University of Alberta

Methodology and natural product synthesis: carbocycles, culpin and sorbicillactone A

by

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ABSTRACT

The first chapter of this thesis describes the development of a general method for indirectly effecting radical carbocyclization of an alkyl chain onto an aromatic ring. This process involves a Birch reductive alkylation of aromatic *tert*-butyl esters, chromium(VI)-mediated oxidation and radical cyclization. The cyclized products are easily aromatized by Saegusa oxidation and treatment with bismuth trichloride. This method forms five- and six-membered benzo-fused carbocycles. Modification allows both formation of non-phenolic products, and the introduction of an additional substituent on the original aromatic ring.

The second chapter describes a method for converting *tert*-butyl benzoates or *tert*-butyl 1-naphthoates into derivatives having a substituted alkyl group in a 1,4-relationship to an alkyl, aryl, alkenyl or alkynyl group. Key steps in the process involve addition of an organometallic species to a cross-conjugated cyclohexadienone followed by treatment with bismuth trichloride, which results in spontaneous decarboxylative aromatization. The method was successfully applied to the synthesis of the antimicrobial fungal metabolite culpin.

The last chapter of this thesis describes synthetic studies towards the marine antileukemic alkaloid, sorbicillactone A. Studies towards the core structure of sorbicillactone A have resulted in a new method of desymmetrization of cross-conjugated cyclohexadienones. The key step involves a highly diastereoselective iodoetherification and radical cyclization, which affords a product that can be elaborated into a γ-lactone.

ACKNOWLEDGEMENTS

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LIST OF ABBREVIATIONS

Ac	acetyl
AcOH	acetic acid
AIBN	2,2'-azobisisobutyronitrile
BINAP	2,2’-bis(diphenylphosphino)-1(*R*), 1’(*R*)-dicyclopentane
Bn	benzyl
Boc	*tert*-butoxycarbonyl
Bu	butyl
t-Bu	*tert*-butyl
CAN	ceric (IV) ammonium nitrate
Cbz	benzyloxycarbonyl
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	*N,N*-dicyclohexylcarbodiimide
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
$(DHQ)_2PYR$	hydroquinine diphenylpyrimidine
Dess-Martin	1,1,1-triacetoxy-1,1-dihydro-1,2-benziodoxo-3(*H*)-one
DFT	density functional theory
DIBAL-H	diisobutylaluminum hydride
DIPT	diisopropyl tartrate
DET	diethyl tartrate
DMAP	4-(dimethylamino)pyridine
DME	ethylene glycol dimethyl ether

DMF	*N*,*N*-dimethylformamide
DMP	2,6-dimethoxypyridine
DOM	directed *ortho* metalation
DPEPhos	bis(2-diphenylphosphinophenyl)ether
Et	ethyl
h	hour
HFIP	1,1,1,3,3,3-hexafluoro-2-propanol
Im	imidazole
KHMDS	potassium hexamethyldisilazide
LDA	lithium diisopropylamide
LTMP	lithium 2,2,6,6-tetramethylpiperidine
Me	methyl
min	minute(s)
MOM	(methoxymethoxy)methyl
mp	melting point
Ms	methanesulfonyl
MS	mass spectrometry
NBS	*N*-bromosuccinimide
NIS	*N*-iodosuccinimide
NMO	4-methylmorpholine *N*-oxide
NMP	*N*-methyl-2-pyrrolidinone
NMR	nuclear magnetic resonance
PCC	pyridinium chlorochromate

PDC	pyridinium dichromate
Pg	protecting group
Ph	phenyl
PPTS	pyridinium *p*-toluenesulfonic acid
RCEM	ring closing enyne metathesis
RCM	ring closing metathesis
SM	starting material
TBAF	tetrabutylammonium fluoride
TBDMS	*tert*-butyldimethylsilyl
TLC	thin layer chromatography
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TMS	trimethylsilyl
Tol	*p*-toluene-
Ts	*p*-toluenesulfonyl
TsOH	*p*-toluenesulfonic acid

Chapter 1

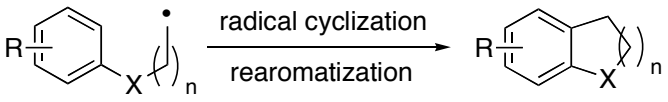
Formal radical closure onto aromatic rings:

A general route to carbocycles

1 INTRODUCTION

1.1 *General*

Cyclization of sp^2 or sp^3 carbon radicals onto double or triple bonds is now a well known synthetic method.[1] However, the corresponding cyclizations onto an aromatic ring (**1.1→1.2**) along the lines summarized in Scheme 1 is a rare and difficult process that requires large amounts of initiator and the mechanism is not fully understood.[2] While there are a significant number of reports[3,4,5] in which the attacking radical is sp^2 hybridized, there does not appear to be a general method for direct closure of sp^3 hybridized carbon radicals onto carbocyclic aromatic rings.



1.1 **1.2**

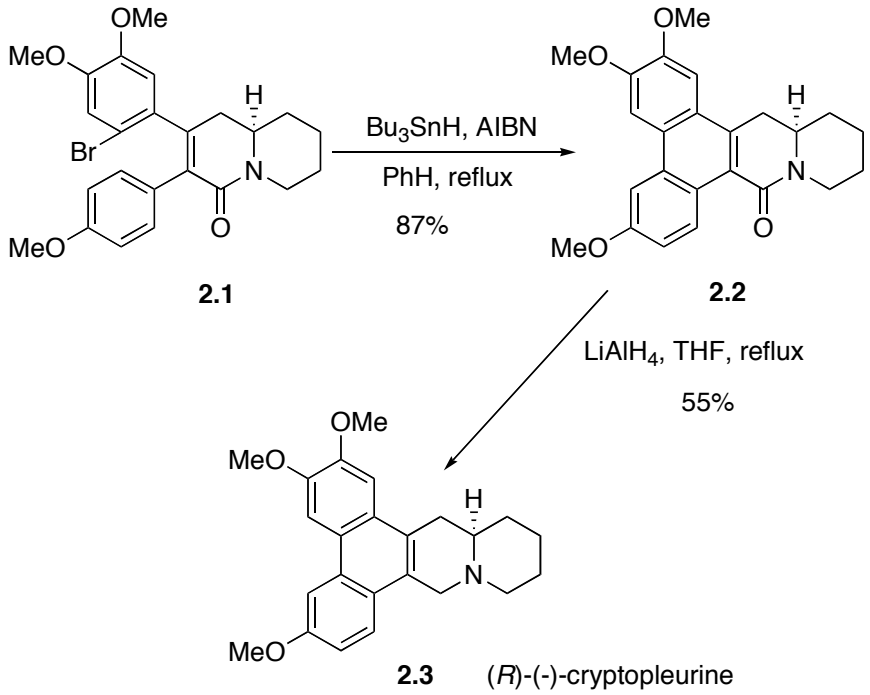
Scheme 1

1.2 *Radical cyclization onto arenes and heteroarenes*

The addition of radicals to arenes and heteroarenes has been of interest for a number of years because of the importance of polycyclic arenes and heteroarenes to the pharmaceutical industry and the occurrence of such systems in natural products.[6] While most radical cyclizations are still carried out using tributyltin hydride, other radical-generating methods are becoming increasingly common.[7]

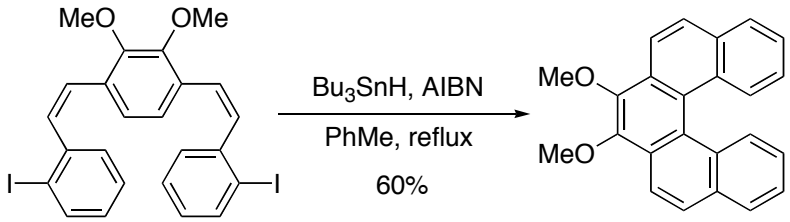
1.2.1 *Aryl radical cyclization*

The addition of aryl radicals onto arenes has been extensively used, with the most common targets being phenanthrene derivatives.[8] For example, construction of the phenanthrene nucleus was first attempted (Scheme 2) through photocyclization ($h\nu$, Et_3N, dioxane) of **2.1** to afford 9-oxocrytopleurine **2.2** in only 54% yield. However, treatment with Bu_3SnH and AIBN effected an intramolecular radical cyclization giving **2.2** in a significantly higher yield (87%). Finally, reduction with $LiAlH_4$ (**2.2→2.3**) completed the first enantioselective synthesis of the alkaloid (*R*)-(-)-cryptopleurine.[9]



Scheme 2

Harrowven *et al.* have recently shown that aryl radical cyclization onto arenes can be used to prepare a range of substituted [5]- and [7]-helicenes, and an example of the former is shown in Scheme 3.[10] In order to ensure that complete double cyclization (**3.1→3.2**) was occurring, 4-5 equiv of Bu_3SnH were required to afford [5]-helicene **3.2** in 60% yield. The driving force of rearomatization after the radical closure overcomes the lack of planarity of helicenes. Helicenes were regarded for many years as little more than an academic curiosity until recently; however, their extraordinary optical, electronic and chelating properties have sparked an interest in their synthesis.[10a]

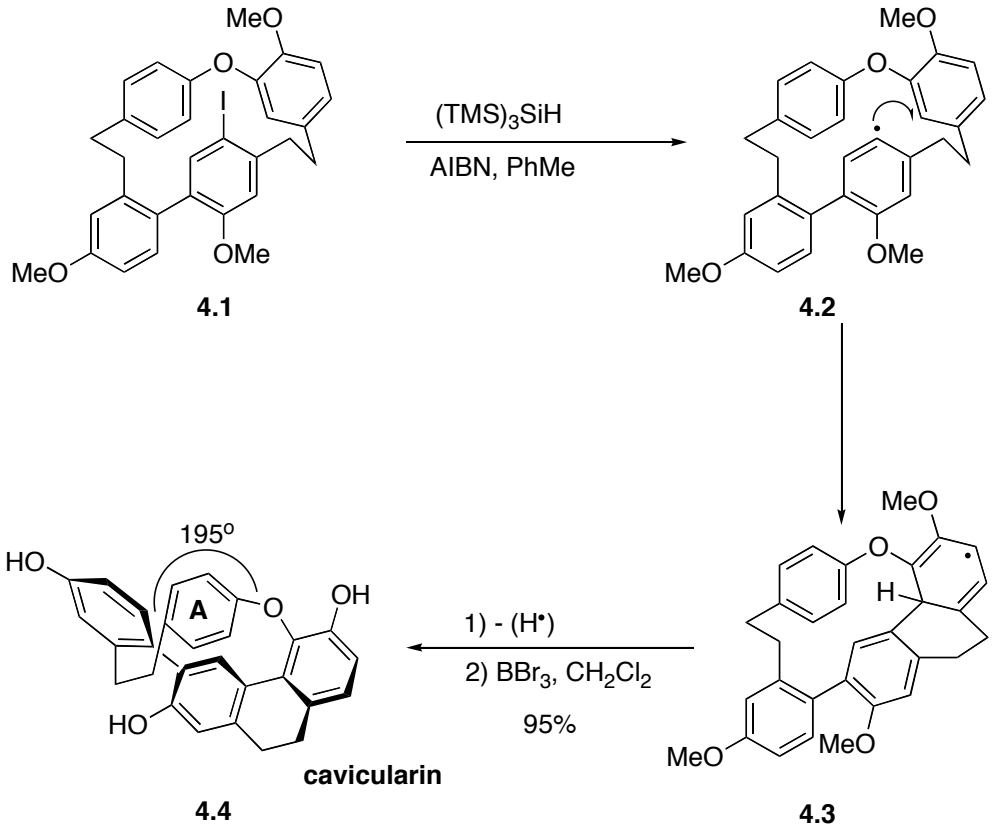


3.1 **3.2**

Scheme 3

The same group reported the use of aryl radical cyclization onto a proximal arene as a way to relieve strain in polyarenes, and this has proved to be valuable in the synthesis of cavicularin (**4.4**) (Scheme 4). Cavicularin is a structurally unusual natural product that comprises a macrocyclic core that imparts considerable strain to the molecule. The key step in the synthesis (**4.1→4.3**), the radical transannular ring contraction, unfortunately gave a 2:1 mixture of the reduced uncyclized and cyclized products. The driving force of

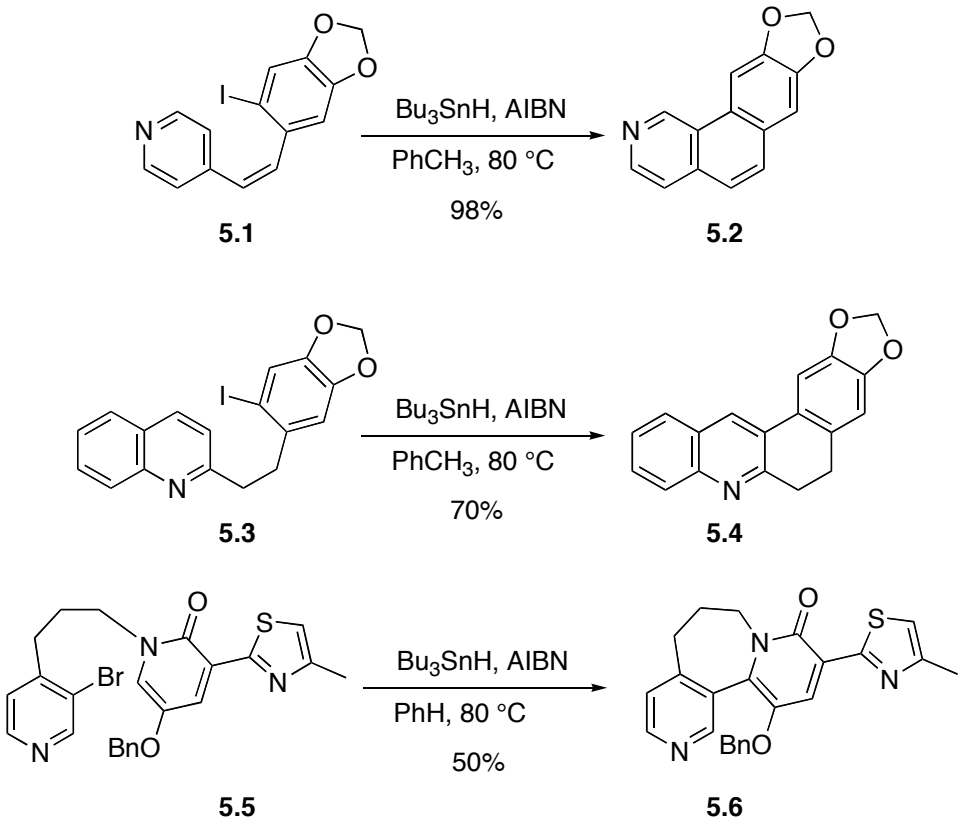
rearomatization overcomes the ring strain in ring **A**. Upon exposure of the inseparable mixture to boron tribromide, the cyclized material gave cavicularin (**4.4**) and the uncyclized component afforded another natural product, the ratio of the two being 2:1, with cavicularin being the minor component.[11]



Scheme 4

Aryl radical cyclization onto heteroarenes such as pyridines,[12] quinolines[13] and pyridinones[14] have been investigated, and Scheme 5 illustrates examples of these radical cyclizations. Intramolecular radical addition to the β-carbon of pyridine (**5.1→5.2**), mediated by tributyltin hydride, gave the cyclized product **5.2** in excellent yield (98%). Intramolecular trigonal radical cyclizations onto

quinolines (cf **5.3→5.4**) are facile processes that open routes to the synthesis of various condensed heterocycles. The authors also pointed out that related attempts to form a five-membered ring were unsuccessful and thus appeared to be more akin to 5-*endo* trigonal processes than 5-*exo* processes. Radical cyclizations with aryl iodides as precursors generally proceed more efficiently than the corresponding reaction with aryl bromides.[13]



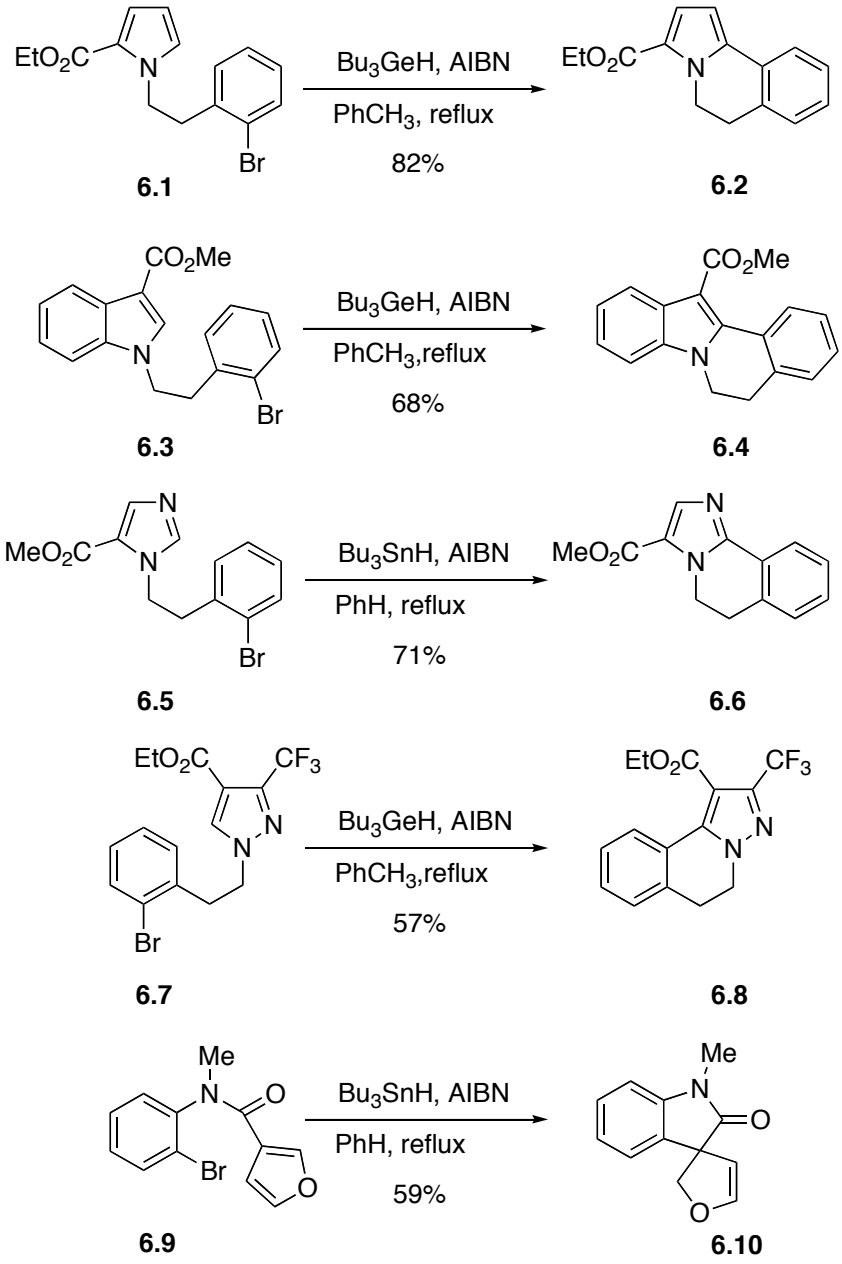
5.1 **5.2** **5.3** **5.4** **5.5** **5.6**

Scheme 5

In the case of the pyridone **5.5**, the uncommon 7-*exo* trigonal closure (**5.5→5.6**) took place in refluxing benzene in the presence of 2 equivalents of Bu_3SnH and a stoichiometric amount of AIBN to afford the cyclized product **5.6**

in 50 % yield, along with the reduced product (replacement of Br with H in **5.5**) in 10% yield.[14]

Aryl radical cyclization onto five-membered ring heteroarenes has also proved to be useful (Scheme 6). Examples of such five-membered heteroarenes



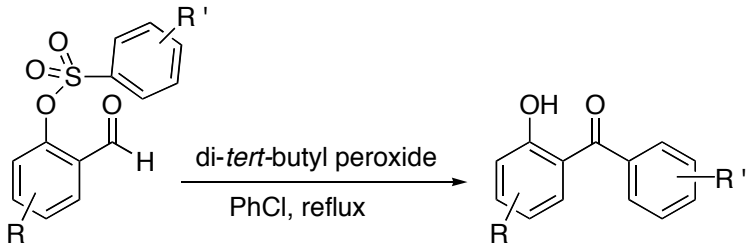
Scheme 6

include pyrroles,[15] indoles,[15] imidazoles,[15] pyrazoles[15] and furans.[16]

Aryl radical cyclizations onto azoles (pyrrole **6.1,** indole **6.3,** imidazole **6.5** and pyrazole **6.7**) proceeded well and tributylgermanium hydride proved to be a better reagent than tributyltin hydride, except for the imidazole case (**6.5→6.6**). However, in the case of furan (**6.9→6.10**), the spirocycle **6.10** was isolated in 59% yield.

1.2.2 Acyl radical cyclization

Acyl radicals[17] have been known for nearly a century but they have only recently emerged as an important tool for organic synthesis and their reactions with arenes have been little studied. Recently, Motherwell and co-workers reported a concise approach for the preparation of hydroxydiarylketones via an intramolecular acyl radical *ipso* substitution (Scheme 7).[18]



7.1 **7.2**

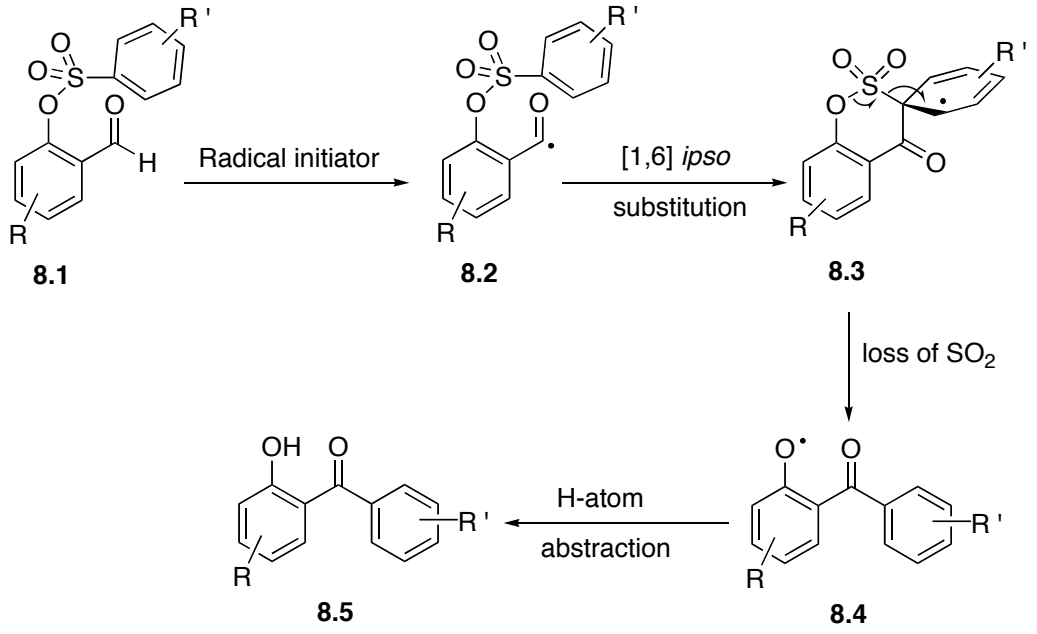
R = H, 3-OMe, 4-OMe, 5-OMe, 6-OMe

R ' = 4-CH_3, 3-CH_3, 2-F, 4-F, 2-NO_2, 4-NO_2, 2-CN

Yield: 28-80%

Scheme 7

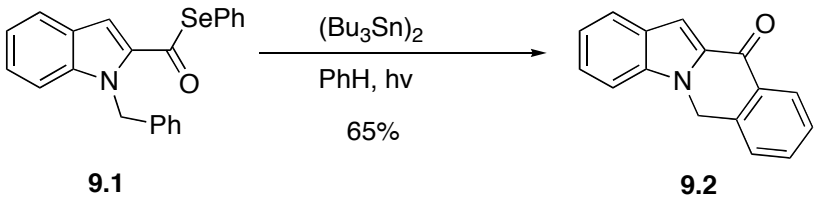
Reaction of sulphonates **7.1** with di-*tert*-butyl peroxide as the radical initiator in refluxing chlorobenzene gave the desired diaryl ketones **7.2** (28-80%). Both electron withdrawing and electron donating groups were well tolerated in the aromatic sulphonyl acceptor ring. It is also of interest to note that products arising from decarbonylation, which is usually a competitive pathway, or [1,7] addition to the sulphonyl substituted acceptor ring were not observed. A proposed mechanism is illustrated in Scheme 8.



Scheme 8

In 2004, Bennasar's group disclosed a cyclization of 2-indolyacyl radical onto arenes as a general approach to polycyclic aryl indolyl ketones, which are common substructures of many natural products and medicinal compounds[19] (Scheme 9). Treatment of selenoester **9.1** under non-reductive cyclization

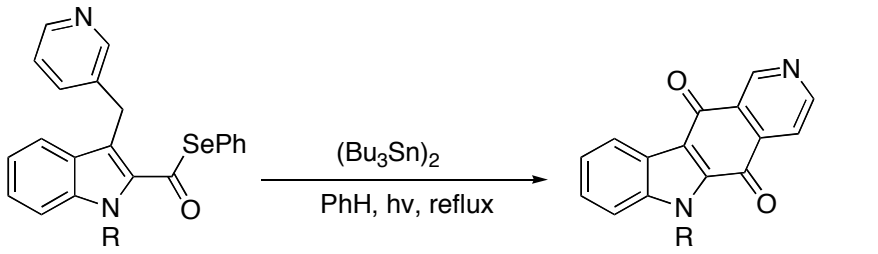
conditions (hexabutylditin, 300W sunlamp) afforded the tetracycle **9.2** in 65% isolated yield with no trace of the competitive reduction product.[20]



9.1 **9.2**

Scheme 9

The same group reported a regioselective intramolecular acyl radical addition onto heteroarenes and applied this strategy in the case of a pyridine ring as a direct entry to ellipticine quinone **10.2** (R = H), a synthetic relay for the anticancer alkaloid ellipticine (Scheme 10).[21]



10.1

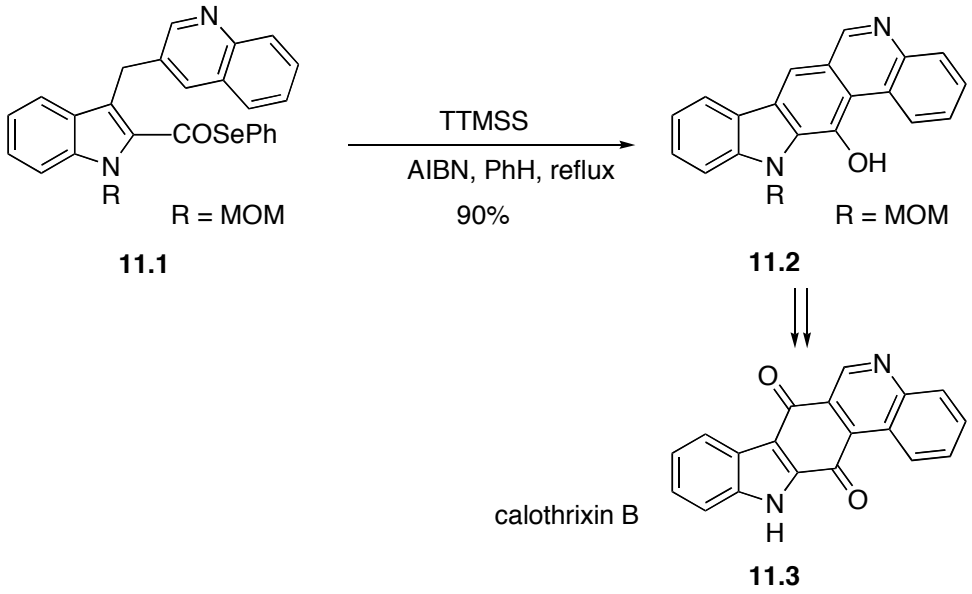
10.2 R = Me, 60%
R = Bn, 42 %
R = H, 10%

Scheme 10

During the radical cyclization, the acyl radical did not decarbonylate but cyclized onto the 4-position of the pyridine ring, followed by an *in situ* oxidation to yield quinones **10.2**. The authors postulated that $Bu_3SnOO^{\cdot}$ radical might

facilitate the required hydrogen abstractions and oxidations. In the case when R = H (Scheme 10), quinone **10.2** (R = H) was isolated in only 10 % yield due to a competitive cyclization onto the 2-position of the pyridine ring. Attempts to improve the yield by using dicumyl peroxide were unsuccessful and starting material was recovered.

Indol-2-yl acyl radicals have also been successfully cyclized onto quinolines (Scheme 11). Treatment of selenoester **11.1** with tris(trimethylsilyl)silane (TTMSS) and AIBN in hot benzene caused cyclization to

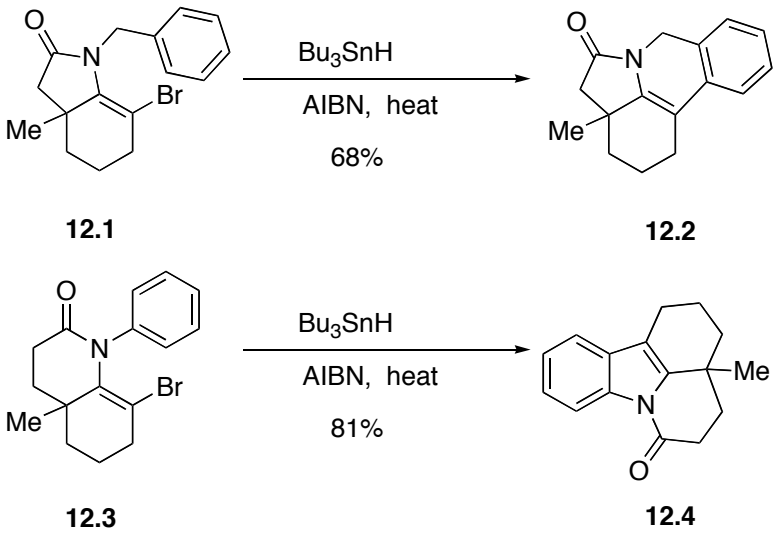


Scheme 11

give the pentacyclic phenol **11.2** which was advanced to the synthesis of calothrixin B, a compound that exhibits potent antimalarial and anticancer properties.[22]

1.2.3 *Alkenyl and imidoyl radical cyclizations*

Recently, Padwa and co-workers showed that alkenyl radical cyclization onto arenes could be used to construct complex systems that possess the characteristic skeleton of the aspidosperma family of alkaloids (Scheme 12). [23]

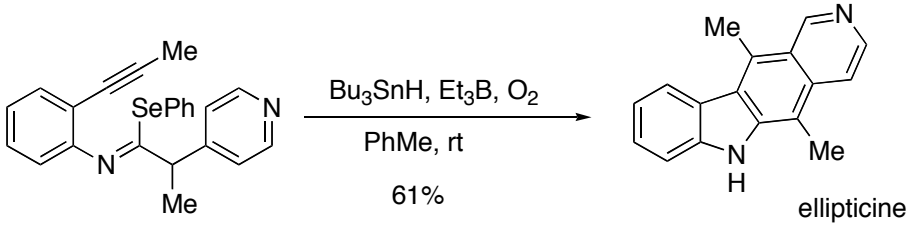


Scheme 12

Exposure of bromo-enamide **12.1** to standard stannane mediated conditions furnished the cyclized product **12.2** in 68% yield together with 27% of the uncyclized reduced product (Br replaced by H in **12.1**). However, the cyclized product **12.4** was obtained in 81% yield under the same reaction conditions.

Imidoyl radicals are attractive intermediates that can be easily formed by addition of carbon- and heteroatom-centered radicals to isonitriles and by hydrogen atom abstraction from imines. These radical species have been extensively used in cyclizations, annulations and cascade reactions for the

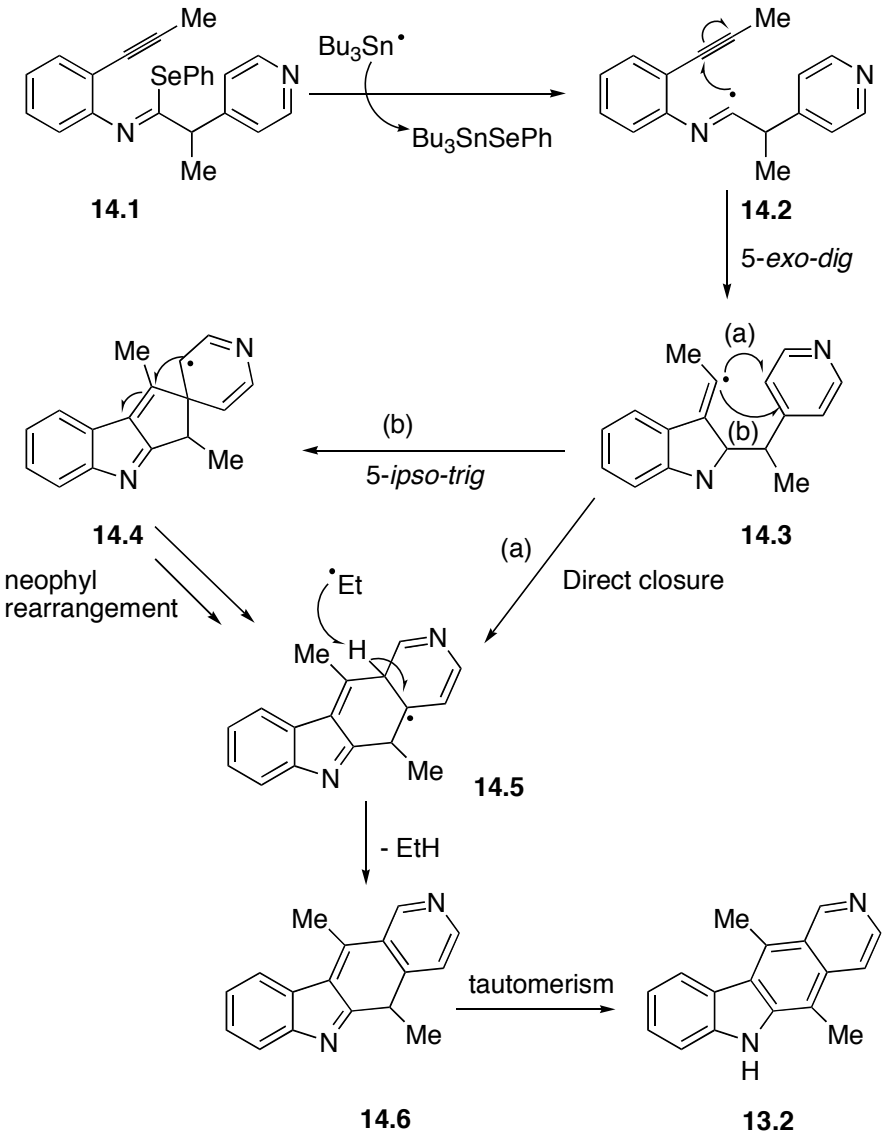
construction of various heterocyclic nitrogen-containing compounds.[24] Bowman and co-workers have demonstrated an intramolecular domino process that involves both imidoyl and alkenyl radicals, for the synthesis of the anticancer alkaloid ellipticine (Scheme 13).[25] Initial radical cyclizations were done with Bu_3SnH and AIBN in refluxing toluene but gave poor yields. However, treatment of **13.1** with Bu_3SnH, Et_3B and O_2 at room temperature successfully yielded the required cyclized product, ellipticine **13.2** in 61% yield.



13.1 **13.2**

Scheme 13

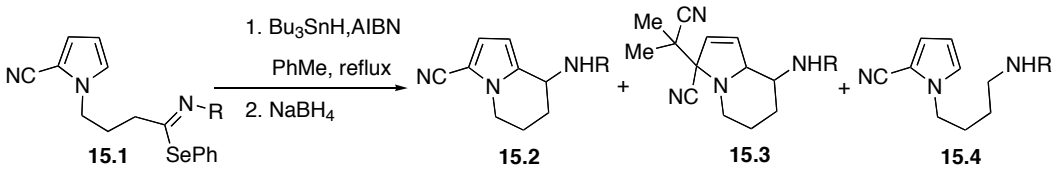
A mechanism was proposed for the radical cascade reaction, as shown in Scheme 14. Under the action of Bu_3SnH, imidoyl selenide **14.1** generates imidoyl radical **14.2**, which undergoes a 5-*exo* digonal cyclization onto the alkyne to give alkenyl radical **14.3**. The akenyl radical **14.3** then undergoes an intramolecular addition onto the pyridine ring via most likely a 5-*ipso trig* cyclization, followed by a neophyl rearrangement (**14.3→14.4**). This method has the advantage that the pyridine ring is substituted in the 4-position and thus, whichever way the neophyl rearrangement takes place, it will provide the desired product. However, a direct cyclization to form a six-membered ring (**14.3→14.5**) cannot be ruled out. The



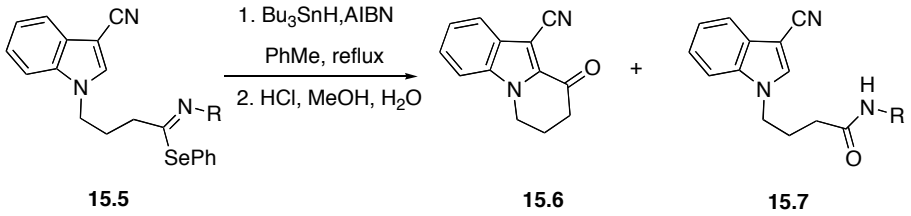
Scheme 14

authors proposed that hydrogen abstraction is facilitated by the ethyl radicals generated from the Et_3B initiator to give **14.6,** which upon rapid tautomerization affords the natural product, ellipticine **13.2.**

Imidoyl selenides, which can be easily prepared from secondary amides, have proved to be useful precursors to imidoyl radicals and have been shown to cyclize onto heteroarenes such as pyrroles and indoles (Scheme 15).[26]



	15.2	15.3	15.4
Mixture:	1.6	1	4.3
Isolated yield:	7%	6%	13%
Combined yield:		70-80 %	



	15.6	15.7
Mixture:	2	1
Isolated yield:	14%	5%
Combined yield:	60-70 %	

Scheme 15

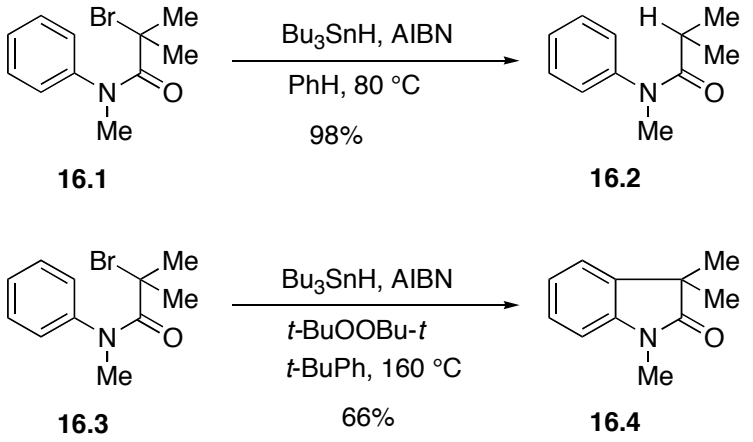
Both pyrrole and indole rings required the presence of an electron withdrawing group in order to activate the rings for nucleophilic attack by imidoyl radicals. After the radical cyclization, the reaction mixture was either reduced with $NaBH_4$ or subjected to acid hydrolysis so that isolation of the products would be easy. The combined yields were good, but isolated yields were poor (Scheme

15) as separation was tedious. Nevertheless, the results indicate that imidoyl radicals cyclize onto activated heteroarenes but further studies are needed to optimize conditions and yields.

1.2.3 *Alkyl radical cyclizations*

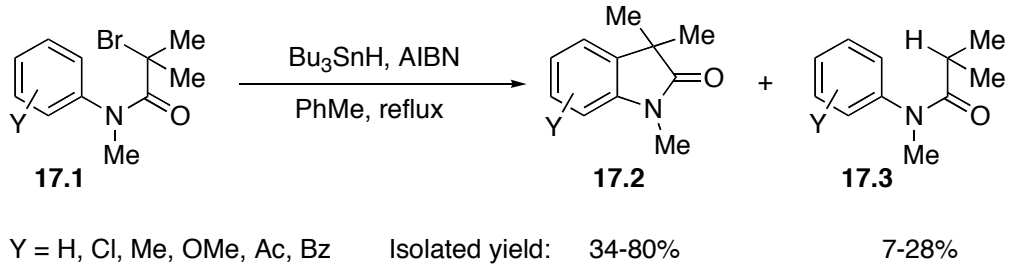
Alkyl radical cyclizations onto arenes are less developed compared to the corresponding cyclization onto heteroarenes.[27] Aryl radical cyclizations have been well studied, as described in section *1.2.1* of this chapter, because aryl radicals are more reactive than alkyl radicals. The addition of alkyl radicals onto arenes is usually too slow to be synthetically useful. This is unfortunate as it has been demonstrated that the use of intramolecular reactions offers good control of regioselectivity.

Beckwith and Storey in 1995 investigated alkyl radical cyclization onto arenes and have shown that the process could provide an entry to indolones (Scheme 16).[28] Heating **16.1** at 80 °C with Bu_3SnH and AIBN gave exclusively the reduction product **16.2** (98% by GC analysis). However, by heating **16.3** at 160 °C in *tert*-butylbenzene and by adding catalytic amounts of di-*tert*-butyl peroxide in small portions over 4 h, the cyclized product **16.4** was obtained in 66% yield. The cyclization yield with Bu_3SnH could be further improved by reducing the effective concentration of tin hydride via slow addition of a mixture of the stannane and di-*tert*-butyl peroxide to a refluxing *tert*-butylbenzene solution. This methodology is limited by the harsh reaction conditions.



Scheme 16

In 2005, the group of Nishio showed that radical cyclization of Beckwith and Storey's substrate **16.1**, slightly modified by having substituents (electron donating or withdrawing) in the *ortho* or *para* positions of the aniline ring, could in fact be done under the standard stannane mediated conditions (Bu_3SnH, AIBN, PhMe) (Scheme 17).[29]

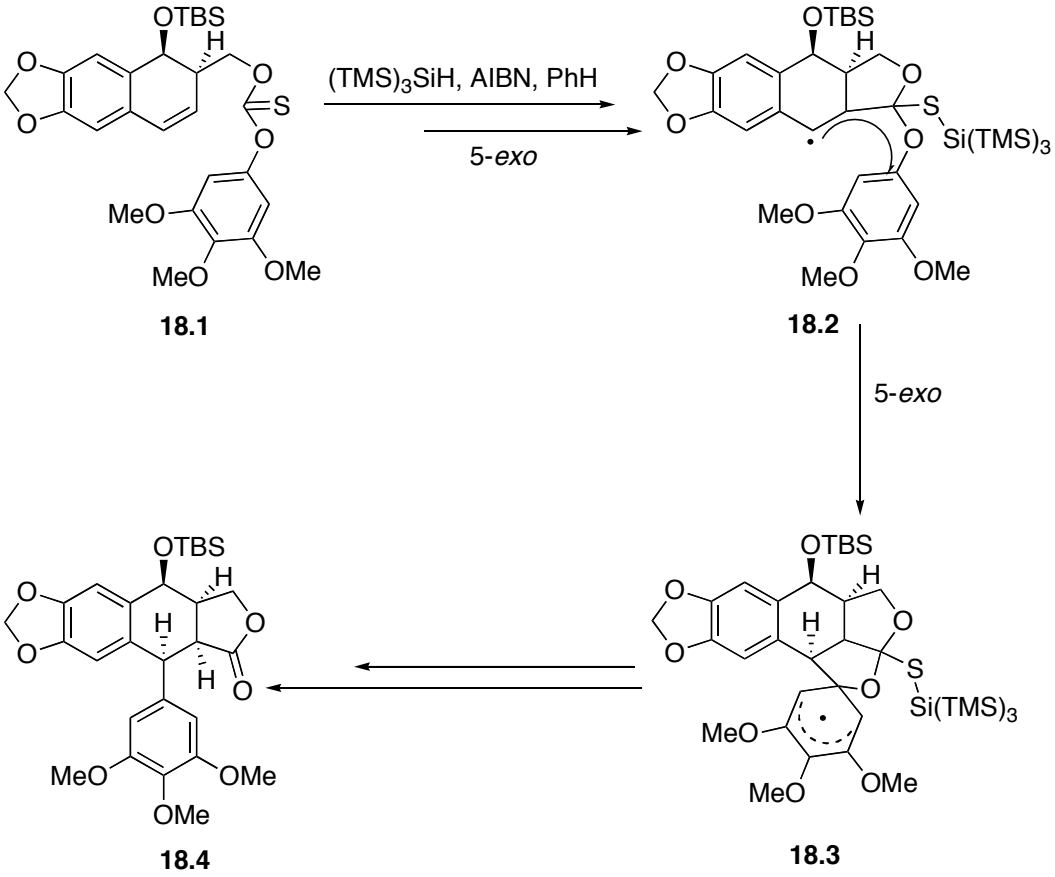


Scheme 17

Cyclization under reductive conditions proceeded reasonably well to afford the cyclized indolones **17.2** (34-80%), with the common by-product being the

reduced uncyclized compound **17.3** (7-28%). The same reaction could be performed with Ni powder in *i*-PrOH with comparable yields.

During synthetic studies on podophyllotoxin, a potent tubulin antimitotic agent, Reynolds and co-workers employed an alkyl radical cyclization onto a proximal arene as a key step in the synthesis (Scheme 18).[30]

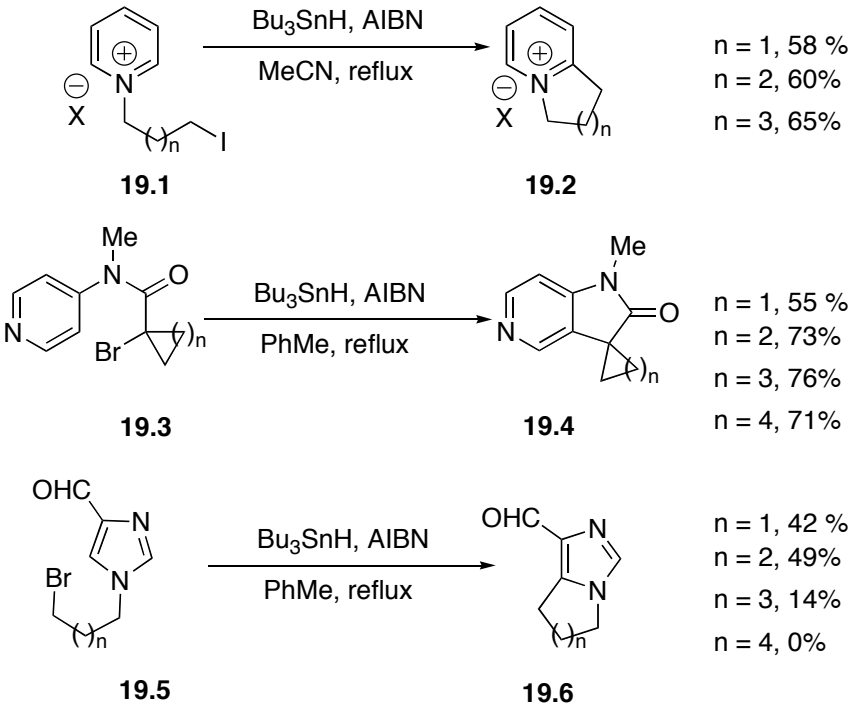


Scheme 18

When thiocarbonate **18.1** was exposed to tris(trimethylsilyl)silane, it first cyclized to a benzylic radical **18.2**, which in turn underwent an *ipso*-substitution

on the pendant aryl ring to give **18.3** and, after elimination of the sulfur unit, afforded the tetrahydronaphthalene lactone **18.4** in 40% yield.

Alkyl radical cyclizations onto heteroarenes have been extensively studied[27] due to the pharmaceutical interest in heteroaromatic compounds. Examples of alkyl radical addition onto pyridinium salts,[31] pyridines[32] and imidazoles[33] are shown in Scheme 19.



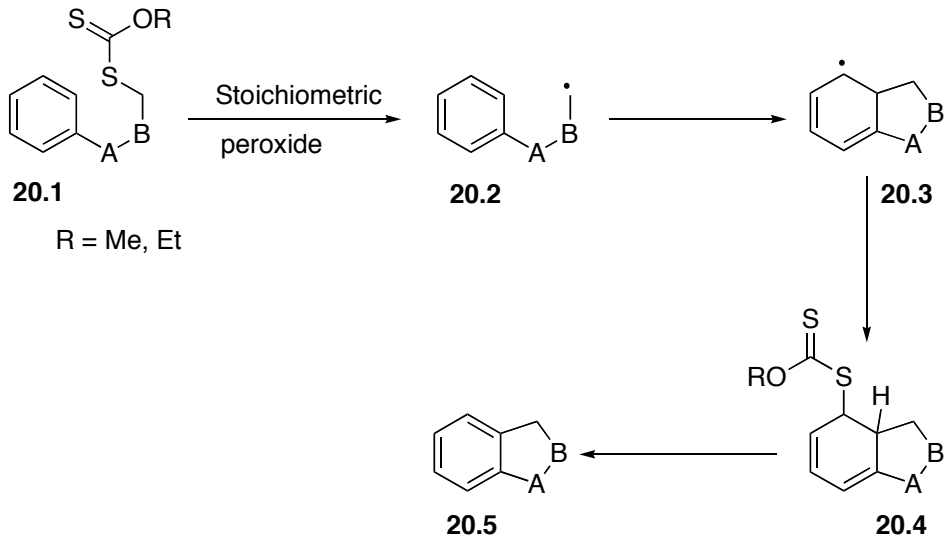
Scheme 19

In all the above examples (Scheme 19), a competing reaction was reduction of the intermediate alkyl radical by Bu_3SnH to give reduced uncyclized products. Formation of a six-membered ring is most favored with little or no

reduction, while attempts to synthesize rings greater than seven-membered gave only the reduced product.

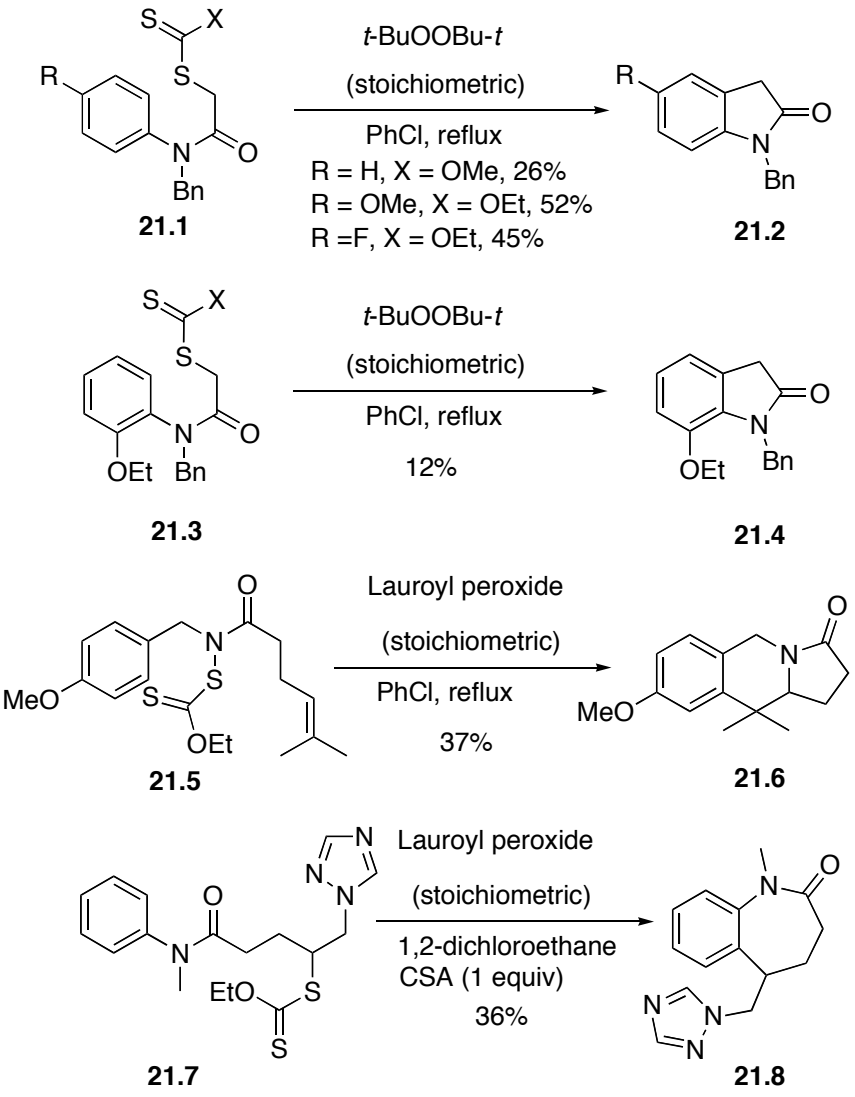
1.3 *Zard's protocol with xanthates and peroxides*

Zard and co-workers have pioneered the area of direct radical cyclization onto an aromatic ring with a long series of publications.[34] This valuable procedure makes use of peroxide, commonly, dilauroyl peroxide (DLP), and xanthate (now classed under the more systematic name, dithiocarbonates) precursors for generating alkyl radicals without using Bu_3SnH or Bu_3GeH. The conditions used strongly favor oxidative rearomatization over competing pathways and this property is useful in additions to aromatic and heteroaromatic rings.



Scheme 20

Another factor favoring Zard's protocol is that the starting xanthate **20.1** (Scheme 20) and the derived radical **20.2** exist in equilibrium, hence can react with each other and keep producing **20.1** and **20.2** again. As such, this process keeps generating the radical intermediate reversibly and, as a consequence, the effective lifetime of the radical in the medium increases considerably. This

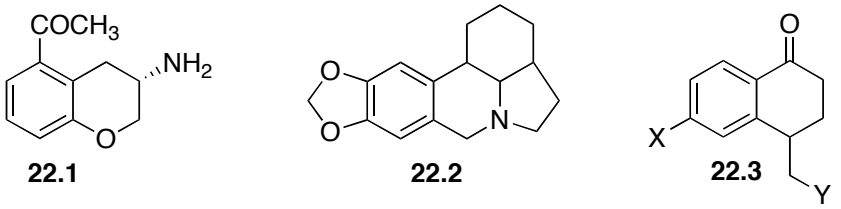


Scheme 21

situation allows the radical to be temporarily 'stored' in case it does not undergo the required slow cyclization onto the aromatic ring. Some typical examples are shown in Scheme 21.[34f, 35]

Five-, six- and seven-membered ring systems are accessible by this process. In the case of **21.7→21.8**, refluxing in 1,2-dichloroethane with 1 equiv of camphorsulphonic acid (CSA) with the gradual addition of a stoichiometric amount of peroxide induced cyclization onto the aromatic ring to afford benzazepinone **21.8** in 36% yield.[36]

Zard's procedure has been applied successfully to natural products such as 3-aminochroman (**22.1**)[37] and lycorane (**22.2**)[34d] as well as intermediates for the synthesis of biologically active substances, such as tetralones (**22.3**)[34b] (Scheme 22).



Scheme 22

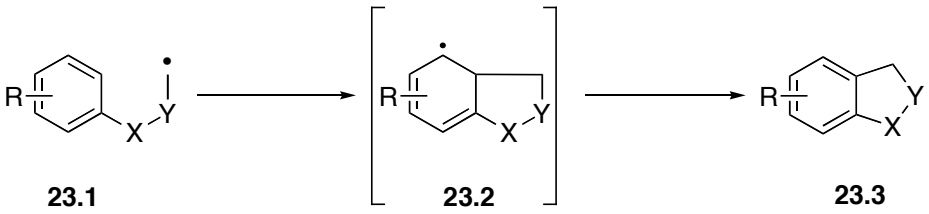
Zard's protocol has a number of advantages[38] such as the fact that no heavy or toxic metals are required, the starting materials are cheap and readily available and the procedure does not require high dilution conditions. However, limitations to this methodology include use of stoichiometric amount of peroxide

and high reaction temperatures. These factors might be incompatible with sensitive functional groups.

2 RESULTS AND DISCUSSION

2.1 *Research Objectives*

As mentioned in the introduction to this chapter, alkyl radical cyclization onto an aromatic ring represents a largely undeveloped, but potentially important, area. Oxidative radical cyclization of an alkyl radical onto a benzene ring, as depicted in Scheme 23 (X,Y = linking chain) would offer a useful route to benzo-fused compounds such as oxygen heterocycles (X = O) or nitrogen heterocycles (X = N) and benzo-fused carbocycles (X = C).

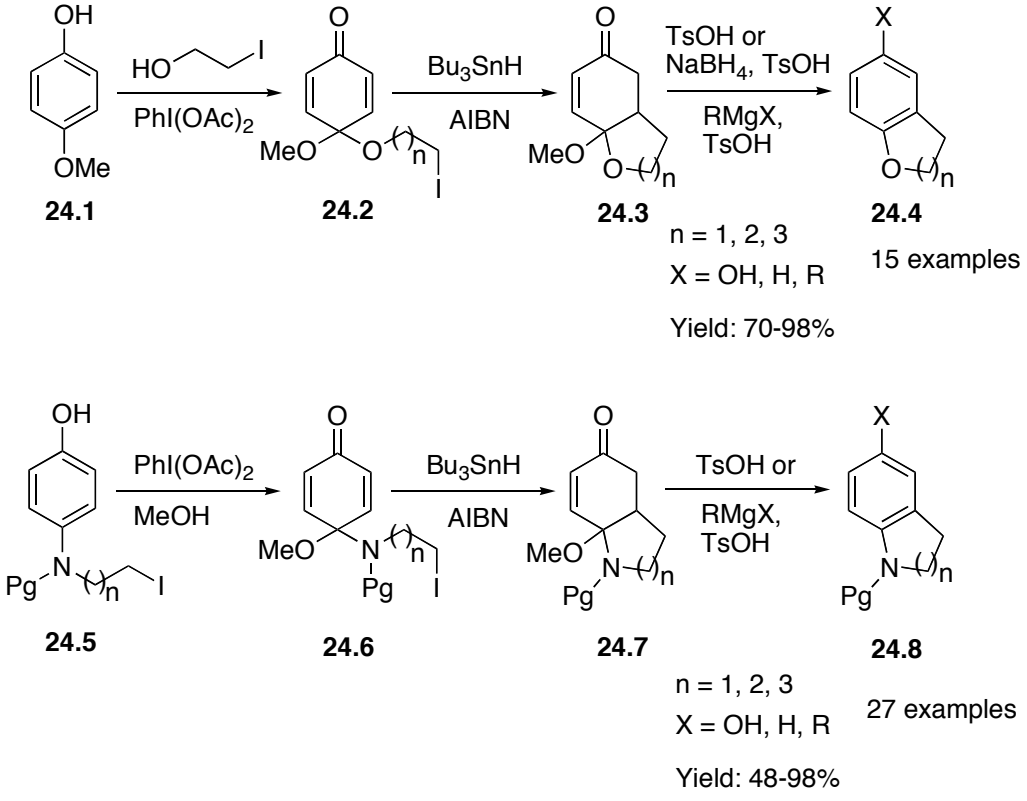


23.1 **23.2** **23.3**

Scheme 23

While this is a known process (**23.1→23.3**), the only method that appears general is Zard's xanthate approach. However, these powerful xanthate-based methods usually require stoichiometric amounts of peroxide as the initiator and quite harsh reaction conditions such as refluxing chloro- or 1,2-dichlorobenzene. For situations where such conditions have to be avoided, the development of a process that functions under the standard mild conditions for radical cyclization (Bu_3SnH, catalytic AIBN, refluxing PhH) would be useful. In this respect, recent publications[39] from this laboratory established an *indirect* method for effecting radical cyclization onto a benzene ring. *Direct* oxidative radical cyclization is a

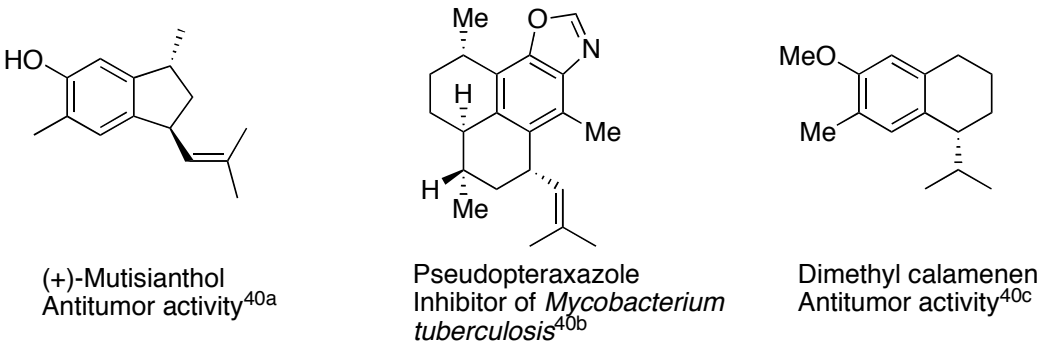
multi-step process with the first step, in all published examples, being cyclization onto the ring (Scheme 23, **23.1→23.2**), followed by oxidation and elimination of a proton (**23.2→23.2**). However, the indirect method developed here has established that if the processes in Scheme 23 are in a different order, that is oxidation first, then radical cyclization, followed by loss of a proton, a quick entry to a range of benzo-fused oxygen-[39a] (**24.4**) and nitrogen heterocycles (**24.8**)[39b,c] is achieved, along the lines summarized in Scheme 24.



Scheme 24

Our objective was now to extend the indirect methodology to an all-carbon case (X = C, Scheme 23) along the same lines as depicted in Scheme 24,

as this would be useful to generate benzo-fused carbocycles. Benzo-fused carbocycles are important structural units in many natural products and Figure 1 illustrates a few examples of such compounds.[40]



(+)-Mutisianthol
Antitumor activity[40a]

Pseudopteraxazole
Inhibitor of *Mycobacterium tuberculosis*[40b]

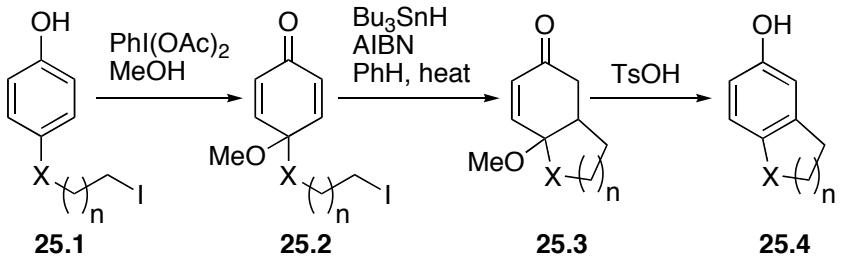
Dimethyl calamenen
Antitumor activity[40c]

Figure 1

2.2 *Development of a general approach to formal radical closure onto aromatic rings*

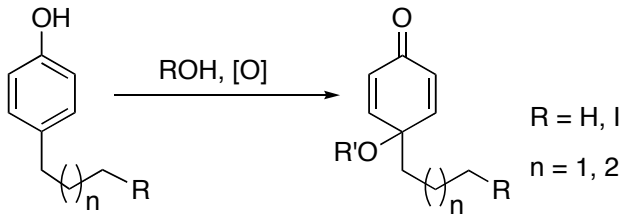
Our objective was to develop a general approach for *indirect* alkyl radical cyclization onto benzene rings and the main requirement was that the method should operate under standard radical cyclization conditions.

The essential steps of the radical method (Scheme 25) developed in this group[39] involved converting the starting benzenoid compound into a cross-conjugated ketone (**25.1→25.2**), which then underwent stannane-mediated radical cyclization under standard conditions (**25.2→25.3**). Finally, treatment with TsOH caused rearomatization (**25.3→25.4**).



Scheme 25

In cases where X = O, the cross-conjugated ketone could be generated as shown, by oxidation in MeOH. Alternatively, if the original benzene ring carried a MeO group *para* to the phenolic OH, then the oxidation must be done in the presence of an α,ω-iodoalcohol in order to generate the cross-conjugated ketones **25.2**. When X = N, a route similar to that of Scheme 25 was followed, but with an additional step in which the nitrogen was first protected as a carbamate before introduction of iodine and oxidation to the cross-conjugated ketone. For the carbocycle case, we decided to explore a similar plan that involves oxidation of *p*-alkyl phenols or *p*-(ω-iodoalkyl) phenols; the latter would be the ideal substrate for studying the radical cyclization step. However, we found that when X = C, oxidation in the sense **25.1→25.2** (Scheme 25) is problematic and proceeds in poor yield (Scheme 26). For example, treatment of **26.1** with hypervalent iodine reagents gave **26.2** in yields of only 15-40%.



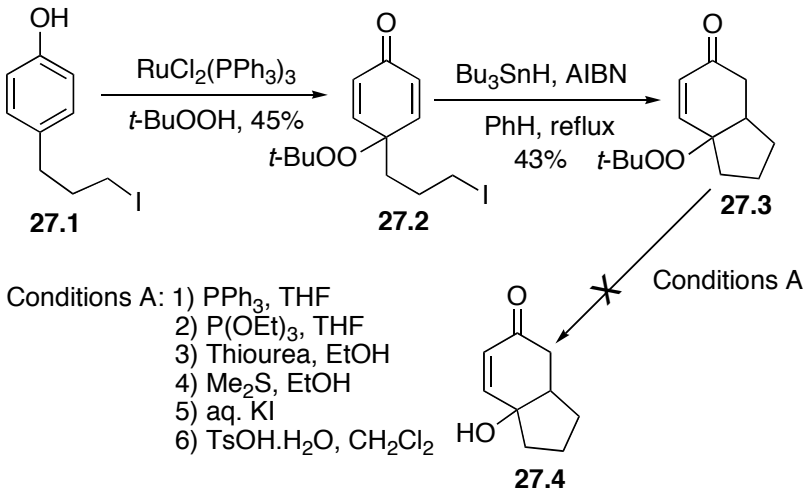
26.1 **26.2**

[O]	R'OH	Yield %
$PhI(OCOCF_3)_2$	H_2O	15
$PhI(OAc)_2$	MeOH	30
$PhI(OCOCF_3)_2$	MeOH	40
$RuCl_2(PPh_3)_3$	*t*-BuOOH	44

Scheme 26

A few examples of such oxidation of *para* alkyl phenols have been reported in the literature to proceed efficiently, but these almost always involve *para* methyl substitution.[41] When the alkyl chain is longer than one carbon, our experiments show that oxidation is usually inefficient, and such examples as we have found in the literature confirm this assessment. The approaches we tried include the use of $PhI(OAc)_2$ in water-MeOH;[41] $PhI(OCOCF_3)_2$ in water-MeCN or in MeOH;[42] and *t*-BuOOH, $RuCl_2(PPh_3)_3$.[43] The best yield obtained was 44%, when using the ruthenium oxidation system with *tert*-butyl hydroperoxide as the external nucleophile. With that compound (**27.2**) in hand, we decided to explore the remaining steps (Scheme 27). Treatment of **27.2** with Bu_3SnH and AIBN in hot benzene afforded the five-membered cyclized product **27.3** in 43% unoptimized yield. However all attempts to cleave hydroperoxide **27.3** to the

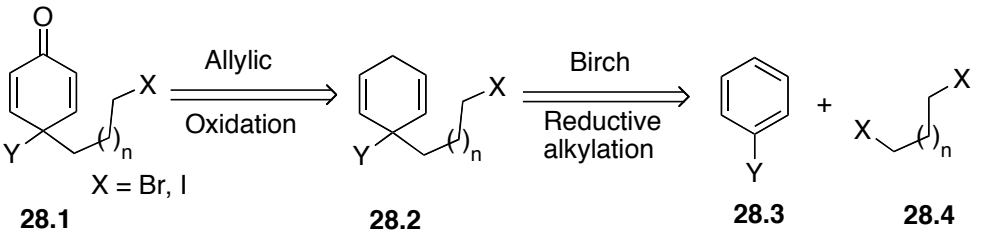
corresponding tertiary alcohol **27.4** were unsuccessful under the various conditions shown in Scheme 27.



Scheme 27

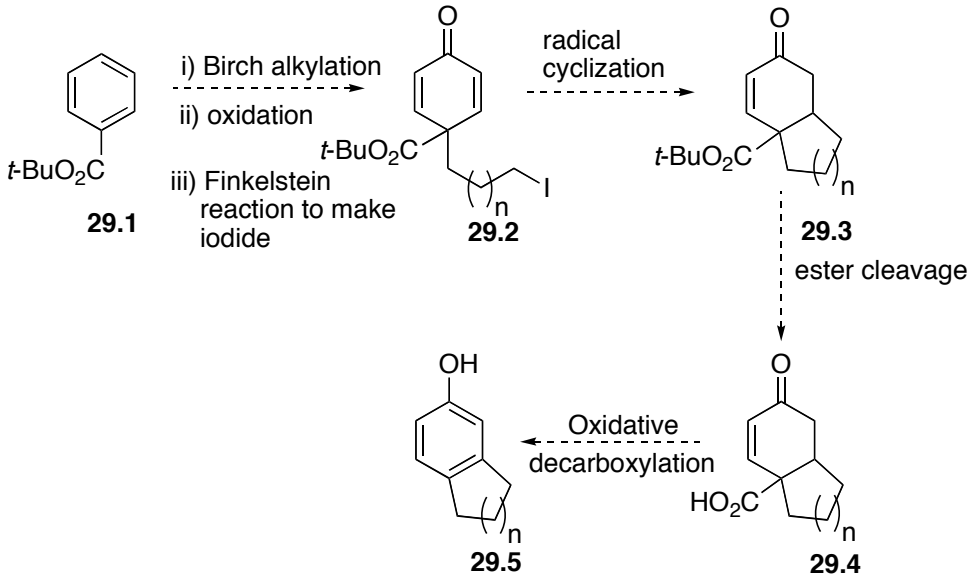
In most cases, starting material or unidentified byproducts were obtained. We thought that by replacing *tert*-butyl hydroxide with cumyl hydroperoxide in the initial oxidation step, cleavage should be easier but, to our surprise, only starting material was obtained in attempts to cleave the radical cyclized hydroperoxide (cf **27.3→27.4**).

Our inability to extend the process of Scheme 25 directly to the all-carbon case caused us to consider alternative key intermediates that conform to the general structure **28.1** (Scheme 28), where Y is a group that can be easily removed in the final process of rearomatization.



Scheme 28

We eventually selected Y = CO_2t-Bu as a suitable candidate for investigation. Such ester derivatives **28.1** ought to be readily available by Birch reductive alkylation[44] of *tert*-butyl benzoate **28.3** with a suitable dihalide **28.4**, followed by allylic oxidation **28.2→28.1**. This choice was guided in part by the fact that preparation of the corresponding methyl esters had already been reported, together with studies on their radical cyclization.[45] Our initial plan is shown in Scheme 29 and we anticipated that after radical cyclization (**29.2→29.3**), removal of the *tert*-butyl group (**29.3→29.4**) and oxidative decarboxylation[46] would give the desired rearomatized product (**29.4→29.5**).



