A General Route to *meta*-(Arylsulfanyl) and *meta*-(Alkylsulfanyl) Substituted Phenols and Synthetic Studies on Sorbicillactones A and B

by

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ABSTRACT

Chapter 1 describes a general route for making *meta*-(arylsulfanyl) and *meta*-(alkylsulfanyl) phenols using DBU assisted aromatization developed in this laboratory. This method is general and enables the construction of the C–S bond without using high temperatures or transition metal catalyst. The method involves *O*-tosylation of cyclohexane-1,3-dione, addition-elimination of a thiolate and bromination at C-2 of the resulting 3-arylsulfanyl- or 3-alkylsulfanylcyclohex-2-en-1-one. Finally, treatment with DBU gives the 3-arylsulfanyl- or 3-alkylsulfanylphenol.

Chapter 2 describes synthetic studies towards the total synthesis of sorbicillactones A and B. Several different approaches were explored to construct the challenging amide quaternary center in the 5-membered lactone ring. During these studies an intramolecular Michael addition was discovered. This key transformation allowed the construction of the carbocyclic core of sorbicillactone A and B in five steps with the correct stereochemistry at all of the stereogenic centers, thus opening the door for the further transformations needed to reach the natural products.

PREFACE

Chapter 1 of this thesis forms part of the research done by Do Van Thanh Nhan at the University of Alberta, with Professor D. L. J. Clive being the supervisor. Chapter 1 of this thesis has been published as Do Van Thanh, N.; Patra, S.; Clive, D. L. J. *Tetrahedron* **2018**, *74*, 4343–4350. Derivatives bearing 4-bromophenyl, 4-methylphenyl and 2-methylphenyl were studied by S. Patra. All other compounds and data collection represent my work. Professor 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 myself. It described several approaches towards sorbicillactones A and B. This part has not been previously published.

In loving memory

I dedicated this thesis to my dear aunt Thanh Tam Do—

a brave and kind soul

ACKNOWLEDGEMENT

First and foremost, I want to give my 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 but also in my life. I have not only been trained how to do experiments, but also how to be a researcher.

I also want to extend my thanks to all the Clive lab member from 2016–2021 for their assistance, useful discussions and friendship.

I would like to offer my thanks to the research support staff of the Department (IR, MS, NMR, elemental analysis laboratories, glass blowing, electronic shop, machine shop and chemical stores), especially Dr. Angelina Morales-Izquierdo for mass spectral characterization, Dr. Michael Ferguson for very beautiful X-ray crystallographic structures and Dr. Mark Miskolzie for his help with NMR problems. I would also like to thank Andrew Yeung for assistance with chemical supplies.

Besides the research support staff, I want to thank Dr. Hayley Wan and Connor Part for their valuable assistance in my Teaching Assistance duties for the last five years.

For all my friend, especially the Mahoutsukai no Yoru translation team, the KEM group, the Hanny group and the Massa group. I want to say “thank you” for all your support over in my Ph.D. journey.

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LIST OF ABBREVIATION

Ac	acetyl
acac	acetylacetonate
AIBN	azobis(isobutyronitrile)
Ala	alanine
APT	attached proton test
Bn	benzyl
Boc	*tert*-butoxycarbonyl
conc	concentrated
CSA	camphorsulfonic acid
dba	dibenzylideneacetone
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	*N*,*N*'-dicyclohexylcarbodiimide
DCM	dichloromethane
DEAD	diethyl azodicarboxylate
DMAP	4-(dimethylamino)pyridine
DMDO	dimethyldioxirane
DME	1,2-dimethoxyethane
DMF	dimethylformamide
DMP	Dess-Martin periodinane
DMSO	dimethylsulfoxide
dr	diasteromeric ratio
EDC	*N*-(3-dimethylaminopropyl)-*N*'-ethylcarbodiimide hydrochloride
EI	electron impact
equiv	equivalent
ESI	electrospray ionization
Et	ethyl
FTIR	Fourier transform infrared spectroscopy
HAT	hydrogen atom transfer
HMDS	hexamethyldisilazide

HMPA	hexamethylphosphoramide
HOBt	1-hydroxybenzotriazole
HPLC	high performance liquid chromatography
IC_{50}	concentration that gives 50% inhibition of an enzyme
i-Pr	isopropyl
LDA	lithium diisopropylamide
LED	light emitting diode
m-CPBA	*meta*-chloroperbenzoic acid
min	minutes
mp	melting point
Ms	methanesulfonyl
NAD	nicotinamide adenine dinucleotide
NBS	*N*-bromosuccinimide
NCS	*N*-chlorosuccinimide
NIS	*N*-iodosuccinimide
ORTEP	Oak Ridge Thermal Ellipsoid Plot
PMB	*para*-methoxybenzyl
r.t.	room temperature
SET	single electron transfer
TBDPS	*tert*-butyldiphenylsilyl
t-Bu	*tert*-butyl
Tf	triflate
TFA	Trifluoroacetic acid
THF	tetrahydrofuran
TMS	trimethylsilyl
tol	tolyl
Ts	toluenesulfonyl
TS	transition state

Chapter 1

A general route to *meta*-(arylsulfanyl)- and *meta*-(alkylsulfanyl)phenols from cyclohexa-1,3-diones

The importance of *meta*-(arylsulfanyl) and *meta*-(alkylsulfanyl)phenols.

A large number of biologically active molecules, such as methionine, cysteine, glutathione, and important drugs like sulfonamides, contains a C–S bond. One subgroup of organosulfur molecules, *meta*-(arylsulfanyl)- and *meta*-(alkylsulfanyl)phenols are important fragments in pharmaceuticals. For example, raloxifene[1] (osteoporosis drug), moxifetin[2] (antidepressant) (Figure 1), KRP-203[3a] (immunosuppresant) and the benzothiophene PPAR[3b] (peroxisome proliferator-activated receptor) agonist all have this moiety as a central building block (Figure 1). Some other phenols of this type may influence intracellular mobilization of Ca^{2+} ions,[4] inhibit the growth of HeLa cells[5] or inhibit 17β-hydroxysteroid dehydrogenase type 1.[6]

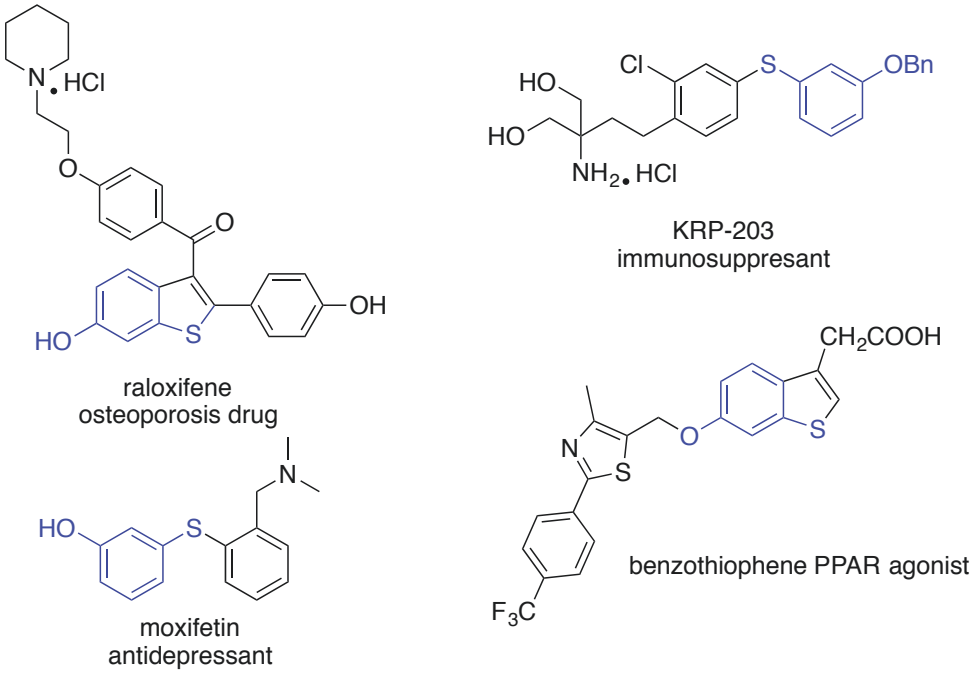


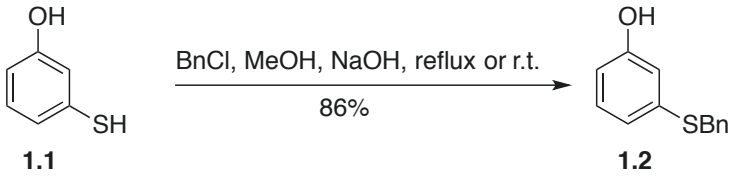
Figure 1. Important drugs containing the *meta*-(arylsulfanyl)phenol unit

Because of the importance of sulfur-containing units, many methodologies to prepare *meta*-sulfanyl phenol building block have been developed. These methodologies can be classified into three categories: (1) making the aryl C–S bond by nucleophilic substitution,

(2) by employing transition metal catalysts, and (3) by dehydrogenative aromatization of cyclohexenone derivatives.

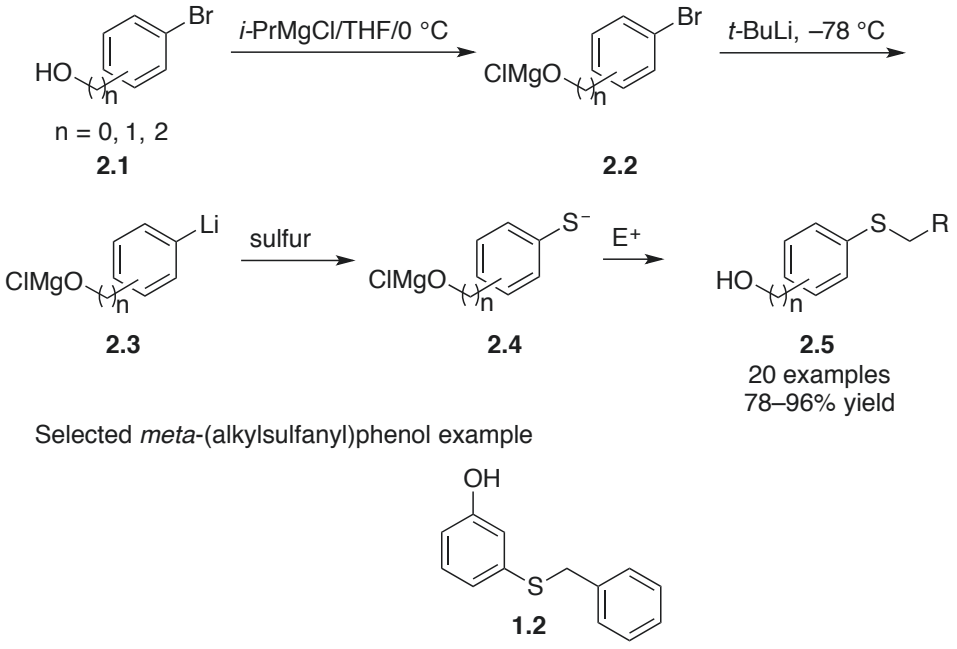
S-Alkylation for making *meta*-(alkylsulfanyl)phenols from thiols and halides.

One of the most frequent ways to make *S*-(alkylsulfanyl)phenols is nucleophilic substitution using a thiol,[7] which is a good nucleophile, in the presence of a base. One such example is presented in Scheme 1.[8]



Scheme 1. Preparing an *meta*-(arylsulfanyl)phenol by nucleophilic substitution

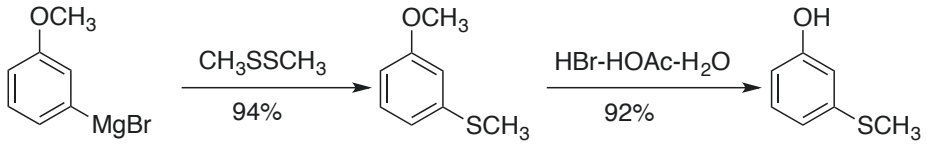
In 2006, Kang and coworkers[9] introduced another way to make *meta*-(alkylsulfanyl)phenols through nucleophilic substitution using (hydroxyalkyl)bromo-benzenes **2.1** as the starting material (Scheme 2).



Scheme 2. Preparation (alkylsulfanyl)phenol derivatives by the method of Kang and coworkers

First, **2.1** was reacted with isopropylmagnesium chloride to deprotonate the terminal OH group. Then the resulting magnesium salts **2.2** undergo lithium-halogen exchange with *t*-BuLi to form aryl lithium salts **2.3** and these are treated with elemental sulfur to give thiolates **2.4**. Finally, **2.4** can be captured by adding an electrophile to afford the *meta*-(alkylsulfanylphenol **2.5** (Scheme 2). By applying this sequence, 3-(benzylsulfanyl)phenol (**1.2**) was made in 96% overall yield in 4 steps. Only primary halides can be used in this methodology.[9]

meta-(Alkylsulfanyl)phenols can be made by reaction between a Grignard reagent and a symmetrical disulfide, a method that was used by Bordwell[10] to make 3-(methylsulfanyl)phenol (**3.3**) (Scheme 3).



3.1 **3.2** **3.3**

Scheme 3. Preparation of *meta*-(methylsulfanyl)phenol by Bordwell

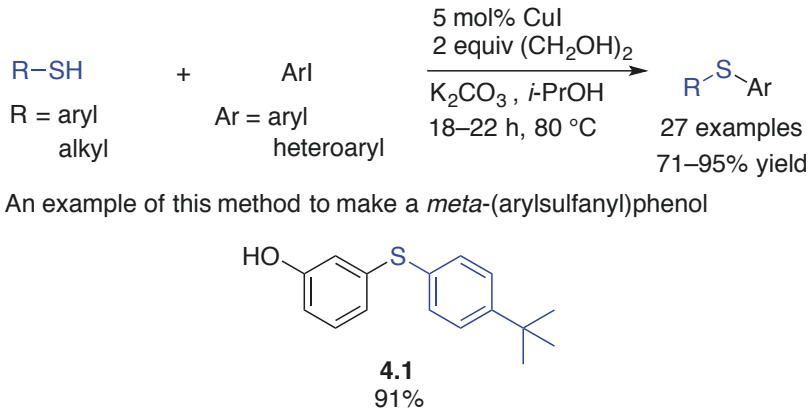
Transition metal catalysts for making *meta*-(arylsulfanyl)- and *meta*-(alkylsulfanyl)phenols and their derivatives.

Nucleophilic substitution methods are useful to make *meta*-(alkylsulfanyl)phenols, but when it comes to *meta*-(arylsulfanyl)phenols these methods are not very efficient. Therefore, recently many routes to arylthioether derivatives with a *meta* hydroxy group have been developed based on transition metal assisted C–S bond formation.[11] The most popular transition metal catalyst is copper (as used in Ullmann or Chan-Lam-Evans coupling), followed by palladium (as in Buchward-Hartwing coupling) and recently nickel has become popular as well. In this section only those procedures related to *meta*-(arylsulfanyl)phenols and *meta*-(alkylsulfanyl)phenols and their derivatives are discussed.

Copper

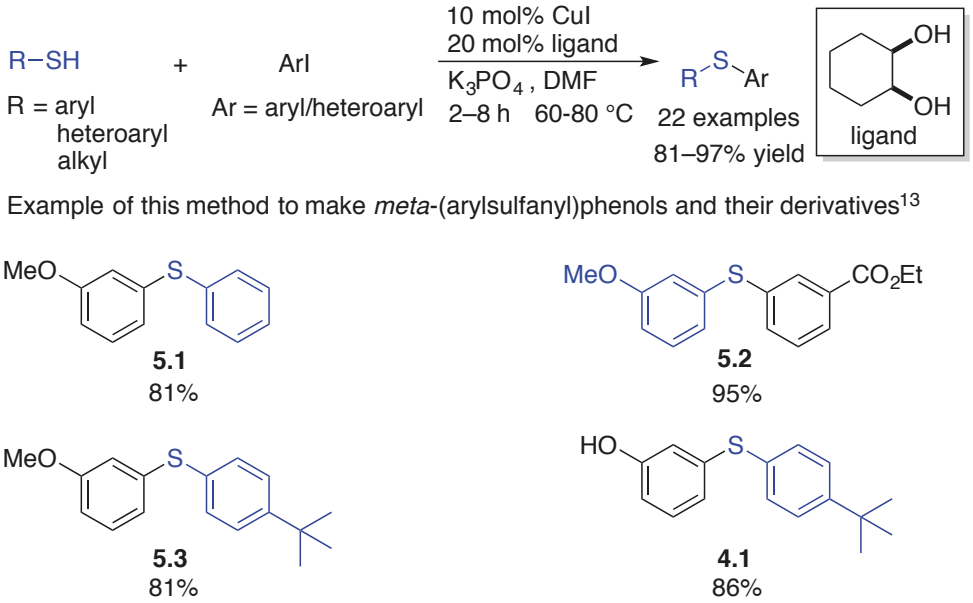
Recently the use of copper salts has become popular for making *meta*-(arylsulfanyl) phenols and their derivatives. The first report came from the Buchwald group,[12] which used air stable CuI as catalyst and ethylene glycol in the presence of K_2CO_3 to perform an aryl C–S coupling between aryl iodides and aryl or alkyl thiols (Scheme 4) to get the desired

thioethers in high yield. Using this methodology, 3-(4-*tert*-butylphenylthio)phenol (**4.1**) was synthesized in 91% yield.[12]



Scheme 4. Buchwald's CuI mediated C–S bond coupling

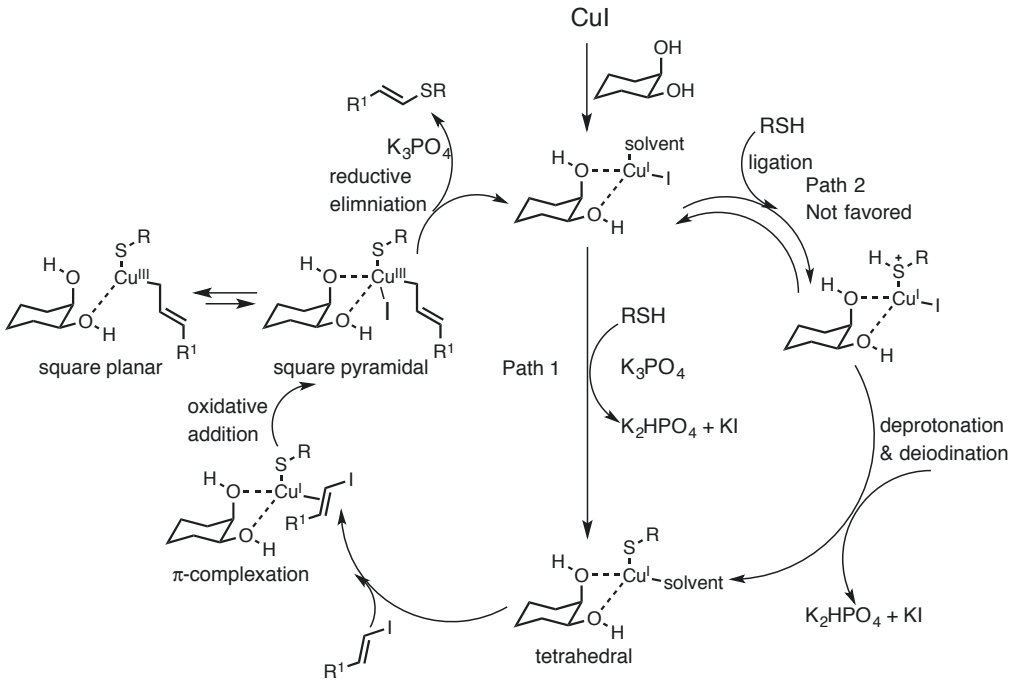
In 2010, Cook and coworkers[13] again choose CuI to promote vinyl and aryl C–S coupling, and this time *cis*-1,2-dihydroxycyclohexanediol was employed as a ligand. Only aryl iodides reacted at low temperature (60–80 °C, 2–8 h), but aryl bromides gave products at an elevated temperature (90–100 °C, 15 h).[13] With this protocol, four *meta*-substituted (arylthio)phenol derivatives **4.1**, **5.1**, **5.2** and **5.3** were prepared in good yield (Scheme 5).



Scheme 5. Making *meta*-(arylsulfanyl) phenols and its derivatives by Cook and coworkers

Many vinyl, aryl, heteroaryl and alkyl halides react with thiols under these conditions to provide a wide range of sulfides including arylvinyl sulflde, diaryl sulfides, heteroaryl sulfides and alkyl sulfides. A convenient feature is that the catalyst can be handled in air. The main disadvantage of this methodology is that aryl chlorides, aryl triflates and aryl boron trifluoride salts do not give any cross coupling products with thiols.[13]

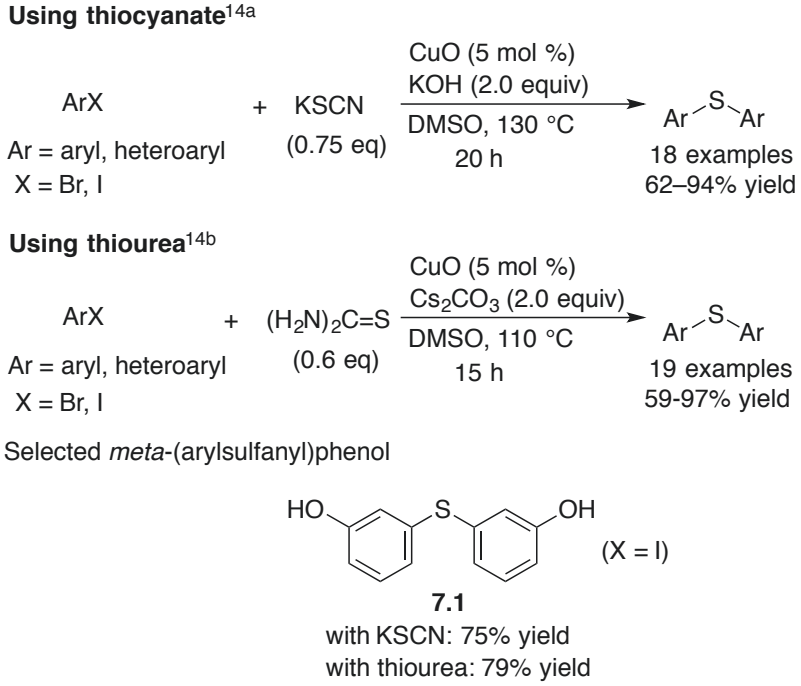
Two plausible mechanisms for the cross coupling are presented in Scheme 6,[13] using a vinyl iodide as an example; however, pathway 2 is ruled out based on previous studies from other groups. Both mechanisms begin with the chelation of CuI by the ligand and solvent to form a tetrahedral intermediate, which undergoes the oxidative addition of vinyl halide or aryl halide to generate a Cu^{III} square planar complex through a square pyramidal Cu^{I} intermediate. A reductive elimination finally takes place to provide the product and regenerate the Cu^{I} species which can then take part in a new catalytic cycle. The *cis* diol ligand was better than the *trans* diol, probably because the *trans*-diol may form a tighter complex with Cu, thereby retarding the oxidative addition step.[13]



Scheme 6. Mechanism of vinyl and aryl C–S bond formation

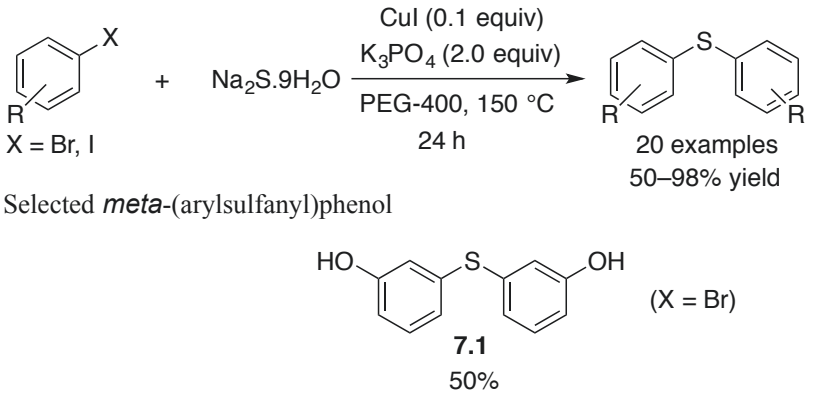
In 2011 Nageswar *et al.* demonstrated that CuO nanoparticles could be used as an efficient catalyst to synthesize symmetric sulfides by reaction between KSCN[14a] or

thiourea[14b] and a broad range of aryl halides at high temperature (110–130 °C) (Scheme 7). The reaction cleanly gives the desired symmetrical diaryl sulfides under ligand-free conditions without using foul smelling thiols and the catalyst can be reused for up to four cycles without loss of activity. Under these conditions the symmetric *meta*-substituted arylthioether derivative **7.1** was formed in 75% yield with KSCN and in 79% yield with thiourea. The authors did not propose mechanisms for these reactions.



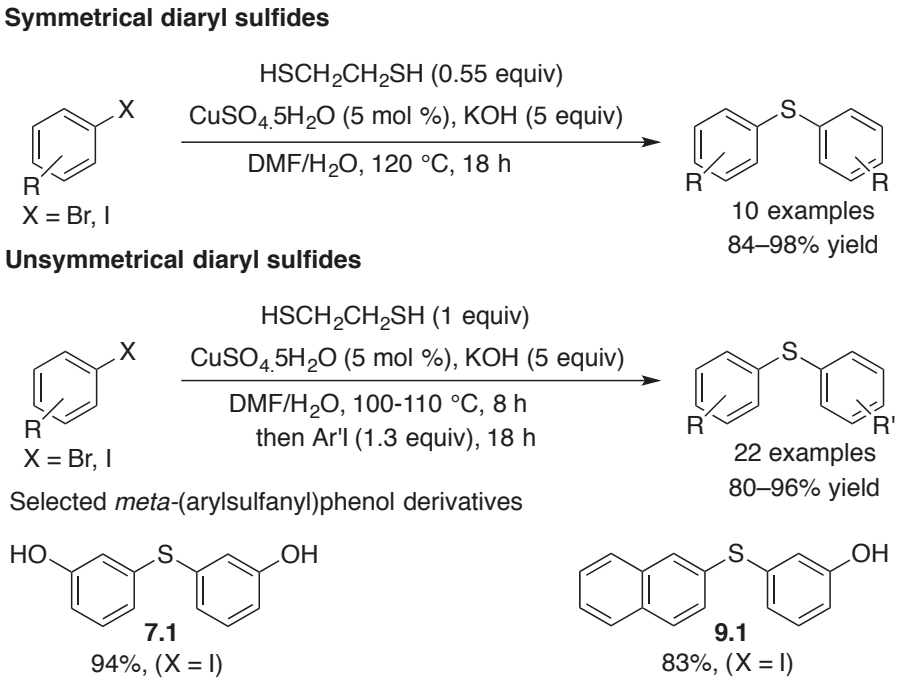
Scheme 7. Nageswar's method to prepare symmetric diaryl ethers using thiocyanate or thiourea and CuO nanoparticles as reusable catalyst

Copper iodide can be used to make symmetric aryl sulfides by reaction between aryl halides and sodium sulfide nonahydrate at 150 °C using PEG-400,[15] a non toxic, cheap, safe and environmentally friendly solvent (Scheme 8). The product is usually obtained through Ullmann coupling in high yield, but in the case of **7.1** the yield was only 50%.



Scheme 8. Symmetric diaryl sulfides preparation using the green solvent PEG-400

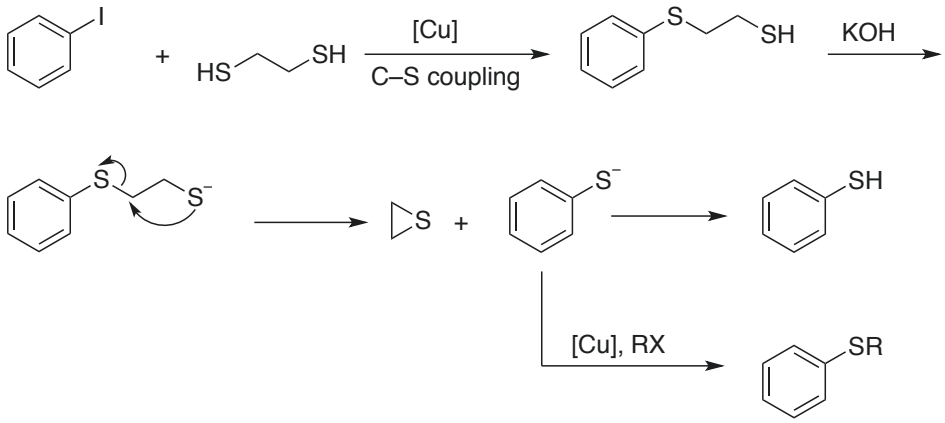
In 2015, Chae and coworkers studied C–S bond formation using $CuSO_4.5H_2O$ as catalyst at elevated temperature in the presence of 1,2-ethanedithiol to prepare a wide range of aryl thioethers and aryl thiols.[16] These conditions showed a broad substrate scope with excellent functional group compatibility; only a simple and available reagent is needed and the products are formed directly from aryl halides (Scheme 9).[16] With this protocol, symmetrical diaryl sulfides such as **7.1** and unsymmetrical products, for example, **9.1**, could



Scheme 9. Synthesis of symmetrical and unsymmetrical aryl sulfides using Chae's methodology

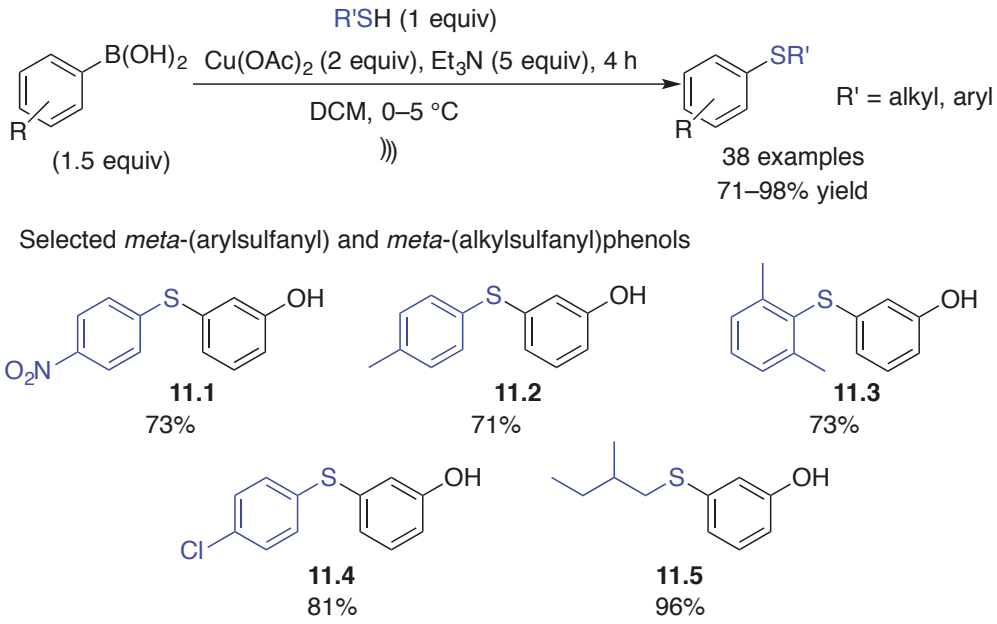
be accessed in high yield. When the amount of 1,2-ethanedithiol is increased to 2 equivalents, thiols become the major product.[16]

From these experimental results, the authors proposed a plausible mechanism to explain the formation of thiophenolate (Scheme 10)[16] via an S_N2 S–C_{alkyl} bond cleavage pathway by the terminal alkyl thiolate in the presence of a base; a thiirane ring and the good leaving group thiophenolate are formed. The thiophenolate can be protonated to give the corresponding thiol or it can react with another aryl or alkyl halide to afford a thioether.



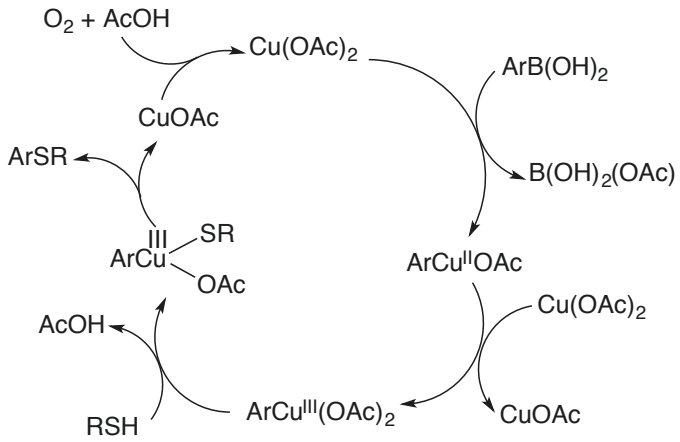
Scheme 10. Mechanism of aryl thiols and aryl thioether formation

In the same year Kabalka[17] reported an ultrasound assisted aryl C–S bond formation by using Chan-Evans-Lam chemistry based on $Cu(OAc)_2$ as catalyst. Many unsymmetrical *S*-arylations of thiols at low temperature (0–5 °C) in open reaction flasks were carried out. Especially, aliphatic thiols could be used as well in this protocol and Scheme 11 shows four *meta*-substituted (arylthio)phenols, **11.1**, **11.2**, **11.3**, **11.4**, and one *meta*-(alkylthiophenol) (**11.5**) synthesized by the Kabalka protocol.[17]



Scheme 11. Kabalka prepared aryl thioethers through Chan-Lam-Evans coupling.

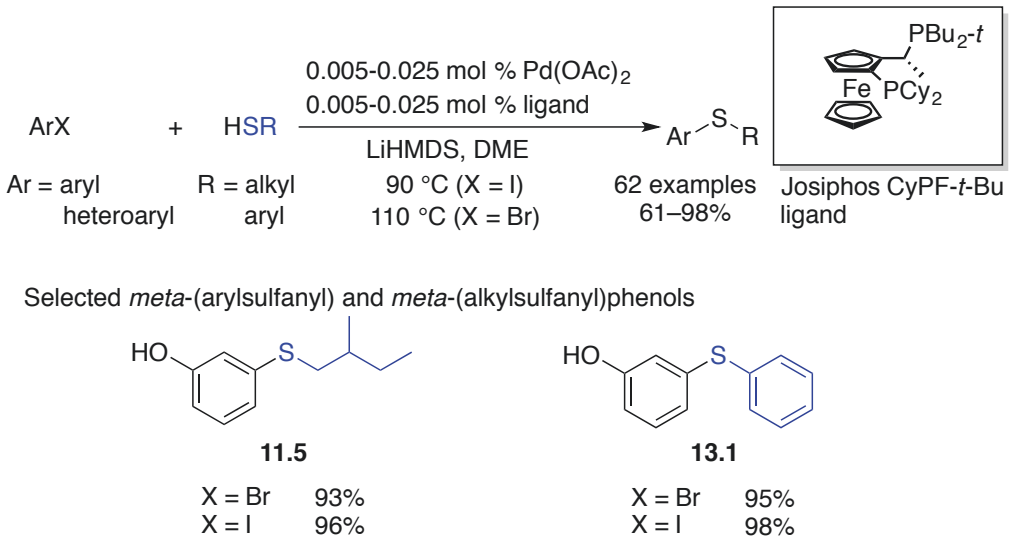
The mechanism for this transformation is shown in Scheme 12.[18] It is believed that a Cu^{III} intermediate is involved.[19] With this methodology, not only can C–S bonds be formed, but also C–N and C–O bonds so as to give access to amines and aryl ethers. The only drawback of the method is that some of the boronic acid counterparts are not commercially available and require independent preparation.



Scheme 12. Chan-Lam-Evans coupling mechanism for aryl thioether formation

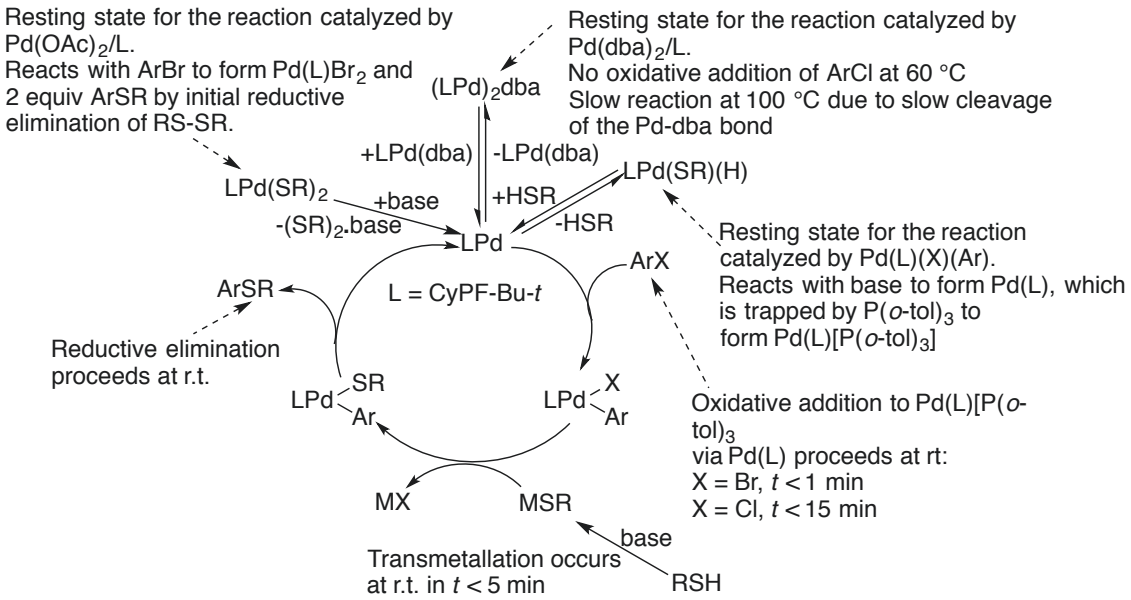
Palladium

The first palladium coupling to prepare *meta*-(arylsulfanyl)phenols and *meta*-(alkylsulfanyl)phenols came from the Hartwig group[20] when they used catalytic amounts of $Pd(OAc)_2$ in the presence of the Josiphos ligand CyPF-*t*-Bu (1-dicyclohexylphosphino-2-di-*tert*-butylphosphinoethylferrocene) to perform the coupling between thiols and aryl halides to afford thioethers in high yield regardless of whether the thiol used was aliphatic (e.g. **11.5**) or aromatic (e.g. **13.1**) (Scheme 13). This is the first example of aryl C–S coupling using a very low catalyst loading and the conditions lead to high turnover numbers (around 100,000).[21]



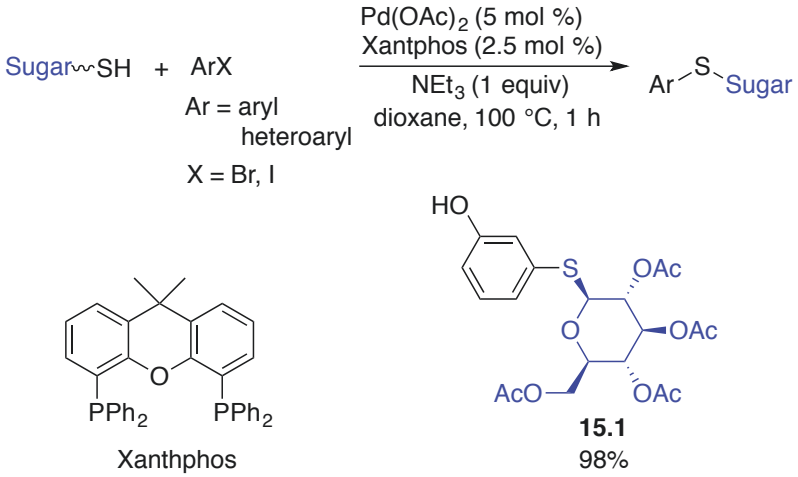
Scheme 13. Palladium mediated C–S coupling by Hartwig and coworkers

A detailed study of the reaction mechanism was undertaken by the Hartwig group.[21] The results showed that the highly restricted backbone conformation, severe steric hindrance and strong electron donicity of the Josiphos ligand CyPF-*t*-Bu gives the best outcome.[20] Through the isolation and reaction of each palladium complex of the catalytic cycle (Scheme 14), it was observed that each step (oxidative addition, transmetallation, reductive elimination) proceeds within minutes at room temperature, but the overall catalytic cycle can only operate at high temperature (90–110 °C). Hence it is clear that the resting state of the reaction lies off the catalytic cycle.[21]

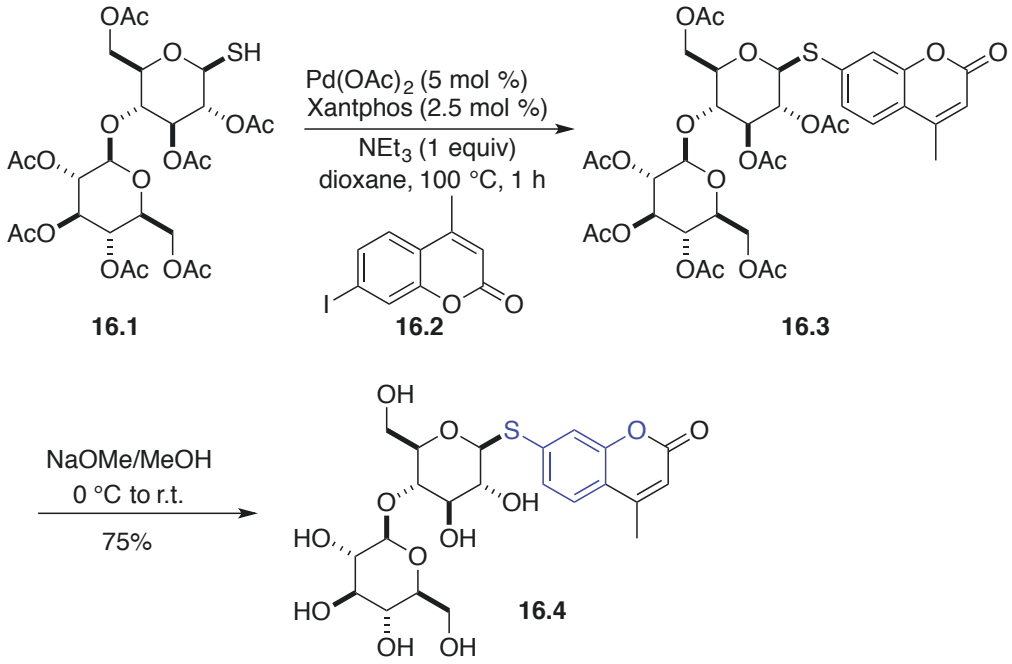


Scheme 14. Detailed mechanistic investigation by Hartwig and coworkers

Many C_{aryl}–S couplings were used to make simple arene derivatives, but very little attention was given to prepare arylthioglycosides, and only one report from Messaoudi and Alami and coworkers tackle this issue.[22] In their study, $Pd(OAc)_2$ and Xantphos [(9,9-dimethyl-9*H*-xanthene-4,5-diyl)bis(diphenylphosphane)] in the presence of triethylamine allowed the coupling reaction between thiosaccharides and aryl halides in dioxane at 100 °C. The method affords not only *meta* derivatives such as **15.1**, but also a wide range of arylthioglycosides in high yield (Scheme 15).[22] This methodology was applied by the authors



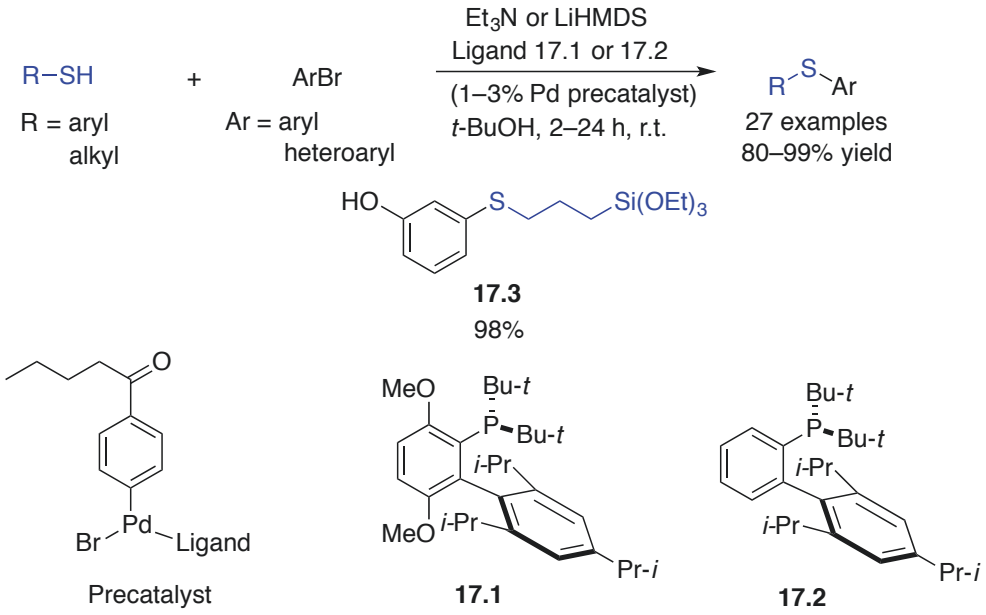
Scheme 15. Thioglycoside formation between thiosaccharides and aryl halides



Scheme 16. Synthesis 4-methyl-7-thioumbelliferyl-β-D-cellobioside using thiosaccharide *S*-arylation methodology

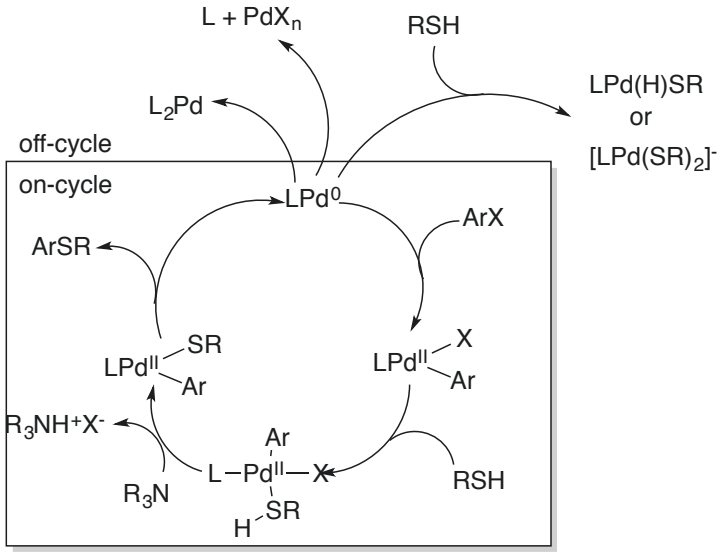
to synthesize 4-methyl-7-thioumbelliferyl-β-D-cellobioside (**16.4**),[22] a fluorescent non-hydrolyzable structural analogue for cellulases (Scheme 16). The compound was made by C–S bond coupling between thiosugar **16.1** and the 7-iodocoumarin **16.2** to afford **16.3** which was hydrolyzed to furnish **16.4** in 75% yield over two steps.

