University of Alberta

Synthesis of Benzo-fused Nitrogen Heterocycles and Substituted Benzenes

by

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FOR LORNA, FOR MARTHA, FOR FAMILY

ABSTRACT

The first chapter of this thesis represents the continued development of a general method for the formation of benzo-fused *N*-heterocycles by formal radical cyclization onto benzene rings. Important stages in this process involve 1) the copper-mediated coupling of various amino alcohols to protected *p*-iodophenols, 2) carbamate-protection of the resulting aryl secondary amine to allow the following oxidation step, 3) the oxidative formation of quinone ketals as radical acceptors, 4) the radical cyclization of pendant iodo-radical triggers onto the cross-conjugated ketone, and 5) the subsequent aromatization of the resulting products into benzo-fused *N*-heterocycles. Various protected 2,3-dihydroindoles—some of which with 2-substitutions—have been synthesized using this methodology. For some examples, it was necessary to repeat the experiments of a previous group member to obtain publication-quality data.

The second chapter describes a new methodology for the formation of regioselectively-substituted benzene rings. Various arene species have been synthesized in *p*-disubstituted, 1,2,4-trisubstituted and 1,2,3,4-tetrasubstituted arrays. Key steps in the methodology include 1) the synthesis of 1,4-diketones by alkylation of various aldehydes and their subsequent reduction and oxidation, 2) addition of organometallic alkenes to 1,4-diketones to form ring closing metathesis (RCM) precursors, and 3) RCM and subsequent aromatization of these cyclized products by double-dehydration to form the desired substituted benzenes. The macrocycle [12]-paracyclophane has also been synthesized using a modified version of the above methodology.

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LIST OF ABBREVIATIONS

ABCN	1,1'-azobis(cyclohexanecarbonitrile)
Ac	acetyl
AcOH	acetic acid
AIBN	2,2'-azobis(isobutyronitrile)
APT	attached proton test
Bn	benzyl
Boc	*tert*-butoxycarbonyl
t-Bu	*t*-butyl
Bz	benzoyl
CAN	ceric ammonium nitrate
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCE	1,1-dichloroethane
DCM	dichloromethane
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DIBAL	diisobutylaluminum hydride
DMAP	4-(dimethylamino)pyridine
DME	1,2-dimethoxyethane
DMF	dimethylformamide
DMSO	dimethyl sulfoxide
EDC	ethylene dichloride
Et	ethyl
FT-IR	Fourier-transform infrared spectroscopy
HMPA	hexamethylphosphoramide
ImH	imidazole
LDA	lithium diisopropylamide

LUMO	lowest unoccupied molecular orbital
MeCN	acetonitrile
MeOH	methanol
Mes	mesityl (1,3,5-trimethylbenzene)
Me_2SO_4	dimethyl sulfate
MOM	methoxymethyl
Ms	mesyl (methylsulfonyl)
NBS	*N*-bromosuccinimide
NIS	*N*-iodosuccinimide
NMR	nuclear magnetic resonance
NMO	4-methylmorpholine *N*-oxide
Ph	phenyl
PhH	benzene
PhMe	toluene
Phth	phthaloyl
Pr	propyl
i-Pr	isopropyl
RCEM	ring closing enyne metathesis
RCM	ring closing metathesis
SET	single electron transfer
SolFC	solvent-free conditions
SOMO	singly occupied molecular orbital
TBAF	tetra-*n*-butyl-ammonium fluoride
TBAI	tetra-*n*-butylammonium iodide
TBS	*t*-butyldimethylsilyl
TLC	thin layer chromatography
TMS	trimethylsilyl

Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
Ts	tosyl (*p*-toluenesulfonyl)
$TsOH \cdot H_2O$	*p*-toluenesulfonic acid
TTMSS	tris(trimethylsilyl)silane

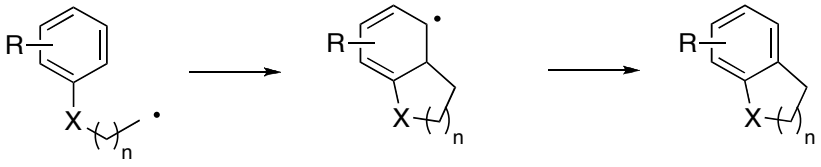
CHAPTER 1

FORMAL RADICAL CYCLIZATIONS ONTO BENZENE RINGS: FORMATION OF BENZO-FUSED NITROGEN HETEROCYCLES

1 INTRODUCTION

1.1 *General*

Radical additions to unsaturated hydrocarbons have become a general synthetic process over the last three decades. Specifically, cyclization of sp^2 and sp^3 radicals onto double and triple bonds is now an integral part of synthetic organic chemistry. By extension, a standard protocol for cyclization onto an aromatic ring (Scheme 1) would be very useful, and would allow for regioselective substitutions that are complimentary to electrophilic aromatic substitutions.



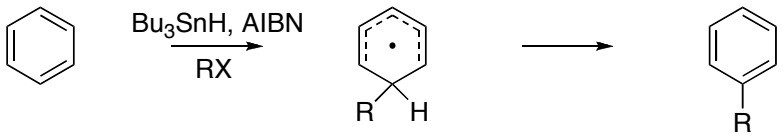
Scheme 1

This type of cyclization remains an uncommon process, however, and most radical additions to benzene rings are inefficient and require large amounts of initiator. Recently, the Clive group has made progress in this area[1] and has developed a protocol for effective formal radical cyclization onto benzene rings. The experimental results detailed in this Chapter represent a continuation of initial studies in this area.[1d]

1.2 *Mechanistic Considerations*

If a radical is able to add to a benzene ring under normal stannane-mediated conditions, a cyclohexadienyl radical is formed. As this radical is stabilized through resonance with the adjoining π-system, it does not participate in effective propagation of the radical chain by hydrogen abstraction from the

stannane. The cyclohexadienyl radical normally undergoes rearomatization to a substituted benzene (Scheme 2), although the mechanism for this process is not properly understood. It is possible that a regioisomeric mixture of cyclohexadienes is formed which is then oxidized to the arene. However, cyclohexadienes form readily by Birch-type reductions and are easily isolated, and so cyclohexadiene oxidation is likely not a significant pathway.



Scheme 2

There is a buildup of the concentration of the radicals and an increase in the chance of homolytic bonding reactions when a propagation step in a radical chain reaction is inefficient. The presence of dimerization and disproportionation products is the result of this radical buildup. In these circumstances, if the substrate is to be effectively consumed, a relatively large amount of chain initiator is required. The tin hydride-mediated addition of radicals to benzene rings therefore requires a disproportionate amount of initiator as a consequence of the formation of long-lived radicals.

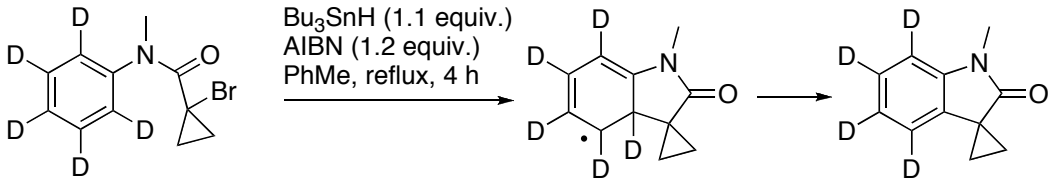
Curran has suggested that the requirement for an excess of initiator may be due to oxidation of the cyclohexadienyl radicals by the initiator, or by a radical derived from the initiator.[2] Bowman has suggested that the cyclohexadienyl radical is deprotonated by the stannane, so as to produce a radical anion, Bu_3Sn^+, and molecular hydrogen (Equation 1).[3] The radical anion can then be aromatized by one of several pathways.

(1) $Bu_3SnH + ArRH\bullet \rightarrow Bu_3Sn^+ + [Ar\text{-}R]\bullet^- + H_2$

These mechanisms are the subject of debate and are not well understood.[4] Detailed studies from the Bowman laboratory have ruled out the mechanism described in Equation 1. The predominant reaction sequence appears to involve the initiator acting as an oxidizing agent, but the exact details remain unclear (Equation 2).[5]

(2) $R'\text{-}N{=}N\text{-}R' + 2ArRH\bullet \rightarrow R'NHNHR' + 2Ar\text{-}R$

Bowman has also reported that in the oxidative radical cyclization of the pentadeuterated compound **3.1**, the azo initiator was at least partially responsible for oxidation of the cyclohexadienyl species **3.2** (Scheme 3).[5] This was confirmed by the presence of 2-cyano-2-deuteriopropane, which was the reduced byproduct of AIBN's reaction with **3.2** to form **3.3**. In this case, tributyltin hydride was used as the hydride source, but the same mechanistic considerations probably apply in the case of alternative hydride sources such as $(Me_3Si)_2SiH$ and Bu_3GeH.

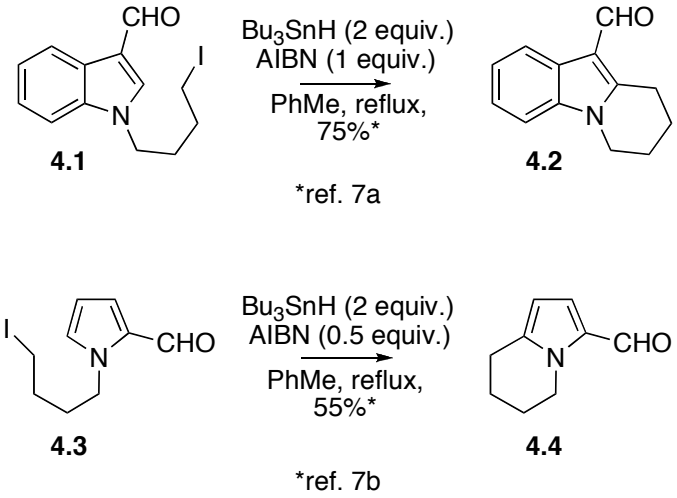


3.1 **3.2** **3.3**, 73%
+ $(CH_3)_2CDCN$, 23%

Scheme 3

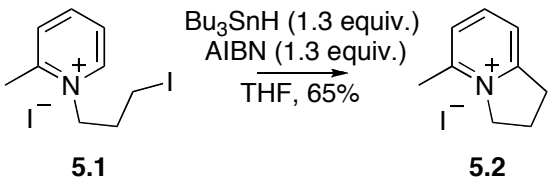
1.3 *Radical Cyclization onto Heteroaromatic Rings*

Radical cyclization onto aromatic heterocycles is a reasonably well-known process; radicals may be oxidatively cyclized onto indoles, imidazoles and pyrroles that contain electron-withdrawing substituents.[6] Typical examples are shown in Scheme 4; it appears that electron withdrawing groups are necessary for this process to be successful, although even then yields can be modest.[7]



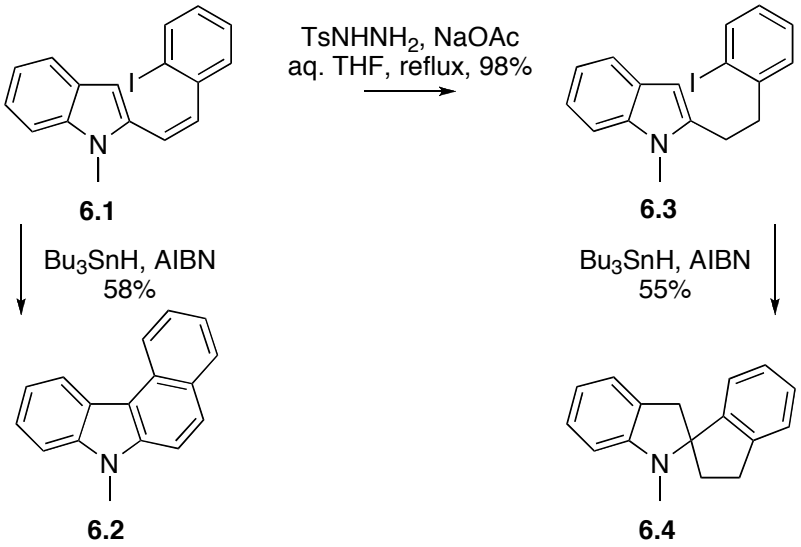
Scheme 4

In the presence of groups that stabilize π-radicals, oxidative radical cyclization onto indoles,[8] pyridines,[9] pyrazoles,[10] pyridones[11] and 1,2,3-triazoles[12] can also be accomplished. Pyridinium salts that are electron-deficient (Scheme 5) readily cyclize when excess AIBN is employed and all the stannane is added at once.[13]



Scheme 5

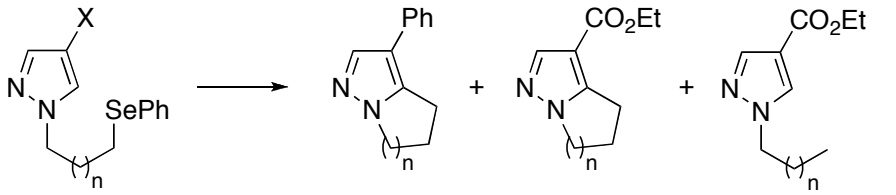
The specific reaction pathway of these cyclizations may be manipulated, as shown in Scheme 6.[8a] Reductive spirocyclization can occur at the C-2 position of the indole ring or oxidative cyclization may occur at C-3, depending on the presence or absence of a double bond in the pendant chain.



Scheme 6

The aforementioned processes work reasonably well, although these reactions are often not general, as shown in Scheme 7. Tin-mediated cyclization of **7.1** (X = Ph, n = 1), using 1.5 equivalents of radical initiator, gives a 38% yield of the natural product withasomnine (**7.2**).[10] If X = CO_2Et (**7.5**, n = 1) however, the reaction gives the undesired reduction product **7.4,** and no cyclized product **7.3**. For the six-membered analogs, **7.6** (X = Ph) was generated in 63% yield, while when X = CO_2Me only 36% of the desired cyclized product (**7.7**) could be isolated, although no undesired reduction product (**7.8**) was detected. When seven-membered ring formation was attempted, if X was Ph, the oxidatively cyclized product **7.9** could be isolated, but only in low yield (37%). Reduction of

7.5 (n = 3) again provided no cyclized product (**7.10**), with the reduction product **7.11** obtained (62%) exclusively.



7.1, X = Ph
7.5, X = CO_2Et

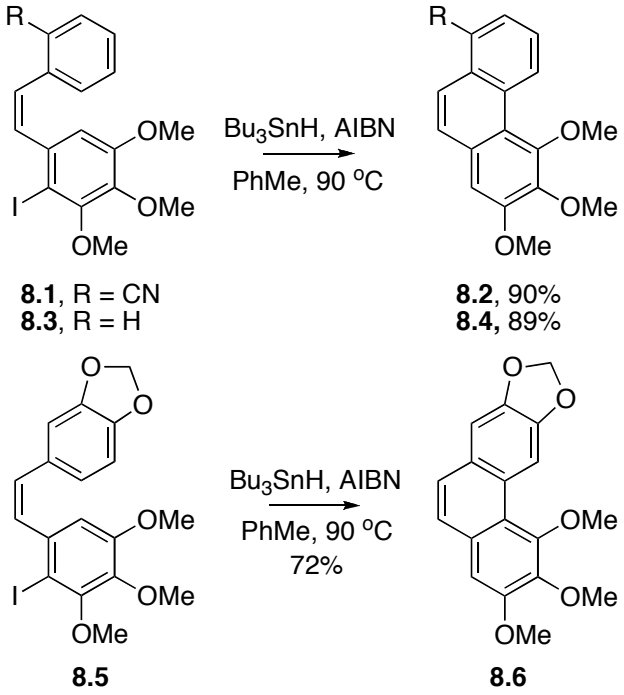
7.2, n = 1, 38% **7.3**, n = 1, 0% **7.4**, n = 1, 73%
7.6, n = 2, 63% **7.7**, n = 2, 36% **7.8**, n = 2, 0%
7.9, n = 3, 37% **7.10**, n = 3, 0% **7.11**, n = 3, 62%

Scheme 7

1.3.1 Attack on a Benzene Ring using typical Radical Cyclization Conditions

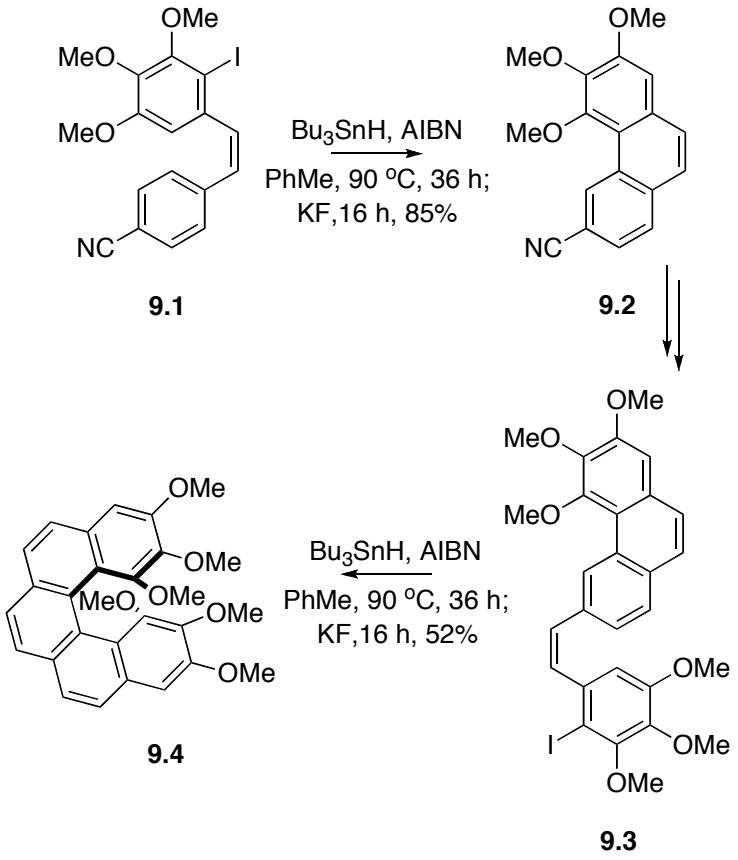
1.3.1.1 Formation of Polyaromatic Compounds

Polyaromatic products may be generated by radical cyclization of a suitably electron rich aryl radical onto arenes that have poor, neutral and rich electron density. As expected, these are oxidative radical cyclizations that presumably occur because the elaborated π-network that results thermodynamically abets rearomatization. The authors of the examples shown in Scheme 8 did not indicate the amount of radical initiator employed.[14]



Scheme 8

The use of *meta*-substituted aromatics generally leads to statistical mixtures of isomers, but cyclization of **8.5** provided **8.6** as the predominant product (72%). The reason for this selectivity is not understood. Nonetheless, it was exploited in a synthesis of helicene **9.4**, using iterative radical cyclizations (Scheme 9). When the *cis*-stilbene **9.3** is treated with Bu_3SnH and an unreported amount of radical initiator, **9.4** is generated in 52% yield. The formation of the strained **9.4** was accompanied by a small amount (17%) of the presumably thermodynamically more stable linear isomer. The authors propose that this selectivity is due to a favored SOMO-LUMO interaction leading to formation of **9.4**. The fact that a product that is clearly strained is generated preferentially when the radical intermediate cyclizes suggests that these cyclizations, and the ultimate loss of hydrogen to provide the aromatic product, are irreversible.[15]

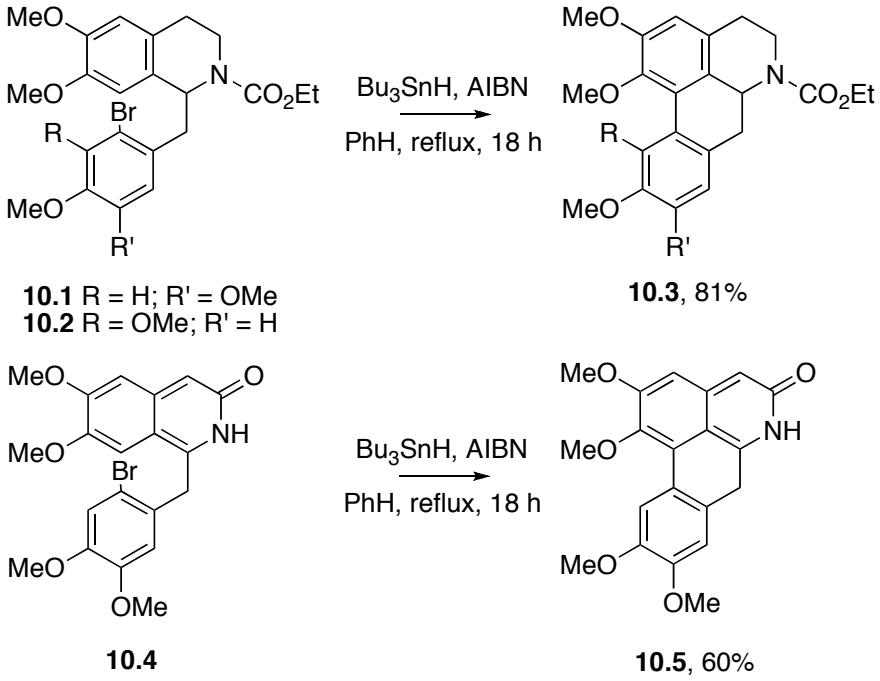


Scheme 9

Biaryl compounds can also be synthesized using standard stannane methodology. With nearly stoichiometric AIBN, conversion of benzyliso-quinoline **10.1** into aporphine **10.3** was accomplished in 81% yield (Scheme 10).[16] When slight changes in the structure of the starting material were made, cyclization was often not observed: rupture of the doubly benzylic carbon-carbon bond occurs if the nitrogen atom is unprotected, for example. Treatment of the modified compound **10.2** under similar conditions resulted in hydrogenolysis of the C-Br bond, preventing cyclization from taking place.

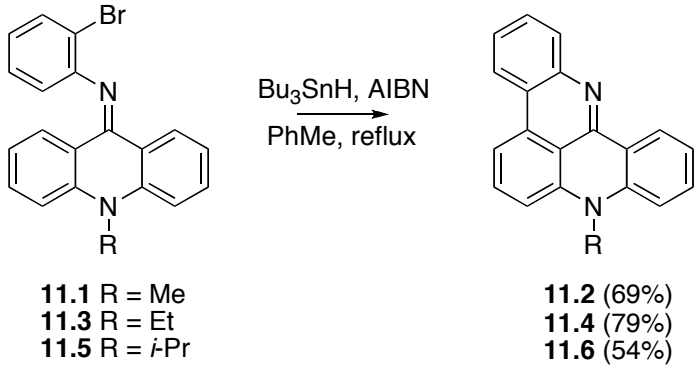
Due to steric restrictions, the conformation required for cyclization may be biased by substituents on the two aromatic rings of starting material **10.2**. The strained polycyclic aromatic helicene **9.4** (Scheme 9) formed readily, however,

and these observations point to a combination of steric effects and subtle electronic differences determining the outcome of such cyclizations. Moderate structural variation (**10.4→10.5**) is usually acceptable.



