A general route to 1,3'-bipyrroles, conversion of cyclohexenone-type systems into phenols and synthetic studies on Coleophomone B

by

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ABSTRACT

Chapter 1 describes a general route for making 1,3'-bipyrroles. This work involves intermolecular conjugate displacement using a special Michael acceptor developed in this laboratory. This method is general and enables the construction of highly substituted 1,3'-bipyrroles. The route was first employed to carry out the total synthesis of Marinopyrrole B by previous laboratory members.

Chapter 2 describes a new family of routes to substituted phenols, including *meta*-substituted phenols, which was discovered during studies on the total synthesis of coleophomone B. This work enables efficient aromatization of 2-bromocyclohex-2-en-1-ones to phenols under very mild conditions. The method has extraordinary broad substrate scope and it is transition-metal free.

Chapter 3 describes synthetic studies towards the total synthesis of coleophomone B. Several different approaches were explored to construct the challenging tricarbonyl system and the strained 11-membered macrocycle. Although the macrocyclization was not achieved, several advanced precursors for cyclization were synthesized and a new aromatization was discovered.

PREFACE

Chapter 1 of this thesis forms part of a research collaboration, led by Dr. Ping Cheng at the University of Alberta, with Professor D. L. J. Clive being the lead collaborator at the University of Alberta. Chapter 1 of this thesis has been published as Cheng, P.; Shao, W.; Clive, D. L. J. "A general route to 1,3'- Bipyrroles." *J. Org. Chem.* **2013**, *78*, 11866–11873. Compound series starting with **22.1** and **22.6** in Chapter 1 were first carried out by Ping Cheng immediately after her graduate studies. Other compounds and data collection were done by myself. D. L. J. Clive was the supervisory author and was involved with concept formation and manuscript composition.

Chapter 2 of this thesis is an original work by Wenjie Shao. It has been published as Shao, W.; Clive, D. L. J. "Synthesis of substituted resorcinol monomethyl ethers from 2-bromo-3-methoxycyclohex-2-en-1-ones." *J. Org. Chem.* **2015**, *80*, 3211–3216. and Shao, W.; Clive, D. L. J. "A Family of Routes to Substituted Phenols, including *meta*-Substituted Phenols." *J. Org. Chem.* **2015**, *80*, 12280-12287. I was responsible for the experiments and data collection. D. L. J. Clive was the supervisory author and was involved with concept formation and manuscript composition.

Chapter 3 of this thesis is an original work by Wenjie Shao. This part has not been previously published.

DEDICATED TO

MY WIFE YUE YIN AND MY FAMILY

ACKNOWLEDGEMENTS

First I would like to give my special thanks to my supervisor Dr. D. L. J. Clive for his strong support throughout my Ph.D. research program. I would not be able to get my Ph.D. without his encouragement and guidance not only in my research area but also in my life. I have not only been trained how to do experiments, but also how to be a real researcher.

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LIST OF ABBREVIATIONS

Ac	Acetyl
Bn	Benzyl
Bu	*n*-Butyl
t-Bu (or Bu-*t*)	*tert*-Butyl
DABCO	1,4-Diazabicyclo[2.2.2]octane
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCC	Dicyclohexylcarbodiimide
DIBAL	Diisobutylaluminum hydride
DMAP	4-Dimethylaminopyridine
DMF	*N*,*N*-Dimethylformamide
DMSO	Dimethyl sulfoxide
FTIR	Fourier transform infrared spectroscopy
KDA	Potassium diisopropylamide
KHMDS	Potassium hexamethyldisilazide
LDA	Lithium diisopropylamide
MRSA	Methicillin-resistant *Staph. aureus*
NFSI	*N*-Fluorobenzenesulfonimide
NaHMDS	Sodium hexamethyldisilazide
NBS	*N*-bromosuccinimide
NCS	*N*-chlorosuccinimide
NMO	*N*-Methyl morpholine-*N*-oxide

PCC	Pyridinium chlorochromate
Pmb	*para*-Methoxybenzyl
SAR	structure-activity relationships
TBAF	Tetrabutylammonium fluoride
THP	Tetrahydropyranyl
TsOH	*p*-Toluenesulfonic acid
Tf	Trifluoromethanesulfonyl
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TOSMIC	Toluenesulfonylmethyl isocyanide
Ts	Toluenesulfonyl

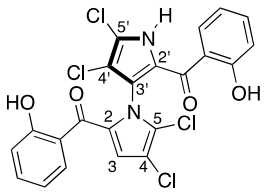
Chapter 1

A general route to 1,3'-bipyrroles

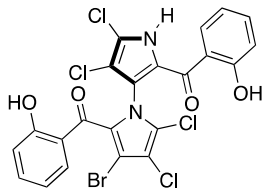
Introduction: Prior literature on the synthesis of 1,3'-bipyrroles

The first part of this Thesis describes a general route to 1,3'-bipyrroles, a project that arose from the total synthesis of marinopyrrole B (**2**) carried out in this laboratory.

The 2008 discovery of marinopyrroles A and B,[1] and the finding that they were extremely active against methicillin-resistant bacteria, generated a great deal of interest in the 1,3'-bipyrrole system because it was felt that it might represent a pharmacophore for drug design.



(-)-marinopyrrole A, (-)-**1**



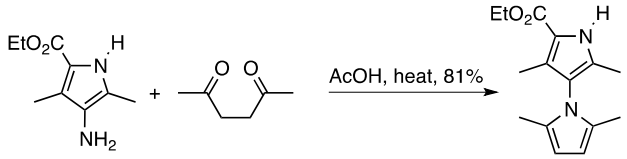
(-)-marinopyrrole B, (-)-**2**

Antibiotics active against methicillin-resistant *Staphylococcus aureus*.

Studies on marinopyrrole synthesis were started promptly after the initial publication on the marinopyrroles, and marinopyrrole A was synthesized along conventional lines, as described later, but attempts to make the more highly substituted marinopyrrole B were unsuccessful until work in this laboratory developed an unusual approach to the system.[2] The route to marinopyrrole B, which is described later, relied on an intermolecular version of a process called intramolecular conjugate displacement developed in this laboratory.[3] When the synthesis of marinopyrrole B, which is based on a method that can accommodate high substitution levels in the lower ring, was finished it was decided — in view of the potential pharmaceutical value of substituted 1,3'-bipyrroles — to see if the approach was general. The biological activity of the marinopyrroles and the possibility that their core structure could serve as a lead in the design of new antibiotics made it worthwhile to generalize, if possible, the route used in the total synthesis. If successful, such a methodology would provide access to numerous analogs for SAR studies.

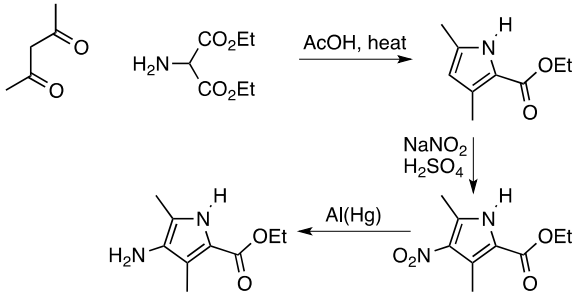
Another reason for undertaking this research was that there are only a few methods for making 1,3'-bipyrroles; evidently, there was very little incentive to prepare such substances until the report of the isolation of marinopyrroles A and B — the first natural products to contain a 1,3'-bipyrrole substructure — and the fact that these substances were active against MRSA. The main prior methods involve the Paal-Knorr or Clauson-Kaas reactions applied to a 3-aminopyrrole, but there are some examples of the use of Ullmann coupling of a halopyrrole with a pyrrole, as well as methods based on the use of TOSMIC.

The earliest 1,3'-bipyrrole synthesis I can find is the report by Treibs,[4] who prepared a single 1,3'-bipyrrole by Paal-Knorr synthesis (Scheme 1).



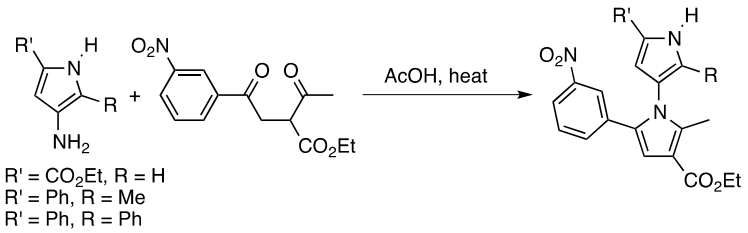
Scheme 1. The first 1,3'-bipyrrole synthesis.

The starting aminopyrrole ester was made by a lengthy route, but the first step is now more conveniently available as follows,[5] while the second and third steps shown are probably the ones used by Treibs.



Scheme 2. Preparation of aminopyrrole ester.

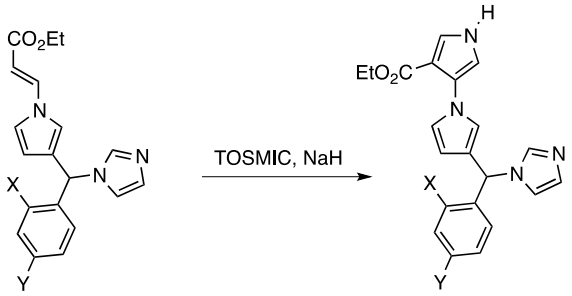
Mingoia *et al*.[6] likewise applied a Paal-Knorr reaction to a group of 3-aminopyrroles (Scheme 3).



Scheme 3. Mingoia's route to 1,3-bipyrroles.

The 1,3'-bipyrroles were converted into pyrrolophenanthridines for use as DNA intercallators.

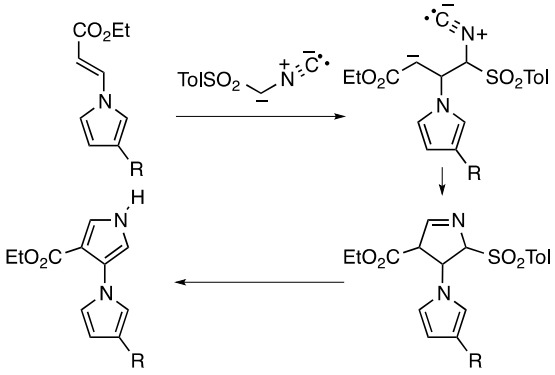
In a study aimed at producing antifungal agents, Di Santo prepared[7] a single 1,3'-bipyrrole by treating an *N*-substituted pyrrole with TOSMIC (Scheme 4).[8]



X,Y various combinations of H, Cl, Me

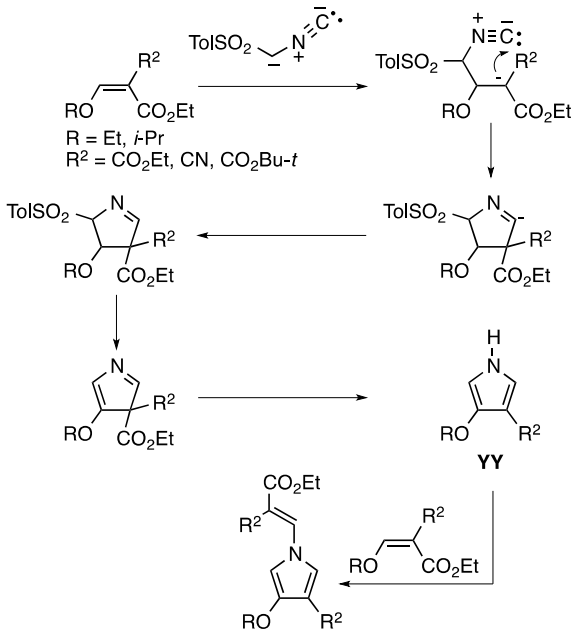
Scheme 4. Di Santo's route to 1,3-bipyrroles.

A plausible mechanism for the reaction with TOSMIC is as follows.[8]



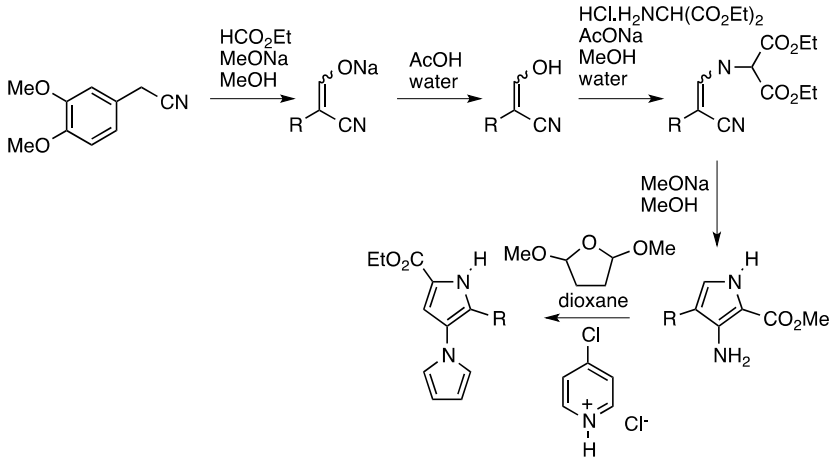
Scheme 5. Mechanism of 1,3'-bipyrrole formation with TOSMIC.

After the report of the isolation of the marinopyrroles several 1,3'-bipyrroles were made by another group (Scheme 6),[9] also using TOSMIC and apparently unaware of the earlier work. The mechanism[8] of the process is also shown in Scheme 6.



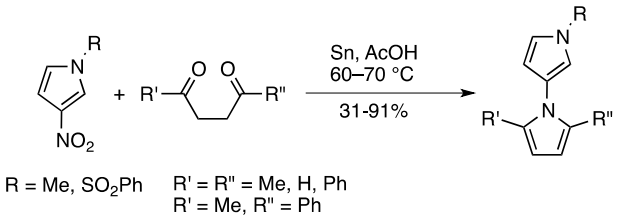
Scheme 6. Mechanism of pyrrole formation with TOSMIC.

A Clauson-Kaas reaction (i.e. acid-catalyzed reaction of an amine with 2,5-dimethoxytetrahyrofuran[10]) was used by Rault[11] to prepare a number of simple 1,3'-bipyrroles as in the following example; the other 1,3'-bipyrroles made had R as various aryl or heteroaryl groups (Scheme 7).



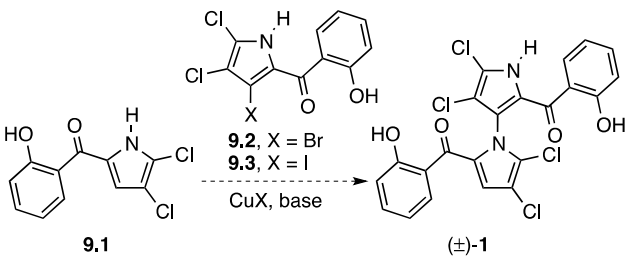
Scheme 7. Use of the Clauson-Kaas reaction.

A very short time after the appearance of their publication in 2008, Fu and Gribble described their Paal-Knorr approach to 1,3'-bipyrroles.[12] In their procedure a 3-nitropyrrole is reduced in AcOH in the presence of a 1,4-diketone or 1,4-dialdehyde so that the intermediate 3-aminopyrrole undergoes the Paal-Knorr reaction in situ (Scheme 8).



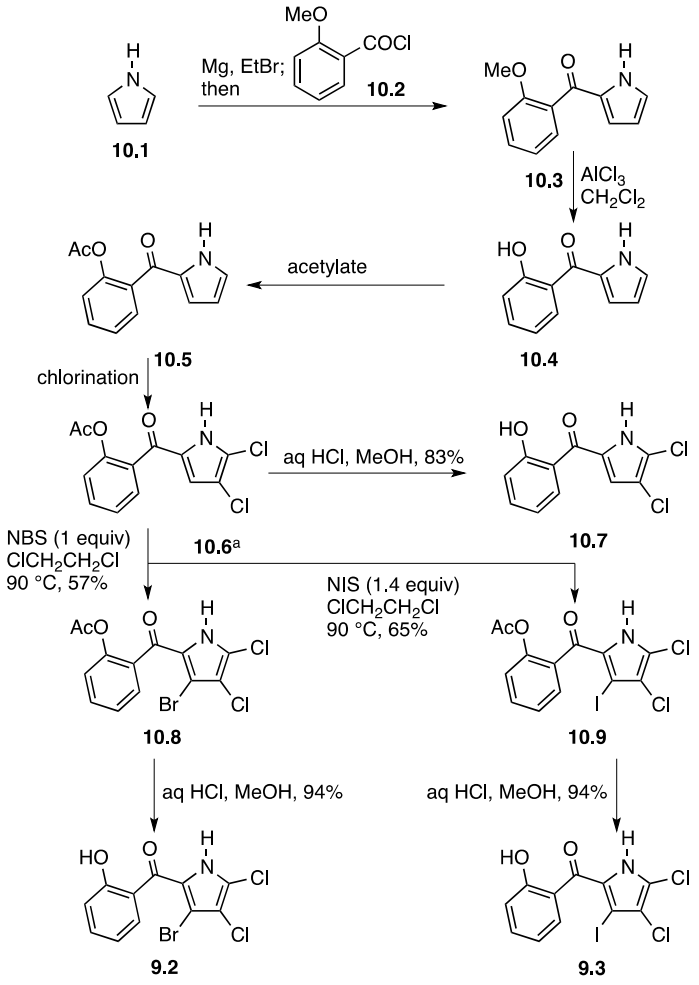
Scheme 8. In situ generation of aminopyrrole for Paal-Knorr synthesis.

The group that isolated the marinopyrroles also made a brief study of synthetic routes to 1,3'-bipyrroles. Their approach was to carry out an Ullmann coupling along the following lines (Scheme 9).[13]



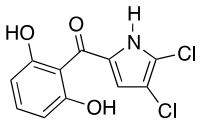
Scheme 9. Ullmann coupling plans for synthesis of marinopyrrole A.

To this end compounds **9.2**, **9.3**, **10.8** and **10.9** were prepared as shown in Scheme 10, largely (up to **10.7**) by analogy to published[14] methods.



[a]Detailed conditions for the preparation of **10.6** are not given.

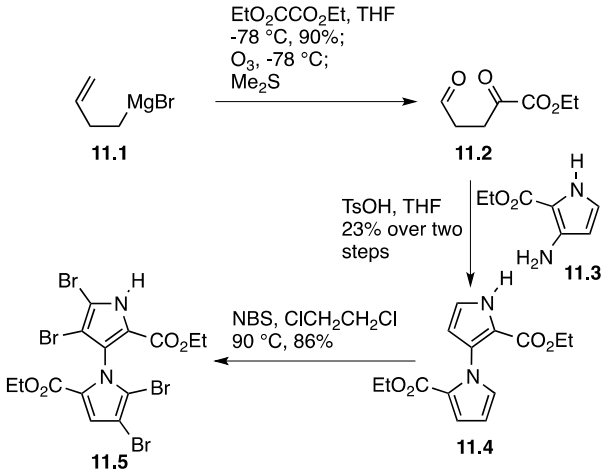
Scheme 10. Synthesis of components of intended Ullmann coupling.



pyoluteorin (**3**)

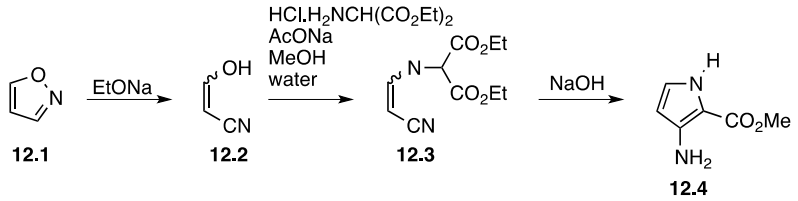
Unfortunately, attempts to effect Ullmann coupling between **10.8**, **10.9**, **9.2** or **9.3** and **10.6** or monodeoxypyoluteorin (**9.1**) were fruitless and it was suggested that this might be due in part to the presence of substituents flanking the coupling site.

Although their attempts to synthesize marinopyrrole A were unsuccessful, the Fenical group did prepare[13] a 1,3'-bipyrrole by the classical method of condensing a 3-aminopyrrole with a 1,4-dicarbonyl compound, as shown in Scheme 11. The 3-aminopyrrole (**11.3**) was made by a literature procedure described below.[15]



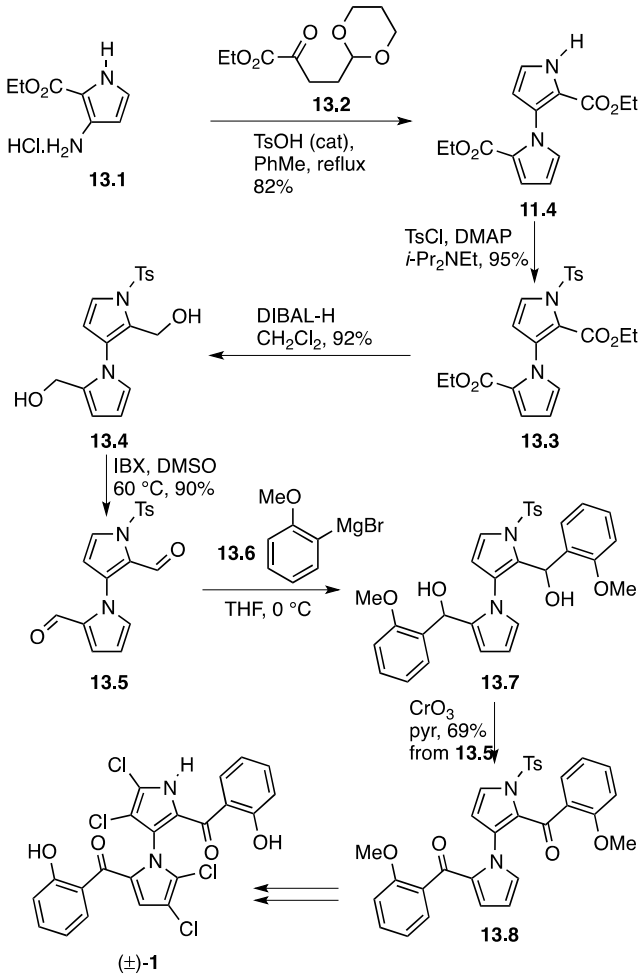
Scheme 11. Synthesis of a 1,3'-bipyrrole by the Fenical group.

Curiously, bipyrrole **11.4** could not be tetrachlorinated, at least with NCS. The 3-aminopyrrole used in the above work was made[15] as shown in Scheme 12.



Scheme 12. Synthesis of methyl 3-aminopyrrole-2-carboxylate.

The next development in the construction of 1,3'-bipyrroles was the synthesis of racemic marinopyrrole A itself,[16] and this was achieved by a slight modification of a Paal-Knorr sequence in the sense that a partially protected 1,4-dicarbonyl compound (**13.2**) was used (Scheme 13).



Scheme 13. Total synthesis of racemic marinopyrrole A.

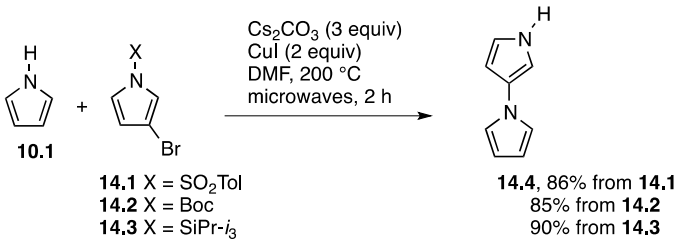
Obviously, the ketal protecting group in **13.2** is removed in situ and so the key step is a Paal-Knorr reaction. The nitrogen of **11.4** was protected as a toluenesulfonamide and the two ester groups were converted by reduction and reoxidation into aldehyde groups so as to set the stage for Grignard addition of *ortho*-anisylmagnesium bromide (**13.5→13.7**). From that point, hydroxyl oxidation, detosylation, tetrachlorination of the pyrrole rings with NCS, and demethylation gave racemic marinopyrrole A. A key observation is that attempts to introduce bromine after the tetrachlorination were unsuccessful, and it has become clear[16,17] that resistance to further halogenation is a general characteristic of tetrachloro- and tetrabromo-1,3'-bipyrroles — at least those that also carry carbonyl substituents at the C-2- and C-2'-positions.

The diol **13.4** has a very curious property: if the oxidation with IBX is done at room temperature only the upper hydroxyl is oxidized. This outcome was later used[18] to advantage by allowing the resulting mono aldehyde to react with a Grignard reagent before oxidizing the other hydroxyl (which, of course, has to be protected before the Grignard reaction); in this way both symmetrically and unsymmetrically arylated 1,3'-bipyrroles were made for SAR studies. In a complementary way, the dialdehyde **13.5** can be ketalized — the bottom aldehyde reacts — so that aryl Grignard reagents can be introduced in a stepwise manner.[19]

Shortly after this synthesis[16] was submitted for publication another route, this time based on Ullman coupling, was reported.[20]

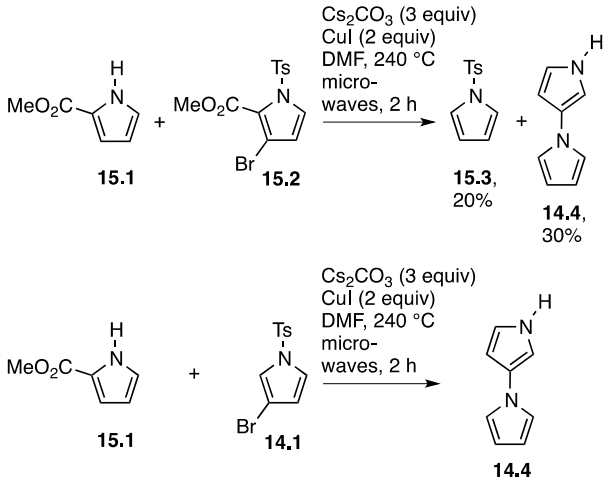
Fenical *et al*. had attempted Ullmann coupling of *polyhalogenated* substrates, but were unsuccessful, as described above; in contrast, the successful use[20] of Ullmann coupling was based on substrates that did not have halogens other than the single bromine needed for the coupling, and in addition, microwave irradiation was employed.

Appropriate conditions were first established with simple compounds. Most attempts were unsuccessful or were unsatisfactory, but it was eventually found that the use of microwave heating was the key, and the following results were obtained (Scheme 14).



Scheme 14. Use of microwaves for Ullmann coupling.

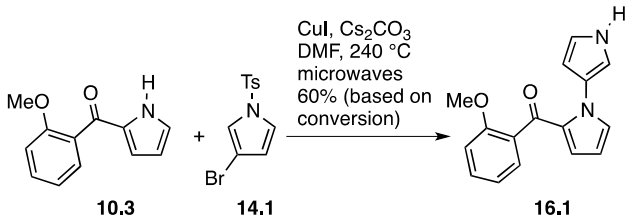
The method was next extended to a pyrrole ester and it was found that a higher temperature was required (240 °C). In addition, ester hydrolysis, decarboxylation and loss of the nitrogen protecting group occurred as shown in Scheme 15.



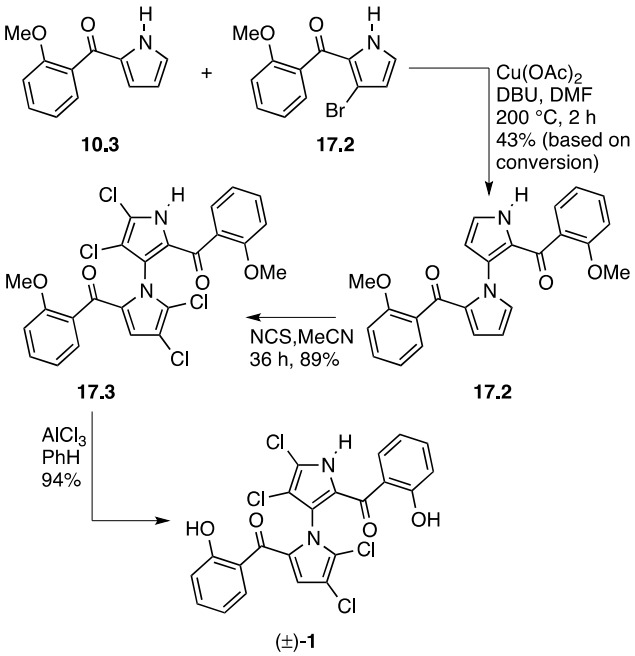
Scheme 15. Further examples of Ullmann coupling to make 1,3'-bipyrroles.

Once the Ullmann conditions had been established, they were applied to the natural product synthesis.

Coupling of the two components **10.3** and **14.1** gave a 60% yield (corrected for recovered starting material) (Scheme 16), but a more convergent approach was achieved by coupling of **10.3** with the more advanced subunit **17.1** (43%) (Scheme 17). The resulting bipyrrole **17.2** was



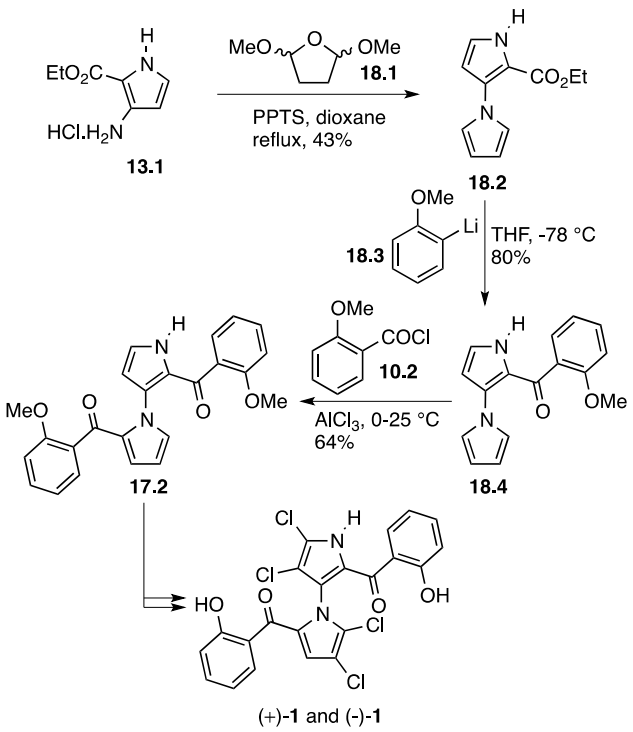
Scheme 16. Ullmann coupling in the synthesis of racemic marinopyrrole A.



Scheme 17. Synthesis of marinopyrrole A via Ullmann coupling.

chlorinated with NCS (89%) reaction, and then demethylation with $AlCl_3$ afforded racemic marinopyrrole A [(±)-**1**].

A short time after the publication of the above microwave-based method, Nicolaou *et al*. reported[17] another synthesis of racemic marinopyrrole A. Like earlier approaches, the route made use of the Clauson-Kaas reaction to form a monosubstituted 1,3'-bipyrrole (Scheme 18).



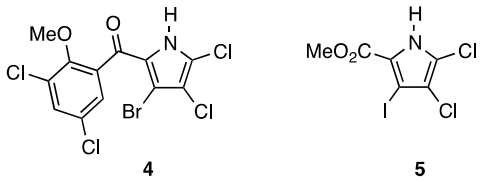
Scheme 18. The Nicolaou route to marinopyrrole A.

Both components for bipyrrole assembly were known compounds and the subsequent steps involved introduction by Grignard reaction of one of the anisoyl groups (**18.2→18.4**) and acylation to attach the other. After chlorination of **17.2**, HPLC resolution on a chiral column, allowed separation of the atropisomers so that demethylation with BBr_3 gave each of the enantiomers of marinopyrrole A. Tetrabromination of **17.2** was also achieved but neither the tetrachloro nor the tetrabromo compounds could be further brominated; consequently, marinopyrrole B was not accessible by the route that leads to marinopyrrole A.

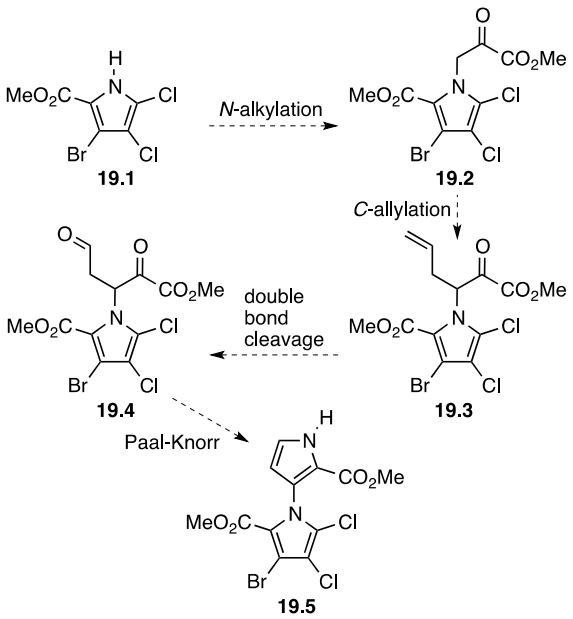
Several analogs of marinopyrrole A were easily made by simple modification of intermediates in the above route, but no new methodologies for 1,3'-bipyrrole assemble were involved. The ability to acylate the unsubstituted pyrrole ring (cf **18.4→17.2**) has been used to generate numerous unsymmetrically substituted analogs.[21]

As indicated above, attempts in other laboratories to prepare marinopyrrole B had been unsuccessful, but a route to this compound was eventually developed[2] in this laboratory. It was based on the fact that a fully halogenated *mono*pyrrole is easily accessible — compounds **4**[22] and **5**[23] were known — so that the difficulties of introducing the bromine onto a fully assembled 1,3'-

bipyrrole could be avoided if a monopyrrole were *N*-alkylated in such a way that the alkyl group attached to the nitrogen was so constituted as to allow formation of a pyrrole ring. Both **4** and **5** had been made before the discovery of the marinopyrroles and their synthesis had nothing to do with the problem of making 1,3'-bipyrroles.



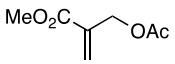
Accordingly, the planned approach was along the lines summarized in Scheme 19.



Scheme 19. Planned route to marinopyrrole B.

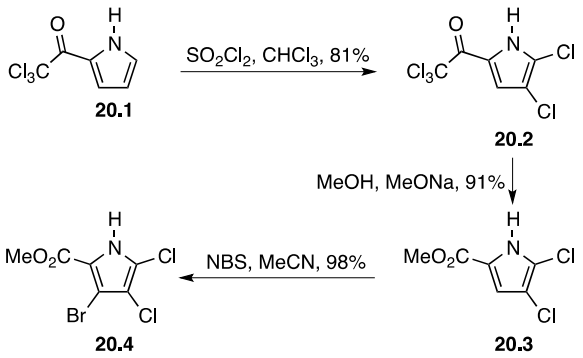
In the event, alkylating the nitrogen of trihalopyrrole **19.1** proved troublesome and the obvious approach of reaction with bromopyruvate did not work. Fortunately, prior work in this laboratory on intramolecular conjugate displacement[3] had familiarized the group with the fact that Michael acceptors carrying an acetate in the allylic position, as in **6** are far more reactive

than ordinary Michael acceptors lacking the acetate leaving group. This characteristic proved to be the key to the development of a route to marinopyrrole B.



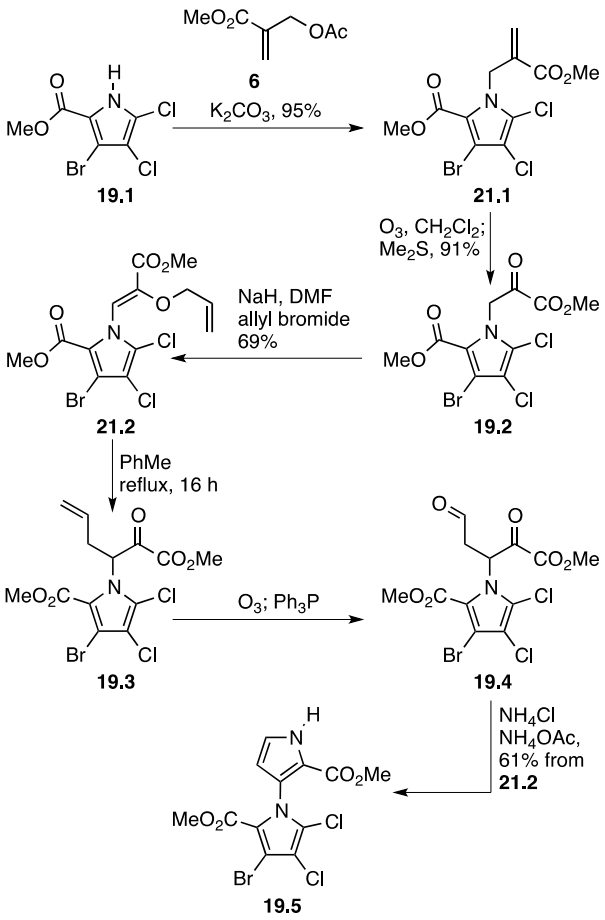
6

The requisite fully substituted monopyrrole was prepared as follows, based on general methods reported in the literature.



Scheme 20. Synthesis of fully halogenated pyrrole needed for synthesis of marinopyrrole B.

When the trihalopyrrole **19.1** was treated with the special Michael acceptor **6**, smooth *N*-alkylation occurred (Scheme 21).



Scheme 21. First phase of the route to marinopyrrole B.

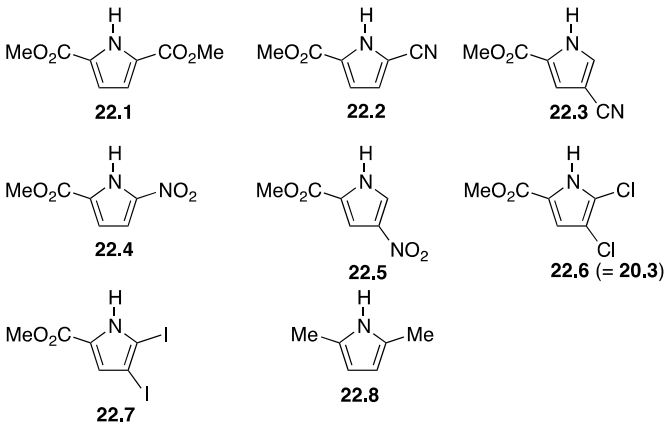
The double bond in **21.1** was cleaved by standard ozonolysis, and allylation generated the *O*-allyl compound **21.2**. This was not a setback, because simply heating in PhMe resulted in Claisen rearrangement to the desired *C*-allyl compound **19.3**. A second application of ozonolytic cleavage produced aldehyde ketone **19.4** which underwent a classical Paal-Knorr reaction to generate the desired 1,3'-bipyrrole **19.5**. That compound was then transformed into the target marinopyrrole B by obvious standard methods already precedented in the published[16] work on marinopyrrole A.

This route is the only one that gives marinopyrrole B and it does this by avoiding the difficulties of fully halogenating a 1,3'-bipyrrole. As such, the route held promise of giving access to an increased range of marinopyrrole analogs for SAR studies; hitherto, such studies have been limited to the marinopyrrole A core. As described in the following Discussion Section of this Thesis, the approach was generalized and extended to a range of substituents.

Results and Discussion

As a result of the successful synthesis of marinopyrrole B in this laboratory and the expectation that 1,3'-bipyrroles might be a fruitful scaffold for development of antibiotics, it was decided to establish if the method used in the marinopyrrole synthesis was indeed general.

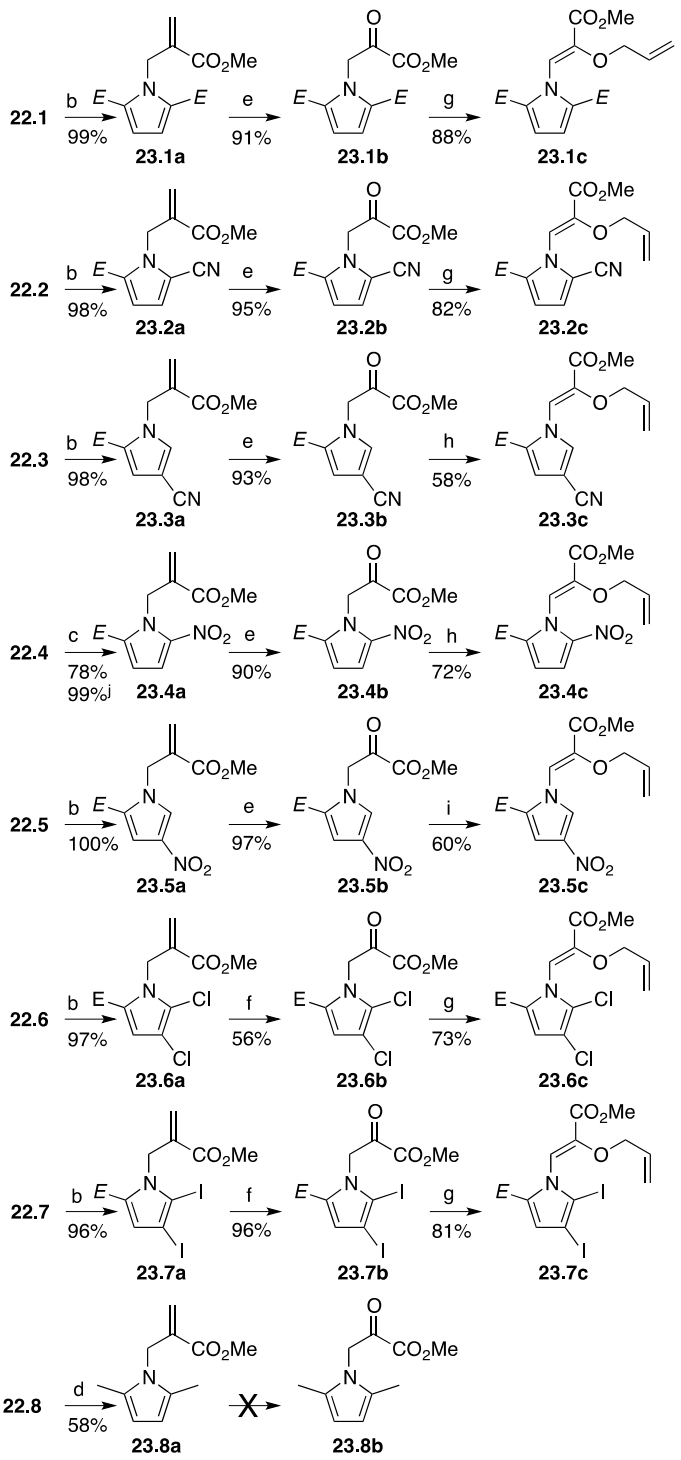
The project started with the preparation of highly substituted monopyrrole units. All these compounds (Scheme 22) were known and their preparation by the literature methods was easily scaled up to gram scale. Most of these monopyrrole units contain electron-withdrawing groups except the dimethyl pyrrole **22.8**. Diiodide pyrrole **22.7** was also examined because it may not tolerate the previous Ullman coupling method and so its successful use in the present approach would illustrate an advantage.



Scheme 22. Starting monopyrrole units for 1,3'-bipyrrole synthesis.

These monopyrroles were transformed into the adducts listed in the following Table[24] by *N*-alkylation in the presence of the special Michael acceptor **6** and K_2CO_3 in refluxing MeCN. The yields were generally excellent, except for the dimethyl pyrrole **22.8** and the 5-nitropyrrole **22.4**, which gave an extremely low yield under my standard K_2CO_3/MeCN conditions. We found that the poor yield for dimethylpyrrole is the result of a side reaction, which is a Michael addition between the initial adduct **23.8a** and the starting dimethylpyrrole. The yield was increased to 58% using NaH as the base and DMF as the solvent. In the case of 5-nitropyrrole **22.4**, the presence of 18-crown-6 (1 equiv) is essential and Na_2CO_3 was used instead of K_2CO_3 in order to get a satisfactory yield. In the absence of the crown ether, only starting material was

recovered in quantitative yield. We found that Na_2CO_3/crown ether gave a much higher yield than the use of K_2CO_3/crown ether, as the latter combination gave only a trace amount of the desired product and the starting material was also largely recovered. Apart from these exceptions, all the *N*-alkylations were done in the same way, and the process is clearly a general one.

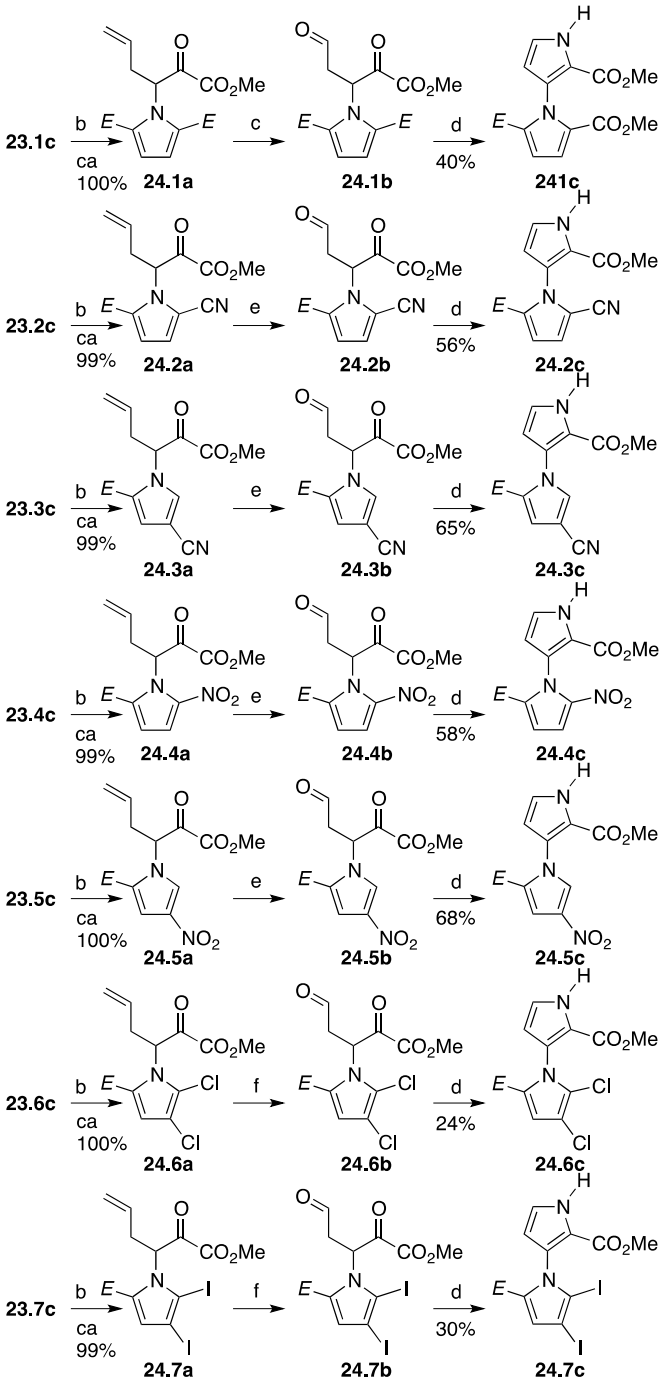


[a]E = CO_2Me. [b]K_2CO_3, MeCN. [c]Na_2CO_3, 18-crown-6, MeCN. [d]NaH, DMF. [e]O_3, Sudan Red 7B; Me_2S. [f]OsO_4, NMO; $Pb(OAc)_4$. [g]NaH, DMF, allyl bromide. [h]K_2CO_3, DMF, allyl bromide. [i]K_2CO_3, 18-crown-6, DMF, allyl bromide. [j]Corrected for recovered **22.4**.

Table 1. Preparation of *O*-allyl ethers.

Double bond cleavage, which is the next step, was usually achieved by ozonolysis and high yields were obtained with the aid of a trace amount Sudan Red 7B[25] as an indicator. Ozonolysis of the dihalo compounds **23.6a**, **23.7a** gave lower yields and so these compounds were converted into their α-ketoesters in two steps: dihydroxylation with OsO_4/NMO[26] and then diol cleavage with $Pb(OAc)_4$. In the case of dimethylpyrrole **23.8a**, several attempts were made to cleave the double bond without interfering with the pyrrole nucleus. Unfortunately, these experiments were unsuccessful. Even with only 1 equiv O_3 delivered to the system via Rubin's apparatus,[27] the pyrrole ring was degraded. Other reagents, such as $RuCl_3/NaIO_4$, $RuCl_3$/Oxone, OsO_4/NMO, led to complex mixtures. At this stage, we concluded that probably our route is not suitable for pyrroles carrying only electron-donating groups.

Allylation of the α-keto esters with allyl bromide afforded the *O*-allyl products in good yields. Efforts were made to optimize the reaction conditions so that we were able to obtain the best results. Depending on the starting materials, K_2CO_3 or NaH were employed and the yields of allylation varied from 58–88%. It is worth noting that in the case of the 4-nitro α-keto ester **23.5b**, 18-crown-6 is necessary, as without this additive, aldol condensation between two molecules of α-keto ester **23.5b** predominates and only a trace of *O*-allyl product **23.5c** was obtained. The geometry of the *O*-allyl products was not established for every case but for one example, the diester product **23.1c**, the *Z* geometry was determined by single crystal X-ray analysis. The double bond geometry of the other compounds was arbitrarily assigned as *Z*, but the actual geometry of the *O*-allyl compounds is of no consequence as the double bond is removed by the subsequent Claisen rearrangement.



[a]E = CO_2Me. [b]PhMe, reflux. [c]O_3,MeOH-CH_2Cl_2, –78 °C; Ph_3P. [d]NH_4OAc, AcOH, yields are calculated over three steps from *O*-allyl ethers. [e]O_3, CH_2Cl_2, Sudan Red 7B, CH_2Cl_2, –78 °C; Me_2S. [f]OsO_4, NMO; $Pb(OAc)_4$.

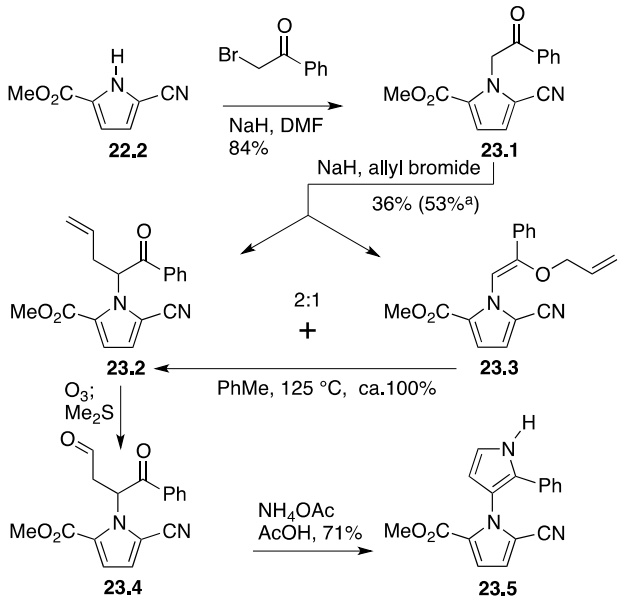
Table 2. Formation of 1,3'-bipyrroles.

The classical Claisen rearrangement of the *O*-allyl vinyl ethers went smoothly in refluxing PhMe, giving almost quantitative yields without any necessity for purification by flash column chromatography. Evaporation of the PhMe solutions gave very clean products, which were used directly in the next step. During this thermal rearrangement, we noticed that *O*-allyl ethers **23.3c** and **23.5c**, both without *two* functional groups flanking the nitrogen atom, showed some tendency to isomerize to their *C*-allyl products **24.3a** and **24.5a** even at room temperature in C_6D_6 and $CDCl_3$. Isomerization of the diiodide **23.7c** into its *C*-allyl product **24.7a** was rather slow, compared with the other examples, but the refluxing time should not be prolonged beyond 40 h in order to achieve best results.

The second double bond cleavage, this time to generate an aldehyde group, was also carried out by two methods: ozonolysis, along with Sudan Red 7B as an indicator or dihydroxylation with OsO_4/NMO, followed by diol cleavage with $Pb(OAc)_4$. The resulting intermediate 1,4-keto aldehydes were rather sensitive and fairly unstable. These aldehydes tended to undergo β-elimination, losing the bottom pyrrole unit. No spectral data were acquired at this stage due to the instability of these keto aldehydes. We tried to reduce the tendency of these 1,4-keto aldehydes to decompose and finally we were fortunate to find that when the oxidation reaction mixtures were worked up at a low temperature (no higher than 15 °C), these compounds could be used immediately in the next step without purification and acceptable yields were obtained (56–68% over three steps). In the case of **24.2a→24.2c**, room temperature work-up gave a 43% yield compared with 56% when worked up at low temperature. The double bond cleavage for halogenated keto aldehydes **24.6a** and **24.7a** was achieved by dihydroxylation and diol cleavage, the same process as for the first double bond cleavage. Even though special manipulation (low temperature technique) was followed during the diol cleavage, Paal-Knorr reaction on these halogenated keto aldehydes resulted in lower yields (24–30% over three steps), probably owing to the more serious decomposition issue. Nevertheless, our approach gave highly substituted 1,3'-bipyrroles, which would be difficult to make by existing methods.

Inspired by the success of our approach to the 1,3'-bipyrrole system, we examined the necessity of having an ester group at C-2' of the newly generated pyrrole ring (top pyrrole ring). α-Bromoacetophenone was used to react with the monopyrrole **22.2**, and this led to the *N*-alkylated substrate **23.1** in 87% yield. Allylation of **23.1** gave both *O*-allyl and *C*-allyl products in 36% yield (56% if corrected for recovered **23.1**) in a ratio of 1:2, and the former was

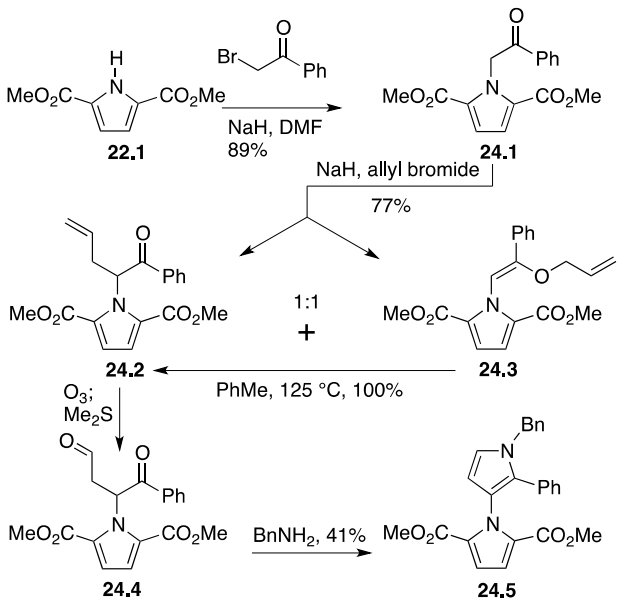
rearranged to the latter product by standard Claisen rearrangement in refluxing PhMe. We were pleased that the double bond cleavage and Paal-Knorr reaction gave the desired 1,3'-bipyrrole product **23.5** in 71% yield. We assume that the presence of the phenyl group somehow lowered the β-elimination tendency observed in the other cases.



[a]Corrected for **23.1**.

Scheme 23. Phenyl-substituted 1,3'-bipyrrole formation.

Compound **24.5** was also made by a similar route as shown in Scheme 26. Allylation of **24.1** also gave both *O*-allyl and *C*-allyl products in 77% yield in a ratio of ca. 1:1 and, as before, the former isomer was converted into the latter by heating in refluxing PhMe. Double bond cleavage by ozone, followed by iodine catalyzed[28] Paal-Knorr reaction with benzylamine, afforded **24.5** in 41% yield over three steps.



Scheme 24. *N*-Protected 1,3'-bipyrrole formation.

Conclusion

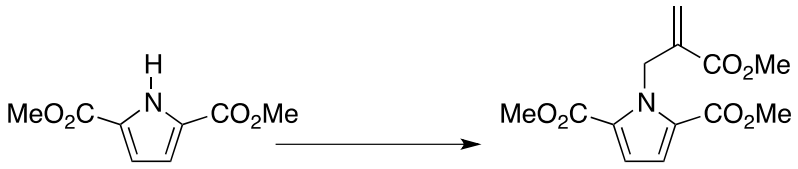
Our results show that we have established a reliable route to generate highly substituted 1,3'-bipyrroles. The essential feature of our approach is that we alkylate the pyrrole nitrogen in such a way that the alkyl group can be elaborated into a substructure that is appropriate to undergo a Paal-Knorr reaction with ammonia. This approach tolerates very well a wide range of electron-withdrawing groups on the initial pyrrole ring. Electron-donating groups (at least methyl) turned out to be unsuitable for our approach, as the double bond of the *N*-alkylated product could not be transformed into the ketone by the methods we tried. It is not essential to have an ester group on the newly-formed pyrrole ring, as a phenyl group can be used equally well. The method described here should be useful in SAR studies based on 1,3'-bipyrroles.

Experimental Section

In order to have all the work on the present methodology in this Thesis I have included the preparation of compound series starting with **22.1** and **22.6**, which were first carried out by Ping Cheng immediately after her graduate studies.[28]

General Procedures. Solvents used for chromatography were distilled before use. Commercial thin layer chromatography plates (silica gel, Merck 60F-254) were used. Silica gel for flash chromatography was Merck type 60 (230–400 mesh). Dry solvents were prepared under an inert atmosphere and transferred by syringe or cannula. The symbols s, d, t and q used for ^{13}C NMR spectra indicate zero, one, two, or three attached hydrogens, respectively, the assignments being made from APT spectra. Solutions were evaporated under water pump vacuum and the residue was then kept under oil pump vacuum. High resolution electrospray mass spectrometry analyses were done on an orthogonal time of flight analyzer.

2,5-Dimethyl 1-(3-methoxy-2-methylidene-3-oxopropyl)-1*H*-pyrrole-2,5-dicarboxylate (23.1a).[24]

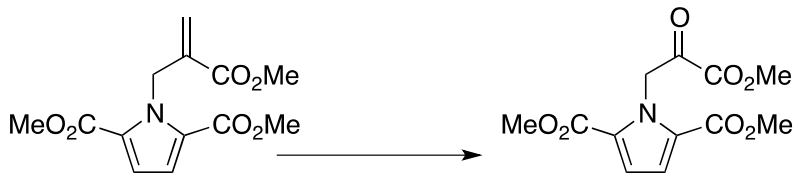


22.1 **23.1a**

A solution of **6**[29] (529.2 mg, 3.348 mmol) in MeCN (5 mL) was added to a stirred suspension of K_2CO_3 (1.25 g, 8.95 mmol) in a solution of **22.1**[30] (408.6 mg, 2.231 mmol) in MeCN (25 mL). The mixture was refluxed for 12 h, cooled, diluted with water and extracted with CH_2Cl_2. The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2.8 x 20 cm), using 1:10 EtOAc-hexanes, gave **23.1a** (621.1 mg, 99%) as a white solid: mp 77–81 °C; FTIR ($CDCl_3$, cast) 1728 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 3.78 (s, 3 H), 3.79 (s, 6 H), 4.69 (apparent t, J = 1.5 Hz, 1 H), 5.73 (apparent t, J = 1.5 Hz, 2 H), 6.11 (apparent t, 1 H), 6.93 (s, 2 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ

46.8 (t), 51.6 (q), 51.9 (q), 116.9 (d), 122.9 (t), 127.4 (s), 138.2 (s), 160.6 (s), 165.6 (s); exact mass (electrospray) *m*/*z* calcd for $C_{13}H_{15}NNaO_6$ $(M + Na)^+$ 304.0792, found 304.0788.

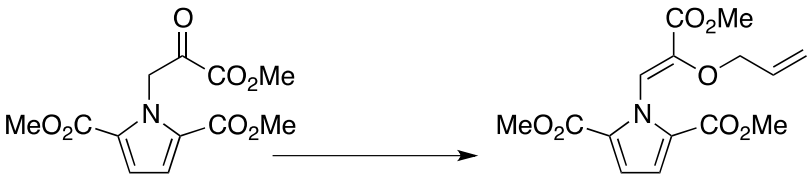
2,5-Dimethyl 1-(3-methoxy-2,3-dioxopropyl)-1*H*-pyrrole-2,5-dicarboxylate (23.1b).



23.1a **23.1b**

A stream of ozonized oxygen was bubbled through a stirred and cooled (-78 °C) solution of **23.1a** (1.17 g, 3.15 mmol) in CH_2Cl_2 (20 mL). After 18 min, the solution became blue, and O_2 was then bubbled through the solution for 20 min to remove the excess of O_3. Me_2S (1.80 mL, 24.2 mmol) was then added, the cold bath was removed, and stirring was continued for 4 h. Evaporation of the solvent and flash chromatography of the residue over silica gel (2.8 x 25 cm), using 1:5 to 3:10 EtOAc-hexanes, gave **23.1b** (625.5 mg, 91%) as a white solid: mp 84–87 °C; FTIR ($CDCl_3$, cast) 1761, 1722 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 3.79 (s, 6 H), 3.94 (s, 3 H), 6.23 (s, 2 H), 6.96 (s, 2 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 51.8 (q), 53.2 (q), 53.5 (t), 117.0 (d), 127.2 (s), 159.9 (s), 161.2 (s), 186.9 (s); exact mass (electrospray) *m*/*z* calcd for $C_{12}H_{13}NNaO_7$ $(M + Na)^+$ 306.0584, found 306.0584.

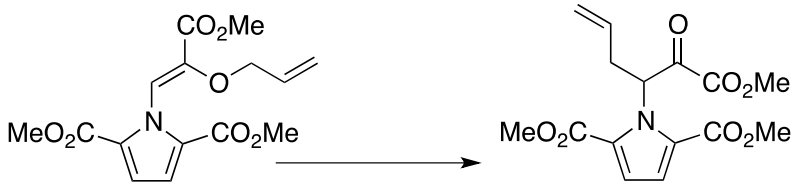
2,5-Dimethyl 1-[(1*Z*)-3-methoxy-3-oxo-2-(prop-2-en-1-yloxy)prop-1-en-1-yl]-1*H*-pyrrole-2,5-dicarboxylate (23.1c).



23.1b **23.1c**

NaH (60% w/w in oil, 16.0 mg, 0.400 mmol) was added to a stirred and cooled (–42 °C) solution of **23.1b** (87.0 mg, 0.307 mmol) in DMF (5 mL). After 20 min, allyl bromide (0.033 mL, 0.38 mmol) was added. The reaction flask was transferred to a single-walled cold bath at –42 °C, and stirring was continued for 2 h, during which time the reaction mixture reached room temperature. Stirring was continued for a further 8 h, saturated aqueous NH_4Cl was added and the mixture was extracted with Et_2O and then with EtOAc. The combined organic extracts were washed with water, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1.8 x 20 cm), using 3:50 to 3:20 EtOAc-hexanes, gave **23.1c** (87.9 mg, 88%) as a white solid: mp 81–84 °C; FTIR ($CDCl_3$, cast) 1732 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 3.79 (s, 6 H), 3.83 (s, 3 H), 4.17 (apparent dt, J = 7.0, 1.0 Hz, 2 H), 4.98–5.04 (m, 2 H), 5.45–5.55 (m, 1 H), 6.90 (s, 2 H), 7.89 (s, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 51.8 (q), 52.3 (q), 72.9 (t), 117.0 (d), 118.2 (t), 123.2 (d), 128.8 (s), 132.6 (d), 141.0 (s), 160.5 (s), 163.5 (s); exact mass (electrospray) m/z calcd for $C_{15}H_{17}NNaO_7$ $(M + Na)^+$ 346.0897, found 346.0895. A sample was crystallized from *i*-Pr_2O for X-ray analysis.

2,5-Dimethyl (±)-1-(1-methoxy-1,2-dioxohex-5-en-3-yl)-1*H*-pyrrole-2,5-dicarboxylate (24.1a).

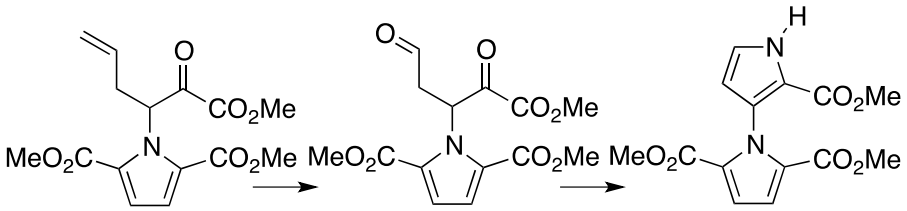


23.1c **24.1a**

A solution of **23.1c** (427.8 mg, 1.323 mmol) in PhMe (10 mL) was stirred and refluxed for 21.5 h and then cooled to room temperature. Evaporation of the solution gave **24.1a** as a white solid (427.6 mg, 100%), which was used directly in the next step: mp 100-102 °C; FTIR ($CDCl_3$, cast) 1759, 1723 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 2.59–2.66 (m, 1 H), 3.19–3.24 (m, 1 H), 3.69 (s, 3 H), 3.83 (s, 6 H), 4.83 (dm, J = 7.0 Hz, 1 H), 4.86 (apparent t, J = 1.0 Hz, 1 H), 5.54–5.63 (m, 1 H), 6.95 (s, 2 H), 7.09 (dd, J = 10.0, 4.5 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 35.4 (t), 52.0 (q), 52.7 (q), 62.3 (d), 117.6 (d), 118.5 (t), 127.2 (s), 132.6 (d), 161.5 (s), 161.6

(s), 188.1 (s); exact mass (electrospray) *m/z* calcd for $C_{15}H_{17}NNaO_7$ $(M + Na)^+$ 346.0897, found 346.089.

2,5-Dimethyl (±)-1-(1-methoxy-1,2,5-trioxopentan-3-yl)-1*H*-pyrrole-2,5-dicarboxylate (24.1b) and 2,5-Dimethyl 1-[2-(methoxycarbonyl)-1*H*-pyrrol-3-yl]-1*H*-pyrrole-2,5-dicarboxylate (24.1c).



24.1a **24.1b** **24.1c**

A stream of ozonized oxygen was bubbled through a stirred and cooled (–78 °C) solution of the above crude keto ester (**24.1a**) (427.6 mg, 1.323 mmol) in a mixture of MeOH (7 mL) and CH_2Cl_2 (7 mL). After 22 min, the solution became blue and O_2 was then bubbled through the solution for 20 min to remove the excess of O_3. Ph_3P (702 mg, 2.65 mmol) was added, the cooling bath was left in place but not recharged, and stirring was continued for 15 h. Evaporation of the solution gave **24.1b** as a yellow residue, which was used directly in the next step.

NH_4OAc (1.62 g, 21.0 mmol) was added to a stirred solution of the above crude keto aldehyde **24.1b** in AcOH (9 mL) and stirring was continued for 30 min. Water was then added and the mixture was extracted with CH_2Cl_2. The combined organic extracts were washed with saturated aqueous $NaHCO_3$ and brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2.2 x 25 cm), using 1:5 to 1:2 EtOAc-hexanes, gave **24.1c** (161.6 mg, 40% over three steps) as a white solid: mp 143–149 °C; FTIR ($CDCl_3$, cast) 3327, 3139, 1736, 1708 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 3.60 (s, 3 H), 3.72 (s, 6 H), 6.29 (apparent t, J = 3.0 Hz, 1 H), 6.92 (apparent t, J = 3.0 Hz, 1 H), 7.02 (s, 2 H), 9.26 (br, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 51.3 (q), 51.5 (q), 110.6 (d), 116.7 (d), 117.6 (s), 120.5 (d), 128.1 (s), 129.1 (s), 159.8 (s), 160.3 (s); exact mass (electrospray) *m/z* calcd for $C_{14}H_{14}N_2NaO_6$ $(M + Na)^+$ 329.0744, found

329.0738. A sample was crystallized from $CHCl_3$ for X-ray analysis.

Methyl 5-cyano-1-(3-methoxy-2-methylidene-3-oxopropyl)-1*H*-pyrrole-2-carboxylate (23.2a).

22.2 **23.2a**

K_2CO_3 (1.98 g, 14.3 mmol) was added to a stirred solution of **22.2**[31] (537 mg, 3.58 mmol) and ester **6**[29] (647 mg, 4.09 mmol) in MeCN (30 mL). The resulting mixture was stirred and refluxed for 10 h, cooled to room temperature, diluted with water and extracted with CH_2Cl_2. The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (3 x 20 cm), using 1:6 EtOAc-hexane, gave **23.2a** (870 mg, 98%) as a white solid: mp 77–80 °C; FTIR ($CDCl_3$, cast) 2227, 1720 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 3.81 (s, 3 H), 3.83 (s, 3 H), 4.93 (apparent t, *J* = 2.0 Hz, 1 H), 5.38 (apparent t, *J* = 2.0 Hz, 2 H), 6.27 (apparent t, *J* = 2.0 Hz, 1 H), 6.82 (d, *J* = 4.0 Hz, 1 H), 6.96 (d, *J* = 4.0 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 47.9 (t), 51.9 (q), 52.2 (q), 110.8 (s), 112.0 (s), 117.5 (d), 118.7 (d), 125.1 (t), 126.7 (s), 136.3 (s), 159.8 (s), 165.1 (s); exact mass (electrospray) *m/z* calcd for $C_{12}H_{12}N_2NaO_4$ $(M + Na)^+$ 271.0689, found 271.0684.

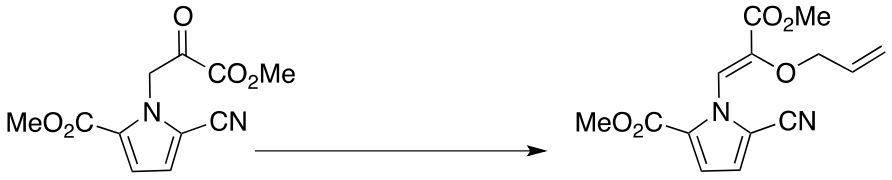
Methyl 5-cyano-1-(3-methoxy-2,3-dioxopropyl)-1*H*-pyrrole-2-carboxylate (23.2b).

23.2a **23.2b**

A slow stream of ozonized oxygen was bubbled via a Pasteur pipette through a stirred

and cooled (–78 °C) solution of **23.2a** (301 mg, 1.21 mmol) and Sudan Red 7B (1.6 mg) in CH_2Cl_2 (24 mL). When the color changed from red to light yellow, the O_3 flow was stopped and O_2 was bubbled through the solution for 15 min at –78 °C. Me_2S (0.45 mL, 6.1 mmol) was then added. The cold bath was left in place, but not recharged, and stirring was continued for 5 h, during which time the reaction mixture reached room temperature. The mixture was washed with water and brine, and the organic extract was dried ($MgSO_4$) and evaporated to give **23.2b** (289 mg, 95%) as an almost white solid that was used directly in the next step: mp 100–105 °C; FTIR ($CDCl_3$, cast) 2229, 1761, 1739, 1713 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 3.81 (s, 3 H), 3.97 (s, 3 H), 5.70 (s, 2 H), 6.85 (d, J = 4.5 Hz, 1 H), 6.98 (d, J = 4.5 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 52.1 (q), 53.5 (q), 54.2 (s), 111.0 (s), 111.8 (s), 117.4 (d), 119.0 (d), 126.5 (s), 159.4 (s), 160.4 (s), 185.1 (s); exact mass (electrospray) m/z calcd for $C_{11}H_{11}N_2O_5$ $(M + H)^+$ 251.0662, found 251.0657.

Methyl 5-cyano-1-[(1*Z*)-3-methoxy-3-oxo-2-(prop-2-en-1-yloxy)prop-1-en-1-yl]-1*H*-pyrrole-2-carboxylate (23.2c).



23.2b **23.2c**

A solution of **23.2b** (780 mg, 3.12 mmol) in DMF (20 mL) was added over 10 min to a stirred and cooled (–40 °C) mixture of NaH (60% w/w in mineral oil, 150 mg, 3.76 mmol) and DMF (16 mL). Stirring at –40 °C was continued for 30 min, and allyl bromide (0.35 mL, 4.13 mmol) was added dropwise over *ca*. 5 min. The cold bath was left in place, but not recharged, and stirring was continued overnight. The reaction mixture was diluted with saturated aqueous NH_4Cl, and extracted with EtOAc. The combined organic extracts were washed with brine, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (3 x 20 cm), using 1:10 EtOAc-hexane to 1:4 EtOAc-hexane, gave **23.2c** (740 mg, 82%) as a white solid: mp 72–75 °C; FTIR ($CDCl_3$, cast) 3136, 2231, 1776, 1728 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 3.84

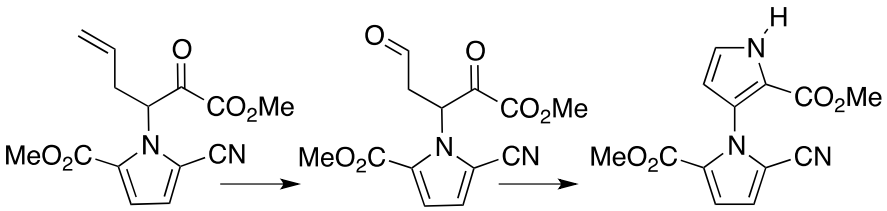
(s, 3 H), 3.87 (s, 3 H), 4.48 (ddd, *J* = 6.0, 1.0, 1.0 Hz, 2 H), 5.12 (ddd, *J* = 10.0, 2.5, 1.0 Hz, 1 H), 5.17 (ddd, *J* = 17.0, 3.0, 1.5 Hz, 1 H), 5.73 (ddt, *J* = 17.5, 10.0, 6.0 Hz, 1 H), 6.87 (d, *J* = 4.0 Hz, 1 H), 6.96 (d, *J* = 4.0 Hz, 1 H), 7.55 (s, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 52.1 (s), 52.6 (s), 110.8 (s), 112.1 (s), 117.3 (d), 118.7 (t), 119.5 (d), 120.0 (d), 127.5 (s), 132.5 (d), 142.9 (s), 159.7 (s), 162.8 (s); exact mass (electrospray) *m*/*z* calcd for $C_{14}H_{15}N_2O_5$ $(M + H)^+$ 291.0975, found 291.0976.

Methyl (±)-5-cyano-1-(1-methoxy-1,2-dioxohex-5-en-3-yl)-1*H*-pyrrole-2-carboxylate (24.2a).

23.2c **24.2a**

A solution of **23.2c** (494 mg, 1.70 mmol) in PhMe (17 mL) was refluxed for 18 h, cooled and evaporated to afford **24.2a** (491 mg, *ca*. 99%) as a thick, light yellow oil: FTIR ($CDCl_3$, cast) 2227, 1736, 1717 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.72–2.84 (m, 1 H), 3.19–3.25 (m, 1 H), 3.78 (s, 3 H), 3.85 (s, 3 H), 4.97–5.02 (m, 2 H), 5.59–5.67 (m, 1 H), 5.97 (br, 1 H), 6.82 (d, *J* = 4.5 Hz, 1 H), 6.97 (d, *J* = 4.0 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 34.6 (t), 52.3 (q), 53.2 (q), 64.4 (d), 111.9 (s), 112.4 (s), 118.3 (d), 119.3 (d), 120.0 (t), 125.9 (s), 131.3 (d), 160.6 (s), 160.8 (s), 186.5 (s); exact mass (electrospray) *m*/*z* calcd for $C_{14}H_{14}N_2NaO_5$ $(M + Na)^+$ 313.0795, found 313.0788.

Methyl (±)-5-cyano-1-(1-methoxy-1,2,5-trioxopentan-3-yl)-1*H*-pyrrole-2-carboxylate (24.2b) and Methyl 5-cyano-1-[2-(methoxycarbonyl)-1*H*-pyrrol-3-yl]-1*H*-pyrrole-2-carboxylate (24.2c).