Scheme 29

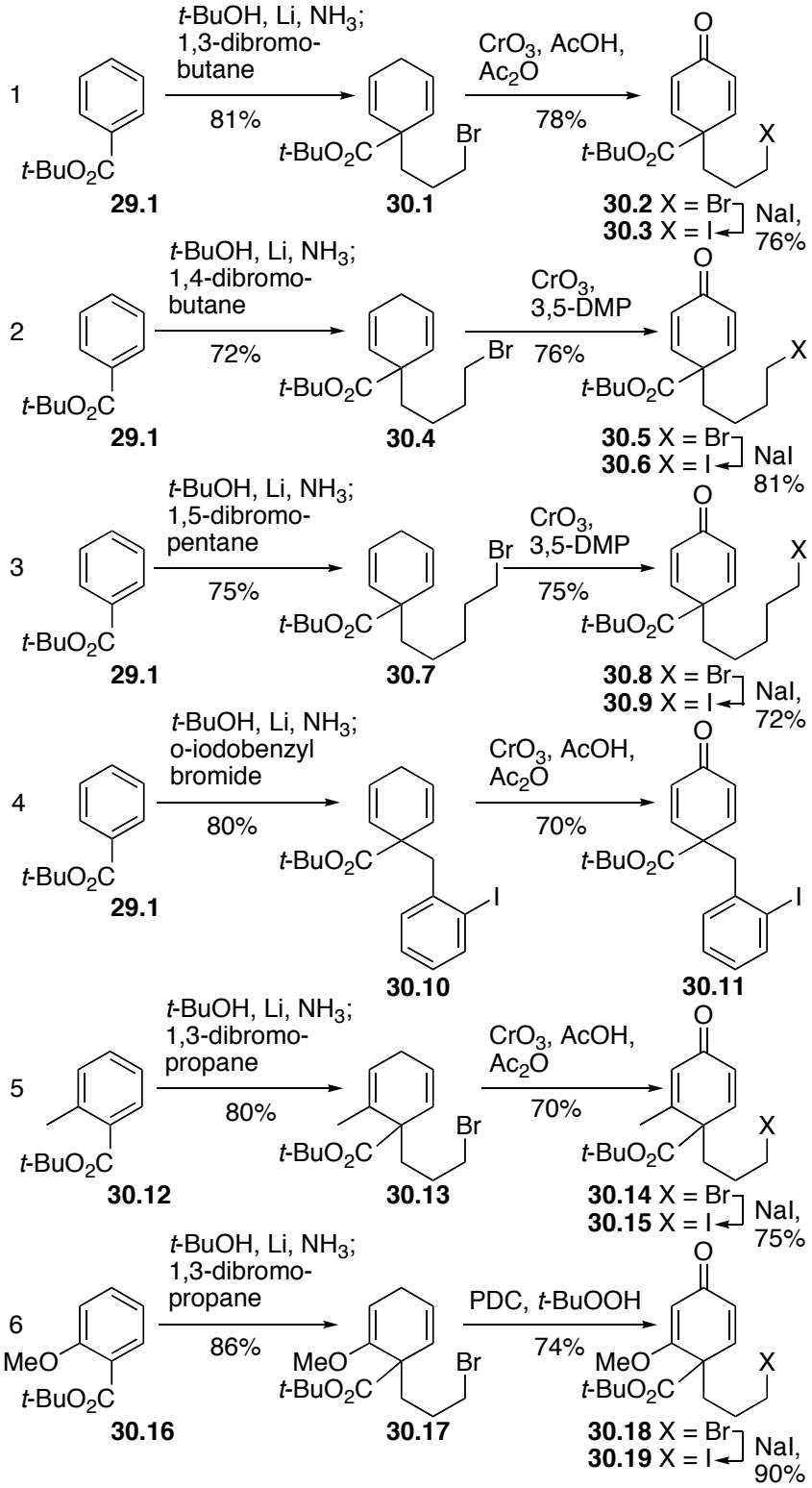
2.2.1 *Formation of radical precursors by Birch reductive alkylation, allylic oxidation and Finkelstein reaction*

Birch reductive alkylation of a number of aromatic *tert*-butyl esters (Scheme 30) with 1,3-dibromopropane, 1,4-dibromobutane or *o*-iodobenzyl bromide proceeded smoothly, giving in most cases yields of at least 80%. This step allows the introduction of an alkyl chain (n > 0) carrying bromine at the end of the chain and thus alleviating the problems we faced in oxidizing *p*-alkyl phenols. However, attempts to carry out Birch reductive alkylation directly with a diiodo alkane instead of a dibromo alkane, gave a complex mixture because of competing double alkylation of the bis-iodide.

The second stage of the process requires oxidation of the 1,4-diene system to a cross-conjugated ketone, and this was best achieved with CrO_3 in AcOH-Ac_2O.[47] In a few cases, better results were obtained under basic conditions with

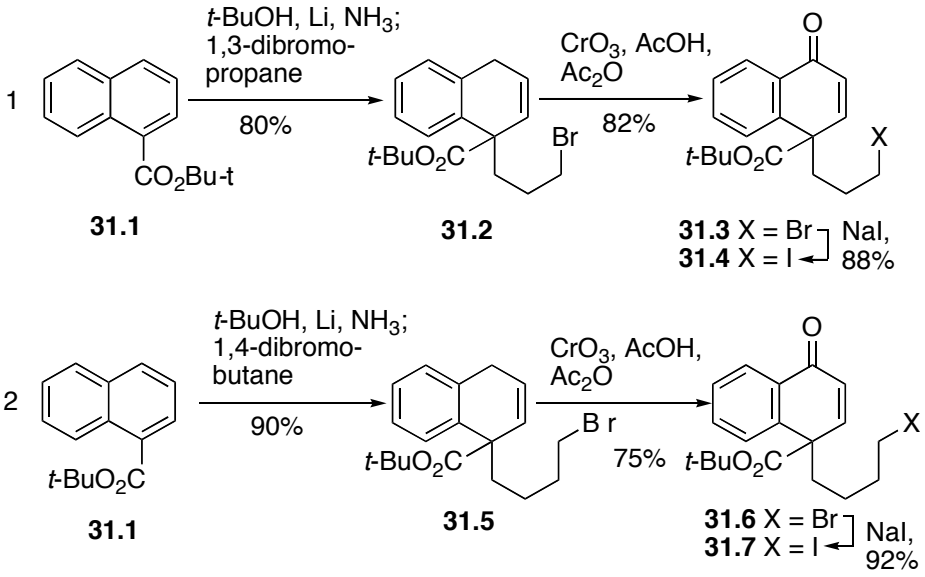
3,5-dimethylpyrazole (DMP) and CrO_3 (Scheme 30, entries 2 and 3).[48] In one example (Scheme 30, entry 6), a combination of PDC-*t*-BuOOH was the best oxidant.[49] The yields for the oxidation range from 70-78%.

Transformation of the bromides into the corresponding iodides was achieved under standard Finkelstein conditions (NaI in refluxing acetone) with yields ranging from 72-90%.


1
t-BuOH, Li, NH3;
1,3-dibromo-
butane
81%
CrO3, AcOH,
Ac2O
78%
t-BuO2C
Br
X
O
29.1
30.1
30.2 X = Br
30.3 X = I
NaI,
76%
2
t-BuOH, Li, NH3;
1,4-dibromo-
butane
72%
CrO3,
3,5-DMP
76%
30.4
30.5 X = Br
30.6 X = I
NaI
81%
3
t-BuOH, Li, NH3;
1,5-dibromo-
pentane
75%
CrO3,
3,5-DMP
75%
30.7
30.8 X = Br
30.9 X = I
NaI,
72%
4
t-BuOH, Li, NH3;
o-iodobenzyl
bromide
80%
CrO3, AcOH,
Ac2O
70%
I
30.10
30.11
5
t-BuOH, Li, NH3;
1,3-dibromo-
propane
80%
CrO3, AcOH,
Ac2O
70%
30.12
30.13
30.14 X = Br
30.15 X = I
NaI,
75%
6
MeO
t-BuOH, Li, NH3;
1,3-dibromo-
propane
86%
PDC, t-BuOOH
74%
30.16
30.17
30.18 X = Br
30.19 X = I
NaI,
90%

Scheme 30

Formation of the cross-conjugated ketone radical precursors was successful with benzenoid systems and substituents such as methyl (Scheme 30, entry 5) and methoxy (Scheme 30, entry 6) groups can be present. Naphthalenoid systems (Scheme 31) also proved to be easily accessible and thus add to the range of substrates available for the radical cyclization step.

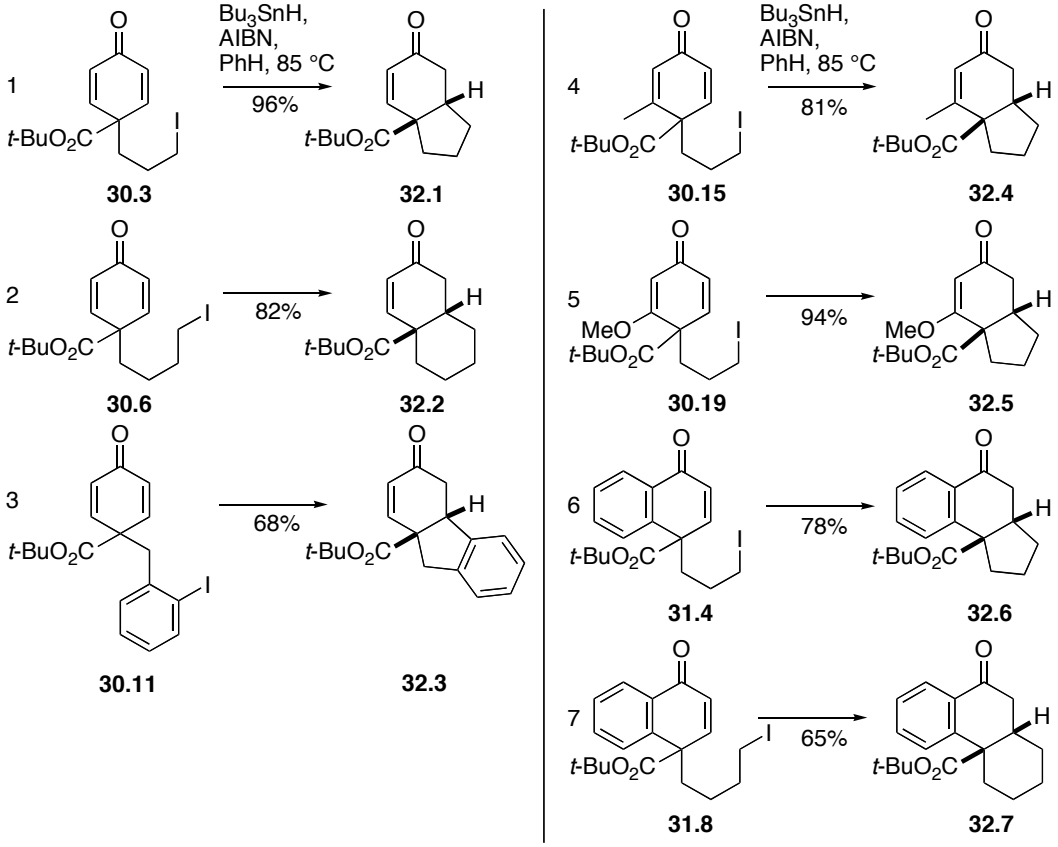


Scheme 31

2.2.2 Radical cyclization of cross-conjugated ketones

In all cases, the radical cyclization step (Scheme 32) was easily carried out by the standard method of slow addition (over 5 h by syringe pump) of a benzene solution of Bu_3SnH containing a catalytic amount of AIBN to a refluxing solution of the substrate in benzene. At the end of the addition, the mixtures were refluxed for an arbitrary period of 3-12 h. Evaporation of the solvent and flash chromatography of the residue over 10% KF-silica gel proved to be the ideal

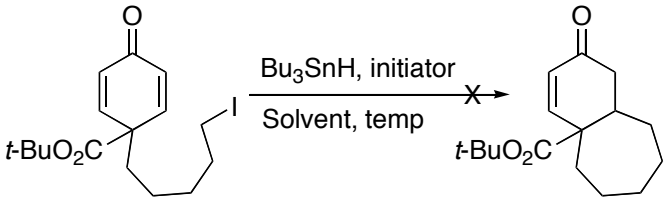
method for isolating pure radical cyclization products. It appears necessary to use iodides since attempts to use bromide **31.3** as a radical precursor gave a poor yield, presumably because bromides react with tributylstannyl radicals about 100 times more slowly than iodides,[45,50] leading to an unfavorable competition between dienone reduction and C-Br homolysis. Five- and six-membered rings are formed in 65-96% yield (Scheme 32). We have also shown that an aryl radical cyclization (Scheme 32, entry 3) is possible.



Scheme 32

Attempts to generate a seven-membered ring (Scheme 33) were unsuccessful. We tried very slow addition of the stannane (over 10 h) in refluxing

benzene, toluene or THF, as well as reactions at room temperature with Et_3B/air as initiator (in ethyl acetate), or at -78 °C with Et_3B/air (in toluene), but always observed simple reduction (replacement of I by H) as by far the major product. 7-*Ex*o-trig cyclizations are not common, but a number are known[51] and it is not clear why the process is unsuccessful in the present case. Because of the failure to form a seven-membered ring, we did not attempt to make an eight-membered ring, as corresponding experiments were also unsuccessful in the oxygen and nitrogen cases (Scheme 24).[39]



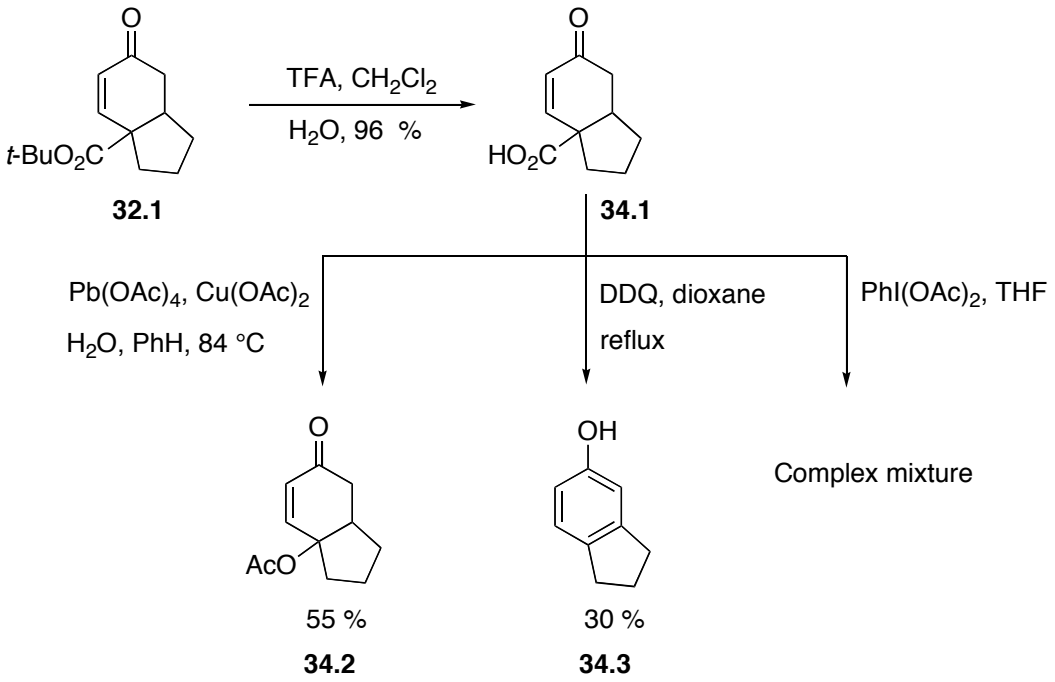
30.9 **33.1**

Initiator	Solvent	Temp	Product
AIBN	PhH	Reflux	Reduced product
AIBN	$PhCH_3$	Reflux	Reduced product
AIBN	THF	Reflux	Reduced product
Et_3B	EtOAc	RT	Complex mixture
Et_3B	$PhCH_3$	-78 °C	Complex mixture

Scheme 33

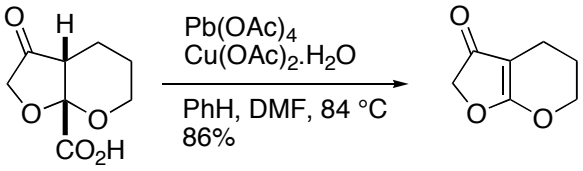
2.2.3 Rearomatization

The next step of our planned sequence — the critical rearomatization — was initially troublesome and several approaches had to be tried. With **32.1** as a test substrate (Scheme 34), we first removed the *tert*-butyl group in the standard



Scheme 34

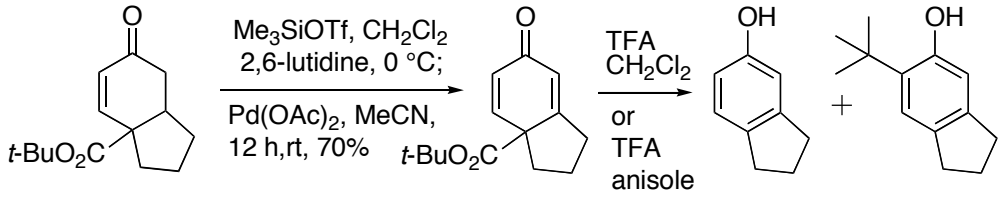
way by treatment with trifluoroacetic acid to afford **34.1** in excellent yield (96%). Exposure of acid **34.1** to the action of $Pb(OAc)_4$ in the presence of $Cu(OAc)_2$ — conditions that had worked well for the conversion of **35.1** into **35.2** (Scheme 35),[46] during a natural product synthesis in this laboratory — did not proceed as expected, but gave instead the acetate **34.2** in 55% yield. This compound was itself resistant to elimination of AcOH under the action of DBU in refluxing toluene. Use of $PhI(OAc)_2$ for the attempted oxidative decarboxylation of **34.1** gave a complex mixture. Treatment of **34.1** with DDQ in refluxing dioxane slowly produced the required aromatized product **34.3**, but in poor yield (33%).



35.1 **35.2**

Scheme 35

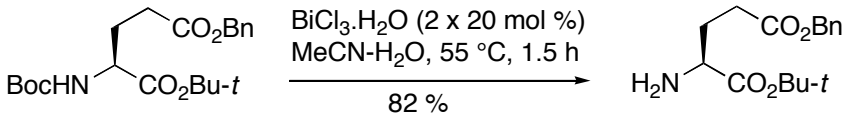
Hence, these initial experiments prompted us to introduce a second double bond before attempting the decarboxylation, because an additional double bond in the ring would facilitate the rearomatization process. To this end, enone **32.1** was subjected to Saegusa oxidation by conversion into the corresponding silyl enol ether, followed by treatment with $Pd(OAc)_2$ (Scheme 36, **32.1→36.1**). The cross-conjugated ketone **36.1** was treated with CF_3CO_2H to remove the *tert*-butyl group and, as expected, the resulting acid underwent spontaneous decarboxylation[52] to afford the desired indanol **34.3** (55%) together with the alkylated byproduct **36.3** in 40% yield. Addition of anisole to suppress formation of this byproduct was ineffective.



32.1 **36.1** **34.3** 55 % **36.3** 40 %

Scheme 36

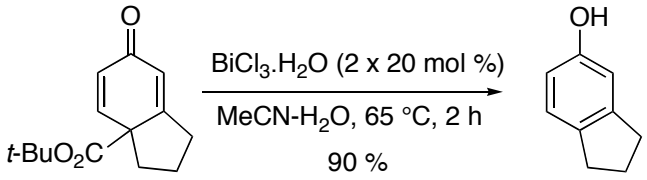
While I was working on this project, a publication from Navath and co-workers reported the use of $BiCl_3.H_2O$ for the smooth chemoselective removal of *N*-Boc groups from protected amino acids and peptides (Scheme 37).[53] In these deprotections[53] prolonged reaction times had to be avoided if the substrate also contained an ordinary *tert*-butyl ester, as cleavage of the latter then started to occur during reaction times longer than 1.5-2 h. However, the authors did not take advantage of this crucial observation as they wanted to show a chemoselective deprotection of *N*-Boc carbamates.



37.1 **37.2**

Scheme 37

With this in mind, our substrate **36.1** was exposed to $BiCl_3.H_2O$ (2 x 20 mol%) in aqueous MeCN at 65 °C. Efficient removal of the *tert*-butyl group occurred as well as decarboxylation to give directly the desired aromatized product **34.3** in 90% yield (Scheme 38) with no trace of the by-product **36.3**. This procedure is simple, uses an inexpensive catalyst ($BiCl_3.H_2O$) and involves the easy work-up procedure of filtration through a pad of Celite. However, we did not establish if the decarboxylation occurred spontaneously or whether the bismuth reagent is involved.

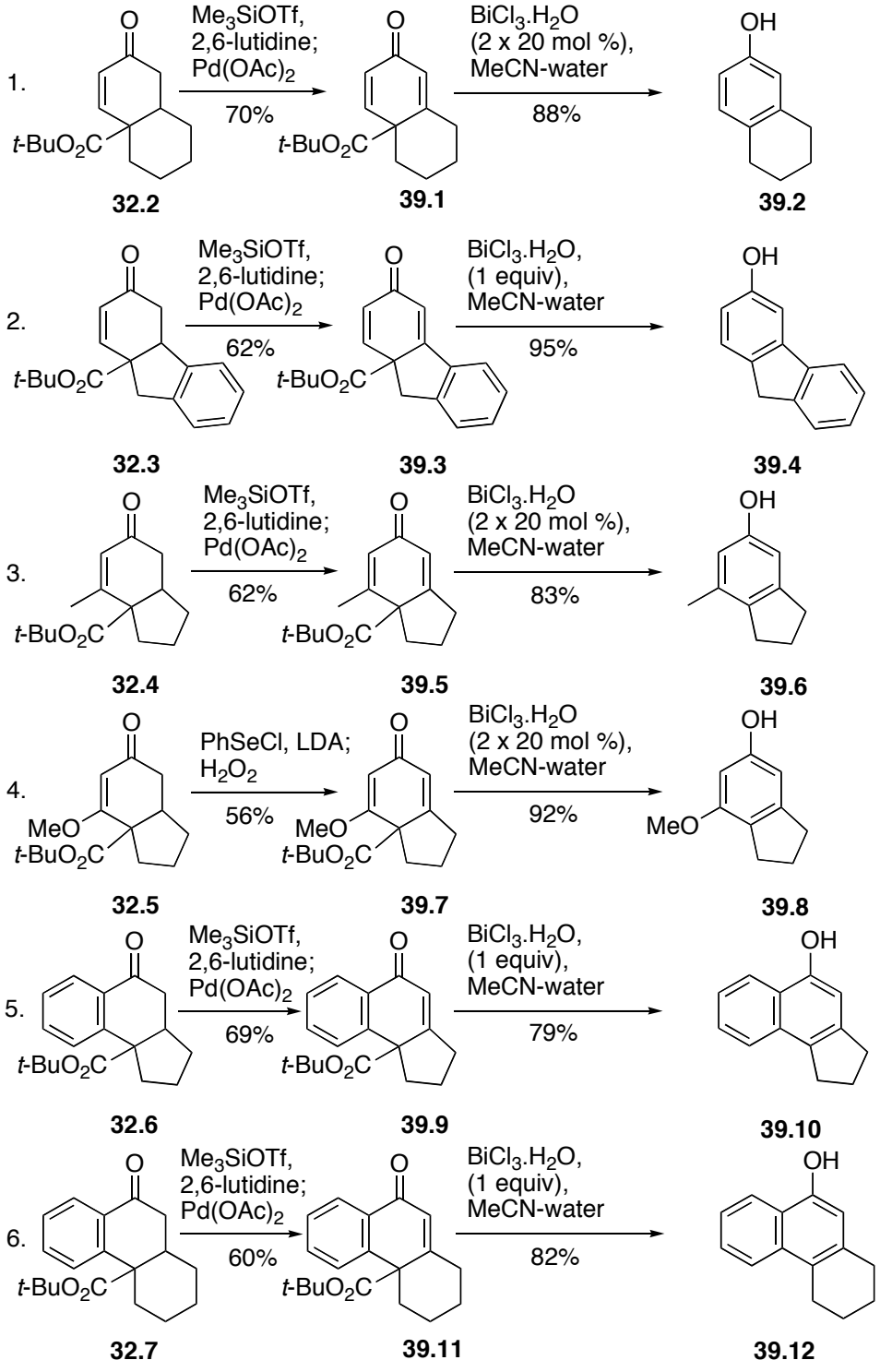


36.1 **34.3**

Scheme 38

With the standard conditions in hand, the method of oxidation (**32.1→36.1**, Scheme 36) was applied to several other enones (Scheme 39) and in all but one case (Scheme 39, entry 6) gave yields a little above 60%. In the case of **32.5** (Scheme 39, entry 4), the silylation step, using either $Me_3SiOSO_2CF_3$ and 2,6-lutidine, or LDA and Me_3SiCl was problematic, but these procedures were not examined exhaustively, since we found that phenylselenation (LDA, PhSeCl) and oxidation (H_2O_2) generated the required double bond, although only in modest yield (56%), presumably because just one of the two intermediate phenyl selenides had the appropriate stereochemistry for *syn* elimination.

The removal of the *tert*-butyl group and decarboxylative aromatization are general and overall yields with our dienones were in the range 79-95% (Scheme 39). In the case of entries 2, 5 and 6, a stoichiometric amount of $BiCl_3.H_2O$ was required for smooth conversion to the aromatized products. In no case did we notice the type of byproduct **36.3** observed with **36.1** when it was treated with CF_3CO_2H. Five- and six-membered benzo-fused carbocycles as well as naphthalenoid carbocycles were successfully synthesized.

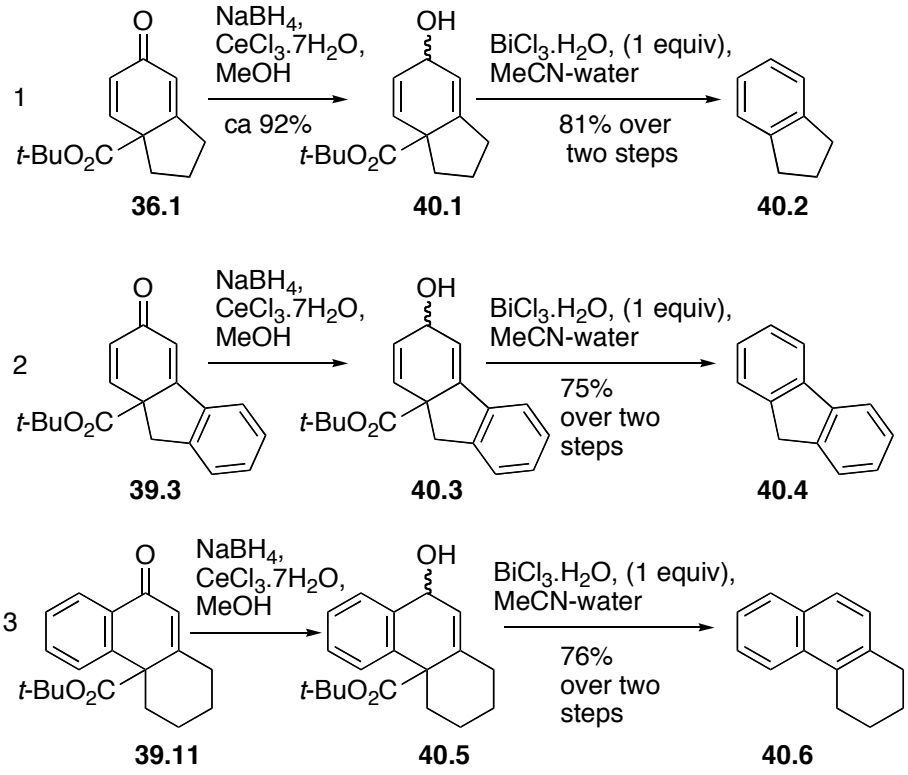

1.
Me3SiOTf,
2,6-lutidine;
Pd(OAc)2
70%
BiCl3.H2O
(2 x 20 mol %),
MeCN-water
88%
t-BuO2C
OH
32.2
39.1
39.2
2.
Me3SiOTf,
2,6-lutidine;
Pd(OAc)2
62%
BiCl3.H2O,
(1 equiv),
MeCN-water
95%
32.3
39.3
39.4
3.
Me3SiOTf,
2,6-lutidine;
Pd(OAc)2
62%
BiCl3.H2O
(2 x 20 mol %),
MeCN-water
83%
32.4
39.5
39.6
4.
PhSeCl, LDA;
H2O2
56%
BiCl3.H2O
(2 x 20 mol %),
MeCN-water
92%
MeO
32.5
39.7
39.8
5.
Me3SiOTf,
2,6-lutidine;
Pd(OAc)2
69%
BiCl3.H2O,
(1 equiv),
MeCN-water
79%
32.6
39.9
39.10
6.
Me3SiOTf,
2,6-lutidine;
Pd(OAc)2
60%
BiCl3.H2O,
(1 equiv),
MeCN-water
82%
32.7
39.11
39.12

Scheme 39

2.2.4 Manipulation of the intermediate dienones before rearomatization

As illustrated in Scheme 39, application of our general process gives phenolic products; the process can, however, be easily diverted to nonphenolic compounds giving products with hydrogen, alkyl or aryl groups in place of the original phenolic hydroxyl.

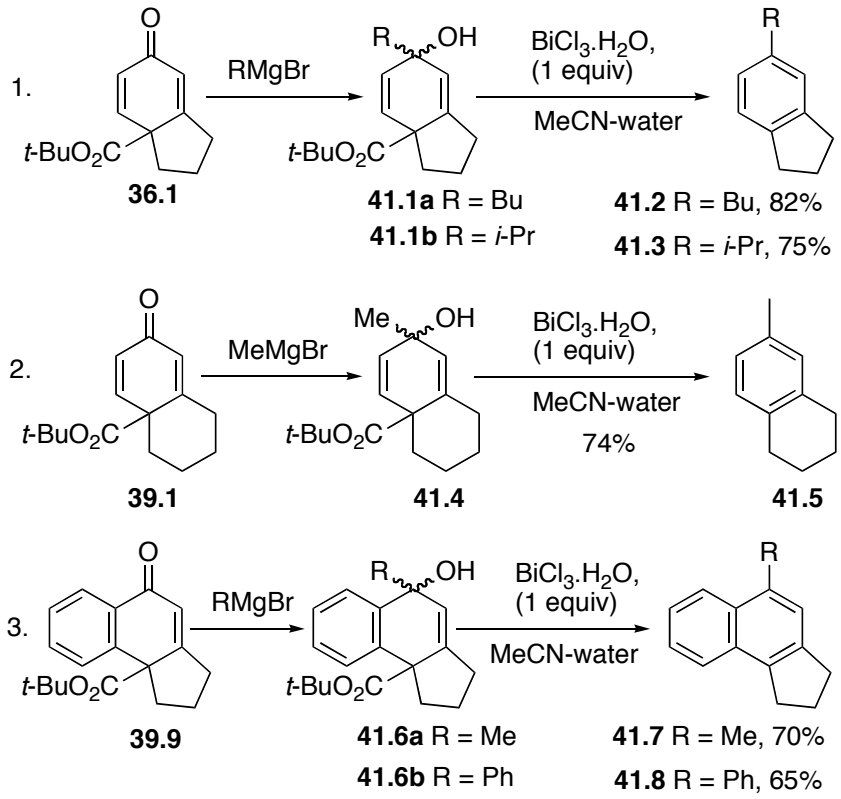
Reduction of the carbonyl of the intermediate dienones under Luche conditions ($NaBH_4$ in the presence of $CeCl_3.7H_2O$) affords hydrocarbons rather than phenols (Scheme 40).



Scheme 40

When the intermediate dienones are treated with Grignard reagents, tertiary alcohols are formed which, upon treatment with $BiCl_3.H_2O$, give

aromatized products carrying an alkyl (**41.2**, **41.3 41.5** and **41.7**) or aryl group (**41.8**) originating from the organometallic reagent (Scheme 41).



Scheme 41

When the intermediate ketone is modified in this way, either by hydride reduction or by carbanion addition, the rearomatization in the presence of $BiCl_3.H_2O$ still occurs efficiently but requires stoichiometric amounts of the reagent.

Another member in our group, Zhenhua Chen, has expanded this methodology (8 examples) and shown that various substituents (aryl, allyl, propargyl) can be introduced in place of the phenolic groups. A noteworthy

example is the introduction of a heteroaryl group (furanyl unit) onto the aromatic ring.[54b]

3 CONCLUSION

We have been able to illustrate a formal alkyl radical cyclization onto an arene (benzene or naphthalene) so as to form benzo-fused carbocycles. This method allows formation of five- and six-membered carbocyclic rings fused onto phenols. The approach is amenable to a number of modifications, and we have developed modifications allowing construction of non-phenolic aromatic species and/or the introduction of alkyl or aryl substituents on the initial aromatic ring, giving access to substitution patterns not easily accessible by other methods. This method also demonstrates the effectiveness of $BiCl_3.H_2O$ for deprotection of *tert*-butyl esters.[54]

4 EXPERIMENTAL

Unless stated to the contrary, the following conditions apply: Reactions were carried out under a slight static pressure of Ar or N_2 that had been purified by passage through a column (3.5 x 42 cm) of R-311 catalyst and then through a similar column of Drierite. All solvents for reactions were dried, as described below. Glassware was dried in an oven (140 °C) for at least 3 h before use and either cooled in a desiccator over Drierite, or assembled quickly, sealed with rubber septa, and allowed to cool under a slight static pressure of Ar or N_2. Reaction mixtures were stirred by Teflon-coated magnetic stirring bars.

Hexane and ethyl acetate used for chromatography were distilled before use.

Products were isolated from solution by evaporation under water aspirator vacuum at, or below, room temperature, using a rotary evaporator.

Microliter syringes were washed with water and acetone, using a suction device to draw the solvents through. Air was then drawn through for 1 min and the syringe was stored under vacuum. The solution to be dispensed was drawn up and expelled, and this operation was repeated several times before drawing up the sample to be used. Cannula transfers were always done under slight pressure (Ar or N_2), not by suction.

Commercial thin layer chromatography (TLC) plates (silica gel, Merck 60F–254) were used. Spots were detected by spraying the plate with a solution of phosphomolybdic acid, followed by charring with a heat gun, or by examination

under UV light. Silica gel for flash chromatography was Merck type 60 (230-400 mesh).

Dry solvents were prepared under an inert atmosphere and transferred by syringe or cannula. Dry THF, Et_2O, PhH, PhMe and dioxane were distilled from sodium and benzophenone ketyl. Dry CH_2Cl_2, Et_3N, *i*-Pr_2NEt and pyridine were distilled from CaH_2. Dry MeOH was distilled from $Mg(OMe)_2$. Acetone was distilled from $KMnO_4$ and dried over 4Å molecular sieves. FT-IR measurements were made from the specified solvent using KBr plates.

The symbols s, d, t, and q used for ^{13}C NMR signals indicate 0, 1, 2, or 3 attached hydrogens, respectively, as based on the APT experiment.

Mass spectra were recorded with Agilent Technologies 6220 Accurate-Mass TOF LC/MS, Perseptive Biosystems Mariner Biospectrometry Workstation, Kratos MS50 or Micromass ZabSpec Hybrid Sector-TOF mass spectrometers.

Compounds isolated by flash chromatography were pure by TLC and, unless otherwise stated, also as judged by high field ^1H and ^{13}C NMR spectra.

General procedure for reductive alkylation.[45]

The apparatus consists of a three-necked round-bottomed flask containing a magnetic stirring bar and fitted with a cold finger condenser fused onto one of the necks. The exit of the condenser was fitted with a drying tube filled with $CaSO_4$. An external mark on the flask indicated the level corresponding to the desired volume of liquid ammonia. The central neck was closed by a septum carrying a nitrogen inlet. The flask was cooled in a dry ice-acetone bath and the

cold finger was charged with dry ice-acetone. Another round-bottomed flask was half-filled with liquid ammonia and several small pieces of Na were added, so as to form a permanently blue solution. This flask was connected via bent adaptors and dry Tygon tubing to the third neck of the other flask. A solution of the starting material in dry THF and *t*-BuOH was injected into the three-necked flask, and liquid ammonia was allowed to condense into the flask. Lithium wire, cut into small pieces, was added rapidly to the vigorously stirred solution. Stirring at -78 °C was continued for 10-15 min, until a dark blue color persisted. The alkyl halide in THF was then added dropwise from a syringe over ca 2 min, and the resulting yellow solution was stirred for 1 h at -78 °C. The cooling bath was removed and the NH_3 was allowed to evaporate under a stream of N_2 (2-3 h). Water was added and the mixture was extracted with Et_2O (4 times). The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel gave the product.

General procedure A for oxidation of the 1,4-cyclohexadienes.[47]

A stirred solution of CrO_3 and Ac_2O in AcOH was cooled to 7 °C and diluted with dry PhH. A solution of the reductive alkylation product in PhH was added dropwise and stirring at 7 °C was continued for 1-3 h (TLC control). The reaction mixture was diluted with EtOAc and carefully quenched with saturated aqueous $NaHCO_3$, washed with water and brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel gave the cross-conjugated ketone.

General procedure B for oxidation of the 1,4-cyclohexadienes.[45]

3,5-Dimethylpyrazole was added in one portion to a stirred and cooled (-20 °C) suspension of dry CrO_3 in CH_2Cl_2. Stirring at -20 °C was continued for 10-20 min, and then the reductive alkylation product in CH_2Cl_2 was added at a fast dropwise rate. Stirring at -20 °C was continued for 30 min (TLC control). The mixture was cooled to 0 °C and aqueous NaOH (5 M) was then added. Stirring at 0 °C was continued for 1 h, and the mixture was then partitioned between Et_2O and water. The aqueous phase was extracted with Et_2O and the combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel gave the cross-conjugated ketone.

General procedure for Finkelstein displacement.

Acetone (distilled from $KMnO_4$ and dried over 4Å molecular sieves) was added to a stirred mixture of the bromide and anhydrous NaI. The mixture was stirred and refluxed for 16-20 h, cooled and partitioned between Et_2O and water. The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel gave the iodide.

General procedure for radical cyclization.

A solution of Bu_3SnH and AIBN in dry PhH was added over 5 h (syringe pump) to a stirred and heated (85 °C) solution of the iodide in PhH. Heating was continued for several h after the addition. Evaporation of the solvent and flash

chromatography of the residue over KF-flash chromatography silica gel (10%$^{w}/_{w}$ KF) gave the cyclized product.

General procedure for Saegusa oxidation.[55]

2,6-Lutidine was added to a stirred and cooled (0 °C) solution of the enone in dry CH_2Cl_2. Neat $Me_3SiOSO_2CF_3$ was then added dropwise over 1 h. After the addition, the mixture was stirred at 0 °C for 1 h and then quenched by addition of saturated aqueous $NaHCO_3$. The mixture was diluted with CH_2Cl_2 and the organic layer was dried ($MgSO_4$) and evaporated, first under waterpump vacuum and then under oilpump vacuum until all lutidine had been removed. The residual enol silane was used without further purification. MeCN was added, followed by $Pd(OAc)_2$, and the mixture was stirred overnight under Ar. The mixture was filtered through a pad of Celite, using CH_2Cl_2. Evaporation of the filtrate and flash chromatography of the residue over silica gel gave the dienone.

General procedure A for rearomatization.

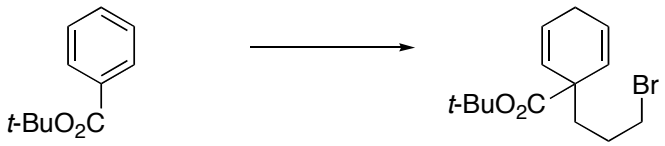
$BiCl_3.H_2O$[53] was added to a solution of the dienone in a mixture of MeCN and water, and the mixture was stirred at 65-70 °C. After 1 h, an additional equal portion of $BiCl_3.H_2O$ was added and stirring at the same temperature was continued until the reaction was complete (TLC control). Solid $NaHCO_3$ was added and mixture was stirred at room temperature for 10 min, and then filtered through a pad of Celite, using CH_2Cl_2. The filtrate was washed with brine, dried

($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel gave the aromatized product.

General procedure B for rearomatization.

Method A was followed in all respects, except that 1 equiv of $BiCl_3.H_2O$ was added initially, and no further addition was made during the course of the reaction.

1-(3-Bromopropyl)cyclohexa-2,5-dienecarboxylic Acid *tert*-Butyl Ester (30.1).

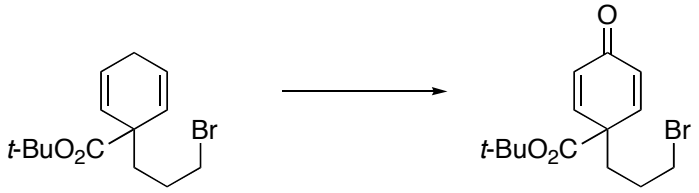


29.1 **30.1**

The general procedure for reductive alkylation was followed, using **29.1** (760 mg, 4.26 mmol) in dry THF (15 mL), *t*-BuOH (0.45 mL, 4.7 mmol), liquid NH_3 (50 mL), Li (63 mg, 8.9 mmol), and 1,3-dibromopropane (1.10 mL, 10.7 mmol) in THF (15 mL). Flash chromatography of the crude product over silica gel (2.5 x 24 cm), using first hexane and then 1:9 EtOAc-hexane, gave **30.1** (1.0 g, 81%) as an oil: FTIR (CH_2Cl_2 cast) 2927, 2854, 1716, 1456, 1265 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.45 (s, 9 H), 1.77-1.79 (m, 4 H), 2.63-2.64 (m, 2 H), 3.36-3.38 (m, 2 H), 5.71 (apparent dt, J = 10.6, 2.1 Hz, 2 H), 5.86-5.90 (m, 2 H);

^{13}C NMR ($CDCl_3$, 100 MHz) δ 26.1 (t), 27.9 (q), 28.0 (t), 33.7 (t), 37.9 (t), 47.9 (s), 80.8 (s), 125.0 (d), 125.7 (d), 127.1 (d), 127.6 (d), 173.5 (s; exact mass *m*/*z* calcd for $C_{14}H_{21}{}^{79}BrNaO_2$ (M + Na) 323.0617, found 323.0618. The ^{13}C NMR spectrum showed two unidentified small peaks at 125.0 and 127.6.

1-(3-Bromopropyl)-4-oxocyclohexa-2,5-dienecarboxylic Acid *tert*-Butyl Ester (30.2).

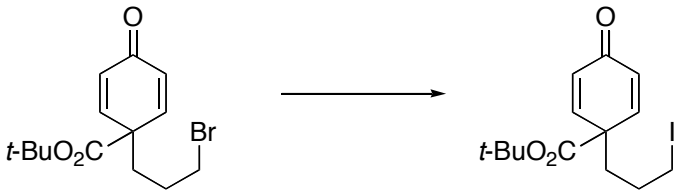


30.1 **30.2**

General procedure A for oxidation was followed, using CrO_3 (1.69 g, 16.9 mmol), Ac_2O (3.0 mL), AcOH (6.3 mL), PhH (10 mL) and **30.1** (1.02 g, 3.39 mmol) in PhH (15 mL), and a reaction time of 1 h. Flash chromatography of the crude product over silica gel (2.5 x 26 cm), using first hexane and then EtOAc-hexane mixtures up to 3:7 EtOAc-hexane, gave **30.2** (0.83 g, 78%) as an oil: FTIR (CH_2Cl_2 cast) 2982, 2918, 1728, 1668, 1457, 1266 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.41 (s, 9 H), 1.70-1.73 (m, 2 H), 1.74-2.05 (m, 2 H), 3.32 (t, *J* = 6.4 Hz, 2 H), 6.30 (d, *J* = 9.9 Hz, 2 H), 6.95 (d, *J* = 9.9 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 27.3 (t), 27.7 (q), 32.6 (t), 36.4 (t), 52.5 (s), 83.3 (s), 130.1 (d), 148.0

(d), 168.6 (s), 184.9 (s); exact mass *m*/*z* calcd for $C_{14}H_{19}{}^{79}BrNaO_3$ (M + Na) 337.0410, found 337.0411.

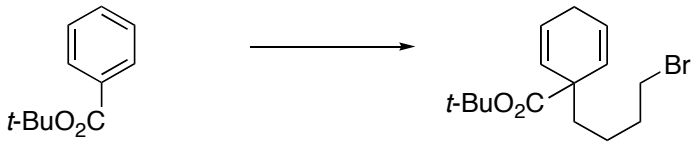
1-(3-Iodopropyl)-4-oxocyclohexa-2,5-dienecarboxylic Acid *tert*-Butyl Ester (30.3).



30.2 **30.3**

The general procedure for Finkelstein displacement was followed, using acetone (20 mL), **30.2** (333 mg, 1.06 mmol) and anhydrous NaI (555 mg, 3.70 mmol), and a reaction time of 16 h. Flash chromatography of the crude product over silica gel (1.5 x 15 cm), using 10% EtOAc-hexane, gave **30.3** (287 mg, 76%) as an oil: FTIR (CH_2Cl_2 cast) 2978, 2933, 1727, 1668, 1516, 1455, 1250 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.45 (s, 9 H), 1.66-1.76 (m, 2 H), 2.02-2.06 (m, 2 H), 3.12 (t, *J* = 6.7 Hz, 2 H), 6.35 (d, *J* = 9.8 Hz, 2 H), 6.97 (d, *J* = 9.8 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 15.0 (t), 27.8 (q), 28.0 (t), 38.7 (t), 52.4 (s), 83.3 (s), 130.1 (d), 148.0 (d), 168.6 (s), 185.0 (s); exact mass *m*/*z* calcd for $C_{14}H_{19}INaO_3$ (M + Na) 385.0271, found 385.0272.

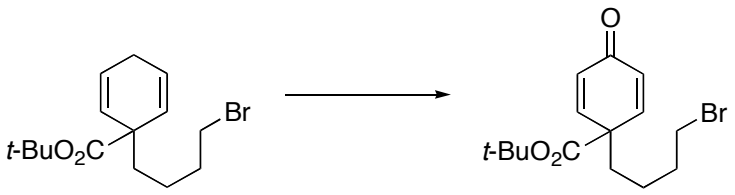
1-(4-Bromobutyl)cyclohexa-2,5-dienecarboxylic Acid *tert*-Butyl Ester (30.4).



29.1 **30.4**

The general procedure for reductive alkylation was followed, using **29.1** (1.02 g, 5.72 mmol) in dry THF (20 mL), *t*-BuOH (0.60 mL, 6.3 mmol), liquid NH_3 (60 mL), Li (0.08 g, 12 mmol), and 1,4-dibromobutane (1.70 mL, 14.3 mmol) in THF (20 mL). Flash chromatography of the crude product over silica gel (2.5 x 24 cm), using first hexane and then 1:9 EtOAc-hexane, gave **30.4** (1.23 g, 72%) as an oil: FTIR (CH_2Cl_2 cast) 2977, 2931, 1723, 1456, 1249 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.32-1.42 (m, 2 H), 1.43 (s, 9 H), 1.59-1.64 (m, 2 H), 1.79-1.86 (m, 2 H), 2.60-2.62 (m, 2 H), 3.37 (t, J = 6.8 Hz, 2 H), 5.69-5.72 (m, 2 H), 5.83-5.91 (m, 2 H); ^{13}C NMR ($CDCl_3$, 100 MHz) (δ 23.1 (t), 26.3 (t), 28.1 (q), 33.1 (t), 33.6 (t), 38.8 (t), 48.4 (s), 80.8 (s), 125.5 (d), 127.6 (d), 174.0 (s); exact mass m/z calcd for $C_{15}H_{23}{}^{79}BrNaO_2$ 314.0881, found 314.0880. The ^{13}C NMR spectrum showed two unidentified small peaks at 125.1 and 127.9.

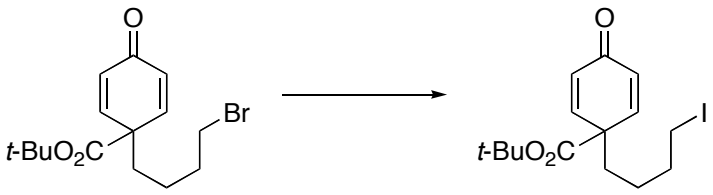
1-(4-Bromobutyl)-4-oxocyclohexa-2,5-dienecarboxylic Acid *tert*-Butyl Ester (30.5).



30.4 **30.5**

General procedure B for oxidation was followed, using 3,5-dimethylpyrazole (3.05 g, 32.0 mmol), CrO_3 (3.17 g, 32.0 mmol), CH_2Cl_2 (30 mL), **30.4** (1.0 g, 3.2 mmol) in CH_2Cl_2 (10 mL), NaOH (5M, 20 mL), and a reaction time of 1 h. Flash chromatography of the crude product over silica gel (2.5 x 24 cm), using first hexane and then EtOAc-hexane mixtures up to 3:7 EtOAc-hexane, gave **30.5** (0.794 g, 76%) as an oil: FTIR (CH_2Cl_2 cast) 2917, 2849, 1726, 1667, 1457, 1259 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.37-1.45 (m, 2 H), 1.46 (s, 9 H), 1.81-1.86 (m, 2 H), 1.90-1.95 (m, 2 H), 3.35 (t, J = 6.6 Hz, 2 H), 6.30 (d, J = 9.8 Hz, 2 H), 6.98 (d, J = 9.8 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 22.8 (t), 27.8 (q), 32.3 (t), 32.7 (t), 37.3 (t), 52.9 (s), 83.2 (s), 129.9 (d), 148.2 (d), 168.9 (s), 185.1 (s); exact mass m/z calcd for $C_{15}H_{21}{}^{79}BrNaO_3$ (M + Na) 351.0566, found 351.0567.

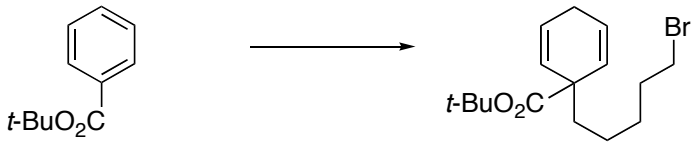
1-(4-Iodobutyl)-4-oxocyclohexa-2,5-dienecarboxylic Acid *tert*-Butyl Ester (30.6).



30.5 **30.6**

The general procedure for Finkelstein displacement was followed, using acetone (15 mL), **30.5** (350 mg, 1.06 mmol) and anhydrous NaI (558 mg, 3.72 mmol), and a reaction time of 15 h. Flash chromatography of the crude product over silica gel (1.5 x 15 cm), using 10% EtOAc-hexane, gave **30.6** (324 mg, 81%) as an oil: FTIR (CH_2Cl_2 cast) 2977, 2932, 1726, 1667, 1629, 1461, 1253 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.34-1.36 (m, 2 H), 1.47 (s, 9 H), 1.79-1.83 (m, 2 H), 1.91-1.96 (m, 2 H), 3.15 (t, J = 6.9 Hz, 2 H), 6.36 (d, J = 10.3 Hz, 2 H), 7.02 (d, J = 10.3 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 5.5 (t), 25.1 (t), 27.8 (q), 33.0 (t), 37.1 (t), 52.9 (s), 83.2 (s), 129.9 (d), 148.2 (d), 169.0 (s), 185.1 (s); exact mass m/z calcd for $C_{15}H_{21}INaO_3$ (M + Na) 399.0428, found 399.0426.

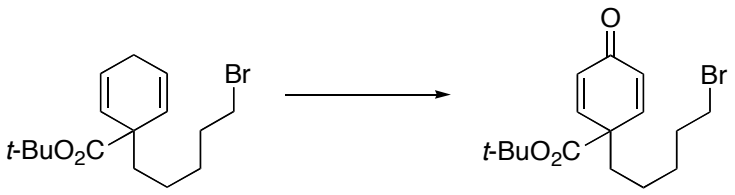
1-(5-Bromopentyl)cyclohexa-2,5-dienecarboxylic Acid *tert*-Butyl Ester (30.7).



29.1 **30.7**

The general procedure for reductive alkylation was followed, using **29.1** (1.00 g, 5.61 mmol) in dry THF (20 mL), *t*-BuOH (0.59 mL, 6.2 mmol), liquid NH_3 (60 mL), Li (82.5 mg, 11.8 mmol), and 1,5-dibromopentane (1.5 mL, 11 mmol) in THF (20 mL). Flash chromatography of the crude product over silica gel (2 x 24 cm), using first hexane and then 1:9 EtOAc-hexane, gave **30.7** (1.38 g, 75%) as an oil: FTIR (CH_2Cl_2 cast) 2934, 2861, 1722, 1368, 1251 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.11-1.23 (m, 2 H), 1.30-1.34 (m, 2 H), 1.39 (s, 9 H), 1.53-1.62 (m, 2 H), 1.74-1.84 (m, 2 H), 2.55-2.58 (m, 2 H), 3.33 (t, J = 6.8 Hz, 2 H), 5.65-5.69 (m, 2 H), 5.76-5.81 (m, 2 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 23.4 (t), 26.2 (t), 27.9 (q), 28.3 (t), 32.6 (t), 33.6 (t), 39.5 (t), 48.3 (s), 80.4 (s), 125.1 (d), 127.6 (d), 173.9 (s); exact mass m/z calcd for $C_{16}H_{25}{}^{79}BrNaO_2$ (M + Na) 351.0930, found 351.0932. The ^{13}C NMR spectrum showed two unidentified small peaks at 125.0 and 127.8.

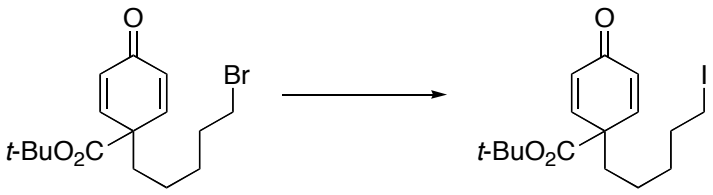
1-(5-Bromopentyl)-4-oxocyclohexa-2,5-dienecarboxylic Acid *tert*-Butyl Ester (30.8).



30.7 **30.8**

General procedure B for oxidation was followed, using 3,5-dimethylpyrazole (957 mg, 9.95 mmol), CrO_3 (995 mg, 9.95 mmol), CH_2Cl_2 (20 mL), **30.7** (327 mg, 0.99 mmol) in CH_2Cl_2 (20 mL), NaOH (5 M, 10 mL), and a reaction time of 1 h. Flash chromatography of the crude product over silica gel (1.5 x 20 cm), using first hexane and then EtOAc-hexane mixtures up to 3:7 EtOAc-hexane, gave **30.8** (256 mg, 75%) as an oil: FTIR ($CDCl_3$ cast) 2917, 2849, 1727, 1668, 1247 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.19-1.29 (m, 2 H), 1.33-1.39 (m, 1 H), 1.41-1.48 (m, 10 H), 1.77-1.84 (m, 2 H), 1.90-1.96 (m, 2 H), 3.37 (t, J = 6.6 Hz, 2 H), 6.33 (d, J = 10.3 Hz, 2 H), 7.00 (d, J = 10.3 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 23.5 (t), 27.9 (q), 28.1 (t), 32.2 (t), 33.4 (t), 38.2 (t), 53.2 (s), 83.1 (s), 129.9 (d), 148.5 (d), 169.2 (s), 185.3 (s); exact mass m/z calcd for $C_{16}H_{23}{}^{79}BrNaO_3$ (M + Na) 365.0723, found 365.0723.

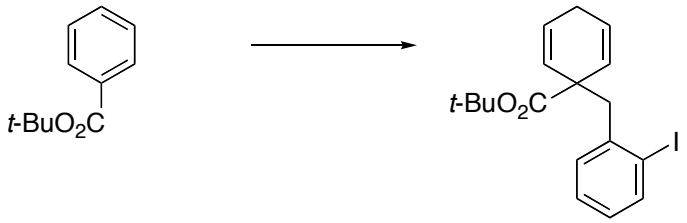
1-(5-Iodopentyl)-4-oxocyclohexa-2,5-dienecarboxylic Acid *tert*-Butyl Ester (30.9).



30.8 **30.9**

The general procedure for Finkelstein displacement was followed, using acetone (20 mL), **30.8** (658 mg, 1.92 mmol) and anhydrous NaI (1.0 g, 6.7 mmol), and a reaction time of 16 h. Flash chromatography of the crude product over silica gel (2 x 18 cm), using 10% EtOAc-hexane, gave **30.9** (539 mg, 72%) as an oil: FTIR ($CDCl_3$ cast) 2933, 2863, 1726, 1668, 1257 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.19-1.28 (m, 2 H), 1.37-1.40 (m, 2 H), 1.47 (s, 9 H), 1.74-1.82 (m, 2 H), 1.90-1.96 (m, 2 H), 3.15 (t, J = 6.9 Hz, 2 H), 6.32-6.35 (m, 2 H), 6.99-7.02 (m, 2 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 6.5 (t), 23.3 (t), 27.9 (q), 30.4 (t), 32.9 (t), 38.2 (t), 53.2 (s), 83.1 (s), 129.9 (d), 148.6 (d), 169.1 (s), 185.3 (s); exact mass m/z calcd for $C_{16}H_{23}INaO_3$ (M + Na) 413.0584, found 413.0585.

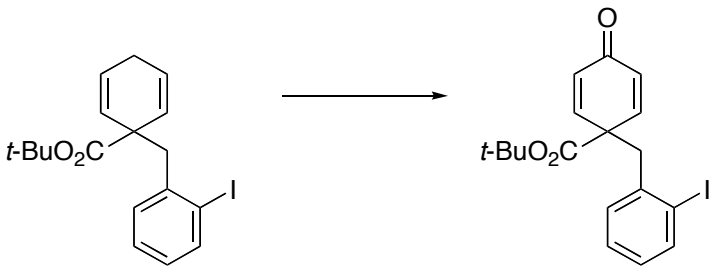
1-(2-Iodobenzyl)cyclohexa-2,5-dienecarboxylic Acid *tert*-Butyl Ester (30.10).



29.1 **30.10**

The general procedure for reductive alkylation was followed, using **29.1** (1.52 g, 8.53 mmol) in dry THF (20 mL), *t*-BuOH (0.89 mL, 9.40 mmol), liquid NH_3 (60 mL), Li (0.12 g, 17 mmol), and *o*-iodobenzyl bromide (5.05 g, 17.0 mmol) in THF (20 mL). Flash chromatography of the crude product over silica gel (4 x 30 cm), using first hexane and then 1:9 EtOAc-hexane, gave **30.10** (2.71 g, 80%) as an oil: FTIR (microscope, cast) 2977, 2930, 1723, 1562, 1471, 1247 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.49 (s, 9 H), 2.18-2.25 (m, 1 H), 2.44-2.51 (m, 1 H), 3.24 (s, 2 H), 5.76-5.79 (m, 2 H), 5.91-5.94 (m, 2 H), 6.83-6.87 (m, 1 H), 7.16-7.23 (m, 2 H), 7.80 (dd, J = 7.9, 1.0 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) (the spectrum shows small impurities) δ 25.8 (t), 27.9 (q), 48.5 (t), 50.2 (s), 81.0 (s), 103.6 (s), 126.0 (d), 126.8 (d), 127.3 (d), 127.9 (d), 130.7 (d), 139.3 (s), 140.2 (s), 173.3 (s); exact mass m/z calcd for $C_{18}H_{21}INaO_2$ (M + Na) 419.0479, found 419.0479.

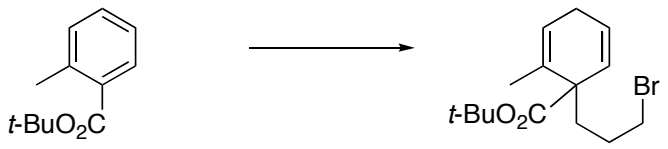
1-(2-Iodobenzyl)-4-oxocyclohexa-2,5-dienecarboxylic Acid *tert*-Butyl Ester (30.11).



30.10 **30.11**

General procedure A for oxidation was followed, using CrO_3 (705 mg, 7.05 mmol), Ac_2O (2.0 mL), AcOH (3.0 mL), PhH (10 mL) and **30.10** (558 mg, 1.41 mmol) in PhH (10 mL), and a reaction time of 4 h. Flash chromatography of the crude product over silica gel (2 x 16 cm), using first hexane and then EtOAc-hexane mixtures up to 3:7 EtOAc-hexane, gave **30.11** (406 mg, 70%) as an oil: FTIR (CH_2Cl_2 cast) 2978, 1727, 1668, 1629, 1248 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.48 (s, 9 H), 3.52 (s, 2 H), 6.23 (d, J = 10.3 Hz, 2 H), 6.91 (ddd, J = 9.1, 7.0, 2.0 Hz, 1 H), 7.13-7.20 (m, 4 H), 7.79 (dd, J = 7.9, 1.0 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 27.9 (q), 47.6 (t), 54.7 (s), 83.6 (s), 102.5 (s), 127.8 (d), 129.1 (d), 130.0 (d), 130.6 (d), 137.6 (s), 139.9 (d), 147.3 (s), 168.5 (s), 185.0 (s); exact mass *m*/*z* calcd for $C_{18}H_{19}INaO_3$ (M + Na) 433.0271, found 403.0270.

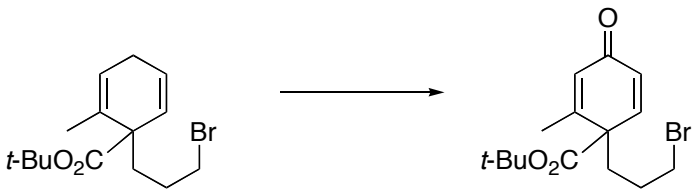
1-(3-Bromopropyl)-2-methylcyclohexa-2,5-dienecarboxylic Acid *tert*-Butyl Ester (30.13).



30.12 **30.13**

The general procedure for reductive alkylation was followed, using **30.12** (1.75 g, 9.11 mmol) in dry THF (20 mL), *t*-BuOH (0.96 mL, 10 mmol), liquid NH_3 (80 mL), Li (0.13 g, 19 mmol), and 1,3-dibromopropane (2.31 mL, 22.8 mmol) in THF (15 mL). Flash chromatography of the crude product over silica gel (4 x 38 cm), using first hexane and then 1:9 EtOAc-hexane, gave **30.13** (2.29 g, 80%) as an oil: FTIR ($CHCl_3$ cast) 2976, 2933, 1723, 1688, 1249 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.43 (s, 9 H), 1.50-1.58 (m, 1 H), 1.64-1.69 (m, 3 H), 1.70-1.76 (m, 2 H), 1.96-2.40 (m, 1 H), 2.56-2.75 (m, 2 H), 3.37-3.43 (m, 2 H), 5.42 (d, J = 9.7 Hz, 1 H), 5.61-5.67 (m, 1 H), 5.85-5.93 (m, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 19.5 (q), 26.9 (t), 27.9 (q), 28.1 (t), 33.1 (t), 34.1 (t), 80.6 (s), 123.2 (d), 126.2 (d), 127.7 (d), 129.9 (s), 130.0 (s), 131.0 (s); exact mass *m*/*z* calcd for $C_{15}H_{23}{}^{79}BrNaO_2$ (M + Na) 337.0774, found 337.0778.

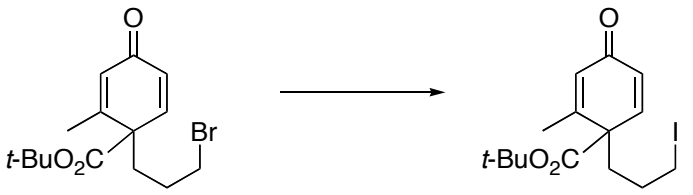
1-(3-Bromopropyl)-2-methyl-4-oxocyclohexa-2,5-dienecarboxylic Acid *tert*-Butyl Ester (30.14).



30.13 **30.14**

General procedure A for oxidation was followed, using CrO_3 (1.69 g, 16.9 mmol), Ac_2O (3.0 mL), AcOH (5.8 mL), PhH (20 mL) and **30.13** (1.06 g, 3.38 mmol) in PhH (20 mL), and a reaction time of 1 h. Flash chromatography of the crude product over silica gel (2.5 x 23 cm), using first hexane and then EtOAc-hexane mixtures up to 3:7 EtOAc-hexane, gave **30.14** (0.778 g, 70%) as a white solid: mp 118-120 °C; FTIR (CH_2Cl_2 cast) 2978, 1730, 1668, 1633, 1247 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.40 (s, 9 H), 1.44-1.49 (m, 1 H), 1.53-1.64 (m, 1 H), 1.97 (s, 3 H), 2.05-2.13 (m, 1 H), 2.24-2.31 (m, 1 H), 3.32-3.38 (m, 2 H), 6.25 (s, 1 H), 6.37 (dd, *J* = 10.0, 1.8 Hz, 1 H), 6.71 (d, *J* = 10.0 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 20.1 (q), 26.8 (t), 27.7 (q), 32.7 (t), 32.9 (t), 56.4 (s), 83.0 (s), 130.1 (d), 130.5 (d), 147.9 (d), 156.3 (s), 168.5 (s), 186.0 (s); exact mass *m*/*z* calcd for $C_{15}H_{21}{}^{79}BrNaO_3$ (M + Na) 351.0566, found 351.0569.

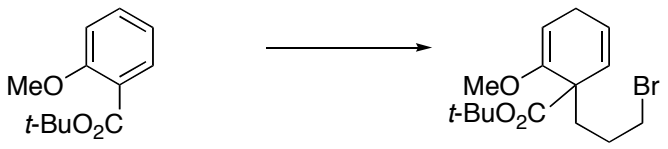
1-(3-Iodopropyl)-2-methyl-4-oxocyclohexa-2,5-dienecarboxylic Acid *tert*-Butyl Ester (30.15).



30.14 **30.15**

The general procedure for Finkelstein displacement was followed, using acetone (15 mL), **30.14** (539 mg, 1.64 mmol) and anhydrous NaI (861 mg, 5.74 mmol), and a reaction time of 17 h. Flash chromatography of the crude product over silica gel (2 x 18 cm), using 10% EtOAc-hexane, gave **30.15** (462 mg, 75%) as a pale yellow oil: FTIR ($CDCl_3$ cast) 2977, 2917, 1730, 1667, 1244 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.43 (s, 9 H), 1.46-1.62 (m, 2 H), 1.99 (s, 3 H), 2.01-2.12 (m, 1 H), 2.19-2.31 (m, 1 H), 3.10-3.16 (m, 2 H), 6.24-6.27 (m, 1 H), 6.37 (dd, J = 10.0, 1.7 Hz, 1 H), 6.72 (d, J = 9.9 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 5.6 (t), 20.0 (q), 27.3 (t), 27.5 (q), 34.7 (t), 56.1 (s), 82.7 (s), 129.9 (d), 130.3 (d), 147.9 (d), 156.2 (s), 168.3 (s), 185.7 (s); exact mass m/z calcd for $C_{15}H_{21}INaO_3$ (M + Na) 399.0428, found 399.0431.

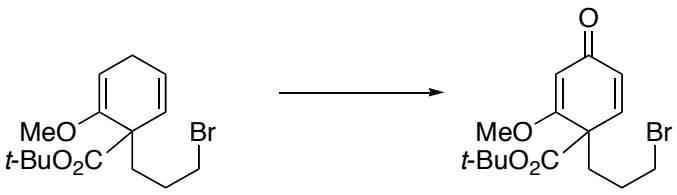
1-(3-Bromopropyl)-2-methoxycyclohexa-2,5-dienecarboxylic Acid *tert*-Butyl Ester (30.17).



30.16 **30.17**

The general procedure for reductive alkylation was followed, using **30.16** (427 mg, 2.05 mmol) in dry THF (15 mL), *t*-BuOH (0.22 mL, 2.26 mmol), liquid NH_3 (50 mL), Li (30.2 mg, 4.31 mmol), and 1,3-dibromopropane (0.52 mL, 5.1 mmol) in THF (15 mL). Flash chromatography of the crude product over silica gel (3 x 21 cm), using first hexane and then 1:9 EtOAc-hexane, gave **30.17** (584 mg, 86%) as an oil: FTIR ($CDCl_3$, cast) 2926, 2935, 1730, 1687, 1649, 1456, 1209 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.42 (s, 9 H), 1.70-1.78 (m, 3 H), 2.07-2.13 (m, 1 H), 2.80-2.86 (m, 2 H), 3.35-3.39 (m, 2 H), 3.55 (s, 3 H), 4.82-4.84 (m, 1 H), 5.37-5.41 (m, 1 H), 5.86-5.90 (m, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 26.5 (t), 27.9 (q), 28.5 (t), 32.9 (t), 34.0 (t), 52.2 (s), 54.2 (q), 80.6 (s), 93.6 (d), 126.8 (d), 127.2 (d), 152.9 (s), 172.4 (s); exact mass *m*/*z* calcd for $C_{15}H_{23}{}^{79}BrNaO_3$ (M + Na) 353.0723, found 353.0724.

1-(3-Bromopropyl)-2-methoxy-4-oxocyclohexa-2,5-dienecarboxylic Acid *tert*-Butyl Ester (30.18).



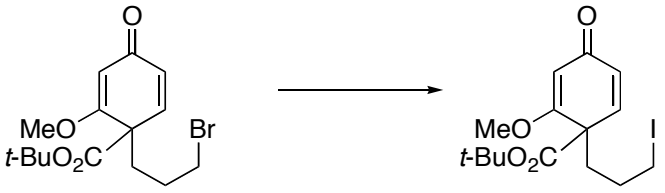
30.17 **30.18**

General procedure A for oxidation was followed, using CrO_3 (1.51 g, 15.1 mmol), Ac_2O (2.6 mL), AcOH (5.2 mL), PhH (15 mL), **30.17** (1.00 g, 3.02 mmol) in PhH (20 mL), and a reaction time of 5 h. Flash chromatography of the crude product over silica gel (2 x 18 cm), using first hexane and then EtOAc-hexane mixtures up to 3:7 EtOAc-hexane, gave **30.18** (646 mg, 62%) as an oil: FTIR ($CDCl_3$, cast) 2977, 2940, 1737, 1660, 1599, 1249 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.39 (s, 9 H), 1.42-1.59 (m, 1 H), 1.60-1.68 (m, 1 H), 2.05-2.12 (m, 1 H), 2.29-2.37 (m, 1 H), 3.33 (t, *J* = 6.6 Hz, 2 H), 3.76 (s, 3 H), 5.68 (d, *J* = 1.4 Hz, 1 H), 6.31 (dd, *J* = 9.9, 1.4 Hz, 1 H), 6.47 (d, *J* = 9.9 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 27.0 (t), 27.6 (q), 32.6 (t), 32.7 (t), 55.7 (s), 55.8 (q), 82.8 (s), 104.2 (d), 130.3 (d), 143.0 (d), 167.5 (s), 173.2 (s), 187.6 (s); exact mass *m*/*z* calcd for $C_{15}H_{21}{}^{79}BrNaO_4$ (M + Na) 367.0515, found 367.0513.

The oxidation was also done using PDC-*t*-BuOOH:[49] Celite (8.0 g) was added to a stirred solution of **30.17** (1.0 g, 3.02 mmol) in PhH (40 mL), followed by PDC (4.55 g, 12.1 mmol) and then *t*-BuOOH (70%, 1.55 mL, 12.1 mmol) was

added dropwise. Stirring was continued for 4 h after the end of the addition, and the mixture was then filtered through a pad of Celite (4 x 6 cm). Evaporation of the filtrate and flash chromatography of the residue over silica gel (2 x 17 cm), using EtOAc-hexane mixtures from 1:9 to 3:7, gave **30.18** (771 mg, 74 %) as an oil identical with material made using CrO_3.

1-(3-Iodopropyl)-2-methoxy-4-oxocyclohexa-2,5-dienecarboxylic Acid *tert*-Butyl Ester (30.19).