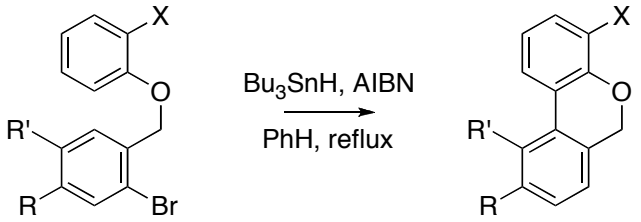
Scheme 10

Polycyclic acridines are accessible using tin hydrides and 10 mol% AIBN in refluxing PhMe with typical examples shown in Scheme 11.[17]



Scheme 11

Aryl radicals generated from *o*-bromobenzyl ethers do not readily provide benzopyrans, but the exceptions shown in Scheme 12 makes it apparent that simple benzene rings (**12.1→12.2**, 48%) are suitable substrates, with electron-donating groups on the radical-bearing ring (**12.3→12.4**) also being tolerated when 1-2 equivalents of stannane, and 0.5-0.6 equivalents of AIBN in refluxing PhH are used. However, the benzene ring accepting the radical may not be substituted, except where an *ortho*-substituted ester derivative (**12.5→12.6**, 30%) is employed. The poor yields are believed to be due to reversibility of the initial radical reaction.[18]



12.1 R = R' = H; X = H
12.3 R, R' = OCH_2O; X = H
12.5 R, R' = OCH_2O; X = CO_2Me

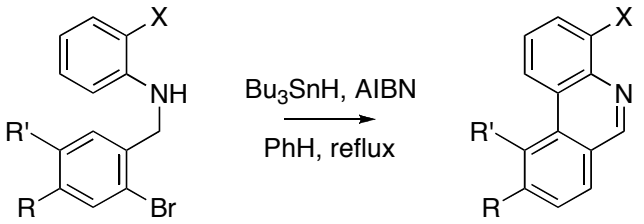
12.2, 48%
12.4, 47%
12.6, 30%

Scheme 12

Bowman *et al*. have also explored the radical cyclization of *o*-bromobenzyl ethers and related compounds, and discovered analogous results—an assortment of products being generated due to the intervention of various rearrangements. When an iodine atom was used as the radical trigger, it did not narrow the product range.[3d]

When the nitrogen equivalent of the transformations shown in Scheme 12 were examined, higher yields are reported (Scheme 13). The process appears to be abetted by the resonance stabilization by the nitrogen of the initial radical

intermediate. A variety of substitutions are tolerated,[19] unlike the previous case (*cf.* Scheme 12).

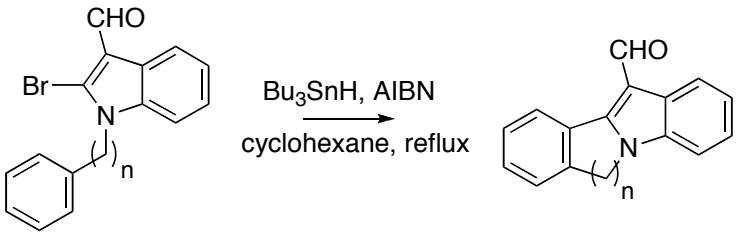


13.1 R, R' = OCH_2O; X = H
13.3 R, R' = OCH_2O; X = OMe

13.2, 66%
13.4, 63%

Scheme 13

Intramolecular addition to unsubstituted benzene rings can occur when a radical is generated from an indole having a suitably placed benzenoid pendant (Scheme 14).[20] Yields fluctuate, based on the length of the connecting alkyl chain. To avoid competitive addition with aromatic solvents, cyclohexane was used as the solvent; the amount of AIBN employed was not documented.[20]

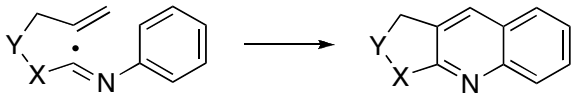


14.1 n = 1
14.3 n = 2
14.5 n = 3
14.7 n = 4

14.2, 25%
14.4, 65%
14.6, 37%
14.8, 0%

Scheme 14

There is a class of radical annulations that are known to produce polycyclic systems (Scheme 15) in which imidoyl radicals **15.1**, produced by several methods, yield a variety of fused quinolines (**15.2**).[21]

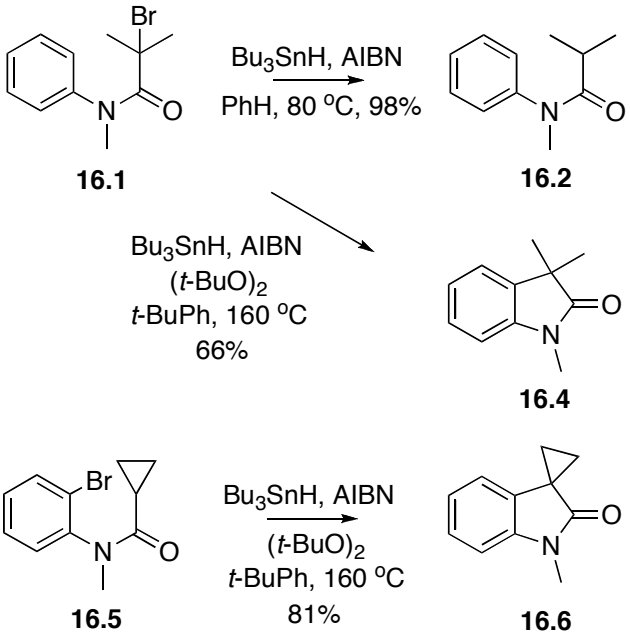


15.1 **15.2**

Scheme 15

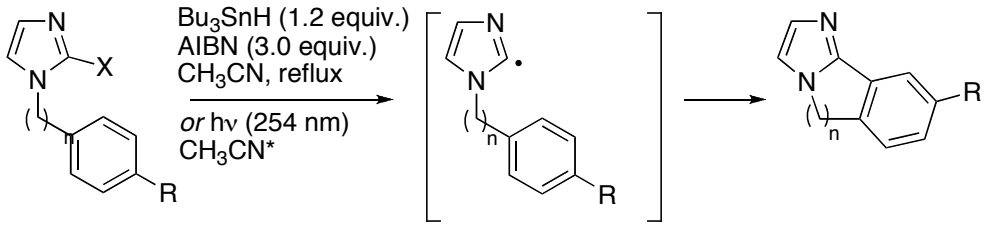
1.3.1.2 *Examples of non-Polyaromatic Products*

Storey and Beckwith heated **16.1** (80 °C) with Bu_3SnH and an unreported amount of AIBN to provide the reduced compound **16.2** (98% yield).[22] When **16.1** and 0.1 M Bu_3SnH in *tert*-butylbenzene were heated (160 °C) while catalytic amounts of di-*tert*-butyl peroxide were added in portions over several hours, the cyclized product **16.4** was obtained (66% yield). Lowering the effective concentration of tin hydride by slow addition of a mixture of stannane and di-*tert*-butyl peroxide to the starting material at 160 °C improved the cyclization yield. This methodology was applied to a process involving radical translocation followed by aromatic substitution to provide easy access to spiro-oxindoles (e.g. **16.6**) from aryl bromides. This approach is, however, limited by the harsh reaction conditions.



Scheme 16

Aldabbagh has reported the superiority of photochemical intramolecular substitutions of imidazol-2-yl radicals, versus those generated using tributyltin hydride and AIBN.[23] Photochemical radical cyclization of halo-imidazoles **17.1**-**17.7** to their annulated counterparts **17.9**-**17.15** provided low to moderate yields (35-66%) and generally very little direct reduction products. These products allow access to corresponding nitroimidazoles which are known bioreductive compounds that can selectively target diseases that occur anaerobically, as well as hypoxic tumors.[24]



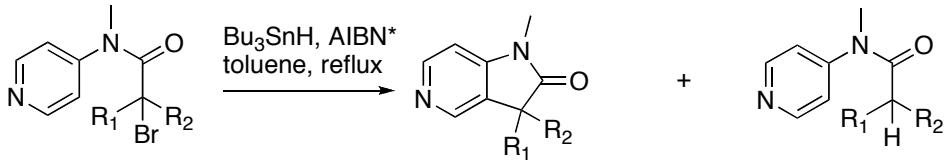
17.1: X = Br, R = H; n = 1
17.2: X = I, R = CF_3; n = 2
17.3: X = Br, R = H; n = 2*
17.4: X = I, R = H; n = 2*
17.5: X = I, R = Cl; n = 2*
17.6: X = I, R = CF_3; n = 2*
17.7: X = I, R = H, n = 3*

17.8

17.9: R = H, n = 1 0%
17.10: R= CF_3, n = 2 21%
17.11: R = H; n = 2 35%*
17.12: R = H; n = 2 61%*
17.13: R = Cl; n = 2 66%*
17.14: R = CF_3; n = 2 53%*
17.15: R = H, n = 3 48%*

Scheme 17

5-Azaoxindoles **18.4-18.6** were synthesized from the corresponding α-bromoamides **18.1-18.3**, derived from pyridines, by homolytic aromatic substitution (Scheme 18).[25] The presence of R-groups (i.e. Me-) that could stabilize the radical formed after the bromine was homolytically abstracted with tributyltin hydride was essential for the formation of 5-azaoxindoles. Satisfactory yields (68%) were achieved in the case of **18.6** with two Me-groups, and only a marginal amount of directly reduced product was seen (**18.9**, 17%).



18.1: $R_1 = R_2 = H$
18.2: R_1 = Me, R_2 = H
18.3: $R_1 = R_2$ = Me

18.4: $R_1 = R_2 = H$ 0%
18.5: R_1 = Me, R_2 = H 7%
18.6: $R_1 = R_2$ = Me 68%

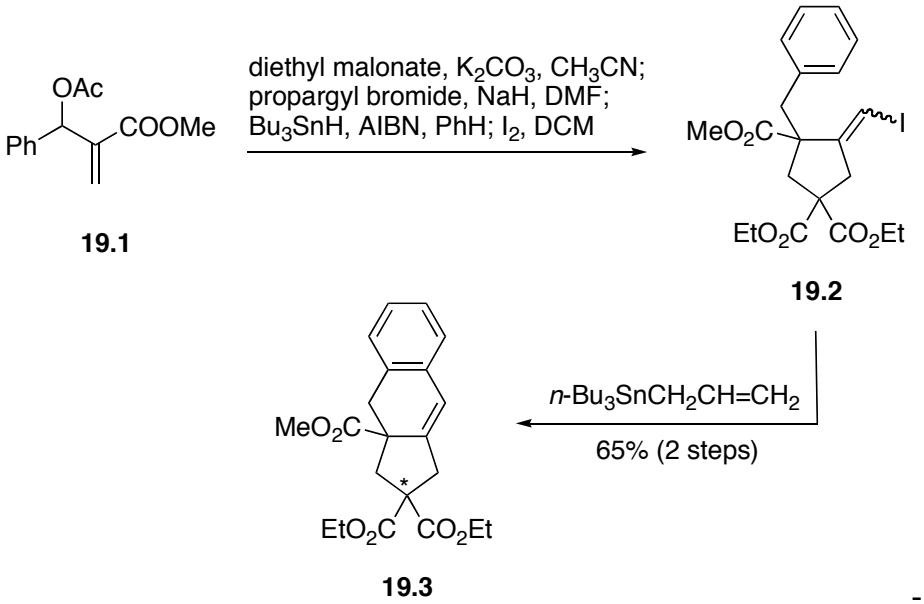
18.7: $R_1 = R_2 = H$ 0%
18.8: R_1 = Me, R_2 = H 24%
18.9: $R_1 = R_2$ = Me 17%

*syringe pumped Bu_3SnH (1.5 equiv.) and AIBN (2.0 equiv.) to substrate (1.0 equiv.) as 0.1 M solution in toluene at reflux.

Scheme 18

Vinyl iodides have been cyclized onto benzene rings in the presence of allyltributylstannane using AIBN (Scheme 19).[26] The substituted

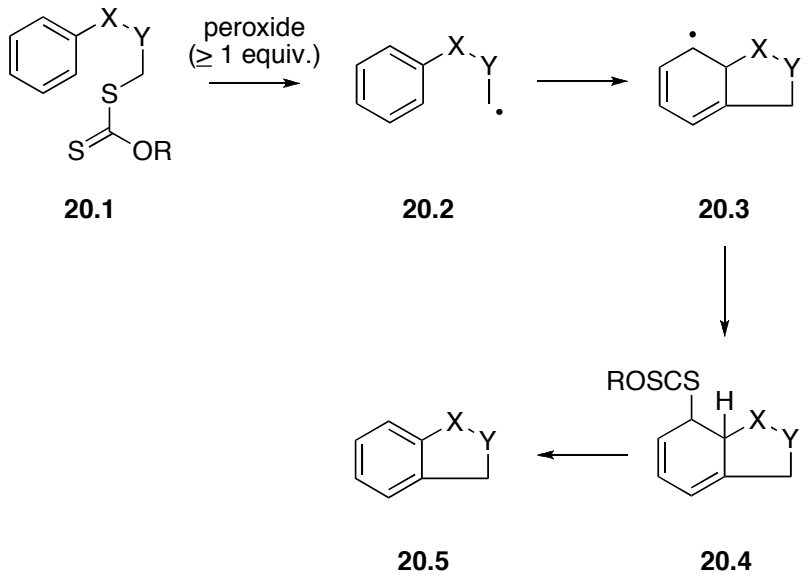
dihydronaphthalene **19.3** was obtained in this way in 65% yield. The method tolerates a variety of substituents on the starting phenyl group as well as on the starred quaternary carbon (see Scheme 19, replacing the ethyl ester groups) where nitrile and methyl esters can be present.



Scheme 19

1.3.2 Application of the Xanthate Method

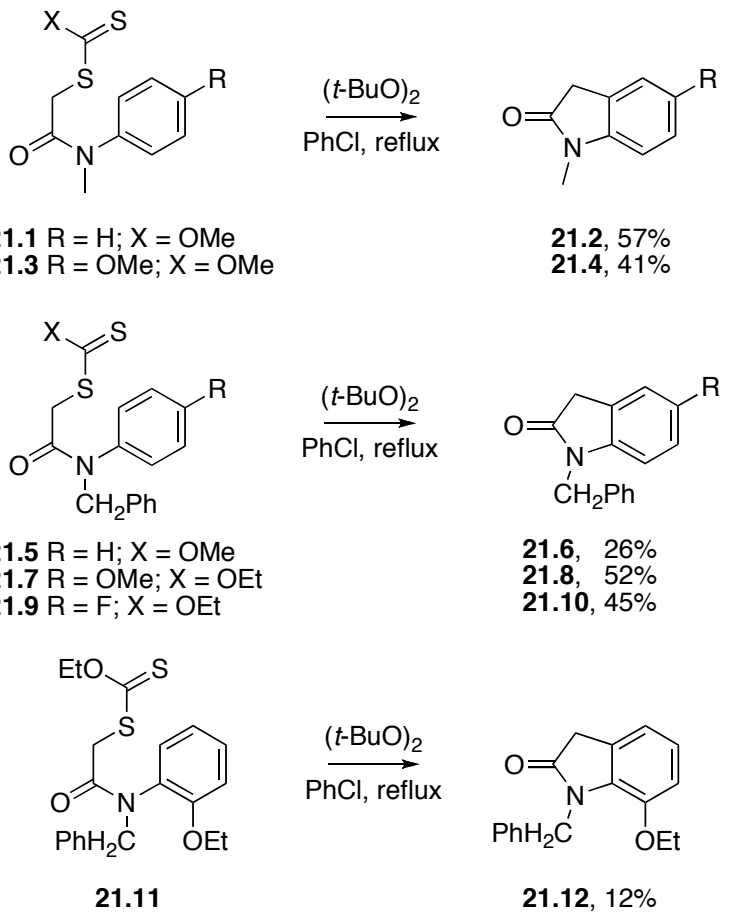
Zard *et al*. have published several papers exploring direct radical cyclization onto an aromatic ring. In this work[27] the radical precursor is a xanthate and the conditions used encourage oxidative rearomatization rather than competing pathways. A factor facilitating this process is that the xanthate (e.g. **20.1**) and its associated radical (**20.2**) exist in equilibrium, which facilitates the process—if they react with each other, **20.1** and **20.2** are produced again.



Scheme 20

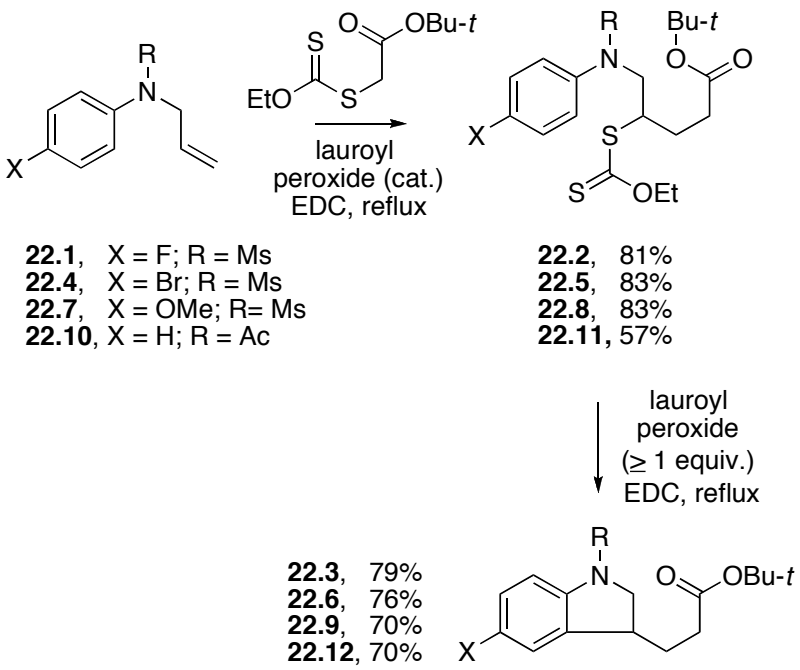
This process generates the radical intermediate in a reversible fashion, which is equivalent to giving the radical a prolonged lifetime, sufficient to overcome conformational factors that slow attack and so the relatively slow ring-closure onto an aromatic ring can take place (**20.2→20.3**). Radical **20.3** is too stable to take part in a chain reaction, therefore its formation is followed by oxidation using peroxide (**20.3→20.5**), or addition of xanthate (**20.3→20.4**) and then aromatization (**20.5**).[28]

This methodology is limited by the inclusion of stoichiometric peroxide and relatively high reaction temperatures—therefore it is likely to be incompatible with sensitive functional groups. Excess peroxide tends to destroy the product once the starting xanthate has been depleted, and so special care must also be taken to monitor the reaction.[29] This protocol does preserve halogen substituents, and is complementary to stannane or silane methodologies that would likely reduce halides.



Scheme 21

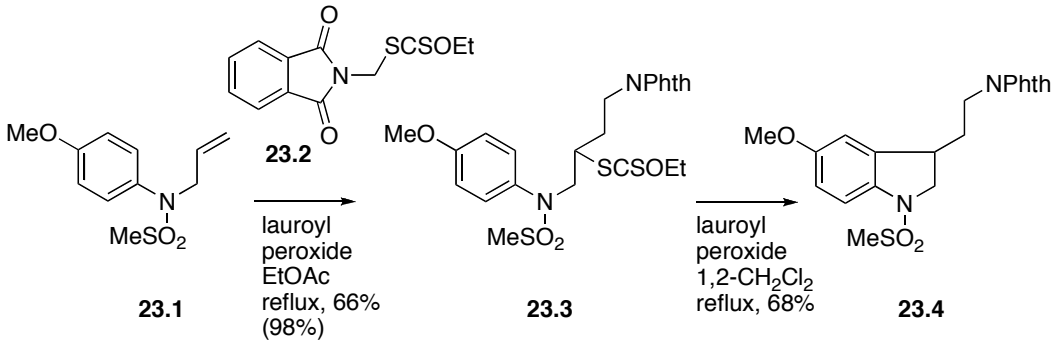
The xanthate method is limited to *para*-substituted aromatic compounds, as *meta*-substitution gives a statistical mixture of regioisomers;[30a] *ortho*-substituted derivatives are susceptible to *ipso*-substitution and give complex mixtures.[30a] The xanthate precursor can be made by intermolecular radical addition, as shown in Scheme 22.[30] The addition of a xanthate by an intermolecular radical process involves a radical chain, which requires only a catalytic amount of peroxide to initiate; in contrast the radical cyclization process requires a stoichiometric amount of peroxide.[30] The yields of the cyclizations summarized below are higher than those for the xanthate-based methodology of Scheme 21. This may be due to the electron-deficient nature of the arene-bound



Scheme 22

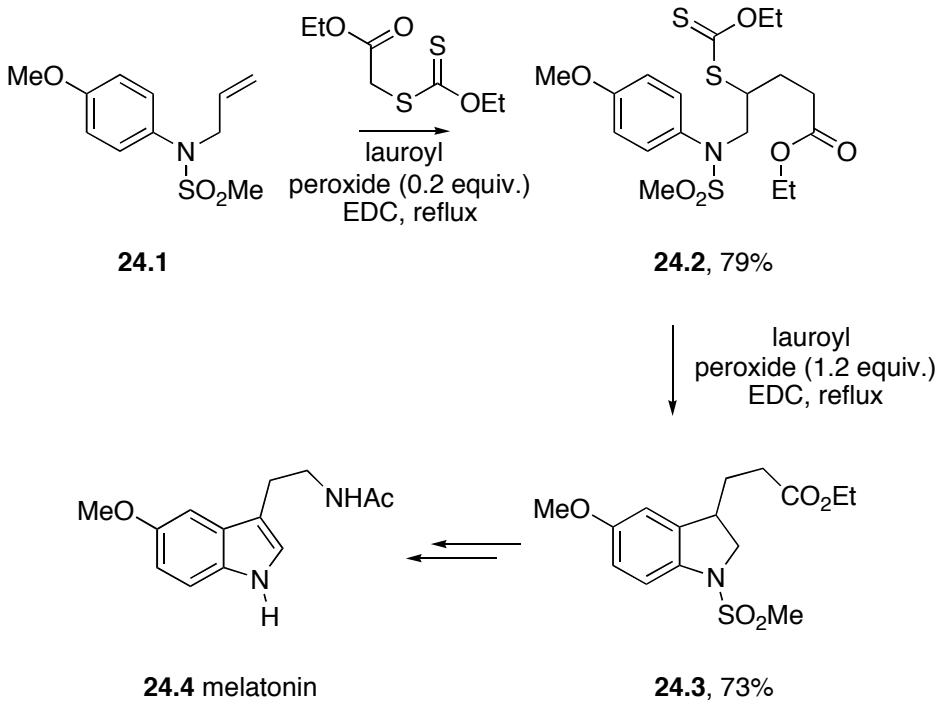
nitrogen which carries an electron-withdrawing substituent.