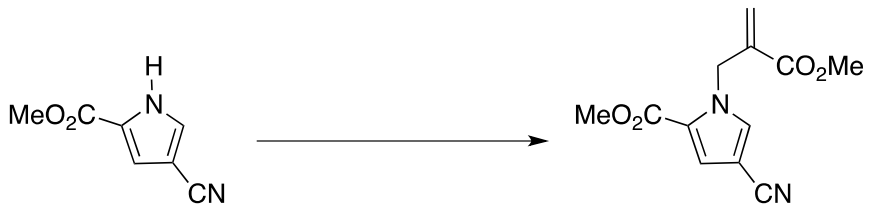


24.2a **24.2b** **24.2c**

A slow stream of ozonized oxygen was bubbled via a Pasteur pipette through a stirred and cooled (–78 °C) solution of **24.2a** (159 mg, 0.548 mmol) and Sudan Red 7B (1 mg) in CH_2Cl_2 (12 mL). When the color changed from red to light yellow, the O_3 flow was stopped and O_2 was bubbled through the solution for 15 min at –78 °C. Me_2S (0.12 mL, 1.6 mmol) was then added. The cold bath was left in place, but not recharged, and stirring was continued for 14 h, during which time the reaction mixture reached room temperature. The mixture was evaporated directly at *ca*. 15 °C to give **24.2b** as a thick, yellow oil, which was used immediately, as follows.

The method for **24.1c** was followed, using NH_4OAc (630 mg, 8.18 mmol), the above crude keto aldehyde **24.2b** in AcOH (6 mL) and a reaction time of 45 min. In this case extraction was done with EtOAc. Flash chromatography of the crude product over silica gel (1 x 20 cm), using 1:4 to 1:2 EtOAc-hexane, gave **24.2c** (83.7 mg, 56% over three steps) as a white solid: mp 149–154 °C; FTIR ($CDCl_3$, cast) 3321, 2229, 1715 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 3.67 (s, 3 H), 3.75 (s, 3 H), 6.36 (dd, *J* = 3.0, 3.0 Hz, 1 H), 6.88 (d, *J* = 4.5 Hz, 1 H), 6.92 (dd, *J* = 3.0, 3.0 Hz, 1 H), 7.01 (d, *J* = 4.5 Hz, 1 H), 9.55 (br, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 51.6 (q), 51.8 (q), 110.2 (d), 112.3 (s), 112.4 (s), 116.9 (d), 117.7 (s), 119.0 (d), 121.2 (d), 125.7 (s), 128.5 (s), 159.5 (s), 159.7 (s); exact mass (electrospray) *m/z* calcd for $C_{13}H_{11}N_3O_4$ $(M + H)^+$ 274.0822, found 274.0823.

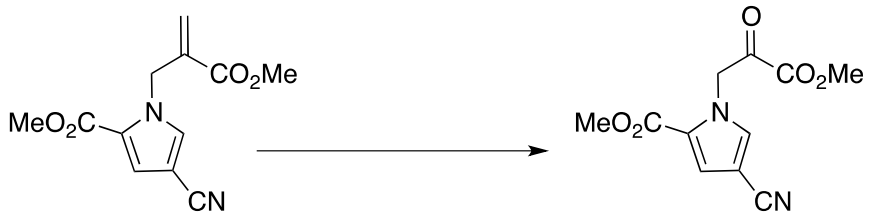
Methyl 4-cyano-1-(3-methoxy-2-methylidene-3-oxopropyl)-1*H*-pyrrole-2-carboxylate (23.3a).



22.3 **23.3a**

The method for **23.2a** was followed, using K_2CO_3 (2.42 g, 17.5 mmol), **22.3**[31] (659 mg, 4.39 mmol) and **6**[29] (763 mg, 4.83 mmol) in MeCN (40 mL). Flash chromatography of the crude product over silica gel (3 x 20 cm), using 1:6 EtOAc-hexane, gave **23.3a** (1.06 g, 98%) as a white solid: mp 92–95 °C; FTIR ($CDCl_3$, cast) 3129, 2232, 1719 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 3.76 (s, 3 H), 3.79 (s, 3 H), 5.20 (apparent t, *J* = 1.5 Hz, 1 H), 5.43 (apparent t, *J* = 1.5 Hz, 1 H), 6.29 (s, 2 H), 7.16 (d, *J* = 2.0 Hz, 1 H), 7.37 (d, *J* = 2.0 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 49.4 (t), 51.7 (q), 52.2 (q), 93.3 (s), 115.0 (s), 120.8 (d), 123.2 (t), 127.7 (s), 134.3 (d), 136.1 (s), 160.0 (s), 165.5 (s); exact mass (electrospray) *m/z* calcd for $C_{12}H_{13}N_2O_4$ $(M + H)^+$ 249.0870, found 249.0872.

Methyl 4-cyano-1-(3-methoxy-2,3-dioxopropyl)-1*H*-pyrrole-2-carboxylate (23.3b).

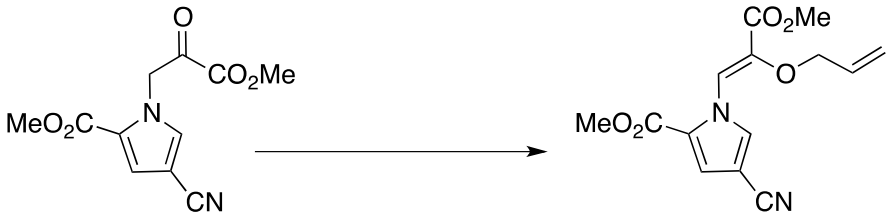


23.3a **23.3b**

The method for **23.2b** was followed, using **23.3a** (750 mg, 3.02 mmol), Sudan Red 7B (2 mg) in CH_2Cl_2 (30 mL) and Me_2S (1.33 mL, 18.1 mmol), with a reduction period of 4 h. Evaporation of the organic extract gave **23.3b** (701 mg, 93%) as an almost white solid that was used directly in the next step: mp 114–115 °C; FTIR ($CDCl_3$, cast) 3133, 2233, 1759, 1738, 1712 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 3.88 (s, 3 H), 3.97 (s, 3 H), 5.53 (s, 2 H), 7.227 (AB q, *J* = 1.74 Hz, $\Delta\nu_{AB}$ = 1.73 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 52.0 (q), 53.6 (q), 56.0 (t),

94.2 (s), 114.6 (s), 120.6 (d), 123.1 (s), 134.1 (d), 159.7 (s), 160.6 (s), 185.2 (s); exact mass (electrospray) *m*/*z* calcd for $C_{11}H_{10}N_2NaO_5$ $(M + Na)^+$ 273.0482, found 273.0483.

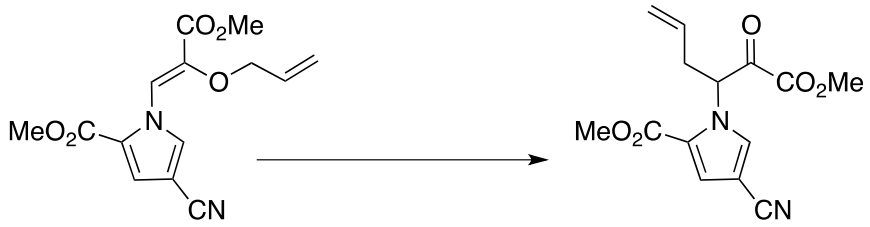
Methyl 4-cyano-1-[(1*Z*)-3-methoxy-3-oxo-2-(prop-2-en-1-yloxy)prop-1-en-1-yl]-1*H*-pyrrole-2-carboxylate (23.3c).



23.3b **23.3c**

A solution of **23.3b** (137 mg, 0.55 mmol) in DMF (5 mL) was added over 10 min to a stirred mixture of K_2CO_3 (77 mg, 0.55 mmol), allyl bromide (0.19 mL, 2.2 mmol) and DMF (10 mL), and stirring was continued for 5 h. The reaction mixture was diluted with water and extracted with EtOAc and the combined organic extracts were washed with brine, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (1 x 20 cm), using 1:10 EtOAc-hexane to 1:5 EtOAc-hexane, gave **23.3c** (98.1 mg, 58%) as a white solid: mp 107–110 °C; FTIR ($CDCl_3$, cast) 3137, 2235, 1724 cm^{-1}; ^1H NMR (C_6D_6, 500 MHz) δ 3.27 (s, 3 H), 3.28 (s, 3 H), 4.22 (ddd, *J* = 6.0, 1.5, 1.0 Hz, 2 H), 4.86 (ddd, *J* = 10.5, 2.5, 1.0 Hz, 1 H), 4.96 (ddd, *J* = 17.0, 2.5, 1.5 Hz, 1 H), 5.54 (ddt, *J* = 17.5, 10.0, 6.0 Hz, 1 H), 6.73 (d, *J* = 1.5 Hz, 1 H), 8.04 (d, *J* = 1.5 Hz, 1 H), 8.56 (s, 1 H); ^{13}C NMR (C_6D_6, 125 MHz) δ 50.9 (q), 51.4 (q), 72.7 (t), 95.8 (s), 114.1 (s), 119.1 (t), 119.7 (d), 120.5 (d), 123.5 (s), 132.3 (d), 133.1 (d), 136.2 (s), 163.0 (s); exact mass (electrospray) *m*/*z* calcd for $C_{14}H_{14}N_2NaO_5$ $(M + Na)^+$ 313.0795, found 313.0792.

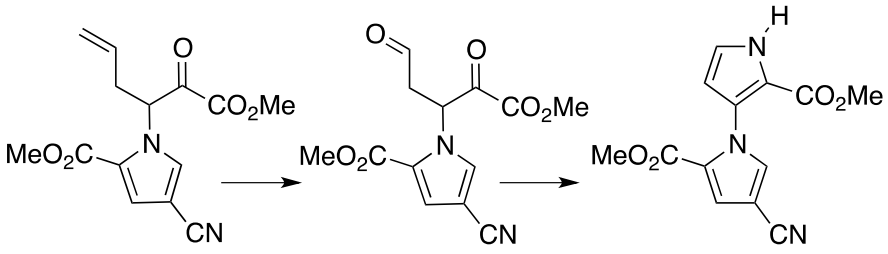
Methyl (±)-4-cyano-1-(1-methoxy-1,2-dioxohex-5-en-3-yl)-1*H*-pyrrole-2-carboxylate (24.3a).



23.3c **24.3a**

A solution of **23.3c** (370 mg, 1.28 mmol) in PhMe (12 mL) was refluxed for 20 h, cooled and evaporated to afford **24.3a** (367 mg, *ca*. 99%) as a thick, light yellow oil that was pure enough for use directly in the next step: FTIR ($CDCl_3$, cast) 2233, 1739, 1709 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 2.70–2.77 (m, 1 H), 3.01–3.07 (m, 1 H), 3.81 (s, 1 H), 3.92 (s, 3 H), 5.15 (ddd, *J* = 7.0, 2.5, 1.0 Hz, 1 H), 5.17 (apparent t, *J* = 2.0 Hz, 1 H), 5.67–5.75 (m, 1 H), 6.47 (dd, *J* = 10.0, 4.5 Hz, 1 H), 7.20 (d, *J* = 2.0 Hz, 1 H), 7.46 (d, *J* = 2.0 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 34.2 (t), 52.1 (q), 53.5 (q), 62.4 (d), 94.1 (s), 114.8 (s), 120.2 (t), 120.9 (d), 123.1 (s), 130.8 (d), 132.2 (d), 160.0 (s), 160.7 (s), 187.8 (s); exact mass (electrospray) *m*/*z* calcd for $C_{14}H_{14}N_2NaO_5$ $(M + Na)^+$ 313.0795, found 313.0794.

Methyl (±)-4-cyano-1-(1-methoxy-1,2,5-trioxopentan-3-yl)-1*H*-pyrrole-2-carboxylate (24.3b) and Methyl 4-cyano-1-[2-(methoxycarbonyl)-1*H*-pyrrol-3-yl]-1*H*-pyrrole-2-carboxylate (24.3c).



24.3a **24.3b** **24.3c**

The procedure for **24.2b** was followed, using, **24.3a** (117 mg, 0.403 mmol), Sudan Red 7B (0.5 mg) in CH_2Cl_2 (20 mL), Me_2S (0.18 mL, 2.5 mmol) and an overnight reduction period. The mixture was evaporated directly at *ca*. 15 °C to give **24.3b** as a thick, yellow oil, which was

used immediately, as follows.

The method for **24.1c** was followed, using NH_4OAc (500 mg, 6.49 mmol), the above crude keto aldehyde **24.3b** in AcOH (8 mL) and a reaction time of 3.5 h. In this case extraction was done with EtOAc. Flash chromatography of the crude product over silica gel (1 x 20 cm), using 1:1 EtOAc-hexane, gave **24.3c** (72.3 mg, 65% over three steps) as a white solid: mp 159–165 °C; FTIR ($CDCl_3$, cast) 3320, 3133, 2234, 1715 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 3.69 (s, 3 H), 3.73 (s, 3 H), 6.31 (apparent t, *J* = 3.0 Hz, 1 H), 6.95 (apparent t, *J* = 3.0 Hz, 1 H), 7.25 (d, *J* = 2.0 Hz, 1 H), 7.32 (d, *J* = 2.0 Hz, 1 H), 9.25 (br, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 51.6 (q), 51.7 (q), 93.8 (s), 109.8 (d), 115.1 (s), 117.3 (s), 119.8 (d), 120.9 (d), 125.5 (s), 127.5 (s), 135.1 (d), 159.6 (s), 159.7 (s); exact mass (electrospray) *m/z* calcd for $C_{13}H_{11}N_3NaO_4$ $(M + Na)^+$ 296.0642, found 296.0638.

Methyl 1-(3-methoxy-2-methylidene-3-oxopropyl)-5-nitro-1*H*-pyrrole-2-carboxylate (23.4a).

22.4 **23.4a**

Na_2CO_3 (242 mg, 2.28 mmol) was added to a stirred solution of **22.4**[32] (195 mg, 1.14 mmol), 18-crown-6 (300 mg, 1.14 mmol) and ester **6**[29] (202 mg, 1.28 mmol) in MeCN (12 mL). The resulting mixture was stirred and refluxed for 36 h, cooled to room temperature, diluted with water and extracted with Et_2O. The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2 x 20 cm), using 1:6 EtOAc-hexane, gave **23.4a** (240 mg, 78% or 99% corrected for recovered **22.4**) as a colorless oil: FTIR ($CDCl_3$, cast) 1722 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 3.75 (s, 3 H), 3.86 (s, 3 H), 4.98 (apparent t, *J* = 1.5 Hz, 1 H), 5.78 (apparent t, *J* = 1.5 Hz, 2 H), 6.21 (apparent t, *J* = 1.5 Hz, 1 H), 6.96 (d, *J* = 4.5 Hz, 1 H), 7.19 (d, *J* = 4.5 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 47.3 (t), 52.1 (q), 52.2 (q), 112.7 (d), 116.2 (d), 124.5 (t), 126.8 (s), 136.5 (s), 140.7 (s), 160.1 (s), 165.2

(s); exact mass (electrospray) *m*/*z* calcd for $C_{11}H_{12}N_2NaO_6$ $(M + Na)^+$ 291.0588, found 291.0581.

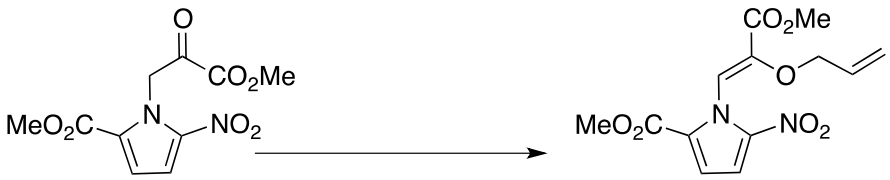
The aqueous layer was acidified with 1.0 M hydrochloric acid and extracted with Et_2O. The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated to give **6** (41.9 mg).

Methyl 1-(3-methoxy-2,3-dioxopropyl)-5-nitro-1*H*-pyrrole-2-carboxylate (23.4b).

23.4a **23.4b**

The method for **23.2b** was followed, using **23.4a** (309 mg, 1.15 mmol), Sudan Red 7B (1 mg) in CH_2Cl_2 (20 mL) and Me_2S (0.5 mL, 7 mmol) and a reduction period of 6 h. In this case, flash chromatography of the crude product over silica gel (2 x 20 cm), using 1:3 EtOAc-hexane, gave **23.4b** (280 mg, 90%) as a white solid: mp 121–123 °C; FTIR ($CDCl_3$, cast) 1761, 1738, 1717 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 3.86 (s, 3 H), 3.98 (s, 3 H), 6.29 (s, 2 H), 7.00 (d, *J* = 4.5 Hz, 1 H), 7.25 (d, *J* = 4.5 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 52.4 (q), 53.5 (q), 54.0 (t), 113.0 (d), 116.4 (d), 126.4 (s), 140.5 (s), 159.4 (s), 160.2 (s), 185.6 (s); exact mass (electrospray) *m*/*z* calcd for $C_{10}H_{10}N_2NaO_7$ $(M + Na)^+$ 293.0380, found 93.0377.

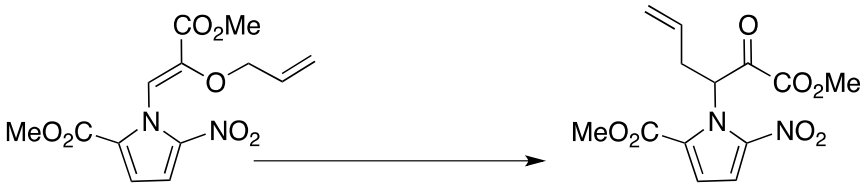
Methyl 1-[(1*Z*)-3-methoxy-3-oxo-2-(prop-2-en-1-yloxy)prop-1-en-1-yl]-5-nitro-1*H*-pyrrole-2-carboxylate (23.4c).



23.4b **23.4c**

The method for **23.3c** was followed, using **23.4b** (249 mg, 0.922 mmol) in DMF (2 mL), and addition time of *ca*. 2 min, allyl bromide (0.16 mL, 1.9 mmol), K_2CO_3 (150 mg, 1.09 mmol) and DMF (10 mL), and a reaction time of 1 h. Flash chromatography of the crude product over silica gel (2 x 15 cm), using 1:2 EtOAc-hexane, gave **23.4c** (206 mg, 72%) as a white solid: mp 52–55 °C; FTIR ($CDCl_3$, cast) 3140, 1731 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 3.847 (s, 3 H), 3.863 (s, 3 H), 4.27 (ddd, *J* = 6.0, 1.0, 1.0 Hz, 2 H), 5.01–5.03 (m, 1 H), 5.04–5.06 (m, 1 H), 5.50 (ddt, *J* = 17.5, 10.0, 6.0 Hz, 1 H), 6.93 (d, *J* = 4.5 Hz, 1 H), 7.12 (d, *J* = 4.5 Hz, 1 H), 7.73 (s, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 52.3 (q), 52.5 (q), 73.0 (t), 112.3 (d), 116.0 (d), 119.0 (t), 127.8 (s), 132.1 (d), 141.2 (s), 142.3 (s), 159.7 (s), 162.6 (s); exact mass (electrospray) *m*/*z* calcd for $C_{13}H_{14}N_2NaO_7$ $(M + Na)^+$ 333.0693, found 333.0686.

Methyl (±)-1-(1-methoxy-1,2-dioxohex-5-en-3-yl)-5-nitro-1*H*-pyrrole-2-carboxylate (24.4a).

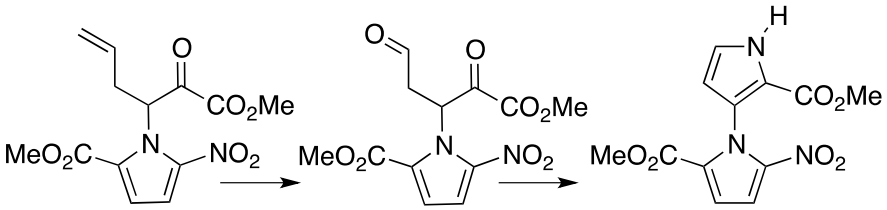


23.4c **24.4a**

A solution of **23.4c** (320 mg, 1.03 mmol) in PhMe (10.3 mL) was refluxed for 36 h, cooled and evaporated to afford **24.4a** (317 mg, *ca*. 99%) as a thick, light yellow oil: FTIR ($CDCl_3$, cast) 1733 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 2.59–2.66 (m, 1 H), 3.25–3.30 (m, 1 H), 3.76 (s, 3 H), 3.91 (s, 3 H), 4.86–4.92 (m, 2 H), 5.57–5.65 (m, 1 H), 6.99 (d, *J* = 5.0 Hz, 1 H), 7.11 (dd, *J* = 10.0, 4.5 Hz, 1 H), 7.21 (d, *J* = 4.5 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 35.1 (t), 52.6 (q), 53.1 (q), 62.9 (d), 113.8 (d), 116.9 (d), 119.6 (t), 126.8 (s), 131.6 (d), 140.3 (s), 161.0 (s), 161.1 (s), 186.2 (s); exact mass (electrospray) *m*/*z* calcd for $C_{13}H_{14}N_2NaO_7$ $(M + Na)^+$ 333.0693, found 333.0686.

Methyl (±)-1-(1-methoxy-1,2,5-trioxopentan-3-yl)-5-nitro-1*H*-pyrrole-2-carboxylate (24.4b) and Methyl 1-[2-(methoxycarbonyl)-1*H*-pyrrol-3-yl]-5-nitro-1*H*-pyrrole-2-

carboxylate (24.4c).

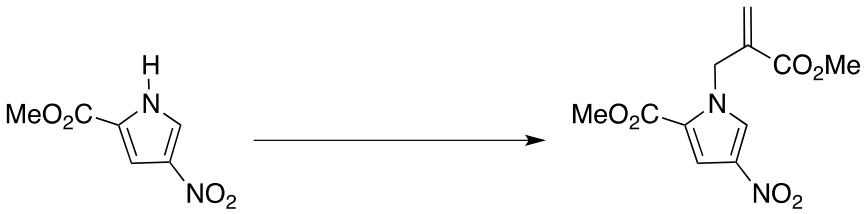


24.4a **24.4b** **24.4c**

The method for **24.2b** was followed, using **24.4a** (95.6 mg, 0.308 mmol), Sudan Red 7B (0.2 mg) in CH_2Cl_2 (10 mL), Me_2S (0.10 mL, 1.4 mmol) and a reduction period of 6 h. The mixture was evaporated directly at *ca*. 15 °C to give **24.4b** as a thick, yellow oil, which was used immediately, as follows.

The method for **24.1c** was followed, using NH_4OAc (360 mg, 468 mmol), the above crude keto aldehyde **24.4b** in AcOH (6 mL) and a reaction time of 3.5 h. (The addition of NH_4OAc was made within *ca*. 2 min of dissolving the keto aldehyde in AcOH.) In this case extraction was done with EtOAc. Flash chromatography of the crude reaction product over silica gel (1 x 15 cm), using 1:3 EtOAc-hexane to 1:2 EtOAc-hexane, gave **24.4c** (52.2 mg, 58% over three steps) as a white solid: mp 127–132 °C; FTIR ($CDCl_3$, cast) 3332, 1717 cm^{-1}; ^1H NMR ($CDCl_3$, 125 MHz) δ 3.63 (s, 3 H), 3.75 (s, 3 H), 6.35 (apparent t, *J* = 3.0 Hz, 1 H), 6.98 (apparent t, *J* = 3.0 Hz, 1 H), 7.02 (d, *J* = 4.5 Hz, 1 H), 7.24 (d, *J* = 4.5 Hz, 1 H), 9.32 (br, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 51.6 (q), 52.0 (q), 110.6 (d), 112.1 (d), 116.0 (d), 117.6 (s), 121.0 (d), 125.7 (s), 128.1 (s), 141.4 (s), 159.5 (s), 159.6 (s); exact mass (electrospray) *m*/*z* calcd for $C_{12}H_{11}N_3NaO_6$ $(M + Na)^+$ 316.0540, found 316.0533.

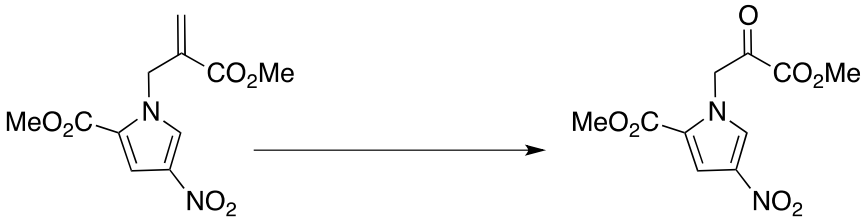
Methyl 1-(3-methoxy-2-methylidene-3-oxopropyl)-4-nitro-1*H*-pyrrole-2-carboxylate (23.5a).



22.5 **23.5a**

The method for **23.2a** was followed, using K_2CO_3 (1.98 g, 14.3 mmol), **22.5**[33] (610 mg, 3.59 mmol) and ester **6**[29] (630 mg, 3.99 mmol) in MeCN (36 mL), and a reflux period of 22 h. Flash chromatography of the crude product over silica gel (3 x 20 cm), using 1:6 EtOAc-hexane, gave **23.5a** (960 mg, 100%) as a white solid: mp 100–103 °C; FTIR ($CDCl_3$, cast) 3137, 1721 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 3.80 (s, 3 H), 3.84 (s, 3 H), 5.25 (s, 2 H), 5.58 (s, 1 H), 6.37 (s, 1 H), 7.44 (d, J = 2.0 Hz, 1 H), 7.74 (d, J = 2.0 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 49.7 (t), 51.9 (q), 52.3 (q), 113.2 (d), 122.2 (t), 127.7 (d), 128.3 (s), 135.7 (s), 135.8 (s), 160.2 (s), 165.4 (s); exact mass (electrospray) m/z calcd for $C_{11}H_{12}N_2NaO_6$ $(M + Na)^+$ 291.0588, found 291.0584.

Methyl 1-(3-methoxy-2,3-dioxopropyl)-4-nitro-1*H*-pyrrole-2-carboxylate (23.5b).

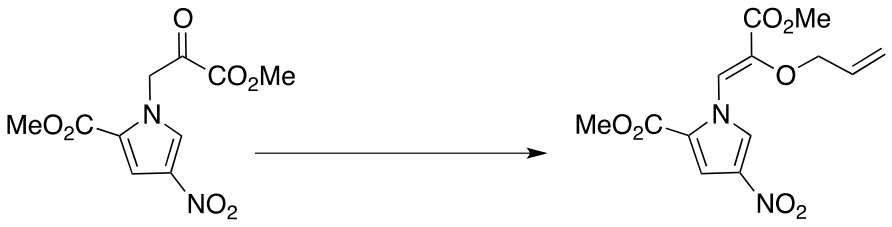


23.5a **23.5b**

The method for **23.2b** was followed, using **23.5a** (960 mg, 3.58 mmol), Sudan Red 7B (1 mg) in CH_2Cl_2 (48 mL) and Me_2S (0.7 mL, 10 mmol), with a reduction period of 6 h. In this case, flash chromatography of the crude product over silica gel (3 x 15 cm), using 1:2 EtOAc-hexane, gave **23.5b** (940 mg, 97%) as a white solid: mp 118–121 °C; FTIR ($CDCl_3$, cast) 3140, 1759, 1738, 1716 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 3.81 (s, 3 H), 3.97 (s, 3 H), 5.56 (s, 2 H), 7.47 (d, J = 2.0 Hz, 1 H), 7.61 (d, J = 2.0 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 52.2 (q), 53.6

(q), 56.3 (t), 113.0 (d), 122.2 (s), 127.7 (d), 136.2 (s), 159.6 (s), 160.7 (s), 185.0 (s); exact mass (electrospray) *m*/*z* calcd for $C_{10}H_{10}N_2NaO_7$ $(M + Na)^+$ 293.0830, found 293.0830.

Methyl 1-[(1*Z*)-3-methoxy-3-oxo-2-(prop-2-en-1-yloxy)prop-1-en-1-yl]-4-nitro-1*H*-pyrrole-2-carboxylate (23.5c).

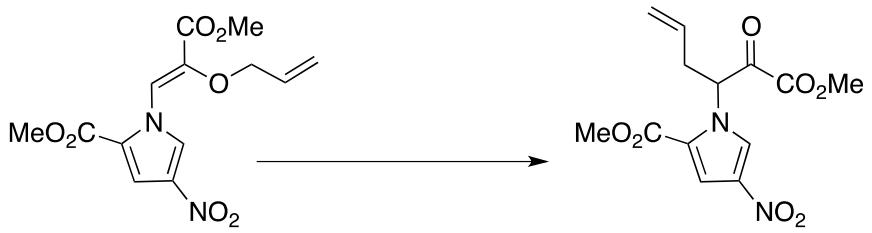


23.5b **23.5c**

A solution of **23.5b** (199 mg, 0.737 mmol) in DMF (5 mL) was added over 10 min to a stirred mixture of K_2CO_3 (102 mg, 0.739 mmol), allyl bromide (0.60 mL, 7.1 mmol), 18-crown-6 (195 mg, 0.739 mmol) and DMF (10 mL). Stirring was continued and the progress of the reaction was monitored by TLC every 10 min. When all of **23.5b** had been consumed (ca 45 min), the reaction mixture was diluted with water and extracted with EtOAc. The combined organic extracts were washed with brine, dried ($MgSO_4$), and evaporated. Crystallization of the residue from Et_2O gave **23.5c** (137 mg, 60%) as a white solid: mp 107–110 °C; FTIR ($CDCl_3$, cast) 3142, 1724 cm^{-1}; ^1H NMR (C_6D_6, 500 MHz) δ 3.25 (s, 3 H), 3.27 (s, 3 H), 4.26 (ddd, *J* = 6.0, 1.5, 1.0 Hz, 2 H), 4.92 (ddd, *J* = 10.5, 2.5, 1.0 Hz, 1 H), 5.04 (ddd, *J* = 17.0, 2.5, 1.5 Hz, 1 H), 5.63 (ddt, *J* = 17.5, 10.0, 6.0 Hz, 1 H), 7.28 (d, *J* = 2.0 Hz, 1 H), 8.51 (dd, *J* = 2.0, 0.5 Hz, 1 H), 8.60 (d, *J* = 0.5 Hz, 1 H); ^{13}C NMR (C_6D_6, 125 MHz) δ 51.0 (q), 51.4 (q), 72.8 (t), 113.2 (d), 119.2 (d), 119.3 (t), 122.4 (s), 126.4 (d), 132.2 (d), 136.7 (s), 137.2 (s), 159.7 (s), 162.8 (s); exact mass (electrospray) *m*/*z* calcd for $C_{13}H_{15}N_2O_7$ $(M + H)^+$ 311.0874, found 311.0871.

Compound **23.5c** is sensitive to silica gel and acidic solvents ($CDCl_3$), and it rearranges to a significant extent within several h in solution ($CDCl_3$) at room temperature.

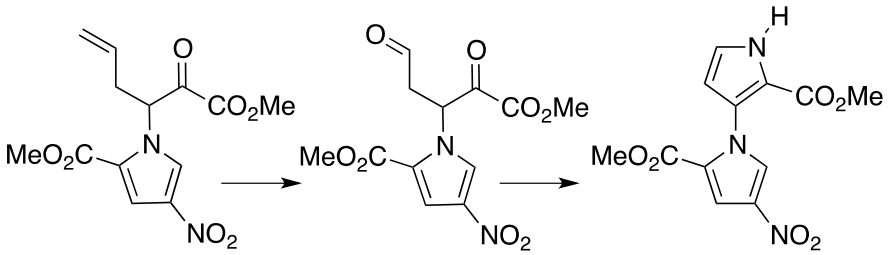
Methyl (±)-1-(1-methoxy-1,2-dioxohex-5-en-3-yl)-4-nitro-1*H*-pyrrole-2-carboxylate (24.5a).



23.5c **24.5a**

A solution of **23.5c** (110 mg, 0.355 mmol) in PhMe (3.6 mL) was refluxed for an arbitrary period of 24 h, cooled and evaporated to afford **24.5a** (110.1 mg, *ca*. 100%) as a thick, light yellow oil: FTIR ($CDCl_3$, cast) 3148, 1739, 1714 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 2.74–2.81 (m, 1 H), 3.05–3.11 (m, 1 H), 3.83 (s, 3 H), 3.94 (s, 3 H), 5.19 (apparent t, *J* = 1.5 Hz, 1 H), 5.22 (ddd, *J* = 7.0, 2.5, 1.0 Hz, 1 H), 5.72–5.80 (m, 1 H), 6.50 (dd, *J* = 10.0, 4.5 Hz, 1 H), 7.47 (d, *J* = 2.0 Hz, 1 H), 7.83 (d, *J* = 2.0 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 34.1 (t), 52.2 (q), 53.6 (q), 62.5 (d), 113.4 (d), 120.5 (t), 122.2 (s), 125.7 (d), 130.6 (d), 136.3 (s), 159.9 (s), 160.9 (s), 187.5 (s); exact mass (electrospray) *m*/*z* calcd for $C_{13}H_{14}N_2NaO_7$ $(M + Na)^+$ 333.0693, found 333.0685.

Methyl (±)-1-(1-methoxy-1,2,5-trioxopentan-3-yl)-4-nitro-1*H*-pyrrole-2-carboxylate (24.5b) and Methyl 1-[2-(methoxycarbonyl)-1*H*-pyrrol-3-yl]-4-nitro-1*H*-pyrrole-2-carboxylate (24.5c).



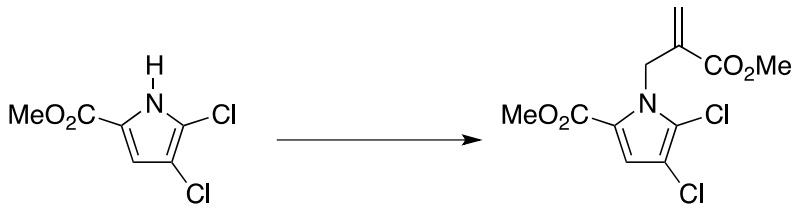
24.5a **24.5b** **24.5c**

The method for **24.2b** was followed, using **24.5a** (73.3 mg, 0.236 mmol), Sudan Red 7B (0.2 mg) in CH_2Cl_2 (6 mL), Me_2S (0.10 mL, 1.4 mmol) and a reduction period of 12 h. The mixture was evaporated directly at *ca*. 15 °C to give **24.5b** as a thick, yellow oil, which was used

immediately, as follows.

The method for **24.1c** was followed, using NH_4OAc (180 mg, 2.34 mmol), the above crude keto aldehyde **24.5b** in AcOH (2 mL) and a reaction time of 3 h. In this case the extraction was done with EtOAc. Flash chromatography of the crude product over silica gel (1 x 15 cm), using 1:1 EtOAc-hexane, gave **24.5c** (46.9 mg, 68% over three steps) as a white solid: mp 168–170 °C; FTIR ($CDCl_3$, cast) 3327, 3142, 1718 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 3.69 (s, 3 H), 3.76 (s, 3 H), 6.33 (apparent t, *J* = 3.0 Hz, 1 H), 6.94 (apparent t, *J* = 3.0 Hz, 1 H), 7.51 (d, *J* = 2.0 Hz, 1 H), 7.69 (d, *J* = 2.0 Hz, 1 H), 9.54 (br, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 51.8 (q), 51.9 (q), 109.5 (d), 112.3 (d), 117.3 (s), 121.2 (d), 124.6 (s), 127.2 (s), 128.6 (d), 136.3 (s), 159.7 (s), 159.8 (s); exact mass (electrospray) *m*/*z* calcd for $C_{12}H_{11}N_3NaO_6$ $(M + Na)^+$ 316.0540, found 316.0533.

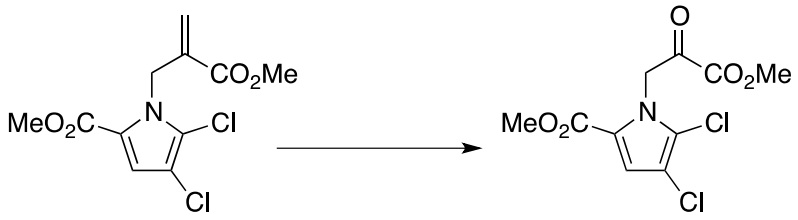
Methyl 4,5-dichloro-1-(3-methoxy-2-methylidene-3-oxopropyl)-1*H*-pyrrole-2-carboxylate (23.6a).[24]



22.6 **23.6a**

The method for **23.1a** was followed, using **6**[29] (515.9 mg, 3.264 mmol) in MeCN (5 mL), K_2CO_3 (1.22 g, 8.74 mmol) and **22.6**[2,23,34] (422 mg, 2.18 mmol) in MeCN (15 mL), and a reflux period of 38 h. Flash chromatography of the crude product over silica gel (2.8 x 20 cm), using first hexane and then 2:25 EtOAc-hexane, gave **23.6a** (618.7 mg, 97%) as a white solid: mp 76–79 °C; FTIR ($CDCl_3$, cast) 1719 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 3.77 (s, 3 H), 3.80 (s, 3 H), 4.82 (apparent t, *J* = 2.0 Hz, 1 H), 5.28 (apparent t, *J* = 2.0 Hz, 2 H), 6.20 (apparent t, *J* = 2.0 Hz, 1 H), 6.95 (s, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 46.3 (t), 51.5 (q), 52.1 (q), 110.5 (s), 116.8 (d), 120.5 (s), 121.8 (s), 124.2 (t), 136.0 (s), 159.6 (s), 165.3 (s); exact mass (electrospray) *m*/*z* calcd for $C_{11}H_{11}Cl_2NNaO_4$ $(M + Na)^+$ 313.9957, found 313.9951.

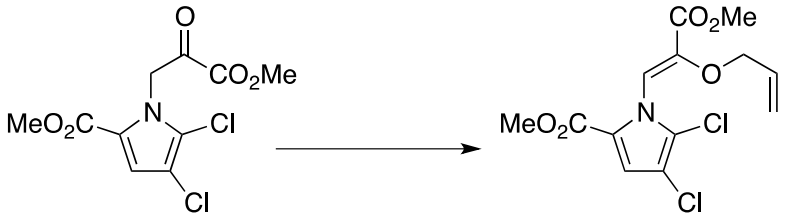
Methyl 4,5-dichloro-1-(3-methoxy-2,3-dioxopropyl)-1*H*-pyrrole-2-carboxylate (23.6b).



23.6a **23.6b**

NMO (921 mg, 7.63 mmol) and OsO_4 (0.1 M in PhMe, 4.24 mL, 0.42 mmol) were added successively to a stirred solution of **23.6a** (619 mg, 2.12 mmol) in a mixture of THF (11 mL) and water (11 mL) (protected from light). After 19 h, the reaction mixture was diluted with EtOAc, washed with water, dried ($MgSO_4$) and evaporated to give a yellow residue. A solution of $Pb(OAc)_4$ (1.22 g, 2.61 mmol) in CH_2Cl_2 (5 mL) was added to a stirred solution of the yellow residue in CH_2Cl_2 (15 mL), and stirring was continued for 20 min in subdued light. The mixture was then filtered through a pad of silica gel, using EtOAc as a rinse. Evaporation of the filtrate and flash chromatography of the residue over silica gel (2.8 x 25 cm), using 1:10 to 1:5 EtOAc-hexanes, gave **23.6b** (538.2 mg, 86%) as a white solid: mp 63–67 °C; FTIR ($CDCl_3$, cast) 3137, 1762, 1738, 1708 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 3.75 (s, 3 H), 3.94 (s, 3 H), 5.63 (s, 2 H), 6.96 (s, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 51.7 (q), 52.7 (t), 53.4 (q), 110.9 (s), 116.9 (d), 120.5 (s), 121.9 (s), 159.7 (s), 160.3 (s), 185.5 (s); exact mass (electrospray) *m*/*z* calcd for $C_{10}H_9Cl_2NNaO_5$ $(M + Na)^+$ 315.9750, found 315.9745.

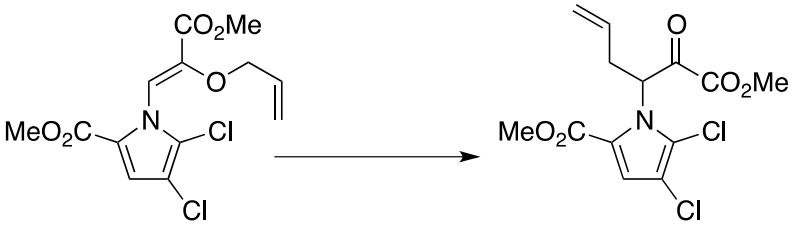
Methyl 4,5-dichloro-1-[(1*Z*)-3-methoxy-3-oxo-2-(prop-2-en-1-yloxy)prop-1-en-1-yl]-1*H*-pyrrole-2-carboxylate (23.6c).



23.6b **23.6c**

NaH (12.7 mg, 60% w/w in oil, 0.322 mmol) was added to a stirred and cooled (–42 °C) solution of **23.6b** (71.8 mg, 0.244 mmol) in DMF (5 mL). After 20 min, allyl bromide (0.026 mL, 0.30 mmol) was added. The cold bath was left in place but not recharged and stirring was continued for 1.5 h, during which time the reaction mixture reached room temperature. Stirring was continued for a further 6.5 h, water was then added and the mixture was extracted with Et_2O. The combined organic extracts were washed with water, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1.2 x 15 cm), using 1:25 to 1:10 EtOAc-hexanes, gave **23.6c** (59.5 mg, 73%) as a colorless oil: FTIR ($CDCl_3$, cast) 1732 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 3.79 (s, 3 H), 3.86 (s, 3 H), 4.31 (ddd, J = 6.0, 1.5, 1.5 Hz, 2 H), 5.08–5.15 (m, 2 H), 5.68 (ddt, J = 17.5, 10.0, 6.0 Hz, 1 H), 6.95 (s, 1 H), 7.31 (s, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 51.7 (q), 52.6 (q), 72.9 (t), 111.8 (s), 117.0 (d), 118.6 (t), 119.2 (d), 121.8 (s), 122.0 (s), 132.4 (d), 143.5 (s), 159.6 (s), 163.0 (s); exact mass (electrospray) m/z calcd for $C_{13}H_{13}Cl_2NNaO_5$ $(M + Na)^+$ 356.0063, found 356.0057.

Methyl (±)-4,5-dichloro-1-(1-methoxy-1,2-dioxohex-5-en-3-yl)-1*H*-pyrrole-2-carboxylate (24.6a).

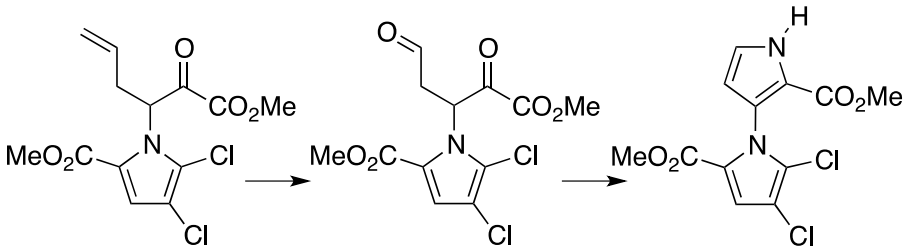


23.6c **24.6a**

A solution of **23.6c** (257.6 mg, 0.7709 mmol) in PhMe (8 mL) was stirred and refluxed

for 20 h and then cooled to room temperature. Evaporation of the solution gave **24.6a** as a light yellow solid (257.6 mg, 100%), which was used directly in the next step: mp 92–96 °C; (crude) FTIR ($CDCl_3$, cast) 3136, 1735, 1708 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 2.66–2.73 (m, 1 H), 3.11–3.16 (m, 1 H), 3.73 (s, 3 H), 3.79 (s, 3 H), 4.94–4.98 (m, 2 H), 5.23–5.61 (m, 1 H), 5.94 (br, 1 H), 6.96 (s, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 34.4 (t), 51.9 (q), 53.0 (q), 62.9 (d), 111.3 (s), 117.9 (d), 119.5 (t), 120.2 (s), 131.7 (d), 160.4 (s), 161.3 (s), 187.4 (s); exact mass (electrospray) *m/z* calcd for $C_{13}H_{13}Cl_2NNaO_5$ $(M + Na)^+$ 356.0063, found 356.0058.

Methyl (±)-4,5-dichloro-1-(1-methoxy-1,2,5-trioxopentan-3-yl)-1*H*-pyrrole-2-carboxylate (24.6b) and Methyl 4,5-dichloro-1-[2-(methoxycarbonyl)-1*H*-pyrrol-3-yl]-1*H*-pyrrole-2-carboxylate (24.6c).



24.6a **24.6b** **24.6c**

NMO (580 mg, 4.96 mmol) and OsO_4 (0.05 M in PhMe, 2.8 mL, 0.14 mmol) were added to a stirred solution of **24.6a** (471 mg, 1.41 mmol) in 1:1 THF-water (16 mL) (protected from light). The yellow mixture was stirred for 6 h, quenched with aqueous $NaHSO_3$ (10% w/v) and extracted with EtOAc. The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated to afford a pale yellow residue (260 mg, 50%). $Pb(OAc)_4$ (320 mg, 0.722 mmol) was added to a stirred and cooled (0 °C) solution of the residue in MeCN (10 mL) and stirring at 0 °C was continued. When all the starting material had reacted (ca 5 min, TLC control, silica, 1:1 EtOAc-hexane), pinacol solution (0.05 M in MeCN, several drops) was added dropwise. When the excess of $Pb(OAc)_4$ had reacted (ca 2 min, TLC control, silica, 1:1 EtOAc-hexane), the mixture was diluted with EtOAc and filtered while still cold through a sintered disc. The organic layer was evaporated at 10 °C to give **24.6b** as a thick, yellow oil, which was used immediately, as follows.

The method for **24.1c** was followed, using NH_4OAc (540 mg, 7.01 mmol), the above crude keto aldehyde **24.6b** in AcOH (8 mL) and a reaction time of 3.5 h. In this case the extraction was done with EtOAc. Flash chromatography of the crude product over silica gel (2 x 15 cm), using 1:3 EtOAc-hexane, gave **24.6c** (107 mg, 24% over three steps) as a white solid: mp 161–165 °C; FTIR ($CDCl_3$, cast) 3308, 3137, 1710 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 3.69 (s, 3 H), 3.71 (s, 3 H), 6.29 (apparent t, *J* = 3.5 Hz, 1 H), 6.98 (apparent t, *J* = 3.5 Hz, 1 H), 7.01 (s, 1 H), 9.26 (br, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 51.4 (q), 51.7 (q), 110.7 (s), 110.9 (d), 116.6 (d), 118.3 (s), 120.9 (d), 122.6 (s), 123.0 (s), 125.6 (s), 159.4 (s), 159.7 (s); exact mass (electrospray) *m*/*z* calcd for $C_{12}H_{10}Cl_2N_2NaO_4$ $(M + Na)^+$ 338.9910, found 338.9908.

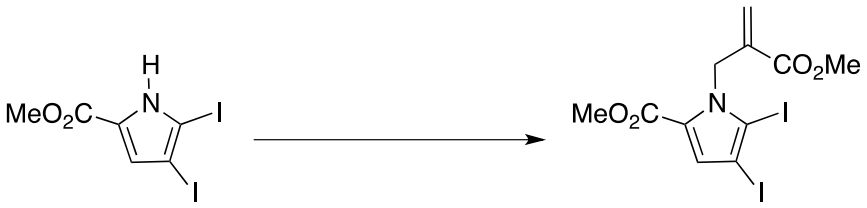
Methyl 4,5-diiodo-1*H*-pyrrole-2-carboxylate (22.7).

- **22.7**

MeONa (167 mg, 3.09 mmol) was added to a stirred and cooled (0 °C) solution of 2,2,2-trichloro-1-(4,5-diiodo-1*H*-pyrrol-2-yl)ethan-1-one[35,36] (1.20 g, 2.58 mmol) in MeOH (26 mL). The cold bath was left in place but not recharged and stirring was continued for 2 h, during which time the reaction mixture reached room temperature. The mixture was evaporated directly and the residue was acidified with dilute hydrochloric acid (1.0 M) and extracted with EtOAc. The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (4 x 15 cm), using 1:5 EtOAc-hexane, gave **22.7** (943 mg, 96%) as a white solid: mp 200–204 °C; FTIR ($CDCl_3$, cast) 3235, 1682 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 3.89 (s, 3 H), 6.93 (d, *J* = 3.0 Hz, 1 H), 9.83 (br, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 52.1 (q), 77.01 (s), 83.3 (s), 123.1 (d), 128.7 (s), 159.7 (s); exact mass (electrospray) *m*/*z* calcd for $C_6H_5I_2NNaO_2$ $(M + Na)^+$ 399.8302, found 399.8301.

Methyl 4,5-diiodo-1-(3-methoxy-2-methylidene-3-oxopropyl)-1*H*-pyrrole-2-carbox-

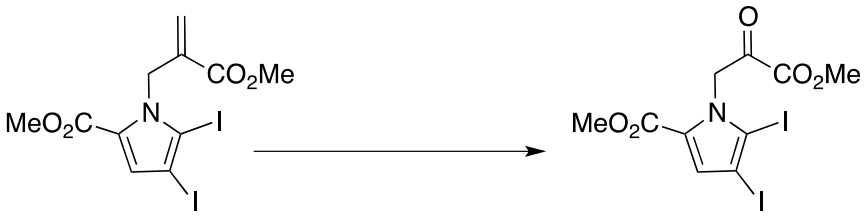
ylate (23.7a).



22.7 **23.7a**

The procedure for **23.2a** was followed, using K_2CO_3 (790 mg, 5.72 mmol), **22.7** (1.08 g, 2.87 mmol) and ester **6**[29] (480 mg, 3.04 mmol) in MeCN (29 mL). At the end of the reaction the extraction was done with Et_2O. Flash chromatography of the crude product over silica gel (3 x 20 cm), using 1:5 EtOAc-hexane, gave **23.7a** (1.30 g, 96%) as a white solid: mp 101–104 °C; FTIR ($CDCl_3$, cast) 1715 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 3.78 (s, 3 H), 3.82 (s, 3 H), 4.73 (apparent t, *J* = 2.0 Hz, 1 H), 5.39 (apparent t, 2 H), 6.22 (apparent t, *J* = 2.0 Hz, 1 H), 7.22 (s, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 51.6 (q), 52.1 (t), 52.2 (q), 76.4 (s), 94.5 (s), 124.5 (t), 126.0 (d), 127.5 (s), 136.2 (s), 159.1 (s), 165.4 (s); exact mass (electrospray) *m*/*z* calcd for $C_{11}H_{11}I_2NNaO_4$ $(M + Na)^+$ 497.8670, found 497.8661.

Methyl 4,5-diiodo-1-(3-methoxy-2,3-dioxopropyl)-1*H*-pyrrole-2-carboxylate (23.7b).

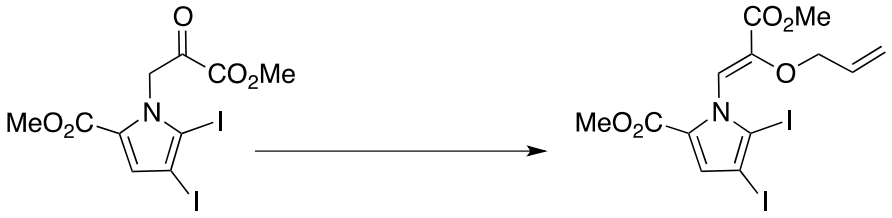


23.7a **23.7b**

NMO (260 mg, 2.22 mmol) and OsO_4 (0.05 M in PhMe, 1.2 mL, 0.06 mmol) were added to a stirred solution of **23.7a** (300 mg, 0.632 mmol) in 1:1 THF-water (7 mL) (protected from light). The yellow mixture was stirred for 36 h and then quenched with aqueous $NaHSO_3$ (10% w/v). The aqueous layer was extracted with EtOAc and the combined organic extracts were

washed with brine, dried ($MgSO_4$) and evaporated. $Pb(OAc)_4$ (310 mg, 0.699 mmol) was added to a stirred and cooled (0 °C) solution of the residue in MeCN (7 mL) and stirring at 0 °C was continued. The reaction was monitored by TLC (silica, 1:1 EtOAc-hexane) and, when all **23.7a** had been consumed (ca 5 min), pinacol (8.3 mg, 0.070 mmol) was added. Stirring was continued for *ca*. 2 min and the mixture was diluted with EtOAc and filtered through a sintered disc. The organic layer was washed with brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2 x 20 cm), using 1:4 EtOAc-hexane, gave **23.7b** (290 mg, 96%) as a white solid: mp 95–98 °C; FTIR ($CDCl_3$, cast) 1758, 1736, 1702 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 3.76 (s, 3 H), 3.97 (s, 3 H), 5.76 (s, 2 H), 7.22 (s, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 51.8 (q), 53.4 (q), 58.7 (t), 76.6 (s), 95.2 (s), 125.9 (d), 127.4 (s), 159.7 (s), 159.8 (s), 185.8 (s); exact mass (electrospray) *m/z* calcd for $C_{10}H_9I_2NNaO_5$ $(M + Na)^+$ 499.8462, found 499.8461.

Methyl 4,5-diiodo-1-[(1*Z*)-3-methoxy-3-oxo-2-(prop-2-en-1-yloxy)prop-1-en-1-yl]-1*H*-pyrrole-2-carboxylate (23.7c).

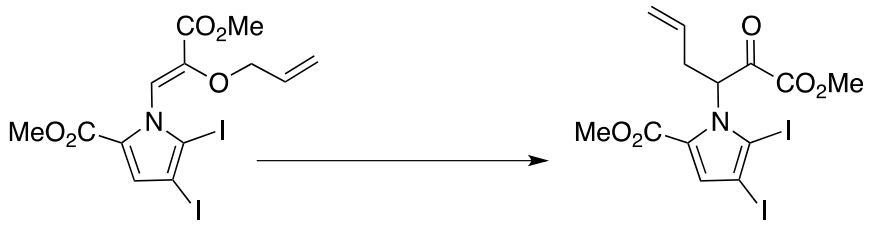


23.7b **23.7c**

The method for **23.6c** was followed, using NaH (60% w/w in mineral oil, 26.2 mg, 0.655 mmol), a reaction temperature of –40 °C, **23.7b** (260 mg, 0.545 mmol), DMF (10 mL), a stirring period of 30 min, allyl bromide (0.06 mL, 0.7 mmol), and a final stirring period of 12 h. In this case the reaction mixture was quenched with saturated aqueous NH_4Cl, and extracted with EtOAc. Flash chromatography of the crude product over silica gel (2 x 15 cm), using 1:6 EtOAc-hexane), gave **23.7c** (227 mg, 81%) as a thick, colorless oil: FTIR ($CDCl_3$, cast) 1730 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 3.79 (s, 3 H), 3.88 (s, 3 H), 4.26 (ddd, *J* = 6.0, 1.5, 1.5 Hz, 2 H), 5.09 (ddd, *J* = 4.5, 3.0, 1.5 Hz, 1 H), 5.12 (ddd, *J* = 6.0, 3.0, 1.5 Hz, 1 H), 5.65 (ddt, *J* = 17.5, 10.0, 6.0 Hz, 1 H), 7.14 (s, 1 H), 7.31 (s, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 51.7 (q), 52.6 (q),

72.9 (t), 77.6 (s), 92.8 (s), 118.6 (t), 123.2 (d), 125.6 (d), 129.5 (s), 132.5 (d), 143.5 (s), 158.9 (s), 163.1 (s); exact mass (electrospray) *m*/*z* calcd for $C_{13}H_{13}I_2NNaO_5$ $(M + Na)^+$ 539.8775, found 539.8776.

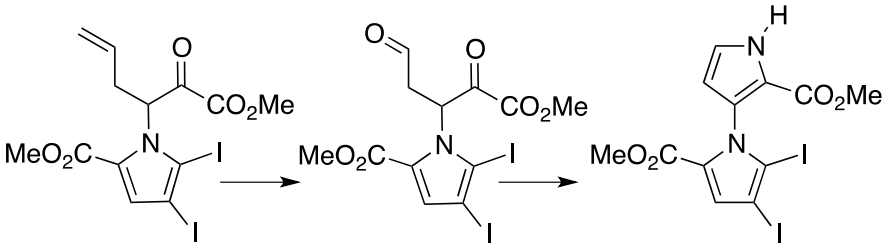
Methyl (±)-4,5-diiodo-1-(1-methoxy-1,2-dioxohex-5-en-3-yl)-1*H*-pyrrole-2-carboxylate (24.7a).



23.7c **24.7a**

A solution of **23.7c** (210 mg, 0.406 mmol) in PhMe (4.1 mL) was refluxed for 42 h in the dark, cooled and evaporated to afford **24.7a** (208.2 mg, *ca*. 99%) as a brown solid: FTIR ($CDCl_3$, cast) 1732, 1705 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 2.69–2.76 (m, 1 H), 3.14–3.19 (m, 1 H), 3.73 (s, 3 H), 3.80 (s, 3 H), 4.95–4.99 (m, 2 H), 5.58–5.67 (m, 1 H), 5.72 (br, 1 H), 7.23 (s, 1 H); ^{13}C NMR ($CDCl_3$, 500 MHz) δ 35.0 (t), 52.0 (q), 53.0 (q), 118.6 (s), 119.4 (t), 127.1 (d), 131.9 (d), 132.5 (d), 159.8 (s), 161.5 (s), 187.6 (s), other expected signals were not observed; exact mass (electrospray) *m*/*z* calcd for $C_{13}H_{13}I_2NNaO_5$ $(M + Na)^+$ 539.8775, found 539.8776. Compound **24.7a** is sensitive to light.

Methyl (±)-4,5-diiodo-1-(1-methoxy-1,2,5-trioxopentan-3-yl)-1*H*-pyrrole-2-carboxylate (24.7b) and Methyl 4,5-diiodo-1-[2-(methoxycarbonyl)-1*H*-pyrrol-3-yl]-1*H*-pyrrole-2-carboxylate (24.7c).

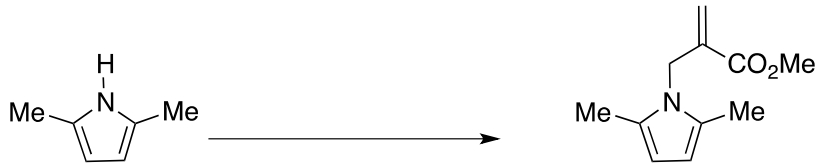


24.7a **24.7b** **24.7c**

The method for **24.6c** was followed, using NMO (160 mg, 1.37 mmol) and OsO_4 (0.05 M in PhMe, 0.8 mL, 0.04 mmol), **24.7a** (210 mg, 0.406 mmol) in 1:1 THF-water (4 mL) (protected from light). The yellow mixture was stirred for 6 h and then quenched with aqueous $NaHSO_3$ (10% w/v). $Pb(OAc)_4$ (180 mg, 0.406 mmol) was added to a stirred and cooled (0 °C) solution of the crude product, which is sensitive to light, in MeCN (5 mL). The reaction was monitored by TLC (silica, 1:1 EtOAc-hexane) and when all of the diol had been consumed (ca 5 min), pinacol solution (0.05 M in MeCN, 5 drops) was added dropwise. When the excess of $Pb(OAc)_4$ had reacted (ca 2 min), the mixture was diluted with EtOAc and the cold reaction mixture was filtered through a sintered disc. The organic layer was quickly washed with saturated aqueous $NaHCO_3$ and brine, dried ($MgSO_4$) and evaporated at 15 °C to give **24.7b** as a thick, yellow oil, which is sensitive to light and was used immediately, as follows.

With the exception that the reaction flask was protected from light, the method for **24.1c** was followed, using NH_4OAc (460 mg, 5.98 mmol), the above crude keto aldehyde **24.7b** in AcOH (4 mL) and and a reaction time of 5 h (protected from light). In this case the extraction was done with EtOAc. The combined organic extracts were washed with saturated aqueous $NaHCO_3$ and brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the crude product over silica gel (1 x 20 cm), using 1:3 EtOAc-hexane, gave **24.7c** (60.7 mg, 30% over three steps) as a white solid: mp 177–182 °C; FTIR ($CDCl_3$, cast) 3308, 1709 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 3.67 (s, 3 H), 3.69 (s, 3 H), 6.24 (apparent t, J = 3.0 Hz, 1 H), 6.98 (apparent t, J = 3.0 Hz, 1 H), 7.22 (s, 1 H), 9.25 (br, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 51.4 (q), 51.7 (q), 76.0 (s), 96.6 (s), 111.0 (d), 118.3 (s), 120.8 (d), 125.4 (d), 129.5 (s), 130.1 (s), 158.8 (s), 159.7 (s); exact mass (electrospray) m/z calcd for $C_{12}H_{10}I_2N_2NaO_4$ $(M + Na)^+$ 522.8622, found 522.8622.

Methyl 2-[(2,5-dimethyl-1*H*-pyrrol-1-yl)methyl]prop-2-enoate (23.8a).



22.8 **23.8a**

NaH (60% w/w in mineral oil 34.0 mg, 0.850 mmol) was added to a cold (0 °C) and stirred solution of **22.8**[37] (freshly distilled, 74 mg, 0.78 mmol) in DMF (2 mL) (N_2 atmosphere, exclusion of oxygen is important). The cold bath was left in place but not recharged and stirring was continued for 1 h. Ester **6**[29] (123 mg, 0.778 mmol) in DMF (2 mL) was added at a fast dropwise rate and stirring was continued for 24 h. The mixture was diluted with water and extracted with Et_2O. The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1 x 12 cm), using 1:10 EtOAc-hexane, gave **23.8a** (87.0 mg, 58%) as a colorless oil: FTIR ($CDCl_3$, cast) 1719 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 2.16 (s, 6 H), 3.86 (s, 3 H), 4.63 (apparent t, J = 2.0 Hz, 2 H), 4.79 (apparent td, J = 2.0, 1.0 Hz, 1 H), 5.85 (s, 2 H), 6.23 (apparent td, J = 2.0, 1.0 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 12.0 (q), 43.7 (t), 52.0 (q), 105.6 (d), 125.0 (t), 127.6 (s), 137.2 (s), 166.0 (s); exact mass (electrospray) m/z calcd for $C_{11}H_{16}NO_2$ $(M + H)^+$ 194.1176, found 194.1176.

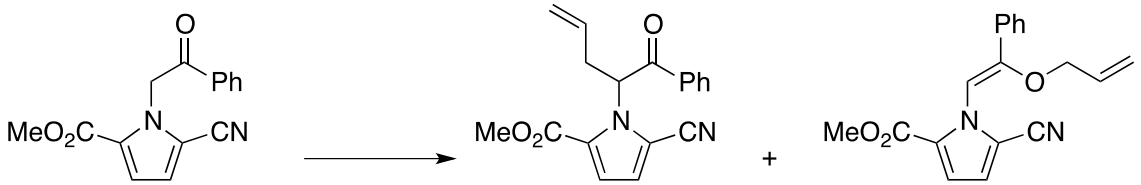
Methyl 5-cyano-1-(2-oxo-2-phenylethyl)-1*H*-pyrrole-2-carboxylate (23.1).

22.2 **23.1**

NaH (60% w/w in mineral oil, 102 mg, 2.55 mmol) was added to a stirred and cooled (0 °C) solution of **22.2**[31] (318 mg, 2.12 mmol) in DMF (21 mL). Stirring at 0 °C was continued for 30 min, and bromoacetophenone (548 mg, 2.75 mmol) was added in one portion. The cold bath was left in place, but not recharged, and stirring was continued for 3.5 h, during which time the reaction mixture reached room temperature. The mixture was diluted with saturated aqueous

NH_4Cl, and extracted with EtOAc. The combined organic extracts were washed with brine, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (3 x 20 cm), using 1:9 EtOAc-hexane to 1:3 EtOAc-hexane, gave **23.1** (477 mg, 84%) as a white solid: mp 110–115 °C; FTIR ($CDCl_3$, cast) 3138, 2226, 1709 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 3.78 (s, 3 H), 5.95 (s, 2 H), 6.87 (d, J = 4.0 Hz, 1 H), 7.02 (d, J = 4.0 Hz, 1 H), 7.52–7.55 (m, 2 H), 7.64–7.67 (m, 1 H), 8.00–8.02 (m, 2 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 51.9 (q), 53.7 (t), 111.3 (s), 112.3 (s), 117.3 (d), 118.7 (d), 127.0 (s), 128.1 (d), 129.0 (d), 134.2 (d), 134.3 (s), 160.5 (s), 191.4 (s); exact mass (electrospray) m/z calcd for $C_{15}H_{12}N_2NaO_3$ $(M + Na)^+$ 291.0740, found 291.0741.

(±)-Methyl 5-cyano-1-(1-oxo-1-phenylpent-4-en-2-yl)-1*H*-pyrrole-2-carboxylate (23.2) and Methyl 5-cyano-1-[(*Z*)-2-phenyl-2-(prop-2-en-1-yloxy)ethenyl]-1*H*-pyrrole-2-carboxylate (23.3).



23.1 **23.2** **23.3**

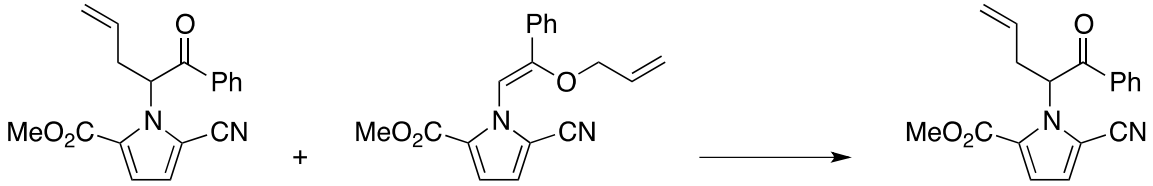
A solution of **23.1** (155 mg, 0.578 mmol) in DMF (4 mL) was added to a stirred and cooled (0 °C) mixture of NaH (60% w/w in mineral oil, 23.3 mg, 0.582 mmol) and DMF (1 mL). Stirring at 0 °C was continued for 30 min and allyl bromide (0.05 mL, 0.6 mmol) in DMF (1 mL) was added over 10 min. The cold bath was left in place, but not recharged, and stirring was continued for 7 h, during which time the reaction mixture reached room temperature. The mixture was diluted with saturated aqueous NH_4Cl and extracted with EtOAc. The combined organic extracts were washed with brine, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (1 x 20 cm), using 1:20 EtOAc-hexane to 1:5 EtOAc-hexane, gave **23.3** (21.6 mg, 12%) and **23.2** (42.7 mg, 24%) as colorless oils. The starting ketone **23.1** (49.4 mg) was recovered.

Compound **23.2** had: FTIR ($CDCl_3$, cast) 2225, 1715 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz)

δ 3.02–3.16 (m, 2 H), 3.86 (s, 3 H), 5.01 (ddd, *J* = 10.0, 2.0, 1.0 Hz, 1 H), 5.06 (ddd, *J* = 17.0, 3.0, 2.0 Hz, 1 H), 5.66–5.72 (m, 1 H), 6.79 (d, *J* = 4.5 Hz, 1 H), 6.93 (d, *J* = 4.5 Hz, 1 H), 7.12 (br, 1 H), 7.41–7.45 (m, 2 H), 7.54 (tt, *J* = 7.5, 1.5 Hz, 1 H), 7.83 (d, *J* = 7.0 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 35.9 (t), 52.1 (q), 62.8 (d), 110.5 (s), 113.2 (s), 117.8 (d), 119.4 (t), 120.2 (d), 126.2 (s), 128.3 (d), 128.8 (d), 132.1 (d), 133.3 (d), 135.3 (s), 161.0 (s), 194.9 (s); exact mass (electrospray) *m*/*z* calcd for $C_{18}H_{17}N_2O_3$ $(M + H)^+$ 309.1234, found 309.1234.

Compound **23.3** had: FTIR ($CDCl_3$, cast) 3135, 2229, 1722 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 3.85 (s, 3 H), 4.16 (ddd, *J* = 6.0, 1.5, 1.5 Hz, 2 H), 5.07–5.13 (m, 2 H), 5.71 (ddt, *J* = 17.5, 10.5, 5.5 Hz, 1 H), 6.61 (s, 1 H), 6.84 (d, *J* = 4.5 Hz, 1 H), 6.96 (d, *J* = 4.5 Hz, 1 H), 7.42–7.43 (m, 3 H), 7.58–7.60 (m, 2 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 51.8 (q), 71.0 (t), 108.1 (d), 111.7 (s), 112.8 (s), 116.6 (d), 117.7 (t), 118.7 (d), 127.4 (s), 127.7 (d), 128.6 (d), 129.8 (d), 132.7 (s), 132.8 (d), 155.0 (s), 160.0 (s); exact mass (electrospray) *m*/*z* calcd for $C_{18}H_{17}N_2O_3$ $(M + H)^+$ 309.1234, found 309.1234.

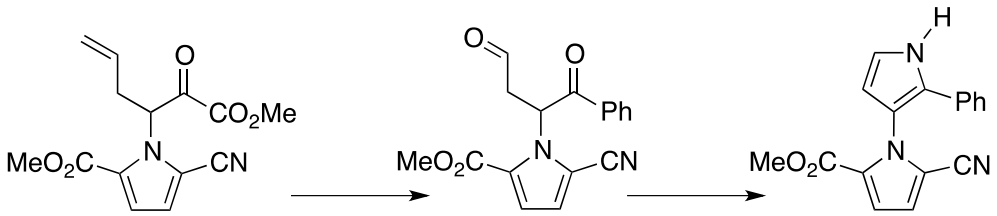
(±)-Methyl 5-cyano-1-(1-oxo-1-phenylpent-4-en-2-yl)-1*H*-pyrrole-2-carboxylate (23.2).



23.2 **23.3** **23.2**

A solution of **23.3** and **23.2** (45.9 mg, 0.149 mmol) in PhMe (1.5 mL) was refluxed for 18 h, cooled and evaporated to afford **23.2** (45.7 mg, *ca*. 99%) as a thick, light yellow oil.

Methyl (±)-5-cyano-1-(1,4-dioxo-1-phenylbutan-2-yl)-1*H*-pyrrole-2-carboxylate (23.4) and Methyl 5-cyano-1-(2-phenyl-1*H*-pyrrol-3-yl)-1*H*-pyrrole-2-carboxylate (23.5).



23.2 **23.4** **23.5**

The method for **23.2b** was followed, using **23.2** (45.7 mg, 0.147 mmol), Sudan Red 7B (ca 0.5 mg) in CH_2Cl_2 (5 mL), Me_2S (0.03 mL, 0.4 mmol) and a reduction period of 8 h. The mixture was evaporated directly at *ca*. 10 °C to give **23.4** as a thick, yellow oil, which was used immediately, as follows.

The method for **24.1c** was followed, using NH_4OAc (110 mg, 1.43 mmol), the above crude keto aldehyde **23.4** in AcOH (3 mL) and a reaction time of 3.5 h. Flash chromatography of the crude product over silica gel (1 x 20 cm), using 1:4 EtOAc-hexane, gave **23.5** (30.6 mg, 71% over three steps) as a white solid: mp 152–156 °C; FTIR ($CDCl_3$, cast) 3369, 3138, 2230, 1716 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 3.70 (s, 3 H), 6.31 (apparent t, J = 3.0 Hz, 1 H), 6.79 (apparent t, J = 3.0 Hz, 1 H), 6.85 (d, J = 4.5 Hz, 1 H), 6.92 (dt, J = 6.5, 1.5 Hz, 2 H), 7.02 (d, J = 4.0 Hz, 1 H), 7.17–7.24 (m, 3 H), 8.62 (br, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 51.8 (q), 109.1 (d), 112.4 (s), 112.7 (s), 117.3 (d), 117.4 (d), 118.0 (s), 118.9 (d), 125.1 (d), 127.2 (d), 127.5 (s), 128.3 (s), 129.0 (d), 130.3 (s), 159.4 (s); exact mass (electrospray) m/z calcd for $C_{17}H_{13}N_3NaO_2$ $(M + Na)^+$ 314.0900, found 314.0898.

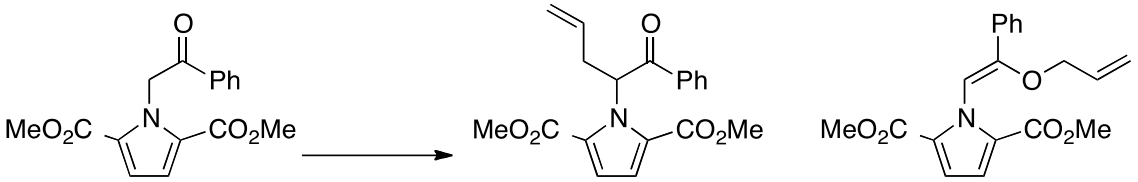
2,5-Dimethyl 1-(2-oxo-2-phenylethyl)-1*H*-pyrrole-2,5-dicarboxylate (24.1).

22.1 **24.1**

The method for **23.1** was followed, using NaH (60% w/w in mineral oil, 80.0 mg, 2.00 mmol), **22.1**[30] (332 mg, 1.82 mmol) in DMF (19 mL), bromoacetophenone (435 mg, 2.18 mmol)

and a reaction time of 6 h. Flash chromatography of the crude product over silica gel (2 x 15 cm), using 1:9 EtOAc-hexane, gave **24.1** (493 mg, 90%) as a white solid: mp 116–121 °C; FTIR ($CDCl_3$, cast) 1723, 1705 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 3.78 (s, 6 H), 6.49 (s, 2 H), 7.01 (s, 2 H), 7.49–7.53 (m, 2 H), 7.61 (tt, *J* = 7.5, 1.5 Hz, 1 H), 8.02–8.04 (m, 2 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 51.6 (q), 53.1 (t), 116.8 (d), 127.6 (s), 128.0 (d), 128.8 (d), 133.6 (d), 135.0 (s), 161.4 (s), 193.5 (s); exact mass (electrospray) *m/z* calcd for $C_{16}H_{16}NO_5$ $(M + H)^+$ 302.1023, found 302.1023.

2,5-Dimethyl (±)-1-(1-oxo-1-phenylpent-4-en-2-yl)-1*H*-pyrrole-2,5-dicarboxylate (24.2) and 2,5-Dimethyl 1-[(*Z*)-2-phenyl-2-(prop-2-en-1-yloxy)ethenyl]-1*H*-pyrrole-2,5-dicarboxylate (24.3).



24.1 **24.2** **24.3**

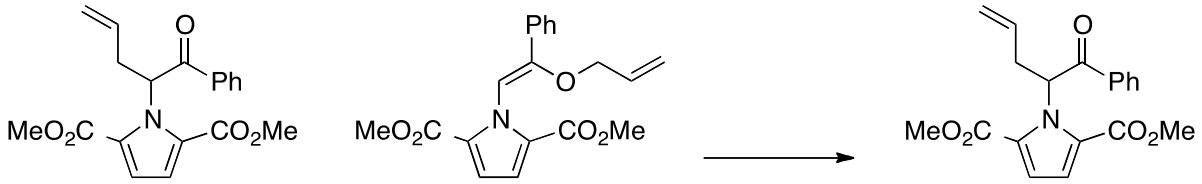
The method for **23.3** and was followed, using **24.1** (320 mg, 1.06 mmol) in DMF (11 mL), NaH (60% w/w in mineral oil, 42.5 mg, 1.06 mmol) and DMF (5 mL), allyl bromide (0.09 mL, 1 mmol) in DMF (10 mL), an addition period of 20 min, and an overnight reaction time. Flash chromatography of the crude product over silica gel (2 x 20 cm), using 1:25 EtOAc-hexane, gave **24.2** (140 mg, 39%) and **24.3** (138 mg, 38%) as colorless oils. Compound **24.2** contained an impurity.