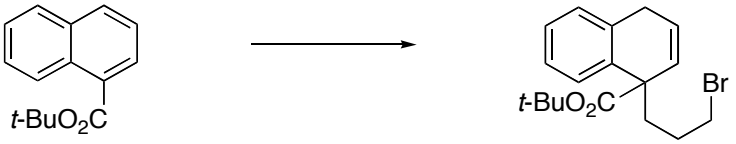


30.18 **30.19**

The general procedure for Finkelstein displacement was followed, using acetone (10 mL), **30.18** (181 mg, 0.52 mmol), anhydrous NaI (275 mg, 1.83 mmol), and a reaction time of 16 h. Flash chromatography of the crude product over silica gel (1.5 x 15 cm), using 10% EtOAc-hexane, gave **30.19** (185 mg, 90%) as an oil: FTIR (CH_2Cl_2, cast) 2976, 2937, 1736, 1660, 1598, 1222 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.34 (s, 9 H), 1.40-1.60 (m, 2 H), 1.97-2.04 (m, 1 H), 2.22-2.29 (m, 1 H), 3.07 (t, J = 6.8 Hz, 2 H), 3.72 (s, 3 H), 5.64 (d, J = 1.3 Hz, 1 H), 6.23 (dd, J = 9.9, 1.5 Hz, 1 H), 6.44 (d, J = 9.9 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 5.3 (t), 27.6 (q), 27.7 (t), 34.8 (t), 55.6 (s), 55.9 (q), 82.8 (s), 104.1

(d), 130.2 (d), 143.0 (d), 167.4 (s), 173.3 (s), 187.6 (s); exact mass *m*/*z* calcd for $C_{15}H_{21}INaO_4$ (M + Na) 415.0377, found 415.0378.

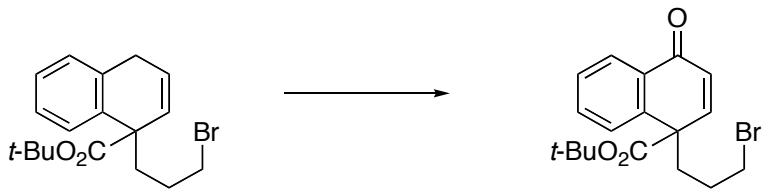
1-(3-Bromopropyl)-1,4-dihydronaphthalene-1-carboxylic Acid *tert*-Butyl Ester (31.2).



31.1 **31.2**

The general procedure for reductive alkylation was followed, using **31.1** (1.1 g, 4.6 mmol) in dry THF (20 mL), *t*-BuOH (0.49 mL, 5.1 mmol), liquid NH_3 (60 mL), Li (70 mg, 9.7 mmol), and 1,3-dibromopropane (1.18 mL, 11.6 mmol) in THF (20 mL). Flash chromatography of the crude product over silica gel (2.5 x 25 cm), using first hexane and then 1:9 EtOAc-hexane, gave **31.2** (1.3 g, 80%) as an oil: FTIR (CH_2Cl_2 cast) 2977, 2932, 1726, 1664, 1599, 1456, 1251 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.36 (s, 9 H), 1.37-1.42 (m, 1 H), 1.58-1.81 (m, 1 H), 1.99-2.09 (m, 1 H), 2.21-2.31 (m, 1 H), 3.30 (t, *J* = 6.8 Hz, 2 H), 3.40-3.43 (m, 2 H), 5.66-5.70 (m, 1 H), 6.12-7.13 (m, 1 H), 7.15-7.18 (m, 3 H), 7.21-7.29 (m, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 27.8 (q), 28.1 (t), 29.8 (t), 33.9 (t), 37.7 (t), 51.4 (s), 80.9 (s), 126.1 (d), 126.3 (d), 126.4 (d), 126.7 (d), 128.1 (d), 128.5 (d), 134.1 (s), 135.2 (s), 173.5 (s); exact mass *m*/*z* calcd for $C_{18}H_{23}{}^{79}BrNaO_2$ (M + Na) 373.0774, found 373.0770.

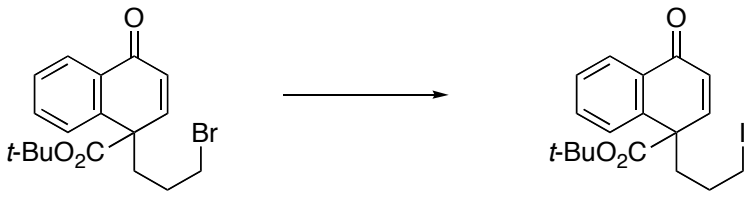
1-(3-Bromopropyl)-4-oxo-1,4-dihydronaphthalene-1-carboxylic Acid *tert*-Butyl Ester (31.3).



31.2 **31.3**

General procedure A for oxidation was followed, using CrO_3 (1.57 g, 15.7 mmol), Ac_2O (3.0 mL), AcOH (6.0 mL), PhH (10 mL) and **31.2** (1.1 mg, 3.1 mmol) in PhH (20 mL), and a reaction time of 2 h. Flash chromatography of the crude product over silica gel (2.5 x 27 cm), using first hexane and then EtOAc-hexane mixtures up to 3:7 EtOAc-hexane, gave **31.3** (0.94 g, 82%) as an oil: FTIR (CH_2Cl_2 cast) 2978, 2932, 1730, 1667, 1456, 1247 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.22-1.26 (m, 1 H), 1.29 (s, 9 H), 1.53-1.61 (m, 1 H), 2.27 (ddd, *J* = 13.7, 11.9, 4.7 Hz, 1 H), 2.39 (ddd, *J* = 13.7, 12.1, 4.7 Hz, 1 H), 2.49-3.24 (m, 2 H), 6.55 (d, *J* = 10.2 Hz, 1 H), 6.90 (d, *J* = 10.2 Hz, 1 H), 7.42 (ddd, *J* = 8.0, 7.0, 1.5 Hz, 1 H), 7.51-7.57 (m, 2 H), 8.16 (dd, *J* = 7.8, 1.4 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 27.2 (t), 27.6 (q), 33.0 (t), 37.0 (t), 53.1 (s), 82.7 (s), 126.4 (d), 126.8 (d), 127.9 (d), 129.9 (d), 131.8 (s), 132.8 (d), 141.5 (s), 148.0 (d), 170.0 (s), 184.3 (s); exact mass *m*/*z* calcd for $C_{18}H_{21}{}^{79}BrNaO_3$ (M + Na) 387.0566, found 387.0564.

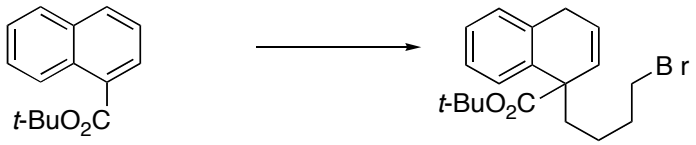
1-(3-Iodopropyl)-4-oxo-1,4-dihydronaphthalene-1-carboxylic Acid *tert*-Butyl Ester (31.4).



31.3 **31.4**

The general procedure for Finkelstein displacement was followed, using acetone (15 mL), **31.3** (421 mg, 1.15 mmol) and anhydrous NaI (605 mg, 4.04 mmol), and a reaction time of 16 h. Flash chromatography of the crude product over silica gel (2 x 20 cm), using 10% EtOAc-hexane, gave **31.4** (418 mg, 88%) as an oil: FTIR (CH_2Cl_2 cast) 2978, 2931, 1729, 1666, 1600, 1244 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.22-1.27 (m, 1 H), 1.32 (s, 9 H), 1.38-1.39 (m, 1 H), 2.26 (ddd, J = 13.8, 11.9, 4.4 Hz, 1 H), 2.46 (ddd, J = 16.7, 12.0, 4.7 Hz, 1 H), 3.03 (t, J = 6.8 Hz, 2 H), 6.60 (d, J = 10.2 Hz, 1 H), 6.91 (d, J = 10.3 Hz, 1 H), 7.46-7.49 (m, 1 H), 7.56-7.60 (m, 2 H), 8.21 (ddd, J = 7.9, 1.5, 0.6 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 5.6 (t), 27.4 (q), 27.6 (t), 39.1 (t), 52.9 (s), 82.6 (s), 126.3 (d), 126.8 (d), 127.8 (d), 129.8 (d), 131.7 (s), 132.7 (d), 141.4 (s), 147.9 (d), 169.9 (s), 184.2 (s); exact mass m/z calcd for $C_{15}H_{21}INaO_3$ (M + Na) 435.0428, found 435.0425.

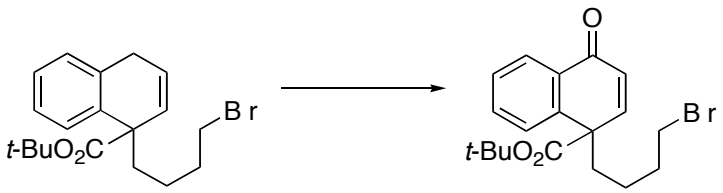
1-(4-Bromobutyl)-1,4-dihydronaphthalene-1-carboxylic Acid *tert*-Butyl Ester (31.5).



31.1 **31.5**

The general procedure for reductive alkylation was followed, using **31.1** (1.79 g, 7.85 mmol) in dry THF (20 mL), *t*-BuOH (0.83 mL, 8.7 mmol), liquid NH_3 (70 mL), Li (0.12 g, 17 mmol), and 1,4-dibromobutane (2.4 mL, 20 mmol) in THF (20 mL). Flash chromatography of the crude product over silica gel (4 x 38 cm), using first hexane and then 1:9 EtOAc-hexane, gave **31.5** (2.56 g, 90%) as an oil: FTIR (CH_2Cl_2, cast) 2977, 2933, 1722, 1454, 1367, 1246 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.97-1.02 (m, 1 H), 1.31-1.33 (m, 1 H), 1.36 (s, 9 H), 1.75-1.83 (m, 2 H), 1.90-1.96 (m, 1 H), 2.09-2.16 (m, 1 H), 3.28-3.33 (m, 2 H), 3.40-3.44 (m, 2 H), 5.70 (ddd, J = 10.1, 2.2, 2.2 Hz, 1 H), 6.10 (ddd, J = 10.1, 3.7, 3.7 Hz, 1 H), 7.14-7.17 (m, 3 H), 7.20-7.32 (m, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 23.0 (t), 27.7 (q), 29.7 (t), 33.0 (t), 33.3 (t), 38.1 (t), 51.6 (s), 80.7 (s), 125.7 (d), 126.1 (d), 126.3 (d), 126.4 (d), 128.2 (d), 128.4 (d), 134.1 (s), 135.5 (s), 173.7 (s); exact mass *m*/*z* calcd for $C_{19}H_{25}{}^{79}BrNaO_2$ (M + Na) 387.0930, found 387.0930.

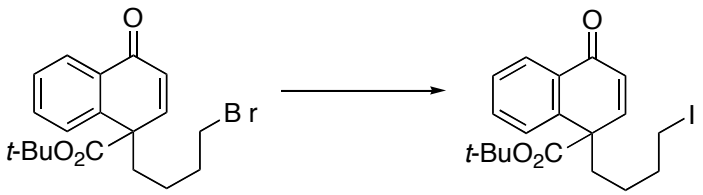
1-(4-Bromobutyl)-4-oxo-1,4-dihydronaphthalene-1-carboxylic Acid *tert*-Butyl Ester (31.6).



31.5 **31.6**

General procedure A for oxidation was followed, using CrO_3 (3.48 g, 34.8 mmol), Ac_2O (6.1 mL), AcOH (10 mL), PhH (10 mL), **31.5** (2.54 g, 6.96 mmol) in PhH (30 mL), and a reaction time of 3 h. Flash chromatography of the crude product over silica gel (4 x 36 cm), using first hexane and then EtOAc-hexane mixtures up to 3:7 EtOAc-hexane, gave **31.6** (1.98 mg, 75%) as an oil: FTIR (CH_2Cl_2, cast) 2977, 2933, 1729, 1667, 1456, 1244 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.82-0.88 (m, 1 H), 1.22-1.25 (m, 1 H), 1.30 (s, 9 H), 1.68-1.70 (m, 2 H), 2.15 (ddd, *J* = 13.6, 12.2, 4.6 Hz, 1 H), 2.30 (ddd, *J* = 13.6, 12.3, 4.9 Hz, 1 H), 3.20-3.28 (m, 2 H), 6.56 (d, *J* = 10.3 Hz, 1 H), 6.92 (d, *J* = 10.3 Hz, 1 H), 7.41-7.46 (m, 1 H), 7.51-7.60 (m, 2 H), 8.16 (ddd, *J* = 7.9, 1.5, 0.6 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 22.6 (t), 27.7 (q), 32.6 (t), 32.8 (t), 37.7 (t), 53.5 (s), 82.5 (s), 126.2 (d), 126.7 (d), 127.7 (d), 129.6 (d), 131.8 (s), 132.6 (d), 141.7 (s), 148.2 (d), 170.2 (s), 184.4 (s); exact mass *m*/*z* calcd for $C_{19}H_{23}{}^{79}BrNaO_3$ (M + Na) 401.0723, found 401.0721.

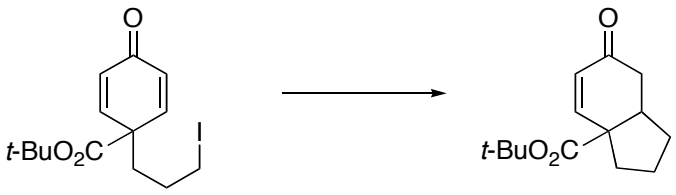
1-(4-Iodobutyl)-4-oxo-1,4-dihydronaphthalene-1-carboxylic Acid *tert*-Butyl Ester (31.7).



31.6 **31.7**

The general procedure for Finkelstein displacement was followed, using acetone (25 mL), **31.6** (1.81 g, 4.75 mmol), anhydrous NaI (2.49 g, 16.6 mmol), and a reaction time of 17 h. Flash chromatography of the crude product over silica gel (2 x 20 cm), using 10% EtOAc-hexane, gave **31.7** (1.86 g, 92%) as an oil: FTIR (CH_2Cl_2, cast) 2925, 2853, 1727, 1665, 1600, 1242 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.81-0.83 (m, 1 H), 1.15-1.20 (m, 1 H), 1.31 (s, 9 H), 1.70-1.75 (m, 2 H), 2.14-2.18 (m, 1 H), 2.25-2.30 (m, 1 H), 3.00-3.05 (m, 2 H), 6.57 (d, J = 11.3 Hz, 1 H), 6.94 (d, J = 11.3 Hz, 1 H), 7.42-7.47 (m, 1 H), 7.52-7.60 (m, 2 H), 8.19 (d, J = 7.8 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 5.6 (t), 24.7 (t), 27.5 (q), 33.2 (t), 37.3 (t), 53.4 (s), 82.4 (s), 126.3 (d), 126.7 (d), 127.7 (d), 129.6 (d), 131.8 (s), 132.7 (d), 141.7 (s), 148.2 (d), 170.2 (s), 184.4 (s); exact mass *m*/*z* calcd for $C_{19}H_{23}INaO_3$ (M + Na) 449.0584, found 449.0584.

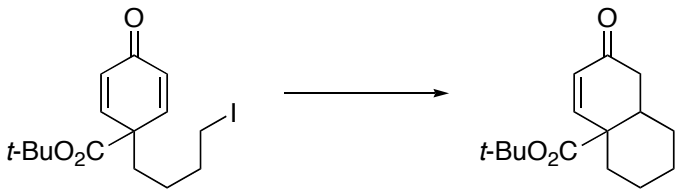
6-Oxo-1,2,3,6,7,7a-hexahydroindene-3a-carboxylic Acid *tert*-Butyl Ester (32.1).



30.3 **32.1**

The general procedure for radical cyclization was followed, using Bu_3SnH (0.17 mL, 0.65 mmol) and AIBN (4.47 mg, 0.027 mmol) in PhH (5 mL), and **30.3** (197 mg, 0.544 mmol) in PhH (15 mL). Heating was continued for 20 h after the addition. Flash chromatography of the crude product over KF-flash chromatography silica gel (10%$^{w}/_{w}$ KF) (1.5 x 15 cm), using 1:9 to 3:7 EtOAc-hexane mixtures, gave **32.1** (123 mg, 96%) as an oil: FTIR (CH_2Cl_2 cast) 2966, 2875, 1722, 1680, 1266 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.36-1.40 (m, 1 H), 1.51 (s, 9 H), 1.53-1.69 (m, 2 H), 1.84-1.98 (m, 2 H), 2.15-2.22 (m, 1 H), 2.38 (dd, *J* = 16.9, 3.2 Hz, 1 H), 2.69 (dd, *J* = 16.8, 5.6 Hz, 1 H), 2.82-2.84 (m, 2 H), 5.95 (d, *J* = 10.2 Hz, 1 H), 6.60 (dd, *J* = 10.2, 1.8 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 23.1 (t), 27.8 (q), 30.5 (t), 38.1 (t), 38.7 (t), 41.1 (d), 54.3 (s), 81.5 (s), 128.5 (d), 149.8 (d), 172.4 (s), 198.4 (s); exact mass *m*/*z* calcd for $C_{14}H_{20}O_3$ 236.1413, found 236.1414.

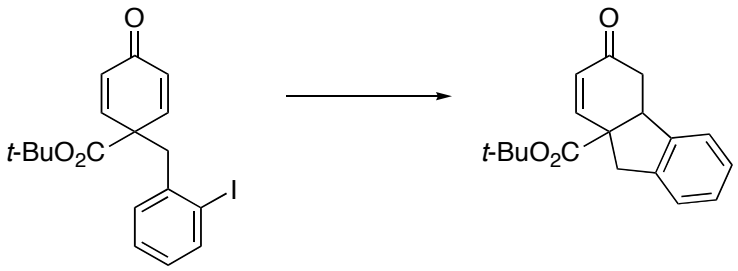
7-Oxo-1,3,4,7,8,8a-hexahydro-2*H*-naphthalene-4a-carboxylic Acid *tert*-Butyl Ester (32.2).



30.6 **32.2**

The general procedure for radical cyclization was followed, using Bu_3SnH (0.18 mL, 0.69 mmol) and AIBN (4.7 mg, 0.03 mmol) in PhH (5 mL), and **30.6** (215 mg, 0.572 mmol) in PhH (15 mL). Heating was continued for 12 h after the addition. Flash chromatography of the crude product over KF-flash chromatography silica gel (10%$^{w}/_{w}$ KF), (1.5 x 15 cm), using 1:9 to 3:7 EtOAc-hexane mixtures, gave **32.2** (117 mg, 82%) as an oil: FTIR (CH_2Cl_2 cast) 2931, 2858, 1720, 1678, 1273, 756 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.31-1.41 (m, 3 H), 1.43 (s, 9 H), 1.56-1.64 (m, 3 H), 1.81-1.85 (m, 2 H), 2.24-2.30 (m, 1 H), 2.54-2.62 (m, 2 H), 5.97 (d, J = 10.2 Hz, 1 H), 6.61 (dd, J = 10.1, 1.3 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.9 (t), 23.6 (t), 27.7 (t), 27.8 (q), 34.5 (t), 36.2 (d), 41.6 (t), 49.3 (s), 81.5 (s), 129.0 (d), 151.3 (d), 172.9 (s), 199.0 (s); exact mass m/z calcd for $C_{15}H_{22}NaO_3$ (M + Na) 273.1461, found 273.1461.

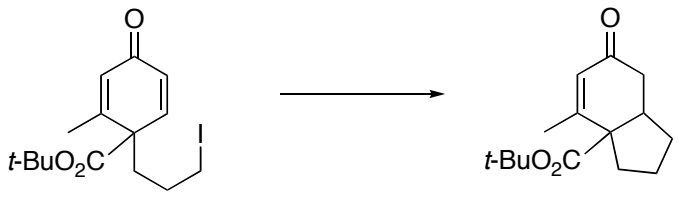
6-Oxo-4b,5,6,9-tetrahydrofluorene-8a-carboxylic Acid *tert*-Butyl Ester (32.3).



30.11 **32.3**

The general procedure for radical cyclization was followed, using Bu_3SnH (0.12 mL, 0.44 mmol) and AIBN (3.0 mg, 0.02 mmol) in PhH (5 mL), and **30.11** (150 mg, 0.37 mmol) in PhH (10 mL). Heating was continued for 10 h after the addition. Flash chromatography of the crude product over KF-flash chromatography silica gel (10%$^{w}/_{w}$ KF) (1.5 x 15 cm), using first hexane and then EtOAc-hexane mixtures up to 3:7 EtOAc-hexane, gave **32.3** (70.7 mg, 68%) as an oil: FTIR (CH_2Cl_2 cast) 2977, 1724, 1689, 1459, 1240 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.52 (s, 9 H), 1.60 (distorted t, *J* = 7.0 Hz, 1 H), 3.01-3.11 (m, 2 H), 3.59 (d, *J* = 15.8 Hz, 1 H), 4.08-4.12 (m, 1 H), 5.94 (d, *J* = 10.2 Hz, 1 H), 6.62 (dd, *J* = 10.2, 1.5 Hz, 1 H), 7.17-7.27 (m, 4 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 27.9 (q), 36.9 (t), 43.2 (t), 45.3 (d), 56.0 (s), 82.2 (s), 123.1 (d), 124.3 (d), 127.1 (d), 127.5 (d), 130.8 (d), 138.5 (s), 142.2 (s), 148.2 (d), 171.4 (s), 196.6 (s); exact mass *m*/*z* calcd for $C_{18}H_{22}NaO_3$ (M + Na) 307.1305, found 307.1303.

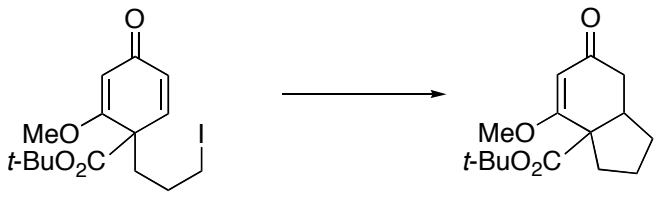
4-Methyl-6-oxo-1,2,3,6,7,7a-hexahydroindene-3a-carboxylic Acid *tert*-Butyl Ester (32.4).



30.15 **32.4**

The general procedure for radical cyclization was followed, using Bu_3SnH (0.31 mL, 1.17 mmol) and AIBN (8.03 mg, 0.05 mmol) in PhH (5 mL), and **30.15** (367 mg, 0.98 mmol) in PhH (10 mL). Heating was continued for 12 h after the addition. Flash chromatography of the crude product over KF-flash chromatography silica gel (10%$^{w}/_{w}$ KF) (1.5 x 20 cm), using 1:9 to 3:7 EtOAc-hexane mixtures, gave **32.4** (197 mg, 81%) as an oil: FTIR (CH_2Cl_2 cast) 2975, 2875, 1724, 1674, 1250 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.33-1.39 (m, 1 H), 1.44 (s, 9 H), 1.52-1.64 (m, 1 H), 1.65-1.74 (m, 1 H), 1.88-1.92 (m, 5 H), 2.35-2.39 (m, 2 H), 2.61-2.67 (m, 2 H), 5.91 (s, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 20.5 (q), 23.0 (t), 27.8 (q), 30.8 (t), 34.5 (t), 38.6 (t), 43.1 (d), 57.9 (s), 81.4 (s), 127.7 (d), 158.7 (s), 172.6 (s), 198.2 (s); exact mass *m*/*z* calcd for $C_{15}H_{22}NaO_3$ (M + Na) 273.1461, found 273.1463.

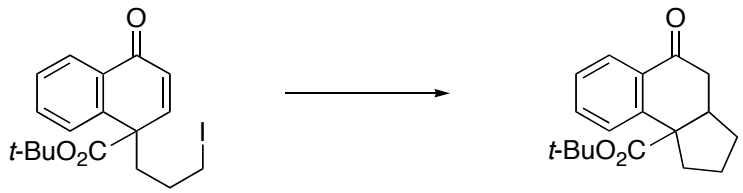
4-Methoxy-6-oxo-1,2,3,6,7,7a-hexahydroindene-3a-carboxylic Acid *tert*-Butyl Ester (32.5).



30.19 **32.5**

The general procedure for radical cyclization was followed, using Bu_3SnH (0.20 mL, 0.61 mmol) and AIBN (10.1 mg, 0.061 mmol) in PhH (5 mL), and **30.19** (241 mg, 0.61 mmol) in PhH (10 mL). Heating was continued for 18 h after the addition. Flash chromatography of the crude product over KF-flash chromatography silica gel (10%$^{w}/_{w}$ KF) (2 x 22 cm), using 1:9 to 3:7 EtOAc-hexane mixtures, gave **32.5** (154 mg, 94%) as an oil: FTIR ($CDCl_3$, cast) 2974, 1732, 1662, 1218 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.41 (s, 9 H), 1.60-1.75 (m, 3 H), 1.86-1.90 (m, 1 H), 2.06-2.19 (m, 1 H), 2.34-2.41 (m, 2 H), 2.59-2.67 (m, 2 H), 3.69 (s, 3 H), 5.41 (s, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 23.3 (t), 27.9 (q), 31.2 (t), 34.1 (t), 38.2 (t), 43.0 (d), 56.1 (q), 57.8 (s), 81.5 (s), 103.0 (d), 171.8 (s), 175.8 (s), 198.3 (s); exact mass *m*/*z* calcd for $C_{14}H_{22}NaO_4$ (M + Na) 289.1410, found 289.1411.

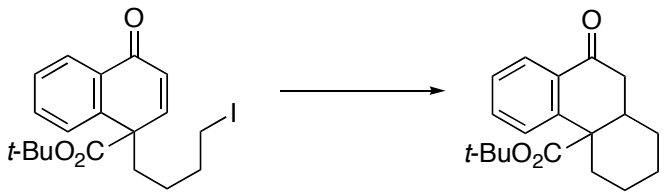
5-Oxo-1,2,3,3a,4,5-hexahydrocyclopenta[*a*]naphthalene-9b-carboxylic Acid *tert*-Butyl Ester (32.6).



31.4 **32.6**

The general procedure for radical cyclization was followed, using Bu_3SnH (0.13 mL, 0.49 mmol) and AIBN (3.3 mg, 0.02 mmol) in PhH (5 mL), and **31.4** (167 mg, 0.41 mmol) in PhH (10 mL). Heating was continued for 12 h after the addition. Flash chromatography of the crude product over KF-flash chromatography silica gel (10%$^{w}/_{w}$ KF) (1.5 x 15 cm), using EtOAc-hexane mixtures, gave **32.6** (90.4 mg, 78%) as an oil: FTIR (CH_2Cl_2 cast) 2974, 2874, 1721, 1690, 1288 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.40 (s, 9 H), 1.43-1.45 (m, 2 H), 1.68-1.73 (m, 1 H), 1.95-2.01 (m, 1 H), 2.17-2.24 (m, 1 H), 2.52-2.66 (m, 2 H), 2.86-2.91 (m, 1 H), 3.04 (dd, *J* = 16.5, 5.5 Hz, 1 H), 7.32 (ddd, *J* = 7.8, 7.2, 1.3 Hz, 1 H), 7.40-7.42 (m, 1 H), 7.53 (ddd, *J* = 7.9, 7.2, 1.5 Hz, 1 H), 7.99 (ddd, *J* = 7.8, 1.5, 0.5 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 22.4 (t), 27.8 (q), 30.5 (t), 38.3 (t), 39.7 (t), 42.3 (d), 56.5 (s), 81.2 (s), 126.5 (d), 127.0 (d), 128.0 (d), 132.0 (s), 133.9 (d), 143.6 (s), 173.7 (s), 197.8 (s); exact mass *m*/*z* calcd for $C_{18}H_{22}NaO_3$ (M + Na) 309.1461, found 309.1464.

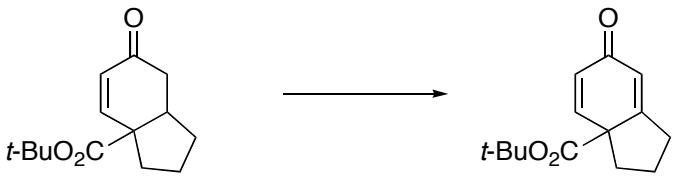
9-Oxo-1,3,4,9,10,10a-hexahydro-2*H*-phenanthrene-4a-carboxylic Acid *tert*-Butyl Ester (32.7).



31.7 **32.7**

The general procedure for radical cyclization was followed, using Bu_3SnH (0.21 mL, 0.77 mmol) and AIBN (10.6 mg, 0.06 mmol) in PhH (5 mL), and **31.7** (275 mg, 0.65 mmol) in PhH (10 mL). Heating was continued for 12 h after the addition. Flash chromatography of the crude product over KF-flash chromatography silica gel (10%$^{w}/_{w}$ KF) (1.5 x 17 cm), using EtOAc-hexane mixtures, gave **32.7** (126 mg, 65%) as an oil: FTIR (CH_2Cl_2, cast) 2934, 2862, 1721, 1692, 1599, 1246 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.24-1.34 (m, 1 H), 1.36 (s, 9 H), 1.39-1.43 (m, 2 H), 1.57-1.61 (m, 3 H), 2.01-2.04 (m, 1 H), 2.22-2.30 (m, 1 H), 2.61 (dd, *J* = 18.2, 7.9 Hz, 1 H), 2.77-2.81 (m, 2 H), 7.34 (ddd, *J* = 7.8, 7.2, 1.2 Hz, 1 H), 7.39-7.41 (m, 1 H), 7.53 (ddd, *J* = 7.9, 7.2, 1.5 Hz, 1 H), 7.81 (ddd, *J* = 7.9, 1.5, 0.5 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.8 (t), 23.1 (t), 27.8 (q), 28.5 (t), 33.0 (t), 37.5 (d), 41.7 (t), 51.4 (s), 81.3 (s), 127.0 (d), 127.1 (d), 127.6 (d), 131.9 (s), 133.7 (d), 143.4 (s), 173.6 (s), 197.8 (s); exact mass *m*/*z* calcd for $C_{19}H_{24}NaO_3$ (M + Na) 323.1618, found 323.1617.

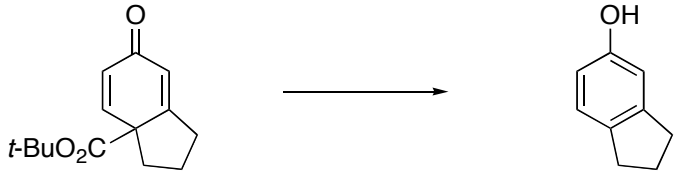
6-Oxo-1,2,3,6-tetrahydroindene-3a-carboxylic Acid *tert*-Butyl Ester (36.1).



32.1 **36.1**

The general procedure for Saegusa oxidation was followed, using 2,6-lutidine (0.16 mL, 1.4 mmol), **32.1** (94 mg, 0.39 mmol), CH_2Cl_2 (5 mL), $Me_3SiOSO_2CF_3$ (0.22 mL, 1.20 mmol), $Pd(OAc)_2$ (88.5 mg, 0.394 mmol) and MeCN (10 mL). Flash chromatography of the crude product over silica gel (1.5 x 12 cm), using 10% EtOAc-hexane, gave **36.1** (65.5 mg, 70%) as an oil: FTIR ($CDCl_3$ cast) 3012, 2979, 1727, 1666, 1641, 1243, 1146 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.37 (s, 9 H), 1.54-1.59 (m, 1 H), 1.91-1.97 (m, 2 H), 2.44-2.60 (m, 2 H), 2.71-2.83 (m, 1 H), 6.14 (s, 1 H), 6.25 (dd, J = 9.8, 1.4 Hz, 1 H), 6.95 (d, J = 9.8 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.9 (t), 27.5 (q), 29.5 (t), 34.3 (t), 59.1 (s), 82.7 (s), 123.7 (d), 130.4 (d), 145.1 (d), 166.9 (s), 168.6 (s) 186.5 (s); exact mass *m*/*z* calcd for $C_{14}H_{18}O_3$ 234.1256, found 234.1261.

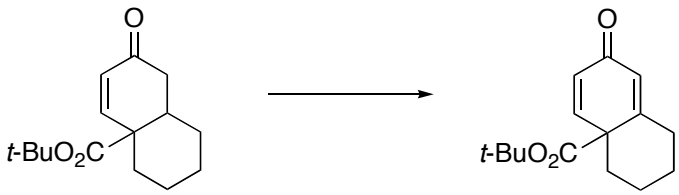
Indan-5-ol (34.3).[56]



36.1 **34.3**

General procedure A for rearomatization was followed, using $BiCl_3.H_2O$ (13.6 mg, 0.041 mmol) and **36.1** (23.6 mg, 0.102 mmol) in MeCN (5 mL) and water (0.1 mL), and a reaction time of 2 h after addition of the second portion of $BiCl_3.H_2O$. Flash chromatography of the crude product over silica gel (1 x 12 cm), using 30% EtOAc-hexane, gave **34.3** (12.3 mg, 90%) as an oil: FTIR (CH_2Cl_2 cast) 3373, 2951, 2845, 1612, 1492 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 2.06-2.12 (m, 2 H), 2.82-2.88 (m, 4 H), 4.40 (s, 1 H), 6.62 (dd, J = 8.1, 2.5 Hz, 1 H), 6.73 (s, 1 H), 7.08 (d, J = 8.0 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 25.7 (t), 31.8 (t), 32.9 (t), 111.3 (d), 112.9 (d), 124.8 (d), 136.2 (s), 145.9 (s), 154.0 (s); exact mass m/z calcd for $C_9H_{10}O$ 134.0732, found 134.0235.

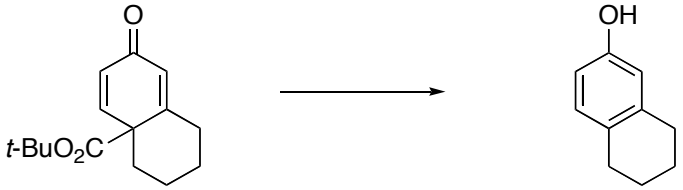
7-Oxo-1,3,4,7-tetrahydro-2*H*-naphthalene-4a-carboxylic Acid *tert*-Butyl Ester (39.1).



32.2 **39.1**

The general procedure for Saegusa oxidation was followed, using 2,6-lutidine (0.20 mL, 1.7 mmol), **32.2** (121 mg, 0.48 mmol), CH_2Cl_2 (10 mL), $Me_3SiOSO_2CF_3$ (0.26 mL, 1.45 mmol), $Pd(OAc)_2$ (108 mg, 0.48 mmol) and MeCN (10 mL). Flash chromatography of the crude product over silica gel (1.5 x 10 cm), using 70% EtOAc-hexane, gave **39.1** (84 mg, 70%) as an oil: FTIR ($CDCl_3$ cast) 2917, 2849, 1728, 1663, 1630, 1254, 1160 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.19-1.35 (m, 2 H), 1.37 (s, 9 H), 1.41-1.56 (m, 1 H), 1.74-1.79 (m, 1 H), 1.95-1.99 (m, 1 H), 2.38-2.62 (m, 3 H), 6.17 (s, 1 H), 6.27 (dd, J = 10.0, 1.7 Hz, 1 H), 6.72 (d, J = 11.0 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 22.8 (t), 27.6 (t), 27.7 (q), 34.6 (t), 37.3 (t), 54.6 (s), 82.7 (s), 125.7 (d), 129.3 (d), 148.8 (d), 162.0 (s), 168.7 (s) 186.5 (s); exact mass m/z calcd for $C_{15}H_{20}NaO_3$ (M + Na) 271.1305, found 271.1307.

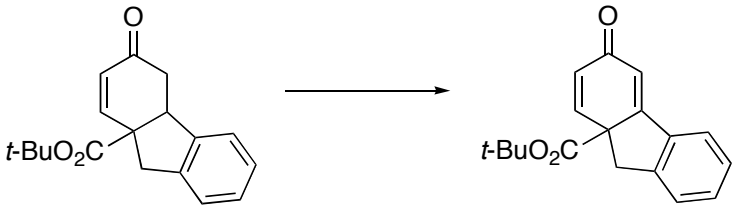
5,6,7,8-Tetrahydronaphthalen-2-ol (39.2).[57]



39.1 **39.2**

General procedure A for rearomatization was followed, using $BiCl_3.H_2O$ (17.8 mg, 53.2 mmol) and **39.1** (33 mg, 133 mmol) in MeCN (5 mL) and water (0.1 mL), and a reaction time of 10 h after addition of the second portion of $BiCl_3.H_2O$. Flash chromatography of the crude product over silica gel (1 x 15 cm), using 10% EtOAc-hexane, gave **39.2** (17.4 mg, 88%) as a white solid: mp 62-63 °C, FTIR (CH_2Cl_2 cast) 3330, 2927, 2856, 1615, 1500 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.76-1.79 (m, 4 H), 2.69-2.72 (m, 4 H), 4.25 (s, 1 H), 6.55 (s, 1 H), 6.59 (dd, J = 8.1, 2.6 Hz, 1 H), 6.93 (d, J = 8.1 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 23.1 (t), 23.4 (t), 28.5 (t), 29.5 (t), 112.7 (d), 115.2 (d), 129.4 (s), 130.1 (d), 138.5 (s), 153.1 (s); exact mass m/z calcd for $C_{10}H_{12}O$ 148.0888, found 148.0889.

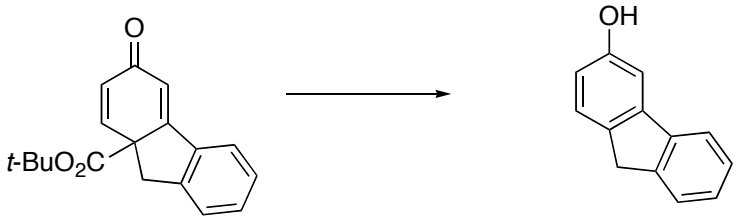
6-Oxo-6,9-dihydrofluorene-8a-carboxylic Acid *tert*-Butyl Ester (39.3).



32.3 **39.3**

The general procedure for Saegusa oxidation was followed, using 2,6-lutidine (0.49 mL, 4.2 mmol), **32.3** (340 mg, 1.20 mmol), CH_2Cl_2 (10 mL), $Me_3SiOSO_2CF_3$ (0.65 mL, 3.6 mmol), $Pd(OAc)_2$ (266 mg, 1.19 mmol) and MeCN (10 mL). Flash chromatography of the crude product over silica gel (1.5 x 15 cm), using 10% EtOAc-hexane, gave **39.3** (210 mg, 62%) as an oil: FTIR ($CHCl_3$ cast) 2981, 2917, 1728, 1652, 1465, 1240 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.24 (s, 9 H), 2.99 (d, J = 15.1 Hz, 1 H), 3.17 (d, J = 15.2 Hz, 1 H), 6.37 (dd, J = 10.3, 1.0 Hz, 1 H), 6.53 (s, 1 H), 7.03 (d, J = 9.7 Hz, 1 H), 7.27-7.29 (m, 1 H), 7.34-7.35 (m, 2 H), 7.55 (d, J = 7.5 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 27.3 (q), 39.2 (t), 51.0 (s), 83.0 (s), 120.0 (d), 122.1 (d), 125.5 (d), 127.6 (d), 131.0 (d), 131.6 (d), 137.3 (s), 143.7 (d), 145.4 (s), 163.0 (s), 168.0 (s), 186.8 (s); exact mass *m*/*z* calcd for $C_{18}H_{18}NaO_3$ (M + Na) 305.1148, found 305.1147.

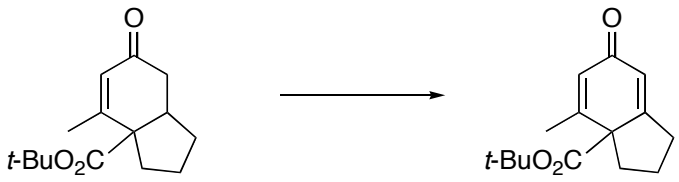
9*H*-Fluoren-3-ol (39.4).[58]



39.3 **39.4**

General procedure A for rearomatization was followed, using $BiCl_3.H_2O$ (19.4 mg, 0.06 mmol) and **39.3** (41 mg, 0.14 mmol) in MeCN (5 mL) and water (0.1 mL), and a reaction time of 3 h after addition of the second portion of $BiCl_3.H_2O$. Flash chromatography of the crude product over silica gel (1 x 15 cm), using 10% EtOAc-hexane, gave **39.4** (25 mg, 95%) as a white solid: mp 143-145 °C (lit.[27] 130-132 °C); FTIR ($CDCl_3$ cast) 3483, 1614, 1451, 1177 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 3.83 (s, 2 H), 4.73 (s, 1 H), 6.79 (dd, *J* = 8.1, 2.5 Hz, 1 H), 7.25 (d, *J* = 2.4 Hz, 1 H), 7.31 (ddd, *J* = 7.4, 7.4, 1.3 Hz, 1 H), 7.32-7.38 (m, 2 H), 7.52-7.55 (m, 1 H), 7.73 (d, *J* = 7.4 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 36.1 (t), 106.6 (d), 114.0 (d), 119.8 (d), 124.9 (d), 125.6 (d), 126.6 (d), 126.8 (d), 135.4 (s), 141.3 (s), 143.2 (s), 144.2 (s), 154.6 (s); exact mass *m*/*z* calcd for $C_{13}H_{10}O$ 182.0732, found 182.0735.

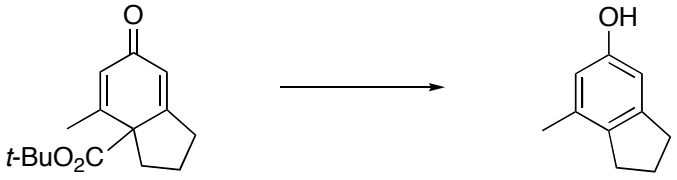
4-Methyl-6-oxo-1,2,3,6-tetrahydroindene-3a-carboxylic Acid *tert*-Butyl Ester (39.5).



32.4 **39.5**

The general procedure for Saegusa oxidation was followed, using 2,6-lutidine (0.27 mL, 2.28 mmol), **32.4** (163 mg, 0.65 mmol), CH_2Cl_2 (10 mL), $Me_3SiOSO_2CF_3$ (0.35 mL, 1.95 mmol), $Pd(OAc)_2$ (145 mg, 0.65 mmol) and MeCN (10 mL). Flash chromatography of the crude product over silica gel (1.5 x 15 cm), using 70% EtOAc-hexane, gave **39.5** (100 mg, 62%) as an oil: FTIR (CH_2Cl_2 cast) 2977, 1726, 1671, 1640, 1236 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.36 (s, 9 H), 1.44-1.56 (m, 1 H), 1.89-1.92 (m, 1 H), 1.93-1.99 (m, 4 H), 2.51-2.54 (m, 1 H), 2.67-2.72 (m, 2 H), 6.07-6.09 (m, 1 H), 6.11-6.13 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 20.0 (q), 21.1 (t), 27.4 (q), 29.2 (t), 32.3 (t), 62.2 (s), 82.4 (s), 123.4 (d), 128.0 (d), 155.4 (s), 166.0 (s), 168.3 (s), 187.7 (s); exact mass *m*/*z* calcd for $C_{15}H_{20}NaO_3$ (M + Na) 271.1305, found 273.1303.

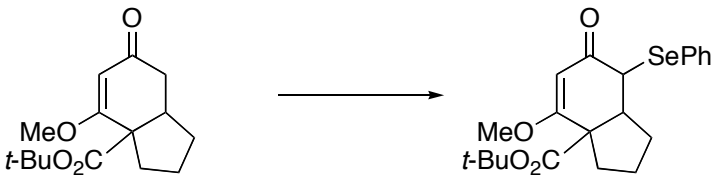
7-Methylindan-5-ol (39.6).[59]



39.5 **39.6**

General procedure A for rearomatization was followed, using $BiCl_3.H_2O$ (16.4 mg, 0.049 mmol) and **39.5** (30.5 mg, 0.123 mmol) in MeCN (5 mL) and water (0.1 mL), and a reaction time of 7 h after addition of the second portion of $BiCl_3.H_2O$. Flash chromatography of the crude product over silica gel (1 x 10 cm), using 30% EtOAc-hexane, gave **39.6** (15.1 mg, 83%) as a white solid: mp 80-82 °C; FTIR ($CDCl_3$ cast) 3302, 2964, 2843, 1605, 1476 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 2.05-2.09 (m, 2 H), 2.22 (s, 3 H), 2.76 (t, J = 7.4 Hz, 2 H), 2.87 (t, J = 7.5 Hz, 2 H), 4.53 (s, 1 H), 6.47 (s, 1 H), 6.56 (s, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 19.2 (q), 25.0 (t), 30.4 (t), 33.1 (t), 108.5 (d), 113.7 (d), 134.6 (s), 135.1 (s), 145.4 (s), 154.2 (s); exact mass m/z calcd for $C_{10}H_{12}O$ 148.0888, found 148.0885.

4-Methoxy-6-oxo-7-phenylselanyl-1,2,3,6,7,7a-hexahydroindene-3a-carboxylic Acid *tert*-Butyl Ester (pre-39.7).



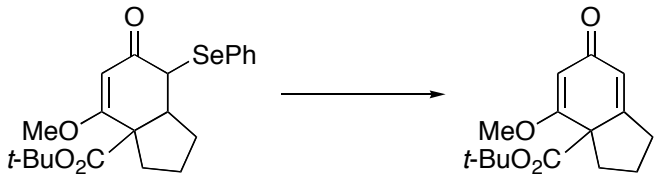
32.5 **pre-39.7**

BuLi (2.5 M in hexane, 0.26 mL, 0.64 mmol) was added dropwise to a stirred and cooled solution (-78 °C) of *i*-Pr_2NH (0.094 mL, 0.69 mmol) in THF (5 mL). Stirring was continued at (-78 °C) for 30 min and a solution of **32.5** (148.9 mg) in THF (3 mL plus 1 mL as a rinse) was added dropwise. Stirring was continued at (-78 °C) for 1 h. PhSeCl (129 mg, 0.67 mmol) in THF (3 mL) was added rapidly and stirring was continued at -78 °C for 1 h. The mixture was quenched with saturated aqueous NH_4Cl and then with water, and extracted with Et_2O (3 times). The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1.5 x 20 cm), using 30% EtOAc-hexane, gave **pre-39.7** as a mixture of isomers [isomer with PhSe and adjacent ring fusion hydrogen cis, 165 mg (70%), isomer with PhSe and adjacent ring fusion hydrogen trans, 28.3 mg (12%)]. The stereochemistry was assigned on the basis that only the cis isomer gave an olefin on oxidation and both isomers had very similar NMR spectra. The cis isomer had: FTIR (CH_2Cl_2, cast) 2926, 1731, 1654, 1265 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.28-1.42 (m, 2 H), 1.51 (s, 9 H), 1.55-1.81 (m, 2 H), 1.99-2.16 (m, 2 H),

2.26-2.42 (m, 1 H), 3.04-3.11 (m, 1 H), 3.71-3.78 (m, 4 H), 5.46 (s, 1 H), 7.24-7.31 (m, 3 H), 7.62-7.68 (m, 2 H); ^{13}C NMR ($CDCl_3$, 100 MHz) (two signals are coincident; spectrum shows some impurity signals) δ 22.6 (t), 27.8 (q), 28.7 (t), 35.3 (t), 47.2 (d), 51.5 (d), 56.5 (d), 59.3 (s), 81.9 (s), 102.7 (d), 127.8 (d), 128.2 (s), 129.1 (d), 134.8 (d), 174.9 (s), 195.0 (s); exact mass *m*/*z* calcd for $C_{21}H_{27}NaO_4Se$ (M + Na) 423.1069, found 423.1072.

The trans isomer was not fully characterized; the integration of the ^{1}H NMR spectrum was poor; the ^{13}C NMR spectrum was very similar to that of the cis isomer: ^{13}C NMR ($CDCl_3$, 100 MHz) δ 22.5 (t), 27.7 (q), 28.6 (t), 35.2 (t), 47.1 (d), 51.4 (d), 56.4 (d), 62.0 (s), 81.8 (s), 102.7 (d), 127.7 (d), 128.1 (s), 129.1 (d), 134.7 (d), 170.7 (s), 174.8 (s), 194.6 (s).

4-Methoxy-6-oxo-1,2,3,6-tetrahydroindene-3a-carboxylic Acid *tert*-Butyl Ester (39.7).

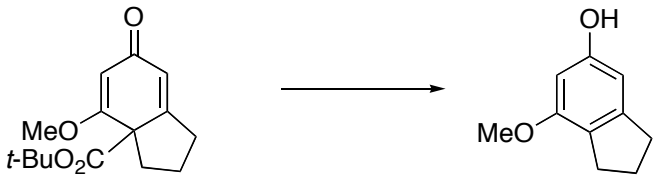


pre-39.7 **39.7**

30% H_2O_2 (0.21 mL) was added dropwise over 5 min to a stirred and cooled (0 °C) solution of **pre-39.7** (presumed to have the PhSe group and adjacent H cis) (83.7 mg, 0.20 mmol) in THF (7 mL) and water (0.7 mL). After

10 min the ice bath was removed and stirring was continued for 2 h. The mixture was cooled to 0 °C and quenched with saturated aqueous $Na_2S_2O_3$ (2 mL). The ice bath was removed and stirring was continued for 10 min. The mixture was diluted with brine (10 mL) and extracted with EtOAc (3 x 10 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1.5 x 15 cm), using 35% EtOAc-hexane, gave **39.7** as an oil (42 mg, 80%): FTIR (CH_2Cl_2, cast) 2926, 2851, 1734, 1670, 1265 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.36 (s, 9 H), 1.57-1.65 (m, 1 H), 1.87-1.94 (m, 1 H), 2.03-2.09 (m, 1 H), 2.44-2.52 (m, 1 H), 2.56-2.62 (m, 1 H), 2.67-2.72 (m, 1 H), 3.71 (s, 3 H), 5.49 (d, *J* = 1.0 Hz, 1 H), 6.04 (s, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) (one signal not observed) δ 21.2 (t), 27.4 (q), 28.7 (t), 31.1 (t), 55.9 (q), 82.4 (s), 101.7 (d), 122.8 (d), 161.1 (s), 167.4 (s), 174.0 (s), 189.3 (s); exact mass *m*/*z* calcd for $C_{15}H_{20}NaO_4$ (M + Na) 287.1254, found 287.1254.

7-Methoxyindan-5-ol (39.8).

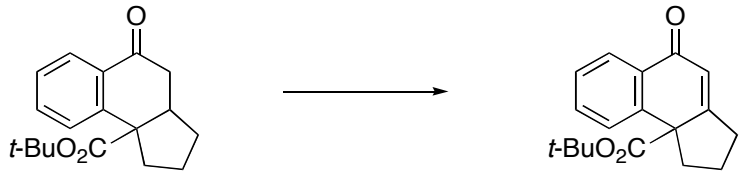


39.7 **39.8**

General procedure A for rearomatization was followed, using $BiCl_3.H_2O$ (20.2 mg, 0.06 mmol), **39.7** (40.0 mg, 0.15 mmol) in MeCN (5 mL) and water

(0.1 mL), and a reaction time of 10 h after addition of the second portion of $BiCl_3.H_2O$. Flash chromatography of the crude product over silica gel (1 x 10 cm), using 30% EtOAc-hexane, gave **39.8** (22.8 mg, 92%) as a white solid: mp 95-97 °C; FTIR ($CHCl_3$, cast) 3303, 2949, 2849, 1613, 1596, 1468 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 2.02-2.10 (m, 2 H), 2.77-2.87 (m, 4 H), 3.79 (s, 3 H), 4.81 (s, 1 H), 6.23 (s, 1 H), 6.33 (s, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 25.0 (t), 28.6 (t), 33.2 (t), 55.1 (q), 96.4 (d), 103.3 (d), 123.7 (s), 146.9 (s), 155.6 (s), 156.4 (s); exact mass *m*/*z* calcd for $C_{10}H_{12}O_2$ 164.0837, found 164.0836.

5-Oxo-1,2,3,5-tetrahydrocyclopenta[*a*]naphthalene-9b-carboxylic Acid *tert*-Butyl Ester (39.9).

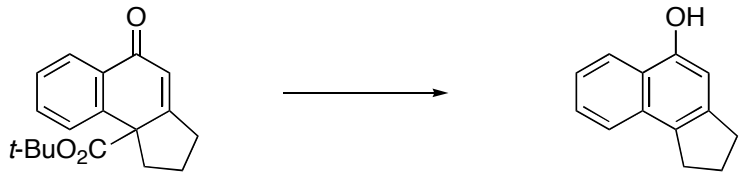


32.6 **39.9**

The general procedure for Saegusa oxidation was followed, using 2,6-lutidine (0.11 mL, 0.95 mmol), **32.6** (78 mg, 0.27 mmol), CH_2Cl_2 (5 mL), $Me_3SiOSO_2CF_3$ (0.15 mL, 0.82 mmol), $Pd(OAc)_2$ (66 mg, 0.27 mmol) and MeCN (5 mL). Flash chromatography of the crude product over silica gel (1.5 x 10 cm), using 10% EtOAc-hexane, gave **39.9** (53.5 mg, 69%) as a white solid: mp 63-64 °C; FTIR (CH_2Cl_2 cast) 2923, 2850, 1725, 1663, 1599, 1246 cm^{-1}; ^1H NMR

($CDCl_3$, 400 MHz) δ 1.22 (s, 9 H), 1.73-2.00 (m, 1 H), 2.01-2.05 (m, 2 H), 2.59-2.68 (m, 1 H), 2.77-2.86 (m, 1 H), 3.11 (ddd, *J* = 8.8, 4.3, 4.3 Hz, 1 H), 6.39 (s, 1 H), 7.41-7.53 (m, 3 H), 8.14 (ddd, *J* = 7.7, 1.4, 0.5 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.8 (t), 27.4 (q), 29.4 (t), 34.4 (t), 59.3 (s), 82.3 (s), 123.7 (d), 126.4 (d), 126.5 (d), 127.6 (d), 131.4 (s), 131.8 (d), 142.0 (s), 166.5 (s), 169.6 (s), 185.8 (s); exact mass *m*/*z* calcd for $C_{18}H_{20}NaO_3$ (M + Na) 307.1305, found 307.1307.

2,3-Dihydro-1*H*-cyclopenta[*a*]naphthalen-5-ol (39.10).[60]

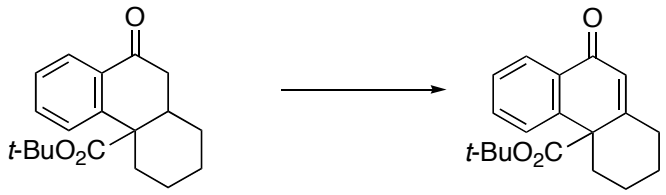


39.9 **39.10**

General procedure B for rearomatization was followed, using $BiCl_3.H_2O$ (17 mg, 0.35 mmol) and **39.9** (99.8 mg, 0.35 mmol) in MeCN (5 mL) and water (0.1 mL), and a reaction time of 10 h. Flash chromatography of the crude product over silica gel (1 x 15 cm), using 10% EtOAc-hexane, gave **39.10** (51.0 mg, 79%) as a solid: mp 119-120 °C; FTIR ($CDCl_3$ cast) 3406, 2951, 2845, 1631, 1594, 1582 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.21-2.26 (m, 2 H), 3.05 (t, *J* = 7.4 Hz, 2 H), 3.18 (t, *J* = 7.4 Hz, 2 H), 5.01 (s, 1 H), 6.78 (s, 1 H), 7.43-7.51 (m, 2 H), 7.73-7.76 (m, 2 H), 8.14-8.18 (m, 2 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 24.4 (t), 30.5 (t), 33.9 (t), 106.2 (d), 122.1 (d), 123.2 (s), 123.9 (d), 124.2 (d), 126.3 (d),

131.0 (s), 131.5 (s), 140.8 (s), 150.3 (s); exact mass *m*/*z* calcd for $C_{13}H_{12}O$ 184.0888, found 184.0889.

9-Oxo-1,3,4,9-tetrahydro-2*H*-phenanthrene-4a-carboxylic Acid *tert*-Butyl Ester (39.11).

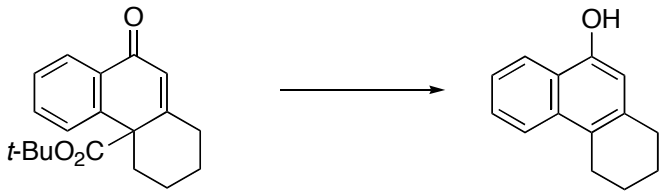


32.7 **39.11**

The general procedure for Saegusa oxidation was followed, using 2,6-lutidine (0.96 mL, 8.2 mmol), **32.7** (705 mg, 2.35 mmol), CH_2Cl_2 (15 mL), $Me_3SiOSO_2CF_3$ (1.3 mL, 7.1 mmol), $Pd(OAc)_2$ (522 mg, 2.33 mmol) and MeCN (10 mL). Flash chromatography of the crude product over silica gel (2.5 x 25 cm), using 10% EtOAc-hexane, gave **39.11** (434 mg, 60%) as an oil: FTIR (CH_2Cl_2, cast) 2935, 2861, 1727, 1663, 1560, 1254 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.28 (s, 9 H), 1.37-1.42 (m, 2 H), 1.81-1.86 (m, 2 H), 2.00-2.60 (m, 1 H), 2.28-2.29 (m, 1 H), 2.60-2.71 (m, 1 H), 2.92-2.97 (m, 1 H), 6.42 (s, 1 H), 7.43-7.59 (m, 1 H), 7.54-7.59 (m, 2 H), 8.21-8.23 (m, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 23.4 (t), 27.4 (q), 27.7 (t), 35.3 (t), 39.6 (t), 53.9 (s), 81.9 (s), 124.9 (d), 125.5 (d), 126.5 (d), 127.6 (d), 130.3 (s), 132.3 (d), 143.8 (s), 161.8 (s), 169.8 (s),

184.9 (s); 2935, 2861, 1727, 1663, 1560, 1254; exact mass *m*/*z* calcd for $C_{19}H_{22}NaO_3$ (M + Na) 321.1461, found 321.1461.

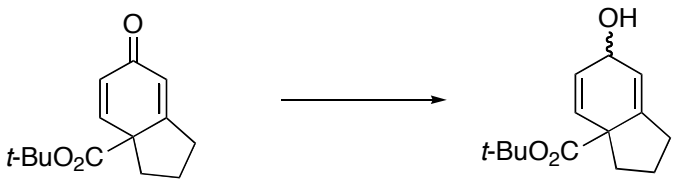
1,2,3,4-Tetrahydrophenanthren-9-ol (39.12).[53]



39.11 **39.12**

General procedure B for rearomatization was followed, using $BiCl_3.H_2O$ (386 mg, 1.16 mmol), **39.11** (345 mg, 1.16 mmol) in MeCN (5 mL) and water (0.1 mL), and a reaction time of 12 h. Flash chromatography of the crude product over silica gel (1.5 x 15 cm), using 10% EtOAc-hexane, gave **39.12** (188 mg, 82%) as an oil: FTIR ($CDCl_3$, cast) 3408, 2929, 2859, 1626, 1599 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.87-1.90 (m, 2 H), 1.97-1.99 (m, 2 H), 2.83 (t, *J* = 6.1 Hz, 2 H), 3.06 (t, *J* = 6.3 Hz, 2 H), 5.40 (s, 1 H), 6.52 (s, 1 H), 7.46-7.51 (m, 1 H), 7.52-7.60 (m, 1 H), 7.97 (d, *J* = 8.4 Hz, 1 H), 8.23 (t, *J* = 8.3 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 22.9 (t), 23.3 (t), 25.2 (t), 30.4 (t), 110.5 (d), 121.8 (d), 122.8 (s), 123.4 (s), 124.1 (d), 125.1 (s), 126.3 (d), 133.6 (s), 134.4 (s), 149.0 (s); exact mass *m*/*z* calcd for $C_{14}H_{14}O$ 198.1045, found 198.1044.

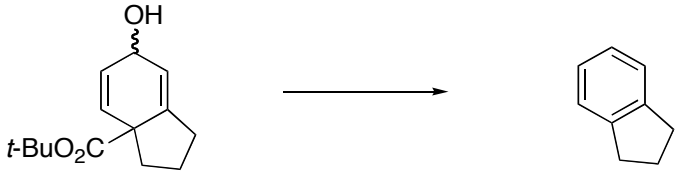
6-Hydroxy-1,2,3,6-tetrahydroindene-3a-carboxylic Acid *tert*-Butyl Ester (40.1).



36.1 **40.1**

$CeCl_3.7H_2O$ (261 mg, 0.70 mmol) and then $NaBH_4$ (13 mg, 0.35 mmol) were added to a stirred and cooled (-78 °C) solution of **36.1** (82 mg, 0.35 mmol) in dry MeOH (5 mL). After the addition, the cold bath was removed and stirring was continued for 25 min. The mixture was quenched slowly with water and extracted with Et_2O. The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. The crude product (**40.1**), which was used directly for the next step, appeared to be a single isomer (^{13}C NMR): FTIR ($CHCl_3$ cast) 3350, 2974, 2872, 1723, 1454, 1250 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.38 (s, 9 H), 1.41-1.47 (m, 1 H), 1.75-1.86 (m, 3 H), 2.28-2.39 (m, 1 H), 2.41-2.50 (m, 2 H), 4.70 (s, 1 H), 5.64 (s, 1 H), 5.92-5.93 (m, 2 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 22.2 (t), 27.7 (q), 28.8 (t), 34.9 (t), 55.6 (s), 65.1 (d), 80.9 (s), 121.6 (d), 128.0 (d), 138.9 (d), 143.3 (s), 172.1 (s); exact mass *m*/*z* calcd for $C_{14}H_{20}NaO_3$ (M + Na) 259.1305, found 259.1304.

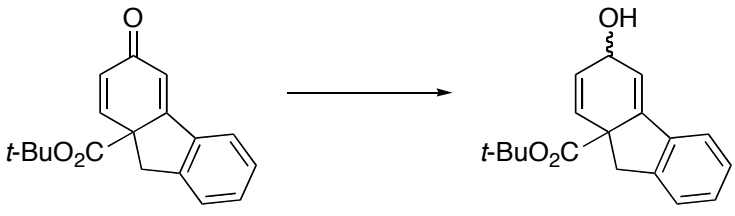
Indan (40.2).



40.1 **40.2**

General procedure B for rearomatization was followed, using $BiCl_3.H_2O$ (99 mg, 0.29 mmol) and **40.1** (70 mg, 0.29 mmol) in MeCN (5 mL) and water (0.1 mL), and a reaction time of 8 h. Flash chromatography of the crude product over silica gel (1.5 x 12 cm), using 10% EtOAc-hexane, gave indan (**40.2**) (28.3 mg, 81%) as an oil: FTIR (CH_2Cl_2 cast) 3021, 2946, 2845, 1483, 1459 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 2.13-2.20 (m, 2 H), 3.01 (t, J = 7.5 Hz, 4 H), 7.39-7.43 (m, 2 H), 7.48-7.52 (m, 2 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 25.6 (t), 33.1 (t), 124.6 (d), 126.2 (d), 144.3 (s).

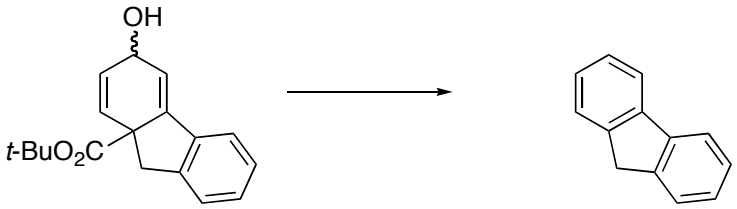
6-Hydroxy-6,9-dihydrofluorene-8a-carboxylic Acid *tert*-Butyl Ester (40.3).



39.9 **40.3**

$CeCl_3.7H_2O$ (263 mg, 0.71 mmol) and then $NaBH_4$ (14.7 mg, 0.39 mmol) were added to a stirred and cooled (-78 °C) solution of **39.9** (99.8 mg, 0.35 mmol) in dry MeOH (5 mL). After the addition, the cold bath was removed and stirring was continued for 25 min. The mixture was quenched slowly with water and extracted with Et_2O. The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. The crude product (**40.3**) was used directly for the next step.

9*H*-Fluorene (40.4).

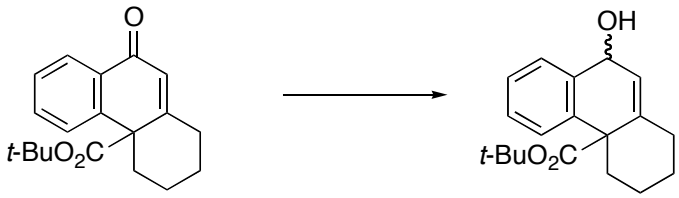


40.3 **40.4**

General procedure B for rearomatization was followed, using $BiCl_3.H_2O$ (112 mg, 0.34 mmol) and **40.3** (96 mg, 0.34 mmol) in MeCN (5 mL) and water (0.1 mL), and a reaction time of 10 h. Flash chromatography of the crude product over silica gel (1.5 x 15 cm), using hexane, gave 9*H*-fluorene (**40.4**) (42 mg, 76%) as a white solid: mp 115-117 °C; FTIR ($CDCl_3$, cast) 3062, 3041, 2919, 2853, 1649, 1597 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 3.94 (s, 2 H), 7.32-7.36 (m, 2 H), 7.39-7.43 (m, 2 H), 7.57-7.59 (m, 2 H), 7.83 (d, J = 7.5 Hz, 2 H); ^{13}C NMR

($CDCl_3$, 100 MHz) δ 36.9 (t), 119.8 (d), 124.9 (d), 126.6 (d), 126.7 (d), 141.6 (s), 143.1 (s); exact mass *m*/*z* calcd for $C_{13}H_{10}$ 166.0783, found 166.0774.

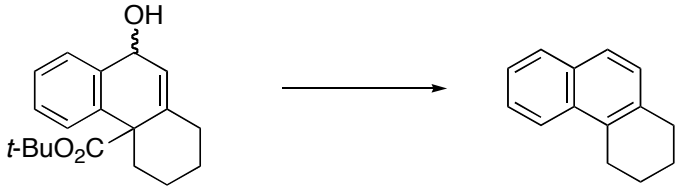
9-Hydroxy-1,3,4,9-tetrahydro-2*H*-phenanthrene-4a-carboxylic Acid *tert*-Butyl Ester (40.5).



39.11 **40.5**

$CeCl_3.7H_2O$ (119 mg, 0.32 mmol) and then $NaBH_4$ (6.8 mg, 0.12 mmol) were added to a stirred and cooled (-78 °C) solution of **39.11** (48 mg, 0.16 mmol) in dry MeOH (5 mL). After the addition, the cold bath was removed and stirring was continued for 40 min. The mixture was quenched slowly with water and extracted with Et_2O. The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. The crude product (**40.5**) was used directly in the next step.

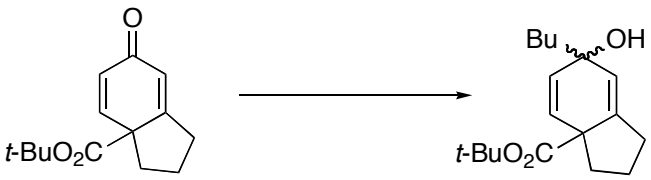
1,2,3,4-Tetrahydrophenanthrene (40.6).[57]



40.5 **40.6**

General procedure B for rearomatization was followed, using $BiCl_3.H_2O$ (57 mg, 0.17 mmol), **40.5** (51 mg, 0.17 mmol) in MeCN (5 mL) and water (0.1 mL), and a reaction time of 6 h. Flash chromatography of the crude product over silica gel (1 x 12 cm), using hexane, gave **40.6** (22 mg, 76%) as an oil: FTIR ($CDCl_3$, cast) 3047, 2927, 2856, 1510, 1457 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.88-1.93 (m, 2 H), 1.95-2.01 (m, 2 H), 2.93 (t, *J* = 6.2 Hz, 2 H), 3.14 (t, *J* = 6.3 Hz, 2 H), 7.21-7.23 (m, 1 H), 7.43-7.53 (m, 2 H), 7.62 (d, *J* = 8.4 Hz, 1 H), 7.80 (d, *J* = 8.6 Hz, 1 H), 7.98 (d, *J* = 8.4 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 22.9 (t), 23.2 (t), 25.6 (t), 30.4 (t), 122.7 (d), 124.6 (d), 125.5 (d), 125.7 (d), 128.2 (d), 128.3 (d), 131.4 (s), 132.0 (s), 132.5(s), 134.2 (s); exact mass *m*/*z* calcd for $C_{14}H_{14}$ 182.1096, found 182.1094.

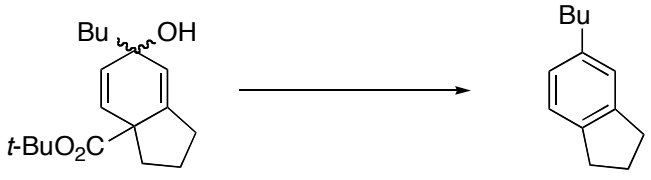
6-Butyl-6-hydroxy-1,2,3,6-tetrahydroindene-3a-carboxylic Acid *tert*-Butyl Ester (41.1a).



36.1 **41.1a**

n-BuMgCl (2 M in THF, 0.15 mL, 0.3 mmol) was added at a fast dropwise rate to a stirred and cooled (-78 °C) solution of **36.1** (58 mg, 0.25 mmol) in Et_2O (5 mL). The cold bath was removed and stirring was continued overnight. The mixture was cooled to 0 °C, quenched by dropwise addition of water, and extracted with Et_2O. The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. The crude product (**41.1a**) was used directly in the next step.

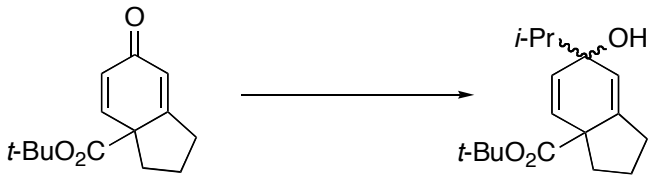
5-Butylindan (41.2).



41.1a **41.2**

General procedure B for rearomatization was followed, using $BiCl_3.H_2O$ (83 mg, 0.25 mmol), **41.1a** (total product from the previous step) in MeCN (5 mL) and water (0.1 mL), and a reaction time of 8 h. Flash chromatography of the crude product over silica gel, using hexane, gave **41.2** (35 mg, 82% over two steps) as an oil: FTIR ($CDCl_3$, cast) 3007, 2956, 2855, 1491, 1458, 1440 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.93 (t, *J* = 7.6 Hz, 3 H), 1.32-1.42 (m, 2 H), 1.56-1.63 (m, 2 H), 2.07 (apparent quintet, *J* = 7.6 Hz, 2 H), 2.58 (t, *J* = 8 Hz, 2 H), 2.86-2.91 (m, 4 H), 6.95-7.15 (m, 3 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.2 (q), 22.7 (t), 25.5 (t), 32.7 (t), 33.1 (t), 34.3 (t), 35.8 (t), 124.3 (d), 124.7 (d), 126.5 (d), 141.1 (s), 141.6 (s), 144.5 (s); exact mass *m*/*z* calcd for $C_{13}H_{18}$ 174.1408, found 174.1408.

6-Hydroxy-6-isopropyl-1,2,3,6-tetrahydroindene-3a-carboxylic Acid *tert*-Butyl Ester (41.1b).

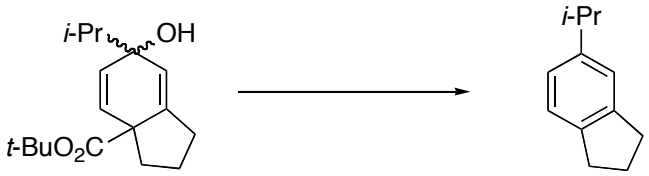


36.1 **41.1b**

i-PrMgBr (2 M in Et_2O, 0.12 mL, 0.24 mmol) was added at a fast dropwise rate to a stirred and cooled (-78 °C) solution of **36.1** (46 mg, 0.20 mmol) in Et_2O (5 mL). The cold bath was removed and stirring was continued overnight.