Zard has also observed that a substituted 2,3-dihydroindole, such as **23.4**, can be obtained from the addition of *S*-phthalimidomethyl xanthate **23.2** to *N*-allylsulfanilide **23.1**, producing xanthate transfer product **23.3** (Scheme 23).[31] Radical cyclization of **23.3**, using lauroyl peroxide as the radical source, provided indoline **23.4**, a useful precursor to melatonin, in moderate yield (68%).



Scheme 23

The xanthate method has aided in the synthesis of melatonin (**24.4**) (Scheme 24)[32] where addition of a xanthate to olefin **24.1** with portionwise addition of lauroyl peroxide provided adduct **24.2** in good yield (79%). Exposure of **24.2** to peroxide in refluxing 1,2-dichloroethane gave indoline **24.3** after ring closure.

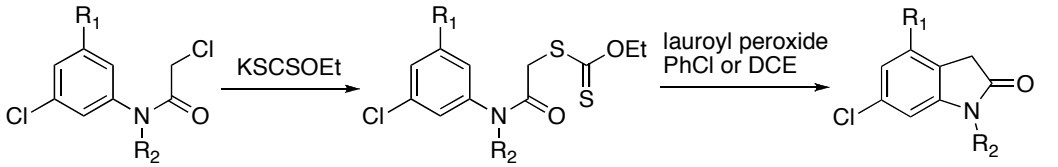


24.1 **24.2**, 79%

24.4 melatonin **24.3**, 73%

Scheme 24

Starting xanthates **25.2** to **25.4**, that were derived from α-chloroamides **25.1**, were also used by Zard to form 7-azaoxindoles.[33] Moderate to good yields were observed in the reaction with lauroyl peroxide to form 7-azaoxindoles **25.5** to **25.7**. These end-products have notable biological activity.[34]



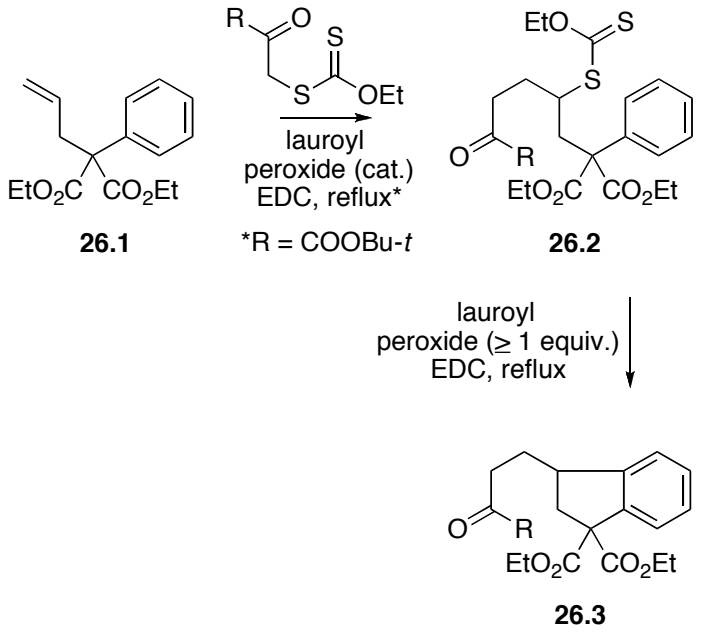
25.1

25.2: R_1 = H, R_2 = cyclopropyl 76%
25.3: R_1 = H, R_2 = *t*-butyl 99%
25.4: R_1 = Cl, R_2 = *t*-butyl 75%

25.5: R_1 = H, R_2 = cyclopropyl 57%
25.6: R_1 = H, R_2 = *t*-butyl 82%
25.7: R_1 = Cl, R_2 = *t*-butyl 74%

Scheme 25

When this approach was applied to indanes, mixed results were obtained with the highest yielding example shown in Scheme 26. It may be possible that the geminal diester group in this example is required for the reaction to proceed reasonably well, but the corresponding process without the geminal substituents was not reported.[30]

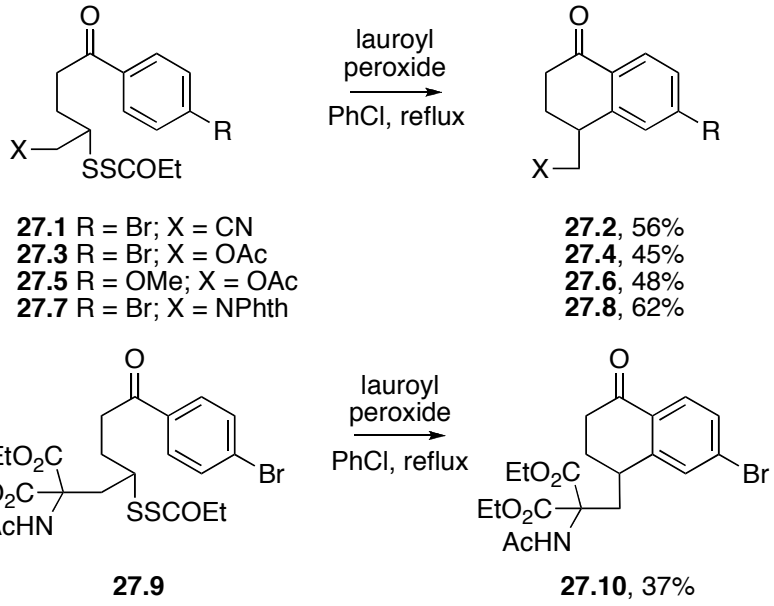


26.1 *R = COOBu-*t* **26.2**

26.3

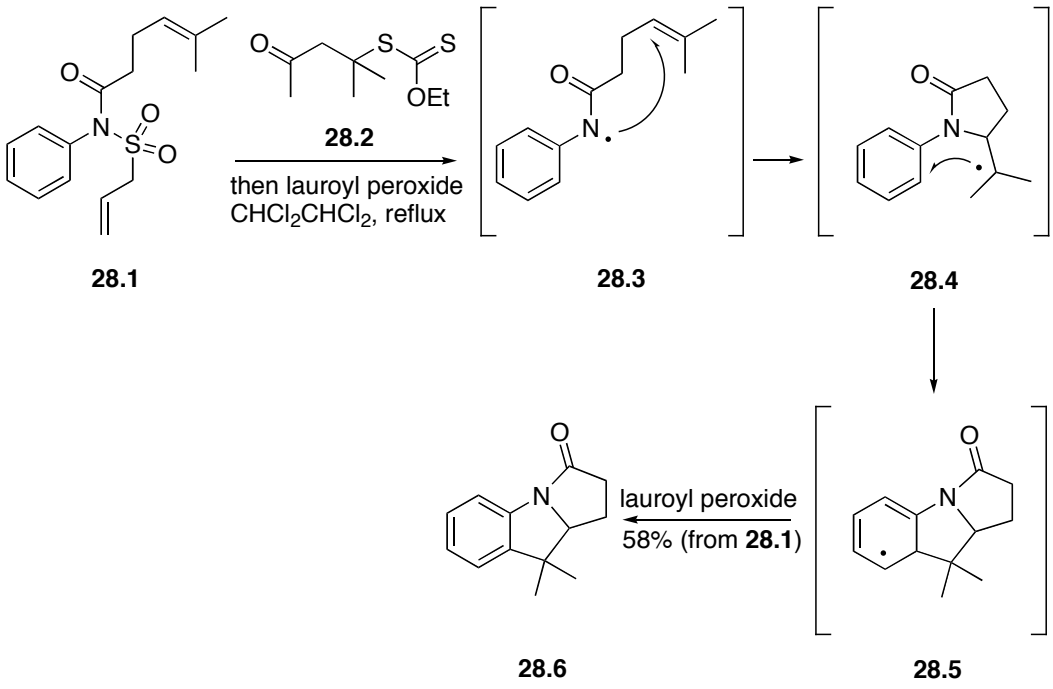
Scheme 26

Various tetralones are also available using this xanthate chemistry (Scheme 27).[29]



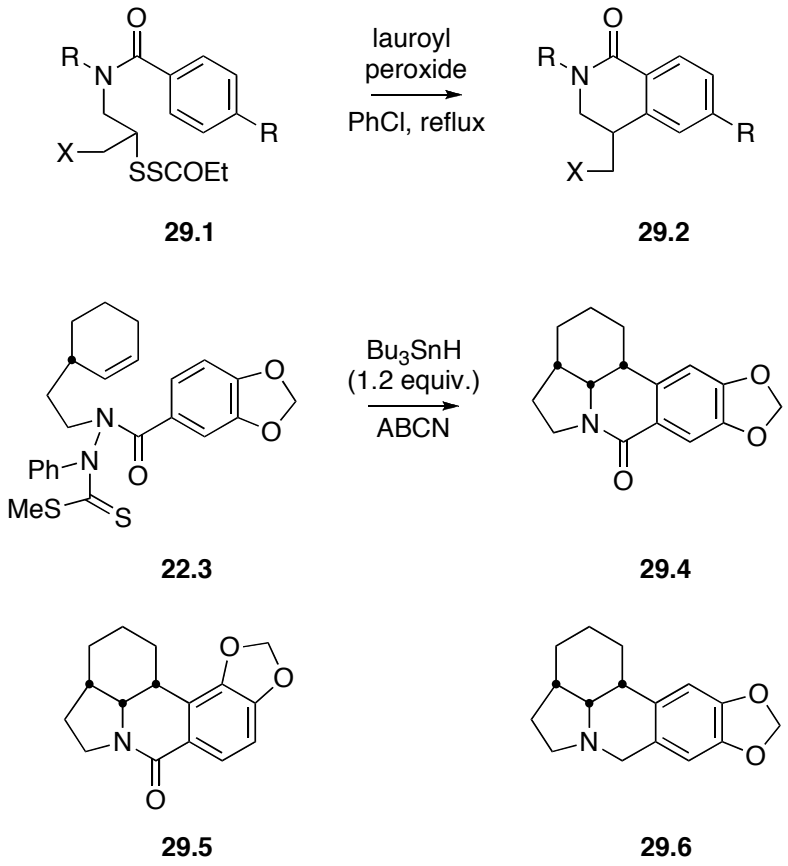
Scheme 27

The allyl sulfonamide **28.1** can be fragmented into sulfonyl radical **28.3** in the presence of a tertiary radical generated by the combination of lauroyl peroxide and **28.2**.[35] Radical **28.3** undergoes ring closure and then cyclizes onto the aromatic ring to finally produce tricyclic lactam **28.6** in 58% overall yield. The peroxide is required in stoichiometric amounts to complete the final aromatization step of the penultimate radical to **28.6**. The best results were obtained when a stabilizing group (here a carbonyl) is present α to nitrogen.



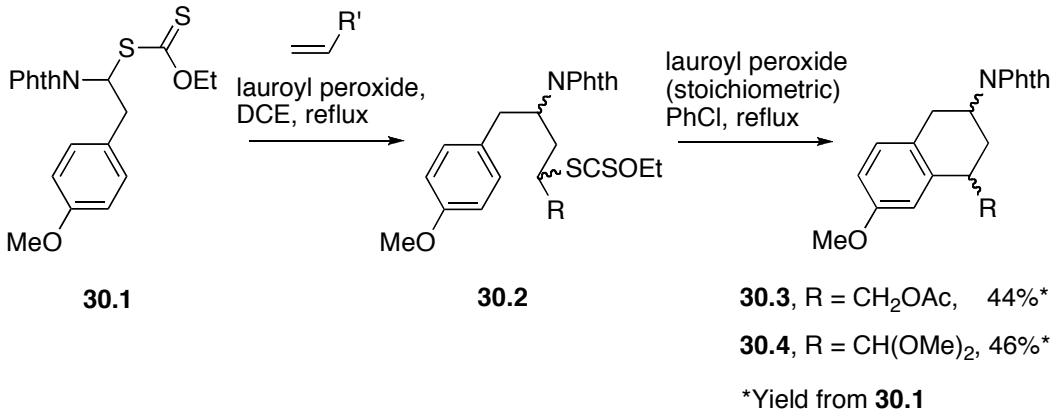
Scheme 28

As shown below (Scheme 29), tetrahydroisoquinolines are also accessible (*cf.* **29.1→29.2**), although yields are modest.[30b] (±)-γ-Lycorane (**29.6**) was synthesized by a variation of this method, using an amidyl radical from **29.3** to begin a radical cascade involving closure first onto an olefin, and then onto an aromatic ring. The radical is generated using a stannane and an equivalent of AIBN rather than peroxide. The reaction provided a 60% yield of **29.4** and its isomer **29.5** (6:4 ratio, respectively).[36] The conversion of **29.4** into γ-lycorane (**29.6**) had been described previously.



Scheme 29

Zard also used xanthates (e.g. **30.1**) to form 2-aminotetralins by adding a further portion of lauroyl peroxide to convert **30.2** into the bicycles **30.3** and **30.4** (Scheme 30).[37] 2-Aminotetralins are part of a family of compounds that have medicinal importance, in most cases, as dopamine agonists. Convenient access to these species had previously been limited.



30.1 **30.2**

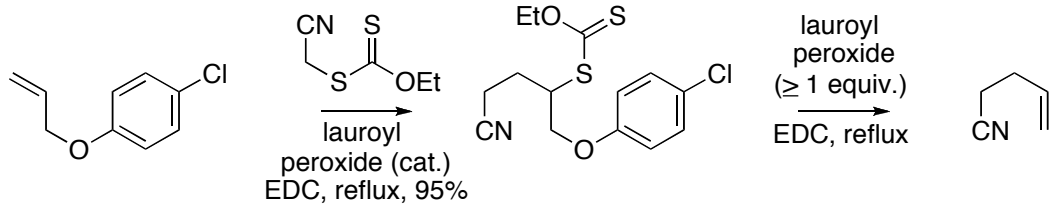
30.3, R = CH_2OAc, 44%*

30.4, R = $CH(OMe)_2$, 46%*

*Yield from **30.1**

Scheme 30

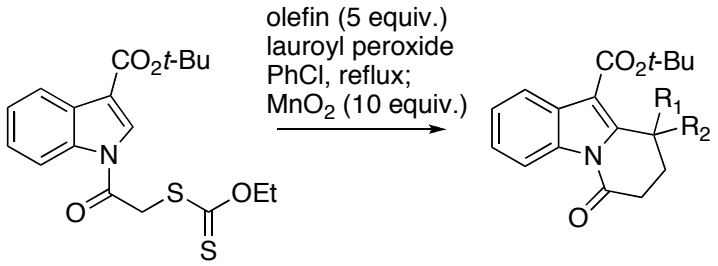
Dihydrobenzofurans cannot be accessed using this approach.[30] Addition of a xanthate to *O*-allyl *p*-chlorophenol **31.1** proceeded efficiently (95%), but the required radical ring closure of **31.2** was not observed under typical conditions. A radical was generated under the oxidative conditions, which, in turn, expelled a *p*-chlorophenoxy radical, thus providing nitrile **31.3** and *p*-chlorophenol.[30]



31.1 **31.2** **31.3**

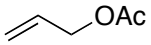
Scheme 31

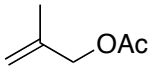
Tricyclic trisubstituted indoles (**32.2**-**32.4**) were also formed in moderate to good yields using indoles bearing *N*-pendant xanthates (**32.1**) in the presence of lauroyl peroxide in chlorobenzene at reflux (Scheme 32).[38] In some, but not all, cases, after the xanthate was completely consumed, manganese(II) oxide was not required to aromatize the intermediate into the final products; however, yields were always better if manganese(II) oxide was employed.

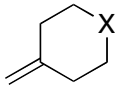
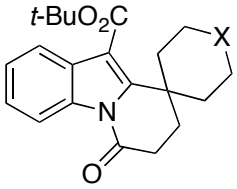


32.1

Product

32.2: olefin =  $R_1 = CH_2OAc$, $R_2 = H$; 69% (49%*)

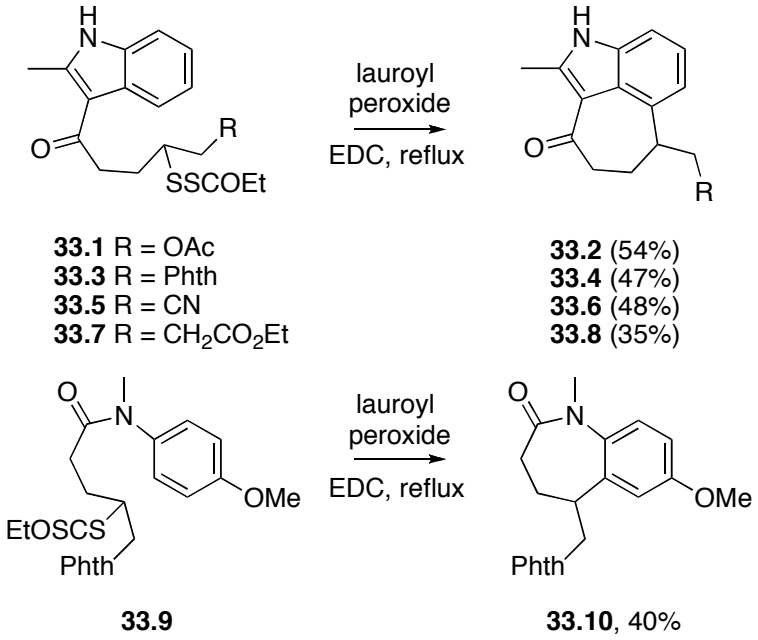
32.3: olefin =  $R_1 = CH_2OAc$, $R_2 = Me$; 74% (49%*)

32.4: olefin =   X = CH_2, 75%
X = NBoc, 79%

*Yield without MnO_2 oxidation

Scheme 32

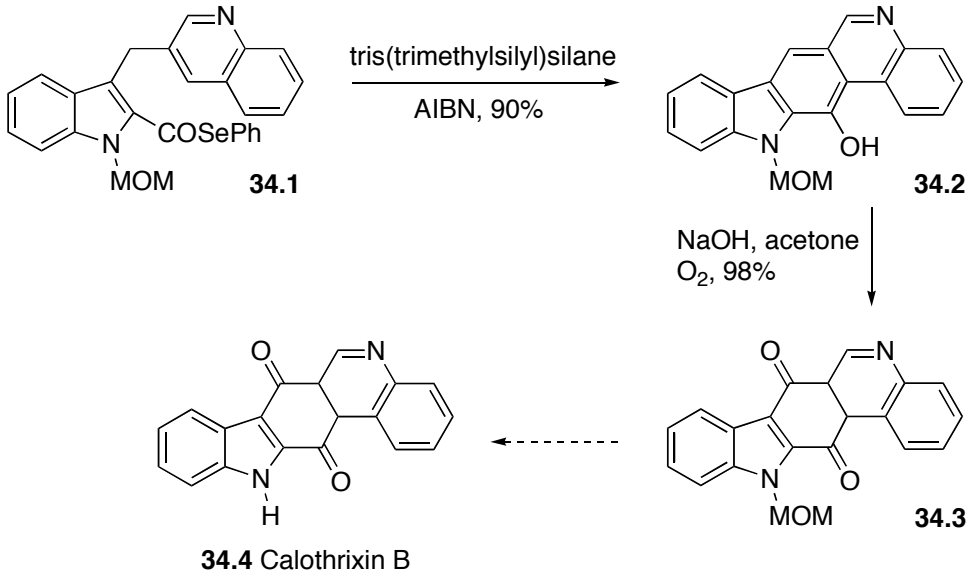
The xanthate method has also recently been applied to make seven-membered rings; yields are very low to modest with typical examples shown in Scheme 33.[39] Seven-membered rings can also be formed by radical addition onto certain aromatic nuclei using stannanes. Pyrrole or imidazole heteroaromatic examples that are successful are activated by an electron-withdrawing group. Chloroamides have also been photolyzed to form seven-membered rings but with mixed results: yields are low and the photolysis likely involves a SET process.[40]



Scheme 33

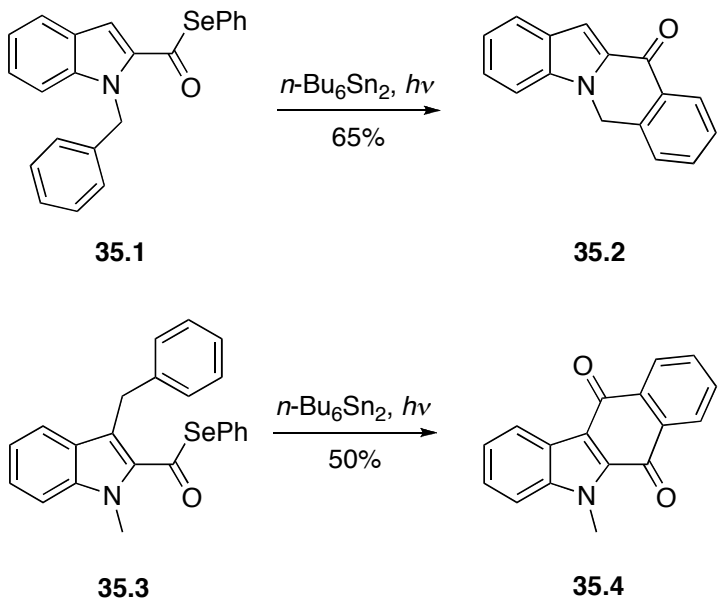
1.3.3 Cyclizations of Radicals from Selenoesters

The selenoester **34.1** has been used to form the calothrixin precursor pentacycle **34.2** in the presence of tributyltin hydride and AIBN.[41] Described as proceeding via a "radical addition—rearomatization—overoxidation" process, **34.2** is formed in a high yield (90%) and is then amenable to near-quantitative oxidation under mild, basic conditions to the quinone **34.3**.