Compound **24.3** had: FTIR ($CDCl_3$, cast) 1734, 1711 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 3.83 (s, 6 H), 3.94 (ddd, *J* = 6.0, 1.5, 1.5 Hz, 2 H), 4.99 (ddd, *J* = 8.0, 3.0, 1.5 Hz, 1 H), 5.02 (apparent t, *J* = 1.5 Hz, 1 H), 5.53–5.61 (m, 1 H), 6.92 (s, 1 H), 6.94 (s, 2 H), 7.37–7.42 (m, 3 H), 7.59–7.61 (m, 2 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 51.6 (q), 70.9 (t), 110.8 (d), 116.3 (d), 117.3 (t), 127.1 (d), 128.6 (d), 128.9 (s), 129.1 (d), 133.2 (d), 133.8 (s), 151.9 (s), 160.8 (s); exact mass (electrospray) *m/z* calcd for $C_{19}H_{19}NNaO_5$ $(M + Na)^+$ 364.1155, found 364.1155.

Compound **24.2** had: FTIR ($CDCl_3$, cast) 1725, 1703 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz)

δ 2.70–2.80 (m, 1 H), 3.37–3.40 (m, 1 H), 3.82 (s, 6 H), 4.84–4.88 (m, 2 H), 5.59–5.69 (m, 1 H), 6.89 (s, 2 H), 7.20 (dd, *J* = 10.0, 4.5 Hz, 1 H), 7.23–7.28 (m, 2 H), 7.37 (tt, *J* = 7.5, 1.5 Hz, 1 H), 7.53–7.56 (m, 2 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 36.2 (t), 51.8 (q), 63.3 (d), 117.7 (d), 118.1 (t), 127.5 (s), 127.6 (d), 128.0 (d), 131.6 (d), 133.7 (d), 137.4 (s), 161.4 (s), 197.0 (s); exact mass (electrospray) *m*/*z* calcd for $C_{19}H_{19}NNaO_5$ $(M + Na)^+$ 364.1155, found 364.1154.

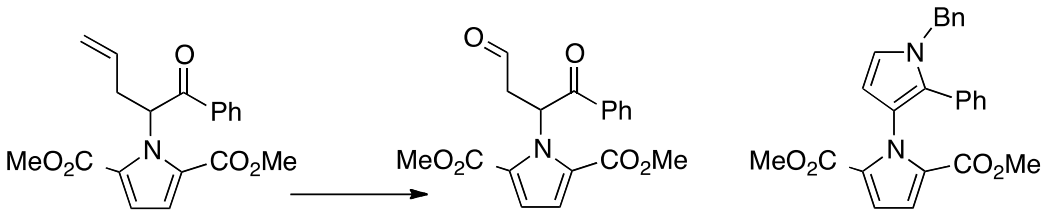
2,5-Dimethyl (±)-1-(1-oxo-1-phenylpent-4-en-2-yl)-1*H*-pyrrole-2,5-dicarboxylate (24.2).



24.2 **24.3** **24.2**

A solution of a mixture of **24.2** and **24.3** (179 mg, 0.525 mmol) in PhMe (6 mL) was refluxed for 13 h, cooled to room temperature and evaporated to give **24.2** as a thick, colorless oil (178 mg, 99%), which was used directly in the next step. Compound **24.2** had same spectral data as above.

2,5-Dimethyl (±)-1-(1,4-dioxo-1-phenylbutan-2-yl)-1*H*-pyrrole-2,5-dicarboxylate (24.4) and 2,5-Dimethyl 1-(1-benzyl-2-phenyl-1*H*-pyrrol-3-yl)-1*H*-pyrrole-2,5-dicarboxylate (24.5).



24.2 **24.4** **24.5**

With the exception that THF was used instead of CH_2Cl_2, the method for **23.2b** was

followed, using **24.2** (75.6 mg, 0.221 mmol), Sudan Red 7B (ca 0.1 mg) in THF (5 mL) and Me_2S (0.03 mL, 0.4 mmol). During the reduction the cold bath was left in place, but not recharged, and stirring was continued for 3 h, during which time the the reaction mixture reached 0 °C. Iodine[28] (5.6 mg, 0.022 mmol) and $BnNH_2$ (0.03 mL, 0.3 mmol) were added. The cold bath was left in place but not recharged and stirring was continued for 4 h. The mixture was diluted with aqueous $NaHSO_3$ (10% w/v) and extracted with EtOAc. The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated at < 12 °C (cold water bath with some ice). The residue was dissolved in MeOH (2 mL) and cooled in an ice bath. $NaBH_4$ (4.2 mg, 0.11 mmol) was added and the cold bath was left in place, but not recharged, and stirring was continued for 2.5 h. The mixture was diluted with saturated aqueous NH_4Cl and extracted with EtOAc. The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1 x 15 cm), using 1:5 EtOAc-hexane, gave **24.5** (37.4 mg, 41% over four steps) as a colorless oil: Compound **24.5** had: FTIR ($CDCl_3$, cast) 1737, 1718 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 3.71 (s, 6 H), 5.07 (s, 2 H), 6.28 (d, J = 3.5 Hz, 1 H), 6.75 (d, J = 3.5 Hz, 1 H), 6.85 (s, 2 H), 7.03–7.08 (m, 4 H), 7.14–7.17 (m, 3 H), 7.22–7.25 (m, 1 H), 7.30–7.33 (m, 2 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 50.9 (q), 51.3 (t), 107.8 (d), 116.4 (d), 119.9 (d), 120.8 (s), 126.2 (d), 127.2 (d), 127.6 (d), 128.1 (d), 128.6 (d), 129.6 (d), 130.2 (s), 130.3 (s), 138.7 (s), 160.2 (s); exact mass (electrospray) m/z calcd for $C_{25}H_{22}N_2NaO_4$ $(M + Na)^+$ 437.1472, found 437.1469.

Compound **24.4** had: FTIR ($CDCl_3$, cast) 1723 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 2.98 (ddd, J = 17.5, 6.0, 1.0 Hz, 1 H); 3.87 (br, 6 H), 3.94 (ddd, J = 17.5, 6.0, 1.0 Hz, 1 H), 6.92 (s, 2 H), 7.27–7.31 (m, 2 H), 7.39–7.44 (m, 2 H), 7.50–7.52 (m, 2 H), 9.89 (t, J = 1.0 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 46.2 (t), 52.0 (q), 59.0 (d), 118.0 (d), 127.5 (d), 127.6 (s), 128.2 (d), 132.1 (d), 136.2 (s), 195.8 (s), 198.4 (d); exact mass (electrospray) m/z calcd for $C_{18}H_{17}NNaO_6$ $(M + Na)^+$ 366.0948, found 366.0944.

References

1 Hughes, C. C.; Prieto-Davo, A.; Jensen, P. R.; Fenical, W. *Org. Lett.* **2008**, *10*, 629–631.

2 Cheng, P.; Clive, D. L. J.; Fernandopulle, S.; Chen, Z. *Chem. Commun.* **2013**, *49*, 558–560.

3 E.g. (a) Clive, D. L. J.; Li, Z.; Yu, M. *J. Org. Chem.* **2007**, *72*, 5608–5617. (b) Prabhudas, B.; Clive, D. L. J. A*ngew. Chem. Int. Ed.* **2007**, *46*, 9295–9297. (c) Wang, L.; Prabhudas, B.; Clive, D. L. J. *J. Am. Chem. Soc.* **2009**, *131*, 6003–6012. (d) Cheng, P.; Clive, D. L. J. *J. Org. Chem.* **2012**, *77*, 3348–3364. (e) Sreedharan, D. T.; Clive, D. L. J. *Org. Biomol. Chem.* **2013**, *11*, 3128–3144.

4 Treibs, A.; Hitzler, O. *Chem. Ber.* **1957**, *90*, 787–788.

5 Robinson, J. A.; McDonald, E. Battersby, A. R. *J. Chem. Soc., Perkin Trans. 1* **1985**, 1699–1709.

6 Mingoia, F. *Tetrahedron* **2001**, *51*, 10147–10153.

7 Santo, R. Di.; Massa, S.; Costi, R.; Simonetti, G.; Retico, A.; Apuzzo, G.; Troccoli, F. *Farmaco* **1994**, *49*, 229–236.

8 van Leusen *Org. Reacts.* **2001**, *57*, 417–666, especially page 459.

9 Qiu, F.; Wu, J.; Zhang, Y.; Hu, M.; Yu, Y. *Tetrahedron Lett.* **2012**, *53*, 446–448.

10 Clauson-Kaas *Acta Chem. Scand.* **1952**, *6*, 667–670.

11 (a) Lisowski, V.; Léonce, S.; Kraus-Berthier, L.; Santos, J. S.-de O.; Pierré, A.; Atassi, G.; Caignard, D.-H.; Renard, P.; Rault, S. *J. Med. Chem.* **2004**, *47*, 1448–1464. (b) Rochais, C.; Lisowski, V.; Dallemagne, P.; Rault, S. *Tetrahedron Lett.* **2004**, *45*, 6353–6356. (c) Cf. Rochais, C.; Lisowski, V.; Dallemagne, P.; Rault, S. *Tetrahedron* **2004**, *60*, 2267–2270. (d) Rochais, C.; Lisowski, V.; Dallemagne, P.; Rault, S. *Bioorg. Med. Chem.* **2006**, *14*, 8162–8175. (e) Rochais, C.; Vu Doc, N.; Lescot, E.; Santos, J. S.-de. O.; Bureau, R.; Meijer, L.; Dallemagne, P.; Rault, S. *Eur. J. Med. Chem.* **2009**, *44*, 708–716.

12 (a) Fu, L.; Gribble, G. W. *Tetrahedron Lett.* **2008**, *49*, 3545–3548. (b) Fu, L.; Gribble, G. W. *Org. Prep. Proced. Int.* **2008**, *40*, 561–566.

13 Hughes, C. C.; Kauffman, C. A.; Jensen, P. R.; Fenical, W. *J. Org. Chem.* **2010**, *75*, 3240–3250.

14 Petruso, S.; Bonanno, S.; Caronna, S.; Ciofalo, M.; Maggio, B.; Schillaci, D. *J. Heterocyclic Chem.* **1994**, *31*, 941–945.

15 Furneaux, R. H.; Tyler, P. C. *J. Org. Chem.* **1999**, *64*, 8411–8412.

16 (a) Cheng, C.; Pan, L.; Chen, Y.; Song, H.; Qin, Y.; Li, R. *J. Comb. Chem.* **2010**, *12*, 541–547. (b) *J. Comb. Chem.* **2010**, *12*, 900. Correction to author list: The designation of the corresponding author and contact information has been changed since publication of the original article.

17 Nicolaou, K. C.; Simmons, N. L.; Chen, J. S.; Haste, N. M.; Nizet, V. *Tetrahedron Lett.* **2011**, *52*, 2041–2043.

18 (a) Cheng, C.; Liu, Y.; Song, H.; Pan, L.; Li, J.; Qin, Y.; Li, R. *Mar. Drugs* **2013**, *11*, 2927–2948. (b) Li, R.; Cheng, C.; Balasis, M. E.; Liu, Y.; Garner, T. P.; Daniel, K. G.; Li, J.; Qin, Y.; Gavathiotis, E.; Sebti, S. M. *Eur. J. Med. Chem.* **2014**, *90*, 315–331.

19 Pan, L.-L.; Cheng, C.-W.; Song, H. *Chemical J. Chinese Universities* **2012**, *33*, 1476–1480.

20 Kanakis, A. A.; Sarli, V. *Org. Lett.* **2010**, *12*, 4872–4875.

21 (a) Liu, Y.; Haste, N. M.; Thienphrapa, W.; Nizet, V.; Hensler, M.; Li, R. *Mar. Drugs* **2012**, *10*, 953–962. (b) Liu, Y.; Haste, N. M.; Thienphrapa, W.; Li, J.; Nizet, V.; Hensler, M.; Li, R. *Mar. Drugs* **2014**, *12*, 2458–2470.

22 Raimondi, M. V.; Schillaci, D.; Petruso, S. *J. Heterocyclic Chem.* **2007**, *44*, 1407–1411.

23 Smith, J. A.; Ng, S.; White, J. *Org. Biomol. Chem.* **2006**, *4*, 2477–2482.

24 This series involving **23.1** and **23.6** were done by Dr. P. Cheng.

25 (a) Veysoglu, T.; Mitscher, L. A.; Swayze, J. K. *Synthesis* **1980**, 807–810. (b) Boer, H.; Kooyman, E. C. *Anal. Chim. Acta* **1951**, *5*, 550–562.

26 Van Rheenen, V.; Kelly, R. C.; Cha, D. Y. *Tetrahedron Lett.* **1976**, *17*, 1973–1976.

27 Rubin, M. B. *J. Chem. Educ.* **1964**, *41*, 388.

28 Banik, B. K.; Samajdar, S.; Banik, I. *J. Org. Chem.* **2004**, *69*, 213–216.

29 (a) Bartrum, H. E.; Adams, H.; Caggiano, L.; Jackson, R. F. W. *Tetrahedron*, 2008, **64**, 3701–3712. (b) Vloon, W. J.; van den Bos, J. C.; Koomen, G.-J.; Pandit, U. K. *Tetrahedron* **1992**, *48*, 8317–8328.

30 Fürstner, A.; Krause, H.; Thiel, O. R. *Tetrahedron* **2002**, *58*, 6373–6380. (b) Hasse, K.; Willis, A. C.; Banwell, M. G. *Eur. J. Org. Chem.* **2011**, 88–99.

31 Loader, C. E.; Anderson, H. J. *Can. J. Chem.* **1981**, *59*, 2673–2976.

32 Schmuck, C.; Dudaczek, J. *Tetrahedron Lett.* **2005**, *46*, 7101–7105.

33 Kumar, R.; Lown, J. W. *Org. Biomol. Chem.* **2003**, *1*, 3327–3342.

34 Bailey, D. M.; Johnson, R. E.; Albertson, N. F. In *Organic Syntheses*; Collect. Vol. 6, 1988, p. 618.

35 The diiodo ester **9** is a new compound, although the parent acid is known. For iodination of 2,2,2-trichloro-1-(1*H*-pyrrol-2-yl)ethan-1-one, see reference 14 and Essa, A. H.; Lerrick, R. I.; Tuna, F.; Harrington, R. W.; Clegg, W.; Hall, M. J. *Chem. Commun.* **2013**, *49*, 2756–2758.

36 Bailey, D. M.; Johnson, R. E. *J. Med. Chem.* **1973**, *16*, 1300–1302.

37 Yang, H.; Baralt, E. J. US Patent 2010256391 A1, 2010 (*Chem. Abstr.* **2010**, *153*, 1256790).

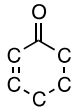
Chapter 2

Conversion of cyclohexenone-type systems into phenols

Introduction: Assessment of prior methods for converting cyclohexenone-type systems into phenols

A number of procedures have been developed for converting cyclohexenones into phenols. In the following I make an assessment of the transformations, the reagents and methods and advantages and range of applicability. The coverage is not exhaustive, but I give numerous examples of the main methods.

For the purpose of this analysis a cyclohexenone-type system is one that contains the subunit **1**, or a tautomer thereof, but I exclude aryl-fused systems in which the indicated double bond is part of an aryl or heteroaryl ring; also excluded, with a few exceptions needed to illustrate the effect of reaction conditions, are the small number of cases where nuclear functionalization of the product (usually bromination or selenenylation) accompanies the aromatization.



1

Summary

#1 Classical dehydrogenation with palladium

#2 Aromatization with DDQ

#3 Aromatization with mercuric acetate

#4 Aromatization using iodine

#5 Aromatization by bromination-dehydrobromination

#6 Aromatization by use of $CuBr_2$

#7 Aromatization with palladium diacetate and palladium bis(trifluoroacetate)

#8 Phenylselenation as an aromatization method

#9 Miscellaneous methods of aromatization

(a) Use of ferric chloride

(b) Reaction of sodium benzoate with haloenones

(c) Heating with sulfur

(d) Use of hot concentrated sulfuric acid

(e) Use of MnO_2

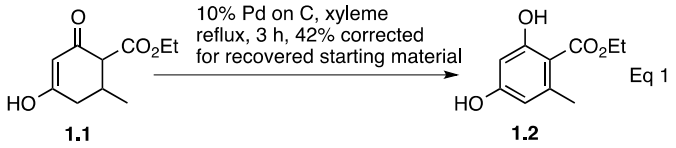
(f) Use of hypervalent iodine reagents

(g) Migration of a pendant double bond

(h) Vanadium catalysts

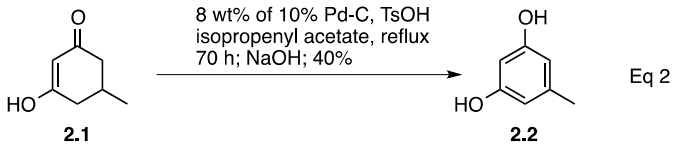
#1 Classical dehydrogenation with palladium

The classical method of dehydrogenation by heating in a high-boiling solvent with Pd-C was used to convert **1.1** into **1.2**.[1] The reaction was slow, and 79% of the starting material was recovered after a reflux period of 3 h in xylene; the corrected yield being 42%. In this case, dehydrogenation with $FeCl_3$, according to a literature procedure, was unsatisfactory (see section on $FeCl_3$), and experiments[2] with MnO_2, DDQ, chloranil, trityl perchlorate, $Hg(OAc)_2$ or $(NH_4)_2Ce(NO_3)_6$ were described as "fruitless".

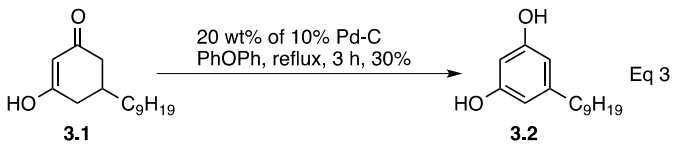


1.1 1.2

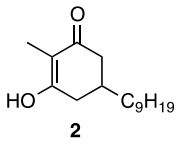
Catalytic dehydrogenation of **2.1** is reported to be unsuccessful,[3] although the aromatization was subsequently carried out (Eq 2) in another laboratory[2] and on the related **3.1**.[2]



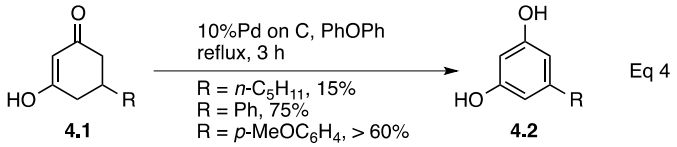
2.1 2.2



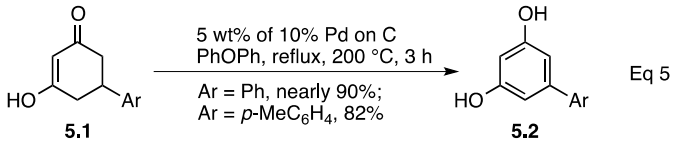
Curiously, **2** gave intractable tars on attempted aromatization with Pd-C.[2]



When heated with Pd-C in diphenyl ether the 5-substituted cyclohexane-1,3-diones **4.1** were aromatized,[5] but when the C-5 substituent was aliphatic the yield was very low. DDQ and chloranil were ineffective and attempts to use these reagents led to recovery of 60–70% of **4.1**.

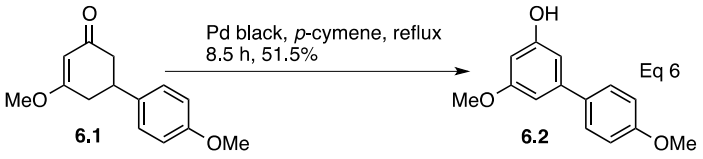


The 5-arylcyclohexane-1,3-diones **5.1** were aromatized at 200 °C.[6]

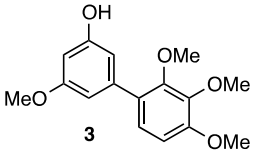


The above examples deal with vinylogous *acids*, but related vinylogous *esters* have also been aromatized.

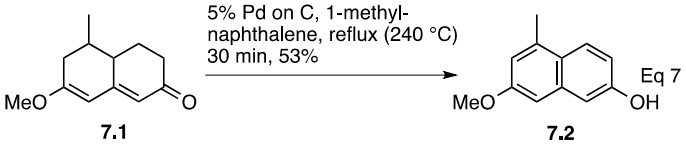
The use of palladium black in a high-boiling solvent was applied for the following transformation.[7]



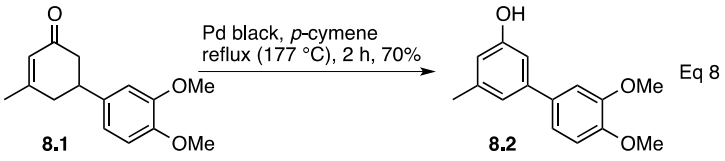
However, the same procedure was unsuccessful for making compound **3**,[7] and it is not clear why this is so. In the case of **3**, DDQ was also unsuccessful, but aromatization was achieved (83%) with $Hg(OAc)_2$ [see section on $Hg(OAc)_2$].



The dienone **7.1** was aromatized to **7.2** by heating with Pd-C in 1-methylnaphthalene.[8]

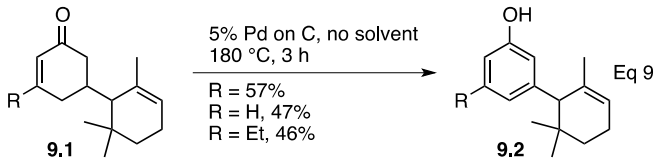


A similar method, but at the lower temperature of 177 °C, was applied to some 5-(monomethoxyphenyl)- and 5-(dimethoxyphenyl)cyclohex-2-en-1-ones.[9] A range of hydrocarbon solvents as well as diphenyl ether, ethylene glycol and diethylene glycol diethyl ether was evaluated and a 2-hour reaction period in *p*-cymene at its reflux temperature (177 °C) gave the most satisfactory results.

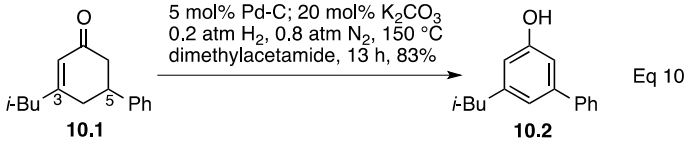


The same conditions were also effective, although in lower yield (38–54%) for 5-alkyl cyclohex-2-en-1-ones where the alkyl group was Me, Et, Pr, *i*-Pr and *n*-C_6H_{13}.[10]

The enone systems **9.1** were aromatized by heating with Pd-C without solvent at 180 °C.[11] In these cases attempts at aromatization using sulfur or DDQ were unsuccessful.

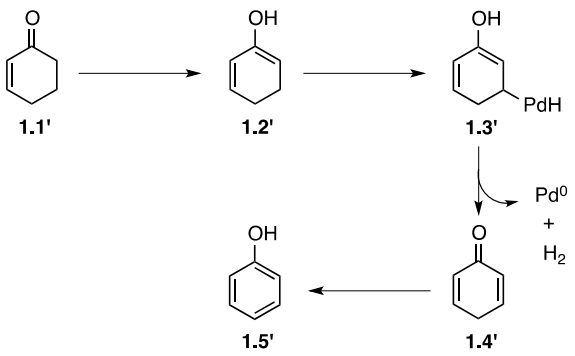


A number of 3,5-disubstituted cyclohex-2-en-1-ones such as **10.1** have been aromatized to phenols, using Pd-C in the presence of K_2CO_3 in dimethylacetamide at 150 °C under an atmosphere of hydrogen.[12]



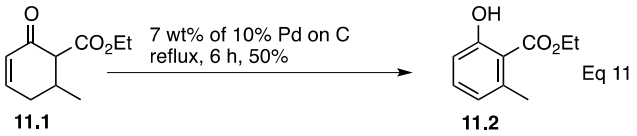
The range of substituents at C-3 included Ph, STol, *o*-HOC_6H_4, *p*-$MeOC_6H_4$, 2-thienyl, 2-furyl, 2-pyrrolyl, HNPh, pyrrolidin-1-yl and morpholin-1-yl. The C-5 substituents were phenyl, 2-furyl, 1-naphthyl with yields being generally above 80%. This is clearly an effective method for thermally and base-stable compounds that lack an easily hydrogenatable substituent.

The mechanism for the Pd-C aromatization of cyclohexenones in a hydrogen atmosphere involves a delicate balance between hydrogenation and dehydrogenation, the key step being insertion of Pd into a C–H bond that is made allylic by enolization (Scheme 1). The authors suggest that H-Pd-H formed but it may be that the hydrogen merely converts a palladium oxide into Pd(0).

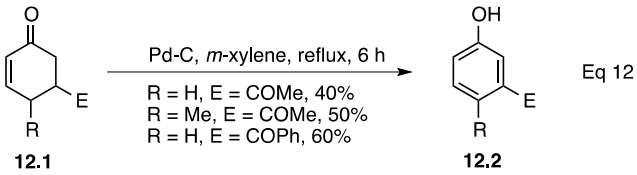


Scheme 1. Mechanism of Pd-C catalyzed aromatization.

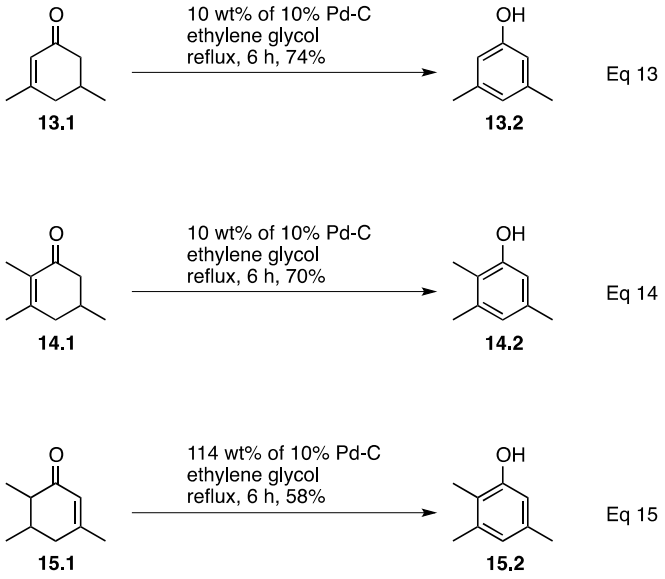
The enone ester **11.1** gave a 50% yield of **11.2** on heating with Pd-C in refluxing mesitylene (165 °C).[13]



The related enones **12.1** were aromatized in refluxing *m*-xylene.[14] In these cases the alternative method of using $CuBr_2$-LiBr in MeCN gave better yields (>70%, see section on $CuBr_2$-LiBr), although it was made clear that there were no attempts to optimize the thermal process.



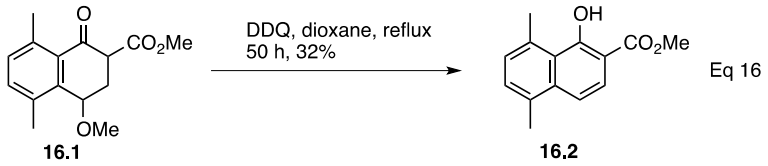
The three closely related enones **13.1**, **14,1** and **15.1** were aromatized by heating in refluxing ethylene glycol;[15] no comment was made about the very different proportions of Pd-C used in the cases of **14.1** and **15.1**. Also, no indication was given as to why the $CuBr_2$-LiBr method (see later) was not used, as in several other aromatizations reported in the same publication.



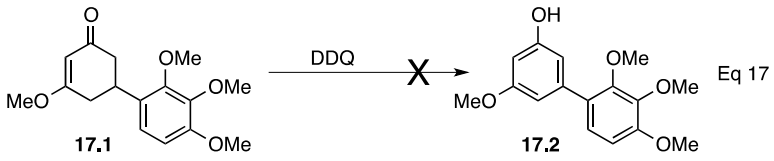
#2 Aromatization with DDQ

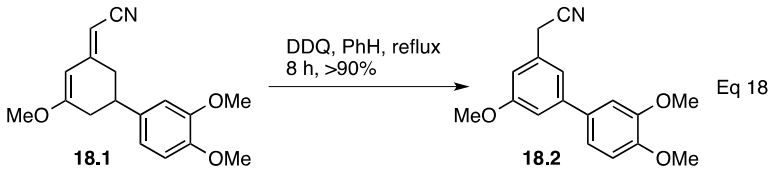
Another classical method for converting a cyclohexenone system into a phenol involves treatment with the high potential quinone DDQ or (much less frequently) chloranil.

Although it is a benzo-fused ketone and, therefore, not within the scope of this review, there is one aromatization (**16.1→16.2**) attributed[16] to the action of DDQ that is most probably just a thermal elimination in which DDQ plays no part.

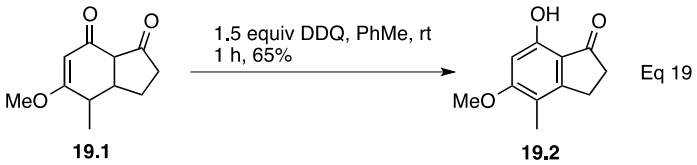


Attempted aromatization of **17.1** with DDQ was unsuccessful[7] but the related **18.1** was aromatized.[17]

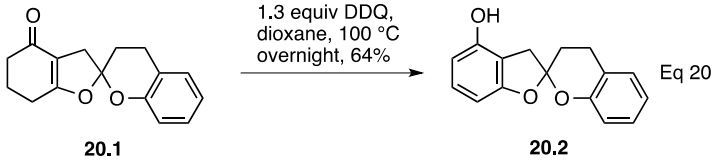




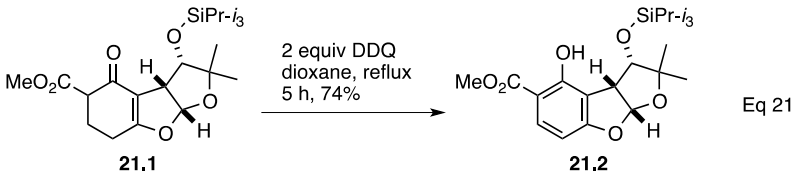
DDQ served to convert **19.1** into **19.2** at room temperature.[18]



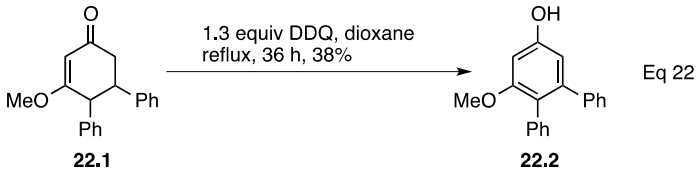
During synthetic studies on γ-rubromycin, enone **20.11** was aromatized in 64% yield with DDQ in dioxane.[19]



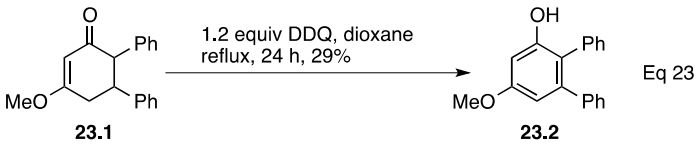
Likewise, in another synthetic study on a natural product, the enone ester **21.1** was aromatized with DDQ under similar conditions to those used for **20.1**.[20]



The simple, and seemingly robust, enone systems **22.1** and **23.1** were aromatized with DDQ in yields of only 38% and 29%, respectively.[21]



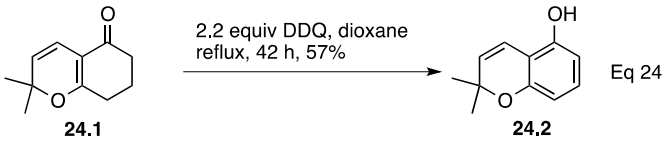
Eq 22



Eq 23

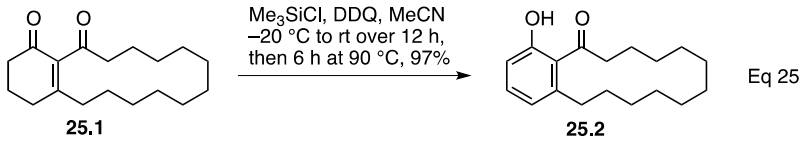
It is not clear why the yields are so poor.

Enone **24.1** was aromatized slowly, but in moderate yield, using DDQ in refluxing dioxane.[22]



Eq 24

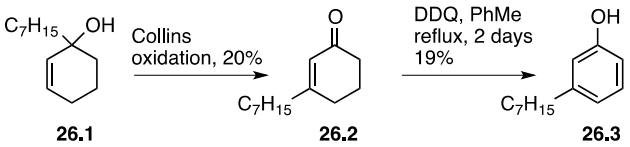
DDQ worked nicely for **25.1** in the presence of Me_3SiCl,[23] but it was not determined if the chlorosilane activated the DDQ or formed a silyl enol ether from the starting ketone. Both reagents were used in stoichiometric amounts. The use of $Pd(OCOCF_3)_2$[24] gave a poor yield (32–43%).[23] A mechanism by which chlorosilanes facilitate dehydrogenation has been proposed for conversion of enones to cross-conjugated ketones.[25]



Eq 25

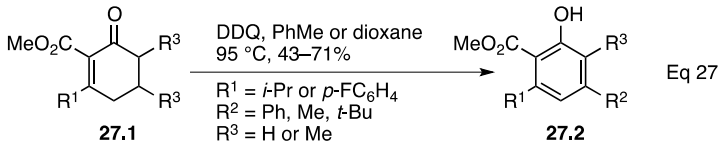
A series of simple 3-alkylcyclohex-2-en-1-ones was aromatized, for antinematodal evaluation, by treatment with DDQ in refluxing benzene.[26] Attempted aromatization of **26.2** with Pd-C "was not fruitful".[26] The other 3-alkylphenols made[26] had straight chain C_{8}-, C_{9}-, C_{10}-, C_{11}-, C_{12}- and C_{-13} substituents in place of the heptyl group of **26.2**. No specific yields for the

aromatization steps with these higher homologs were given, but the outcome of each of the steps was stated to be comparable to those for the preparation of **26.2**.



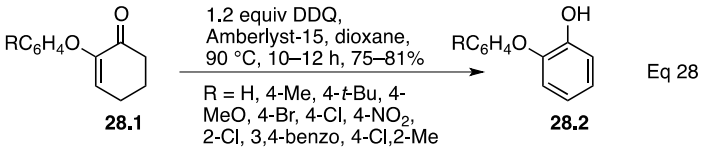
26.1 **26.2** **26.3** Eq 26

A series of enone esters **27.11** was aromatized at 95 °C in PhMe or dioxane.[27] In these cases heating (175 °C) with sulfur or use of Pd-C or Pt-C in decalin at 200 °C was "much less effective".[27]



27.1 **27.2** Eq 27

Some 2-aryloxyphenols have therapeutic applications[28] and a number of simple 2-aryloxycyclohexenones **28.1** have been aromatized with DDQ activated with the solid acid Amberlyst-15. In the absence of the activator there was no reaction,[28] *t*-BuMe$_2$SiCl was also tried[28] as an activator,[25] but this approach led to a complex mixture.



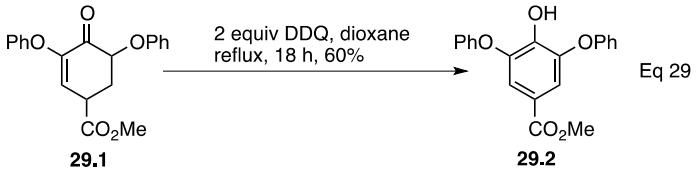
28.1 **28.2** Eq 28

The temperature is important in these experiments,[28] with 90 °C being optimum. Several other oxidants were examined: I_2 in methanol gave a 10% yield of 2-phenoxyphenol together with other unspecified products. Use of I_2 in acetonitrile at room temperature or at reflux failed to give the phenol and most of the starting material was recovered. Some phenol **28.2** was formed on treating **28.1** with CuBr-LiBr in DMF at 90 °C for 10 h, but the yield was only 30%. Dehydrogenation with 10 wt% of 10% Pd-C in refluxing ethylene glycol for 2 h gave the desired

phenol in 10% yield. Finally, **28.1** (R = H) was found to be largely inert to IBX (even in excess) in DMSO at 80 °C.

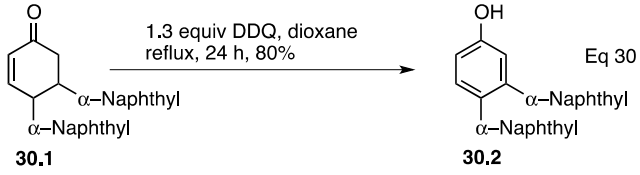
The DDQ-Amberlyst procedure was also examined in a variety of solvents. Polar solvents (DMF, MeOH, AcOH) did not result in any improvement and, in the non-polar solvent PhMe, the yield was very low.

The bis-phenoxy phenol **29.2** was generated in 60% yield by dearomatization of **29.1** with DDQ.[29]



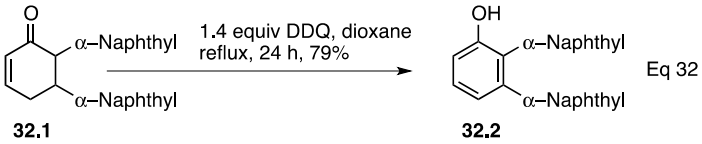
29.1 **29.2**

The group of related naphthyl-substituted enones **30.1**, **31.1**, **32.1** and **33.1** were aromatized in widely different yields and, again, the reason for the differences is unclear.[30]

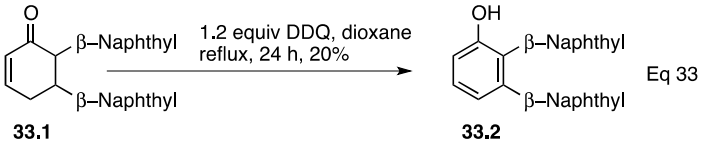


30.1 **30.2**

31.1 **31.2**

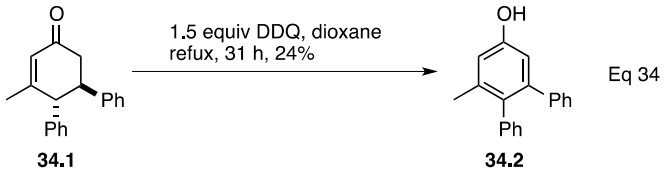


32.1 **32.2**



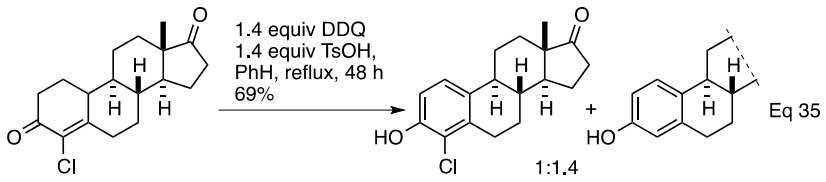
33.1 **33.2**

A low yield was also observed for the diphenyl enone **34.1**.[31]



34.1 **34.2**

The chloroenone **35.1** was aromatized with DDQ in the presence of TsOH.[32] In this case the dechlorinated analog **35.3** (estrone) was also produced, presumably via the $\Delta^{3,5(10)}$ dienol, followed by reprotonation at C-4 and elimination.

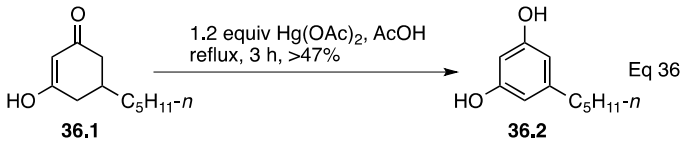


35.1 **35.2** **35.3**

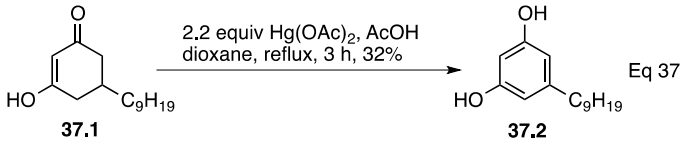
The above examples show that stoichiometric DDQ usually effects aromatization in refluxing dioxane, but the reaction is slow and the yields are rarely very high. Also, seemingly minor structural changes can have a dramatic effect on the yield, and even with thermally robust compounds, the outcome can be poor for no apparent reason.

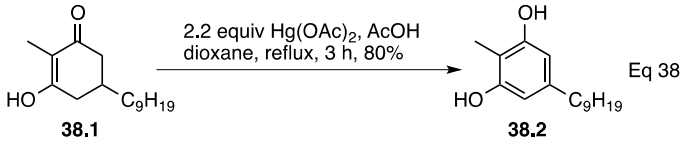
#3 Aromatization with mercuric acetate

An early example of the use of $Hg(OAc)_2$ in stoichiometric amount to effect aromatization is the formation of olivetol (**36.2**).[33,34]

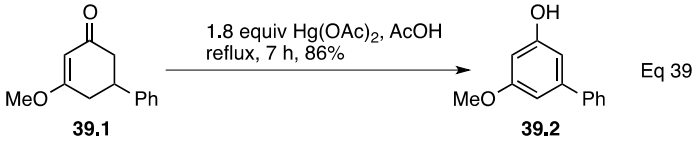


The unpredictable performance of $Hg(OAc)_2$ is illustrated by the examples in Eqs 37 and 38, which differ widely in efficiency.[2] It is not clear why the C-2 methyl substituent of **38.1** should exert a beneficial effect.

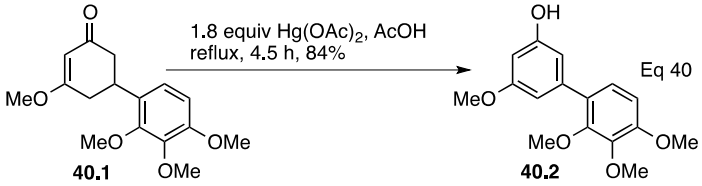




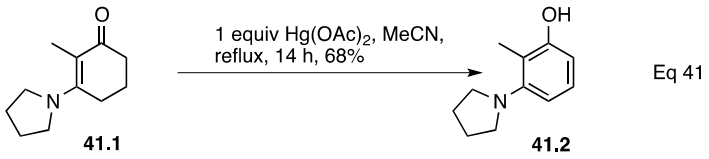
The oxidation also works with vinylogous esters (e.g. **39.1**) under similarly harsh conditions.[35]



In the case of compound **40.1**, aromatization with $Hg(OAc)_2$ was very effective;[7] in contrast, use of platinum black or DDQ was unsuccessful.



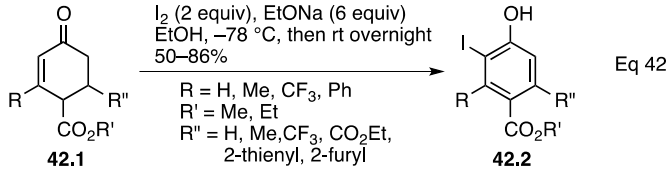
In related aromatizations, a number of simple vinylogous amides were aromatized[36] in 35–78% yield, by heating in refluxing acetonitrile with an equivalent of $Hg(OAc)_2$ for 12–20 h; the transformation **41.1→41.2** being typical.



Eq 41

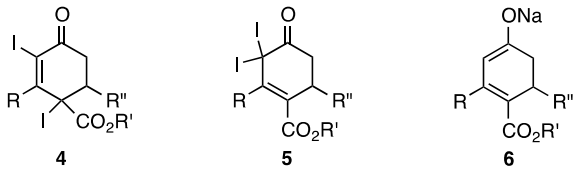
#4 Aromatization using iodine

The use of iodine to convert cyclohexenone systems into aromatics has been reviewed.[37] Generally, phenol ethers are formed, rather than phenols, but a number of cyclohexenones carrying an ester group are converted into iodophenols in the presence of base.[38]

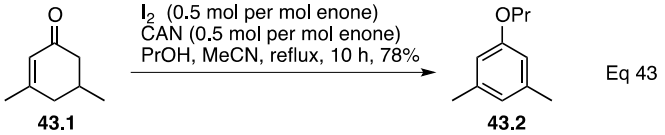


Eq 42

These reactions (Eq 42) are considered to proceed via either or both of the diiodoketones **4** and **5**. Use of less than 2 equiv of iodine led to incomplete consumption of the starting material. An electron-withdrawing group at C-4 is essential and the preferential formation of the more stable linearly conjugated dienolate **6** accounts for the regiochemical iodination.

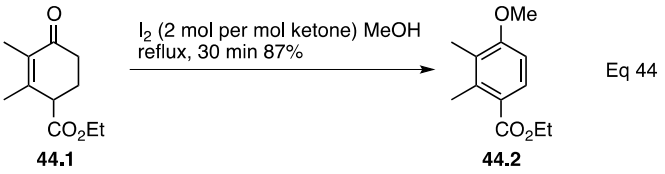


The use of I_2 and $(NH_4)_2Ce(NO_2)_6$ led to phenol ethers, as shown by the conversion **43.1→43.2**.[39]



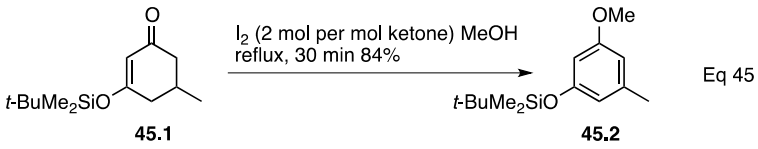
Eq 43

A range of cyclohexenones carrying an ester group at C-4 have been aromatized[40] with I_2 in refluxing MeOH (30 min, 85–90%). Methyl ethers are formed, and a typical example is the formation of **44.2**.



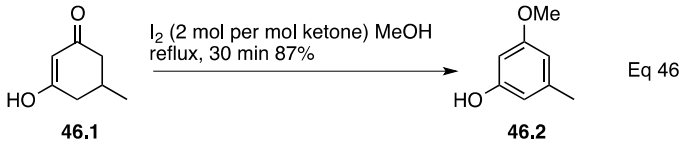
Eq 44

In a subsequent publication[41] the examples reported did not contain an ester group; the example shown in Eq 45 is most relevant to the formation of phenols because, in principle, the silyl ether **45.2** can be desilylated to afford a phenol.



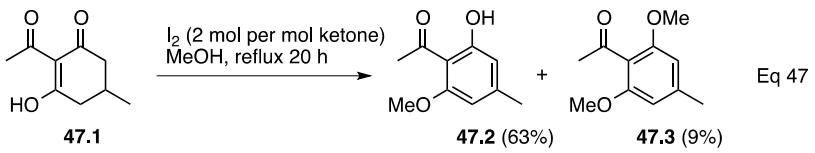
Eq 45

Similarly, cyclohexane-1,3-diones give 3-methoxyphenols on treatment with I_2 in MeOH (Eq 46).[41]

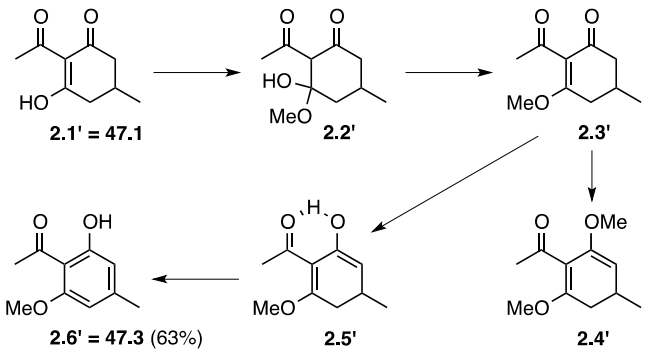


Eq 46

2-Acylcylohexane-1,3-diones behaved differently on treatment with I_2 in refluxing MeOH; in the simple cases examined[42] (**47.1**) a 1,3-*dimethoxy*benzene (**47.3**), was a significant product and in some cases the major product.

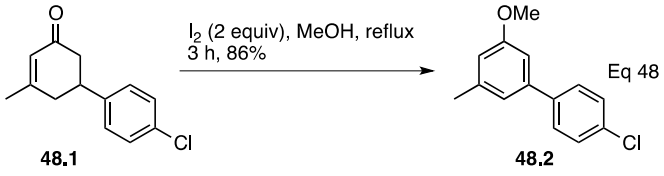


Possibly, an intermediate enol (**2.5'**) formed from **2.3'**, and stabilized by intramolecular hydrogen bonding, is the species that leads to the formation of a phenol. It is proposed[42] that **2.3'** is also converted into a bis-enol ether **2.4'** which is the precursor of the corresponding aromatic compound **2.6'** (= **47.3**).

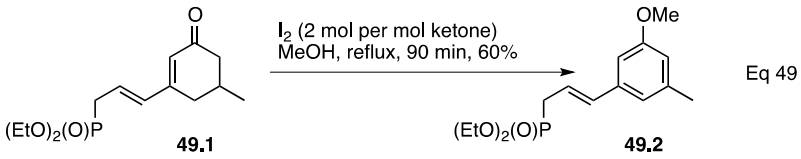


Scheme 2. Mechanism of iodine-catalyzed aromatization.

Several closely related biphenyl methyl ethers have been prepared by iodine-mediated aromatization, as illustrated in Eq 48.[43]

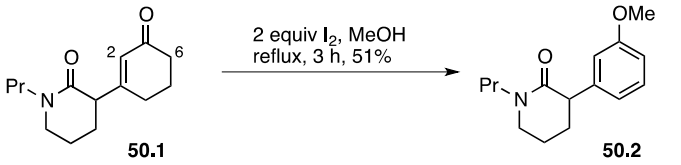


The more highly functionalized aromatic **49.2** is also available by the iodine-based method.[44]



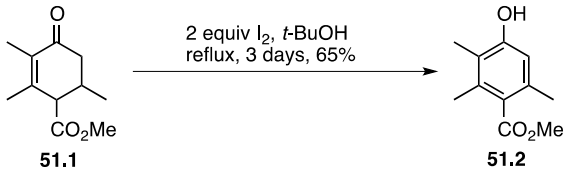
Eq 49

The lactam enone **50.1** gave the aromatic methyl ether **50.2**, but experiments with the corresponding C-2 or C-6 methylated enones were unsuccessful.[45]



Eq 50

Although aromatization by reaction with I_2 in MeOH normally leads to the formation of methyl ethers, several analogs of Hagemann's ester were examined in *t*-BuOH and these experiments led directly to phenols, a typical example being the conversion **51.1→51.2**.[15]



Eq 51

The aromatization is slow and the two other related examples that were reported[15] required 3 and 5 days, respectively.

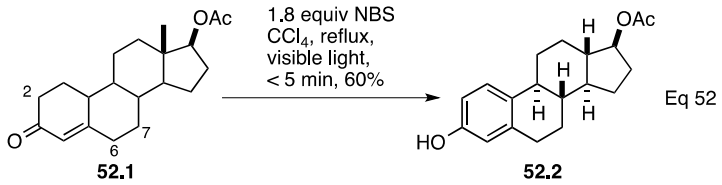
We suspect that the lesser tendency of *t*-BuOH compared with MeOH to form an intermediate hemiketal is the reason why phenols are formed in *t*-BuOH.

#5 Aromatization by bromination-dehydrobromination

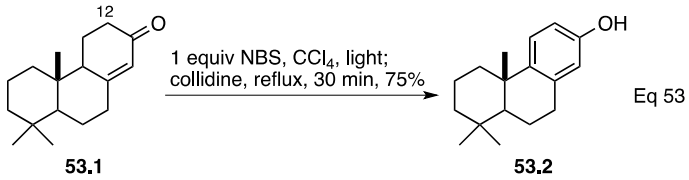
Bromination with Br_2 or NBS, followed by elimination of HBr is another classical method for aromatization, and several modifications of this general approach have been reported.

The action of NBS on the steroidal enone **52.1** for a very short time at the reflux temperature of CCl_4 gave estradiol-17-acetate.[46] Possibly, bromination at C-2 (for which a

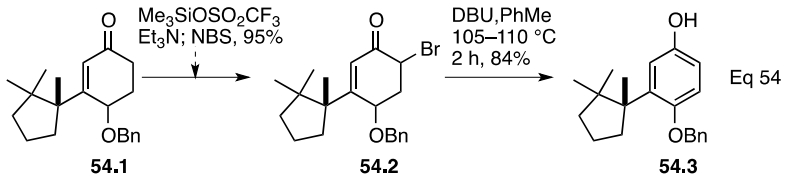
number of mechanisms can be envisaged), followed by thermal dehydrobromination, gives a cross-conjugated ketone that tautomerizes to the phenol. The crude product appeared to contain a C-6–C-7 double bond (which was saturated by hydrogenation), as would be expected from competing allylic bromination at C-6.



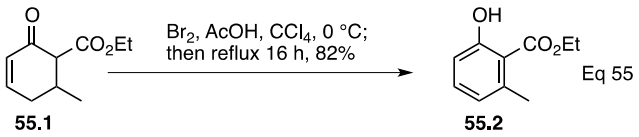
In a related process, the podocarp-8(14)-en-13-one **53.1** was aromatized[47] by bromination, presumably at C-12, and then dehydrobrominated in refluxing collidine.



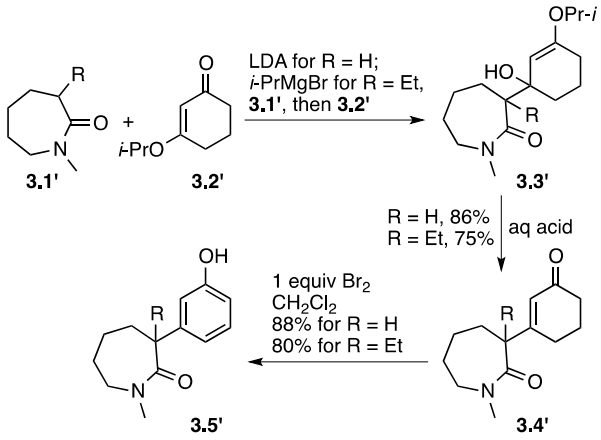
α-Bromination of **54.1** was effected by forming the trimethylsilyl enol ether and treating that with NBS at –30 °C.[48] When the resulting bromide **54.2** was heated with DBU in PhMe for 2 h the phenol was formed in high yield. When the standard selenium-based methodology (see later) was tried[48] on the same enone the yield was lower (40% after selenation, oxidation and selenoxide fragmentation).



In another slight modification of the bromination-dehydrobromination method, keto ester **55.1** was aromatized[49] by bromination at 0 °C and then heating while removing the liberated HBr with a stream of nitrogen.

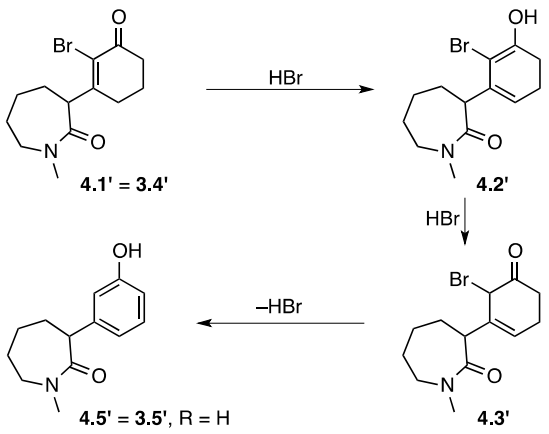


A report relevant to the research described in the Discussion Section of this Thesis is the observation[50] that the lactams **3.1'** can be condensed with enone **3.2'**. The products (**3.4'**) were treated with Br_2 in CH_2Cl_2 to give **3.5'**. The method was applied to a number of lactams differing in the size of the lactam ring.



Scheme 3. Mechanism of aromatization by bromination-dehydrobromination.

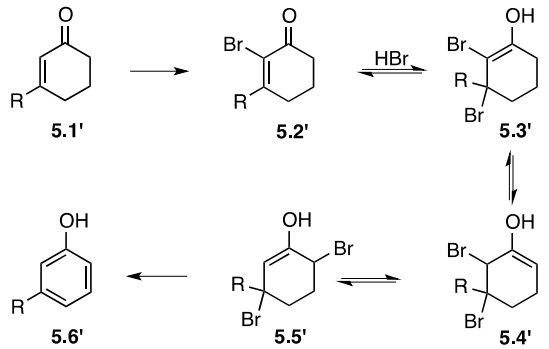
The HBr generated in the bromination step must catalyze deconjugation of the intermediate 2-bromocyclohex-2-en-1-one, which then looses HBr, one possibility being summarized in Scheme 4.



Scheme 4. Mechanism of HBr in aromatization.

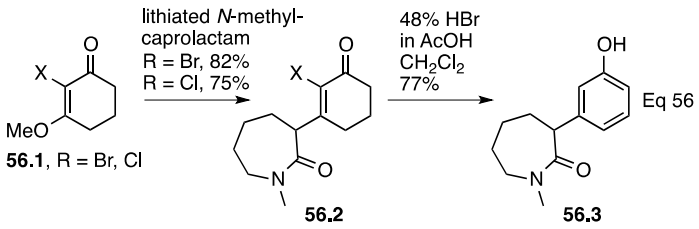
Several other methods for aromatization were tested on **3.4'** (R = H): Br_2 in methanolic benzene, $CuBr_2$, $CuCl_2$ (with or without LiBr or LiCl) in various solvents, and NBS, but the best method proved to be use of 1 equiv of Br_2, the stoichiometry being controlled to avoid halogenation of the product phenol.

A later paper from the same laboratory[51] reported that the bromination could also be done in AcOH. Additionally, the bromine could be generated in situ using aqueous $KBrO_3$ and HBr and, in that case, the bromo enone **4.1'** was isolated (67%). Under anhydrous conditions, bromination would generate HBr, and the following mechanism (Scheme 5) was proposed for the resulting aromatization under anhydrous conditions.



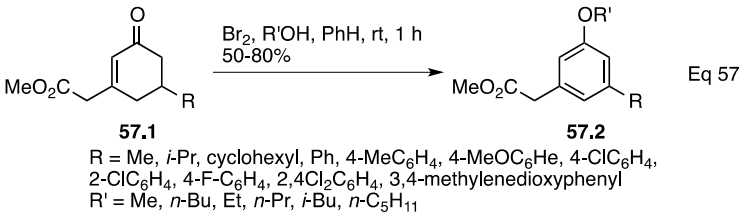
Scheme 5. Mechanism of aromatization by bromination-dehydrobromination.

In this later publication[51] it was reported that lithiation of *N*-methylcaprolactam with LDA and reaction with **56.1** gave the enones **56.2** after aqueous acidic workup. These were smoothly aromatized by treatment with 48% HBr in CH_2Cl_2 or AcOH.



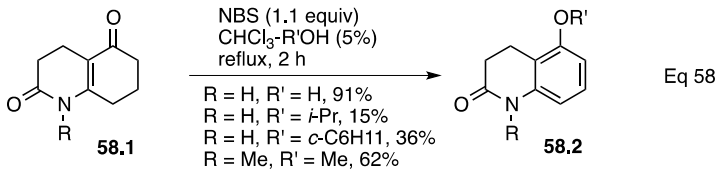
The corresponding sequence with *lithiated* 2-ethyl-*N*-methylcaprolactam failed in the first step (cf **56.1→56.2**), but the magnesium salt (as opposed to the lithium salt) did react as required and the adducts were smoothly aromatized with 48% HBr in CH_2Cl_2 (no yields given). This sequence involves one of the very few reports of an organometallic reagent reacting with a 2-halocyclohex-2-en-1-one; I have been able to locate only a few[52,53,54,55,56,57] others.

The bromination method was also applied to the enones **57.1**.[58] The bromination was



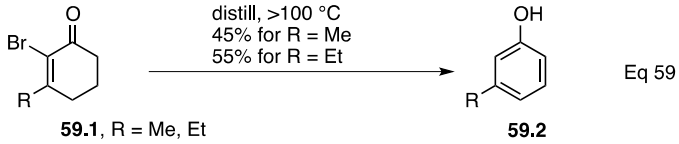
done in an alcohol solvent and aromatization and simultaneous *O*-alkylation occurred.[59] Evidently, at some stage a hemiacetal is formed. When a primary or secondary alcohol, other than methanol, was used ester exchange was also observed, and so the crude mixtures were immediately hydrolyzed to give the acids.

Ether formation was also observed in the following cases (Eq 58).[60]



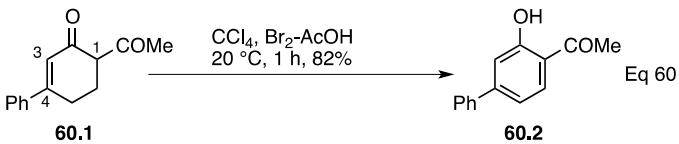
When the reaction was conducted in pure chloroform, without any alcohol, the corresponding phenol was formed (R = Me, 62%). When *t*-BuOH was the alcohol, the phenol was also produced (R = H, 54%).

Distillation of the bromoenones **59.1** gave the corresponding phenols.[57]



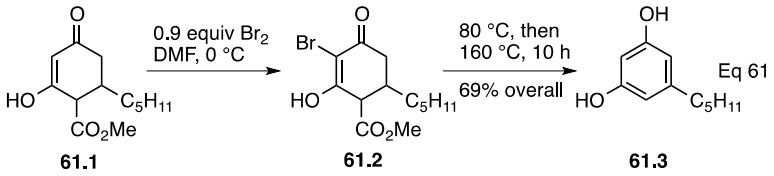
The bromoenones **59.1** were prepared from 2-bromocyclohexane-1,3-dione by reaction with MeMgI or EtMgBr, followed by workup with dilute acid in yields of 47% (R = Me) and 70% (R = Et). This is the only case where this particular method of preparing a bromoenone is followed by aromatization—the sequence used in one of the examples of my own research (see Discussion section of this chapter of the Thesis). In the present case the conditions are harsh and the yields are not very good.

Treatment of several 6-acetylcyclohex-2-en-1-ones with Br_2-AcOH in CCl_4 at room temperature gave the corresponding phenols (Eq 60).[61] With the 3-phenyl-substituted example **60.1** the yield was high, but was below 50% with the 3-methyl-, 3,4-dimethyl-, 3-ethyl-4-methyl- and 4-ethyl-3-methyl-substituted analogs.

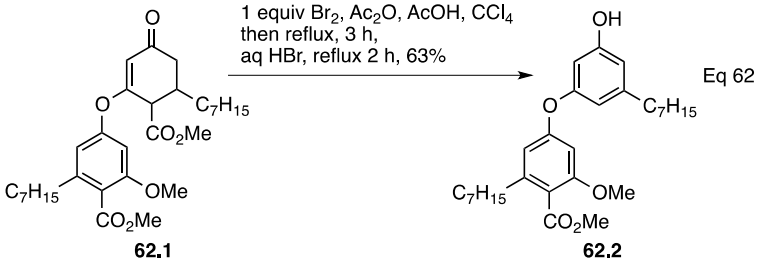


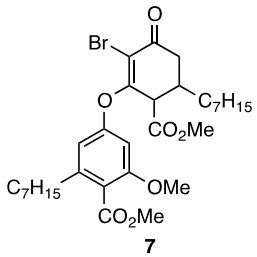
When the ketone **61.1** was treated with Br_2 in DMF at 0 °C the bromide **61.2** was formed and, on raising the temperature to 80 °C and then to 160 °C, phenol **61.3** was produced in 69%

yield from **61.1**.[62] During the first heating period decarbomethoxylation occurs, and during the second heating period HBr is lost, presumably via double bond migration to the β,γ position with respect to the carbonyl carbon.

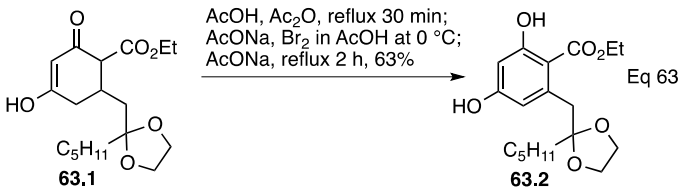


Bromination was also used to aromatize the aryloxy ketone **62.1**.[63] Presumably, bromide **7** is an intermediate,[64] but it is not clear at which stage the decarbomethoxylation occurs; we assume it is likely to be before aromatization so as to account for the fact that only one ester group is lost.



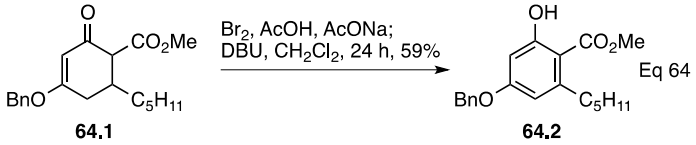


The keto ester **63.1** was aromatized in a similar way, by acetylation and the use of AcONa as a buffer to protect the acid-sensitive acetal group.[65]

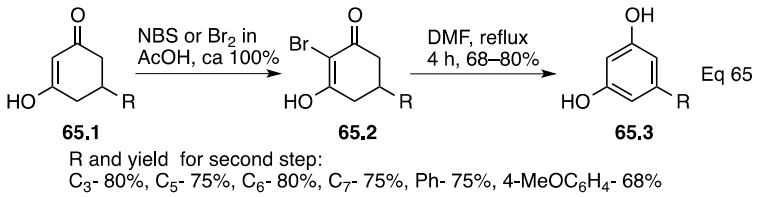


The site of the initial bromination probably corresponds to the site in **7**, and again, the elimination of bromine must involve prior movement of the double bond.

An alternative to thermal dehydrobromination is the use of DBU at room temperature (Eq 64).[66] Again the site of the initial bromination was not identified; it may be α to the ester group.

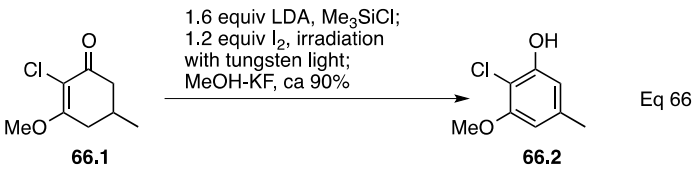


Some very simple cyclohexane-1,3-diones have been aromatized by bromination and heating in DMF (Eq 65).[5]



The dehydrobromination step (**65.2→65.3**) must involve movement of the double bond out of conjugation. In these studies both DDQ and chloranil were "ineffective" and dehydrogenation with Pd-C in refluxing Ph_2O gave only a 15% yield for the test case **65.1**, R = C_5H_{11}. For **65.1**, R = Ph or 4-$MeOC_6H_4$ the Pd-C method gave 75% and >60% yield, respectively.

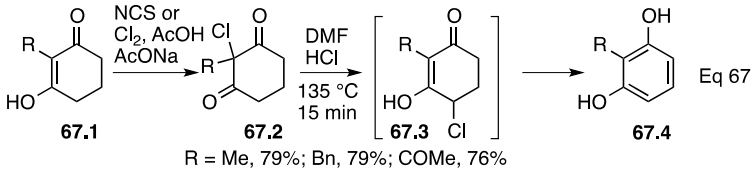
Iodine, instead of Br_2, has also been used to generate phenols (Eq 66).[67]



Eq 66

Presumably, this transformation involves thermal elimination from an α-iodocyclohexenone and silylation of the resulting phenolic tautomer.

In a few cases, chlorination has been used to effect aromatization (Eq 67).[68]



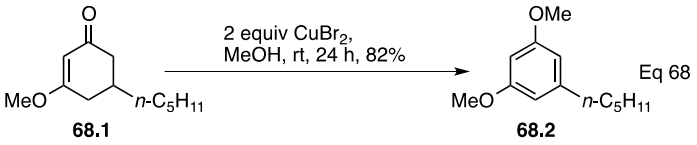
R = Me, 79%; Bn, 79%; COMe, 76%

Eq 67

The simple 2-substituted cyclohexane-1,3-diones were chlorinated with NCS or, in the case where R = Bn, with Cl_2 in AcOH buffered with AcONa. It was suggested that the resulting 2-chloro compounds rearranged on heating with HCl in DMF and then lost HCl to give the phenols in good yield. The outcome of the initial chlorination was very sensitive to the reaction conditions, at least for the cases tested (R = Me, Bn). A later study examined the mechanism of chlorination and rearrangement in DMF-HCl.[69]

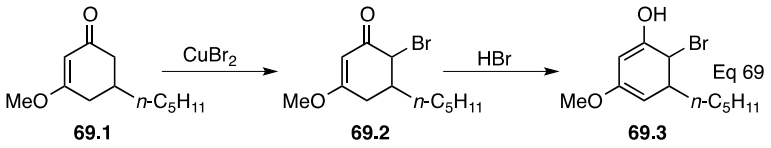
#6 Aromatization by use of $CuBr_2$

The enone **68.1** was converted by treatment with 2 equiv $CuBr_2$ in MeOH into the methyl ether **68.2**.[62]

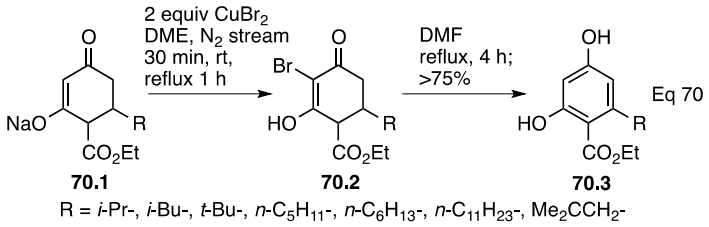


Eq 68

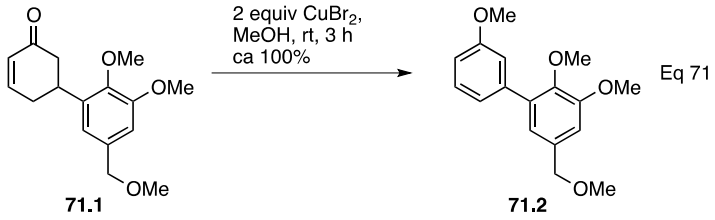
The mechanism by which $CuBr_2$ effects halogenation (of carbonyl compounds) does not appear to have been established,[70] but a plausible pathway for the aromatization is via the allylic bromide **69.3**.



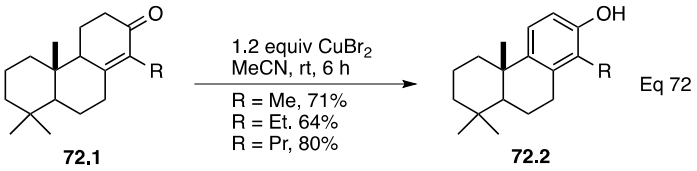
When the sodium salt **70.1** was treated with $CuBr_2$ in DME it was reported to form the bromide **70.2**, and this underwent efficient aromatization in refluxing DMF.[71] Decarboxylation of the products was easily effected by saponification and brief heating with aqueous sulfuric acid.



The cyclohexenone **71.1** was aromatized by treatment with 2 equiv $CuBr_2$ in MeOH, the product being the phenol methyl ether.[17]



The enones **72.1** were aromatized[47] with $CuBr_2$ in MeCN at room temp; in these cases bromination with NBS and treatment with collidine, a process that was satisfactory for R = H, was not successful. No hydroxylic solvent was used and consequently the product was a phenol rather than the corresponding ether.

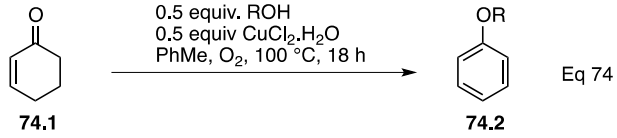


Eq 72

Enone **73.1** gave the aromatic methyl ether on reaction with $CuBr_2$ in MeOH. Use of EtOH or benzyl alcohol gave the ethyl and benzyl ethers, respectively, but use of aqueous dioxane did not give the phenol.[72]

Eq 73

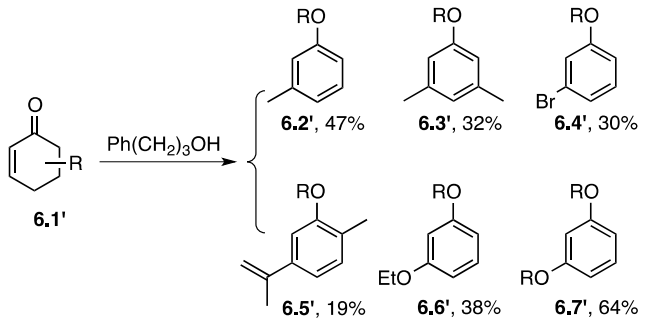
Aromatization to form aryl *ethers* can also be done with $CuCl_2.H_2O$ in the presence of O_2 and an alcohol (Eq 74).[73]



Eq 74

ROH = primary alkyl, benzylic, secondary alcohol, 33–100%.

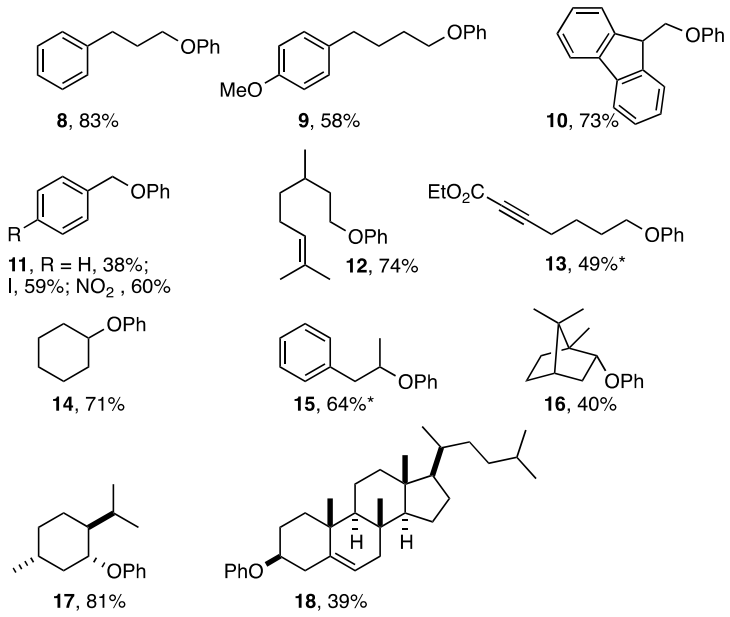
Arylalkyl alcohols $Ar(CH_2)_nOH$, in which the benzene ring carries I, MeO or NO_2 are satisfactory alcohols and an alkyl chain bearing CO_2Me, NHTs or incorporating a triple or double bond can also be used, but the reaction does not work for a tertiary alcohol.[73] Various substituted cyclohexenones were also examined, leading to the following ethers (Scheme 6).



Scheme 6. Substrate scope of aromatization reaction.

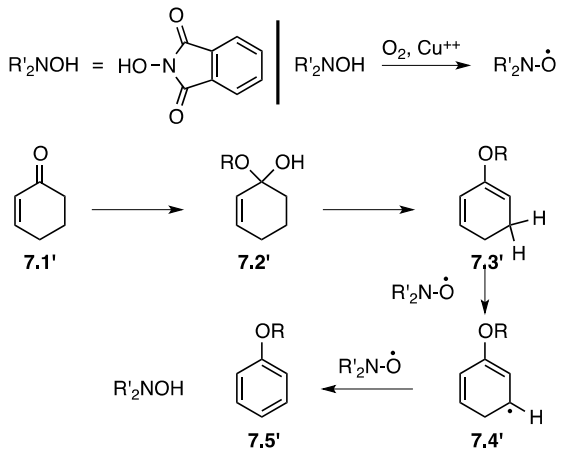
As shown, even double etherification can be done (using cyclohexane-1,3-dione).[73]

The amount of copper reagent can be lowered and an effective procedure along such lines was developed, based on the use of 10 mol% $Cu(OTf)_2$, 20 mol% *N*-hydroxyphthalimide and 1 equiv each of KI and water, an O_2 atmosphere (sealed tube) and a reaction time of 18 h at 100 °C. Under these conditions, the following yields were obtained with cyclohexenone and a variety of alcohols.