The mixture was cooled to 0 °C, quenched by dropwise addition of water, and extracted with Et_2O. The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. The crude product (**41.1b**) was used directly in the next step.

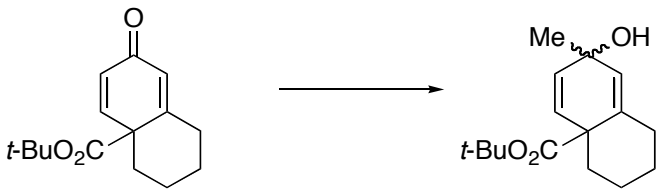
5-Isopropylindan (41.3).[61]



41.1b **41.3**

General procedure B for rearomatization was followed, using $BiCl_3.H_2O$ (65 mg, 0.2 mmol), **41.1b** (total product from the previous step) in MeCN (5 mL) and water (0.1 mL), and a reaction time of 2 h. Flash chromatography of the crude product over silica gel (1.5 x 12 cm), using hexane, gave **41.3** (23 mg, 75%) as an oil: FTIR ($CDCl_3$, cast) 3008, 2958, 2867, 1493, 1460 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.25 (d, J = 7.0 Hz, 6 H), 2.07 (apparent quintet, J = 7.5 Hz, 2 H), 2.85-2.92 (m, 5 H), 7.02-7.16 (m, 3 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 24.3 (q), 25.5 (t), 32.5 (t), 32.9 (t), 34.0 (d), 122.3 (d), 124.1 (d), 124.3 (d), 141.6 (s), 144.3 (s), 147.0 (s); exact mass m/z calcd for $C_{12}H_{16}$ 160.1252, found 160.1250.

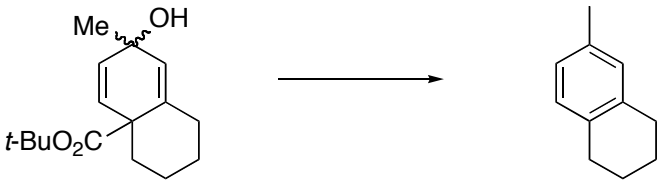
7-Hydroxy-7-methyl-1,3,4,7-tetrahydro-2*H*-naphthalene-4a-carboxylic Acid *tert*-Butyl Ester (41.4).



39.1 **41.4**

MeMgBr (3 M in THF, 0.20 mL, 0.60 mmol) was added at a fast dropwise rate to a stirred and cooled (-78 °C) solution of **39.1** (100 mg, 0.40 mmol) in Et_2O (5 mL). The cold bath was removed and stirring was continued for 2 h. The mixture was cooled to 0 °C, quenched slowly with water, and extracted with Et_2O. The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. The crude product (**41.4**) was used directly in the next step.

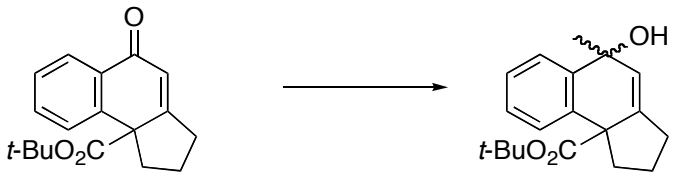
6-Methyl-1,2,3,4-tetrahydronaphthalene (41.5).[62]



41.4 **41.5**

General procedure B for rearomatization was followed, using $BiCl_3.H_2O$ (117 mg, 0.35 mmol), **41.4** (total product from the previous steps) in MeCN (5 mL) and water (0.1 mL), and a reaction time of 9 h. Flash chromatography of the crude product over silica gel (1.5 x 15 cm), using hexane, gave **41.5** (38 mg, 74%) as an oil: FTIR ($CHCl_3$, cast) 3000, 2925, 2857, 1505, 1449 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.78-1.83 (m, 4 H), 2.30 (s, 3 H), 2.73-2.77 (m, 4 H), 6.91 (s, 1 H), 6.94-6.97 (m, 2 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 20.8 (q), 23.2 (t), 23.3 (t), 28.9 (t), 29.3 (t), 126.1 (d), 128.9 (d), 129.6 (d), 133.9 (s), 134.7 (s), 136.8 (s).

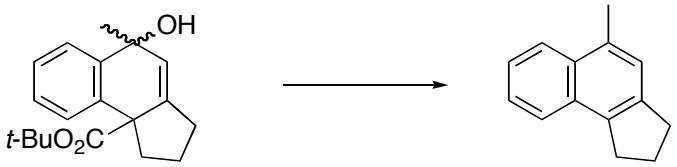
5-Hydroxy-5-methyl-1,2,3,5-tetrahydrocyclopenta[*a*]naphthalene-9b-carboxylic Acid *tert*-Butyl Ester (41.6a).



39.9 **41.6a**

MeMgBr (3 M in THF, 0.17 mL, 0.50 mmol) was added at a fast dropwise rate to a stirred and cooled (-78 °C) solution of **39.9** (95 mg, 0.34 mmol) in Et_2O (10 mL). The cold bath was removed and stirring was continued for 40 min. The mixture was cooled to 0 °C, quenched slowly with water, and extracted with Et_2O. The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. The crude product (**41.6a**) was used directly in the next step.

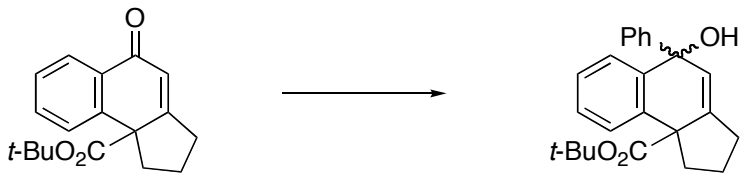
5-Methyl-2,3-dihydro-1*H*-cyclopenta[*a*]naphthalene (41.7).



41.6a **41.7**

General procedure B for rearomatization was followed, using $BiCl_3.H_2O$ (88.4 mg, 0.265 mmol), **41.6a** (79.6 mg, 0.265 mmol) in MeCN (5 mL) and water (0.1 mL), and a reaction time of 4 h. Flash chromatography of the crude product over silica gel (1 x 12 cm), using hexane, gave **41.7** (33.6 mg, 70%) as an oil: FTIR ($CDCl_3$, cast) 3008, 2947, 2845, 1592, 1439 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 2.21-2.28 (m, 2 H), 2.70 (s, 3 H), 3.09 (t, J = 7.4 Hz, 2 H), 3.25 (t, J = 7.4 Hz, 2 H), 7.28 (s, 1 H), 7.45-7.53 (m, 2 H), 7.81-7.83 (m, 1 H), 7.99-8.02 (m, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 19.5 (q), 24.4 (t), 31.0 (t), 33.8 (t), 124.0 (d), 124.4 (d), 124.6 (d), 124.8 (d), 125.4 (d), 130.5 (s), 131.4 (s), 132.6 (s), 137.4(s), 140.5 (s); exact mass *m*/*z* calcd for $C_{14}H_{14}$ 182.1096, found 182.1125.

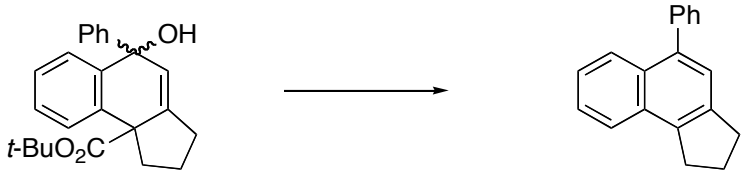
5-Hydroxy-5-phenyl-1,2,3,5-tetrahydrocyclopenta[*a*]naphthalene-9b-carboxylic Acid *tert*-Butyl Ester (41.6b).



39.9 **41.6b**

PhMgCl (2 M in THF, 0.14 mL, 0.29 mmol) was added at a fast dropwise rate to a stirred and cooled (-78 °C) solution of **39.9** (54 mg, 0.19 mmol) in THF (10 mL). The cold bath was removed and stirring was continued for 1 h. The mixture was cooled to 0 °C, quenched slowly with water, and extracted with Et_2O. The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. The crude product (**41.6b**) was used directly for the next step.

5-Phenyl-2,3-dihydro-1*H*-cyclopenta[*a*]naphthalene (41.8).[63]



41.6b **41.8**

General procedure B for rearomatization was followed, using $BiCl_3.H_2O$ (46 mg, 0.14 mmol) and **41.6b** (50 mg, 0.14 mmol) in MeCN (5 mL) and water

(0.1 mL), and a reaction time of 12 h. Flash chromatography of the crude product over silica gel (1 x 10 cm), using 10% EtOAc-hexane, gave **41.8** (22 mg, 65%) as an oil: FTIR ($CHCl_3$ cast) 3058, 2921, 2848, 1591, 1576, 784 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.27-2.32 (m, 2 H), 3.16 (t, J = 7.4 Hz, 2 H), 3.32 (t, J = 7.5 Hz, 2 H), 7.34-7.43 (m, 3 H), 7.48-7.53 (m, 5 H), 7.85-7.90 (m, 2 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 24.6 (t), 31.3 (t), 33.9 (t), 124.5 (d), 124.7 (d), 124.8 (d), 125.8 (d), 126.8 (d), 127.0 (d), 128.2 (d), 130.3 (d), 130.6 (s), 130.7 (s), 139.1 (s), 139.2 (s), 140.5 (s), 141.4 (s); exact mass m/z calcd for $C_{19}H_{16}$ 244.1252, found 244.1249.

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Chapter 2

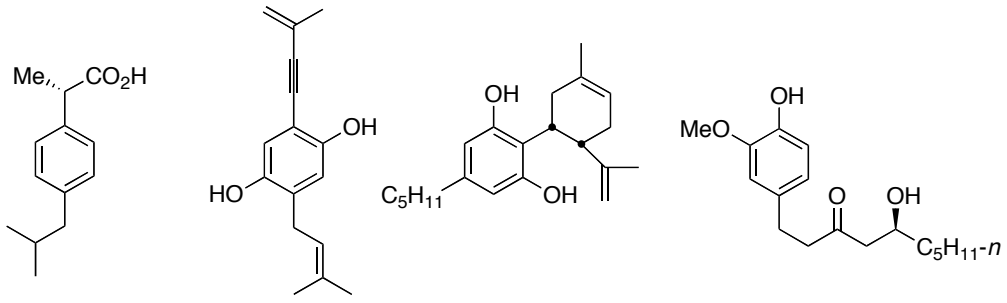
A route to 1,4-disubstituted aromatics:

Application to the synthesis of the antibiotic culpin

1 INTRODUCTION

1.1 *General*

Studies on the structure, reactions, and synthesis of aromatic compounds are deep-rooted in the history of organic chemistry since the time of Kekulé's dream a century ago.[1] Many modern synthetic targets, in particular those relevant to agrochemical and pharmaceutical preparations, either are benzenoid or incorporate an aromatic component (Scheme 1).[2] In this respect, commercially available aromatic substances are modified in a variety of ways, such as functional group introduction into a mono- or disubstituted material and attachment of chains either to existing functionality or directly onto the ring.[3] The regiospecific preparation of polyfunctionalized aromatic compounds remains a challenge in organic synthesis.



(+)-ibuprofen[2a] — Antiinflammatory agent

culpin[2b] — Antibiotic

3,4-*cis*-cannabidiol[2c] — Important bioactivities

[6]-gingerol[2d] — Induces apoptosis

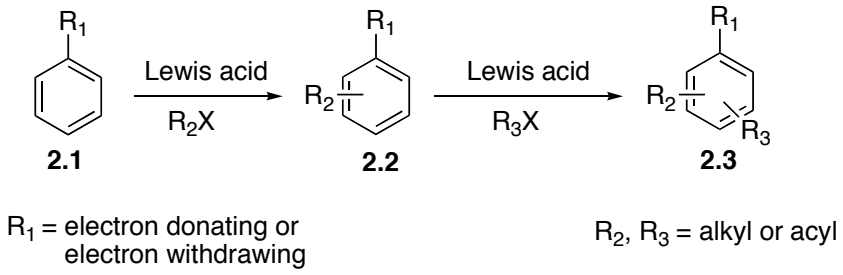
Scheme 1

1.3 *Synthesis of benzene derivatives from pre-existing arenes*

Classical approaches for the preparation of benzene derivatives are based on conventional electrophilic or nucleophilic substitutions, catalyzed coupling reactions, and metalation-functionalization reactions.

1.2.1 *Friedel-Crafts reaction*

Electrophilic aromatic substitution, which is represented by the classical Friedel-Crafts reaction (Friedel-Crafts alkylation or acylation), is a very important means for preparing substituted aromatic compounds (Scheme 2).[4]



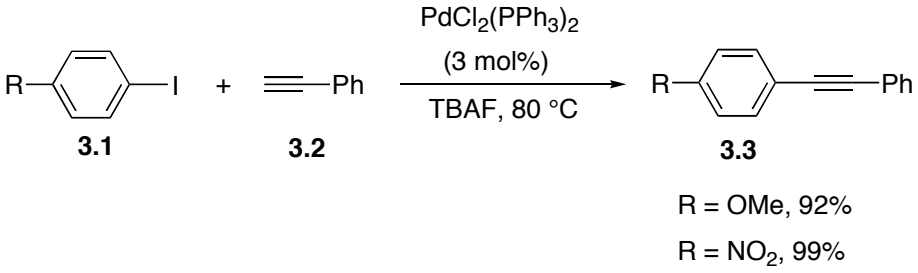
Scheme 2

The construction of polysubstituted benzenes has been mainly achieved by stepwise introduction of substituents onto the aromatic ring (**2.1**→**2.3**) in the presence of a Lewis acid. However, the reaction conditions are often harsh and the regiochemical outcome is nonselective. High regioselectivity can only be achieved by careful choice of the reagents and the synthetic route; sometimes this requires several protection and deprotection steps.

1.2.2 Catalyzed cross coupling reactions

Transition metal catalyzed cross-coupling reactions are very important carbon-carbon bond forming reactions in organic synthesis. In the course of the last several decades, there has been an explosion of transition metal catalyzed cross-coupling reactions,[5] and only the most recent work on the preparation of benzene derivatives will be described below.

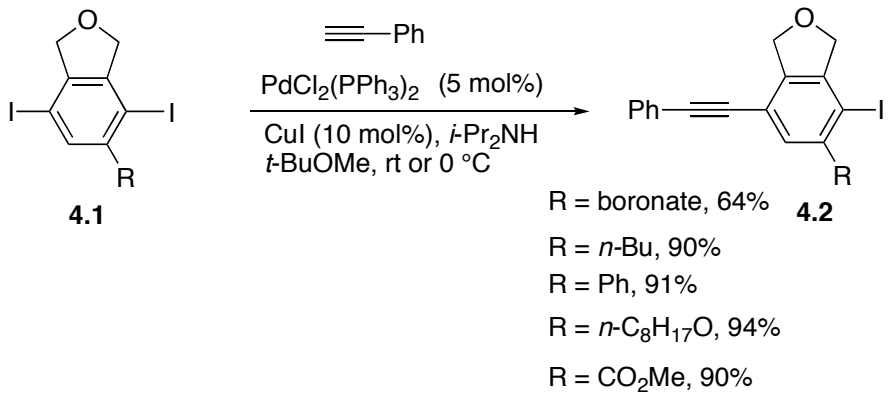
Li and co-workers have recently found a general method for the rapid Sonogashira cross-coupling reaction of aryl halides with terminal alkynes (Scheme 3).[6] Li's protocol proceeds under copper-, amine-, and solvent-free conditions, but three equivalents of TBAF are required for the smooth conversion to products. The authors argued that the beneficial roles of TBAF are presumably activation of the Pd(0) species with generation of an anionic Pd species and deprotonation of the acidic terminal hydrogen of the alkyne.



Scheme 3

Yamamoto and Hattori in 2008 disclosed a palladium-catalyzed site selective Sonogashira coupling of substituted diiodobenzenes **4.1** with phenylacetylene in the synthesis of multiply functionalized benzenes **4.2** (Scheme 4).[7] In this reaction, the two carbon-iodine bonds are perfectly differentiated from

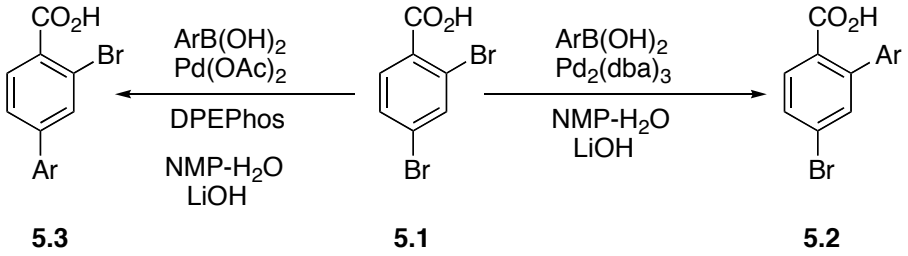
one another because of the difference in their steric environment imposed by the substituent R.



4.1 **4.2**

Scheme 4

Houpis and co-workers reported highly selective carboxyl-directed cross-coupling reactions of 2,4-dibromobenzoic acids with arylboronic acids for the synthesis of trisubstituted benzoic acid derivatives (Scheme 5).[8]



5.3 **5.1** **5.2**

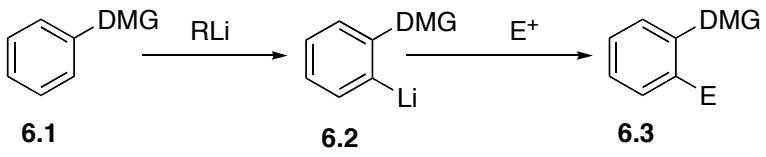
Scheme 5

The carboxylate anion is used as a directing group in the coupling reaction to selectively form *ortho*-substituted derivatives in 50-80% yield. After extensive screening studies, they found that solvent, base and the number of equivalents of

base are the determining factors for the success of the reaction. Interestingly, with a combination of palladium diacetate and DPEPhos as catalyst (**5.1→5.3**), the directing effect could be reversed to give *para*-substituted derivatives **5.3**. At present, the exact nature of the active catalytic species is unknown.

1.2.3 Directed ortho metalation (DOM)

Directed *ortho* metalation (DOM) is another synthetic method that has been extensively studied. This approach is very useful for introducing substituents regioselectively at the *ortho* position.[3] The DOM reaction consists of deprotonation of a site *ortho* to a heteroatom-containing directed metalated group (DMG) **6.1** by using an alkyllithium base, leading to an *ortho*-lithiated species **6.2**. These *ortho*-lithiated species can be trapped by electrophilic reagents to give 1,2-disubstituted benzene derivatives **6.3**, after which the DMG can be retained, converted to a different functional group or in some cases removed. Good DMG's are strong complexing or chelating groups that have the effect of increasing the kinetic acidity of protons in the *ortho* position.

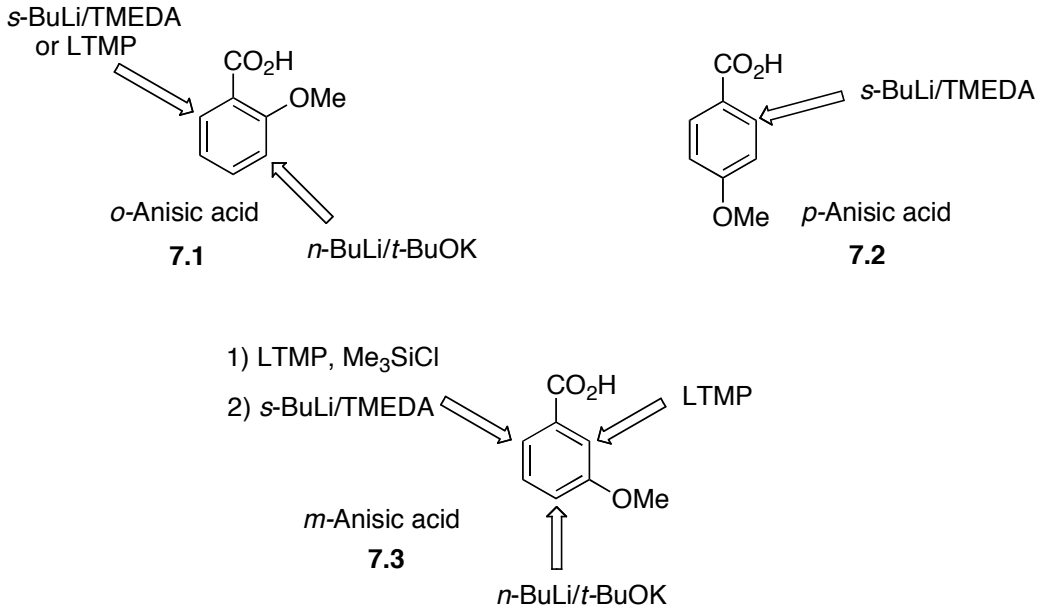


6.1 **6.2** **6.3**

Scheme 6

Mortier and co-workers have recently demonstrated, after extensive investigations, a general, direct, and regioselective synthesis of substituted

methoxybenzoic acids by *ortho* metalation of *o*-**7.1**, *m*-**7.3**, and *p*-anisic acids (**7.2**) (Scheme 7).[9] By judicious choice of base, metalation temperature and exposure times, the metalation can be selectively directed to either of the *ortho* positions. These methods open routes to very simple methoxybenzoic acids with a number of functionalities that are not otherwise easily available.



Scheme 7

Directed *ortho* metalation remains a powerful strategy; however, the scope of this reaction is clearly restricted by its nature: predicting sites of metalation in multiply substituted aromatics is difficult and remains a synthetic challenge.

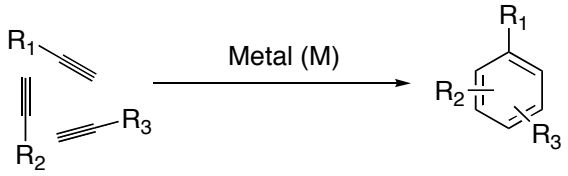
1.3 *Synthesis of benzene derivatives from acyclic precursors*

The classical approach for the preparation of benzene derivatives is based on aromatic substitution in which a substituent is introduced onto a pre-existing arene. However, the main limitation is the frequent difficulty in controlling regioselectivity on the aromatic ring. In this respect, building up the aromatic moiety from acyclic precursors has become of interest to the synthetic community. Modern approaches have been developed by regioselective construction of the aromatic skeleton from linear components, in which the substitution pattern of the final product is dictated by the structures and functionalities of the precursors.

1.3.1 *Synthesis of benzene derivatives via cycloaddition reactions*

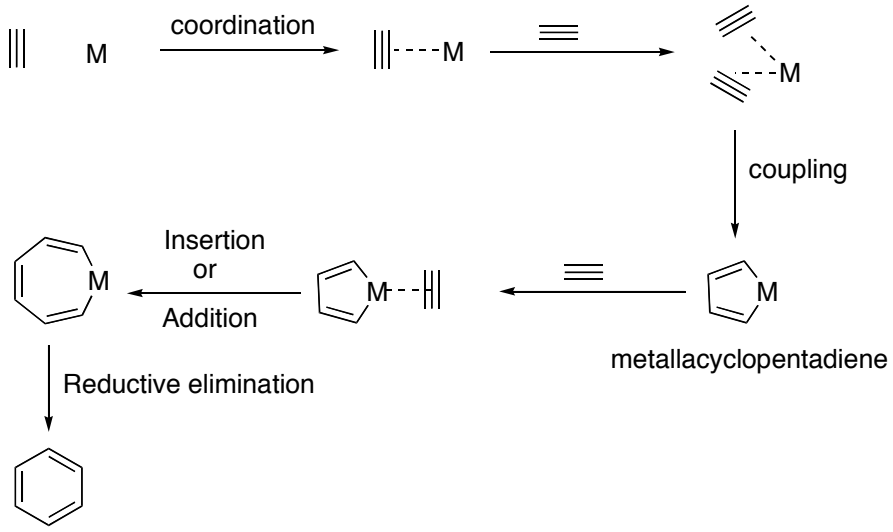
Cycloaddition reactions are a powerful means for quickly assembling small acyclic precursors into complex cyclic molecules. Transition metal catalyzed [2+2+2] cyclotrimerization and [4+2] cycloadditions are the two most common approaches for the regioselective synthesis of polysubstituted benzene derivatives.

In 1948, Reppe *et al*. disclosed the first transition metal (nickel) catalyzed [2+2+2] cyclotrimerization of acetylenes (Scheme 8), which offers a reliable and straightforward synthetic entry to substituted aromatic derivatives.[10]



Scheme 8

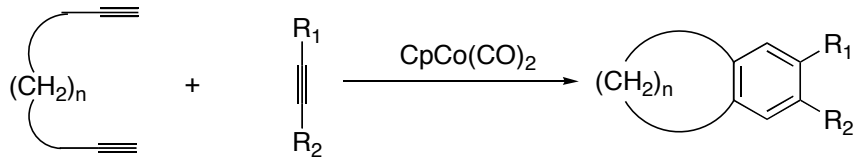
In this reaction, three carbon-carbon bonds of the aromatic ring are formed in a single step. Based on the results of several investigators, the mechanism of this reaction, which is catalyzed by low-valent transition metal complexes, has been proposed as described in Scheme 9.[11]



Scheme 9

In 1975, Vollhardt and co-workers reported that cobalt complexes could also be used to catalyze [2+2+2] cycloadditions involving α,ω-diynes to form annulated benzenes **10.3** (Scheme 10).[12] The reaction worked best for n = 3 and 4, and a range of substituents (R = H, alkyl, aryl, vinyl, CH_2OH, CO_2R', NR',

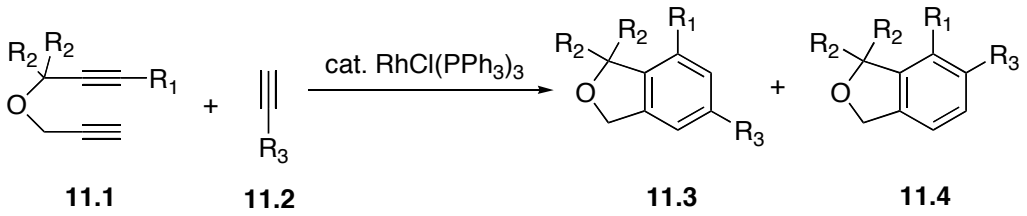
SR') was tolerated. However, the yields dropped considerably when bulky substituents, such as $Si(CH_3)_3$ were present at the terminal position of the diyne.



10.1 n = 2, 3, 4, 5 **10.2** **10.3** yield: 30-95%

Scheme 10

Since the discovery of the cyclotrimerization reaction by Reppe *et al*,[10] this reaction has been rapidly expanded for many C-C bond forming reactions. McDonald and co-workers showed a notable *meta* selectivity in the rhodium-catalyzed cyclotrimerization of oxodiynes with alkynes (Scheme 11).[13] The regioselectivity of the reaction and the reactivity of the substrate are highly dependent on the steric bulk of the substituents attached to the substrates.



11.1 **11.2** **11.3** **11.4**

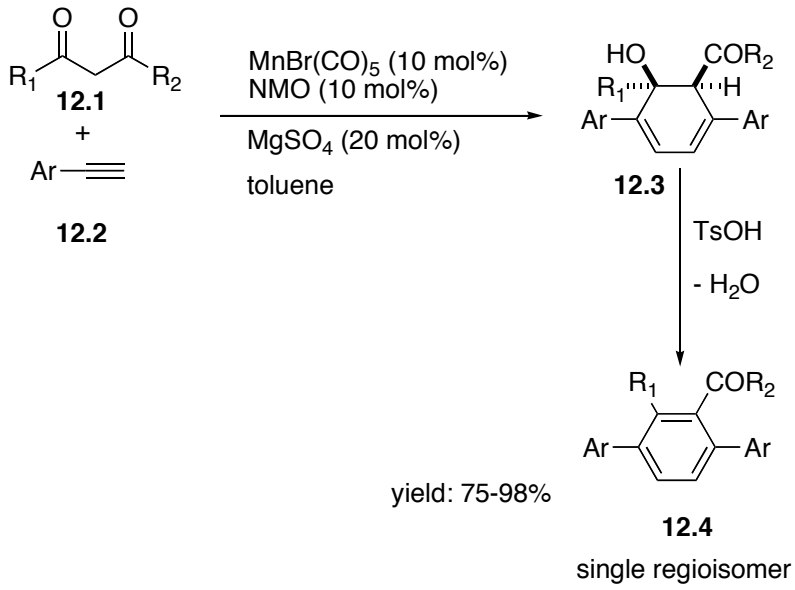
R_1	R_2	R_3	**Yield of 11.3 + 11.4 (%)**	**Ratio 11.3 : 11.4**
Me	H	*n*-Bu	35	1.7 : 1
Me	H	$C(CH_3)_2OH$	54	**11.3** only
Me	H	CH_2OH	53	1.8 : 1
$C(CH_3)_2OH$	H	*n*-Bu	36	**11.3** only
$C(CH_3)_2OH$	H	$C(CH_3)_2OH$	60	**11.3** only
OEt	Me	*n*-Bu	61	4 : 1
OEt	Me	$C(CH_3)_2OH$	53	**11.3** only

Scheme 11

This methodology was applied in the [2+2+2] cyclotrimerization of carbohydrate derivatives with alkynes for the synthesis of *C*-acyl glycosides.[14]

Recently, Nakamura and co-workers reported the manganese-catalyzed [2+2+2] annulation of 1,3-dicarbonyl compounds with terminal alkynes for an efficient and regioselective synthesis of substituted benzene derivative (Scheme 12).[15] This reaction formally resembles the well-known [2+2+2] cyclotrimerization but differs in the sense that the enol form of the dicarbonyl

compound is incorporated into the benzene ring with the removal of one mole of water.

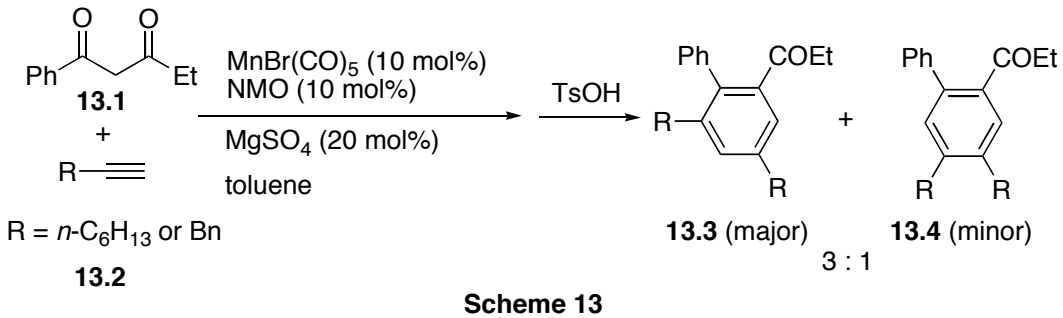


Scheme 12

Treatment of 1, 3-dicarbonyl compound **12.1** with 2 mol of aryl alkyne **12.2** in the presence of a catalytic amount of $MnBr(CO)_5$, NMO and $MgSO_4$ in toluene afforded the *p*-terphenyl derivatives **12.4** after dehydration with perfect regioselectivity in good to excellent yield. The reaction first generates a cis-cyclohexadienol intermediate **12.3** as an exclusive stereo- and regioisomer, which is then dehydrated in situ in the presence of TsOH to give the single regioisomeric **12.4** and water. This arene synthesis is greatly accelerated by NMO and the presence of anhydrous $MgSO_4$ improves the yield by removing water and suppressing side reactions (such as hydrolysis of the ester group in the product).

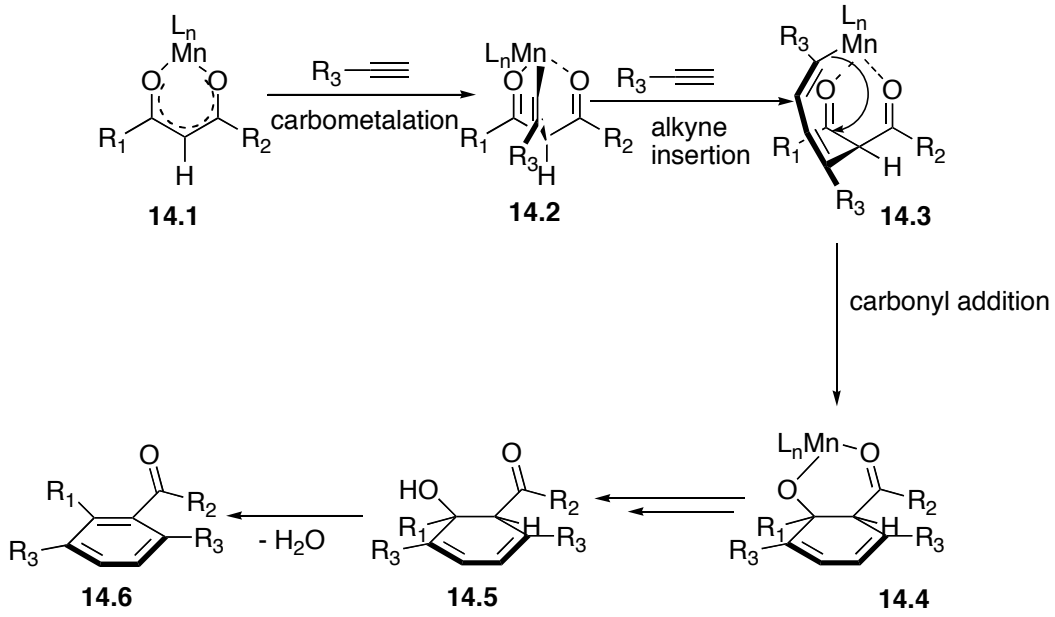
However, when the same reaction was done with an alkyl alkyne, a lower

regioselectivity was observed to give *para* (**13.3**) and *meta* isomers (**13.4**) in an ca. 3:1 ratio (Scheme 13).



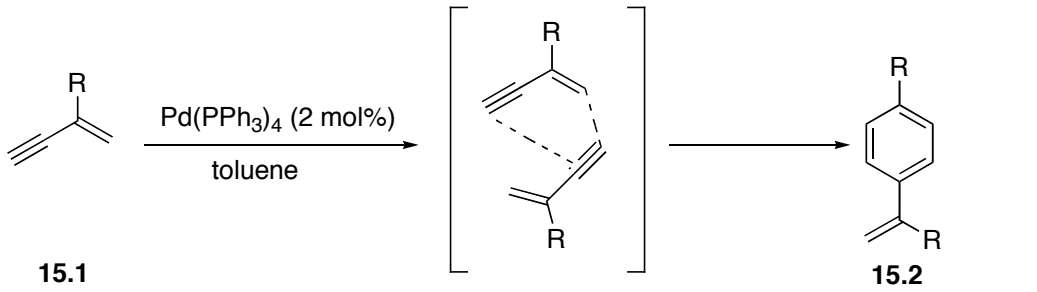
Scheme 13

At that time, due to lack of experimental evidence, the Nakamura's group was unable to provide mechanistic evidence to account for the cis stereochemistry of the cyclohexadienol intermediate and the high regioselectivity. But early this year, after extensive experiments and density functional calculations (DFT), the same group proposed a mechanism (Scheme 14), which involves sequential carbometalation reactions of a manganese enolate **14.1** followed by intramolecular carbonyl addition (**14.3.→14.4**) of the organomanganese intermediate.[16]



Scheme 14

[4+2] Cycloadditions have also been shown to be useful approaches for the regioselective synthesis of benzene derivatives. Yamamoto *et al.* found that conjugated enynes were excellent substrates for the formal [4+2] cycloaddition in the presence of a palladium catalyst (Scheme 15). The reaction is highly regioselective and gives 1,4-disubstituted benzenes (**15.2**) as single isomers in good to high yields.[17]

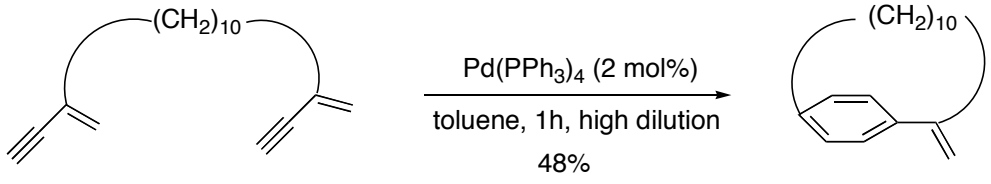


15.1 **15.2**

R	Isolated yield (%)
n-Hex	77
Me	70
$(CH_3)_2C(OH)CH_2CH_3$	81
$CH_3COCH_2CH_3$	82

Scheme 15

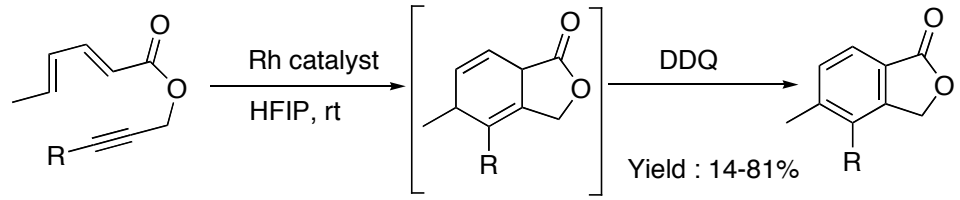
Yamamoto applied this approach for a short entry to the synthesis of cyclophanes (Scheme 16, **16.1→16.2**).



16.1 **16.2**

Scheme 16

Saito and co-workers described the Diels-Alder cyclization of esters such as **17.1** (Scheme 17). The reaction proceeded at room temperature using a cationic rhodium catalyst in hexafluoroisopropanol (HFIP) as solvent. The adduct **17.2** has a tendency to aromatize, hence the cyclization was most conveniently worked up in the presence of DDQ to give **17.3**.[18]



17.1 **17.2** **17.3**

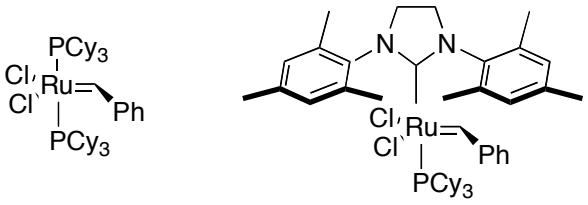
R = H, Me, Ph, TBS

Scheme 17

The best yield (81%) was obtained when R = H and, as the bulkiness of R increases, the yield drops considerably (R = Ph, TBS, 11%, 14% respectively). However, the yield can be improved if the reaction is done in trifluoroethanol as solvent.

1.3.2 Synthesis of benzene derivatives via ring closing metathesis

Ring closing metathesis (RCM) has become a very important method for constructing cyclic compounds of various sizes.[19] The success of this reaction is largely due to the discovery by Grubbs *et al*. of active well-defined ruthenium catalysts, namely Grubb's first (**18.1**) and second (**18.2**) generation catalysts (Scheme 18). The application of RCM for building up the aromatic moiety from acyclic precursors has emerged as an interesting strategy, mainly because of high reactivity and functional group tolerance of the catalysts.



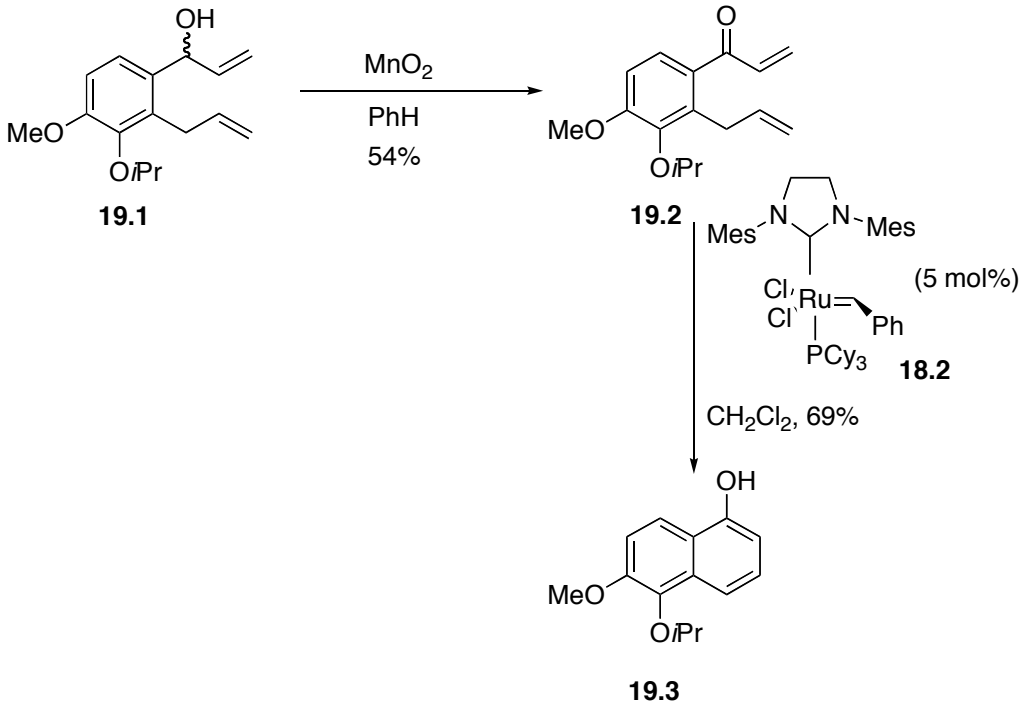
18.1 **18.2**

Scheme 18

An examination of the literature reveals that RCM has been mainly used for the construction of heteroaromatics such as pyrroles, furans, quinolines and indoles, and there are very few reports on the synthesis of benzene derivatives.[20] Construction of an aromatic ring by RCM followed four main strategies. First, ring closure followed by an aromatization via oxidation (Scheme 21, **21.4→21.6**); second, RCM to give an appropriate cyclic compound, and then elimination of suitably placed leaving groups (Scheme 21, **21.1→21.3**); third, construction of new rings fused to existing aromatic frameworks (Scheme 23, **23.1→23.2**), and finally, a combination of RCM with tautomerization of the products (Scheme 19, **19.1→19.3** and Scheme 20, **20.1→20.3**).

The last approach, that is, RCM combines with tautomerization of the products, is an elegant way of making aromatic compounds directly and so far only carbocyclic arenes have been prepared in this way. In 2003, Van Otterlo and co-workers reported the first example of making aromatic compounds via an RCM/tautomerization approach.[21] During their study on the synthesis of benzo-fused bicyclic compounds using RCM, they also demonstrated one example of making a naphthol derivative (**19.3**) in 69% yield (Scheme 19). Thus, an allylic

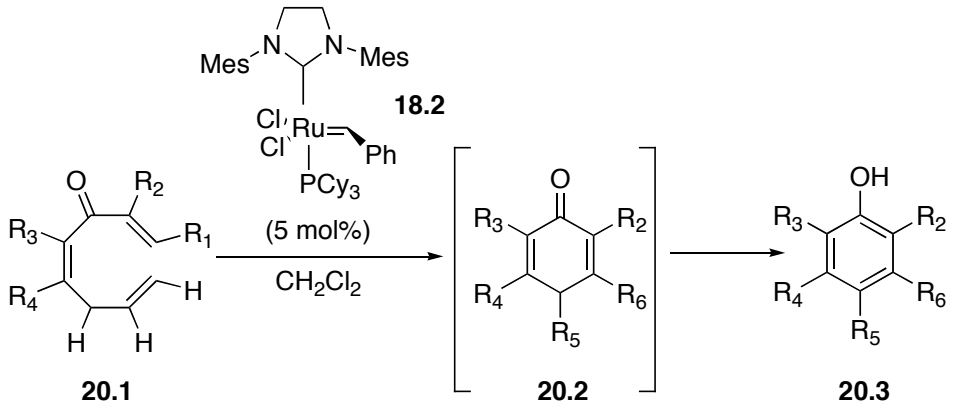
oxidation of alcohol **19.1** with MnO_2 followed by RCM using Grubbs's second generation catalyst **18.2**, gave naphthol **19.3**, which was presumably formed by tautomerization of the corresponding cyclic ketone intermediate derived from **19.2**.



Scheme 19

In 2005, Imamoto *et al.* used the same approach for constructing a series of substituted phenol derivatives.[22] When a range of substituted trienes **20.1** were subjected to RCM with Grubbs's second generation catalyst (**18.2)** in dichloromethane, the ketone intermediates **20.2** were formed, which spontaneously tautomerized to the desired phenols **20.3** (Scheme 20). In most cases, the reaction proceeded in very good yields. Substituents such as alkyl,

phenyl, silyl and alkyloxy could be placed on the ring to a maximum of three groups in total.



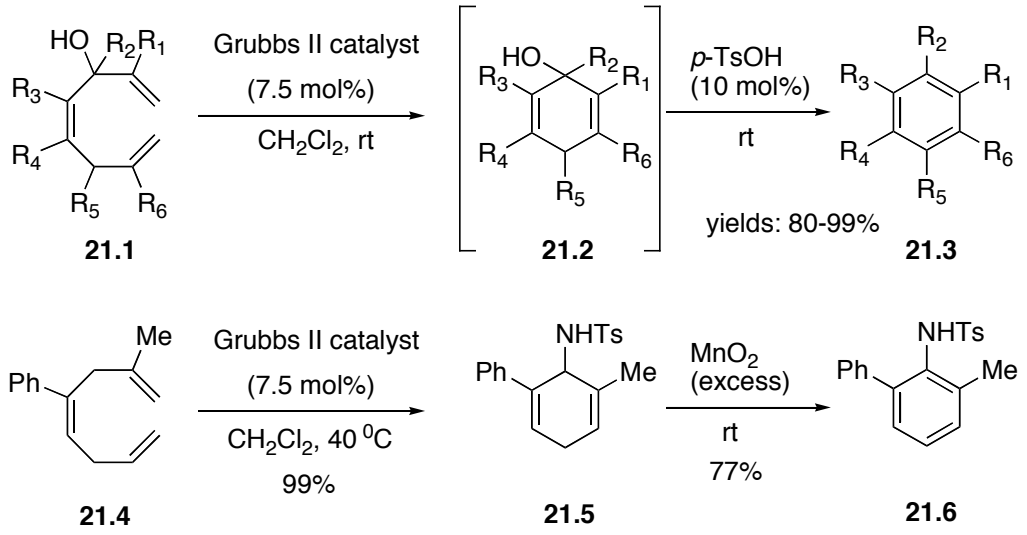
R_1	R_2	R_3	R_4	Yield %
H	H	Ph	H	90
H	Me	^{n}Pr	^{n}Pr	92
H	Et	$SiMe_3$	H	97
H	C_2H_4OAc	Ph	H	98

Scheme 20

The same group in 2006 reported a tandem RCM/dehydration and RCM/oxidation processes for the synthesis of a variety of substituted benzene derivatives (Scheme 21).[23] Treatment of trienols **21.1** with Grubbs' first generation catalyst (**18.1)** in dichloromethane at room temperature gave the

intermediate dienols **21.2**, which were dehydrated in the presence of a catalytic amount of TsOH to afford the desired benzene derivatives **21.3**. The tandem RCM/dehydration process appears to be general with a number of substrates (alkyl, aryl and alkyloxy). The reaction proceeds in very good to excellent yields (80-99%).

In some cases, increasing the steric bulk on the terminal olefins led to a decrease in reaction rate in the RCM step. However, this problem was solved by using Grubbs' second generation catalyst **(18.2**). Mono-, di- and trisubstituted benzene derivatives were accessible by this method.

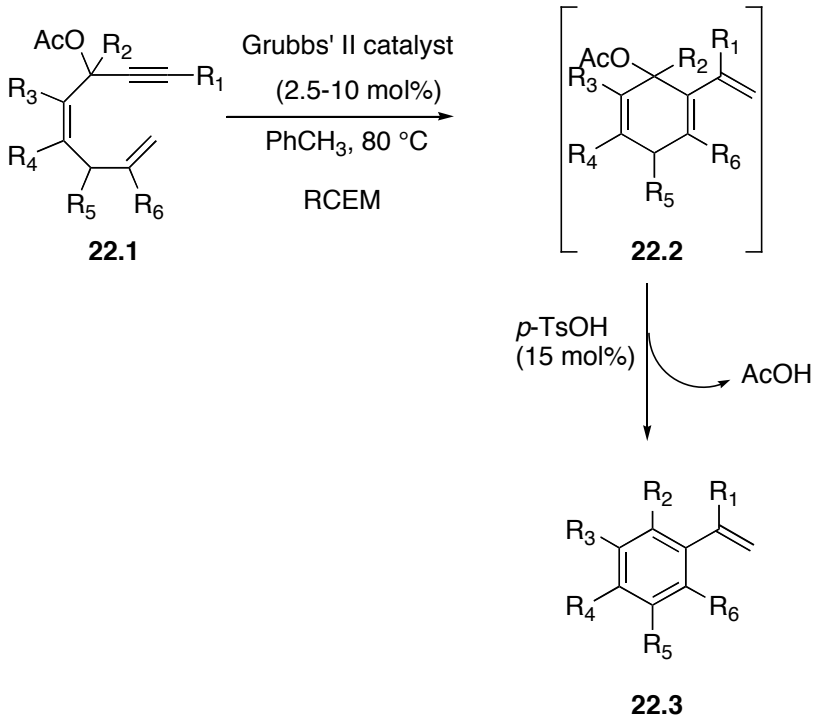


Scheme 21

The methodology was also applied to the synthesis of aniline derivative **21.6** via a RCM/oxidation process (Scheme 21, **21.4→21.6**). In this case,

oxidation of **21.5** with excess MnO_2 gave the corresponding aniline derivative **21.6**.

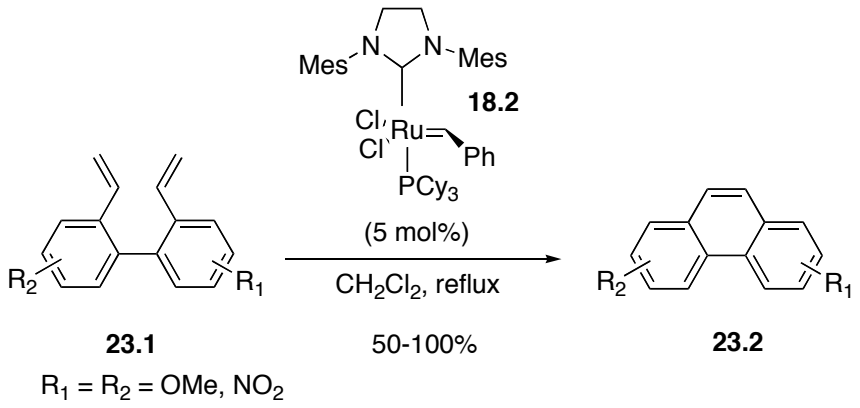
Imamoto's group also recently described the synthesis of substituted styrenes by a ring closing enyne metathesis/elimination strategy (Scheme 22).[24]



Scheme 22

Reaction was found to proceed best at 80 °C as attempts to carry out the reaction at room temperature gave a lower yield. Elimination of the acetate group drives the aromatization step. Introduction of an alkyl, aryl, pyridyl, haloalkyl or an ester group at the R_1 position was accomplished without any problems because of the great functional group tolerance of the catalyst. However, reactivity was decreased when R_1 is hydrogen and R_6 is methyl (34%).

The use of RCM to construct a new ring that is appended to an existing unsaturated framework can also result in the formation of a new aromatic ring. Luliano and co-workers described RCM of 2,2'-divinylbiphenyls **23.1** to give differently substituted phenanthrenes **23.2** (Scheme 23).[25] 2,2'-Divinylbiphenyls **23.1** were easily prepared by Wittig olefination of benzaldehyde precursors.



23.1
$R_1 = R_2 = OMe, NO_2$

50-100%

23.2

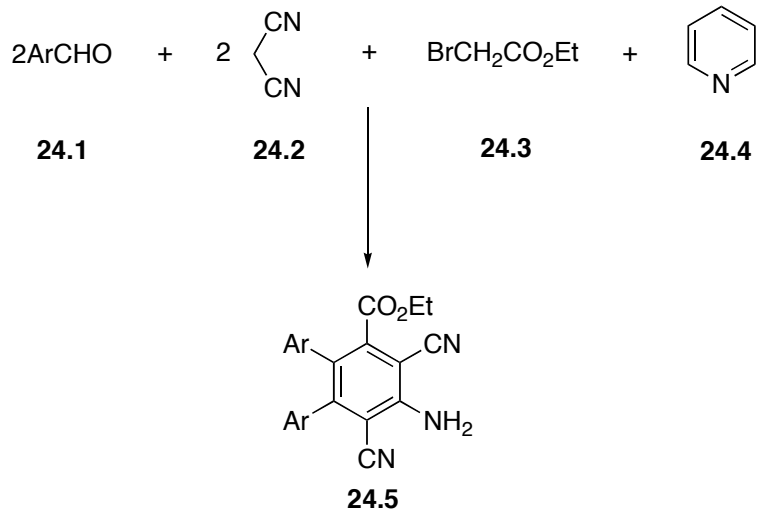
Scheme 23

Reaction proceeded under mild conditions and is independent of both the nature and position of the groups located on the biphenyl moiety. The only limitation of this methodology is that it is impossible to form phenanthrenes having substituents at positions 9 and 10.

1.4 Miscellaneous reactions

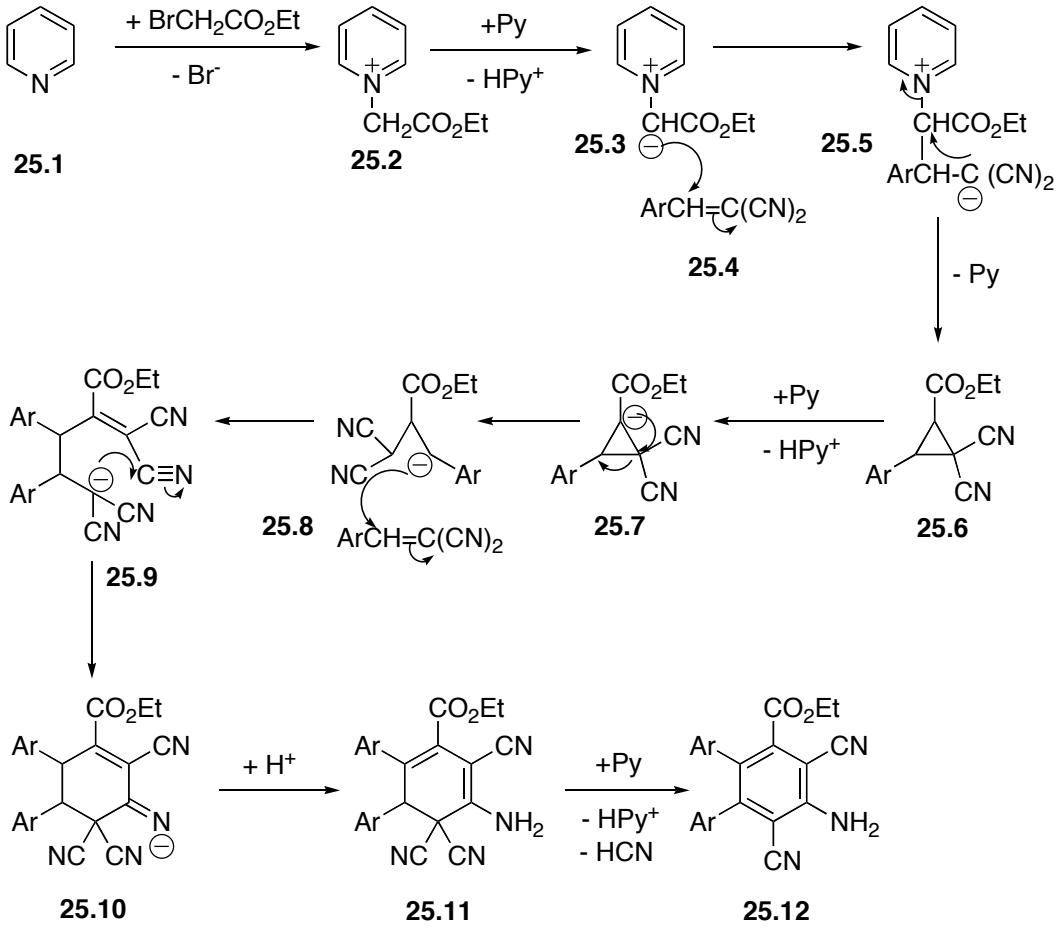
Recently, Yan and co-workers reported a one-pot multi-component cyclization reaction of pyridine (**24.4**), ethyl α-bromoacetate (**24.3**), malononitrile (**24.2**) and aromatic aldehyde **24.1** in refluxing acetonitrile to prepare

polysubstituted benzene derivatives **24.5** (Scheme 24).[28] The reaction proceeded in moderate yields (31-53%).



Scheme 24

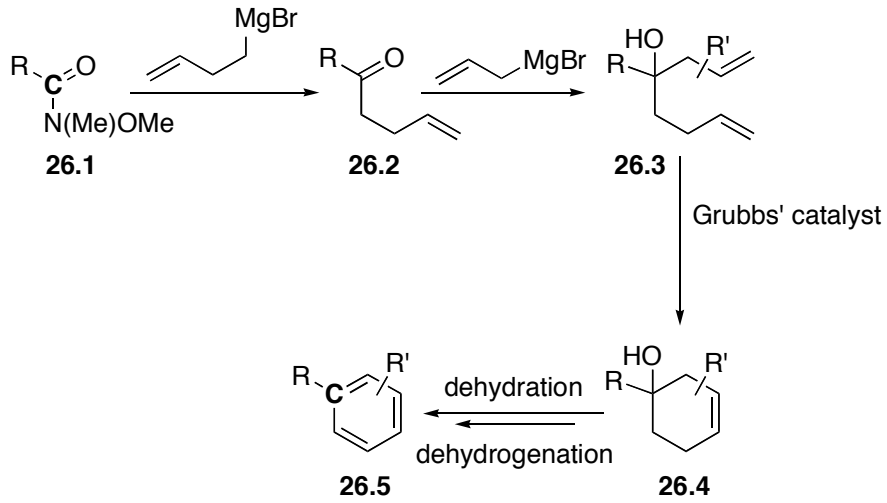
The authors proposed a mechanism for the one-pot four component reaction, as depicted in Scheme 25. The key steps in the mechanism involve a Knoevenagel condensation to form **25.4**, a Michael addition (**25.3→25.4**) followed by cyclopropane formation (**25.5→25.6**), an intramolecular addition (**25.9→25.10**) to give a six-membered carbocycle and, finally, an aromatization process (**25.11→25.12**). The presence of the two cyano groups is vital for the reaction sequence, particularly, in the final steps, where they act as strongly electron withdrawing and leaving groups to favor aromatization. This mechanism was supported by the isolation of key intermediates, such as the cyclopropane **25.6** and the six-membered ring system **25.11**, as well as the final aromatized product **25.12** for an X-ray diffraction analysis.



Scheme 25

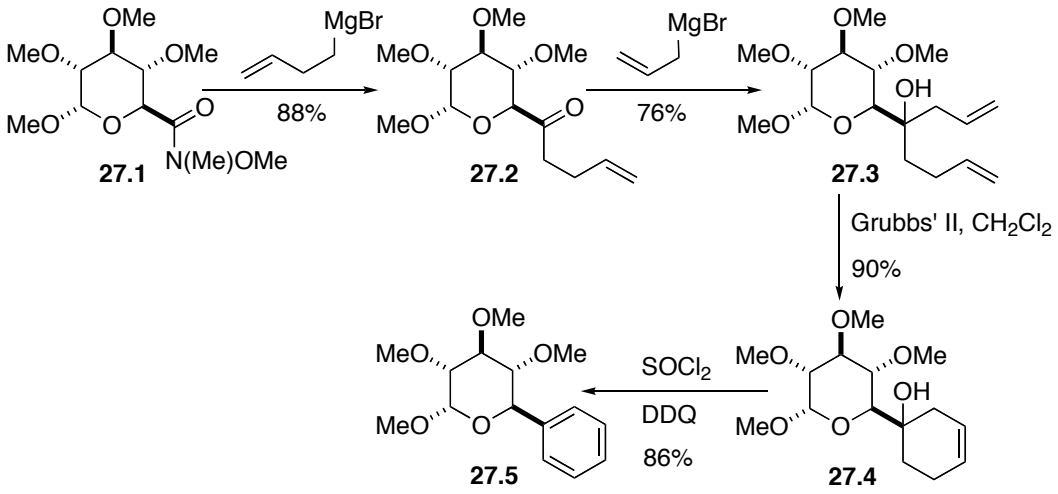
This year, Clive and Pham have shown that benzene derivatives can be formed from esters and acids via the intermediacy of their corresponding Weinreb amides (Scheme 26).[27] A special feature of this methodology is that the benzene ring formed incorporates the amide carbonyl carbon. The process involves treatment of the ester-derived Weinreb amides **26.1** with 3-butenylmagnesium bromide and an allylic Grignard reagent (**26.1→26.3**), followed by ring closing metathesis (**26.3→26.4**) using 5 mol% Grubbs I or Grubbs II, and dehydration and dehydrogenation (**26.4→26.5**). The dehydration and rearomatization can be

done under acidic conditions with a mixture of $TsOH.H_2O$ and DDQ, or in two steps with $SOCl_2$/pyridine, followed by treatment with DDQ.



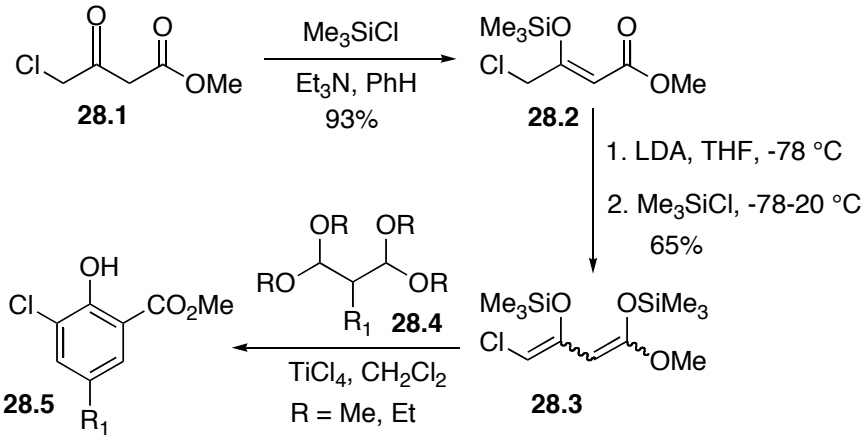
Scheme 26

The overall sequence proceeds with good yields and the method allows the formation of *ortho*- and *meta*-disubstituted benzenes. This method was applied to carbohydrate substrates, and gives easy access to *C*-5 aryl pyranosides with retention of stereochemistry (Scheme 27, **27.1→27.5**). Some carbohydrates derivatives with *C*-5 aryl groups are known[28] to inhibit sodium glucose co-transporter type 2, and might provide a mechanism to lower the elevated blood glucose levels of patients with diabetes.[29]



Scheme 27

Langer *et al*. have recently shown that a variety of highly substituted chlorinated arenes could be regioselectively prepared by one pot cyclizations of the first 4-chloro-1,3-bis(trimethylsilyloxy)-1,3-butadiene (Scheme 28).[30] Functionalized chloroarenes are of great pharmacological relevance.[31] Thus, silylation of commercially available methyl 4-chloroacetoacetate (**28.1**) gave the silyl enol ether **28.2** in 93% yield. Deprotonation of **28.2** with LDA followed by addition of chlorotrimethylsilane, afforded diene **28.3** which, upon $TiCl_3$-mediated [3+3] cyclization in the presence of compound **28.4**, gave the desired 3-chlorosalicylates **28.5** in moderate yields. A noteworthy feature is that the chloro groups proved to be compatible with the reaction conditions and the diene **28.3** can be stored at -20 °C for several weeks.



Scheme 28

The above examples are an arbitrary selection of recently developed methods. There are, however, many other approaches (benzannulation reactions such as the [3+2+1] Dötz reaction of Fischer carbene complexes,[32a] Danheiser alkyne-cyclobutanone [4+2] cyclization,[32b] [3+3] cyclocondensation of biselectrophiles with bisnucleophiles[32c] and 1,6-electrocyclic reaction[32d]) for the construction of benzene derivatives, but the regiospecific preparation of polyfuctionalized aromatic compounds remains a synthetic challenge. Some of these methodologies have been applied in the synthesis of natural products.[33]

2 RESULTS AND DISCUSSION

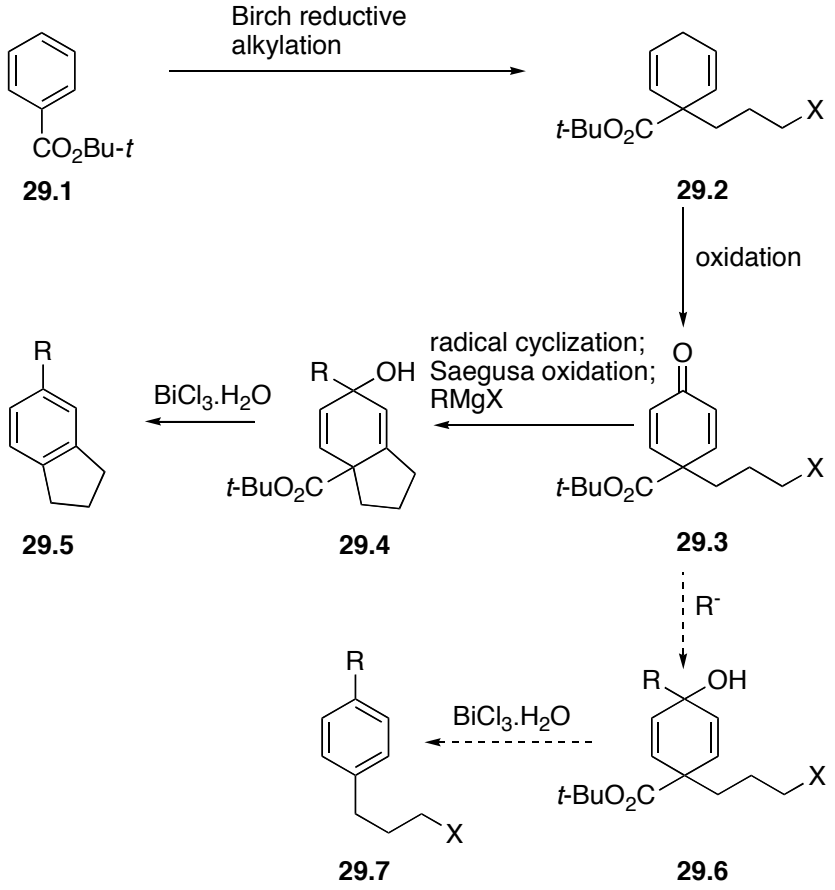
2.1 *Research Objectives*

Although many approaches are available for the synthesis of substituted aromatics,[4] the general importance of such compounds (fundamental structures of natural products, functional materials, pharmacological and industrial relevance) leaves considerable room for the development of new synthetic procedures. Many synthetic routes for the preparation of benzene derivatives suffer from a long multistep reaction sequence, low yields of target products and, in particular, serious regiochemical issues. Herein, we report a method that starts with *tert*-butyl benzoates or *tert*-butyl 1-naphthoates and allows the introduction of two carbon substituents in a 1,4-relationship.

2.2 *Principle of the method*

During our recent work on formation of benzo-fused carbocycles,[34] $BiCl_3.H_2O$ was used as a reagent for deprotection of *tert*-butyl esters and to our delight, decarboxylation and rearomatization took place simultaneously (Scheme 29). Several cross-conjugated dienones of type **29.3** have been prepared in this laboratory by alkylative Birch reduction (**29.1→29.2**), followed by allylic oxidation (**29.2→29.3**).[34] Some of these dienones were then elaborated into the alcohols **29.4**, which underwent spontaneous decarboxylative aromatization (**29.4→29.5**) on heating (70-80 °C) with $BiCl_3.H_2O$ (1.0 equiv), a reagent previously known to be useful for chemoselective deprotection of *tert*-butyl carbamates.[35] This earlier work was aimed specifically at the preparation of

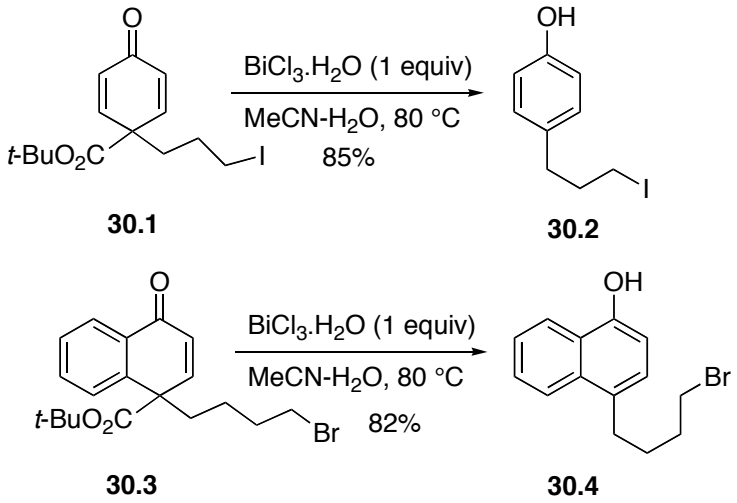
benzo-fused carbocycles (such as **29.5**), but the facility of the decarboxylative aromatization step (**29.4→29.5**) suggested that monocyclic compounds of type **29.6**, which would also be readily available from the cross-conjugated dienones **29.3** by Grignard or organolithium addition, might likewise be aromatized to give access to *para*-disubstituted benzenes **29.7**.



Scheme 29

This key deprotection-decarboxylation and aromatization step (**29.4→29.5**) mediated by $BiCl_3.H_2O$ works well in cyclic systems, where the *tert*-butyl ester group is flanked between two rings, and so we decided to carry out

some test experiments to investigate if the reaction would work in the case of monocyclic systems (**29.6**). Treatment of simple benzenoid- (**30.1**) and naphthalenoid- (**30.3**) dienones in MeCN-H_2O with stoichiometric amounts of $BiCl_3.H_2O$ afforded the desired *para*-alkyl phenol derivatives (**30.2**, **30.4**) in very good yields (Scheme 30).

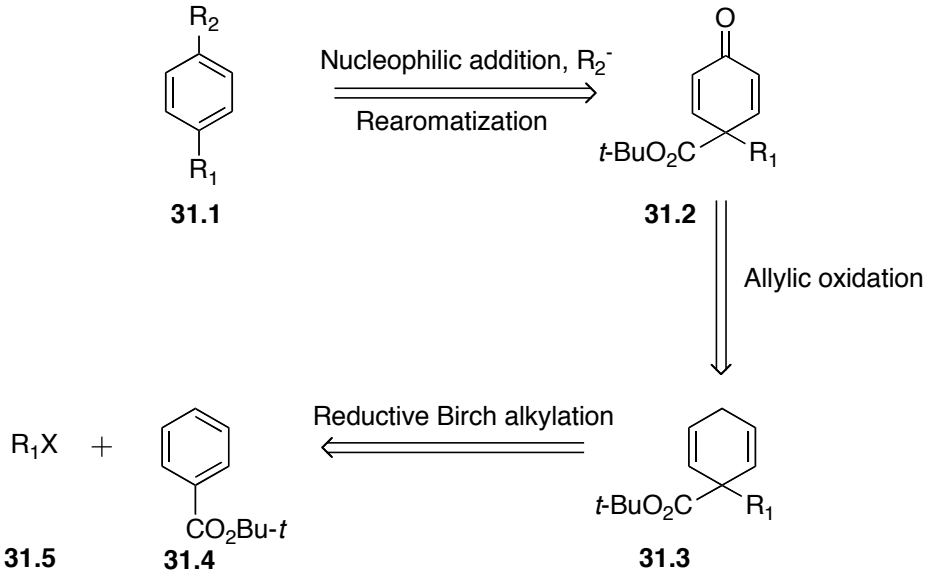


Scheme 30

Attempts to do the same reaction in the presence of TFA or $Bi(OTf)_3$ resulted in a low yield. The absence of a small amount of water in the reaction medium led to a decrease in rate and a lower yield. Hence, the optimized conditions are a stoichiometric amount of $BiCl_3.H_2O$, a mixture of acetonitrile and water (5:0.1) as the solvent system, and a temperature of 70-80 °C. While the test experiments (Scheme 30) showed that we can easily prepared *para*-alkyl phenols, we were more interested in the regioselective preparation of disubstituted aromatics having two carbon substituents in a 1,4-relationship. These 1,4-

disubstituted aromatics are important structural units of natural products (cf Scheme 1).