Scheme 34

2-Indoylacyl radicals that are generated by reaction of selenoesters **35.1** and **35.3** with hexabutylditin in the presence of light, have been observed to undergo a ring closure with pendant benzenes to form polycyclic aryl indolyl ketones **35.2** and **35.4**, respectively, in moderate yields.[42] Annulations onto aromatic rings using acyl radicals have seen limited use compared to that of aryl and alkyl radicals, but the method[42] allows access to the substructures of many natural and medicinal compounds which contain an acyl-aryl functionality.

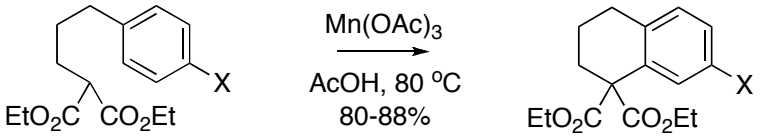


Scheme 35

1.3.4 Cyclizations of Radicals from β-Dicarbonyl Compounds

Cyclization using free radicals can be applied to benzene rings when the initial radical is both generated *and* terminated oxidatively.[43] This large subject has been reviewed.[43]

When β-dicarbonyl compounds are employed, a proton is abstracted and the resulting anion is oxidized by a metal to form a radical. In this strategy, the radical precursor is readily generated but the use of oxidant (often in excess) can cause undesired further oxidation.[44]

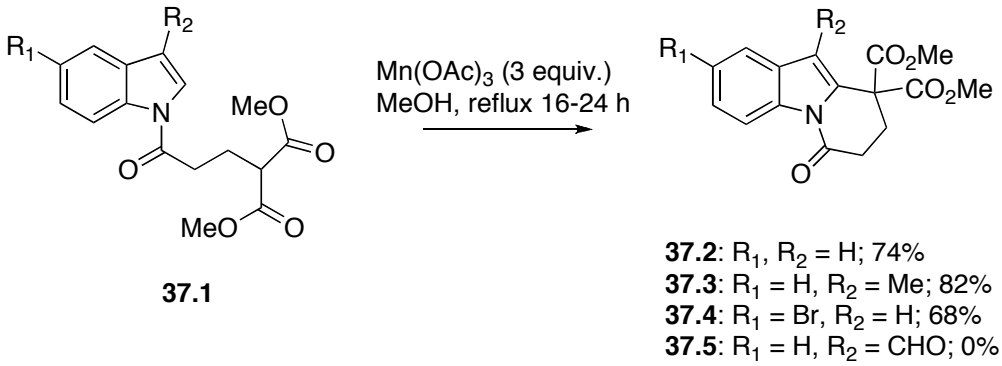


36.1 X = H, OMe, NO_2, NHCOMe

36.2

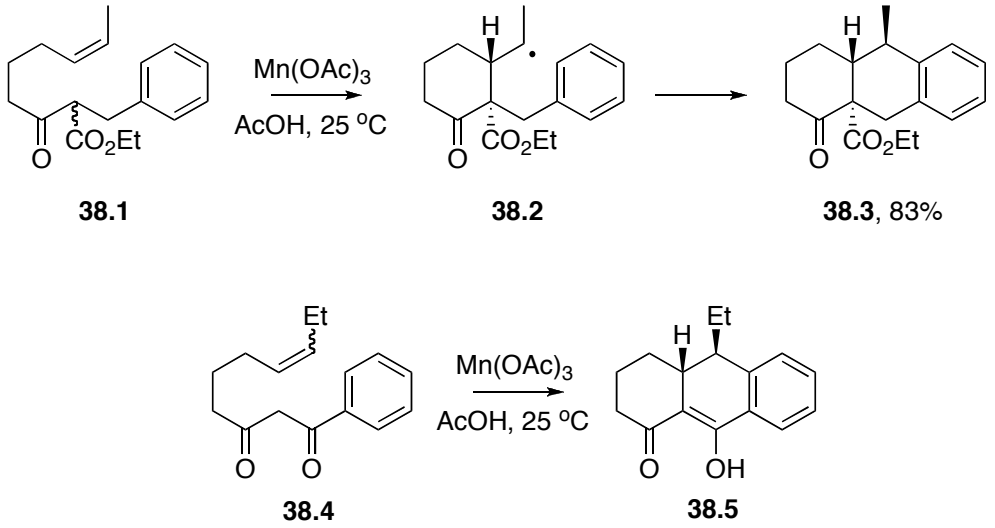
Scheme 36

The Kerr group has reported[45] that *N*-acyl indoles (**37.1**) undergo oxidative radical cyclizations in the presence of $Mn(OAc)_3$, when heated at reflux in methanol, to produce 2-annulated indoles (Scheme 37). They also observed that the reactions could be carried out in acetic acid at reflux with the manganese(III) reagent with satisfactory yields. All substrates reported provided good yields except for the case of the indole-3-carboxaldehyde, **37.5**, which decomposed under the reaction conditions.



Scheme 37

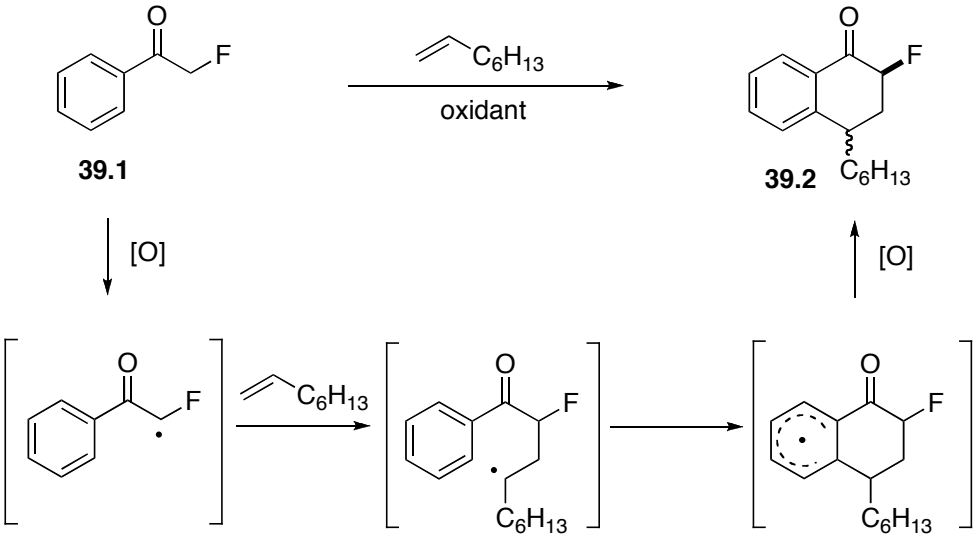
Tandem oxidative cyclizations can be used to make more complex targets. Oxidative cyclization of **38.1** with $Mn(OAc)_3$ in AcOH generates a cyclohexanemethyl radical **38.2** that adds to the aromatic ring to provide **38.3** in 83% yield and as a single stereoisomer (Scheme 38). Oxidative cyclization of either the *E*- or *Z*-isomer of **38.4** similarly provides **38.5** in 85% yield.[46]



Scheme 38

1.3.5 Cyclization onto an Aromatic Ring by a Cascade Process

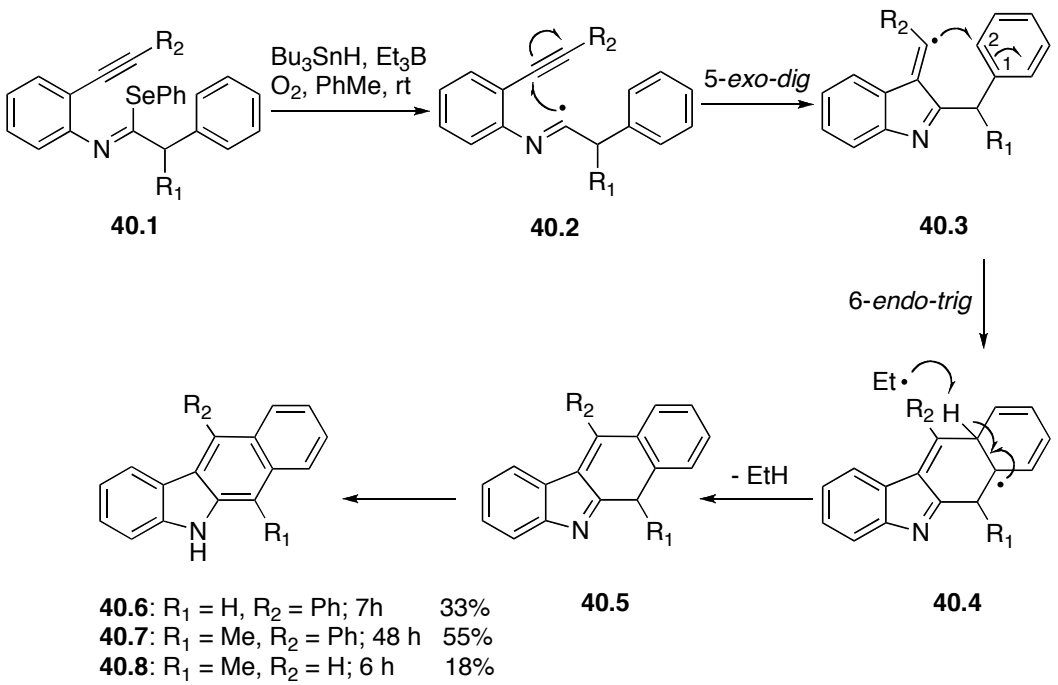
α–Fluoroacetophenone **39.1** and 1-octene have been combined to make 2-fluorotetralones **39.2** in an oxidative radical cyclization process employed by Heinrich *et al*.[47] Anhydrous manganese(III) acetate [$Mn(OAc)_3$], ceric ammonium nitrate (CAN) and $Mn_3O(OAc)_7$ were evaluated under a variety of conditions, and it was found that manganese(III) oxide (5 equiv.) in the presence of hot acetic acid with added potassium acetate provided quantitative yields. Substituted 2-tetralones have been used as intermediates in the synthesis of fluorohydrins that are, themselves, constituents of many biologically active compounds.[48]



Conditions	Yield
1. $Mn(OAc)_3$ (4 equiv.), AcOH, sealed tube, 140 °C, 30 min	29%
2. CAN, (2 equiv.), CH_3CN, sealed tube, 100 °C, 30 min	0%
3. $Mn_3O(OAc)_7$ (3 equiv.), AcOH-KOAc, sealed tube, 140 °C, 30 min	47%
4. $Mn(OAc)_3$ (3 equiv.), AcOH-KOAc, sealed tube, 140 °C, 30 min	50%
5. $Mn(OAc)_3$ (5 equiv.), AcOH-KOAc, sealed tube, 140 °C, 15 min	100%

Scheme 39

Bowman *et al*. have observed that imidoyl selenides **40.1** can be used as radical precursors for the formation of substituted indoles when exposed to tributyltin hydride in the presence of Et_3B and O_2.[49] The yields for the radical cyclization are highly dependent on the presence of a radical stabilizing group (e.g. Ph-) at the terminal position of the alkyne. At best, only low to moderate yields were achieved [*cf.* **40.6** (33%) and **40.7** (55%)]. It is also possible that **40.3** undergoes 5-*ipso*-*trigonal* attack onto the 1-position of the phenyl ring; neophyl rearrangement then still provides the radical **40.4**.

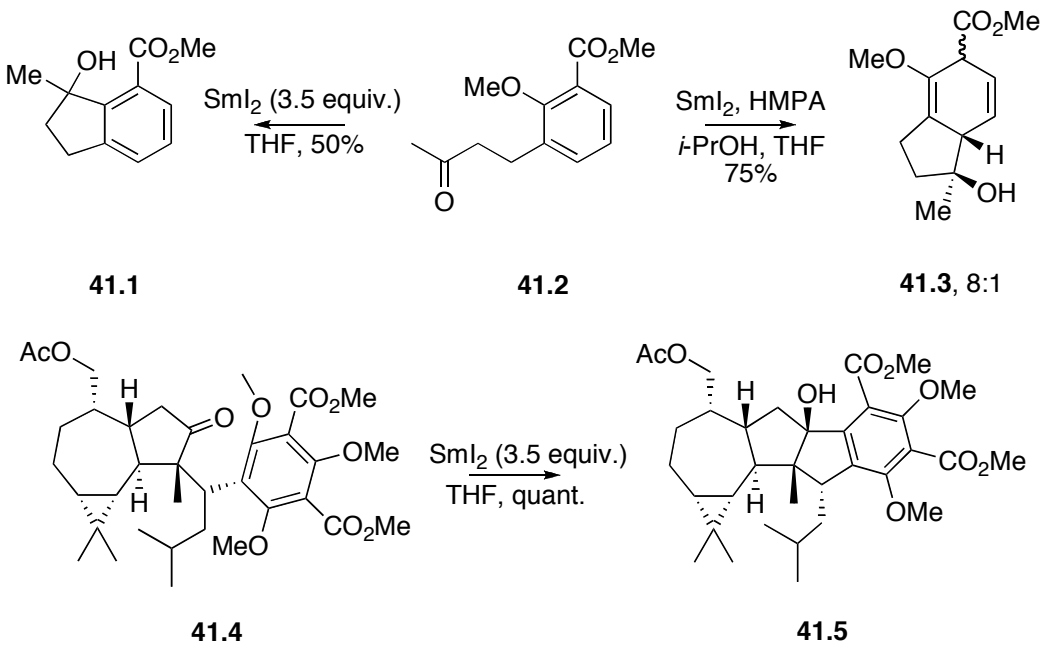


Scheme 40

1.3.6 *Cyclization onto an Aromatic Ring using Samarium(II)*

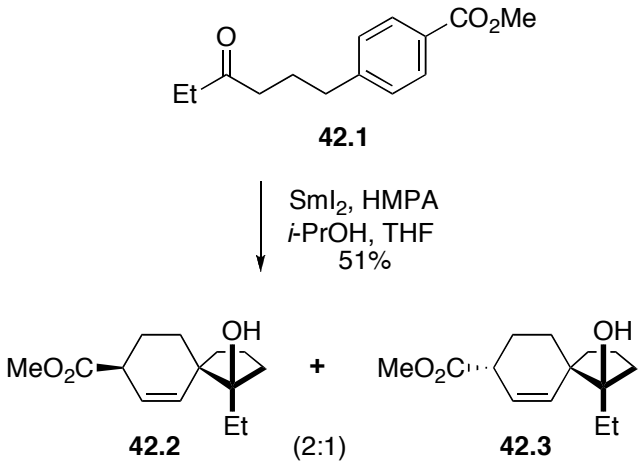
If an aromatic ring bears an electron-withdrawing group, samarium(II) diiodide can be used to effect intramolecular radical cyclization, but only a few examples of this methodology have been reported.[50]

A ketyl radical can attack selectively the *ortho* or *para* positions of an aromatic ring that bears an electron-withdrawing substituent, depending on the reaction conditions.[51] If **41.2** is treated with SmI_2 in THF, the *ipso*-substituted product **41.1** is generated through attack *ortho* to the ester group (50%). This *ipso*-substitution is effective in more complex cases (*cf.* **41.4→41.5**) and the successful outcome appears to be due to the samarium ion's unique chelating ability: it likely causes the appropriate reactant substructures to be close together and also facilitates the elimination of methanol.[51] Treatment of **41.2** with *i*-PrOH (2 equiv.), SmI_2 (5 equiv.) and HMPA (18 equiv.) generated cyclohexadiene **41.3** in 75% yield by attack *para* to the ester functionality.



Scheme 41

This procedure has been applied to the synthesis of spirocycles and again favors *para* attack to the electron-withdrawing group. It is possible that addition of HMPA and isopropanol interferes with the methoxy lone pairs and prevents them from interacting with the samarium, an interaction that would favor a pathway that is not controlled by chelation. A typical example is shown in Scheme 42 where ketone **42.1** undergoes cyclization using the conditions indicated. The cyclization product, which is a radical, is reduced by SmI_2 to give a mixture of diastereoisomeric alcohols **42.2** and **42.3** (2:1, respectively).[52]

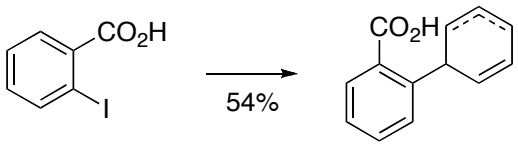


Scheme 42

1.4 Radical Cyclization onto an Aromatic Ring without Rearomatization

Cases where the intermediate cyclohexadienyl radical is trapped without aromatization have been reported by Crich (*cf.* Scheme 2).[4] The methodology uses catalytic PhSeSePh which generates PhSeH that facilitates hydrogen atom donation to the intermediate cyclohexadienyl radical.

For intermolecular examples, slow addition of a tributyltin hydride and AIBN solution to an aryl iodide and 20 mol% PhSeSePh over 12 h is required (Scheme 43). In the most successful example, with **43.1**, *o*-(cyclohexadienyl)benzoic acid **43.2** was produced in a yield of 54%. Kinetic trapping of the cyclohexadienyl radical at the internal site explains the observed 10:1 ratio of non-conjugated to conjugated dienes. The intermolecular process is limited to iodoarenes as the radical precursor, and benzene as the radical acceptor—the intramolecular version was low yielding and lead to a complex mixture of products.

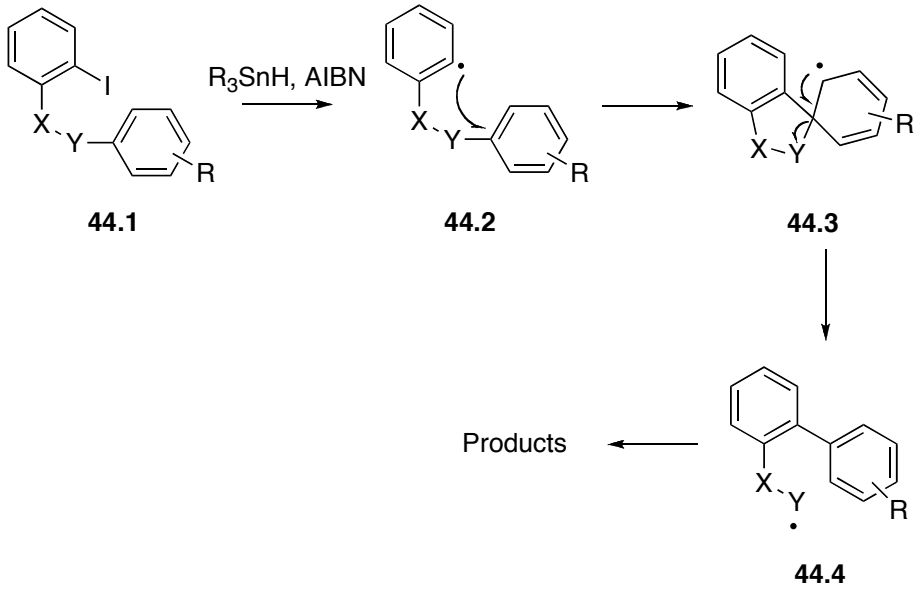


43.1 **43.2**

Scheme 43

1.5 Radical Attack on a Benzene Ring with ipso-Substitution

The radical mechanism of intramolecular transfer of aryl groups is well established. This transfer is a consequence of *ipso* attack onto an aromatic ring, and the majority of the studies involve attaching the radical segment to an aromatic acceptor that bears an effective leaving group. A typical generic case is shown in Scheme 44 and numerous specific examples are reported in the literature.[53]

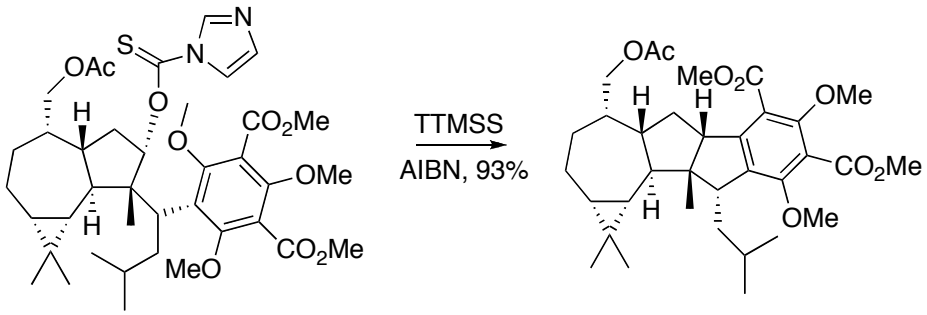


44.1 **44.2** **44.3** **44.4**

Scheme 44

However, the process shown in Scheme 45, does not appear to be generalizable and the outcome is highly dependent on the steric influence of the

thiocarbamate starting material and the conformation of the radical intermediate. This *ipso* process is improved if one can shorten the gap between the methoxy group and the radical—something that samarium effectively accomplishes with its strong chelating ability (*cf.* Section 1.3.4).[51]

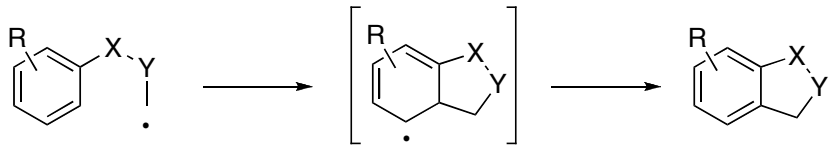


45.1 **45.2**

Scheme 45

1.6 Early Investigations in the Clive Group

A useful route to benzo-fused products would be available if one could readily achieve the oxidative cyclization of an alkyl radical onto a benzene ring along the lines of Scheme 46. This is a known process, as discussed in the introduction to this chapter. Prior to 2006, however, the only method that appeared to be general was Zard's xanthate methodology. Although very useful, this process is best applied to benzene rings that are *para*-substituted, and which contain no features sensitive to peroxides or the usually required high temperatures.



46.1, X,Y = linking units **46.2** **46.3**

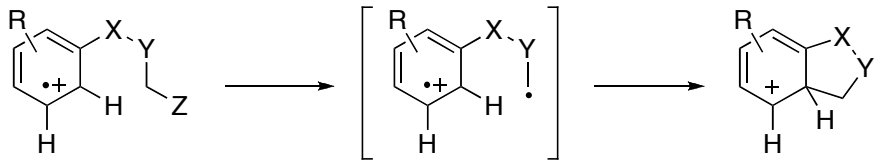
Scheme 46

Radical cyclization is impeded by the energy required to destroy the aromaticity of the starting material (**46.1→46.2**). In addition, the cyclized radical **46.2** may undergo a number of undesired reactions. There was a need for a general protocol that could be performed employing classical stannane radical cyclization conditions.