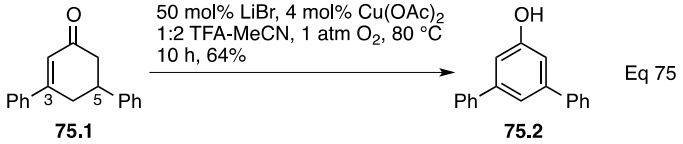
* Reaction at 120 °C instead of 100 °C.

The mechanism proposed for this reaction is summarized in the following Scheme.



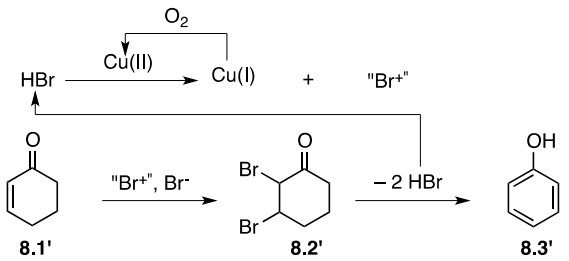
Scheme 7. Mechanism of copper-catalyzed aromatization.

Conversion of cyclohexenones into phenols can also be achieved by copper-catalyzed bromination, a typical example being **75.1→75.2**.[74]



Besides a phenyl group at C-3, the case of a C-3 hydrogen was also examined. The C-5 substituents were 4-$MeOC_6H_4$-, 4-$O_2NC_6H_4$-, 4-BuC_6H_4-, 2-thienyl, H and isopropenyl. In a few cases C-4 carried a CO_2Me group. Although prolonged heating in the presence of CF_3CO_2H is required, yields are often high; they varied from 46% to 97% (average, 68%). The highest yield (97%) was obtained with a C-5 isopropenyl group and it is not clear if acid-catalyzed migration of the pendant double bond, rather than bromination-dehydrobromination, accounts for the outcome. If the amount of LiBr is too large the phenolic products are often brominated; the optimum amount of LiBr is 50 mol%.

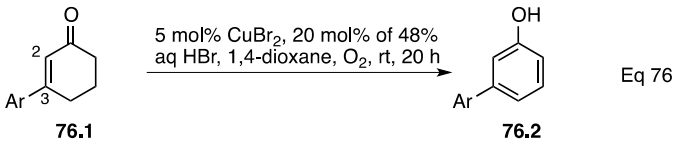
In this procedure LiBr in the presence of acid generates HBr which is oxidized to a source of electrophilic bromine, and the following brief mechanistic scheme was proposed (Scheme 8).



Scheme 8. Mechanism of aromatization in the presence of LiBr.

The intermediate dibromide is aromatized in the absence of LiBr, under otherwise identical conditions. Aromatization of the dibromide to phenol is very slow in the absence of Cu(II) ions, suggesting that the copper ions also play a role in the loss of HBr.

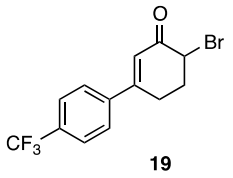
A mechanistically related process (Eq 76) employs a catalytic amount of $CuBr_2$ (5 mol%), 20 mol% of 48% aqueous HBr, and an oxygen atmosphere.[75] The reaction occurs at room temperature.



A number of examples were studied with simple C-3 or C-2 aryl, heteroaryl or benzyl substituents and, in a few cases, with an alkyl or benzyl group at C-4. Yields were very high, generally above 90%, giving access to substituted phenols including those with a *meta* substituent. Several disubstituted phenols were also prepared, again in good yield. If an excess of HBr is used, the phenolic product is brominated.

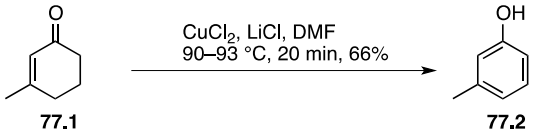
A sample of bromide **19** was aromatized quantitatively in 30 min when subject to the above reaction conditions; however, in the absence of HBr there was no reaction, but in the absence of $CuBr_2$ aromatization was again quantitative. These observations suggest that bromination occurs first in the standard reaction to generate compounds of type **19** and that an HBr-mediated dehydrobromination then takes place; finally, tautomerization generates the phenol. The mechanisms for the bromination (which probably occurs slowly) and dehydrobromination are not known; in fact, several mechanistic proposals for bromination (in other contexts) by $CuBr_2$ have been suggested,[76] but without any definite conclusions. This

proposal differs from that of Scheme 8 because it does not involve bromine addition to the double bond.



19

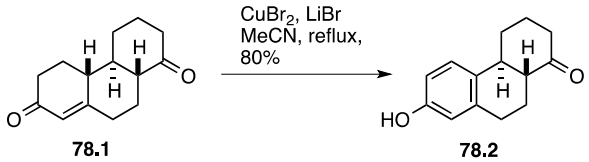
Use of $CuCl_2$ and LiCl in DMF leads directly to phenols, but the scope of this process was not explored and only cyclohexenone itself and 3-methylcyclohex-2-en-1-one were examined.[77] No intermediate chloro compounds were detected.



77.1 **77.2** Eq 77

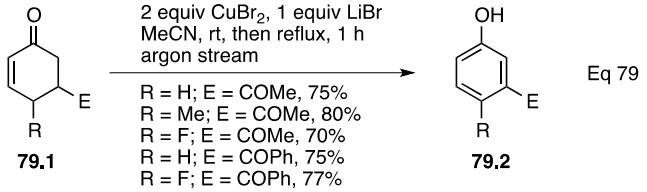
The above process was subsequently investigated further[78] and it was found that aromatization of **77.1** could be achieved in better yield within 1 h by using CuBr-LiBr instead of the chlorides and by using MeCN at reflux rather than DMF at 80–90 °C. The process was conducted under a stream of nitrogen. The reaction is stated to be inhibited by CuBr and HBr.

When applied to polycyclic compounds only the cyclohexenone subunit is modified, as in the conversion **78.1→78.2**.[78]

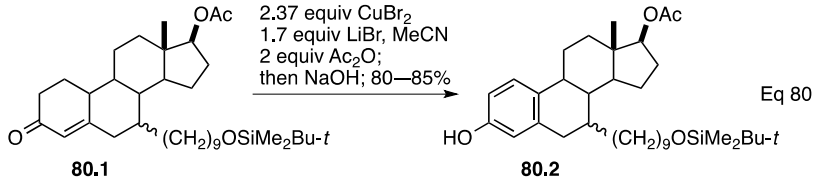


78.1 **78.2** Eq 78

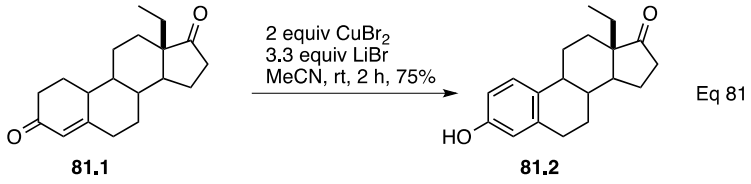
The $CuBr_2$-LiBr method was very effective for the following aromatizations[14] (Eq 79) and the yields were better than those obtained with Pd-C in refluxing *m*-xylene.



The $CuBr_2$-LiBr method has been used on an industrial scale in the synthesis of the anticancer drug fulvestrant, the following reaction (Eq 80) being carried out in batches of several hundred kg.[79] The acetylation step was done to decrease the reactivity of the product phenol so as to suppress bromination of the phenol. At the end of the reaction, thiourea was added before saponification in order to precipitate copper species.

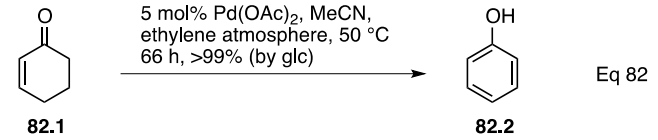


A structurally related example is the aromatization of the 18-homoestrone derivative **81.1** which occurred in good yield and without bromination α to the C-17 carbonyl.[80]



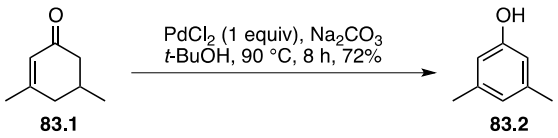
#7 Aromatization with palladium diacetate and palladium bis(trifluoroacetate)

During a study[81] on the Pd(II)-catalyzed oxidation of cyclohexanone to cyclohex-2-en-1-one it was observed that conversion to phenol could be effected in the presence of ethylene, using 5 mol% of $Pd(OAc)_2$ in acetonitrile at 50 °C. The reaction (Eq 82) was slow (66 h) but the yield was >99%. This was the only example studied, and so the general utility of this process remains to be established.



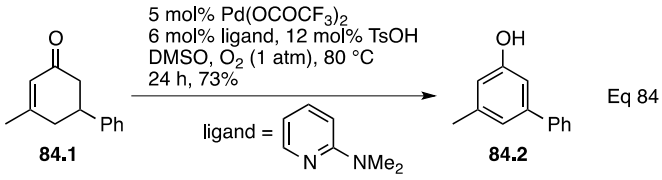
Eq 82

Aromatization with 1 equiv of $PdCl_2$ has also been reported (Eq 83),[82] but large scale applications would be prohibitively expensive.



Eq 83

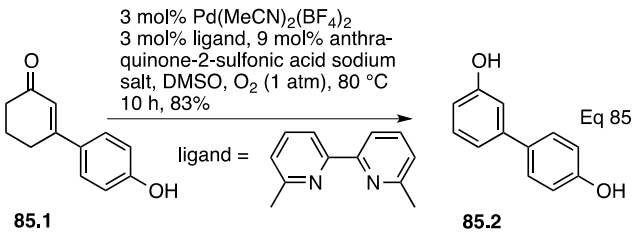
Methods that are catalytic in palladium offer a more promising approach and the use of $Pd(OCOCF_3)_2$ has been studied[24] in this regard (Eq 84). Oxygen is used as the terminal oxidant. While the reactions are slow, the yields are satisfactory (57–96%), and the method offers an



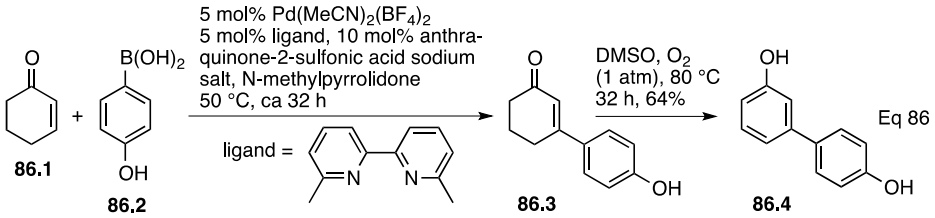
Eq 84

attractive route to 3,5-disubstituted phenols. Such compounds, when derivatized on the phenolic oxygen, sometimes have important biological properties, but are not readily available by other methods.[24] The nature of the ligand is important and 2-(dimethylamino)pyridine in the presence of TsOH gave best results. It was speculated that the role of the TsOH is to protonate the coordinated ligand, making it more electron-deficient, a factor that should facilitate the two key steps in the dehydrogenation — the C–H insertion and β-hydride elimination. Further research was devoted to the mechanism of the aromatization.[83]

In a later publication[84] a different catalyst and ligand system was developed (Eq 85).[84]



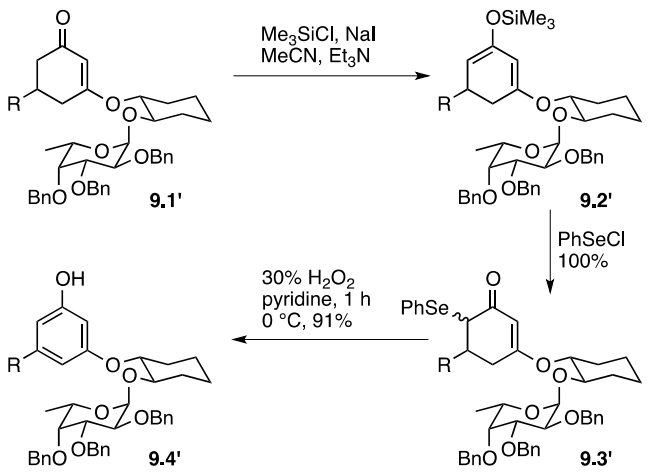
The aim of this research was to find a catalyst that would serve equally well for Heck coupling of a boronic acid with a cyclohexenone so as to afford a 3-arylcyclohex-2-en-1-one (e.g. **85.1**) that could be directly aromatized in situ to a *meta*-substituted phenol. In the event, the above catalyst served this purpose admirably (Eq 86).[84]



The catalyst system could also be used simply for the aromatization step on cyclohexenones made by methods other than by a Heck reaction.

#8 Phenylselenation as an aromatization method

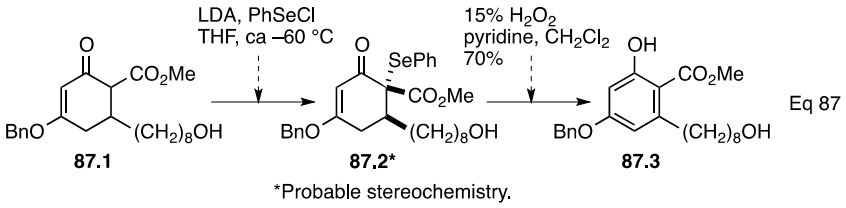
Another standard aromatization method is the α-phenylselenation of an enone, followed by oxidation of the selenide so as to generate a double bond. The phenylselanyl group can also be introduced via a silyl enol ether.[85] Even though the substrate **9.1'** (R = H) is highly functionalized each step goes in good yield.



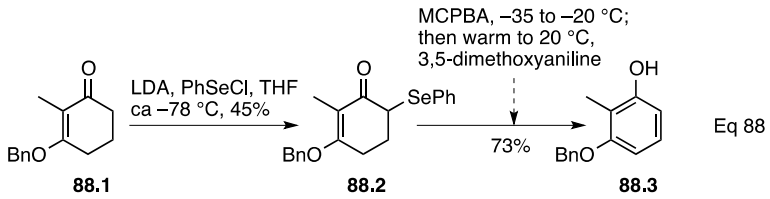
Scheme 9. Aromatization by selenation.

Related enones **9.1'** (R = Ph, *i*-Pr) were aromatized in the same way, but no yields were specified.

Sometimes the PhSe group is introduced via a lithium enolate (Eq 87).[86]

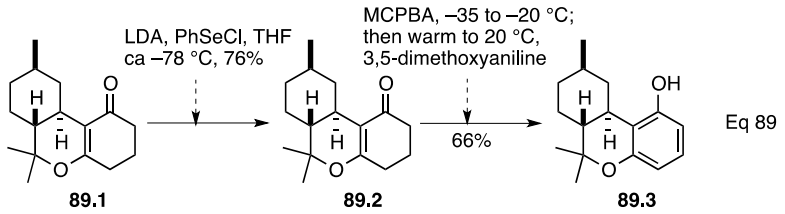


For this selenium-based method special conditions are sometimes necessary in the final oxidation step, as in the following examples (Eqs 88 and 89).[87]



It is not clear why the yield in the first step (**88.1→88.2**) is so low. In the second step, 3,5-dimethoxyaniline was used to trap the PhSeOH formed in the selenoxide elimination; in the absence of this trapping agent the phenolic product is selenated.

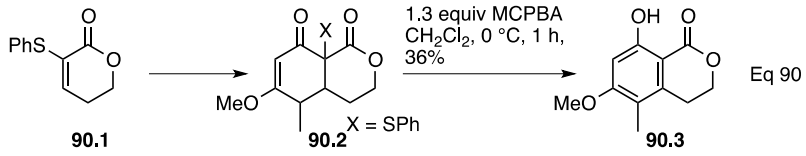
The same method was applied to make a compound having much of the carbon skeleton of the tetrahydrocannabinols (E 89).[87]



A similar transformation was attempted by brominating **89.1** (using an unspecified method), but it was impossible to suppress bromination of the phenolic product.

The need for the dimethoxyaniline trapping agent contrasts with the use of H_2O_2 in the case of **87.3** above, where no trapping agent was called for.[86]

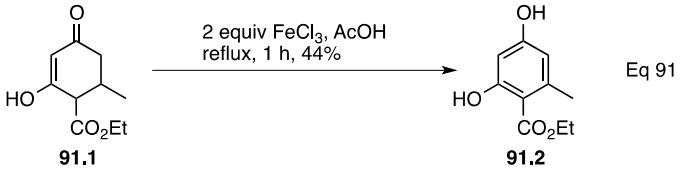
An analogous sulfoxide elimination has been reported (Eq 90).[18] In this case the sulfur-containing substrate (**90.2**) was made by a Diels-Alder cycloaddition on **90.1**; the corresponding cycloaddition using a substrate having a PhSe group instead of PhS was unsuccessful.



#9 Miscellaneous methods of aromatization

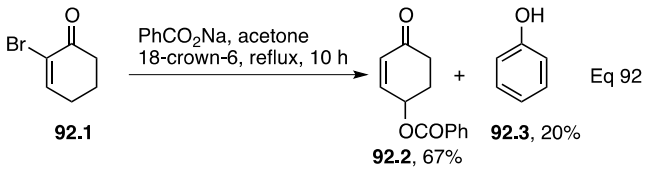
(a) Use of ferric chloride

The use of ferric chloride to aromatize **90.1** was reported a long time ago.[88] The same experiment was repeated almost 30 years later in another laboratory,[89] but attempts to improve the yield were unsuccessful.[89]

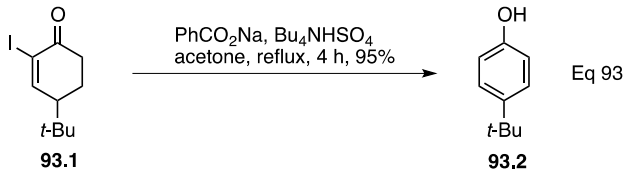


(b) Reaction of sodium benzoate with haloenones

During studies on α- and γ-benzoyloxylation of 2-halocyclohex-2-en-1-ones[90] the following incidental transformations were reported (Eqs 92 and 93).



92.1 **92.2**, 67% **92.3**, 20%

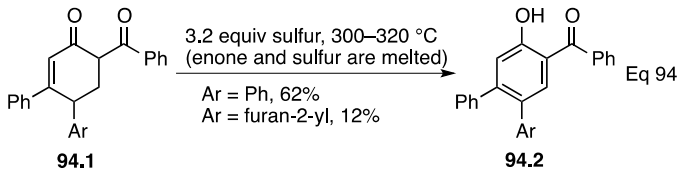


93.1 **93.2**

The process does not appear to be general and a substituent at C-4 is required for a satisfactory yield of the phenol (Eq 93); only the two phenols shown above were reported.

(c) Heating with sulfur

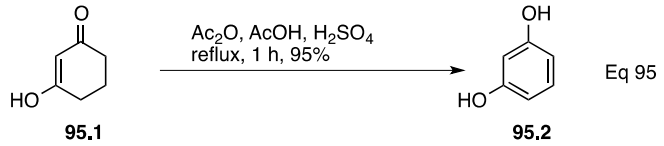
Heating with sulfur to a high temperature has been used to aromatize cyclohexenones,[91] and, although it is a classical method of dehydrogenation, it is a harsh and unattractive procedure.

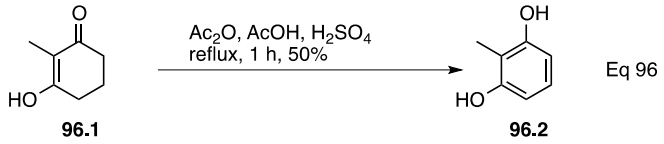


94.1 **94.2**

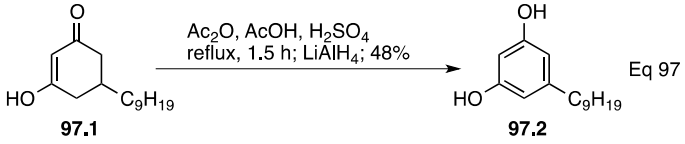
(d) Use of hot concentrated sulfuric acid

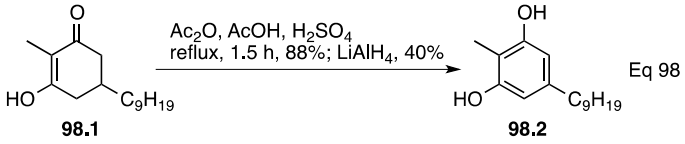
A few 1,3-dihydroxybenzenes were formed in good yield when the corresponding cyclohexan-1,3-diones were heated for 1 h with concentrated H_2SO_4 in Ac_2O-AcOH.[4] The mechanistic pathway involves sulfonylation at C-4 of **95.1**, followed by E1 elimination. The

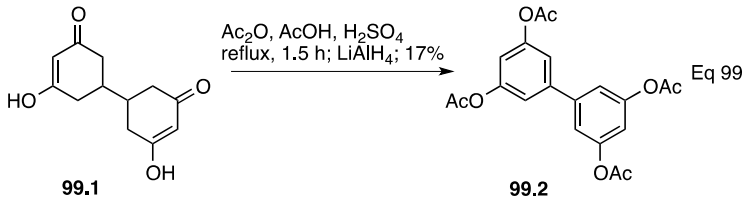




method is obviously of limited value for acid-sensitive compounds, but it has seen some use with robust substrates (Eqs 97–99).[2]



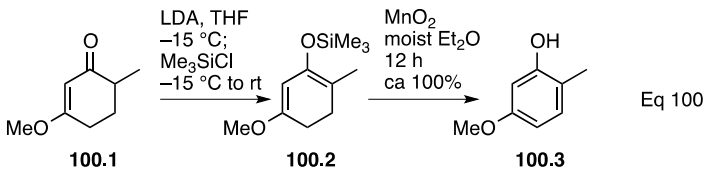




Aromatization of **99.1** was unexpectedly difficult,[2] both $Hg(OAc)_2$ and Pd-C in refluxing Ph_2O gave intractable material and, as shown, the Ac_2O-AcOH-H_2SO_4 method gave a very low yield.

(e) Use of MnO_2

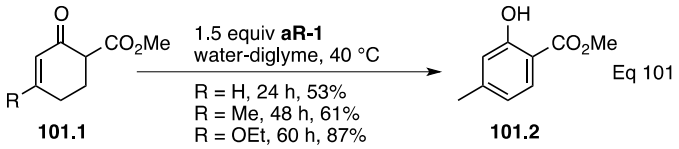
Aromatization of a silyl enol ether has been effected with MnO_2 (Eq 100).[67]



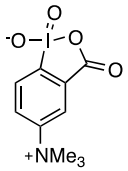
Eq 100

(f) Use of hypervalent iodine reagents

A few β-ketoesters have been aromatized with the water-soluble hypervalent iodine reagent **20** (Eq 101).[92]

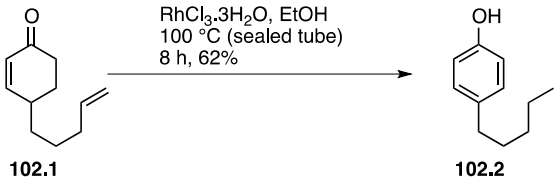


Eq 101



(g) Migration of a pendant double bond

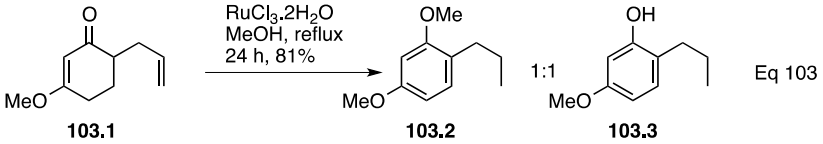
A number of cases have been reported in which a pendant double bond is made to migrate into a cyclohexenone ring, so as to produce the corresponding phenol; a typical example is shown in Eq 102.[93]



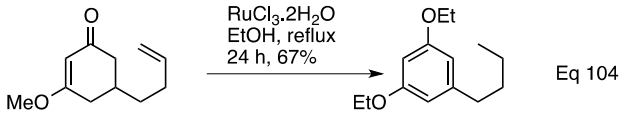
Eq 102

It is known that $RhCl_3 \cdot 3H_2O$ reacts with EtOH to form a rhodium hydride species and HCl.[94]

Several related isomerizations were reported by another group[95] and it was found that the outcome is very sensitive to the reaction conditions and substrate structure: compound **103.1** gave a mixture of the phenol and its *O*-methyl ether, while **104.1** gave only the phenolic diethyl ether, and some compounds failed to aromatize. The formation of **104.2** indicates the intervention of an acid-catalyzed enol ether equilibration. The method does not appear to be general.



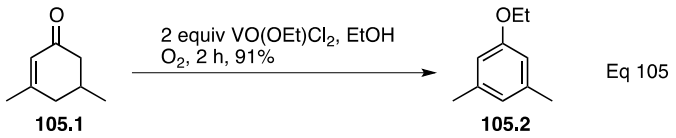
103.1 **103.2** **103.3**



104.1 **104.5**

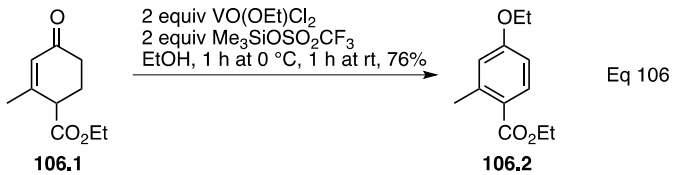
(h) Vanadium catalysts

Several cyclohexenones have been aromatized using vanadium oxidizing agents. With 1 or more equiv of $VO(OEt)Cl_2$, in the presence of O_2, the products are phenol ethers (Eq 105).[96]



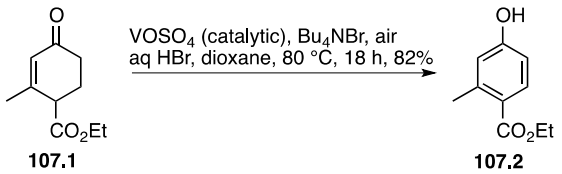
105.1 **105.2**

The type of ether formed is determined by the alcohol used as the solvent. The same transformation can be done in the absence of oxygen if at least 1 equivalent of $Me_3SiOSO_2CF_3$ is present (Eq 106).[97]



106.1 **106.2**

The reaction can also be done catalytically[98] (Eq 107) and, under the conditions used, the product is a phenol rather than a phenol ether, but the range of enones has not been adequately explored for either of these vanadium-mediated reactions.



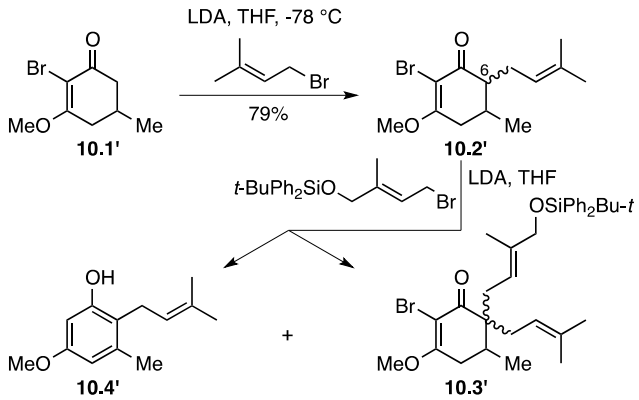
107.1 **107.2** Eq 107

Conclusion

Clearly, the aromatization of cyclohexenones is difficult and the numerous observations described in this survey show that harsh conditions are frequently required, and the method described in the following Discussion chapter is a valuable alternative approach that is widely applicable and that uses mild conditions.

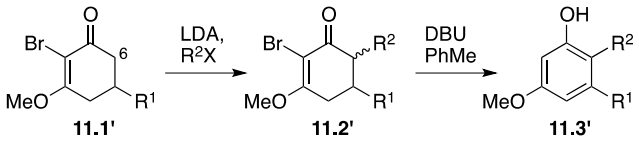
Results and Discussion

As described in Chapter 3 of this Thesis alkylation of bromoenone system **10.1'** with an allylic bromide worked well, but attempts to carry out a second alkylation gave a mixture of the desired product **10.3'** and the phenol **10.4'**. I found that one of the isomers of **10.2'** was more easily alkylated to **10.3'** and so I treated **10.2'** with DBU in the hope of equilibrating the material and, possibly, increasing the proportion of the more easily alkylated isomer. In the event **10.2'** was converted into **10.4'**. These observations indicated that 2-bromoenone systems could be alkylated and then aromatized under very attractive conditions.



Scheme 10. First example of aromatization.

Inspired by the smooth and previously unappreciated aromatization of a 2-bromo-3-methoxycyclohex-2-en-1-one to a phenol, we decided to examine the generality of this reaction. The starting materials, **11.1'** could be easily made from 3-methoxycyclohex-2-en-1-ones by bromination with NBS,[54] and the next experiments in the sequence are very straightforward: a) alkylation at C-6 with LDA and an alkyl halide in THF at –78 °C and b) aromatization with 2.0 equiv DBU in PhMe at room temperature (Scheme 11).



R_1 = Me, Et; R_2 = alkyl halide

Scheme 11. General route to resorcinol derivatives.

Several methods were tried for the alkylation step in order to get a satisfactory yield. We used compound **10.1'** and prenyl bromide as a test case and we found that deprotonation at –78 °C for 1 h only, followed by addition of the halide, gave 51% yield. Best results were obtained only by adhering exactly to the following optimized procedure: the starting material, 2-bromo-3-methoxycyclohex-2-en-1-one **10.1'** was deprotonated by LDA over 3 h, during which time the temperature was increased from –78 °C to 0 °C. Then the solution was recooled to –78 °C and the alkyl halide was added. In some cases a temperature of –78 °C was maintained, but in other cases the mixture was allowed to reach room temperature. We tried the alkylation with a number of simple halides, which are listed in Table 1. These were known compounds except for **22**; a few are commercially available and the others were made by the literature procedures; and both **21** and **22** were needed in my work on coleophomone, as described in Chapter 3 of this Thesis.

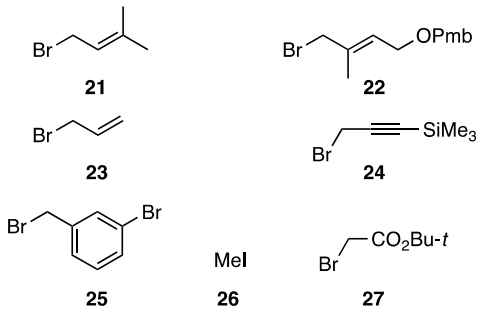


Table 1. Alkyl halides used for the alkylation step.

Under the optimized conditions, the yields were generally good (they varied from 70–79%) for all the examples. We did not optimize the reaction conditions for the aromatization as the yield was already very good (85%), using the initial conditions we had examined. However, we did study the relationship between reaction temperature and yield in the DBU-induced aromatization. Although the reaction went to completion faster at high temperature in PhMe (80 °C for 1 h; 50 °C for 4 h), we found it is more convenient to do this reaction at room temperature for an overnight period. The reaction was clean and the results are shown in Table 2.

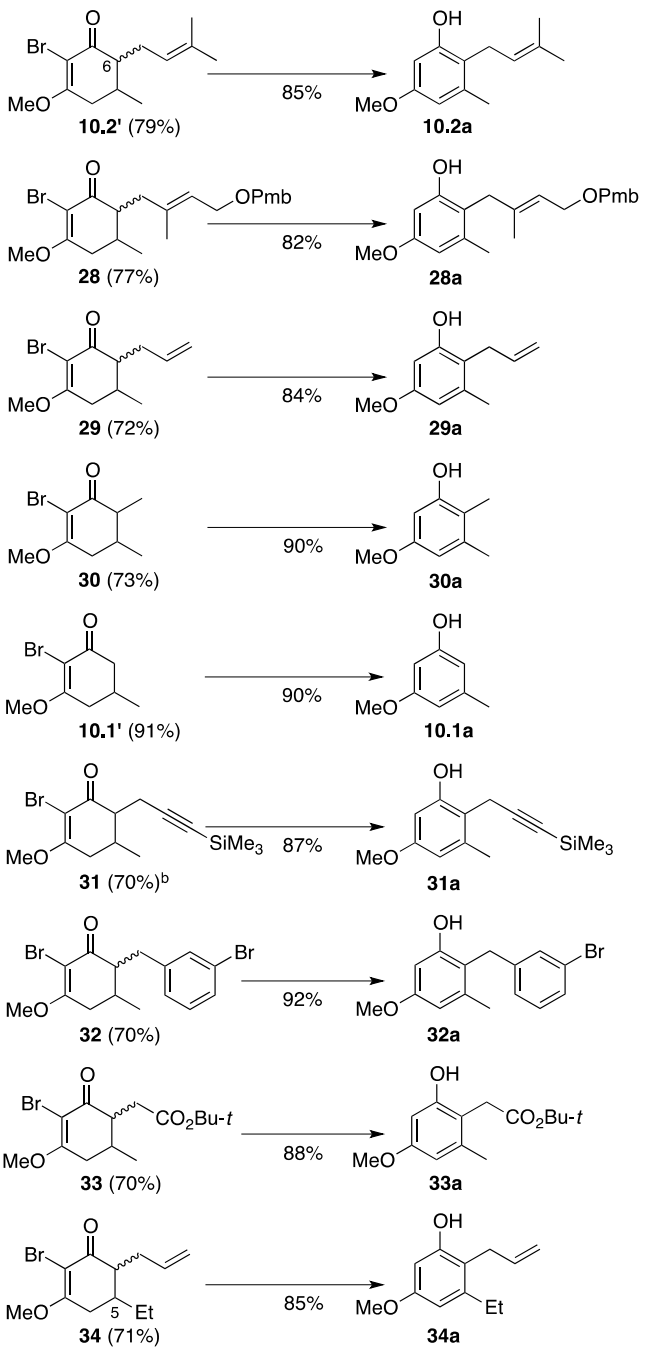


Table 2. Yields for alkylation and aromatization.

Reactive halides, such as allylic, propargylic, and benzylic bromides are suitable. We also attempted to use butyl bromide and butyl iodide for the alkylation step, but these experiments were unsuccessful and no alkylation occurred. The alkylation products consist of two inseparable diastereoisomers, and so it was difficult to tell if minor signals in the NMR

spectra came from minor impurities or from the minor diastereoisomer. If it was the former, the impurity amount must be small as the aromatization steps always gave high yields (82%–92%).

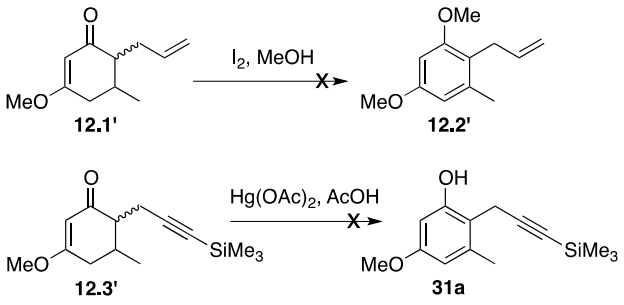
The preparation of compound **28a** is of special interest. Our method gave 82% yield of the desired phenol. This is a case were DDQ may not be a suitable reagent for aromatization, as the Pmb group is normally removed by the action of DDQ.

The substituent at C-5 does not have to be a methyl group, our choice was simply based on the fact that compound **10.1'** was a starting material in my studies on coleophomone B. An ethyl group is also acceptable (see **34→34a**) and probably any alkyl or aryl substituent would be accommodated provided no feature was sensitive to LDA or to NBS — the reagent used to introduce the bromine. The transformation of **34** to **34a** gave 85% yield while it is 84% for the Me example (**29→29a**).

From the examples studied, we conclude that the functional group introduced at C-6 has very little influence, if any, on the aromatization; the yields were always high.

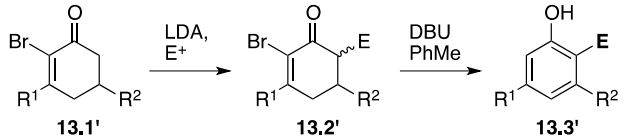
As indicated in the introduction there are a number of methods available for aromatizing cyclohexenone systems into phenols and so we decided to make a brief comparison of two known methods with our approach.

Compound **12.1'** and compound **12.3'** were treated with I_2/MeOH and with $Hg(OAc)_2$/AcOH (Scheme 12). Both reactions afforded complex mixtures, either at room temperature or at the reflux temperature of the respective solvents, which are the thermal conditions reported in the literature. The ^1H NMR spectra of the crude reaction mixtures did not show the presence of any aromatized products. These tests show that existing methods, at least those based on DDQ, I_2/MeOH and $Hg(OAc)_2$, are not compatible with certain side-chain functional groups. In contrast, our approach gave very good yields for these transformations.



Scheme 12. Attempted aromatization of cyclohexenones with I_2 or $Hg(OAc)_2$.

During the course of the above work we realized that the mildness of the aromatization step might allow the use of electrophiles other than simple carbon units. If this were the case the application of our method would be greatly expanded. In the event, we found that the electrophiles used for the C-6 alkylation step were not at all limited to active alkyl halides, but also could be extended to a very broad range of heteroatoms, such as N, F, S, Se, O. In other words, our approach could be used to make regiospecifically aryl-heteroatom bonds as well. During this research we also found that the MeO group at C-3 is not necessary. Again, all the reactions of the initial enolate with electrophiles are very straightforward and we put a variety of functional groups at the C-6 position using the optimized alkylation conditions mentioned above. Our results are summarized in Scheme 13 and Tables 3 and 4.



Scheme 13. General routes to heteroatom-containing phenols.

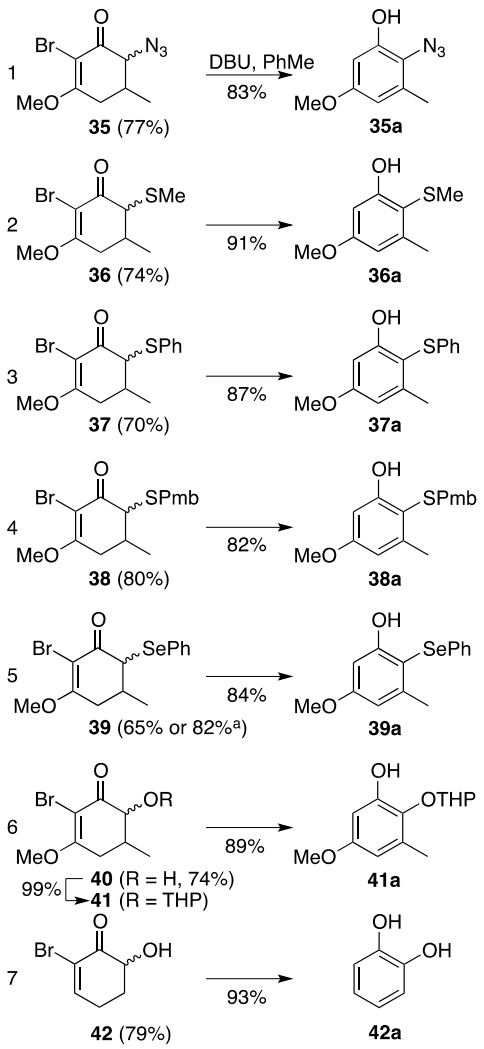
Sulfenylation (Table 3, entries 2, 3, 4) of 2-bromo-3-methoxycyclohex-2-en-1-one was easily done by deprotonation with LDA and treatment with $RSSO_2Tol$. This type of reagent has often been used in this laboratory in connection with an ongoing natural product synthesis. The reagents are known and they are easy to prepare by literature methods and are bench-stable.[99] Aromatization of the sulfur-containing enones was smooth and fast, and led to 82–91% yields of the desired aromatized products. The selenium example (**39)** was also done in a similar way, using the standard method of sulfenylating a ketone (LDA and then PhSeCl).

For the sulfur and selenium-containing bromocyclohexenones, the aromatization reactions are much faster, going to completion within 20 min to 2 h. The azide compound **35** was prepared by treating the enolate with 2,4,6-triisopropylbenzenesulfonyl azide[100] to obtain the azide in 77% yield. We also tried $TolSO_2N_3$[101] as the azide source but only got 31% yield of the desired product. Compound **35** was converted into azido phenol **35a** in good yield within 5 h.

α-Hydroxylation of compound **10.1'** (via its lithium enolate) with *N*-sulfonyl-oxaziridine[102] gave **40** as a mixture of diastereoisomers in 74% yield. However, the resulting α-

hydroxy compound could not be aromatized. Under our standard conditions (2.0 equiv DBU in PhMe), the α-hydroxy compound only gave a complex mixture. Therefore we protected **40** with *t*-butylchlorodiphenylsilane but the following aromatization afforded only a trace amount of the phenolic product. Fortunately, when THP was employed as a protecting group, the aromatization turned out to be very efficient and compound **41a** was obtained in very good yield. This example, whose three hydroxyl groups were differentially protected, enables further selective functionalization, which would be difficult to achieved by previously existing aromatization methods.

It is worth noting that although we had difficulty in aromatizing the α-hydroxy compound **40**, we did not encounter any problem when dealing with the simple α-hydroxyl bromoenone **42**, and catechol was generated in excellent yield without the necessity of using a protecting group. Evidently, the presence of the C-3 alkoxy group does have an influence, presumably by modifying the electronic properties of the carbonyl.

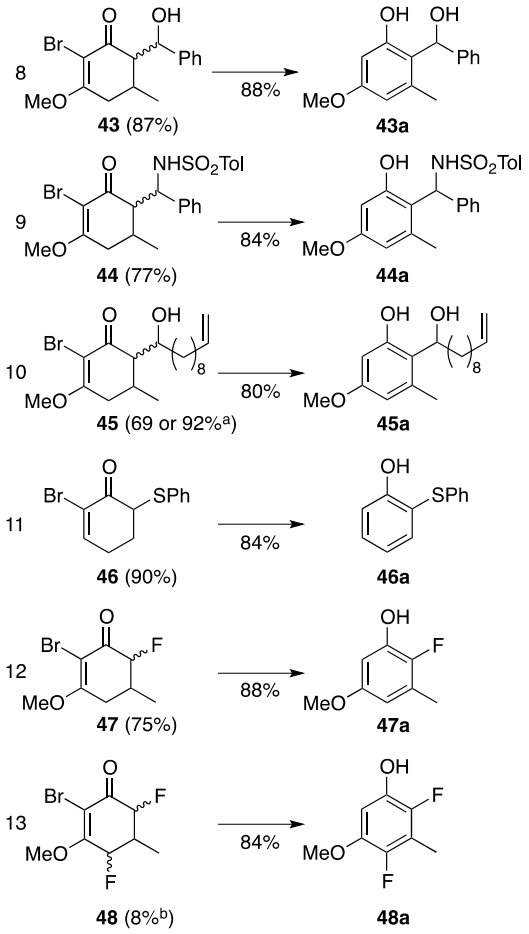


[a]Yield corrected for recovered **39**

Table 3. Aromatization of heteroatom-containing bromoenones.

When **10.1'** was treated either with benzaldehyde or an aliphatic aldehyde, the aldol products (Table 4, compounds **43** and **45**) were obtained in 87% and 69% yield, respectively. We were concerned that the aldol compounds **43** and **45** would suffer dehydration, especially compound **43**. In the case of **43** it is reasonable that the dehydration tendency would be enhanced by the fact that the product would then have a conjugated system. Fortunately, such side reactions did not occur for either **43** or **45**. Instead, both aldols underwent aromatization and gave the desired products in satisfactory yields.

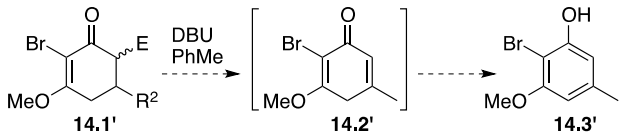
Likewise, the sulfonamide **44** was converted to the phenol in 84% yield. Fluorination of **10.1'** with the commercially available reagent *N*-fluorobenzenesulfonimide [NFSI, $FN(SO_2Ph)_2$] gave two fluorine-substituted products. The monofluoro compound **47** was obtained as the major product while the difluoro compound **48** was formed in minor amount. Even when we used only 1 equiv NFSI, the fluorination reaction still gave the difluoro compound as a byproduct. However, the amount could be suppressed to 8% by only using 1.05 equiv NFSI and, under these conditions, the monofluoro compound **47** was obtained in 75% yield. Both of these fluoro compounds were transformed into the fluorophenols under standard conditions in 88% and 84% yield, respectively.



[a]Yield corrected for recovered **45**. [b]Yield was suppressed by using 1.05 equiv NFSI on purpose.

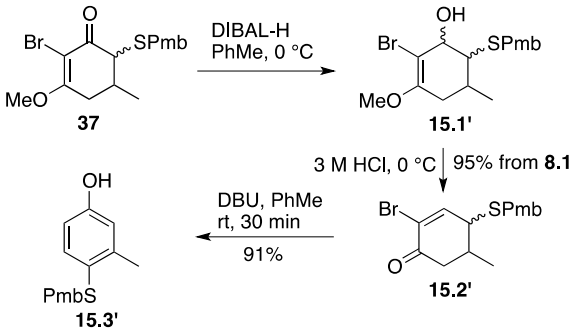
Table 4. Aromatization of heteroatom-containing bromoenones, continued.

For some of the heteroatom electrophiles, there is the potential for elimination within the six-membered ring, as shown in Scheme 14. Fortunately, for all our examples, such elimination did not occur at all. However, when the heteroatom is bromine (E = Br), this side reaction did occur and it gave **14.3'** as the major product (ca 88% yield).



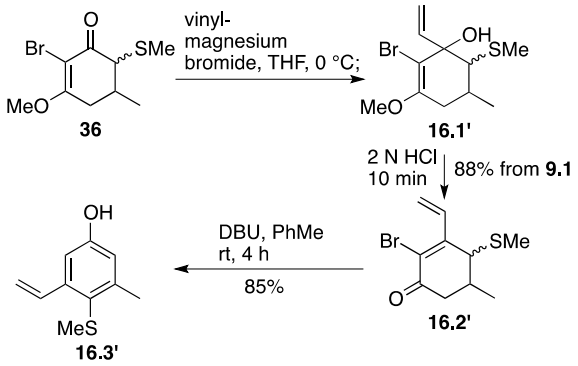
Scheme 14. Potential undesired elimination reaction.

Different substitution patterns of the aromatic product can be easily achieved by manipulation of the 2-bromo-3-methoxycyclohexe-2-en-1-one derivatives. For example, when treated with DIBAL-H in PhMe, followed by working up with 3 M HCl at 0 °C, bromoenone **37** was converted into **15.2'** in less than 10 min in 95% yield. Compound **15.2'** was exposed to the standard aromatization conditions (2.0 equiv DBU in PhMe) and it gave **15.3'** in 91% yield. DIBAL-H reduction of bromoenones does not seem to have been reported before and we find that use of DIBAL-H in PhMe is critical; when we used DIBAL-H in CH_2Cl_2 the reaction was not clean. In the final product (**15.3'**), the PmbS group is *para* to the hydroxyl group and also, we did not observe any tendency of the PmbS unit to undergo elimination during the aromatization step. The overall transformation is so efficient that it gave 87% over two steps from **37** to **15.3'**.



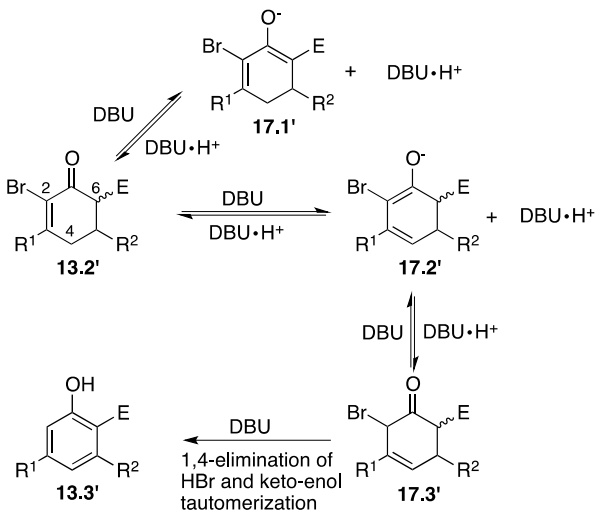
Scheme 15. Preparation of *para*-substituted phenol **15.3'**.

What is more important, our approach could be used to achieve *meta* functionalization of highly substituted phenolic compounds. As indicated in the introduction section there are not many examples of efficient aromatization of cyclohexenones to make *meta*-substituted phenols and, although the principle has been recognized, it is not widely used and I assume that this is because prior methods for aromatization are unattractive, involving either thermally harsh conditions or often giving poor yields. As summarized in Scheme 16, compound **36** was reacted with a Grignard reagent, followed by acid hydrolysis, and DBU then induced aromatization to generate **16.2'**. *Meta*-substituted phenol **16.3'** was obtained in 75% yield for the overall transformation (**36→16.3'**). Such a transformation is another important feature of our approach and without doubt, our route to substituted phenols will be complementary to the existing methods based on electrophilic substitution and modification of the substituents.



Scheme 16. Preparation of *meta*-substituted phenol, **16.3'**.

We proposed a plausible mechanism for this transformation and we assume that this process involves deprotonation at C-4 of compound **13.2'** as the first step, then deconjugation and HBr elimination to afford the phenolic product **13.3'**. The acidity of the C-4 and C-6 hydrogens is key to this process, as well as the pK_a value of the base. Among the different bases we have tried, only DBU gave the desired product, while pyridine, Et_3N, NaH or KHMDS gave only starting material or complex mixtures.



Scheme 17. Proposed mechanism for the aromatization.

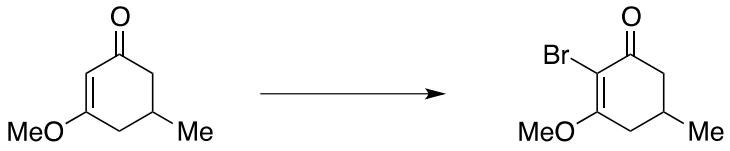
Conclusion

In summary, I have developed a highly efficient but simple process that converts bromoenone systems into the corresponding aromatics under very mild conditions. Such a process is transition-metal free and it has extraordinarily broad substrate scope. The substitution pattern can be easily changed by treating the initial bromo compounds with DIBAL-H or a Grignard reagent (RMgX). When a Grignard reagent is employed, the newly introduced functional group is *meta* to the final phenolic hydroxyl. This route to *meta*-functionalized phenols is now being explored in this laboratory by other chemists.

Experimental section

General Procedures. Solvents used for chromatography were distilled before use. Commercial thin layer chromatography plates (silica gel, Merck 60F-254) were used. Silica gel for flash chromatography was Merck type 60 (230–400 mesh). Dry solvents were prepared under an inert atmosphere and transferred by syringe or cannula. The symbols s, d, t and q used for ^{13}C NMR spectra indicate zero, one, two, or three attached hydrogens, respectively, the assignments being made from APT spectra. Solutions were evaporated under water pump vacuum and the residue was then kept under oil pump vacuum. High resolution electrospray mass spectrometric analyses were done with an orthogonal time of flight analyzer and electron ionization mass spectra were measured with a double-focusing sector mass spectrometer.

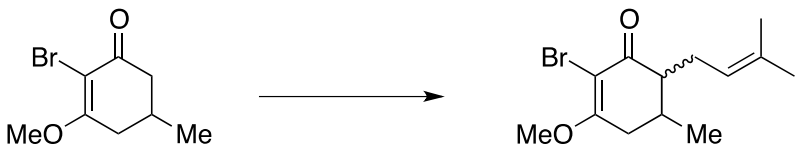
2-Bromo-3-methoxy-5-methylcyclohex-2-en-1-one (10.1').



- **10.1'**

NBS (4.35 g, 24.4 mmol) was added in one portion to a stirred and cooled (0 °C) solution of 3-methoxy-5-methycyclohex-2-en-1-one[8,103] (2.85 g, 20.3 mmol) in CH_2Cl_2 (14 mL). Stirring at 0 °C was continued for 2 h with protection from light. The reaction mixture was diluted with saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2. The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. Crystallization of the residue from MeOH gave **10.1'** (4.05 g, 91%) as a white solid: 97–100 °C; FTIR ($CDCl_3$, cast) 1653, 1615 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.17 (d, J = 6.5 Hz, 3 H), 2.21–2.33 (m, 3 H), 2.65–2.69 (m, 1 H), 2.78–2.85 (m, 1 H), 3.97 (s, 3 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 20.8 (q), 28.1 (d), 34.7 (t), 44.8 (t), 56.3 (q), 102.7 (s), 172.1 (s), 190.9 (s); exact mass (electron ionization) *m*/*z* calcd for $C_8H_{11}{}^{79}BrO_2$ $(M)^+$ 217.9942, found 217.9941.

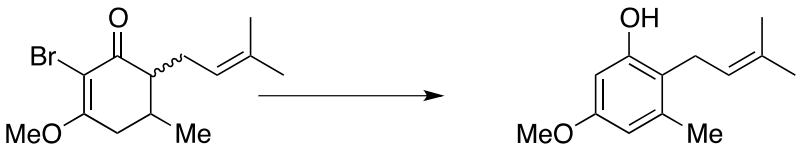
2-Bromo-3-methoxy-5-methyl-6-(3-methylbut-2-en-1-yl)cyclohex-2-ene-1-one (10.2').



10.1' **10.2'**

n-BuLi (2.50 M in hexanes, 2.60 mL, 6.50 mmol) was added dropwise to a stirred and cooled (–78 °C) solution of *i*-Pr_2NH (0.93 mL, 6.64 mmol) in THF (10 mL). Stirring at –78 °C was continued for 30 min and then a solution of **10.1'** (1.10 g, 5.02 mmol) in THF (5 mL) was added dropwise. The cold bath was not recharged so that the temperature rose to 0 °C over 2 h. The mixture was then recooled to –78 °C and a solution of prenyl bromide (2.24 mL, 19.4 mmol) in THF (5 mL) was added dropwise. The cold bath was left in place, but not recharged, and stirring was continued for 6 h. The reaction mixture was diluted with saturated aqueous NH_4Cl and extracted with EtOAc. The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (3 x 15 cm), using 1:4 EtOAc-hexanes, gave **10.2'** (1.14 g, 79%) as a pale yellow solid: FTIR ($CDCl_3$, cast) 1659, 1592 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ (major isomer) 1.13 (d, J = 6.5 Hz, 3 H), 1.65 (s, 3 H), 1.69 (s, 3 H), 2.17–2.27 (m, 2 H), 2.32–2.41 (m, 2 H), 2.48–2.59 (m, 1 H), 2.83 (dd, J = 17.5, 5.0 Hz, 1 H), 3.95 (s, 3 H) 5.02–5.06 (m, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ (major isomer) 17.8 (q), 17.9 (q), 25.8 (q), 27.0 (t), 30.1 (d), 33.0 (t), 52.6 (d), 56.1 (q), 102.2 (s), 120.7 (d), 133.5 (s), 170.3 (s), 192.6 (s); exact mass (electrospray) m/z calcd for $C_{13}H_{19}{}^{79}BrNaO_2$ $(M + Na)^+$ 309.0461, found 309.0457.

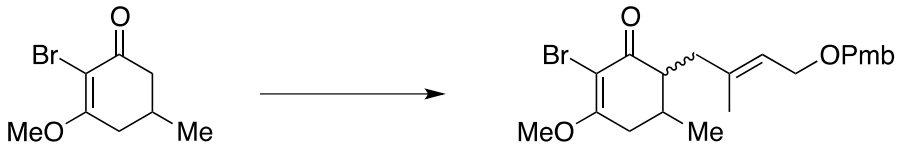
5-Methoxy-3-methyl-2-(3-methylbut-2-en-1-yl)phenol (10.4').[104]



10.2' **10.4'**

DBU (304 mg, 2.00 mmol) was added to a stirred solution of **10.2'** (287 mg, 1.00 mmol) in PhMe (2 mL). Stirring was continued overnight and the mixture was diluted with hydrochloric acid (5%) and extracted thoroughly with EtOAc. The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1.8 x 10 cm), using 1:3 EtOAc-hexanes, gave **10.4'** (175 mg, 85%) as a thick oil: FTIR ($CDCl_3$, cast) 3419, 1614, 1590 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.74 (s, 3 H), 1.81 (s, 3 H), 2.27 (s, 3 H), 3.30 (d, *J* = 8.5 Hz, 2 H), 3.75 (s, 3 H), 5.12 (s, 1 H), 5.13–5.17 (m, 1 H), 6.28 (d, *J* = 3.0 Hz, 1 H), 6.35 (d, *J* = 3.0 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 17.8 (q), 20.3 (q), 25.2 (t), 25.7 (q), 55.2 (q), 99.5 (d), 108.5 (d), 117.8 (s), 122.1 (d), 133.8 (s), 138.1 (s), 155.2 (s), 158.4 (s); exact mass (electron ionization) *m/z* calcd for $C_{13}H_{18}O_2$ $(M)^+$ 206.1306, found 206.1304.

2-Bromo-3-methoxy-6-[(2*E*)-4-[4(methoxyphenyl)methoxy]-2-methylbut-2-en-1-yl]-5-methylcyclohex-2-en-1-one (28).

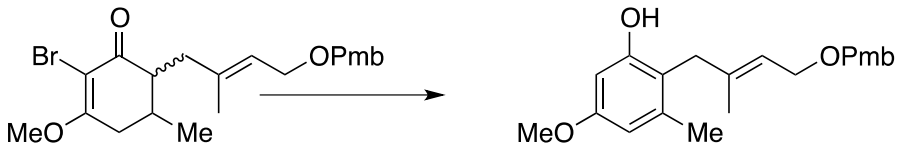


10.1' **28**

The procedure for compound **10.2'** was followed, using *n*-BuLi (2.50 M in hexanes, 0.28 mL, 0.70 mmol), *i*-Pr_2NH (0.12 mL, 0.85 mmol) in THF (2 mL), a solution of **10.1'** (138 mg, 0.63 mmol) in THF (2 mL) and a solution of **22** (468 mg, 1.64 mmol) in THF (2 mL). The mixture was left overnight after the addition of **22** and then worked up Flash chromatography of the residue over silica gel (1.8 x 10 cm), using 1:4 EtOAc-hexanes, gave **28** (205 mg, 77%) as a colorless oil: FTIR ($CDCl_3$, cast) 1659, 1611, 1589 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ (major isomer) 1.11 (d, *J* = 7.0 Hz, 3 H), 1.63 (s, 3 H), 2.14–2.26 (m, 1 H), 2.29–2.47 (m, 4 H), 2.84 (dd, *J* = 18, 5.5 Hz, 1 H), 3.80 (s, 3 H), 3.93 (s, 3 H), 4.01 (s, 2 H) 4.42 (s, 2 H), 5.40–5.43 (m, 1 H), 6.87 (d, *J* = 9.0 Hz, 2 H), 7.26 (d, *J* = 8.5 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ (major isomer) 16.1 (q), 20.0 (q), 29.1 (d), 31.2 (t), 40.1 (t), 50.5 (d), 55.2 (q), 56.2 (q), 66.2 (t), 71.9 (t), 101.2

(s), 113.7 (d), 124.2 (d), 129.4 (d), 130.4 (s), 137.0 (s), 159.2 (s), 169.7 (s), 192.9 (s); exact mass (electrospray) *m*/*z* calcd for $C_{21}H_{28}{}^{79}BrO_4$ $(M + H)^+$ 423.1165, found 423.1166.

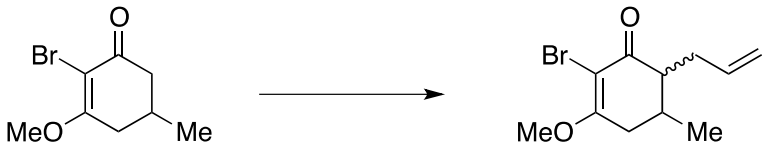
5-Methoxy-2-[(2*E*)-4-[(4-methoxyphenyl)methoxy]-2-methylbut-2-en-1-yl]-3-methylphenol (28a).



28 **28a**

The procedure for **10.4'** was followed, using DBU (151 mg, 0.993 mmol) and a solution of **28** (200 mg, 0.473 mmol) in PhMe (1.5 mL). Workup and flash chromatography of the residue over silica gel (1.8 x 10 cm), using 1:3 EtOAc-hexanes, gave **28a** (133 mg, 82%) as a thick oil: FTIR ($CDCl_3$, cast) 3353, 1613, 1589 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.67 (s, 3 H), 2.23 (s, 3 H), 3.32 (s, 2 H), 3.74 (s, 3 H), 3.80 (s, 3 H), 4.01 (d, *J* = 3.0 Hz, 2 H), 4.40 (s, 2 H), 5.13 (s, 1 H), 5.32–5.36 (m, 1 H), 6.26 (d, *J* = 3.0 Hz, 1 H), 6.35 (d, *J* = 3.0 Hz, 1 H), 6.86 (d, *J* = 6.0 Hz, 2 H), 7.24 (d, *J* = 6.0 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 16.7 (q), 20.2 (q), 35.5 (t), 55.1 (q), 55.2 (q), 66.1 (t), 71.7 (t), 99.5 (d), 108.5 (d), 113.7 (d), 115.6 (s), 121.7 (d), 129.4 (d), 130.4 (s), 138.6 (s), 139.1 (s), 155.5 (s), 158.7 (s), 159.1 (s); exact mass (electrospray) *m*/*z* calcd for $C_{21}H_{25}O_4^-$ $(M - H)^-$ 341.1758, found 341.1761.

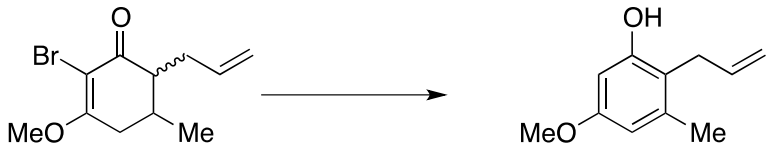
2-Bromo-3-methoxy-5-methyl-6-(prop-2-en-1-yl)cyclohex-2-ene-1-one (29).



10.1' **29**

The procedure for compound **10.2'** was followed, using *n*-BuLi (2.50 M in hexanes, 0.60 mL, 1.50 mmol), *i*-Pr_2NH (0.25 mL, 1.78 mmol) in THF (6 mL), a solution of **10.1'** (293 mg, 1.35 mmol) in THF (3 mL) and a solution of allyl bromide (0.40 ml, 4.63 mmol) in THF (3 mL). The mixture was left overnight after the addition of the allyl bromide and then worked up. Flash chromatography of the residue over silica gel (1.8 x 13 cm), using 1:5 EtOAc-hexanes, gave **29** (249 mg, 72%) as a thick oil: FTIR ($CDCl_3$, cast) 3076, 1649, 1587 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ (major isomer) 1.13 (d, *J* = 6.5 Hz, 3 H), 2.17–2.27 (m, 2 H), 2.33–2.39 (m, 2 H), 2.66–2.70 (m, 1 H), 2.82 (dd, *J* = 17.5, 5.0 Hz, 1 H), 3.93 (s, 3 H), 5.02–5.10 (m, 2 H), 5.67–5.75 (m, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ (major isomer) 19.4 (q), 30.0 (d), 32.4 (t), 33.3 (t), 51.7 (d), 56.1 (q), 102.3 (s), 117.2 (t), 135.0 (d), 170.5 (s), 192.0 (s); exact mass (electron ionization) *m/z* calcd for $C_{11}H_{15}{}^{79}BrO_2$ $(M)^+$ 258.0255, found 258.0257.

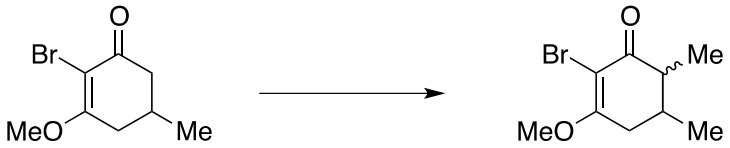
5-Methoxy-3-methyl-2-(prop-2-en-1-yl)phenol (29a).[105]



29 **29a**

The procedure for **10.4'** was followed, using DBU (100 mg, 0.658 mmol) and a solution of **29** (81.5 mg, 0.318 mmol) in PhMe (1 mL). Workup and flash chromatography of the residue over silica gel (1 x 10 cm), using 1:3 EtOAc-hexanes, gave **29a** (46.8 mg, 84%) as a thick oil: ^1H NMR ($CDCl_3$, 500 MHz) δ 2.26 (s, 3 H), 3.36 (d, *J* = 7.5 Hz, 2 H), 3.75 (s, 3 H), 5.00–5.08 (m, 2 H), 5.90–6.00 (m, 1 H), 6.28 (d, *J* = 3.5 Hz, 1 H), 6.37 (d, *J* = 3.5 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 19.9 (q), 30.1 (t), 55.2 (q), 99.5 (d), 108.5 (d), 115.2 (t), 116.0 (s), 135.9 (d), 138.8 (s), 154.9 (s), 158.6 (s).

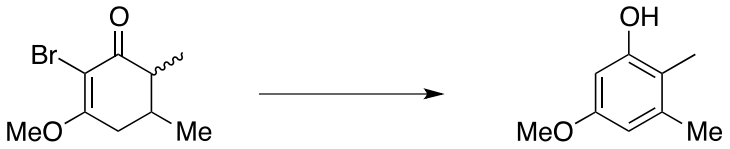
2-Bromo-3-methoxy-5,6-dimethylcyclohex-2-en-1-one (30).



10.1' **30**

The procedure for compound **10.2'** was followed, using *n*-BuLi (2.50 M in hexanes, 0.63 mL, 1.57 mmol), *i*-Pr_2NH (0.26 mL, 1.85 mmol) in THF (6 mL), a solution of **10.1'** (313 mg, 1.43 mmol) in THF (3 mL) and a solution of MeI (0.20 ml, 3.21 mmol) in THF (2 mL). The mixture was left overnight after the addition of MeI and then worked up. Flash chromatography of the residue over silica gel (1.8 x 13 cm), using 1:5 EtOAc-hexanes, gave **30** (243 mg, 73%) as a white solid: FTIR ($CDCl_3$, cast) 1654, 1590 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ (major isomer) 1.17 (d, *J* = 6.5 Hz, 3 H), 1.24 (d, *J* = 7.0 Hz, 3 H), 1.92–1.98 (m, 1 H), 2.12–2.18 (m, 1 H), 2.36 (dd, *J* = 17.5, 10.0 Hz, 1 H), 2.83 (dd, *J* = 17.5, 9.5 Hz, 1 H), 3.95 (s, 3 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ (major isomer) 13.4 (q), 19.7 (q), 34.0 (d), 34.4 (t), 47.4 (d), 56.1 (q), 102.3 (s), 170.7 (s), 193.1 (s); exact mass (electron ionization) *m/z* calcd for $C_9H_{13}{}^{79}BrO_2$ $(M)^+$ 232.0098, found 232.0097.

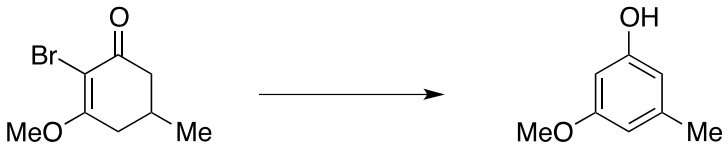
5-Methoxy-2,3-dimethylphenol (30a).[106]



30 **30a**

The procedure for **10.4'** was followed, using DBU (330 mg, 2.17 mmol) and a solution of **30** (241 mg, 1.03 mmol) in PhMe (2 mL). Workup and flash chromatography of the residue over silica gel (1.8 x 10 cm), using 1:5 EtOAc-hexanes, gave **30a** (141 mg, 90%) as a white solid: mp 94–95 °C (lit.[106] 93–93.5 °C); ^1H NMR ($CDCl_3$, 500 MHz) δ 2.08 (s, 3 H), 2.24 (s, 3 H), 3.74 (s, 3 H), 4.64 (s, 1 H), 6.25 (d, *J* = 2.5 Hz, 1 H), 6.35 (d, *J* = 2.5 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 10.8 (q), 20.4 (q), 55.2 (q), 98.9 (d), 108.0 (d), 114.3 (s), 138.8 (s), 154.2 (s), 157.9 (s).

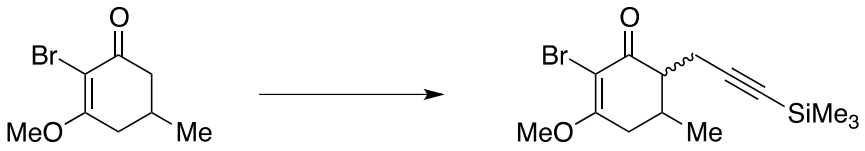
3-Methoxy-5-methylphenol (10.1a).[107]



10.1' **10.1a**

The procedure for **10.4'** was followed, using DBU (114 mg, 0.75 mmol), and a solution of **10.1'** (77.2 mg, 0.357 mmol) in PhMe (1 mL). Workup and flash chromatography of the residue over silica gel (1 x 8 cm), using 1:3 EtOAc-hexanes, gave **10.1a** (43.4 mg, 90%) as a thick oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.28 (s, 3 H), 3.77 (s, 3 H), 5.16 (br s, 1 H), 6.25 (dd, *J* = 2.5 Hz, 1 H), 6.28 (s, 1 H), 6.34 (s, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 21.5 (q), 55.2 (q), 98.6 (d), 107.3 (d), 108.6 (d), 140.6 (s), 156.5 (s), 160.8 (s).

2-Bromo-3-methoxy-5-methyl-6-[3-(trimethylsilyl)prop-2-yn-1-yl]cyclohex-2-en-1-one (31).

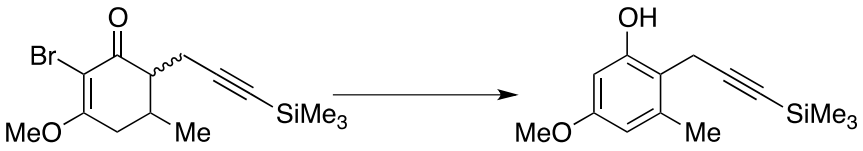


10.1' **31**

The procedure for compound **10.2'** was followed, using *n*-BuLi (2.50 M in hexanes, 0.51 mL, 1.27 mmol), *i*-Pr_2NH (0.20 mL, 1.43 mmol) in THF (3 mL), a solution of **10.1'** (257 mg, 1.17 mmol) in THF (3 mL) and a solution of propargylic bromide (750 mg, 3.93 mmol) in THF (3 mL). The mixture was left overnight after the addition of propargylic bromide and then worked up. Flash chromatography of the residue over silica gel (1.8 x 13 cm), using 1:4 EtOAc-hexanes, gave **31** (270 mg, 70%) as a white solid: FTIR ($CDCl_3$, cast) 2169, 1649, 1582 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ (major isomer) 0.13 (s, 9 H), 1.23 (d, *J* = 6.5 Hz, 3 H), 2.22–2.90 (m, 1 H), 2.39–2.42 (m, 2 H), 2.65 (dd, *J* = 17.0, 4.5 Hz, 1 H), 2.86–2.91 (m, 2 H), 3.97 (s, 3 H); ^{13}C

NMR ($CDCl_3$, 125 MHz) δ (major isomer) 0.1 (q), 18.8 (t), 19.5 (q), 30.9 (d), 33.8 (t), 50.9 (d), 56.2 (q), 86.5 (s), 102.2 (s), 103.5 (s), 170.9 (s), 190.3 (s); exact mass (electron ionization) *m/z* calcd for $C_{14}H_{21}{}^{79}BrO_2Si$ $(M)^+$ 328.0494, found 328.0487.

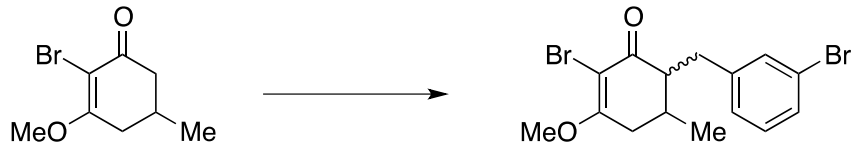
5-Methoxy-3-methyl-2-[3-(trimethylsilyl)prop-2-yn-1-yl]phenol (31a).



31 **31a**

The procedure for **10.4'** was followed, using DBU (119 mg, 0.735 mmol) and a solution of **31** (121 mg, 0.368 mmol) in PhMe (1 mL). Workup and flash chromatography of the residue over silica gel (1 x 10 cm), using 1:5 EtOAc-hexanes, gave **31a** (79.3 mg, 87%) as a thick oil: FTIR ($CDCl_3$, cast) 3444, 2170, 1615, 1592 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.15 (s, 9 H), 2.28 (s, 3 H), 3.53 (s, 2 H), 3.75 (s, 3 H), 5.88 (s, 1 H), 6.34 (d, J = 2.5 Hz, 1 H), 6.37 (d, J = 2.5 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ –0.05 (q), 17.2 (t), 20.3 (q), 55.2 (q), 87.2 (s), 100.1 (d), 103.4 (s), 108.8 (d), 113.1 (s), 138.0 (s), 155.4 (s), 159.0 (s); exact mass (electrospray) *m/z* calcd for $C_{14}H_{19}O_2Si$ $(M - H)^-$ 247.1160, found 247.1161.

2-Bromo-6-[(3-bromophenyl)methyl]-3-methoxy-5-methylcyclohex-2-en-1-one (32).

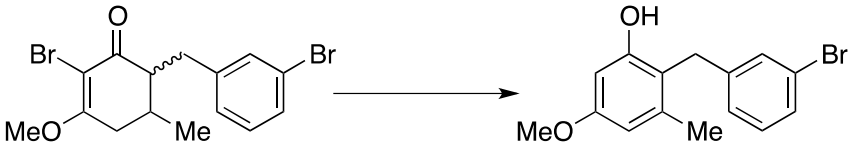


10.1' **32**

The procedure for compound **10.2'** was followed, using *n*-BuLi (2.50 M in hexanes, 0.32 mL, 0.80 mmol), *i*-Pr_2NH (0.13 mL, 0.93 mmol) in THF (2 mL), a solution of **10.1'** (161 mg, 0.735 mmol) in THF (2 mL) and a solution of 3-bromobenzyl bromide (550 mg, 2.20 mmol) in

THF (2 mL). The mixture was left overnight after the addition of 3-bromobenzyl bromide and then worked up. Flash chromatography of the residue over silica gel (1.8 x 13 cm), using 1:4 EtOAc-hexanes, gave **32** (199 mg, 70%) as a white solid: FTIR ($CDCl_3$, cast) 1659, 1590 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ (major isomer) 1.12 (d, J = 7.0 Hz, 3 H), 2.03–2.07 (m, 1 H), 2.36–2.56 (m, 2 H), 2.74–3.00 (m, 3 H), 3.93 (s, 3 H), 7.15–7.16 (m, 2 H), 7.33–7.37 (m, 2 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ (major isomer) 20.0 (q), 29.6 (d), 32.6 (t), 34.4 (t), 53.8 (d), 56.3 (q), 101.9 (s), 122.4 (s), 127.9 (d), 129.4 (d), 130.0 (d), 132.1 (d), 141.6 (s), 170.4 (s), 192.0 (s); exact mass (electron ionization) m/z calcd for $C_{15}H_{16}{}^{79}Br_2O_2$ $(M)^+$ 385.9516, found 385.9522.