A simple retrosynthetic analysis is depicted in Scheme 31, where **31.1** could arise from the cross-conjugated cyclohexadienone **31.2** via addition of an organometallic species followed by treatment with $BiCl_3.H_2O$. Compound **31.2**, in turn, could arise from Birch reductive alkylation of a simple *tert*-butyl benzoate (**31.4**) and allylic oxidation of the resulting diene **31.3**.

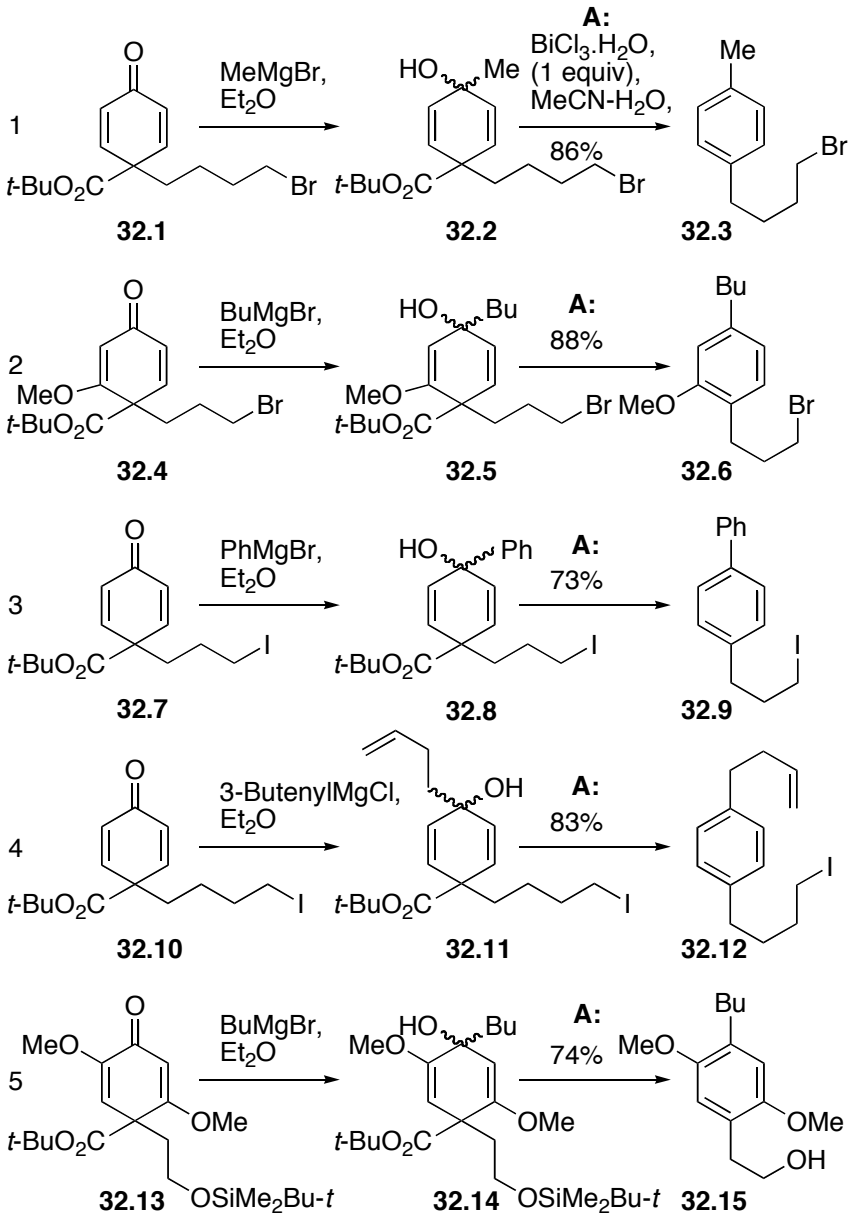


Scheme 31

2.3 Formation of 1,4-disubstituted aromatics

Most of the cross-conjugated ketones we have examined were available from our earlier study — hence the presence of a bromine or iodine atom at the end of the first alkyl chain. All the dienones were prepared by a Birch reduction/alkylation sequence, followed by oxidation with CrO_3-AcOH or PDC-*t*-

BuOOH, using procedures described in Chapter 1.[34] The cross-conjugated ketones react efficiently with Grignard reagents to produce the expected alcohols as a mixture of diastereoisomers (Scheme 32). The formation of a mixture is of no consequence, however, because treatment with 1 equiv of $BiCl_3.H_2O$ in MeCN-water at 70-80 °C transforms the alcohols smoothly into the desired aromatized products. The overall yield for the two steps — Grignard addition and aromatization — is generally above 73%. We did not establish if the bismuth salt plays a role in the decarboxylation or is involved only in removal of the *tert*-butyl group.



Scheme 32

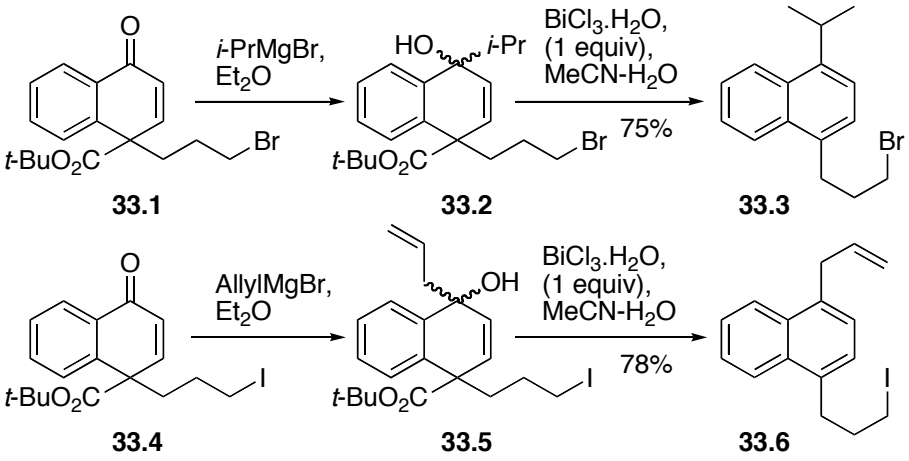
Entries 1-3 (Scheme 32) show that 1,4-disubstituted aromatics are formed having substituted alkyl groups *para* to alkyl, aryl and alkenyl groups respectively. A noteworthy feature of our method is that halogens are compatible with the reaction conditions. Moreover, substituents (such as methoxy groups) on

the starting *tert*-butyl benzoate (Entry 3) are tolerated and our experiments show that at the end of the reaction sequence, a trisubstituted or tetrasubstituted benzene derivative can be prepared as well. Entry 5 (**32.13→32.15**) indicates that a *tert*-butyldimethylsilyl group is removed in the presence of a stoichiometric amount of $BiCl_3.H_2O$. A literature search reveals that other bismuth salts, such as $Bi(OTf)_3$[36] (in MeOH) and $BiBr_3$[37] (in wet MeCN) are known to cleave *tert*-butyldimethylsilyl ethers, but $BiCl_3$ (in catalytic amounts) in MeOH is reported[36] to have no effect on this protecting group.

A 1,2-alkyl shift[38] in cross-conjugated dienones is known to occur under acidic conditions or on heating. However, in none of our cases did we observe any rearrangement during the aromatization step mediated by $BiCl_3.H_2O$, and this observation shows the effectiveness of the bismuth reagent.

2.3.1 *Formation of 1,4-disubstituted naphthalene derivatives*

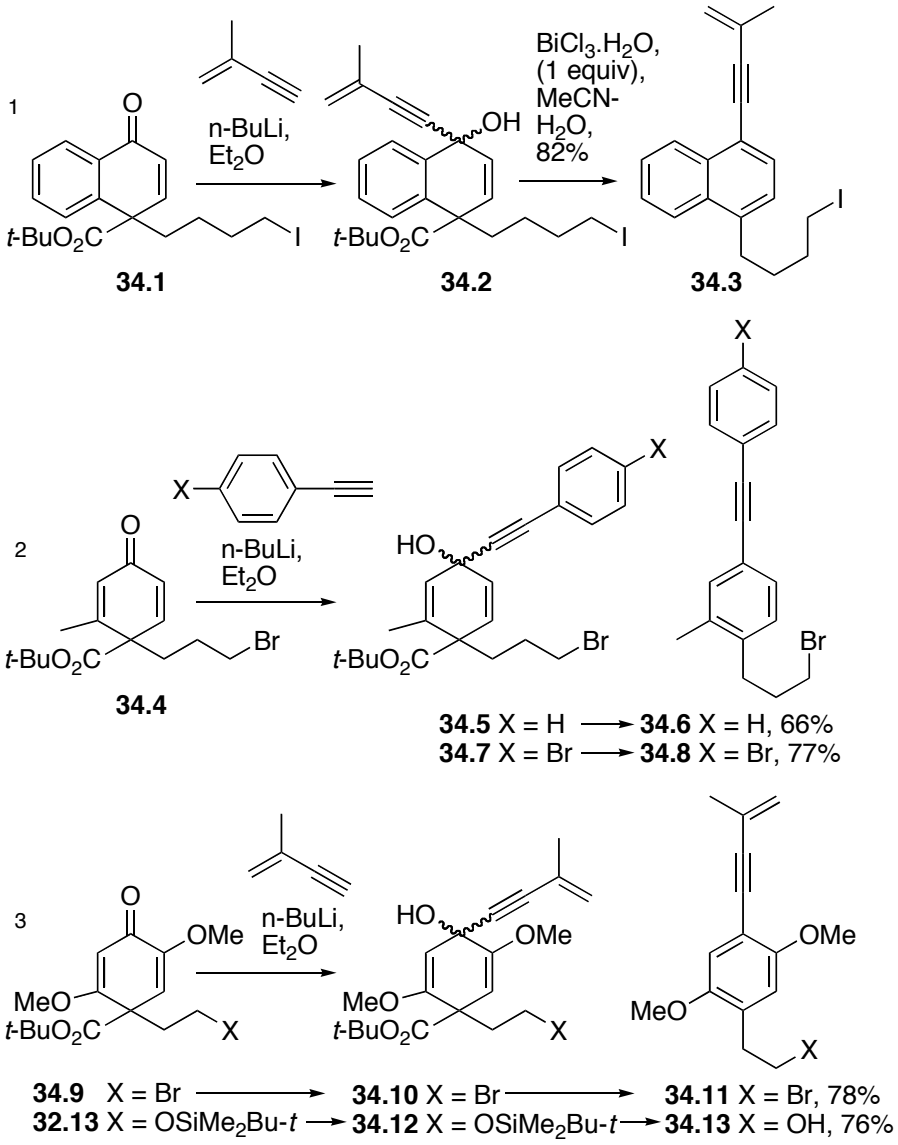
Strategies for the construction of substituted naphthalenes are limited and in the literature only a few methods have been described. They often have some disadvantages, including tedious reaction conditions, low yield, and a lack of commercial key intermediates.[39] Our method is also applicable to the construction of naphthalene derivatives if one starts with a simple *tert*-butyl 1-naphthoate (Scheme 33) and the method can be used to introduce an alkyl or alkenyl group in good yield.



Scheme 33

2.3.2 Formation of acetylenic compounds

Introduction of an acetylenic group onto an aromatic ring can be achieved via the Sonogashira cross coupling reaction of an aryl halide and a terminal alkyne in the presence of a palladium catalyst, a copper(I) cocatalyst and an amine base. Our method, however, does allow the formation of acetylenic compounds (Scheme 34) via a non-transition metal mediated process. The conversion **34.4→34.8** shows that the substructure that is being incorporated can itself bear a metal-sensitive substituent, such as a halogen (Br); this would have been problematic in the case of transition metal catalyzed cross coupling processes, but the formation of substituted alkyl-alkynyl derivatives in a 1,4 relationship was achieved in good yields by the present method.

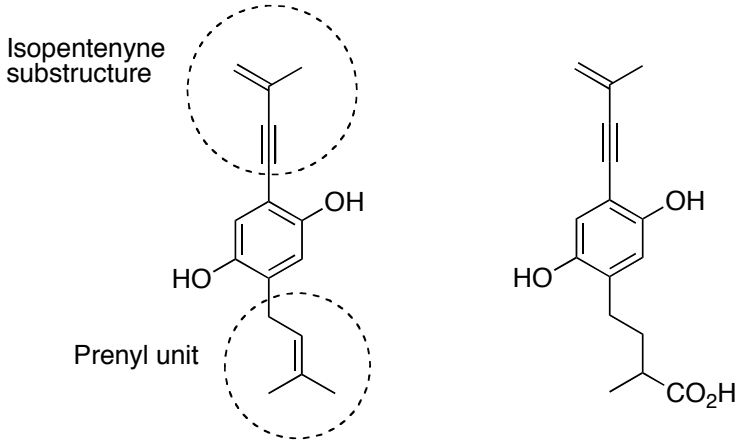


Scheme 34

2.4 Synthesis of the antibiotic culpin

Our method was then applied to the synthesis of the hydroquinone antibiotic culpin (**35.1**).[2c] Culpin was isolated from a soil sample in 1989 during the course of screening for new antifungal agents. It is produced by a species of *Preussia* isolated from a soil sample obtained in Culpeper, Virginia. A patent by

Johnson *et al* [40] disclosed that culpin has weak antimicrobial activity against a variety of bacteria and fungi, and combats bacterial infections in mammalian species, such as domesticated animals and humans. In addition, culpin was useful as a disinfectant and for suppressing the growth of susceptible microorganisms on, for example, surgical instruments. Closely related to culpin is serialynic acid (**35.2**), which was isolated from the fungus *Antrodia serialis* in 2007 and shown to exhibit weak activity against phytopathogenic fungal strains.[41] Culpin possesses an isopentenyne side chain and a prenyl fragment in a 1,4-relationship on an aromatic ring, and thus becomes a potential target for our methodology (Scheme 35). No synthesis of culpin had been reported before our own work.

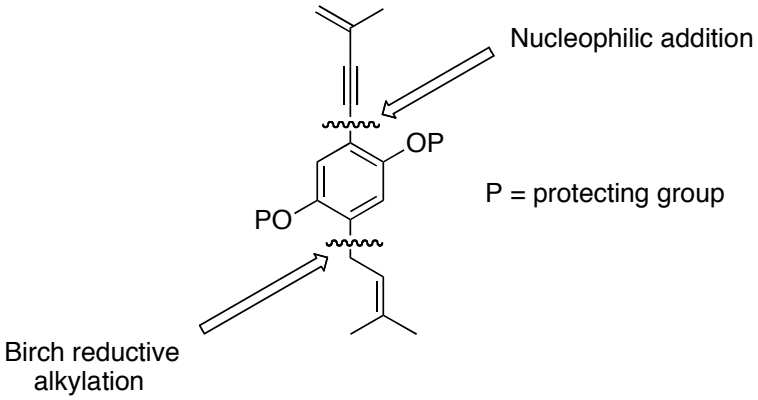


Culpin **35.1** Serialynic acid **35.2**

Scheme 35

Our initial plan is depicted in Scheme 36, where the isopentenyne substructure would be introduced via a nucleophilic addition to the corresponding cross-conjugated dienone, and the prenyl unit via a Birch reductive alkylation in

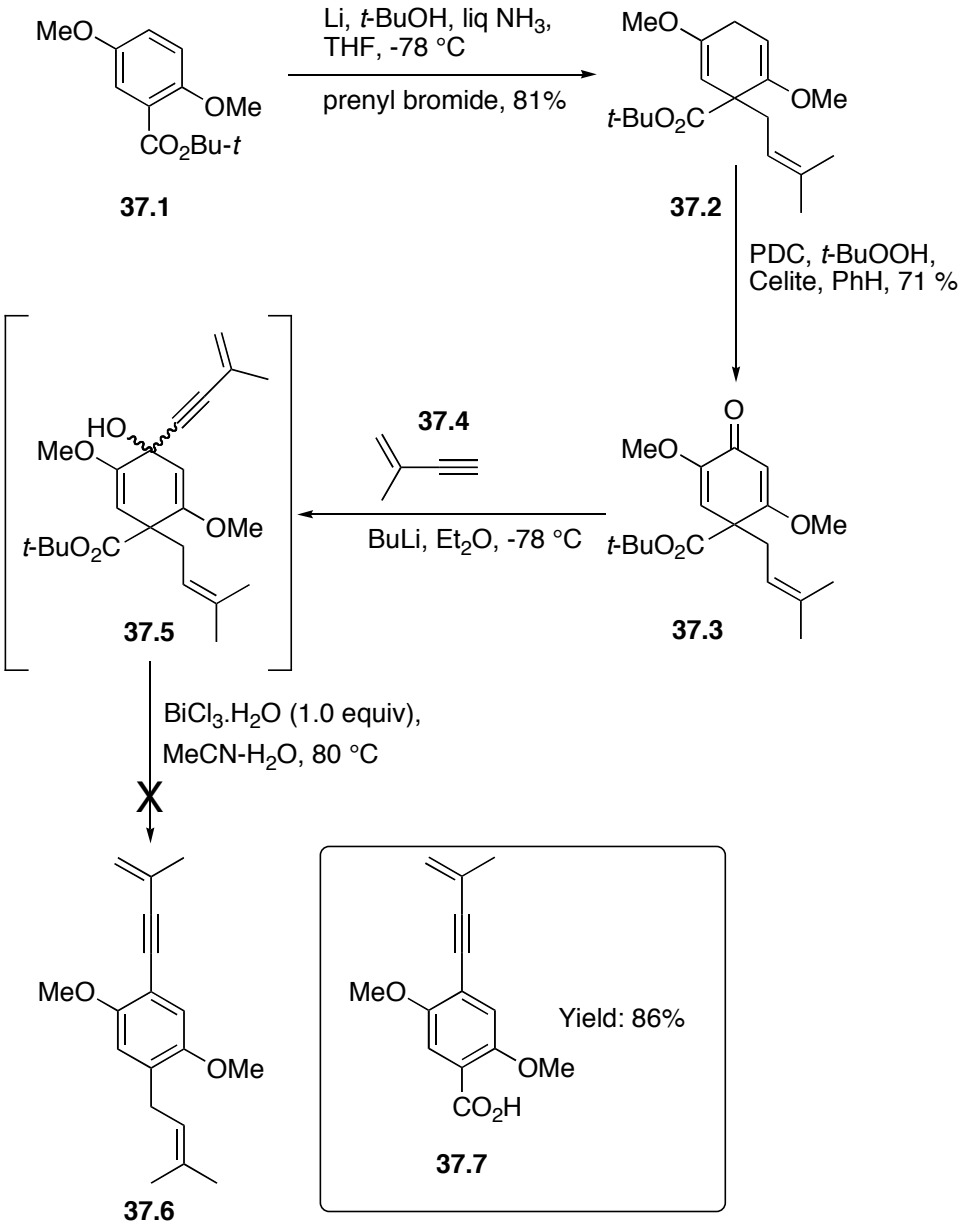
the presence of prenylbromide. The phenolic hydroxyl groups would be initially capped with a protecting group or a precursor of the phenol (such as a methoxy group).



Scheme 36

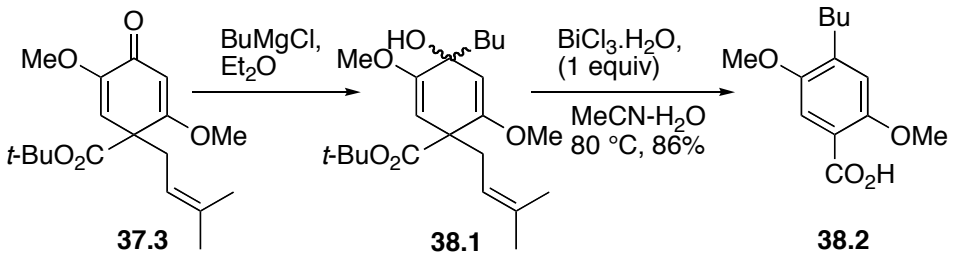
Thus, an attempted synthesis of culpin began with Birch reduction of 2,5-dimethoxy *tert*-butyl benzoate (**37.1**) and the resulting intermediate anion was trapped by alkylation with prenyl bromide to afford diene **37.2** in 81% yield. Allylic oxidation of the cycclohexadiene unit of **37.2**, using PDC-*t*-BuOOH, served to produce the desired cross-conjugated ketone **37.3** in good yield. Treatment of ketone **37.3** with the alkynyllithium derived from **37.4** in diethyl ether at -78 °C gave the tertiary alcohol intermediate **37.5** (reaction monitored by IR spectroscopy) which, upon reaction with $BiCl_3.H_2O$, did not proceed as expected and no trace of compound **37.6** was observed. The latter would have required just one step to complete the synthesis of culpin. Instead, what we isolated was the carboxylic acid derivative **37.7**. Formation of the acid derivative **37.7** can be rationalized by assuming that loss of the prenyl fragment is faster than

the decarboxylation step. Attempts to minimize the formation of **37.7** by decreasing the temperature or amount of $BiCl_3.H_2O$ were unsuccessful, and only compound **37.7** was isolated.



Scheme 37

This preference for the loss of a prenyl unit (we did not test other allylic substituents), rather than decarboxylation, appears to be general, as compound **38.1** behaved in a similar way (Scheme 38). The acid **38.2** was obtained in 86% yield on treatment with $BiCl_3.H_2O$.

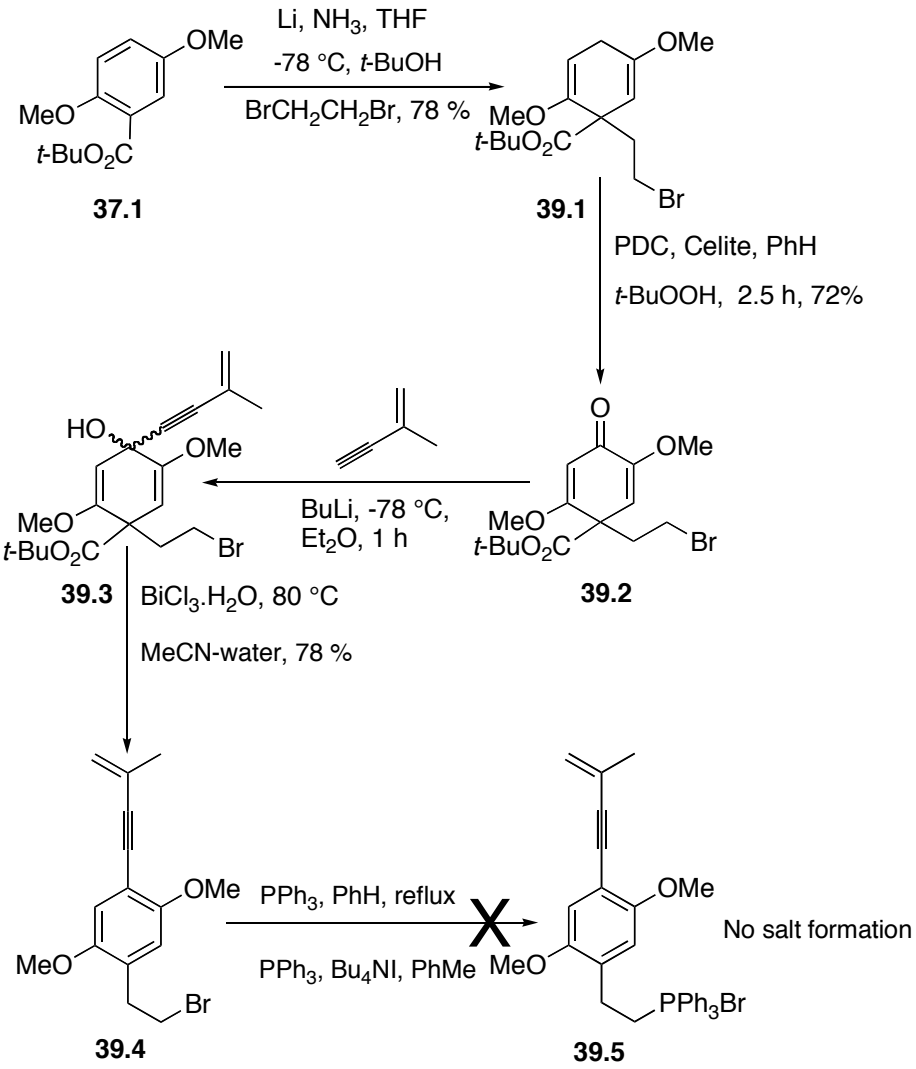


37.3 **38.1** **38.2**

Scheme 38

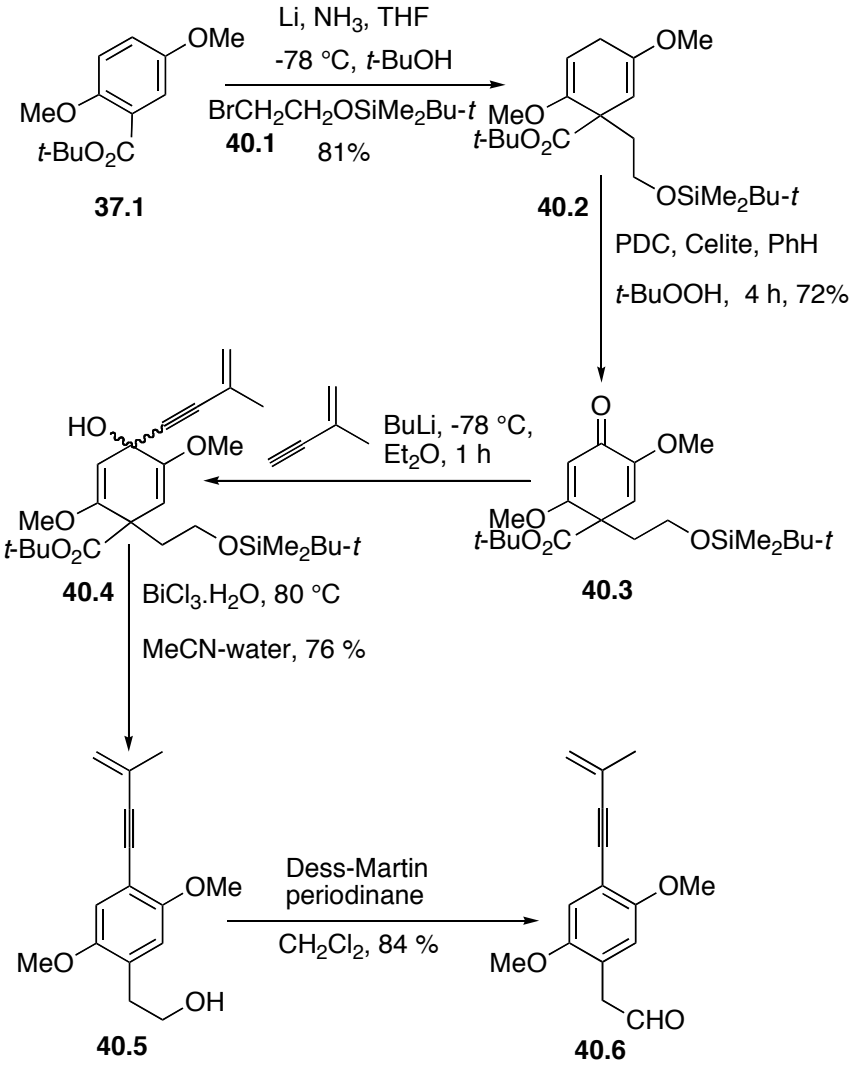
This unexpected result necessitated a different approach in which the prenyl unit of culpin would be elaborated *after* the rearomatization step. Taking advantage of Birch reductive alkylation, which provides an opportunity to introduce different chains on the ring, our plan was to have a bromine atom at the end of a chain that would eventually be converted to a phosphonium salt and the latter would be a good precursor for a subsequent Wittig reaction to install the prenyl fragment. With this in mind, Birch reductive alkylation in the presence of 1,2 dibromoethane gave diene **39.1** in good yield (Scheme 39). The usual sequence of reactions was repeated — oxidation, nucleophilic attack of an alkynyl species and rearomatization mediated by $BiCl_3.H_2O$ — to provide the desired aromatized product **39.4** (78% over 2 steps). Unfortunately, all attempts to generate the phosphonium salt **39.5** in the presence of triphenylphosphine

(refluxing in PhH for several days or use of a catalytic amount of *tert*-butyl ammonium iodide), were unsuccessful. No salt formation was observed and only starting material was recovered. Addition of acetone directly to a solution of starting material and triphenylphosphine that had been refluxing for 3 days resulted in no reaction.



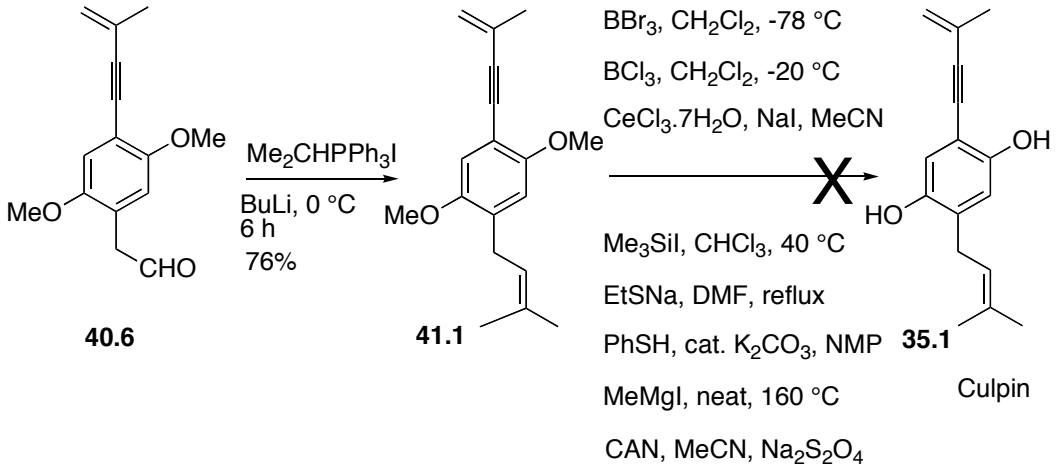
Scheme 39

At this stage, we reasoned that if we reverse the Wittig process, that is, if we have an aldehyde group at the end of the chain attached to the eventual aromatic ring, then Wittig reaction with the appropriate phosphonium reagent should install the desired prenyl unit. To this end, Birch alkylation (**37.1→40.2**) was done in the presence of the bromosilylated derivative **40.1**, as the silyl protected primary alcohol would be a precursor for the aldehyde group later in the synthesis (Scheme 40).



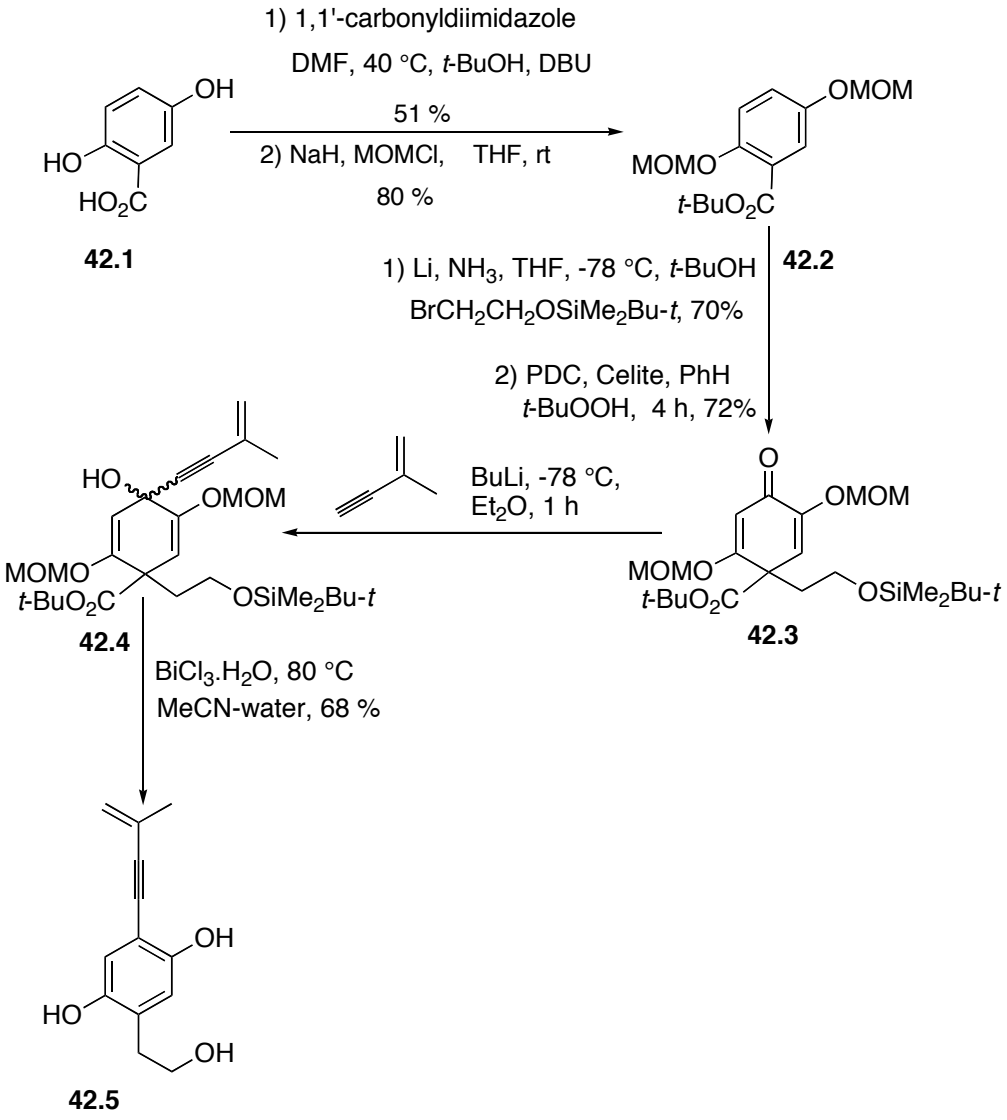
Scheme 40

Upon reaction of the tertiary alcohol intermediate **40.4** with $BiCl_3.H_2O$, deprotection of the *tert*-butyl ester, decarboxylation, rearomatization and deprotection of the *tert*-butyldimethylsilyl group all occurred, to afford the desired aromatized alcohol derivative in 76% yield. Alcohol **40.5** was smoothly transformed into the corresponding aldehyde **40.6** upon oxidation with Dess-Martin periodinane (DMP). Treatment of the aldehyde with the isopropylidenetriphenylphosphorane finally installed the prenyl unit to give compound **41.1** (Scheme 41), which is the precursor of culpin (**35.1**). However, demethylation (**41.1→35.1**) to release culpin (**35.1**) was problematic. We tried various standard conditions (acidic, basic and nucleophilic) for demethylation, but in all cases obtained either a complex mixture or recovered the starting material. We suspect that the enediyne fragment is sensitive to the demethylation conditions, as in one case, the crude proton NMR spectrum showed loss of this fragment.



Scheme 41

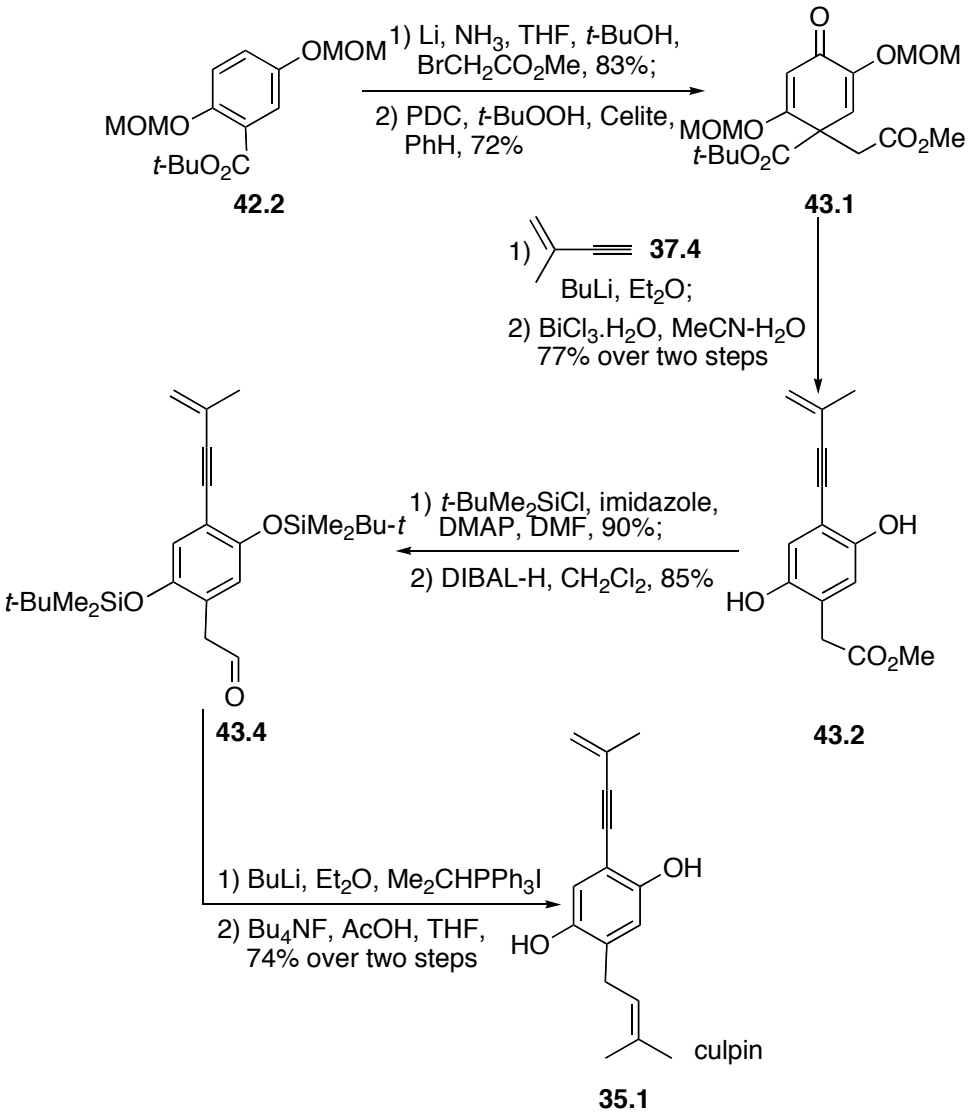
Our efforts to synthesize culpin continued and we decided to use a different protecting group; specifically, we opted to prepare the bis-MOM ether **42.2** since the latter can be easily synthesized in gram quantities from gentisic acid **42.1** (Scheme 42).



Scheme 42

The same sequence of reactions as used before were repeated (Scheme 42) and during the rearomatization step (**42.4→42.5**), the unexpected loss of the MOM groups was observed to give triol **42.5** (68%). Further manipulation of triol **42.5** was problematic due to its instability under various reaction conditions.

The results so far implied that the sensitivity of the culpin structure imposes several restrictions on the types of protecting groups that can be used for the phenolic oxygens. With bis-MOM ether **42.2** still in hand, we decided to attempt Birch alkylation with $BrCH_2CO_2Me$. This approach was successful, and our eventual route to culpin is shown in Scheme 43.



Scheme 43

Reaction of **43.1** with the lithium salt of the acetylene **37.4**, and treatment with $BiCl_3.H_2O$ under our standard conditions, resulted not only in aromatization but also in loss of the MOM groups. Accordingly, the resulting bis-phenol **43.2** was silylated and the ester side-chain was elaborated to the required prenyl unit by standard reactions (DIBAL reduction of the ester to the corresponding

aldehyde and Wittig olefination). Finally, desilylation, using TBAF furnished culpin (**35.1**).

While we expect that culpin should be more easily accessible by transition-metal-catalyzed coupling reactions, using a suitably protected 2,5-dihalo-1,4-benzenediol, our synthesis, nevertheless reveals interesting features of the general reaction we have developed for making 1,4-disubstituted aromatics.

3 CONCLUSION

We have been able to illustrate a method for converting *tert*-butyl benzoates or *tert*-butyl 1-naphthoates into derivatives having a substituted alkyl group in a 1,4-relationship to an alkyl, aryl, alkenyl or alkynyl group. The key step is a one-pot deprotection of a *tert*-butyl ester followed by spontaneous decarboxylative aromatization mediated by $BiCl_3.H_2O$. Our method has been applied to the synthesis of the antimicrobial fungal metabolite culpin. The work on culpin also served to identify a limitation in the nature of the groups that survive the decarboxylative aromatization in the presence of $BiCl_3.H_2O$.[42]

4 EXPERIMENTAL

Unless stated to the contrary, the following conditions apply: Reactions were carried out under a slight static pressure of Ar or N_2 that had been purified by passage through a column (3.5 x 42 cm) of R-311 catalyst and then through a similar column of Drierite. All solvents for reactions were dried, as described below. Glassware was dried in an oven (140 °C) for at least 3 h before use and either cooled in a desiccator over Drierite, or assembled quickly, sealed with rubber septa, and allowed to cool under a slight static pressure of Ar or N_2. Reaction mixtures were stirred by Teflon-coated magnetic stirring bars.

Hexane and ethyl acetate used for chromatography were distilled before use.

Products were isolated from solution by evaporation under water aspirator vacuum at, or below, room temperature, using a rotary evaporator.

Microliter syringes were washed with water and acetone, using a suction device to draw the solvents through. Air was then drawn through for 1 min and the syringe was stored under vacuum. The solution to be dispensed was drawn up and expelled, and this operation was repeated several times before drawing up the sample to be used. Cannula transfers were always done under slight pressure (Ar or N_2), not by suction.

Commercial thin layer chromatography (TLC) plates (silica gel, Merck 60F–254) were used. Spots were detected by spraying the plate with a solution of phosphomolybdic acid, followed by charring with a heat gun, or by examination

under UV light. Silica gel for flash chromatography was Merck type 60 (230-400 mesh).

Dry solvents were prepared under an inert atmosphere and transferred by syringe or cannula. Dry THF, Et_2O, PhH, PhMe and dioxane were distilled from sodium and benzophenone ketyl. Dry CH_2Cl_2, Et_3N, *i*-Pr_2NEt and pyridine were distilled from CaH_2. Dry MeOH was distilled from $Mg(OMe)_2$. FT-IR measurements were made from the specified solvent using KBr plates.

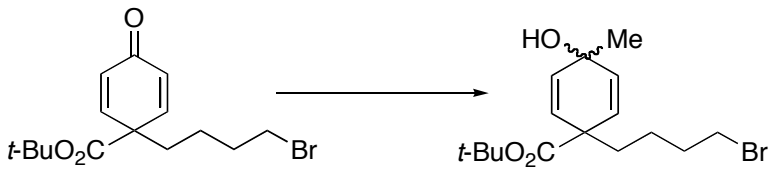
The symbols s, d, t, and q used for ^{13}C NMR signals indicate 0, 1, 2, or 3 attached hydrogens, respectively, as based on the APT experiment.

Mass spectra were recorded with Agilent Technologies 6220 Accurate-Mass TOF LC/MS, Perseptive Biosystems Mariner Biospectrometry Workstation, Kratos MS50 or Micromass ZabSpec Hybrid Sector-TOF mass spectrometers.

General procedure for rearomatization.

$BiCl_3.H_2O$[34] (1 equiv) was added to a solution of the intermediate tertiary alcohol in a mixture of MeCN (5 mL) and water (0.1 mL), and the mixture was stirred at 75-80 °C for 1-12 h until reaction was complete (TLC control). The mixture was filtered through Celite, using CH_2Cl_2, and the filtrate was washed with brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel gave the aromatized product.

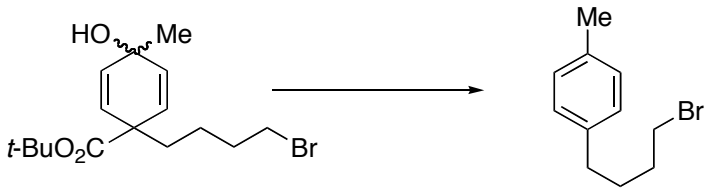
***tert*-Butyl 1-(4-Bromobutyl)-4-hydroxy-4-methylcyclohexa-2,5-diene-carboxylate (32.2).**



32.1 **32.2**

MeMgBr (3 M in Et_2O, 0.11 mL, 0.33 mmol) was added at a fast dropwise rate to a stirred and cooled (-78 °C) solution of **32.1** (100 mg, 0.30 mmol) in Et_2O (5 mL). The cold bath was removed and stirring was continued for 2 h at room temperature. The mixture was cooled to 0 °C, quenched slowly with water, and extracted with Et_2O. The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. The crude product (**32.2**) was used directly in the next step.

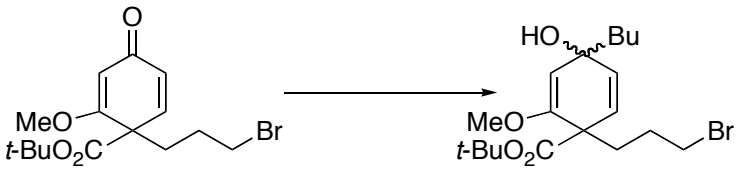
1-(4-Bromobutyl)-4-methylbenzene (32.3).[43]



32.2 **32.3**

The general procedure for rearomatization was followed, using $BiCl_3.H_2O$ (101 mg, 0.30 mmol) and **32.2** (total product from the previous step) in MeCN (5 mL) and water (0.1 mL), and a reaction time of 8 h. Flash chromatography of the crude product over silica gel (1.5 x 15 cm), using 10% EtOAc-hexane, gave **32.3** (59 mg, 86%) as an oil: FTIR (microscope, cast) 3005, 2934, 2859, 1515, 1457 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.76-1.78 (m, 2 H), 1.88-1.89 (m, 2 H), 2.33 (s, 3 H), 2.61 (t, *J* = 7.7 Hz, 2 H), 3.42 (t, *J* = 6.7 Hz, 2 H), 7.08-7.10 (m, 4 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 20.9 (q), 29.8 (t), 32.1 (t), 33.6 (t), 33.4 (t), 128.1 (d), 128.9 (d), 135.2 (s), 138.6 (s); exact mass *m/z* calcd for $C_{11}H_{15}{}^{79}Br$ 226.0357, found 226.0357.

***tert*-Butyl 1-(3-Bromopropyl)-4-butyl-4-hydroxy-2-methoxycyclohexa-2,5-dienecarboxylate (32.5).**

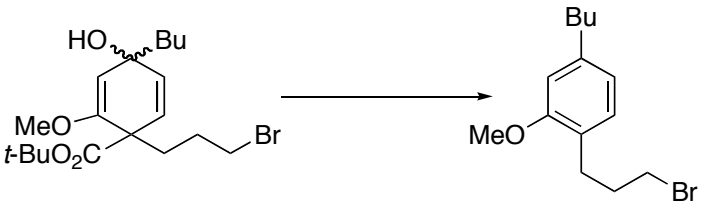


32.4 **32.5**

BuMgBr (2 M in THF, 0.09 mL, 0.17 mmol) was added at a fast dropwise rate to a stirred and cooled (-78 °C) solution of **32.4** (54 mg, 0.16 mmol) in Et_2O (10 mL). The cold bath was removed and stirring was continued for 1.5 h. The mixture was cooled to 0 °C, quenched slowly with water, and extracted with

Et_2O. The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. The crude product (**32.5**) was used directly in the next step.

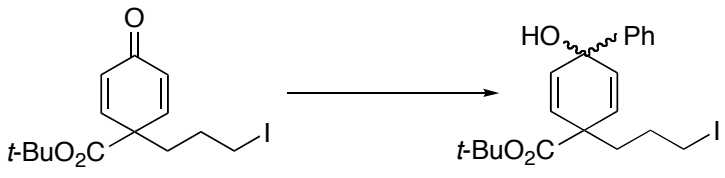
1-(3-Bromopropyl)-4-butyl-2-methoxybenzene (32.6).



32.5 **32.6**

The general procedure for rearomatization was followed, using $BiCl_3.H_2O$ (53 mg, 0.16 mmol) and **32.5** (total product from the previous step) in MeCN (5 mL) and water (0.1 mL), and a reaction time of 6 h. Flash chromatography of the crude product over silica gel (1 x 12 cm), using 10% EtOAc-hexane, gave **32.6** (39 mg, 88%) as an oil: FTIR (microscope, cast) 2999, 2956, 2856, 1612, 1580, 1509, 1260 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.94 (t, J = 7.3 Hz, 3 H), 1.36-1.41 (m, 2 H), 1.54-1.62 (m, 2 H), 2.11-2.16 (m, 2 H), 2.59 (t, J = 7.6 Hz, 2 H), 2.72 (t, J = 7.2 Hz, 2 H), 3.40 (t, J = 6.8 Hz, 2 H), 3.82 (s, 3 H), 6.67 (s, 1 H), 6.71 (d, J = 7.5 Hz, 1 H), 7.04 (d, J = 7.5 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.9 (q), 22.4 (t), 28.5 (t), 32.7 (t), 33.6 (t), 33.7 (t), 35.6 (t), 55.1 (q), 110.5 (d), 120.1 (d), 125.9 (s), 129.8 (d), 142.4 (s), 157.2 (s); exact mass m/z calcd for $C_{14}H_{21}{}^{79}Br$ 284.0776, found 284.0776.

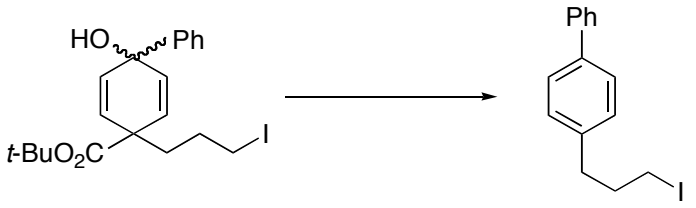
***tert*-Butyl 4-Hydroxy-1-(3-iodopropyl)-4-phenylcyclohexa-2,5-diene-carboxylate (32.8).**



32.7 **32.8**

PhMgBr (2 M in THF, 0.15 mL, 0.30 mmol) was added at a fast dropwise rate to a stirred and cooled (-78 °C) solution of **32.7** (100 mg, 0.28 mmol) in Et_2O (6 mL). The cold bath was removed and stirring was continued for 5 h. The mixture was cooled to 0 °C, quenched slowly with water, and extracted with Et_2O. The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. The crude product (**32.8**) was used directly in the next step.

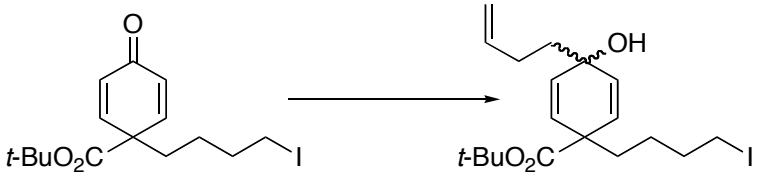
4-(3-Iodopropyl)biphenyl (32.9).[44]



32.8 **32.9**

The general procedure for rearomatization was followed, using $BiCl_3.H_2O$ (92 mg, 0.28 mmol) and **32.8** (total product from the previous step) in MeCN (5 mL) and water (0.1 mL), and a reaction time of 12 h. Flash chromatography of the crude product over silica gel (1.5 x 12 cm), using hexane, gave **32.9** (65 mg, 73%) as an oil: FTIR (microscope, cast) 3028, 2955, 2852, 1486, 1449 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.15-2.20 (m, 2 H), 2.78 (t, *J* = 7.4 Hz, 2 H), 3.21 (t, *J* = 6.8 Hz, 2 H), 7.29-7.36 (m, 2 H), 7.41-7.46 (m, 2 H), 7.52-7.60 (m, 5 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 6.2 (t), 34.7 (t), 35.7 (t), 126.9 (d), 127.0 (d), 127.1 (d), 128.6 (d), 128.9 (d), 139.1 (s), 139.4 (s), 140.8 (s); exact mass *m*/*z* calcd for $C_{15}H_{15}I$ 322.0219, found 322.0220.

***tert*-Butyl 4-(But-3-enyl)-4-hydroxy-1-(4-iodobutyl)cyclohexa-2,5-dienecarboxylate (32.11).**

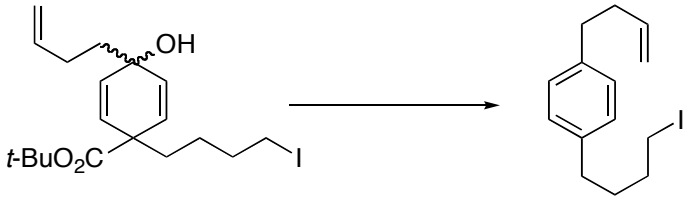


32.10 **32.11**

3-Butenylmagnesium bromide (0.5 M in THF, 1.87 mL, 0.93 mmol) was added at a fast dropwise rate to a stirred and cooled (-78 °C) solution of **32.10** (293 mg, 0.78 mmol) in Et_2O (10 mL). The cold bath was removed and stirring was continued for 5 h. The mixture was cooled to 0 °C, quenched slowly with

water, and extracted with Et_2O. The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. The crude product (**32.11**) was used directly in the next step.

1-(But-3-enyl)-4-(4-iodobutyl)benzene (32.12).

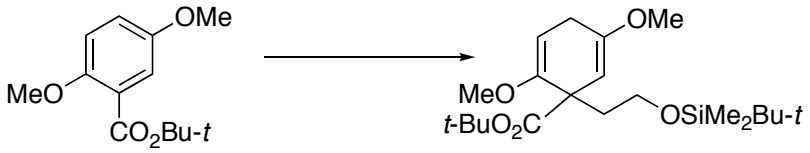


32.11 **32.12**

The general procedure for rearomatization was followed, using $BiCl_3.H_2O$ (260 mg, 0.78 mmol) and **32.11** (total product from the previous step) in MeCN (5 mL) and water (0.1 mL), and a reaction time of 8 h. Flash chromatography of the crude product over silica gel (1.5 x 15 cm), using 35% EtOAc-hexane, gave **32.12** (203 mg, 83%) as an oil: FTIR ($CDCl_3$, cast) 3049, 2932, 2855, 1640, 1514, 1452 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.70-1.76 (m, 2 H), 1.86-1.91 (m, 2 H), 2.34-2.42 (m, 2 H), 2.62 (t, J = 7.6 Hz, 2 H), 2.70 (t, J = 7.8 Hz, 2 H), 3.21 (t, J = 6.9 Hz, 2 H), 4.99 (dddd, J = 10.2, 1.5, 1.3, 1.3 Hz, 1 H), 5.06 (dddd, J = 17.1, 1.5, 1.5, 1.5 Hz, 1 H), 5.88 (dddd, J = 16.8, 10.2, 6.6, 6.6 Hz, 1 H), 7.09-7.14 (m, 4 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 6.7 (t), 32.1 (t), 32.9 (t), 34.3 (t), 34.9 (t), 35.4 (t), 114.7 (t), 128.2 (d), 128.3 (d), 138.1 (d), 139.1 (s), 139.3 (s); exact mass m/z calcd for $C_{14}H_{19}I$ 314.0532, found 314.0536.

***tert*-Butyl 1-[2-[(*tert*-Butyldimethylsilyl)oxy]ethyl]-2,5-dimethoxy-4-oxocyclohexa-2,5-dienecarboxylate (32.13).**

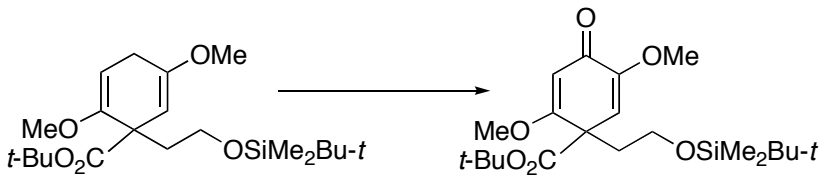
(a) *tert*-Butyl 1-[2-[(*tert*-Butyldimethylsilyl)oxy]ethyl]-2,5-dimethoxy-cyclohexa-2,5-dienecarboxylate.



37.1 **-**

A solution of **37.1** (1.00 g, 4.20 mmol) in a mixture of dry THF (20 mL) and *t*-BuOH (0.44 mL, 4.6 mmol) was injected into the three-necked flask, and liquid NH_3 (40 mL) was allowed to condense into the flask. Lithium wire (73.5 mg, 10.5 mmol), cut into small pieces, was added rapidly to the vigorously stirred solution. Stirring at -78 °C was continued for 30 min, by which time a dark blue color persisted. $BrCH_2CH_2OSiMe_2Bu$-*t* (1.5 g, 6.3 mmol) in THF (5 mL) was then added dropwise from a syringe over ca 2 min, and the resulting solution was stirred for 1 h at -78 °C. The cooling bath was removed and the NH_3 was allowed to evaporate under a stream of N_2 (2-3 h). Water was added and the mixture was extracted with Et_2O (4 times). The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. The crude product [*tert*-butyl 1-[2-[(*tert*-butyldimethylsilyl)oxy]ethyl]-2,5-dimethoxycyclo-hexa-2,5-dienecarboxylate] was used directly in the next step.

(b) *tert*-Butyl 1-[2-[(*tert*-Butyldimethylsilyl)oxy]ethyl]-2,5-dimethoxy-4-oxocyclohexa-2,5-dienecarboxylate (32.13).

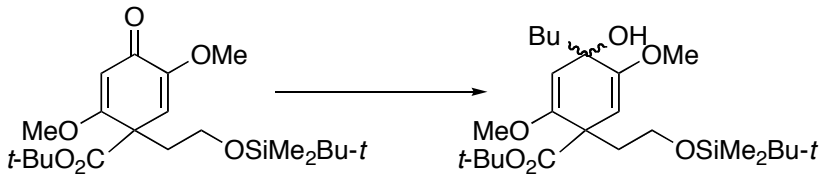


-- **32.13**

Celite (1.0 g) and then PDC (6.32 g, 16.8 mmol) were added to a stirred solution of *tert*-butyl 1-[2-[(*tert*-butyldimethylsilyl)oxy]ethyl]-2,5-dimethoxycyclohexa-2,5-dienecarboxylate (total product from the previous step) in PhH (20 mL). *t*-BuOOH (5-6 M in decane, 3.06 mL, 16.8 mmol) was added and the resulting solution was stirred at room temperature for 4 h. The mixture was filtered through Celite, and the solid was washed twice with CH_2Cl_2 (2 x 30 mL). Evaporation of the filtrate and flash chromatography of the residue over silica gel (2.5 x 25 cm), using first hexane and then EtOAc-hexane mixtures up to 1:1 EtOAc-hexane, gave **32.13** (1.26 g, 73%) as a white solid: mp 65-67 °C; FTIR ($CDCl_3$, microscope) 2935, 2955, 1736, 1662, 1646, 1210 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ -0.24 (s, 6 H), 0.84 (s, 9 H), 1.38 (s, 9 H), 2.20-2.27 (m, 1 H), 2.42-2.49 (m, 1 H), 3.37-3.48 (m, 2 H), 3.67 (s, 3 H), 3.74 (s, 3 H), 5.38 (s, 1 H), 5.70 (s, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ -5.41 (q), -5.47 (q), 18.3 (t), 25.9 (q), 27.7 (q), 37.7 (s), 54.3 (s), 55.3 (q), 56.1 (q), 59.1 (t), 82.5 (s), 103.9 (d),

110.3 (d), 151.6 (s), 168.8 (s), 173.9 (s), 182.3 (s); exact mass *m*/*z* calcd for $C_{21}H_{36}NaO_6Si$ (M + Na) 435.2173, found 435.2171.

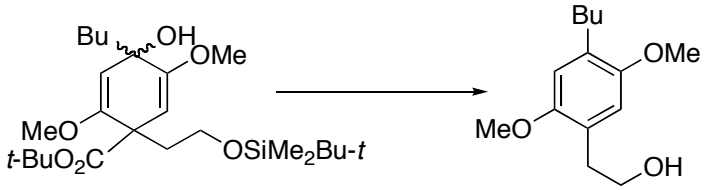
***tert*-Butyl 4-Butyl-1-[2-[(*tert*-butyldimethylsilyl)oxy]ethyl]-4-hydroxy-2,5-dimethoxycyclohexa-2,5-dienecarboxylate (32.14).**



32.13 **32.14**

BuMgBr (2 M in THF, 0.07 mL, 0.15 mmol) was added at a fast dropwise rate to a stirred and cooled (-78 °C) solution of **32.13** (50 mg, 0.12 mmol) in Et_2O (5 mL). The cold bath was removed and stirring was continued for 1 h. The mixture was cooled to 0 °C, quenched slowly with water, and extracted with Et_2O. The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. The crude product (**32.14**) was used directly in the next step.

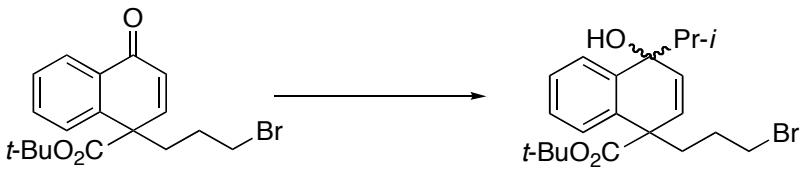
2-(4-Butyl-2,5-dimethoxyphenyl)ethanol (32.15).



32.14 **32.15**

The general procedure for rearomatization was followed, using $BiCl_3.H_2O$ (40 mg, 0.12 mmol) and **32.14** (total product from the previous step) in MeCN (5 mL) and water (0.1 mL), and a reaction time of 1 h. Flash chromatography of the crude product over silica gel (1.5 x 16 cm), using 30% EtOAc-hexane, gave **32.15** (21 mg, 74%) as an oil: FTIR ($CDCl_3$, microscope) 3380, 2955, 2932, 2859, 1507, 1465, 1213 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.94 (t, *J* = 7.3 Hz, 3 H), 1.35-1.41 (m, 2 H), 1.54-1.58 (m, 2 H), 1.91 (s, 1 H), 2.59 (t, *J* = 7.8 Hz, 2 H), 2.88 (t, *J* = 6.3 Hz, 2 H), 3.79 (s, 3 H), 3.80 (s, 3 H), 3.83 (t, *J* = 6.3 Hz, 2 H), 6.69 (s, 2 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.0 (q), 22.7 (t), 29.9 (t), 32.4 (t), 34.2 (t), 56.1 (q), 56.2 (q), 63.1 (t), 113.1 (d), 113.9 (d), 124.8 (s), 130.4 (s), 151.4 (s), 151.5 (s); exact mass *m*/*z* calcd for $C_{14}H_{22}O_3$ 238.1569, found 238.1569.

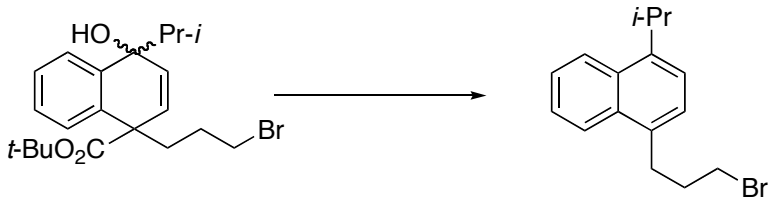
***tert*-Butyl 1-(3-Bromopropyl)-1,4-dihydro-4-hydroxy-4-isopropyl-naphthalene-1-carboxylate (33.2).**



33.1 **33.2**

i-PrMgBr (2.0 M in Et_2O, 0.21 mL, 0.43 mmol) was added at a fast dropwise rate to a stirred and cooled (-78 °C) solution of **33.1** (130 mg, 0.36 mmol) in Et_2O (10 mL). The cold bath was removed and stirring was continued for 3 h. The mixture was cooled to 0 °C, quenched slowly with water, and extracted with Et_2O. The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. The crude product (**33.2**) was used directly in the next step.

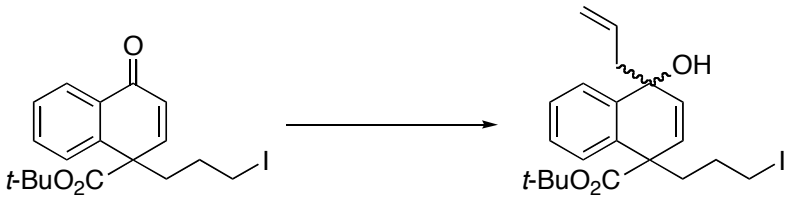
1-(3-Bromopropyl)-4-isopropylnaphthalene (33.3).



33.2 **33.3**

The general procedure for rearomatization was followed, using $BiCl_3.H_2O$ (119 mg, 0.36 mmol) and **33.2** (total product from the previous step) in MeCN (5 mL) and water (0.1 mL), and a reaction time of 8 h. Flash chromatography of the crude product over silica gel (1.5 x 15 cm), using hexane, gave **33.3** (78 mg, 75%) as an oil; FTIR ($CDCl_3$, microscope) 3073, 2962, 2870, 1597, 1517, 1459 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.41 (d, J = 6.9 Hz, 6 H), 2.28-2.35 (m, 2 H), 3.24 (t, J = 7.3 Hz, 2 H), 3.49 (t, J = 6.5 Hz, 2 H), 3.72-3.79 (m, 1 H), 7.36 (s, 2 H), 7.51-7.56 (m, 2 H), 8.07-8.11 (m, 1 H), 8.17-8.21 (m, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) (two aromatic signals coincident) δ 23.5 (q), 28.3 (d), 31.2 (t), 33.3 (t), 33.6 (t), 121.3 (d), 124.0 (d), 124.3 (d), 125.2 (d), 126.2 (d), 131.7 (s), 131.9 (s), 134.2 (s), 143.3 (s); exact mass m/z calcd for $C_{16}H_{19}{}^{79}Br$ 290.0670, found 290.0671.

***tert*-Butyl 4-Allyl-1,4-dihydro-4-hydroxy-1-(3-iodopropyl)naphthalene-1-carboxylate (33.5).**

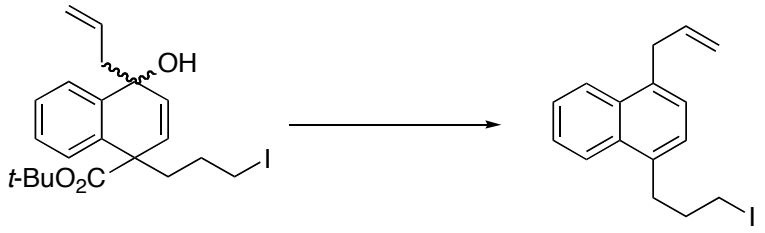


33.4 **33.5**

Allylmagnesium bromide (1.0 M in Et_2O, 0.39 mL, 0.39 mmol) was added at a fast dropwise rate to a stirred and cooled (-78 °C) solution of **33.4** (148 mg,

0.36 mmol) in Et_2O (10 mL). The cold bath was removed and stirring was continued for 4 h. The mixture was cooled to 0 °C, quenched slowly with water, and extracted with Et_2O. The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. The crude product (**33.5**) was used directly in the next step.

1-Allyl-4-(3-iodopropyl)naphthalene (33.6).

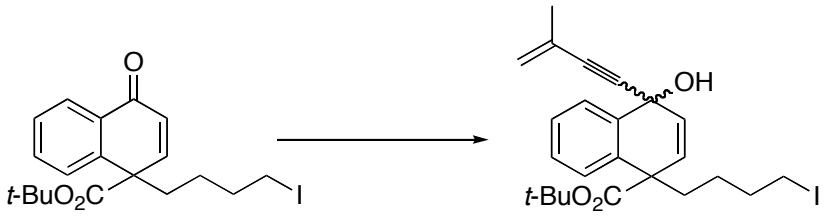


33.5 **33.6**

The general procedure for rearomatization was followed, using $BiCl_3.H_2O$ (120 mg, 0.36 mmol) and **33.5** (total product from the previous step) in MeCN (5 mL) and water (0.1 mL), and a reaction time of 7 h. Flash chromatography of the crude product over silica gel (1.5 x 15 cm), using hexane, gave **33.6** (94 mg, 78%) as an oil: FTIR ($CDCl_3$, microscope) 3074, 3004, 2924, 2852, 1638, 1596, 1458 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 2.24-2.28 (m, 2 H), 3.19 (t, J = 7.4 Hz, 2 H), 3.25 (t, J = 6.7 Hz, 2 H), 3.83 (d, J = 6.5 Hz, 2 H), 5.08-5.13 (m, 2 H), 6.11 (dddd, J = 17.3, 10.8, 6.3, 6.3 Hz, 1 H), 7.28-7.33 (m, 2 H), 7.50-7.56 (m, 2 H), 8.05-8.08 (m, 2 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 6.7 (t), 33.4 (t), 34.1 (t), 37.2 (t), 116.0 (t), 124.2 (d), 124.8 (d), 125.4 (d), 125.5 (d), 125.8 (d), 126.1 (d), 131.9 (s),

132.3 (s), 134.8 (s), 135.1 (s), 136.1 (d); exact mass *m*/*z* calcd for $C_{16}H_{17}I$ 336.0375, found 336.0374.

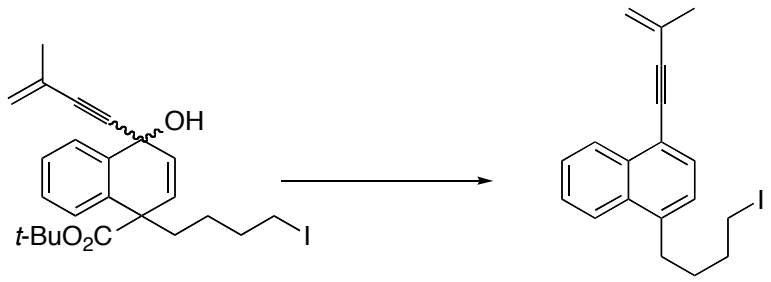
4-(4-Iodobutyl)-1-(3-methylbut-3-en-1-ynyl)-1,4-dihydronaphthalen-1-ol (34.2).



34.1 **34.2**

n-BuLi (1.6 M in hexane, 0.60 mL, 0.97 mmol) was added at a fast dropwise rate to a stirred and cooled (-78 °C) solution of 2-methyl-1-buten-3-yne (0.09 mL, 0.97 mmol) in Et_2O (10 mL). The resulting solution was stirred at -78 °C for 1 h. A solution of **34.1** (206 mg, 0.48 mmol) in Et_2O (3 mL) was added dropwise and stirring t -78 °C was continued for 2 h. The mixture was quenched slowly with saturated aqueous NH_4Cl and extracted with Et_2O. The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. The crude product (**34.2**) was used directly in the next step.

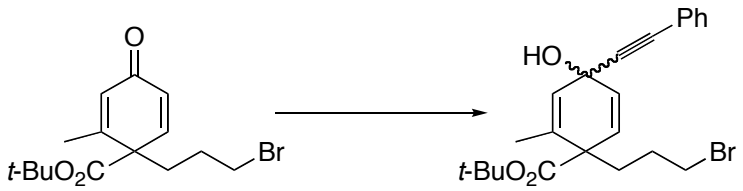
1-(4-Iodobutyl)-4-(3-methylbut-3-en-1-ynyl)naphthalene (34.3).