1.6.1 Early Development of an Indirect Approach to Radical Cyclization onto a Benzene Ring

The goal of the initial researchers on this project (Fletcher, Peng and Wingert) was to develop a general methodology for oxidative radical cyclization onto benzenes. It was hoped that *any* radical-bearing carbon chain could be made to cyclize onto an aromatic ring using the traditional stannane-based protocol.

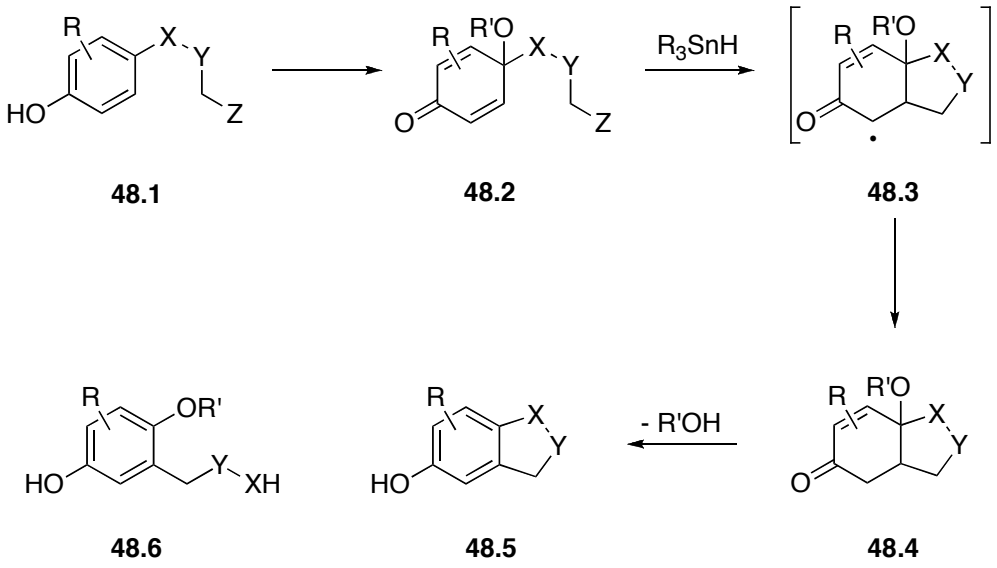
It was understood that oxidative radical cyclization is a multi-step process and that the most common first step was cyclization onto the ring (Scheme 46, **46.1→46.2**), and *then* oxidative removal of the proton (**46.2→46.3**). It was realized that if the order of these processes were changed then some of the difficulties in the steps **46.1→46.3** could be avoided (*cf*. Scheme 47). If **47.1** could first be generated oxidatively and *then* radical cyclization carried out (**47.2→47.3**), the intermediate **47.3** would readily lose a proton to regenerate the aromatic ring. Some practical difficulties remained with this rearranged sequence, but a useful approach was established by temporary modification of the benzene ring into an entity that readily underwent radical cyclization.



47.1 **47.2** **47.3**

Scheme 47

A methodology that relies on oxidation of a phenol to a cross-conjugated ketone was investigated.[54] Transformations comparable to **48.1→48.2** (Scheme 48) are well studied in cases where X is oxygen and such oxidations dearomatize the benzene ring and generate a dienone. The double bonds of **48.2** are activated by the ketone functionality allowing for reaction with an incoming nucleophilic radical. The intermediate **48.3** formed by radical cyclization was anticipated to acquire a hydrogen atom from the stannane reagent, thus propagating the chain reaction. It is well established that α-keto radicals undergo radical chain processes,[55] and so participation of **48.3** in a radical chain process was expected. Homolytic fission of the C-Z bond in intermediate **48.2** might be competitive with stannane-mediated dienone reduction. Intermediate **48.4** should be in the proper oxidation state to undergo acid or base catalyzed aromatization, to provide a phenol (**48.5)**. Formation of **48.5** could also be complicated if the expulsion of substituent X in **48.4** were favored so that the undesired **48.6** would be generated rather than **48.5**. The reaction **48.1→48.2** is a well-studied oxidation process if X is oxygen. Fletcher first tested[56] a related sequence using *p*-alkoxyphenols to eventually form benzo-fused heterocycles containing oxygen (**48.5**; X = O, Y = C).



Scheme 48

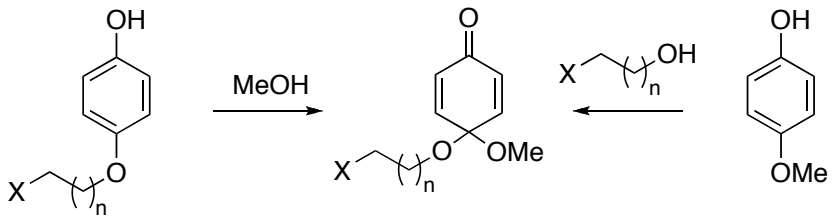
1.6.2 Formation of Benzo-fused Oxygen Heterocycles

The indirect method from the initial studies discussed above allowed for formal radical cyclization onto a benzene ring and represented a powerful method for making benzo-fused oxygen heterocycles under standard radical cyclization conditions.[1a] These studies also preceded future work featuring benzo-fused nitrogen heterocycles and analogous completely carbon-based compounds. The individual steps of the method are discussed in the following sections, beginning with the formation of cross-conjugated ketones that readily undergo radical reactions.

1.6.3 Oxidation of Phenols to Cross-Conjugated Ketones

Cross-conjugated enones **49.2** that carry two alkoxy groups (Scheme 49) can be generated from a phenol bearing a *p*-alkoxy substituent that already possesses a terminal halogen (**49.1**). In this sequence, the oxidation is done in MeOH to provide the quinone ketal (Scheme 49, **49.1→49.2**). It is also possible

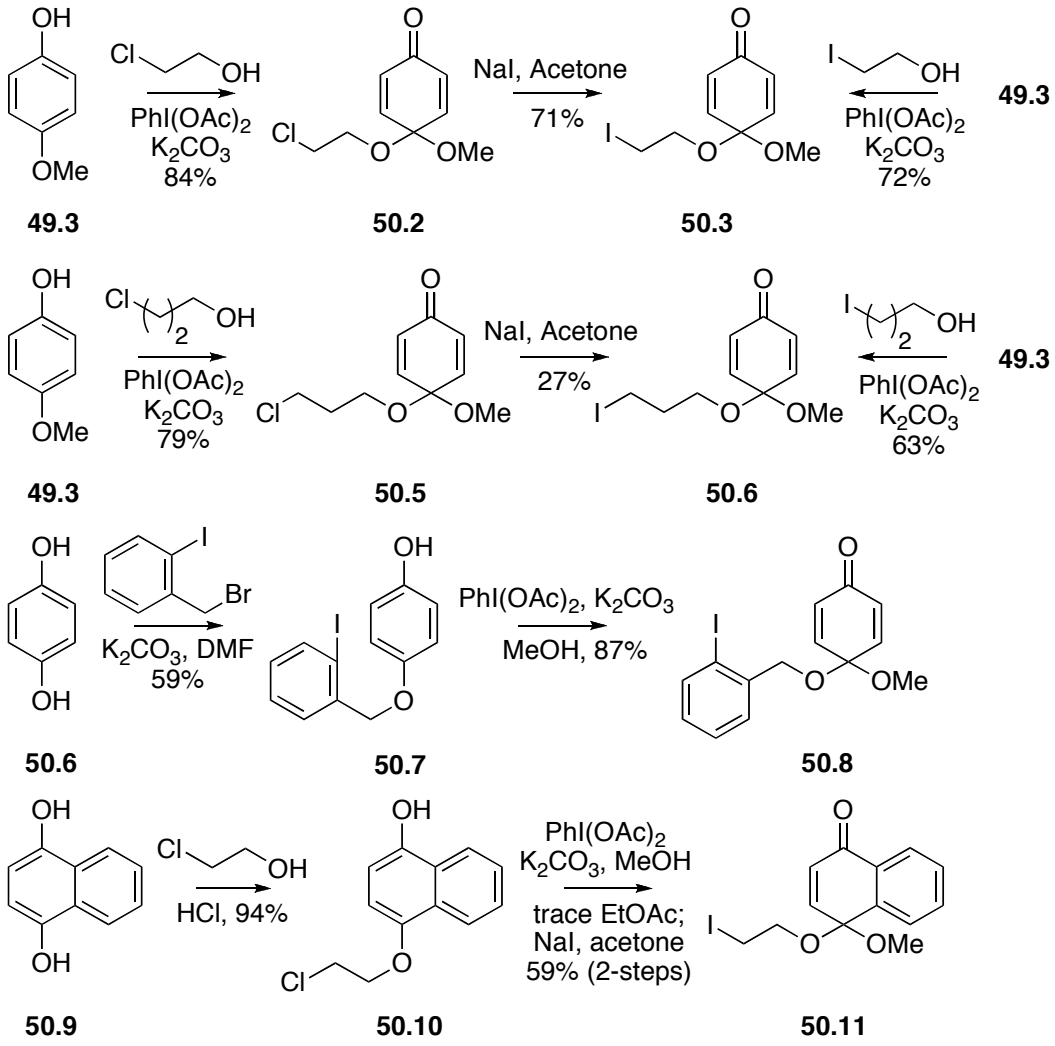
to achieve this transformation by the addition of α,ω-halo alcohols to *p*-methoxyphenols (Scheme 49, **49.3→49.2**).[1a,b]



49.1 **49.2** **49.3**

Scheme 49

Initial studies of these approaches by Fletcher are shown in Scheme 50 (for both transformations of the type **49.1→49.2** and **49.3→49.2**) where $PhI(OAc)_2$ (*ca.* 1.1 equiv.) was used as the oxidizing agent to form the quinone ketals.[57] As these intermediates are acid-sensitive, the oxidation was done in the presence of K_2CO_3 (*ca.* 2.2 equiv.) with a small amount of Et_3N added to all solvents used during chromatography.

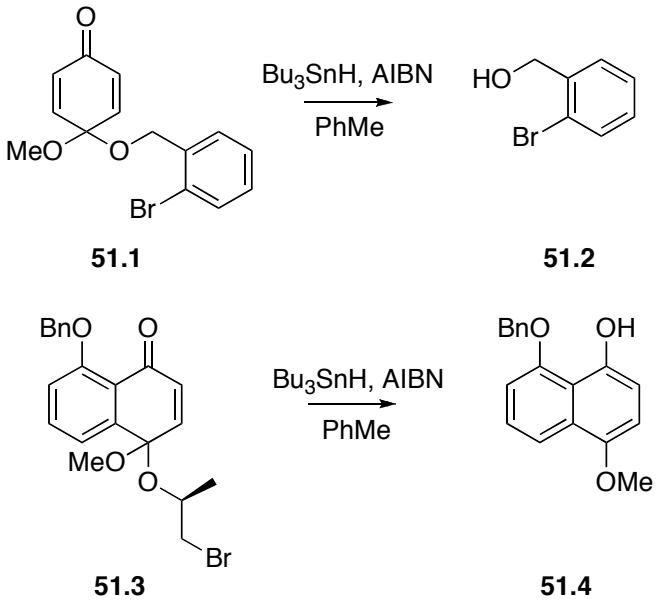


Scheme 50

The oxidations were effectively carried out in the presence of iodo alcohols (**49.3→50.3**, **49.3→50.6**) except with 4-iodobutanol, which preferentially reacted with $PhI(OAc)_2$. Chloro alcohols were satisfactory starting materials, and could be converted into the corresponding iodides by Finkelstein reaction with anhydrous NaI.

1.6.4 Radical Cyclization and Rearomatization of Cross-Conjugated Ketones

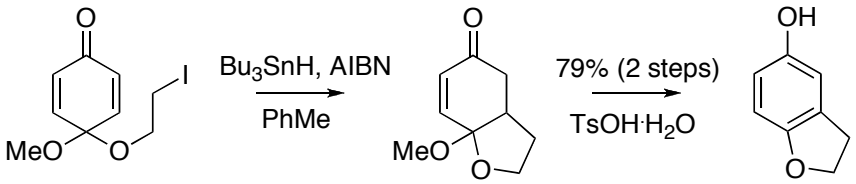
The early studies on radical cyclization of cross-conjugated ketones used standard conditions (slow addition of stannane at 85°C) and yields were generally above 75%. It was necessary to use iodides in these reactions. The use of bromides was examined (Scheme 51) without observing any cyclization products. Preferential reduction of the dienone system was assumed to take place in these cases.



Scheme 51

The ultimate formation of dihydrobenzofuran rings was readily accomplished by acid-catalyzed aromatization (Scheme 52). $TsOH{\cdot}H_2O$ was found to be satisfactory in all cases, but CH_3CO_2H and HCO_2H also yielded the aromatized products. The penultimate α,β-unsaturated radical cyclization product is highly acid labile and $CDCl_3$ and even silica gel caused aromatization in several cases. As yields for the aromatization were generally very high (*ca*. 87%) it was possible to use the crude radical cyclization products directly (**50.3→52.3**)

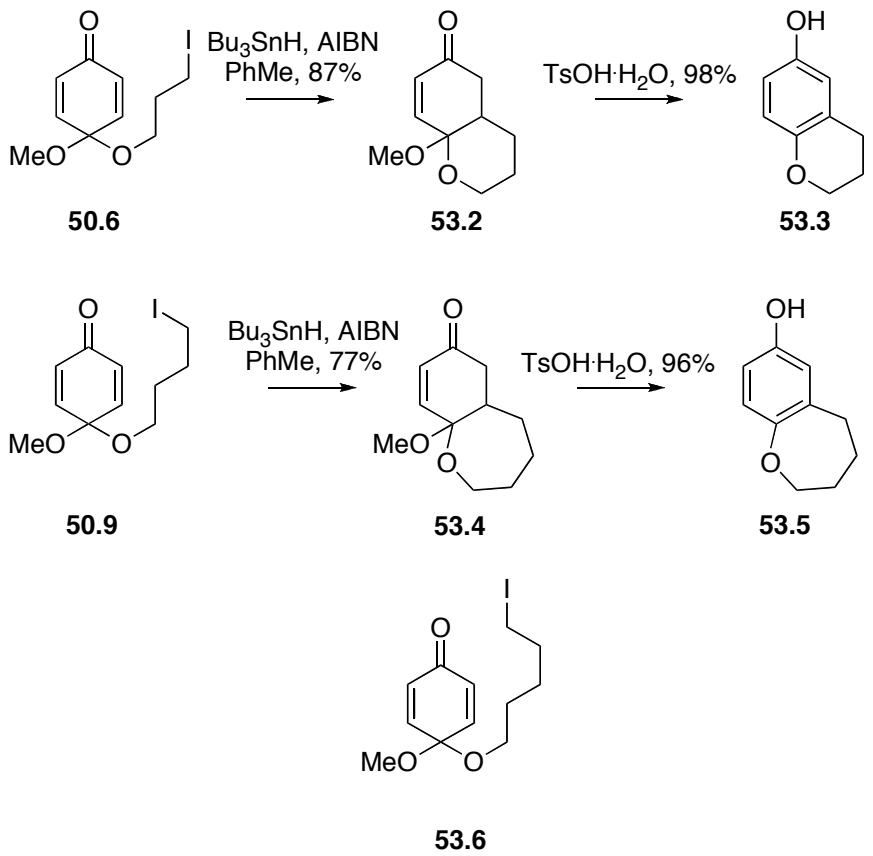
without purification. If pure penultimate products were desired, yields were sometimes slightly reduced by partial aromatization. This can be minimized by keeping these acid-sensitive compounds under mildly basic conditions.



50.3 **52.2** **52.3**

Scheme 52

Radical cyclization also readily allowed access to six- and seven-membered heterocyclic rings and these products were smoothly aromatized, using the aforementioned general conditions (Scheme 53). This is particularly noteworthy since formation of 7-membered rings by radical cyclization can be problematic. The analogous iodide **53.6** failed to undergo radical ring closure to form an 8-membered ring.

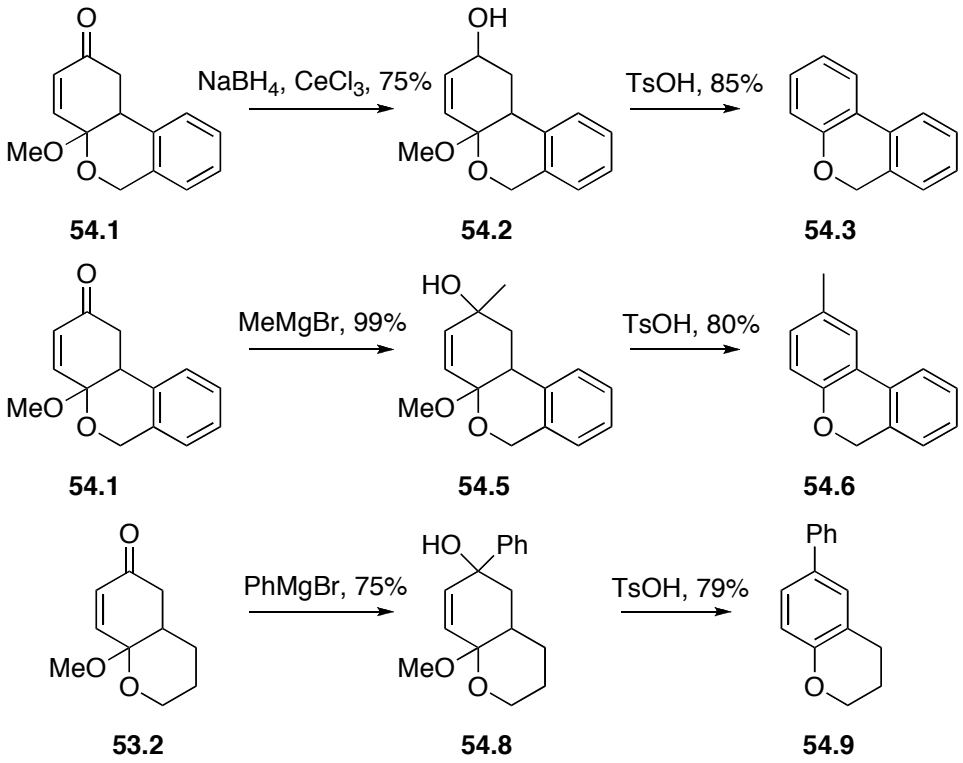


Scheme 53

1.7 Manipulation of the Radical Cyclization Products before Aromatization

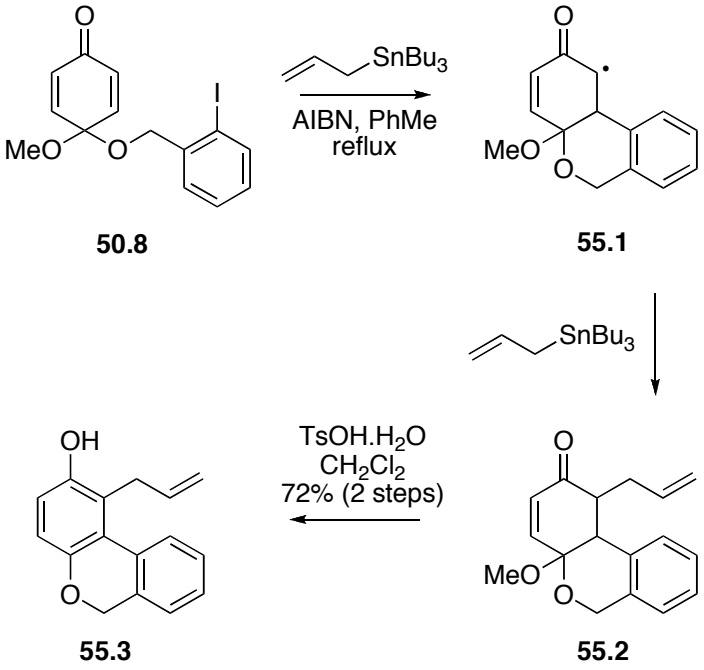
As illustrated above, application of the general radical cyclization/aromatization process to *p*-alkoxyphenols allows easy access to phenols. It can, however, be modified so as to easily form products with hydrogen, alkyl or aryl groups substituting for the phenolic hydroxyl.

If the radical cyclization products are reduced with $NaBH_4$ in the presence of $CeCl_3 \cdot 7H_2O$ (**54.1→54.2**), aromatization of the alcohol that results leads to loss of the hydroxyl group (**54.2→54.3**). A tertiary alcohol is formed when the radical cyclization products are treated with a Grignard reagent (**54.1→54.5**, **53.2→54.8**). Aromatization then yields products that bear an alkyl or aryl group derived from the organometallic nucleophile (**54.5→54.6**, **54.8→54.9**).



Scheme 54

The intermediate radical arising from the closure step can be trapped as well,[58] as seen in the case of iodide **50.8** (Scheme 55). Here **50.8** is heated with AIBN and allyltributyltin, producing radical **55.1** which undergoes Keck allylation, to ultimately give **55.3** after acid-mediated aromatization.

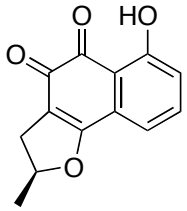


Scheme 55

The aforementioned examples show that the discussed radical cyclization strategy allows effective access to benzo-fused oxygen heterocycles. It also provides access to benzenes with substitution patterns that may not be easily accessible by other methodologies.

1.8 *Natural Product Synthetic Applications: Nocardione A*

Fletcher explored the synthesis of the natural *o*-quinone (-)-nocardione A (**56.1**) using the above methodology.[59] One previous synthesis of the optically pure material had been reported,[60] and it was revealed that the structure is sensitive and readily racemizes at the methyl position. Despite the norcardione A appearing more easily accessible by our method, it was a more demanding test of this strategy than previous examples.