In 2019, Buchwald and coworkers[23] reported a palladium catalyst to make C–S bonds with aliphatic and aromatic thiols using chelating bisphosphine ligands like *t*-BuBrettPhos (**17.1**) or *t*-BuXphos (**17.2**) and triethylamine (for aliphatic thiols) or LiHMDS (for aromatic thiols). The reaction occurred smoothly at room temperature (Scheme 17) with a wide range of thiols and aryl bromides. The *meta*-(alkylsulfanyl)phenol **17.3** was obtained in 98% yield.



Scheme 17. Making C–S bond at room temperature using Buchwald conditions

In their mechanistic studies, Buchwald *et al*. found out that the effectiveness of a given catalyst is not well-predicted by the distribution of ligand (Pd-bound or free) in the catalytic resting state. They did not observe any free ligand in almost every case and monophosphine ligands gave better results than bisphosphine ligands[20, 21] because bisphosphine ligands tend to form the alternative, stable off-cycle species: a L_2Pd dimer or

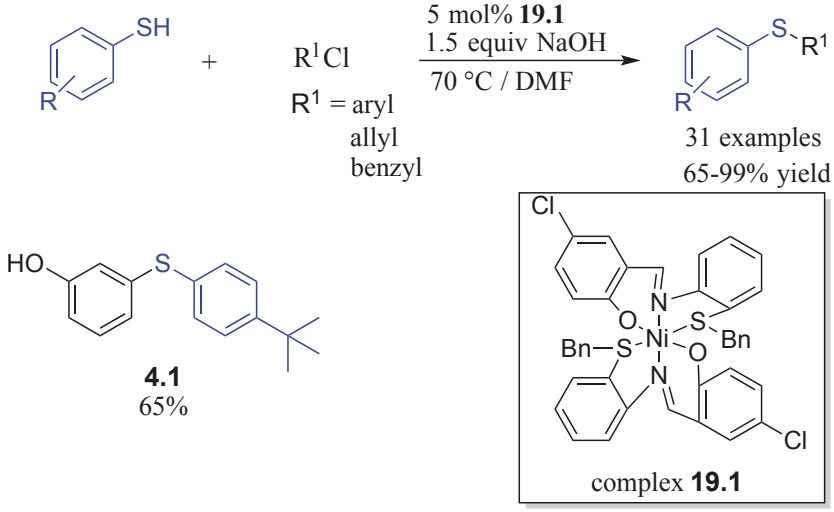


Scheme 18. Mechanism for *S*-arylation according to Buchwald and coworkers

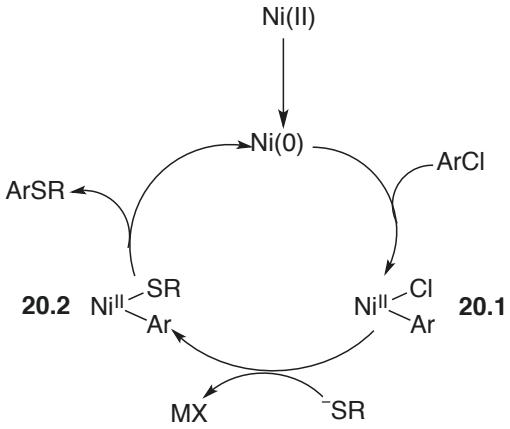
hydridopalladium thiolate. Based on the information they obtained, the Buchwald group proposed the coupling mechanism shown in Scheme 18.[23]

Nickel

In a search for different transition metals to replace expensive palladium, nickel was found to be one of the most suitable candidates. But up to now, there are only a few reports about nickel catalysts being used to create *meta* C_{aryl}–S bonds. The first one comes from Gogoi and coworkers in 2014 when they used a nickel-Schiff base complex NiL_2 (**19.1**)[24] to perform the coupling between organic chlorides and aryl thiols (Scheme 19) at 70 °C. This is the only report using cheap and readily available aryl chlorides as coupling partners. This methodology allowed different types of chlorides, namely aryl, benzyl and allyl chlorides, to participate; and it was found that benzyl chlorides are the most reactive. The *meta*-(arylsulfanyl)phenol derivative **4.1** was formed in 65% yield by this method; and the proposed mechanism is shown in Scheme 20.[25]

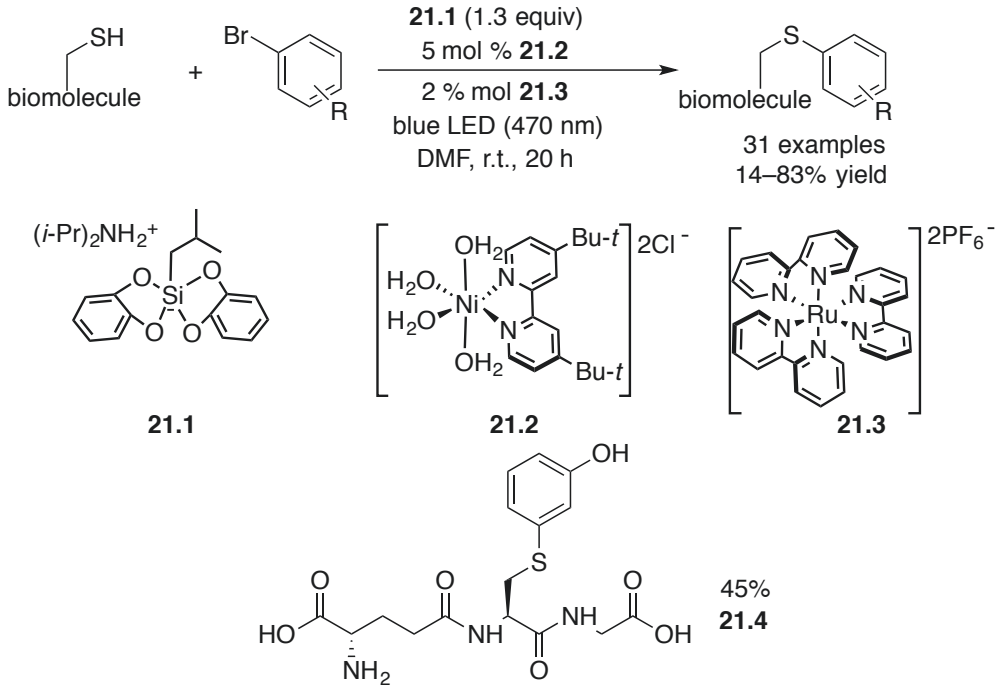


Scheme 19. Nickel catalyst promoted C–S coupling



Scheme 20. Mechanism of nickel promoted aryl C–S coupling

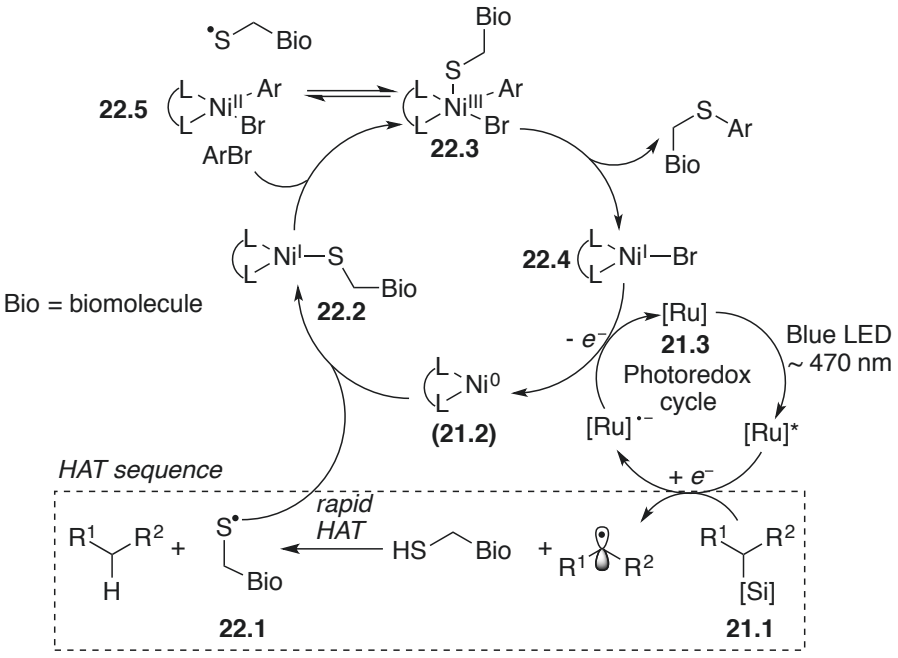
The only report related to *meta*-sulfanylphenols involving Ni/photoredox dual-catalyzed cross coupling initiated by photon absorption was described by the Molander[26] group in 2018. The reaction takes place in the presence of hydrogen atom transfer reagent **21.1**, nickel cross coupling catalyst **21.2** and photoredox catalyst **21.3**. With this methodology, different biomolecules, drugs, peptides or biological probes bearing a thiol group could be *S*-arylated regardless of the nature of the thiol group. In one example,



Scheme 21. Thioarylation biomolecules using photoredox cross coupling by Molander and coworkers[26]

glutathione reacted with 3-bromophenol to give the corresponding thioether **21.4** in 45% yield (Scheme 21).

In contrast to the cross coupling mechanism, in the photoredox mechanism the Ru photocatalyst **21.3** absorbs a photon to become an excited state beginning the catalytic cycle, and this is followed followed by oxidation of the hydrogen atom transfer (HAT) reagent **21.1** via a single electron transfer mechanism (SET). Rapid H-atom abstraction from the SH group of the biomolecule generates a thiyl radical **22.1**, which adds to Ni(0) complex **21.2** to give **22.2**. This is followed by Ni(I) oxidative addition to the aryl bromide to form **22.3**. Reductive elimination from the Ni(III) species and a final SET closes the catalytic cycle (Scheme 22).[26]

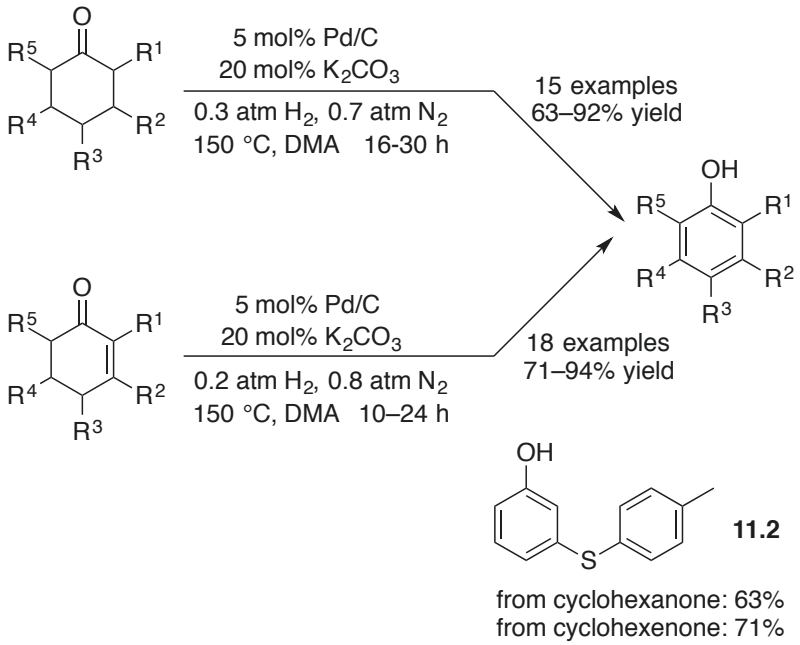


Scheme 22. Mechanism of the photoredox cross coupling reaction

Making *meta*-(arylsulfanyl)- and *meta*-(alkylsulfanyl)phenols and their derivatives by dehydrogenation.

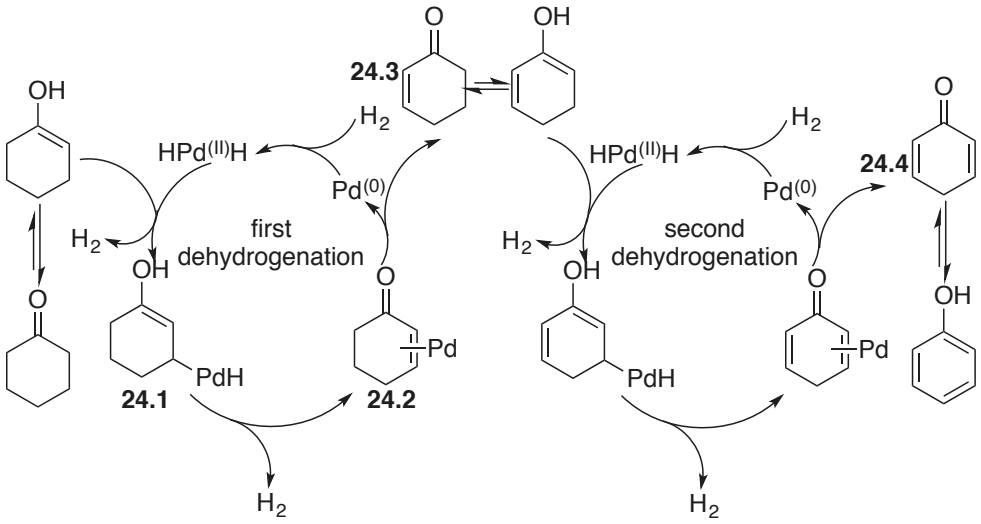
Besides the cross coupling reaction, *meta*-(arylsulfanyl)- and *meta*-(alkylsulfanyl)phenols can be prepared through dehydrogenation of cyclohexanone derivatives. The first report was from Liu and coworkers in 2015,[27] in which they used commercial Pd/C in combination with H_2, which leads to a great increase in catalyst activity (Scheme 23). This methodology does not require an oxidant or hydrogen acceptor, and

therefore no overoxidation occurs and many easily oxidized functional groups should remain intact. Using this procedure, *meta*-(arylsulfanyl)phenol **11.2** was formed in 63% and 71% yield from cyclohexanone and cyclohex-2-en-one, respectively.[27]



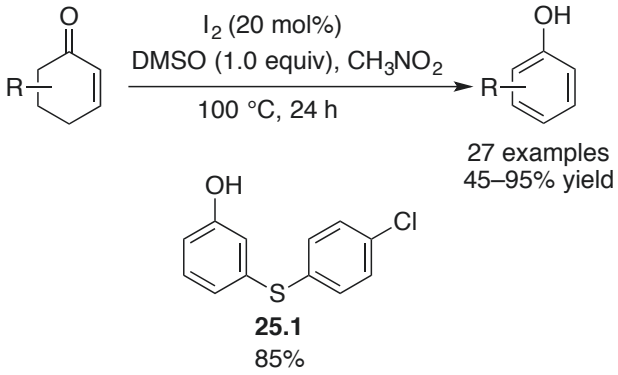
Scheme 23. Formation of *meta*-(sulfanyl)phenols by dehydrogenation cyclohexanone and cyclohexenone derivatives

A detailed mechanism of this reaction cannot yet be presented, but Liu proposed a potential mechanism (Scheme 24).[27] The reaction starts with a keto-enol tautomeric equilibrium under basic conditions. Pd(0) now reacts with hydrogen gas to generate a HPd(II)H species, which may undergo dehydrogenative palladation of the β-position of cyclohexanone to generate the intermediate **24.1**. Compound **24.1** is subsequently converted to key intermediate **24.2**; meanwhile H_2 is released. Intermediate **24.2** rapidly dissociates leading to Pd(0) and intermediate **24.3**. Sequentially, the second dehydrogenation of **24.3**, a process similar to the first dehydrogenation, results in the generation of **24.4**, which tautomerizes to the target product.



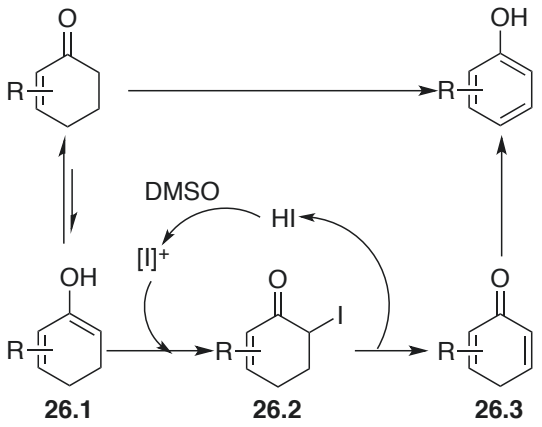
Scheme 24. Dehydrogenation aromatization mechanism with Pd/C and H_2

In 2016, Jiao and coworkers reported a metal-free dehydrogenative aromatization of cyclohexenone derivatives using iodine in DMSO at 100 °C. Not only *meta*-substituted but also *ortho*- and *para*-substituted compounds could be made in high yield. This approach was used to prepare 3-(4-chlorophenylthio)phenol (**25.1**) in 85% yield (Scheme 25).[28]



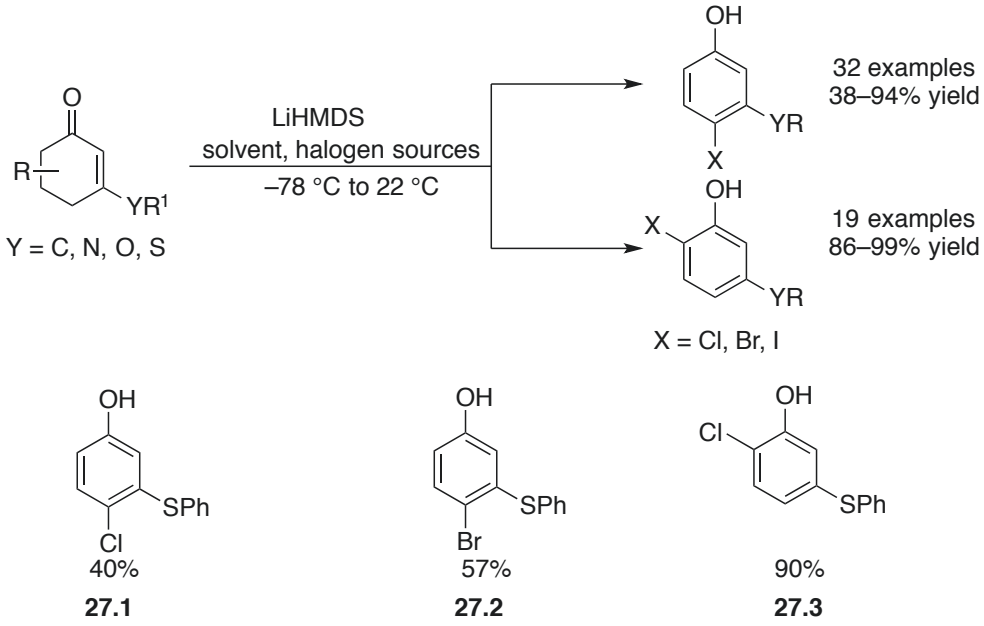
Scheme 25. Iodine dehydrogenative aromatization of cyclohexenone derivatives

A possible mechanism is presented in Scheme 26.[28] Initially, cyclohexenone undergoes keto-enol tautomerism to form **26.1**, followed by electrophilic iodization to afford α-iodocyclohexenone **26.2**, which subsequently eliminated HI to give intermediate **26.3**. Species **26.3** quickly tautomerizes to the phenol product.[28]



Scheme 26. Mechanism of the iodine dehydrogenative aromatization reaction

Another method is to aromatize vinylogous esters of 3-substituted cyclohex-2-en-1-ones to haloresorcinols as reported by Mohr and coworkers in 2016.[29] They used a strong base (LiHMDS) and halogen sources to synthesize 4- or 6-haloresorcinols in good to high yield (Scheme 27). When this methodology was applied to prepare *meta*-(arylsulfanyl)phenols only the 6-chloro product **27.3** could be obtained in high yield, the 4-bromo- (**27.2)** and 4-chloro- (**27.1**) compounds being obtained in modest yields. A mechanistic study showed that this reaction goes through a dihalogenated species.[29]

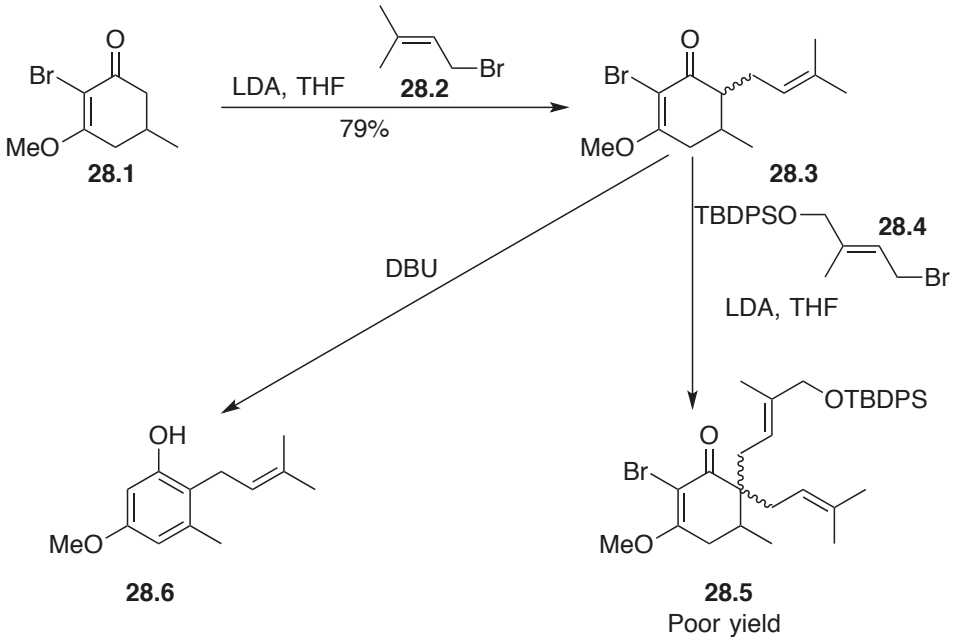


Scheme 27. Mohr's vinylogous ester aromatize halogenation

Our synthetic approach to polysubstituted phenols including *meta*-substituted phenols from cyclohexane-1,3-dione

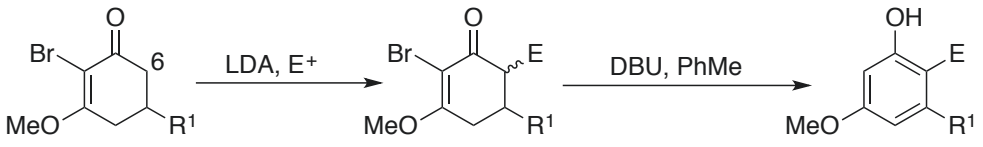
A general way to make polysubstituted phenols

In 2015, a member of our group, Dr Wenjie Shao, reported that while trying to alkylate ketone **28.3** with allylic halide **28.4**, the yield of **28.5** was low, but one epimer of **28.3** behaved better than the other. Therefore, he tried to equilibrate the epimer mixture **28.3** by treatment with DBU to see if the more useful epimer would become the major component. Surprisingly, the product was the phenol **28.6** (Scheme 28).[30]



Scheme 28. The discovery of a way to make polysubstituted phenols

The conversion of **28.3** into **28.6** represented a method for making resorcinol



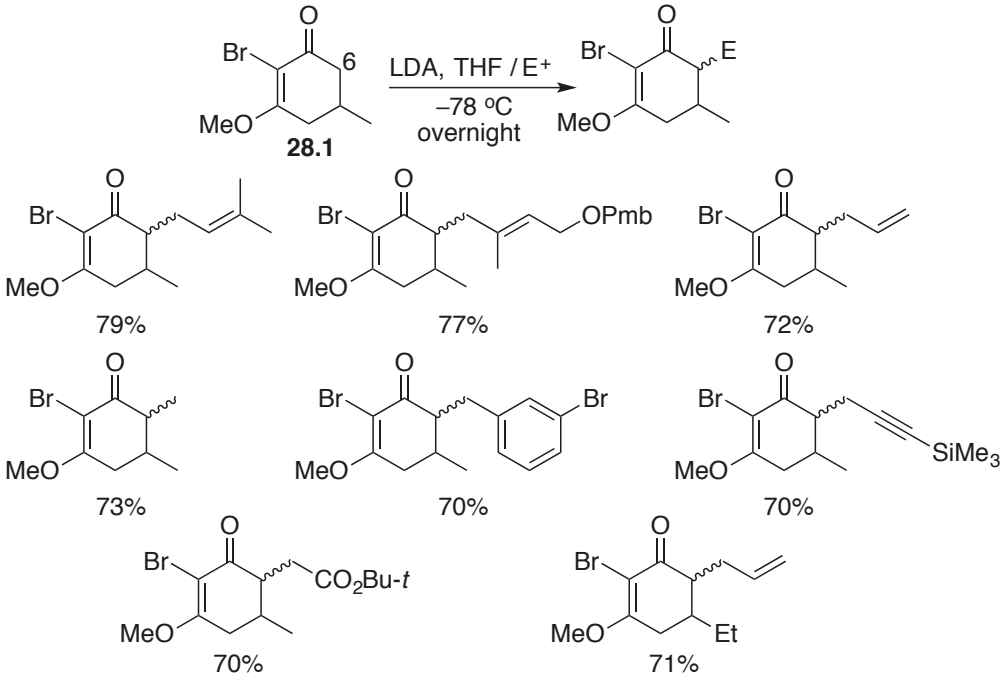
R^1 = H, Me, Et

E^+ = A large variety of electrophiles

Scheme 29. A general family of routes to substituted phenols

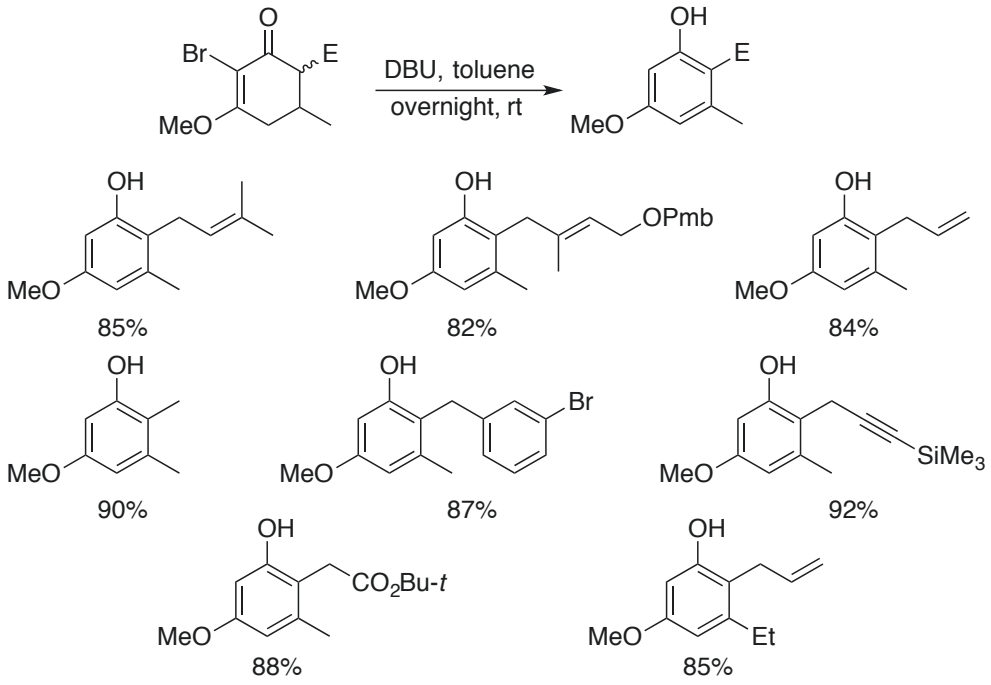
monomethyl ethers in a regiocontrolled way, along the lines shown in Scheme 29.[30, 31]

A number of examples were examined in which the starting bromo ketone—usually bromo ketone **28.1**—was alkylated with reactive halides such as allylic, propargylic and benzylic halides as well as methyl iodide and an α-bromoester (Scheme 30).[30] The only limitation he uncovered was the need for a *reactive* alkylating agent; methyl iodide worked well but attempted alkylation with 1-bromobutane was unsuccessful.

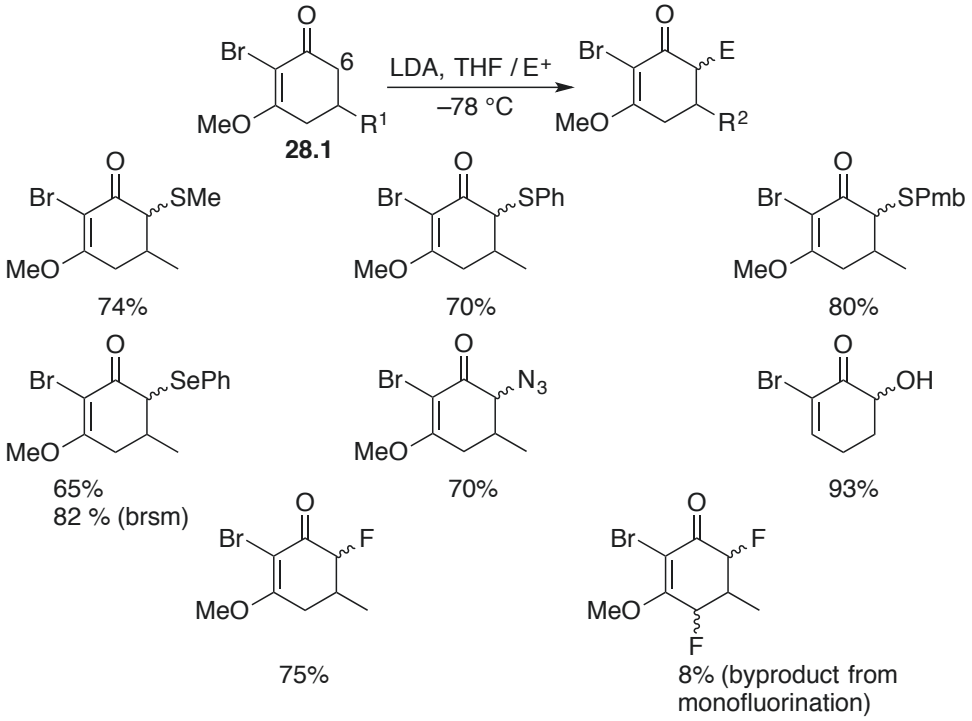


Scheme 30. C_6-alkylation of bromoenone **28.1** by reactive halides

In one case, the starting bromo ketone had an ethyl group instead of the methyl of **28.1**; in that case the alkylation yield with allyl bromide was 71% and the yield for aromatization was 85% (Scheme 31).[30]

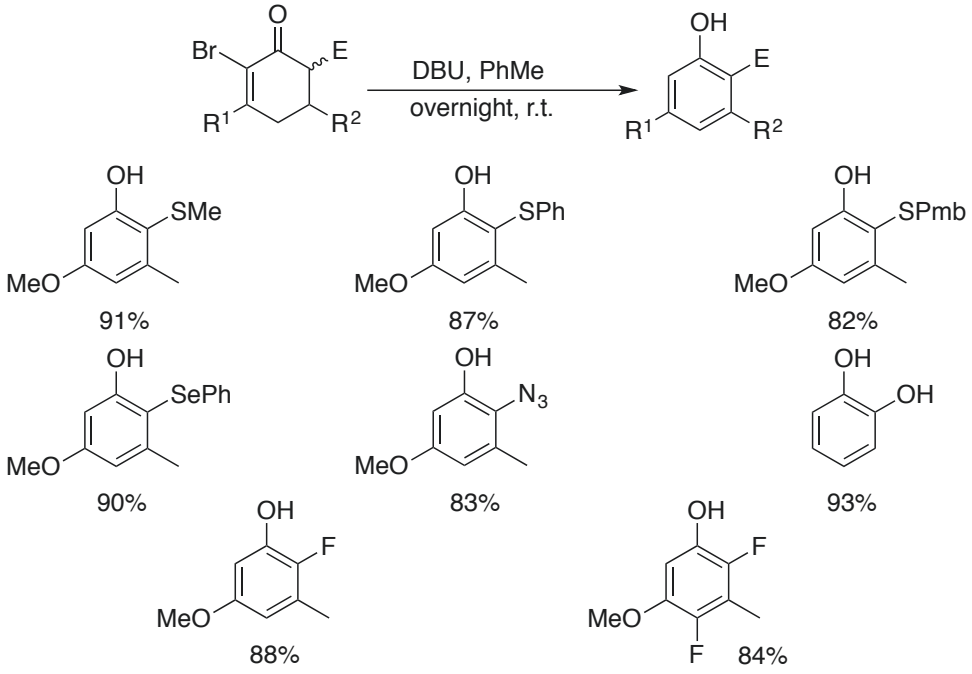


Scheme 31. Aromatization of various bromoenones



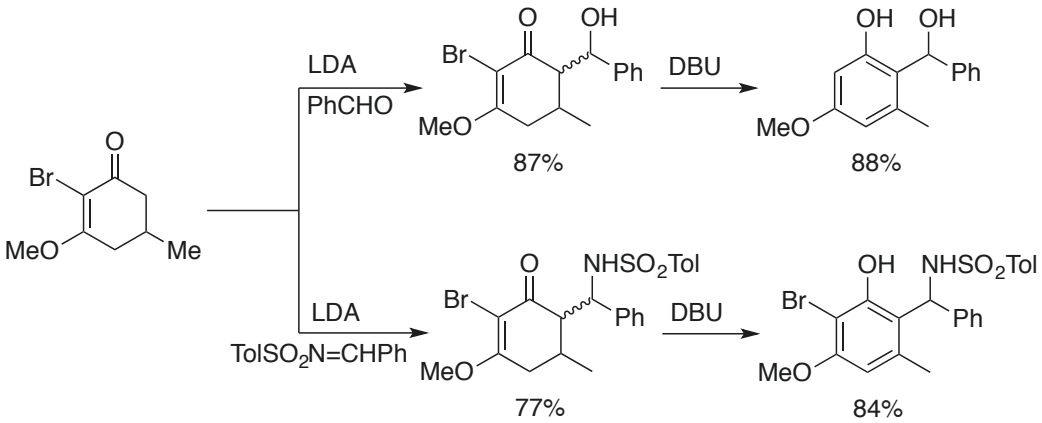
Scheme 32. Functionalization at C_6 with a variety of electrophiles (the difluoro derivative was the side product when **27.1** was monofluorinated with 1.05 eq of fluorinating agent).