34.2 **34.3**

The general procedure for rearomatization was followed, using $BiCl_3.H_2O$ (161 mg, 0.48 mmol) and **34.2** (total product from the previous step) in MeCN (5 mL) and water (0.1 mL), and a reaction time of 4 h. Flash chromatography of the crude product over silica gel (1.5 x 18 cm), using 10% EtOAc-hexane, gave **34.3** (148 mg, 82%) as an oil: FTIR ($CDCl_3$, microscope) 3063, 2938, 2864, 2196, 1610, 1584, 1511 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.85-1.97 (m, 4 H), 2.11 (s, 3 H), 3.10 (t, J = 7.5 Hz, 2 H), 3.23 (t, J = 6.8 Hz, 2 H), 5.37-5.38 (m, 1 H), 5.50-5.52 (m, 1 H), 7.28-7.30 (m, 1 H), 7.54-7.62 (m, 3 H), 8.04 (dd, J = 2.6, 7.1 Hz, 1 H), 8.38 (dd, J = 2.6, 7.3 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) (there are two pairs of coincident signals) δ 6.3 (t), 23.6 (q), 31.3 (t), 32.0 (t), 33.3 (t), 86.6 (s), 95.1 (s), 119.4 (s), 121.7 (s), 123.9 (d), 125.4 (d), 126.2 (d), 126.9 (d), 129.9 (d), 131.5 (s), 133.5 (s), 138.9 (s); exact mass m/z calcd for $C_{19}H_{19}I$ 374.0532, found 374.0529.

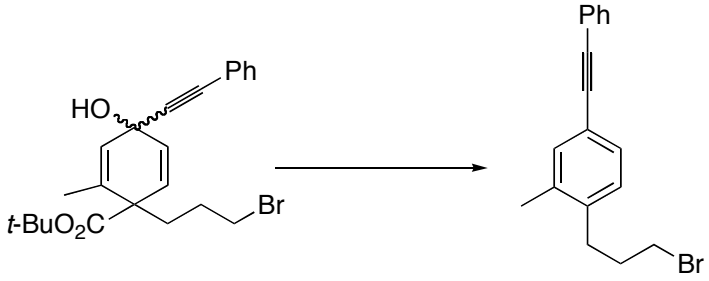
***tert*-Butyl 1-(3-Bromopropyl)-4-hydroxy-2-methyl-4-(phenylethynyl)-cyclohexa-2,5-dienecarboxylate (34.5).**



34.4 **34.5**

n-BuLi (2.5 M in hexane, 0.20 mL, 0.49 mmol) was added at a fast dropwise rate to a stirred and cooled (-78 °C) solution of phenylacetylene (0.05 mL, 0.49 mmol) in THF (5.0 mL). The resulting solution was stirred at this temperature for 1 h. A solution of **34.4** (109 mg, 0.33 mmol) in Et_2O (3 mL) was added dropwise and stirring was continued for 2 h. The mixture was quenched slowly with saturated aqueous NH_4Cl and extracted with Et_2O. The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. The crude product (**34.5**) was used directly in the next step.

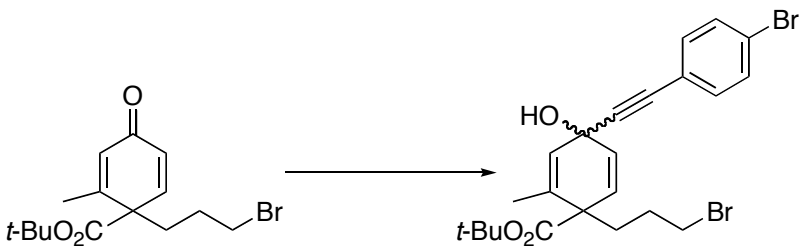
1-(3-Bromopropyl)-2-methyl-4-(phenylethynyl)benzene (34.6).



34.5 **34.6**

The general procedure for rearomatization was followed, using $BiCl_3.H_2O$ (111 mg, 0.33 mmol) and **34.5** (total product from the previous step) in MeCN (5 mL) and water (0.1 mL), and a reaction time of 4 h. Flash chromatography of the crude product over silica gel (1.5 x 11 cm), using 50% EtOAc-hexane, gave **34.6** (68.4 mg, 66% over 2 steps) as an oil: FTIR ($CDCl_3$, microscope) 2925, 2854, 2208, 1502, 1443 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.08-2.18 (m, 2 H), 2.33 (s, 3 H), 2.79 (t, J = 7.8 Hz, 2 H), 3.45 (t, J = 6.4 Hz, 2 H), 7.15 (d, J = 7.8 Hz, 1 H), 7.33-7.34 (m, 5 H), 7.51-7.59 (m, 2 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 19.1 (q), 31.4 (t), 32.8 (t), 33.2 (t), 88.8 (s), 89.4 (s), 121.1 (s), 123.4 (s), 128.1 (d), 128.2 (d), 129.0 (d), 129.2 (d), 131.5 (d), 133.4 (d), 136.1 (s), 139.4 (s); exact mass m/z calcd for $C_{18}H_{17}{}^{79}Br$ 312.0512, found 312.0511.

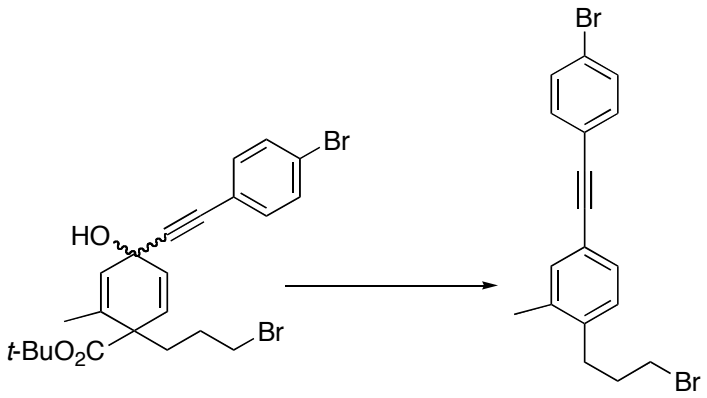
***tert*-Butyl 4-[(4-Bromophenyl)ethynyl]-1-(3-bromopropyl)-4-hydroxy-2-methylcyclohexa-2,5-dienecarboxylate (34.7**).



34.4 **34.7**

(4-Bromophenyl)acetylene (227 mg, 1.25 mmol) was added to a stirred and cooled (-78 °C) solution of LDA [from *n*-BuLi (2.5 M in hexane), 0.55 mL, 1.4 mmol) and *i*-Pr_2NH (0.19 mL, 1.4 mmol) in THF (3.0 mL)]. The resulting mixture was stirred at -78 °C for 1 h. A solution of **34.4** (495 mg, 1.51 mmol) in THF (2 mL) was added dropwise and stirring was continued for 2 h. The mixture was quenched by slow addition of saturated aqueous NH_4Cl, and extracted with Et_2O. The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. The crude product (**34.7**) was used directly in the next step.

4-[(4-Bromophenyl)ethynyl]-1-(3-bromopropyl)-2-methylbenzene (34.8).

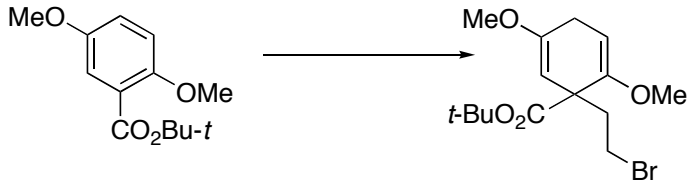


34.7 **34.8**

The general procedure for rearomatization was followed, using $BiCl_3.H_2O$ (418 mg, 1.25 mmol) and **34.7** (total product from the previous step) in MeCN (5 mL) and water (0.1 mL), and a reaction time of 2 h. Flash chromatography of the crude product over silica gel (1.5 x 11 cm), using 90% EtOAc-hexane, gave **34.8** (439 mg, 77% over 2 steps) as an oil: FTIR ($CDCl_3$, microscope) 2925, 2868, 2211, 1502, 1484 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.05-2.18 (m, 2 H), 2.33 (s, 3 H), 2.79 (t, J = 7.3 Hz, 2 H), 3.45 (t, J = 6.5 Hz, 2 H), 7.15 (d, J = 7.8 Hz, 1 H), 7.28-7.39 (m, 4 H), 7.46-7.49 (m, 2 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 19.5 (q), 31.8 (t), 33.1 (t), 33.5 (t), 88.0 (s), 90.8 (s), 120.9 (s), 122.4 (s), 122.6 (s), 129.3 (d), 129.4 (d), 131.8 (d), 133.1 (d), 133.6 (d), 136.4 (s), 139.9 (s); exact mass *m*/*z* calcd for $C_{18}H_{16}{}^{79}Br_2$ 389.9619, found 389.9618.

***tert*-Butyl 1-(2-Bromoethyl)-2,5-dimethoxy-4-oxocyclohexa-2,5-diene-carboxylate (34.9).**

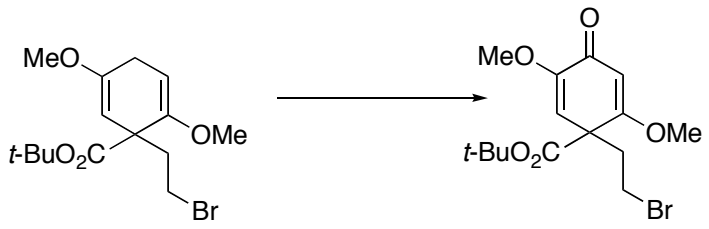
(a) *t e r t*-Butyl (2-Bromoethyl)-2,5-dimethoxy-1-cyclohexa-2,5-diene-carboxylate.



37.1 **--**

A solution of **37.1** (1.03 g, 4.33 mmol) in a mixture of dry THF (20 mL) and *t*-BuOH (0.46 mL, 4.8 mmol) was injected into the three-necked flask and liquid NH_3 (60 mL) was allowed to condense into the flask. Lithium wire (75.7 mg, 10.8 mmol), cut into small pieces, was added rapidly with vigorous stirring. Stirring at -78 °C was continued for 1 h, by which time a dark blue color persisted. 1,2-Dibromoethane (1.5 mL, 17 mmol) in THF (3 mL) was then added dropwise from a syringe over ca 3 min, and the resulting solution was stirred for 2 h at -78 °C. The cooling bath was removed and the NH_3 was allowed to evaporate under a stream of N_2 (2-3 h). Water was added and the mixture was extracted with Et_2O (3 times). The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. The crude product [*tert*-butyl (2-bromoethyl)-2,5-dimethoxy-1-cyclohexa-2,5-dienecarboxylate] was used directly in the next step.

(b) *tert*-Butyl (2-Bromoethyl)-2,5-dimethoxy-1-4-oxocyclohexa-2,5-diene-carboxylate (34.9).

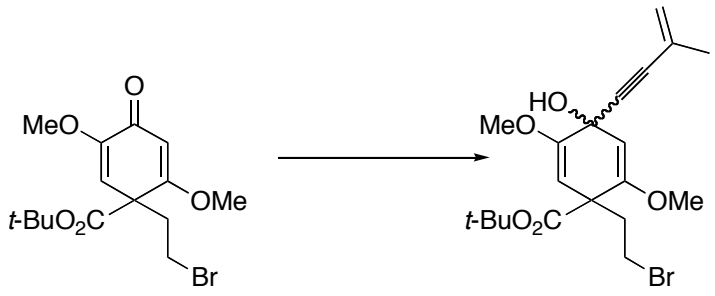


-- **34.9**

Celite (1.0 g) and then PDC (6.52 g, 17.3 mmol) were added to a stirred solution of *tert*-butyl (2-bromoethyl)-2,5-dimethoxy-1-cyclohexa-2,5-dienecarboxylate (total product from the previous step) in PhH (30 mL). *t*-BuOOH (5.5 M in decane, 3.14 mL, 17.3 mmol) was added and the resulting mixture was stirred at room temperature for 2.5 h. The mixture was filtered through Celite, and the solid was washed with CH_2Cl_2 (2 x 30 mL). Evaporation of the filtrate and flash chromatography of the residue over silica gel (2.5 x 20 cm), using first hexane and then EtOAc-hexane mixtures up to 1:1 EtOAc-hexane, gave **34.9** (1.12 g, 72% over 2 steps) as a white solid: mp 156-157 °C; FTIR ($CDCl_3$, microscope) 2979, 2937, 2849, 1735, 1644, 1611, 1199 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.38 (s, 9 H), 2.50-2.57 (m, 1 H), 2.71-2.79 (m, 1 H), 2.99-3.06 (m, 1 H), 3.10-3.17 (m, 1 H), 3.69 (s, 3 H), 3.77 (s, 3 H), 5.32 (s, 1 H), 5.74 (s, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 26.2 (t), 27.6 (q), 37.9 (t), 55.3 (q), 55.7 (s), 56.3 (q), 82.9 (s), 104.4 (d), 108.6 (d), 152.2 (s), 167.9 (s), 172.4 (s),

181.7 (s); exact mass *m*/*z* calcd for $C_{15}H_{21}{}^{79}BrNaO_5$ (M + Na) 383.0465, found 383.0463.

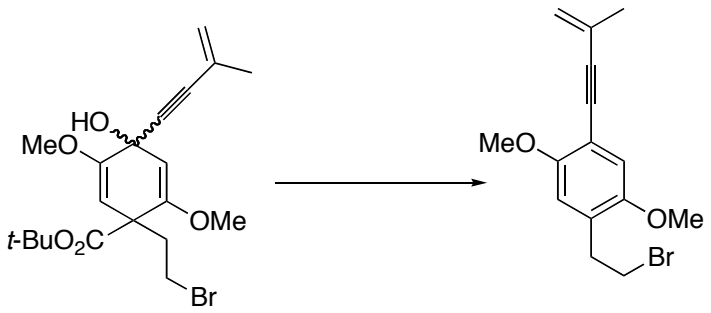
***tert*-Butyl 1-(2-Bromoethyl)-4-hydroxy-2,5-dimethoxy-4-(3-methylbut-3-en-1-ynyl)cyclohexa-2,5-dienecarboxylate (34.10).**



34.9 **34.10**

n-BuLi (1.6 M in hexane, 1.54 mL, 2.47 mmol) was added at a fast dropwise rate to a stirred and cooled (-78 °C) solution of 2-methyl-1-buten-3-yne (0.23 mL, 2.47 mmol) in Et_2O (10 mL). The resulting solution was stirred at -78 °C for 1 h. A solution of **34.9** (445 mg, 1.23 mmol) in Et_2O (3 mL) was added dropwise and stirring was continued for 3 h. The mixture was quenched slowly with saturated aqueous NH_4Cl and extracted with Et_2O. The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. The crude product (**34.10**) was used directly in the next step.

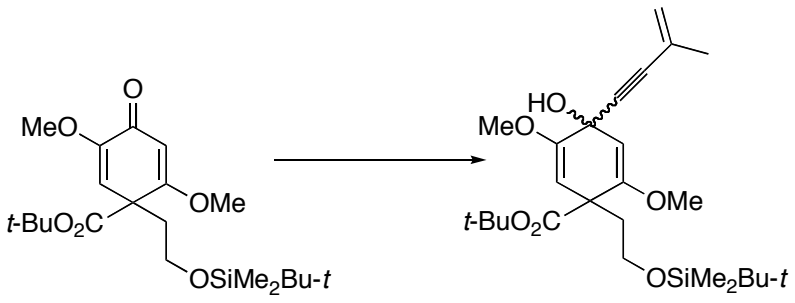
1-(2-Bromoethyl)-2,5-dimethoxy-4-(3-methylbut-3-en-1-ynyl)benzene (34.11).



34.10 **34.11**

The general procedure for rearomatization was followed, using $BiCl_3.H_2O$ (410 mg, 1.23 mmol) and **34.10** (total product from the previous step) in MeCN (5 mL) and water (0.1 mL), and a reaction time of 1 h. Flash chromatography of the crude product over silica gel (1.5 x 15 cm), using 50% EtOAc-hexane, gave **34.11** (296 mg, 78% over 2 steps) as an oil: FTIR ($CDCl_3$, microscope) 2958, 2924, 2854, 1506, 1468, 1222 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 2.01 (s, 3 H), 3.15 (t, *J* = 7.6 Hz, 2 H), 3.56 (t, *J* = 7.6 Hz, 2 H), 3.79 (s, 3 H), 3.86 (s, 3 H), 5.30-5.31 (m, 1 H), 5.42-5.43 (m, 1 H), 6.70 (s, 1 H), 6.89 (s, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 23.4 (q), 31.6 (t), 34.8 (t), 55.7 (q), 56.5 (q), 84.5 (s), 94.5 (s), 111.2 (s), 114.1 (d), 115.1 (d), 121.8 (s), 126.8 (s), 128.7 (s), 151.0 (t), 153.9 (s); exact mass *m*/*z* calcd for $C_{15}H_{17}{}^{79}BrO_2$ 308.0412, found 308.0416.

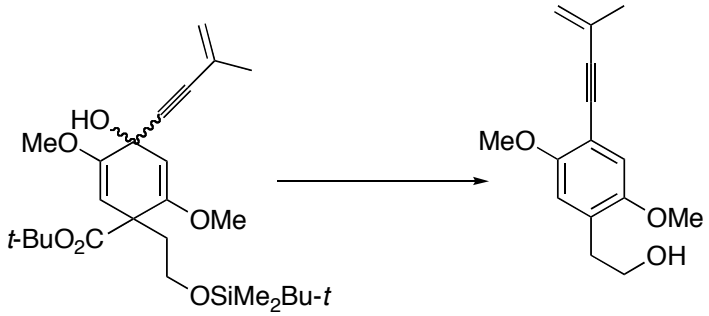
***tert*-Butyl 1-[2-[(*tert*-Butyldimethylsilyl)oxy]ethyl]-4-hydroxy-2,5-dimethoxy-4-(3-methylbut-3-en-1-ynyl)cyclohexa-2,5-dienecarboxylate (34.12).**



32.13 **34.12**

n-BuLi (1.6 M in hexane, 0.42 mL, 0.68 mmol) was added at a fast dropwise rate to a stirred and cooled (-78 °C) solution of 2-methyl-1-buten-3-yne (0.064 mL, 0.68 mmol) in Et_2O (5 mL). The resulting solution was stirred at -78 °C for 1 h. A solution of **32.13** (140 mg, 0.34 mmol) in Et_2O (3 mL) was added dropwise and stirring was continued for 2 h. The mixture was quenched slowly with saturated aqueous NH_4Cl and extracted with Et_2O. The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. The crude product (**34.12**) was used directly in the next step.

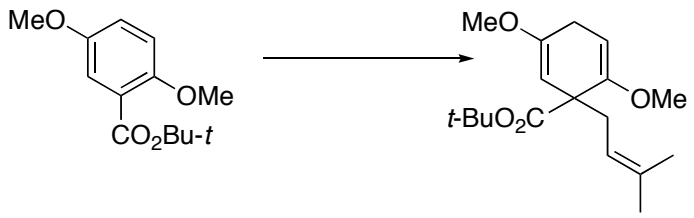
2-[2,5-Dimethoxy-4-(3-methylbut-3-en-1-ynyl)phenyl]ethanol (34.13).



34.12 **34.13**

The general procedure for rearomatization was followed, using $BiCl_3.H_2O$ (114 mg, 0.34 mmol) and **34.12** (total product from the previous step) in MeCN (5 mL) and water (0.1 mL), and a reaction time of 1 h. Flash chromatography of the crude product over silica gel (1 x 15 cm), using 50% EtOAc-hexane, gave **34.13** (63.5 mg, 76% over 2 steps) as an oil: FTIR ($CHCl_3$, microscope) 3389, 2933, 2850, 2203, 1505, 1218 cm^{-1}; ^1H NMR (CDCl3, 400 MHz) δ 1.75-1.85, (m, 1 H), 2.01 (s, 3 H), 2.89 (t, J = 6.4 Hz, 2 H), 3.79 (s, 3 H), 3.81-3.82 (m, 2 H), 3.84 (s, 3 H), 5.29-5.30 (m, 1 H), 5.41-5.42 (m, 1 H), 6.72 (s, 1 H), 6.90 (s, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 23.5 (q), 34.5 (t), 55.9 (q), 56.6 (q), 62.7 (t), 84.7 (s), 94.4 (s), 110.8 (s), 114.4 (d), 115.3 (d), 121.8 (s), 126.9 (s), 129.0 (s), 151.2 (t), 154.2 (s); exact mass *m*/*z* calcd for $C_{15}H_{18}NaO_3$ (M + Na) 269.1148, found 269.1148.

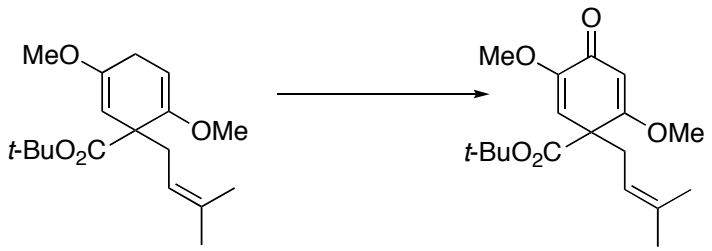
***tert*-Butyl 2,5-Dimethoxy-1-(3-methylbut-2-enyl)cyclohexa-2,5-diene-carboxylate (37.2).**



37.1 **37.2**

A solution of **37.1** (805 mg, 3.38 mmol) in dry THF (15 mL) and *t*-BuOH (0.32 mL, 3.38 mmol) was injected into the three-necked flask, and liquid NH_3 (20 mL) was allowed to condense into the flask. Lithium wire (0.05 g, 7.1 mmol), cut into small pieces, was added rapidly to the vigorously stirred solution. Stirring at -78 °C was continued for 1 h, by which time a dark blue color persisted. Prenyl bromide (0.58 mL, 5.1 mmol) in THF (3 mL) was then added dropwise from a syringe over ca 2 min, and the resulting solution was stirred for 2 h at -78 °C. The cooling bath was removed and the NH_3 was allowed to evaporate under a stream of N_2 (2-3 h). Water was added and the mixture was extracted with Et_2O (3 times). The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. The crude product (**37.2**) was used directly in the next step.

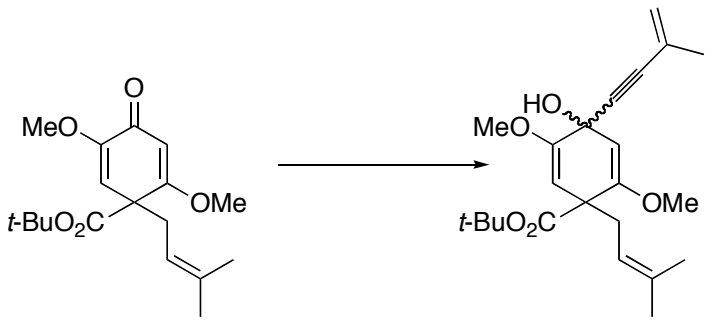
***tert*-Butyl 2,5-Dimethoxy-1-(3-methylbut-2-enyl)-4-oxocyclohexa-2,5-dienecarboxylate (37.3).**



37.2 **37.3**

Celite (1.0 g) and then PDC (5.09 g, 13.5 mmol) were added to a stirred solution of **37.2** (total product from the previous step) in PhH (25 mL). *t*-BuOOH (7.76 M in decane, 1.74 mL, 13.5 mmol) was added and the resulting mixture was stirred at room temperature for 3 h. The mixture was filtered through Celite, and the solid was washed with CH_2Cl_2 (2 x 30 mL). Evaporation of the filtrate and flash chromatography of the residue over silica gel (1.5 x 15 cm), using first hexane and then EtOAc-hexane mixtures up to 1:1 EtOAc-hexane, gave **37.3** (773 mg, 71% over 2 steps) as a white solid: mp 154-155 °C; FTIR ($CDCl_3$, microscope) 2974, 2849, 1725, 1657, 1609, 1371, 1256 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.40 (s, 9 H), 1.57 (s, 6 H), 2.64 (dd, J = 6.8, 14.3 Hz, 1 H), 2.84 (dd, J = 8.1, 14.4 Hz, 1 H), 3.64 (s, 3 H), 3.70 (s, 3 H), 4.71-4.75 (m, 1 H), 5.32 (s, 1 H), 5.66 (s, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 17.8 (q), 25.7 (q), 27.6 (q), 33.8 (t), 55.1 (q), 55.9 (q), 56.0 (s), 82.2 (s), 103.8 (d), 110.3 (d), 116.9 (d), 135.4 (s), 151.7 (s), 169.1 (s), 174.0 (s), 182.5 (s); exact mass m/z calcd for $C_{18}H_{26}NaO_5$ (M + Na) 345.1672, found 345.1672.

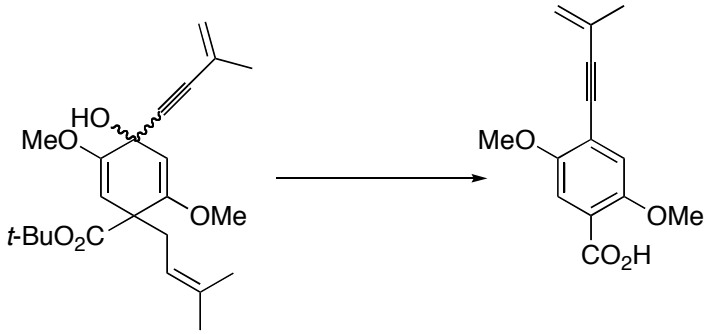
***tert*-Butyl 4-Hydroxy-2,5-dimethoxy-1-(3-methylbut-2-enyl)-4-(3-methylbut-3-en-1-ynyl)cyclohexa-2,5-dienecarboxylate (37.5).**



37.3 **37.5**

n-BuLi (2.5 M in hexane, 0.50 mL, 1.24 mmol) was added at a fast dropwise rate to a stirred and cooled (-78 °C) solution of 2-methyl-1-buten-3-yne (0.12 mL, 1.24 mmol) in Et_2O (5 mL). The resulting solution was stirred at -78 °C for 1 h. A solution of **37.3** (200 mg, 0.62 mmol) in Et_2O (3 mL) was added dropwise and stirring was continued for 2 h. The mixture was quenched slowly with saturated aqueous NH_4Cl and extracted with Et_2O. The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. The crude product (**37.5**) was used directly in the next step.

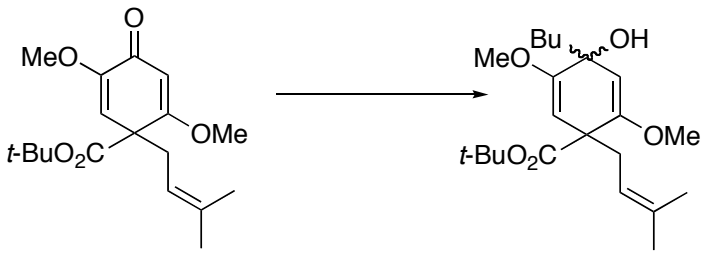
2,5-Dimethoxy-4-(3-methylbut-3-en-1-ynyl)benzoic Acid (37.7).



37.5 **37.7**

The general procedure for rearomatization was followed, using $BiCl_3.H_2O$ (207 mg, 0.62 mmol) and **37.5** (total product from the previous step) in MeCN (5 mL) and water (0.1 mL), and a reaction time of 6 h. Flash chromatography of the crude product over silica gel (1 x 10 cm), using 50% EtOAc-hexane, gave **37.7** (131 mg, 86% over 2 steps) as a solid: FTIR ($CDCl_3$, microscope) 3255, 2976, 2957, 2250, 1729, 1447, 1226 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.07 (s, 3 H), 3.95 (s, 3 H), 4.10 (s, 3 H), 5.42-5.44 (m, 1 H), 5.53-5.54 (m, 1 H), 7.14 (s, 1 H), 7.69 (s, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 23.2 (q), 56.5 (q), 57.3 (q), 83.3 (s), 98.3 (s), 114.5 (d), 116.6 (d), 117.6 (s), 119.0 (s), 123.5 (s), 126.4 (s), 151.5 (t), 154.7 (s), 164.9 (s); exact mass *m/z* calcd for $C_{14}H_{14}O_4$ (M + Na) 246.0892, found 246.0899.

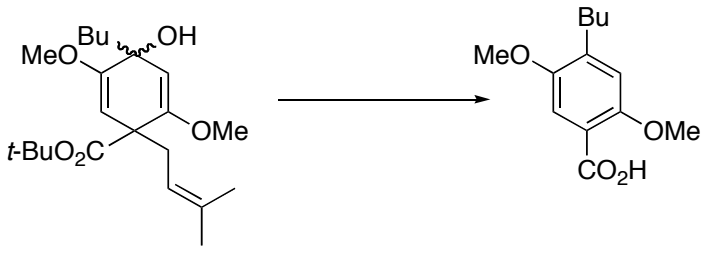
***tert*-Butyl 4-Butyl-4-hydroxy-2,5-dimethoxycyclohexa-2,5-diene-carboxylate (38.1).**



37.3 **38.1**

BuMgCl (2 M in THF, 0.12 mL, 0.25 mmol) was added at a fast dropwise rate to a stirred and cooled (-78 °C) solution of **37.3** (66 mg, 0.21 mmol) in Et_2O (5 mL). The cold bath was removed and stirring was continued for 1 h. The mixture was cooled to 0 °C, quenched slowly with water, and extracted with Et_2O. The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. The crude product (**38.1**) was used directly in the next step.

4-Butyl-2,5-dimethoxybenzoic acid (38.2).

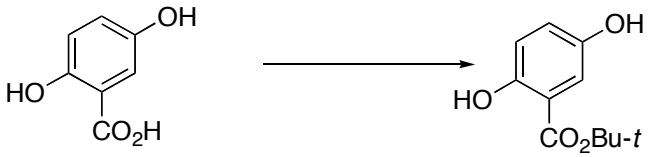


38.1 **38.2**

The general procedure for rearomatization was followed, using $BiCl_3.H_2O$ (68 mg, 0.21 mmol) and **38.1** (total product from the previous step) in MeCN (5 mL) and water (0.1 mL), and a reaction time of 5 h. Flash chromatography of the crude product over silica gel (1 x 12 cm), using 50% EtOAc-hexane, gave **38.2** (43 mg, 86%) as an oil: FTIR (microscope, cast) 3300-2592, 1686, 1570, 1504, 1240 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.95 (t, *J* = 7.3 Hz, 3 H), 1.37-1.40 (m, 2 H), 1.55-1.60 (m, 2 H), 2.66 (t, *J* = 7.7 Hz, 2 H), 3.85 (s, 3 H), 4.05 (s, 3 H), 6.85 (s, 1 H), 7.60 (s, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.8 (q), 22.5 (t), 30.3 (t), 31.6 (t), 55.8 (q), 57.1 (q), 113.5 (d), 113.7 (d), 115.1 (s), 139.7 (s), 152.0 (s), 152.3 (s), 165.4 (s); exact mass *m/z* calcd for $C_{13}H_{18}O_4$ 238.1205, found 238.1205.

***tert*-Butyl 2,5-Bis(methoxymethoxy)benzoate (42.2).**[45]

(a) ***tert*-Butyl 2,5-dihydroxybenzoate.**

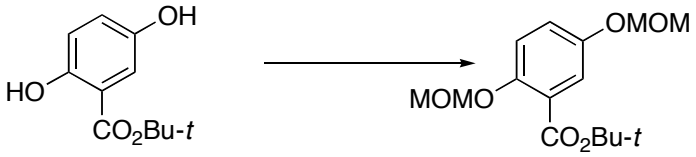


42.1 -

A solution of **42.1** (3.00 g, 19.5 mmol) and 1,1'-carbonyldiimidazole (3.16 g, 19.5 mmol) in dry DMF (20 mL) was heated at 40 °C under Ar for 1 h. *t*-BuOH (3.73 mL, 38.9 mmol) and DBU (2.91 mL, 19.5 mmol) were then added and stirring at 40 °C was continued for 24 h. The mixture was diluted with Et_2O (100 mL), washed with aqueous $NaHCO_3$ (100 mL), dried ($MgSO_4$) and

evaporated. Flash chromatography of the residue over silica gel (3 x 25 cm), using first hexane and then EtOAc-hexane mixtures up to 3:7 EtOAc-hexane, gave *tert*-butyl 2,5-dihydroxybenzoate (2.4 g, 58%) as a solid: mp 77-78 °C; FTIR ($CDCl_3$, microscope) 3405, 2979, 2935, 1672, 1617, 1486, 1274 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.61 (s, 9 H), 5.40 (s, 1 H), 6.86 (d, J = 8.9 Hz, 1 H), 6.98 (dd, J = 3.2, 8.9 Hz, 1 H), 7.27 (d, J = 3.1 Hz, 1 H), 10.69 (s, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 28.1 (q), 82.9 (s), 113.7 (s), 115.1 (d), 118.2 (d), 123.3 (d), 147.5 (s), 155.5 (s), 169.2 (s); exact mass m/z calcd for $C_{11}H_{14}NaO_4$ (M + Na) 233.0784, found 233.0783.

(b) *tert*-Butyl 2,5-Bis(methoxymethoxy)benzoate (42.2).



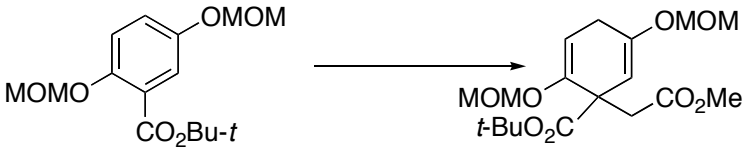
- **42.2**

A solution of gentisic acid *tert*-butyl ester (1.50 g, 7.14 mmol) in dry THF (10 mL) was added to a suspension of NaH (60%w/w in oil, 0.86 g, 35.7 mmol) in dry THF (20 mL) and the mixture was stirred for 1 h (Ar atmosphere). Chloromethyl methyl ether (1.74 mL, 22.9 mmol) was added slowly and stirring was continued overnight. Water and saturated aqueous NH_4Cl were added to adjust the pH to about 7. The mixture was extracted with Et_2O and the combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. Flash

chromatography of the residue over silica gel (3 x 20 cm), using first hexane and then EtOAc-hexane mixtures up to 3:7 EtOAc-hexane, gave **42.2** (1.81 g, 85%) as an oil: FTIR ($CDCl_3$, microscope) 2977, 2905, 1724, 1496, 1252 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.57 (s, 9 H), 3.46 (s, 3 H), 3.51 (s, 3 H), 5.12 (s, 2 H), 5.14 (s, 2 H), 7.08-7.09 (m, 2 H), 7.38 (s, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 28.1 (q), 55.8 (q), 56.0 (q), 81.2 (s), 94.9 (t), 96.0 (t), 118.6 (d), 118.7 (d), 124.6 (d), 151.1 (s), 151.6 (s), 165.0 (s); exact mass *m*/*z* calcd for $C_{15}H_{22}NaO_6$ (M + Na) 321.1309, found 321.1310.

***tert*-Butyl 1-[(Methoxycarbonyl)methyl]-2,5-bis(methoxymethoxy)-4-oxocyclohexa-2,5-dienecarboxylate (43.1).**

(a) *tert*-Butyl 1-[(Methoxycarbonyl)methyl]-2,5-bis(methoxymethoxy)-cyclohexa-2,5-dienecarboxylate.



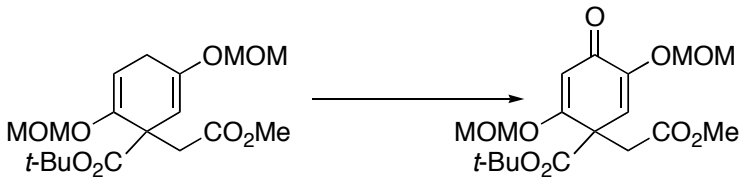
42.2 -

The apparatus consists of a three-necked round-bottomed flask containing a magnetic stirring bar and fitted with a cold finger condenser fused onto one of the necks. The exit of the condenser carried a drying tube filled $CaSO_4$. An external mark on the flask indicated the level corresponding to the desired volume of liquid NH_3. The central neck was closed by a septum carrying a nitrogen inlet.

The flask was cooled in a dry ice-acetone bath and the cold finger condenser was charged with dry ice-acetone. Another round-bottomed flask was half-filled with liquid NH_3 and several small pieces of Na were added, so as to form a permanently blue solution. This flask was connected via bent adaptors and dry Tygon tubing to the third neck of the other flask. A solution of **42.2** (1.77 g, 5.94 mmol) in dry THF (20 mL) and *t*-BuOH (0.60 mL, 5.94 mmol) was injected into the three-necked flask, and liquid NH_3 (40 mL) was allowed to condense into the flask. Lithium wire (0.17 g, 24 mmol), cut into small pieces, was added rapidly to the vigorously stirred solution. Stirring at -78 °C was continued for 1 h, by which time a dark blue color persisted. A solution of $BrCH_2CO_2CH_3$ (1.7 mL, 18 mmol) in THF (5 mL) was then added dropwise from a syringe over ca 2 min, and the resulting solution was stirred for 2 h at -78 °C. The cooling bath was removed and the NH_3 was allowed to evaporate under a stream of N_2 (2-3 h). Water was added and the mixture was extracted with Et_2O (3 times). The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2.5 x 18 cm), using 50% EtOAc-hexane, gave *tert*-butyl 1-[(methoxycarbonyl)methyl]-2,5-bis(methoxymethoxy)-cyclohexa-2,5-dienecarboxylate (1.8 g, 83%) as an oil: FTIR ($CDCl_3$, microscope) 2954, 2902, 1731, 1665, 1392, 1368, 1251 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.42 (s, 9 H), 2.82-2.87 (m, 3 H), 3.39 (s, 3 H), 3.41 (s, 3 H), 3.60 (s, 3 H), 3.66-3.68 (m, 1 H), 4.93-4.97 (m, 5 H), 5.10-5.18 (m, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 27.7 (q), 27.9 (t), 40.4 (t), 51.1 (q), 51.3 (s), 55.7 (q), 55.8 (q), 81.0 (s), 93.4 (t), 94.1 (t), 96.5 (d), 98.9 (d), 150.0 (s), 152.1 (s), 171.2 (s),

171.3 (s); exact mass *m*/*z* calcd for $C_{18}H_{28}NaO_8$ (M + Na) 395.1676, found 395.1675.

(b) *tert*-Butyl 1-[(Methoxycarbonyl)methyl]-2,5-bis(methoxymethoxy)-4-oxocyclohexa-2,5-dienecarboxylate (43.1).



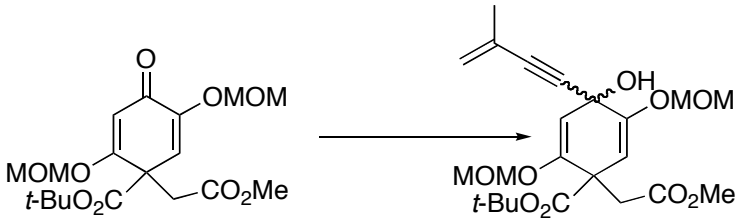
-- **43.1**

Celite (1.0 g) and then PDC (2.18 g, 5.81 mmol) were added to a stirred solution of *tert*-butyl 1-[(methoxycarbonyl)methyl]-2,5-bis(methoxymethoxy)-cyclohexa-2,5-dienecarboxylate (540 mg, 1.45 mmol) in PhH (15 mL). *t*-BuOOH (7.76 M in decane, 0.75 mL, 5.8 mmol) was added and stirring at room temperature was continued for 4 h. The mixture was filtered through Celite, and the solid was washed CH_2Cl_2 (2 x 30 mL) and evaporated. Flash chromatography of the residue over silica gel (1.5 x 18 cm), using first hexane and then EtOAc-hexane mixtures up to 1:1 EtOAc-hexane, gave **43.1** (403 mg, 72%) as an oil: FTIR ($CDCl_3$, microscope) 2978, 2832, 1737, 1665, 1615, 1370, 1250 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.40 (s, 9 H), 3.06-3.10 (m, 2 H), 3.42 (s, 3 H), 3.43 (s, 3 H), 3.60 (s, 3 H), 5.10-5.12 (m, 4 H), 5.95 (s, 1 H), 6.10 (s, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 27.7 (q), 39.8 (t), 51.7 (q), 53.6 (s), 56.0 (q), 56.9 (q), 83.3

(s), 94.4 (t), 94.9 (t), 106.7 (d), 115.2 (d), 149.2 (s), 167.2 (s), 169.3 (s), 169.7 (s), 182.0 (s); exact mass *m*/*z* calcd for $C_{18}H_{26}NaO_9$ (M + Na) 409.1469, found 409.1469.

2-[2,5-Dihydroxy-4-(3-methylbut-3-en-1-ynyl)phenyl]acetic Acid Methyl Ester (43.2).

(a) *tert*-Butyl 4-Hydroxy-1-[(methoxycarbonyl)methyl]-2,5-bis(methoxy-methoxy)-4-(3-methylbut-3-en-1-ynyl)cyclohexa-2,5-dienecarboxylate.

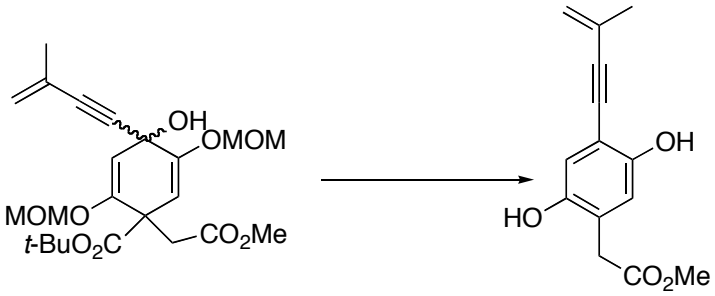


43.1 **--**

n-BuLi (2.5 M in hexane, 0.35 mL, 0.88 mmol) was added at a fast dropwise rate to a stirred and cooled (-78 °C) solution of 2-methyl-1-buten-3-yne (0.08 mL, 0.88 mmol) in Et_2O (5 mL). The resulting solution was stirred at -78 °C for 1 h. A solution of **43.1** (169 mg, 0.44 mmol) in Et_2O (3 mL) was added dropwise and stirring was continued for 3 h. The mixture was quenched slowly with saturated aqueous NH_4Cl and extracted with Et_2O. The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. The crude product [*tert*-butyl 4-hydroxy-1-[(methoxycarbonyl)methyl]-2,5-bis(methoxy-

methoxy)-4-(3-methylbut-3-en-1-ynyl)cyclohexa-2,5-dienecarboxylate] was used directly in the next step.

(b) 2-[2,5-Dihydroxy-4-(3-methylbut-3-en-1-ynyl)phenyl]acetic Acid Methyl Ester (43.2).



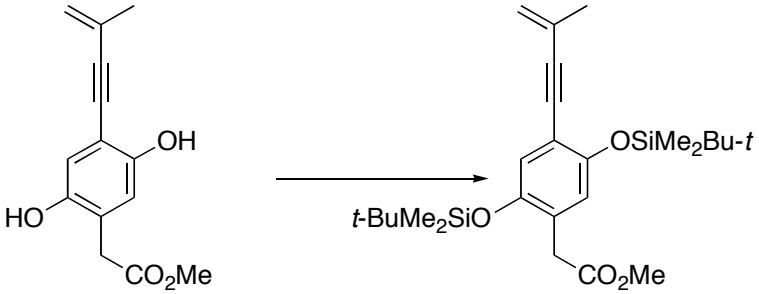
- **43.2**

The general procedure for rearomatization was followed, using $BiCl_3.H_2O$ (131 mg, 0.44 mmol) and *tert*-butyl 4-hydroxy-1-[(methoxycarbonyl)methyl]-2,5-bis(methoxymethoxy)-4-(3-methylbut-3-en-1-ynyl)cyclohexa-2,5-dienecarboxylate (total product from the previous step) in MeCN (5 mL) and water (0.1 mL), and a reaction time of 3 h. Flash chromatography of the crude product over silica gel (1 x 10 cm), using 30% EtOAc-hexane, gave **43.2** (83 mg, 77%) as an oil: FTIR ($CDCl_3$, microscope) 3398, 2954, 2924, 2196, 1716, 1431, 1199 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.01 (s, 3 H), 3.64 (s, 2 H), 3.76 (s, 3 H), 5.35-5.37 (m, 2 H), 5.43 (s, 1 H), 6.71 (s, 1 H), 6.87 (s, 1 H), 6.92 (s, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 23.4 (q), 37.7 (t), 52.8 (q), 81.7 (s), 97.6 (s), 109.5

(s), 116.6 (d), 119.9 (d), 123.0 (s), 123.7 (s), 126.1 (s), 148.2 (t), 150.6 (s), 173.8 (s); exact mass *m*/*z* calcd for $C_{14}H_{14}NaO_4$ (M + Na) 269.0784, found 269.0786.

[2,5-Bis[(*tert*-butyldimethylsilyl)oxy]-4-(3-methylbut-3-en-1-ynyl)-phenyl]acetaldehyde (43.4).

(a) [2,5-Bis[(*tert*-butyldimethylsilyl)oxy]-4-(3-methylbut-3-en-1-ynyl)-phenyl]acetic Acid Methyl Ester.

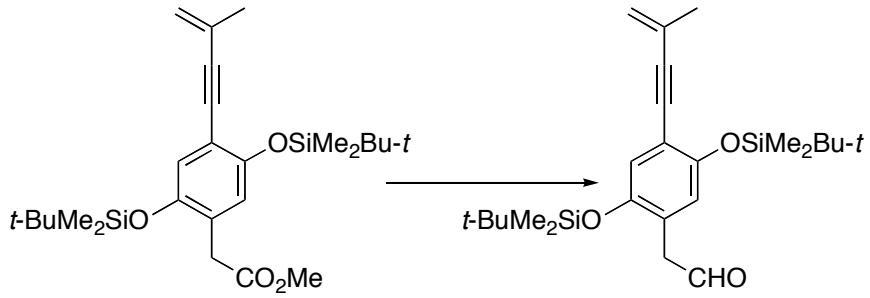


43.2 **-**

Ester **43.2** (30 mg, 0.12 mmol), imidazole (33 mg, 0.48 mmol), *t*-$BuMe_2SiCl$ (54 mg, 0.36 mmol), and DMAP (2.9 mg, 0.02 mmol) were dissolved in anhydrous DMF (5 mL) and the solution was heated at 50 °C for 18 h. The mixture was poured into water and extracted with Et_2O. The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1 x 12 cm), using 10% EtOAc-hexane, gave [2,5-bis[(*tert*-butyldimethylsilyl)oxy]-4-(3-methylbut-3-en-1-ynyl)-phenyl]acetic acid methyl ester (51 mg, 90%) as an oil: FTIR ($CDCl_3$, microscope) 2955, 2931, 2859, 2204, 1744, 1498, 1435, 1255 cm^{-1}; ^1H NMR

($CDCl_3$, 300 MHz) δ -0.22 (s, 12 H), 0.99 (s, 9 H), 1.02 (s, 9 H), 1.98 (s, 3 H), 3.55 (s, 2 H), 3.66 (s, 3 H), 5.26-5.28 (m, 1 H), 5.36-5.37 (m, 1 H), 6.67 (s, 1 H), 6.78 (s, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ -4.38 (q), -4.30 (q), 18.2 (s), 23.5 (q), 25.68 (q), 25.72 (q), 35.8 (t), 51.8 (q), 85.7 (s), 93.7 (s), 114.7 (s), 121.5 (s), 121.9 (d), 122.1 (d), 126.6 (s), 127.1 (s), 147.4 (t), 150.2 (s), 171.5 (s); exact mass *m*/*z* calcd for $C_{26}H_{42}NaO_4Si_2$ (M + Na) 497.2514, found 497.2516.

(b) [2,5-Bis[(*tert*-butyldimethylsilyl)oxy]-4-(3-methylbut-3-en-1-ynyl)-phenyl]acetaldehyde (43.4).



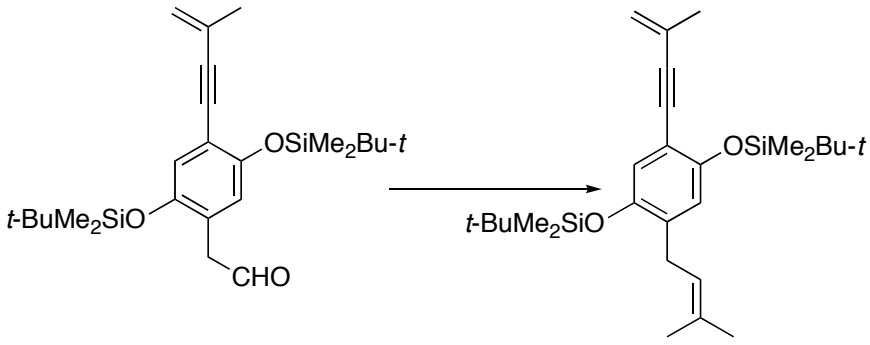
- **43.4**

DIBAL-H (1.0 M in CH_2Cl_2, 0.10 mL, 0.10 mmol) was added slowly to a stirred and cooled (-78 °C) solution of [2,5-bis[(*tert*-butyldimethylsilyl)oxy]-4-(3-methylbut-3-en-1-ynyl)phenyl]acetic acid methyl ester (46 mg, 0.10 mmol) in Et_2O (5 mL) and stirring at -78 °C was continued for 3 h. The mixture was quenched slowly with MeOH at 0 °C, followed by addition of 20% aqueous potassium tartrate solution, and then extracted with Et_2O. The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. Flash

chromatography of the residue over silica gel (1 x 10 cm), using 100% hexane, gave **43.4** (37 mg, 85%) as an oil: FTIR ($CDCl_3$, microscope) 2956, 2896, 2859, 2197, 1729, 1498, 1403, 1256 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.23 (s, 12 H), 0.98 (s, 9 H), 1.02 (s, 9 H), 1.99 (s, 3 H), 3.56 (s, 2 H), 5.28-5.29 (m, 1 H), 5.37-5.39 (m, 1 H), 6.59 (s, 1 H), 6.84 (s, 1 H), 9.65 (s, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) (two signals are coincident) δ -4.35 (q), -4.21 (q), 18.2 (s), 23.5 (q), 25.70 (q), 25.73 (q), 45.7 (t), 85.5 (s), 94.0 (s), 115.3 (s), 121.7 (s), 122.2 (d), 122.3 (d), 124.7 (s), 127.0 (s), 147.7 (t), 150.5 (s), 199.3 (s); exact mass *m*/*z* calcd for $C_{25}H_{40}NaO_3Si_2$ (M + Na) 467.2516, found 467.2516.

2-(3-Methylbut-2-enyl)-5-(3-methylbut-3-en-1-ynyl)benzene-1,4-diol (35.1) (culpin).[40]

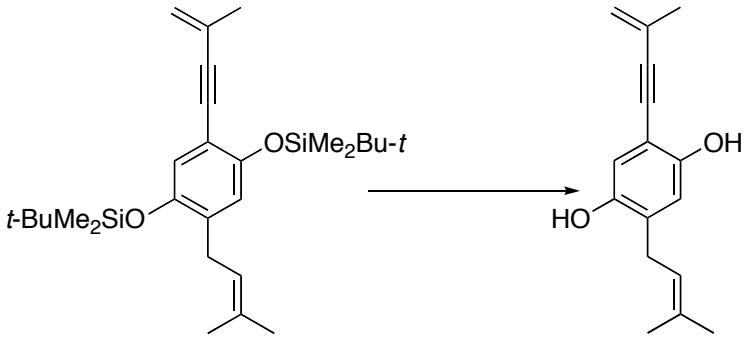
(a) 1,4-Bis[(*tert*-butyldimethylsilyl)oxy]-2-(3-methylbut-2-enyl)-5-(3-methylbut-3-en-1-ynyl)benzene.



43.4 **-**

n-BuLi (2.5 M in hexane, 0.054 mL, 0.135 mmol) was added at a fast dropwise rate to a stirred and cooled (0 °C) solution of $Me_2CHPPh_3^+I^-$ (58.4 mg, 0.135 mmol) in THF (5 mL). The resulting solution was stirred at -78 °C for 1 h. A solution of **43.4** (30 mg, 0.07 mmol) in THF (1 mL) was added dropwise and stirring was continued for 5 h, the cold bath being left in place but not recharged. The mixture was quenched with water and extracted with Et_2O. The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. The crude product [1,4-bis[(*tert*-butyldimethylsilyl)oxy]-2-(3-methylbut-2-enyl)-5-(3-methylbut-3-en-1-ynyl)benzene] was used directly in the next step.

(b) 2-(3-Methylbut-2-enyl)-5-(3-methylbut-3-en-1-ynyl)benzene-1,4-diol (35.1) (culpin).[40]



- **35.1**

Bu_4NF (1.0 M in THF, 0.17 mL, 0.17 mmol) was added slowly to a stirred and cooled (0 °C) solution of 1,4-bis[(*tert*-butyldimethylsilyl)oxy]-2-(3-methylbut-2-enyl)-5-(3-methylbut-3-en-1-ynyl)benzene (total product from the

previous step) and a few drops of AcOH in THF (3 mL). The mixture was stirred for 6 h, quenched with water and extracted with Et_2O. The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1 x 8 cm), using 30% EtOAc-hexane, gave **35.1** (12 mg, 74%) as a white solid which decomposed in C_6D_6 during acquisition of the ^{13}C NMR spectrum: FTIR (C_6D_6, microscope) 3420, 2959, 2927, 2856, 2195, 1507 cm^{-1}; ^1H NMR (C_6D_6, 400 MHz) δ 1.45 (s, 3 H), 1.52 (br s, 3 H), 1.69-1.70 (m, 3 H), 3.17 (d, J = 7.6 Hz, 2 H), 3.94 (s, 1 H), 5.00-5.01 (m, 1 H), 5.18-5.23 (m, 1 H), 5.26-5.27 (m, 1 H), 5.36 (s, 1 H), 6.53 (s, 1 H), 6.85 (s, 1 H); ^{13}C NMR (C_6D_6, 100 MHz) δ 17.6 (q), 23.4 (q), 25.7 (q), 29.5 (t), 83.0 (s), 101.9 (s), 107.6 (s), 116.4 (d), 117.5 (d), 121.8 (d), 122.4 (s), 126.8 (s), 131.2 (s), 138.4 (s), 147.8 (t), 151.7 (s); exact mass m/z calcd for $C_{16}H_{18}NaO_2$ (M + Na) 265.1199, found 265.1199.

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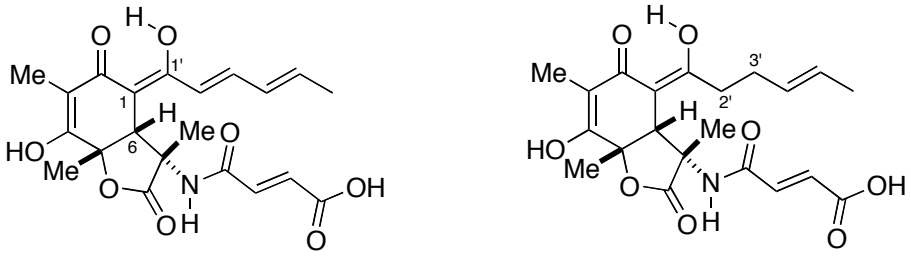
Chapter 3

Synthetic studies related to the marine alkaloid, sorbicillactone A: A method for desymmetrization of cross-conjugated cyclohexadienones

1 INTRODUCTION

1.1 *Isolation, biological properties and biotechnological production of sorbicillactone A*

In the search for novel bioactive compounds from sponge-derived micro-organisms, Bringmann and co-workers recently identified the first members of a new class of secondary metabolites, the sorbicillin-derived alkaloids sorbicillactone A (**1.1**) and its 2',3'-dihydro analog sorbicillactone B (**1.2**).[1a,b,c]



Sorbicillactone A (1.1) **Sorbicillactone B (1.2)**

Scheme 1

Sorbicillactone A (**1.1**) was first detected in a salt-water culture of a *Penicillium chrysogenum* strain isolated from a specimen of the Mediterranean sponge *Ircinia fasciculata* (Porifera).[2] Structural studies were undertaken by Bringmann's group whereby extensive 2D NMR and mass spectrometry measurements served to identify the structure of **1.1** and **1.2**. The absolute configurations of the compounds were elucidated by quantum chemical calculation of circular dichroism (CD) spectra.[1]

Sorbicillactone A (**1.1**) was found to exhibit highly selective activity against the murine leukemic lymphoblast cell line L5178y with an IC_{50} of 2.2

μg/mL, while the structurally related sorbicillactone B (**1.2**) exhibited a significantly lower activity with an IC_{50} value of >10 μg/ mL. Besides its cytotoxicity, sorbicillactone A (**1.1**) also shows high anti-HIV activity. In the concentration range 0.3-3.0 μg/mL, sorbicillactone A protected human T lymphocytes (H9 cells) against the cytopathic effect of HIV-1 and inhibited the expression of viral proteins.[2,3] The effect of sorbicillactone A on calcium ions in primary neurons revealed that it could be considered as a promising neuroprotective compound. Overall, the biological properties of sorbicillactone A are that it shows selective anti-leukemic activity without showing notable cytotoxicity and it also has antiviral and neuroprotective properties. It could, therefore, be a potential new lead structure in medicinal chemistry.[1]

The initial amounts of sorbicillactone A produced were approximately 4 mg L^{-1} (range 2-6 mg L^{-1}) culture broth in surface liquid cultures. In order to increase the yield and to adapt the production to amounts sufficient for ongoing preclinical and structure-activity relationship studies, the Bergmann group developed an efficient process for the biotechnological large-scale production and isolation of pure sorbicillactone A. By this method, they were able to isolate 100 g of pure sorbicillactone A for clinical studies on this potential antitumoral drug.[1b]

Until now, there is no reported total synthesis of sorbicillactone A (**1.1**) and we decided to explore methods for its synthesis as it is a structurally and biologically interesting target. Looking closely at sorbicillactone A, we realized that a good starting point would be construction of the sorbicillinoid core, which is comprised of the six-membered cyclohexenone and the five-membered lactone

ring. Furthermore, establishing the stereochemistry at the ring fusion would be a key step. Thus, we realized that a desymmetrization process would be a promising start, as described below.

1.4 Desymmetrization reactions

Desymmetrization is a useful approach to synthesize complex compounds in a single operation whereby at least two new stereogenic centers are formed. Chiral quaternary centers can be obtained with high selectivity. The stereoinduction occurs via a covalently bound chiral moiety or by using chiral reagents (Figure 1).

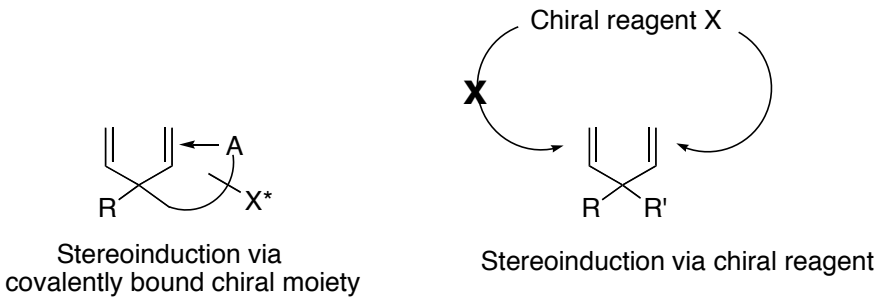


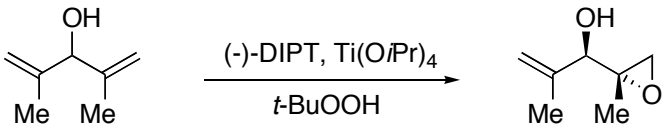
Figure 1. Differentiation of double bonds

Desymmetrization[4] of an achiral molecule to yield an enantiomerically enriched product has proven to be a powerful synthetic tool. In general, to achieve an enantioselective symmetry breaking synthetic operation, two enantiotopic functional groups must be differentiated. By far the greatest number of enantioselective desymmetrizations involved the formation of a carbon-

heteroatom bond, and perhaps, not surprisingly, the formation of a carbon-oxygen linkage is the most common bond construction. Desymmetrization reactions via formation of carbon-carbon bonds are less developed.[5]

1.2.1 Desymmetrization reactions involving the formation of a carbon-heteroatom bond

The desymmetrization of *meso*-dienes by enantioselective epoxidation has received considerable attention.[6,7] Schreiber had been instrumental in using the Sharpless asymmetric epoxidation to desymmetrize *meso*-dienes. Reaction of the simple diene **2.1** under standard Sharpless conditions led to the formation of enantiomerically enriched epoxide **2.2** (Scheme 2). Schreiber showed that as the reaction time increased, so did the amount of di-epoxides formed with the consequence that the ee of mono-epoxide **2.2** increased.

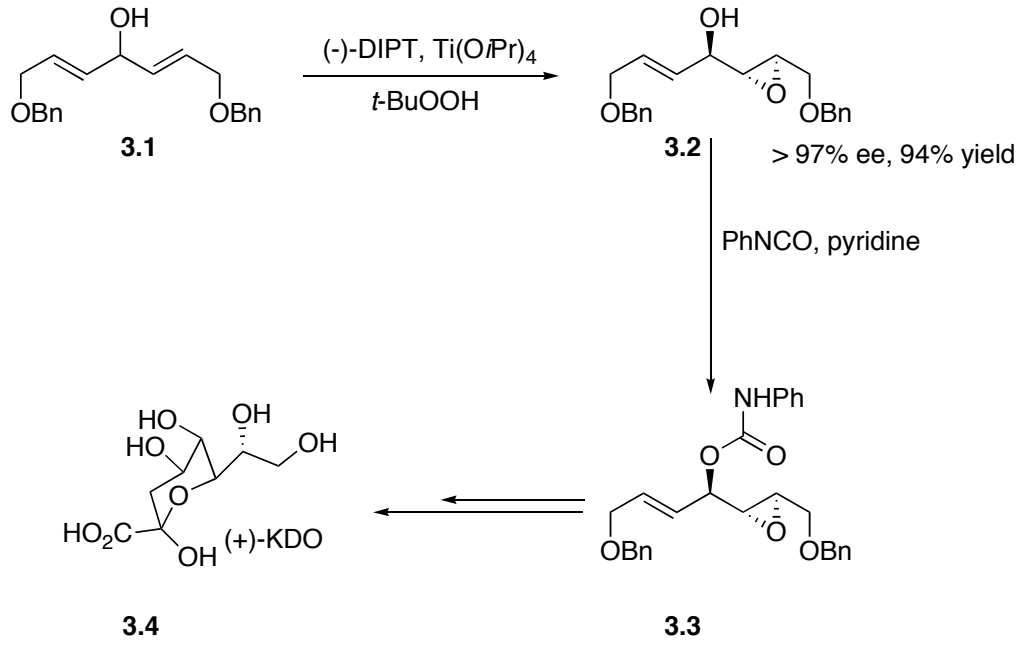


2.1 **2.2**

Time (h)	ee (%)	de (%)
0.5	88	99
1.0	94	99
1.5	99.3	99

Scheme 2

This approach has been applied to a wide range of diene substrates and the synthetic utility had been demonstrated. For example, desymmetrization of diene **3.1** afforded the desired mono-epoxide **3.2** in 94% yield and > 97% ee (Scheme 3).

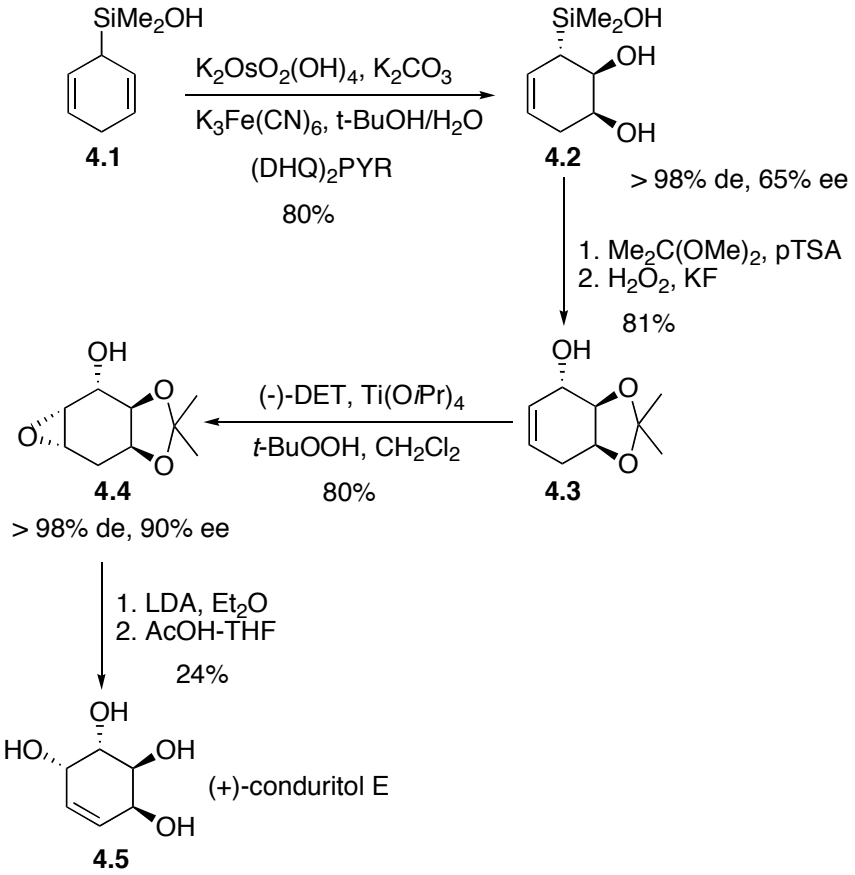


Scheme 3

The key desymmetrization step (**3.1→3.2**) established the absolute configuration of two stereocentres in a single operation and mono-epoxide **3.2** was advanced through several steps to complete an enantioselective synthesis of 2-deoxy-D-*manno*-2-octulosonic acid, KDO.[6]

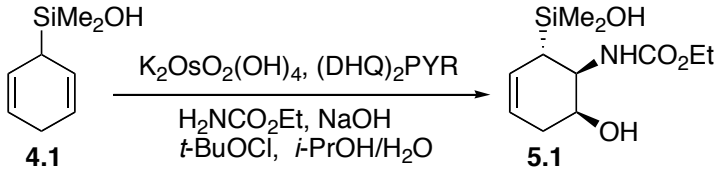
Desymmetrization of *meso*-dienes has also been demonstrated by the use of Sharpless asymmetric dihydroxylation (AD).[8] Landais has pioneered the use of the AD reaction to selectively produce enantiomerically enriched diols from

silylated cyclohexadiene **4.1**. Treatment of silanol **4.1** under Sharpless AD conditions[9] gave diol **4.2** in 80% yield with excellent diastereoselectivity (> 98% de). The addition occurred *anti* to the silyl group with moderate enantioselectivity (65% ee). The diol **4.2** was used as a precursor for the synthesis of various natural products.[10] For example, diol **4.2** was advanced through five steps to provide (+)-conduritol E **4.5** (Scheme 4). The enantiomeric excess was increased from the 65% obtained after the initial desymmetrizing AD by the use of a Sharpless asymmetric epoxidation of allylic alcohol **4.3**. Eventually, the natural product **4.5** was obtained with >99% ee.



Scheme 4

Landais's group has also developed the Sharpless asymmetric aminohydroxylation (AA) as a desymmmetrising tool. Reaction of silanol **4.1** under AA conditions afforded amino alcohol **5.1** (Scheme 5) as a single diastereomer with high regioselectivity. Enantiotopic group differentiation occurred with moderate selectivity (68% ee).[11]

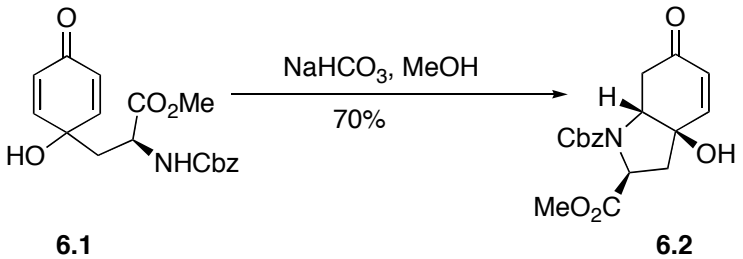


4.1 **5.1**

(75% , 68% ee)

Scheme 5

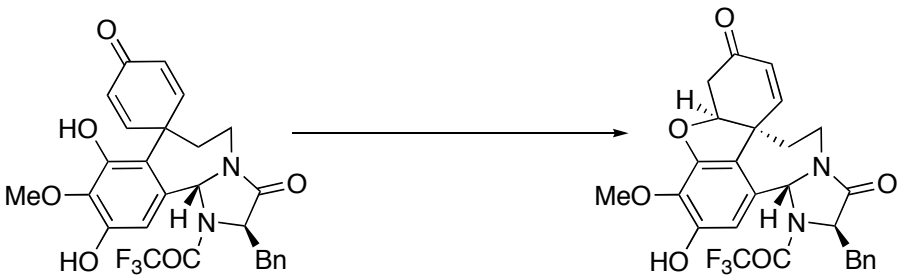
Wipf reported a highly stereoselective intramolecular addition of carbamates onto dienones, which were easily prepared from the corresponding amino acids.[12,13] Michael acceptor **6.1** underwent a stereoselective 1,4-addition under basic conditions to give bicycle **6.2** as the only detectable isomer (Scheme 6).



6.1 **6.2**

Scheme 6

Node recently reported a group-selective 1,4-phenol addition onto dienone **7.1** to afford the desired cyclized product **7.2** in 95% yield as a single isomer (Scheme 7).[14]



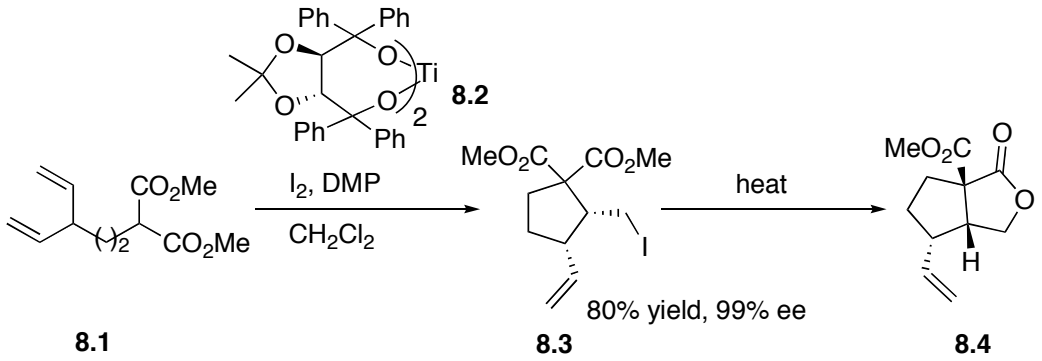
7.1 **7.2**

Scheme 7

1.2.2 *Desymmetrization reactions involving the formation of a carbon-carbon bond*

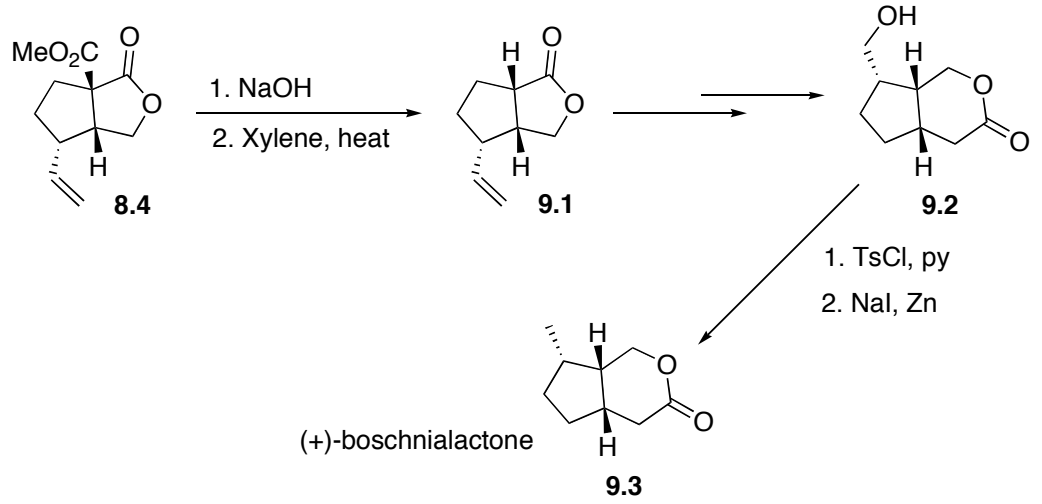
The stereoselective formation of all-carbon quaternary stereogenic centers represents a significant challenge.[15] In the past few years, desymmetrization has become a useful tool to create these chiral carbon quaternary centers with high selectivity.