(*S*)-(-)-**56.1**

Scheme 56

The nocardiones also represent useful synthetic targets as they generally posses noteworthy biological properties. They are known inhibitors of cdc25B phosphatases, which control cell cycle progression and regulation. Three cdc25 genes are present in human cells: cdc25A, B, and C. Each of these functions at a specific phase of cell division[61] and acts by removal of phosphate groups from threonine and tyrosine residues that activate cyclin-dependent kinases.[62]

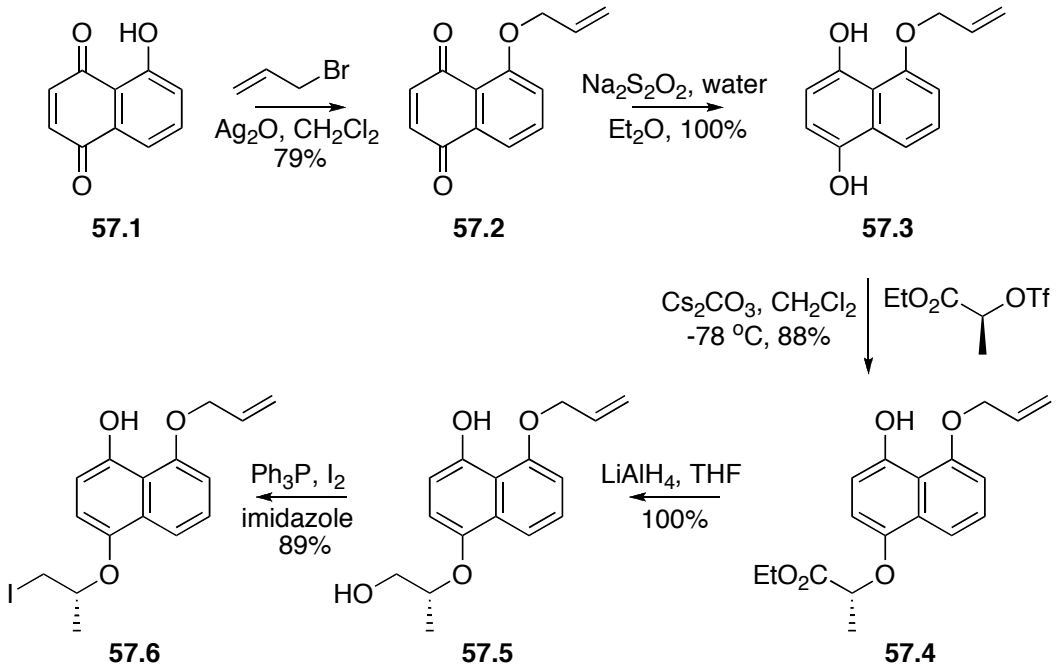
Cdc25B is expressed throughout the cell cycle, with enhanced expression in the G_1–S-phase. Cdc25B has oncogenic properties, and is over-expressed in a many human cancers including colorectal, gastric, lung, ovarian and prostate cancers, as well as non-Hodgkin's lymphoma and some melanomas.[63] Extensive studies have shown that in cancers of the head, neck and breast, there is significantly elevated expression of cdc25B.[64,65] The over-expression of cdc25B in a large fraction of tumors suggests that expression of cdc25 phosphatases may play a significant role in cancer development through its unchecked deregulation.[64] Therefore, the synthesis and study norcardiones is of potential importance to cancer chemotherapy.

1.8.1 Total Synthesis of Nocardione A

Fletcher's approach to norcardione A was to use formal radical cyclization onto a benzene ring to form the delicate dihydrofuran ring (**58.3→58.4**). After this key step, he followed Tanada and Mori's plan[60] but also explored the use of

several protecting groups for the phenolic hydroxyl. Ultimately, he prepared *ent*-nocardione A (**58.6**) in 22% overall yield from readily available juglone.

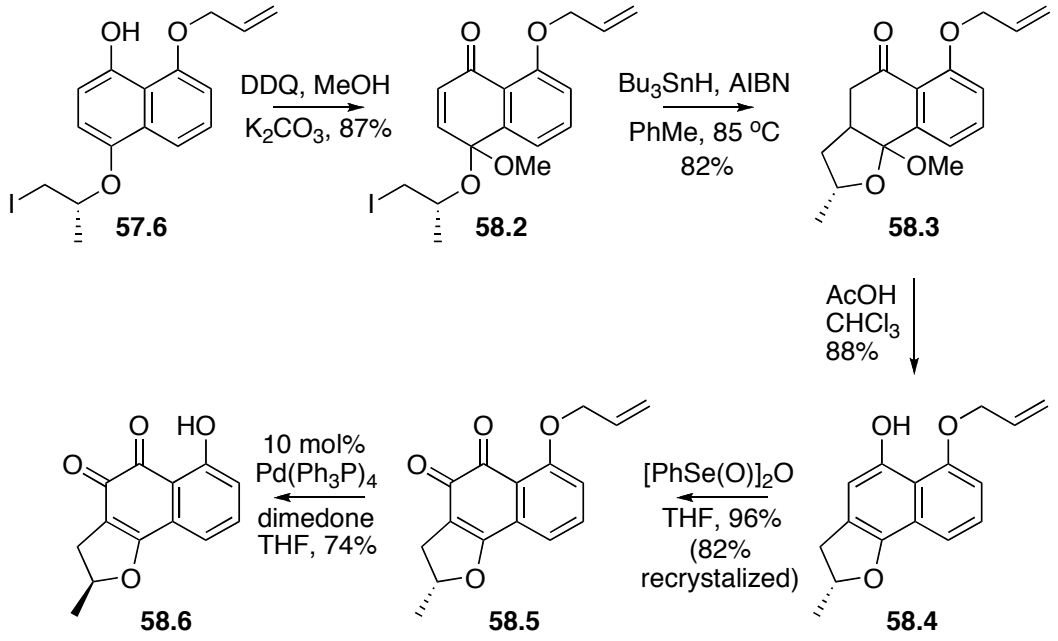
The synthetic route that led to *ent*-nocardione A is summarized in Schemes 57 and 58. The synthesis begins with the readily available natural product juglone (**57.1**), which was then protected as an allyl ether (Ag_2O, allyl bromide, 79%). It was reduced to the hydroquinone oxidation level ($Na_2S_2O_4$) (**57.1→57.3**), which was alkylated using the trifluoromethanesulfonate derived[66] from (-)-ethyl lactate (**57.3→57.4**). Ester **57.4** was reduced (Scheme 57, $LiAlH_4$, 100%, **57.4→57.5**) and then iodide **57.6** was easily obtained by reaction with I_2, Ph_3P and imidazole (89%).



Scheme 57

At this point, oxidation of **57.6** with DDQ in MeOH provided **58.2** (Scheme 58), which was required for the radical cyclization step (87%). Radical cyclization of **58.2** (Scheme 58) by the typical protocol gave the desired product

58.3 in 82% yield. Quantitative aromatization (^{1}H NMR) of **58.3** to **58.4** happened spontaneously upon storing the cyclization product in (mildly acidic) $CDCl_3$. Intentional rearomatization (**58.3→58.4**) was easily achieved by using AcOH in $CHCl_3$ at room temperature (88%). Naphthol **58.4** was oxidized (96%) to the *o*-quinone **58.5** using $[PhSe(O)]_2O$ in the same fashion as in Mori's synthesis.[60] The quinone was recrystallized and treated with $(Ph_3P)_4Pd$ and dimedone to remove the allyl protecting group and provide *ent*-nocardione A (**58.6**, 74%).



Scheme 58

Using oxidative radical cyclization to construct a substituted aromatic system allowed for construction of *ent*-nocardione A **58.6** in an overall yield of 22% from juglone (**57.1**). This is approximately ten times the yield of Mori's synthesis, showing that the radical cyclization procedure can overcome the limitations of previously established methods in constructing substituted benzo-fused dihydrofuran rings.

1.9 Formation of Benzo-Fused Nitrogen Heterocycles

The processes described previously allow the formation of benzo-fused oxygen heterocycles. As many biologically active molecules contain benzo-fused nitrogen heterocycles, easy access to these structures would be very useful and so the extension of Fletcher's method to the formation of dihydrindoles and their analogues appeared especially worthwhile. What follows is the initial synthetic studies by Fletcher that allowed for extension of the original general method (*cf.* Scheme 48) to saturated nitrogen-containing benzo-fused heterocycles.

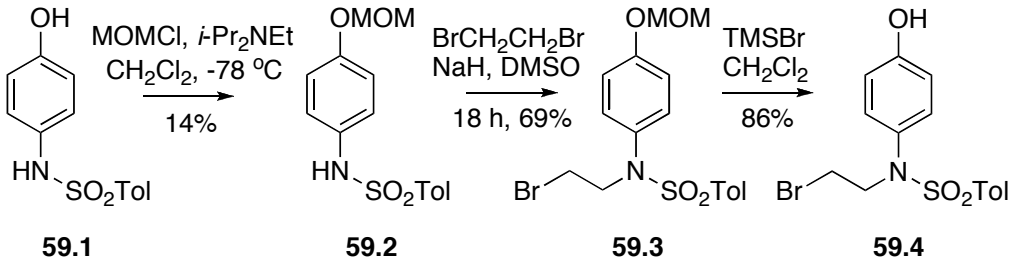
1.9.1 Synthetic Overview

Unlike the above oxidations, which feature phenols with oxygen-containing chains (Scheme 48, X = O, **48.1→48.2**), the analogous oxidation when X is nitrogen had not been previously well-studied. As nitrogen is trivalent, it meant that X would have an extra substituent, probably in the form of a protecting group, and so a practical synthetic route to **48.1** (with free phenol, X = NR, and Z = I) needed to be established.

1.9.2 Establishing Routes to p-Amino Phenols

The primary concern was formation of a phenolic aniline that carried an alkyl chain with a terminal halogen. The alkylation was achieved when a tosyl-protected amine starting material was used. Selective protection of the phenol moiety of **59.1** gave **59.2** in low yield, and the compound was then alkylated with 1,2-dibromoethane (**59.2→59.3**). After removal of the MOM protecting group, the oxidation precursor **59.4** was treated with $PhI(OAc)_2$, K_2CO_3, MeOH but no oxidation product was formed. When DDQ in MeOH was employed, as seen previously in the nocardione A synthesis, there was also no formation of the desired product. The use of other oxidizing agents such as CAN, $Tl(NO_3)_3$, or

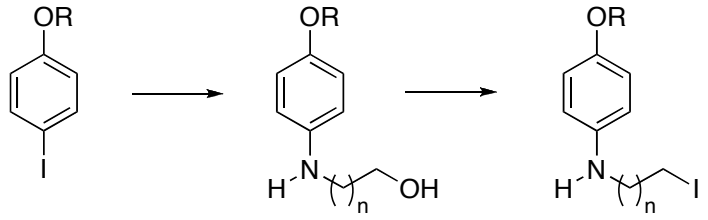
$Pb(OAc)_4$ was also unsuccessful. The formation of cross-conjugated ketones in this series appears to require protecting groups other than sulfonates.



59.1 **59.2** **59.3** **59.4**

Scheme 59

It also appeared that a general procedure based on the alkylation of a preexisting aniline nitrogen was likely to be problematic. Fletcher instead surveyed several synthetic routes towards **48.1** (X = N) and eventually settled on that shown in Scheme 60. An advantage of this approach was that the amine and/or aryl iodide could be manipulated before the coupling step. One could also make use of natural amino acids and their derivatives, which could be readily turned into enantiomerically pure amino alcohol building blocks useful for coupling.



60.1 **60.2** **60.3**

Scheme 60

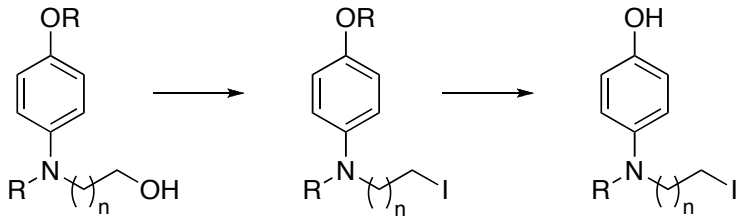
In order to implement the sequence shown in Scheme 60, several copper-mediated coupling procedures were explored. Ma's method,[67] which uses amino

acids as ligands, was found to be particularly suitable. When these conditions were used, the coupling of amino alcohols that were *unprotected* with *O*-protected *p*-iodophenols occurred very well. The compatibility of this coupling procedure with unprotected alcohols — a quality that is clearly very useful — is shown below (Scheme 62). The presence of the free hydroxyl appears to help the cross-coupling reaction while later acting as a useful handle for further modification. Amino alcohols also generally allowed the reaction to proceed at lower temperatures and frequently required shorter reaction times. It is plausible that this is due to the lone pair on the oxygen atom causing the amino alcohol to behave like a bidentate chelator to the metal catalyst. This should facilitate coupling once oxidative addition of copper to the C-I bond has occurred. The yields of these coupling reactions were comparable to the yields reported for unfunctionalized examples from Ma's studies.[67]

When reactions are done on a small scale (*ca.* <1 g of aryl iodide) the above coupling procedure seems to work most effectively at a concentration of 1.0 M or less for the aryl iodide. When higher dilutions are used, sluggish reactions and depressed yields were observed. If these reactions are done on scales using more than 1.0 g of aryl iodide, higher dilutions (*ca.* 0.5-0.75 M) are necessary to maintain reasonable yields. It was also found in several cases that the pendant iodide could be formed before or after protection of the amine nitrogen (*cf.* Scheme 60), a feature that confers additional flexibility to the procedure.

When MOM ethers are used for protection of the phenol, Me_3SiBr readily removed the protecting group. Although Scheme 61 outlines reactions where protected iodophenols are converted to *p*-aminoiodophenols (**61.2→61.3**), procedures were also developed that do not require phenol protection, and

secondary amides have been used instead of amines in order to shorten the overall route.[56]



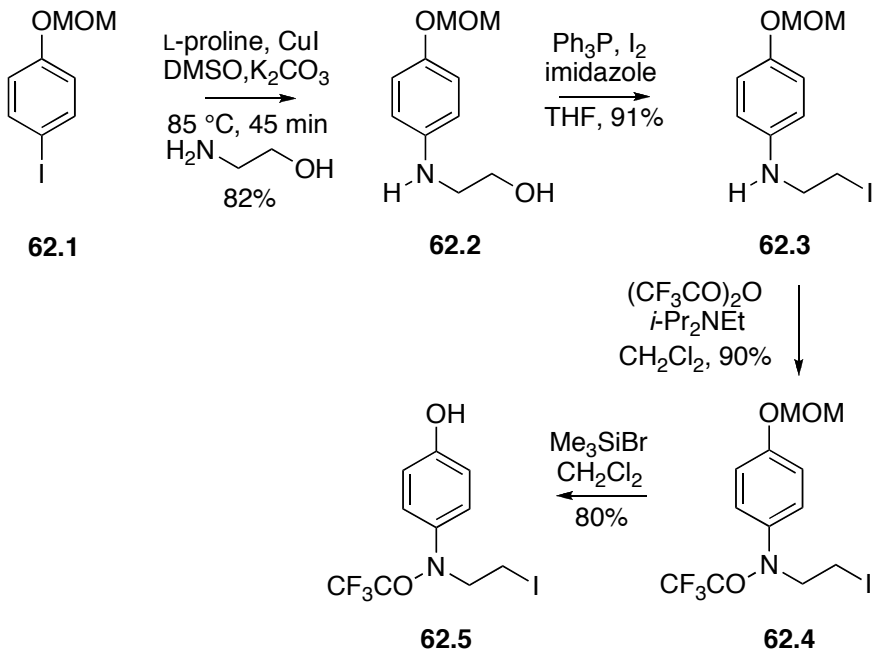
61.1 **61.2** **61.3**

Scheme 61

1.9.3 The First Generation Studies by Fletcher

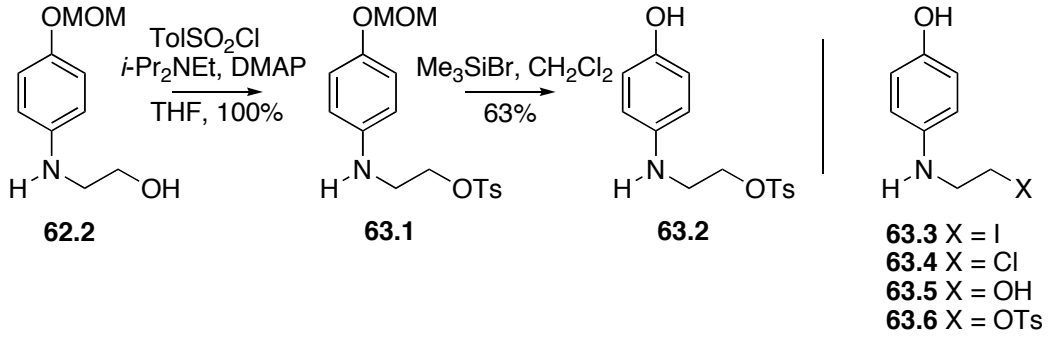
1.9.3.1 p-Amino Phenol Preparation

Ma's procedure was used to prepare substrates to examine the oxidation process by cross coupling 2-aminoethanol with **62.1**.[67] The resultant product was formed rapidly (less than 1 hour) at 85 °C, providing **62.2** in 82% yield. The iodide was formed using a standard protocol (**62.3**, 91%) and the nitrogen, which could potentially displace the iodide of **62.3**, was promptly protected (**62.4**, 90%). Iodide **62.4** can be deprotected to give **62.5** with Me_3SiCl (80%); treatment with BBr_3 was also effective (74% yield).



Scheme 62

It was discovered that the phenolic hydroxyl group of **62.3** must be protected; the free phenol analogue of **62.3** could not be isolated in a separate experiment. When **62.3** and its chloro analogue were deprotected with Me_3SiBr by Fletcher with hopes to form **63.3** or **63.4**, respectively (Scheme 63), decomposition products were formed. Only when the amine is protected, can the phenolic oxygen be unmasked (*cf.* **62.4→62.5**).

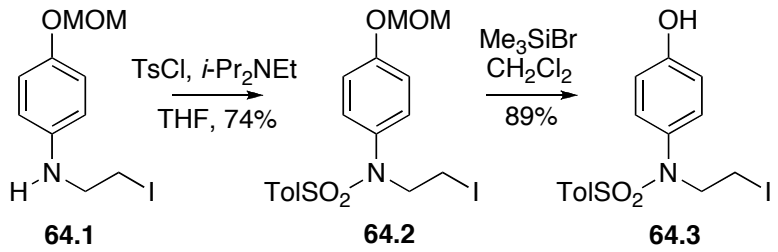


Scheme 63

1.9.3.2 *Oxidation of p-Amino Phenols*

The oxidation to form the cross-conjugated ketones **48.2** (X = NR) was then investigated. While oxidations of the type **48.1→48.2**, where X is oxygen, have been reported, there were far fewer examples featuring nitrogen in place of oxygen. These examples were found in synthetic work of Myers and Danishefsky on the formation of the dynemicin A chromophore.[68]

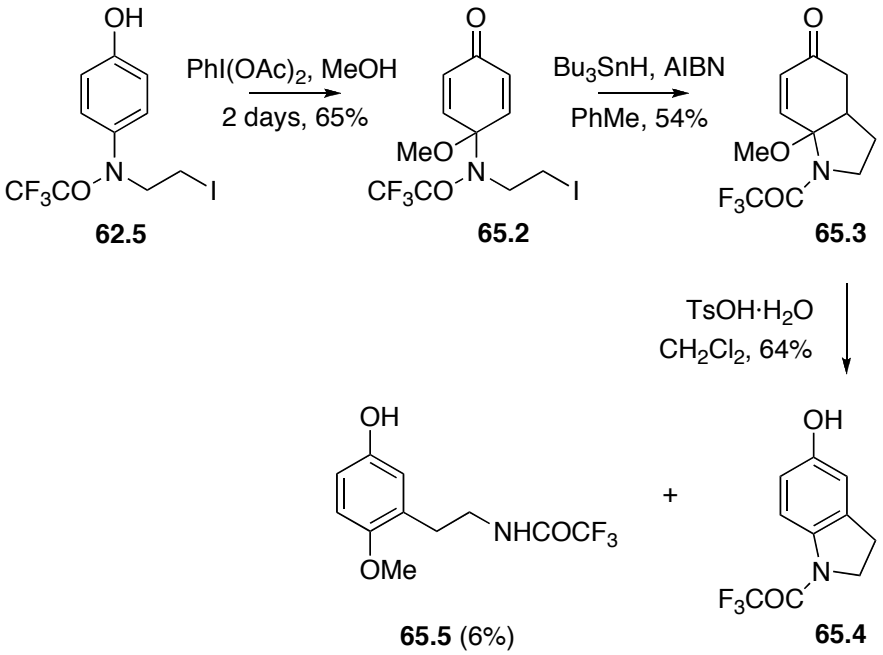
Although the oxidation of *N*-tosyl bromide **59.4**, shown previously, was unsuccessful, oxidation of the *N*-tosyl iodide **64.3** (Scheme 64), was attempted. When $PhI(OAc)_2$ was used in the absence of base, **64.3** was not oxidized. When the more powerful oxidizing agent $PhI(OCOCF_3)_2$ was used, starting material was recovered.



64.1 **64.2** **64.3**

Scheme 64

The *N*-trifluoroacetoxy protected phenol (**62.5**) series was then investigated. In the absence of base, oxidation was found to proceed slowly (48 hours) using $PhI(OAc)_2$ in MeOH, providing a 65% yield (Scheme 65). Use of $PhI(OCOCF_3)_2$ gave the same product over a much shorter period (30 min) but provided **65.2** in only 53% yield.



Scheme 65

1.9.3.3 *Radical Cyclization and Aromatization*

Radical cyclization of **65.2→65.3**, using tributyltin hydride and AIBN, appeared to work, but provided only a 54% yield after multiple flash chromatography to remove tin byproducts. The process of aromatization can theoretically proceed in two ways, depending on whether the methoxy group (**48.4→48.5**, Scheme 48) or the amino unit (**48.4→48.6**) is expelled. When **65.3** is rearomatized using catalytic TsOH·H_2O, bicycle **65.4** was the major product (64% yield). The minor uncyclized product was **65.5** (6% yield). Complete selectivity for the desired rearomatized **65.4** was only observed when 4Å molecular sieves were used along with the acid.

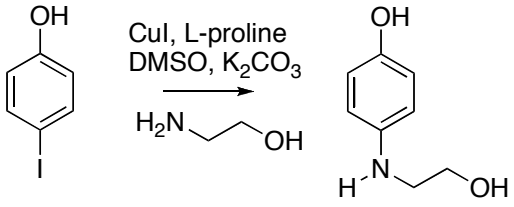
Due to the various problems encountered while using the trifluoroacetoxy protecting group (e.g. moderate yields, sluggish reactions), Fletcher decided to investigate other methods of *N*-group protection.