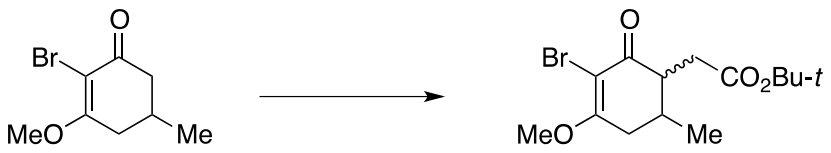
2-[(3-Bromophenyl)methyl]-5-methoxy-3-methylphenol (32a).



32 **32a**

The procedure for **10.4'** was followed, using DBU (150 mg, 0.987 mmol) and a solution of **32** (191 mg, 0.492 mmol) in PhMe (2 mL). Workup and flash chromatography of the residue over silica gel (1.8 x 10 cm), using 1:5 EtOAc-hexanes, gave **32a** (139 mg, 92%) as a white solid: mp 115–117 °C; FTIR ($CDCl_3$, cast) 3402, 3057, 1615, 1592 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 2.21 (s, 3 H), 3.77 (s, 3 H), 3.95 (s, 2 H), 4.60 (s, 1 H), 6.26 (d, J = 2.5, 1 H), 6.38 (d, J = 2.5, 1 H), 7.06–7.12 (m, 2 H), 7.28–7.30 (m, 2 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 20.2 (q), 31.0 (t), 55.2 (q), 99.5 (d), 108.5 (d), 116.8 (s), 122.6 (s), 126.7 (d), 129.0 (d), 129.9 (d), 131.0 (d), 139.4 (s), 142.9 (s), 154.5 (s), 158.8 (s); exact mass (electron ionization) m/z calcd for $C_{15}H_{15}{}^{79}BrO_2$ $(M)^+$ 306.0255, found 306.0250.

***tert*-Butyl-2-(3-bromo-4-methoxy-6-methyl-2-oxocyclohex-3-en-1-yl)acetate (33).**



10.1' **33**

The procedure for compound **10.2'** was followed, using *n*-BuLi (2.50 M in hexanes, 0.30 mL, 0.75 mmol), *i*-Pr_2NH (0.12 mL, 0.856 mmol) in THF (2 mL), a solution of **10.1'** (146 mg, 0.667 mmol) in THF (2 mL) and a solution of *tert*-butyl bromoacetate (0.31 ml, 2.10 mmol) in THF (2 mL). The mixture was left overnight after the addition of the *tert*-butyl bromoacetate and then worked up. Flash chromatography of the residue over silica gel (1.8 x 13 cm), using 1:3 EtOAc-hexanes, gave **33** (178 mg, 70%) as a thick oil: FTIR ($CDCl_3$, cast) 1726, 1664, 1593 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ (major isomer) 1.14 (d, J = 6.5 Hz, 3 H), 1.46 (s, 9 H), 2.15–2.20 (m, 1 H), 2.37 (dd, J = 17.5, 10.5 Hz, 1 H), 2.46 (dd, J = 11.0, 5.5, 1 H), 2.56–2.61 (m, 1 H), 2.76–2.82 (m, 1 H), 3.94 (s, 3 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ (major isomer) 19.4 (q), 28.0 (q), 32.3 (d), 33.9 (t), 34.8 (t), 49.3 (d), 56.2 (q), 80.6 (s), 102.1 (s), 170.9 (s), 171.6 (s), 191.1 (s); exact mass (electrospray) m/z calcd for $C_{14}H_{22}{}^{79}BrO_4$ $(M + H)^+$ 333.0696, found 333.0690.

***tert*-Butyl 2-(2-hydroxy-4-methoxy-6-methylphenyl)acetate (33a).**

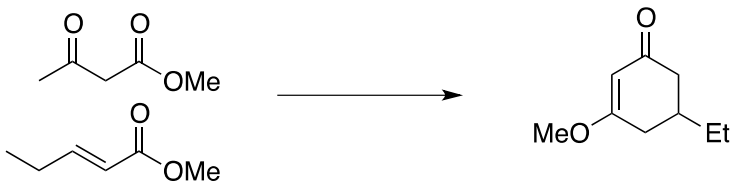
33 **33a**

The procedure for **10.4'** was followed, using DBU (155 mg, 1.02 mmol) and a solution of **33** (167 mg, 0.50 mmol) in PhMe (2 mL). Workup and flash chromatography of the residue over silica gel (1.8 x 10 cm), using 1:4 EtOAc-hexanes, gave **33a** (111 mg, 88%) as an off-white solid: mp 72–74 °C; FTIR ($CDCl_3$, cast) 3411, 1732, 1702, 1616, 1594 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.45 (s, 9 H), 2.29 (s, 3 H), 3.53 (s, 2 H), 3.75 (s, 3 H), 6.35 (d, J = 2.5, 1 H), 6.40 (d, J

= 2.0, 1 H), 7.44 (s, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 20.3 (q), 27.9 (q), 34.2 (t), 55.1 (q), 82.4 (s), 100.7 (d), 108.9 (d), 112.5 (s), 138.3 (s), 156.5 (s), 159.3 (s), 173.4 (s); exact mass (electrospray) *m/z* calcd for $C_{14}H_{19}O_4$ $(M - H)^-$ 251.1289, found 251.1285.

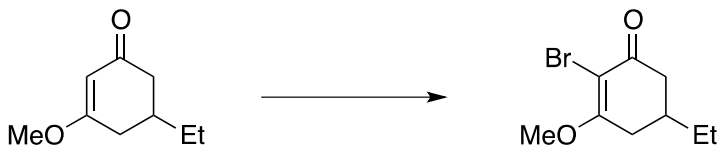
2-Bromo-5-ethyl-3-methoxy-6-(prop-2-en-1-yl)cyclohex-2-ene-1-one (34).

(a) Preparation of 5-ethyl-3-methoxycyclohex-2-en-1-one.



EtONa was prepared by dissolving Na (150 mg, 6.52 mmol) in ice-cold EtOH (7 mL). Then ethyl acetoacetate (0.84 mL, 860 mg, 6.61 mmol) and methyl 2-pentenoate (846 mg, 6.61 mmol) were added by syringe to the resulting stirred solution. The mixtures was refluxed for 6 h (N_2 atmosphere) and then evaporated. The residue was dissolved in water (4 ml) and KOH (730 mg, 13.0 mmol) was added. The solution was refluxed for 1 h and then cooled. Concentrated H_2SO_4 was added carefully to adjust the pH to 1. The solution was refluxed for 2 h, cooled to room temperature, and extracted thoroughly with EtOAc. The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. The residue was dissolved in MeOH (5 mL) and $(MeO)_3CH$ (0.72 mL, 700 mg, 6.61 mmol) was added. The solution was stirred for 24 h at room temperature and then evaporated. Flash chromatography of the residue over silica gel (1.8 x 12 cm), using 2:3 EtOAc-hexanes, gave 5-ethyl-3-methoxycyclohex-2-en-1-one (350 mg, 41% over two steps) as a colorless, thick oil: FTIR ($CDCl_3$, cast) 1734, 1655, 1609 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.95 (t, *J* = 9.5 Hz, 3 H), 1.40–1.47 (m, 2 H), 2.01–2.20 (m, 3 H), 2.42–2.50 (m, 2 H), 3.70 (s, 3 H), 5.37 (d, *J* = 1.6 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 11.1 (q), 28.0 (t), 34.9 (t), 35.4 (d), 43.0 (t), 55.7 (q), 102.1 (s), 178.2 (s), 199.7 (s); exact mass (electron ionization) *m/z* calcd for $C_9H_{14}O_2$ $(M)^+$ 154.0993, found 154.0995.

(b) Preparation of 2-bromo-5-ethyl-3-methoxycyclohex-2-en-1-one.



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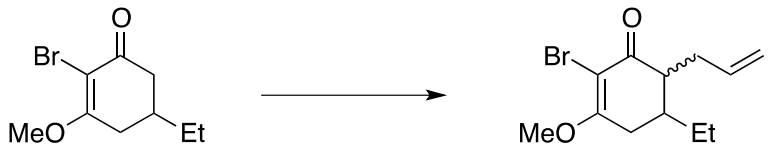
NBS (166 mg, 0.932 mmol) was added in one portion to a stirred and cooled (0 °C) solution of 5-ethyl-3-methoxycyclohex-2-en-1-one (120 mg, 0.779 mmol) in CH_2Cl_2 (4 mL). Stirring at 0 °C was continued for 3.5 h with protection from light and the mixture was then diluted with saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2. The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1.8 x 12 cm), using 2:3 EtOAc-hexanes, gave 2-bromo-5-ethyl-3-methoxycyclohex-2-en-1-one (165 mg, 91%) as a white solid: mp 100–103 °C; FTIR ($CDCl_3$, cast) 1733, 1662, 1585 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.98 (t, J = 7.5 Hz, 3 H), 1.48–1.52 (m, 2 H), 2.04–2.12 (m, 1 H), 2.21 (dd, J = 16.0, 12.5 Hz, 1 H), 2.32 (dd, J = 17.0, 10.0 Hz, 1 H), 2.69–2.85 (m, 2 H), 3.97 (s, 3 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 11.1 (q), 28.0 (t), 32.7 (t), 34.5 (d), 42.6 (t), 56.3 (q), 102.6 (s), 172.4 (s), 191.0 (s); exact mass (electron ionization) *m/z* calcd for $C_{15}H_{15}{}^{79}BrO_2$ $(M)^+$ 306.0255, found 306.0250.

(c) 2-Bromo-5-ethyl-3-methoxy-6-(prop-2-en-1-yl)cyclohex-2-ene-1-one (34).



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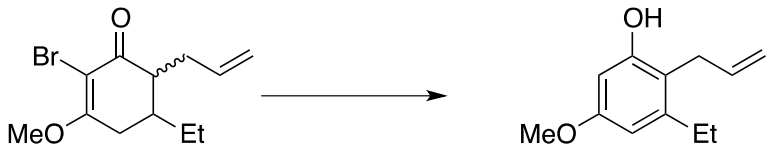
34

The procedure for compound **10.2'** was followed, using *n*-BuLi (2.50 M in hexanes, 0.20 mL, 0.50 mmol), *i*-Pr_2NH (0.08 mL, 0.57 mmol) in THF (2 mL), 2-bromo-5-ethyl-3-methoxycyclohex-2-en-1-one (103 mg, 0.442 mmol) in THF (2 mL) and allyl bromide (267 mg, 2.20 mmol) in THF (1 mL). The mixture was left overnight after the addition of allyl bromide and then worked up. Flash chromatography of the residue over silica gel (1 x 12 cm), using 1:3

EtOAc-hexanes, gave **34** (85.6 mg, 71%) as a white solid which was a mixture of diastereoisomers: FTIR ($CDCl_3$, cast) 3075, 1646, 1613, 1587 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ (major isomer) 0.95 (t, *J* = 7.5 Hz, 3 H), 1.59–1.64 (m, 2 H), 2.01–2.04 (m, 1 H), 2.37–2.49 (m, 3 H), 2.52–2.58 (m, 1 H), 2.83 (dd, *J* = 17.5, 5.5, 1 H), 3.96 (s, 3 H), 5.05–5.11 (m, 2 H), 5.71–5.76 (m, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ (major isomer) 10.9 (q), 25.3 (t), 29.2 (t), 33.2 (t), 35.7 (d), 49.8 (d), 56.1 (q), 101.7 (s), 117.2 (t), 135.2 (d), 170.4 (s), 192.5 (s); exact mass (electron ionization) *m/z* calcd for $C_{12}H_{17}{}^{79}BrO_2$ $(M)^+$ 272.0412, found 272.0408.

3-Ethyl-5-methoxy-2-(prop-2-en-1-yl)phenol (34a).



34 **34a**

The procedure for **10.4'** was followed, using DBU (91.3 mg, 0.60 mmol) and **34** (82.0 mg, 0.30 mmol) in PhMe (1 mL). Workup and flash chromatography of the residue over silica gel (1 x 10 cm), using 1:6 EtOAc-hexanes, gave **34a** (49.0 mg, 85%) as a thick oil: FTIR ($CDCl_3$, cast) 3431, 3077, 3001, 1636, 1616, 1589 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.18 (t, *J* = 9.0 Hz, 3 H), 2.59 (q, *J* = 7.5 Hz, 2 H), 3.37 (dt, *J* = 6.0, 1.5 Hz, 2 H), 3.76 (s, 3 H), 4.88 (s, 1 H), 5.03–5.10 (m, 2 H), 5.98 (ddt, *J* = 17.0, 10.0, 6.0 Hz, 1 H), 6.29 (d, *J* = 2.5 Hz, 1 H), 6.39 (d, *J* = 2.5 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 15.3 (q), 26.5 (t), 29.7 (t), 55.2 (q), 99.4 (d), 107.1 (d), 115.1 (s), 115.6 (s), 136.5 (d), 144.8 (s), 155.2 (s), 159.0 (s); exact mass (electrospray) *m/z* calcd for $C_{12}H_{15}O_2$ $(M)^+$ 191.1078, found 191.1079.

6-Azido-2-bromo-3-methoxy-5-methylcyclohex-2-en-1-one (35).

10.1' **35**

n-BuLi (2.5 M in hexanes, 0.13 mL, 0.325 mmol) was added dropwise to a stirred and cooled (–78 °C) solution of *i*-Pr_2NH (0.05 mL, 0.357 mmol) in THF (1.5 mL). Stirring at –78 °C was continued for 30 min and then a solution of **10.1'** (65 mg, 0.297 mmol) in THF (1.5 mL) was added dropwise over < 1 min. The cold bath was left in place, but not recharged, so that the temperature rose to 0 °C over 2 h. The mixture was then recooled to –78 °C and a solution of 2,4,6-triisopropylbenzenesulfonyl azide[100] (180 mg, 0.582 mmol) in THF (1.5 mL) was added dropwise over < 1 min. The cold bath was left in place, but not recharged, and stirring was continued for 1 h, by which point the temperature had risen to –20 °C. A solution of AcOH in THF (1 N, 0.33 mL) was added and the solvent was evaporated. Flash chromatography of the residue over silica gel (1 × 15 cm), using 1:3 EtOAc–hexanes, gave **35** (59.5 mg, 77%) as a pale yellow oil: FTIR ($CDCl_3$, cast) 2104, 1668 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ (major isomer) 1.15 (d, *J* = 7.0 Hz, 3 H), 2.34–2.40 (m, 1 H), 2.50–2.55 (m, 1 H), 2.62–2.90 (m, 1 H), 3.97 (s, 3 H), 4.04–4.05 (m, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ (major isomer) 15.9 (q), 31.0 (t), 33.0 (d), 56.7 (d), 66.7 (q), 100.0 (s), 172.8 (s), 186.6 (s); exact mass (electron ionization) *m/z* calcd for $C_8H_{10}O_2{}^{79}BrN_3$ $(M)^+$ 258.9956, found 258.9951.

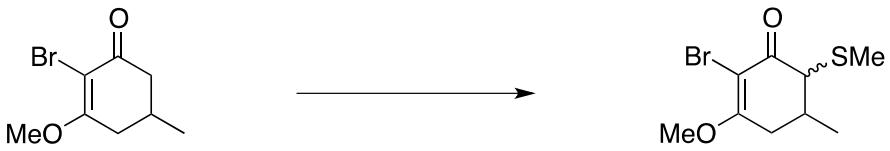
2-Azido-5-methoxy-3-methylphenol (35a).

35 **35a**

DBU (67 mg, 0.44 mmol) was added to a stirred solution of **35** (56.1 mg, 0.215 mmol) in PhMe (1 mL). Stirring was continued for 1 h and the reaction mixture was diluted with 5%

hydrochloric acid and extracted with EtOAc. The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1 × 15 cm), using 1:5 EtOAc-hexanes, gave **35a** (32.1 mg, 83%) as a pale yellow, thick oil: FTIR ($CDCl_3$, cast) 3366, 2115, 1614 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 2.34 (s, 3 H), 3.74 (s, 3 H), 5.40 (br s, 1 H), 6.29 (d, J = 3.0 Hz, 1 H), 6.34 (d, J = 3.0 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 17.1 (q), 56.3 (q), 99.3 (d), 108.6 (d), 127.7 (s), 163.2 (s), 172.0 (s); exact mass (electrospray) m/z calcd for $C_8H_8O_2N_3$ $(M - H)^-$ 178.0622, found 178.0621.

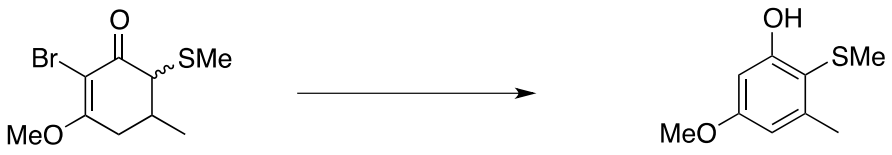
2-Bromo-3-methoxy-5-methyl-6-(methylsulfanyl)cyclohex-2-en-1-one (36).



10.1' **36**

n-BuLi (2.5 M in hexanes, 0.13 mL, 0.325 mmol) was added dropwise to a stirred and cooled (–78 °C) solution of *i*-Pr_2NH (0.05 mL, 0.357 mmol) in THF (2.0 mL). Stirring at –78 °C was continued for 30 min and then a solution of **10.1'** (65 mg, 0.297 mmol) in THF (2.0 mL) was added dropwise over < 1 min. The cold bath was left in place, but not recharged, so that the temperature rose to 0 °C over 2.5 h. The mixture was then recooled to –78 °C and a solution of $TolSO_2SMe$[99b] (132 mg, 0.653 mmol) in THF (2.0 mL) was added dropwise over < 1 min. The cold bath was left in place, but not recharged, and stirring was continued for 4 h, during which the mixture reached room temperature. The reaction mixture was diluted with saturated aqueous NH_4Cl and extracted with EtOAc. The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1 × 15 cm), using 1:3 EtOAc–hexanes, gave **36** (58.2 mg, 74%) as a pale yellow oil: FTIR ($CDCl_3$, cast) 1655 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ (major isomer) 1.20 (d, J = 7.0 Hz, 3 H), 2.15 (s, 3 H), 2.42–3.05 (m, 3 H), 3.25–3.34 (m, 1 H), 3.93 (s, 3 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ (major isomer) 14.2 (q), 19.6 (q), 31.0 (t), 31.5 (d), 54.5 (d), 56.3 (q), 99.7 (s), 169.0 (s), 187.3 (s); exact mass (electron ionization) m/z calcd for $C_9H_{13}O_2{}^{79}BrS$ $(M)^+$ 263.9819, found 263.9813.

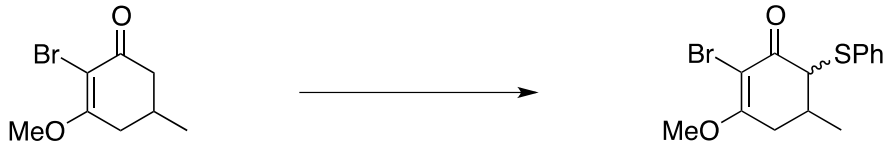
5-Methoxy-3-methyl-2-(methylsulfanyl)phenol (36a).



36 **36a**

DBU (35.6 mg, 0.234 mmol) was added to a stirred solution of **36** (31 mg, 0.117 mmol) in PhMe (1 mL). Stirring was continued for 1 h and the reaction mixture was diluted with 5% hydrochloric acid and extracted with EtOAc. The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1 × 15 cm), using 1:4 EtOAc-hexanes, gave **36a** (19.6 mg, 91%) as a colorless oil: FTIR ($CDCl_3$, cast) 3374, 1608 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 2.16 (s, 3 H), 2.48 (s, 3 H), 3.77 (s, 3 H), 6.40 (d, J = 3.0 Hz, 1 H), 6.43 (d, J = 3.0 Hz, 1 H), 7.14 (s, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 18.7 (q), 20.9 (q), 55.2 (q), 97.3 (d), 108.7 (d), 111.4 (s), 144.1 (s), 158.2 (s), 161.2 (s); exact mass (electrospray) m/z calcd for $C_9H_{11}O_2S$ $(M - H)^-$ 183.0485, found 183.0488.

2-Bromo-3-methoxy-5-methyl-6-(phenylsulfanyl)cyclohex-2-en-1-one (37).

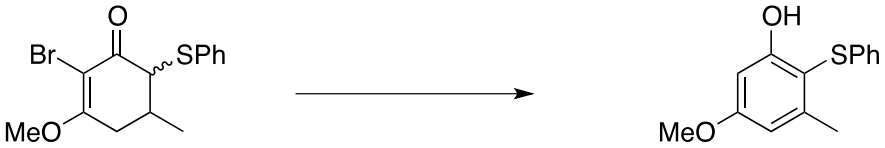


10.1' **37**

n-BuLi (2.5 M in hexanes, 0.13 mL, 0.325 mmol) was added dropwise to a stirred and cooled (–78 °C) solution of *i*-Pr_2NH (0.05 mL, 0.357 mmol) in THF (2.0 mL). Stirring at –78 °C was continued for 30 min and then a solution of **10.1'** (65 mg, 0.297 mmol) in THF (1.5 mL) was added dropwise over < 1 min. The cold bath was left in place, but not recharged, so that the temperature rose to 0 °C over 2.5 h. The mixture was then recooled to –78 °C and a solution of $TolSO_2SPh$[99b] (123 mg, 0.442 mmol) in THF (1.5 mL) was added dropwise over < 1 min. The

cold bath was left in place, but not recharged, and stirring was continued for 3 h, during which the mixture reached room temperature. The reaction mixture was diluted with saturated aqueous NH_4Cl and extracted with EtOAc. The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1 × 15 cm), using 1:5 EtOAc–hexanes, gave **37** (67.8 mg, 70%) as a pale yellow oil: FTIR ($CDCl_3$, cast) 1664 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ (major isomer) 1.12 (d, J = 7.0 Hz, 3 H), 2.38–2.42 (m, 1 H), 2.51–2.53 (m, 1 H), 3.18–3.22 (m, 1 H), 3.96–3.72 (m, 1 H), 4.18 (s, 3 H), 7.36–7.38 (m, 3 H), 7.46–7.48 (m, 2 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ (major isomer) 19.4 (q), 33.0 (d), 39.5 (t), 50.7 (d), 56.6 (q), 104.8 (s), 128.9 (d), 129.6 (d), 132.5 (s), 132.8 (d), 167.1 (s), 189.5 (s); exact mass (electron ionization) m/z calcd for $C_{14}H_{15}O_2{}^{79}BrS$ $(M)^+$ 325.9976, found 325.9973.

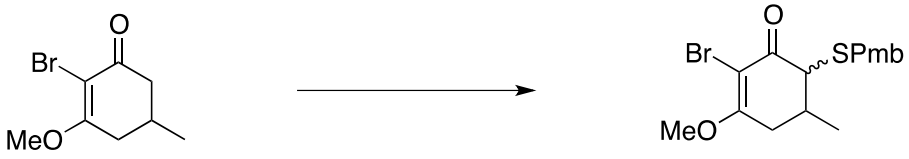
5-Methoxy-3-methyl-2-(phenylsulfanyl)phenol (37a).



37 **37a**

DBU (61.6 mg, 0.405 mmol) was added to a stirred solution of **37** (60.3 mg, 0.184 mmol) in PhMe (1 mL). Stirring was continued for 2 h and the reaction mixture was diluted with 5% hydrochloric acid and extracted with EtOAc. The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (0.8 × 10 cm), using 1:4 EtOAc-hexanes, gave **37a** (39.5 mg, 87%) as a white solid: mp 102–104 °C; FTIR ($CDCl_3$, cast) 3359 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 2.37 (s, 3 H), 3.78 (s, 3 H), 4.83 (br s, 1 H), 6.38 (d, J = 2.5 Hz, 1 H), 6.44 (d, J = 2.5 Hz, 1 H), 6.96–6.98 (m, 2 H), 7.02–7.06 (m, 1 H), 7.15–7.18 (m, 2 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 21.4 (q), 56.2 (q), 97.4 (d), 109.7 (d), 110.2 (s), 124.4 (d), 125.5 (d), 128.6 (d), 138.6 (s), 146.6 (s), 157.6 (s), 162.2 (s); exact mass (electrospray) m/z calcd for $C_{14}H_{13}O_2S$ $(M - H)^-$ 245.0642, found 245.0640. Anal. Calcd for $C_{14}H_{14}O_2S$: C, 68.26; H, 5.73; S, 13.02. Found: C, 68.47; H, 5.73; S, 12.88.

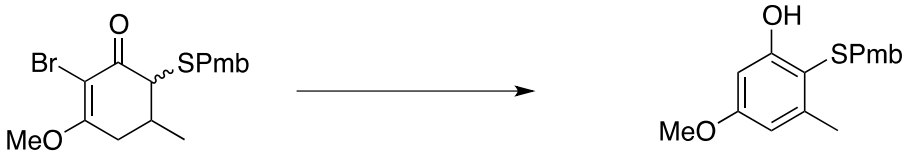
2-Bromo-3-methoxy-6-{[(4-methoxyphenyl)methyl]sulfanyl}-5-methylcyclohex-2-en-1-one (38).



10.1' **38**

n-BuLi (2.5 M in hexanes, 0.13 mL, 0.325 mmol) was added dropwise to a stirred and cooled (–78 °C) solution of *i*-Pr_2NH (0.05 mL, 0.357 mmol) in THF (2.0 mL). Stirring at –78 °C was continued for 30 min and then a solution of **10.1'** (65 mg, 0.297 mmol) in THF (1.5 mL) was added dropwise over < 1 min. The cold bath was left in place, but not recharged, so that the temperature rose to 0 °C over 3.5 h. The mixture was then recooled to –78 °C and a solution of $TolSO_2SPmb$[99c] (113 mg, 0.387 mmol) in THF (1.5 mL) was added dropwise over < 1 min. The cold bath was left in place, but not recharged, and stirring was continued for 1 h, by which point the temperature had risen to –20 °C. The reaction mixture was diluted with saturated aqueous NH_4Cl and extracted with EtOAc. The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1 × 15 cm), using 1:3 EtOAc–hexanes, gave **38** (84.3 mg, 80%) as a colorless oil: FTIR ($CDCl_3$, cast) 1657, 1609 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ (major isomer) 1.12 (d, J = 6.8 Hz, 3 H), 2.32–2.57 (m, 2 H), 2.93–2.99 (m, 1 H), 3.21–3.28 (m, 1 H), 3.68–3.84 (m, 5 H), 3.91 (s, 3 H), 6.82–6.85 (m, 2 H), 7.29–7.32 (m, 2 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ (major isomer) 19.7 (q), 31.1 (t), 31.9 (d), 34.1 (t), 51.5 (d), 55.3 (q), 56.4 (q), 99.9 (s), 113.8 (d), 129.4 (s), 130.4 (d), 158.7 (s), 169.1 (s), 187.7 (s); exact mass (electrospray) m/z calcd for $C_{16}H_{20}O_3{}^{79}BrS$ $(M + H)^+$ 371.0311, found 371.0309.

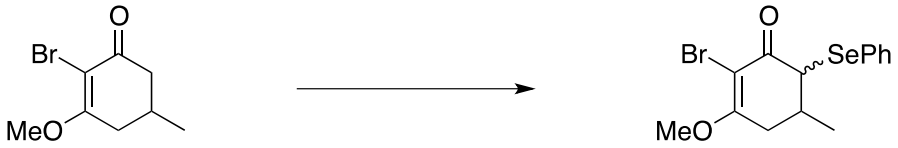
5-Methoxy-2-{[(4-methoxyphenyl)methyl]sulfanyl}-3-methylphenol (38a).



38 **38a**

DBU (50.9 mg, 0.335 mmol) was added to a stirred solution of **38** (58.0 mg, 0.163 mmol) in PhMe (1 mL). Stirring was continued for 2 h and the reaction mixture was diluted with 5% hydrochloric acid and extracted with EtOAc. The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (0.8 × 10 cm), using 1:4 EtOAc-hexanes, gave **38a** (36.7 mg, 82%) as a white solid: mp 48–50 °C; FTIR ($CDCl_3$, cast) 3377, 1614 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 2.25 (s, 3 H), 3.67 (s, 2 H), 3.77 (s, 3 H), 3.78 (s, 3 H), 6.35 (dd, *J* = 3.0, 0.5 Hz, 1 H), 6.38 (dd, *J* = 3.0, 0.5 Hz, 1 H), 6.77–6.78 (m, 2 H), 6.93 (s, 1 H), 6.97–6.99 (m, 2 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 21.1 (q), 39.7 (t), 55.2 (q), 55.3 (q), 97.2 (d), 108.6 (d), 109.4 (s), 113.9 (d), 129.7 (s), 129.9 (d), 144.9 (s), 158.7 (s), 158.9 (s), 161.4 (s); exact mass (electrospray) *m/z* calcd for $C_{16}H_{17}O_3S$ $(M - H)^-$ 289.0904, found 289.0902.

2-Bromo-3-methoxy-5-methyl-6-(phenylselenyl)cyclohex-2-en-1-one (39).

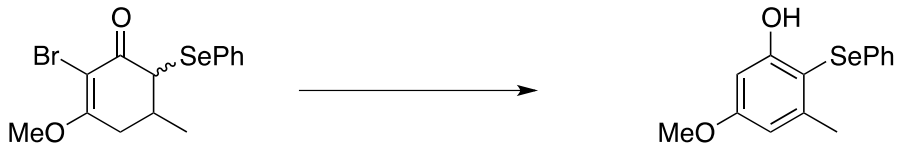


10.1' **39**

n-BuLi (2.5 M in hexanes, 0.13 mL, 0.325 mmol) was added dropwise to a stirred and cooled (–78 °C) solution of *i*-Pr_2NH (0.05 mL, 0.357 mmol) in THF (2.0 mL). Stirring at –78 °C was continued for 30 min and then a solution of **10.1'** (65 mg, 0.297 mmol) in THF (2.0 mL) was added dropwise over < 1 min. The cold bath was left in place, but not recharged, so that the temperature rose to 0 °C over 2.5 h. The mixture was then recooled to –78 °C and a solution of PhSeCl (113 mg, 0.590 mmol) in THF (2.0 mL) was added dropwise over < 1 min. The cold

bath was left in place, but not recharged, and stirring was continued for 4 h, during which the mixture reached room temperature. The reaction mixture was diluted with saturated aqueous NH_4Cl and extracted with EtOAc. The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1 × 15 cm), using 1:3 EtOAc–hexanes, gave **39** [72.1 mg, 65%, or 82% corrected for recovered **10.1'** (11.1 mg)]) as a pale yellow oil: FTIR ($CDCl_3$, cast) 1657 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ (major isomer) 1.17 (d, J = 7.0 Hz, 3 H), 2.42–3.01 (m, 3 H), 3.87–3.91 (m, 4 H), 7.26–7.33 (m, 3 H), 7.59–7.61 (m, 2 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ (major isomer) 19.9 (q), 31.2 (t), 32.4 (d), 52.0 (d), 56.4 (q), 100.7 (s), 127.6 (s), 128.6 (d), 129.2 (d), 135.5 (d), 171.1 (s), 187.5 (s); exact mass (electron ionization) m/z calcd for $C_{14}H_{15}O_2{}^{79}Br^{80}Se$ $(M)^+$ 373.9421, found 373.9420.

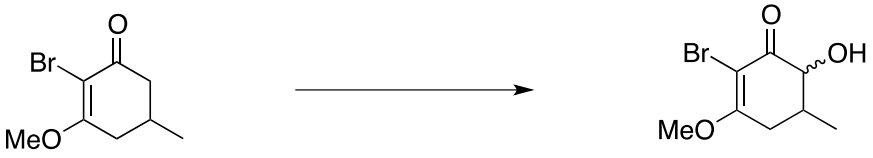
5-Methoxy-3-methyl-2-(phenylselenyl)phenol (39a).



39 **39a**

DBU (45 mg, 0.296 mmol) was added to a stirred solution of **39** (50.3 mg, 0.134 mmol) in PhMe (1 mL). Stirring was continued for 8 h and the reaction mixture was diluted with 5% hydrochloric acid and extracted with EtOAc. The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (0.8 × 10 cm), using 1:10 EtOAc-hexanes, gave **39a** (33.3 mg, 84%) as a white solid: mp 74–76 °C; FTIR ($CDCl_3$, cast) 3384, 1602 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 2.41 (s, 3 H), 3.81 (s, 3 H), 6.49 (d, J = 3.0 Hz, 1 H), 6.52 (d, J = 3.0 Hz, 1 H), 6.79 (s, 1 H), 7.12–7.21 (m, 5 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 23.6 (q), 55.3 (q), 97.3 (d), 107.1 (s), 109.1 (d), 126.4 (d), 128.5 (d), 129.4 (d), 131.1 (s), 145.2 (s), 158.4 (s), 162.3 (s); exact mass (electrospray) m/z calcd for $C_{14}H_{13}O_2{}^{80}Se$ $(M - H)^-$ 293.0086, found 293.0091. A sample was recrystallized from hexane for combustion analysis. Anal. Calcd for $C_{14}H_{14}O_2Se$: C, 57.37; H, 4.81. Found: C, 57.25; H, 4.82. Another sample was crystallized from hexane-CH_2Cl_2 for X-ray analysis.

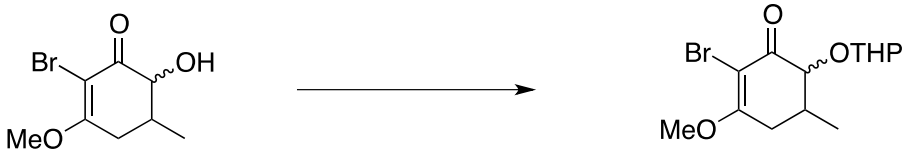
2-Bromo-6-hydroxy-3-methoxy-5-methylcyclohex-2-en-1-one (40).



10.1' **40**

n-BuLi (2.5 M in hexanes, 0.26 mL, 0.65 mmol) was added dropwise to a stirred and cooled (–78 °C) solution of *i*-Pr_2NH (0.10 mL, 0.713 mmol) in THF (3.0 mL). Stirring at –78 °C was continued for 30 min and then a solution of **10.1'** (130 mg, 0.594 mmol) in THF (3.0 mL) was added dropwise over < 1 min. The cold bath was left in place, but not recharged, so that the temperature rose to 0 °C over 3.5 h. The mixture was then recooled to –78 °C and a solution of 2-(4-methylbenzenesulfonyl)-3-phenyloxaziridine)[102] (250 mg, 0.909 mmol) in THF (3.0 mL) was added dropwise over < 1 min. The cold bath was left in place, but not recharged, and stirring was continued for 4 h, during which the mixture reached room temperature. The reaction mixture was diluted with saturated aqueous $NaHCO_3$ and extracted with EtOAc. The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1 × 15 cm), using 1:1 EtOAc-hexanes, gave **40** (103.3 mg, 74%) as a colorless oil: FTIR ($CDCl_3$, cast) 3346, 1666 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.00 (d, *J* = 7.0 Hz, 3 H), 2.71–2.75 (m, 2 H), 2.92 (dd, *J* = 18.0, 5.5 Hz, 1 H), 3.75 (br s, 1 H), 3.99 (s, 3 H), 4.31 (d, *J* = 5.0 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 11.9 (q), 32.4 (d), 32.6 (t), 56.6 (q), 74.5 (d), 97.8 (s), 171.1 (s), 191.9 (s); exact mass (electrospray) *m/z* calcd for $C_8H_{10}O_3{}^{79}Br$ $(M - H)^-$ 232.9819, found 232.9816.

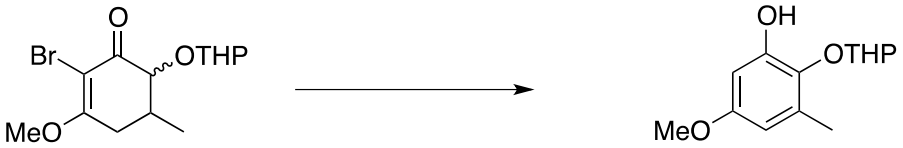
2-Bromo-3-methoxy-5-methyl-6-(oxan-2-yloxy)cyclohex-2-en-1-one (41).



40 **41**

3,4-Dihydropyran (20 mg, 0.208 mmol) and pyridinium *p*-toluenesulfonate (0.8 mg, 0.0032 mmol) were added to a stirred solution of **40** (40.1 mg, 0.171 mmol) in CH_2Cl_2 (2 mL). Stirring was continued for 5 h and the reaction mixture was then diluted with saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2. The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated to give **41** (55.9 mg, ca 99%) as an oil that was a mixture of isomers (^{1}H NMR) which was used directly in the next step.

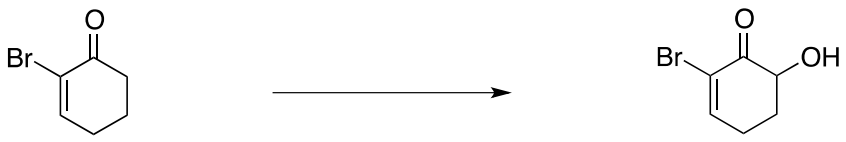
5-Methoxy-3-methyl-2-(oxan-2-yloxy)phenol (41a).



41 **41a**

DBU (111 mg, 0.730 mmol) was added to a stirred solution of **41** (55.9 mg, ca 0.171 mmol) in PhMe (1 mL). Stirring was continued overnight and the reaction mixture was diluted with ice-cold saturated aqueous NH_4Cl and extracted with EtOAc. The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (0.8 × 10 cm), using 1:10 EtOAc-hexanes, gave **41a** (37.9 mg, 89%) as a colorless, thick oil: FTIR ($CDCl_3$, cast) 3327, 1620 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.55–2.06 (m, 6 H), 2.19 (s, 3 H), 3.55–3.60 (m, 1 H), 3.73 (s, 3 H), 4.14–4.16 (m, 1 H), 4.64 (dd, *J* = 8.5, 2.5 Hz, 1 H), 6.24 (d, *J* = 2.5 Hz, 1 H), 6.38 (d, *J* = 3.0 Hz, 1 H), 7.91 (s, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 16.6 (q), 21.4 (t), 24.7 (t), 31.4 (t), 55.4 (q), 66.4 (t), 100.1 (d), 104.9 (d), 107.2 (d), 132.0 (s), 138.1 (s), 150.3 (s), 156.7 (s); exact mass (electrospray) *m*/*z* calcd for $C_{13}H_{17}O_4$ $(M - H)^-$ 237.1132, found 237.1130.

2-Bromo-6-hydroxycyclohex-2-en-1-one (42).



-- **42**

n-BuLi (2.5 M in hexanes, 0.21 mL, 0.525 mmol) was added dropwise to a stirred and cooled (–78 °C) solution of *i*-Pr_2NH (0.09 mL, 0.642 mmol) in THF (3.0 mL). Stirring at –78 °C was continued for 30 min and then a solution of 2-bromocyclohex-2-en-1-one[108] (85.2 mg, 0.487 mmol) in THF (3.0 mL) was added dropwise over < 1 min. Stirring at –78 °C was continued for 1 h and oxaziridine 2-(4-methylbenzenesulfonyl)-3-phenyloxaziridine)[102] (102 mg, 0.584 mmol) in THF (3.0 mL) was added dropwise over < 1 min. The cold bath was left in place, but not recharged, and stirring was continued for 4 h, during which the mixture reached room temperature. The reaction mixture was diluted with saturated aqueous NH_4Cl and extracted with EtOAc. The combined organic extracts were washed with ice-cold aqueous 0.1%w/v NaOH and brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1 × 15 cm), using 1:3 EtOAc–hexanes, gave **42** (73.4 mg, 79%) as a colorless oil: FTIR ($CDCl_3$, cast) 3482 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.94–2.04 (m, 1 H), 2.40–2.46 (m, 1 H), 2.55–2.58 (m, 2 H), 3.57 (d, *J* = 2.0 Hz, 1 H), 4.30 (ddd, *J* = 13.5, 5.5, 1.5 Hz, 1 H), 7.40–7.42 (m, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 26.7 (t), 30.7 (t), 73.3 (d), 120.2 (s), 152.2 (d), 193.9 (s); exact mass (electron ionization) *m*/*z* calcd for $C_6H_7O_2{}^{79}Br$ $(M)^+$ 189.9629, found 189.9629.

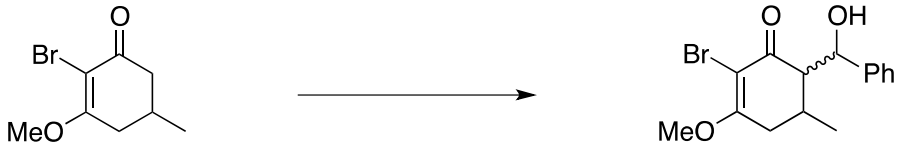
Benzene-1,2-diol (42a).[109]

42 **42a**

DBU (120 mg, 0.789 mmol) was added to a stirred solution of **42** (69.9 mg, 0.366 mmol) in PhMe (1 mL). Stirring was continued overnight and the reaction mixture was diluted with a few (5—6) drops of AcOH. The PhMe and excess of AcOH were evaporated, and flash chromatography of the residue over silica gel (0.8 × 10 cm), using 1:1 EtOAc-hexanes, gave **42a** (37.4 mg, 93%) as an off-white solid: mp 102–104 °C; ^1H NMR ($CDCl_3$, 500 MHz) δ 5.09 (s, 2

H), 6.81–6.83 (m, 2 H), 6.87–6.88 (m, 2 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 115.5 (d), 121.3 (d), 143.5 (s).

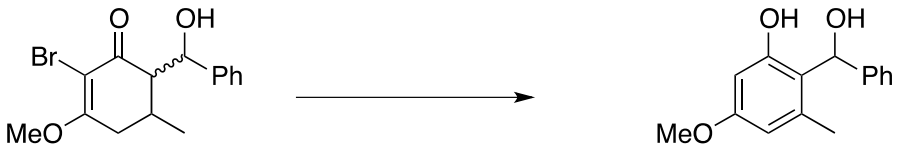
2-Bromo-6-[hydroxy(phenyl)methyl]-3-methoxy-5-methylcyclohex-2-en-1-one (43).



10.1' **43**

n-BuLi (2.5 M in hexanes, 0.26 mL, 0.650 mmol) was added dropwise to a stirred and cooled (–78 °C) solution of *i*-Pr_2NH (0.10 mL, 0.714 mmol) in THF (3.0 mL). Stirring at –78 °C was continued for 30 min and then a solution of **10.1'** (131 mg, 0.598 mmol) in THF (3.0 mL) was added dropwise over < 1 min. The cold bath was left in place, but not recharged, so that the temperature rose to 0 °C over 3.5 h. The mixture was then recooled to –78 °C and PhCHO (0.24 mL, 2.39 mmol) was added dropwise over < 1 min. Stirring was continued for 20 min at –78 °C. A solution of AcOH in THF (1 N, 0.65 mL) was added and the solvent was evaporated. The residue was partitioned between water and EtOAc and the combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1 × 15 cm), using 1:3 EtOAc–hexanes, gave **43** (143 mg, 87%) as a white solid: FTIR ($CDCl_3$, cast) 3438, 1652 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ (major isomer) 1.07 (d, J = 7.0 Hz, 3 H), 2.03–2.40 (m, 2 H), 2.66–2.90 (m, 2 H), 3.16 (br s, 1 H), 3.94 (s, 3 H), 4.81–5.08 (m, 1 H), 7.26–7.37 (m, 5 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ (major isomer) 20.6 (q), 28.0 (d), 31.8 (t), 56.4 (d), 59.5 (q), 74.7 (d), 101.4 (s), 126.5 (d), 128.1 (d), 128.7 (d), 141.7 (s), 171.2 (s), 192.6 (s); exact mass (electron ionization) *m*/*z* calcd for $C_{15}H_{17}O_3{}^{79}Br$ $(M)^+$ 324.0361, found 324.0356.

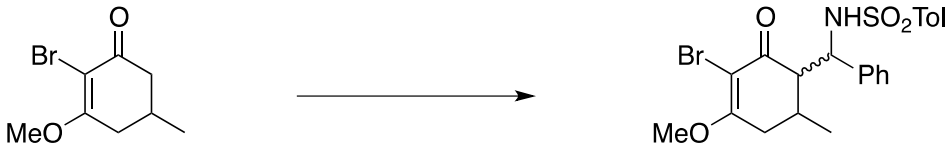
2-[Hydroxy(phenyl)methyl]-5-methoxy-3-methylphenol (43a).



43 **43a**

DBU (0.10 mL, 0.696 mmol) was added to a stirred solution of **43** (113 mg, 0.348 mmol) in PhMe (1.5 mL). Stirring was continued overnight and the reaction mixture was diluted with 5% hydrochloric acid and extracted with EtOAc. The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1 × 10 cm), using 1:4 EtOAc-hexanes, gave **43a** (74.6 mg, 88%) as a white solid: mp 113–115 °C; FTIR ($CDCl_3$, cast) 3319, 1623 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 2.15 (s, 3 H), 2.72 (d, *J* = 3.0 Hz, 1 H), 3.77 (s, 3 H), 6.17 (d, *J* = 2.5 Hz, 1 H), 6.29 (dd, *J* = 2.5, 1.0 Hz, 1 H), 6.38 (d, *J* = 2.5 Hz, 1 H), 7.30–7.37 (m, 5 H), 8.59 (s, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 19.9 (q), 55.2 (q), 74.6 (d), 100.7 (d), 108.6 (d), 116.4 (s), 127.1 (d), 128.3 (d), 128.8 (d), 136.8 (s), 141.2 (s), 157.7 (s), 160.1 (s); exact mass (electrospray) *m/z* calcd for $C_{15}H_{15}O_3$ $(M - H)^-$ 243.1027, found 243.1026. A sample was recrystallized from hexane for combustion analysis. Anal. Calcd for $C_{15}H_{16}O_3$: C, 73.75; H, 6.60. Found: C, 73.38; H, 6.56.

***N*-[(3-Bromo-4-methoxy-6-methyl-2-oxocyclohex-3-en-1-yl)(phenyl)methyl]-4-methylbenzene-1-sulfonamide (44)**.

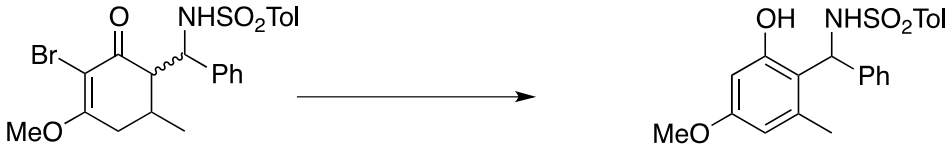


10.1' **44**

n-BuLi (2.5 M in hexanes, 0.26 mL, 0.650 mmol) was added dropwise to a stirred and cooled (–78 °C) solution of *i*-Pr_2NH (0.10 mL, 0.714 mmol) in THF (3.0 mL). Stirring at –78 °C was continued for 30 min and then a solution of **10.1'** (130 mg, 0.598 mmol) in THF (3.0 mL) was added dropwise over < 1 min. The cold bath was left in place, but not recharged, so that the

temperature rose to 0 °C over 3.5 h. The mixture was then recooled to –78 °C and a solution of *N*-(toluenesulfonyl)benzaldimine[110] (300 mg, 1.16 mmol) in THF (2.0 mL) was added dropwise over < 1 min. The cold bath was left in place, but not recharged, and stirring was continued for 1 h, by which point the temperature had risen to –20 °C. The reaction mixture was diluted with saturated aqueous $NaHCO_3$ and extracted with EtOAc. The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1 × 15 cm), using 1:1 EtOAc–hexanes, gave **44** (218.5 mg, 77%) as a colorless oil: FTIR ($CDCl_3$, cast) 3358, 1657 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ (major isomer) 1.26 (d, *J* = 6.5 Hz, 3 H), 2.41–2.39 (m, 5 H), 2.57 (dd, *J* = 8.5, 5.0 Hz, 1 H), 2.83 (dd, *J* = 8.5, 5.0 Hz, 1 H), 3.94 (s, 3 H), 4.67 (dd, *J* = 8.0, 5.0 Hz, 1 H), 5.78 (d, *J* = 8.0 Hz, 1 H), 7.04–7.11 (m, 7 H), 7.44–7.45 (m, 2 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ (major isomer) 19.9 (q), 21.4 (q), 29.3 (d), 33.3 (t), 56.4 (d), 56.5 (q), 58.9 (d), 101.6 (s), 126.9 (d), 127.0 (d), 127.1 (d), 128.2 (d), 129.2 (d), 137.6 (s), 139.5 (s), 142.9 (s), 171.4 (s), 191.4 (s); exact mass (electrospray) *m/z* calcd for $C_{22}H_{25}O_4{}^{79}BrNS$ $(M + H)^+$ 478.0682, found 478.0687.

***N*-[(2-Hydroxy-4-methoxy-6-methylphenyl)(phenyl)methyl]-4-methylbenzene-1-sulfonamide (44a)**.

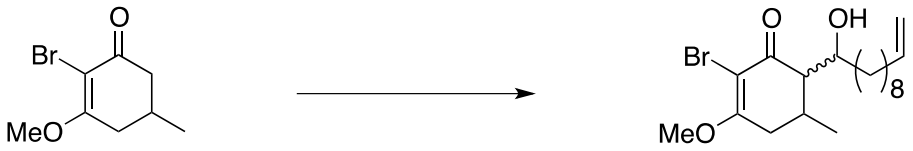


44 **44a**

DBU (148 mg, 0.966 mmol) was added to a stirred solution of **44** (210 mg, 0.439 mmol) in PhMe (3 mL). Stirring was continued overnight and the reaction mixture was diluted with 5% hydrochloric acid and extracted with EtOAc. The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1 × 10 cm), using 1:5 EtOAc-hexanes, gave **44a** (147 mg, 84%) as a white solid: mp 58–60 °C; FTIR ($CDCl_3$, cast) 3326, 1614 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 2.11 (s, 3 H), 2.32 (s, 3 H), 3.69 (s, 3 H), 5.68 (s, 1 H), 5.76 (d, *J* = 9.5 Hz, 1 H), 6.00 (d, *J* = 2.5 Hz, 1 H), 6.17 (d, *J* = 2.5

Hz, 1 H), 6.25 (d, *J* = 9.5 Hz, 1 H), 7.04 (d, *J* = 8.0 Hz, 2 H), 7.22–7.26 (m, 5 H), 7.52–7.54 (m, 2 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 20.1 (q), 21.4 (q), 55.2 (q), 55.4 (d), 100.5 (d), 108.4 (d), 117.0 (s), 126.6 (d), 126.8 (d), 127.3 (d), 128.4 (d), 129.1 (d), 137.2 (s), 138.3 (s), 140.1 (s), 142.9 (s), 154.3 (s), 159.6 (s); exact mass (electrospray) *m*/*z* calcd for $C_{22}H_{22}NO_4S$ $(M - H)^-$ 396.1275, found 396.1282.

2-Bromo-6-(1-hydroxyundec-10-en-1-yl)-3-methoxy-5-methylcyclohex-2-en-1-one (45).

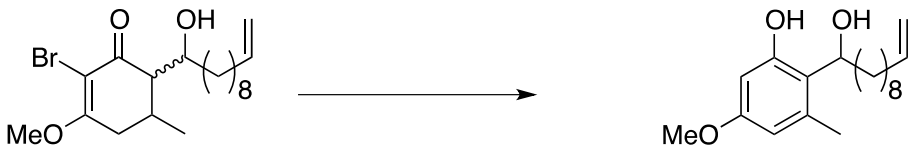


10.1' **45**

n-BuLi (2.5 M in hexanes, 0.13 mL, 0.325 mmol) was added dropwise to a stirred and cooled (–78 °C) solution of *i*-Pr_2NH (0.05 mL, 0.357 mmol) in THF (1.5 mL). Stirring at –78 °C was continued for 30 min and then a solution of **10.1'** (65 mg, 0.298 mmol) in THF (1.5 mL) was added dropwise over < 1 min. The cold bath was left in place, but not recharged, so that the temperature rose to 0 °C over 4.5 h. The mixture was then recooled to –78 °C and a solution of undec-10-enal (74.8 mg, 0.445 mmol) in THF (1.5 mL) was added dropwise over < 1 min. The cold bath was left in place, and stirring at –78 °C was continued for 10 min. A solution of AcOH in THF (1 N, 0.33 mL) was added and the solvent was evaporated. The residue was partitioned between water and EtOAc and the combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1 × 15 cm), using 1:3 EtOAc–hexanes, gave **45** [79.3 mg, 69% or 92% corrected for recovered **10.1'** (14.8 mg)] as a colorless oil: FTIR ($CDCl_3$, cast) 3485, 1653 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.18 (d, *J* = 6.4 Hz, 3 H), 1.25–1.79 (m, 14 H), 2.00–2.24 (m, 4 H), 2.36–2.43 (m, 2 H), 2.87–2.90 (m, 1 H), 3.82 (br s, 1 H), 3.94 (s, 3 H), 4.90–5.00 (m, 2 H), 5.75–5.85 (m, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 20.3 (q), 26.1 (t), 28.9 (t), 29.1 (t), 29.4 (t), 29.5 (t), 29.6 (t), 29.9 (d), 33.8 (t), 33.8 (t),

36.4 (t), 56.3 (d), 57.2 (q), 71.4 (d), 102.3 (s), 114.1 (t), 139.2 (d), 171.4 (s), 192.7 (s); exact mass (electron ionization) *m*/*z* calcd for $C_{19}H_{31}O_3{}^{79}Br$ $(M)^+$ 386.1456, found 386.1450.

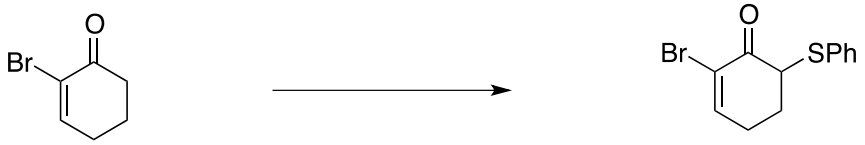
2-(1-Hydroxyundec-10-en-1-yl)-5-methoxy-3-methylphenol (45a).



45 **45a**

DBU (17.8 mg, 0.117 mmol) was added to a stirred solution of **45** (22.7 mg, 0.0587 mmol) in PhMe (2 mL). Stirring was continued overnight and the reaction mixture was diluted with 5% hydrochloric acid and extracted with EtOAc. The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (0.8 × 10 cm), using 1:4 EtOAc-hexanes, gave **45a** (14.3 mg, 80%) as a thick oil: FTIR ($CDCl_3$, cast) 3435, 3177, 1627 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.26–1.37 (m, 12 H), 1.62–1.72 (m, 1 H), 1.88–2.60 (m, 3 H), 2.19 (s, 3 H), 2.36 (d, *J* = 3.0 Hz, 1 H), 3.75 (s, 3 H), 4.92–5.00 (m, 2 H), 5.08–5.10 (m, 1 H), 5.78–5.84 (m, 1 H), 6.24 (d, *J* = 2.5 Hz, 1 H), 6.32 (d, *J* = 2.5 Hz, 1 H), 8.49 (s, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 19.8 (q), 26.0 (t), 28.9 (t), 29.1 (t), 29.4 (t), 29.4 (t), 29.5 (t), 33.8 (t), 36.3 (t), 55.2 (q), 72.7 (d), 100.6 (d), 108.3 (d), 114.1 (t), 118.3 (s), 135.8 (s), 139.2 (d), 157.5 (s), 159.6 (s); exact mass (electrospray) *m*/*z* calcd for $C_{19}H_{29}O_3$ $(M - H)^-$ 305.2122, found 305.2123.

2-Bromo-6-(phenylsulfanyl)cyclohex-2-en-1-one (46).



-- **46**

n-BuLi (2.5 M in hexanes, 0.26 mL, 0.650 mmol) was added dropwise to a stirred and cooled (–78 °C) solution of *i*-Pr_2NH (0.10 mL, 0.714 mmol) in THF (3.0 mL). Stirring at –78 °C was continued for 30 min and then a solution of 2-bromocyclohex-2-enone[108] (96 mg, 0.548 mmol) in THF (3.0 mL) was added dropwise over < 1 min. The cold bath was left in place, but not recharged, so that the temperature rose to 0 °C over 3.5 h. The mixture was then recooled to –78 °C and PhCHO (0.24 mL, 2.39 mmol) was added dropwise over < 1 min. The cold bath was left in place, but not recharged, and stirring was continued for 4 h, during which the mixture reached room temperature. The reaction mixture was diluted with saturated aqueous NH_4Cl and extracted with EtOAc. The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1 × 15 cm), using 1:8 EtOAc–hexanes, gave **46** (139.5 mg, 90%) as a colorless oil: FTIR ($CDCl_3$, cast) 1684 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 2.28–2.32 (m, 1 H), 2.46–2.49 (m, 2 H), 2.71–2.77 (m, 1 H), 4.04 (dd, *J* = 4.5 Hz, 1 H), 7.32–7.37 (m, 4 H), 7.48–7.50 (m, 2 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 25.9 (t), 28.7 (t), 53.2 (d), 122.1 (s), 128.4 (d), 129.2 (d), 132.2 (s), 133.5 (d), 149.5 (d), 186.9 (s); exact mass (electron ionization) *m/z* calcd for $C_{12}H_{11}O^{79}BrS$ $(M)^+$ 281.9714, found 281.9716.

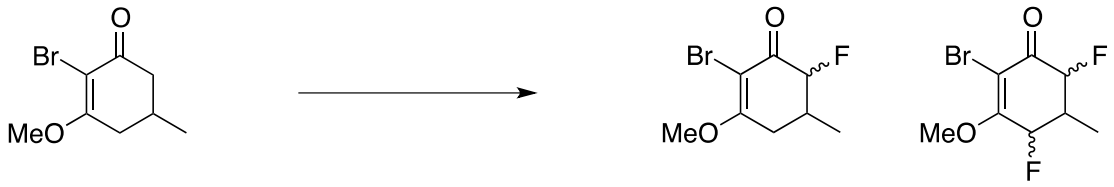
2-(Phenylsulfanyl)phenol (46a).[111]

46 **46a**

DBU (89 mg, 0.585 mmol) was added to a stirred solution of **46** (83.4 mg, 0.293 mmol) in PhMe (2 mL). Stirring was continued for 30 min and the reaction mixture was diluted with 5% hydrochloric acid and extracted with EtOAc. The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (0.8 × 10 cm), using 1:15 EtOAc-hexanes, gave **46a** (50.3 mg, 84%) as a pale yellow oil: FTIR ($CDCl_3$, cast) 3424, 1595 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 6.50 (s, 1 H), 6.96 (ddd, *J* = 7.5, 1.5 Hz, 1 H), 7.06–7.10 (m, 3 H), 7.14–7.17 (m, 1 H), 7.22–7.25 (m, 3 H), 7.36–7.40 (m, 1 H),

7.53 (dd, J = 7.5 Hz, 1.5 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 115.6 (d), 116.3 (s), 121.3 (d), 126.2 (d), 126.9 (d), 129.2 (d), 132.3 (d), 135.9 (s), 136.9 (d), 157.3 (s); exact mass (electrospray) m/z calcd for $C_{12}H_9OS$ $(M - H)^-$ 201.0380, found 201.0387.

2-Bromo-6-fluoro-3-methoxy-5-methylcyclohex-2-en-1-one (47) and 2-Bromo-4,6-difluoro-3-methoxy-5-methylcyclohex-2-en-1-one (48).



10.1' **47** **48**

n-BuLi (2.5 M in hexanes, 0.26 mL, 0.65 mmol) was added dropwise to a stirred and cooled (–78 °C) solution of *i*-Pr_2NH (0.10 mL, 0.713 mmol) in THF (3.0 mL). Stirring at –78 °C was continued for 30 min and then a solution of **10.1'** (130 mg, 0.594 mmol) in THF (3.0 mL) was added dropwise over < 1 min. The cold bath was left in place, but not recharged, so that the temperature rose to 0 °C over 3.5 h. The mixture was then recooled to –78 °C and a solution of commercial *N*-fluorobenzenesulfonimide (196 mg, 0.622 mmol) in THF (3.0 mL) was added dropwise over < 1 min. The cold bath was left in place, but not recharged, and stirring was continued for 4 h, during which the mixture reached room temperature. The reaction mixture was diluted with saturated aqueous $NaHCO_3$ and extracted with EtOAc. The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1 × 15 cm), using 1:3 EtOAc–hexanes, gave **47** (105 mg, 75%) and **48** (12 mg, 8%) as colorless oils: Compound **47** had: FTIR ($CDCl_3$, cast) 1677 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.22 and 1.29 (d, J = 7.0 Hz, integration together 3 H), 2.37–2.96 (m, 3 H), 3.98 and 3.99 (s, integration together 3 H), 4.59 (dd, J = 48.5, 11.5 Hz) and 4.82 (dd, J = 49.5, 3.0 Hz) integration together 1 H; ^{13}C NMR ($CDCl_3$, 125 MHz) δ (major isomer) 14.6 (q), 30.8 (t), 32.3 (d), 56.7 (q), 91.1 (d), 100.2 (s), 171.9 (s), 185.6 (s); ^{19}F NMR ($CDCl_3$, 468.6 MHz) δ –194.1 (m), –199.9 (m); exact mass (electron ionization) m/z calcd for $C_8H_{10}O_2{}^{79}BrF$ $(M)^+$ 235.9848, found 235.9852. Compound **48** had: FTIR ($CDCl_3$, cast) 1698 cm^{-1}; ^{1}H NMR

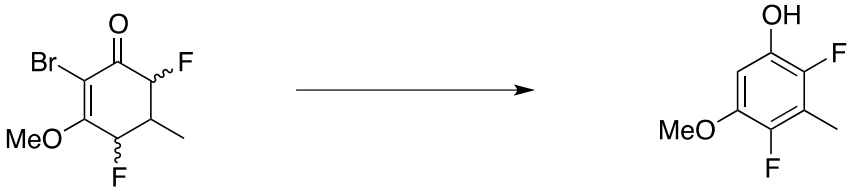
($CDCl_3$, 500 MHz) δ (major isomer) 1.13 (d, *J* = 7.0 Hz, 3 H), 2.54–3.00 (m, 1 H), 4.12 (s, 3 H), 4.91–5.41 (m, 2 H); the ^{13}C NMR ($CDCl_3$, 125 MHz) was too complicated to be informative; exact mass (electron ionization) *m*/*z* calcd for $C_8H_9O_2{}^{79}BrF_2$ $(M)^+$ 253.9754, found 253.9753.

2-Fluoro-5-methoxy-3-methylphenol (47a).

47 **47a**

DBU (98 mg, 0.644 mmol) was added to a stirred solution of **47** (75.4 mg, 0.318 mmol) in PhMe (1.5 mL). Stirring was continued overnight and the reaction mixture was diluted with 5% hydrochloric acid and extracted with EtOAc. The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1 × 15 cm), using 1:5 EtOAc-hexanes, gave **47a** (43.5 mg, 88%) as a colorless, thick oil: FTIR ($CDCl_3$, cast) 3390, 1604 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 2.24 (dt, *J* = 2.5, 0.5 Hz, 3 H), 3.73 (s, 3 H), 5.02 (br s, 1 H), 6.23–6.25 (m, 1 H), 6.39–6.41 (m, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 14.6 (q), 55.6 (q), 100.2 (d), 107.4 (d), 125.4 (s), 143.7 (s), 145.5 (s), 155.6 (s); ^{19}F NMR ($CDCl_3$, 468.6 MHz) δ –155.8 (apparent s); exact mass (electrospray) *m*/*z* calcd for $C_8H_8O_2F$ $(M - H)^-$ 155.0514, found 155.0514.

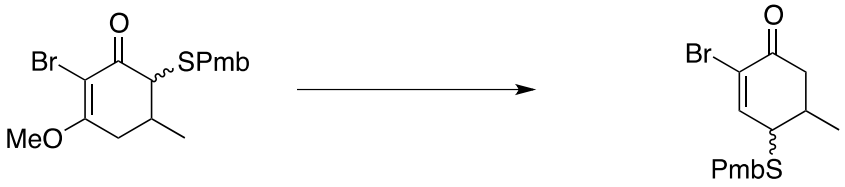
2,4-Difluoro-5-methoxy-3-methylphenol (48a).



48 **48a**

DBU (50.6 mg, 0.333 mmol) was added to a stirred solution of **48** (42.4 mg, 0.166 mmol) in PhMe (1 mL). Stirring was continued overnight and the reaction mixture was diluted with 5% hydrochloric acid and extracted with EtOAc. The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1 × 15 cm), using 1:5 EtOAc-hexanes, gave **48a** (24.4 mg, 84%) as a colorless, thick oil: FTIR ($CDCl_3$, cast) 3429, 1613 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 2.21 (t, J = 2.5 Hz, 3 H), 3.82 (s, 3 H), 4.86 (br s, 1 H), 6.50 (t, J = 10.0 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 7.6 (q), 56.7 (q), 99.4 (d), 114.1 (s), 138.9 (s), 142.1 (s), 143.9 (s), 145.3 (s); ^{19}F NMR ($CDCl_3$, 376.1 MHz) δ –147.2 (t), –152.8 (t); exact mass (electrospray) m/z calcd for $C_8H_7O_2F_2$ $M - H)^-$ 173.0420, found 173.0419.

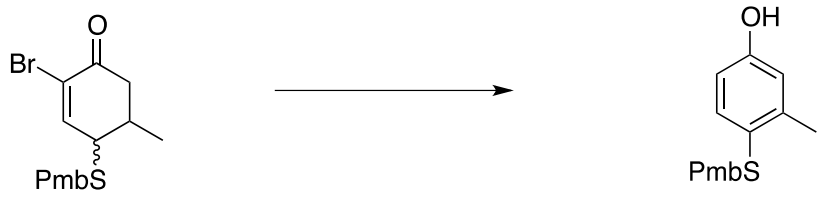
2-Bromo-4-{[(4-methoxyphenyl)methyl]sufanyl}-5-methylcyclohex-2-en-1-one (15.2').



37 **15.2'**

DIBAL-H (1.0 M in hexanes, 0.21 mL) was added over < 1 min to a stirred solution of **37** (74.0 mg, 0.20 mmol) in PhMe at 0 °C. The mixture was stirred for 5 min, diluted at 0 °C with 3 N hydrochloric acid, stirred for 5 min and extracted with EtOAc. The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (0.8 × 12 cm), using 1:4 EtOAc-hexanes, gave **15.2'** (64.4 mg, 95%) as a colorless, thick oil: FTIR ($CDCl_3$, cast) 1678 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ (major isomer) 1.11 (d, J = 7.0 Hz, 3 H), 2.65–2.39 (m, 1 H), 2.49–2.92 (m, 2 H), 3.12–3.36 (m, 1 H), 3.78 (s, 2 H), 3.81 (s, 3 H), 6.86–6.89 (m, 2 H), 7.18–7.26 (m, 3 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ (major isomer) 19.2 (q), 34.9 (d), 35.3 (t), 43.6 (t), 48.9 (d), 55.3 (q), 114.2 (d), 123.4 (s), 129.1 (s), 130.1 (d), 149.3 (d), 159.1 (s), 190.5 (s); exact mass (electron ionization) m/z calcd for $C_{15}H_{17}O_2S^{81}Br$ $(M)^+$ 342.0112, found 342.0111.

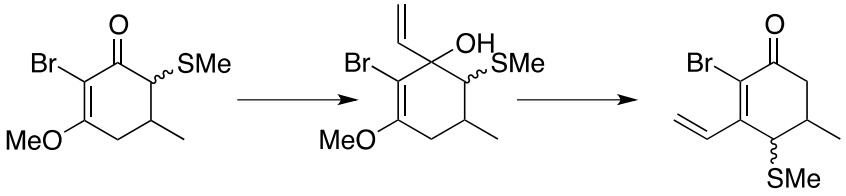
4-{[(4-Methoxyphenyl)methyl]sulfanyl}-3-methylphenol (15.3').



15.2' **15.3'**

DBU (57.2 mg, 0.376 mmol) was added to a stirred solution of **15.2'** (60.3 mg, 0.184 mmol) in PhMe (1 mL). Stirring was continued for 30 min and the reaction mixture was diluted with aqueous NH_4Cl and extracted with EtOAc. The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (0.8 × 12 cm), using 1:4 EtOAc-hexanes, gave **15.3'** (41.6 mg, 91%) as a white solid: mp 81–83 °C; FTIR ($CDCl_3$, cast) 3397, 1609 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 2.28 (s, 3 H), 3.78 (s, 3 H), 3.87 (s, 2 H), 4.68 (br s, 1 H), 6.58 (ddd, J = 10.5, 3.5, 0.5 Hz, 1 H), 6.67 (dd, J = 3.5, 0.5 Hz, 1 H), 6.77–6.79 (m, 2 H), 7.06–7.08 (m, 2 H), 7.19 (d, J = 10.5 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 20.8 (q), 39.9 (t), 55.3 (q), 113.4 (d), 113.8 (d), 117.1 (d), 125.8 (s), 130.0 (d), 130.1 (s), 135.0 (d), 142.5 (s), 155.1 (s), 158.6 (s); exact mass (electrospray) *m/z* calcd for $C_{15}H_{15}O_2S$ M – H)$^-$ 259.0798, found 259.0797.

2-Bromo-3-ethenyl-5-methyl-4-(methylsulfanyl)cyclohex-2-en-1-one (16.2').

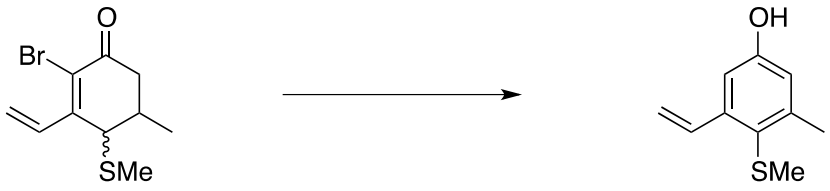


36 **16.2'**

Vinylmagnesium bromide solution (1.0 M in THF, 0.15 mL) was added dropwise over < 1 min to a stirred solution of **36** (26.0 mg, 0.098 mmol) in THF (2.0 mL) and stirring at 0 °C was continued for 1 h. The ice bath was left in place, but not recharged, and stirring was continued for 12 h, during which the mixture reached room temperature. The reaction mixture was diluted

with 2 N hydrochloric acid, stirred for 10 min and extracted with EtOAc. The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (0.5 × 10 cm), using 1:5 EtOAc-hexanes, gave **16.2'** (22.5 mg, 88%) as a colorless, thick oil: FTIR ($CDCl_3$, cast) 1676 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ (major isomer) 1.23 (d, J = 6.5 Hz, 3 H), 2.15 (s, 3 H), 2.47–3.35 (m, 3 H), 3.68–3.74 (m, 1 H), 5.74 (d, J = 11.0 Hz, 1 H), 5.98 (d, J = 17.5 Hz, 1 H), 7.13 (dd, J = 17.5, 11.0 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ (major isomer) 17.5 (q), 18.5 (q), 34.3 (d), 41.4 (t), 49.7 (d), 123.7 (t), 125.8 (s), 135.6 (d), 153.3 (s), 191.2 (s); exact mass (electron ionization) m/z calcd for $C_{10}H_{13}OS^{81}Br$ $(M)^+$ 261.9850, found 261.9852.

3-Ethenyl-5-methyl-4-(methylsulfanyl)phenol (16.3').



16.2' **16.3'**

DBU (29.3 mg, 0.192 mmol) was added to a stirred solution of **16.2'** (25.1 mg, 0.096 mmol) in PhMe (0.5 mL). Stirring was continued for 4 h and the reaction mixture was diluted with saturated aqueous NH_4Cl and extracted with EtOAc. The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (0.5 × 12 cm), using 1:5 EtOAc-hexanes, gave **16.3'** (14.7 mg, 85%) as a white solid: mp 98–101 °C; FTIR ($CDCl_3$, cast) 3375, 1598 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 2.16 (s, 3 H), 2.51 (s, 3 H), 4.73 (s, 1 H), 5.32 (dd, J = 11.2, 1.6 Hz, 1 H), 5.63 (d, J = 11.2, 1.6 Hz, 1 H), 6.69 (d, J = 2.8 Hz, 1 H), 6.89 (d, J = 2.8 Hz, 1 H), 7.50 (dd, J = 17.6, 10.8 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 19.3 (q), 21.7 (q), 110.6 (d), 115.7 (t), 116.9 (d), 126.2 (s), 136.3 (d), 143.7 (s), 144.7 (s), 155.4 (s); exact mass (electrospray) m/z calcd for $C_{10}H_{11}OS$ $M - H)^-$ 179.0538, found 179.0536.

References

1 Mirrington, R. N.; Ritchie, E.; Shoppee, C. W.; Sternhell, S.; Taylor, W. C. *Aust. J. Chem.* **1966**, *19*, 1265–1284.

2 Cleaver, L.; Croft, J. A.; Ritchie, E.; Taylor, W. C. *Aust. J. Chem.* **1976**, *29*, 1989–2001.

3 Quoted in reference 4.

4 Kablaoui, M. S. *J. Org. Chem.* **1974**, *39*, 3696–3698.

5 Chandrasekharan, V.; Unnikrishnan, P.; Shah, G. D.; Bhattacharyya, S. C. *Indian J. Chem.* **1978**, *16B*, 970–972.

6 Nilsson, M.; Norin, T. *Acta Chem. Scand.* **1963**, *17*, 1157–1159.

7 Itoh, Y.; Brossi, A.; Hamel, E.; Lin, C. M. *Helv. Chim. Acta* **1988**, *71*, 1199–1209.

8 Takahashi, K.; Suzuki, T.; Hirama, M. *Tetrahedron Lett.* **1992**, *33*, 4603–4604.

9 Horning, E. C.; Horning, M. G. *J. Am. Chem. Soc.* **1947**, *69*, 1359–1361.

10 Horning, E. C.; Horning, M. G., Walker, G. N. *J. Am. Chem. Soc.* **1949**, *71*, 169–171.

11 Kim, B.-T.; Asami, T.; Morita, K.; Soh, C.-H.; Murofushi, N. *Biosci. Biotech. Biochem.* **1992**, *56*, 624–629.

12 Zhang, J.; Jiang, Q.; Yang, D.; Zhao, X.; Dong, Y.; Liu, R. *Chem. Sci.* **2015**, *6*, 4674–4680.

13 Bohlmann, F.; Prezewowsky, K. *Chem. Ber.* **1964**, *97*, 1176–1178.

14 Bennetau, B.; Rajarison, F.; Dunoguès *Tetrahedron* **1994**, *50*, 1179–1188.

15 Majetich, G.; Allen, S. *ARKIVOC* **2010**, (iv), 104–124.

16 Banerjee, A. K.; Vera, W. J.; Cabrera, E. V.; Sanchez, J. L. *J. Chem. Res.* **2010**, 243–245.

17 Gerecke, M.; Brossi, A. *Helv. Chim. Acta* **1979**, *62*, 1549–1558.

18 Nelson, P. H.; Carr, S. F.; Devens, B. H.; Eugui, E. M.; Franco, F.; Gonzalez, C.; Hawley, R. C.; Loughhead, D. G.; Milan, D. J.; Papp, E.; Patterson, J. W.; Rouhafza, S.; Sjogren, E. B.; Smith, D. B.; Stephenson, R. A.; Talamas, F. X.; Waltos, A.-M.; Weikert, R. J.; Wu, J. C. *J. Med. Chem.* **1996**, *39*, 4181–4196.