Taguchi and co-workers have developed a desymmetrizing iodocarbocyclization of bisalkenylated malonates (Scheme 8).[16] Reaction of malonate **8.1** with 20 mol% of Ti-TADDOLate **8.2** in the presence of iodine and 2,6-dimethoxypyridine (DMP) gave the cyclopentane **8.3** in very good yield (80%) and excellent enantioselectivity (99% ee). Upon heating **8.3**, lactone **8.4** was obtained in excellent yield.



Scheme 8

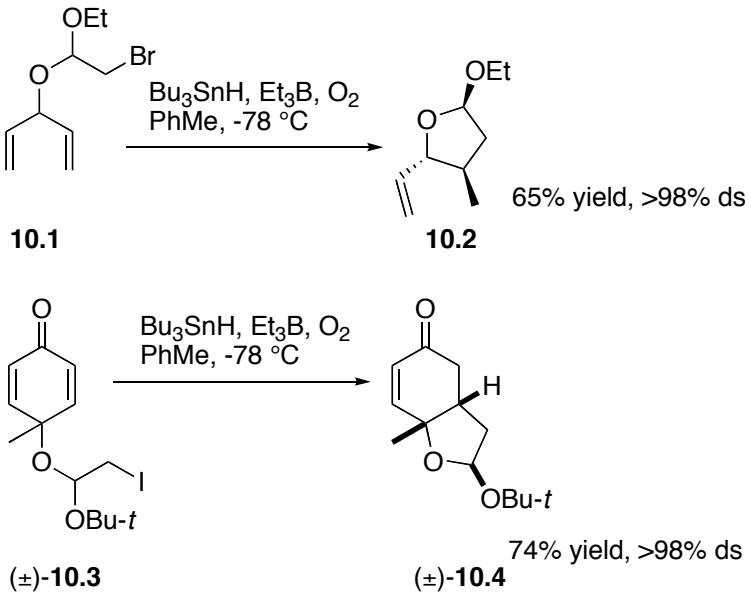
Lactone **8.4** was used as a precursor in a short synthesis of (+)-boschnialactone **9.3** (Scheme 9).



Scheme 9

Renaud and co-workers have investigated a novel desymmetrization strategy based on regioselective and diastereoselective formation of a carbon-carbon bond in both open and cyclic systems.[17] This approach takes advantage of a group selective radical addition based on a concept recently reported by

Curran's group.[18] Stork-Ueno radical cyclization of bromoacetal **10.1** gave the trisubstituted tetrahydrofuran **10.2** with very high diastereoselectivity (>98%) at -78 °C (Scheme 10). Renaud found that this reaction was temperature dependent. For example, running the same reaction (**10.1→10.2**) at 80 °C (Bu_3SnH, AIBN) afforded **10.2** in 61% yield and 86% ds. The cyclic radical precursor **10.3** also gave excellent levels of stereocontrol at low temperature (**10.3→10.4**).



Scheme 10

The key element for the control of the stereochemical outcome in the above radical reactions is the acetal center and this can be rationalized by the reacting conformations of type A (Beckwith-Houk type) and B for the open and cyclic systems, respectively (Figure 2).

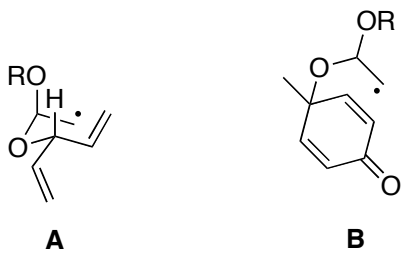
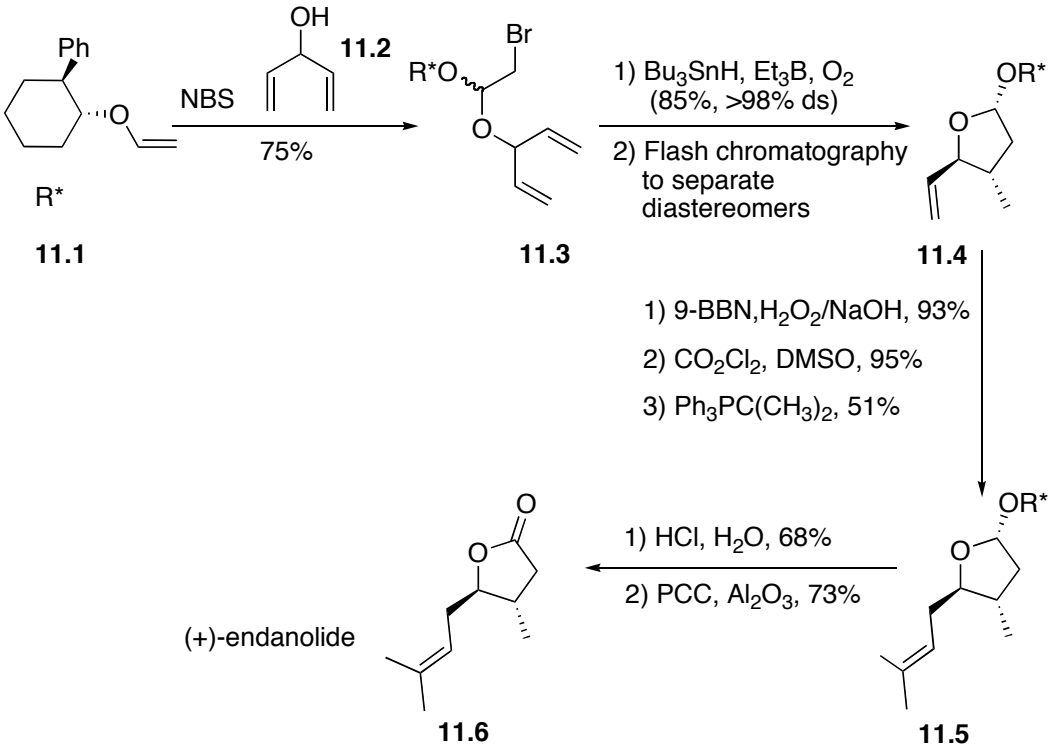


Figure 2. Stereochemical model for radical cyclizations

The above examples involve racemic compounds and the reactions are *diastereoselective*. However, if a single enantiomer were to be used, the processes would then become *enantioselective*, and this fact serves to identify the problem of making enantiomerically pure Stork haloacetals.

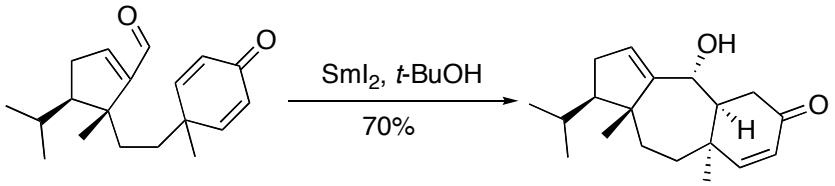
Renaud showed the utility of the above approach summarized in Scheme 10 for the synthesis of optically pure lactones such as (+)-eldanolide, the pheromone of the male African sugarcane stem borer *Eldana saccharina*; his route is summarized in Scheme 11.[17,19]



Scheme 11

The optically pure vinyl ether **11.1** gave a 1:1 diastereoisomeric mixture when treated with NBS in the presence of symmetrical alcohol **11.2**, but each diastereoisomer of **11.3** underwent highly diastereoselective (ds >98%) ring closure. Chromatographic separation of the cyclization products (which are diastereoisomers) afforded **11.4**, which was then used for the synthesis of the natural product, (+)-eldanolide **11.6**. The main limitation of Renaud's approach is that the diastereoselectivity of the haloacetalization step (**11.1→11.3**) is not controlled and hence separation of the diastereomers by chromatography is necessary. This limitation is addressed in my own research described in the Discussion Section.

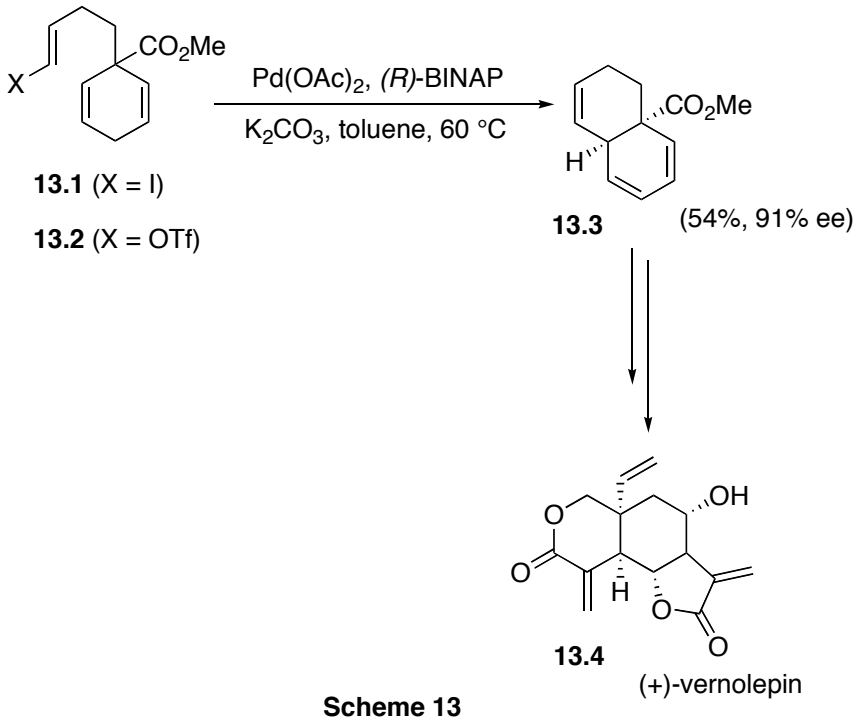
Lee and co-workers showed that ketyl radical cyclization of optically pure aldehyde **12.1** in the presence of samarium diiodide gave the 5-7-6 tricyclic core intermediate of guanacastepenes **12.2** in 70% yield as the only isomer (Scheme 12).[20] This example is different from Renaud's in the sense that the starting material contains asymmetric carbons that are preserved in the final natural product, and the process is simply an example of diastereoselection with an optically pure starting material.



12.1 **12.2**

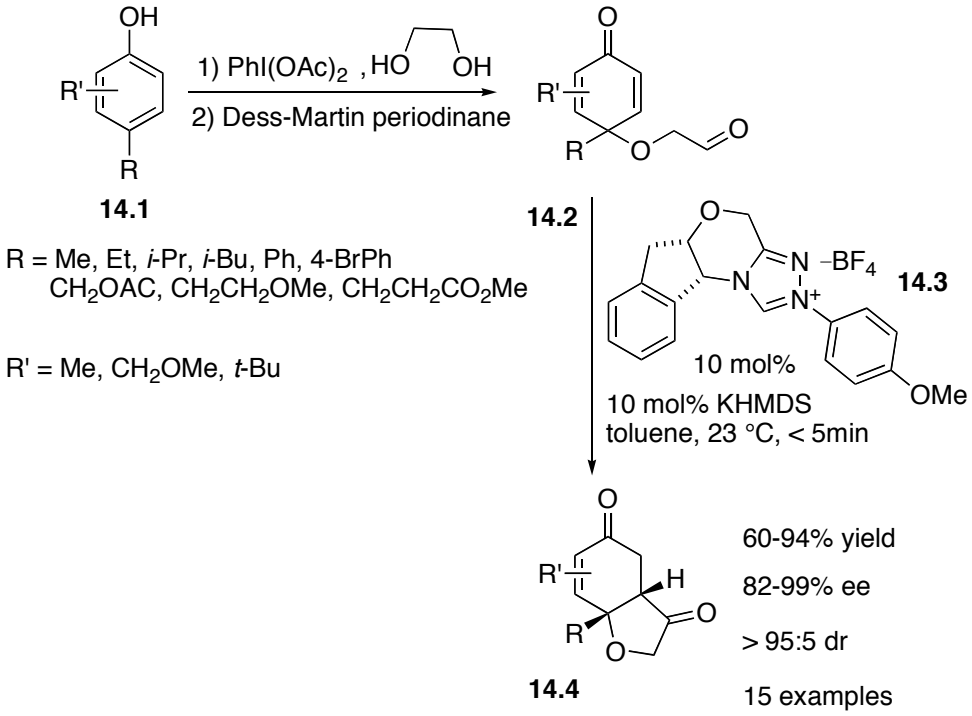
Scheme 12

Shibasaki reported an asymmetric Heck reaction for the desymmetrization of 1,4-cyclohexadienes (Scheme 13). Treatment of the cyclohexadienes in the presence of (*R*)-BINAP as a chiral ligand, in a palladium-mediated desymmetrization reaction, gave decalin derivatives with good asymmetric induction. The Shibasaki group found that by replacing the iodide **13.1** by a triflate **13.2** and modifying the reaction conditions, improved selectivity was achieved.[21] Thus, decalin derivative **13.3** was obtained in 54% yield with 91% enantiomeric excess. This desymmetrization strategy was then successfully applied to the first asymmetric synthesis of (+)-vernolepin **13.4**.



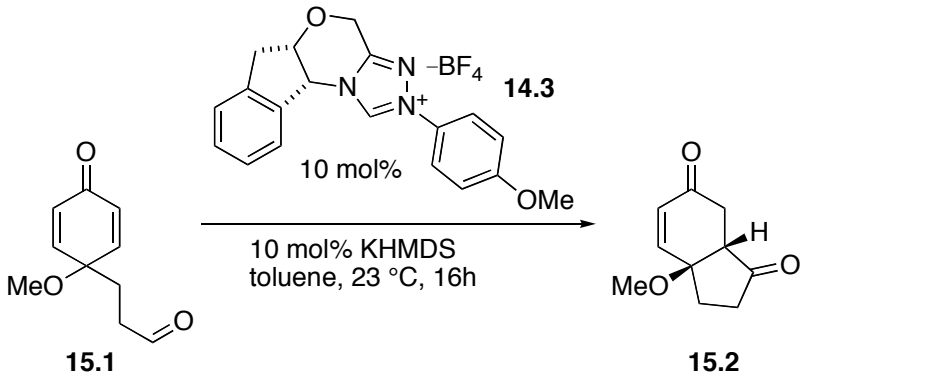
Scheme 13

In 2006, Rovis demonstrated an asymmetric synthesis of hydrobenzofuranones via desymmetrization of cyclohexadienones using an intramolecular Stetter reaction (Scheme 14).[22] A number of cross-conjugated dienone derivatives (**14.2)** were prepared from hypervalent iodine oxidation reactions in the presence of ethylene glycol to afford the dienone alcohols (usually in poor yield) which, upon treatment with Dess-Martin reagent, gave the corresponding aldehydes (**14.1→14.2**, 9-43% over two steps). This step sets the stage for the asymmetric Stetter reaction. Cyclization was achieved in less than 5 min in the presence of the aminoindanol-derived triazolium salt **14.3** as catalyst and KHMDS in toluene at room temperature (**14.2→14.4**). The desired cyclized products **14.4** were obtained in very good yields and excellent enantioselectivities.



Scheme 14

Although most substrates are oxygen tethered-substrates, the same group has also shown that carbocycles are also accessible (Scheme 15), for example, when **15.1** was subjected under the same reaction conditions, hydrindane **15.2** was isolated in good yield. However, there is no example of nitrogen-tethered substrates being investigated.

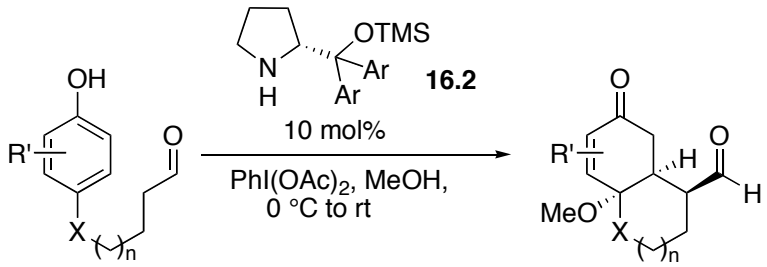


Scheme 15

Rovis's asymmetric intramolecular desymmetrizing Stetter reaction strategy gave hydrobenzofurans with quaternary stereocenters in high enantioselectivities and diastereoselectivities. These hydrobenzofurans are important core skeletons found in many natural products.[23]

Along the same lines as Rovis, Gaunt and co-workers in 2007 reported a process that directly transforms a *para*-substituted phenol to a highly functionalized chiral molecule.[24] This process involves an oxidative dearomatization followed by an amine-catalyzed enantioselective desymmetrizing Michael reaction (Scheme 16). Reaction of phenol derivatives **16.1** with 1 equiv of $PhI(OAc)_2$ and 10 mol% of (*R*)-proline type catalyst **16.2** delivered the cyclized products **16.3** with exquisite control of stereochemistry (>20:1 dr and 99% ee). They also found that the above reaction proceeded well in MeOH and this highlighted the importance of protic media in controlling the stereoselectivity in the desymmetrization step. In contrast to Rovis's work, Gaunt's strategy allows access to oxygen and nitrogen heterocycles as well as carbocycles.

However, a main limitation is that substitution on the phenolic ring was not well tolerated, for example, when 2,6-dimethylphenol (**16.1**, R' = Me) was tested, a poor enantioselectivity (40% ee) was observed for the cyclized product (**16.3**, R' = Me).



16.1

X = C, O, N

n = 0,1, 2

R' = Me

16.3 52-84% yield

97-99% ee

> 20:1 dr

10 examples

Scheme 16

The stereochemistry of the catalytic enantioselective process could be rationalized as shown by Gaunt's proposed model (Figure 3) via a transition state (vide infra) that involves an endo-like attack onto the *Si* face of the meso-cyclohexadienone.

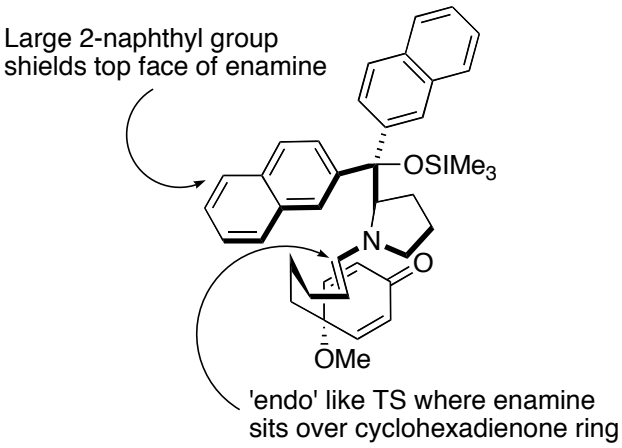


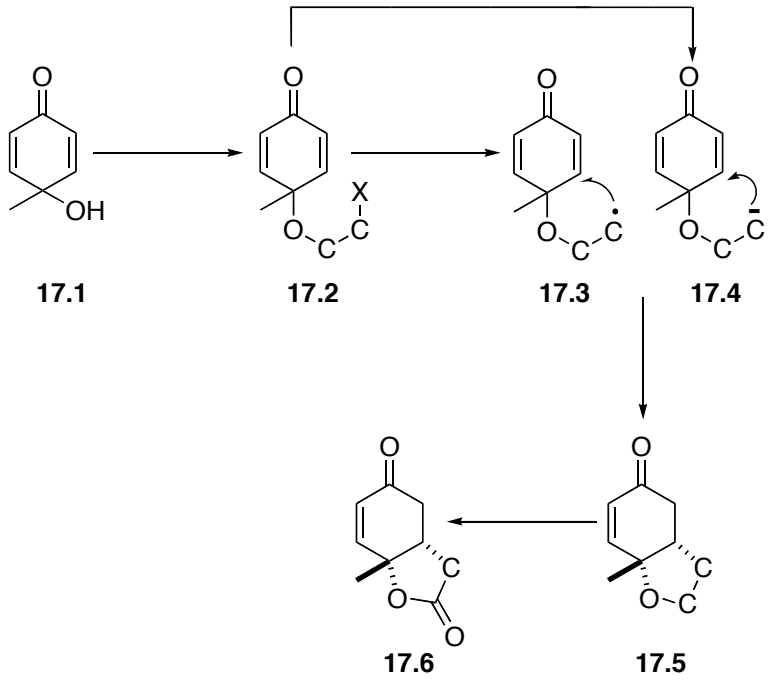
Figure 3. Gaunt's proposed stereochemical model

Overall, Gaunt's strategy, which starts with a flat molecule that is devoid of architectural complexity, gives via a one-step transformation a complex non-racemic molecular structure with excellent control of three new stereogenic centers. This strategy is currently under investigation in Gaunt's laboratory for the application to the synthesis of natural products.

2 RESULTS AND DISCUSSION

2.1 *Research Objectives*

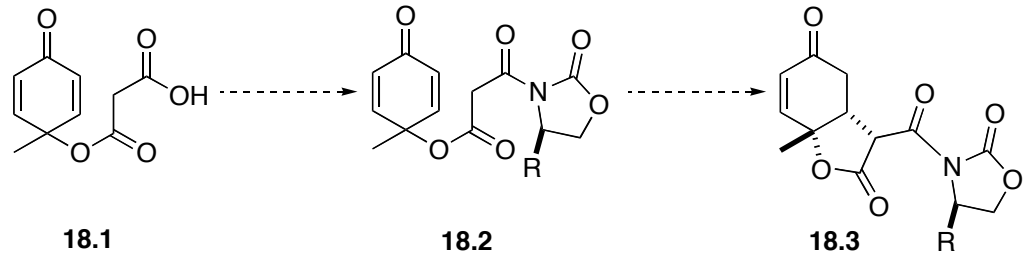
As part of the preliminary planning for a synthesis of the antileukemic agent sorbicillactone A (**1.1**),[1] a decision was made to investigate desymmetrizing processes along the lines summarized in Scheme 17, where X is a homolyzable substituent (Br or I) for a diastereoselective radical reaction (**17.2→17.3**) or X is H for an ionic Michael addition (**17.2→17.4**). We were hoping that these desymmetrization processes, in the presence of a chiral auxiliary, would allow control of stereochemistry in the ring closure. In a single operation, two new stereogenic centers are created and after removal or degradation of the chiral auxiliary, the product would be elaborated into a γ-lactone (**17.5→17.6**).



Scheme 17

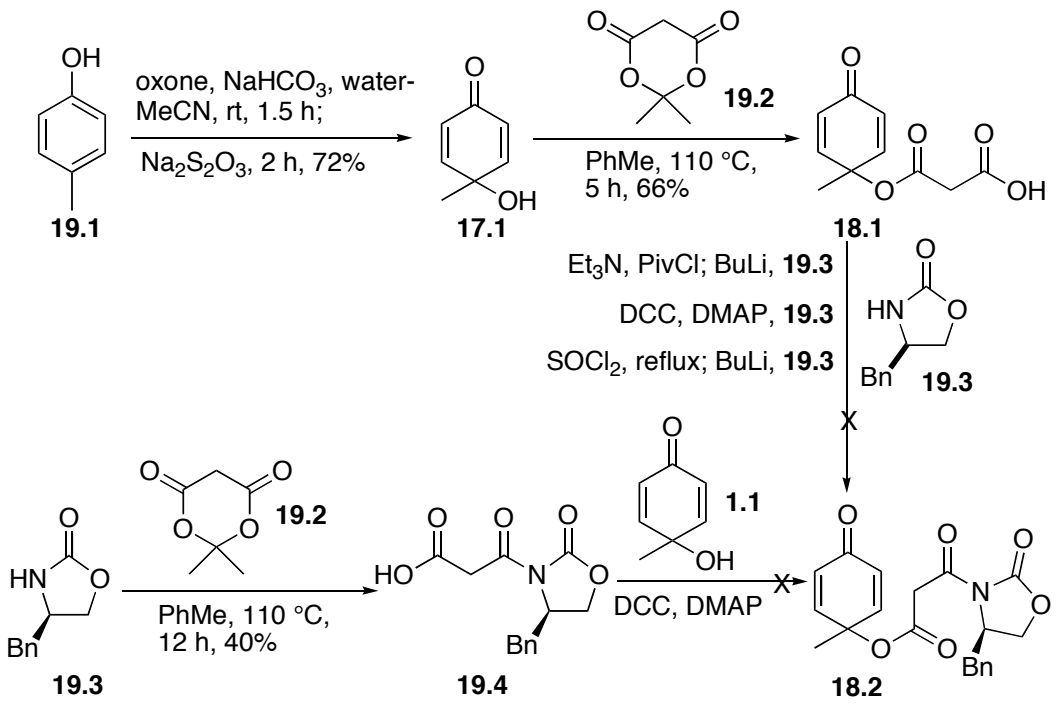
2.2 *Use of Evans's chiral auxiliary for an ionic Michael addition desymmetrization process*

Our investigation began with the use of Evans's oxazolidinone as the chiral auxiliary in the hope that it would dictate the stereochemistry of the ring closure via a Michael addition (**18.2→18.3**), as shown in Scheme 18.



Scheme 18

Cyclohexadienone **17.1** was readily available by oxidation of *p*-cresol with Oxone in MeCN and water, a procedure recently developed by Carreño and co-workers.[25] Treatment of cyclohexadienone **17.1** with Meldrum's acid (**19.2**) in refluxing PhMe gave the half ester **18.1** in 66% yield (Scheme 19). However, attempts to couple compound **18.1** with (*R*)-4-benzyl-2-oxazolidinone (**19.3**) under various conditions failed to generate the key intermediate **18.2**. Attempting to reverse the process by first heating (*R*)-4-benzyl-2-oxazolidinone **19.3** with Meldrum's acid (**19.2**) to give compound **19.4**, and then coupling with cyclohexadienone **17.1**, was also unsuccessful (**19.4→18.2**).



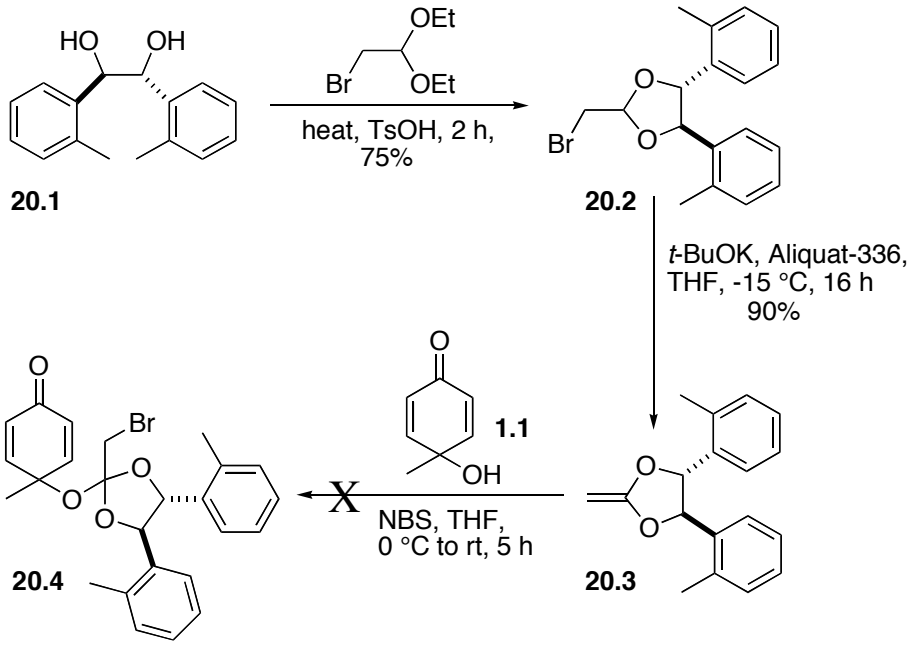
Scheme 19

As we could not prepare the key intermediate **18.2**, we were unable to study the planned stereoselective intramolecular 1,4-addition process, and so we turned our attention to the use of a different chiral auxiliary.

2.3 Use of auxiliary-based C_2 symmetric ketene acetal for a radical addition process

Further consideration suggested that cyclic ketene acetals such as **20.3** were worth examining. They had been used in stereoselective cycloaddition reactions[26] and in the asymmetric synthesis of terpenoids.[27] Another special feature of ketene acetals was that the carbon-carbon double bond is highly polarized and most ketene acetals are susceptible to attack by protic substrates; for example, reaction of cyclic ketene acetals with MeOH gave the corresponding

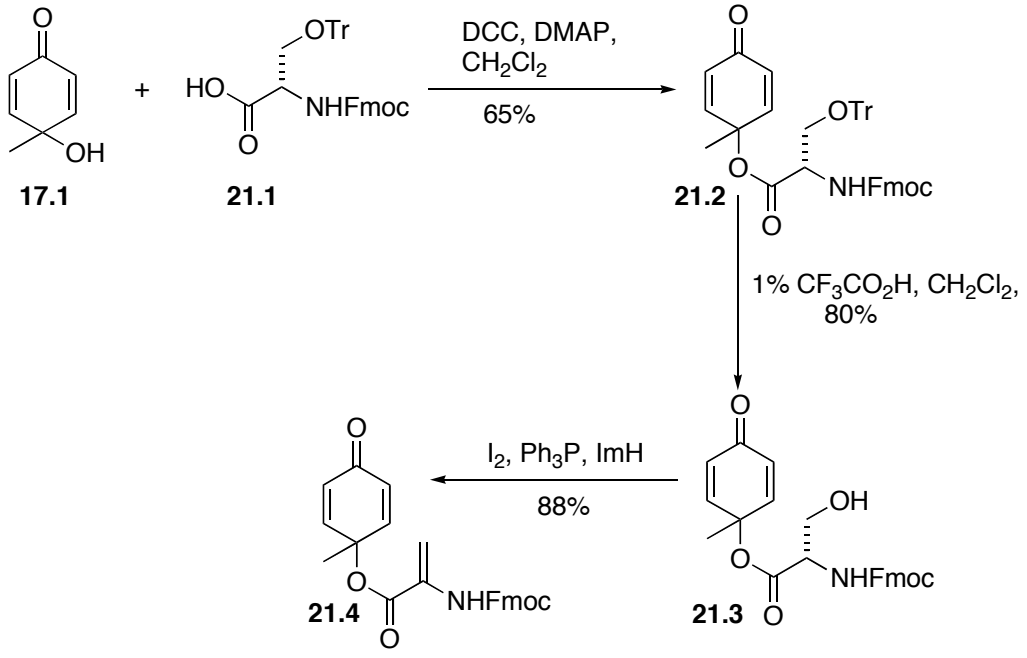
cyclic orthoacetates in fairly good yield (65-98%).[28] Based on this observation, we reasoned that treatment of the cyclic ketene acetal **20.3** with cyclohexadienone **17.1** in the presence of NBS should afford the bromo intermediate **20.4** which would set the stage for a diastereoselective radical cyclization. To this end, the diol **20.1** was converted into the bromo acetal **20.2** in 75% yield and the latter was dehydrobrominated (**20.2→20.3**) using the method developed by Bailey and Zhou[29] to give the cyclic ketene acetal **20.3** in 90% yield (Scheme 20). The compound was unstable and had to be used immediately for the next step. Unfortunately, reaction of ketene acetal **20.3** with cyclohexadienone **17.1** in the presence of NBS in THF did not proceed as expected, but instead gave a complex mixture, possibly because of the instability of the cyclic ketene acetal **20.3** and its competing or dominating polymerization.[30]



Scheme 20

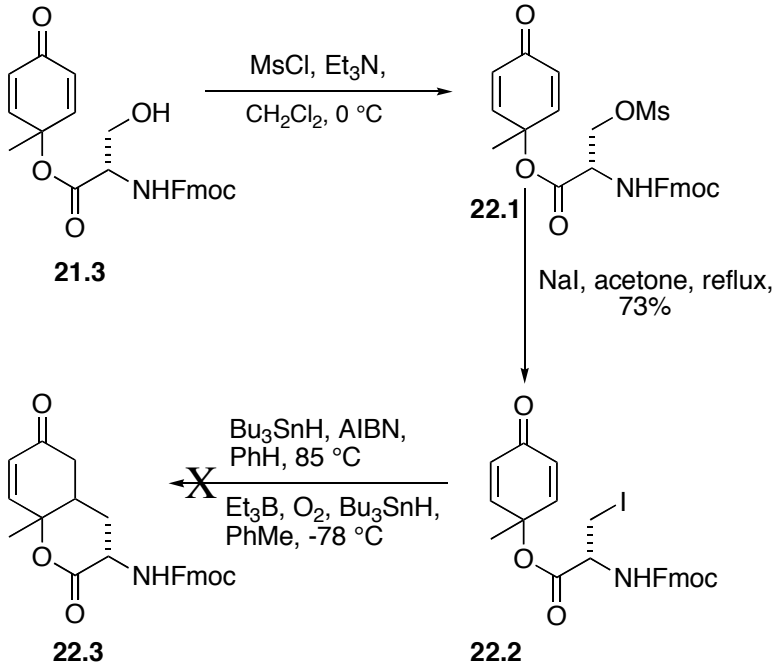
2.4 *Use of an amino acid as a source of chirality*

On looking closely at sorbicillactone A, we realized that an amino acid could potentially be used to construct the lactone unit with the hope that it would control the stereochemistry of the ring closure. To this end, treatment of the commercially available serine diprotected derivative **21.1** with the enone **17.1** in the presence of DCC and DMAP gave the desired coupling product **21.2** in 65% yield (Scheme 21). Removal of the trityl group was achieved using 1% CF_3CO_2H to afford the monoprotected compound **21.3** (79%). Conversion of the hydroxyl group of **21.3** to the corresponding iodide under standard conditions (I_2, PPh_3, ImH) for a subsequent radical cyclization failed to give the desired iodo product but instead the eliminated product **21.4** was isolated in 88% yield.



Scheme 21

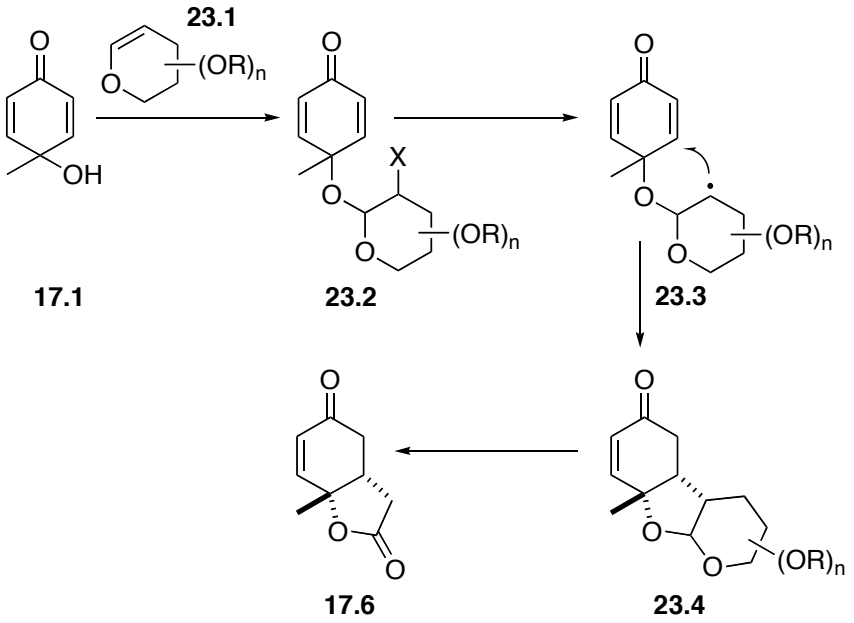
However, this problem was overcome by first converting the hydroxyl group of **21.3** to a mesylate (**22.1**) followed by displacement with sodium iodide in refluxing acetone to give the iodo radical precursor **22.2** in 73% yield (Scheme 22). Attempted radical cyclization (**22.2**→**22.3**) under standard conditions (Bu_3SnH, AIBN, PhH, 85 °C) did not proceed as expected but instead gave a complex mixture. At this stage, we suspected that the iodide might be decomposing on heating and thus we attempted the radical cyclization in the presence of Et_3B and oxygen as the radical initiator at a low temperature (-78 °C), but these conditions gave mainly recovered starting material along with reduced product (replacement of I by H) and so this route was abandoned.



Scheme 22

2.5 *Use of glycals as a source of chirality*

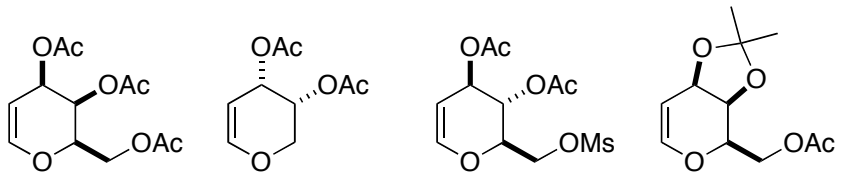
Glycals have been extensively used in natural product synthesis and it has been shown that they are very useful components of the chiral pool.[31] As mentioned in the introduction section of this chapter, the work done by Renaud and co-workers showed that differentiation in cyclohexadienes could be obtained using the Stork-Ueno reaction, whereby the chiral centre at the acyclic acetal steers the addition reaction perfectly.[19] Thus, our plan was to make use of a cyclic acetal, which we expected would be a better auxiliary because it is rigidified compared with an acyclic acetal. On this basis, glycals **23.1** appeared to be good candidates for investigation. However, implementation of this plan requires a method for functionalizing the tertiary hydroxyl of **17.1** in a way that sets the stage for the radical cyclization (**23.2→23.3**), and the cyclization must be



Scheme 23

diastereoselective (Scheme 23). Finally, the cyclization product should also provide opportunities for degradation to release the required lactone **17.6**.

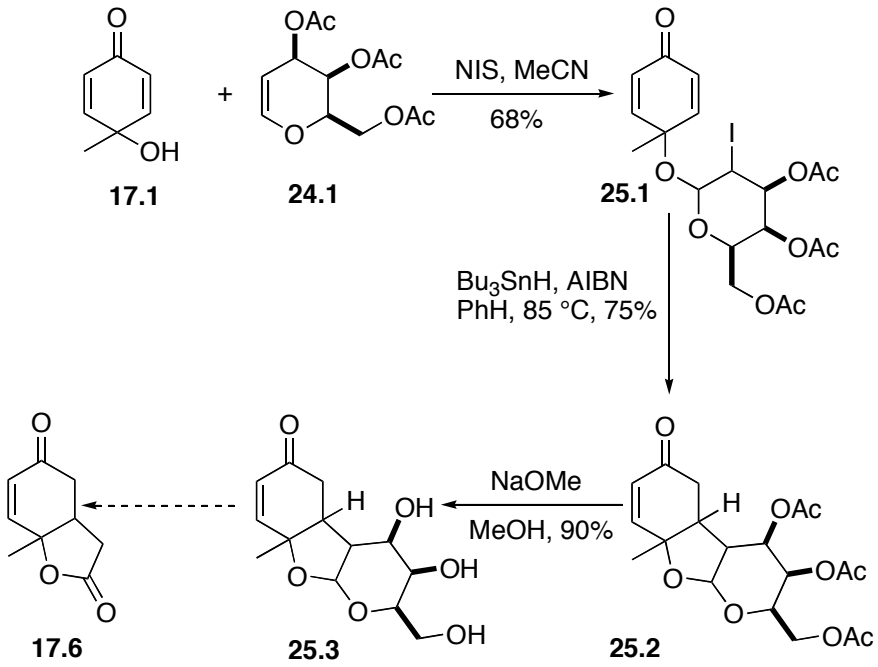
Accordingly, a brief experimental survey of several glycals was made (Scheme 24). We examined first the glycals **24.1** to **24.4**, and began with D-galactal triacetate[32] **(24.1),** as a sample happened to be available in the laboratory.



24.1 **24.2** **24.3** **24.4**

Scheme 24

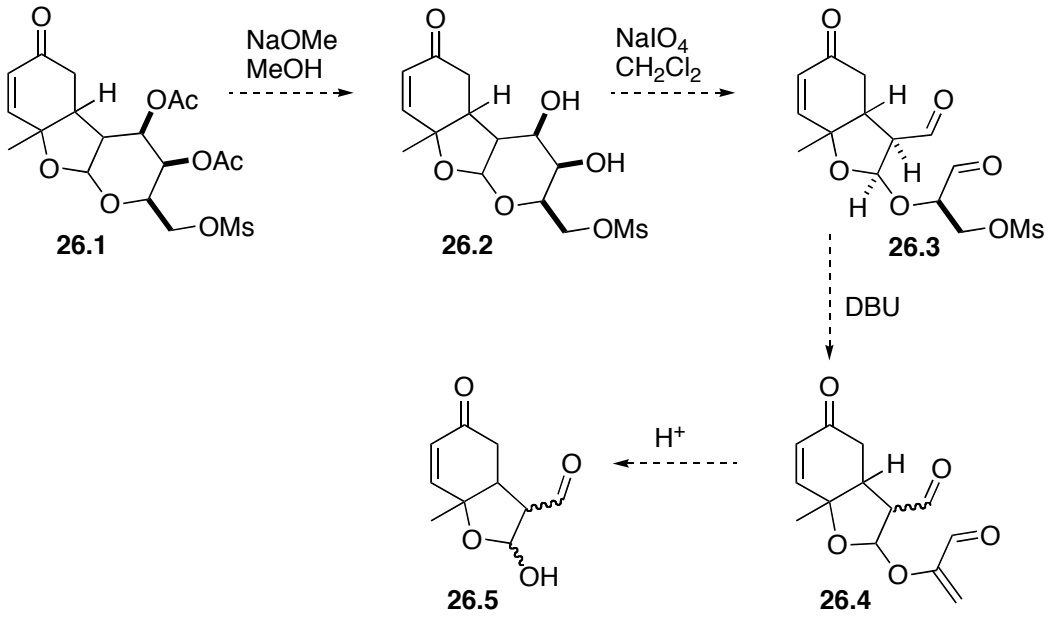
The cross-conjugated ketone **17.1** reacted with D-galactal triacetate (**24.1)** in the presence of NIS in MeCN to give iodide **25.1** in 68% yield as a single isomer whose full stereochemistry was not established (Scheme 25). Iodide **25.1** underwent radical cyclization under standard stannane-mediated conditions, giving the cyclized product **25.2** as a single isomer (75%). Treatment of **25.2** with sodium methoxide in MeOH afforded the desired triol **25.3** in 90% yield. At first, isolation of the triol was problematic but later we found that quenching the reaction with an Amberlite resin made isolation of the diol easier. However, attempts to degrade the derived triol **25.3** to the lactone **17.6** were unsuccessful. For example, treatment of triol **25.3** with sodium periodate or sodium periodate supported on silica[33] in MeOH gave a complex mixture.



Scheme 25

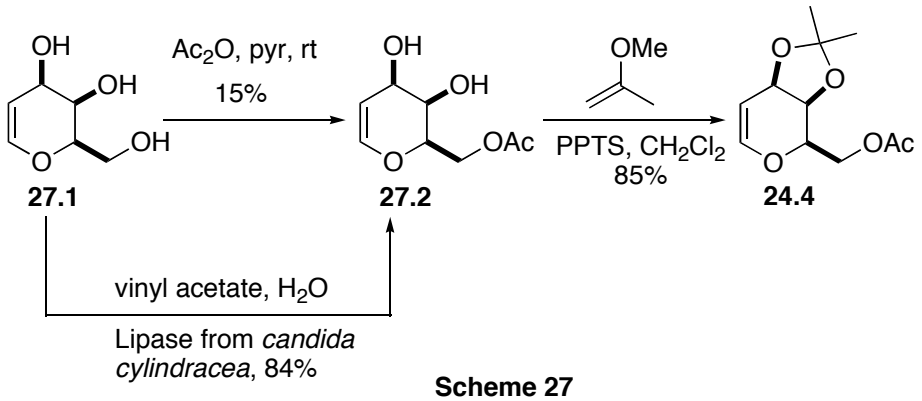
Suspecting that degradation of a *diol*, rather than a *triol*, might be simpler, we then planned to repeat the sequence of Scheme 25 with the arabinal diacetate **24.2**. However, the first step (the iodoetherification) produced a mixture of two isomers, suggesting that the presence of a C-6 substituent on the glycal is important for stereochemical control.

The di-*O*-acetyl-D-glucal derivative **24.3** was examined next, this compound being chosen because it is easily prepared and the methanesulfonyloxy group might facilitate the degradation process, after radical cyclization (**26.1→26.5**), along the lines summarized in Scheme 26.



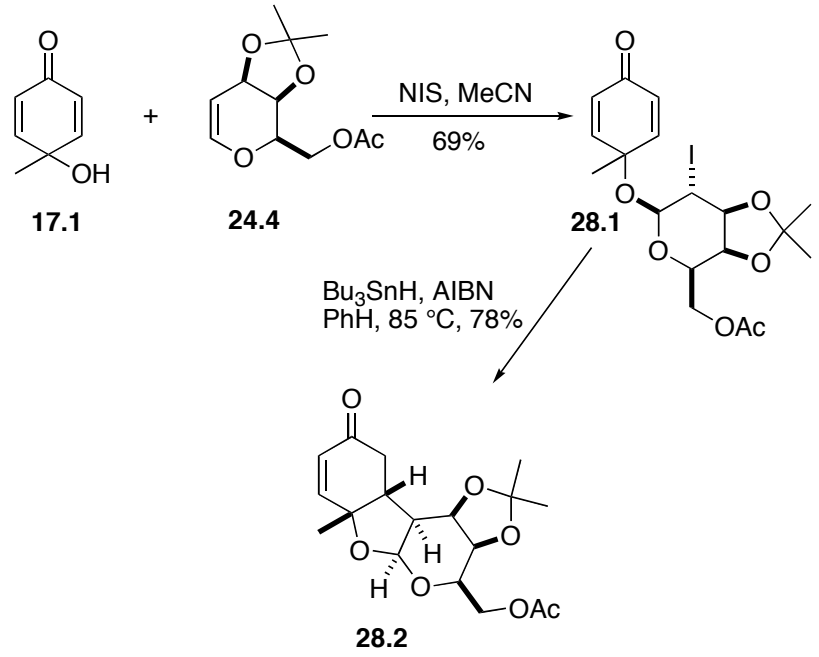
Scheme 26

Surprisingly, the iodoetherification (cf **17.1→25.1**) did not work — at least, in the two attempts we made — and so we returned to the galactal series and used compound **24.4**. Our hope was that the large ketal protecting group would foster a high degree of stereoselectivity in both the iodoetherification and radical cyclization steps, and might also be easily removable to afford a diol with the C-6 acetoxy group intact. Glycal **24.4** was first prepared (Scheme 27) by treatment of D-galactal **27.1** with acetic anhydride in pyridine to give the desired monoacetate glycal **27.2** in only 15% yield, accompanied by a mixture of glycal diacetates. A modified route made use of an enzymatic reaction[34] of compound **27.1** in the presence of vinyl acetate and Lipase from *candida cylindracea* (LCC) to give **27.2** in 84% yield. Reaction of **27.2** with 2-methoxypropene and PPTS in CH_2Cl_2 afforded the required protected glycal **24.4** (85%).



Scheme 27

In the presence of NIS, the tertiary alcohol **17.1** reacted with glycal **24.4** to provide a single iodo ether **28.1** (69%) that underwent stannane-mediated radical cyclization under standard conditions to afford the cyclized product **28.2** as a single isomer in 75% yield (Scheme 28).



Scheme 28

The cyclized product **28.2** was crystalline and its stereochemistry was tentatively determined by transverse rotating frame nuclear Overhauser effect (TROESY) measurements. Figure 4 summarizes the key interactions that were used to establish the stereochemistry, in particular, the absence of a correlation between the methyl hydrogens and the hydrogen of the acetal centre. The assignment was later confirmed by X-ray analysis (Figures 5 and 6).

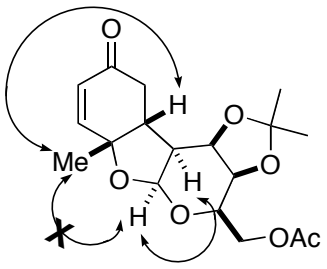


Figure 4: TROESY correlations for product **28.2**

On this basis, the stereochemistry of its precursor **28.1** is assumed to be as shown (Scheme 28). The stereochemical course proposed for the iodoetherification (**17.1→28.1**) is in line with prior observations made with a related galactal.[35]

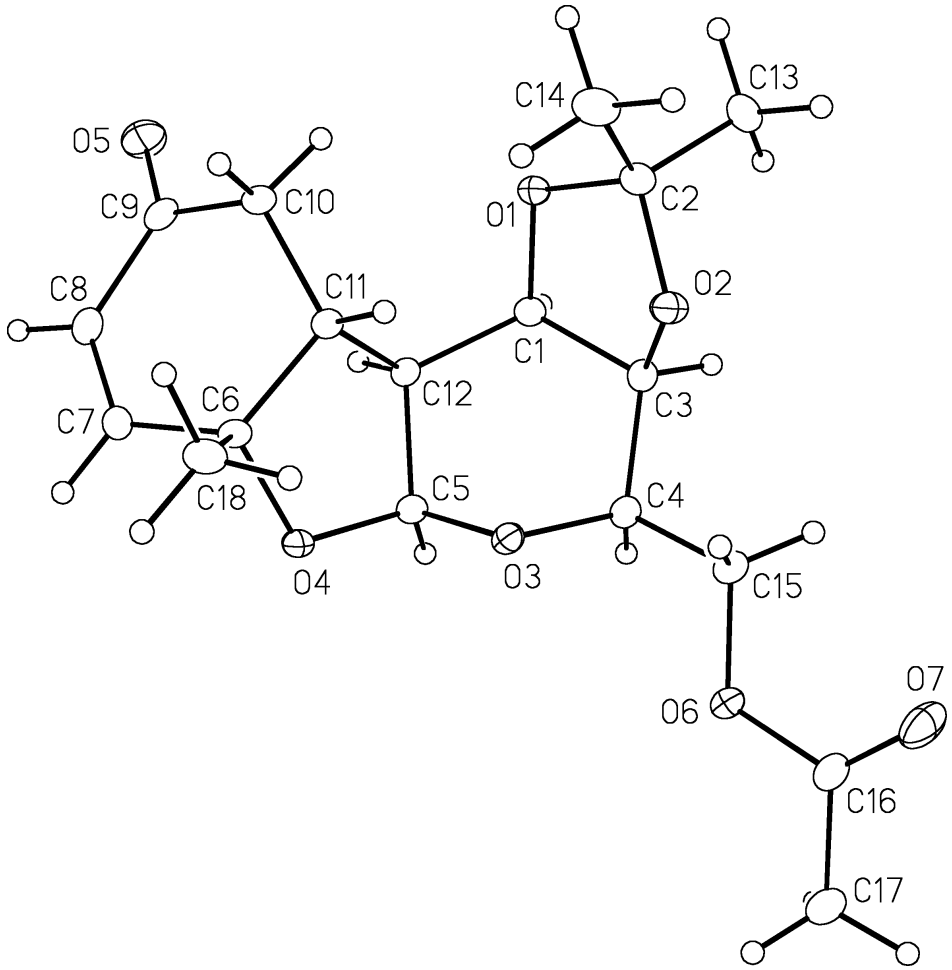


Figure 5: X-Ray structure of compound **28.2** (perspective view)

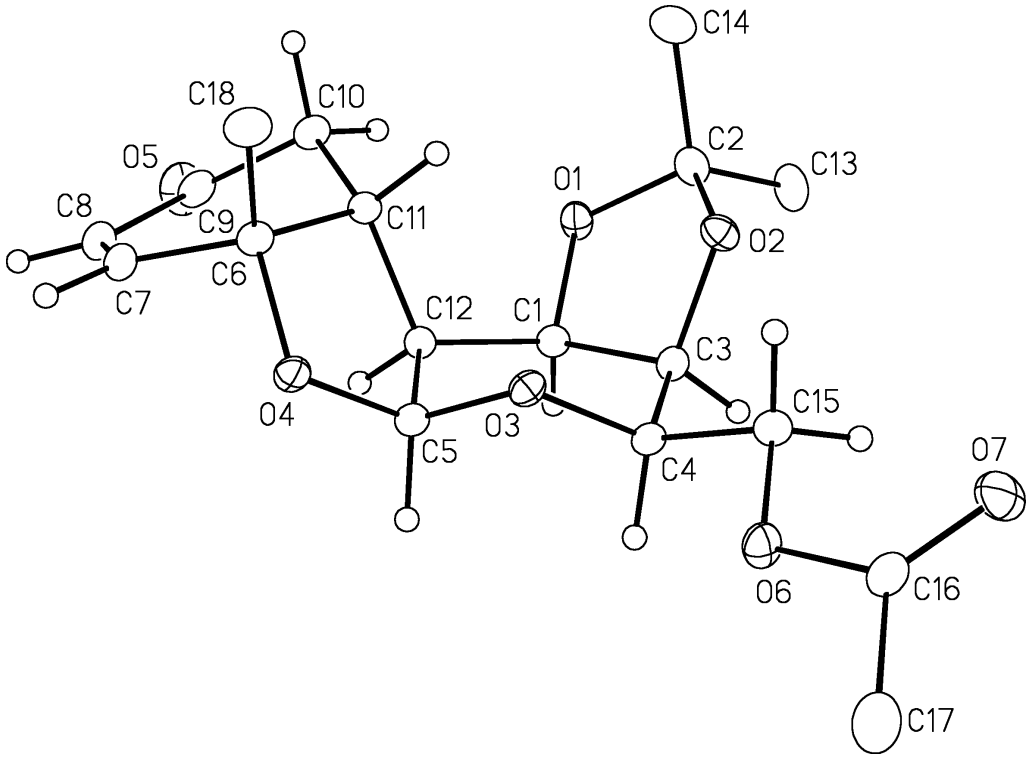
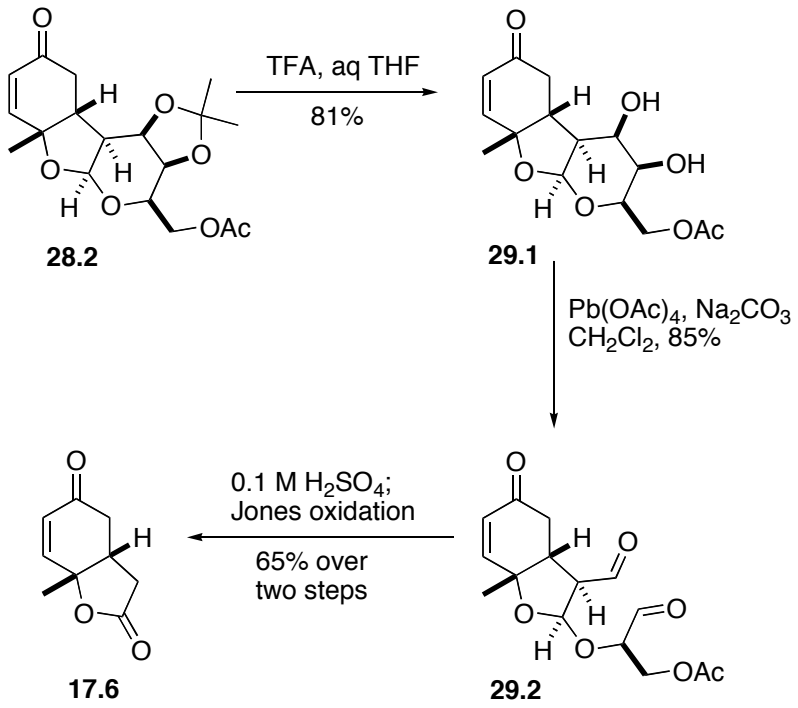


Figure 6: X-Ray structure of compound **28.2** (alternate view, methyl hydrogens have been omitted)

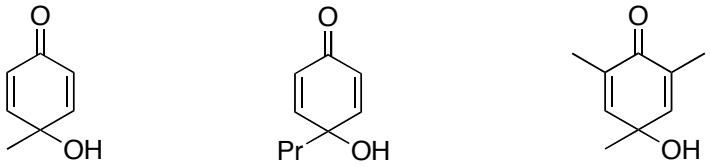
The next step in our planned sequence is to degrade the sugar unit to the required lactone. Acid hydrolysis of **28.2** served to release the diol **29.1** (Scheme 29). This ketal hydrolysis was also tried with TsOH-MeOH and PPTS-MeOH, but neither of these systems gave the diol. With CF_3CO_2H, however, the hydrolysis was efficient (81%) and the diol was then easily cleaved by treatment with $Pb(OAc)_4$ in the presence of Na_2CO_3 to dialdehyde **29.2** (85%). We initially experienced difficulty in further degrading the dialdehyde. Experiments using CF_3CO_2H in aqueous THF, aqueous HCl-THF, and $BiCl_3.H_2O$-MeOH were all unsuccessful, but we eventually found that acid hydrolysis with dilute H_2SO_4,

followed by Jones oxidation of the resulting crude product, gave the lactone **17.6** in 65% yield over the two steps. This model study has established the required stereochemistry of the sorbicillinoid core of sorbicillactone A (**1.1)**.



Scheme 29

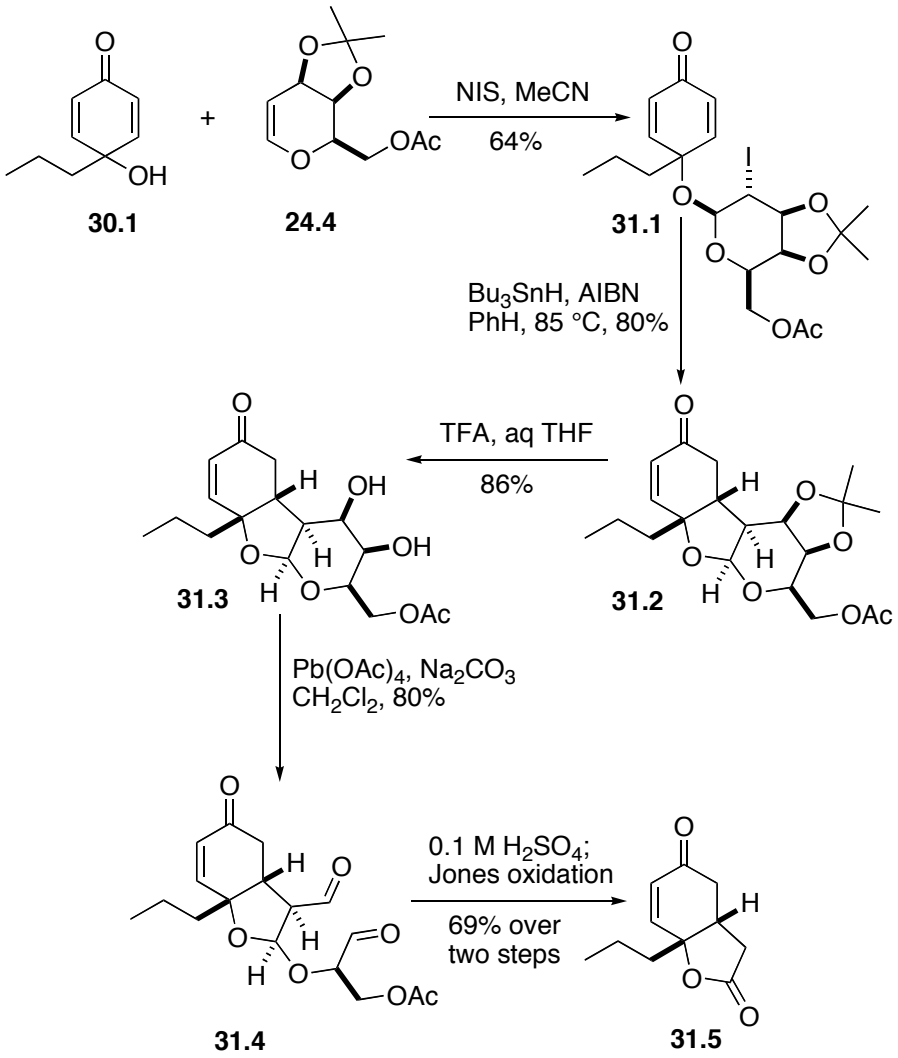
The above reaction sequence (Schemes 28 and 29) for desymmetrization of cross-conjugated ketones of type **17.1** is general, and was next applied to the two additional substrates[36] **30.1** and **30.2**[25] (Scheme 30).



17.1 **30.1** **30.2**

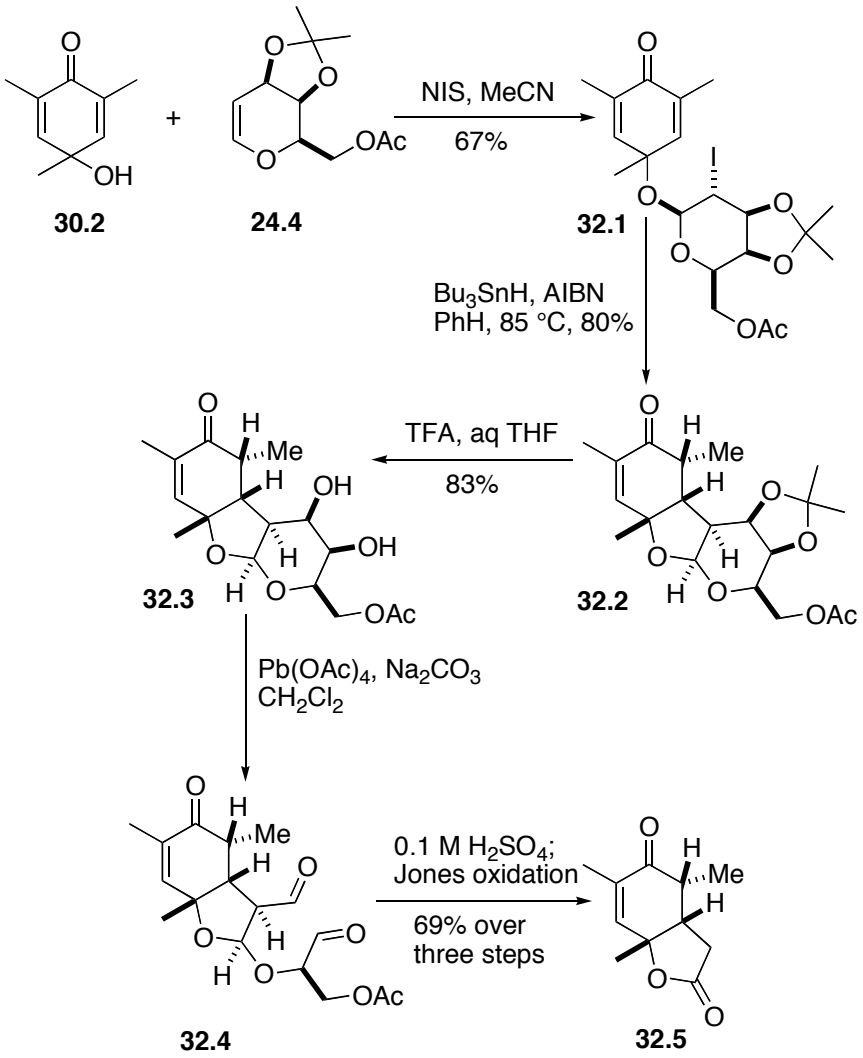
Scheme 30

In the case of the propyl series (Scheme 31), the iodoetherification step (**30.1→31.1**) gave the desired coupling product **31.1** in 64% yield, predominantly as a single isomer (dr 18.4:1; ^{1}H NMR). Iodide **31.1** then underwent stannane-mediated radical cyclization to afford the cyclized product **31.2** as a single isomer (80%). The stereochemistry of compound **31.2** was arbitrarily assigned as shown, by analogy with the established stereochemistry for compound **28.2**. Degradation of the sugar moiety proceeded as expected, giving the desired lactone in good yield.



Scheme 31

The substrate that we examined next was the 2,6-dimethylcyclohexadienone derivative (**30.2**) as this would allow the construction of three strereogenic centres in the final lactone product. This substrate (**30.2**) behaved well and gave a single isomer in both the iodoetherification (**30.2→32.1**) and radical cyclization (**32.1→32.2**) steps (Scheme 32).



Scheme 32

However, during cleavage of diol **32.3**, the corresponding dialdehyde **32.4** was unstable and hence, the crude mixture was used directly for the next step to release the lactone **32.5**. The stereochemistry of the cyclized product **32.2** was tentatively determined by TROESY measurements and Figure 7 summarizes the key correlations.

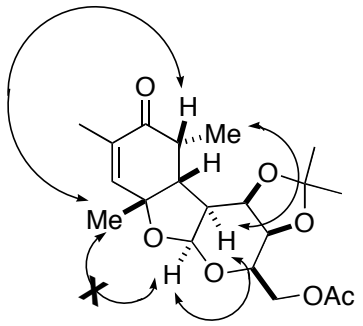


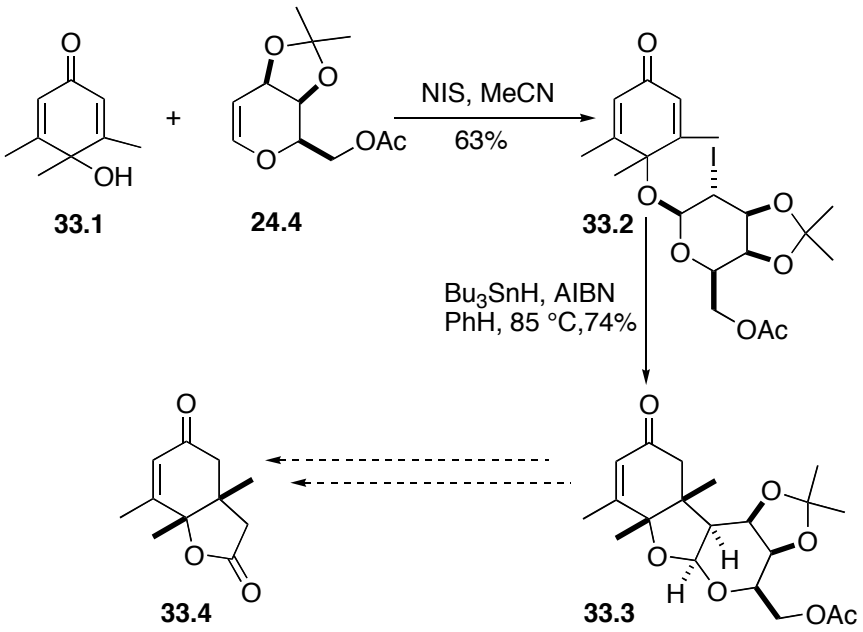
Figure 7: TROESY correlations for product **32.2**

3 CONCLUSION

The model study on the sorbicillinoid core of the marine alkaloid, sorbicillactone A has resulted in a new method for the desymmetrization of cross-conjugated cyclohexadienones. In this desymmetrization strategy, stereoinduction occurs via a covalently bound chiral sugar moiety. The key steps involve a highly controlled iodoetherification and diastereoselective radical cyclization. The stereochemistry of the radical cyclized product was confirmed by X-ray analysis in one case. In a single operation, at least two new stereogenic centers are formed and chiral quaternary carbons can be generated with high selectivity. Degradation of the sugar moiety allows the formation of γ-lactones, which are key structural units of natural products. While this methodology is still at an early stage, further experiments need to be done to define the scope of the reaction.

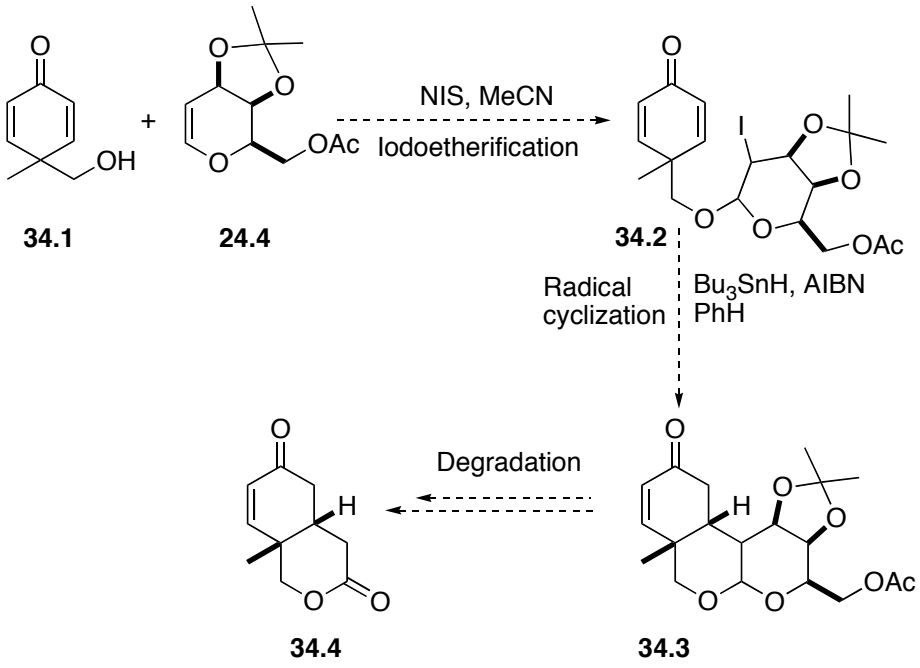
4 FUTURE RESEARCH

Another good substrate to be investigated would be the 3,5-dimethyl cyclohexadienone derivative (**33.1**) as the latter would allow the stereoselective formation of two quaternary stereogenic centres in the final lactone product **33.4**. This route has been briefly examined, as depicted in Scheme 33.



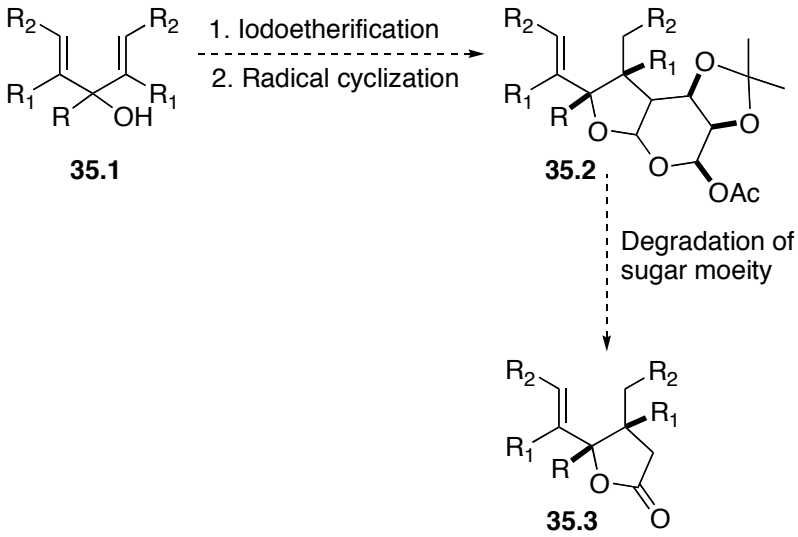
Scheme 33

The desymmetrization methodology gives access to a 5-membered lactone fused onto a 6-membered ring, however, the method can probably be extended to construct a 6-membered lactone fused onto a 6-membered ring (**34.4**), along the lines summarized in Scheme 34.