Reactive alkylating agents are not the only electrophiles that can be used to place a substituent at C-6 of the starting bromo ketone.[31] A number of electrophiles were examined and it was found that nitrogen, sulfur, oxygen and fluorine are easily attached to C-6 (Scheme 32), and that the subsequent aromatization proceeds smoothly in high yield (Scheme 33).[31]



Scheme 33. Aromatization of C-6 substituted bromoenones by DBU

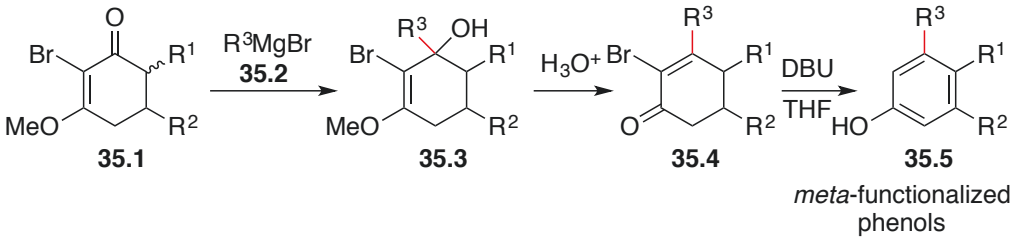
The starting bromo ketone can be condensed with aldehydes or *N*-sulfonyl imines and aromatization occurs efficiently without any dehydration or loss of *p*-toluenesulfonamide (Scheme 34).[31]



Scheme 34. Aromatization of sensitive substrates without undesired elimination

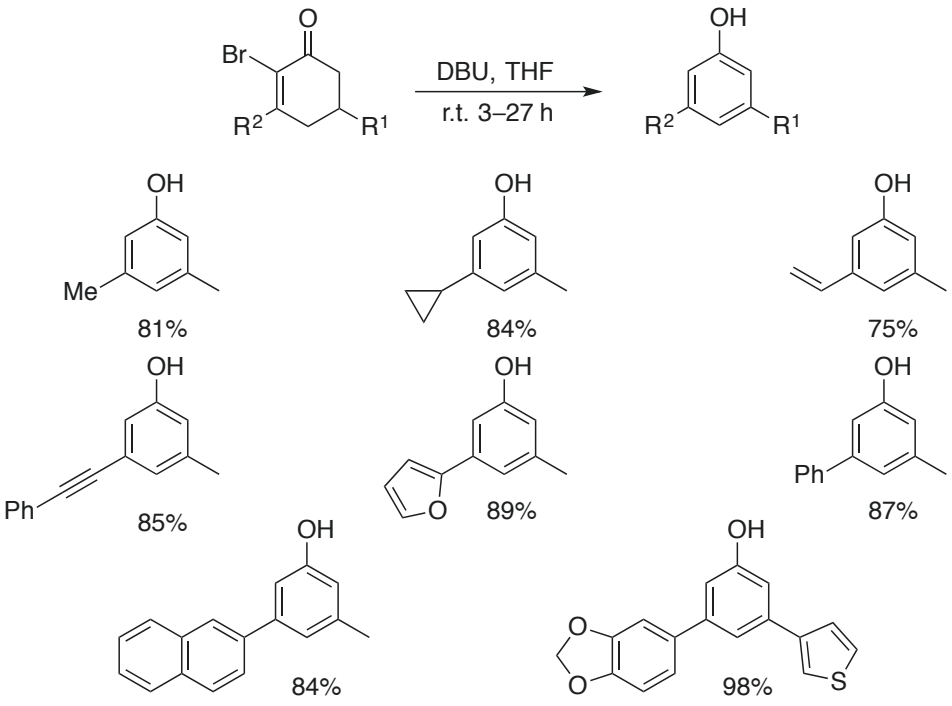
Using DBU-mediated aromatization to make *meta*-substituted phenols

In an attempt to widen the scope, another group member, Guojun Yu, found that the ketones which were made by deprotonation and reaction with an electrophile can be modified very easily by addition of an organolithium to the carbonyl group so that, on treatment with acid and then DBU, a *meta*-alkylated or *meta*-arylated phenol is formed. Phenols of this type are not readily available by classical electrophilic substitution because of the *ortho*/*para* directing effect of the phenolic oxygen or of the corresponding *O*-methyl ether. The route to *meta*-substituted phenols is summarized in generic form by Scheme 35.[32] The method simply involves treating the intermediate ketones **35.1** with a Grignard reagent **35.2** and the intermediate **35.3** is then quenched with mild acid to effect rearrangement to furnish **35.4**; this is then followed by reaction with DBU to deliver the desired phenol **35.5**.[32]

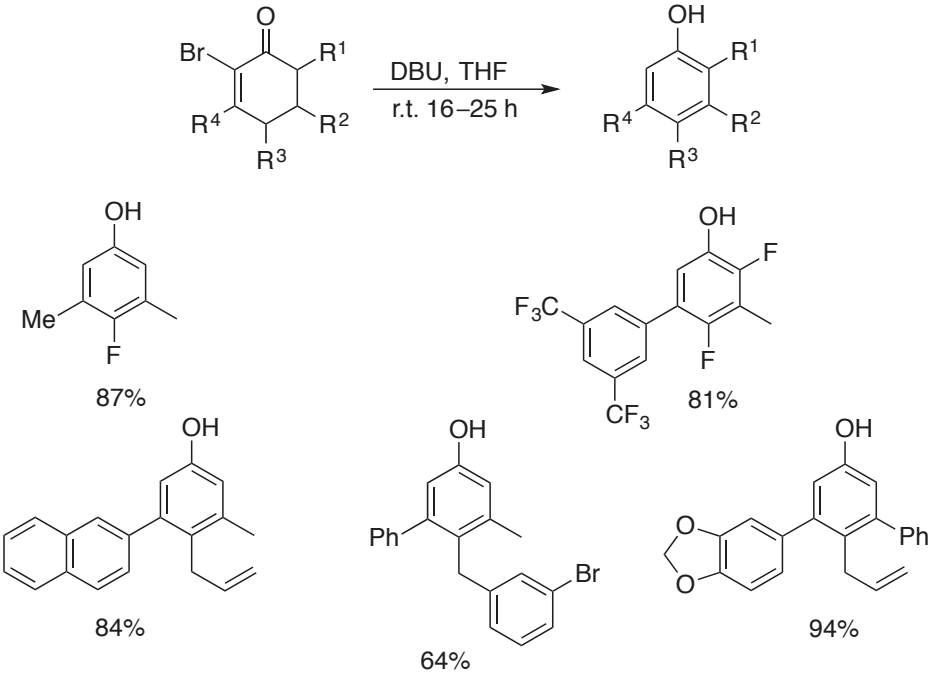


Scheme 35. A general route to synthesize *meta*-functionalized phenols

It was shown that the C5 methyl substituent in the starting bromo ketone plays no role and some compounds where that substituent is an aromatic group were made as well. Many examples of this organometallic carbonyl addition-acid hydrolysis and aromatization sequence to make *meta*-substituted phenols are presented in Scheme 36. This route to *meta*-substituted phenols also works with highly substituted cyclohexenones (Scheme 37).[32]



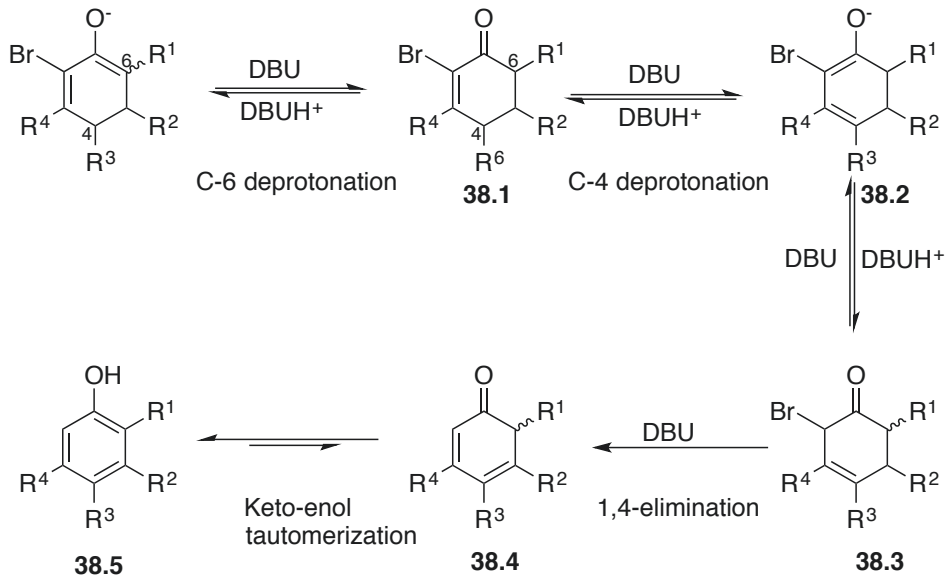
Scheme 36. Some *meta*-substituted phenols made by Yu



Scheme 37. Highly substituted phenols accessed by Yu

The proposed mechanism of the aromatization involves deprotonation at C4 or C6, but only C4 deprotonation of **38.1** can lead to aromatization product **38.5** through

intermediate **38.4**, which is formed by 1,4-elimination from **38.3**, itself formed by tautomerization of **38.2** in the presence of protonated DBU (Scheme 38).[32]



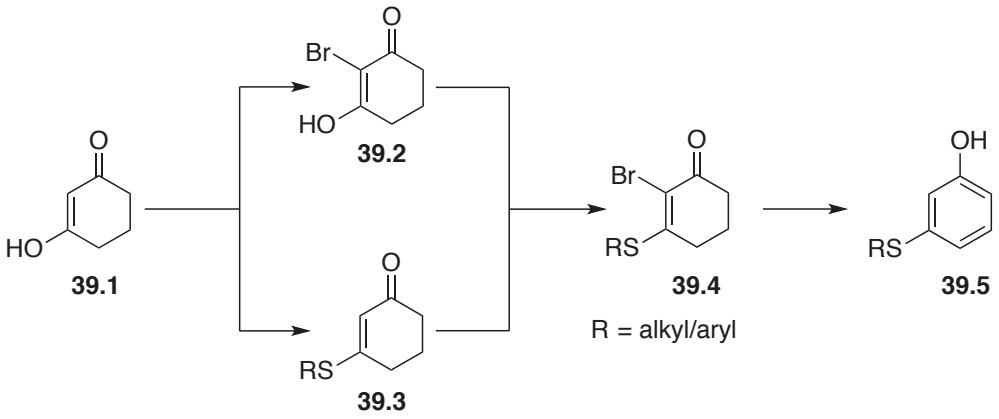
Scheme 38. Proposed mechanism for the DBU aromatization

Conclusion

There are many methodologies that have been used to make *meta*-(arylsulfanyl) and *meta*-(alkylsulfanyl)phenols. But those methodologies usually need a high temperature, a heavy metal catalyst, or they have limited scope or are not environmentally benign. *meta*-(Arylsulfanyl) and *meta*-(alkylsulfanyl)phenols are useful building blocks in the pharmaceutical industry and there is a need for routes to using mild and environmentally friendly conditions.

Results and discussions

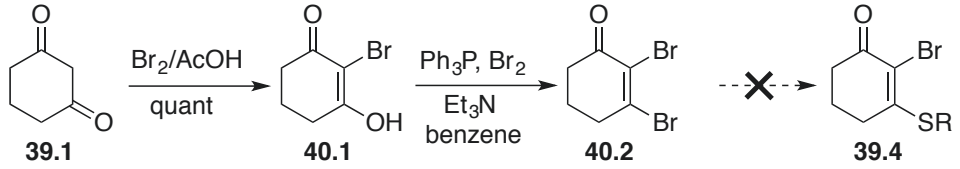
Based on the aromatization conditions reported from this laboratory,[30, 31, 32] I have extended the methodology to synthesize *meta*-(arylsulfanyl)- and *meta*-(alkylsulfanyl)phenols by treatment 2-bromo-3-(arylsulfanyl)cyclohex-2-en-1-ones (**39.4)** or the corresponding alkylsulfanyl compounds with DBU at room temperature. There are two ways to approach compound **39.4**, namely, by introducing the bromine before or after the sulfur unit, and both possibilities were investigated.



Scheme 39. Two approaches to synthesize *meta*-(arylsulfanyl) and *meta*-(alkylsulfanyl)phenols

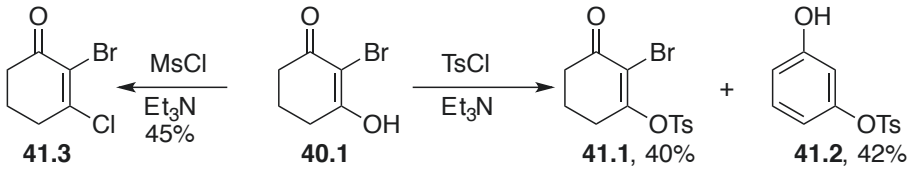
Introduction of bromine first

Cyclohexan-1,3-dione (**39.1**) was easily brominated, usually in near quantitative yield, by treatment with Br_2 in AcOH.[33] After that, the monobromide was converted to dibromide **40.1**[34] to introduce the sulfur unit through an addition-elimination process. However, this approach was unsatisfactory as the dibromide could not be stored without decomposition (Scheme 40).



Scheme 40. Attempted synthesis of bromoenones **39.4** by nucleophilic displacement using dibromide **40.2**

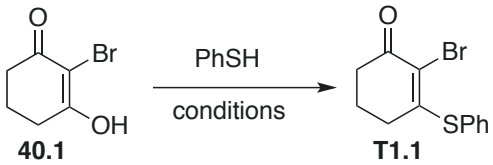
Therefore, the bromo tosylate **41.1** was prepared by using Et_3N and TsCl, but the yield was poor (40%) and the desired product was accompanied by the known tosyloxy phenol[35] **41.2**. Changing the conditions to the use of Et_3N and MsCl leads to 3-chloro-2-bromocyclohexenone (**41.3**) as the only product in 45% yield (Scheme 41).



Scheme 41. Formation of 2-bromo-, 3-(tosyloxy) and 3-chloroenones

Several attempts were then made to introduce the sulfur unit directly using **40.1**, but only simple treatment of **40.1** with 1 equivalent PhSH in methanol for 24 hours afforded the desired product **T1.1** in satisfactory yield (60%). All the attempts are summarized in Table 1.

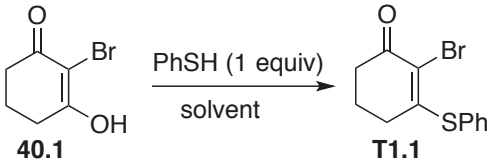
Table 1. Introduction of the phenylthio (PhS^-) unit



Conditions	Yield	Reference
PhSH, Ph_3P, DEAD	20 %	36
PhSH, DCC	desired product forms but cannot be purified	37
PhSH, HOBt, pyridine	No reaction	38
$(PhS)_2$, Ph_3P	8% desired product + debromination product	39
MeOH, PhSH	60%	

To increase the yield, variation of the solvent was examined, and MeOH was found to be the best. From Table 2 it is clear that the reaction works only in protic solvents.

Table 2. Solvent optimization for the PhSH displacement reaction

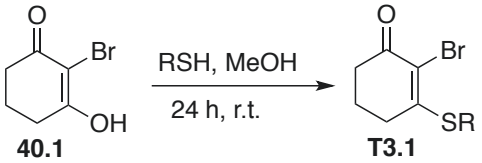


40.1 **T1.1**

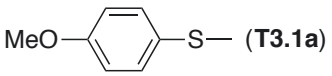
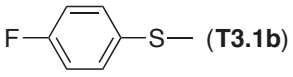
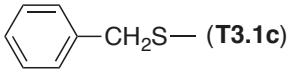
Solvent	**Yield**
MeOH	73 %
MeCN	No reaction
CF_3CH_2OH	65% (impure)
EtOH	65% (impure)
DMF	No reaction
DMSO	No reaction

Next, I tried to expand the scope, and some of the results are summarized in Table 3. Only *tert*-butyl thiol did not react. The others gave acceptable yields of the corresponding sulfides.

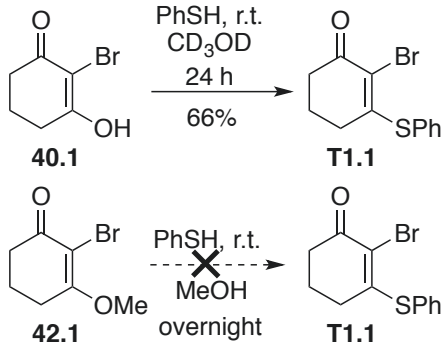
Table 3. Reaction of 2-bromocyclohexa-1,3-dione with some thiols



40.1 **T3.1**

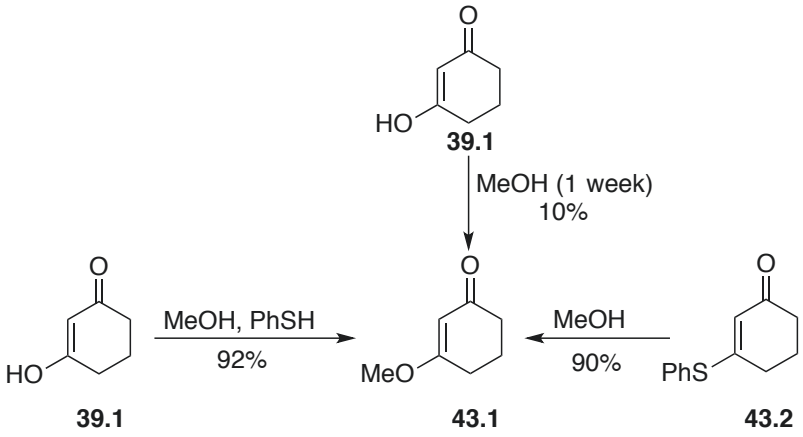
R	**Yield**
 (**T3.1a**)	75 %
 (**T3.1b**)	57%
 (**T3.1c**)	67%
Me_3CS— (**T3.1d**)	0%

The mechanism of this unusual transformation was investigated as well. Firstly the solvent was changed to CD_3OD, and the product **T1.1** was isolated in 66% yield but did not incorporate any deuterium. So I wondered if the observed formation of **T1.1** was the result of replacement OH by OMe, followed by displacement of the methoxy group. To test this possibility PhSH was added to a methanol solution of **42.1**. However, as judged by TLC analysis, none of the desired product **T1.1** had been formed (Scheme 42).



Scheme 42. Attempted to investigate the mechanism

In related experiments (Scheme 43), cyclohexane-1,3-dione (**39.1**) was stored in MeOH for one week, but only 10% of **43.1** was formed. But, when PhSH (1 equiv) was added the product **43.1** was formed in 92% yield after an overnight reaction period. In another experiment, vinylogous ester **43.1** was formed in 90% yield after keeping the keto sulfide **43.2** in MeOH overnight.



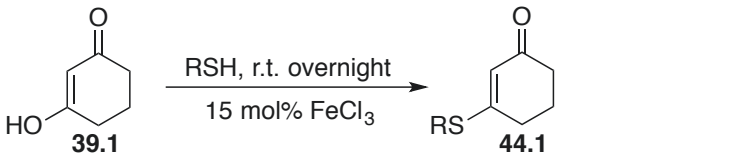
Scheme 43. Experiments to explore the unusual displacement mechanism

This observation caused me to store the bromoenones **T1.1** in MeOH to see if incursion of PhS/MeO exchange was responsible for the modest yield of **T1.1**, but this material was found to be stable in MeOH.

The outcome of these experiment forced me to turn to an alternative approach in which the bromine is introduced after the sulfur unit.

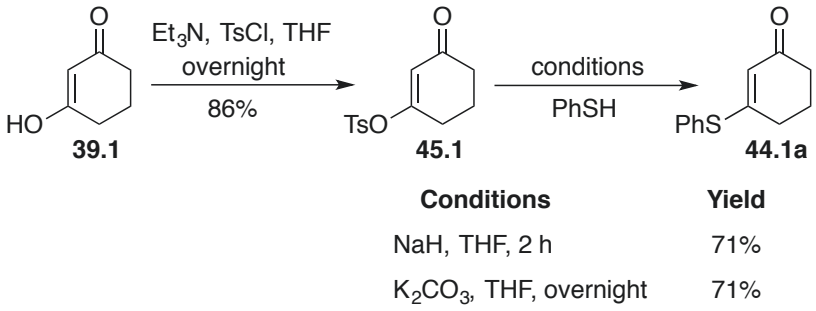
Introduction of sulfur first

At first, I tried to attach the sulfur unit through the solvent-free reaction between a thiol and cyclohexane-1,3-dione (**39.1**) using $FeCl_3$ as catalyst.[40] This method afforded the desired product in good yield (Scheme 44), but because some thiols are solids, this procedure is not general.



Scheme 44. Preparation of 3-(arylsulfanyl)cyclohexenone under solvent-free conditions

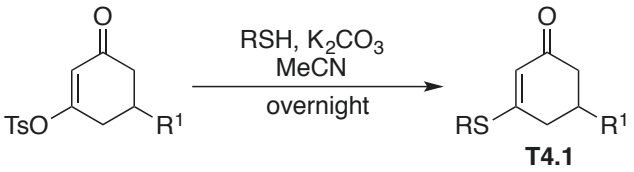
At this point I decided to make 3-(tosyloxy)cyclohexenone[41] in the hope that displacement with a thiol would give the desired product (**44.1**). Some results for screening to establish the best conditions for nucleophilic displacement are presented in Scheme 45.



Scheme 45. Screening conditions for the nucleophilic displacement reaction

Although the outcome of the two experiments is the same, K_2CO_3/THF[42, 43] is more environmental friendly than NaH, and so this system was used with a number of thiols. The results are summarized in Table 4.

Table 4. Preparation of 3-(arylsulfanyl)- and 3-(alkylsulfanyl)cyclohexenones through addition-elimination of the corresponding tosylate



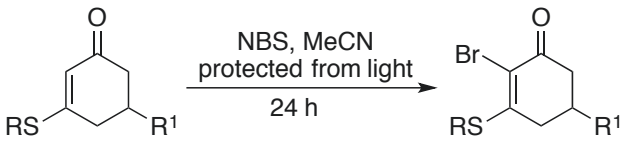
T4.1

R		**R^1**	**yield** (%)
Ph	**44.1a**	H	71
4-MeOC$_6$H$_4$	**44.1b**	H	90
4-FC$_6$H$_4$	**T4.1a**	H	90
4-BrC$_6$H$_4$	**T4.1b**	H	78
4-MeC$_6$H$_4$	**T4.1c**	H	93
2-MeC$_6$H$_4$	**T4.1d**	H	93
2-MeO$_2$CC$_6$H$_4$	**T4.1e**	H	85
Bn	**T4.1f**	H	82
t-Bu	**T4.1g**	H	40
Ph	**T4.1h**	Ph	81*

* The corresponding tosylate was made in 93% yield

The next step is the introduction of bromine at C2. In the case of the simplest example (**43.2**), bromination with NBS in CCl_4 had been reported,[44] but because of the presence of the sulfur atom, which could trigger unwanted side reactions,[45] I was uncertain about the generality of this methodology. However, by changing the solvent to acetonitrile and protecting the reaction flask from light it was possible to carry out bromination at C2 regardless of the electron-donating or electron-withdrawing substituent in the arylsulfanyl group. In comparison, use of NBS in CCl_4 gave lower yields (60%) in the several experiments tried with 3-(phenylthio)cyclohex-2-en-1-one.

Table 5. Bromination 3-(arylsulfanyl)- and 3-(alkylsulfanyl)cyclohexenones to the corresponding bromoenones

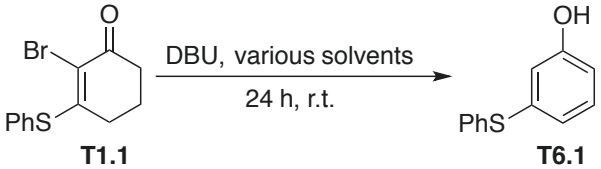


R	**R¹**	**yield** (%)
Ph	H	72[(a)]
4-$MeOC_6H_4$	H	74
4-FC_6H_4	H	73
4-BrC_6H_4	H	78
4-MeC_6H_4	H	74
2-MeC_6H_4	H	82
2-$MeO_2CC_6H_4$	H	60
Bn	H	72
t-Bu	H	42[(b)]
Ph	Ph	77

[(a)] NBS/CCl_4 gave only 60% yield after 24 h
[(b)] The main product was the disulfide of the corresponding bromoenone

Finally the aromatization with DBU was studied[30, 31, 32] with the simplest substrate **T1.1**. I began by investigating the effect of changing the solvent, but such changes had very little effect (Table 6); the individual solvents acetonitrile and dimethylformamide gave the best results. In the event I choose acetonitrile for the aromatization reaction because it is easier to remove and happens to be more environmentally friendly.[46]

Table 6. Effect of solvent on the DBU aromatization reaction

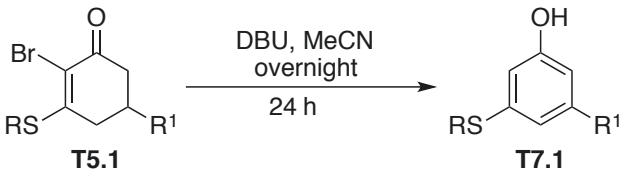


T1.1 **T6.1**

Solvent:	toluene	CH_2Cl_2	THF	MeCN	DMF
Yield:	83%	85%	85%	90%	90%

Using these conditions, the DBU-induced aromatization was applied to the bromoenones which are listed in Table 5 and the results are collected in Table 7.

Table 7. Aromatization of 2-bromo-3-(arylsulfanyl)cyclohex-2-en-1-ones and 2-bromo-3-(alkylsulfanyl)cyclohex-2-en-1-ones with DBU.



T5.1 **T7.1**

R		**R^1**	**yield** (%)
Ph	**T6.1**	H	90
4-$MeOC_6H_4$	**T7.1a**	H	86
4-FC_6H_4	**T7.1b**	H	60
4-BrC_6H_4	**T7.1c**	H	79
4-MeC_6H_4	**T7.1d**	H	75
2-MeC_6H_4	**T7.1e**	H	78
2-$MeO_2CC_6H_4$	**T7.1f**	H	72
Bn	**T7.1g**	H	65
t-Bu	**T7.1h**	H	25
Ph	**T7.1i**	Ph	63

Conclusion

In conclusion, *meta*-(arylsulfanyl)phenols and *meta*-(alkylsulfanyl)phenols were made in good yield, with the exception of 3-(*tert*-butyl)phenol, from cyclohexane-1,3-dione by converting it into the corresponding tosylate. This compound could itself be converted into 3-(arylsulfanyl)- and 3-(alkylsulfanyl)cyclohex-2-en-1-ones by treatment with a thiol and K_2CO_3 in MeCN. Bromination with NBS in MeCN and treatment with DBU provides the *meta*-(sulfanyl)phenols. This reaction sequence operates under mild and environmentally friendly conditions, without the need of heavy metals or expensive catalysts.

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 (N_2) 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. Gradient flash chromatography was done by stepwise small increases in the proportion of the more polar solvent, as described for the individual experiments. NBS was recrystallized from water.[47]

3-(Phenylsulfanyl)cyclohex-2-en-1-one (44.1a).[40]

45.1 **44.1a**

PhSH (0.055 mL, 0.50 mmol) was added to a stirred mixture of tosylate **45.1** (133 mg, 0.50 mmol), K_2CO_3 (413 mg, 2.50 mmol) and dry MeCN (1 mL) and stirring was continued overnight (N_2 atmosphere). Water (10 mL) was added and stirring was continued for 15 min. The mixture was extracted with EtOAc (3 × 15 mL) and the combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1 × 25 cm), using 4:1 hexane-EtOAc, gave 3-(phenylsulfanyl)cyclohex-2-en-1-one (**44.1a**) (72 mg, 71%) as an oil: ^1H NMR ($CDCl_3$, 400 MHz) δ 2.01–2.07 (m, 2 H), 2.34–2.38 (m, 2 H), 2.52 (td, *J* = 6.0, 0.8 Hz, 2 H), 7.40–7.48 (m, 5 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 22.9, 30.2, 37.2, 120.9, 128.0, 129.8, 130.1, 135.5, 166.8, 196.0.

2-Bromo-3-(phenylsulfanyl)cyclohex-2-en-1-one (T1.1).[44a]

44.1a **T1.1**

3-(Phenylsulfanyl)cyclohex-2-en-1-one (**44.1a**) (102 mg, 0.50 mmol) and freshly crystallized NBS (98 mg, 0.55 mmol) were placed in a round-bottomed flask containing a magnetic stirrer. Dry MeCN (1.0 mL) was added and the mixture was stirred for 24 h (N_2 atmosphere) with protection from light (flask wrapped in aluminum foil). EtOAc (15 mL) was added and the mixture was washed successively with aqueous $Na_2S_2O_3$ (1 M), saturated aqueous $NaHCO_3$, and brine. The organic extract was dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (3 × 15 cm), using 4:1 hexane-EtOAc, gave 2-bromo-3-(phenylsulfanyl)cyclohex-2-en-1-one (**T1.1**) (102 mg, 72%) as a solid: mp 112–113 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.93–1.97 (m, 2 H), 2.20 (t, *J* = 6.5 Hz, 2 H), 2.56 (t, *J* = 6.0 Hz, 2 H), 7.43–7.58 (m, 5 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 22.5, 32.2, 37.1, 116.8, 129.1, 129.7, 130.4, 136.0, 164.3, 187.7.

3-(Phenylsulfanyl)phenol (T6.1).[20]

T1.1 **T6.1**

DBU (0.032 mL, 0.212 mmol) was injected into a stirred solution of 2-bromo-3-(phenylsulfanyl)cyclohex-2-en-1-one (**T1.1**) (30 mg, 0.11 mmol) in dry MeCN (1.0 mL) and stirring was continued overnight (N_2 atmosphere). The mixture was diluted with hydrochloric acid (5%, 10 mL) and stirring was continued for 15 min. The mixture was extracted with EtOAc (3 × 15 mL) 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 successively hexane (ca 20 mL), 5% EtOAc-hexane (ca 50 mL) and 10% EtOAc-hexane (ca 100 mL), gave the desired product 3-(phenylsulfanyl)phenol (**T7.1a**) (19 mg, 89%) as an oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.98 (br s, 1 H), 6.70–6.80 (m, 1 H), 6.85–6.86 (m, 1 H), 6.98–7.00 (m, 1 H), 7.26 (t, *J* = 8.0 Hz, 1 H), 7.36–7.51 (m, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 113.9, 116.9, 122.7, 127.5, 129.3, 130.2, 131.9, 134.8, 137.89, 156.0.

3-[(4-Fluorophenyl)sulfanyl]cyclohex-2-en-1-one (T4.1a).[48]

45.1 **T4.1a**

The procedure for making 3-(phenylsulfanyl)cyclohex-2-en-1-one was followed exactly, using 4-fluorobenzene-1-thiol (0.042 mL, 0.50 mmol), tosylate **45.1** (133 mg, 0.50 mmol), K_2CO_3 (413 mg, 2.50 mmol) and dry MeCN (1 mL). Water (10 mL) was added and stirring was continued for 15 min. Flash chromatography of the crude product over silica gel (3 × 15 cm), using 4:1 hexane-EtOAc, gave 3-[(4-fluorophenyl)sulfanyl]cyclohex-2-en-1-one (**T4.1a**) (100 mg, 90%) as an oil: FTIR ($CDCl_3$, cast) 2949, 1659, 1589, 1491, 1324, 1227, 1187 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 2.03–2.06 (m, 2 H), 2.37 (t, J = 6.5 Hz, 2 H), 2.50–2.52 (m, 2 H), 5.41 (s, 1 H), 7.10–7.13 (m, 2 H), 7.44–7.47 (m, 2 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 23.0 (t), 30.2 (t), 37.3 (t), 117.2 (d, $^2J_{CF}$ = 22.2 Hz), 120.9 (d, $^4J_{CF}$ = 3.6 Hz), 123.4 (d), 137.7 (d, $^3J_{CF}$ = 8.5 Hz), 164.0 (d, $^1J_{CF}$ = 252.0 Hz), 165.0 (s), 166.7 (s), 196.0 (s); exact mass (EI) m/z calcd for $C_{12}H_{14}FOS$ (M^+) 222.0515, found 222.0515.

2-Bromo-3-[(4-fluorophenyl)sulfanyl]cyclohex-2-en-1-one (T3.1b).

T4.1a **T3.1b**

The procedure for making 2-bromo-3-(phenylsulfanyl)cyclohex-2-en-1-one was followed exactly, using 3-[(4-fluorophenyl)sulfanyl]cyclohex-2-en-1-one (**T4.1a**) (60 mg, 0.27 mmol), freshly crystallized NBS (53 mg, 0.30 mmol) and dry MeCN (1.0 mL). Flash chromatography of the crude product over silica gel (3 × 15 cm), using 4:1 hexane-EtOAc, gave 2-bromo-3-[(4-fluorophenyl)sulfanyl]cyclohex-2-en-1-one (**T3.1b**) (60 mg, 73%) as a solid: mp 135–136 °C; FTIR ($CDCl_3$, cast) 3097, 3070, 2956, 2935, 1665, 1588, 1543, 1491, 1266, 1222, 1185 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.95 (quintet, J = 6.5 Hz, 2 H), 2.16–2.19 (m, 2 H), 2.55 (t, J = 6.5 Hz, 2 H), 7.12–7.15 (m, 2 H), 7.54–7.56 (m, 2 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 22.5 (t), 32.2 (t), 37.1 (t), 117.02 (d, $^2J_{CF}$ = 22.1 Hz), 117.03 (s), 124.6 (d, $^4J_{CF}$ = 3.6 Hz), 138.2 (d, $^3J_{CF}$ = 8.7 Hz), 163.8 (s), 164.1 (d, $^1J_{CF}$ = 252.6 Hz), 187.6 (s); exact mass (EI) m/z calcd for $C_{12}H_{10}{}^{81}BrFOS$ (M^+) 301.9599, found 301.9597.

3-[(4-Fluorophenyl)sulfanyl]phenol (T7.1b).

T3.1b **T7.1b**

The procedure for making 3-(phenylsulfanyl)phenol was followed exactly, using DBU (0.088 mL, 0.590 mmol) and 2-bromo-3-[(4-fluorophenyl)sulfanyl]cyclohex-2-en-1-one (**T3.1b**) (88.4 mg, 0.294 mmol) in dry MeCN (1.0 mL). Flash chromatography of the crude product over silica gel (1 × 15 cm), using 3:7 hexane-CH_2Cl_2, gave 3-[(4-fluorophenyl)sulfanyl]phenol (**T7.1b**) (39 mg, 60%) as an oil: FTIR ($CDCl_3$, cast) 3380, 3092, 1589, 1489, 1474, 1439, 1225, 1156 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 4.81 (s, 1 H), 6.65–6.67 (m, 2 H), 6.80–6.82 (m, 1 H), 7.02–7.06 (m, 1 H), 7.14 (td, J = 8.0, 1.0 Hz, 1 H), 7.40–7.43 (m, 2 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 113.7 (d), 115.9 (d), 116.5 (d), 116.6 (d, $^2J_{CF}$ = 22.4 Hz), 121.7 (d), 129.3 (d, $^4J_{CF}$ = 3.4 Hz), 130.2 (d), 134.9 (d, $^3J_{CF}$ = 8.5 Hz), 138.7 (d), 156.0 (s), 162.7 (d, $^1J_{CF}$ = 248.5 Hz); exact mass (EI) *m/z* calcd for $C_{12}H_9OFS$ (M^+) 220.0358, found 220.0355.

3-[(4-Methoxyphenyl)sulfanyl]cyclohex-2-en-1-one (44.1b).[40]

45.1 **44.1b**

The procedure for making 3-(phenylsulfanyl)cyclohex-2-en-1-one was followed exactly, using 4-methoxybenzene-1-thiol (0.12 mL, 1.00 mmol), tosylate **45.1** (266 mg, 1.00 mmol), K_2CO_3 (826 mg, 5.00 mmol) and dry MeCN (2 mL) Flash chromatography of the crude product over silica gel (3 × 15 cm), using 4:1 hexane-EtOAc, gave 3-[(4-methoxyphenyl)sulfanyl]cyclohex-2-en-1-one (**44.1b**) (210 mg, 90%) as an oil: FTIR ($CDCl_3$, cast) 3004, 2962, 1654, 1587, 1578, 1494, 1325, 1290, 1250 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 2.04 (quintet, J = 6.5 Hz, 2 H), 2.36 (t, J = 6.5 Hz, 2 H), 2.49–2.51 (m, 2 H), 3.82 (s, 3 H), 5.42 (s, 1 H), 6.90–6.93 (m, 2 H), 7.36–7.38 (m, 2 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 22.9 (t), 30.1 (t), 37.3 (t), 55.4 (q), 115.5 (d), 118.5 (s), 120.6 (d), 137.0 (d), 161.2 (s), 168.0 (s), 196.1 (s); exact mass (EI) *m/z* calcd for $C_{13}H_{14}O_2S$ (M^+) 234.0715, found 234.0718.

2-Bromo-3-[(4-methoxyphenyl)sulfanyl]cyclohex-2-en-1-one (T3.1a).

44.1b **T3.1a**

The procedure for making 2-bromo-3-(phenylsulfanyl)cyclohex-2-en-1-one was followed exactly, using 3-[(4-methoxyphenyl)sulfanyl]cyclohex-2-en-1-one (**44.1b**) (86.2 mg, 0.353 mmol), freshly crystallized NBS (69.2 mg, 0.389 mmol) and dry MeCN (1.0 mL). Flash chromatography of the crude product over silica gel (3 × 15 cm), using 4:1 hexane-EtOAc, gave 2-bromo-3-[(4-methoxyphenyl)sulfanyl]cyclohex-2-en-1-one (**T3.1a**) (81.9 mg, 74%) as a solid: mp 115–117 °C; FTIR ($CDCl_3$, cast) 2971, 2947, 1662, 1590, 1454, 1438, 1253, 1187 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.93 (quintet, J = 6.4 Hz, 2 H), 2.18 (t, J = 6.4 Hz, 2 H), 2.53 (t, J = 6.4 Hz, 2 H), 3.84 (s, 3 H), 6.94 (d, J = 8.8 Hz, 2 H), 7.46 (d, J = 8.8 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 22.5 (d), 32.1 (d), 37.2 (d), 55.5 (q), 115.2 (d), 116.2 (s), 119.7 (s), 137.6 (d), 161.4 (s), 165.6 (s), 187.7 (s); exact mass (EI) m/z calcd for $C_{13}H_{13}{}^{81}BrO_2S$ (M^+) 313.9799, found 313.9796.

3-[(4-Methoxyphenyl)sulfanyl]phenol (T7.1a).

T3.1a **T7.1a**

The procedure for making 3-(phenylsulfanyl)phenol was followed exactly, using DBU (0.035 mL, 0.240 mmol) and 2-bromo-3-[(4-methoxyphenyl)sulfanyl]cyclohex-2-en-1-one (**T3.1a**) (37.5 mg, 0.120 mmol) in dry MeCN (1.0 mL). Flash chromatography of the crude product over silica gel (1 × 15 cm), using successively hexane (ca 20 mL), 5% EtOAc-hexane (ca 50 mL) and 10% EtOAc-hexane (ca 100 mL), gave 3-[(4-methoxyphenyl)sulfanyl]phenol (**T7.1a**) (24 mg, 86%) as an oil: FTIR ($CDCl_3$, cast) 3396, 1591, 1493, 1439, 1289, 1248, 1173 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 3.85 (s, 3 H), 4.92 (br s, 1 H), 6.57–6.60 (m, 2 H), 6.74 (ddd, J = 5.0, 1.5, 1.0 Hz, 1 H), 6.90 (dd, J = 9.0, 3.0 Hz, 2 H); 7.10 (t, J = 8.0 Hz, 1 H), 7.43 (dd, J = 9.0, 3.0 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 55.4 (q), 112.8 (d), 114.4 (d), 115.1 (d), 120.2 (d), 123.6 (s), 130.0 (d), 135.9 (d), 140.6 (s), 156.0 (s), 160.1 (s); exact mass (EI) m/z calcd for $C_{13}H_{12}O_2S$ (M^+) 232.0558, found 232.0561.

3-[(4-Bromophenyl)sulfanyl]cyclohex-2-en-1-one (T4.1b).

45.1 **T4.1b**

The procedure for making 3-(phenylsulfanyl)cyclohex-2-en-1-one was followed exactly, using 4-bromobenzene-1-thiol (378 mg, 2.00 mmol), tosylate **45.1** (532 mg, 2.00 mmol), K_2CO_3 (1.652 g, 10 mmol) and dry MeCN (4 mL). Flash chromatography of the crude product over silica gel (2 × 25 cm), using 4:1 hexane-EtOAc, gave 3-[(4-bromophenyl)sulfanyl]cyclohex-2-en-1-one (**T4.1b**) (443 mg, 78%) as an oil: FTIR ($CDCl_3$, cast) 3076, 2950, 2889, 1649, 1579 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 2.03–2.08 (m, 2 H), 2.38 (dd, J = 7.5, 1.0 Hz, 2 H), 2.51 (ddd, J = 7.5, 6.0, 1.0 Hz, 2 H), 5.45 (apparent t, J = 1.5 Hz, 1 H), 7.33–7.35 (m, 2 H), 7.54–7.57 (m, 2 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 22.9 (t), 30.2 (t), 37.2 (t), 121.1 (d), 125.0 (s), 127.1 (s), 133.1 (d), 137.0 (d), 165.9 (s), 195.9 (s); exact mass (EI) m/z calcd for $C_{12}H_{11}{}^{81}BrOS$ (M^+) 283.9694, found 283.9691.

2-Bromo-3-[(4-bromophenyl)sulfanyl]cyclohex-2-en-1-one (T5.1a).

T4.1b **T5.1a**

The procedure for making 2-bromo-3-(phenylsulfanyl)cyclohex-2-en-1-one was followed exactly, using 3-[(4-bromophenyl)sulfanyl]cyclohex-2-en-1-one (**T4.1b**) (200 mg, 0.710 mmol), freshly crystallized NBS (151 mg, 0.840 mmol) and dry MeCN (1.5 mL). Flash chromatography of the crude product over silica gel (1.2 × 25 cm), using 4:1 hexane-EtOAc, gave 2-bromo-3-[(4-bromophenyl)sulfanyl]cyclohex-2-en-1-one (**T5.1a**) (100 mg, 78%) as a solid: mp 118–120 °C; FTIR ($CDCl_3$, cast) 3079, 3060, 2957, 2931, 1666, 1538 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.94–1.99 (m, 2 H), 2.20 (dd, J = 6.0, 6.0 Hz, 2 H), 2.55–2.58 (m, 2 H), 7.41–7.44 (m, 2 H), 7.57–7.60 (m, 2 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 22.5 (t), 32.3 (t), 37.1 (t), 117.4 (s), 125.4 (s), 128.2 (s), 132.9 (d), 137.4 (d), 163.0 (s), 187.6 (s); exact mass (EI) m/z calcd for $C_{12}H_{10}{}^{79}BrOS$ $(M + H)^+$ 360.8894, found 360.8892.

3-[(4-Bromophenyl)sulfanyl]phenol (T7.1c).

T5.1a **T7.1c**

The procedure for making 3-(phenylsulfanyl)phenol was followed exactly, using DBU (0.08 mL, 0.53 mmol) and 2-bromo-3-[(4-bromophenyl)sulfanyl]cyclohex-2-en-1-one

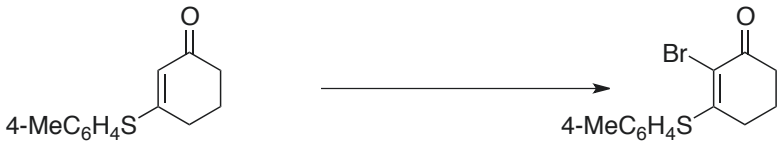
(**T5.1a**) (97 mg, 0.26 mmol) in dry MeCN (1.5 mL). Flash chromatography of the crude product over silica gel (1 × 30 cm), using successively hexane (ca 20 mL), 5% EtOAc-hexane (ca 50 mL) and 10% EtOAc-hexane (ca 100 mL), gave 3-[(4-bromophenyl)sulfanyl]phenol (**T7.1c**) (60 mg, 79%) as an oil: FTIR ($CDCl_3$, cast) 3375, 3059, 2954, 2925, 1583, 1472 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 4.84 (br s, 1 H), 6.72 (ddd, *J* = 8.0, 2.5, 0.5 Hz, 1 H), 6.77 (m, 1 H), 6.90 (ddd, *J* = 8.0, 1.5, 0.5 Hz, 1 H), 7.16–7.26 (m, 3 H), 7.43 (dt, *J* = 9.0, 2.0 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 114.5 (d), 117.4 (d), 121.4 (s), 123.2 (d), 130.4 (d), 132.4 (d), 132.9 (d), 134.5 (s), 136.8 (s), 156.0 (s); exact mass (EI) *m*/*z* calcd for $C_{12}H_8{}^{79}BrOS$ $(M - H)^-$ 278.9485, found 278.9477.

3-[(4-Methylphenyl)sulfanyl]cyclohex-2-en-1-one (T4.1c).[40]

45.1 **T4.1c**

The procedure for making 3-(phenylsulfanyl)cyclohex-2-en-1-one was followed exactly, using 4-methylbenzene-1-thiol (248 mg, 2.00 mmol), tosylate **45.1** (532 mg, 2.00 mmol), K_2CO_3 (1.652 g, 10.00 mmol) and dry MeCN (4 mL). Flash chromatography of the crude product over silica gel (2 × 25 cm), using 4:1 hexane-EtOAc, gave 3-[(4-methylphenyl)sulfanyl]cyclohex-2-en-1-one (**T4.1c**) (401 mg, 93%) as a solid: mp 45–48 °C; FTIR ($CDCl_3$, cast) 3023, 2948, 2866, 1659, 1578 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 2.02–2.07 (apparent dt, *J* = 13.0, 6.0 Hz, 2 H), 2.35–2.38 (m, 1 H), 2.38 (s, 3 H), 2.52 (ddd, *J* = 6.0, 6.0, 1.0 Hz, 2 H), 5.46 (apparent t, *J* = 1.0 Hz, 1 H), 7.21–7.23 (m, 2 H), 7.35 (dt, *J* = 8.0, 2.0 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 21.3 (q), 23.0 (t), 30.2 (t), 37.3 (t), 120.7 (d), 124.4 (s), 130.7 (d), 135.4 (d), 140.6 (s), 167.5 (s), 196.1 (s); exact mass (EI) *m*/*z* calcd for $C_{13}H_{14}OS$ (M^+) 218.0765, found 218.0766.