19 Lindsey, C. C.; Wu, K. L.; Pettus, T. R. R. *Org. Lett.* **2006**, *8*, 2365–2367.

20 Pirrung, M. C.; Lee, Y. R. *J. Am. Chem. Soc.* **1995**, *117*, 4814–4821.

21 Zimmerman, H. E.; Pasteris, R. J. *J. Org. Chem.* **1980**, *45*, 4876–4891.

22 Schuda, P. F.; Price, W. A. *J. Org. Chem.* **1987**, *52*, 1972–1979.

23 Persich, P.; Llaveria, J.; Lhermet, R.; de Haro, T.; Stade, R.; Kondoh, A.; Fürstner, A. *Chem. Eur. J.* **2013**, *19*, 13047–13058.

24 Izawa, Y.; Pun, D.; Stahl, S. S. *Science* **2011**, *333*, 209–213.

25 Chen, K.; Liu, C.; Deng, L.; Xu, G. *Steroids* **2010**, *75*, 513–516.

26 Takaishi, K.; Alen, Y.; Kaazu, K.; Baba, N.; Nakajima, S. *Biosci. Biotech. Biochem.* **2004**, *68*, 2398–2400.

27 Robl *Tetrahedron Lett.* **1990**, *3*1, 3421–3424.

28 Jadhav, P. J.; Samant, S. D. *Russian J. Org. Chem.* **2014**, *50*, 1301–1305.

29 Olsen, R. K.; Shao, R.-l. *J. Org. Chem.* **1996**, *61*, 5852–5856.

30 Zimmerman, H. E.; Lynch, D. C. *J. Am Chem. Soc.* **1985**, *107*, 7745–7756.

31 Zimmerman, H. E.; Sebek, P. *J. Am Chem. Soc.* **1997**, *119*, 3677–3690.

32 Bourban, C. Y. M.; Hanson, J. R.; Hitchcock, P. B. *J. Chem. Res., Miniprint* **1990**, 2050–2066.

33 Liebman, A. A.; Malarek, D. H.; Dorsky, A. M.; Kaegi, H. H. *J. Labelled Compounds* **1971**, *7*, 241–246.

34 Brossi, A.; Focella, V.; Focella, A.; Teitel, S. US 3,729,519, 1973 (example 31).

35 Lebeuf, R.; Robert, F.; Landais, Y. *Org. Lett.* **2005**, *7*, 4557–4560.

36 Iida, H.; Yuasa, Y.; Kibayashi. C. *Synthesis* **1982**, 471–472.

37 Mphahlele, M. J. *Molecules* **2009**, *14*, 5308–5322.

38 Hegde, S. G.; Kassim, A. M.; Kennedy, A. I. *Tetrahedron* **2011**, *5*7, 1689–1698.

39 Horiuchi, C. A.; Fukinishi, H.; Kajita, M.; Yamaguchi, A.; Kiyomiya, H.; Kiji, S. *Chem. Lett.* **1991**, 1921–1924.

40 Kotnis, A. S. *Tetrahedron Lett.* **1990**, *31*, 481–484.

41 Kotnis, A. S. *Tetrahedron Lett.* **1991**, *32*, 3441–3444.

42 Kim, J. M.; Lee, K. Y.; Kim, J. N. *Bull. Korean Chem. Soc.* **2003**, *24*, 1057–1058.

43 Tamura, Y.; Yoshimoto, Y. *Chem. Ind. (London)* **1980**, 888–889.

44 Mphahlele, M. J.; Modro, T. A. *J. Chem. Soc., Perkin Trans. 1* **1996**, 2261–2264.

45 Tecle, H.; Bergmeier, S. C.; Wise, L. D. *J. Heterocyclic Chem.* **1989**, *26*, 1125–1128.

46 Hartman, J. A.; Tomasewski, A. J.; Dreiding, A. S. *J. Am. Chem. Soc.* **1956**, *78*, 5662–5666.

47 Evans, G. B.; Furneaux, R. H.; Gravestock, M. B.; Lynch, G. P.; Scott, G. K. *Bioorg. Med. Chem.* **1999**, *7*, 1953–1964.

48 Abad, A.; Agulló, C.; Cuñat, A. C.; Perni, R. H. *Tetrahedron: Asymmetry* **2000**, *11*, 1607–1615.

49 Hauser, F.; Pogany, S. A. *Synthesis* **1980**, 814–815.

50 (a) Bradley, G.; Cavalla, J. F.; Edington, T.; Shepherd, R. G.; White, A. C. *Eur. J. Med. Chem.* **1980**, *15*, 375–385. (b) Shepherd, R. G. US 4,463,177, 1984.

51 Shepherd, R. G.; White, A. C. *J. Chem. Soc., Perkin Trans. 1* **1987**, 2153–2155.

52 Schepens, W.; Van Haver, D.; Vandewalle, M.; Bouillon, R.; Verstuyf, A.; De Clercq, P. J. *Org. Lett.* **2006**, *8*, 4247–4250.

53 Hatae, N.; Suzuki, I.; Choshi, T.; Hibino, S.; Okada, C.; Toyota, E. *Tetrahedron Lett.* 2014, *55*, 4146–4148.

54 Hara, R.; Furukawa, T.; Kashima, H.; Kusama, H.; Horiguchi, Y.; Kuwajima, I. *J. Am. Chem. Soc.* **1999**, *21*, 3072–3082.

55 Nishikawa, T.; Isobe, M. *Tetrahedron* **1994**, *50*, 5621–5632.

56 Paquette, L. A.; Zon, G. *J. Am. Chem. Soc.* **1974**, *96*, 224–233.

57 Nazarov, I. N.; Zav'ialov, S. I. *Bull. Acad. Sci. USSR* **1958**, 186–189.

58 Tamura, Y.; Yoshimoto, Y.; Kunimoto, K.; Tada, S.; Tomita, T.; Wada, T.; Seto, E.; Murayama, M.; Shibata, Y.; Nomura, A.; Ohata, K. *J. Med. Chem.* **1977**, *20*, 709–714.

59 Cf. Tamura, Y.; Yoshimoto, Y.,; Suzuki, M.; Terasima, M. *Chem. Ind. (London)* **1970**, 1410.

60 Tamura, Y.; Terashima, M.; Higuchi, Y.; Ozaki, K. *Chem. Ind. (London)* **1970**, 1435.

61 Lacey, R. N. *J. Chem. Soc.* **1960**, 1625–1633.

62 Focella, A.; Teitel, S.; Brossi, A. *J. Org. Chem.* **1977**, *42*, 3456–3457.

63 Elix, J. A.; Jones, A. J.; Lajide, L.; Coppins, B. J.; James, P. W. *Aust. J. Chem.* **1984**, *37*, 2349–2364.

64 Dyke. H. J.; Elix, J. A.; Marcuccio, S. M.; Whitton, A. A. *Aust. J. Chem.* **1987**, *40*, 431–434.

65 Elix, J. A.; Jayanthia, V. K. *Aust. J. Chem.* **1987**, *40*, 1851–1859.

66 Carvalho, C. F.; Sargent, M. V. *J. Chem. Soc., Perkin Trans. 1* **1984**, 1621–1626.

67 Boers, R. B.; Gast, P.; Hoff, A. J.; de Groot, H. J. M.; Lugtenburg, J. *Eur. J. Org. Chem.* **2002**, 189–202.

68 Schamp, N.; Verhé, R.; De Buyck, L. *Tetrahedron* **1973**, *29*, 3857–3859.

69 De Buyck, L.; Verhé, R.; DeKimpe, N.; Schamp, N. *Bull. Soc. Chim. Belg.* **1980**, *89*, 307–322.

70 (a) Fort, A. W. *J. Org. Chem.* **1960**, *26*, 332–334. (b) Castro, C. E.; Gaughan, E. J.; Owsley, D. C. *J. Org. Chem.* **1965**, *50*, 587–592.

71 Marmor, R. S. *J. Org. Chem.* **1972**, *37*, 2901–2904.

72 Brossi, A.; Bruderer, H.; Rachlin, A. I.; Teitel, S. *Tetrahedron* **1968**, *24*, 4277–4284.

73 Simon, M.-O.; Girard, S. A.; Li, C.-J. *Angew. Chem. Int. Ed.* **2012**, *51*, 7537–7540.

74 Tong, H.-C.; Reddy, K. R.; Liu, S.-T. *Eur. J. Org. Chem.* **2014**, 3256–3261.

75 Kikushima, K.; Nishina, Y. *RSC Advances* **2013**, *3*, 20150–20156.

76 (a) Koyano, T. *Bull. Chem. Soc. Jpn.* **1971**, *44*, 1158–1160. (b) Baird, W. C., Jr.; Surridge, J. H.; Buza, M. *J. Org. Chem.* **1971**, *36*, 3324–3330. (c) Kojima, Y.; Kawaguchi, S. *Bull. Chem. Soc. Jpn.* **1972**, *45*, 1293–1299. (d) Kojima, Y.; Usui, K.; Kawaguchi, S. *Bull. Chem. Soc. Jpn.* **1972**, *45*, 3127–3130. (e) Yang, L.; Lu, Z.; Stahl, S. S. *Chem. Commun.* **2009**, 6460–6462.

77 Kosower, E. M.; Wu, G.-S. *J. Org. Chem.* **1963**, *28*, 633–638.

78 Bondon, D.; Pietrasanta, Y.; Pucci, B. *Tetrahedron Lett.* **1977**, *18*, 821–824.

79 Brazier, E. J.; Hogan, P. J.; Leung, C. W.; O'Kearney-McMullen, A.; Norton, A. K.; Powell, L.; Robinson, G. E.; Williams, E. G. *Org. Process Res. Devel.* **2010**, *14*, 544–552.

80 Ali, H.; Rousseau, J.; Lafrenière, J.; van Lier, J. E. *Steroids* **2000**, *65*, 74–84.

81 Hayashi, M.; Yamada, K.; Nakayama, S. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1501–1503.

82 Shan, S. *Jingxi Shiyou Huagong Jinzhan* **2005**, *6*, 24–25. *Chem. Abstr.* **146**, 401642.

83 Pun, D.; Diao, T.; Stahl, S. S. *J. Am. Chem. Soc.* **2013**, *135*, 8213–8221.

84 Izawa, Y.; Zheng, C.; Stahl, S. S. *Angew. Chem. Int. Ed.* **2013**, *52*, 3672–3675.

85 Bänteli, R.; Ernst, B. *Tetrahedron Lett.* **1997**, *38*, 4059–4061.

86 Gerlach, H.; Thalimann, A. *Helv. Chim. Acta* **1977**, *60*, 2866–2871.

87 Tietze, L. F.; von Kiedrowski, G.; Berger, B. *Tetrahedron Lett.* **1982**, *23*, 51–54.

88 Pfau, A. St. *Helv. Chim. Acta* **1933**, *16*, 282–286.

89 Smith, C. R., Jr. *J. Org. Chem.* **1960**, *25*, 588–591.

90 Hayashi, Y.; Shoji, M.; Kishida, S. *Tetrahedron Lett.* **2005**, *46*, 681–685.

91 Ivanov, C.; Tcholakova, T. *Synthesis* **1981**, 392–394.

92 Cui, L.-Q.; Dong, Z.-L.; Zhang, C. *Org. Lett.* **2011**, *13*, 6488–6491.

93 Grieco, P. A.; Marinovic, N. *Tetrahedron Lett*. **1978**, *19*, 2545–2548.

94 Trebellas, J. C.; Olechowski, J. R.; Jonassen, H. B.; Moore, D. W. *J. Organometallic Chem*. **1967**, *9*, 153–158.

95 Blagbrough, I. S.; Pattenden, G.; Raphael, R. A. *Tetrahedron Lett*. **1982**, *23*, 4843–4846.

96 Hirao, T.; Mori, M.; Ohshiro, Y. *J. Org. Chem*. **1990**, *50*, 358–360.

97 Hirao, T.; Mori, M.; Ohshiro, Y. *Chem. Lett*. **1991**, 783–784.

98 Moriuchi, T.; Kikushima, K.; Kajikawa, T.; Hirao, T. *Tetrahedron Lett*. **2009**, *50*, 7385–7387.

99 (a) Fujiki, K.; Tanifuji, N.; Sasaki, Y.; Yokoyama, T. *Synthesis* **2002**, 343–348. (b) Back, T. G.; Collins, S.; Vijaya Krishna, M. *Can. J. Chem*. **1987**, *65*, 38–42. (c) Kimura, S.; Bill, E.; Bothe, E.; Weyhermüller, T.; Wiegardt, K. *J. Am. Chem. Soc*. **2001**, *123*, 6025–6039.

100 Stone, M. J.; van Dyk, M. S.; Booth, P. M.; Williams, D. H. *J. Chem. Soc., Perkin Tran*s. I **1991**, 1629–1635.

101 Bélanger, D.; Tong, X.; Soumaré, S.; Dory, Y. L; Zhao, Y. *Chem. Eur. J*. **2009**, *15*, 4428–4436.

102 Kiss, E.; Marko, I. E.; Guillaume, M. Tetrahedron 2011, 67, 9173–9178.

103 Tada, M.; Takakuwa, T.; Nagai, M.; Yoshii, T. *Agric. Biol. Chem*. **1990**, *54*, 3061–3063.

104 Synthesis: Nicolaou, K. C.; Montagnon, T.; Vassilicogiannakis, G.; Mathison, C. J. N. *J. Am. Chem. Soc*. **2005**, *127*, 8872–8888.

105 Biswas, B.; Sarkar, D.; Venkateswaran, R. V. *Tetrahedron* **2008**, *64*, 3212–3216. This publication reports that Claisen rearrangement (200 °C) of 1-methoxy-3-methyl-5-(prop-2-en-1-yloxy)benzene does not stop at the first stage and that appreciable amounts of 3-methoxy-5-methyl-4-(prop-2-en-1-yl)phenol are formed.

106 Witty, T. R.; Remers, W. A. *J. Med. Chem*. **1973**, *16*, 1280–1284.

107 Mirrington, R. N.; Feutrill, G. I. *Organic Syntheses*; Wiley: New York, 1988; *Collect. Vol*. 6, p 859–861.

108 Nicolaou, K. C.; Ding, H.; Richard, J.-A.; Chen, D. Y.-K. *J. Am. Chem. Soc*. **2010**, *132*, 3815–3818.

109 Kofler, A. *Chem. Ber*. **1943**, *76*, 871–873.

110 Chemla, F.; Hebbe, V.; Normant, J.-F. *Synthesis* **2000**, 75–77.

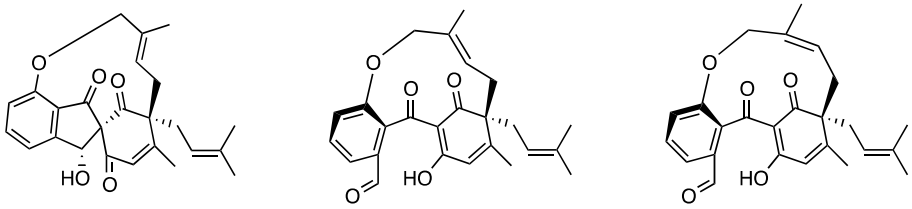
111 Feng, Y.; Wang, H.; Sun, F.; Li, Y.; Fu, X.; Jin, K. *Tetrahedron* **2009**, *65*, 9737–9741.

Chapter 3

Synthetic studies on Coleophomone B

Introduction: Synthesis of the coleophomones

In 1998, a Japanese company, Shionogi Pharmaceutical Co., revealed three structurally novel and unusual secondary metabolites (Scheme 1, **1.1–1.3**) in a Japanese patent.[1] These three natural compounds had been isolated from a *Stachybotrys cylindrospora* fungal broth and assigned as Shionogi I-1, Shionogi I-2 and Shionogi I-3, respectively. The interesting biological activities, including antifungal action, and the ability to inhibit the serine protease enzyme, heart chymase, which accounts for the conversion of angiotensin I to angiotensin II,[2] aroused great attention. The latter biological property made these compounds potential leads for development of drugs to treat hypertension and congestive heart failure.

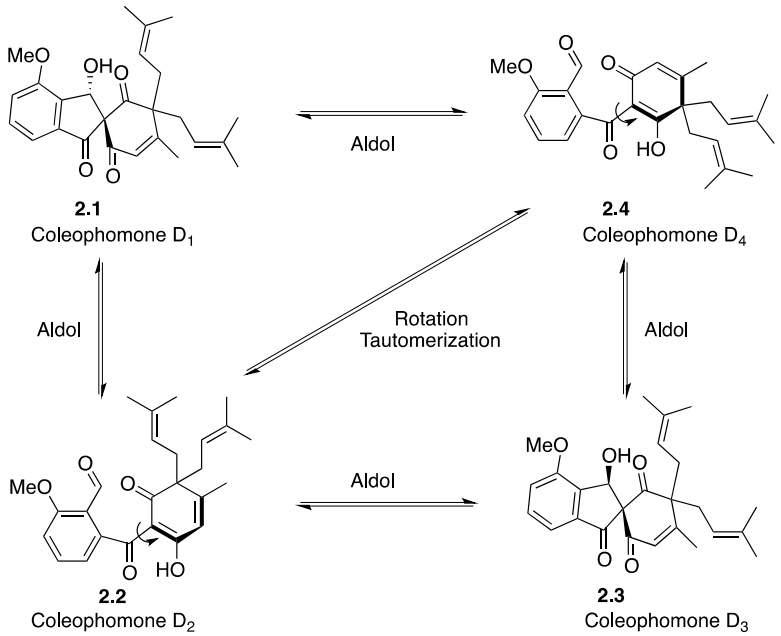


Scheme 1. Structures of Coleophomones A, B and C.

These three natural products, which consist of a strained, rigid macrocycle fused on an aryl ring, a highly unsaturated six-membered ring and the unique tricarbonyl system are interesting and very challenging targets for synthetic chemists.

It is reported that coleophomone A (**1.1**) and coleophomone B (**1.2**) interconvert in MeCN-H_2O.[3] Coleophomone B (**1.2**) predominates at pH > 7 and the tautomerization does not occur when the pH is lower than 3. It is suspected that the conversion **1.2→1.1** happens by a stereospecific aldol condensation and there is no evidence for the presence of another diastereoisomer of Coleophomone A in *in vitro* experiments.

In 1999, the same company reported another patent,[4] describing the discovery of a fourth metabolite, coleophomone D. Being different from the other three coleophomones, coleophomone D, exists as a mixture of constitutional isomers that undergo rapid interconversion through a facile aldol-retro-aldol type reaction. Compared with the other metabolites, coleophomone D does not have a strained macrocycle and also its substitution pattern is different.



Scheme 2. Aldol-retro-aldol reaction of Coleophomone D.

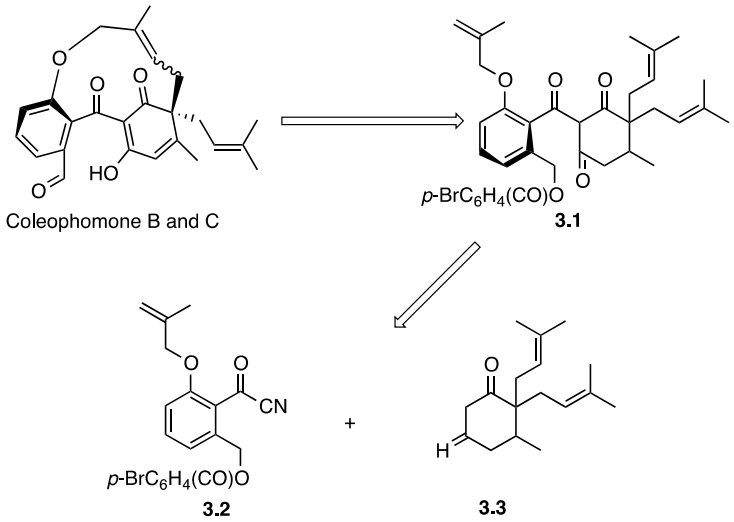
One year later, in 2000, a drug discovery team from Merck published a paper in *Tetrahedron Letters* focusing on the isolation and structure identification of coleophomones A and B,[3] apparently unaware of the previously existing Japanese patent. This team isolated these natural products from fermentation of *Coleophoma sp*, a fungus isolated in the Sierra Villuercas in Spain, therefore, the compounds were called coleophomones. In their *Tetrahedron Letters* paper, it was reported that these compounds showed weak antibacterial activity, owing to their ability to inhibit a crucial bacterial transglycosylase enzyme. To avoid confusion, the two Shionogi compounds, **1.3** and **2**, were designated coleophomones C and D.[5]

Attracted by the challenging strained macrocycle and unique tricarbonyl system, along with the biological activity of these nature products, we decided to work on the total synthesis of

coleophomone B. Up to now, the only reported total synthesis of (racemic) coleophomones B, C and D[6] comes from Nicolaou's group.

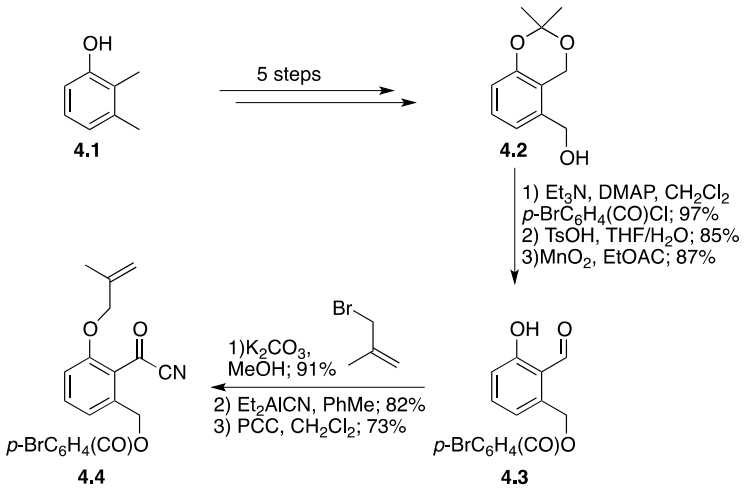
Total Syntheses of Coleophomones B, C and D by the Nicolaou Group[5,6]

According to the retrosynthetic analysis shown in Scheme 3, the total synthesis of coleophomones B and C would be based on two key steps: a ring-closing metathesis and a *C*-acylation onto an 1,3-dicarbonyl system. Macrocyclization would be carried out by ring-closing metathesis from compound **3.1**, which itself was to be synthesized by a *C*-acylation reaction between 1,3-dicarbonyl compound **3.3** and acyl cyanide **3.2**.[7]



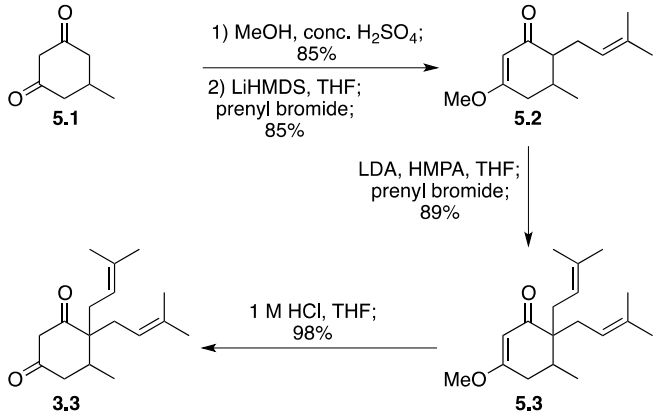
Scheme 3. Retroanalysis of coleophomone B by the Nicolaou group.

The trisubstituted aromatic compound **3.2** was synthesized from commercially available 2,3-dimethylphenol. Compound **4.1** was converted into the benzyl alcohol **4.2** in five steps according to published literature.[8] *p*-Bromobenzoylation of **4.2**, deprotection of the acetonide, and MnO_2 oxidation gave the desired benzaldehyde **4.3** in 72% overall yield. Alkylation with 3-bromo-2-methylpropene, followed by treatment with Nagata's reagent (Et_2AlCN) and PCC oxidation resulted in the formation of acyl cyanide **4.4** as the final product.



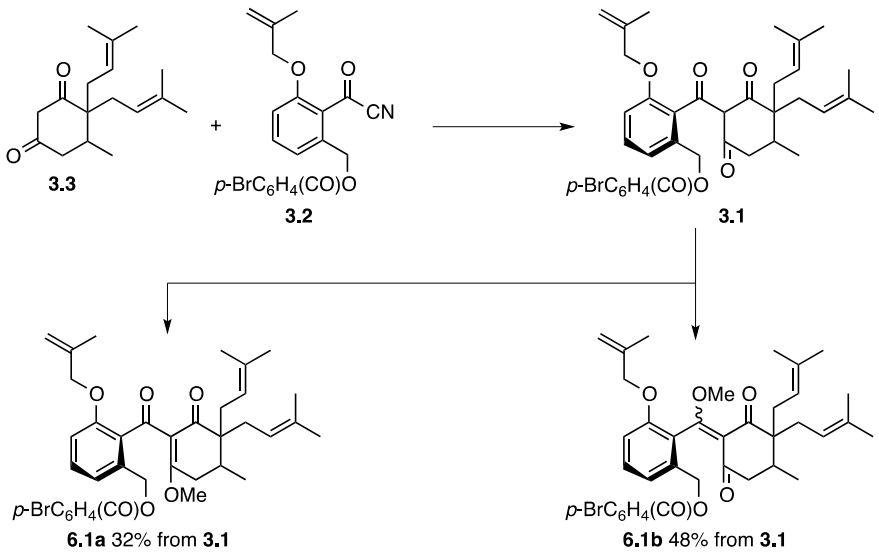
Scheme 4. Synthesis of acyl cyanide **4.4**.

The right hand building block, the substituted 1,3-cyclohexanedione **3.3** was prepared from 5-methyl-1,3-cyclohexanedione. Methylation of **5.1**, followed by bisalkylation with prenyl bromide, afforded the vinylogous ester derivative **5.3**. Hydrolysis of **5.3** with 1 M HCl generated the cyclic the 1,3-diketone **5.4** as the final product in 98% yield.



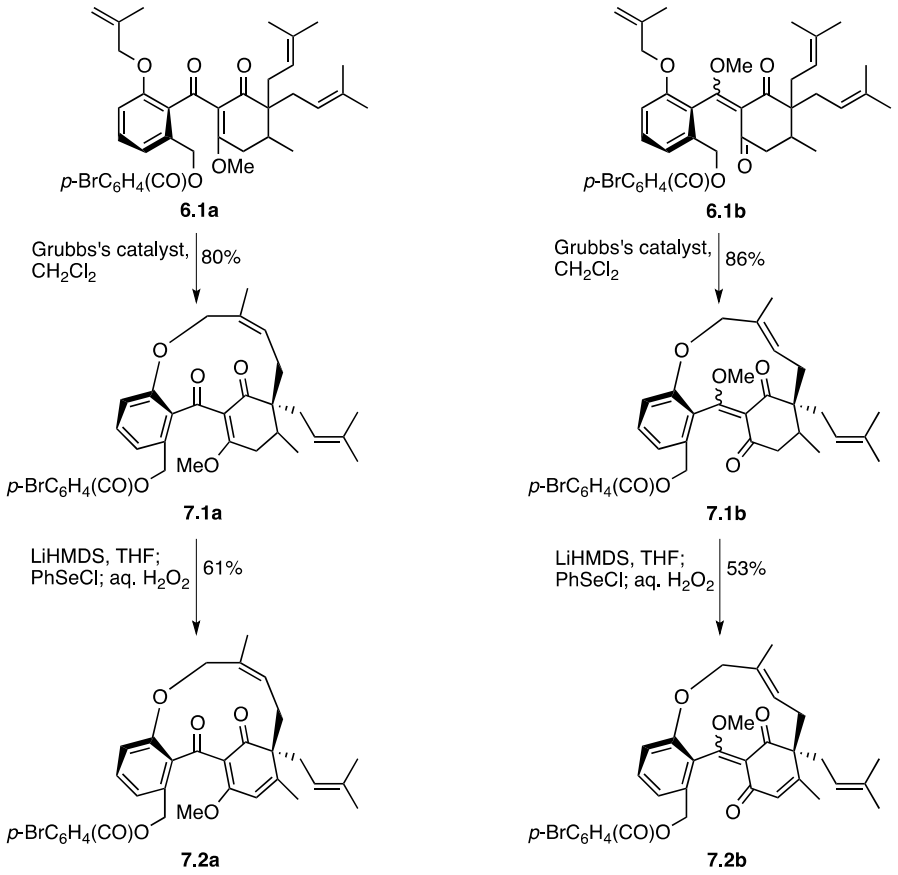
Scheme 5. Synthesis of bisalkylated cyclic 1,3-diketone **3.3**.

With the two building blocks in hand, the tricarbonyl compound **3.1** was generated by a *C*-acylation reaction, which is facilitated by DMAP. Methylation of the tricarbonyl intermediate **3.1** with diazomethane gave two vinylogous esters **6.1a** and **6.1b** as major products.



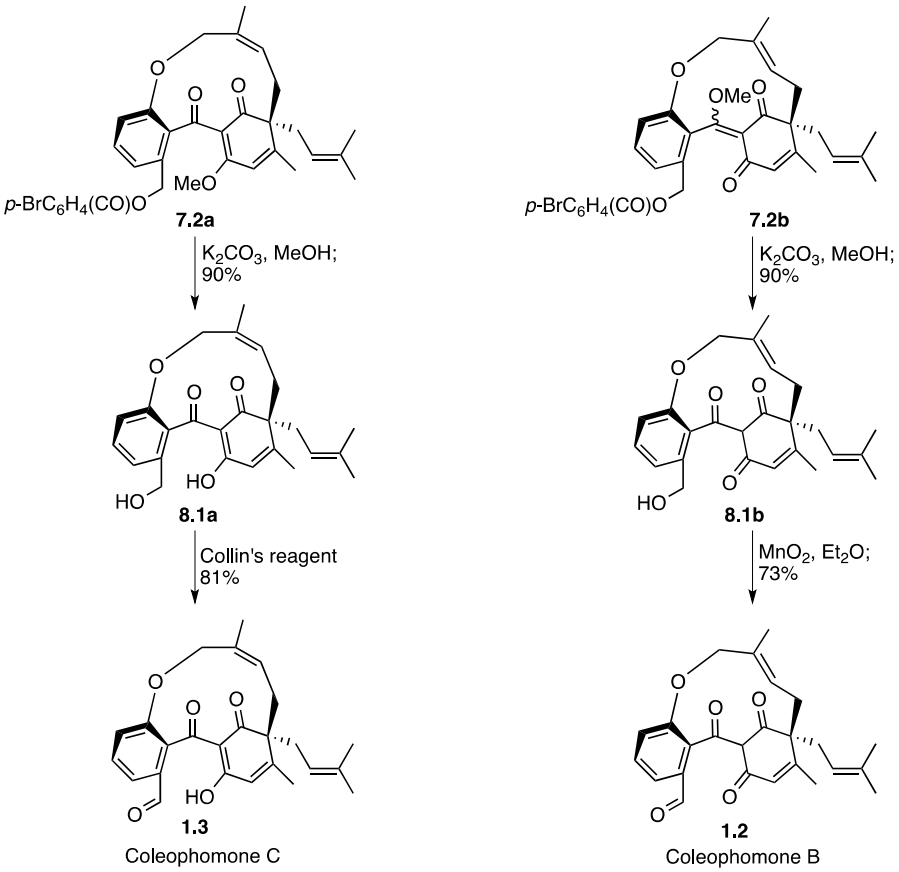
Scheme 6. Synthesis of tricarbonyl system.

These two olefins **6.1a** and **6.1b** were each treated with the second generation Grubbs' catalyst. Under the standard metathesis reaction conditions, compound **6.1a** gave the *Z* product **7.1a** while compound **6.1b** furnished the *E* product **7.1b**. The double bond within the right-hand cyclohexanedione substructure was made by treating each of these metathesis products with $(Me_3Si)_2NLi$, followed by PhSeCl and then an excess of aqueous H_2O_2.



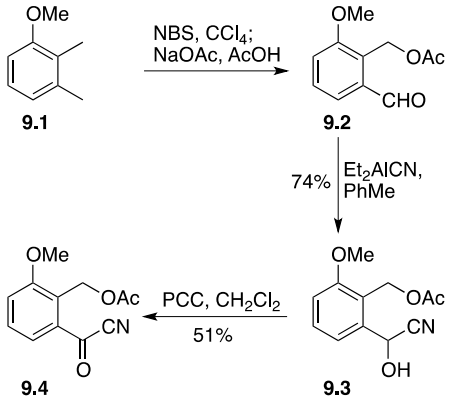
Scheme 7. Construction of skeletons of Coleophomone B and C.

When exposed to K_2CO_3 in MeOH, the methyl ester and *p*-bromobenzoyl groups were removed at the same time and the resulting alcohols were oxidized to the final aldehydes (Scheme 8). For compound **8.1a**, the Collins reagent was employed for the oxidation and it furnished coleophomone C. MnO_2 was used to convert compound **8.1b** into coleophomone B in 73% yield.



Scheme 8. Total synthesis of coleophomones B and C.

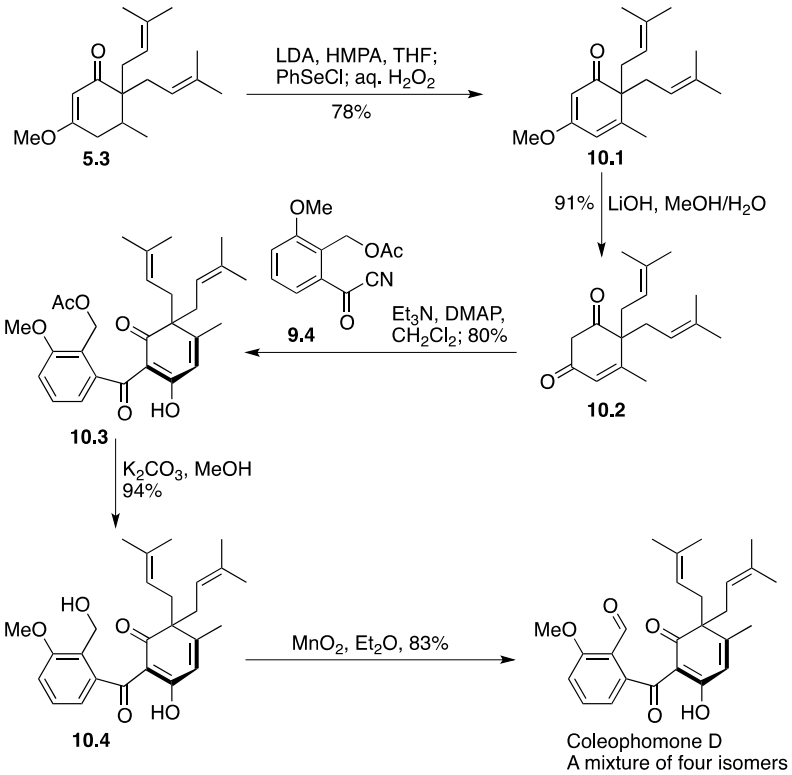
The total synthesis of coleophomone D was also described in the same paper.[5] Inspired by the *C*-acylation reaction between an acyl cyanide and a 1,3-diketone, coleophomone D was synthesized by the following route. The left-hand building block, the benzoyl cyanide **9.4**, was



Scheme 9. Preparation of acyl cyanide **9.4**.

made from 2,3-dimethylanisole (**9.1**) which was transformed into aldehyde **9.2** via a two-step literature method.[7] Then treatment with Nagata's reagent (Et_2AlCN), followed by PCC oxidation, gave the benzoyl cyanide **9.4**.

The other building block, the 1,3-cyclohexenedione **10.2**, was made in two steps from the vinylogous ester **5.3**. Compound **5.3** was deprotonated with LDA in the presence of HMPA (Scheme 10), and the resulting enolate was trapped with PhSeCl. The intermediate phenyl selenide was oxidized in situ with an excess of aqueous H_2O_2 to form the corresponding selenoxide which underwent *syn*-elimination to afford the desired unsaturated vinylogous ester **10.1**. Hydrolysis with LiOH in MeOH and water gave the desired cyclic 1,3-diketone **10.2**, and it was reacted with the benzoyl cyanide **9.4** to form the *C*-acyl product **10.3**. Deprotection with K_2CO_3 and oxidation with MnO_2 afforded coleophomone D as a mixture of four constitutional isomers.



Scheme 10. Total synthesis of Coleophomone D.

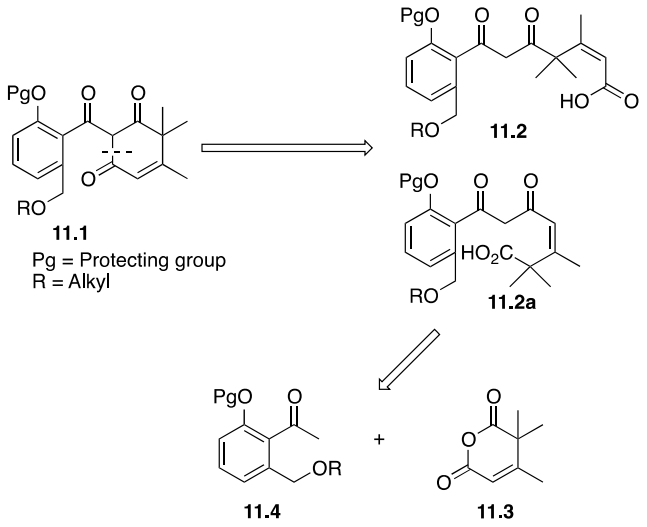
No other syntheses of the coleophomones have been reported.

Results and Discussion

When synthetic studies were carried out in this group, we faced two major challenges posed by the structure of coleophomone B. One is the macrocyclization to generate the 11-membered ring with the desired trans double bond geometry, and the second one is the construction of the tethered tricarbonyl moiety. In order to solve these two challenges, we have studied several approaches as discussed below.

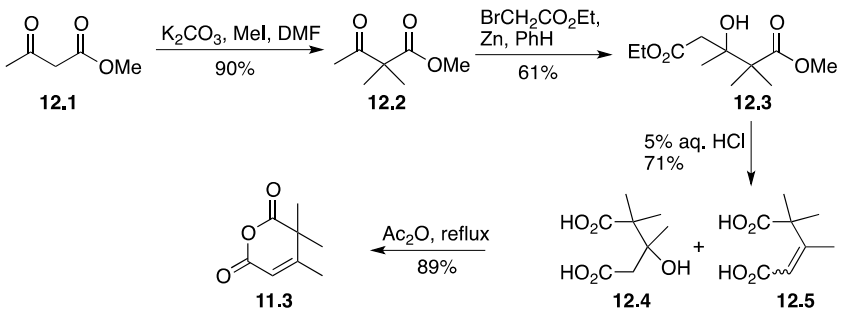
First generation approach

In our first attempt, we tried to construct the tricarbonyl core by an intramolecular acylation of a linear 1,3-diketone. We first carried out a model study on a simple structure. From the retroanalysis summarized in Scheme 11, the tricarbonyl compound **11.1** could be derived from the carboxylic acid **11.2** or its regioisomer **11.2a**, which would be made from the simple precursors **11.3** and **11.4**.



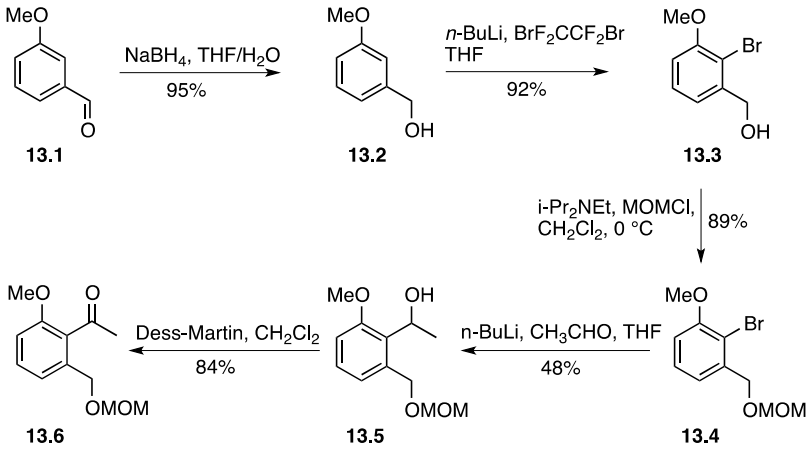
Scheme 11. Retroanalysis for intramolecular acylation reaction.

The synthetic route to anhydride **11.3** is shown in Scheme 12. Double methylation of **12.1** gave **12.2**, which was converted into diester **12.3** by Reformatsky reaction. Hydrolysis with 5% aqueous HCl gave the corresponding dicarboxylic acid, and heating with Ac_2O was employed to effect the final cyclization to **11.3**.



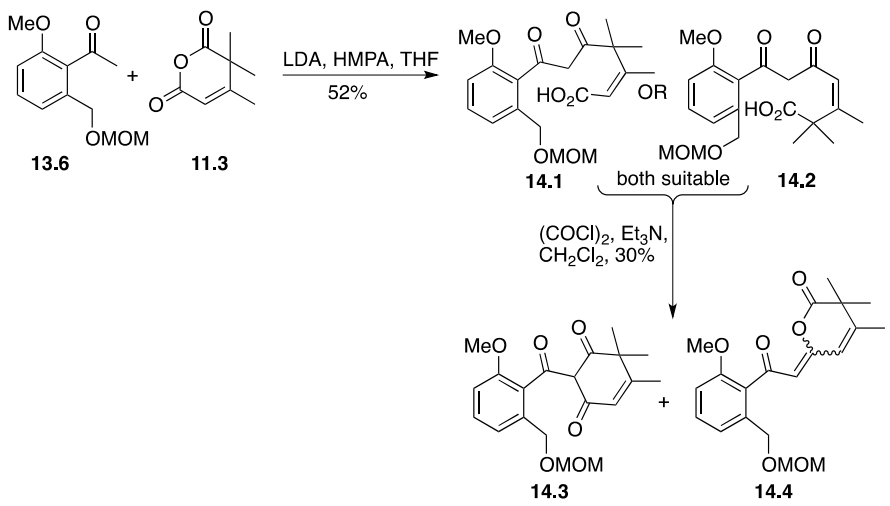
Scheme 12. Preparation of cyclic anhydride **11.3**.

The other piece, the substituted benzophenone **13.6**[9] was made by the following route from *m*-anisaldehyde (**13.1**). The transformation **13.4→13.5** gave a low yield, probably due to steric effects.



Scheme 13. Preparation of benzophenone derivative.

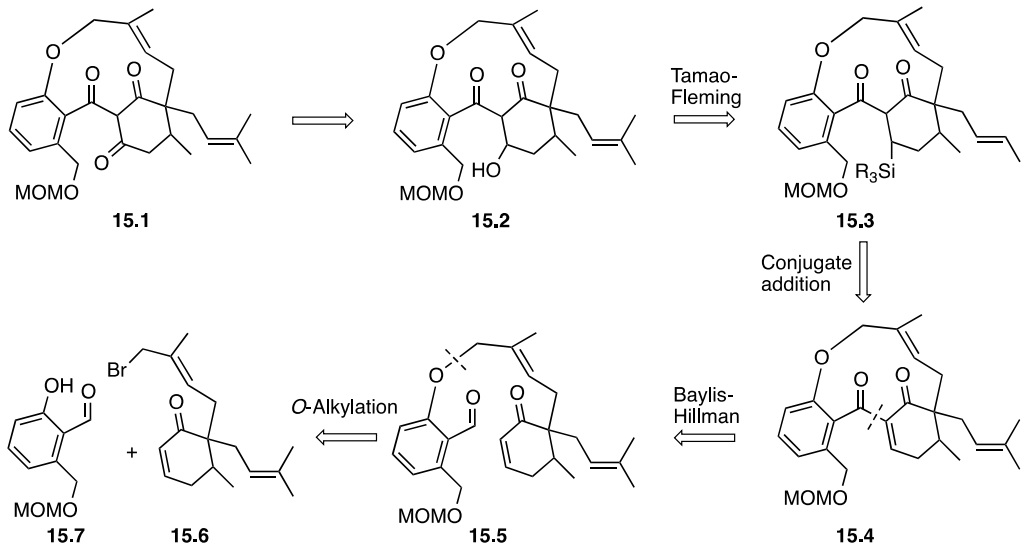
The acylation reaction between **13.6** and **11.3** gave the desired carboxylic acid in 52% yield. At this stage, I did not establish which isomer was obtained, but both isomers should lead to the same product in the next step. However, the cyclization turned out to be not as successful as I had expected. After purification by column chromatography, the product was isolated in only 30% yield. We tried to optimize the yield for this reaction, but these attempts failed to give any improvement. We could not distinguish between several possible structures (**14.3** and *E*-**14.4** and *Z*-**14,4**) and the material was an oil so that X-ray analysis was not applicable. Thus, we decided to abandon this route.



Scheme 14. Intramolecular acylation reaction of carboxylic acids **14.1**/**14.2**.

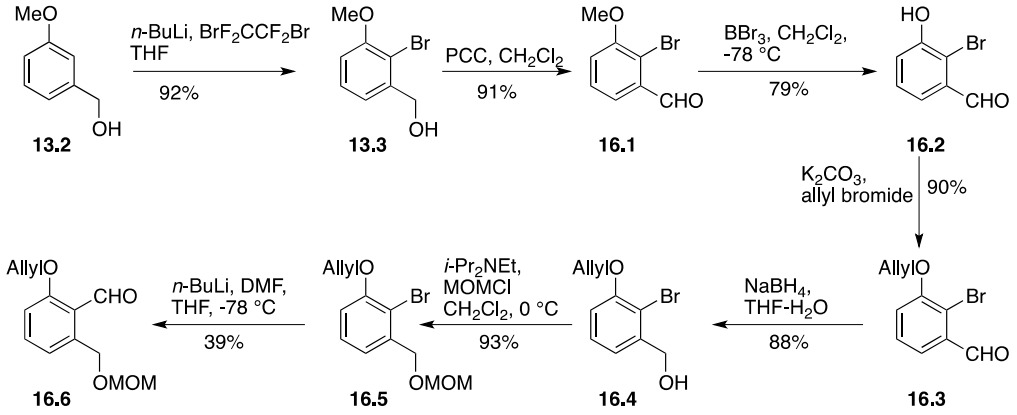
Second generation approach

In our second approach (Scheme 15), we tried to construct the tricarbonyl core structure at a late stage while first forming the top ether bond (see dotted line in **15.5**). Formation of the ether bond early in the synthesis would be easy, because it is an ordinary *O*-alkylation (**15.7** + **15.6**→**15.5**). We planned to use an intramolecular Baylis-Hillman reaction (**15.5**→**15.4**) to make the strained 11-membered ring.



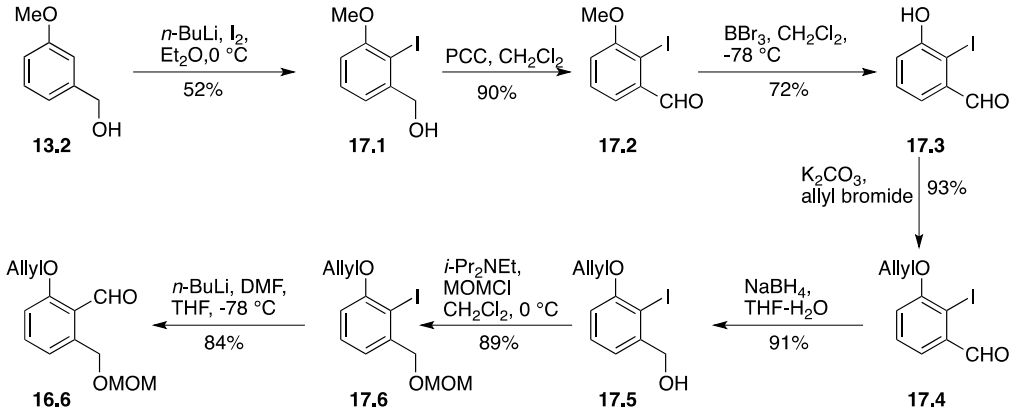
Scheme 15. Retroanalysis for intramolecular Baylis-Hillman reaction.

A protected version (**16.6**) of the left hand building block, **15.7** was made from the benzyl alcohol **13.2**. Bromination and oxidation gave the aldehyde **16.1**. This aldehyde was deprotected, allylated and reduced to the corresponding benzyl alcohol **16.4**. The alcohol was further protected by reaction with MOMCl and, after lithium-halogen exchange, the resulting carbanion was trapped with DMF to generate the desired building block **16.6**, which is a protected form of **15.7**. All the reactions went smoothly except for the last reaction, which only gave 39% yield.



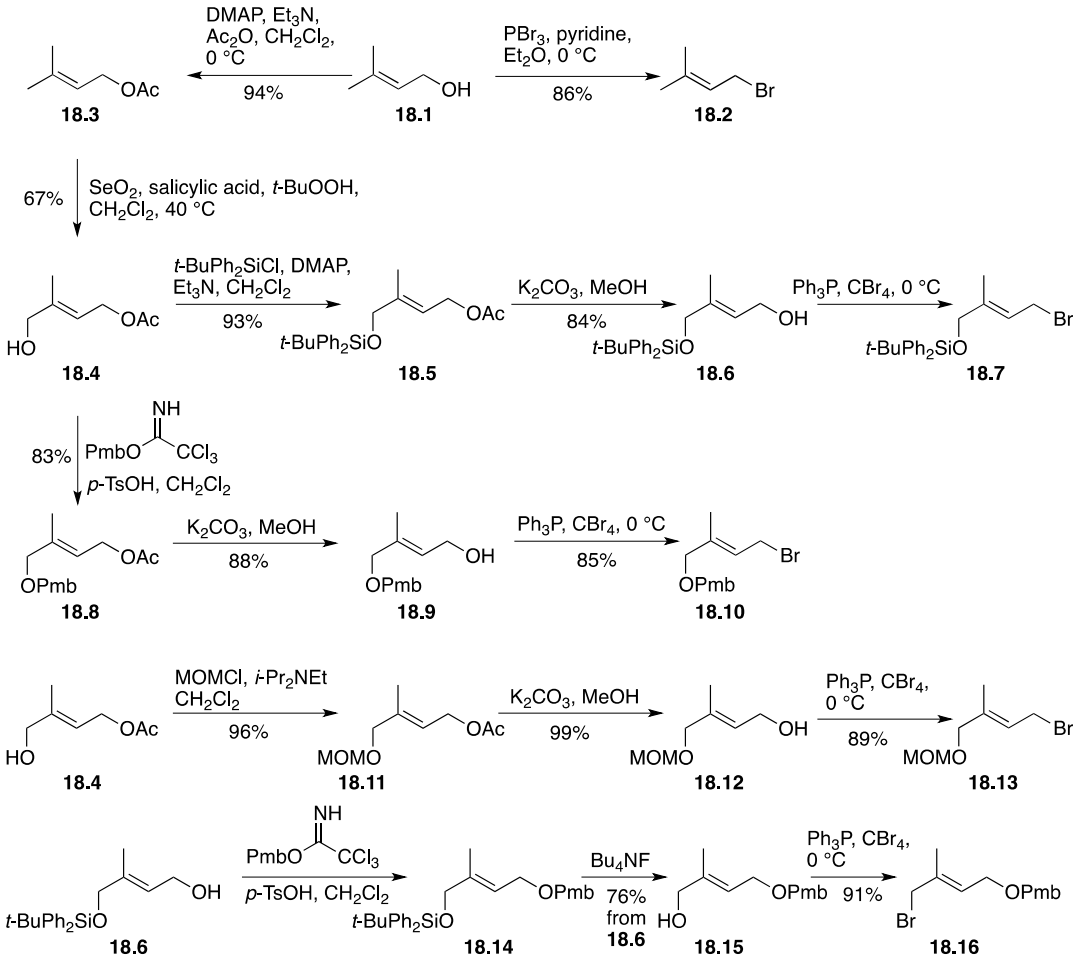
Scheme 16. Preparation of aldehyde building block **16.6**.

In order to optimize the yield, we repeated the sequence by replacing the bromine with iodine (Scheme 17), as the lithium-iodide exchange gave a more reactive carbanion compared with lithium-bromide exchange. The reaction sequence is the same as for the bromine case, except that when iodine is present instead of bromine, the last acylation reaction gave 84% yield.



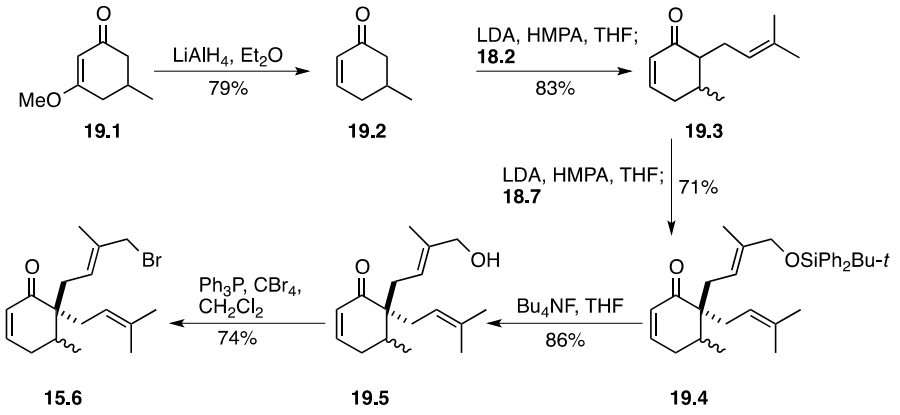
Scheme 17. Preparation of aldehyde building block **16.6** by lithium-iodine exchange.

With compound **16.6** in hand, we started to make the other building block, the dialkylated cyclohexenone **15.6**. We first made two side chains, **18.2** and **18.7**, which are allylic bromide derivatives, by the following pathway. One of the side chains, **18.2**, was made from prenol with PBr_3 in 86% yield. The other one, **18.7**, was synthesized in several steps. Acetylation of prenol with Ac_2O gave the known acetate[10] **18.3** in 94% yield. The acetate was oxidized[11] to the allylic alcohol **18.4** with SeO_2/*t*-BuOOH and the resulting hydroxyl group was protected by reaction with *t*-$BuPh_2SiCl$. Deacetylation with K_2CO_3 in MeOH generated allyl alcohol **18.6** in 84% yield. Finally, the alcohol was converted into the bromide **18.7** with Ph_3P and CBr_4 in 92% yield. For convenience, also listed in Scheme 18 are the preparation of other side chains **18.10**, **18.13** and **18.16** that we used in later approaches.



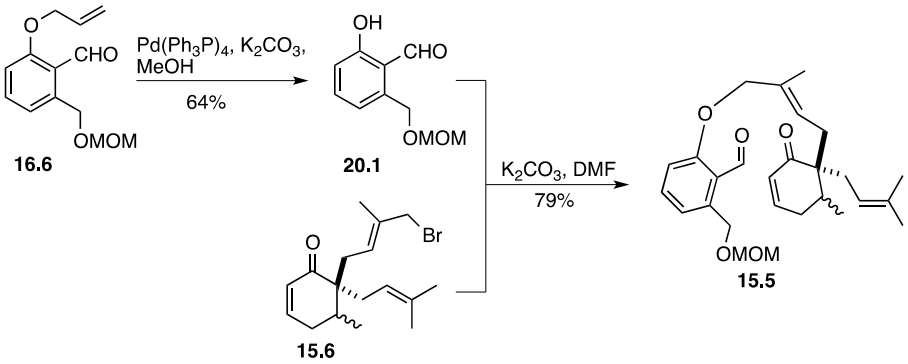
Scheme 18. Preparation of side chains.

After making the two allyl subunits **18.2** and **18.7**, we prepared the other building block **15.6** from the vinylogous ester **19.1**. Reduction with $LiAH_4$ gave cyclohexenone **19.2** in 79% yield, and double alkylation of **19.2** with **18.2** and then with **18.7** gave the dialkylated cyclohexenone **19.4** in 71% yield as a mixture of diastereoisomers. The hydroxyl group was deprotected by the action of Bu_4NF and the corresponding allylic alcohol was converted into bromide **15.6** in 74% yield.



Scheme 19. Preparation of doubly alkylated cyclohexenone **15.6**.

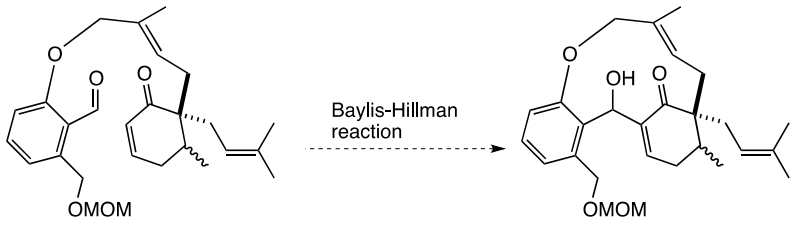
With two building blocks **15.6** and **16.6** in hand, we made the key intermediate **15.5** by deallylation of **16.6** and an *O*-alkylation reaction (**20.1** + **15.6**). The desired compound **15.5** was obtained in 79% yield.



Scheme 20. Ether bond formation by *O*-alkylation.

However, we could not cyclize **15.5** under various Baylis-Hillman conditions.[12] Under most of the conditions, such as use of MgI_2/TMEDA/DMAP,[13] DABCO and DBU, only starting

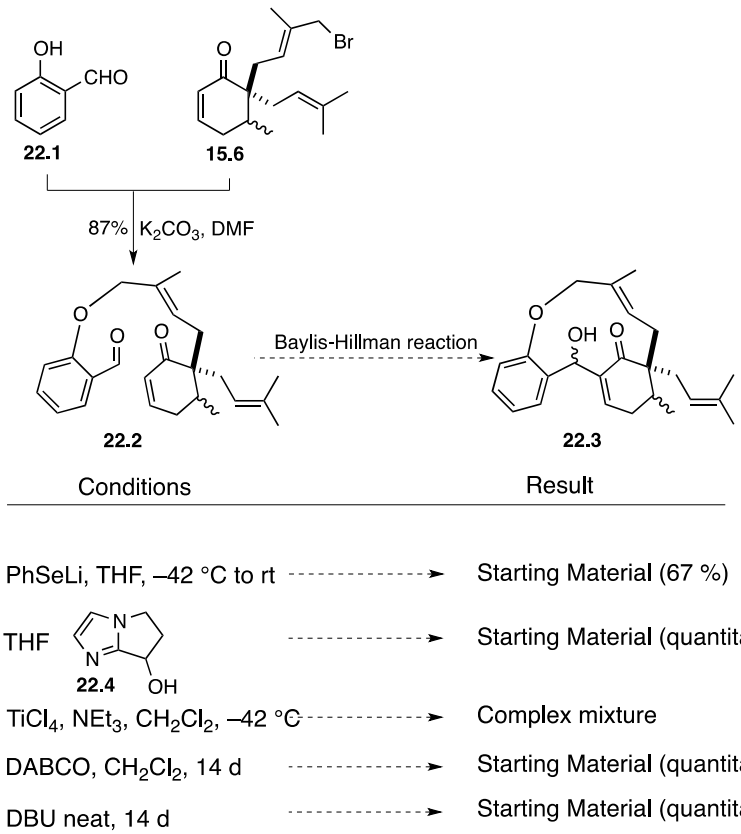
material was recovered in quantitative yield. Cyclization in the presence of $TiCl_4$ gave a complex mixture and an experiment with Bu_3P gave only 27% of the recovered aldehyde and no other identifiable products.



Conditions		Result
MgI_2, TMEDA, DMAP, MeOH	⟶	Starting Material (quantitative)
Bu_3P, MeOH	⟶	Starting Material (27 %)
$TiCl_4$, CH_2Cl_2	⟶	Complex mixture
DABCO, CH_2Cl_2	⟶	Starting Material (quantitative)
DBU, CH_2Cl_2	⟶	Starting Material (quantitative)

Scheme 21. Intramolecular Baylis-Hillman reaction.

Based on the results of these experiments, we assume that the initial aldehyde group, flanked by two other functional groups, is probably too hindered and it may not be accessible. To test this assumption, we then simplified the aldehyde by removing one of the flanking substituents. To this end we used commercially available 2-hydroxybenzaldehyde and made compound **22.2**.



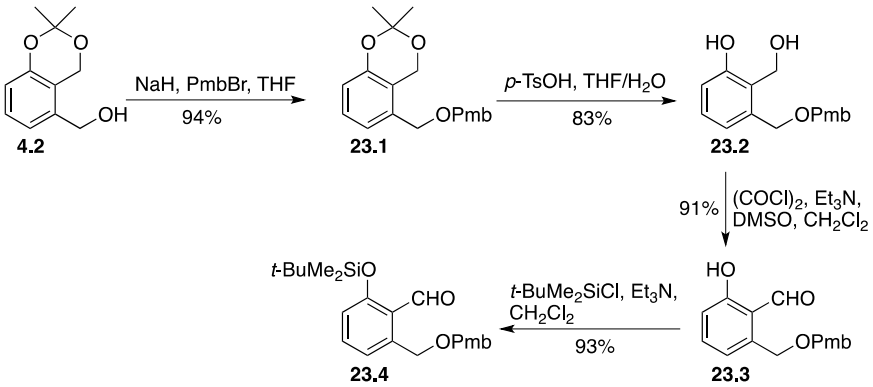
Scheme 22. Model study of intramolecular Baylis -Hillman reaction.

However, even with the less hindered aldehyde **22.2**, the intramolecular Baylis-Hillman reaction did not occur. PhSeLi as the Baylis-Hillman promoter gave 67% recovery of starting material and DABCO and DBU each gave starting material in quantitative yield after 14 days. In the presence of the special catalyst, hydroxyl imidazole **22.4**, again only quantitative recovery of starting material was observed. When **22.2** was exposed to $Et_3N/TiCl_4$, it decomposed to a complex mixture. At this stage, we suspected that development of the strained 11-membered ring in the desired cyclic product thwarts the intramolecular Baylis-Hillman reaction.

Third generation approach

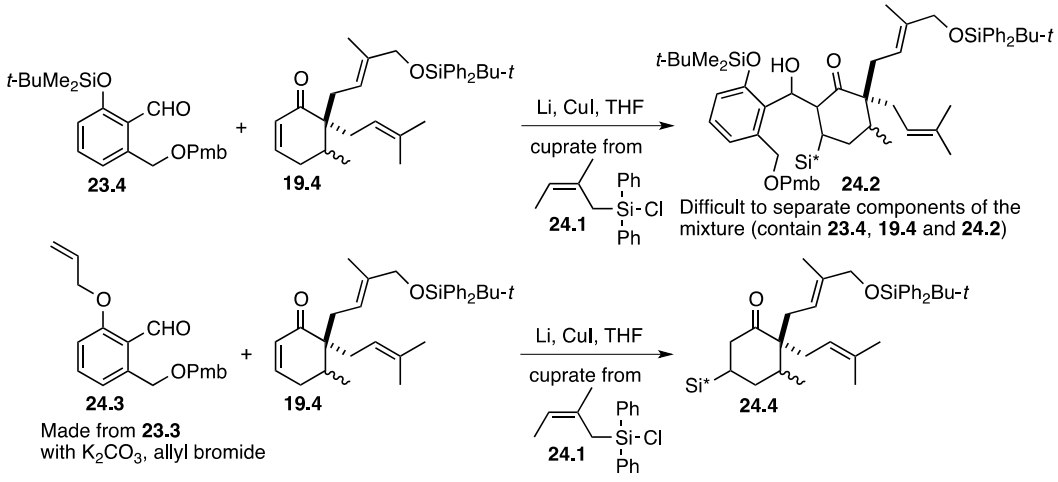
Since the intramolecular Baylis-Hillman reaction did not give the desired cyclic compound, we considered the strategy of *intermolecular* conjugate addition to construct the tricarbonyl system first, followed by macrocyclization. To this end, we modified the protecting groups of the aromatic building block. We started from the known benzylic alcohol **4.2**[8] and protected the hydroxyl with a Pmb group (**4.2→23.1**). Hydrolysis of **23.1** gave diol **23.2** in 83%

yield. The benzylic hydroxyl was oxidized to the aldehyde by Swern oxidation in 91% yield and the resulting phenolic compound **23.3** was protected by silylation with *t*-$BuMe_2SiCl$.



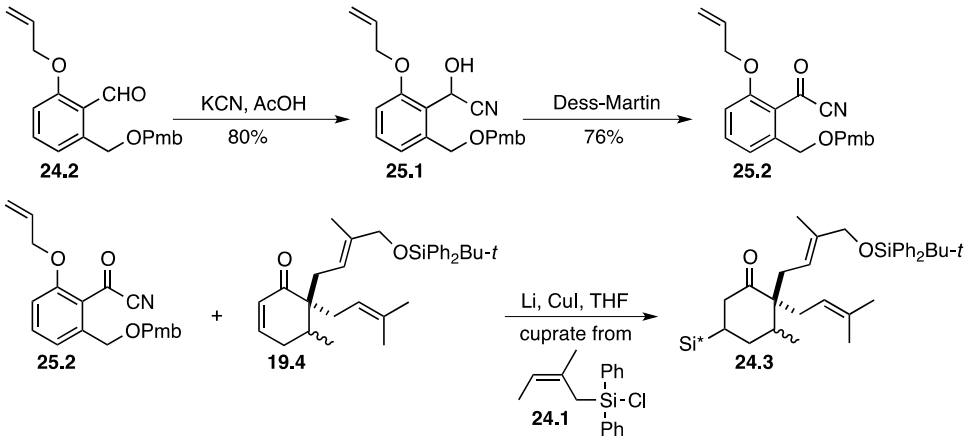
Scheme 23. Preparation of benzaldehyde **23.4** for intermolecular conjugate addition.

We tried to first link the two units, aldehyde **23.4** and cyclohexenone **19.4** by conjugate addition. A silyl cuprate[14] derived from **24.1** was used as the nucleophile; however, the reaction appeared (high resolution mass) to give only a mixture of both starting materials and product and it was impossible to separate the desired compound **24.2** from the others. In order to solve the separation problem, we used a different protecting group, an allyl group, instead of the *t*-$BuMe_2Si$-group. Unfortunately, the allyl protected benzaldehyde **24.3** only gave **24.4** as the silicon adduct on treatment with the silyl cuprate.



Scheme 24. Intermolecular conjugate addition with allylic silicon unit.

We suspect that the benzaldehyde **24.3** is not reactive enough, and so we prepared the acyl cyanide as the trapping reagent instead of the aldehyde for the conjugate addition.

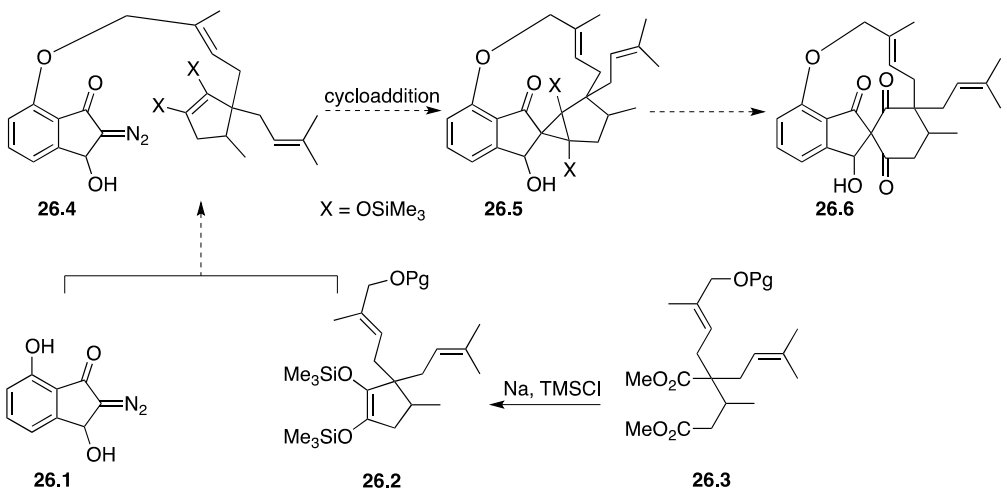


Scheme 25. Attempted intermolecular conjugate addition with acyl cyanide **25.2**.

The aldehyde was transformed into the cyanohydrin **25.1** and oxidation with the Dess-Martin reagent then generated the desired acyl cyanide **25.2** in 76% yield. However, the attempted conjugate addition gave the same result as **24.2**; only the silicon adduct was isolated and the desired product was not detected. At this stage, we assumed that steric hindrance prevents the enolate from trapping the aldehyde or acyl cyanide and we decided to try another approach.

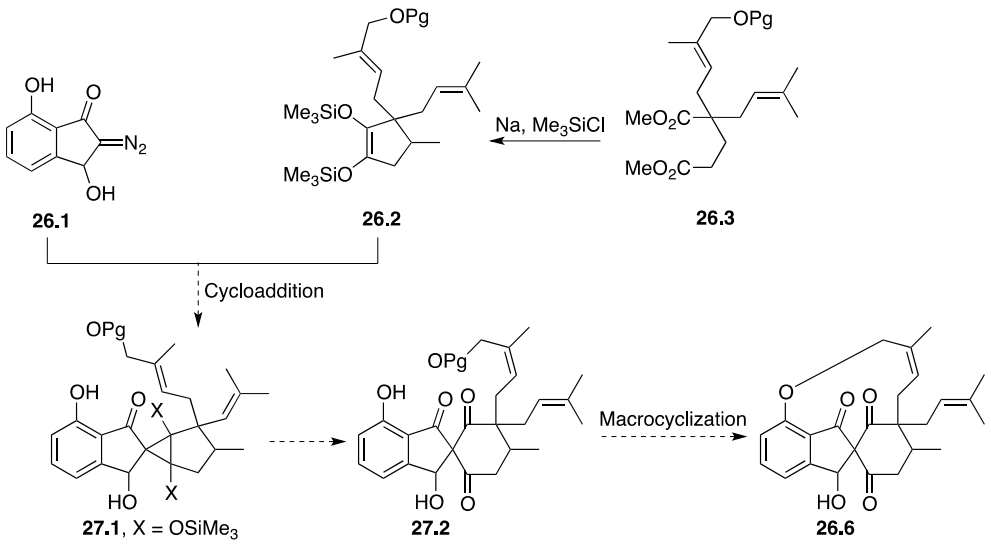
Fourth generation approach

In our fourth approach, we planned to construct the challenging tricarbonyl core structure via a carbene intermediate in order to solve the difficulty of forming the tricarbonyl structure.



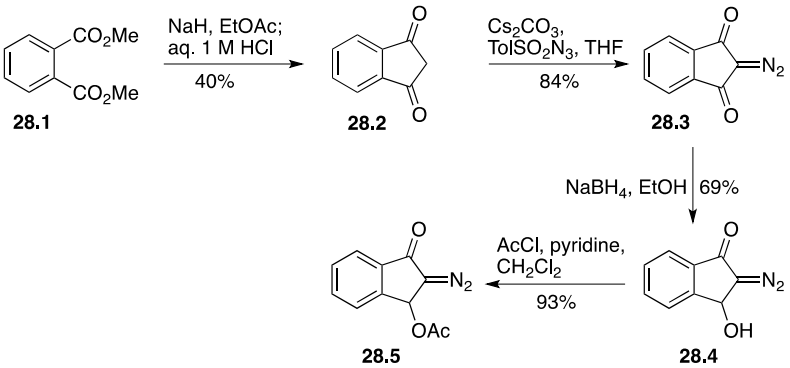
Scheme 26. Intramolecular cycloaddition pathway.

The idea was to prepared two building blocks, **26.1** and **26.2**. Compound **26.1** is a diazo compound which could be converted into a carbene under Rh or Cu catalysis. The other component, **26.2**, is a bis siloxy enol ether, which we felt could be made from diester **26.3** via treatment with Na/Me_3SiCl. The cycloaddition, if successful, should give [3,1]-bicyclic compound **26.5** with two -$OSiMe_3$ groups. Addition of the simple carbene MeCH: to a bis silyl enol ether has been reported for a different ring size of the bis silyl enol ether.[15] The bicyclic system should be convertible into the corresponding tricarbonyl system via a diol cleavage pathway. We also considered an alternative intermolecular pathway to implement this idea, as shown in Scheme 27. The cycloaddition could be done first and we would then build the tricarbonyl system **27.2** before the macrocyclization.



Scheme 27. Intermolecular cycloaddition pathway.

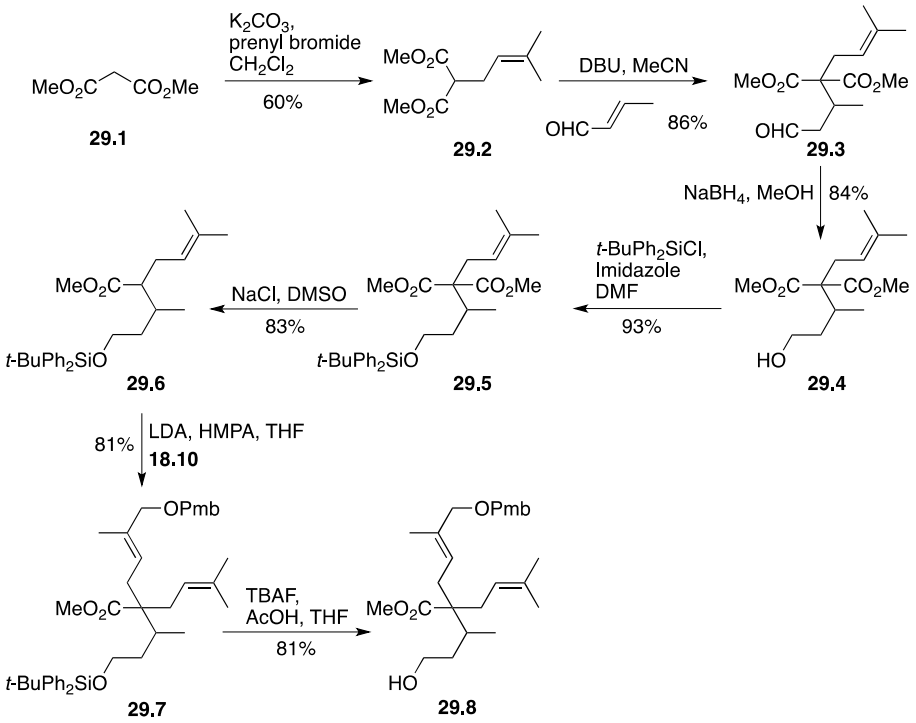
We first carried out a model study on a simple compound to test our approach. The synthesis of the aromatic diazo compound was easily achieved from the commercially available diester **28.1**. Treatment with NaH in EtOAc, followed by 1 M aqueous HCl, afforded cyclic 1,3-diketone **28.2** in 40% yield. The diketone was then exposed to $TolSO_2N_3$, with Cs_2CO_3 as a base. This procedure afforded diazo compound **28.3** in 84% yield. One of the ketone carbonyls in **28.3** was reduced to the alcohol by $NaBH_4$ and protected by acetylation with AcCl.



Scheme 28. Preparation of diazo building blocks.