Scheme 34

While the desymmetrization process has been mainly investigated with cyclic systems (cyclohexadienone), it remains to be seen how acyclic systems such as **35.1** would behave in our standard route (Scheme 35). Desymmetrization of these acyclic diene systems will allow access to substituted vinyl butyrolactone derivatives **35.3**, which are important structural motifs in natural product synthesis.[37]



35.1 **35.2** **35.3**

Scheme 35

5 EXPERIMENTAL

Unless stated to the contrary, the following conditions apply: Reactions were carried out under a slight static pressure of Ar or N_2 that had been purified by passage through a column (3.5 x 42 cm) of R3-11 catalyst and then through a similar column of Drierite. All solvents for reactions were dried, as described below. Glassware was dried in an oven for at least 3 h before use (120 °C) and either cooled in desiccators over Drierite, or assembled quickly, sealed with rubber septa, and allowed to cool under a slight static pressure of Ar. Reaction mixtures were stirred with Teflon-coated magnetic stirring bars.

Hexane used for chromatography was distilled before use.

Products were isolated from solution by evaporation under water aspirator vacuum at room temperature, using a rotary evaporator.

Microliter syringes were washed with water and acetone using a suction device to draw the solvents through. Then air was sucked through for 1 min. The solution to be dispensed was drawn up and expelled, and this operation was repeated several times before drawing up the sample to be used. Cannula transfers were always done under slight pressure (Ar), not by suction.

Commercial thin layer chromatography (TLC) plates (silica gel, Merck 60F-254) were used. Spots were detected by spraying the plate with a solution of phosphomolybdic acid, followed by charring on a hot plate, or by examination under UV light. Silica gel for flash chromatography was Merck type 60 (230-400 mesh).

Dry solvents were prepared under an inert atmosphere and transferred by dry syringes fitted with oven-dried needles, or cannula. Dry PhH was distilled from sodium and benzophenone ketyl. Dry MeCN and CH_2Cl_2 were distilled from CaH_2. Dry MeOH was distilled from $Mg(OMe)_2$. Acetone was distilled from $KMnO_4$ and dried over 4Å molecular sieves. All other solvents were used as purchased.

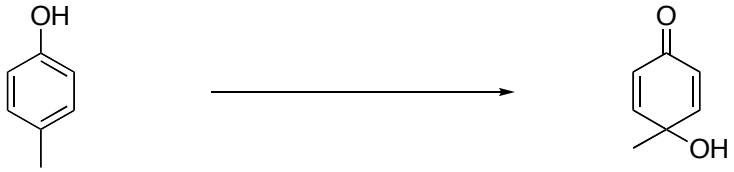
FTIR measurements were recorded on a Nicolet 7000 FTIR instrument. Measurements were made as casts from the specified solvent.

^1H nuclear magnetic resonance spectra were recorded with Varian INOVA-300 (at 300 MHz), Varian INOVA-400 (at 400 MHz), Varian INOVA-500 (at 500 MHz) spectrometers in the specified deuterated solvent. ^{13}C spectra were recorded with Varian INOVA-400 (at 100 MHz), Varian INOVA-500 (at 125 MHz). The symbols s, d, t, and q used for ^{13}C NMR signals indicate 0, 1, 2, or 3 attached hydrogens, respectively, which are assigned based on the APT experiment.

Mass spectra were recorded with Agilent Technologies 6220 Accurate-Mass TOF LC/MS, Perseptive Biosystems Mariner Biospectrometry Workstation, Kratos MS50 or Micromass ZabSpec Hybrid Sector-TOF mass spectrometers.

Compounds isolated by flash chromatography were pure by TLC and, unless otherwise stated, also as judged by high field ^1H and ^{13}C NMR spectra.

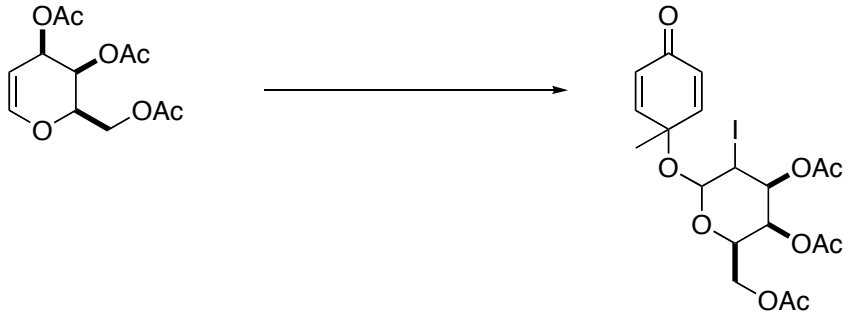
4-Hydroxy-4-methylcyclohexa-2,5-dienone (17.1).[25]



***p*-cresol** **17.1**

A mixture of Oxone (28.4 g, 46.2 mmol) and $NaHCO_3$ (11.6 g, 139 mmol) was added over ca 3 min to a vigorously stirred solution of *p*-cresol (0.97 mL, 9.3 mmol) in MeCN (10 mL) and water (40 mL). The flask was immediately closed with a septum attached via a needle to an empty balloon to avoid loss of generated singlet oxygen. Vigorous stirring was continued until all the phenol had reacted (TLC control). The mixture was diluted with water (15 mL), solid $Na_2S_2O_3$ (14.6 g, 92.47 mmol) was added and stirring was continued for 1 h. The mixture was then partitioned between EtOAc and water and the aqueous phase was extracted with EtOAc. The combined organic extracts were washed with brine, dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (2 x 18 cm), using 50% EtOAc-hexane, gave **17.1** (825 mg, 72%) as a pale yellow solid: mp 77-78 °C, FTIR (microscope, cast) 3410, 2978, 2925, 1674, 1640, 1373 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.49 (s, 3 H), 2.04 (s, 1 H), 6.15 (d, J = 10.2 Hz, 2 H), 6.88 (d, J = 10.1 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 26.6 (q), 67.1 (s), 127.1 (d), 151.9 (d), 185.2 (s).

1-Methyl-4-oxocyclohexa-2,5-dienyl 3,4,6-Tri-*O*-acetyl-2-deoxy-2-iodo-β-D-galactopyranoside (25.1).

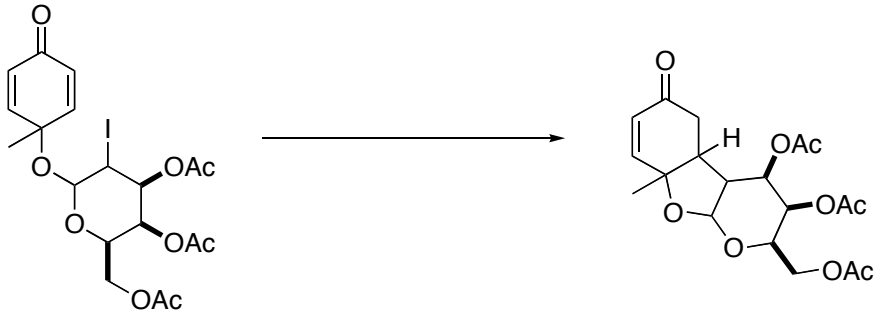


24.1 **25.1**

NIS (1.25 g, 5.58 mmol) was added to a stirred solution of D-galactal triacetate **24.1** (1.24 g, 4.56 mmol) in MeCN (20 mL) and the mixture was stirred at room temperature for 15 min. The cross conjugated enone **17.1** (461 mg, 3.72 mmol) was added and stirring was continued for 12 h. The mixture was diluted with Et_2O, washed with saturated aqueous $Na_2S_2O_3$ and brine, dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (2.5 x 18 cm), using 50% EtOAc-hexane, gave **25.1** (1.62 g, 68%) as an oil, which was a single isomer: $[\alpha]_D$ = 63.1 (*c* 3.09, $CHCl_3$); FTIR **(**microscope, cast**)** 2982, 1749, 1675, 1373, 1231 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.50 (s, 3 H), 2.07 (s, 3 H), 2.08 (s, 3 H), 2.15 (s, 3 H), 4.11-4.13 (m, 1 H), 4.17-4.12 (m, 2 H), 4.41 (ddd, *J* = 7.6, 5.6, 2.0 Hz, 1 H), 4.97 (t, *J* = 4.5 Hz, 1 H), 5.22 (d, *J* = 1.6 Hz, 1 H), 5.37 (t, *J* = 2.8 Hz, 1 H), 6.20 (dd, *J* = 10.2, 1.9 Hz, 1 H), 6.34 (dd, *J* = 10.2, 1.9 Hz, 1 H), 6.74 (dd, *J* = 10.2, 3.1 Hz, 1 H), 6.89 (dd, *J* = 10.3, 3.1 Hz, 1 H); ^{13}C NMR

($CDCl_3$, 100 MHz) δ 20.5 (q), 20.7 (q), 20.8 (q), 21.6 (d), 26.1 (q), 61.8 (t), 65.1 (d), 65.2 (d), 67.2 (d), 73.6 (s), 99.1 (d), 128.1 (d), 130.7 (d), 148.4 (d), 150.2 (d), 169.3 (s), 170.0 (s), 170.1 (s), 184.5 (s); exact mass (electrospray) *m*/*z* calcd for $C_{19}H_{23}INaO_9$ (M + Na) 545.0279, found 545.0280.

Acetic Acid (3,4-Diacetoxy-3,4,4a,4b,5,6,8a,9a-octahydro-8a-methyl-6-oxo-2*H*-1,9-dioxafluoren-2-yl)methyl Ester (25.2).

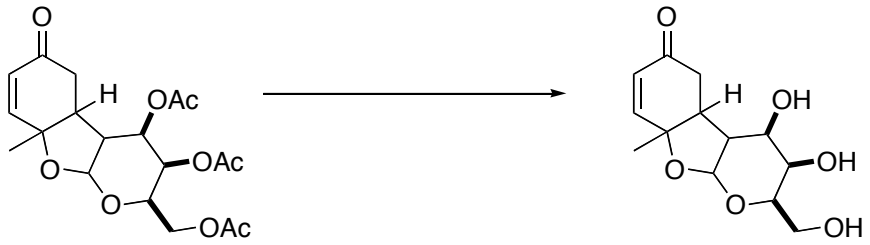


25.1 **25.2**

A solution of Bu_3SnH (0.22 mL, 0.848 mmol) and AIBN (11.6 mg, 0.071 mmol) in PhH (10 mL) was added over 1 h by syringe pump to a stirred and heated (85 °C) solution of **25.1** (369 mg, 0.707 mmol) in PhH (5 mL). Heating was continued for 12 h after the addition. Evaporation of the solvent and flash chromatography of the residue over KF-flash chromatography silica gel (10%w/w KF), using 50% EtOAc-hexane, gave the cyclized product **25.2** (209.1 mg, 75%) as an oil, which was a single isomer: $[\alpha]_D$ = 61.2 (*c* 2.16, $CHCl_3$); FTIR (microscope, cast) 2973, 1747, 1686, 1372, 1235 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.56 (s, 3 H), 2.01 (s, 6 H), 2.07 (s, 3 H), 2.21-2.24 (m, 1 H), 2.50-2.59

(m, 2 H), 2.62-2.70 (m, 1 H), 4.10 (dd, *J* = 11.4, 6.1 Hz, 1 H), 4.20 (dd, *J* = 11.4, 7.3 Hz, 1 H), 4.31 (ddd, *J* = 6.2, 6.2, 3.6 Hz, 1 H), 4.98 (dd, *J* = 7.6, 2.8 Hz, 1 H), 5.33 (d, *J* = 5.1 Hz, 1 H), 5.41 (dd, *J* = 3.5, 2.9 Hz, 1 H), 5.94 (dd, *J* = 10.3, 0.9 Hz, 1 H), 6.55 (dd, *J* = 10.3, 1.5 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 20.5 (q), 20.6 (q), 20.7 (q), 25.0 (q), 37.4 (t), 45.7 (d), 46.9 (d), 60.8 (t), 65.8 (d), 70.4 (d), 72.3 (d), 78.6 (s), 97.8 (d), 127.9 (d), 150.6 (d), 169.6 (s), 170.1 (s), 170.4 (s), 196.0 (s); exact mass (electrospray) *m*/*z* calcd for $C_{19}H_{24}NaO_9$ (M + Na) 419.1313, found 419.1315.

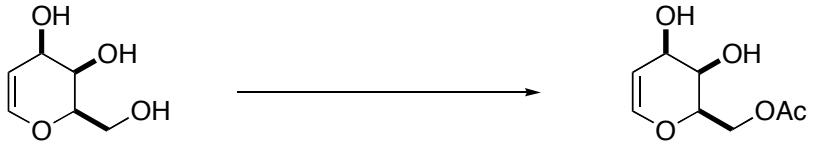
3,4,4a,4b,8a,9a-Hexahydro-3,4-dihydroxy-2-hydroxymethyl-8a-methyl-2*H*,5*H*-1,9-dioxafluoren-6-one (25.3).



25.2 **25.3**

MeONa (125 mg, 2.31 mmol) was added to a stirred solution of **25.2** (229 mg, 0.579 mmol) in dry MeOH (10 mL) and stirring was continued for 3. Amberlite (IR 120) was carefully added until the pH was 7, and the mixture was filtered. Evaporation of the filtrate gave crude **25.3** as white foam, which was used directly for the next step: FTIR (microscope, cast) 3395, 2934, 1713, 1675, 1377, 1236 cm^{-1}.

1-*O*-Acetyl-2,6-anhydro-5-deoxy-D-*arabino*-hex-5-enitol (27.2).[34]



27.1 **27.2**

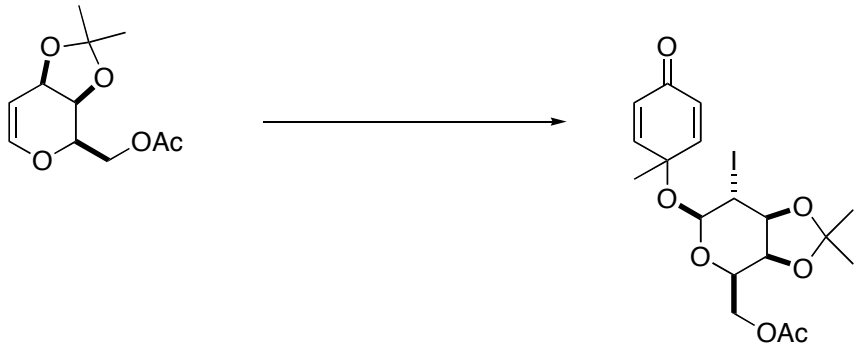
Vinyl acetate (25 mL) and powdered 4Å molecular sieves (4.00 g) were added to a stirred solution of **27.1** (2.00 g, 13.7 mmol) in water (2 mL). Lipase (from *Candida cylindracea*, LCC, 1.6 g) was added and the mixture was stirred for 45 min at room temperature. The mixture was then diluted with EtOAc, filtered and evaporated. Flash chromatography of the residue over silica gel (3 x 19 cm), using 50% EtOAc-hexane, gave **27.2** (2.16 g, 84%) as a white foam: FTIR **(**microscope, cast**)** 3438, 2941, 1739, 1649, 1371, 1242 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.12 (s, 3 H), 2.34 (d, J = 8.6 Hz, 1 H), 2.44 (d, J = 6.9 Hz, 1 H), 3.92 (t, J = 5.2 Hz, 1 H), 4.10 (t, J = 5.9 Hz, 1 H), 4.33 (dd, J = 11.7, 7.1 Hz, 1 H), 4.43 (dd, J = 11.7, 5.4 Hz, 2 H), 4.74 (ddd, J = 6.2, 1.8, 1.8 Hz, 1 H), 6.40 (dd, J = 6.2, 1.8 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 20.9 (q), 63.4 (t), 63.9 (d), 65.2 (d), 74.5 (d), 103.0 (d), 144.5 (d), 171.2 (s); exact mass (electrospray) m/z calcd for $C_8H_{12}NaO_5$ (M + Na) 211.0577, found 211.0575.

1-*O*-Acetyl-2,6-anhydro-5-deoxy-3,4-*O*-(1-methylethylidene)-D-*arabino*-hex-5-enitol (24.4).

27.2 **24.4**

2-Methoxypropene (0.46 mL, 4.8 mmol) and PPTS (252 mg, 1.00 mmol) were added to a stirred and cooled (0 °C) solution of **27.2** (755 mg, 4.02 mmol) in dry CH_2Cl_2 (20 mL). After 30 min the ice bath was removed and stirring was continued for 4 h. Additional 2-methoxypropene (0.38 mL, 4.02 mmol) was added and stirring was continued for 12 h. Evaporation of the solvent and flash chromatography of the residue over silica gel (2 x 15 cm), using 10% EtOAc-hexane, gave **24.4** (764 mg, 84%) as an oil: $[\alpha]_D$ = 13.4 (*c* 5.19, $CHCl_3$); FTIR **(**microscope, cast**)** 2986, 2938, 1745, 1649, 1371, 1229 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.34 (s, 3 H), 1.45 (s, 3 H), 2.10 (s, 3 H), 4.10-4.25 (m, 1 H), 4.23-4.27 (m, 1 H), 4.30-4.42 (m, 2 H), 4.65 (dd, *J* = 6.2, 3.0 Hz, 1 H), 4.80 (ddd, *J* = 6.2, 2.9, 1.4 Hz, 1 H), 6.39 (d, *J* = 6.3 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 20.9 (q), 26.8 (q), 27.9 (q), 64.2 (t), 68.5 (d), 72.5 (d), 72.7 (d), 102.6 (d), 110.7 (s), 144.5 (d), 170.7 (s); exact mass (electrospray) *m*/*z* calcd for $C_{11}H_{16}NaO_5$ (M + Na) 251.0890, found 251.0894.

1-Methyl-4-oxocyclohexa-2,5-dienyl-6-*O*-Acetyl-2-deoxy-2-iodo-3,4-*O*-(1-methylethylidene)-β-D-galactopyranoside (28.1).

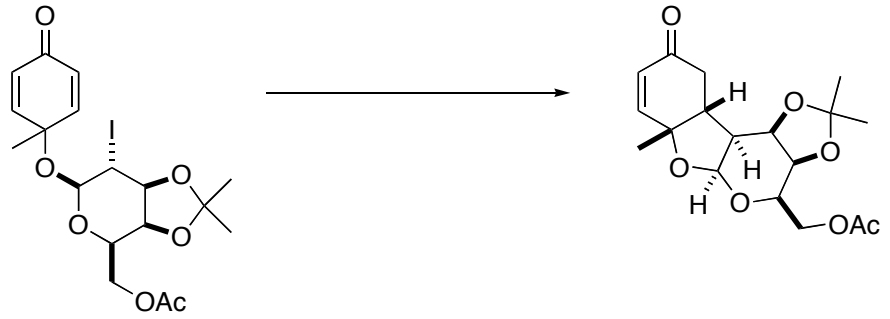


24.4 **28.1**

NIS (403 mg, 1.79 mmol) was added to a stirred solution of D-galactal triacetate **24.4** (340 mg, 1.49 mmol) in MeCN (15 mL) and the mixture was stirred at room temperature for 20 min. The cross conjugated enone **17.1** (203 mg, 1.64 mmol) was added and stirring was continued for 12 h. The mixture was diluted with Et_2O, washed with saturated aqueous $Na_2S_2O_3$ and brine, dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (1.5 x 19 cm), using 30% EtOAc-hexane, gave **28.1** (494 mg, 69%) as an oil, which was a single isomer: $[\alpha]_D$ = 8.8 (*c* 4.57, $CHCl_3$); FTIR **(**microscope, cast**)** 2987, 2935, 1742, 1672, 1383, 1244 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.32 (s, 3 H), 1.48 (s, 3 H), 1.50 (s, 3 H), 2.06 (s, 3 H), 3.73 (t, *J* = 9.4 Hz, 1 H), 3.84-3.88 (m, 2 H), 4.21-4.29 (m, 3 H), 4.46 (dd, *J* = 8.8, 5.0 Hz, 1 H), 6.08 (dd, *J* = 10.2, 2.0 Hz, 1 H), 6.30 (dd, *J* = 10.1, 2.5 Hz, 1 H), 6.95-7.04 (m, 2 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 20.7 (d), 25.9 (q), 26.0 (q), 28.2 (q), 32.6 (q), 63.3 (t), 71.6

(d), 73.3 (d), 74.1 (s), 82.2 (d), 98.6 (d), 110.6 (s), 127.0 (d), 130.3 (d), 149.4 (d), 151.7 (d), 170.5 (s), 185.1 (s); exact mass (electrospray) *m*/*z* calcd for $C_{18}H_{23}INaO_7$ (M + Na) 501.0381, found 501.0386.

Acetic Acid (3a*R*,4*R*,5a*S*,6a*R*,10a*R*,10b*S*,10c*R*)-(3a,5a,6a,9,10,10a,10b,10c-Octahydro-2,2,6a-trimethyl-1,3,5,6-tetraoxa-9-oxo-4*H*-cyclopenta[*c*]fluoren-4-yl)methyl Ester (28.2).

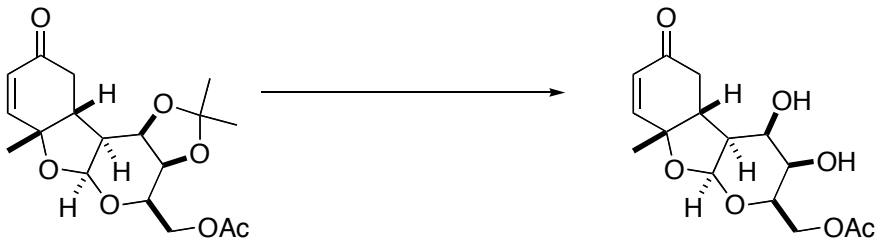


28.1 **28.2**

A solution of Bu_3SnH (0.13 mL, 0.49 mmol) and AIBN (3.37 mg, 0.021 mmol) in PhH (5 mL) was added over 2 h by syringe pump to a stirred and heated (85 °C) solution of **28.1** (196 mg, 0.41 mmol) in PhH (5 mL). Heating was continued for 4 h after the addition. Evaporation of the solvent and flash chromatography of the residue over KF-flash chromatography silica gel (10%w/w KF), using 50% EtOAc-hexane, gave the cyclized product **28.2** (113 mg, 78%) as a white solid, which was a single isomer: mp 165-167 °C, $[\alpha]_D$ = 46.3 (*c* 0.51, $CHCl_3$); FTIR **(**microscope, cast**)** 2986, 2940, 1740, 1682, 1371, 1246 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.29 (s, 3 H), 1.45 (s, 3 H), 1.55 (s, 3 H), 2.05 (s, 3

H), 2.26 (ddd, *J* = 12.0, 8.0, 4.0 Hz, 1 H), 2.55 (dd, *J* = 17.5, 6.5 Hz, 1 H), 2.82 (ddt, *J* = 12.0, 6.0, 1.5 Hz, 1 H), 3.03 (ddd, *J* = 17.5, 1.5, 1.5 Hz, 1 H), 3.75 (ddd, *J* = 7.0, 4.0, 2.5 Hz, 1 H), 4.08 (dd, *J* = 7.0, 2.5 Hz, 1 H), 4.23 (dd, *J* = 12.0, 8.0 Hz, 1 H), 4.35 (dd, *J* = 12.0, 4.0 Hz, 1 H), 4.56 (dd, *J* = 7.5, 7.0 Hz, 1 H), 4.91 (d, *J* = 4.5 Hz, 1 H), 5.86 (dd, *J* = 10.5, 1.0 Hz, 1 H), 6.55 (dd, *J* = 10.0, 2.0 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 20.9 (q), 24.7 (q), 25.1 (q), 25.9 (q), 37.2 (t), 43.9 (d), 44.1 (d), 63.7 (t), 70.6 (d), 71.1 (d), 71.9 (d), 80.2 (s), 101.1 (d), 109.5 (s), 126.8 (d), 151.4 (d), 170.9 (s), 197.5 (s); exact mass (electrospray) *m*/*z* calcd for $C_{18}H_{24}NaO_7$ (M + Na) 375.1414, found 375.1413.

Acetic Acid (2*R*,3*R*,4*R*,4a*S*,4b*R*,8a*R*,9a*S*)-(3,4,4a,4b,5,6,8a,9a-Octahydro-3,4-dihydroxy-8a-methyl-6-oxo-2*H*-1,9-dioxafluoren-2-yl)methyl Ester (29.1).

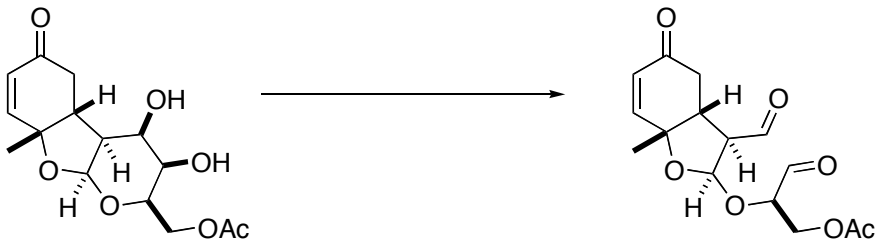


28.2 **29.1**

CF_3CO_2H (0.03 mL, 0.36 mmol) was added to a stirred and cooled (0 °C) solution of **28.2** (53.3 mg, 0.151 mmol) in 4:1 THF-water (2.5 mL). The ice bath was removed and stirring was continued for 12 h. Evaporation of the solvent and flash chromatography of the residue over silica gel (1 x 18 cm), using 50%

EtOAc-hexane, gave **29.1** (38.6 mg, 81%) as a white solid: mp 145-147 °C, FTIR (microscope, cast) 3461, 2971, 2897, 1737, 1674, 1373, 1240 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.58 (s, 3 H), 2.05 (s, 3 H), 2.42 (ddd, *J* = 12.4, 6.0, 3.4 Hz, 1 H), 2.62 (dd, *J* = 17.1, 5.9 Hz, 1 H), 2.91 (s, 2 H), 3.17 (d, *J* = 17.4 Hz, 1 H), 3.35 (dd, *J* = 12.7, 6.0 Hz, 1 H), 3.54 (t, *J* = 6.5 Hz, 1 H), 3.79 (d, *J* = 3.7 Hz, 1 H), 4.08 (dd, *J* = 6.2, 4.0 Hz, 1 H), 4.22 (dd, *J* = 11.4, 6.5 Hz, 1 H), 4.46 (dd, *J* = 11.6, 6.2 Hz, 1 H), 5.01 (d, *J* = 3.4 Hz, 1 H), 5.86 (d, *J* = 10.3 Hz, 1 H), 6.57 (dd, *J* = 10.3, 1.3 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 20.9 (q), 25.6 (q), 37.6 (t), 43.3 (d), 46.9 (d), 63.3 (t), 67.4 (d), 68.7 (d), 71.2 (d), 82.4 (s), 101.0 (d), 126.0 (d), 151.8 (d), 171.6 (s), 198.6 (s); exact mass (electrospray) *m*/*z* calcd for $C_{15}H_{20}NaO_7$ (M + Na) 335.1101, found 375.1103.

Acetic Acid (2*R*)-2-[(2*S*,3*S*,3a*R*,7a*S*)-(3-Formyl-2,3,3a,4,5,7a-hexahydro-7a-methyl-5-oxobenzofuran-2-yl)oxy]-3-oxopropyl Ester (29.2).

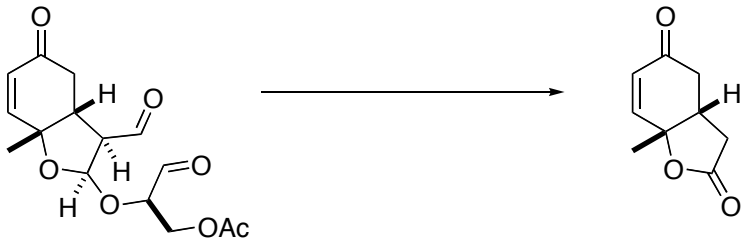


29.1 **29.2**

Na_2CO_3 (28.9 mg, 0.273 mmol) and then $Pb(OAc)_4$ (60.5 mg, 0.137 mmol) were added to a stirred and cooled (-78 °C) solution of **29.1** (28.4 mg, 0.091 mmol) in CH_2Cl_2 (3 mL) and stirring was continued at -78 °C for 2 h.

Evaporation of the solvent and flash chromatography of the residue over silica gel (1 x 16 cm), using 50% EtOAc-hexane, gave **29.2** (24 mg, 85%) as an oil: $[\alpha]_D$ = 26.1 (*c* 1.19, $CHCl_3$); FTIR **(**microscope, cast**)** 2971, 2931, 1739, 1681, 1374, 1236 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.60 (s, 3 H), 2.07 (s, 3 H), 2.65-2.77 (m, 2 H), 3.05 (ddd, *J* = 12.2, 5.1, 1.1 Hz, 1 H), 3.14-3.21 (m, 1 H), 4.34 (dd, *J* = 11.7, 4.8 Hz, 1 H), 4.42 (t, *J* = 4.8 Hz, 1 H), 4.50 (dd, *J* = 11.7, 3.9 Hz, 1 H), 5.50 (d, *J* = 5.0 Hz, 1 H), 5.89 (dd, *J* = 10.3, 0.6 Hz, 1 H), 6.51 (dd, *J* = 10.3, 1.8 Hz, 1 H), 9.64 (s, 1 H), 9.81 (d, *J* = 1.1 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 20.6 (q), 25.4 (q), 35.9 (t), 41.2 (d), 59.5 (d), 62.2 (t), 78.9 (d), 81.5 (s), 100.4 (d), 126.8 (d), 150.1 (d), 170.4 (s), 195.9 (s), 196.2 (d), 198.1 (d); exact mass (electrospray) *m*/*z* calcd for $C_{15}H_{18}NaO_7$ (M + Na) 333.0945, found 333.0942.

(3a*R*,7a*S*)-3a,7a-Dihydro-7a-methyl-3*H*,4*H*-benzofuran-2,5-dione (17.6).

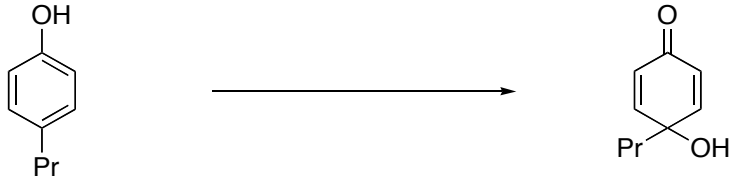


29.2 **17.6**

H_2SO_4 (0.1 M, 0.5 mL) was added to a stirred solution of **29.2** (55 mg, 0.18 mmol) in THF (3 mL) and stirring was continued for 4 h. The mixture was evaporated and the residue was used directly for the next step.

Jones reagent (ca 7.0 M, 0.076 mL, 0.532 mmol) was added to a stirred and cooled (-78 °C) solution of the above residue in acetone (5 mL) and stirring was continued for 30 min at -78 °C. The cold bath was removed and stirring was continued for 12 h. The mixture was quenched with MeOH (1 mL), diluted with EtOAc (5 mL), washed with aqueous NaOH (0.1N, 5 mL) and brine, dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (1 x 15 cm), using 30% EtOAc-hexane, gave **17.6** (19.73 mg, 67%) as a white solid: mp 114-115 °C, $[\alpha]_D$ = 29.1 (*c* 1.20, $CHCl_3$); FTIR **(**microscope, cast**)** 2979, 2932, 1776, 1683, 1379, 1254 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.69 (s, 3 H), 2.43 (dd, *J* = 17.5, 11.7 Hz, 1 H), 2.61 (dd, *J* = 17.3, 3.2 Hz, 1 H), 2.67-2.76 (m, 2 H), 2.89-2.98 (m, 1 H), 6.10 (dd, *J* = 10.3, 0.8 Hz, 1 H), 6.68 (dd, *J* = 10.3, 1.8 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 24.2 (q), 34.7 (t), 36.8 (t), 40.9 (d), 81.5 (s), 129.2 (d), 146.5 (d), 173.6 (s), 194.9 (s); exact mass (electrospray) *m*/*z* calcd for $C_9H_{10}NaO_3$ (M + Na) 189.0522, found 189.0522.

4-Hydroxy-4-propylcyclohexa-2,5-dienone (30.1).[25]

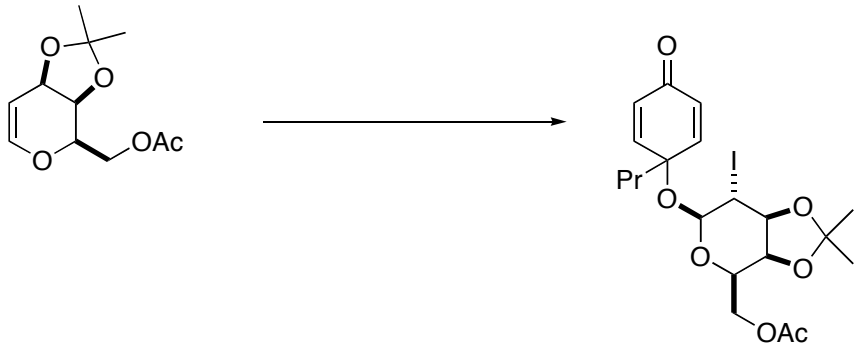


***p*-propylphenol** **30.1**

A mixture of Oxone (45.2 g, 73.4 mmol) and $NaHCO_3$ (18.5 g, 220 mmol) was added over ca 3 min to a vigorously stirred solution of *p*-propylphenol (2.00 g, 14.7 mmol) in MeCN (10 mL) and water (45 mL). The flask was immediately closed with a septum attached via a needle to an empty balloon to avoid loss of generated singlet oxygen. Vigorous stirring was continued until all the phenol had reacted (TLC control). The mixture was diluted with water (20 mL), solid $Na_2S_2O_3$ (36.4 g, 147 mmol) was added and stirring was continued for 2 h. The mixture was then partitioned between EtOAc and water and the aqueous phase was extracted with EtOAc. The combined organic extracts were washed with brine, dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (2 x 25 cm), using 10% EtOAc-hexane, gave **30.1** (1.45 g, 65%) as an oil: FTIR (microscope, cast) 3390, 2962, 2935, 1700, 1670, 1396 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.92 (t, J = 7.3 Hz, 3 H), 1.27-1.33 (m, 2 H), 1.70-1.76 (m, 2 H), 2.33 (s, 1 H), 6.18 (dd, J = 10.2, 1.0 Hz, 2 H), 6.81 (dd, J = 10.2, 1.0 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 14.2 (q), 17.0 (t), 42.0 (t), 69.9 (s), 128.2 (d),

151.4 (d), 185.7 (s)); exact mass (electrospray) *m*/*z* calcd for $C_9H_{12}NaO_2$ (M + Na) 175.0729, found 175.0730.

4-Oxo-1-propylcyclohexa-2,5-dienyl 6-*O*-Acetyl-2-deoxy-2-iodo-3,4-*O*-(1-methylethylidene)-β-D-galactopyranoside (31.1).

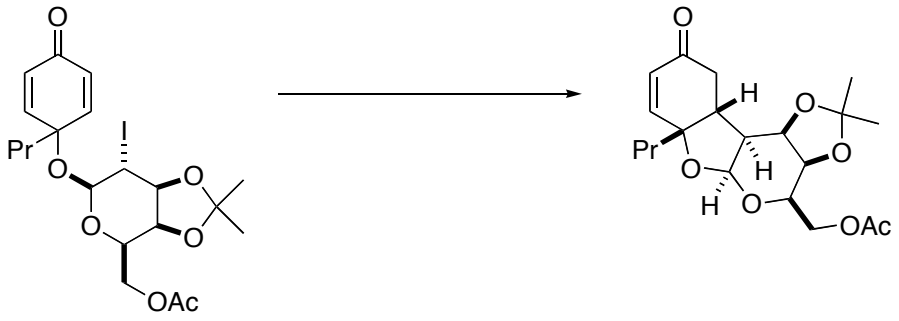


24.4 **31.1**

NIS (309 mg, 1.37 mmol) was added to a stirred solution of **24.4** (157 mg, 0.69 mmol) in MeCN (5 mL) and the mixture was stirred at room temperature for 15 min. The cross conjugated enone **30.1** (115 mg, 0.752 mmol) was added and stirring was continued for 12 h. The mixture was diluted with Et_2O, washed with saturated aqueous $Na_2S_2O_3$ and brine, dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (1.5 x 20 cm), using 30% EtOAc-hexane, gave **31.1** (222 mg, 64%) as a white foam, which was an 18.4:1 mixture of isomers (^{1}H NMR): FTIR **(**microscope, cast**)** 2986, 2972, 1742, 1671, 1382, 1243 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.90 (t, *J* = 7.3 Hz, 3 H), 1.26-1.42 (m, 2 H), 1.32 (s, 3 H), 1.41 (s, 3 H), 1.68-1.80 (m, 2 H), 2.08 (s, 3 H), 3.76 (t, *J* = 8.9

Hz, 1 H), 3.83 (ddd, *J* = 8.0, 3.8, 2.1 Hz, 1 H), 3.87 (dd, *J* = 2.1, 5.1 Hz, 1 H), 4.18-4.31 (m, 3 H), 4.46 (dd, *J* = 8.9, 5.1 Hz, 1 H), 6.13 (dd, *J* = 10.2, 2.0 Hz, 1 H), 6.36 (dd, *J* = 9.2, 2.1 Hz, 1 H), 6.98 (d, *J* = 10.3 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.2 (d), 16.8 (t), 20.7 (q), 26.0 (q), 28.2 (q), 32.7 (q), 41.4 (t), 63.3 (t), 71.6 (d), 73.4 (d), 74.1 (s), 82.2 (d), 98.4 (d), 110.7 (s), 127.8 (d), 131.3 (d), 148.7 (d), 151.4 (d), 170.5 (s), 185.4 (s); exact mass (electrospray) *m*/*z* calcd for $C_{20}H_{27}INaO_7$ (M + Na) 529.0694, found 529.0694.

Acetic Acid (3a*S*, 4*R*,5a*S*,6a*S*,10a*R*,10b*S*,10c*R*)-(3a,5a,6a,9,10,10a, 10b,10c-Octahydro-2,2-dimethyl-1,3,5,6-tetraoxa-9-oxo-6a-propyl-4*H*-cyclo-penta[*c*]fluoren-4-yl)methyl Ester (31.2).

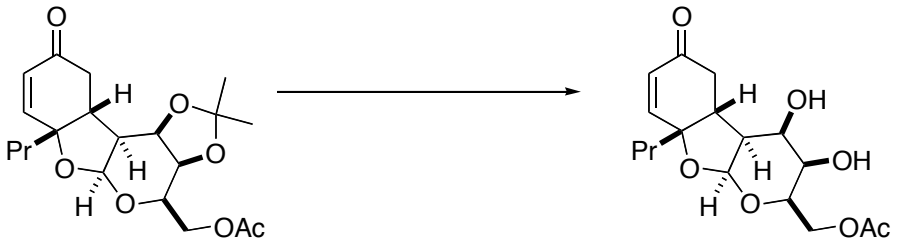


31.1 **31.2**

A solution of Bu_3SnH (0.06 mL, 0.23 mmol) and AIBN (1.55 mg, 0.01 mmol) in PhH (5 mL) was added over 2 h by syringe pump to a stirred and heated (85 °C) solution of **31.1** (96 mg, 0.19 mmol) in PhH (5 mL). Heating was continued for 12 h after the addition. Evaporation of the solvent and flash chromatography of the residue over KF-flash chromatography silica gel (10%w/w

KF), using 50% EtOAc-hexane, gave the cyclized product **31.2** (57.4 mg, 80%) as an oil, which was a single isomer: $[\alpha]_D$ = 33.4 (*c* 0.51, $CHCl_3$); FTIR **(**microscope, cast**)** 2961, 2937, 1741, 1683, 1382, 1248 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.96 (t, *J* = 7.2 Hz, 3 H), 1.30 (s, 3 H), 1.46 (s, 3 H), 1.47-1.49 (m, 2 H), 1.71-1.79 (m, 1 H), 1.81-1.89 (m, 1 H), 2.03 (s, 3 H), 2.24 (ddd, *J* = 11.6, 7.8, 4.4 Hz, 1 H), 2.54 (dd, *J* = 17.6, 6.2 Hz, 1 H), 2.85-2.92 (m, 1 H), 3.02 (dd, *J* = 17.6, 1.2 Hz, 1 H), 3.74 (ddd, *J* = 6.9, 4.3, 2.6 Hz, 1 H), 4.08 (dd, *J* = 6.8, 2.6 Hz, 1 H), 4.25 (dd, *J* = 11.8, 7.5 Hz, 1 H), 4.35 (dd, *J* = 11.8, 4.3 Hz, 1 H), 4.56 (t, *J* = 7.0 Hz, 1 H), 4.91 (d, *J* = 4.5 Hz, 1 H), 5.92 (dd, *J* = 10.3, 1.0 Hz, 1 H), 6.58 (dd, *J* = 10.3, 1.8 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.5 (q), 17.2 (t), 20.9 (q), 24.8 (q), 26.0 (q), 37.6 (t), 40.9 (t), 42.0 (d), 44.1 (d), 63.7 (t), 70.7 (d), 71.0 (d), 72.0 (d), 82.4 (s), 100.9 (d), 109.5 (s), 127.5 (d), 151.0 (d), 170.9 (s), 197.8 (s); exact mass (electrospray) *m*/*z* calcd for $C_{20}H_{28}NaO_7$ (M + Na) 403.1727, found 403.1722.

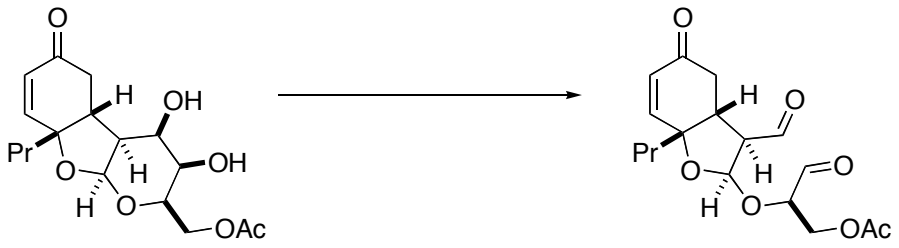
Acetic Acid (2*R*,3*R*,4*R*,4a*S*,4b*R*,8a*R*,9a*S*)-(3,4,4a,4b,5,6,8a,9a-Octahydro-3,4-dihydroxy-1,9-dioxa-6-oxo-8a-propyl-2*H*-fluoren-2-yl)methyl ester (31.3).



31.2 **31.3**

CF_3CO_2H (0.076 mL, 0.999 mmol) was added to a stirred and cooled (0 °C) solution of **31.2** (45 mg, 0.12 mmol) in 4:1 THF-water (3 mL). The ice bath was removed and stirring was continued for 12 h. Evaporation of the solvent and flash chromatography of the residue over silica gel (1 x 10 cm), using 50% EtOAc-hexane, gave **31.3** (34.6 mg, 86%) as an oil: $[\alpha]_D$ = 9.5 (*c* 1.15, $CHCl_3$); FTIR **(**microscope, cast**)** 3461, 2962, 2903, 1738, 1675, 1373, 1240 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.97 (t, *J* = 7.3 Hz, 3 H), 1.48-1.54 (m, 2 H), 1.77-1.83 (m, 2 H), 2.07 (s, 3 H), 2.39-2.46 (m, 3 H), 2.60 (dd, *J* = 17.4, 6.3 Hz, 1 H), 3.15 (d, *J* = 17.4 Hz, 1 H), 3.36 (dd, *J* = 12.3, 6.2 Hz, 1 H), 3.52 (t, *J* = 6.4 Hz, 1 H), 3.76 (d, *J* = 3.6 Hz, 1 H), 4.06 (dd, *J* = 6.0, 3.9 Hz, 1 H), 4.18 (dd, *J* = 11.4, 6.2 Hz, 1 H), 4.48 (dd, *J* = 11.5, 6.8 Hz, 1 H), 4.98 (d, *J* = 3.6 Hz, 1 H), 5.85 (d, *J* = 10.3 Hz, 1 H), 6.58 (dd, *J* = 10.3, 1.6 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 14.5 (q), 17.2 (t), 20.9 (q), 38.0 (t), 41.3 (t), 41.5 (d), 47.1 (d), 63.0 (t), 67.4 (d), 68.8 (d), 71.0 (d), 84.7 (s), 100.7 (d), 126.7 (d), 151.1 (d), 171.6 (s), 198.8 (s); exact mass (electrospray) *m*/*z* calcd for $C_{17}H_{24}NaO_7$ (M + Na) 363.1414, found 363.1414.

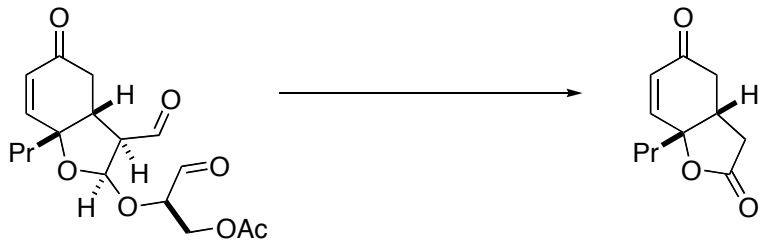
Acetic Acid (2*R*)-2-[(2*S*,3*S*,3a*R*,7a*S*)-2-[(3-Formyl-2,3,3a,4,5,7a-hexahydro-5-oxo-7a-propylbenzofuran-2-yl)oxy]-3-oxopropyl Ester (31.4).



31.3 **31.4**

Na_2CO_3 (14.3 mg, 0.14 mmol) and then $Pb(OAc)_4$ (29.9 mg, 0.067 mmol) were added to a stirred and cooled (-78 °C) solution of **31.3** (15.3 mg, 0.045 mmol) in CH_2Cl_2 (2 mL) and stirring was continued at -78 °C for 5 h. Evaporation of the solvent and flash chromatography of the residue over silica gel (1 x 10 cm), using 50% EtOAc-hexane, gave **31.4** (12.2 mg, 80%) as an oil: $[\alpha]_D$ = 28.9 (*c* 0.92, $CHCl_3$); FTIR **(**microscope, cast**)** 2962, 2935, 1741, 1682, 1382, 1240 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.99 (t, *J* = 7.1 Hz, 3 H), 1.26-1.32 (m, 1 H), 1.44-1.56 (m, 2 H), 1.72-1.82 (m, 1 H), 1.86-1.94 (m, 1 H), 2.04 (s, 3 H), 2.67-2.74 (m, 2 H), 3.18-3.23 (m, 1 H), 3.41 (dd, *J* = 12.2, 5.1 Hz, 1 H), 4.36 (dd, *J* = 11.3, 4.1 Hz, 1 H), 4.42-4.48 (m, 1 H), 5.51 (d, *J* = 4.8 Hz, 1 H), 5.94 (d, *J* = 10.3 Hz, 1 H), 6.54 (d, *J* = 10.3 Hz, 1 H), 9.64 (s, 1 H), 9.81 (s, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 14.5 (q), 17.4 (t), 20.6 (q), 36.4 (t), 39.5 (d), 41.5 (t), 59.8 (d), 62.2 (t), 78.9 (d), 83.8 (s), 100.2 (d), 127.6 (d), 149.7 (d), 170.4 (s), 196.2 (s), 196.3 (d), 198.1 (d); exact mass (electrospray) *m*/*z* calcd for $C_{17}H_{22}NaO_7$ (M + Na) 361.0945, found 361.0942.

(3a*R*,7a*S*)-3a,7a-Dihydro7a-propyl-3*H*,4*H*-benzofuran-2,5-dione (31.5).



31.4 **31.5**

H_2SO_4 (0.1 M, 0.2 mL) was added to a stirred solution of **31.4** (10.4 mg, 0.031 mmol) in THF (1.5 mL) and stirring was continued for 6 h. The mixture was evaporated and the residue was used directly for the next step.

Jones reagent (ca 7.0 M, 0.013 mL, 0.093 mmol) was added to a stirred and cooled (-78 °C) solution of the above residue in acetone (2 mL) and stirring was continued for 30 min at -78 °C. The cold bath was removed and stirring was continued for 12 h. The mixture was quenched with MeOH (1 mL), diluted with EtOAc (5 mL), washed with aqueous NaOH (0.1 N, 5 mL), and brine, dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (1 x 12 cm), using 30% EtOAc-hexane, gave **31.5** (3.9 mg, 64%) as an oil: $[\alpha]_D$ = 30.2 (*c* 2.59, $CHCl_3$); FTIR **(**microscope, cast**)** 2963, 2875, 1780, 1685, 1228 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.03 (t, *J* = 7.3 Hz, 3 H), 1.51-1.57 (m, 2 H), 1.82-1.87 (m, 1 H), 1.92-1.97 (m, 1 H), 2.42 (dd, *J* = 17.5, 11.9 Hz, 1 H), 2.60 (dd, *J* = 17.5, 2.9 Hz, 1 H), 2.65-2.76 (m, 2 H), 2.93-3.20 (m, 1 H), 6.13 (dd, *J* = 10.4, 1.0 Hz, 1 H), 6.68 (dd, *J* = 10.4, 1.8 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz)

δ 14.3 (q), 17.1 (t), 34.8 (t), 37.1 (t), 38.9 (d), 40.0 (t), 83.8 (s), 129.7 (d), 145.9 (d), 173.8 (s), 195.1 (s); exact mass) *m*/*z* calcd for $C_{11}H_{14}O_3$ 194.0943, found 194.0942.

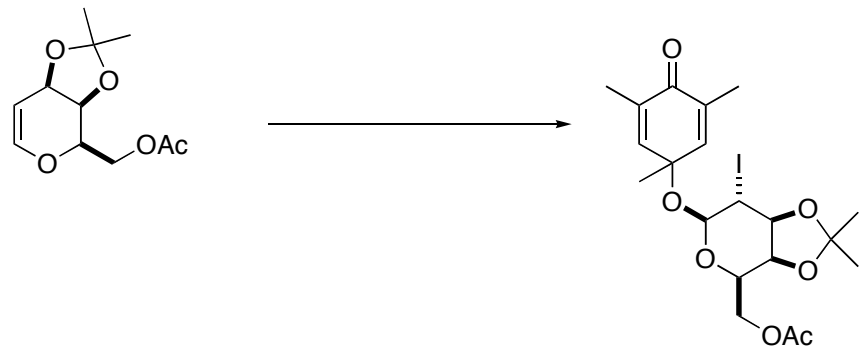
4-Hydroxy-2,4,6-trimethylcyclohexa-2,5-dienone (30.2).[25]

2,4,6-trimethylphenol **30.2**

A mixture of Oxone (45 g, 73 mmol) and $NaHCO_3$ (18.5 g, 220 mmol) was added over ca 3 min to a vigorously stirred solution of 2,4,6-trimethylphenol (2.00 g, 14.7 mmol) in MeCN (10 mL) and water (43 mL). The flask was immediately closed with a septum attached via a needle to an empty balloon to avoid loss of generated singlet oxygen. Vigorous stirring was continued until all the phenol had reacted (TLC control). The mixture was diluted with water (20 mL), solid $Na_2S_2O_3$ (36.4 g, 147 mmol) was added and stirring was continued for 1 h. The mixture was then partitioned between EtOAc and water and the aqueous phase was extracted with EtOAc. The combined organic extracts were washed with brine, dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (2 x 22 cm), using 10% EtOAc-hexane, gave **30.2** (1.9 g, 86%) as a pale yellow solid: mp 41-43 °C, FTIR (microscope, cast) 3410, 2978, 2925, 1674, 1640, 1373, 1210 cm^{-1}; ^1H NMR

($CDCl_3$, 400 MHz) δ 1.34 (s, 3 H), 1.75 (s, 6 H), 3.18 (s, 1 H), 6.56 (s, 2 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 15.7 (q), 27.0 (q), 66.9 (s), 132.9 (s), 148.0 (d), 187.0 (s).

1,3,5-Trimethyl-4-oxocyclohexa-2,5-dienyl 6-*O*-Acetyl-2-deoxy-2-iodo-3,4-*O*-(1-methylethylidene)-β-D-galactopyranoside (32.1).

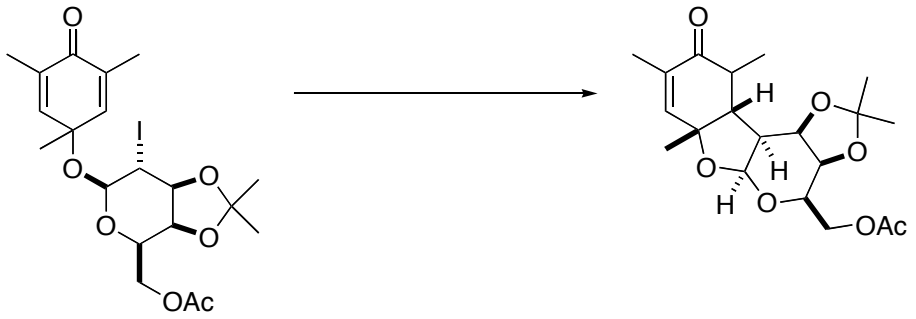


24.4 **32.1**

NIS (371 mg, 1.65 mmol) was added to a stirred solution of **24.4** (313 mg, 1.37 mmol) in MeCN (10 mL) and the mixture was stirred at room temperature for 15 min. The cross conjugated enone **30.2** (261 mg, 1.72 mmol) was added and stirring was continued for 12 h. The mixture was diluted with Et_2O, washed with saturated aqueous $Na_2S_2O_3$ and brine, dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (1.5 x 19 cm), using 30% EtOAc-hexane, gave **32.1** (463 mg, 67%) as a yellow oil, which was a single isomer: $[\alpha]_D$ = -4.4 (*c* 9.4, $CHCl_3$); FTIR **(**microscope, cast**)** 2985, 2930, 1743, 1674, 1643, 1372, 1243 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.31 (s, 3 H), 1.38 (s, 3 H),

1.39 (s, 3 H), 1.89 (d, *J* = 1.3 Hz, 3 H), 1.92 (d, *J* = 1.3 Hz, 3 H), 2.05 (s, 3 H), 3.76 (t, *J* = 9.2 Hz, 1 H), 3.82 (ddd, *J* = 7.6, 3.8, 2.2 Hz, 1 H), 3.86 (dd, *J* = 5.0, 2.1 Hz, 1 H), 4.18-4.23 (m, 2 H), 4.30 (dd, *J* = 12.0, 3.9 Hz, 1 H), 4.46 (dd, *J* = 8.8, 5.0 Hz, 1 H), 6.76-6.77 (m, 2 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 15.8 (q), 16.0 (q), 20.9 (q), 26.0 (q), 26.2 (q), 28.2 (q), 33.1 (d), 63.7 (t), 71.5 (d), 73.5 (d), 74.3 (s), 82.2 (d), 98.1 (d), 110.5 (s), 134.0 (s), 136.3 (s), 144.9 (d), 146.2 (d), 170.6 (s), 186.6 (s); exact mass (electrospray) *m*/*z* calcd for $C_{20}H_{27}INaO_7$ (M + Na) 529.1000, found 529.1001.

Acetic Acid (3a*R*,4*R*,5a*S*,6a*S*,10*R*,10a*S*,10b*S*,10c*R*)-(3a,5a,6a,9,10,10a, 10b,10c-Octahydro-2,2,6a,8,10-pentamethyl-1,3,5,6-tetraoxa-9-oxo-4*H*-cyclo-penta[*c*]fluoren-4-yl)methyl Ester (32.2).

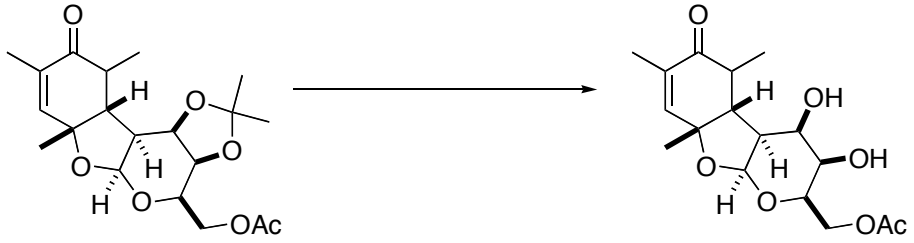


32.1 **32.2**

A solution of Bu_3SnH (0.06 mL, 0.23 mmol) and AIBN (1.61 mg, 0.01 mmol) in PhH (5 mL) was added over 2 h by syringe pump to a stirred and heated (85 °C) solution of **32.1** (98.9 mg, 0.19 mmol) in PhH (5 mL). Heating was continued for 10 h after the addition. Evaporation of the solvent and flash

chromatography of the residue over KF-flash chromatography silica gel (10%w/w KF), using 70% EtOAc-hexane, gave the cyclized product **32.2** (59.4 mg, 80%) as a white foam, which was a single isomer: $[\alpha]_D$ = -16.0 (*c* 2.88, $CHCl_3$); FTIR **(**microscope, cast**)** 2980, 2935, 1741, 1680, 1369, 1241 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.17 (d, *J* = 6.8 Hz, 3 H), 1.27 (s, 3 H), 1.44 (s, 3 H), 1.51 (s, 3 H), 1.71 (s, 3 H), 1.72-1.79 (m, 1 H), 2.00 (s, 3 H), 2.99 (ddd, *J* = 13.4, 6.8, 6.8 Hz, 1 H), 2.97-3.00 (m, 1 H), 3.44-3.47 (m, 1 H), 4.31-4.43 (m, 2 H), 4.51 (dd, *J* = 11.9, 4.2 Hz, 1 H), 4.69 (t, *J* = 6.2 Hz, 1 H), 5.18 (d, *J* = 6.6 Hz, 1 H), 6.26 (s, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 13.0 (q), 15.6 (q), 23.2 (q), 25.0 (q), 25.1 (q), 26.6 (q), 40.6 (d), 41.5 (d), 49.7 (d), 63.2 (t), 71.6 (d), 72.5 (d), 73.3 (d), 79.1 (s), 101.4 (d), 109.0 (s), 134.9 (s), 145.6 (d), 170.9 (s), 200.7 (s); exact mass (electrospray) *m*/*z* calcd for $C_{20}H_{28}NaO_7$ (M + Na) 403.1727, found 403.1726.

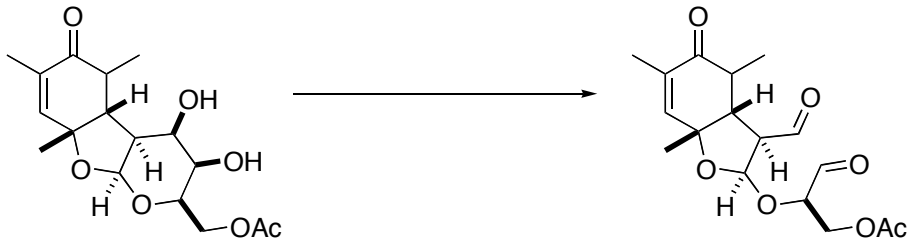
Acetic Acid (2*R*,3*R*,4*R*,4a*S*,4b*S*,8a*S*)-(3,4,4a,4b,5,6,8a,9a-Octahydro-3,4-dihydroxy-5,7,8a-trimethyl-6-oxo-2*H*-1,9-dioxafluoren-2-yl)methyl Ester (32.3).



32.2 **32.3**

CF_3CO_2H (0.076 mL, 0.999 mmol) was added to a stirred and cooled (0 °C) solution of **32.2** (152 mg, 0.399 mmol) in 4:1 THF-water (5 mL). The ice bath was removed and stirring was continued for 12 h. Evaporation of the solvent and flash chromatography of the residue over silica gel (1.5 x 15 cm), using 50% EtOAc-hexane, gave **32.3** (113 mg, 83%) as an oil: $[\alpha]_D$ = -14.9 (*c* 0.45, $CHCl_3$); FTIR **(**microscope, cast**)** 3472, 2979, 2934, 1743, 1679, 1379, 1247 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.22 (d, *J* = 6.8 Hz, 3 H), 1.31 (s, 3 H), 1.48 (s, 3 H), 1.77 (s, 3 H), 1.83-1.87 (m, 1 H), 2.74-2.77 (m, 1 H), 3.03 (ddd, *J* = 8.5, 4.9, 2.0 Hz, 1 H), 3.07-3.20 (br s, 2 H), 3.36-3.43 (m, 1 H), 3.71-3.80 (m, 1 H), 3.81-3.91 (m, 1 H), 4.15 (dd, *J* = 7.2, 2.6 Hz, 1 H), 4.46 (t, *J* = 5.3 Hz, 1 H), 4.95 (d, *J* = 6.6 Hz, 1 H), 6.30 (s, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 13.1 (q), 15.6 (q), 23.3 (q), 24.9 (q), 40.7 (d), 41.6 (d), 49.7 (d), 61.8 (t), 73.2 (d), 75.2 (d), 76.8 (d), 79.2 (s), 101.5 (d), 135.1 (s), 145.6 (d), 171.5 (s), 200.8 (s); exact mass (electrospray) *m*/*z* calcd for $C_{17}H_{24}NaO_7$ (M + Na) 363.1101, found 363.1103.

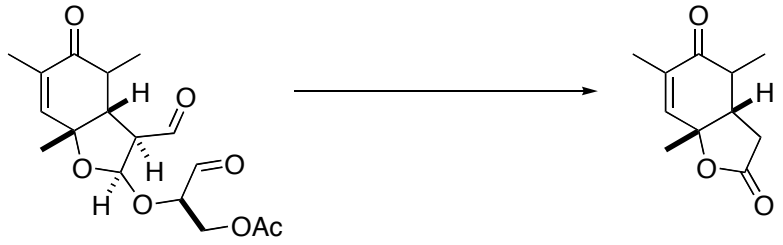
Acetic Acid (2*R*)-2-[(2*S*,3*S*,3a*R*,7a*S*)-(3-Formyl-2,3,3a,4,5,7a-hexa-hydro-4,6,7a-trimethyl-5-oxobenzofuran-2-yl)oxy]-3-oxopropyl Ester (32.4).



32.3 **32.4**

Na_2CO_3 (12.4 mg, 0.117 mmol) and then $Pb(OAc)_4$ (25.9 mg, 0.059 mmol) were added to a stirred and cooled (-78 °C) solution of **32.3** (13.3 mg, 0.039 mmol) in CH_2Cl_2 (2 mL) and stirring was continued at -78 °C for 4 h. Evaporation of the solvent gave crude **32.4**, which was directly for the next step.

(3a*S*,7a*S*)-3a,7a-Dihydro-4,6,7a-trimethyl-3*H*,4*H*-benzofuran-2,5-dione (32.5).



32.4 **32.5**

H_2SO_4 (0.1 M, 0.5 mL) was added to a stirred solution of **32.4** (10.5 mg, 0.031 mmol) in THF (2 mL) and stirring was continued for 4 h. The mixture was evaporated and the residue was used directly for the next step.

Jones reagent (ca 7.0 M, 0.013 mL, 0.093 mmol) was added to a stirred and cooled (-78 °C) solution of the above residue in acetone (2 mL) and stirring was continued for 30 min at -78 °C. The cold bath was removed and stirring was continued for 12 h. The mixture was quenched with MeOH (1 mL), diluted with EtOAc (5 mL), washed with aqueous NaOH (0.1 N, 5 mL) and brine, dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (1 x 10 cm), using 30% EtOAc-hexane, gave **32.5** (5.2 mg, 69% over 3 steps) as an

oil: $[\alpha]_D$ = -54.1 (*c* 0.51, $CHCl_3$); FTIR (microscope, cast) 2924, 2852, 1771, 1682, 1684, 1381, 1221 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.18 (d, *J* = 6.8 Hz, 3 H), 1.68 (s, 3 H), 1.83 (s, 3 H), 2.20 (dd, *J* = 17.4, 12.6 Hz, 1 H), 2.61 (dd, *J* = 17.4, 8.3 Hz, 1 H), 2.74-2.80 (m, 1 H), 2.83-2.90 (m, 1 H), 6.34 (s, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.3 (q), 15.8 (q), 24.2 (q), 32.0 (t), 40.4 (d), 48.1 (d), 82.8 (s), 131.0 (s), 140.7 (d), 174.2 (s), 198.2 (s); exact mass *m*/*z* calcd for $C_{11}H_{14}O_3$ 194.0943, found 194.0941.

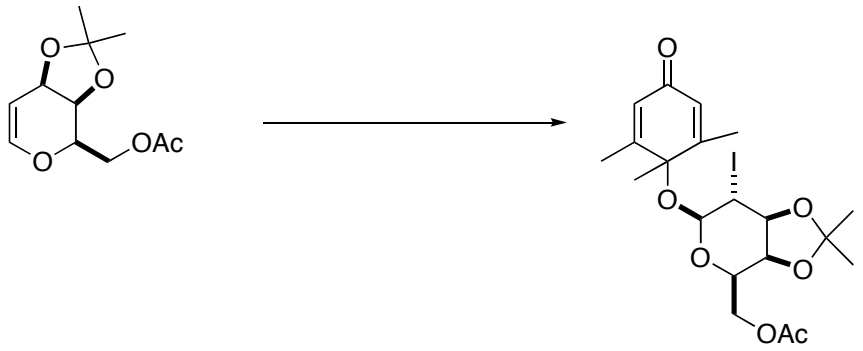
4-Hydroxy-3,4,5-trimethylcyclohexa-2,5-dienone (33.1).[25]

3,4,5-trimethylphenol **33.1**

A mixture of Oxone (45 g, 73 mmol) and $NaHCO_3$ (18.5 g, 220 mmol) was added over ca 3 min to a vigorously stirred solution of 3,4,5-trimethylphenol (2.00 g, 14.7 mmol) in MeCN (20 mL) and water (32 mL). The flask was immediately closed with a septum attached via a needle to an empty balloon to avoid loss of generated singlet oxygen. Vigorous stirring was continued until all the phenol had reacted (TLC control). The mixture was diluted with water (15 mL), solid $Na_2S_2O_3$ (36.5 g, 147 mmol) was added and stirring was continued for 2 h. The mixture was then partitioned between EtOAc and water and the aqueous phase was extracted with EtOAc. The combined organic extracts were washed

with brine, dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (2 x 20 cm), using 50% EtOAc-hexane, gave **33.1** (1.81 g, 81%) as a white solid: mp 66-68 °C, FTIR (microscope, cast) 3265, 2989, 2923, 1666, 1610, 1381, 1167 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.30 (s, 3 H), 1.98 (s, 6 H), 4.33 (s, 1 H), 5.75 (s, 2 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 18.2 (q), 26.1 (q), 71.4 (s), 125.1 (d), 165.0 (s), 186.1 (s); exact mass *m*/*z* calcd for $C_9H_{12}O_2$ 152.0837, found 152.0837.

3,4,5-Trimethyl-4-oxocyclohexa-2,5-dienyl 6-*O*-Acetyl-2-deoxy-2-iodo-3,4-*O*-(1-methylethylidene)-β-D-galactopyranoside (33.2).

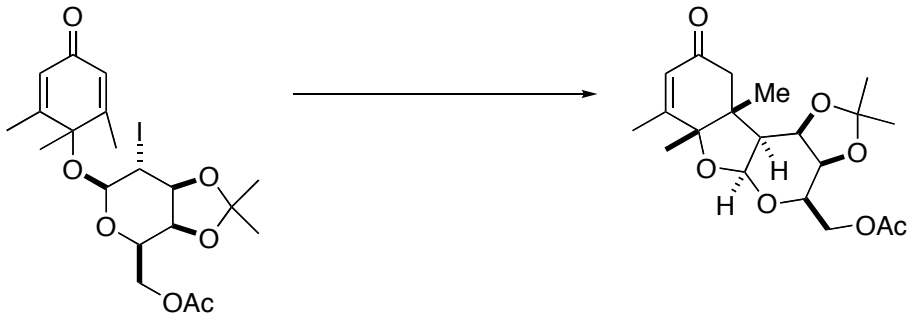


24.4 **33.2**

NIS (338 mg, 1.50 mmol) was added to a stirred solution of **24.4** (171 mg, 0.75 mmol) in MeCN (10 mL) and the mixture was stirred at room temperature for 15 min. The cross conjugated enone **33.1** (123 mg, 0.83 mmol) was added and stirring was continued for 12 h. The mixture was diluted with Et_2O, washed with saturated aqueous $Na_2S_2O_3$ and brine, dried (Na_2SO_4) and evaporated. Flash

chromatography of the residue over silica gel (2.0 x 19 cm), using 30% EtOAc-hexane, gave **33.2** (240 mg, 63%) as an oil, which was a single isomer: $[\alpha]_D$ = 53.3 (*c* 0.48, $CHCl_3$); FTIR **(**microscope, cast**)** 2992, 2926, 1738, 1670, 1620, 1374, 1241 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.28 (s, 3 H), 1.43 (s, 3 H), 1.46 (s, 3 H), 2.04 (s, 6 H), 2.18 (s, 3 H), 3.68-3.74 (m, 1 H), 3.83 (dd, *J* = 5.1, 2.2 Hz, 1 H), 4.06-4.10 (m, 1 H), 4.17 (d, *J* = 9.1 Hz, 1 H), 4.24 (dd, *J* = 12.3, 2.9 Hz, 1 H), 4.41 (dd, *J* = 8.9, 5.0 Hz, 1 H), 4.48-4.60 (m, 1 H), 5.88 (d, *J* = 1.3 Hz, 1 H), 6.16 (d, *J* = 1.3 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 19.4 (q), 20.9 (q), 24.4 (d), 26.0 (q), 26.1 (q), 28.2 (q), 32.0 (q), 63.8 (t), 71.9 (d), 73.5 (d), 74.3 (s), 82.0 (d), 98.3 (d), 110.4 (s), 125.3 (d), 130.7 (d), 156.7 (s), 163.4 (s), 171.0 (s), 185.3 (s); exact mass (electrospray) *m*/*z* calcd for $C_{20}H_{27}INaO_7$ (M + Na) 529.0694, found 529.0694.

Acetic Acid (3a*R*,4*R*,5a*S*,6a*R*,10a*R*,10b*S*,10c*R*)-(3a,5a,6a,9,10,10a, 10b,10c-Octahydro-2,2,6a,7,10a-pentamethyl-1,3,5,6-tetraoxa-9-oxo-4*H*-cyclopenta[*c*]-fluoren-4-yl)methyl Ester (33.3).



33.2 **33.3**

A solution of Bu_3SnH (0.12 mL, 0.46 mmol) and AIBN (3.18 mg, 0.02 mmol) in PhH (5 mL) was added over 2 h by syringe pump to a stirred and heated (85 °C) solution of **33.2** (196 mg, 0.39 mmol) in PhH (5 mL). Heating was continued for 12 h after the addition. Evaporation of the solvent and flash chromatography of the residue over KF-flash chromatography silica gel (10%w/w KF), using 50% EtOAc-hexane, gave the cyclized product **33.3** (108.77 mg, 74%) as a pale yellow oil: $[\alpha]_D$ = 62.9 (*c* 1.99, $CHCl_3$); FTIR **(**microscope, cast**)** 2983, 2935, 1739, 1664, 1372, 1242 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.19 (s, 3 H), 1.26 (s, 3 H), 1.34 (s, 3 H), 1.39 (s, 3 H), 1.44-1.56 (m, 1 H), 2.03 (s, 3 H), 2.08 (s, 3 H), 2.27 (d, *J* = 18.9 Hz, 1 H), 2.80 (d, *J* = 18.9 Hz, 1 H), 3.40-3.44 (m, 1 H), 4.08-4.15 (m, 2 H), 4.28 (dd, *J* = 11.9, 4.2 Hz, 1 H), 4.41 (dd, *J* = 4.9, 6.7 Hz, 1 H), 5.31 (d, *J* = 6.7 Hz, 1 H), 6.26 (s, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 19.6 (q), 21.0 (q), 22.9 (q), 24.6 (q), 26.3 (q), 30.5 (q), 43.4 (t), 47.4 (s), 49.8 (d), 63.2 (t), 70.7 (d), 71.9 (d), 72.4 (d), 85.5 (s), 102.2 (d), 109.5 (s), 127.3 (d), 162.3 (s), 171.0 (s), 195.7 (s); exact mass (electrospray) *m*/*z* calcd for $C_{20}H_{28}NaO_7$ (M + Na) 403.1727, found 403.1729.

6 REFERENCES

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