2-Bromo-3-[(4-methylphenyl)sulfanyl]cyclohex-2-en-1-one (T5.1b).



T4.1c **T5.1b**

The procedure for making 2-bromo-3-(phenylsulfanyl)cyclohex-2-en-1-one was followed exactly, using 3-[(4-methylphenyl)sulfanyl]cyclohex-2-en-1-one (**T4.1c**) (209 mg,

1.00 mmol), freshly crystallized NBS (195 mg, 1.10 mmol) and dry MeCN (1.5 mL). Flash chromatography of the crude product over silica gel (1.2 × 25 cm), using 4:1 hexane-EtOAc, gave 2-bromo-3-[(4-methylphenyl)sulfanyl]cyclohex-2-en-1-one (**T5.1b**) (210 mg, 74%) as a solid: mp 128–130 °C; FTIR ($CDCl_3$, cast) 3052, 3033, 2956, 2931, 1662, 1542 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.91–2.0 (m, 2 H), 2.20 (dd, *J* = 6.0, 6.0 Hz, 2 H), 2.41 (s, 3 H), 2.55 (dd, *J* = 7.0, 7.0 Hz, 2 H), 7.23–7.25 (m, 2 H), 7.42–7.44 (m, 2 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 21.4 (q), 22.5 (t), 32.1 (t), 37.2 (t), 116.5 (s), 125.6 (s), 130.4 (d), 135.9 (d), 140.9 (s), 164.9 (s), 187.7 (s); exact mass (EI) *m*/*z* calcd for $C_{13}H_{13}{}^{81}BrOS$ (M^+) 297.9850, found 297.9851.

3-[(4-Methylphenyl)sulfanyl]phenol (T7.1d).[27]

T5.1b **T7.1d**

The procedure for making 3-(phenylsulfanyl)phenol was followed exactly, using DBU (0.10 mL, 0.67 mmol) and 2-bromo-3-[(4-methylphenyl)sulfanyl]cyclohex-2-en-1-one (**T5.1b**) (102 mg, 0.33 mmol) in dry MeCN (1.5 mL). Flash chromatography of the crude product over silica gel (1 × 30 cm), using successively hexane (ca 20 mL), 5% EtOAc-hexane (ca 50 mL) and 10% EtOAc-hexane (ca 100 mL), gave 3-[(4-methylphenyl)sulfanyl]phenol (**T7.1d**) (56 mg, 75%) as an oil: FTIR ($CDCl_3$, cast) 3383, 3022, 2920, 2862, 1584, 1474 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 2.37 (s, 3 H), 4.90 (br s, 1 H), 6.63–6.68 (m, 2 H), 6.82–6.85 (m, 1 H), 7.11–7.17 (m, 3 H), 7.35 (dd, *J* = 6.5, 2.0 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 21.2 (q), 113.4 (d), 115.7 (d), 121.6 (d), 130.1 (d), 130.2 (d), 130.3 (s), 133.1 (d), 138.1 (s), 139.2 (s), 155.9 (s); exact mass (electrospray) *m*/*z* calcd for $C_{13}H_{11}OS$ $(M - H)^-$ 215.0536, found 215.0534.

3-[(2-Methylphenyl)sulfanyl]cyclohex-2-en-1-one (T4.1d).

45.1 **T4.1d**

The procedure for making 3-(phenylsulfanyl)cyclohex-2-en-1-one was followed exactly, using 2-methylbenzene-1-thiol (0.30 mL, 2.46 mmol), tosylate **45.1** (655 mg, 2.45

mmol), K_2CO_3 (1.70 g, 12.3 mmol) and dry MeCN (4 mL). Flash chromatography of the crude product over silica gel (2 × 25 cm), using 4:1 hexane-EtOAc, gave 3-[(2-methylphenyl)sulfanyl]cyclohex-2-en-1-one (**T4.1d**) (500 mg, 93%) as an oil: FTIR ($CDCl_3$, cast) 3059, 2949, 2866, 1656, 1578 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 2.06 (quintet, J = 6.5 Hz, 2 H), 2.37–2.39 (m, 5 H), 2.54 (td, J = 6.0, 1.0 Hz, 2 H), 5.32 (apparent t, J = 1.0 Hz, 1 H), 7.21–7.24 (m, 2 H), 7.30–7.37 (m, 2 H), 7.46 (ddd, J = 7.5, 1.0, 0.5 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 20.4 (q), 23.0 (t), 30.2 (t), 37.3 (t), 120.4 (d), 127.3 (s), 127.3 (d), 130.8 (d), 131.2 (d), 136.6 (d), 142.7 (s), 165.9 (s), 196.1 (s); exact mass (EI) *m*/*z* calcd for $C_{13}H_{14}OS$ (M^+) 218.0765, found 218.0765.

2-Bromo-3-[(2-methylphenyl)sulfanyl]cyclohex-2-en-1-one (T5.1c).

T4.1d **T5.1c**

The procedure for making 2-bromo-3-(phenylsulfanyl)cyclohex-2-en-1-one was followed exactly, using 3-[(2-methylphenyl)sulfanyl]cyclohex-2-en-1-one (**T4.1d**) (224 mg, 1.03 mmol), freshly crystallized NBS (200 mg, 1.13 mmol) and dry MeCN (1.5 mL). Flash chromatography of the crude product over silica gel (1.2 × 25 cm), using 4:1 hexane-EtOAc, gave 2-bromo-3-[(2-methylphenyl)sulfanyl]cyclohex-2-en-1-one (**T5.1c**) (250 mg, 82%) as a solid: mp 111–113 °C; FTIR ($CDCl_3$, cast) 3060, 3011, 2950, 2923, 1671, 1537 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.91–1.96 (m, 2 H), 2.1 (t, J = 6.0 Hz, 2 H), 2.45 (s, 3 H), 2.56 (dd, J = 7.5, 6.0 Hz, 2 H), 7.25–7.27 (m, 2 H), 7.33–7.37 (m, 1 H), 7.40 (ddd, J = 7.5, 1.5, 1.5 Hz, 1 H), 7.54 (dd, J = 7.5, 1.5 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 21.2 (q), 22.5 (t), 31.7 (t), 37.2 (t), 117.3 (s), 127.2 (d), 128.7 (s), 130.9 (d), 131.2 (d), 137.0 (d), 143.1 (s), 164.4 (s), 187.7 (s); exact mass (EI) *m*/*z* calcd for $C_{13}H_{13}{}^{79}BrOS$ (M^+) 295.9871, found 295.9872.

3-[(2-Methylphenyl)sulfanyl]phenol (T7.1e).

T5.1c **T7.1e**

The procedure for making 3-(phenylsulfanyl)phenol was followed exactly, using DBU (0.10 mL, 0.67 mmol) and 2-bromo-3-[(2-methylphenyl)sulfanyl]cyclohex-2-en-1-one (**T5.1c**) (95 mg, 0.32 mmol) in dry MeCN (1.5 mL). Flash chromatography of the crude product over silica gel (1 × 30 cm), using successively hexane (ca 20 mL), 5% EtOAc-hexane (ca 50 mL) and 10% EtOAc-hexane (ca 100 mL), gave 3-[(2-methylphenyl)sulfanyl]phenol (**T7.1e**) (54 mg, 78%) as an oil: FTIR ($CDCl_3$, cast) 3376, 3060, 2961, 2923, 1584, 1473 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 2.42 (s, 3 H), 4.95 (br s, 1 H), 6.62–6.63 (m, 1 H), 6.66 (dd, *J* = 8.0, 1.0 Hz, 1 H), 6.80 (dd, *J* = 8.0, 1.0 Hz, 1 H), 7.15 (t, *J* = 8.0 Hz, 1 H), 7.17–7.21 (m, 1 H), 7.25–7.32 (m, 2 H), 7.45 (d, *J* = 8.0 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 20.7 (q), 113.3 (d), 115.5 (d), 121.4 (d), 126.8 (d), 128.5 (d), 130.2 (d), 130.8 (d), 132.8 (s), 134.0 (d), 138.3 (s), 140.8 (s), 156.0 (s); exact mass (electrospray) *m*/*z* calcd for $C_{13}H_{11}OS$ $(M - H)^-$ 215.0536, found 215.0538.

Methyl 2-[(3-oxocyclohex-1-en-1-yl)sulfanyl]benzoate (T4.1e).

45.1 **T4.1e**

The procedure for making 3-(phenylsulfanyl)cyclohex-2-en-1-one was followed exactly, using methyl 2-sulfanylbenzoate[49] (168 mg, 1.00 mmol), tosylate **45.1** (266 mg, 1.00 mmol), K_2CO_3 (826 mg, 5.00 mmol) and dry MeCN (2 mL). Flash chromatography of the crude product over silica gel (3 × 15 cm), using 4:1 hexane-EtOAc, gave methyl 2-[(3-oxocyclohex-1-en-1-yl)sulfanyl]benzoate (**T4.1e**) (222.5 mg, 85%) as an oil: FTIR ($CDCl_3$, cast) 1731, 1656, 1578, 1467, 1293, 1271 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 2.05 (quintet, *J* = 6.5 Hz, 2 H), 2.38 (t, *J* = 6.5 Hz, 1 H), 2.52–2.54 (m, 2 H), 3.88 (s, 3 H), 5.57 (s, 1 H), 7.46–7.58 (m, 2 H); 7.89 (dd, *J* = 6.0, 1.5 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 22.9 (t), 30.4 (t), 37.2 (t), 52.5 (q), 122.4 (d), 129.2 (d), 129.8 (s), 131.2 (d), 132.4 (d), 135.2 (s), 137.1 (d), 165.6 (s), 166.5 (s), 196.3 (s); exact mass (EI) *m*/*z* calcd for $C_{14}H_{14}O_3S$ (M^+) 262.0664, found 262.0663.

Methyl 2-[(2-bromo-3-oxocyclohex-1-en-1-yl)sulfanyl]benzoate (T5.1d).

T4.1e **T5.1d**

The procedure for making 2-bromo-3-(phenylsulfanyl)cyclohex-2-en-1-one was followed exactly, using methyl 2-[(3-oxocyclohex-1-en-1-yl)sulfanyl]benzoate (**T4.1e**) (204.4 mg, 0.780 mmol), freshly crystallized NBS (153.6 mg, 0.860 mmol) and dry MeCN (1 mL). Flash chromatography of the crude product over silica gel (3 × 15 cm), using 4:1 hexane-EtOAc, gave methyl 2-[(2-bromo-3-oxocyclohex-1-en-1-yl)sulfanyl]benzoate (**T5.1d**) (160 mg, 60%) as a solid: mp 117–120 °C; FTIR ($CDCl_3$, cast) 3089, 1726, 1668, 1569, 1351, 1136, 1118 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.95 (quintet, J = 6.0 Hz, 2 H), 2.26 (t, J = 6.0 Hz, 2 H), 2.57 (t, J = 6.5 Hz, 2 H), 3.90 (s, 3 H), 5.57 (s, 1 H), 7.54–7.56 (m, 2 H), 7.64–7.66 (m, 1 H), 7.87–7.89 (m, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 22.6 (t), 32.3 (t), 37.3 (t), 52.8 (q), 117.5 (s), 129.2 (s), 130.5 (d), 130.8 (d), 132.1 (d), 136.7 (s), 137.8 (d), 164.4 (s), 166.9 (s), 188.0 (s); exact mass (EI) m/z calcd for $C_{14}H_{13}{}^{81}BrO_3S$ (M^+) 341.9748, found 341.9752.

Methyl 2-[(3-hydroxyphenyl)sulfanyl]benzoate (T7.1f).[50]

T5.1d **T7.1f**

The procedure for making 3-(phenylsulfanyl)phenol was followed exactly, using DBU (0.08 mL, 0.54 mmol) and methyl 2-[(2-bromo-3-oxocyclohex-1-en-1-yl)sulfanyl]benzoate (**T5.1d**) (92 mg, 0.27 mmol) in dry MeCN (1 mL). Flash chromatography of the crude product over silica gel (3 × 20 cm), using successively hexane (ca 100 mL), 5% EtOAc-hexane (ca 100 mL) and 10% EtOAc-hexane (ca 100 mL) and 20% EtOAc-hexane (ca 100 mL), gave methyl 2-[(3-hydroxyphenyl)sulfanyl]benzoate (**T7.1f**) (50.5 mg, 72%) as an oil: FTIR ($CDCl_3$, cast) 3409, 1714, 1693, 1587, 1307, 1273, 1255 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 3.97 (s, 3 H), 5.24 (br s, 1 H), 6.89–6.92 (m, 2 H), 7.08–7.14 (m, 3 H), 7.24–7.31 (m, 2 H), 7.96 (dd, J = 6.5, 1.5 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 52.3 (q), 116.4 (d), 121.9 (d), 124.5 (d), 126.9 (s), 127.6 (d), 127.8 (d), 130.8 (d), 131.0 (d), 132.5 (d), 133.9 (s), 142.9 (s), 156.5 (s), 167.2 (s); exact mass (EI) m/z calcd for $C_{14}H_{12}O_3S$ (M^+) 260.0507, found 260.0508.

3-(Benzylsulfanyl)cyclohex-2-en-1-one (T4.1f).

45.1 **T4.1f**

The procedure for making 3-(phenylsulfanyl)cyclohex-2-en-1-one was followed exactly, using phenylmethanethiol (0.12 mL, 1.0 mmol), tosylate **45.1** (266 mg, 1.00 mmol), K_2CO_3 (826 mg, 5.00 mmol) and dry MeCN (2 mL). Flash chromatography of the crude product over silica gel (3 × 15 cm), using 4:1 hexane-EtOAc, gave 3-(benzylsulfanyl)cyclohex-2-en-1-one (**T4.1f**) (179 mg, 82%) as a solid: mp 75–77 °C; FTIR ($CDCl_3$, cast) 3054, 1654, 1573, 1452, 1295, 1264 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 2.03 (quintet, J = 6.0 Hz, 2 H), 2.40 (t, J = 6.0 Hz, 2 H), 2.45–2.47 (m, 2 H), 4.03 (s, 2 H), 5.95 (s 1 H), 7.26–7.34 (m, 5 H; ^{13}C NMR ($CDCl_3$, 125 MHz) δ 23.0 (t), 30.7 (t), 35.9 (t), 37.4 (t), 120.0 (d), 127.8 (d), 128.9 (d), 134.7 (s), 165.2 (s), 195.8 (s); exact mass (EI) *m*/*z* calcd for $C_{13}H_{14}OS$ (M^+) 218.0765, found 218.0767.

3-(Benzylsulfanyl)-2-bromocyclohex-2-en-1-one (T3.1c).

T4.1f **T3.1c**

The procedure for making 2-bromo-3-(phenylsulfanyl)cyclohex-2-en-1-one was followed exactly, using 3-(benzylsulfanyl)cyclohex-2-en-1-one (**T4.1f**) (54.5 mg, 0.250 mmol), freshly crystallized NBS (49.2 mg, 0.275 mmol) and dry MeCN (1.0 mL). Flash chromatography of the crude product over silica gel (3 × 15 cm), using 4:1 hexane-EtOAc, gave 3-(benzylsulfanyl)-2-bromocyclohex-2-en-1-one (**T3.1c**) (54 mg, 72%) as a solid: mp 112-114 °C; FTIR ($CDCl_3$, cast) 2950, 2666, 1667, 1532, 1494, 1453, 1261, 1184 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 2.07 (quintet, J = 6.5 Hz, 2 H), 2.55–2.58 (m, 2 H), 2.70 (t, J = 6.0 Hz, 2 H), 4.15 (s, 2 H), 7.30–7.38 (m, 5 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 22.4 (t), 31.2 (t), 36.6 (t), 36.9 (t), 117.1 (s), 127.9 (d), 128.8 (d), 129.0 (d), 135.0 (s), 163.7 (s), 187.3 (s); exact mass (EI) *m*/*z* calcd for $C_{13}H_{13}{}^{81}BrOS$ (M^+) 297.9850, found 297.9856.

3-(Benzylsulfanyl)phenol (T7.1g).[52]

T3.1c **T7.1g**

The procedure for making 3-(phenylsulfanyl)phenol was followed exactly, using DBU (0.050 mL, 0.318 mmol) and 3-(benzylsulfanyl)-2-bromocyclohex-2-en-1-one (**T3.1c**) (31.5 mg, 0.106 mmol) in dry MeCN (1.0 mL). Flash chromatography of the crude product over silica gel (1 × 15 cm), using 3:7 hexane-CH_2Cl_2, gave 3-(benzylsulfanyl)phenol (**T7.1g**) (15 mg, 65%) as an oil: FTIR ($CDCl_3$, cast) 3386, 3084, 3061, 1581, 1493, 1475, 1247, 1216 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 4.12 (s, 2 H), 4.90 (br s, 1 H), 6.64 (dd, *J* = 8.0, 2.0 Hz, 1 H), 6.78 (t, *J* = 2.0 Hz, 1 H), 6.88 (d, *J* = 8.0 Hz, 1 H), 7.13 (t, *J* = 8.0 Hz, 1 H), 7.23–7.33 (m, 5 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 38.7 (t), 113.4 (d), 116.1 (d), 121.8 (d), 127.3 (d), 128.6 (d), 128.9 (d), 129.9 (d), 137.3 (s), 138.2 (s) 155.8 (s); exact mass (EI) *m*/*z* calcd for $C_{13}H_{12}OS$ (M^+) 216.0609, found 216.0605.

5-Phenyl-3-(phenylsulfanyl)cyclohex-2-en-1-one (T4.1h).

(a) 3-Oxo-5-phenylcyclohex-1-en-1-yl 4-methylbenzene-1-sulfonate (No number mentioned in the discussion).[53]

Et_3N (0.5 mL, 3.6 mmol) was added to a stirred solution of commercial 3-hydroxy-5-phenylcyclohex-2-en-1-one (565 mg, 3.00 mmol) and TsCl (573 mg, 3.00 mmol) in dry THF (10 mL), and stirring was continued overnight (N_2 atmosphere). Water (15 mL) was added and stirring was continued for 30 min. The mixture was extracted with Et_2O (3 × 20 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated to afford 3-oxo-5-phenylcyclohex-1-en-1-yl 4-methylbenzene-1-sulfonate (946.5 mg, 92%) as a solid, which was used directly in the next step. The material had: mp 86–88 °C; FTIR ($CDCl_3$, cast) 3063, 1678, 1635, 1426, 1376, 1194, 1179 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 2.48 (s, 3 H), 2.56 (dd, *J* = 16.0, 13.0 Hz, 1 H), 2.65 (dd, *J* = 16.0, 4.0 Hz, 1 H), 2.74 (dd, *J* = 6.5, 1.5 Hz, 2 H), 3.31–3.38 (m, 1 H), 5.90 (s, 1 H), 7.17–7.19 (m, 2 H), 7.25–7.28 (m, 1 H), 7.32–7.39 (m, 4 H), 7.81–7.84 (m, 2 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 21.8 (d), 36.4 (t), 39.2 (q), 43.6 (t), 116.6 (d), 126.6 (d), 127.4 (d), 128.3 (d), 129.0 (d), 130.2 (d), 132.5 (s),

141.6 (s), 146.3 (s), 167.3 (s), 197.8 (s); exact mass (EI) *m*/*z* calcd for $C_{19}H_{18}O_4S$ (M^+) 342.0926, found 342.0926.

(b) 5-Phenyl-3-(phenylsulfanyl)cyclohex-2-en-1-one (T4.1h).

T4.1h

The procedure for making 3-(phenylsulfanyl)cyclohex-2-en-1-one was followed exactly, using PhSH (0.105 mL, 1.00 mmol), 3-oxo-5-phenylcyclohex-1-en-1-yl 4-methylbenzene-1-sulfonate (342 mg, 1.00 mmol), K_2CO_3 (826 mg, 12.3 mmol) and dry MeCN (2 mL). Flash chromatography of the crude product over silica gel (3 × 15 cm), using 4:1 hexane-EtOAc, gave 5-phenyl-3-(phenylsulfanyl)cyclohex-2-en-1-one (**T4.1h**) (234.2 mg, 80%) as a solid: mp 85–87 °C; FTIR ($CDCl_3$, cast) 3059, 3028, 1653, 1577, 1440, 1290, 1255, 1040 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 2.58–2.83 (m, 4 H), 3.37–3.44 (m, 1 H), 5.56 (d, *J* = 1.5 Hz, 1 H), 7.24–7.29 (m, 3 H), 7.34–7.37 (m, 2 H), 7.42–7.45 (m, 3 H), 7.49–7.51 (m, 2 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 37.8 (s), 41.0 (d), 44.2 (s), 120.7 (d), 126.8 (d), 127.2 (d), 127.9 (d), 128.9 (s), 130.0 (d), 130.3 (d), 135.5 (d), 142.6 (s), 166.0 (s), 195.5 (s); exact mass (EI) *m*/*z* calcd for $C_{18}H_{16}OS$ (M^+) 280.0922, found 280.0923.

2-Bromo-5-phenyl-3-(phenylsulfanyl)cyclohex-2-en-1-one (T5.1e).

T4.1h **T5.1e**

The procedure for making 2-bromo-3-(phenylsulfanyl)cyclohex-2-en-1-one was followed exactly, using 5-phenyl-3-(phenylsulfanyl)cyclohex-2-en-1-one (**T4.1h**) (200 mg, 0.714 mmol), freshly crystallized NBS (140.6 mg, 0.786 mmol) and dry MeCN (1.0 mL). Flash chromatography of the crude product over silica gel (3 × 15 cm), using 9:1 hexane-EtOAc, gave 2-bromo-5-phenyl-3-(phenylsulfanyl)cyclohex-2-en-1-one (**T5.1e**) (197 mg, 77%) as a solid: mp 128–132 °C; FTIR ($CDCl_3$, cast) 3059, 1671, 1538, 1453, 1440, 1264, 1242 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 2.39–2.48 (m, 2 H), 2.76 (dd, *J* = 16.0, 13.0 Hz, 1 H), 2.87 (ddd, *J* = 11.5, 4.0, 1.5 Hz, 1 H), 3.30–3.37 (m, 1 H), 7.06–7.08 (m, 2 H), 7.20–7.30 (m, 3 H), 7.38–7.46 (m, 3 H), 7.52–7.55 (m, 2 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 39.2 (t),

40.4 (d), 43.9 (t), 116.9 (d), 126.6 (d), 127.3 (d), 128.8 (d), 128.9 (s), 129.8 (d), 130.6 (d), 135.9 (d), 141.8 (s), 163.0 (s), 187.2 (s); exact mass (EI) *m*/*z* calcd for $C_{18}H_{15}{}^{81}BrOS$ (M^+) 360.0006, found 360.0002.

5-Phenyl-3-(phenylsulfanyl)phenol (T7.1i).

T5.1e **T7.1i**

The procedure for making 3-(phenylsulfanyl)phenol was followed exactly, using DBU (0.025 mL, 0.17 mmol) and 2-bromo-5-phenyl-3-(phenylsulfanyl)cyclohex-2-en-1-one (**T5.1e**) (30.6 mg, 0.085 mmol) in dry MeCN (1.0 mL). Flash chromatography of the crude product over silica gel (1 × 15 cm), using 3:7 hexane-CH_2Cl_2, gave 5-phenyl-3-(phenylsulfanyl)phenol (**T7.1i)** (17 mg, 63%) as an oil: FTIR ($CDCl_3$, cast) 3391, 3059, 2953, 1586, 1570, 1476, 1449, 1196 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 4.83 (s, 1 H), 6.71 (dd, *J* = 2.0, 1.5 Hz, 1 H), 6.91 (dd, *J* = 2.0, 1.5 Hz, 1 H), 7.15 (t, *J* = 1.5 Hz, 1 H), 7.27–7.36 (m, 4 H), 7.40–7.45 (m, 4 H), 7.50–7.52 (m, 2 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 112.9 (d), 115.7 (d), 121.6 (d), 127.1 (d), 127.6 (d), 127.8 (d), 128.8 (d), 129.4 (d), 132.0 (d), 134.7 (s), 138.4 (s), 140.1 (s), 143.7 (s), 156.3 (s); exact mass (EI) *m*/*z* calcd for $C_{18}H_{14}OS$ (M^+) 278.0765, found 279.0771.

3-(*tert*-Butylsulfanyl)cyclohex-2-en-1-one (T4.1g).

45.1 **T4.1g**

The procedure for making 3-(phenylsulfanyl)cyclohex-2-en-1-one was followed exactly, using 2-methylpropane-2-thiol (0.11 mL, 1.00 mmol), tosylate **45.1** (266 mg, 1.00 mmol), K_2CO_3 (826 mg, 5.00 mmol) and dry MeCN (2 mL). Flash chromatography of the crude product over silica gel (3 × 15 cm), using 4:1 hexane-EtOAc, gave 3-(*tert*-butylsulfanyl)cyclohex-2-en-1-one (**T4.1g**) (73.4 mg, 40%) as an oil: FTIR ($CDCl_3$, cast) 2963, 1659, 1570, 1457, 1338 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.48 (s, 9 H), 1.99 (quintet *J* = 6.0 Hz, 2 H), 2.36–2.38 (m, 4 H), 6.11 (s, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ

22.8 (t), 30.4 (q), 31.7 (t), 37.2 (t), 47.4 (s), 122.6 (d), 164.5 (s), 196.0 (s); exact mass (EI) *m*/*z* calcd for $C_{10}H_{16}OS$ (M^+) 184.0922, found 184.0922.

2-Bromo-3-(*tert*-butylsulfanyl)cyclohex-2-en-1-one (T3.1d).

T4.1g **T3.1d**

The procedure for making 2-bromo-3-(phenylsulfanyl)cyclohex-2-en-1-one was followed exactly, using 3-(*tert*-butylsulfanyl)cyclohex-2-en-1-one (**T4.1g**) (65 mg, 0.35 mmol), freshly crystallized NBS (63.2 mg, 0.350 mmol) and dry MeCN (0.5 mL). Flash chromatography of the crude product over silica gel (3 × 15 cm), using 4:1 hexane-EtOAc, gave 2-bromo-3-(*tert*-butylsulfanyl)cyclohex-2-en-1-one (**T3.1d**) (40 mg, 42%) as a solid: mp 102–103 °C; FTIR ($CDCl_3$, cast) 2965, 1661, 1517, 1472, 1262, 1248 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.56 (s, 9 H), 2.09 (quintet, *J* = 6.0 Hz, 2 H), 2.60 (t, *J* = 6.0 Hz, 2 H), 2.93 (t, *J* = 6.0 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 22.8 (t), 32.3 (q), 32.9 (t), 37.4 (t), 49.6 (s), 119.2 (s), 164.6 (s), 187.8 (s); exact mass (EI) *m*/*z* calcd for $C_{10}H_{15}{}^{81}BrOS$ (M^+) 264.0006, found 264.0004.

3-(*tert*-Butylsulfanyl)phenol (T7.1h).

T3.1d **T7.1h**

The procedure for making 3-(phenylsulfanyl)phenol was followed exactly, using DBU (0.034 mL, 0.226 mmol) and 2-bromo-3-(*tert*-butylsulfanyl)cyclohex-2-en-1-one (**T3.1d**) (29.5 mg, 0.113 mmol) in dry MeCN (1 mL). Flash chromatography of the crude product over silica gel (1 × 15 cm), using 2:8 hexane-CH_2Cl_2, gave 3-(*tert*-butylsulfanyl)phenol (**T7.1h**) (5 mg, 25%) as an oil: FTIR ($CDCl_3$, cast) 3355, 2961, 1583, 1469, 1456, 1245, 1210, 1159 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.29 (s, 9 H), 4.76 (s, 1 H), 6.84 (dd, *J* = 8.0, 2.5 Hz, 1 H), 7.03 (t, *J* = 1.5 Hz, 1 H), 7.11 (d, *J* = 7.5 Hz, 1 H), 7.20 (t, *J* = 8.0 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 31.0 (q), 46.1 (s), 115.9 (d), 124.0 (d), 129.4

(d), 129.9 (d), 134.1 (s), 155.2 (s); exact mass (EI) *m*/*z* calcd for $C_{10}H_{14}OS$ (M^+) 182.0765, found 182.0764.

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Chapter 2

Synthetic studies on sorbicillactone A and sorbicillactone B

Isolation and bioactivities of sorbicillactone A and sorbicillactone B.

In 2005, Bringmann and coworkers[1] reported two new sorbicillinoid alkaloids, namely sorbicillactone A (**1.1**) and sorbicillactone B (**1.2**) (Figure 1). The compounds were isolated from *Penicillum chrysogenum*, one of the most widespread fungal species, by using preparative HPLC. Compounds **1.1** and **1.2** are members of a large family of fungal natural products called sorbicillinoids; the chemistry of these substances has been reviewed in detail by Harned.[2]

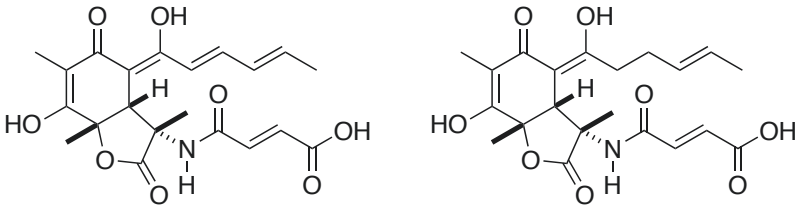


Figure 1. The structure of sorbicillactones A and B

After isolation and characterization of the two compounds, Bringmann and coworkers[1] continued to study their biolactivities. Sorbicillactone A (**1.1**) has cytotoxic and cytostatic activity against several tumor cell lines, namely murine leukemic lymphoblast L5187y, rat adrenal pheochromocytoma PC12 cells, human T lymphocytes H9 cells and human cervix carcinoma HeLa S3 cells. While sorbicillactone A displays selective cytotoxicity against murine leukemic lymphoblast L5187y (IC_{50} = 2.2 μg/mL), the IC_{50} values with the other cell lines are all above 10 μg/mL. The structurally related sorbicillactone B (**1.2)** exhibited a significantly lower activity than **1.1**, with IC_{50} values all above 10 μg/mL. These results indicate the importance of the fully unsaturated side chain for cytotoxic activity.

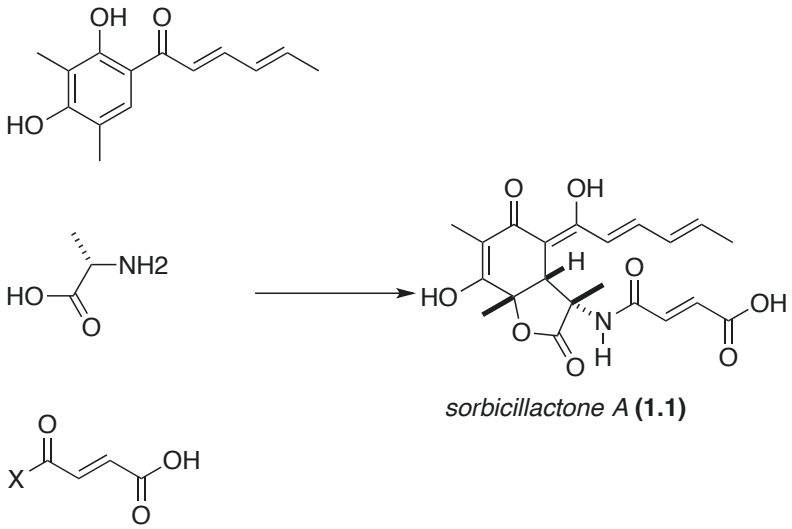
Besides its cytotoxicity, **1.1** also shows high anti-HIV activity;[1] in the concentration range between 0.3 and 3.0 μg/L, **1.1** protected human T lymphocytes (H9 cells) against the cytopathic effect of HIV-1 and inhibited the expression of viral proteins.

Finally, and most interestingly, **1.1** shows that it could block the effects of both serotonin and L-glutamic acid on calcium concentrations in primary neurons by decreasing the [Ca^{2+}] level (approximately 50%).[1] The role of serotonin,[3] L-glutamic acid[4] and the increase of calcium concentrations[5] in neuronal cell death were already known. Therefore, these *in vivo* results suggests that **1.1** could serve as a neuroprotective agent, which could be used in the treatment of stroke.[6]

Because of the amazing bioactivity of sorbicillactone A, it has been passed for human trials.[7] Bringmann and coworkers[8] developed a large scale fermentation method which has produced 100 g of pure **1.1**. The cost of separating **1.2** from **1.1** is high and collecting the marine fungus is difficult; the compound was not developed.[9]

Biosynthesis of sorbicillactone A and B.

The molecular structures of **1.1** and **1.2** suggested that their biosynthetic origin could be from sorbicillin, L-alanine and a fumaric acid precursor (Scheme 1).[1] To confirm this hypothesis, Bringmann *et al*.[1] performed feeding experiments with [$^{13}C_3$]-L-alanine, [$^{13}C_2$]-acetate and [methyl-^{13}C]-L-methionine after optimization of the growth conditions of the fungus to afford **1.1** as the major metabolite.

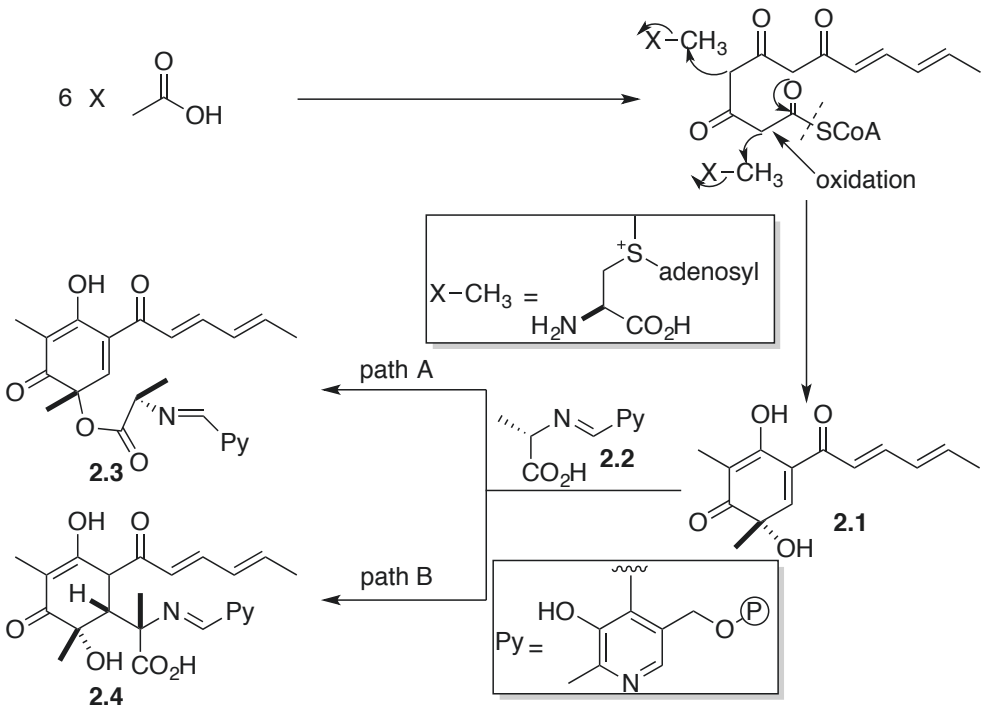


sorbicillactone A **(1.1)**

Scheme 1. Proposed biosynthesis of sorbicillactone A from sorbicillin, L-alanine and a fumaric acid precursor

Based on the feeding experiments, Bringmann proposed a biosynthetic pathway to **1.1**[1] via oxidative dearomatization of sorbicillin to provide sorbicillinol (**2.1**, Scheme 2).

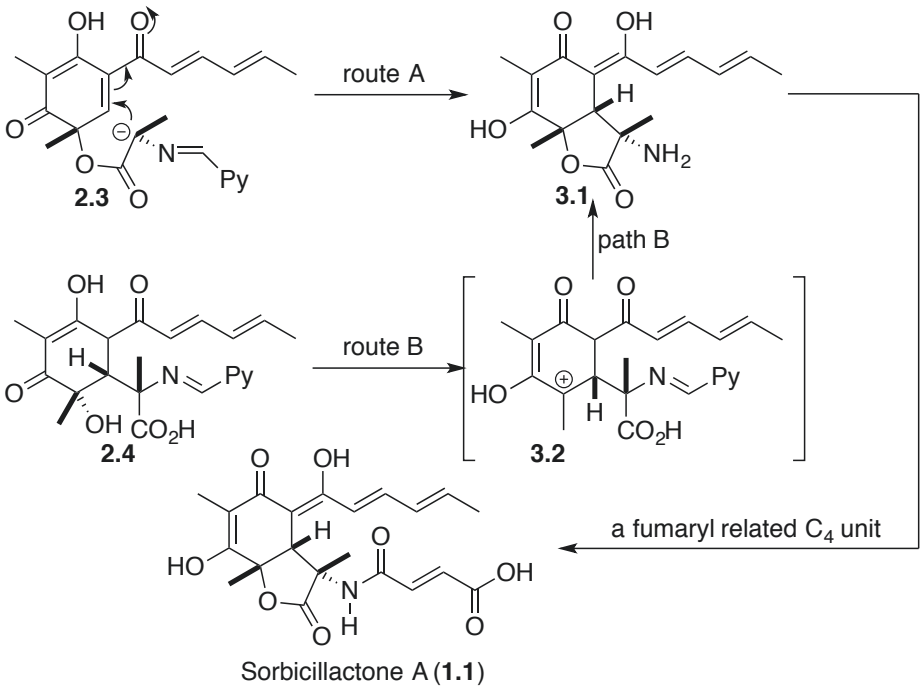
Compound **2.1** is proposed to undergo esterification with alanine derivative **2.2** which could be activated with pyridoxal phosphate to give the intermediate **2.3** (route A). In another plausible pathway, **2.2** could be deprotonated first and then undergo Michael addition to afford **2.4** (route B). These two routes to make the 5-membered lactone are shown in Scheme 2.



Scheme 2. Two possible routes to make the 5-membered lactone in sorbicillactone A biosynthesis

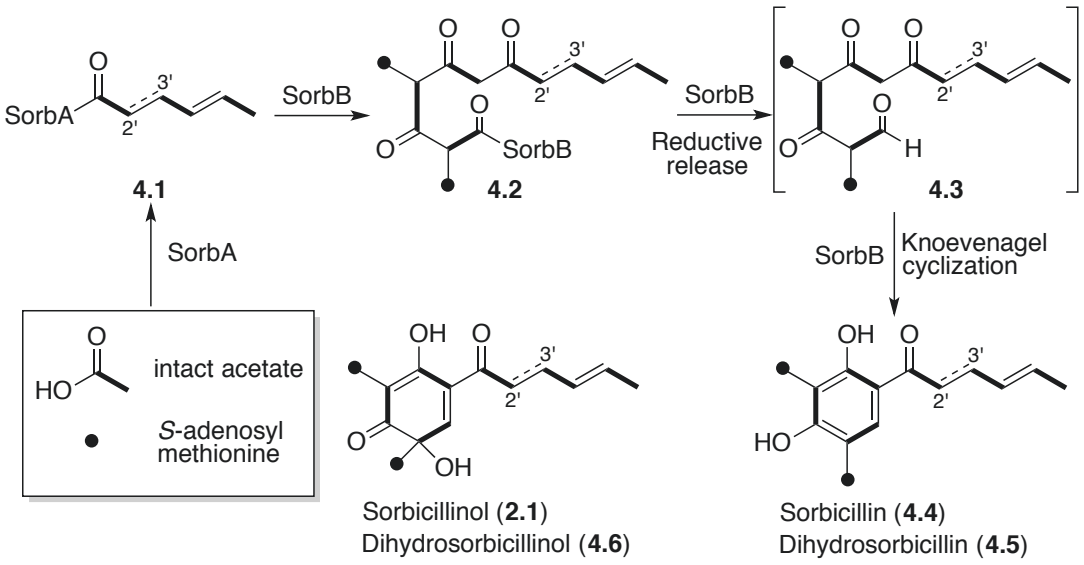
In the next step, it is likely that intermediate **2.3** is deprotonated at the α position in the alanine portion, followed by intramolecular Michael addition to give intermediate **3.1** (route A). The same intermediate could be formed from **2.4** through carbocation **3.2**, followed by ring-closure to form the lactone (route B). Finally, a fumaryl C4-unit is attached to the free amino group to provide sorbicillactone A (Scheme 3). Although the two routes seem to be reasonable, it should be pointed out that route B involves the unstable carbocation **3.2**, which is adjacent to an electron withdrawing group (carbonyl group in this case), and so this route is less favorable. Moreover, the labeling pattern of the amide side chain seems to be non-symmetric, which indicates that this residue is derived, at least partially, from an unsymmetric compound. This hypothesis was later confirmed when [$^{13}C_4$]-fumaric acid was

used in feeding experiments; these did not lead to fumaryl labeling in the amide side chain, hence the fumaryl side chain does not come from fumaric acid itself. In summary, the origin of the C_4 fumaryl unit remains unknown.[1]



Scheme 3. Biosynthesis of sorbicillactone A through two possible pathways

The Bringmann biosynthetic hypothesis can only explain the formation of **1.1**, but it does not give a satisfactory explanation for the co-isolated natural product **1.2**. This concern remained unanswered until 2014, when Cox and coworkers[10] proposed a new biosynthetic route to the key metabolite sorbicillinol (**2.1**) in *Penicillum chrysogenum*, based on the Bringmann feeding experiments[1] and their own observations (Scheme 4). Two intermediates **4.1** and **4.2** are formed from acetate and *S*-adenosyl methionine by two polyketide enzymes SorbA and SorbB. Compound **4.2** is then transformed into **4.3**, a polyketide aldehyde, which can undergo Knoevenagel cyclisation catalyzed by SorbB to afford sorbicillin (**4.4**) and dihydrosorbicillin (**4.5**). Those two products are then oxidized by SorbC to provide sorbicillinol (**2.1**), which then leads to sorbicillactone A (**1.1**), and dihydrosorbicillinol (**4.6**), which would give sorbicillactone **B** (**1.2**). The proposed biosynthetic route to **2.1** can explain the formation of dihydrosorbicillinol (**4.6**) which leads to the side product sorbicillactone B (**1.2**). This proposal was confirmed later by Driessen who identified the gene responsible for sorbicillinoid production in a strain of *P. chrysogenum*.[11]



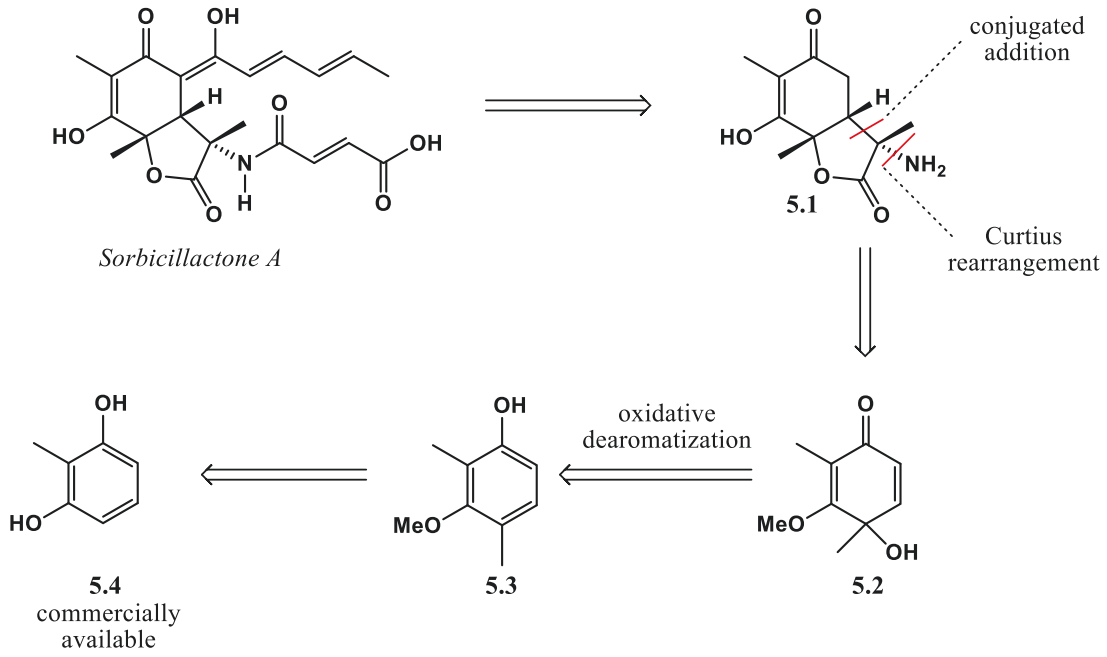
Scheme 4. Cox's sorbicillinol biosynthesis proposal[10]

The synthesis of Sorbicillactone A and its bicyclic core.