However, we encountered some difficulties when we tried to synthesize the the required bis siloxy enol ether. Compound **26.3**, the precursor of the bis siloxy enol ether, has two side

chains α to one of the ester groups and much effort was required to synthesize such a compound. We decided to use Pmb as a protecting group instead of *t*-BuPh$_2$Si because we suspected that the silicon unit would not survive the following conditions during the synthesis.

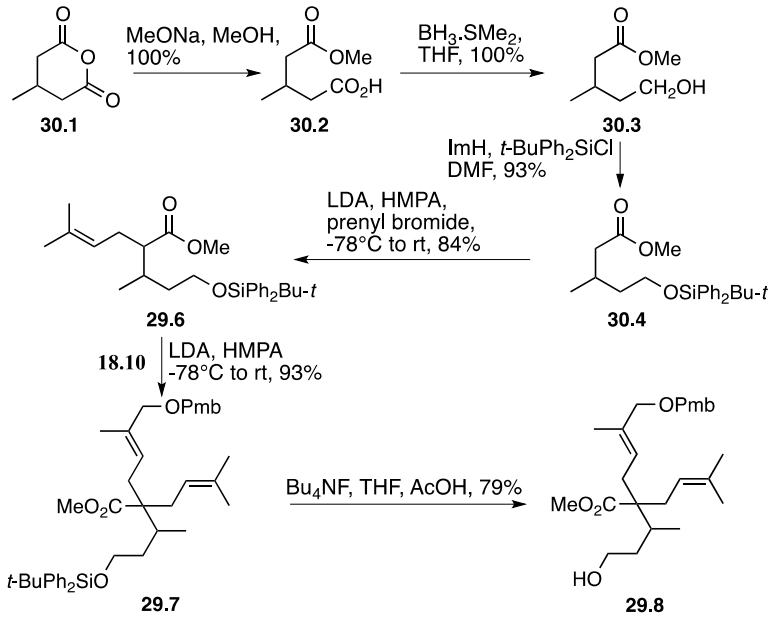


Scheme 29. Synthesis of bis siloxy enol ether precursor.

Dimethyl malonate was alkylated with prenyl bromide and the resulting product **29.2** underwent Michael addition to crotonaldehyde to afford diester **29.3** in 86% yield. The aldehyde was reduced and then the resulting alcohol was protected by silylation with *t*-BuPh$_2$SiCl in 93% yield (**29.4→29.5**). The following Krapcho decarboxylation gave mono ester **29.6** which was alkylated with **18.10** to afford the bis alkylated mono ester **29.7**. Deprotection with Bu$_4$NF gave the desired compound **29.8**, which could be converted to a diester by oxidation. However, when we tried to scale up this route, we found that the Krapcho decarboxylation did not work very well and sometimes we could not get the desired monoester **29.6**.

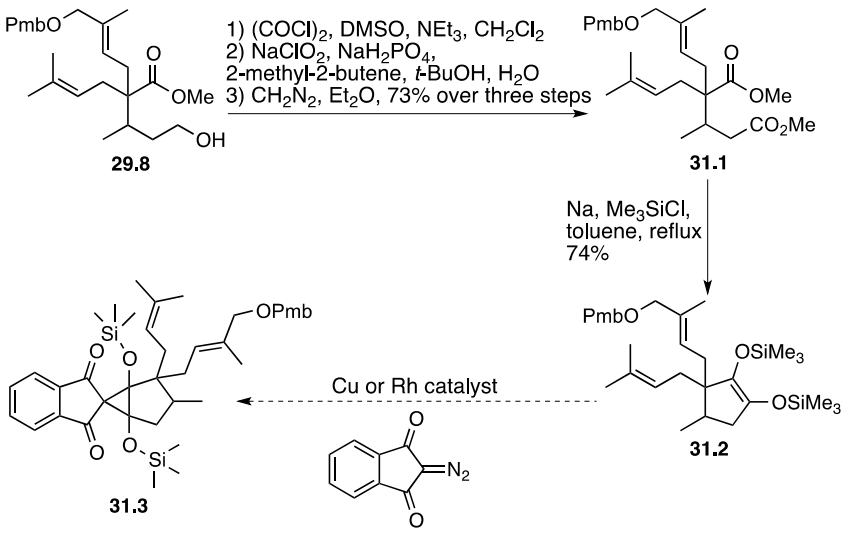
In order to solve this problem, we developed another route to synthesize **29.8**. This route started with the hydrolysis of methyl glutaric anhydride **(30.1)**. The carboxylic acid **30.2** was reduced to the alcohol by BH$_3$ and the hydroxyl group was protected by reaction with *t*-BuPh$_2$SiCl. The following steps were the same as in the previous route of Scheme 29, and the

present modified route also leads to the desired intermediate **29.8**. This route is much shorter and is reproducible.



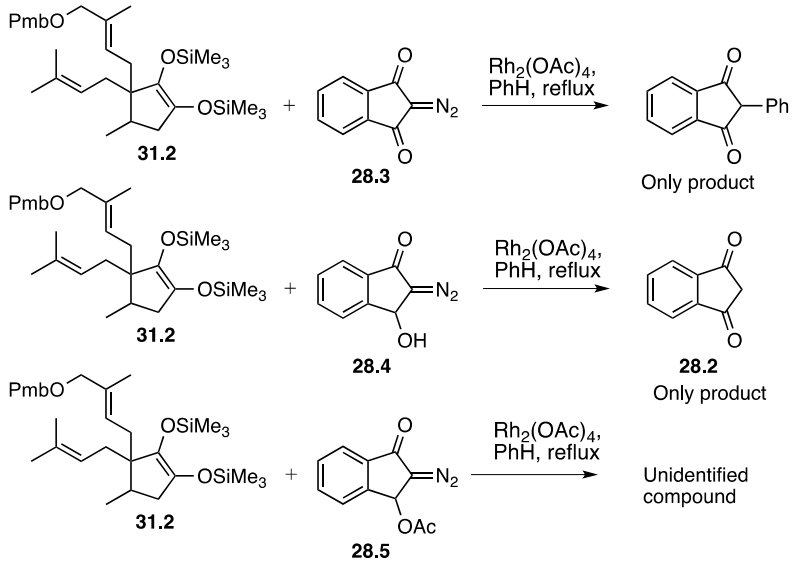
Scheme 30. Alternate route to bis siloxy enol ether precursor.

We then transformed alcohol **29.8** into the diester **31.1** by oxidation and methylation. The alcohol was first oxidized to an aldehyde by the Swern method, and the aldehyde was further oxidized to a carboxyl which was methylated with diazomethane. The diester **31.1** was obtained in 73% yield over three steps. The conversion of **31.1** to **31.2** by acyloin reaction was achieved by treatment with Na/Me_3SiCl[16] in refluxing PhMe.



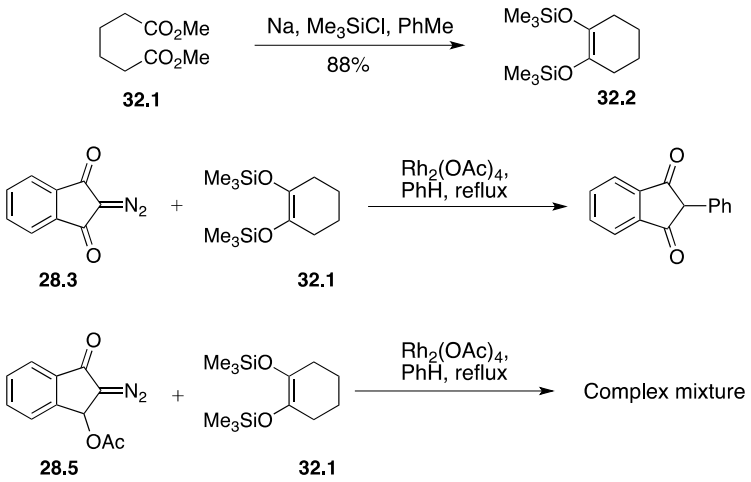
Scheme 31. Preparation of bis siloxy enol ether **31.2**.

With compound **31.2** in hand, we decided to carry out the cycloaddition with different diazo compounds. However, the following three experiments only gave undesired products or unidentified compounds. For the first entry, 1,3-diketone **28.3** was used as the carbene source and it reacted only with with benzene. The second entry shows the diketone as the only product, while the third experiment gave an unidentified product. We suspected that probably the C=C double bond in the bis siloxy compound is not accessible to a large carbene due to the flanking siloxy groups.



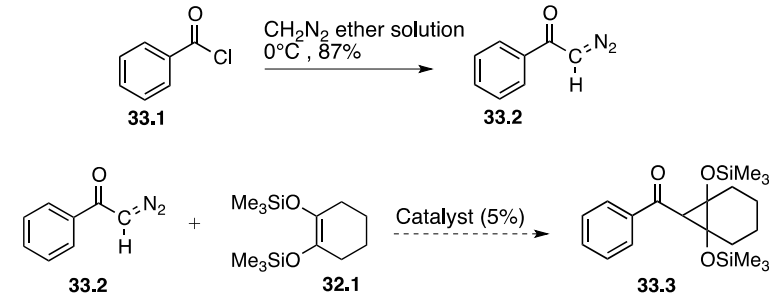
Scheme 32 (part 1). Attempted intermolecular cycloaddition via a carbene.

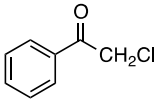
Considering the possible steric effects, we tried the bis siloxy compound **32.2** which is known to react with the simple carbene CH_3CH:.[15] However, the result for the cycloaddition experiment was still not helpful. C-H insertion with benzene occurred with diketone **28.3** and the acyl protected diazo **28.5** only gave a complex mixture.



Scheme 32 (part 2). Model study of intermolecular cycloaddition.

The diazo compound was also modified and the diazo ketone **33.2** was prepared from benzoyl chloride by reaction with diazomethane. The cycloaddition between diazo **33.2** and bis siloxy enol ether **32.1** was unsuccessful. The carbene intermediate reacted with the solvent when chloroform was used. When $Cu(acac)_2$ was used as a catalyst and in the presence of over 10 equiv **32.1**, only a trace amount of the desired product **33.3** was obtained. When $Rh_2(OAc)_4$ was employed as the catalyst, the reaction did not give any desired product.



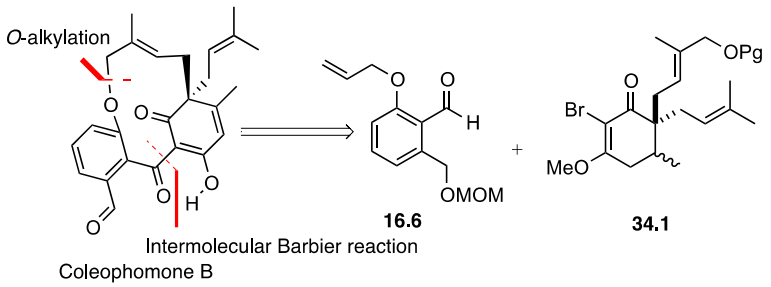
Entry	Solvent	Catalyst	Result
1	$CHCl_3$	$Rh_2(OAc)_4$	
2	benzene	$Cu(acac)_2$	Trace (with over 10 equiv **32.1**)
3	benzene	$Rh_2(OAc)_4$	Complex mixture
4	toluene	$Cu(acac)_2$	No desired product (with 0.5 equiv **32.1**)

Scheme 33. Model study of intermolecular cycloaddition (continued).

We tried to remove the Pmb group of the bis siloxy enol ether **31.2** with DDQ with the intention of converting the resulting alcohol into a bromide, but the siloxy group seems to be incompatible with the reaction conditions even though this particular siloxy enol ether is stable enough to be chromatographed over silica gel. Considering the difficulty of the cycloadditions on the model studies, we decided to abandon this route.

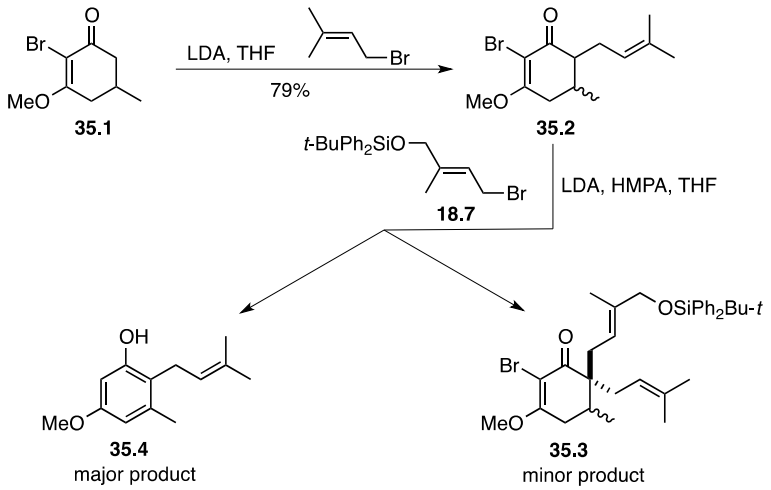
Fifth generation approach

In this approach, we decided to use an intermolecular Barbier reaction and then do a cycloetherification to generate the macrocyclic system. Our retroanalysis is shown in Scheme 34. We planned to construct the tricarbonyl system by Barbier reaction between **16.6** and **34.1**. The later macrocyclization would be achieved by cycloetherification. We have already described the synthesis of **16.6** in the previous discussion and we now examined a route to synthesize the bisalkylated bromoenone system **34.1**.



Scheme 34. Retroanalysis for intermolecular Barbier reaction.

In our synthetic route to **35.3**, we started from the 2-bromoenone **35.1**, whose synthesis has already been described in the second Chapter of this Thesis. The first alkylation went very well under optimized conditions and it gave a 79% yield of the desired mono alkylated bromoenone **35.2**. However, we found that the second alkylation did not work in the way we expected. Instead of generating dialkylated bromoenone **35.3**, we got a large amount of the aromatic compound **35.4**.



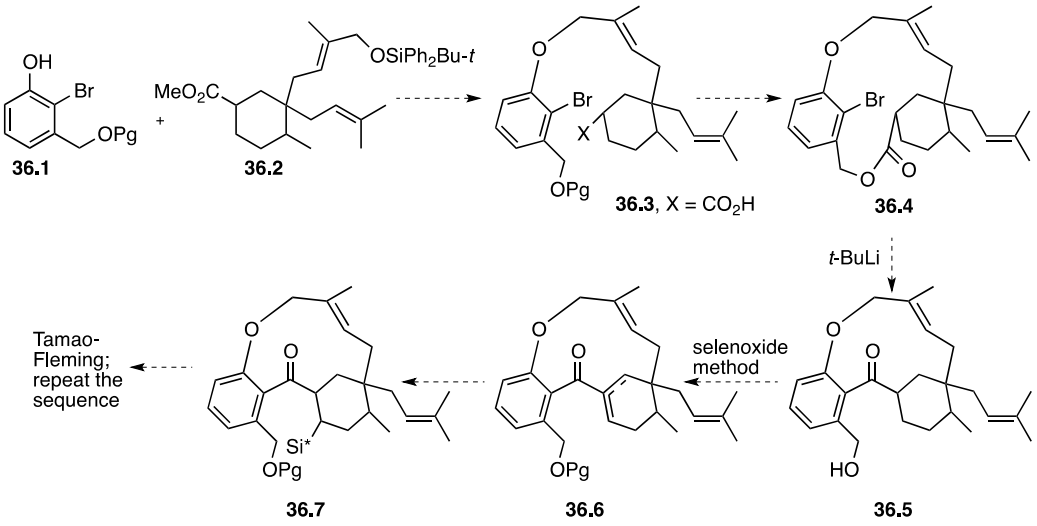
Scheme 35. Double alkylation of 2-bromo cyclohexenone system.

In order to make the dialkylation give a better yield, we tried several different bases, for example NaH, KHMDS, KDA, LiHMDS. We also tried to carry out the alkylation at different temperatures. But none of these attempts was successful. Compound **35.2** was a mixture of trans and cis isomers, and we eventually recognized that these two isomers behaved differently in the alkylation. The trans isomer of **35.2** underwent both alkylation and aromatization with

LDA/HMPA. The cis isomer only undergoes aromatization under the above conditions. We tried to equilibrate the cis and trans isomer mixture with DBU, and this experiment, which did not effect equilibration, led to the discovery of a general route to substituted phenols discussed in Chapter 2. Since we could not doubly alkylate **35.2** smoothly, we did not continue trying to optimize the alkylation and decided to study a new approach.

Sixth generation approach

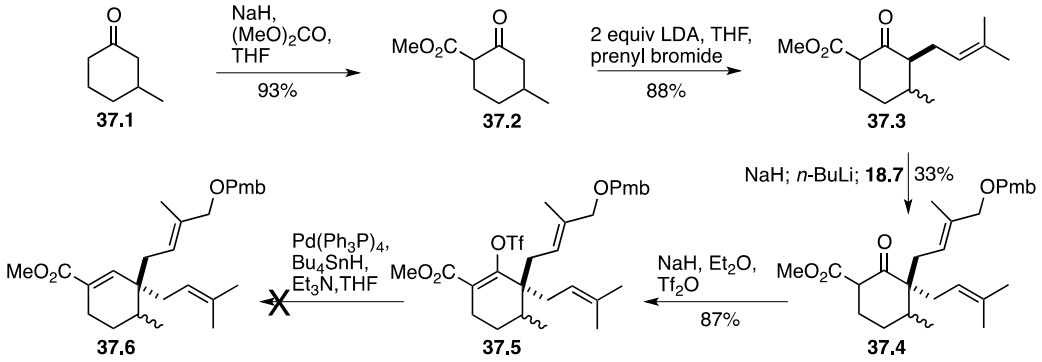
We planned a route based on ring contraction (**36.4→36.5**) and installation of the oxygens by conjugate addition of a silicon unit (**36.6→36.7**), followed by Tamao-Fleming oxidation and a repetition of this sequence. Such a route would enable us to construct a less strained carbon skeleton corresponding to coleophomone B, while leaving the tricarbonyl system to be installed at later stage. The intramolecular macrolactonization should be easier to achieve, for the ring size is larger and less strained. The subsequent intramolecular acyl transfer (**36.4→36.5**) would give the desired carbon skeleton of coleophomone B without some of the rigidifying double bonds.



Scheme 36. Synthetic plan for intramolecular acyl transfer.

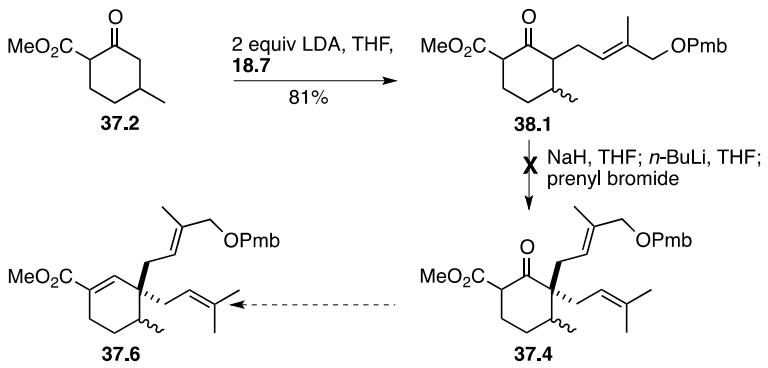
The aromatic building block **36.1** is easy to make and its analogs, with different protecting groups, had already been prepared, as discussed previously. The synthesis of **36.2** is challenging, as the dialkyl side chains were remote to the methyl ester. We first examined a

route via Weiler alkylation to form **36.2**. The cyclic keto ester (Scheme 37) was made from 3-methylcyclohexanone in 93% yield by the action of NaH and dimethyl carbonate (**37.1→37.2**). Then 2 equiv LDA was used to generate the dianion, and prenyl bromide was added to quench the dianion. The first alkylation gave **37.3** in 88% yield as a mixture of enol-keto isomers. However, the second Weiler alkylation was not as good as the first one, for it only gave **37.4** in 33% yield, and from the ^{1}H NMR and ^{13}C NMR spectra, **37.4** was found to contain some minor impurity which could not be removed to give a pure product. The ketone was converted to the enol triflate with NaH and triflic anhydride and compound **37.5** was used directly in the next step without column chromatography. The attempt to remove the OTf group was unsuccessful and we suspect that the impurity within compounds **37.4** and **37.5** was responsible.



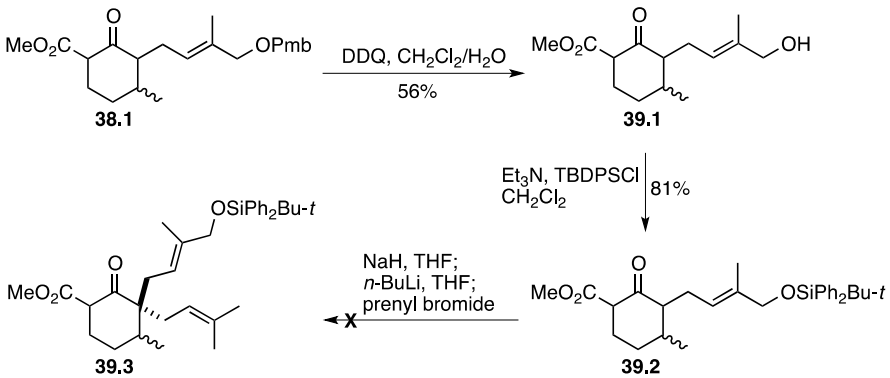
Scheme 37. Double Weiler alkylation on cyclic keto ester system.

Because the yield (33%) and purity after the second alkylation were unsatisfactory, we decided to attach the Pmb side chain first and see if this route would solve the problems. The first Weiler alkylation went smoothly (**37.2→38.1**) and the yield is very good. However, in the presence of the Pmb side chain, the second alkylation did not occur. From TLC analysis, several products were formed, and NMR spectra showed complicated signals. We suspected that the Pmb protecting group is not compatible with the generated carbanion and a different protecting group would be required.



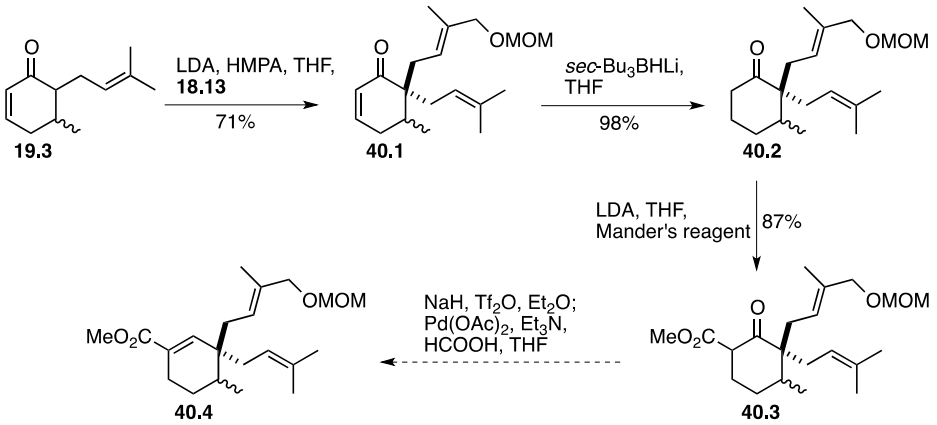
Scheme 38. Attempted double Weiler alkylation via a different sequence.

We removed the Pmb group with DDQ and reprotected the allylic alcohol by silylation with *t*-BuPh$_2$SiCl. Compound **39.2** was exposed to the Weiler alkylation conditions, but the result was the same as in the Pmb example. TLC analysis and NMR experiments showed that the second alkylation conditions led to decomposition of the cyclic ketone ester system.



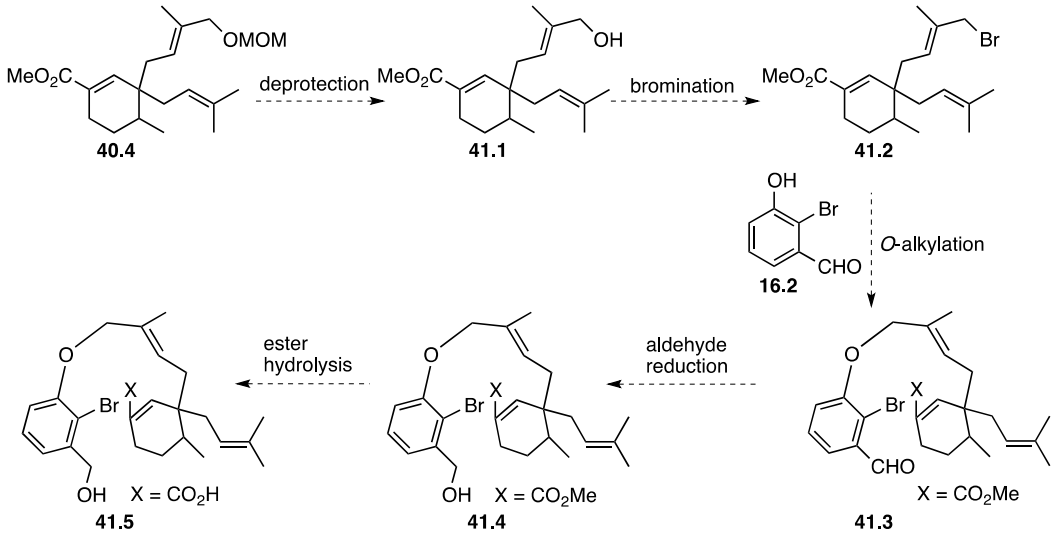
Scheme 39. Double Weiler alkylation with different protecting group.

In order to solve the decomposition problem, we circumvented the double Weiler alkylation step by doing the double alkylation on cyclohexenone first, and then attaching the methyl ester with Mander's reagent. The second alkylation of an initial cyclohexenone **19.3** gave **40.1** in 71% yield. Then the double bond within the ring was removed by treatment with L-Selectride in 98% yield. Finally, the methyl ester was installed by treating the enolate, generated from **40.2**, with Mander's reagent and we got **40.3** in 87% yield.



Scheme 40. Cyclic keto ester synthesis by using Mander's reagent.

In the future, we plan to convert the cyclic keto ester **40.3** to the desired unsaturated methyl ester **40.4**. The MOM group will be removed and the resulting allyl alcohol will be transformed to the bromide **41.2**. *O*-Alkylation with **16.2** and reduction should give the benzyl alcohol **41.4**. Ester hydrolysis with NaOH or LiOH will generate the carboxylic acid **41.5** as a precursor for cycloesterification.



Scheme 41. Proposed route to macrolide precursor.

Conclusion

We have investigated the challenging macrocyclization by several intramolecular and intermolecular methods. Pathways for constructing the tricarbonyl system were also explored extensively. One of the attempts led to the discovery of a general aromatization method, which was covered in Chapter 2 of the Thesis. Although we have not been able to generate macrocyclic systems, a number of advanced cyclization precursors were synthesized, and further attempts to effect macrocyclization will be continued in this laboratory.

Experimental section

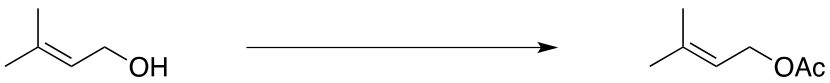
General Procedures. Solvents used for chromatography were distilled before use. Commercial thin layer chromatography plates (silica gel, Merck 60F-254) were used. Silica gel for flash chromatography was Merck type 60 (230–400 mesh). Dry solvents were prepared under an inert atmosphere and transferred by syringe or cannula. The symbols s, d, t and q used for ^{13}C NMR spectra indicate zero, one, two, or three attached hydrogens, respectively, the assignments being made from APT spectra. Solutions were evaporated under water pump vacuum and the residue was then kept under oil pump vacuum. High resolution electrospray mass spectrometry analyses were done on an orthogonal time of flight analyzer.

1-Bromo-3-methylbut-2-ene (18.2).[17]

18.1 **18.2**

PBr_3 (7.5 mL, 79.0 mmol) was added dropwise to a stirred and cooled (0 °C) solution of pyridine (3.0 mL, 37.0 mmol) and prenol (18.2 mL, 174 mmol) in Et_2O (90 mL). The cold bath was left in place but not recharged and the mixture was stirred overnight during which the mixture attained room temp. The reaction mixture was diluted with saturated aqueous $NaHCO_3$ and extracted with Et_2O. The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. Vacuum distillation gave **18.2**[17] (22.3 g, 86%) as a colorless liquid, which was kept in the freezer and stabilized by a small amount of silver wool: ^1H NMR ($CDCl_3$, 500 MHz) δ 1.73 (m, 3 H), 1.77 (m, 3 H), 4.00 (s, 2 H), 4.02 (s, 2 H), 5.52–5.53 (m, 1 H).

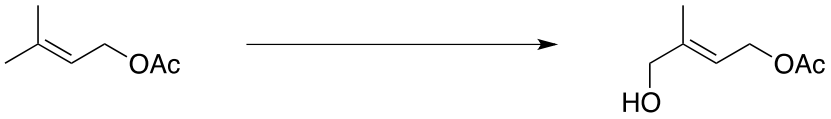
3-Methylbut-2-en-1-yl acetate (18.3).[10]



18.1 **18.3**

DMAP (1.50 g, 12.3 mmol), Et_3N (30.0 mL, 214 mmol) and Ac_2O (17.5 mL, 185 mmol) were added to a stirred and cooled (0 °C) solution of prenol (**18.1**) (10.7 g, 124 mmol) in CH_2Cl_2 (150 mL). The cold bath was left in place but not recharged and stirring was continued overnight during which the mixture attained room temp. The reaction mixture was diluted with saturated aqueous NH_4Cl and extracted with CH_2Cl_2. The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated to give **18.3**[10] (14.9 g, 94%) as a pale yellow liquid, which was used without purification.

(2*E*)-4-Hydroxy-3-methylbut-2-en-1-yl acetate (18.4).[11]



18.3 **18.4**

Salicylic acid (1.6 g, 11.7 mmol), *t*-BuOOH (70% w/w in water, 26 mL, 187 mmol) and SeO_2 (3.2 g, 29.2 mmol) were added to a stirred solution of **18.3** (14.9 g, 117 mmol) in CH_2Cl_2 (100 mL) at room temp. Then the mixture was warmed to 40 °C and and stirred at this temp for 36 h. The reaction mixture was diluted with saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2. The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. $NaBH_4$ (4.4 g, 117 mmol) was added in 4 portions over 20 min to a stirred and cooled (0 °C) solution of the above reaction residue in MeOH (50 mL). The resulting mixture stirred for 2 h at 0 °C, diluted with saturated aqueous NH_4Cl and extracted with Et_2O. The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated to give **18.4**[11] (11.3 g, 67%) as a pale yellow liquid, which was used without purification: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.78 (s, 3 H), 2.02 (s, 3 H), 4.04 (s, 2 H), 4.62 (m, 2 H), 5.61 (m, 1 H).

(2*E*)-4-[*tert*-Butyldiphenylsilyl)oxy]-3-methylbut-2-en-1-yl acetate (18.5).[18]

18.4 **18.5**

DMAP (92.5 mg, 0.76 mmol), Et_3N (3.2 mL, 22.8 mmol) and *t*-$BuPh_2SiCl$ (2.30 g, 8.34 mmol) were added to a stirred solution of **18.4** (1.09 g, 7.58 mmol) in CH_2Cl_2 (15 mL) at room temp. The mixture stirred for 8 h, diluted with saturated aqueous NH_4Cl and extracted with CH_2Cl_2. The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (3 × 15 cm), using 1:8 EtOAc-hexanes, gave **18.5** (2.70 g, 93%) as a colorless oil: FTIR ($CDCl_3$, cast) 3071, 1741 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.10 (s, 9 H), 1.67 (s, 3 H), 2.01 (s, 3 H), 4.10 (s, 2 H), 4.73–4.74 (m, 2 H), 5.78–5.79 (m, 1 H), 7.93–7.45 (m, 6 H), 7.68–7.70 (m, 4 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 13.67 (q), 19.3 (s), 21.0 (q), 26.8 (q), 60.9 (t), 67.9 (t), 117.4 (d), 127.6 (d), 129.6 (d), 133.5 (s), 135.5 (d), 140.4 (s), 171.0 (s); exact mass (electrospray) *m*/*z* calcd for $C_{23}H_{30}NaO_3Si$ $(M + Na)^+$ 405.1850, found 405.1856.

(2*E*)-4-[*tert*-Butyldiphenylsilyl)oxy]-3-methylbut-2-en-1-ol (18.6).[18]

18.5 **18.6**

K_2CO_3 (1.94 g, 14.1 mmol) was added to a stirred solution of **18.5** (2.70 g, 7.04 mmol) in MeOH (15 mL) at room temp. The resulting mixture was stirred for 6 h, diluted with saturated aqueous NH_4Cl and extracted with Et_2O. The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (3 × 15 cm), using 1:3 EtOAc-hexanes, gave **18.6**[18] (2.01 g, 84%) as a colorless oil: ^1H NMR ($CDCl_3$, 500 MHz) δ 1.08 (s, 9 H), 1.63 (s, 3 H), 4.06 (s, 2 H), 4.21–4.23 (m, 2 H), 5.75–5.80 (m, 1 H), 7.38–7.42 (m, 6 H), 7.65–7.69 (m, 4 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 13.6 (q), 19.3 (s), 26.8 (q), 59.1 (t), 68.0 (t), 122.4 (d), 127.7 (d), 129.7 (d), 133.6 (s), 135.5 (d), 137.9 (s).

{[(2*E*)-4-Bromo-2-methylbut-2-en-1-yl]oxy)(*tert*-butyl)diphenylsilane (18.7).[19]

18.6 **18.7**

Ph_3P (1.69 g, 6.47 mmol) and CBr_4 (2.15 g, 6.47 mmol) were added to a stirred and cooled (0 °C) solution of **18.6** (2.01 g, 5.88 mmol) in CH_2Cl_2 (20 mL). The ice bath was left in place, but not recharged, and stirring was continued for 6 h during which time the mixture attained room temp. Evaporation of the solvent and flash chromatography of the residue over silica gel (3 × 15 cm), using 1:20 EtOAc-hexanes, gave **18.7** (2.18 g, 92%) as a colorless oil: FTIR ($CDCl_3$, cast) 3070 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.08 (s, 9 H), 1.67 (s, 3 H), 4.06–4.10 (m, 4 H), 5.93–5.94 (m, 1 H), 7.26–7.44 (m, 6 H), 7.66–7.69 (m, 4 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 13.1 (q), 19.3 (t), 26.8 (q), 28.6 (s), 67.7 (t), 119.4 (d), 127.7 (d), 129.7 (d), 133.4 (s), 135.5 (d), 141.4 (s).

(2*E*)-4-[(4-Methoxyphenyl)methoxy]-3-methylbut-2-en-1-yl acetate (18.8).[18]

18.4 **18.8**

p-TsOH (56 mg, 0.326 mmol) was added to a mixture of **18.4** (940 mg, 6.53 mmol) and 4-methoxybenzyl 2,2,2-trichloroacetimidate (2.02 g, 7.18 mmol) in CH_2Cl_2 (10 mL). The resulting mixture was stirred for 13 h, diluted with saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2. The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (3 × 15 cm), using 1:8 EtOAc–hexanes, gave **18.8** (1.43 g, 83%) as a colorless oil.

(2*E*)-4-[(4-Methoxyphenyl)methoxy]-3-methylbut-2-en-1-ol (18.9).[20]

18.8 **18.9**

K_2CO_3 (1.50 g, 10.9 mmol) was added to a stirred solution of **18.8** (1.43 g, 5.44 mmol) in MeOH (12 mL)and stirring was continued for 5 h. The reaction mixture was diluted with saturated aqueous NH_4Cl and extracted with EtOAc. The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2 × 15 cm), using 1:1 EtOAc–hexanes, gave **18.9** (1.06 g, 88%) as a colorless oil: FTIR ($CDCl_3$, cast) 3393 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.70 (s, 3 H), 3.80 (s, 3 H), 3.89 (s, 2 H), 4.20–4.22 (m, 2 H), 4.41 (s, 2 H), 5.67–5.69 (m, 1 H), 6.87 (d, *J* = 7.0 Hz, 2 H), 7.27 (d, *J* = 7.0 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 14.0 (q), 55.3 (q), 59.1 (t), 71.6 (t), 75.1 (t), 113.8 (d), 126.0 (d), 129.3 (d), 130.4 (s), 135.8 (s), 159.2 (s); exact mass (electron ionization) *m*/*z* calcd for $C_{13}H_{18}O_3$ $(M)^+$ 222.1256, found 222.1256.

1-({[(2*E*)-4-Bromo-2-methylbut-2-en-1-yl]oxy}methyl)-4-methoxybenzene (18.10).

18.9 **18.10**

Ph_3P (1.12 g, 4.26 mmol) and CBr_4 (1.41 g, 4.26 mmol) were added to a stirred and cooled (0 °C) solution of **18.9** (0.86 g, 3.87 mmol) in CH_2Cl_2 (15 mL). The ice bath was left in place, but not recharged, and stirring was continued for 3 h during which the mixture attained room temp. Evaporation of the solvent and flash chromatography of the residue over silica gel (2 × 15 cm), using 1:10 EtOAc–hexanes, gave **18.10** (0.94 g, 85%) as a colorless oil: FTIR ($CDCl_3$, cast) 1612 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.75 (s, 3 H), 3.80 (s, 3 H), 3.91 (s, 2 H), 4.02–4.04 (m, 2 H), 4.41 (s, 2 H), 5.81–5.82 (m, 1 H), 6.89 (d, *J* = 7.0 Hz, 2 H), 7.27 (d, *J* = 7.0 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 13.6 (q), 28.1 (t), 55.3 (q), 71.6 (t), 74.4 (t), 113.8 (d),

122.5 (d), 129.4 (d), 130.2 (s), 139.4 (s), 159.2 (s); exact mass (electron ionization) *m*/*z* calcd for $C_{13}H_{17}BrO_2$ $(M)^+$ 286.0391, found 286.0394.

(2*E*)-4-(Methoxymethoxy)-1-methylbut-2-en-1-yl acetate (18.11).[21]

18.4 **18.11**

MOMCl (1.50 mL, 19.1 mmol) and *i*-Pr_2NEt (4.50 mL, 26.04 mmol) were added in that order to a stirred and cooled (0 °C) solution of **18.4** (2.50 g, 17.36 mmol) in CH_2Cl_2 (35 mL). The ice bath was left in place, but not recharged, and stirring was continued overnight during which the mixture attained room temp. The mixture was diluted with saturated aqueous NH_4Cl and extracted with CH_2Cl_2. The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2 × 15 cm), using 1:4 EtOAc–hexanes, gave **18.11**[21] (3.12 g, 96%) as a colorless oil.

(2*E*)-4-(Methoxymethoxy)-3-methylbut-2-en-1-ol (18.12).[21]

18.11 **18.12**

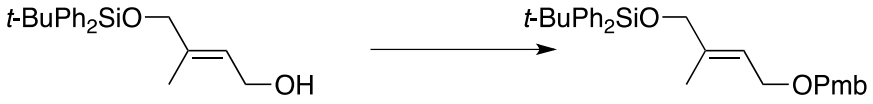
K_2CO_3 (6.90 g, 49.8 mmol) was added to a solution of **18.11** (3.12 g, 16.6 mmol) in MeOH (40 mL) and the mixture was stirred for 5 h at room temp. The reaction mixture was diluted with saturated aqueous NH_4Cl and extracted with EtOAc. The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated to give **18.12**[21] (2.39 g, 99%) as a colorless oil.

{[(2*E*)-4-Bromo-2-methylbut-2-en-1-yl]oxy}(methoxy)methane (18.13).

18.12 **18.13**

$MeSO_2Cl$ (1.50 mL, 19.6 mmol) and Et_3N (3.0 mL, 26.2 mmol) were added to a stirred and cooled (–40 °C) solution of **18.12** (1.91 g, 13.1 mmol) in THF (24 mL). Stirring at –40 °C was continued for 1 h and a solution of LiBr (4.8 g, 39.3 mmol) in THF (24 mL) was then added added.[22] The cold bath was left in place, but not recharged, and stirring was continued overnight, during which the mixture attained room temp. The mixture was diluted with saturated aqueous NH_4Cl and extracted with Et_2O. The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2 × 15 cm), using 1:5 EtOAc–hexanes, gave **18.13** (2.44 g, 89%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.75 (s, 3 H), 3.37 (s, 3 H), 3.98 (s, 2 H), 4.03 (d, *J* = 10.5 Hz, 2 H), 4.63 (s, 2 H), 5.81–5.82 (m, 1 H).

***tert*-Butyl ({[(2*E*)-4-[(methoxyphenyl)methoxy]-2-methylbut-2-en-1-yl]oxy})diphenylsilane (18.14).**



18.6 **18.14**

4-Methoxybenzyl 2,2,2-trichloroacetimidate (729 mg, 2.59 mmol) in CH_2Cl_2 (3 mL) and *p*-TsOH.H_2O (41.6 mg, 0.22 mmol) were added to a stirred and cooled (0 °C) solution of **18.6** (735 mg, 2.16 mmol) in CH_2Cl_2 (6 mL). Stirring was continued for 4.5 h, and the mixture was diluted with water and extracted with CH_2Cl_2. The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (3 x 15 cm), using 1:5 EtOAc-hexanes, gave **18.14** (863 mg, ca 87%) as a colorless oil which contained a minor impurity. The material was used directly for next step.

(2*E*)-4-[(4-Methoxyphenyl)methoxy]-2-methylbut-2-en-1-ol (18.15).[23]

18.14 **18.15**

Bu_4NF (1.0 M in THF, 2.20 mL, 2.20 mmol)) was added to a stirred and cooled solution of **18.14** (863 mg, 1.88 mmol) in THF (10 mL). Stirring was continued for 12 h, and the mixture was diluted with saturated aqueous NH_4Cl and extracted with EtOAc. The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (3 x 15 cm), using 1:1 EtOAc-hexanes, gave **18.15**[23] (363 mg, 76% over two steps) as a colorless oil: FTIR ($CDCl_3$, cast) 3395, 1612 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.44 (br s, 1 H), 1.67 (s, 3 H), 3.80 (s, 3 H), 4.02–4.06 (m, 4 H), 4.45 (s, 2 H), 5.64–5.67 (m, 1 H), 6.88 (d, *J* = 9.0 Hz, 2 H), 7.27 (d, *J* = 9.0 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 13.9 (q), 55.3 (q), 65.9 (t), 68.1 (t), 72.0 (t), 113.8 (d), 121.6 (d), 129.4 (d), 130.4 (s), 139.1 (s), 159.2 (s); exact mass (electrospray) *m*/*z* calcd for $C_{13}H_{18}NaO_3$ $(M + Na)^+$ 245.1148, found 245.1154.

1-({[(2*E*)-4-Bromo-3-methylbut-2-en-1-yl]oxy}methyl)-4-methoxybenzene (18.16).[24]

18.15 **18.16**

Ph_3P (227 mg, 0.866 mmol) and CBr_4 (240 mg, 0.723 mmol) were added to a stirred and cooled solution of **18.15** (160 mg, 0.723 mmol) in CH_2Cl_2 (7 mL). Stirring was continued for 3.5 h and the solvent was then evaporated. Flash chromatography of the residue over silica gel (1.8 x 15 cm), using 1:12 EtOAc-hexanes, gave **18.16**[24] (187 mg, 91%) as a colorless oil: FTIR ($CDCl_3$, cast) 1612 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.78 (s, 3 H), 3.80 (s, 3 H), 3.96 (s, 2 H), 4.02 (d, *J* = 6.5 Hz, 2 H), 4.44 (s, 2 H), 5.78–5.80 (m, 1 H), 6.88 (d, *J* = 7.5 Hz, 2 H), 7.26 (d, *J* = 7.5 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 15.1 (q), 40.2 (t), 55.3 (q), 66.1 (t), 72.1 (t), 113.8

(d), 127.3 (d), 129.4 (d), 130.1 (s), 135.5 (s), 159.3 (s); exact mass (electron ionization) *m*/*z* calcd for $C_{13}H_{17}{}^{81}BrO_2$ $(M)^+$ 286.0391, found 286.0400.

(3-Methoxyphenyl)methanol (13.2).[25]

13.1 **13.2**

Compound **13.2** was made (95%) by the literature method.[25]

(2-Bromo-3-methoxyphenyl)methanol (13.3).[26]

13.2 **13.3**

Compound **13.3** was made (92%) by the literature method.[26]

2-Bromo-1-methoxy-3-[(methoxymethoxy)methyl]benzene (13.4).

13.3 **13.4**

MOMCl (0.31 mL, 4.08 mmol) and *i*-Pr_2NEt (0.70 mL, 4.02 mmol) were added in that order to a stirred and cooled (0 °C) solution of **13.3** (0.439 g, 2.02 mmol) in CH_2Cl_2 (10 mL). The cold bath was left in place but not recharged and stirring was continued overnight during

which the mixture attained room temp. The mixture was diluted with saturated aqueous NH_4Cl and extracted with CH_2Cl_2. The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1 × 15 cm), using 1:7 EtOAc–hexanes, gave **13.4** (0.461 g, 89%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 3.43 (s, 3 H), 3.90 (s, 3 H), 4.69 (s, 2 H), 4.77 (s, 2 H), 6.85 (dd, *J* = 6.8, 2.0 Hz, 1 H), 7.12 (dd, *J* = 6.8, 2.0 Hz, 1 H), 7.28 (t, *J* = 6.8 Hz, 1 H).

1-{2-Methoxy-6-[(methoxymethoxy)methyl]phenylethan-1-ol (13.5).

13.4 **13.5**

n-BuLi (1.82 M in hexane, 1.40 mL, 2.55 mmol) was added dropwise to a stirred and cooled (–78 °C) solution of **13.4** (0.604 g, 2.31 mmol) in THF (10 mL). The mixture was stirred for 80 min at the same temp and then MeCHO (0.4 mL, 7.1 mmol) was added. The cold bath was left in place, but not recharged, and stirring was continued overnight during which the mixture attained room temp. The reaction mixture was diluted with saturated aqueous NH_4Cl and extracted with Et_2O. The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1 × 15 cm), using 1:2 EtOAc–hexanes, gave **13.5** (0.248 g, 48%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.55–1.58 (d, *J* = 7.0 Hz, 3 H), 3.39 (s, 3 H), 3.79 (d, *J* = 11 Hz, 1 H), 3.88 (s, 3 H), 4.55 (d, *J* = 11 Hz, 1 H), 4.65–4.69 (m, 3 H), 5.10–5.13 (m, 1 H), 6.89 (d, *J* = 8.5 Hz, 1 H), 6.94 (d, *J* = 8.5 Hz, 1 H), 7.21 (t, *J* = 8.5 Hz, 1 H).

1-{2-Methoxy-6-[(methoxymethoxy)methyl]phenylethan-1-one (13.6).[9]

13.5 **13.6**

Dess-Martin periodinane (0.563 g, 1.26 mmol) was added to a stirred solution of **13.5** (0.214 g, 0.946 mmol) in CH_2Cl_2 (18 mL) and stirring was continued overnight. The resulting mixture was diluted with aqueous KOH (1 N, 20 mL) and extracted with CH_2Cl_2. The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (0.8 × 15 cm), using 1:3 EtOAc–hexanes, gave **13.6**[9] (0.178 g, 84%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.50 (s, 3 H), 3.36 (s, 3 H), 3.82 (s, 3 H), 4.53 (s, 2 H), 4.61 (s, 2 H), 6.87 (d, *J* = 8.5 Hz, 1 H), 6.98 (d, *J* = 8.5 Hz, 1 H), 7.29 (t, *J* = 8.5 Hz, 1 H).

(2-Iodo-3-methoxyphenyl)methanol (17.1).[26]

13.2 **17.1**

Compound **17.1** was made (52%) by the literature method.[26]

2-Iodo-3-methoxybenzaldehyde (17.2).[27]

17.1 **17.2**

A mixture of PCC (0.259 g, 1.19 mmol) and Celite (0.229 g) was added in three portions over 5 min to a vigorously stirred and cooled (0 °C) solution of **17.1** (0.134 g, 0.507 mmol) in CH_2Cl_2 (5 mL). Vigorous stirring at 0 °C was continued for 1 h, the ice bath was removed and stirring was continued for 2 h. The mixture was filtered through a sintered disc funnel and the

solid was washed with CH_2Cl_2. Evaporation of the filtrate and flash chromatography of the residue over silica gel (0.8 × 15 cm), using 1:4 EtOAc–hexanes, gave **17.2**[27] (0.119 g, 90%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 3.97 (s, 3 H), 7.07 (d, *J* = 7.0 Hz, 1 H), 7.41 (t, *J* = 7.0 Hz, 1 H), 7.52 (d, *J* = 7.0 Hz, 1 H), 10.2 (s, 1 H).

3-Hydroxy-2-iodobenzaldehyde (17.3).[28]

17.2 **17.3**

BBr_3 (1.0 M in CH_2Cl_2, 0.90 mL, 0.90 mmol) was added to a stirred and cooled (–78 °C) solution of **17.2** (0.118 g, 0.45 mmol) in CH_2Cl_2. The cold bath was left in place but not recharged and stirring was continued overnight during which the mixture attained room temp. The reaction mixture was diluted with saturated aqueous NH_4Cl and extracted with Et_2O. The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (0.6 × 15 cm), using 1:4 EtOAc–hexanes, gave **17.3**[28] (80.2 mg, 72%) as a white solid: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.84 (s, 1 H), 7.29 (dd, *J* = 7.0, 1.5 Hz, 1 H), 7.38 (t, *J* = 7.0 Hz, 1 H), 7.48 (dd, *J* = 7.0, 1.5 Hz, 1 H).

2-Iodo-3-(prop-2-en-1-yloxy)benzaldehyde (17.4).[28]

17.3 **17.4**

Compound **17.4** was made (93%) by the literature method.[28]

[2-Iodo-3-(prop-2-en-1-yloxy)phenyl]methanol (17.5).

17.4 **17.5**

$NaBH_4$ (5.2 mg, 0.14 mmol) was added to a stirred solution of **17.4** (63 mg, 0.22 mmol) in THF/water (3:1 v/v, 4 mL). The resulting mixture was stirred for 1 h, diluted with water and extracted with Et_2O. The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated to give **17.5** (57 mg, 91%) as a white solid, which was used directly in the next step: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.03 (t, *J* = 6.5 Hz, 1 H), 4.61-4.62 (m, 2 H), 4.72 (d, *J* = 7.0 Hz, 2 H), 5.30-5.33 (m, 1 H), 5.52–5.56 (m, 1 H), 6.03-6.09 (m, 1 H), 6.76 (d, *J* = 8.5 Hz, 1 H), 7.09 (d, *J* = 8.5 Hz, 1 H), 7.29 (t, *J* = 8.5 Hz, 1 H).

2-Iodo-1-[(methoxymethoxy)methyl]-3-(prop-2-en-1-yloxy)benzene (17.6).

17.5 **17.6**

MOMCl (0.03 mL, 0.39 mmol) and *i*-Pr_2NEt (0.06 mL, 0.34 mmol) were added to a stirred and cooled (0 °C) mixture of **17.5** (46 mg, 0.16 mmol) in CH_2Cl_2 (10 mL). The cold bath was left in place but not recharged and stirring was continued overnight during which the mixture attained room temp. The reaction mixture was diluted with saturated aqueous NH_4Cl and extracted with CH_2Cl_2. The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (0.5 × 15 cm), using 1:7 EtOAc–hexanes, gave **17.6** (47.1 g, 89%) as a colorless oil: FTIR ($CDCl_3$, cast) 3072, 1568 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 3.46 (s, 3 H), 4.64 (dd, *J* = 3.0, 1.5 Hz, 2 H), 4.67 (s, 2

H), 4.80 (s, 2 H), 5.32–5.35 (m, 1 H), 5.44–5.63 (m, 1 H), 6.06–6.12 (m, 1 H), 6.76–6.78 (m, 1 H), 7.11–7.13 (m, 1 H), 7.27–7.28 (m, 1 H), 7.30–7.31 (m, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 55.6 (q), 69.9 (t), 73.7 (t), 90.6 (s), 96.2 (t), 111.5 (d), 117.6 (s), 121.4 (d), 129.0 (d), 132.6 (d), 142.3 (s), 157.0 (s).

2-[(Methoxymethoxy)methyl]-6-(prop-2-en-1-yloxy)benzaldehyde (16.6).

17.6 **16.6**

n-BuLi (2.5 M in hexane, 0.06 mL, 0.15 mmol) was added dropwise to a stirred and cooled (–78 °C) solution of **17.6** (44 mg, 0.13 mmol) in THF (3 mL). Stirring was continued for 80 min. and then DMF (0.20 mL, 2.58 mmol) was added. The cold bath was left in place but not recharged and stirring was continued overnight during which the mixture attained room temp. The reaction mixture was diluted with saturated aqueous NH_4Cl and extracted with Et_2O. The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (0.5 × 15 cm), using 1:5 EtOAc–hexanes, gave **16.6** (26.1 mg, 84%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 3.44 (s, 3 H), 4.63 (dd, *J* = 3.0, 1.5 Hz, 2 H), 4.80 (s, 2 H), 5.01 (s, 2 H), 5.33–5.36 (m, 1 H), 5.44–5.48 (m, 1 H), 6.05–6.12 (m, 1 H), 6.95 (d, *J* = 8.5 Hz, 1 H), 7.35 (d, *J* = 8.5 Hz, 1 H), 10.70 (s, 1 H); exact mass (electrospray) *m*/*z* calcd for $C_{13}H_{16}NaO_4$ $(M + Na)^+$ 259.0941, found 259.0941.

2-Bromo-3-methoxybenzaldehyde (16.1).[29]

13.3 **16.1**

A mixture of PCC (3.45 g, 16.0 mmol) and Celite (3.0 g) was added in three portions over 5 min. to a vigorously stirred and cooled (0 °C) solution of **13.3** (1.51 g, 6.96 mmol) in CH_2Cl_2 (30 mL). Vigorous stirring at 0 °C was continued for 1 h, the ice bath was removed and stirring was continued for 2 h. The mixture was filtered through a sintered disc funnel and the solid was washed with CH_2Cl_2. Evaporation of the filtrate and flash chromatography of the residue over silica gel (2 × 15 cm), using 1:4 EtOAc–hexanes, gave **16.1**[29] (1.36 g, 91%) as a white solid.

2-Bromo-3-hydroxybenzaldehyde (16.2).[30]

16.1 **16.2**

BBr_3 (1.0 M in CH_2Cl_2, 6.5 mL, 6.5 mmol) was added to a stirred and cooled (–78 °C) solution of **16.1** (1.36 g, 6.32 mmol) in CH_2Cl_2 (24 mL). The cold bath was left in place but not recharged and stirring was continued for 3 h during which the mixture reached about –20 °C. The reaction mixture was diluted with saturated aqueous NH_4Cl and extracted with CH_2Cl_2. The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1 × 15 cm), using 1:5 EtOAc–hexanes, gave **16.2** (1.01 g, 79%) as a white solid.

2-Bromo-3-(prop-2-en-1-yloxy)benzaldehyde (16.3).[31]

16.2 **16.3**

K_2CO_3 (1.39 g, 10.1 mmol) was added to a stirred mixture of **16.2** (1.01 g, 5.02 mmol) and allyl bromide (0.85 mL, 10.0 mmol) in DMF (20 mL), and stirring was continued overnight. The mixture was diluted with water and extracted with Et_2O and the combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1 × 15 cm), using 1:4 EtOAc–hexanes, gave **16.3** (1.09 g, 90%) as a white solid.

[2-Bromo-3-(prop-2-en-1-yloxy)phenyl]methanol (16.4).[31]

16.3 **16.4**

$NaBH_4$ (85.1 mg, 2.25 mmol) was added to a stirred solution of **16.3** (1.08 g, 4.48 mmol) in THF/H_2O (9.0 mL, 8:1 v/v) and stirring was continued for 1 h. The mixture was diluted with water and extracted with Et_2O, and the combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1 × 15 cm), using 1:4 EtOAc–hexanes, gave **16.4** (0.947 g, 88%) as a white solid.

2-Bromo-1-[(methoxymethoxy)methyl]-3-(prop-2-en-1-yloxy)benzene (16.5).

16.4 **16.5**

MOMCl (0.25 mL, 3.30 mmol) and *i*-Pr_2NEt (0.57 mL, 3.30 mmol) were added to a stirred and cooled (0 °C) mixture of **16.4** (0.401 g, 1.65 mmol) in CH_2Cl_2 (10 mL). The cold bath was left in place but not recharged and stirring was continued overnight during which the mixture attained room temp. The reaction mixture was diluted with saturated aqueous NH_4Cl and extracted with CH_2Cl_2. The combined organic extracts were washed with brine, dried

($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (0.5 × 15 cm), using 1:7 EtOAc–hexanes, gave **16.5** (0.44, 93%) as a colorless oil.

2-[(Methoxymethoxy)methyl]-6-(prop-2-en-1-yloxy)benzaldehyde (16.6).

16.5 **16.6**

n-BuLi (2.5 M in hexane, 0.74 mL, 1.85 mmol) was added dropwise to a stirred and cooled (–78 °C) solution of **16.5** (0.44 g, 0.13 mmol) in THF (6.0 mL). Stirring was continued for 80 min and then DMF (0.20 mL, 2.58 mmol) was added. The cold bath was left in place but not recharged and stirring was continued overnight during which the mixture attained room temp. The reaction mixture was diluted with saturated aqueous NH_4Cl and extracted with Et_2O. The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (0.5 × 15 cm), using 1:5 EtOAc–hexanes, gave **16.6** (0.14 g, 39%) as a colorless oil, spectroscopically identical to material made from **17.6**.

2-Hydroxy-6-[(methoxymethoxy)methyl]benzaldehyde (20.1).

16.6 **20.1**

$Pd(PPh_3)_4$ (82 mg, 0.071 mmol) was added to a stirred mixture of K_2CO_3 (0.588 g, 4.26 mmol) and **16.6** (0.335 g, 1.42 mmol) in MeOH (6 mL). The mixture was stirred overnight, diluted with 1.0 N hydrochloric acid and extracted with Et_2O. The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2 × 15 cm), using 1:7 EtOAc–hexanes, gave **20.1** (0.178 g, 64%) as a yellow oil:

FTIR ($CDCl_3$, cast) 3048, 2825, 2771, 1647 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 3.40 (s, 3 H), 4.69 (s, 2 H), 4.84 (s, 2 H), 6.90 (d, J = 7.5 Hz, 1 H), 6.96 (d, J = 7.5 Hz, 1 H), 7.45 (t, J = 7.5 Hz, 1 H), 10.36 (s, 1 H), 11.92 (s, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 55.7 (q), 66.2 (t), 95.7 (t), 118.0 (s), 118.7 (d), 121.1 (d), 136.9 (d), 140.8 (s), 163.4 (s), 195.9 (d); exact mass (electrospray) m/z calcd for $C_{10}H_{12}NaO_4$ $(M + Na)^+$ 219.0628, found 219.0628.

5-{[(4-Methoxyphenyl)methoxy]methyl}-2,2-dimethyl-2,4-dihydro-1,3-benzodioxine (23.1).[32]

4.2 **23.1**

Compound **23.1** was made (94%) by the literature method.[32]

2-(Hydroxymethyl)-3-{[(4-methoxyphenyl)methoxy]methyl}phenol (23.2).[32]

23.1 s**23.2**

The product was made (83%) by the literature method.[32]

2-Hydroxy-6-{[(4-methoxyphenyl)methoxy]methyl}benzaldehyde (23.3).[32]

23.2 **23.3**

Compound **23.3** was made (91%) by the literature method.[32]

2-[(*tert*-Butyldimethylsilyl)oxy]-6-{[(4-methoxyphenyl)methoxy]methyl}benzaldehyde (23.4).

23.3 **23.4**

t-$BuMe_2SiCl$ (0.573 g, 3.80 mmol) and Et_3N (1.0 mL, 7.0 mmol) were added to a stirred and cooled (0 °C) mixture of **23.3** (0.942 g, 3.46 mmol) in CH_2Cl_2 (17 mL). The ice bath was left in place, but not recharged, and stirring was continued overnight during which the mixture attained room temp. The reaction mixture was diluted with saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2. The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1 × 15 cm), using 1:8 EtOAc–hexanes, gave **23.4** (1.24 g, 93%) as a colorless oil: FTIR ($CDCl_3$, cast) 2859, 1683 cm^{-1}; ^{13}C NMR ($CDCl_3$, 125 MHz) δ –4.22 (q), 18.3 (s), 25.7 (q), 55.3 (q), 69.6 (t), 72.6 (t), 113.8 (d), 118.4 (d), 119.7 (d), 124.1 (s), 129.2 (d), 130.5 (s), 134.9 (d), 143.2 (s), 159.1 (s), 160.0 (s), 192.3 (d).

2-{[(4-Methoxyphenyl)methoxy]methyl}-6-(prop-2-en-1-yloxy)benzaldehyde (24.3).

23.3 **24.3**

K_2CO_3 (0.335 g, 2.42 mmol) was added to a stirred mixture of **23.3** (0.22 g, 0.809 mmol) and allyl bromide (0.09 mL, 1.0 mmol) in DMF (8 mL). Stirring was continued overnight and the mixture was diluted with water and extracted with Et_2O. The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1 × 15 cm), using 1:4 EtOAc–hexanes, gave **24.3** (0.222 g, 88%) as a thick oil: FTIR ($CDCl_3$, cast) 2869, 2837, 1683 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 3.83 (s, 3 H), 4.61 (s, 2 H), 4.66–4.67 (m, 2 H), 4.96 (m, 2 H), 5.35–5.44 (m, 2 H), 6.02–6.08 (m, 1 H), 6.90–6.92 (m, 3 H), 7.34–7.25 (m, 3 H), 10.7 (s, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 55.3 (q), 69.5 (t), 69.9 (t), 72.6 (t), 111.3 (d), 113.8 (d), 118.0 (s), 119.2 (d), 121.9 (s), 129.2 (d), 130.5 (s), 132.4 (d), 135.0 (d), 143.2 (s), 159.2 (s), 162.0 (s), 191.9 (d); exact mass (electrospray) *m*/*z* calcd for $C_{19}H_{20}O_4$ $(M + Na)^+$ 335.1259, found 335.1254.

2-Hydroxy-2-(2-{[(4-methoxyphenyl)methoxy]methyl}-6-(prop-2-en-1-yloxy)phenyl)-acetonitrile (25.1).

24.3 **25.1**

KCN (7.5 mg, 0.12 mmol) and AcOH (1 drop) were added to a stirred and cooled (0 °C) solution of **24.3** (30 mg, 0.096 mmol) in MeOH (1 mL). Stirring at 0 °C was continued for 10 min and the solvent was then evaporated at room temp. The residue was diluted with saturated aqueous $NaHCO_3$ and extracted with EtOAc. Evaporation of the solvent and flash chromatography of the residue over silica gel (0.5 × 15 cm), using 1:3 EtOAc–hexanes, gave **25.1** (26.1 mg, 80%) as a thick oil: FTIR ($CDCl_3$, cast) 3411 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 3.80 (s, 3 H), 4.67–4.65 (m, 5 H), 5.07 (d, J = 14.5 Hz, 1 H), 5.34 (d, J = 14.5 Hz, 1 H), 5.41–5.46 (m, 2 H), 6.03–6.09 (m, 2 H), 6.88–6.97 (m, 4 H), 7.28–7.32 (m, 3 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 55.3 (q), 56.2 (d), 69.9 (t), 71.0 (t), 72.4 (t), 113.3 (d), 114.0 (d), 118.5 (s), 119.6 (s), 123.4 (d), 124.5 (s), 128.7 (s), 130.0 (d), 130.5 (d), 132.2 (d), 137.3 (s), 156.4 (s), 159.6 (s); exact mass (electrospray) *m*/*z* calcd for $C_{20}H_{21}NNaO_4$ $(M + Na)^+$ 362.1369, found 362.1363.

2-{[(4-Methoxyphenyl)methoxy]methyl}-6-(prop-2-en-1-yloxy)phenyl)benzoyl cyanide (25.2).

25.1 **25.2**

Dess–Martin periodinane (16.9 mg, 0.04 mmol) was added to a stirred mixture of **25.1** (12.3 mg, 0.036 mmol) in CH_2Cl_2 (1 mL). Stirring was continued for 5 min and the mixture was diluted with 30% aqueous $Na_2S_2O_3$ and extracted with CH_2Cl_2. The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (0.5 × 15 cm), using 1:5 EtOAc–hexanes, gave **25.2** (9.3 mg, 76%) as a thick oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 3.81 (s, 3 H), 4.50 (s, 2 H), 4.72 (s, 2 H), 4.73 (t, *J* = 1.5 Hz, 2 H), 5.35–5.44 (m, 2 H), 6.02–6.08 (m, 1 H), 6.89 (d, *J* = 8.5 Hz, 1 H), 6.98–6.99 (m, 1 H), 7.18–7.20 (m, 1 H), 7.27 (t, *J* = 8.5 Hz, 2 H), 7.51 (t, *J* = 8.5 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 55.3 (q), 69.0 (t), 70.4 (t), 72.8 (t), 112.3 (d), 113.9 (d), 114.6 (s), 118.8 (s), 120.6 (d), 122.6 (s), 129.6 (s), 129.6 (d), 131.7 (d), 135.1 (d), 142.4 (s), 159.3 (s), 159.4 (s), 168.0 (s).

2,2-Dimethyl-3-oxobutanoate (12.2).[33]

12.1 **12.2**

This product was made (90%) by the literature method.[33]

5-Ethyl 1-methyl-3-hydroxy-2,3,3-trimethylpentanedioate (12.3).

12.2 **12.3**

Zn powder (1.18 g, 18.06 mmol) and a catalytic amount of I_2 (ca. 13 mg) were added to a stirred solution of **12.2** (1.3013 g, 9.03 mmol) in PhH (10 mL).[34] The mixture was heated to reflux and a solution of $BrCH_2CO_2Et$ (1.30 mL, 11.7 mmol) in PhH (2 mL) was added dropwise over 15 min. The resulting mixture was refluxed and stirred overnight, cooled to room temp, diluted with 1.0 N hydrochloric acid and extracted with Et_2O. The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2 × 15 cm), using 1:5 EtOAc-hexanes, gave **12.3** (1.2687 g, 61%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.22-1.29 (m, 12 H), 2.49 (m, 1 H), 2.68 (m, 1 H), 3.71 (s, 3 H), 4.14-4.19 (m, 3 H).

3-Hydroxy-2,2,3-trimethylpentanedioate (12.4) and 3,4,4-Trimethylpent-2-enedioic acid (12.5).[35]

12.3 **12.4** **12.5**

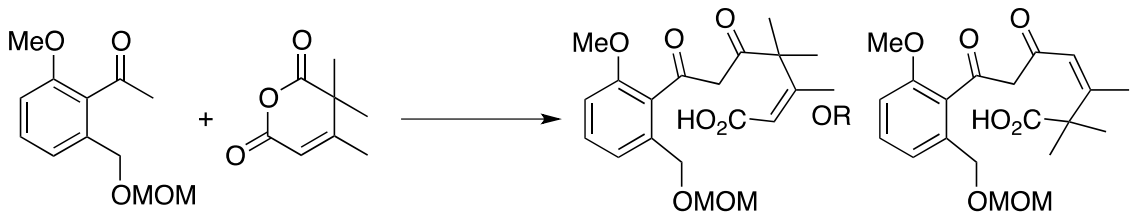
Dilute hydrochloric acid (5%, 5 mL) was added to a stirred solution of **12.3** (0.2241 g, 0.966 mmol) and the mixture was refluxed for 24 h, cooled to room temp and extracted with Et_2O. The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated to give a mixture of **12.4** and **12.5** (0.1207 g, 71%) as a thick oil. As this was a mixture of two compounds, both of which lead to the same product in the next step, the material was used without characterization.

3,3,4-Trimethyl-3,6-dihydro-2*H*-pyran-2,6-dione (11.3).[36]

12.4 **12.5** **11.3**

A solution of **12.4** and **12.5** (0.1032 g, 0.543 mmol) in Ac_2O (6 mL) was refluxed overnight and cooled to room temp. The solvent was removed by vacuum distillation (oil bath at 90 °C, protection from moisture, water pump) and flash chromatography of the residue over silica gel (1 × 15 cm), using 1:3 EtOAc-hexanes, gave **11.3**[36] (83.2 mg, 89%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.51 (s, 6 H), 2.03 (s, 3 H), 5.96 (s, 1 H).

(2*Z*)-7-{2-Methoxy-6-[(methoxymethoxy)methyl]phenyl}-3,4,4-trimethyl-5,7-dioxohept-2-enoic acid (14.1) or (3*Z*)-7-{2-Methoxy-6-[(methoxymethoxy)methyl]phenyl}-2,2,3-trimethyl-5,7-dioxohept-3-enoic acid (14.2).

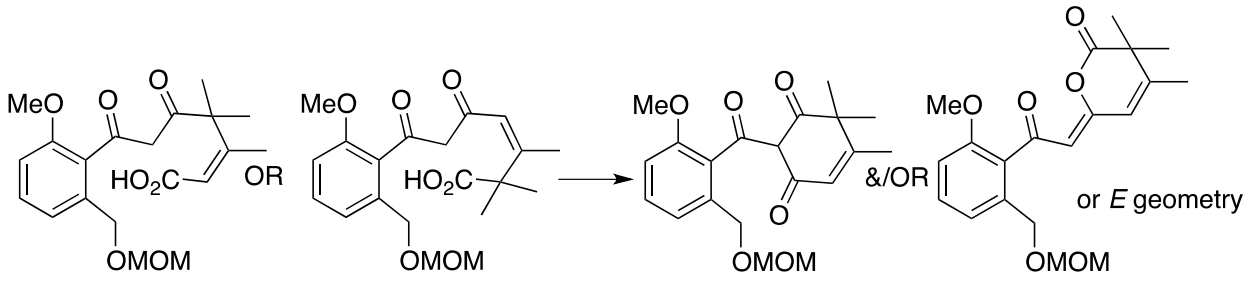


13.6 **11.3** **14.1** **14.2**

n-BuLi (2.50 M in hexanes, 0.77 mL, 1.92 mmol) was added dropwise to a stirred and cooled (–78 °C) solution of *i*-Pr_2NH (0.29 mL, 2.07 mmol) in THF (4.5 mL). Stirring at –78 °C was continued for 30 min and then a solution of **13.6** (0.4289 g, 1.91 mmol) in THF (1.5 mL) was added dropwise. Stirring at –78 °C was continued for 2 h and a solution of **11.3** (0.1341 g, 0.87 mmol) in THF (1 mL) was added. The cold bath was left in place, but not recharged, and stirring was continued overnight during which the mixture attained room temp. The reaction mixture was diluted with saturated aqueous NH_4Cl and extracted with Et_2O. The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2 × 15 cm), using 1:4 EtOAc-hexanes, gave **14.1** or **14.2** (0.1706 g,

52%) as a pale yellow oil. We did not distinguish between the two structures. The material had: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.13 (s, 3 H), 1.25 (s, 3 H), 1.95 (s, 3 H), 3.11 (d, *J* = 17.5 Hz, 1 H), 3.40 (s, 3 H), 3.67 (d, *J* = 17.5 Hz, 1 H), 3.87 (s, 3 H), 4.58–4.73 (m, 4 H), 5.82 (s, 1 H), 6.92 (d, *J* = 7.5 Hz, 1 H), 7.07 (d, *J* = 7.5 Hz, 1 H), 7.39 (t, *J* = 7.5 Hz, 1 H); exact mass (electrospray) *m*/*z* calcd for $C_{20}H_{26}NaO_7$ $(M + Na)^+$ 401.1571, found 401.1561.

2-{2-Methoxy-6-[(methoxymethoxy)methyl]benzoyl}-5,6,6-trimethylcyclohex-4-ene-1,3-dione (14.3) or (6*Z*)- or (6*E*)-6-(2-{2-Methoxy-6-[(methoxymethoxy)methyl]phenyl}-2-oxoethylidene)-3,3,4-trimethyl-3,6-dihydro-2*H*-pyran-2-one (14.4).



14.1 **14.2** **14.3** **14.4**

$(COCl)_2$ (0.02 mL, 0.225 mmol) was added to a stirred solution of **14.1/14.2** (17.2 mg, 0.0455 mmol) in CH_2Cl_2 (2 mL) and stirring was continued for 6 h. Et_3N (0.03 mL, 0.21 mmol) was added and stirring was continued overnight. The reaction mixture was diluted with saturated aqueous NH_4Cl and extracted with CH_2Cl_2. The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. Preparative TLC of the residue (analytical silica gel plate), using 1:2 EtOAc-hexanes, gave **14.3/14.4** (4.8 mg, 30%) as a pale yellow oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.41 (s, 6 H), 2.02 (s, 3 H), 3.38 (s, 3 H), 4.61 (s, 2 H), 4.65 (s, 2 H), 6.10 (s, 1 H), 6.90 (d, J = 7.0 Hz, 1 H), 7.10 (d, J = 7.0 Hz, 1 H), 7.35 (t, J = 7.0 Hz, 1 H), 7.49 (s, 1 H); exact mass (electrospray) *m*/*z* calcd for $C_{20}H_{24}NaO_6$ $(M + Na)^+$ 383.1463, found 383.1465.

Methyl 5-[(*tert*-Butyldiphenylsilyl)oxy]-3-methylpentanoate (30.4).

30.3 **30.4**

Imidazole (69.5 mg, 1.5 mmol) and *t*-$BuPh_2SiCl$ (0.27 mL, 1.07 mmol) were added to a stirred solution of **30.3** (see later for preparation) (0.13 g, 0.89 mmol) in DMF (2 mL) and stirring was continued for 5 h. The reaction mixture was diluted with saturated aqueous NH_4Cl and extracted with Et_2O. The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1 × 15 cm), using 1:10 EtOAc-hexanes, gave **30.4** (0.220 g, 64%) as a colorless oil: FTIR ($CDCl_3$, cast) 3017, 1738 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.93 (d, *J* = 7.0 Hz, 3 H), 1.12 (s, 9 H), 1.44–1.54 (m, 1 H), 1.59–1.62 (m, 1 H), 2.11–2.35 (m, 3 H), 3.68 (s, 3 H), 3.70 (m, 2 H), 7.38–7.42 (m, 6 H), 7.65–7.70 (m, 4 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 19.2 (s), 19.7 (q), 16.8 (q), 27.3 (d), 39.1 (t), 41.5 (t), 61.8 (t), 127.6 (d), 127.7 (d), 133.9 (s), 135.5 (d), 173.5 (s); exact mass (electrospray) *m/z* calcd for $C_{23}H_{32}NaO_3Si$ $(M + Na)^+$ 407.2009, found 407.2013.

5-Methoxy-3-methyl-5-oxopentanoic acid (30.2).[37]

30.1 **30.2**

MeONa (25.3 mg, 0.468 mmol) was added to a stirred solution of **30.1** (3.00 g, 23.4 mmol) in MeOH (30 mL). Stirring was continued for 36 h, the solvent was evaporated and the residue was partitioned between saturated aqueous NH_4Cl and Et_2O. The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated to give **30.2**[37] (3.74 g, 100%) as a colorless oil, which was used directly in the next step: FTIR ($CDCl_3$, cast) 2959 (broad), 1738, 1710 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.06 (d, *J* = 7.0 Hz, 3 H), 2.92–2.44 (m, 5 H), 3.68 (s,

3 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 19.8 (d), 27.1 (q), 40.5 (t), 40.5 (t), 51.5 (q), 172.8 (s), 178.5 (s); exact mass (electrospray) *m/z* calcd for $C_7H_{11}O_4$ $(M - H)^-$ 159.0660, found 159.0663.