1.9.4 Second Generation Studies

Carbamate protection of nitrogen was then explored, as reported in the aminophenol oxidations by Myers and Danishefsky. Carbamates can be formed even when a hydroxyl group is present and so the formation of unstable iodoamines (*cf*. **62.3**) can be avoided. Under these conditions, Ma's procedure[67] was also attempted with both unprotected amino alcohols and iodophenols (i.e. phenolic oxygen unprotected, e.g. **66.1**).

1.9.4.1 Cross-Coupling to Form unprotected Amino(hydroxyalkyl) Phenols and subsequent Manipulation

In the reaction **66.1→66.2** (Scheme 66), Fletcher was able to achieve an 81% yield of the coupled product when 5 equivalents of the (inexpensive) amine were used at mild temperature (3 h at 55 °C). Exploratory work had shown that keeping the reaction temperature below 60 °C inhibited formation of byproducts.

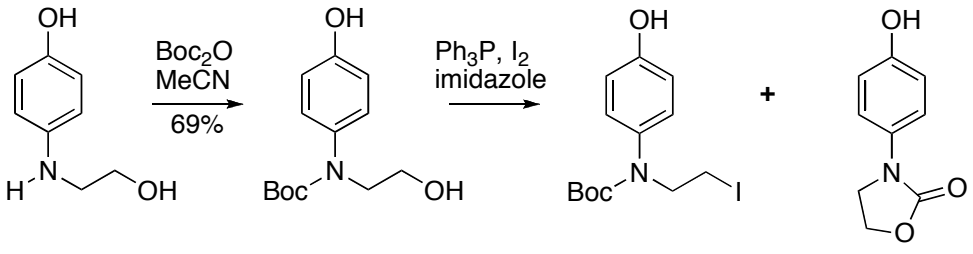


66.1 **66.2**

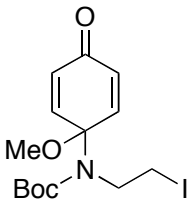
Scheme 66

Use of the Boc group was first investigated, where treatment of **66.2** with Boc_2O in MeCN gave **67.2** in moderate yield (69%). When the iodide was formed by the usual procedure, the yield was low (28%) and the major product was the undesired cyclic carbonate **67.4**. Clearly, the Boc group participated in the iodination reaction involving Ph_3P and I_2, resulting in the undesired bicycle.

It was also found that when the minor product **67.3** was placed under oxidizing conditions, **67.5** was not formed.



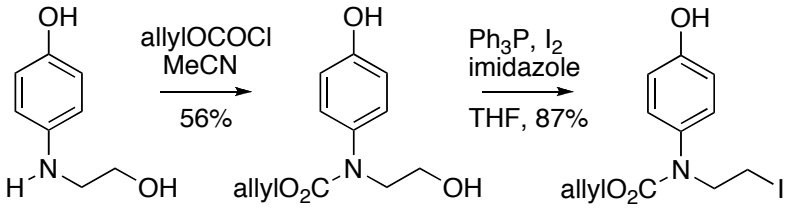
66.2 **67.2** **67.3** (28%) **67.4**



67.5

Scheme 67

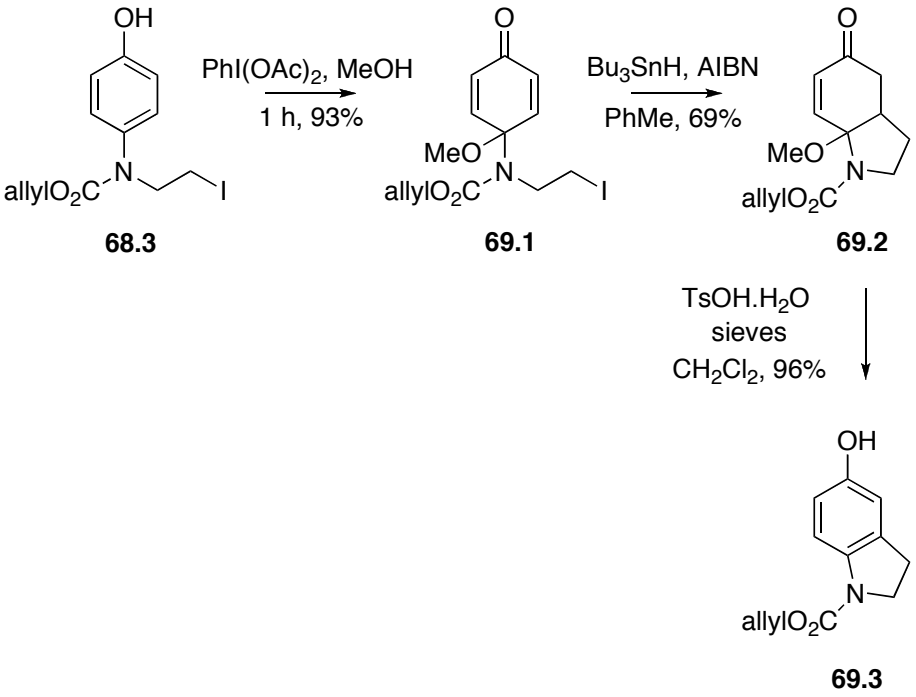
The alloc group was also used for formation of **68.2** but proved to be less selective than desired (**66.2→68.2**) and provided a moderate yield by addition of allyl chloroformate to the starting material in CH_3CN (56%). Formation of iodide **68.3** was high-yielding if an excess of the reagents (2.5 equiv.) was used.



66.2 **68.2** **68.3**

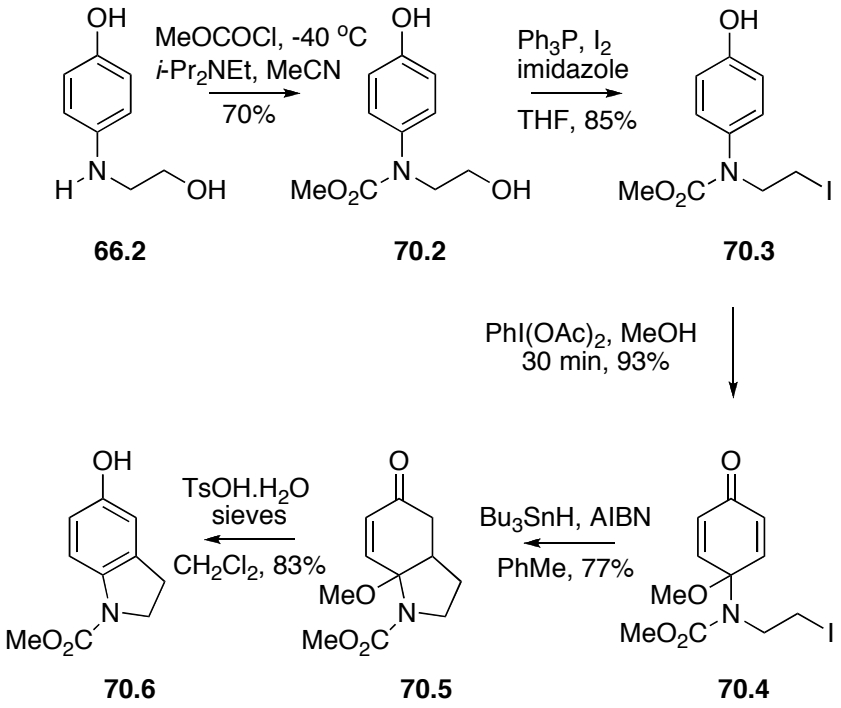
Scheme 68

The transformation **68.3→69.1** was efficient using $PhI(OAc)_2$ (1 h, 93%) and the product is readily converted into the desired aromatic phenol (**69.3**) (Scheme 69). The radical cyclization step (**69.1→69.2**, 69%) and rearomatization (**69.2→69.3**, 96%) were easily achieved.



Scheme 69

Methyl carbamates were also found to be useful for *N*-protection (Scheme 70) and the conversion **66.2→70.2** was achieved when MeOCOCl and base are added sequentially in portions. For best results, 0.6 equiv. of methyl chloroformate is added to **66.2** at -40 °C, followed by a brief (30 min) warming period to 0 °C, then addition of base (0.6 equiv.) and addition of another portion of the chloroformate (-40 °C). Formation of iodide **70.3** followed by oxidation, radical cyclization, and rearomatization steps (**70.3→70.6**) using the established procedure worked very effectively.

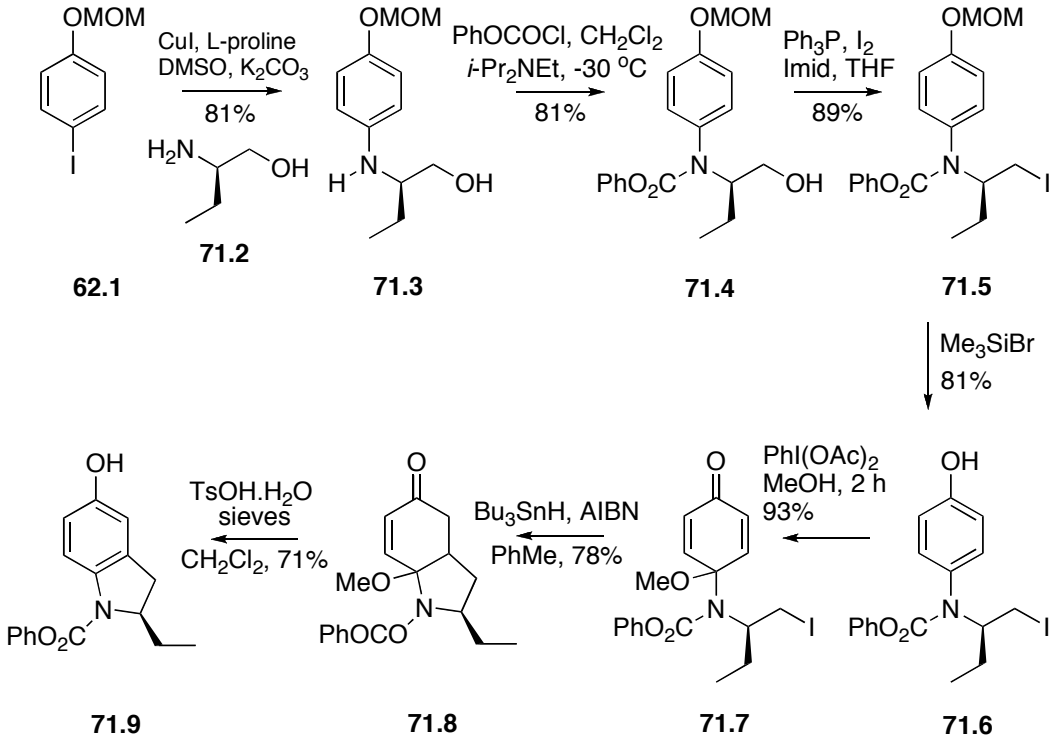


Scheme 70

1.9.5 Substituted Dihydroindole Synthesis

Amines with substituents can be used in place of 2-aminoethanol. It is desirable to first protect the iodophenol with a MOM group in these cases. Coupling of protected iodophenol **62.1** with 2-aminobutanol (**71.2**) to form **71.3** proceeds readily (81% yield) when the reaction mixture is heated (80 °C) for longer periods of time (14 h) (Scheme 71). Unfortunately, with increased steric bulk next to the nitrogen, the following conversion of the amino alcohol **71.3** to the *N*-protected iodo species is less straightforward. The protection of the nitrogen is best done before iodination, to avoid formation of undesirable side-products. Protection of **71.3** as a phenyl carbamate (**71.3→71.4**) occurred smoothly (81%) and iodination of **71.4** using the standard method provided **71.5** in good yield (89%). Phenol **71.6** was obtained by MOM-deprotection using Me_3SiBr (81%). The following oxidation of **71.6** occurred readily, but isolation

of the product **71.7** was difficult due to decomposition when the solution was concentrated to dryness. Concentration and/or prolonged storage of oxidation product **71.7** and its analogs is to be avoided, as the material should be used immediately after isolation to minimize decomposition. Radical cyclization of **71.7** yielded a stable ketone **71.8** (78%) that was then aromatized to **71.9** (71%).

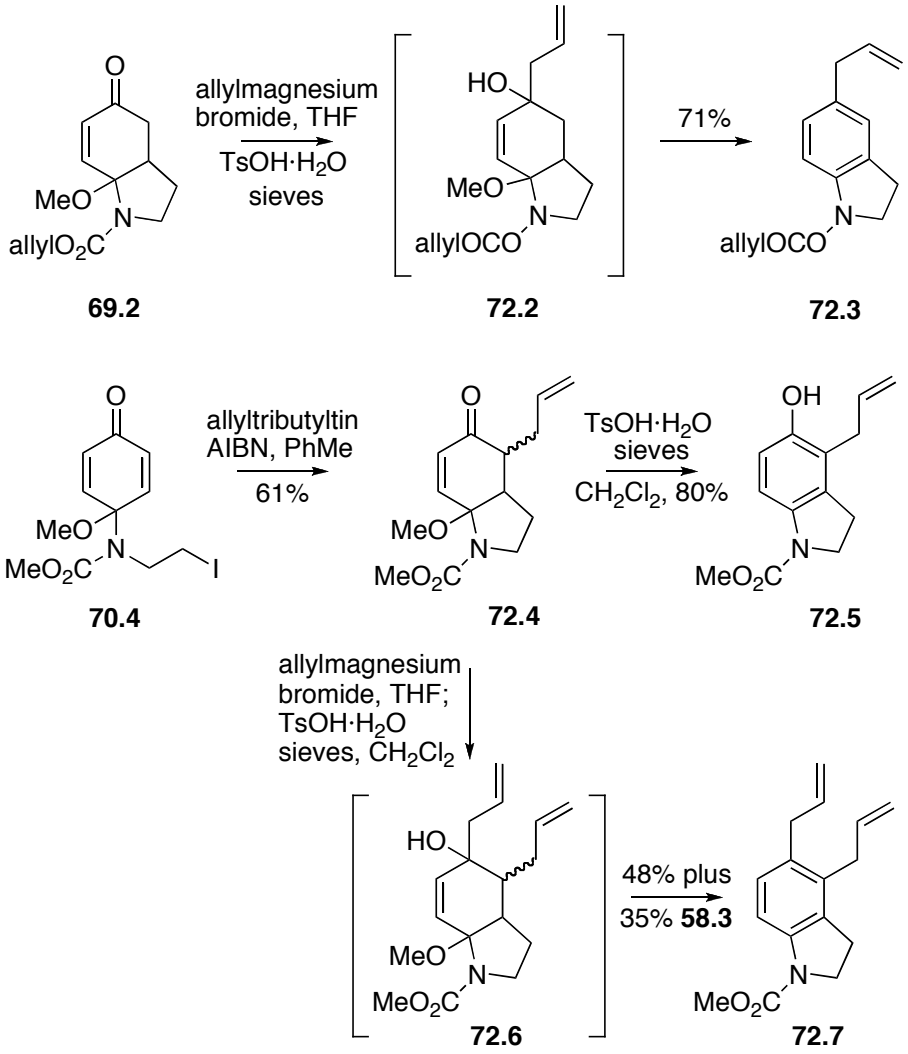


Scheme 71

1.9.6 Radical Cyclization Product Manipulation before Aromatization

Fletcher expanded the method so that it can accommodate the generation of compounds carrying carbon substituents instead of the phenolic hydroxyl group (see Scheme 72, **69.2→72.3**). The intermediate radical arising from the radical closure step can also be trapped, leading to 1,2,3,4-tetrasubstituted products such as **72.5** and **72.7** from iodide **70.4** (Scheme 72). Keck allylation occurs when the iodide **70.4** is exposed to standard free radical conditions in the presence of

allyltributyltin and gave **72.4** in moderate yield (61%); the following aromatization reaction to form **72.5** went efficiently (80%).



Scheme 72

Modifications involving not only intermediate radical interception but also the use of a Grignard reagent, can also be applied to the same starting iodide (Scheme 72, **70.4→72.5** and **72.7**). Processes like this provide products that can be even further elaborated.

2 RESULTS AND DISCUSSION

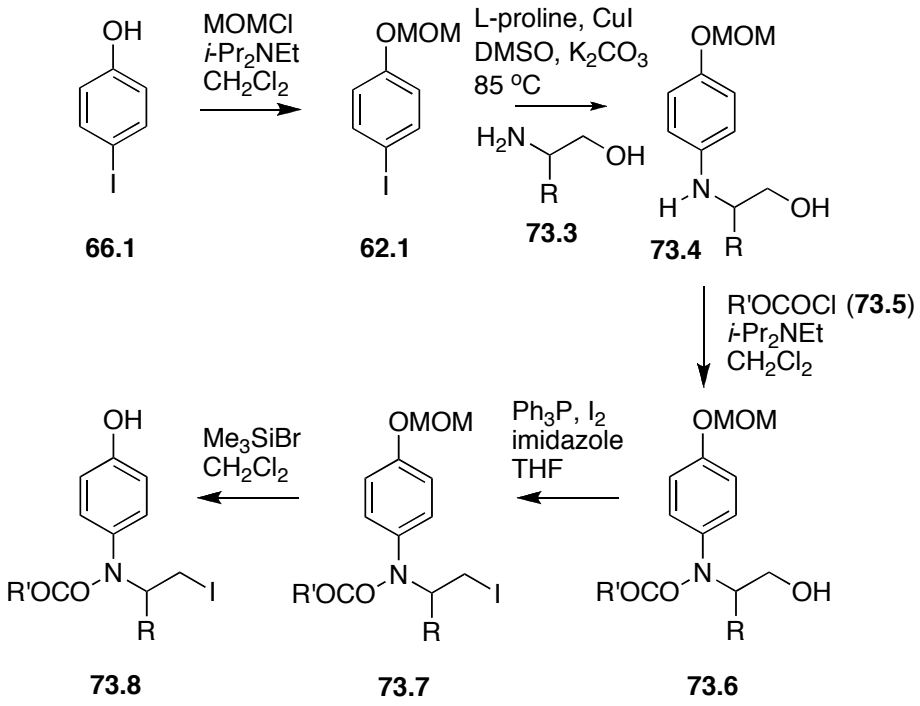
2.1 *Objectives*

The work of Fletcher *et al.*[1a,b] was expanded and improved in our study of the formation of benzo-fused nitrogen heterocycles. Several new complete examples were carried out and generally featured modification of the alkyl substituent on the non-aromatic carbon α to the nitrogen and/or use of a different *N*-protecting group. In some cases, higher quality spectral data of the initial compounds were required due to the presence of impurities and other spurious signals in the original traces, and/or yields needed to be raised. These improved results were then published.[1d] As this work was the result of additional experiments from the initial starting materials, these results are also discussed, despite being initially investigated by Fletcher.

2.2 *Formation of Benzo-fused 5-Membered N-Heterocycles: Overview*

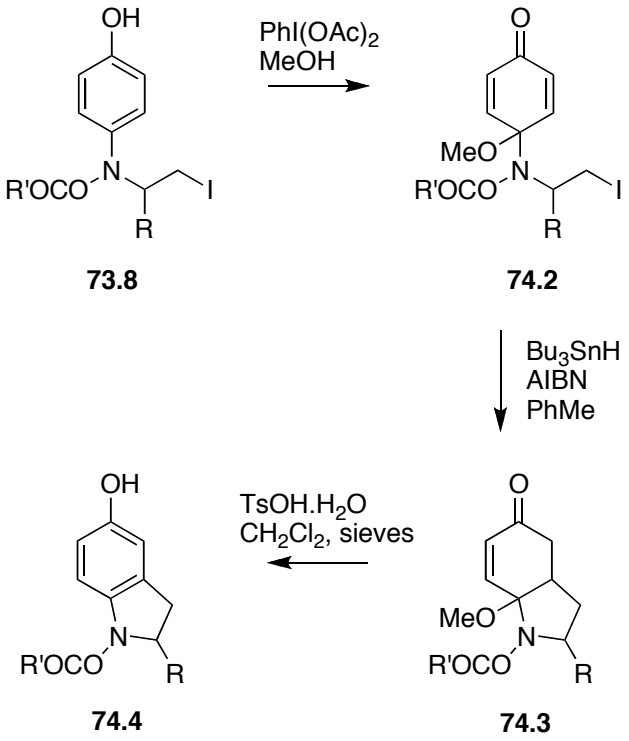
Further examples of benzo-fused 5-membered *N*-heterocyclic compounds were formed based on the prior protocol.[1] An amino alcohol **73.3** (R = H or aliphatic group) was first coupled to the protected iodophenol **62.1** by a modified version of Ma's copper-mediated method[66] to provide aromatic amino alcohol **73.4** (Scheme 73). This secondary amine was then protected using methyl-, allyl- or phenyl chloroformate (**73.5**, R' = Me, allyl, Ph) in the presence of Hünig's base, to provide the requisite carbamate **73.6**, which was then converted into the corresponding iodide **73.7** in the standard way. The MOM protecting group was

then removed using trimethylsilyl bromide to provide the unprotected, elaborated phenol **73.8**.



Scheme 73

Phenols **73.8** (R' = Me, allyl, Ph) were oxidized to **74.2** using phenyliodo diacetate in methanol (Scheme 74). Radical cyclization to enone **74.3** was then carried out under standard conditions, and subsequent exposure to $TsOH \cdot H_2O$ provided the desired aromatized phenols **74.4**. In some cases these three final steps were done without extensive purification of the intermediates due the unstable nature of **74.2** and **74.3** and the yield was calculated after the final product **74.4** was formed.



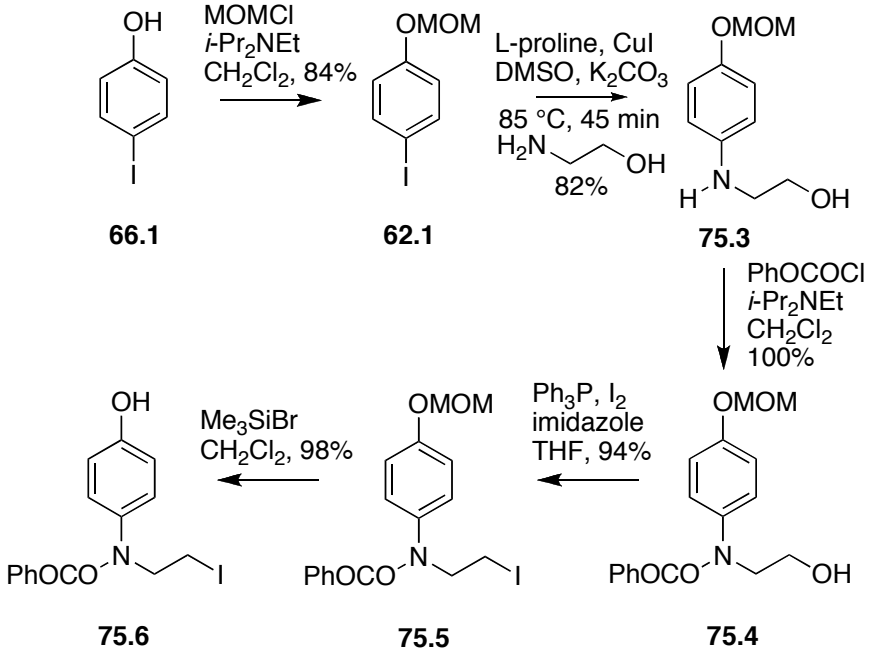
Scheme 74

Apart from using various *N*-protecting groups (R' = Me, allyl, Ph) and altering the R-group α to the nitrogen, manipulation of **74.3** was also carried out before aromatization, to give a phenyl ring carrying hydrogen instead of hydroxyl (see Section 2.6).