Sorbicillactone A possess potent bioactivity and a total synthesis of this natural product would pave the way for modifying the structure so as to identify the most important features responsible for its biological activity. But after many years of effort, the total synthesis of this "deceptively simple molecule",[12] with two of three vicinal stereocenters quarternary, is a challenging task. Only one total synthesis of (±)-**1.1** and three approaches to the bicyclic core of **1.1** and **1.2** have been reported so far. However, the synthesized natural product was clearly not pure, as judged by its ^{1}H NMR spectrum.

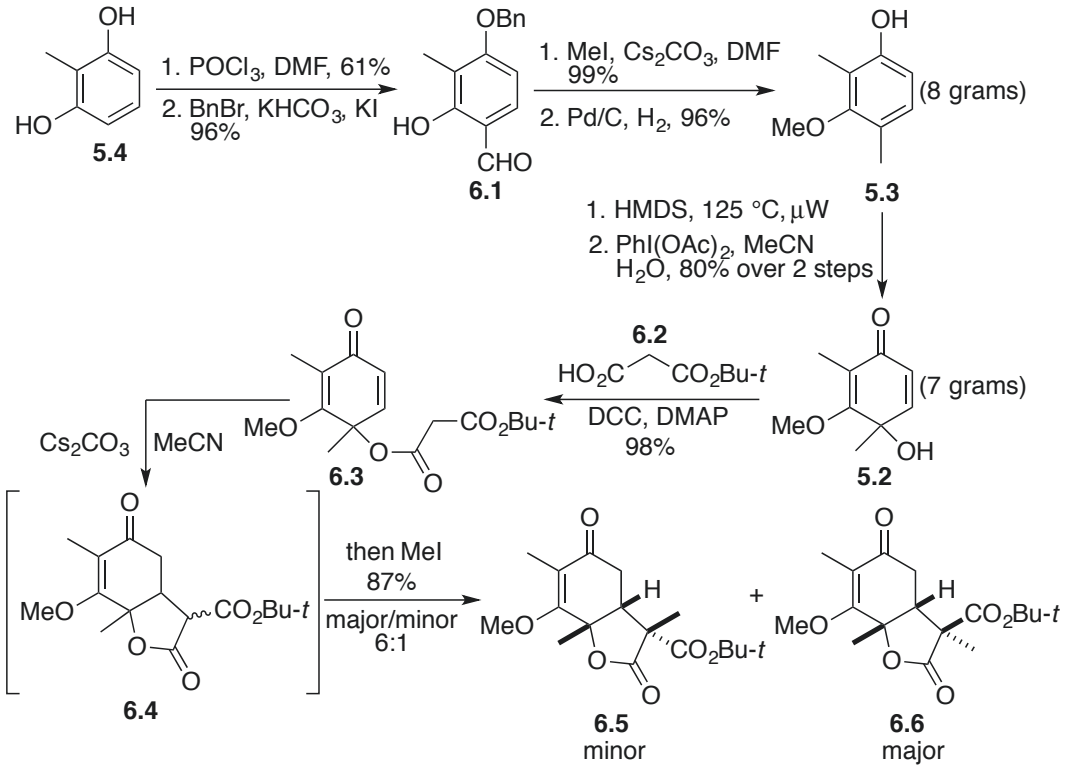
Harned's total synthesis of (±)-sorbicillactone A

In 2011, Harned and coworkers[12, 13] reported a concise synthesis of **1.1**, and up to now it still remains the only total synthesis of the compound. Harned's route was based on intramolecular Michael addition to afford a 5-membered lactone ring and Curtius rearrangement to reach the key intermediate **5.1** from **5.2**, which in turn was made by dearomatization of **5.3**. He explored the Michael addition in more detail in a follow-up paper.[14] The polysubstituted aromatic ring **5.3** could be traced back to 2-methyl resorcinol (**5.4**), a commercially available material. From key intermediate **5.1**, only amidation to put the fumaryl side chain and aldol condensation to set up the sorbyl side chain needed to be done to reach **1.1**. The synthetic route is outlined in Scheme 5.



Scheme 5. Harned's plan to approach sorbicillactone A[13]

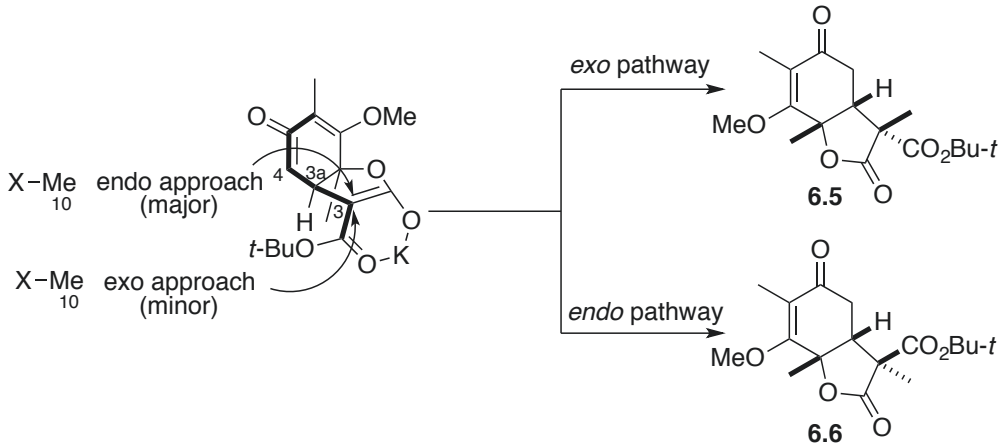
A formyl group was installed on 2-methylresorcinol (**5.4**) by $POCl_3$/DMF, and then selective benzylation of the less hindered hydroxyl was carried out (Scheme 6). Methylation of the other hydroxyl group and exhaustive hydrogenolysis then give **5.3**. This sequence could be scaled up to give an 8-g batch of material. Oxidative dearomatization took place on treatment with $PhI(OAc)_2$ in $(Me_3Si)_2NH$ under microwave assistance to give quinol **5.2** in high yield. When the reaction was scaled up **5.2** could be made in 7-g batches. The tertiary hydroxyl underwent Steglich esterification with malonic acid *t*-butyl ester (**6.2**) to generate dienone **6.3**. This dienone cyclized on treatment with Cs_2CO_3 through an intramolecular Michael addition to afford the intermediate **6.4**, which could be methylated *in situ* with iodomethane to provide the two epimers **6.5** and **6.6**. Although the one-pot Michael addition/methylation did give the desired core of sorbicillactone A (**1.1**), unfortunately, the undesired epimer with the wrong stereochemistry α to the lactone carbonyl, compound **6.6**, was the major product (6:1 ratio); this result greatly reduced the efficiency of the synthesis. In the end, by working on a large scale to compensate for the unfavorable product ratio, the Harned group was able to get over 1 g of the desired product (**6.5**) possessing the correct stereochemistry.[13]



Scheme 6. Synthesis of sorbicillactone A core structure[13]

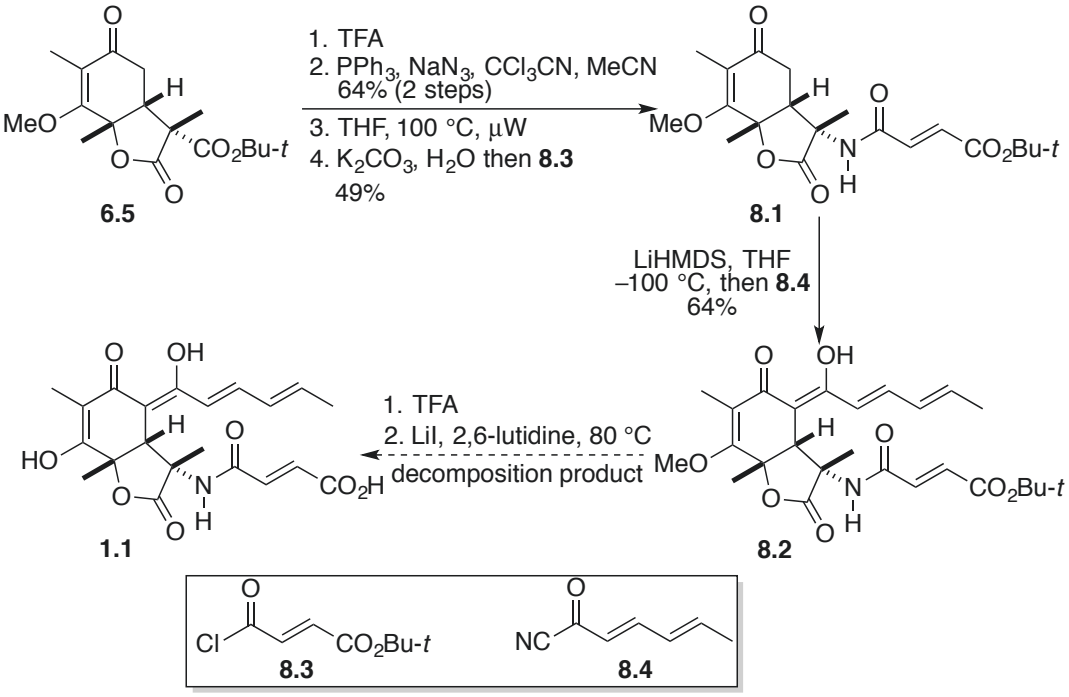
It had been hoped that the alkylation of **6.4** would occur by approach from the convex (*exo*) face, which should be less shielded, to generate the correct stereochemistry in the five membered ring, and so the experimental result[13] was unexpected. Later on, Harned and coworkers[15] proposed a possible explanation for the origin of this unusual selectivity. They found that only for methylation with methyl iodide does the alkylation favor the *endo* product. Computational studies using M06-2X (using K^+ as counterion) show that the *endo* approach is 0.4 kcal mol^{-1} more favorable than the *exo* approach. One reason could be that in the *endo* transition state, the dihedral angle between the C3–CO_2Bu-*t* carbon-carbon bond and the C3a–C4 bond is 75° (Scheme 7); in contrast, in the *exo* transition state, the dihedral angle is only 15°. The compression of the dihedral angle creates a torsional strain and increases the energy of the *exo* transition state. Another reason could be that the angle between the approaching electrophile and the five-membered ring is larger (115°) in the transition state for endo approach than it is in the exo approach, for which the calculations suggest 104°; hence the larger angle avoids excessive steric hindrance with the cyclohexenone ring as the methyl group approaches C3. However, when the size of electrophile becomes bigger, the steric clash with the cyclohexenone ring would favor an *exo*

approach. An account of stereoselectivity governed by torsional control was summarized by Houk[16] and later such torsional control was exploited by Harned in his briarane diterpenoid synthesis study.[17]



Scheme 7. A possible explanation for the unexpected alkylation selectivity[15]

With around 1 g of **6.5** in hand, the ester group was hydrolyzed to liberate the carboxylic acid, which was transformed *in situ* into an acyl azide. This material underwent



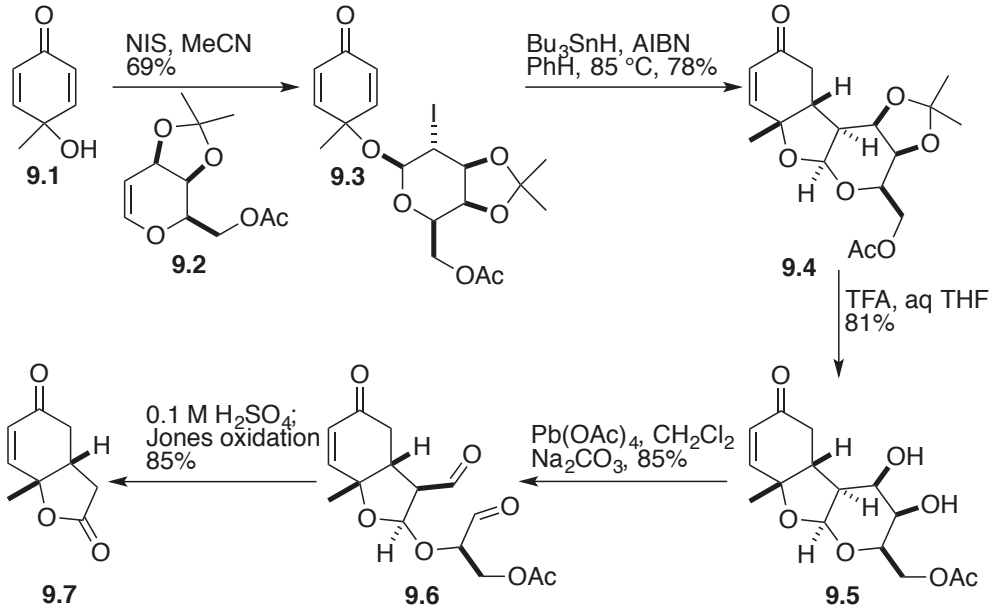
Scheme 8. Final steps in Harned's sorbicillactone A synthesis

Curtius rearrangement on microwave irradiation, and acylation of the free amine by **8.3** afforded the amide **8.1**. The sorbyl side chain was attached by deprotonation of **8.1** with LiHMDS and acylation with **8.4** to give **8.2** (Scheme 8).[13]

The last two steps are removal of two protecting groups. Cleavage the *tert*-butyl ester protecting group with TFA went smoothly, but the last demethylation was always accompanied by a significant amount of decomposition to an unknown compound, although the same conditions worked well in the *epi*-series. According to Harned, the synthetic material is unstable so he could not get reasonable NMR data.[12]

Attempt to synthesize the core of sorbicillactone A and B

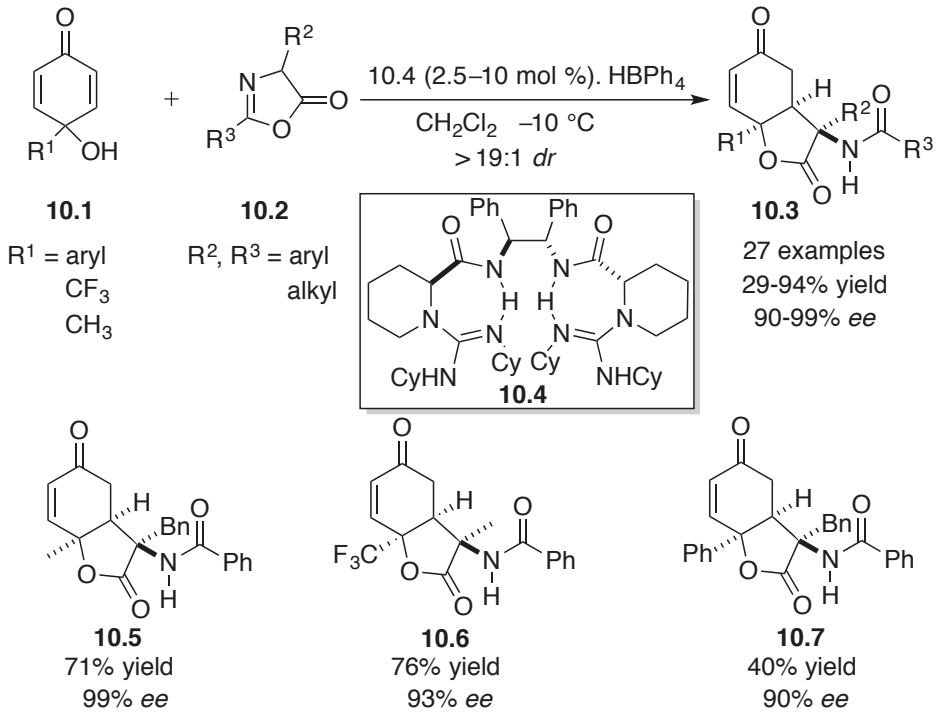
There are three reports on the construction of the optically pure bicyclic core structure of **1.1** and **1.2**. The Clive group[18] was the first to address this challenge by performing a radical cyclization of the intermediate **9.3** (single isomer), which was formed by reaction between tertiary alcohol **9.1** and chiral auxiliary **9.2** in the presence of NIS. The radical cyclization of **9.3** in the presence of Bu_3SnH/AIBN afforded **9.4**. Subsequently, treatment of **9.4** with aqueous TFA afforded diol **9.5**, which could be cleaved further by $Pb(OAc)_4$ to give dialdehyde **9.6**. It was found that acid hydrolysis with 0.1 M H_2SO_4, followed by Jones oxidation, led to **9.7**, which possesses the same absolute configuration as the core structure of sorbicillactone A.



Scheme 9. Clive's approach to construct the optically pure bicyclic core of sorbicillactone A

The main reason for this stereochemical outcome is the use of galactal derivative **9.2** as a chiral auxiliary, in which the bulky ketal unit fosters a high degree of stereoselectivity in both the iodoetherification and radical cyclization.[18]

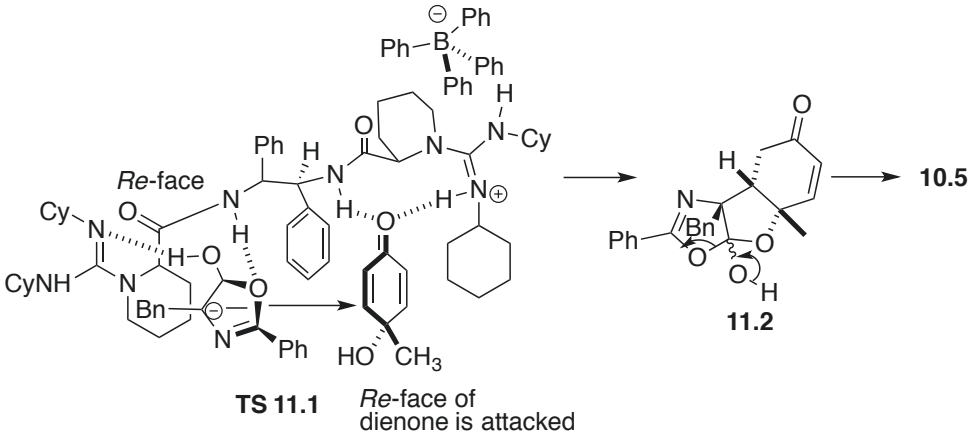
Nine years after the first report from our group,[18] Liu and coworkes[19] studied the domino conjugate addition/lactonization between *p*-quinol **10.1** and the azlactone derivative **10.2** in the presence of guanidine derivative **10.4** as catalyst to afford a series of bicyclic lactones **10.3** with the relative configuration of three newly constructed chiral centers consistent with natural products **1.1** and **1.2** (Scheme 10). Although this reaction did not work very well when R^1 is an aryl group (40% yield), the approach could provide direct access to the key chiral structure of sorbicillactone.



Scheme 10. Domino conjugate addition/lactonization to construct optically pure sorbicillactone bicyclic core and some selected examples

The authors proposed a bifunctional catalyst model, based on ^{1}H NMR evidence, to explain the stereoselectivity of this reaction (Scheme 11).[19] The model clearly shows that the basic guanidine unit accelerates the enolization of the azlactone, and is in contact with the enolized form as a hydrogen acceptor. At the same time the vicinal amide bonds to the ring oxygen of the enolized azlactone via another hydrogen bond. The guanidinium salt and

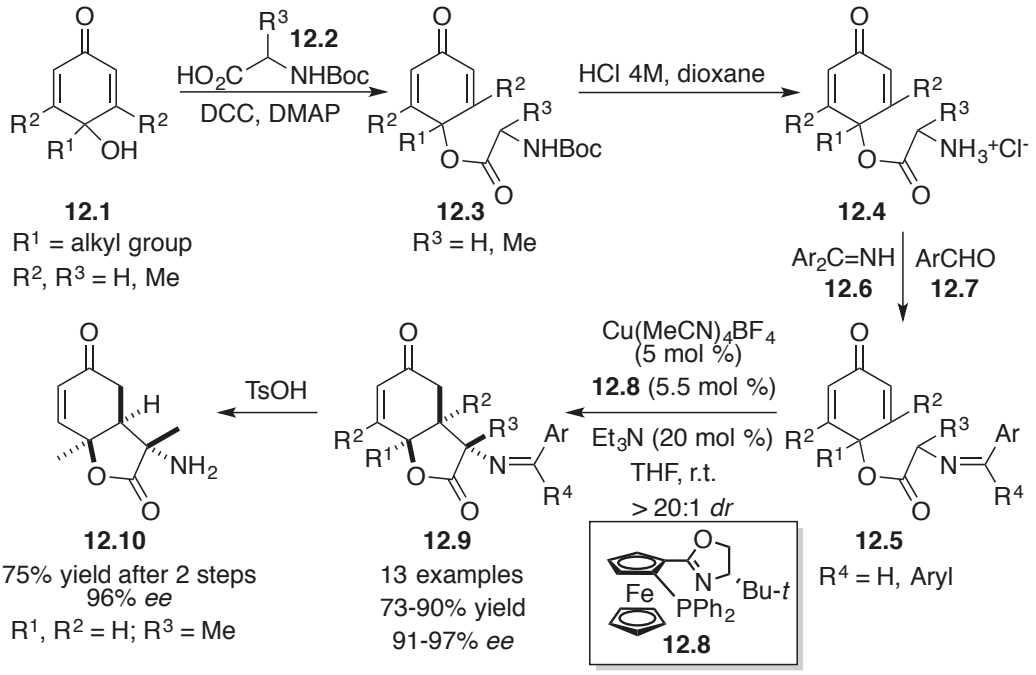
neighboring amide provide double hydrogen bonds to contact the carbonyl group in the *p*-quinol **10.1** (with R^1 = Me). An intermolecular conjugate addition between azlactone and *p*-quinol takes place *via* a *Re–Re* face contact. The phenyl group and cyclohexyl group underneath engender steric hindrance to discriminate between the faces of the *para*-substituted of *p*-quinol, thus desymmetrization of *p*-quinol occurs (TS **11.1**). Next, the hydroxyl group of the *p*-quinol attacks the carbonyl group of the azlactone through intermediate **11.2** to provide product **10.5** with the desired stereochemistry.[19]



Scheme 11. A possible transition state model to explain the stereoselectivity of domino conjugate addition/lactonization reaction.

Not long after Liu's study, Li[20] reported an enantioselective intramolecular conjugate addition at room temperature of an iminoester precursor, which could be synthesized from readily available materials. The iminoester **12.5** was prepared as follow: firstly, esterification between *p*-quinol **12.1** and *N*-Boc protected amino acid **12.2** at room temperature gave ester **12.3**. Deprotection with 4 M HCl in dioxane afforded the hydrochloride salt **12.4**. The salt could be transformed into the corresponding iminoester by treatment with symmetric diarylimine **12.6** or aromatic aldehyde **12.7** to afford the desired compound **12.5**. This material was cyclized in the presence of $Cu(MeCN)_4BF_4$ and the Phosferrox ligand **12.8** with triethylamine as a base in dichloromethane to afford the product **12.9**. The imine group in compound **12.9** was easily be hydrolyzed by treatment with TsOH to give the corresponding amine **12.10** (Scheme 12). Although the product does not possess the relative configuration of **1.1**, this approach is the first reported enantioselective

intramolecular conjugate addition of an iminoester. The author did not give any explanation for the observed stereoselectivity.

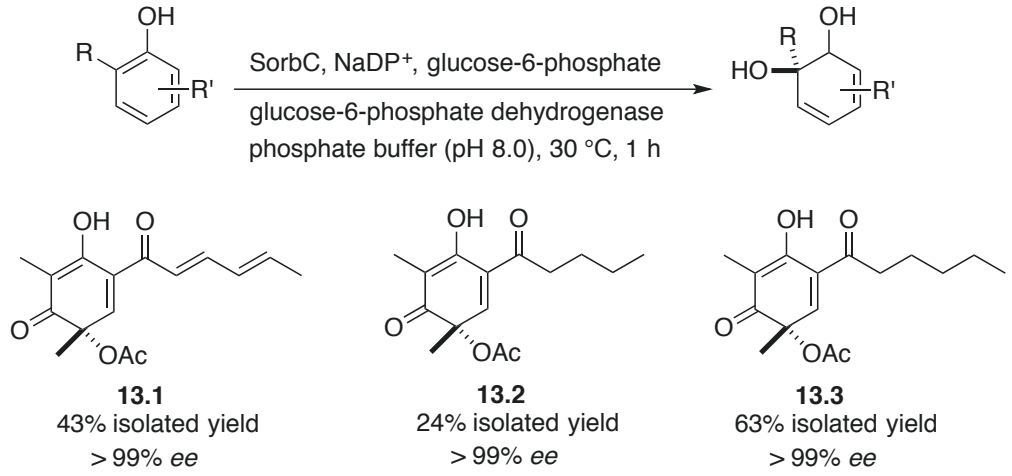


Scheme 12. Li's approach to the sorbicillactone core[20]

Sorbicillinol, the key common biosynthetic intermediate to sorbicillinoid natural products

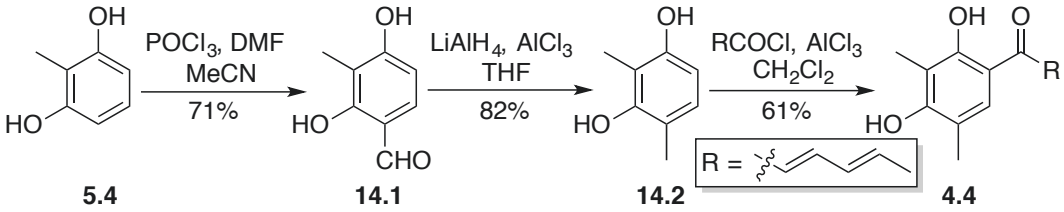
In 2001, Abe[21] proposed that sorbicillinol (**2.1**) could serve as a key intermediate in the biosynthesis of many sorbicillinoid natural products, including sorbicillactone A (**1.1**) and sorbicillactone B (**1.2**), and this suggestion was used later by the Bringmann group.[1] Therefore a direct route to sorbicillinol (**2.1**) could be an attractive biomimetic synthetic route to approach not only sorbicillactones **1.1** and **1.2**, and it could also serve as a common intermediate to synthesize other sorbicillinoid natural products.

The work by Cox[14] firmly established the role of the enzyme SorbC as a biocatalyst for enantioselective dearomatization of phenols. Narayan and coworkers[22] were the first to utilize this enzyme to synthesize some sorbicillinol derivatives (Scheme 13). Although the product formed with an *ee* of >99% the isolated yields were not very high.



Scheme 13. Selected examples of Narayan's enantioselective dearomatization of phenols using SorbC

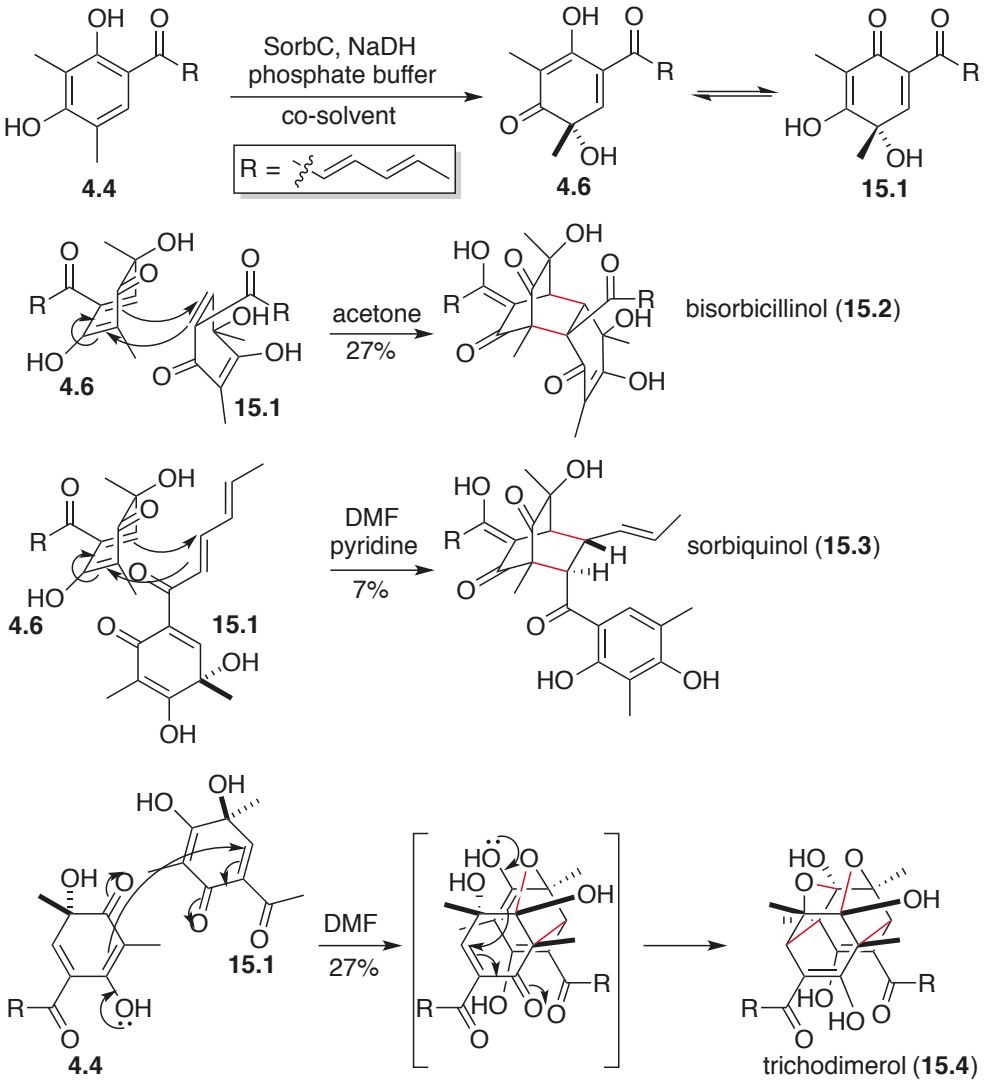
From 2017 to 2020, the Gulder group[23] published a series of chemoenzymatic total syntheses of a variety of sorbicillinoid natural products, using SorbC. This was achieved by enantioselective dearomatization of sorbicillin (**4.4**), which could be prepared from 2-methylresorcinol (**5.4**). The first step was a Vilsmeier-Haack reaction and this was followed by lithium aluminum hydride reduction of the newly inserted formyl group to afford **14.2**. Finally, acylation of **14.2** with sorbyl chloride gave sorbicillin (**4.4**) (Scheme 14).[23a]



Scheme 14. Gulder's synthesis of sorbicillin

When sorbicillin (**4.4**) was treated with SorbC in the presence of NADH and a phosphate buffer (pH = 8) in the presence of a cosolvent to dissolve **4.4** three sorbicillinoid natural products were formed depending on the conditions used.[23a] When the cosolvent is acetone, Diels-Alder cycloaddition between two tautomeric *p*-quinols **4.4** and **15.1** afforded bisorbicillinol (**15.2**) in 27% yield. If the co-solvent was DMF and pyridine was then added and the mixture heated at reflux for 2 h, sorbiquinol (**15.3**) could be isolated in 7% yield, and this appears to be the first synthesis of the compound. When DMF was the only co-solvent

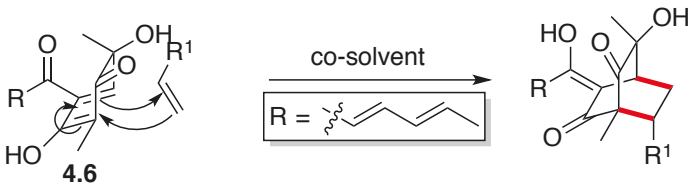
trichodimerol (**15.4**) became the main product, which was formed through a domino sequence of ketalization and two Michael additions (Scheme 15).



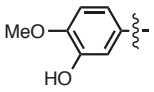
Scheme 15. Chemoenzymatic synthesis of bisorbicillinol, sorbiquinol and trichodimerol by dimerization of sorbicillinol.

Sorbicillinol (**4.6**) is a highly reactive diene, and Gulder and coworkers[23b, 23d] utilized this characteristic to approach some other sorbicillinoid natural products by changing the dienophiles. Three more natural sorbcillinoids: sorbicatechol A, rezishanone B and rezishanone C were successfully synthesized by this methodology (Table 1).

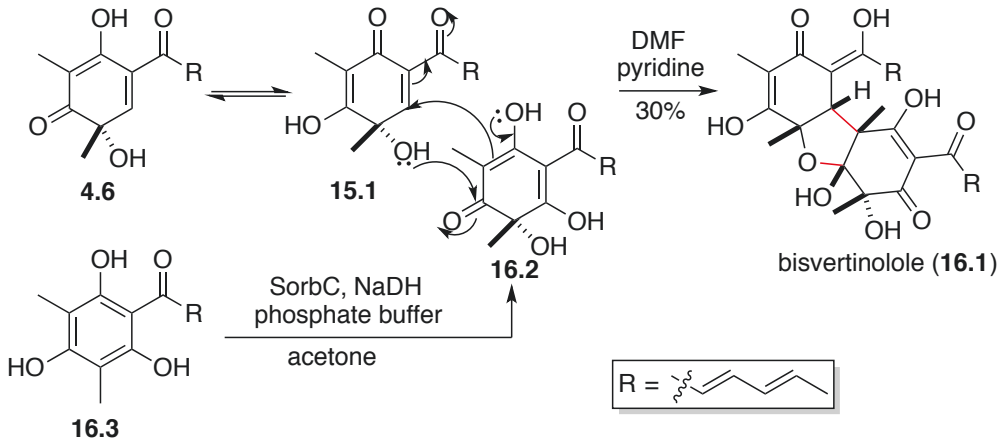
Table 1. Some other sorbicillinoid natural products synthesized by Diels-Alder reaction between sorbicillinol and different dienophiles[23b]



4.6

R^1	co-solvent	yield	natural product
n-BuO	DMF	32%	rezishanone B
EtO	DMF	29%	rezishanone C
	acetone	30%	sorbicatechol A

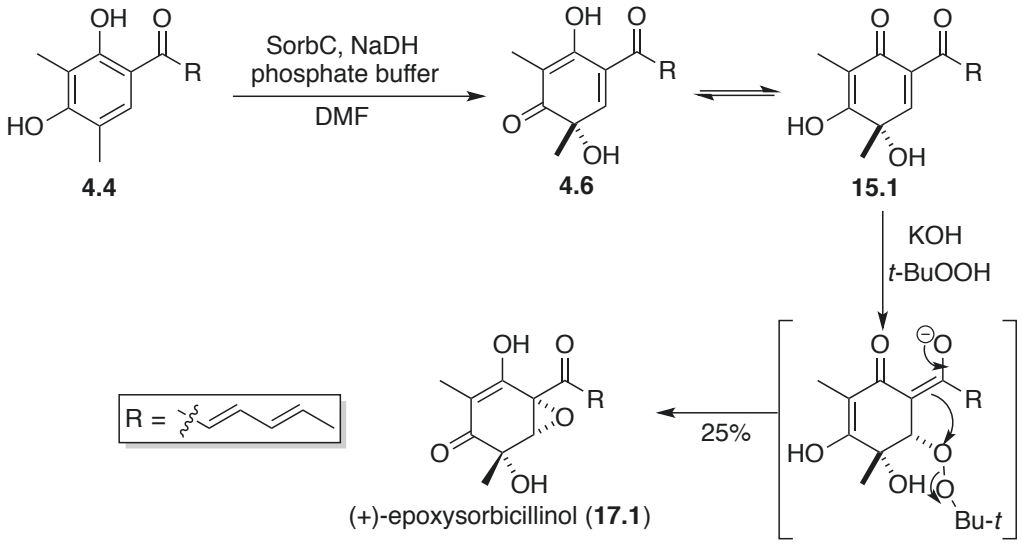
Another sorbicillinoid natural product that could be produced from the common intermediate **4.6** is bisvertinolole (**16.1**). This synthesis was done by treatment of a DMF solution of **4.6** with oxosorbicillinol (**16.2**) in the presence of pyridine. Compound **16.2** was synthesized by chemoenzymatic oxidative dearomatization of phloroglucinol derivative **16.3** with SorbC. The formation of **16.1** occurred by a highly selective Michael addition/ketalization domino reaction between tautomer **15.1** and **16.2**. This is the first total synthesis of **16.1**.[23b]



Scheme 16. The first total synthesis of bisvertinolole by chemoenzymatic synthesis.

One other sorbicillinoid natural product that was synthesized from **4.6** is (+)-epoxysorbicillinol (**17.1**).[23b] This time an external nucleophile, *t*-$BuOO^-$, was introduced to

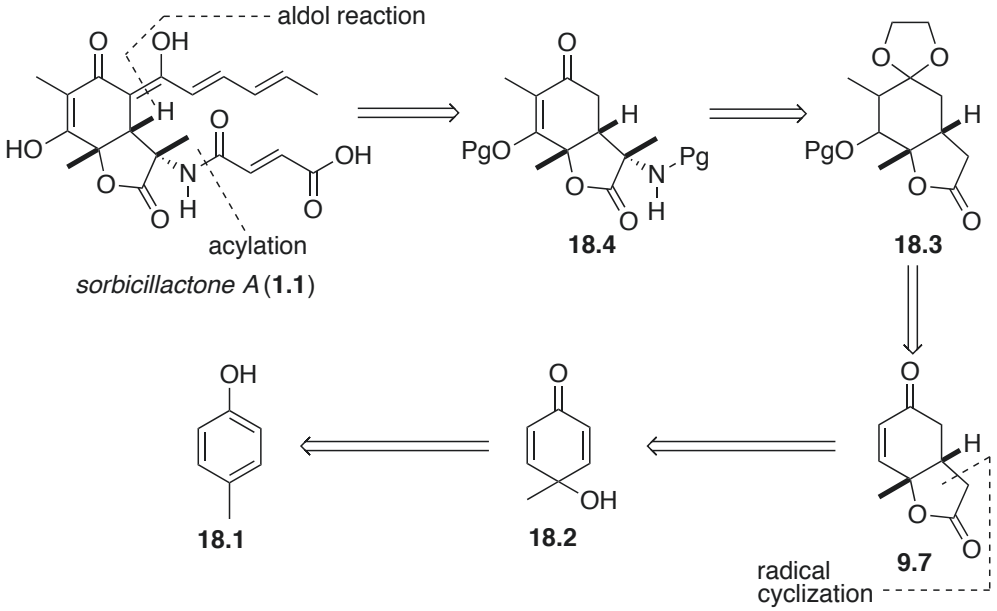
react with **4.6** to give an epoxide through a Weitz-Scheffer epoxidation. The tertiary alcohol functional group in **4.6** directs attack of the peroxide anion to the same side by precomplexation (Scheme 17).