Methyl 5-Hydroxy-3-methylpentanoate (30.3).[38]

30.2 **30.3**

A solution of $BH_3.SMe_2$ (2 M in THF, 0.56 mL, 1.12 mmol) was added to a stirred and cooled (–10 °C) solution of **30.2** (0.17 g, 1.06 mmol) in THF (5 mL). The cold bath was left in place, but not recharged, and stirring was continued overnight during which the mixture attained room temp. The mixture was diluted with MeOH. The solvent was evaporated, and the residue was partitioned between saturated aqueous $NaHCO_3$ and Et_2O. The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated to give **30.3**[38] (0.15 g, 99%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.98 (d, J = 7.0 Hz, 3 H), 1.46–1.59 (m, 2 H), 1.84 (br s, 1 H), 2.11–2.35 (m, 3 H), 3.66 (s, 3 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 20.0 (q), 27.0 (d), 39.4 (t), 41.3 (t), 51.5 (q), 60.5 (t), 173.7 (s).

1,3-Dimethyl 2-(3-Methylbut-2-en-1-yl)propanedioate (29.2).[39]

29.1 **29.2**

The product was made (60%) by the literature method.[39]

1,3-Dimethyl 2-(3-Methylbut-2-en-1-yl)-2-(4-oxobutan-2-yl)propanedioate (29.3).

29.2 **29.3**

DBU (31.4 mg, 0.2 mmol) and crotonaldehyde (0.09 mL, 1.1 mmol) were added to a stirred solution of **29.2** (0.20 g, 1.0 mmol) in MeCN (3 mL). Stirring was continued for 2 days and the solvent was evaporated. The residue partitioned between saturated aqueous NH_4Cl and Et_2O. The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. to give **29.3** (0.231 g, 86%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.96 (d, J = 7.0 Hz, 3 H), 1.62 (s, 3 H), 1.71 (s, 3 H), 2.19–2.21 (m, 1 H), 2.68–2.69 (m, 2 H), 2.80–2.86 (m, 2 H), 3.71 (s, 3 H), 3.75 (s, 3 H), 5.01–5.04 (m, 1 H), 9.74 (s, 1 H).

1,3-Dimethyl 2-(4-Hydroxybutan-2-yl)-2-(3-methylbut-2-en-1-yl)propanedioate (29.4).

29.3 **29.4**

$NaBH_4$ (13 mg, 0.344 mmol) was added to a stirred and cooled (0 °C) solution of **29.3** (0.182 g, 0.674 mmol) in MeOH (3 mL) and stirring was continued for 4 h. The reaction mixture was diluted with saturated aqueous NH_4Cl and extracted with Et_2O. The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1 × 15 cm), using 1:1 EtOAc-hexanes, gave **29.4** (0.154 g, 84%) as a colorless oil: FTIR ($CDCl_3$, cast) 3445, 1729 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.93 (d, J = 7.0 Hz, 3 H), 1.19–1.21 (m, 1 H), 1.57 (s, 3 H), 1.65 (s, 3 H), 1.82–1.94 (m, 2 H), 2.21–2.24 (m,

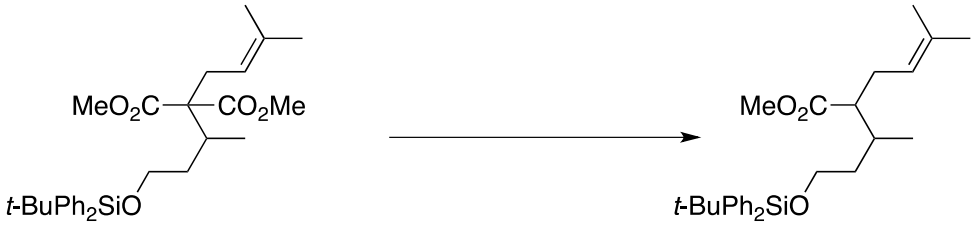
1 H), 2.61 (d, J = 7.5 Hz, 2 H), 3.56–3.72 (m, 8 H), 4.98–5.01 (m, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 15.2 (q), 17.7 (d), 26.0 (q), 32.2 (t), 33.0 (q), 36.3 (t), 51.9 (q), 52.0 (q), 61.2 (t), 62.0 (s), 118.1 (d), 134.9 (s), 171.3 (s), 171.9 (s); exact mass (electrospray) m/z calcd for $C_{13}H_{21}O_4$ $(M + H)^+$ 241.1435, found 241.1434.

1,3-Dimethyl 2-{4-[(*tert*-Butyldiphenylsilyl)oxy]butan-2-yl}-2-(3-methylbut-2-en-1-yl)propanedioate (29.5).

29.4 **29.5**

Imidazole (21 mg, 0.35 mmol) and *t*-$BuPh_2SiCl$ (0.08 mL, 0.319 mmol) were added to a stirred solution of **29.4** (72.3 mg, 0.266 mmol) in DMF (3 mL) and stirring was continued overnight. The reaction mixture was diluted with saturated aqueous NH_4Cl and extracted with Et_2O. The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1 × 15 cm), using 1:9 EtOAc-hexanes, gave **29.5** (0.127 g, 93%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.88 (d, J = 7.0 Hz, 3 H), 1.05 (s, 9 H), 1.09–1.11 (m, 1 H), 1.06 (s, 3 H), 1.67 (s, 3 H), 1.90–1.93 (m, 1 H), 2.30–2.32 (m, 1 H), 2.61 (d, J = 7.0 Hz, 2 H), 3.67–3.69 (m, 7 H), 5.02–5.04 (m, 1 H), 7.37–7.42 (m, 6 H), 7.66–7.68 (m, 4 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 15.2, 17.7, 19.2, 26.0, 26.8, 32.6, 33.6, 35.5, 51.8, 51.9, 62.4, 118.6, 127.6, 129.5, 134.0, 134.5, 135.6, 171.5, 171.6.

Methyl 2-{4-[(*tert*-Butyldiphenylsilyl)oxy]butan-2-yl}-5-methylhex-4-anoate (29.6).



29.5 **29.6**

Water (2 drops) was added to a stirred mixture of **29.5** (73 mg, 0.143 mmol) and NaCl (16.7 mg, 0.286 mmol) in DMSO (1.5 mL).[40] The mixture was heated to 180 °C (oil bath) and stirring was continued for 13 h. The reaction mixture was cooled, diluted with water and extracted with Et_2O. The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1 × 15 cm), using 1:15 EtOAc-hexanes, gave **29.6** (53.7 mg, 83%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.85–0.88 (m, 3 H), 1.05 (s, 9 H), 1.60–2.32 (m, 12 H), 3.63 (s, 3 H), 3.68–3.72 (m, 2 H), 5.00–5.03 (m, 1 H), 7.38–7.40 (m, 6 H), 7.66–7.68 (m, 4 H).

Methyl 2-{4-[(*tert*-Butyldiphenylsilyl)oxy]butan-2-yl}-5-methylhex-4-anoate (29.6).

30.4 **29.6**

n-BuLi (2.50 M in hexanes, 0.75 mL, 1.875 mmol) was added dropwise to a stirred and cooled (–78 °C) solution of *i*-Pr_2NH (0.29 mL, 2.07 mmol) in THF (16 mL). Stirring at –78 °C was continued for 30 min and then a solution of **30.4** (0.600 g, 1.56 mmol) in THF (8 mL) was added dropwise. Stirring at –78 °C was continued for 1 h and a solution of prenyl bromide (0.27 mL, 2.34 mmol) and HMPA (2.0 mL, 11.5 mmol) in THF (1 mL) was added. The cold bath was left in place, but not recharged, and stirring was continued overnight during which the mixture attained room temp. The reaction mixture was diluted with saturated aqueous NH_4Cl and

extracted with Et_2O. The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (3 × 15 cm), using 1:15 EtOAc-hexanes, gave **29.6** (0.643 g, 91%) as a pale yellow oil, spectroscopically identical to material made from **29.5**.

Methyl 2-{4-[(*tert*-Butyldiphenylsilyl)oxy]butan-2-yl}-2-[(2*E*)-4-[(4-methoxyphenyl)-methoxy]-3-methylbut-2-en-1-yl]-5-methylhex-4-enoate (29.7).

29.6 **29.7**

n-BuLi (2.50 M in hexanes, 2.20 mL, 5.50 mmol) was added dropwise to a stirred and cooled (–78 °C) solution of *i*-Pr_2NH (0.85 mL, 6.05 mmol) in THF (50 mL). Stirring at –78 °C was continued for 30 min and then a solution of **29.6** (2.26 g, 5.00 mmol) in THF (8 mL) was added dropwise. Stirring was continued for 6 h and a solution of **18.10** (1.85 g, 6.50 mmol) and HMPA (2.0 mL, 11.5 mmol) in THF (8 mL) was added. The cold bath was left in place, but not recharged, and stirring was continued overnight during which the mixture attained room temp. The reaction mixture was diluted with saturated aqueous NH_4Cl and extracted with Et_2O. The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (3 × 15 cm), using 1:12 EtOAc-hexanes, gave **29.7** (2.66 g, 81%) as a pale yellow oil: FTIR ($CDCl_3$, cast) 3070, 3047, 1726 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.84 (d, J = 7.0 Hz, 3 H), 1.06 (s, 9 H), 1.60 (s, 3 H), 1.68 (s, 6 H), 1.68–2.50 (m, 5 H), 3.65 (s, 3 H), 3.81 (s, 3 H), 3.86 (s, 2 H), 4.35 (s, 2 H), 5.10–5.12 (m, 1 H), 5.38–5.41 (m, 1 H), 6.86–6.89 (m, 2 H), 7.24–7.27 (m, 2 H), 7.38–7.41 (m, 6 H), 7.66–7.68 (m, 4 H); exact mass (electrospray) *m/z* calcd for $C_{33}H_{50}NO_2Si$ $(M + H)^+$ 520.3596, found 520.3605.

Methyl 2-(4-Hydroxybutan-2-yl)-2-[(2*E*)-4-[(4-methoxyphenyl)methoxy]-3-methylbut-2-en-1-yl]-5-methylhex-4-enoate (29.8).

29.7 **29.8**

Bu_4NF (1.0 N in THF, 6.70 mL, 6.70 mmol) was added to a stirred mixture of **29.7** (3.667 g, 5.59 mmol) and AcOH (0.35 mL, 6.15 mmol) in THF (30 mL) and stirring was continued for 24 h. The mixture was diluted with saturated aqueous NH_4Cl and extracted with Et_2O. The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (3 × 15 cm), using 1:3 EtOAc-hexanes, gave **29.8** (1.91 g, 81%) as a pale yellow oil: FTIR ($CDCl_3$, cast) 3432, 1725 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.95 (d, *J* = 7.0 Hz, 3 H), 1.61 (s, 3 H), 1.68–1.70 (m, 6 H), 1.80–2.00 (m, 2 H), 2.16–2.25 (m, 4 H), 3.66–3.68 (m, 1 H), 3.68 (s, 3 H), 3.69–3.71 (m, 1 H), 3.82 (s, 3 H), 3.87 (s, 2 H), 4.37 (s, 2 H), 5.10–5.12 (m, 1 H), 5.39–5.41 (m, 1 H), 6.90 (d, *J* = 7.5 Hz, 2 H), 7.27 (d, *J* = 7.5 Hz, 2 H); exact mass (electrospray) *m*/*z* calcd for $C_{25}H_{38}NaO_5$ $(M + Na)^+$ 441.2607, found 441.2611.

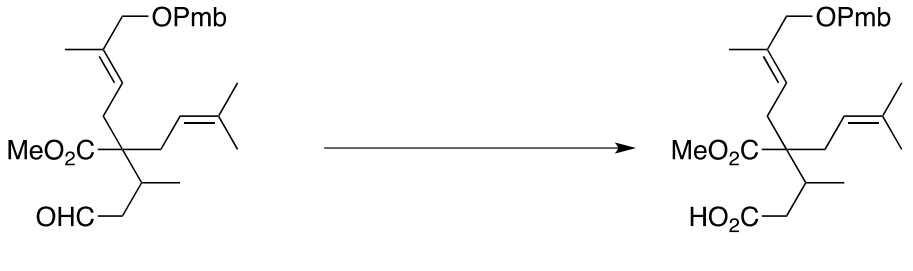
1,5-Dimethyl 2-[(2*E*)-4-[(4-methoxyphenyl)methoxy]-3-methylbut-2-en-1-yl]-3-methyl-2-(3-methylbut-2-en-1-yl)pentanedioate (31.1).

(a) Methyl 2-[(2*E*)-4-[(4-methoxyphenyl)methoxy-3-methylbut-2-en-1-yl]-5-methyl-2-(4-oxobutan-2-yl)hex-4-enoate.

29.8 **-**

DMSO (0.79 mL, 11.2 mmol) was added to a stirred and cooled (–78 °C) solution of $(COCl)_2$ (0.49 mL, 5.61 mmol) in CH_2Cl_2 (20 mL) and stirring was continued for 15 min. A solution of **29.8** (1.556 g, 3.72 mmol) in CH_2Cl_2 (20 mL) was added and stirring at –78 °C was continued for 15 min. Et_3N (3.13 mL, 22.2 mmol) was added mixture and stirring at –78 °C was continued for 1 h. The reaction mixture was diluted with saturated aqueous NH_4Cl and extracted with Et_2O. The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated to give methyl 2-[(2*E*)-4-[(4-methoxyphenyl)methoxy-3-methylbut-2-en-1-yl]-5-methyl-2-(4-oxobutan-2-yl)hex-4-enoate (1.41 g, 91%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.93 (d, *J* = 7.0 Hz, 3 H), 1.59 (s, 3 H), 1.67–1.68 (m, 6 H), 2.20–2.85 (m, 7 H), 3.67 (s, 3 H), 3.79 (s, 3 H), 3.86 (s, 2 H), 4.34 (s, 2 H), 5.00–5.03 (m, 1 H), 5.37–5.41 (m, 1 H), 6.86 (d, *J* = 8.8 Hz, 2 H), 7.27 (d, *J* = 8.8 Hz, 2 H), 9.70 (s, 1 H).

(b) 4-(Methoxycarbonyl)-4-[(2*E*)-4-[(4-methoxyphenyl)methoxy]-3-methylbut-2-en-1-yl]-3,7-dimethyloct-6-enoate.



- **-**

2-Methyl-2-butene (2.0 N in THF, 5.00 mL) and a solution of $NaClO_2$ (0.42 g, 4.64 mmol) and NaH_2PO_4 (0.42 g, 3.50 mmol) in water (12 mL) were added dropwise to a solution of the above aldehyde (0.334 g, 0.938 mmol) in *t*-BuOH (20 mL). Stirring was continued for 10 min,

much of the organic solvent was evaporated and the residue was extracted with Et_2O. The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated to give 4-(methoxycarbonyl)-4-[(2*E*)-4-[(4-methoxyphenyl)methoxy]-3-methylbut-2-en-1-yl]-3,7-dimethyloct-6-enoate (0.332 g, 95%) as a colorless oil, which was used directly in the next step.

(c) 1,5-Dimethyl 2-[(2*E*)-4-[(4-methoxyphenyl)methoxy]-3-methylbut-2-en-1-yl]-3-methyl-2-(3-methylbut-2-en-1-yl)pentanedioate (31.1).

- **31.1**

CH_2N_2 gas was bubbled through a stirred and cooled (0 °C) solution of the above acid (0.332 g, 0.89 mmol) in Et_2O (9 mL). Evaporation of the solvent gave **31.1** (0.256 g, 75%) as a colorless oil: FTIR ($CDCl_3$, cast) 1734 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.96 (d, *J*= 7.0 Hz, 3 H), 1.60–1.61 (m, 3 H), 1.68–1.71 (m, 6 H), 2.08–2.16 (m, 1 H), 2.25–2.50 (m, 6 H), 3.68–3.69 (m, 6 H), 3.82–3.88 (m, 3 H), 3.89 (s, 2 H), 4.37 (d, *J* = 4.0 Hz, 2 H), 5.00–5.10 (m, 1 H), 5.38–5.42 (m, 1 H), 6.99–6.90 (m, 2 H), 7.26–7.28 (m, 2 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 51.6 (q), 51.7 (q), 93.8 (s), 109.8 (d), 115.1 (s), 117.3 (s), 119.8 (d), 120.9 (d), 125.5 (s), 127.5 (s), 135.1 (d), 159.6 (s), 159.7 (s); exact mass (electrospray) *m/z* calcd for $C_{26}H_{38}NaO_6$ $(M + Na)^+$ 469.2561, found 469.2553.

({5-[(2*E*)-4-[(4-Methoxyphenyl)methoxy]-3-methylbut-2-en-1-yl]-4-methyl-5-(3-methylbut-2-en-1-yl)-2-[(trimethylsilyl)oxy]cyclopent-1-en-1-yl}oxy)trimethylsilane (31.2).

31.1 **31.2**

Na (small pieces, 30.8 mg, 1.34 mmol) was added to PhMe (3 mL) and the mixture was refluxed to generate sodium sand, and the mixture was then cooled to room temp. A solution of **31.1** (0.1156 g, 0.259 mmol) and Me_3SiCl (0.17 mL, 1.04 mmol) in PhMe (3 mL) was added to the sodium sand and the resulting mixture was refluxed for 3 h. The reaction mixture was cooled to room temp and filtered under Ar through a sintered disc. The filtrate was evaporated to give **31.2** (0.102 g, 74%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.185 (m, 3 H), 0.94 (d, *J* = 7.0 Hz, 3 H), 1.26 (m, 3 H), 1.59–1.70 (m, 6 H), 1.85–2.24 (m, 7 H), 3.80 (s, 3 H), 3.89 (d, *J* = 2.4 Hz, 2 H), 4.35 (d, *J* = 5.2 Hz, 2 H), 5.18–5.22 (m, 1 H), 5.40–5.58 (m, 1 H), 6.88 (d, *J* = 8.0 Hz, 2 H), 7.24 (d, *J* = 8.0 Hz, 2 H).

2,3-Dihydro-1*H*-indene-1,3-dione (28.2).[41]

28.1 **28.2**

The product was made (40%) by the literature method.[41]

2-(λ^5-Diazynylidene)-1*H*-indene-1,3(2*H*)-dione (28.3).[42]

28.2 **28.3**

The product was made (84%) by the literature method.[42]

3-Hydroxy-2-(λ^5-Diazynylidene)-2,3-dihydro-1*H*-inden-1-one (28.4).[43]

28.3 **28.4**

The product was made (69%) by the literature method.[43]

3-Oxo-2-(λ^5-Diazynylidene)-2,3-dihydro-1*H*-inden-1-yl Acetate (28.5).

28.4 **28.5**

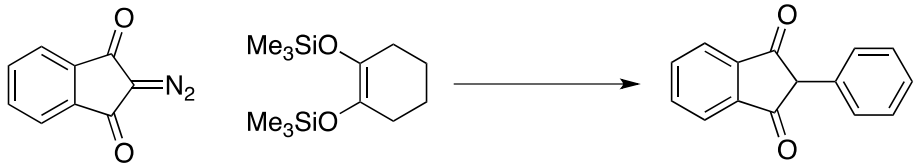
MeCOCl (15.7 mg, 0.20 mmol) and pyridine (0.02 mL, 0.20 mmol) were added to a stirred solution of **28.4** (17.4 mg, 0.10 mmol) in CH_2Cl_2 (1 mL) and stirring was continued for 13 h. The mixture was diluted with saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2. The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated to give **28.5** (20.9 mg, 93%) as a pale yellow oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.20 (s, 3 H), 6.79 (s, 1 H), 7.57–7.59 (m, 2 H), 7.66 (t, J = 7.5 Hz, 1 H), 7.81 (d, J = 7.5 Hz, 1 H).

Trimethyl({2-[(trimethylsilyl)oxy]cyclohex-1-en-1-yl}oxy)silane (32.2).[16]

32.1 **32.2**

The product was made (88%) by the literature method.[16]

2-Phenyl-2,3-dihydro-1*H*-indene-1,3-dione (32.3).[44]



28.3 **32.2** **32.3**

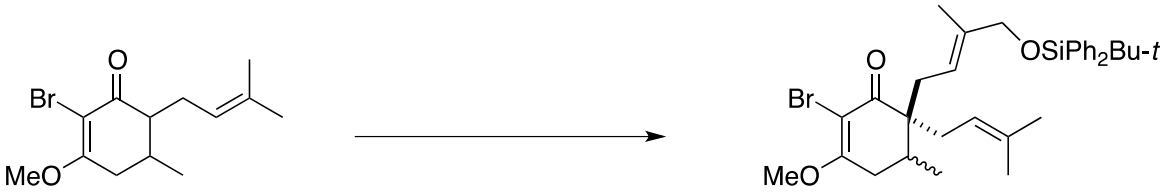
A solution of **28.3** (34.4 mg, 0.20 mmol) in PhH (1 mL) was added over 2 h to a stirred and refluxing solution of **32.2** (516 mg, 2.0 mmol) and $Rh_2(OAc)_4$ (1.3 mg, 0.003 mmol) in PhH (1 mL). Refluxing was continued for 7.5 h. The mixture was evaporated and the residue was partitioned between brine and EtOAc. The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1 × 15 cm), using 1:3 EtOAc-hexane gave **32.3**[44] (2 mg): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 4.25 (s, 1 H), 7.17–7.20 (m, 2 H), 7.30–7.35 (m, 3 H), 7.90 (dd, *J* = 7.0, 4.0 Hz, 2 H), 8.07 (dd, *J* = 7.0, 4.0 Hz, 2 H).

2-Diazo-1-phenylethan-1-one (33.2).[45]

33.1 **33.2**

The product was made (87%) by the literature method.[45]

2-Bromo-6-[(6*E*)-4-[(*tert*-butyldiphenylsilyl)oxy]-3-methylbut-2-en-1-yl]-3-methoxy-5-methyl-6-(3-methylbut-2-en-1-yl)cyclohex-2-en-1-one (35.3).



35.2 **35.3**

n-BuLi (2.50 M in hexanes, 0.07 mL, 0.175 mmol) was added dropwise to a stirred and cooled (–78 °C) solution of *i*-Pr_2NH (0.03 mL, 0.214 mmol) in THF (3 mL). Stirring at –78 °C was continued for 30 min and then a solution of **35.2** (41 mg, 0.143 mmol) in THF (3 mL) was added dropwise. Stirring was continued for 1 h and a solution of **18.7** (75 mg, 0.186 mmol) in THF (3 mL) was added. The cold bath was left in place, but not recharged, and stirring was continued overnight. The reaction mixture was diluted with saturated aqueous NH_4Cl and extracted with Et_2O. The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (0.5 × 15 cm), using 1:10 EtOAc-hexanes, gave **35.3** (35.2 mg, 41%) as a pale yellow oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.03–1.07 (m, 12 H), 1.55–1.67 (m, 9 H), 2.01–2.80 (m, 7 H), 3.85–3.90 (m, 3 H), 4.01–4.03 (m, 2 H), 4.91–5.08 (m, 1 H), 5.22–5.50 (m, 1 H), 7.35–7.40 (m, 6 H), 7.62–7.67 (m, 4 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 13.7 (q), 15.3 (q), 15.6 (q), 17.9 (q), 18.0 (q), 19.3 (s), 26.0 (q), 26.9 (q), 30.0 (t), 30.2 (t), 31.5 (t), 32.3 (t), 32.4 (d), 32.7 (d), 52.2 (t), 55.9 (q), 68.7 (t), 69.1 (t), 102.7 (s), 118.3 (d), 118.7 (d), 119.8 (d), 120.0 (d), 127.6 (d), 127.7 (d), 129.5 (d), 129.6 (d), 133.6 (s), 133.8 (s), 133.9 (s), 134.0 (s), 134.1 (s), 135.5 (d), 136.1 (s), 136.4 (d), 169.5 (s), 169.6 (s), 193.9 (s), 194.3 (s); exact mass *m*/*z* calcd for $C_{34}H_{45}{}^{81}BrNaO_3Si$ 610.23010, found 610.23053.

5-Methylcyclohex-2-en-1-one (19.2).[46]

19.1 **19.2**

A solution of **19.1** (0.98 g, 7.0 mmol) in Et_2O (3 mL) was added to a stirred suspension of $LiAlH_4$ (82.4 mg, 1.96 mmol) in Et_2O (4 mL) and stirring was continued overnight. The mixture was diluted with enough dilute hydrochloric acid (4 M) to adjust the pH to 1, and the solution and extracted with Et_2O. The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2 × 15 cm), using 1:1 Et_2O -hexanes, gave **19.2**[46] (0.61 g, 79%) as a pale yellow oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.07 (d, *J* = 7.0 Hz, 3 H), 1.99–2.08 (m, 2 H), 2.11–2.40 (m, 1 H), 2.42–2.50 (m, 2 H), 5.99–6.02 (m, 1 H), 6.93–6.97 (m, 1 H).

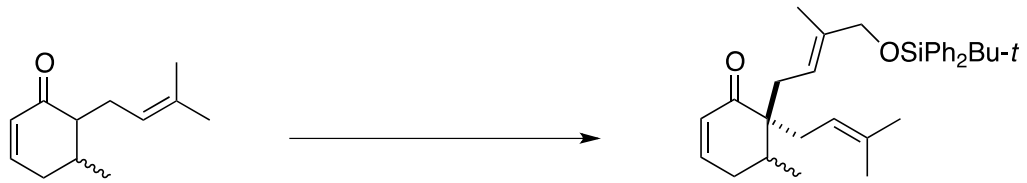
5-Methyl-6-(3-methylbut-2-en-1-yl)cyclohex-2-en-1-one (19.3).

19.2 **19.3**

n-BuLi (2.50 M in hexanes, 2.00 mL, 5.00 mmol) was added dropwise to a stirred and cooled (–78 °C) solution of *i*-Pr_2NH (0.98 mL, 7.01 mmol) in THF (16 mL). Stirring at –78 °C was continued for 30 min and then a solution of **19.2** (0.50 g, 4.55 mmol) in THF (10 mL) was added dropwise. Stirring at –78 °C was continued for 3 h and a solution of **18.2** (1.10 g, 9.10 mmol) and HMPA (0.87 mL, 5.00 mmol) in THF (4 mL) was added. The cold bath was left in place, but not recharged, and stirring was continued overnight. The reaction mixture was diluted with saturated aqueous NH_4Cl and extracted with Et_2O. The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2 × 15 cm), using 1:10 EtOAc-hexanes, gave **19.3** (0.672 g, 83%) as a pale yellow oil: FTIR ($CDCl_3$, cast) 1677 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.04 (d, J = 7.0 Hz, 3 H), 1.58–

1.69 (m, 9 H), 2.04–2.47 (m, 6 H), 5.04–5.07 (m, 1 H), 5.96–5.99 (m, 1 H), 6.82–6.85 (m, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 17.8 (d), 19.7 (q), 25.8 (q), 26.2 (t), 32.3 (q), 32.6 (t), 53.7 (d), 121.2 (d), 129.2 (d), 133.0 (s), 147.8 (d), 201.4 (s); exact mass (electrospray) *m*/*z* calcd for $C_{12}H_{19}O$ $(M + H)^+$ 179.1431, found 179.1430.

6-[(2*E*)-4-[(*tert*-Butyldiphenylsilyl)oxy]-3-methylbut-2-en-1-yl]-6-(3-methylbut-2-en-1-yl)cyclohex-2-en-1-one (19.4).



19.3 **19.4**

n-BuLi (2.50 M in hexanes, 1.70 mL, 4.30 mmol) was added dropwise to a stirred and cooled (–78 °C) solution of *i*-Pr_2NH (0.67 mL, 4.74 mmol) in THF (3 mL). Stirring at –78 °C was continued for 30 min and then a solution of **19.3** (0.511 g, 2.87 mmol) in THF (3 mL) was added dropwise. Stirring at –78 °C was continued for 3 h and a solution of **18.7** (1.86 g, 4.59 mmol) and HMPA (1.00 mL, 5.74 mmol) in THF (3 mL) was added. The cold bath was left in place, but not recharged, and stirring was continued overnight. The reaction mixture was diluted with saturated aqueous NH_4Cl and extracted with Et_2O. The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (3 × 15 cm), using 1:25 EtOAc-hexanes, gave **19.4** (1.02 g, 71%) as a pale yellow oil: FTIR ($CDCl_3$, cast) 3007, 1675 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.97–1.06 (m, 3 H), 1.55–1.68 (m, 9 H), 2.10–2.70 (m, 7 H), 4.01–4.04 (m, 2 H), 4.92–5.05 (m, 1 H), 5.27–5.44 (m, 1 H), 5.90–5.94 (m, 1 H), 6.74–6.78 (m, 1 H), 7.33–7.42 (m, 6 H), 7.64–7.68 (m, 4 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 13.7, 15.2, 17.9, 19.3, 26.0, 26.8, 28.2, 28.7, 31.8, 34.4, 52.3, 69.1, 118.7, 118.9, 127.5, 129.0, 129.5, 133.7, 134.0, 135.5, 136.0, 146.7, 202.8; exact mass (electrospray) *m*/*z* calcd for $C_{33}H_{44}NaO_2Si$ $(M + Na)^+$ 523.2998, found 523.3003.

6-[(2*E*)-4-Hydroxy-3-methylbut-2-en-1-yl]-6-(3-methylbut-2-en-1-yl)cyclohex-2-en-1-one (19.5).

19.4 **19.5**

Bu_4NF (1.0 N in THF, 3.10 mL, 3.10 mmol) was added to a stirred solution of **19.4** (1.28 g, 2.56 mmol) in THF (10 mL) and stirring was continued for 13 h. The mixture was diluted with saturated aqueous NH_4Cl and extracted with Et_2O. The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (3 × 15 cm), using 1:2 EtOAc-hexanes, gave **19.5** (0.577 g, 86%) as a pale yellow oil: FTIR ($CDCl_3$, cast) 3433, 3031, 1667 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.97 (d, J = 7.0 Hz, 3 H), 1.57–1.67 (m, 9 H), 2.09–2.43 (m, 7 H), 3.96 (d, J = 11.5 Hz, 2 H), 4.89–5.00 (m, 1 H), 5.21–5.33 (m, 1 H), 5.90–5.93 (m, 1 H), 6.76–6.79 (m, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 13.8, 15.2, 17.9, 26.0, 28.3, 30.5, 31.8, 34.3, 52.2, 69.0, 119.0, 120.5, 121.9, 129.0, 133.6, 136.9, 147.0, 203.0; exact mass (electrospray) m/z calcd for $C_{17}H_{26}O_2Na$ $(M + Na)^+$ 285.1825, found 285.1825.

6-[(2*E*)-4-Bromo-3-methylbut-2-en-1-yl]-6-(3-methylbut-2-en-1-yl)cyclohex-2-en-1-one (15.6).

19.5 **15.6**

Ph_3P (0.21 g, 0.796 mmol) and CBr_4 (0.265 g, 0.796 mmol) were added to a stirred and cooled (0 °C) solution of **19.5** (0.19 g, 0.725 mmol) in CH_2Cl_2 (3 mL) and stirring was continued

for 1 h. Evaporation of the solvent and flash chromatography of the residue over silica gel (1 × 15 cm), using 1:8 EtOAc-hexanes, gave **15.6** (0.174 g, 74%) as a pale yellow oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.96–0.98 (m, 3 H), 1.56–1.76 (m, 9 H), 2.10–2.27 (m, 7 H), 3.92–3.95 (m, 2 H), 4.90–5.00 (m, 1 H), 5.41–5.56 (m, 1 H), 5.92–5.94 (m, 1 H), 6.77–6.79 (m, 1 H).

2-(Methoxymethoxy)-6-{[(2*E*)-2-methyl-4-[6-methyl-1-(3-methylbut-2-en-1-yl)-2-oxocyclohex-3-en-1-yl]but-2-en-1-yl]oxy}benzaldehyde (15.5).

20.1 **15.6** **15.5**

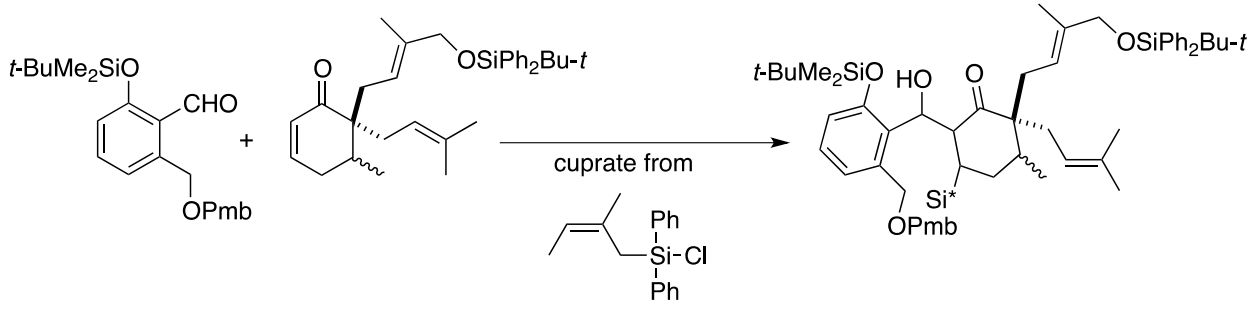
K_2CO_3 (47.1 mg, 0.342 mmol) was added to a stirred solution of **20.1** (24.5 mg, 0.1254 mmol) and **15.6** (35.0 mg, 0.114 mmol) in DMF (2 mL) and stirring was continued for 5 h. The mixture was diluted with water and extracted with Et_2O. The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1 × 15 cm), using 1:8 EtOAc-hexanes, gave **15.5** (37.5 mg, 79%) as a pale yellow oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.97–0.99 (m, 3 H), 1.58–1.76 (m, 9 H), 2.10–2.71 (m, 7 H), 3.41 (s, 3 H), 4.45–4.50 (m, 2 H), 4.78 (s, 2 H), 4.95–5.03 (m, 3 H), 5.40–5.56 (m, 1 H), 5.95–5.99 (m, 1 H), 6.78–6.81 (m, 1 H), 6.85–6.89 (m, 1 H), 7.30–7.34 (m, 1 H), 7.46–7.58 (m, 1 H), 10.62–10.64 (m, 1 H); exact mass (electrospray) *m/z* calcd for $C_{27}H_{36}NaO_5$ $(M + Na)^+$ 463.2454, found 463.2455.

2-{[(2*E*)-2-Methyl-4-[6-methyl-1-(3-methylbut-2-en-1-yl)-2-oxocyclohex-3-en-1-yl]but-2-en-1-yl]oxy}benzaldehyde (22.3).

22.1 **15.6** **22.3**

K_2CO_3 (0.22 g, 1.60 mmol) was added to a stirred solution of **22.1** (78.4 mg, 0.642 mmol) and **15.6** (0.174 g, 0.535 mmol) in DMF (3 mL) and stirring was continued for 13 h. The mixture was diluted with water and extracted with Et_2O. The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1 × 15 cm), using 1:8 EtOAc–hexanes, gave **22.3** (0.17 g, 87%) as a thick oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.94–0.97 (m, 3 H), 1.57–1.75 (m, 9 H), 2.03–2.70 (m, 8 H), 4.47–4.50 (m, 2 H), 4.90–5.00 (m, 1 H), 5.38–5.57 (m, 1 H), 5.91–5.94 (m, 1 H), 6.75–7.00 (m, 3 H), 7.51–7.52 (m, 1 H), 7.81–7.83 (m, 1 H), 10.48–10.50 (m, 1 H).

2-({2-[(*tert*-Butyldimethylsilyl)oxy]-6-{[(4-methoxyphenyl)methoxy]methyl}phenyl}-(hydroxy)methyl)-6-[(2*E*)-4-[(*tert*-butyldiphenylsilyl)oxy]-3-methylbut-2-en-1-yl]-5-methyl-3-{[(2*Z*)-2-methylbut-2-en-1-yl]diphenylsilyl}cyclohexan-1-one (24.2).



23.4 **19.4** **24.1** **24.2**

A solution of **19.4** (105 mg, 0.21 mmol) in THF (2 mL) was added to a stirred and cooled (–78 °C) THF solution (0.166 M, 0.63 mL) of the cuprate derived from **24.1**.[47] Stirring at –78 °C was continued for 1 h. A solution of **23.4** (162 mg, 0.42 mmol) in THF (2 mL) was added dropwise and stirring was continued overnight, during which time the mixture attained room

temperature. The reaction mixture was diluted with saturated aqueous NH_4Cl and extracted with EtOAc. The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1 × 15 cm), using 1:5 EtOAc–hexanes, gave an oil which appeared (high resolution mass) to be a mixture of **23.4**, **19.4** and **24.2**. Exact mass (electrospray) *m*/*z* calcd for **24.2**, $C_{72}H_{94}NaO_6Si_3$ $(M + Na)^+$ 1161.6275, found 1161.6250.

Methyl 4-Methyl-2-oxocyclohexane-1-carboxylate (37.2).[48]

37.1 **37.2**

Compound **37.2** was made (93%) by the literature method.[48]

Methyl 4-Methyl-3-(3-methylbut-2-en-1-yl)-2-oxocyclohexane-1-carboxylate (37.3).

37.2 **37.3**

n-BuLi (2.5 M in hexanes, 2.2 mL, 5.45 mmol) was added dropwise to a stirred and cooled (0 °C) solution of *i*-Pr_2NH (0.77 mL, 5.45 mmol) in THF (10 mL). Stirring at 0 °C was continued for 30 min and then a solution of **37.2** (0.44 g, 2.597 mmol) in THF (10 mL) was added dropwise over 5 min. The mixture was stirred at 0 °C for 1 h and a solution of prenyl bromide (0.33 mL, 2.597 mmol) in THF (3 mL) was added dropwise over 5 min. The cold bath was left in place, but not recharged, and stirring was continued for 1 h. The reaction mixture was diluted with saturated aqueous NH_4Cl and extracted with Et_2O. The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2 × 15 cm), using 1:15 ether–hexanes, gave **37.3** (0.542 g, 88%) as a pale yellow

oil: FTIR ($CDCl_3$, cast) 1750, 1715, 1656 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.95–1.08 (m, 3 H), 1.20–1.30 (m, 1 H), 1.61–1.69 (m, 7 H), 2.00–2.39 (m, 5 H), 3.73–3.75 (m, 3 H), 5.01–5.04 (m, 1 H); exact mass (electrospray) *m/z* calcd for $C_{14}H_{22}NaO_3$ $(M + Na)^+$ 261.1461, found 261.1455. The ^{13}C NMR spectrum was complicated by the presence of both keto and enol forms of diastereoisomers.

Methyl 3-[(2*E*)-4-[(4-Methoxyphenyl)methoxy]-3-methylbut-2-en-1-yl]-4-methyl-3-(3-methylbut-2-en-1-yl)-2-oxocyclohexane-1-carboxylate (37.4).

37.3 **37.4**

A solution of **37.3** (0.119 g, 0.50 mmol) in THF (2 mL) was added to a stirred and cooled (0 °C) suspension of NaH (60% w/w in mineral oil, 22 mg, 0.55 mmol) in THF (2 mL). The mixture was stirred for 15 min and then cooled to –78 °C. *n*-BuLi (2.5 M in hexanes, 0.22 mL, 0.545 mmol) was added and the stirred mixture was warmed to 0 °C over 1 h (by removing pieces of dry ice from the cold bath. A solution of **18.7** (0.171 g, 0.60 mmol) in THF (2 mL) was added at 0 °C, the cold bath was left in place, but not recharged, and stirring was continued overnight during which the mixture attained room temp. The mixture was diluted with saturated aqueous NH_4Cl and extracted with Et_2O. The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1 × 15 cm), using 1:10 EtOAc–hexanes, gave **37.4** (73.1 mg, 33%) as a pale yellow oil: ^1H NMR ($CDCl_3$, 500 MHz) δ 0.99–2.45 (m, 22 H), 3.69 (s, 3 H), 3.76 (s, 3 H), 3.82–3.89 (m, 2 H), 5.00–5.04 (m, 1 H), 5.38–5.41 (m, 1 H), 6.88–6.90 (m, 2 H), 7.25–7.28 (m, 2 H), 12.3 (s, 1 H). The ^{13}C NMR spectrum was complicated by the presence of both keto and enol forms of diastereoisomers.

Methyl 3-[(2*E*)-4-[(4-Methoxyphenyl)methoxy]-3-methylbut-2-en-1-yl]-4-methyl-3-(3-methylbut-2-en-1-yl)-2-(trifluoromethanesulfonyloxy)cyclohex-1-ene-1-carboxylate (37.5).

37.4 **37.5**

A solution of **37.4** (35 mg, 0.079 mmol) in Et_2O (2 mL) was added to a stirred and cooled (0 °C) suspension of NaH (60% w/w in mineral oil, 4.0 mg, 0.103 mmol) in Et_2O (2 mL) and stirring was continued for 30 min. $(CF_3SO_2)_2O$ (0.016 mL, 0.095 mmol) was added and stirring was continued for 1 h.[49] The mixture was diluted with water and extracted with Et_2O. The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated to give **37.5** (39.6 mg, 87%) as a pale yellow oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.945–1.04 (m, 3 H), 1.63–1.70 (m, 9 H), 1.80–2.65 (m, 9 H), 3.69–3.91 (m, 8 H), 4.36–4.39 (m, 2 H), 5.00–5.09 (m, 1 H), 5.38–5.42 (m, 1 H), 6.88–6.90 (m, 2 H), 7.26–7.28 (m, 2 H).

Methyl 3-[(2*E*)-4-[(4-Methoxyphenyl)methoxy]-3-methylbut-2-en-1-yl]-4-methyl-2-oxocyclohexane-1-carboxylate (38.1).

37.2 **38.1**

n-BuLi (2.5 M in hexanes, 0.80 mL, 2.10 mmol) was added dropwise to a stirred and cooled (0 °C) solution of *i*-Pr_2NH (0.30 mL, 2.10 mmol) in THF (2 mL). Stirring at 0 °C was continued for 30 min and then a solution of **37.2** (0.17 g, 1.0 mmol) in THF (2 mL) was added dropwise over 5 min. The mixture was stirred at 0 °C for 1 h and a solution of **18.7** (0.31 g, 1.1

mmol) in THF (2 mL) was added dropwise over 5 min. The cold bath was left in place, but not recharged, and stirring was continued for 2 h. The reaction mixture was diluted with saturated aqueous NH_4Cl and extracted with Et_2O. The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2 × 15 cm), using 1:6 Et_2O–hexanes, gave **38.1** (0.304 g, 81%) as a pale yellow oil: FTIR ($CDCl_3$, cast) 1747, 1654 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.98 (d, *J* = 7.0 Hz, 1 H), 1.68–2.47 (m, 10 H), 3.70 (s, 3 H), 3.74 (s, 3 H), 3.80 (s, 2 H), 4.34 (s, 2 H), 5.37–5.38 (m, 1 H), 6.87 (d, *J* = 7.0 Hz, 2 H), 7.24 (d, *J* = 7.0 Hz, 2 H), 12.3 (s, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 14.7 (q), 19.8 (q), 20.5 (t), 27.5 (t), 28.5 (t), 30.5 (d), 45.8 (d), 51.4 (q), 55.2 (q), 70.8 (t), 75.8 (t), 97.7 (t), 113.7 (q), 125.5 (d), 129.3 (d), 130.6 (s), 133.9 (s), 159.1 (s), 173.1 (s), 173.5 (s); exact mass (electrospray) *m*/*z* calcd for $C_{22}H_{30}NaO_5$ $(M + Na)^+$ 397.1985, found 397.1980.

6-[(2*E*)-4-(Methoxymethoxy)-3-methylbut-2-en-1-yl]-5-methyl-6-(3-methylbut-2-en-1-yl)cyclohex-2-en-1-one (40.1).

19.3 **40.1**

n-BuLi (2.5 M in hexanes, 0.68 mL, 1.70 mmol) was added dropwise to a stirred and cooled (–78 °C) solution of *i*-Pr_2NH (0.26 mL, 1.87 mmol) in THF (2 mL). Stirring at –78 °C was continued for 30 min and then a solution of **19.3** (0.202 g, 1.13 mmol) in THF (2 mL) was added dropwise over 5 min. The mixture was stirred at –78 °C for 3.5 h and a solution of **18.13** (0.355 g, 1.70 mmol) and HMPA (0.39 mL, 2.26 mmol) in THF (2 mL) was added dropwise over 5 min. The cold bath was left in place, but not recharged, and stirring was continued for 2 h. The reaction mixture was diluted with saturated aqueous NH_4Cl and extracted with Et_2O. The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1 × 15 cm), using 1:4 Et_2O–hexanes, gave **40.1** (0.247 g, 71%) as a pale yellow oil: FTIR ($CDCl_3$, cast) 1675 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz)

δ 0.96–0.98 (m, 3 H), 1.58–1.68 (m, 9 H), 2.09–2.62 (m, 7 H), 3.33–3.36 (m, 3 H), 3.88–3.91 (m, 2 H), 4.56–4.59 (m, 2 H), 4.90–5.01 (m, 1 H), 5.21–5.39 (m, 1 H), 5.93–5.96 (m, 1 H), 6.76–6.79 (m, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 14.1 (d), 15.2 (q), 17.9 (q), 26.0 (q), 28.2 (s), 30.4 (t), 31.8 (t), 34.3 (q), 52.1 (t), 52.2 (t), 73.3 (t), 95.1 (t), 118.7 (d), 123.0 (d), 128.9 (d), 133.2 (s), 133.9 (s), 146.7 (d), 202.8 (s); exact mass (electron ionization) *m*/*z* calcd for $C_{19}H_{30}O_3$ $(M)^+$ 306.2194, found 306.2195.

2-[(2*E*)-4-(Methoxymethoxy)-3-methylbut-2-en-1-yl]-3-methyl-2-(3-methylbut-2-en-1-yl)cyclohexan-1-one (40.2).

40.1 **40.2**

L-Selectride (1.0 N in THF, 0.77 mL, 0.77 mmol) was added to a stirred and cooled (–78 °C) solution of **40.1** (0.215 g, 0.703 mmol) in THF (7 mL). Stirring at –78 °C was continued for 1 h. The reaction mixture was diluted with saturated aqueous NH_4Cl and extracted with Et_2O. The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated to give **40.2** (0.210 g, 98%) as a pale yellow oil, which was used directly in the next step: FTIR ($CDCl_3$, cast) 1705 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.94 (d, *J* = 7.0 Hz, 3 H), 1.61–1.63 (m, 3 H), 1.68–1.69 (m, 6 H), 1.70–2.59 (m, 11 H), 3.38 (s, 3 H), 3.92 (s, 2 H), 4.60 (s, 2 H), 4.91–4.96 (m, 1 H), 5.23–5.31 (m, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 14.1 (d), 15.6 (q), 17.9 (q), 24.5 (t), 26.0 (q), 28.7 (t), 29.0 (t), 31.2 (t), 37.8 (q), 55.2 (q), 55.7 (s), 73.5 (t), 95.2 (t), 118.5 (d), 124.8 (d), 133.2 (s), 134.2 (s), 214.7 (s); exact mass (electrospary) *m*/*z* calcd for $C_{19}H_{32}NaO_3$ $(M + Na)^+$ 331.3244, found 331.2248.

Methyl 3-[(2*E*)-4-(Methoxymethoxy)-3-methylbut-2-en-1-yl]-4-methyl-3-(3-methylbut-2-en-1-yl)-2-oxocyclohexane-1-carboxylate (40.3).

40.2 **40.3**

n-BuLi (2.5 M in hexanes, 0.22 mL, 0.55 mmol) was added dropwise to a stirred and cooled (–78 °C) solution of *i*-Pr_2NH (0.09 mL, 0.65 mmol) in THF (3 mL). Stirring at –78 °C was continued for 30 min and then a solution of **40.2** (0.154 g, 0.50 mmol) in THF (3 mL) was added dropwise over 5 min. The mixture was stirred at 0 °C for 2 h and a solution of MeOCOCN (0.05 mL, 0.60 mmol) and HMPA (0.09 mL, 0.05 mmol) in THF (1 mL) was added dropwise over 5 min. The cold bath was left in place, but not recharged, and stirring was continued for 2 h. The reaction mixture was diluted with saturated aqueous NH_4Cl and extracted with Et_2O. The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1 × 15 cm), using 1:4 EtOAc–hexanes, gave **40.3** (0.167 g, 87%) as a pale yellow oil which contains some impurity that makes it unsuitable for the next step: FTIR ($CDCl_3$, cast) 1749, 1709, 1652 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.92–0.93 (m, 3 H), 1.47–1.67 (m, 14 H), 2.26–2.31 (m, 7 H), 3.36–3.39 (m, 3 H), 3.72–3.73 (m, 3 H), 3.90–3.92 (m, 2 H), 4.56–4.58 (m, 2 H), 4.90–5.01 (m, 1 H), 5.21–5.39 (m, 1 H), 12.5 (s, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 14.1 (d), 16.0 (q), 17.8 (q), 22.1 (t), 26.0 (t), 26.7 (q), 33.3 (t), 34.0 (q), 34.7 (t), 46.3 (s), 51.4 (q), 55.2 (q), 73.4 (t), 95.1 (t), 120.6 (d), 125.1 (d), 131.8 (s), 133.4 (s), 173.3 (s), 175.6 (s); exact mass (electrospray) *m/z* calcd for $C_{21}H_{34}NaO_5$ $(M + Na)^+$ 389.2298, found 389.2300.

Methyl 3-[(2*E*)-4-Hydroxy-3-methylbut-2-en-1-yl]-4-methyl-2-oxocyclohexane-1-carboxylate (39.1).

38.1 **39.1**

Water (0.4 mL) and DDQ (0.18 g, 0.80 mmol) were added to a stirred solution of **38.1** (0.148 g, 0.396 mmol) in CH_2Cl_2 (4 mL) and stirring was continued for 4 h. The mixture was diluted with saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2. The solvent was evaporated and the residue was dissolved in MeOH (3 mL) and the solution was stirred and cooled to – 78 °C. $CeCl_3$ (0.38 g, 1.0 mmol) and $NaBH_4$ (28 mg, 0.74 mmol) were added and stirring at –78 °C was continued for 1 h. The mixture was diluted with saturated aqueous NH_4Cl and extracted with Et_2O. The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1 × 15 cm), using 1:15 EtOAc–hexanes, gave **39.1** (0.56 g, 56%) as a pale yellow oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.99–1.16 (m, 3 H), 1.70–2.43 (m, 13 H), 3.73–3.79 (m, 3 H), 4.00–4.02 (m, 2 H), 5.38–5.41 (m, 1 H).

Methyl 3-[(2*E*)-4-[(*tert*-Butyldiphenylsilyl)oxy]-3-methylbut-2-en-1-yl]-4-methyl-2-oxocyclohexane-1-carboxylate (39.2).

39.1 **39.2**

Et_3N (0.10 mL, 0.66 mmol) and *t*-$BuPh_2SiCl$ were added to a stirred solution of **39.1** (56 mg, 0.22 mmol) in CH_2Cl_2 (3 mL). The mixture was stirred for 4 h, diluted with saturated aqueous NH_4Cl and extracted with CH_2Cl_2. The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1 × 15 cm), using 1:8 EtOAc–hexanes, gave **39.2** (88 mg, 81%) as a pale yellow oil as a mixture of keto and enol diastereoisomers.: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.81–1.11 (m, 9 H), 1.47–1.76 (m, 6 H), 2.03–2.81 (m, 3 H), 3.57–3.83 (m, 3 H), 4.04–4.09 (m, 2 H), 5.35–5.48 (m, 1 H), 7.37–7.46 (m, 6 H), 7.70–7.72 (m, 4 H).

References

1 Kamigakinai, T.; Nakashima, M.; Tani, H. Japanese patent JP 10101666 A2, 1998

2 Urata, H.; Kinoshita, A.; Misono, K. S.; Bumpus, F. M.; Husain, A. *J. Biol. Chem.* **1990**, *265*, 22348–22357.

3 Wilson, K. E.; Tsou, N. N.; Guan, Z.; Ruby, C. L.; Pelaez, F.; Gorrochategui, J.; Vicente, F.; Onishi, H. R. *Tetrahedron Lett.* **2000**, *41*, 8705–8709.

4 Kamigaichi, T.; Nakashima, M.; Tani, H. Japanese patent JP 11158109 A2, 1999.

5 Nicoalou, K. C.; Montagnon, T.; Vassilikiannakis, G.; Mathison, C. J. N. *J. Am. Chem. Soc.* **2005**, *127*, 8872–8888.

6 Nicolaou, K. C.; Montagnon, T.; Vassilikogiannakis, G. *Chem. Commun.* **2002**, 2478–2479.

7 Tang, Q.; Sen, S. E. *Tetrahedron Lett.* **1998**, *39*, 2249–2252.

8 Suzuki, M.; Sugiyama, T.; Watanabe, M.; Murayama, T.; Yamashita, K. *Agric. Biol. Chem.* **1987**, *51*, 1121–1127

9 Coutts, S. J.; Wallace, T. W. *Tetrahedron* **1994**, *50*, 11755–11780.

10 Kann, N.; Rein, T.; Akermark, B.; Helquist, P. *J. Org. Chem.* **1990**, *55*, 5312–5323.

11 Mechelke, M. F.; Wiemer, D. F. *J. Org. Chem.* **1999**, *64*, 4821–4829.

12 Basavaiah, D.; Veeraraghavaiah, G. *Chem. Soc. Rev.* **2012**, *41*, 68–78.

13 Bugarin, A.; Conell, B. T. *J. Org. Chem.* **2009**, *74*, 4638–4641.

14 (a) Fleming, I.; Winter, S. B. D. *J. Chem. Soc., Perkin Trans 1*, **1998**, 2687–2700. (b) Ojima, I; Kumagai, M. *J. Organometal. Chem.*, **1978**, *157*, 359–372.

15 Wang, X.; Butler, S. C.; Gallucci, J. C.; Paquette, L. A. *J. Org. Chem.* **2009**, *74*, 6825–6830.

16 Matzeit, A.; Schäfer, H. J.; Amatore, C. *Synthesis* **1995**, 1432–1444.

17 Chow, S. Y.; Williams, H. J.; Huang, Q.; Nanda, S.; Scott, A. I. *J. Org. Chem.* 2005, *70*, 9997–10003.

18 Shao, W.; Clive, D. L. J. *J. Org. Chem.* **2015**, *80*, 3211–3216.

19 Serra, S. *Tetrahedron: Asymmetry* **2014**, *25*, 1561–1572.

20 Raghavan, S.; Sreekanth, T. *Tetrahedron Lett.* **2008**, *49*, 1169–1174.

21 Pichlmair, S.; de Lera Ruiz, M.; Vilotijevic, I.; Paquette, L. A. *Tetrahedron* **2006**, *62*, 5791–5802.

22 Cf. Martínez, M. M.; Hoppe, D. *Eur. J. Org. Chem.* **2015**, 1427–1443.

23 Nanda, S.; Scott, A. I. *Tetrahedron: Asymmetry* **2004**, *15*, 963–970.

24 This compound has previously been generated in situ. See reference 23.

25 Parihar, S.; Kumar, A.; Chaturvedi, A. K.; Sachan, N. K.; Luqman, S.; Changkija, B.; Manohar, M.; Prakash, O.; Chanda, D.; Khan, F.; Chanotiya, C. S.; Shankar, K.; Dwivedi, A.; Konwar, R.; Negi, A. S. *J. Steroid Biochem. Mol. Biol.* **2013**, *137*, 332–344.

26 Neufeind, S.; Hülsken, N.; Neudörfl, J.-M.; Schlörer, N.; Schmaltz, H.-G. *Chem. Eur. J.* **2011**, *17*, 2633–2641.

27 Fan, Y. C.; Kwon, O. *Org. Lett.* **2015**, *17*, 2058–2061.

28 Zhao, J.; Bane, S.; Snyder, J. P.; Hu, H.; Mukherjee, K.; Slebodnick, C.; Kingston, D. G. I. *Bioorg. Med. Chem.* **2011**, *19*, 7664–7678.

29 (a) Fischer, F. R.; Nuckolls, C. *Angew. Chem. Int. Ed.* **2010**, *49*, 7257–7260. (b) Myers, A. I.; Nelson, T. D.; Moorlag, H.; Rawson, D. J. Meier, A. *Tetrahedron* **2004**, *60*, 4459–4473.

30 (a) van Otterlo, W. S. L.; Michael, J. P.; Fernandes, M. A.; de Konig, C. B. *Tetrahedron Lett.* **2004**, *45*, 5091–5094. (b) Stavrakov, G.; Keller, M.; Breit, B. *Eur. J. Org. Chem.* **2007**, 5726–5733.

31 Yuen, T.-Y.; Yang, S.-H.; Brimble, M. A. *Angew. Chem., Int. Ed.* **2011**, *50*, 8350–8353.

32 (a) Fouche, M.; Masse, F.; Roth, H.-J. *Org. Lett.* **2015**, *17*, 4936–4939. (b) Nomiya, M.; Murakami, T.; Takada, N.; Okuno, T.; Harada, Y.; Hashimoto, M. *J. Org. Chem.* **2008**, *73*, 5039–5047.

33 van Goor, F. F.; Burton, W. L. US 2011/98311 A1, 2011.

34 Cf. Inagaki, H.; Miyauchi, S.; Miyauchi, R. N.; Kawato, H. C.; Ohki, H.; Matsuhashi, N.; Kawakami, K.; Takahashi, H.; Takemura, M. *J. Med. Chem.* **2003**, *46*, 1005–1015.

35 (a) Perkin, W. H., jun.; Thorpe, J. F. *J. Chem. Soc., Trans.* **1897**, *71*, 1177–1194, especially p. 1177. (b) Perkin, W.H., jun.; Thorpe, J. F. *J. Chem. Soc., Trans.* **1899**, *75*, 63–66.

36 Packer, J.; Sargent, J. D. *J. Chem. Soc.* **1933**, 556–557.

37 Nakayama, Y.; Kumar, G. B.; Kobyashi, Y. *J. Org. Chem.* **2000**, *65*, 707–715.

38 Barba, O. *et al.* WO2010/103334 A1, 2010

39 Millán, A.; de Cienfuegos, A.; Miguel, D.; Campaña, A. G.; Cueva, J. M. *Org. Lett.* **2012**, *14*, 5984–5987.

40 Lautens, M; Hughes, G.; Zunic, V. *Can. J. Chem.* **2000**, *78*, 868–883.

41 Padmanabhan, P. V; Ramana, D. V.; Ramadasa, S. R. *Indian J. Chem. Section B* **1983**, *22*, 1–4.

42 Lee, J. C.; Yuk, J. Y. *Synth. Commun.* **1995**, *25*, 1511–1515.

43 Severin, T.; Lerche, H. *Chem. Ber.* **1970**, *103*, 2148–2151.

44 Rosenfeld, M. J.; Shankar, B. K. R.; Schechter, H. *J. Org. Chem.* **1988**, *53*, 2699–2705.

45 Newman, M. S.; Beal, III, P. *J. Am. Chem. Soc.* **1949**, *71*, 1506–1507.

46 (a) Musser, A. K.; Fuchs, P. L. *J. Org. Chem.* **1982**, *47*, 3121–3131. (b) Watson, I. D. G.; Yudin, A. K. *J. Am. Chem. Soc.* **2005**, *127*, 17516–17529.

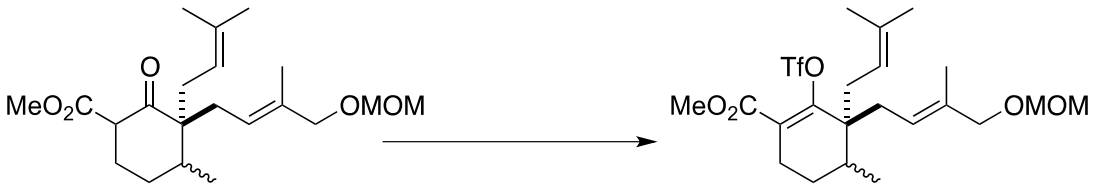
47 Yu, G.; Clive, D. L. J. *Org. Biomol. Chem.* **2016**, *17*, 1653–1664.

48 Oishi, S.; Nelson, S. D. *J. Org. Chem.* **1992**, *57*, 2744–2747.

49 Cf. Jasperse, C. P.; Curran, D. P. *J. Am. Chem. Soc.* **1990**, *112*, 5601–5609.

Experimental work done between submission of the Thesis and the defense

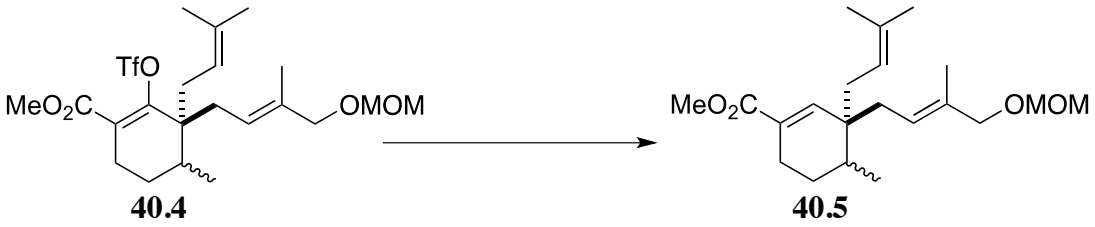
Methyl 3-[(2*E*)-4-(Methoxymethoxy)-3-methylbut-2-en-1-yl]-4-methyl-3-(3-methylbut-2-en-1-yl)-2-(trifluoromethanesulfonyloxy)cyclohex-1-ene-1-carboxylate (40.3).



40.3 **40.4**

A solution of **40.3** (100 mg, 0.273 mmol) was added to a stirred and cooled (0 °C) slurry of NaH (60% w/w in oil, 32.8 mg, 0.82 mmol) in Et_2O (2 mL). Stirring at 0 °C was continued for 30 min and $(CF_3SO_2)_2O$ (0.06 mL, 0.357 mmol) was added. The mixture stirred for 30 min at 0 °C, the ice bath was removed and stirring was continued for 30 min. The mixture was diluted with water and extracted with EtOAc. The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (0.8 × 15 cm), using 1:7 EtOAc-hexanes, gave **40.4** (0.129 g, 95%) as a colorless oil: FTIR ($CDCl_3$, cast) 1762, 1734 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.95 (d, J = 7.0 Hz, 3 H), 1.56–1.70 (m, 12 H), 2.25–2.61 (m, 6 H), 3.36 (s, 3 H), 3.77 (s, 3 H), 3.93 (s, 2 H), 4.59 (s, 2 H), 4.98–5.16 (m, 1 H), 5.38–5.43 (m, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 14.2 (q), 15.7 (q), 17.9 (q), 25.6 (t), 25.9 (q), 26.0 (t), 34.8 (t), 35.2 (d), 44.3 (s), 46.4 (t), 52.3 (q), 55.2 (q), 73.1 (t), 95.3 (t), 120.6 (d), 122.7 (d), 126.0 (s), 132.3 (s), 135.0 (s), 152.6 (s), 166.2 (s); exact mass (electrospray) m/z calcd for $C_{22}H_{33}F_3NaO_7$ $(M + Na)^+$ 521.1791, found 521.1785.

Methyl 3-[(2*E*)-4-(Methoxymethoxy)-3-methylbut-2-en-1-yl]-4-methyl-3-(3-methylbut-2-en-1-yl)cyclohex-1-ene-1-carboxylate (40.5).



40.4 **40.5**

$Pd(OAc)_2$ (3.1 mg, 0.014 mmol), Ph_3P (7.1 mg, 0.028 mmol) and Et_3N (0.12 mL, 0.813 mmol) were added to a stirred solution of **40.4** (135 mg, 0.271 mmol) in THF (6 mL). The mixture was stirred for 15 min and then HCO_2H (0.021 mL, 0.542 mmol) was added. The mixture heated at 65 °C for 6 h and then cooled to room temperature. The solvent was evaporated and the residue was partitioned between water and CH_2Cl_2. The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (0.8 × 15 cm), using 1:7 EtOAc-hexanes, gave **40.5** (97.2 mg, 98%) as a colorless oil: FTIR ($CDCl_3$, cast) 1715 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.67–0.96 (m, 6 H), 1.57–1.71 (m, 9 H), 2.01–2.25 (m, 6 H), 3.37 (s, 3 H), 3.74 (s, 3 H), 3.90–3.96 (m, 2 H), 4.57–4.62 (m, 2 H), 5.15–5.31 (m, 2 H), 6.68 (s, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 14.2 (q), 21.7 (t), 22.6 (q), 25.8 (t), 26.7 (q), 33.3 (q), 33.9 (s), 34.3 (d), 42.6 (t), 44.6 (t), 51.5 (q), 55.0 (q), 73.3 (t), 95.3 (t), 124.1 (d), 129.1 (s), 133.6 (s), 137.7 (d), 144.3 (d), 160.4 (s), 168.0 (s).

Methyl 3-[(2*E*)-4-Hydroxy-3-methylbut-2-en-1-yl]-4-methyl-3-(3-methylbut-2-en-1-yl)cyclohex-1-ene-1-carboxylate (41.1).

40.5 **41.1**

PPTS (309 mg, 1.23 mmol) was added to a stirred solution of **40.5** (90.2 mg, 0.246 mmol) in *t*-BuOH (5 mL) and the mixture was stirred for 30 min and then refluxed for 9 h, cooled to room temperature and diluted with Et_2O. The mixture was washed with brine and the organic layer was dried over $MgSO_4$. Flash chromatography of the residue over silica gel (0.8 × 15 cm),

using 1:7 EtOAc-hexanes, gave **41.1** (64.2 mg, 81%) as a colorless oil: FTIR ($CDCl_3$, cast) 3440, 1715 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.90 (d, *J* = 7.0 Hz, 3 H), 0.95–0.97 (m, 2 H), 1.40–1.56 (m, 1 H), 1.64–1.71 (m, 9 H), 2.00–2.58 (m, 6 H), 3.73 (s, 3 H), 3.97 (s, 2 H), 5.18–5.22 (m, 2 H), 6.73 (s, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 13.9 (q), 15.4 (q), 17.9 (q), 23.9 (t), 26.0 (q), 26.7 (q), 33.4 (d), 34.0 (t), 35.3 (s), 42.6 (t), 51.5 (q), 69.1 (t), 120.1 (d), 122.5 (d), 129.6 (s), 133.5 (s), 136.8 (s), 147.3 (d), 168.0 (s); exact mass (electrospray) *m/z* calcd for $C_{19}H_{30}NaO_3$ $(M + Na)^+$ 329.2087, found 329.2086.

Methyl 3-[(2*E*)-4-Bromo-3-methylbut-2-en-1-yl]-4-methyl-3-(3-methylbut-2-en-1-yl)cyclohex-1-ene-1-carboxylate (41.2).

41.1 **41.2**

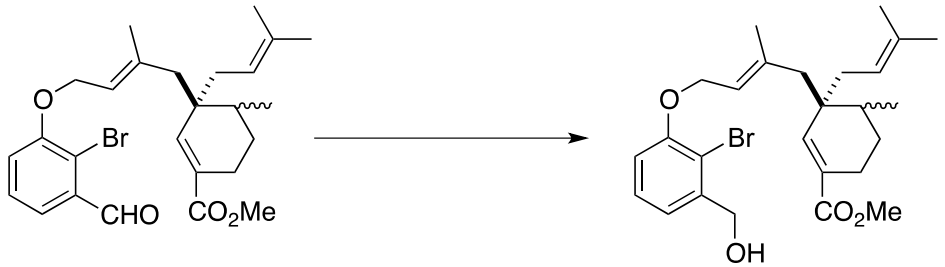
Ph_3P (61 mg, 0.23 mmol) and CBr_4 (77 mg, 0.23 mmol) were added to a stirred and cooled (0 °C) solution of **41.1** (62.2 mg, 0.193 mmol) in CH_2Cl_2 (4 mL). The ice bath was left in place, but not recharged, and stirring was continued for 6 h during which time the mixture attained room temp. Evaporation of the solvent and flash chromatography of the residue over silica gel (0.5 × 15 cm), using 1:12 EtOAc-hexanes, gave **41.2** (64 mg, 86%) as a colorless oil: FTIR ($CDCl_3$, cast) 1715 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.90 (d, *J* = 7.0 Hz, 3 H), 0.94–0.97 (m, 2 H), 1.58–1.76 (m, 10 H), 1.98–2.36 (m, 6 H), 3.75 (s, 3 H), 3.94 (s, 2 H), 5.12–5.41 (m, 2 H), 6.72 (s, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 14.9 (q), 15.0 (q), 15.9 (q), 23.9 (t), 26.0 (q), 26.7 (t), 33.6 (t), 34.0 (d), 36.0 (s), 41.6 (t), 45.1 (t), 51.6 (q), 119.8 (d), 127.3 (d), 129.9 (s), 133.7 (s), 134.2 (s), 146.8 (d), 167.9 (s); exact mass (electrospray) *m/z* calcd for $C_{19}H_{29}BrNaO_2$ $(M + Na)^+$ 391.1243, found 391.1245.

Methyl 3-[(2*E*)-4-(2-Bromo-3-formylphenoxy)-3-methylbut-2-en-1-yl]-4-methyl-3-(3-methylbut-2-en-1-yl)cyclohex-1-ene-1-carboxylate (41.3).

41.2 **41.3**

K_2CO_3 (23 mg, 0.166 mmol) and **16.2** (27 mg, 0.134 mmol) were added to a stirred solution of **41.2** (41.4 mg, 0.112 mmol) in DMF (3 mL). Stirring was continued overnight and the mixture was diluted with water and extracted with EtOAc. The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (0.5 × 8 cm), using 1:7 EtOAc-hexanes, gave **41.3** (47.7 mg, 87%) as a colorless oil: FTIR ($CDCl_3$, cast) 2864, 1713, 1694 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.83–0.96 (m, 6 H), 1.45–1.76 (m, 9 H), 2.02–2.35 (m, 6 H), 3.73 (s, 3 H), 4.50–4.54 (m, 2 H), 5.16–5.43 (m, 2 H), 6.72 (s, 1 H), 7.05–7.11 (m, 1 H), 7.28–7.34 (m, 1 H), 7.50 (d, *J* = 8.0 Hz, 1 H), 10.43 (s, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 14.0 (q), 14.1 (q), 15.9 (q), 24.0 (t), 26.6 (q), 26.7 (t), 33.5 (d), 34.0 (t), 35.3 (s), 42.7 (t), 51.5 (q), 76.7 (t), 117.8 (s), 118.7 (d), 121.4 (d), 125.9 (d), 128.0 (d), 129.2 (s), 130.4 (s), 133.7 (s), 137.8 (s), 140.3 (d), 147.1 (d), 167.9 (s), 168.0 (s), 192.3 (d); exact mass (electrospray) *m*/*z* calcd for $C_{26}H_{33}BrNaO_4$ $(M + Na)^+$ 511.1454, found 511.1461.

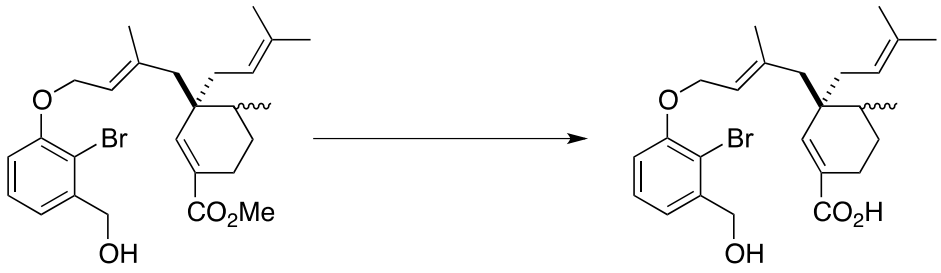
Methyl 3-[(2*E*)-4-[2-Bromo-3-(hydroxymethyl)phenoxy]-2-methylbut-2-en-1-yl]-4-methyl-3-(3-methylbut-2-en-1-yl)cyclohex-1-ene-1-carboxylate (41.4).



41.3 **41.4**

$NaBH_4$ (2 mg, 0.053 mmol) was added to a stirred and cooled (0 °C) solution of **41.3** (40 mg, 0.079 mmol). After 10 min, the solvent was evaporated and the residue was partitioned between water and EtOAc. The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated to give **41.4** (36.9 mg, 92%) as a colorless oil: FTIR ($CDCl_3$, cast) 3422, 1714 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.82–0.96 (m, 6 H), 1.57–1.74 (m, 9 H), 1.93–2.40 (m, 7 H), 3.41 (s, 1 H), 3.73 (s, 3 H), 4.46–4.50 (m, 2 H), 4.74–4.76 (m, 2 H), 5.15–5.38 (m, 2 H), 6.60–6.81 (m, 2 H), 7.06–7.08 (m, 1 H), 7.21–7.26 (m, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 13.9 (q), 14.7 (q), 17.9 (q), 24.0 (q), 24.7 (t), 31.5 (d), 33.3 (t), 35.2 (t), 42.8 (t), 45.0 (s), 51.6 (q), 65.3 (t), 74.6 (t), 112.5 (s), 112.7 (d), 120.0 (d), 120.8 (d), 124.7 (d), 127.8 (d), 129.3 (s), 130.3 (s), 132.2 (s), 140.1 (s), 145.1 (d), 154.8 (s), 168.0 (s); exact mass (electrospray) *m*/*z* calcd for $C_{26}H_{35}BrNaO_4$ $(M + Na)^+$ 513.1611, found 513.1612.

3-[(2*E*)-4-[2-Bromo-3-(hydroxymethyl)phenoxy]-2-methylbut-2-en-1-yl]-4-methyl-3-(3-methylbut-2-en-1-yl)cyclohex-1-ene-1-carboxylic acid (41.5).



41.4 **41.5**

LiOH (2.2 mg, 0.091 mmol) was added to a stirred solution of **41.4** (5.8 mg, 0.0118 mmol) in MeOH (0.9 mL) and water (0.3 mL). Stirring was continued for 24 h and the solvent was evaporated. The residue was partitioned between hydrochloric solution (1 N) and Et_2O. The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated to give **41.5** (3.8 mg, 67%) as a colorless oil: FTIR ($CDCl_3$, cast) 3353, 1688 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.82–0.95 (m, 3 H), 1.26 (s, 2 H), 1.57–1.71 (m, 9 H), 1.91–2.36 (m, 7 H), 2.63 (s, 1 H), 4.50 (d, *J* = 18.5 Hz, 2 H), 4.74–4.77 (m, 2 H), 5.13–5.15 (m, 1 H), 5.35–5.62 (m, 1 H), 6.75 (d, *J* = 8.5 Hz, 1 H), 6.79 (s, 1 H), 7.04–7.08 (m, 1 H), 7.18–7.23 (m, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 13.9 (q), 17.9 (q), 23.7 (s), 26.0 (q), 26.6 (t), 29.2 (q), 31.7 (d), 33.3 (t), 43.1 (t), 53.8 (t),

69.6 (t), 74.2 (t), 112.5 (s), 112.7 (d), 112.9 (d), 120.1 (d), 120.9 (d), 124.4 (d), 127.9 (d), 132.0 (s), 133.8 (s), 133.9 (s), 154.7 (s), 210.8 (s); exact mass (electrospray) *m*/*z* calcd for $C_{25}H_{32}BrNaO_4$ $(M - H)^-$ 475.1489, found 475.1484.