Scheme 17. Chemoenzymatic stereoselective total synthesis of (+)-epoxysorbicillinol

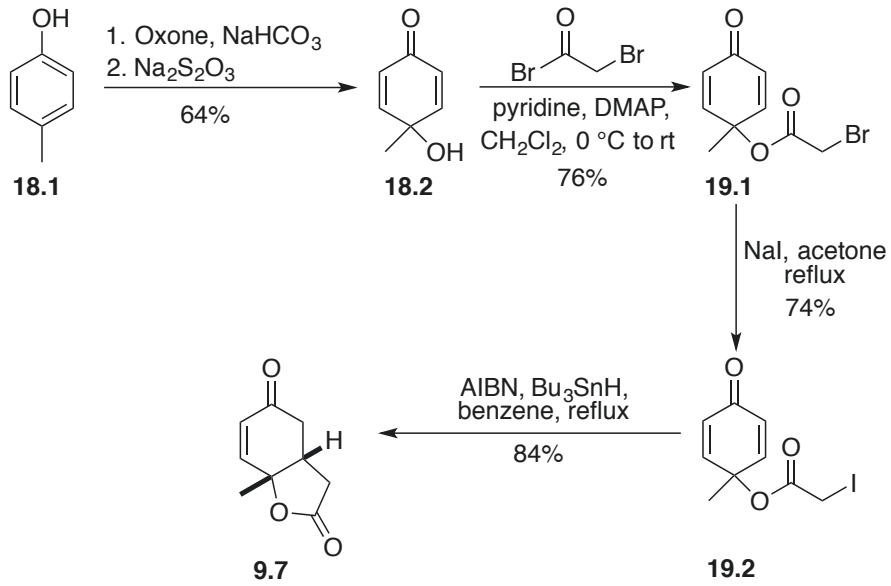
Our synthetic approach to sorbicillactone A and B

In connection with our procedure to prepare optically active sorbicillactone the bicyclic core was first made in optically pure form,[18] and Dr Dinesh Sreedharan was the first one in our group to try to elaborate the core into sorbicillactone A.[24] His plan (see Scheme 18) was to make **9.7** by radical cyclization from *p*-cresol (**18.1**), which was commercially available. The next thing to do is to form the quarternary amine with the correct stereochemistry and from there he would proceed to sorbicillactone A (**1.1**). His plan, was tried first with racemic material (Scheme 18).



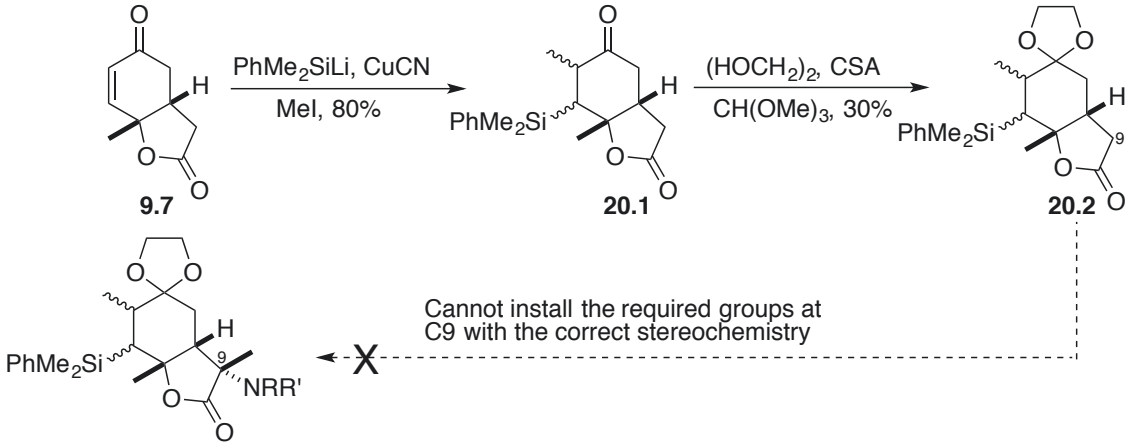
Scheme 18. Dr Sreedharan's plan to approach sorbicillactone A

Dearomatization of *p*-cresol (**18.1**) with Oxone in the presence of $NaHCO_3$ afforded **18.2** in 64% yield (Scheme 19). Esterification of the tertiary alcohol with bromoacetyl bromide in pyridine then gave acyl bromide **19.1**, which was converted into acyl iodide **19.2** by Finkelstein reaction. The radical cyclization of **19.2** worked smoothly to produce racemic bicyclic lactone **9.7** in 84% yield.



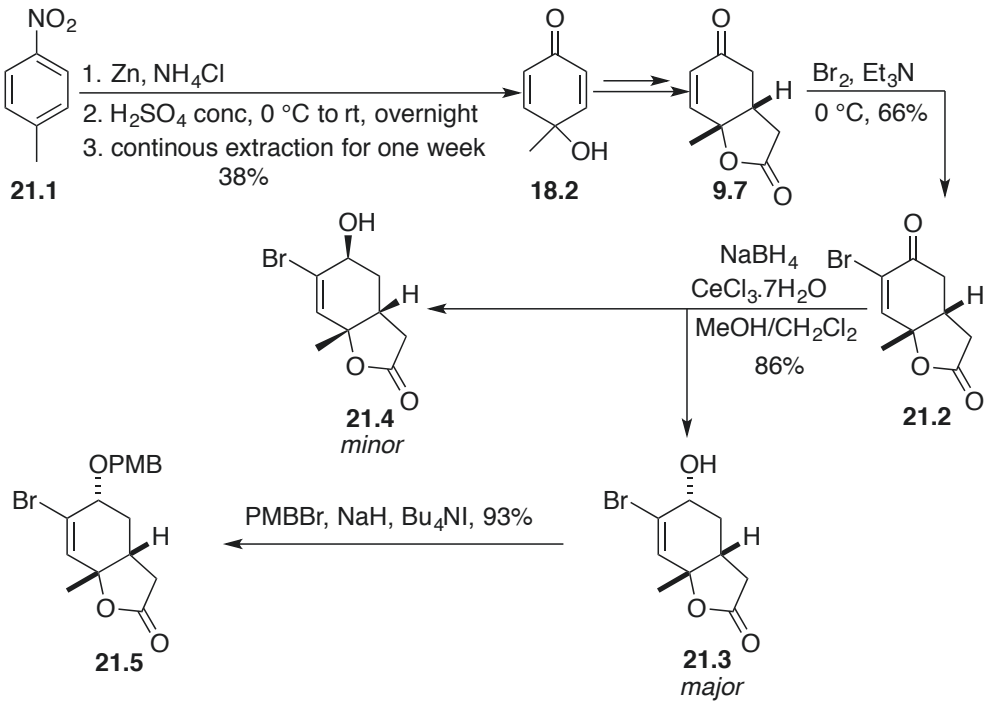
Scheme 19. Preparation of racemic bicyclic sorbicillactone core by Dr Sreedharan

In the next step, Dr Sreedharan tried to functionalize the six-membered ring by organosilicon conjugate addition and enolate trapping by MeI, so that the silicon unit could be converted later into the required functional group of sorbicillactones A and B by a methodology developed in our group.[25] Protection of the ketone group in **20.1** was done by treatment with ethylene glycol and CSA to afford ketal **20.2**. However, despite many attempts, it was impossible to install both the amino and methyl groups onto the lactone ring with the correct stereochemistry (Scheme 20).[24]



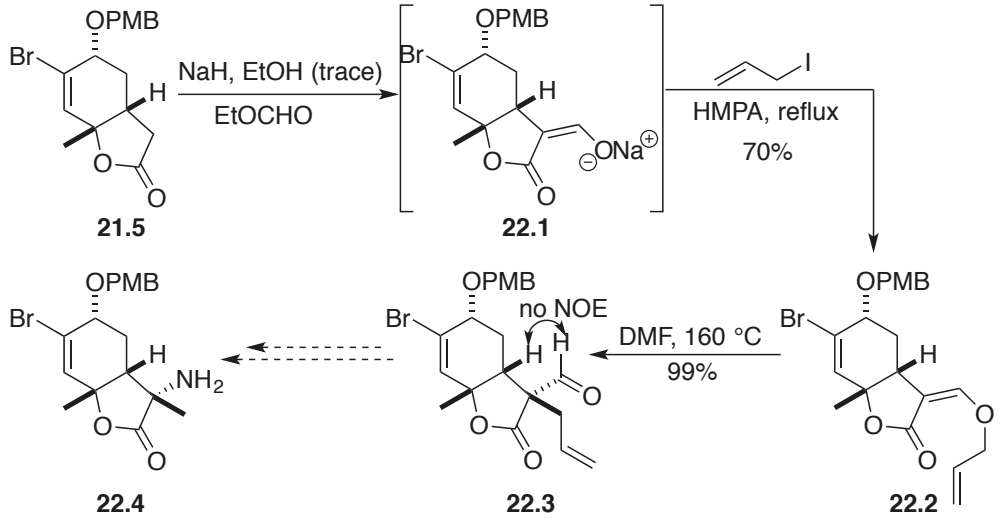
Scheme 20. Dr Sreedharan's approach to sorbicillactone A

Because the approach of Dr Sreedharan was unsatisfactory, Dr JongMyoung Chea[26] decided to modify Dr Sreedharan's route to improve its efficiency. In the dearomatization step, he choose 4-nitrotoluene (**21.1**) instead of *p*-cresol (**18.1**) due to the fact that variable yields with *p*-cresol made the process unsuitable for preparing **18.2** on a big scale. 4-Nitrotoluene was dearomatized according to the procedure of Takahashi *et al*.[27] to produce **18.2** in acceptable and reproducible yields on large scale (38% with 20 g *p*-nitrotoluene). Compound **18.2** was converted into **9.7** through the same route as used by Dr Sreedharan. In the next step, **9.7** was brominated, instead of being subjected to conjugate addition, to afford bromoenone **21.2**. Luche reduction of **21.2** gave a mixture of two alcohols **21.3** and **21.4** (1.4:1 *dr*), which could be separated by column chromatography. The hydroxyl group in the major isomer (**21.3**) was protected as a *p*-methoxybenzyl ether using NaH and PMBBr in the presence of Bu_4NI to give **21.5** (Scheme 21).[26]



Scheme 21. Dr JongMyoung's preparation of bromide **21.5**

Bromide **21.5** was converted into allyl ether **22.2** in two steps through intermediate **22.1** in 70% overall yield. Heating **22.2** in DMF at reflux triggered the Claisen rearrangement to afford **22.3**, which could serve as a starting point to access key intermediate **22.4** (Scheme 22).[26]



Scheme 22. Preparation of allylic aldehyde **22.3** by Claisen rearrangement

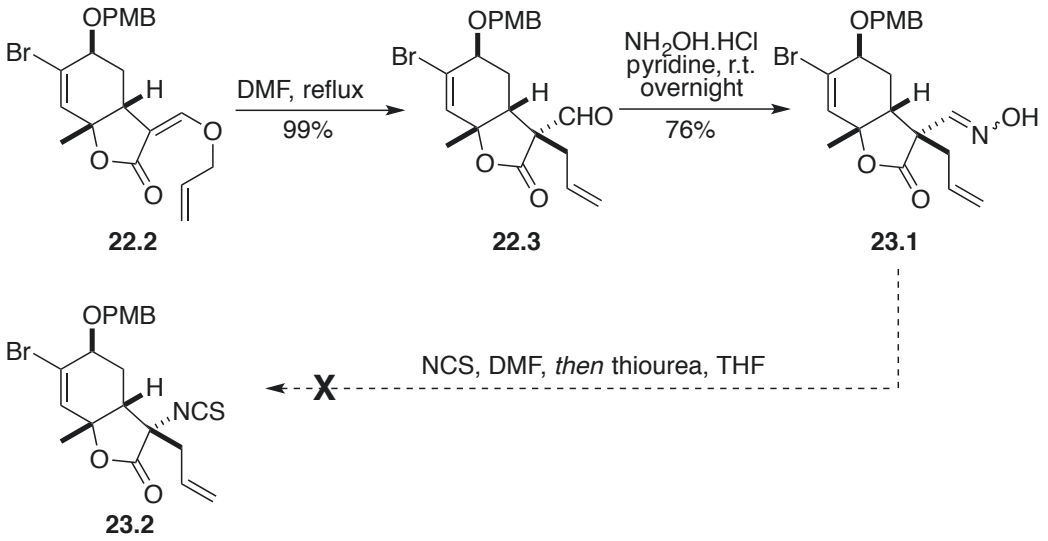
Conclusion

Several approaches were tried to solve the synthetic problems posed by sorbicillactone A, but all the approaches have serious weaknesses. Recently, however, our group found a remarkable and welcome result by way of an unusual Claisen rearrangement (**22.2**→**22.3**), and it appeared that the stage was set to complete the functionality at the quaternary carbon center in the lactone ring.

Results and discussion

First generation approach

In continuing from the point reached by Dr. JongMyoung, compound **22.3** was converted into oxime **23.1**,[28] in order to attempt rearrangement into isothiocyanate **23.2** by treatment with NCS and triethylamine,[29] but in the event only the starting material was recovered from this experiment (Scheme 23).



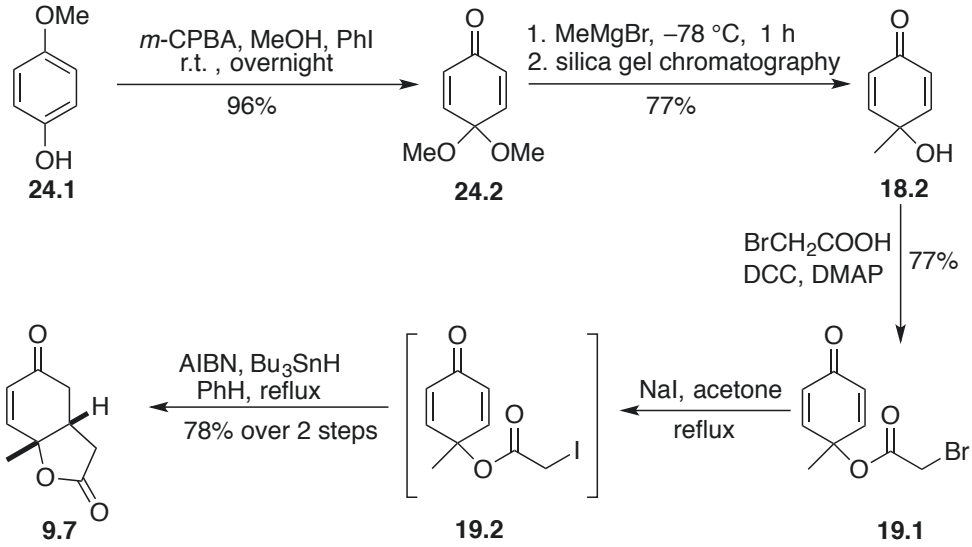
Scheme 23. Failure to convert aldoxime into isothiocyanate

Second generation approach

The failure of the oxime to isothiocyanate rearrangement forced me to re-evaluate the original plan. The first problem is that the preparation of **18.2** was too long, and it took at least a week to produce enough materials for the next step. The second one is the acylation **18.2→19.1** which initially appeared to work in good yield, subsequently gave only mediocre yields (ca 50%). I also questioned the need for the bromination step. The bromine had been introduced to improve the yield in the subsequent Luche reduction but I decided to check if the bromination was indeed necessary and I modified the original route in the following way.

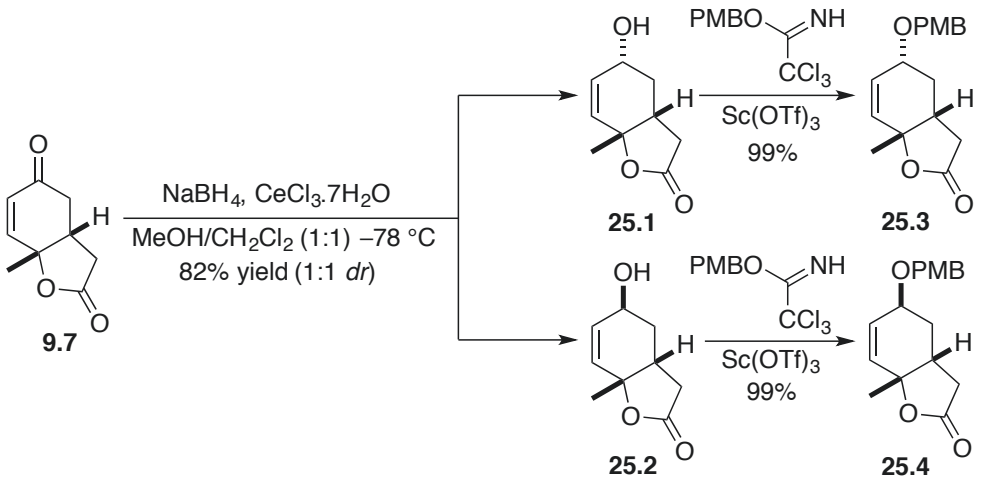
Thus, my own synthetic studies (Scheme 24) began with dearomatization of *p*-methoxyphenol (**24.1**) with *m*-CPBA and iodobenzene in methanol to afford monoketal **24.2** in 96% yield.[30] This monoketal had already been converted into **18.2** by reaction with MeLi,[31] but MeLi is quite expensive and so I tried to replace it with the cheaper MeMgBr at

–78 °C; the resulting tertiary alcohol **18.2** was furnished in 77% yield. This compound was subjected to DCC esterification with bromoacetic acid in the presence of 10 mol % DMAP to afford acyl bromide **19.1** in 77% yield. When the amount of DMAP[32] was only 1 mol % the yield was 60%. The acyl bromide **19.1** was subjected to a Finkelstein reaction to afford **19.2**, which was use directly for the radical cyclization, giving the bicyclic lactone **9.7** in an overall yield of 78% over the two steps. This approach which I developed increased the efficiency of the preparation of **9.7** because all steps could be done in good yield and were easy to scale up (Scheme 24).



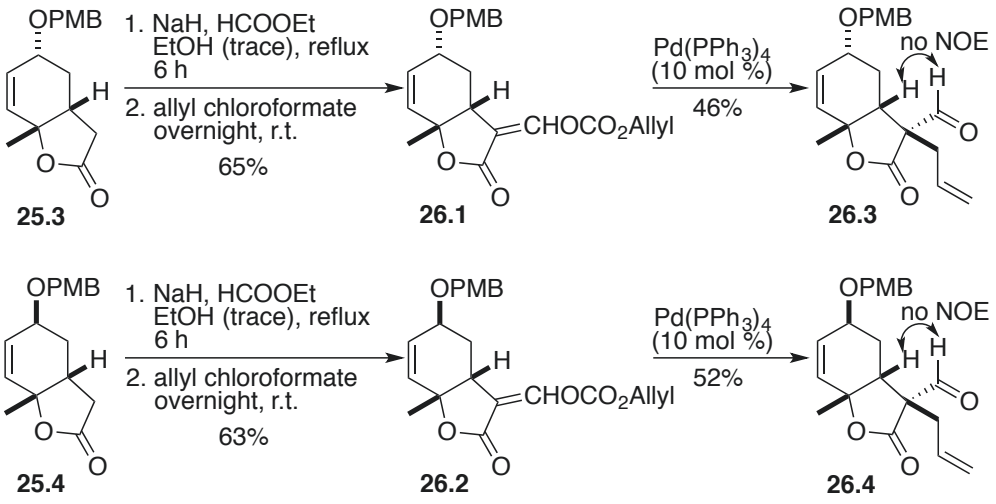
Scheme 24. My own approach to access bicyclic lactone **9.7**

Direct Luche reduction of **9.7** using $NaBH_4$ and $CeCl_3.7H_2O$[33] afforded two diastereomeric alcohols **25.1** and **25.2** (82% yield, 1:1 *dr*), which could be separated by flash chromatography. These two alcohols were protected as the *p*-methoxybenzyl ethers **25.3** and **25.4** using the trichloroacetimidate derivative of PMB alcohol in the presence of 5 mol % $Sc(OTf)_3$.[34] The protection reaction finished within 15 minutes to give the corresponding PMB ethers in almost quantitative yield (Scheme 25).



Scheme 25. The preparation of two diastereomers PMB ethers

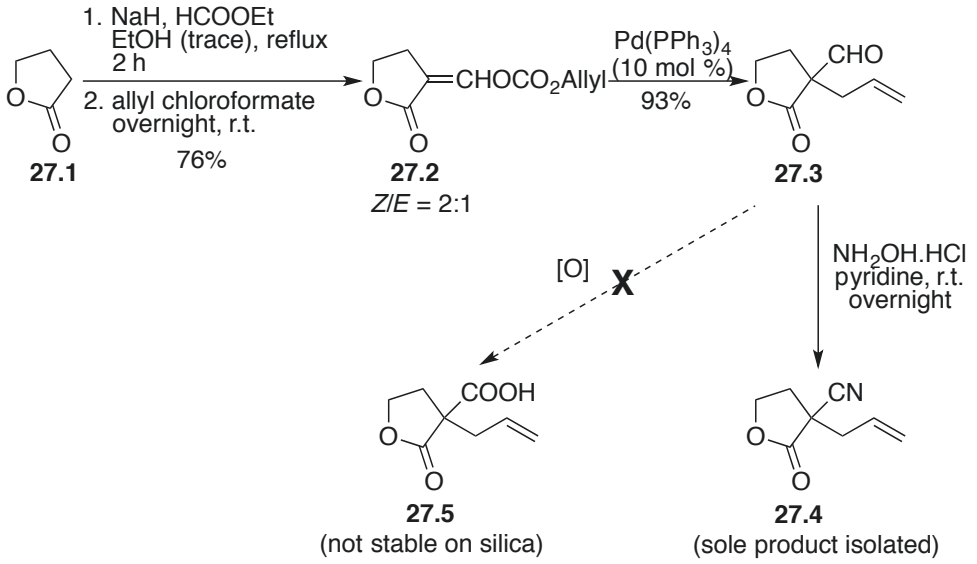
At this point, I decided to make the desired allylic aldehyde by using mild conditions instead heating the corresponding allyl ether in DMF at reflux. Therefore a palladium mediated allyl carbonate rearrangement to make α-quaternary γ-butyrolactones reported from Cossy's group was chosen.[35] I applied the Cossy methodology to the two PMB ethers **25.3** and **25.4** to obtain the corresponding allylic aldehydes **26.3** and **26.4** as the sole isomers via the allyl carbonates **26.1** and **26.2** (both as mixtures of *E* and *Z* isomers).



Scheme 26. Application of Cossy's methodology to make allyl aldehydes under mild conditions.

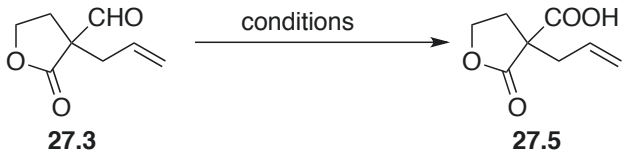
Compound **25.4** gave a slightly better yield of the aldehyde than **25.3** (Scheme 26). Hence the alcohol **25.2** was used from this point and the alcohol **25.1** was oxidized back to the parent bicyclic ketone **9.7** by Dess-Martin oxidation[36] (80% yield) to maximize the material output.

A model study was conducted to find out the best way to convert the aldehyde group into an amine. Treatment of butyrolactone (**27.1**) in refluxing THF with NaH/HCOOEt and allyl chloroformate gave allyl carbonate **27.2** as a 2:1 *Z*:*E* isomer mixture. This material rearranged with loss of CO_2 in the presence of $Pd(PPh_3)_4$ to afford the desired allyl aldehyde **27.3** as a single isomer. I planned to convert **27.3** into an oxime suitable for conversion into an isothiocyanate, but when I applied the conditions reported by Castle *et al.*[28] for oxime formation to aldehyde **27.3** the compound was converted into nitrile **27.4** as the sole product (Scheme 27). Therefore I tried to oxidize aldehyde **27.3** into the corresponding acid in order to use a Curtius rearrangement, but the acid turned out to be unstable during attempted purification by silica gel chromatography. However, I was able to find conditions for the Pinnick oxidation that gave an acceptably pure product after workup. My experiments to establish these conditions are collected in Table 2.



Scheme 27. Trying to convert the aldehyde into amine

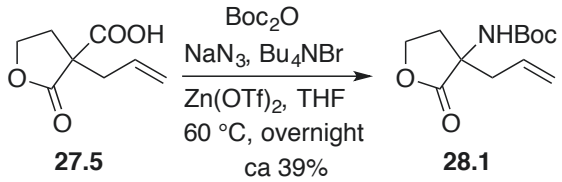
Table 2. Screening conditions to oxidize aldehyde **27.3** into carboxylic acid **27.5**



27.3 **27.5**

Conditions	Yield	Reference
$NaClO_2$, $NaH_2PO_4.H_2O$ *t*-BuOH/THF, 0 °C–r.t 2-methylbut-2-ene	ca 81% but not pure	37
$NaClO_2$, $NaH_2PO_4.H_2O$ H_2O/*t*-BuOH/THF, 0 °C 2-methylbut-2-ene	ca 100% but not pure	38
Oxone, DMF, r.t.	Only SM	39
$NaClO_2$, $NaH_2PO_4.H_2O$ H_2O_2/MeCN, 0 °C 2-methylbut-2-ene	Only SM	40
PDC, DMF, r.t.	Only SM	41
$NaClO_2$, $NaH_2PO_4.H_2O$ *t*-BuOH/H_2O, 0 °C–r.t. resorcinol	91.5% fairly pure	42

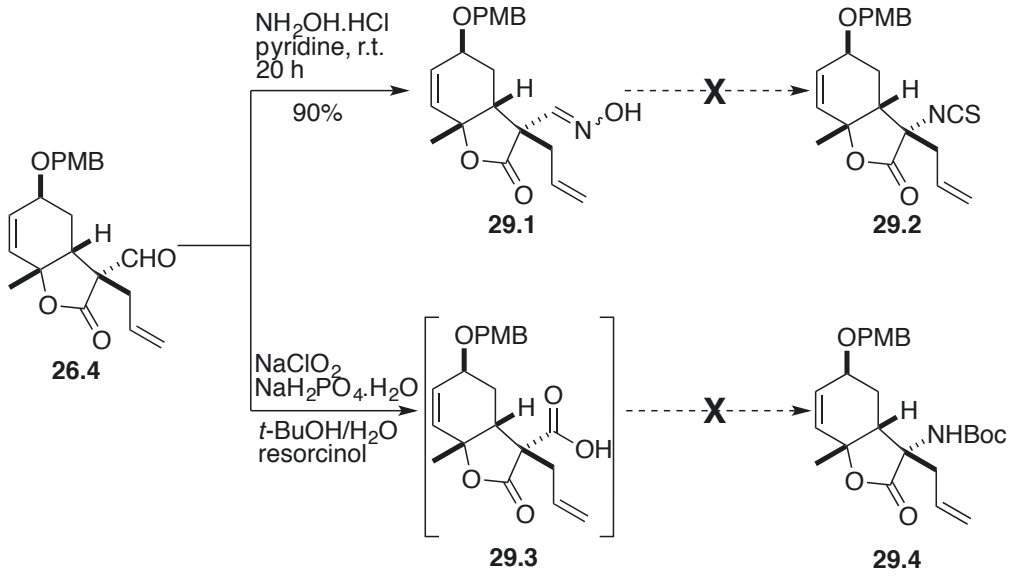
The fairly pure (^{1}H NMR) acid **27.5** was subjected to the usual steps of a Curtius rearrangement using the conditions reported by Lebel[43] to afford impure carbamate **28.1** in low yield (Scheme 28).



27.5 **28.1**

Scheme 28. Curtius rearrangement to convert a tertiary acid to the corresponding carbamate

Based on the result of this model study, I tried to apply the same conditions to the allyl aldehyde **26.4**. Although the oxime formation did not work well in the model, the aldoxime **29.1** was formed under the reported conditions[28] in 90% yield. But again, only starting material was recovered in the attempted rearrangement of the aldoxime to the isocyanate **29.2** under several different conditions.[29, 44] The Curtius rearrangement process, which worked in the model, afford a complex mixture with **29.3** (Scheme 29).



Scheme 29. Unsuccessful attempts to form the tertiary carbon–nitrogen bond

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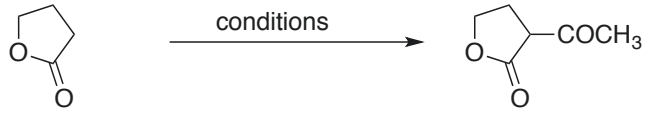
Table 3. Acetylation γ-butyrolactone



27.1 **T3.1**

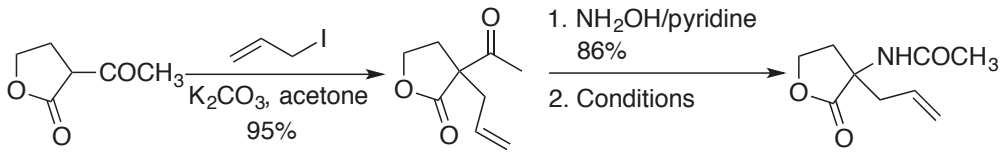
Conditions	Yield	Reference
NaHMDS, Ac_2O	No **T3.1** detected	45
LDA, MeCOCl	28%	
LDA, Ac_2O	41%	
LDA, Ac_2O, HMPA	41%	
LDA, MeCHO, then DMP	40%	46
LDA, MeCHO, HMPA then DMP	46%	

After the above observations, I decided to introduce the nitrogen onto the lactone ring through a Schmidt or a Beckmann rearrangement. Therefore another model study was set up to test these possibilities. The acylation of γ-butyrolactone (**27.1**) to make 2-acetylbutyrolactone (**T3.1**) is not an easy task (Table 3).

A careful study from the Feringa[47] group showed that the yield of the acetylation cannot surpass 45%. Therefore, I decided to install the acetyl side chain by the two-step method summarized in the last entry of Table 3, which in the event gave a slightly better result.

The 2-acetylbutyrolactone (**T3.1**) was allylated by allyl iodide using K_2CO_3 in acetone[48] and then treatment with NH_2OH/pyridine furnished **T4.1**, which was used to investigate the Beckmann rearrangement. Bismuth triflate at room temperature in acetonitrile provided the best outcome (Table 4).

Table 4. Investigate the Beckmann and Schmidt rearrangement

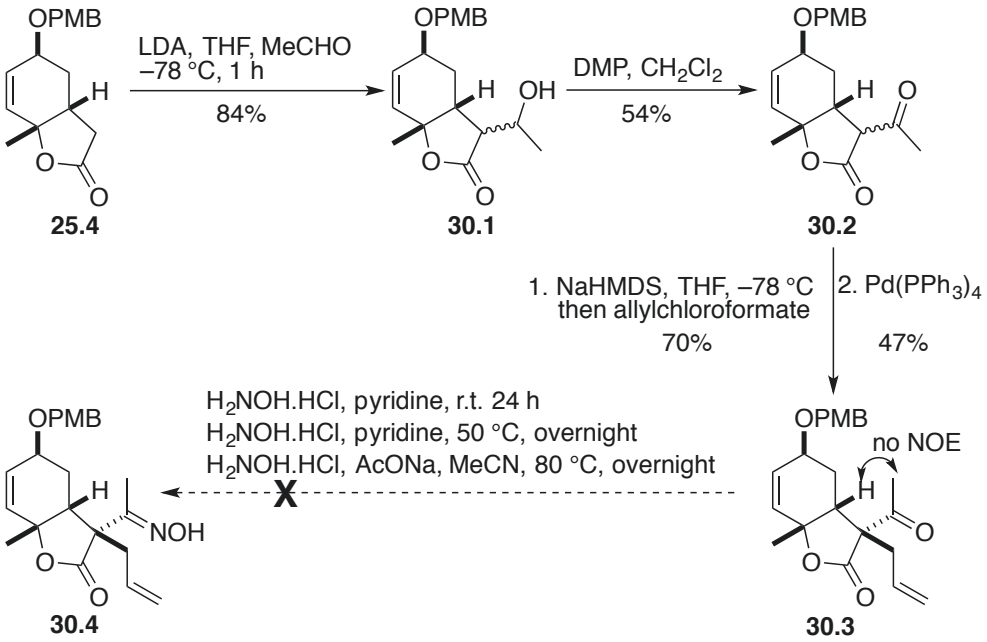


T3.1 **T4.1** **T4.2**

Conditions for second step	Overall Yield of T4.2	Reference
NaN_3, $MeSO_3H$, $CHCl_3$, 0 °C	Complex mixture	49*
TsCl, pyridine, then *i*-PrOH, reflux	SM recovered	50
$Sc(OTf)_3$, MeCN, 80 °C	SM recovered	
$Bi(OTf)_3$, MeCN, 80 °C	58%	
$Bi(OTf)_3$, MeCN, r.t.	66%	

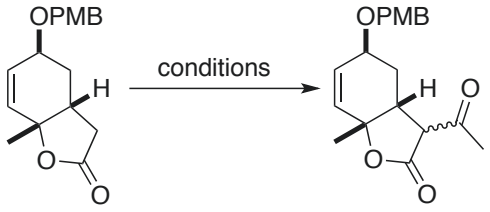
* **T4.1** was used without conversion to the oxime

After the model study, I embarked on the challenge of putting the nitrogen onto the lactone ring of **25.4** through $Bi(OTf)_3$ mediated Beckmann rearrangement. Compound **25.4** underwent aldol condensation with acetaldehyde to afford a mixture of inseparable alcohol isomers **30.1** in 84% yield. The alcohol mixture **30.1** was oxidized to the corresponding ketone by DMP to furnish **30.2** in 54% yield. Ketone **30.2** was subjected to the palladium mediated rearrangement[35] conditions reported by Cossy and gave the quaternary allyl ketone **30.3**. But all my efforts to make the oxime from **30.3** were thwarted (Scheme 30).



Scheme 30. Route to oxime **30.4**

Table 5. Reexamination of the acetylation reaction



Conditions	**Yield**
LiHMDS (1.2 eq) then AcCl	No DP detected
NaHMDS (2 eq) then AcCl	38%
LDA (2.4 eq), MeCHO then DMP	50%
LDA (2.4 eq), *N*-acetylimidazole	57%*

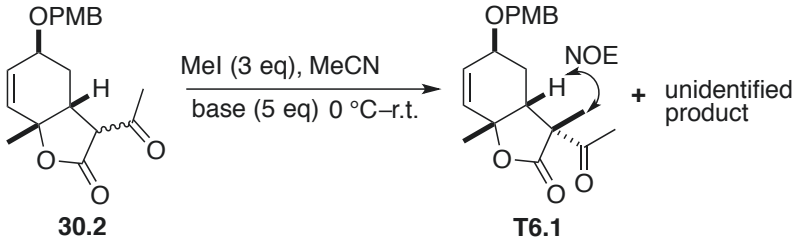
* Only one isomer detected by ^{1}H NMR

I assumed that oxime formation did not take place because the carbonyl is in a sterically inaccessible position underneath the six-membered ring and is also shielded by the allyl group. Therefore, instead of using an allyl group, I decided to use a methyl group instead. I re-examined the aldol-oxidation sequence, and were pleased to find that the reagent

N-acylimidazoles gave 57% yield of the desired product **30.2** as a single isomer (^{1}H NMR) (Table 5).

With satisfactory conditions for introducing the acetyl group in hand the next step was alkylation with MeI to set up the quaternary center. The reaction afforded the desired quaternary center with the correct relative stereochemistry (based on NOE observations), but it also gave another product with molecular formula $C_{19}H_{21}O_5$ whose structure was not deduced (Table 6).

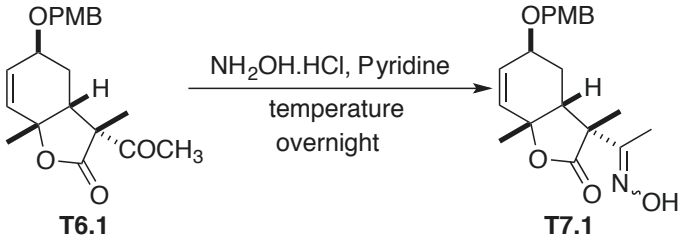
Table 6. Methylation **30.2** by MeI



30.2 **T6.1**

Base	Time	Yield of T6.1
K_2CO_3	3 h	46% (4:1 *dr*)
K_2CO_3	overnight	39% (4:1 *dr*)
Cs_2CO_3	overnight	43% (8:1 *dr*)

Table 7. Investigate the formation of oxime **T7.1**



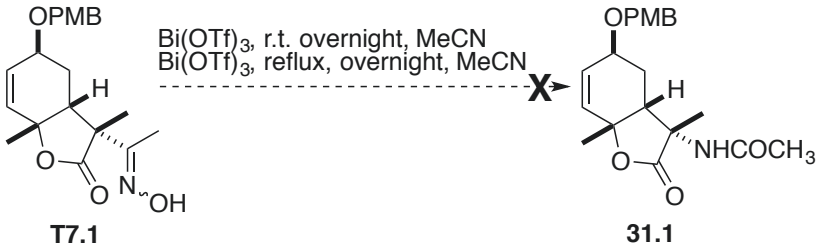
T6.1 **T7.1**

Temperature	Yield of T7.1
room temperature	No reaction
60 °C	32%*
reflux	80%

* Reaction was stopped after 24 h

The conversion from **T6.1** to its corresponding oxime was investigated next. The formation of oxime **T7.1** is sow at room temperature, but increasing the temperature led to a better yield of **T7.1**, which was a mixture of two inseparable geometric isomers (Table 7).

The oxime mixture **T7.1** was subjected to conditions for a $Bi(OTf)_3$ mediated Beckmann rearrangement. But much to my disappointment, no sign of the desired Beckmann rearrangement product was detected, and so my efforts to set up the carbon–nitrogen bond in the five-membered lactone was again unsuccessful (Scheme 31).

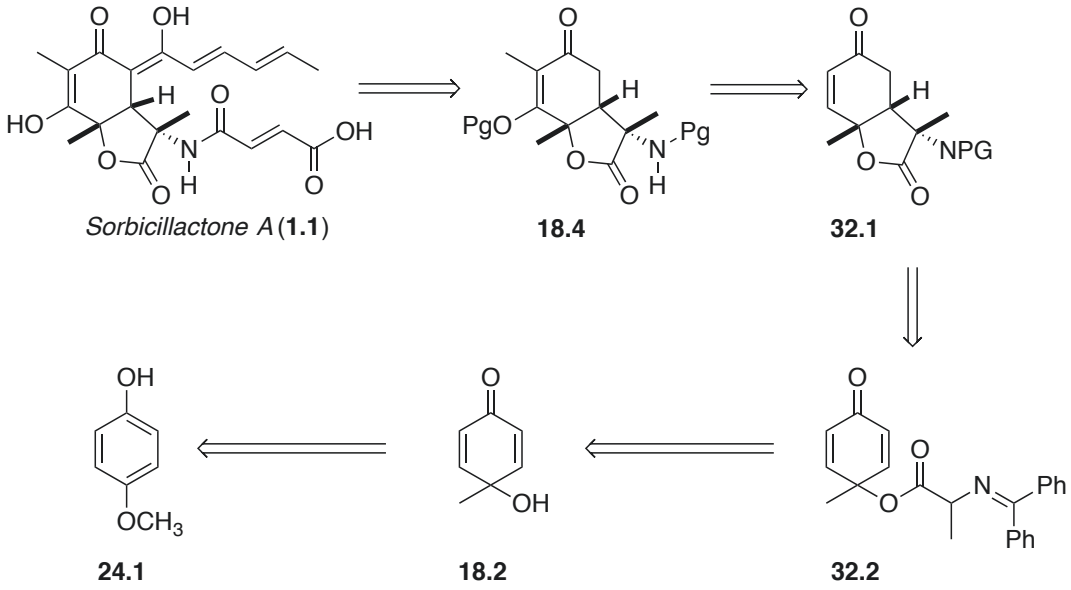


T7.1 **31.1**

Scheme 31. Failure to make the desired amide **31.1**

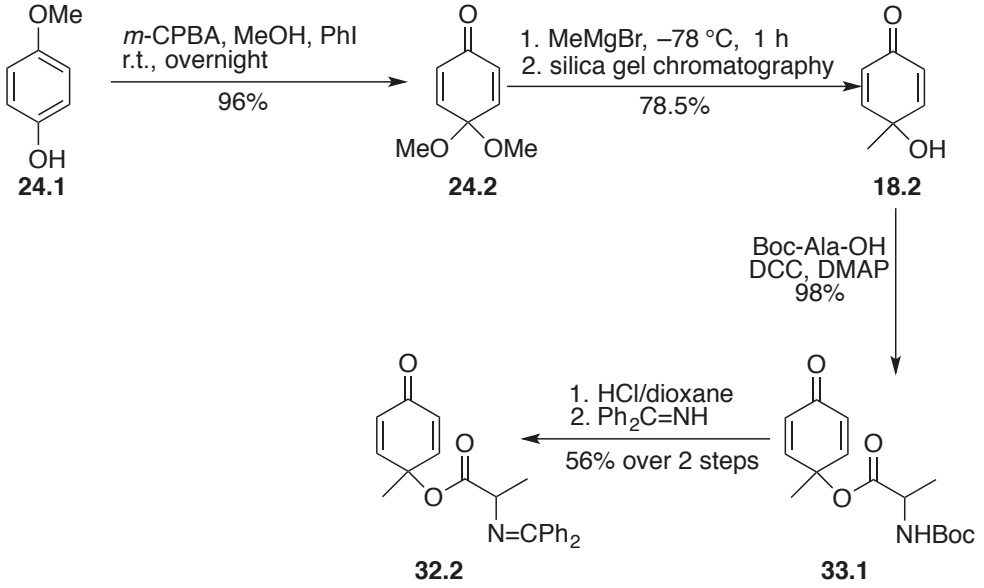
Third generation approach

At this point, I decided to abandon the approach using the bicyclic compound **9.7** as the key intermediate because of the difficulty of constructing the quaternary stereogenic center in the lactone ring with the correct stereochemistry. Inspired by Bringmann's biosynthetic hypothesis,[1] in which the key step is an intramolecular Michael addition, I sought to try such a reaction with compound **32.2** to make **32.1** with all the stereocenters set up correctly in only one step. This new approach is summarized in Scheme 32.



Scheme 32: New approach to synthesis sorbicillactone A

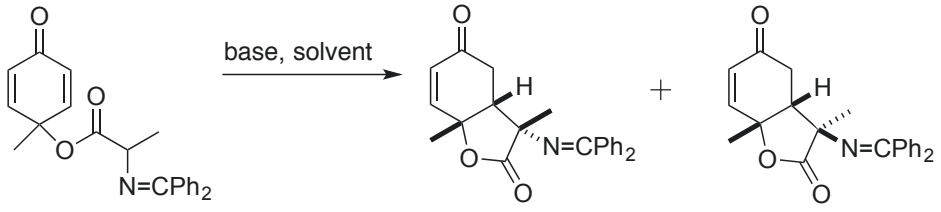
Like the second generation approach, compound **24.1** could be easily converted into alcohol **18.2** in a large scale operation (Scheme 33). Esterification of **18.2** with racemic Boc-Ala-OH afforded **33.1**, which could be deprotected by HCl/dioxane and the crude amine salt was treated with benzophenone imine to give the corresponding Schiff base **32.2**.[20] (Scheme 33)



Scheme 33: The preparation of Schiff base **32.2**

A brief optimization of the key intramolecular Michael addition of substrate **32.2** is summarized in Table 8. Fortunately, the key intermediate **32.1** was formed with the correct stereochemistry when **32.2** was treated with DBU for 48 h. Cyclization could also be achieved with Cs_2CO_3 but that reagent gave a 1:1 mixture of the two diastereoisomers **32.1** and **T8.1**.

Table 8. Intramolecular Michael addition of Schiff base **32.2**



32.2 **32.1** **T8.1**

Base	**Solvent**	**Time**	**Yield**
Cs_2CO_3[14]	MeCN	Overnight	Complex mixture
K_2CO_3	THF	Overnight	No reaction
Cs_2CO_3[51]	THF	Overnight	70% (1:1 mixture of **32.1** and **T8.1**)
DBU	THF	48 h	78%

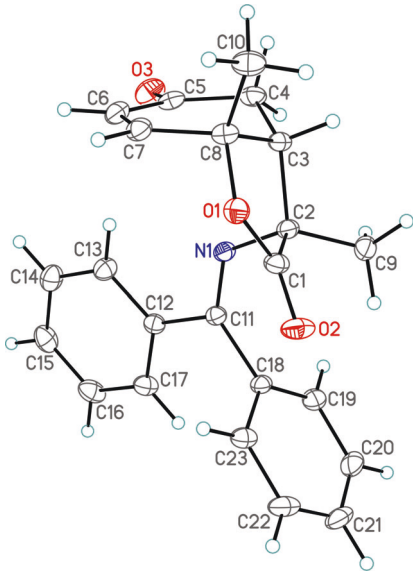
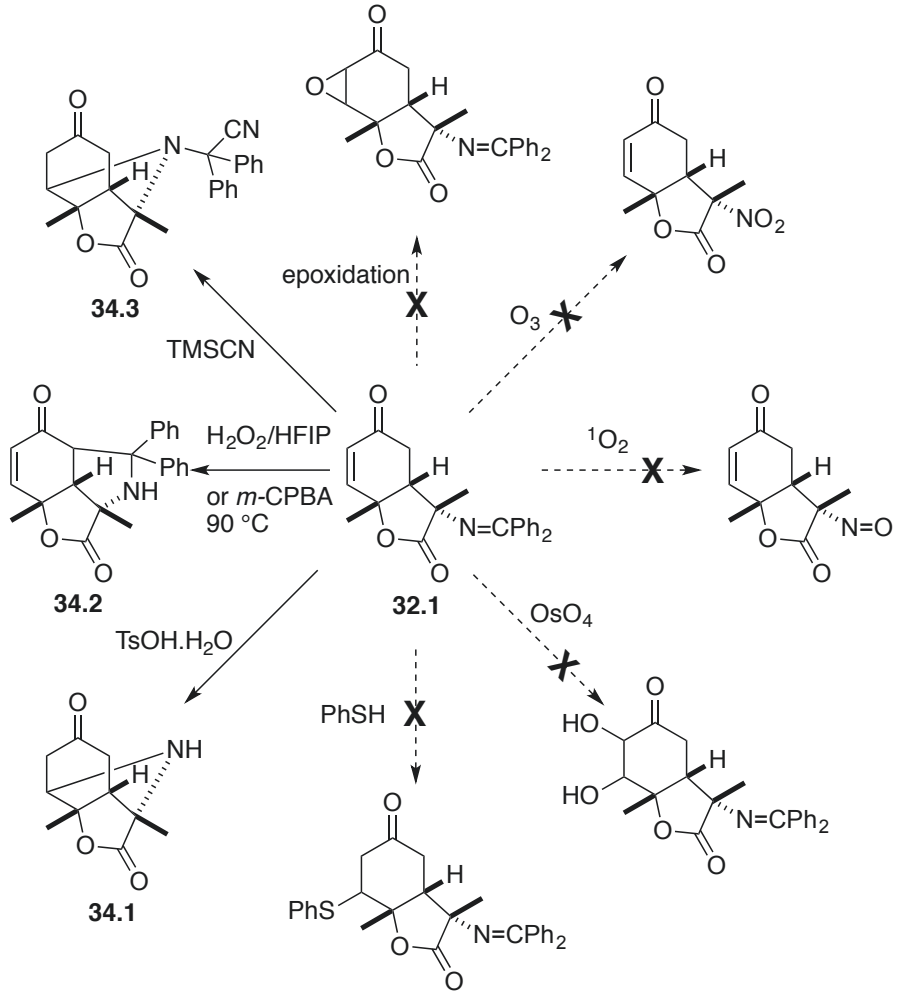


Figure 2. ORTEP diagram of compound **32.1**

The stereochemistry of product **32.1** was confirmed by X-ray analysis (Figure 2). The stereochemical outcome of the cyclization is in stark contrast to the one reported by Li;[20] perhaps the absence of a transition metal complex is responsible in my case. With the stereochemistry of **32.1** confirmed, I have been successful in finding a way to approach the carbocyclic core of sorbicillactone A and B in a short route that is easy to scale up.

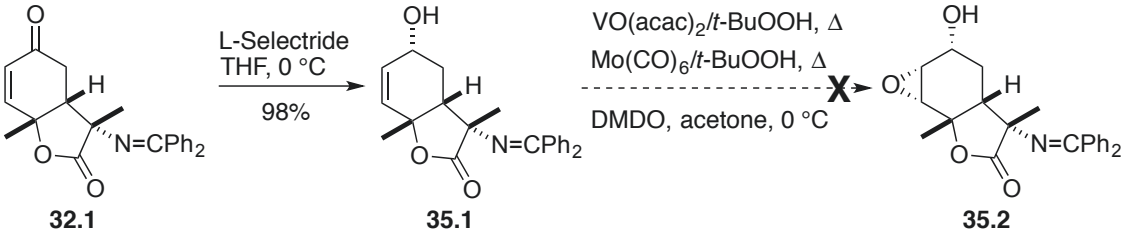


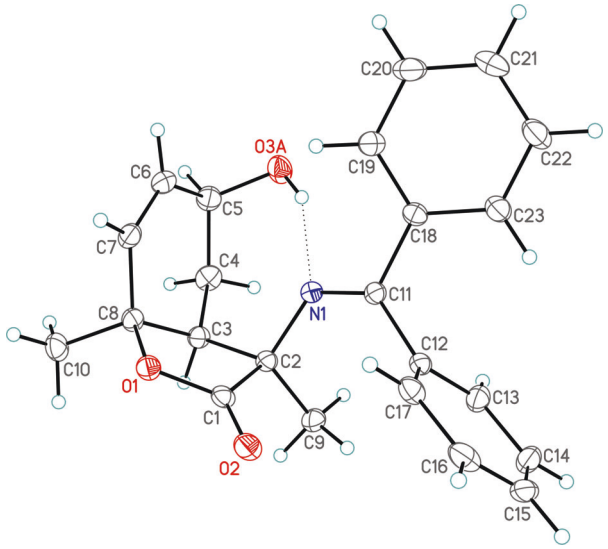
Scheme 34: Unsuccessful attempts to functionalize the double bond

The next task was to functionalize the carbon-carbon double bond in the six-membered ring to form a cyclohexane-1,3-dione derivative. I expected that this could be done without problem, but it turns out to be an extremely difficult task. Compound **32.1** was surprisingly inert and starting material was recovered from experiments involving Julia-Colonna epoxidation,[19, 52] ozone, singlet oxygen,[53] OsO_4, PhSH,[54] dimethyldioxirane,[55] and sodium perborate.[56] Remove of the imine group with $TsOH.H_2O$ triggered an intramolecular

aza-Michael addition to afford **34.1**. With *m*-CPBA[57] and also with H_2O_2/HFIP[58] the tricyclic compound **34.2** was formed as the sole product, and with TMSCN the cyanide ion attacked the C=N bond instead of the carbonyl and gave **34.3** whose structure was confirmed by X-ray analysis.

Because of the apparently hindered nature of the C=C bond in the cyclohexenone ring, I decided to install the oxygen through allylic epoxidation which occurs intramolecularly. Enone **32.1** was reduced with L-Selectride to give the iminoalcohol **35.1**, but attempted epoxidation with $VO(acac)_2$/*t*-BuOOH[59a] or $Mo(CO)_6$/*t*-BuOOH,[59b] both of which operate by an intramolecular delivery of an oxygen, or with dimethyldioxirane[59c] gave back compound **32.1** instead of the desired epoxide **35.2** (Scheme 35). Therefore the stereochemistry of the hydroxyl group in the cyclohexene ring was judged to be unsuited for directed epoxidation, a process which has been thoroughly investigated.[60]

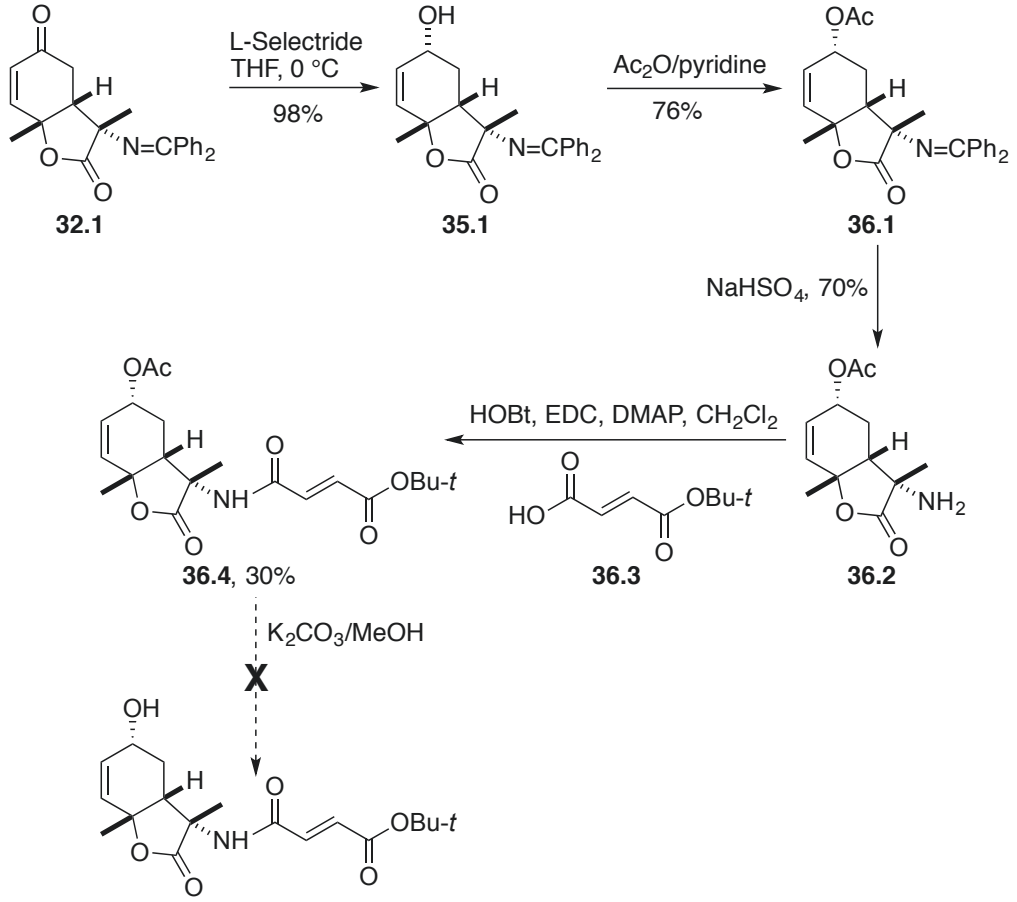




Scheme 35: (i) Unsuccessful attempts to epoxidize alcohol **35.1** and (ii) its ORTEP diagram

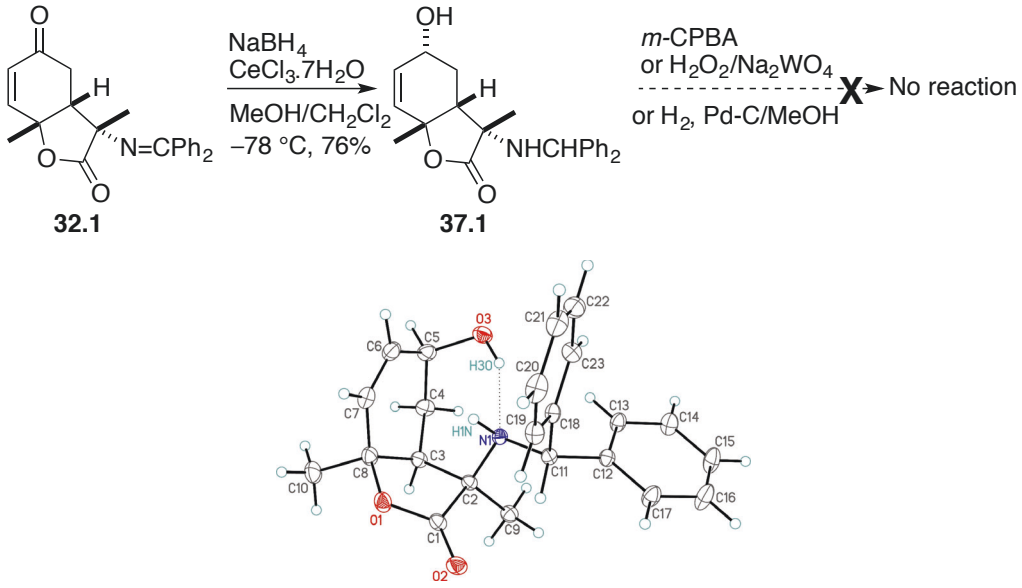
Another route to try to install the oxygen on the 6-membered ring was evaluated. Alcohol **35.1** was acetylated with Ac_2O/pyridine to give **36.1**, which was hydrolyzed by

$NaHSO_4/H_2O$ to afford the amine **36.2**. The fumaryl side chain was attached to **36.2** through amidation coupling with **36.3**, but this reaction is very sluggish, and amide **36.4** was isolated in only 30% yield, perhaps due to the shielded nature of the tertiary amine group. Compound **36.4** was deacetylated by treatment with K_2CO_3/MeOH to give an unidentified product without the double bond in the amide side chain. I did not establish if this was the result of an intramolecular Michael addition of the newly released hydroxyl group onto the amide side chain.



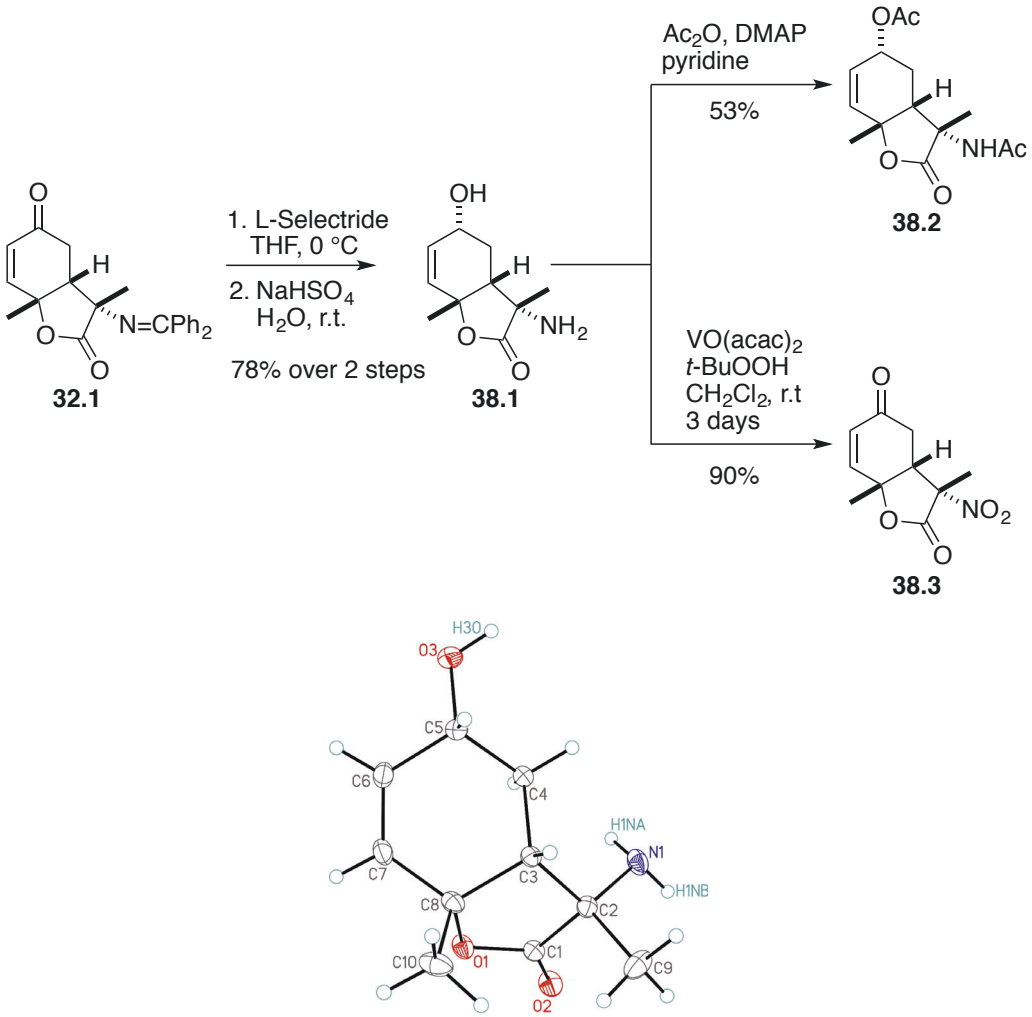
Scheme 36: Another attempted strategy to reach sorbicillactone A

When **32.1** was subjected to Luche reduction, the aminoalcohol **37.1** was formed, but attempts to oxidize **37.1** to the corresponding hydroxylamine turned out to be ineffective with *m*-CPBA[61a] or H_2O_2/Na_2WO_4,[61b] the standard reagents for this transformation. Removal of the Ph_2CH group in **37.1** by hydrogenolysis did not work and only starting material was recovered under the conditions used (room temperature, 1 atmosphere) (Scheme 37).



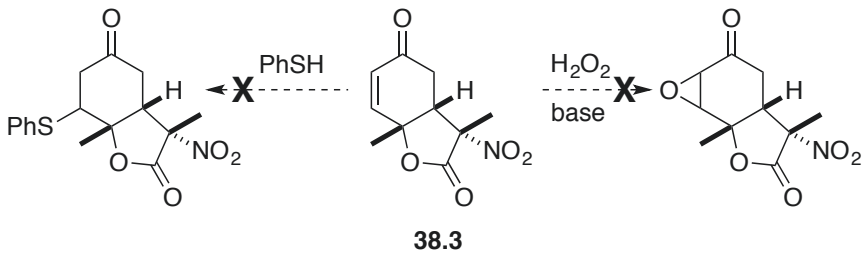
Scheme 37: Synthesized aminoalcohol **37.1** (and its ORTEP diagram) and its unsuccessful subsequent transformation

From all the unsuccessful attempts it is clear that the imine protecting group $N=CPh_2$ needs to be removed before going further. But deprotection of compound **32.1** leads to a spontaneous intramolecular Michael addition to give **34.1** (see Scheme 34), and so the C=O group in **32.1** should be reduced first, followed by deprotection of the nitrogen. These two reactions could be done without isolating the intermediate and afforded the amine **38.1** in 78% yield over the two steps (Scheme 38). The amino alcohol could be bis-acetylated with Ac_2O/DMAP but the product **38.2** was formed in a modest yield (53%). Surprisingly, the nitroketone **38.3** was formed from an attempted Sharpless epoxidation[59a] in 90% yield after a reaction period of 3 days and this transformation opens the door for further operations.



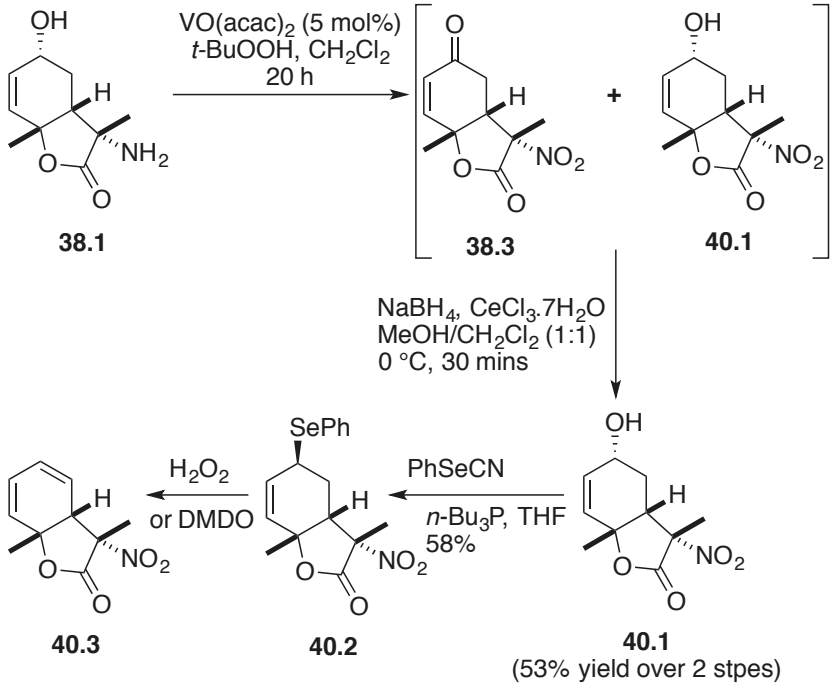
Scheme 38: Formation of aminoalcohol **38.1** (and its ORTEP diagram) and its subsequent transformation

Although the nitro group is less sterically demanding than the imine N=CPh$_2$ group, it was disappointing to find that conjugate addition of PhSH[54] or Julia–Collona epoxidation[19, 52] only gave back the starting materials (Scheme 39).



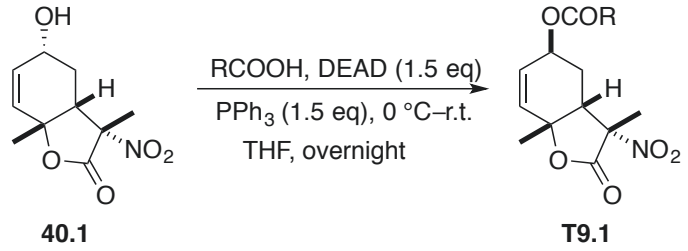
Scheme 39: Unsuccessful attempt to functionalize the nitroketone

By carefully examining the X-rays structure of **38.1** I suspected that the failure of Sharpless directed epoxidation was because the OH group is too far from the double bond. Consequently inversion of the stereochemistry of the alcohol group ought to solve the problem. Therefore I tried to stop the oxidation of the amine after 20 h (TLC show that there is no starting material remaining at that point) to get the nitroalcohol **40.1**, but in the event, I produced only a mixture of **38.3** and **40.1**, which was hard to separate into its components. Eventually, I treated the crude mixture of **38.3** and **40.1** under Luche reduction conditions to produce only **40.1** in 53% yield over two steps. Selenide **40.2** was synthesized in 58% yield by treatment of **40.1** with PhSeCN/*n*-Bu_3P so as to set the stage for a 1,3-allylic transportation, which was developed in our group [62] However, oxidization of the selenide with H_2O_2 or dimethyldioxirane gave the diene **40.3** as the sole product instead of the rearranged allylic alcohol.



Scheme 40: Unsuccessful 1,3-allylic transportation

Table 9. Optimization of the Mitsunobu reaction



40.1 **T9.1**

RCOOH		**yield**	**reference**
O_2N—C$_6$H$_4$—COOH	(**T9.1a**)	*trace*	63
HCOOH	(**T9.1b**)	*No reaction*	64
3,5-$(O_2N)_2$—C$_6$H$_3$—COOH	(**T9.1c**)	84%	65

Having failed with the selenoxide-based 1,3-allyl transportation, I turned to the Mitsunobu inversion. Although esterification with *p*-nitrobenzoic acid gave a very poor yield, the trace of solid product **41.2** was enough for me to confirm by X-ray analysis that inversion of the alcohol had indeed occurred (Figure 3). Further optimization of the Mitsunobu reaction by changes to the carboxylic acid component identified 3,5-dinitrobenzoic acid as a much better reagent (Table 9).

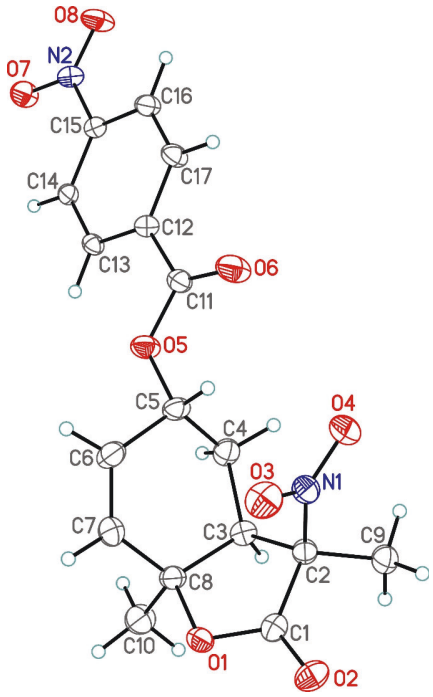
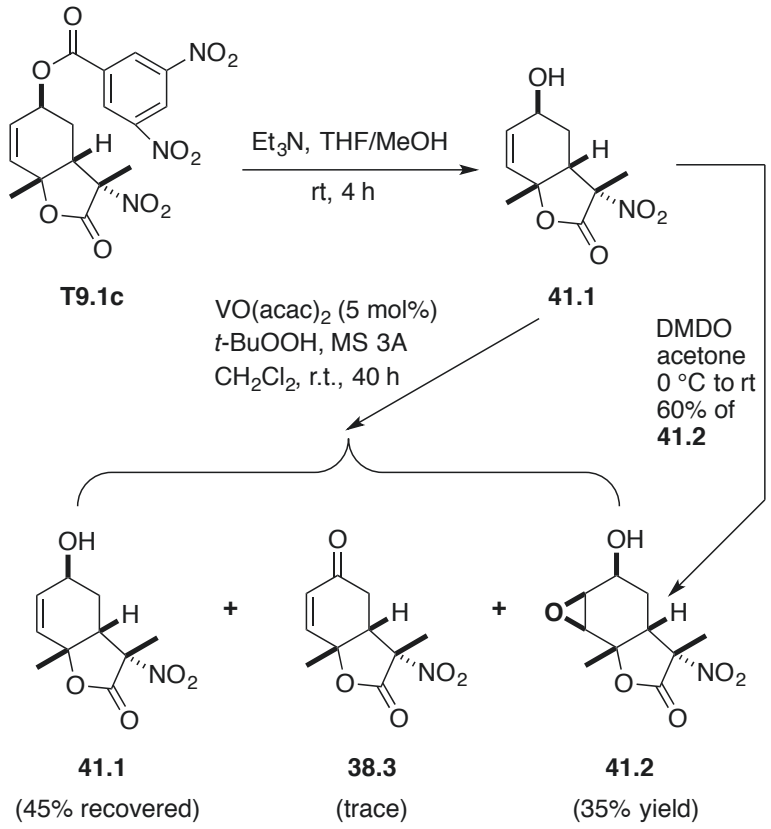


Figure 3. X-ray structure of *p*-nitrobenzoate ester **T9.1**, R = 4-$O_2NC_6H_4$

At first, I tried to hydrolyze the dinitrobenzoate to get alcohol **41.1** by using K_2CO_3/MeOH, but the desired alcohol was formed in only 23% yield. On switching to Et_3N in THF/MeOH (1:1)[66] **41.1** was obtained in 86% yield. This time, epoxidation of **41.1** under the Sharpless conditions gave the corresponding epoxide **41.2** in 35% yield after 40 h, 45% yield of recovered starting material **41.1** and traces of the ketone **38.3** (Scheme 41). Fortunately, use of dimethyldioxirane was even more successful and gave **41.2** in 60% yield and only traces of **38.3** were detected.



Scheme 41: Successful epoxidation of the cyclohexane ring core of sorbicillactones A and B

Conclusion

During the expedition to conquer sorbicillactones A and B, I found a bioinspired intramolecular Michael addition which could directly establish three stereogenic centers (two of them are quaternary) in only one step. This discovery helped me quickly construct the core of sorbicillactones A and B in 5 steps overall, that could be easily to scaled up. The Sharpless epoxidation experiment with the aminoalcohol **38.1** unexpectedly gave nitroketone **38.3**, which could be converted to alcohol **40.1**. Conversion of **40.1** to its alcohol epimer **41.1** via Mitsunobu inversion opened a way to successfully functionalize the double bond in the cyclohexene ring. With this, only the methyl and two side chains remain to be attached, and two natural products sorbicillactone A and B now seem within reach. Again, this work shows that simple synthetic pathways can be very hard to find.[67]

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 (N_2) 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. Gradient flash chromatography was done by stepwise small increases in the proportion of the more polar solvent, as described for the individual experiments.

4,4-Dimethoxycyclohexa-2,5-dien-1-one (24.2).[30]

24.1 **24.2**

m-CPBA (70–75%, 14.45 g, 64.52 mmol) was added to PhI (1 mL, 3.23 mmol) in bench MeOH (150 mL), and *p*-methoxyphenol (4.0 g, 32.26 mmol) was added in one lot to the stirred solution. Stirring at room temperature was continued overnight. At that point no starting phenol remained (tlc control, silica, 3:7 EtOAc-hexane) and the precipitate was filtered off. The filtrate was evaporated and saturated aqueous $NaHCO_3$ (100 mL) was added to the residue. The mixture was extracted with CH_2Cl_2 (2 × 70 mL) and the combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (5 × 15 cm), using first 1:9 EtOAc-hexane (1000 mL) and then 2:8 EtOAc-hexane, gave **24.2** (4.77 g, 96%) as a yellow oil: ^1H NMR ($CDCl_3$, 500 MHz,) δ 6.82 (d, J = 10.4 Hz, 2 H), 6.28 (d, J = 10.3 Hz, 2 H), 3.38 (s, 6 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 185.2 (s), 143.3 (d), 130.1 (d), 92.6 (s), 50.5 (q).

4-Hydroxy-4-methylcyclohexa-2,5-dien-1-one (18.2).[31]

24.2 **18.2**

A solution of **24.2** (4.87 g, 31.63 mmol) in dry THF (40 mL) was added dropwise over 5 min by syringe to a stirred and cooled (–78 °C) solution of MeMgBr (3 M in Et_2O, 19 mL, 57 mmol) in THF (20 mL). Stirring at –78 °C was continued for 1 h and the cooling bath was then removed and saturated aqueous NH_4Cl (75 mL) was poured into the reaction mixture. Stirring was continued for 30 min and the mixture was extracted with EtOAc (3 × 80). The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (5 × 15 cm), using 1:1 EtOAc-hexane, gave **18.2** (3.07 g, 78.5%) as a brown solid: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.89 (d, J = 10.1 Hz, 2 H), 6.15 (d, J = 10.1 Hz, 2 H), 2.04 (s, 1 H), 1.50 (s, 3 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 185.3 (s), 151.9 (d), 127.4 (d), 67.3 (s), 26.8 (q).

1-Methyl-4-oxo-cyclohexa-2,5-dien-1-yl 2-bromoacetate (19.1).[68]

18.2 **19.1**

Bromoacetic acid (4.03 g, 29.0 mmol) was added in one lot to a stirred solution of **18.2** (2.40 g, 19.4 mmol) in dry CH_2Cl_2 (50 mL) and then DCC (5.98 g, 29.0 mmol) and DMAP (237 mg, 1.94 mmol) were added, each in one lot. Stirring at room temperature was continued for 2.5 h and the mixture was then diluted with Et_2O (50 mL). The resulting mixture was filtered and evaporated. Flash chromatography of the residue over silica gel (5 × 15 cm), using 3:7 EtOAc-hexane, gave **19.1** (3.63 g, 77%) as a brown solid: mp 70–72 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.90 (d, J = 10.2 Hz, 2 H), 6.28 (d, J = 10.2 Hz, 2 H), 3.81 (s, 2 H), 1.62 (s, 3 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 184.7 (s), 165.7 (s), 147.6 (d), 128.8 (d), 75.9 (s), 26.1 (t) 25.7 (q).

(3a*R,7a*S**)-7a-Methyl-2,3,3a,4,5,7a-hexahydro-1-benzofuran-2,5-dione (9.7).**[18]

19.1 **9.7**

All steps in the following experiment were done with protection from light. Dry acetone (100 mL) was added to a round-bottomed flask containing **19.1** (1.97 g, 8.07 mmol) and NaI (4.84 g, 32.2 mmol). The flask was fitted with a reflux condenser (N_2 atmosphere) and the mixture was refluxed for 6 h, by which point no starting material remained (tlc, silica, 3:7 EtOAc-hexane). The solvent was evaporated and the residue was swirled with EtOAc (150 mL) and the mixture was filtered through a pad (1 × 4 cm wide) of Celite. The filtrate was washed with water and brine, dried ($MgSO_4$), and evaporated. The residue was dissolved in bench PhH (250 mL). The solution was refluxed (N_2 atmosphere) and a solution of Bu_3SnH (2.1 mL, 8.07 mmol) and AIBN (132.6 mg, 0.81 mmol) in dry PhH (20 mL) was added by syringe pump over 10 h from a 24-mL syringe. Refluxing was continued for another 6 h and the mixture was cooled and evaporated. Flash chromatography of the residue over silica gel (5 × 15 cm), using 2:3 EtOAc-hexane., gave **9.7** (1.04 g, 78% over two steps) as a solid: mp 110–112 °C; FTIR (CH_2Cl_2, cast) 2978, 1771, 1682, 1419, 1309 cm^{-1}; ^1H NMR ($CDCl_3$, 700 MHz) δ 6.65 (dd, *J* = 10.3, 1.9 Hz, 1 H), 6.08 (dd, *J* = 10.4, 1.0 Hz, 1 H), 2.96–2.88 (m, 1 H), 2.77–2.67 (m, 2 H), 2.61 (ddd, *J* = 17.4, 3.0, 1.0 Hz, 1 H), 2.42 (dd, *J* = 17.5, 11.8 Hz, 1 H), 1.68 (s, 3 H); ^{13}C NMR ($CDCl_3$, 175 MHz) δ 195.0 (s), 173.7 (s), 146.5 (d), 129.2 (d), 81.5 (s), 40.9 (d), 36.8 (t), 34.8 (t), 24.2 (q); exact mass (EI) *m*/*z* calcd for $C_9H_{10}O_3$ (M^+) 166.0630, found 166.0631.

(3a*R,7a*S**)-5-Hydroxy-7a-methyl-2,3,3a,4,5,7a-hexahydro-1-benzofuran-2-one (25.1 and 25.2).**

9.7 **25.1** and **25.2**

A solution of **9.7** (360 mg, 2.17 mmol) in bench CH_2Cl_2 (20 mL) was added in one portion to a stirred and cooled (–78 °C) solution of $CeCl_3.7H_2O$ (4.84 g, 13 mmol) in bench MeOH (20 mL). $NaBH_4$ (201.4 mg, 5.41 mmol) was added in one portion and stirring at –78 °C was continued for 1 h. Water (20 mL) and solid $NaHSO_4$ (2 g) were added and the cooling bath was removed. Stirring was continued for another 5 min and the mixture was then extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (3 × 30 cm), using 2:3 EtOAc-hexane, gave the β-alcohol **25.2** (149.7 mg, 41%) as an oil and the α-alcohol (149.4 mg, 41%) as a white solid.

The α-alcohol **25.1** (less polar isomer) had: FTIR (CH_2Cl_2, cast) 3422, 1770, 1447, 1079 cm^{-1}; ^1H NMR ($CDCl_3$, 700 MHz) δ 5.98 (ddd, *J* = 10.2, 2.4, 1.0 Hz, 1 H), 5.78 (dd, *J* = 10.1, 1.8 Hz, 1 H), 4.30–4.24 (m, 1 H), 2.90 (dd, *J* = 17.8, 8.3 Hz, 1 H), 2.57 (dd, *J* = 17.7, 4.1 Hz, 1 H), 2.41–2.35 (m, 1 H), 2.07–2.02 (m, 1 H), 1.60–1.51 (m, 3 H), 1.44 (s, 3 H). ^{13}C NMR ($CDCl_3$, 175 MHz) δ 175.5 (s), 134.4 (d), 129.0 (d), 81.6 (s), 64.8 (d), 37.7 (d), 35.9 (t), 34.1 (t), 26.2 (q); exact mass (ESI) *m*/*z* calcd for $C_9H_{12}NaO_3$ ($M+Na^+$) 191.0679 found 191.0679.

The β-alcohol **25.2** (more polar isomer) had: FTIR (CH_2Cl_2, cast) 3433, 1766, 1421, 1089 cm^{-1}; ^1H NMR ($CDCl_3$, 700 MHz) δ 5.96 (ddd, *J* = 10.2, 3.3, 0.9 Hz, 1 H), 5.77 (ddd, *J* = 10.2, 1.6, 0.8 Hz, 1 H), 4.39–4.36 (m, 1 H), 2.74–2.64 (m, 2 H), 2.39 (dd, *J* = 16.8, 7.9 Hz, 1 H), 2.08–2.01 (m, 1 H), 1.78 (ddd, *J* = 13.9, 7.5, 4.2 Hz, 1 H), 1.62 (d, *J* = 5.3 Hz, 1H), 1.52 (s, 3 H); ^{13}C NMR ($CDCl_3$, 175 MHz) δ 175.4 (s), 132.2 (d), 130.5 (d), 82.4 (s), 62.6 (d), 38.1 (d), 33.9 (t), 32.3 (t), 26.0 (q); exact mass (ESI) *m*/*z* calcd for $C_9H_{12}NaO_3$ ($M+Na^+$) 191.0679 found 191.0680.

(3a*R,7a*S**)-7a-Methyl-2,3,3a,4,5,7a-hexahydro-1-benzofuran-2,5-dione (9.7)**.

25.1 **9.7**

Dess-Martin reagent (954 mg, 2.25 mmol) was added in one lot to a stirred and cooled (0 °C) solution of **25.1** (252 mg, 1.50 mmol) in dry CH_2Cl_2 (15 mL). The ice bath was removed and stirring was continued for 1 h (monitoring by ^1H NMR. The reaction mixture was diluted with CH_2Cl_2 and washed with saturated aqueous $NaHCO_3$, aqueous $Na_2S_2O_3$ (1 M) and brine. The organic extract was dried ($MgSO_4$) and evaporated. Flash

chromatography of the residue over silica gel (2 × 15 cm), using 2:3 EtOAc-hexane, gave **9.7** (199 mg, 80%) as a solid.

(3a*R,5*R**,7a*S**)-5-[(4-Methoxyphenyl)methoxy]-7a-Methyl-2,3,3a,4,5,7a-hexahydro-1-benzofuran-2-one (25.1).**

25.1 **25.3**

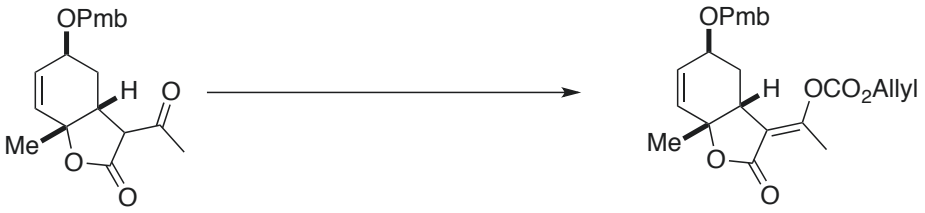
A solution of **25.1** (95.2 mg, 0.566 mmol) in dry DMF (1 mL) was injected dropwise into a stirred and cooled (0 °C) slurry of NaH (60%$^{w}/_{w}$ in mineral oil, 40.8 mg, 1.02 mmol) in DMF (1 mL). After 5 min bubbling stopped and neat PmbBr[69] (0.1 mL, 0.694 mmol) was injected rapidly. The ice bath was left in place but not recharged and stirring was continued overnight by which time no starting alcohol remained (tlc, silica, 3:7 EtOAc-hexane). Water (20 mL) was added dropwise and the mixture was 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 2:8 EtOAc-hexane to 3:7 EtOAc-hexane, gave **25.3** (131.7 mg, 81%) as a solid: mp 52–55 °C; FTIR (CH_2Cl_2, cast) 2934, 1769, 1621, 1513, 1287 cm^{-1}; ^1H NMR ($CDCl_3$, 700 MHz) δ 7.25 (d, *J* = 8.6 Hz, 2 H), 6.88 (d, *J* = 8.6 Hz, 2 H), 6.04 (dd, *J* = 10.2, 2.9 Hz, 1 H), 5.77 (dd, *J* = 10.2, 1.6 Hz, 1 H), 4.52 (s, 2 H), 3.94 (dddd, *J* = 6.5, 4.8, 2.9, 1.7 Hz, 1 H), 3.81 (s, 3 H), 2.83–2.71 (m, 2 H), 2.41–2.34 (m, 1 H), 1.97 (dt, *J* = 13.7, 4.7 Hz, 1 H), 1.77 (ddd, *J* = 13.7, 8.8, 6.5 Hz, 1 H), 1.43 (s, 3 H); ^{13}C NMR ($CDCl_3$, 175 MHz) δ 175.6 (s), 159.4 (s), 131.2 (d), 130.2 (s), 129.7 (d), 129.2 (d), 114.0 (d), 82.0 (s), 70.4 (t), 70.2 (d), 55.4 (q), 37.9 (d), 35.5 (t), 29.7 (t), 26.0 (q); exact mass (EI) *m*/*z* calcd for $C_{17}H_{20}O_4$ (M^+) 288.1362, found 288.1361.

(3a*R,5*S**,7a*S**)-5-[(4-Methoxyphenyl)methoxy]-7a-Methyl-2,3,3a,4,5,7a-hexahydro-1-benzofuran-2-one (25.4).**

25.2 **25.4**

(4-Methoxyphenyl)methyl 2,2,2-trichloroethanimidate[70] (580.34 mg, 2.05 mmol) and $Sc(OTf)_3$ (33.7 mg, 0.0685 mmol) were added sequentially to a stirred solution of **25.2** (230 mg, 1.37 mmol) in dry PhMe (6 mL) (N_2 atmosphere). Stirring was continued for 15 min (tlc monitoring, silica, 2:3 EtOAc-hexane) and the solvent was then evaporated at ca 40 °C. Flash chromatography of the residue over silica gel (2 × 15 cm), using 1:4 EtOAc-hexane, gave the **25.4** (384.6 mg, 98%) as an oil: FTIR (CH_2Cl_2, cast) 2933, 1767, 1612, 1530, 1285 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.31–7.25 (m, 2 H), 6.91 (d, *J* = 8.6 Hz, 2 H), 6.06 (dd, *J* = 10.2, 3.6 Hz, 1 H), 5.82 (dd, *J* = 10.1, 1.4 Hz, 1 H), 4.54 (s, 2 H), 4.10–4.03 (m, 1 H), 3.83 (s, 3 H), 2.85–2.61 (m, 2 H), 2.37 (dd, *J* = 16.9, 7.0 Hz, 1 H), 2.03–1.86 (m, 2 H), 1.53 (s, 3 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 175.5 (s), 159.4 (s), 130.9 (d), 130.20 (s), 130.19 (d), 129.3 (d), 114.0 (d), 82.6 (s), 70.5 (t), 68.7 (d), 55.3 (q), 37.8 (d), 34.2 (t), 29.6 (t), 26.0 (q); exact mass (ESI) *m*/*z* calcd for $C_{17}H_{20}NaO_4$ (M+Na) 311.1254 found 311.1254.

(3a*R,5*S**,7a*R**)-5-[(4-Methoxyphenyl)methoxy]-7a-methyl-2-oxo-2,3,3a,4,5,7a-hexahydro-1-benzofuran-3-ylidene]methyl but-3-enoate (26.2).**

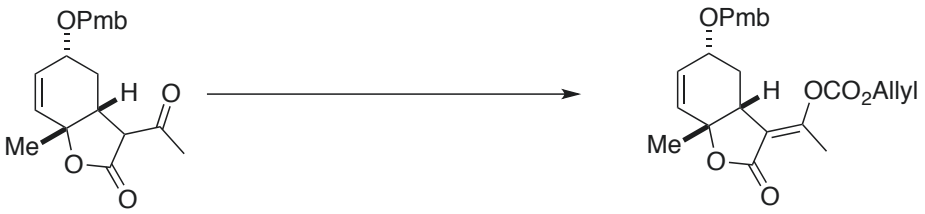


25.4 **26.2**

A solution of **25.4** (220 mg, 0.770 mmol) in THF (20 mL) was added dropwise to a stirred slurry of NaH (60%$^w/_w$ in mineral oil, 61.6 mg, 1.54 mmol) in THF (5 mL) (N_2 atmosphere). After the addition the reaction flask was lowered into an oil bath set at 40 °C. Dry EtOH (1 drop) was injected and when the resulting bubbling had subsided neat EtOCHO (0.14 mL, 1.69 mmol) was injected rapidly and the mixture was refluxed for 5 h. The mixture was cooled and evaporated. The residue was dissolved in THF (20 mL), allyl chloroformate (0.41 mL, 3.85 mmol) was injected rapidly and the mixture was stirred overnight (N_2 atmosphere). Brine (30 mL) was added and the mixture was extracted with Et_2O. The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2 × 15 cm), using 1:9 EtOAc-hexane, gave **26.2** (147.4 mg, 54%) as an oil, which was a single isomer: ^1H NMR ($CDCl_3$, 700 MHz) δ 7.30–7.24 (m, 3 H), 6.89 (d, *J* = 8.6 Hz, 2 H), 6.02–5.92 (m, 2 H), 5.78 (dd, *J* = 10.3, 1.5 Hz, 1 H), 5.43 (dd, *J* = 17.2, 1.4 Hz, 1 H), 5.34 (dd, *J* = 10.4, 1.2 Hz, 1 H), 4.75 (dd, *J* = 6.2, 1.3 Hz, 2 H), 4.04–3.99 (m, 1 H), 3.81 (s, 3 H), 3.20 (ddd, *J* = 7.0, 4.7, 2.3 Hz, 1 H), 2.09–2.02 (m, 1 H), 1.92 (ddd, *J* = 14.0, 7.3, 4.7 Hz, 1 H), 1.51 (s, 3 H); ^{13}C NMR ($CDCl_3$, 175 MHz) δ

165.8 (s), 159.5 (s), 152.0 (s), 141.0 (d), 131.0 (d), 130.7 (d), 130.5 (d), 130.1 (s), 129.5 (d), 120.3 (t), 114.1 (s), 114.0 (d), 80.5 (s), 70.8 (t), 70.2 (t), 68.3 (d), 55.3 (q), 41.0 (d), 30.5 (t), 26.4 (q).

(3a*R,5*R**,7a*R**)-5-[(4-Methoxyphenyl)methoxy]-7a-methyl-2-oxo-2,3,3a,4,5,7a-hexahydro-1-benzofuran-3-ylidene]methyl but-3-enoate (26.3).**



26.1 **26.3**

A solution of **26.1** (105 mg, 0.360 mmol) in THF (10 mL) was added dropwise to a stirred slurry of NaH (60%$^{w}/_{w}$ in mineral oil, 29.16 mg, 0.73 mmol) in THF (5 mL) (N_2 atmosphere). After the addition the reaction flask was lowered into an oil bath set at 40 °C. Dry EtOH (1 drop) was injected and when the resulting bubbling had subsided neat EtOCHO (0.07 mL, 0.87 mmol) was injected rapidly and the mixture was refluxed for 5 h. The mixture was cooled and evaporated. The residue was dissolved in THF (10 mL), allyl chloroformate (0.12 mL, 1.13 mmol) was injected rapidly and the mixture was stirred overnight (N_2 atmosphere). Brine (20 mL) was added and the mixture was extracted with Et_2O. The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2 × 15 cm), using 1:9 EtOAc-hexane, gave **26.3** (94.4 mg, 65%) as an oil, which was a single isomer: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.45 (d, *J* = 1.4 Hz, 1 H), 7.27 (d, *J* = 8.6 Hz, 2 H), 6.90 (d, *J* = 8.6 Hz, 2 H), 6.08 (ddd, *J* = 10.2, 1.9, 1.1 Hz, 1 H), 6.02–5.92 (m, 1 H), 5.80 (dd, *J* = 10.3, 2.0 Hz, 1 H), 5.44 (dd, *J* = 17.2, 1.4 Hz, 1 H), 5.35 (dd, *J* = 10.4, 1.2 Hz, 1 H), 4.76 (d, *J* = 5.9 Hz, 2 H), 4.54 (d, *J* = 2.6 Hz, 2 H), 4.02–3.95 (m, 1 H), 3.83 (s, 3 H), 2.86 (ddd, *J* = 11.7, 5.2, 1.5 Hz, 1 H), 2.14–2.07 (m, 1H), 1.73 (ddd, *J* = 13.0, 11.7, 9.2 Hz, 1 H), 1.41 (s, 3 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 165.3 (s), 159.3 (s), 151.9 (s), 141.8 (d), 133.4 (d), 130.5 (d), 130.1 (s), 129.2 (d), 128.5 (d), 120.2 (t), 115.5 (s), 113.9 (d), 79.2 (s), 70.7 (d), 70.2 (t), 70.1 (t), 55.3 (q), 41.3 (d), 33.2 (t), 27.5 (q).

(3*R,3a*R**,5*S**,7a*R**)-5-[(4-Methoxyphenyl)methoxy]-7a-methyl-2-oxo-3-(prop-2-en-1-yl)-2,3,3a,4,5,7a-hexahydro-1-benzofuran-3-carbaldehyde (26.4).**

26.2 **26.4**

A solution of **26.2** (64.4 mg, 0.162 mmol) in THF (10 mL) was injected into a stirred solution of $Pd(PPh_3)_4$ (18.7 mg, 0.0162 mmol) in THF (5 mL) and stirring was continued for 24 h (N_2 atmosphere). The mixture was diluted with brine and extracted with EtOAc. The combined organic extracts washed with brine, dried ($MgSO_4$) and evaporated. Flash chromatography over silica gel (2 × 15 cm), using 1:4 EtOAc-hexane, gave **26.4** (33.6 mg, 52%) as an oil: ^{1}H NMR ($CDCl_3$, 700 MHz) δ 9.62 (s, 1 H), 7.25–7.22 (m, 2 H), 6.90–6.86 (m, 2 H), 5.90–5.87 (m, 2 H), 5.74 (dddd, *J* = 16.7, 10.1, 8.2, 6.5 Hz, 1 H), 5.28–5.20 (m, 2 H), 4.47 (d, *J* = 1.9 Hz, 2 H), 3.80 (s, 3 H), 3.77 (ddd, *J* = 8.2, 6.0, 1.9 Hz, 1 H), 2.77 (dd, *J* = 6.2, 3.8 Hz, 1 H), 2.67–2.57 (m, 2 H), 2.30–2.25 (m, 1 H), 1.92 (ddd, *J* = 14.6, 8.5, 6.1 Hz, 1 H), 1.55 (s, 3 H); ^{13}C NMR ($CDCl_3$, 175 MHz) δ 196.7 (d), 173.5 (s), 159.5 (s), 132.3 (d), 131.2 (d), 130.0 (s), 129.6 (d), 129.5 (d), 121.4 (t), 114.0 (d), 81.1 (s), 70.8 (t), 69.1 (d), 63.0 (s), 55.3 (q), 46.5 (d), 36.3 (t), 27.02 (t), 26.6 (q).

(3*R,3a*R**,5*S**,7a*R**)-3-[(Hydroxyimino)methyl]-5-[(4-methoxyphenyl)methoxy]-7a-methyl-3-(prop-2-en-1-yl)-2,3,3a,4,5,7a-hexahydro-1-benzofuran-2-one (29.1).**

26.4 **29.1**

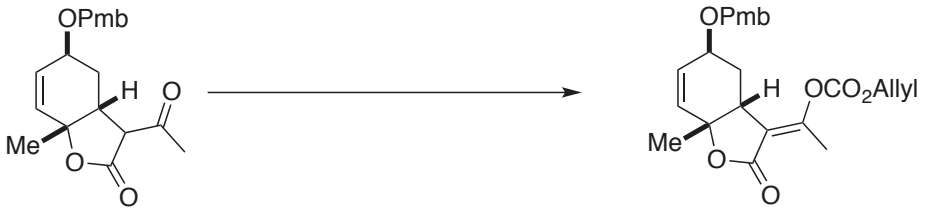
Only ^{1}H NMR of the product recorded showing it is a mixture of *E* and *Z* oximes. The spectrum was of poor quality.

(3a*R,5*S**,7a*R**)-3-Acetyl-5-[(4-methoxyphenyl)methoxy]-7a-methyl-2,3,3a,4,5,7a-hexahydro-1-benzofuran-2-one (30.2).**

25.4 **30.2**

A solution of LDA was prepared by addition of *n*-BuLi (2.5 M in hexanes, 0.64 mL, 1.53 mmol) to a stirred and cooled (0 °C) solution of *i*-Pr_2NH (0.214 mL, 1.53 mmol) in THF (8 mL). After 30 min the reaction flask was transferred to a cold bath at –78 °C. A solution of **25.4** (181.7 mg, 0.637 mmol) in THF (2 mL) was injected at a fast dropwise rate and stirring was continued for 1 h. Then a solution of ImAc (210.15 mg, 1.91 mmol) in THF (3 mL) was injected also at a fast dropwise rate. Stirring at –78 °C was continued for 1 h, saturated aqueous NH_4Cl was added and the mixture was extracted with EtOAc (3 × 20 mL). 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-hexane, gave **30.2** (118.7 mg, 57%) as an oil: FTIR (CH_2Cl_2, cast) 2931, 1763, 1719, 1612, 1530, 1301 cm^{-1}; ^1H NMR ($CDCl_3$, 700 MHz) δ 7.25 (d, *J* = 8.6 Hz, 2 H), 6.88 (d, *J* = 8.6 Hz, 2 H), 5.97 (ddd, *J* = 10.4, 2.5, 1.3 Hz, 1 H), 5.77–5.71 (m, 1 H), 4.55–4.47 (m, 2 H), 4.02 (ddd, *J* = 9.3, 5.3, 2.6 Hz, 1 H), 3.81 (s, 3 H), 3.49 (d, *J* = 10.9 Hz, 1 H), 3.16–3.09 (m, 1 H), 2.45 (s, 3 H), 2.24–2.16 (m, 2 H), 1.84 (ddd, *J* = 13.8, 9.3, 4.3 Hz, 1H), 1.54 (s, 3 H); ^{13}C NMR ($CDCl_3$, 175 MHz) δ 200.3 (s), 170.5 (s), 159.5 (s), 130.8 (d), 130.7 (d), 129.9 (s), 129.4 (d), 114.0 (d), 81.9 (s), 70.5 (t), 68.9 (d), 57.1 (q), 55.4 (d), 40.7 (d), 29.9 (q), 28.22 (t), 25.6 (q); exact mass (EI) *m*/*z* calcd for $C_{19}H_{22}O_5$ (M^+) 330.1467 found 330.1467.

1-[(3a*R,5*S**,7a*R**)-5-[(4-Methoxyphenyl)methoxy]-7a-methyl-2-oxo-2,3,3a,4,5,7a-hexahydro-1-benzofuran-3-ylidene]ethyl prop-2-en-1-yl carbonate.**



30.2 –

$(Me_3Si)_2NNa$ (1 M in Et_2O, 0.21 mL, 0.21 mmol) was injected dropwise into a stirred and cooled (–78 °C) solution of **30.2** (34 mg, 0.103 mmol) in THF (5 mL). Stirring was continued for 1 h and then neat allyl chloroformate (0.033 mL, 0.31 mmol) was injected rapidly. Stirring at –78 °C was continued for 30 min and saturated aqueous NH_4Cl (10 mL) was added. The mixture was 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 × 15 cm), using 1:9 EtOAc-hexane, gave the desired product (26.4 mg, 70%) as an oil: The ^{1}H NMR spectrum was messy, in part because of the presence of two isomers, but the material was used directly in the next step.

(3*R,3a*R**,5*S**,7a*R**)-3-Acetyl-5-[(4-methoxyphenyl)methoxy]-7a-methyl-3-(prop-2-en-1-yl)-2,3,3a,4,5,7a-hexahydro-1-benzofuran-2-one (30.3).**

–

30.3

$Pd(PPh_3)_4$ (13.3 mg, 9.05 μmole) was tipped into a stirred solution of the starting material (26.4 mg, 0.06 mmol) in dry THF (5 mL) and stirring was continued overnight (N_2 atmosphere). At this point examination by tlc (silica, 3:7 EtOAc-hexane) showed that all starting material had reacted. The mixture was diluted with brine and extracted with EtOAc. The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1 × 15 cm), using 1:9 EtOAc-hexane, gave **30.3** (15.7 mg, 70%) as an oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.31–7.24 (m, 2 H), 6.91 (d, J = 8.6 Hz, 2 H), 5.90–5.84 (m, 2 H), 5.75 (dddd, J = 16.5, 10.2, 8.6, 6.1 Hz, 1 H), 5.30–5.17 (m, 2 H), 4.55–4.43 (m, 2 H), 3.85–3.77 (m, 4 H), 2.74 (dt, J = 6.3, 3.1 Hz, 1 H), 2.71–2.63 (m, 1 H), 2.55 (dd, J = 14.0, 8.6 Hz, 1 H), 2.52–2.43 (m, 1 H), 2.24 (s, 3 H), 1.84 (ddd, J = 14.7, 8.5, 6.4 Hz, 1 H), 1.55 (s, 3 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 206.2 (s), 175.9 (s), 159.4 (s), 132.0 (d), 131.7 (d), 130.4 (d), 130.2 (s), 129.5 (d), 121.4 (t), 114.0 (d), 80.8 (s), 71.0 (t), 68.4 (d), 62.9 (s), 55.3 (q), 47.7 (d), 39.9 (t), 30.5 (q), 27.2 (q), 26.6 (t).

(3*R,3a*R**,5*S**,7a*R**)-3-Acetyl-5-[(4-methoxyphenyl)methoxy]-3,7a-dimethyl-2,3,3a,4,5,7a-hexahydro-1-benzofuran-2-one (T6.1).**

30.2 **T6.1**

A solution of **30.2** (37 mg, 0.112 mmol) in dry MeCN (2 mL) was added rapidly to a stirred and cooled (0 °C) portion of Cs_2CO_3 (109.6 mg, 0.336 mmol). Neat MeI (021 μL, 0.336 mmol) was injected rapidly. The ice bath was left in place but not recharged and stirring was continued overnight. At this point examination by tlc (silica, 2:3 EtOAc-hexane) showed that all **30.2** had reacted. The mixture was diluted with water and extracted with EtOAc. The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1 × 15 cm), using 1:4 EtOAc-hexane, gave **T6.1** (16.4 mg, 42.5%) as an oil which was a 8:1 mixture of diastereoisomers in favor of the desired stereochemistry. A pure sample of the major product was isolated from the next step and had: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.24 (d, *J* = 8.4 Hz, 3 H), 6.88 (d, *J* = 8.5 Hz, 2 H), 5.93–5.83 (m, 2 H), 4.51–4.41 (m, 2 H), 3.80 (s, 3 H), 2.54 (t, *J* = 5.4 Hz, 1 H), 2.40–2.28 (m, 2 H), 2.21 (s, 3 H), 1.87 (ddd, *J* = 14.1, 7.6, 6.2 Hz, 1 H), 1.57 (s, 3 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 206.4 (s), 177.1 (s), 159.4 (s), 131.6 (d), 130.2 (s), 130.1 (d), 129.5 (d), 114.0 (d), 80.6 (s), 70.7 (t), 68.2 (d), 59.4 (s), 55.5 (q), 51.9 (d), 30.0 (q), 27.9 (q), 27.0 (t), 23.72 (q); exact mass (ESI) *m*/*z* calcd for $C_{20}H_{24}NaO_5$ ($M+Na^+$) 367.1516 found 367.1517.

1-Methyl-4-oxocyclohexa-2,5-dien-1-yl 2-{[(*tert*-butoxy)carbonyl]amino}propanoate (33.1).

18.2 **33.1**

DCC (5.04 g, 24.45 mmol) and DMAP (199 mg, 1.63 mmol) were added to a stirred solution of **18.2** (2.03 g, 16.3 mmol) and *N*-Boc-alanine (4.63 g, 24.45 mmol) in bench CH_2Cl_2 (41 mL) and stirring was continued for 1 h (without protection from air). The

mixture was then filtered through a pad of Celite using Et_2O as a rinse. The combined filtrates were evaporated and flash chromatography of the residue over silica gel (5 × 15 cm), using 3:7 EtOAc-hexane, gave **33.1** (4.71 g, 98%) as a crystalline solid: mp 68–70 °C; FTIR (CH_2Cl_2, cast) 3344, 1753, 1712, 1668, 1518, 1164 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 6.87 (ddd, *J* = 35.5, 10.0, 2.8 Hz, 2 H), 6.24 (dt, *J* = 10.5, 2.2 Hz, 2 H), 4.92 (s, 1 H), 4.31–4.22 (m, 1 H), 1.58 (s, 3 H), 1.44 (s, 9 H), 1.39 (d, *J* = 7.2 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 184.9 (s), 172.1 (s), 155.2 (s), 148.6 (d), 148.3 (d), 128.6 (d), 128.4 (d), 80.1 (s), 75.1 (s), 49.4 (d), 28.4 (q), 26.3 (q), 18.5 (q); exact mass (ESI) *m*/*z* calcd for $C_{15}H_{21}NNaO_5$ ($M+Na^+$) 318.1312 found 318.1315.

1-Methyl-4-oxocyclohexa-2,5-dien-1-yl 2-[(diphenylmethylidene)amino]propanoate (32.2).

33.1 **32.2**

(a) Removal of Boc group.

A stock mixture of concentrated hydrochloric acid (33.3 mL) and dioxane (66.7 mL) was prepared. This experiment should be done on no more than 750 mg of **33.1**; larger scale experiments give a lower yield.

Compound **33.1** (720 mg, 2.20 mmol) was dissolved in the stock solution (5 mL) and stirring was continued for 45 min by which point tlc analysis (silica, 1:1 EtOAc-hexane) showed that the reaction was complete. The mixture was evaporated at room temperature, under an oil pump vacuum. When solid material began to form the reaction flask was connected directly to an oil pump and kept under vacuum for 5 h.

(b) Formation of the imine **32.2**.

The resulting crude amine was dissolved in dry CH_2Cl_2 (10 mL). The solution was stirred and anhydrous $MgSO_4$ (587 mg, 4.40 mmol) and $Ph_2C{=}NH$ (0.49 mL, 2.64 mmol) were added (N_2 atmosphere). Stirring was continued for 20 h and the mixture was then filtered through a pad of Celite, using CH_2Cl_2 as a rinse. The experiment was repeated on exactly the same scale and the two filtered solutions were combined. Evaporation of the filtrate and flash chromatography of the residue over silica gel (3 × 15 cm), using first 1:20 EtOAc-hexane (1000 mL), then 1:10 EtOAc-hexane (220 mL) and finally 1:4 EtOAc-hexane, gave **32.2** (1.00 g, 56%) as an oil: FTIR (CH_2Cl_2, cast) 2984, 1749, 1669, 1446, 1280, 1164

cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.65–7.62 (m, 2 H), 7.51–7.46 (m, 3 H), 7.43–7.38 (m, 1 H), 7.36–7.31 (m, 2 H), 7.19–7.16 (m, 2 H), 6.88–6.84 (m, 2 H), 6.26–6.21 (m, 2 H), 4.14 (q, *J* = 6.7 Hz, 1 H), 1.55 (s, 3 H), 1.42 (d, *J* = 6.7 Hz, 3 H); ^{13}C NMR ($CDCl_3$; 125 MHz) δ 185.0 (s), 171.4 (s), 170.2 (s), 149.0 (d), 148.9 (d), 139.4 (s), 136.2 (s), 130.5 (d), 128.81 (d), 128.79 (d), 128.4 (d), 128.28 (d), 128.26 (d), 128.16 (d), 127.7 (d), 74.6 (s), 60.7 (d), 26.3 (q), 19.0 (q); exact mass (ESI) *m*/*z* calcd for $C_{23}H_{22}NO_3$ ($M+H^+$) 360.1594 found 360.1590.

(3*S,3a*R**,7a*R**)-3-[(Diphenylmethylidene)amino]-3,7a-dimethyl-2,3,3a,4,5,7a-hexahydro-1-benzofuran-2,5-dione (32.1).**

32.2 **32.1**

Desired isomer

DBU (0.88 mL, 5.92 mmol) was injected into a stirred solution of **32.2** (708.6 mg, 1.97 mmol) in dry THF (49 mL) and stirring was continued for 48 h (N_2 atmosphere. The solvent was evaporated and the residue was dissolved in CH_2Cl_2 (30 mL). The solution was washed with water and brine, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (3 × 15 cm), using 2:3 EtOAc-hexane, gave **32.1** (551.3 mg, 78%) as a solid: 171–173 °C; FTIR (CH_2Cl_2, cast) 2977, 1777, 1685, 1632, 1280 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.50–7.41 (m, 3 H), 7.40–7.27 (m, 5 H), 7.15–7.10 (m, 2 H), 6.65 (dd, *J* = 10.4, 1.5 Hz, 1 H), 5.97 (d, *J* = 10.3 Hz, 1 H), 3.07 (d, *J* = 16.1 Hz, 1 H), 2.83–2.72 (m, 2 H), 1.65 (s, 3 H), 1.36 (s, 3 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 194.3 (s), 174.4 (s), 167.7 (s), 145.9 (d), 139.5 (s), 136.5 (s), 130.6 (d), 129.6 (d), 128.81 (d), 128.77 (d), 128.02 (d), 127.93 (d), 127.4 (d), 79.3 (s), 67.1 (s), 54.5 (d), 33.7 (t), 26.82 (q), 23.7 (q); exact mass (ESI) *m*/*z* calcd for $C_{23}H_{22}NO_3$ ($M+H^+$) 360.1594 found 360.1595.

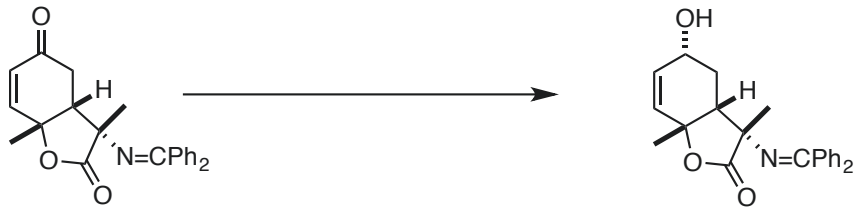
Undesired isomer

When the cyclization was done using Cs_2CO_3 a 1:1 mixture of diastereoisomers was obtained.

Cs_2CO_3 (4.13 g, 12.68 mmol) was added to a stirred solution of **32.2** (910.3 mg, 2.54 mmol) in dry THF (60 mL) and stirring was continued for 20 h (N_2 atmosphere. Water (30 mL) was added, the organic phase was separated and the aqueous phase was extracted with EtOAc. The combined organic phases were dried ($MgSO_4$) and evaporated. Flash

chromatography of the residue over silica gel (2 × 15 cm), using 1:4 EtOAc-hexane, gave **T8.1** (310.3 mg, 35%) as a solid and the diastereoisomer (310.5 mg, 35%) as an oil: FTIR (CH_2Cl_2, cast) 2981, 1775, 1687, 1624, 1281 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.61–7.56 (m, 2 H), 7.49 (tt, *J* = 4.9, 3.2 Hz, 3 H), 7.45–7.38 (m, 1 H), 7.33 (t, *J* = 7.5 Hz, 2 H), 7.29–7.24 (m, 3 H), 6.66–6.60 (m, 1 H), 6.05 (d, *J* = 10.4 Hz, 1 H), 3.26 (dt, *J* = 6.2, 2.1 Hz, 1 H), 2.69–2.51 (m, 2 H), 1.46 (s, 3 H), 1.41 (s, 3 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 195.5 (s), 176.6 (s), 168.9 (s), 147.7 (d), 140.4 (s), 136.8 (s), 130.7 (d), 129.2 (d), 129.0 (d), 128.8 (d), 128.7 (d), 128.4 (d), 128.1 (d), 78.0 (s), 67.7 (s), 51.4 (d), 34.2 (t), 26.1 (q), 22.7 (q); exact mass (ESI) *m*/*z* calcd for $C_{23}H_{22}NO_3$ ($M+H^+$) 360.1594 found 360.1587.

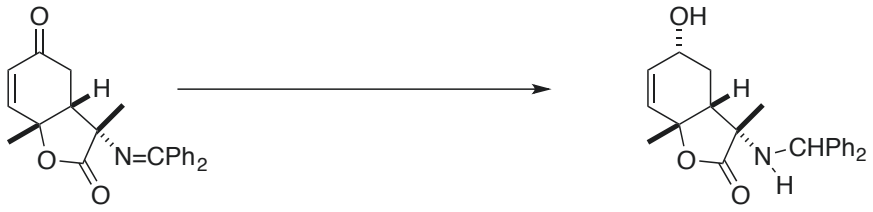
(3*S,3a*R**,5*R**,7a*R**)-3-[(Diphenylmethylidene)amino]-5-hydroxy-3,7a-dimethyl-2,3,3a,4,5,7a-hexahydro-1-benzofuran-2-one (32.1).**



32.1 **35.1**

L-Selectride (1 M in THF, 0.30 mL, 0.30 mmol) was added dropwise to a stirred and cooled (0 °C) solution of **32.1** (71.8 mg, 0.2 mmol) in dry THF (5) (N_2 atmosphere). After 15 min examination by tlc (silica, 1:1 EtOAc-hexane) showed that reaction was complete. Saturated aqueous NH_4Cl (20 mL) was added to the reaction mixture, which was then extracted with EtOAc. The combine organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2 × 15 cm), using 1:1 EtOAc-hexane, gave **35.1** (71.2 mg, 98%) as a solid: mp 148–151 °C; FTIR (CH_2Cl_2, cast) 3405, 1770, 1629, 1596, 1281 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.50–7.39 (m, 6 H), 7.37–7.33 (m, 2 H), 7.17 (dt, *J* = 6.6, 1.6 Hz, 2 H), 5.89 (dt, *J* = 10.3, 1.4 Hz, 1 H), 5.78 (ddd, *J* = 10.3, 3.8, 1.2 Hz, 1 H), 5.08 (d, *J* = 11.2 Hz, 1 H), 4.01 (ddd, *J* = 10.5, 6.9, 4.1 Hz, 1 H), 2.48 (dt, *J* = 16.3, 6.8 Hz, 1 H), 2.40–2.35 (m, 2 H), 1.47 (s, 3 H), 1.44 (s, 3 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 175.3 (s), 170.5 (s), 140.4 (s), 136.5 (s), 131.5 (d), 131.0 (d), 129.1 (d), 128.5 (d), 128.4 (d), 127.9 (d), 80.3 (s), 66.9 (s), 60.2 (d), 51.6 (d), 27.8 (t), 27.4 (q), 25.2 (q); exact mass (ESI) *m*/*z* calcd for $C_{23}H_{24}NO_3$ ($M+H^+$) 362.1751 found 362.1741.

(3*S,3a*R**,5*R**,7a*R**)-3-[(Diphenylmethyl)amino]-5-hydroxy-3,7a-dimethyl-2,3,3a,4,5,7a-hexahydro-1-benzofuran-2-one (37.1).**



32.1 **37.1**

A solution of **32.1** (60 mg, 0.167 mmol) in CH_2Cl_2 (3 mL) was added to a stirred and cooled (0 °C) solution of $CeCl_3.7H_2O$ (372.6 mg, 1 mmol) in MeOH (3 mL). $NaBH_4$ (46.6 mg, 1.25 mmol) was added in one portion (N_2 atmosphere). The ice bath was left in place, but not recharged, and stirring was continued overnight. $NaHSO_4$ (1 g, 7.24 mmol) and water (15 mL) were added and the mixture was extracted with CH_2Cl_2. The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2 × 15 cm), using 3:7 EtOAc-hexane, gave **37.1** (46 mg, 76%) as a solid: mp 50–53 °C; FTIR (CH_2Cl_2, cast) 3292, 1759, 1476, 1057 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.49–7.45 (m, 2 H), 7.35 (t, *J* = 7.6 Hz, 2 H), 7.30–7.24 (m, 3 H), 7.23–7.16 (m, 3 H), 5.88–5.77 (m, 2 H), 5.52 (s, 1 H), 4.15 (dd, *J* = 6.7, 3.3 Hz, 1 H), 2.43 (dt, *J* = 16.0, 6.6 Hz, 1 H), 2.32 (dt, *J* = 6.3, 1.7 Hz, 1 H), 2.24 (dd, *J* = 16.1, 2.1 Hz, 1 H), 1.47 (s, 3 H), 1.16 (s, 3 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 176.4 (s), 143.9 (s), 143.6 (s), 132.6 (d), 130.9 (d), 129.1 (d), 128.7 (d), 127.6 (d), 127.2 (d), 127.1 (d), 127.0 (d), 80.3 (s), 61.8 (d), 61.2 (s), 59.6 (d), 50.2 (d), 26.9 (t), 26.8 (q), 20.5 (q); exact mass (ESI) *m/z* calcd for $C_{23}H_{26}NO_3$ ($M+H^+$) 364.1907 found 364.1904.

(3*S,3a*R**,5*R**,7a*R**)-3-Amino-5-hydroxy-3,7a-dimethyl-2,3,3a,4,5,7a-hexahydro-1-benzofuran-2-one (38.1).**

32.1 **38.1**

L-Selectride (1 M, 0.65 mL, 0.65 mmol) was added dropwise to a stirred and cooled (0 °C) solution of **32.1** (155 mg, 0.430 mmol) in dry THF (10 mL). After 15 min tlc examination (silica, 1:1 EtOAc, hexane) showed that all **32.1** had reacted. Water (15 mL) and $NaHSO_4$ (1.2 g, 8.64 mmol) were added and the ice bath was removed. Stirring was continued for 10 min and the mixture was extracted with EtOAc. The aqueous phase was basified with solid $NaHCO_3$ to pH 8. The resulting mixture was extracted with EtOAc. The

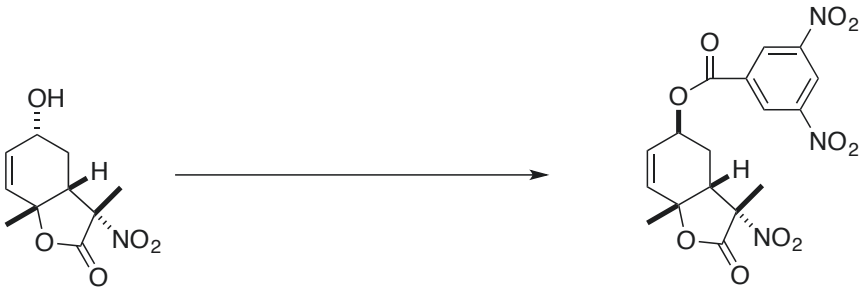
combined organic extracts were dried (Na_2SO_4) and evaporated to give the **38.1** (66.5 mg, 78%) as a solid: mp 121–125 °C; FTIR (CH_2Cl_2, cast) 3346, 1766, 1377, 1049 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 5.91 (ddd, *J* = 10.4, 4.0, 1.4 Hz, 1 H), 5.83 (dt, *J* = 10.3, 1.4 Hz, 1 H), 4.07–4.01 (m, 1 H), 3.03 (s, 3 H), 2.34 (dt, *J* = 16.0, 6.4 Hz, 1 H), 2.24 (dt, *J* = 6.1, 1.9 Hz, 1 H), 2.09–2.02 (m, 1 H), 1.47 (s, 3 H), 1.37 (s, 3 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 179.0 (s), 132.7 (d), 129.7 (d), 81.1 (s), 59.2 (d), 56.4 (s), 48.6 (d), 26.9 (t), 26.4 (q), 23.4 (q); exact mass (ESI) *m*/*z* calcd for $C_{10}H_{16}NO_3$ ($M+H^+$) 198.1125 found 198.1126.

(3*S,3a*R**,5*R**,7a*R**)-5-Hydroxy-3,7a-dimethyl-3-nitro-2,3,3a,4,5,7a-hexahydro-1-benzofuran-2-one (40.1).**

38.1 **40.1**

CH_2Cl_2 (20 mL) was added to a flask containing compound **38.1** (176.5 mg, 0.895 mmol), $VO(acac)_2$ (13.9 mg, 0.052 mmol) and powdered oven-dried 3Å molecular sieves (1.5 g). The mixture was stirred at room temperature and *t*-BuOOH (5 M in decane, 0.90 mL, 4.48 mmol) was added at a fast dropwise rate to generate a red solution which became yellow after ca 15 min. Stirring was continued for 20 h. The mixture was filtered through a Celite pad using CH_2Cl_2 as a rinse. The filtrate was evaporated, the residue was dissolved in CH_2Cl_2 (5 mL) and the solution was added to a stirred and cooled (0 °C) solution of $CeCl_3.7H_2O$ (999.4 mg, 2.7 mmol) in MeOH (5 mL). $NaBH_4$ (51.0 mg, 1.34 mmol) was added in one lot and stirring was continued for 1 h. Water (10 mL) was added and then solid $NaHSO_4$ (600 mg). Stirring was continued for ca 10 min and the mixture was extracted with CH_2Cl_2. The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2 × 15 cm), using 2:3 hexane-EtOAc, gave **40.1** (146 mg, 72% over two steps) as a white solid: mp 107–110 °C; FTIR (CH_2Cl_2, cast) 3416, 1782, 1554, 1100 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 6.03–5.91 (m, 1 H), 5.84 (dd, *J* = 10.2, 2.2 Hz, 1 H), 4.20 (dd, *J* = 9.0, 4.8 Hz, 1 H), 2.68–2.52 (m, 1 H), 2.11–1.97 (m, 4 H), 1.67–1.47 (m, 4 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 168.3 (s), 135.1 (d), 128.2 (d), 93.3 (s), 79.8 (s), 64.0 (d), 48.3 (d), 30.7 (t), 29.3 (q), 23.9 (q), exact mass (ESI) *m*/*z* calcd for $C_{10}H_{13}ClNO_5$ ($M+Cl^-$) 262.0488 found 262.0484.

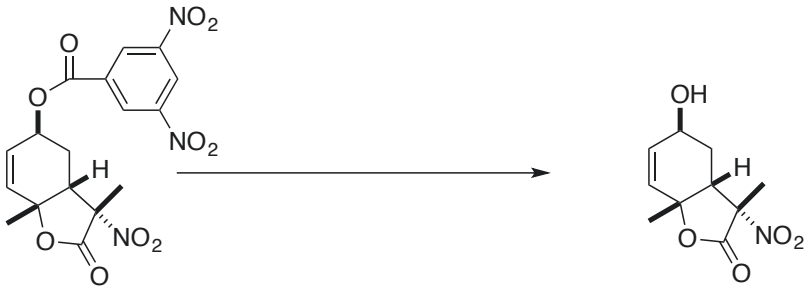
(3*S,3a*R**,5*S**,7a*R**)-3,7a-dimethyl-3-nitro-2-oxo-2,3,3a,4,5,7a-hexahydro-1-benzofuran-5-yl 3,5-dinitrobenzoate (T9.1c).**



40.1 **T9.1c**

THF (5 mL) was added to a flask containing **40.1** (84.7 mg, 0.373 mmol), 3,5-dinitrobenzoic acid (118.6 mg, 0.56 mmol) and Ph_3P (146.7 mg, 0.56 mmol) and the mixture was then stirred and cooled in an ice bath. DEAD (0.09 mL, 0.56 mmol) was added in one lot. The ice bath was left in place but not recharged and stirring was continued overnight. Evaporation of the solvent and flash chromatography of the residue over silica gel (2 × 25 cm), using 7:3 hexane-EtOAc, gave **T9.1c** (132.3 mg, 84%) as a white solid: mp 195-199 °C; FTIR (CH_2Cl_2, cast) 1784, 1730, 1549, 1278 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 9.25 (t, *J* = 2.1 Hz, 1 H), 9.11 (d, *J* = 2.1 Hz, 2 H), 6.08 (ddd, *J* = 10.5, 1.7, 1.0 Hz, 1 H), 5.99 (ddd, *J* = 10.5, 3.3, 0.9 Hz, 1 H), 5.59–5.54 (m, 1 H), 2.86–2.81 (m, 1 H), 2.73 (dddd, *J* = 14.9, 6.4, 4.0, 0.9 Hz, 1 H), 2.21 (ddd, *J* = 15.0, 8.1, 6.9 Hz, 1 H), 1.98 (s, 3 H), 1.71 (s, 3 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 167.6 (s), 161.7 (s), 148.8 (s), 133.4 (s), 132.4 (d), 129.5 (d), 127.1 (d), 122.8 (d), 91.1 (s), 80.1 (s), 66.5 (d), 50.9 (d), 28.2 (q), 25.3 (t), 22.7 (q), exact mass (ESI) *m*/*z* calcd for $C_{17}H_{15}ClN_3O_{10}$ ($M+Cl^-$) 456.0451 found 456.0455.

(3*S,3a*R**,5*S**,7a*R**)-5-Hydroxy-3,7a-dimethyl-3-mitro-2,3,3a,4,5,7a-hexahydro-1-benzofuran-2-one (41.1).**



T9.1c **41.1**

Et_3N (0.13 mL, 0.942 mmol) was added in one lot to stirred solution of **T9.1c** (132.3 mg, 0.314 mmol) in 1:1 THF-MeOH (10 mL) and stirring was continued for 5 h. Evaporation of the solvent and flash chromatography of the residue over silica gel (2 × 15 cm), using 3:2 hexane-EtOAc, gave **41.1** (59 mg, 83%) as a solid: mp 110-113 °C; FTIR (CH_2Cl_2, cast) 3470, 1777, 1551, 1064 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 5.91 (dd, *J* = 10.4, 3.1 Hz, 1 H), 5.85 (dt, *J* = 10.3, 1.2 Hz, 1 H), 4.29–4.23 (m, 1 H), 2.79 (dd, *J* = 6.7, 4.3 Hz, 1 H), 2.46–2.39 (m, 1 H), 1.98–1.90 (m, 4 H), 1.64 (s, 3 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 168.2 (s), 132.4 (d), 129.2 (d), 91.4 (s), 80.8 (s), 60.5 (d), 51.0 (d), 28.8 (t), 28.4 (q), 22.9 (q), exact mass (ESI) *m*/*z* calcd for $C_{10}H_{13}ClNO_5$ ($M+Cl^-$) 262.0488 found 262.0481.

(1*S,2*S**,4*S**,5*S**,7*R**,8*S**)-5-Hydroxy-1,8-dimethyl-8-nitro-3,10-dioxatricyclo-[5.3.0.0^{2,4}]decan-9-one (41.2).**

41.1 **41.2**

An acetone solution of dimethyldioxirane was prepared as follows: $NaHCO_3$ (30 g, 35.7 mmol) was added to a 1-L three-necked flask containing acetone (60 mL), water (50 mL) and a magnetic stirrer. The flask was cooled in an ice bath and, with vigorous stirring, Oxone (60 g, 9.75 mmol) was added in five equal portions at 3-min intervals. Three min after the last addition the ice bath was removed and the flask was fitted with a distillation head and take-off carrying a receiving flask which was immersed in a cold bath at –78 °C. The take-off was connected to the house vacuum and a moderate vacuum was applied so that the acetone and DMDO distilled over. The distillation was continued until bubbling ceased in the reaction flask by which time ca 40–50 mL of yellow distillate had been collected.

A cooled (–20 °C) solution of dimethyldioxirane in acetone (6 mL), prepared as above, was added to **41.1** (51 mg, 0.225 mmol) immersed in an ice bath and the resulting solution was stirred for 20 h, the ice bath being left in place but not recharged. Evaporation of the solvent and flash chromatography of the residue over silica gel (1 × 15 cm), using 1:1 hexane-EtOAc, gave **41.2** (33 mg, 60%) as a white solid: mp 168–170 °C; FTIR (CH_2Cl_2, cast) 3488, 1768, 1563, 1121, 1098 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 3.94 (dddd, *J* = 10.7, 8.4, 6.5, 2.2 Hz, 1 H), 3.49 (dd, *J* = 3.8, 1.3 Hz, 1 H), 3.38 (dd, *J* = 4.0, 2.2 Hz, 1 H), 2.42 (dt, *J* = 6.1, 1.9 Hz, 1 H), 2.15 (dddd, *J* = 15.1, 6.5, 2.4, 0.8 Hz, 1 H), 1.83 (s, 3 H), 1.70–1.62 (m, 5 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 168.0 (s), 90.5 (s), 79.0 (s), 61.5 (d), 58.3 (d), 56.5 (d),

52.5 (d), 25.3 (q), 23.8 (t), 21.8 (q), exact mass (ESI) *m*/*z* calcd for $C_{10}H_{13}ClNO_6$ ($M+Cl^-$) 278.0437 found 262.0429.

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