2.3 Synthesis of Simple Dihydroindoles

Unsubstituted dihydroindole **76.4** (*cf.* Scheme 76) was formed (Schemes 75 and 76) by first coupling 2-aminoethanol to MOM-protected **66.1**, using the standard copper-mediated procedure which provided a high yield (82%) for joining the two relatively unhindered units (Scheme 75). Protection of the resulting amine **75.3** to form **75.4** occurred quantitatively, and iodination

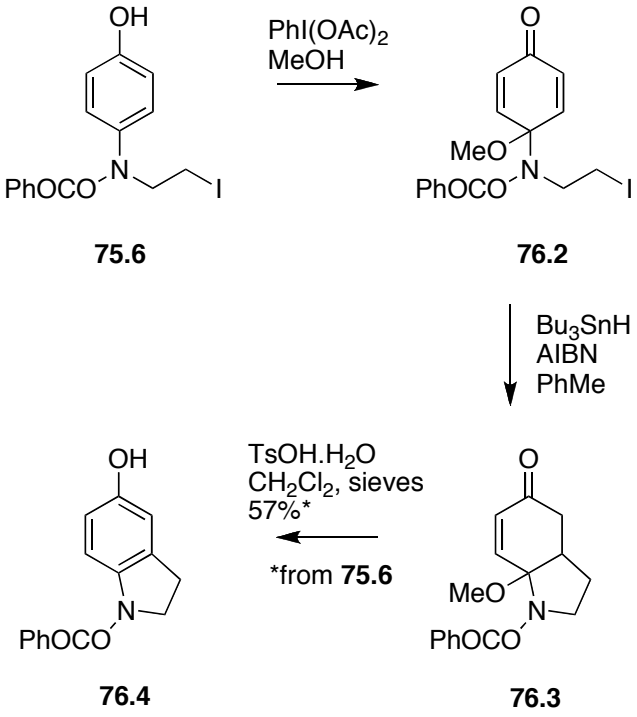
(**75.4**→**75.5**) and MOM-deprotection (**75.5**→**75.6**) occurred in the expected high yields.



Scheme 75

Phenol **75.6** was oxidized to **76.2** using phenyliodo diacetate in methanol. As **76.2** decomposes upon concentration of its solutions, its yield was not calculated, despite being purified by flash chromatography. After purification, the selected fractions were evaporated to *near-dryness*. At this point, dry PhMe was added and evaporated to *near-dryness* and the process was repeated at least three times to drive off residual chromatography eluent. Finally, the volume of dry PhMe needed for the radical cyclization reaction was added and the cyclization was carried out using the standard method to form **76.3**. This process of repetitive evaporation of PhMe was use for all the following examples. The radical cyclization product **76.3** was purified by flash chromatography using 10%

finely ground KF/90% silica gel to remove residual tin byproducts. As **76.3** had partially aromatized to **76.4** in the presence of the mildly acidic silica, fractions containing both products were combined, evaporated, and subjected to the action of $TsOH \cdot H_2O$ to provide **76.4** in 57% yield (over three steps).

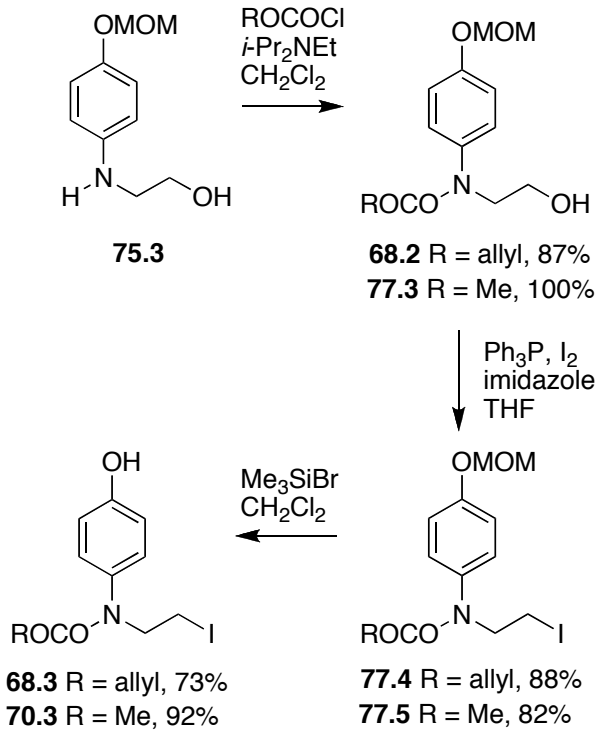


Scheme 76

Analogs of α-unsubstituted dihydroindole **76.4** featuring different carbamate protection groups were also generated. These experiments were carried out for the purpose of improving Fletcher's yields and/or the quality of his spectra.

Allyl carbamate-protected amine **68.2** was formed from **75.3** in good yield using allyl chloroformate (87%) (Scheme 77). Subsequent iodination to form **77.4** similarly went without incident (88%), and MOM-deprotection of **77.4** with Me_3SiBr gave **68.3** (73%). Methyl carbamate-protected amine **77.3** was also

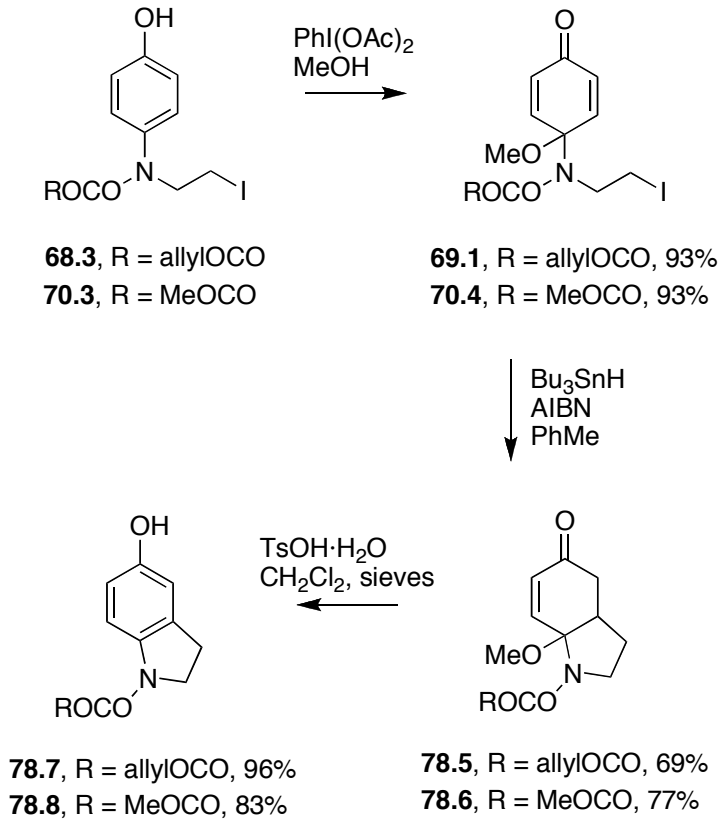
formed from **75.3**, using MeOCOCl, and the yield was quantitative. Iodination (**77.3**→**77.5**, 82%) and MOM-deprotection (**77.5**→**70.3**, 92%) were carried out without incident.



Scheme 77

Compounds **68.3** and **70.3** were both oxidized using the standard method to form **69.1** and **70.4**, respectively, both in 93% yield. In each case, the oxidation products were isolable and their solutions could be concentrated for a short period while their purity and yields were being assessed. Radical cyclization of **69.1** provided the allyl carbamate-protected enone **78.5** (69%), which could be purified without significant aromatization into **78.7**. Exposure of **78.5** to mild acid provided the desired phenol **78.7** in 96% yield. Likewise, radical cyclization of **70.4** under standard conditions, provided isolable enone

78.6 in 77% yield. Exposure to mild acid provided phenol **78.8** in good yield (83%).



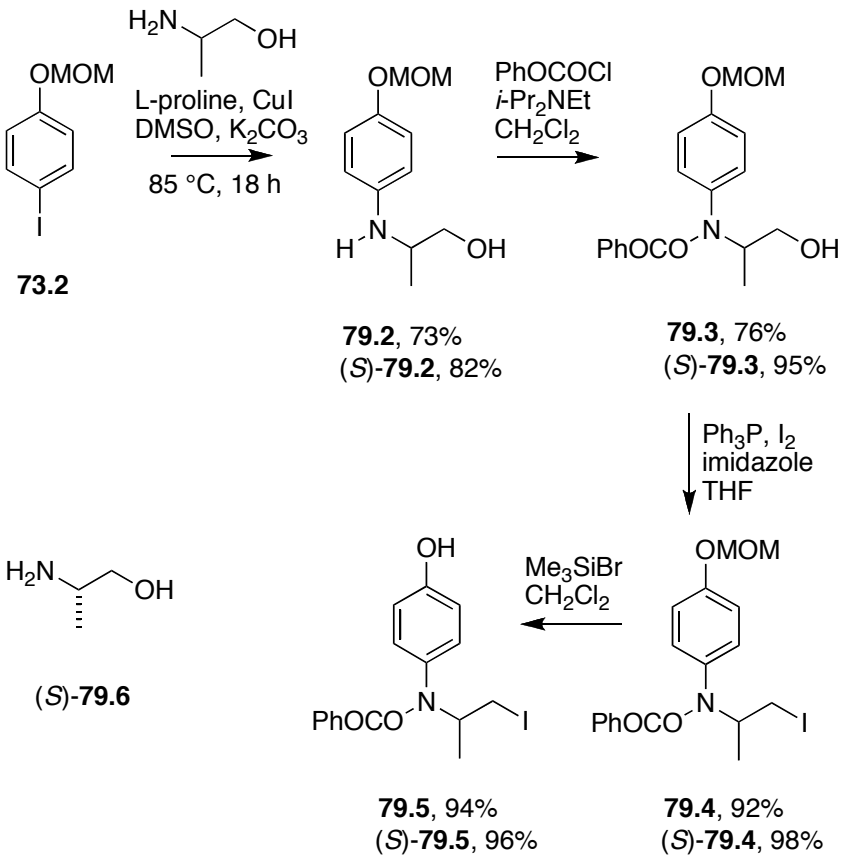
Scheme 78

2.4 *Synthesis of Substituted Dihydroindoles*

The formation of dihydroindoles with simple alkyl substituents α to the benzo-fused nitrogen was achieved by coupling several substituted amino alcohols to protected iodophenol **62.1**. As will be described, it is possible to add a number of different substituents at this position, but steric factors impose limitations once attempts are made to install isopropyl or *tert*-butyl groups. In the former case, the bulk of the isopropyl group inhibits protection of the nitrogen and complicates the sequence of surrounding reaction steps (see Scheme 85). In the latter case, the *tert*-butyl substituted amino alcohol is very difficult to install at the

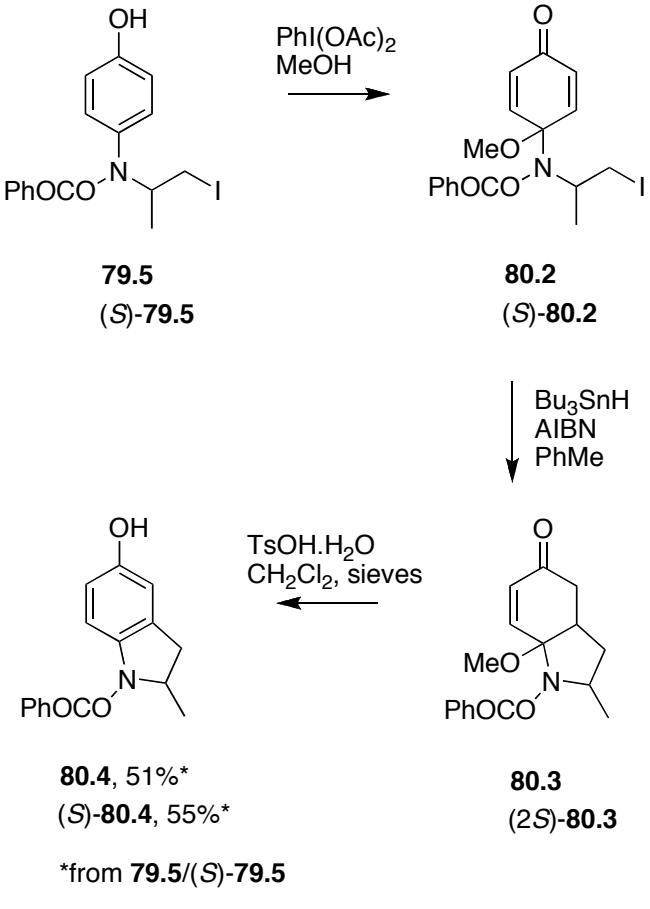
initial coupling stage, leading to the need for forcing conditions and low yields (see Scheme 87). Subsequent protection of the nitrogen was not possible, however.

In the simplest case, racemic 2-aminopropanol was coupled to **62.1** (to eventually give final product **80.4**, Scheme 80). The coupled product was then protected with PhOCOCl to provide **79.3** (76%), and this was iodinated using the standard procedure (**79.4**, 92%) and MOM-deprotected using Me_3SiBr (**79.5**, 94%). Similarly, satisfactory yields were achieved when optically pure amino alcohol (*S*)-**79.2** was used in the initial coupling procedure, to eventually give intermediate iodophenol (*S*)-**79.5**. Amino alcohol (*S*)-**79.6** was easily obtained via the reduction of the carboxylic acid group of alanine to the requisite alcohol.



Scheme 79

The carbamate-protected iodophenols **79.5** and (*S*)-**79.5** were then oxidized with $PhI(OAc)_2$, using the usual conditions, to provide intermediates **80.2** and (*S*)-**80.2**, respectively, whose solutions were not concentrated to dryness after chromatographic purification. Exposure to radical cyclization conditions then provided enones **80.3** and (2*S*)-**80.3**, respectively, which were purified using 10% finely ground KF/90% silica gel to remove tin byproducts. Due to partial decomposition into the aromatized final products, yields for the aforementioned compounds were not calculated. Exposure of the readily aromatized **80.3** and (2*S*)-**80.3** to acidic conditions ultimately provided phenols **80.4** and (*S*)-**80.4** in good overall (three-steps) yields (51% and 55%, respectively).



79.5
(*S*)-**79.5**

80.2
(*S*)-**80.2**

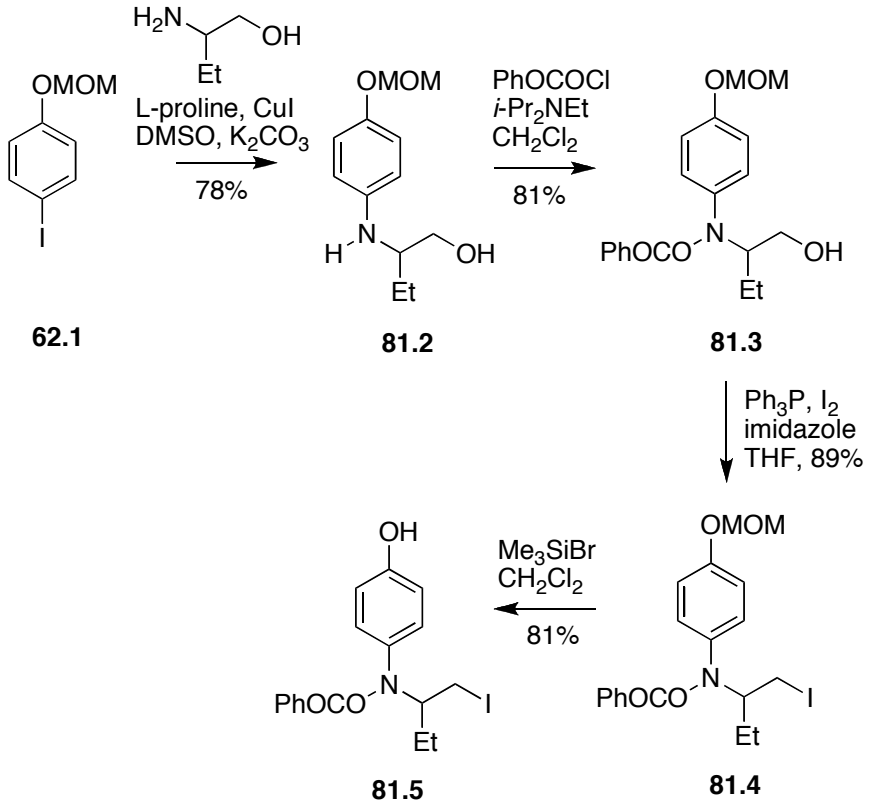
80.4, 51%*
(*S*)-**80.4**, 55%*

*from **79.5**/(*S*)-**79.5**

80.3
(2*S*)-**80.3**

Scheme 80

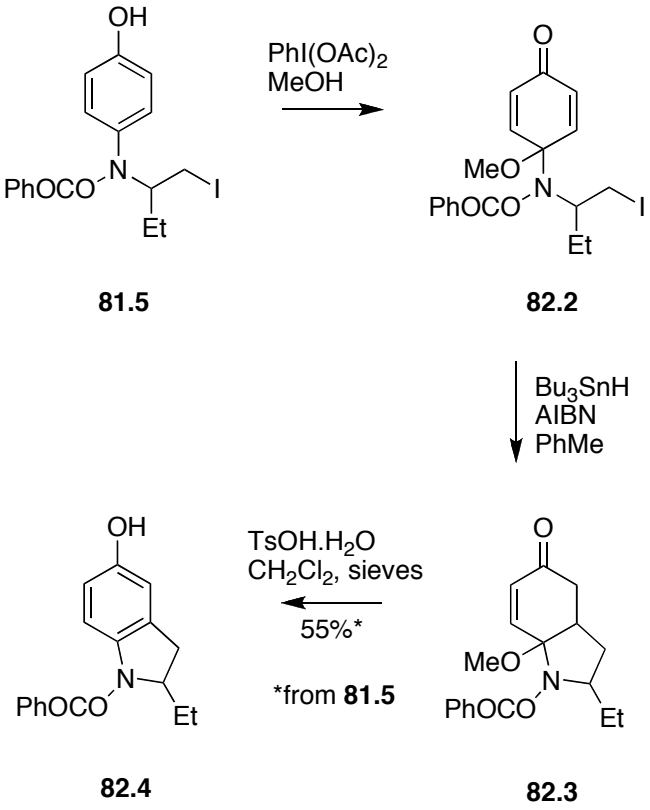
Ethyl-substituted dihydroindole **82.4** (see Scheme 82) was formed along the same lines as above, in order to improve the yields and spectral data of previous experiments in this group. 2-Aminobutanol was coupled to **62.1** using the standard procedure in good yield (78%). Phenyl carbamate protection of **81.2** to **81.3** occurred in good yield (89%). Subsequent conversion of **81.3** to iodide **81.4** and then to the MOM-deprotected compound **81.5** also occurred in good yields (89% and 81%, respectively).



Scheme 81

Oxidation of **81.5** to **82.2** using the normal conditions occurred readily. The yield of **82.2** was not calculated as, after purification by chromatography, the solution was not concentrated to dryness. Exposure of **82.2** to standard radical cyclization conditions then provided enone **82.3**, which was purified over 10%

finely ground KF/90% silica gel, resulting in partially aromatized **82.3**. The partially aromatized material was then subjected to mild acidic conditions to form the desired phenol **82.4** in 55% yield (over three steps).



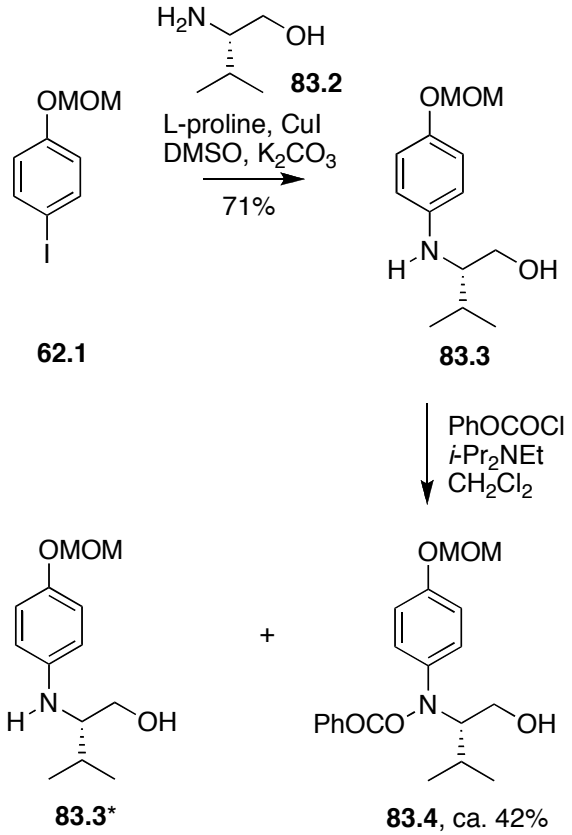
Scheme 82

2.5 Attempted Synthesis of Sterically Crowded Substituted Dihydroindoles

The synthesis of dihydroindoles with bulky alkyl groups α to nitrogen was attempted. In the case of **86.4** (see Scheme 86), where an isopropyl group is present on the ring, difficulties were faced in the protection of the nitrogen. While possible to achieve, the selective protection of the secondary nitrogen over the hydroxyl was thwarted by the presence of the isopropyl group and an indirect method had to be used (see later). In the case of **87.3** (see Scheme 87), which bears a *tert*-butyl group α to nitrogen, the coupling procedure was made difficult

by the steric bulk of the alkyl substituent, leading to low yields, even under forcing conditions. Subsequent protection of the nitrogen functionality, however, could not be achieved.

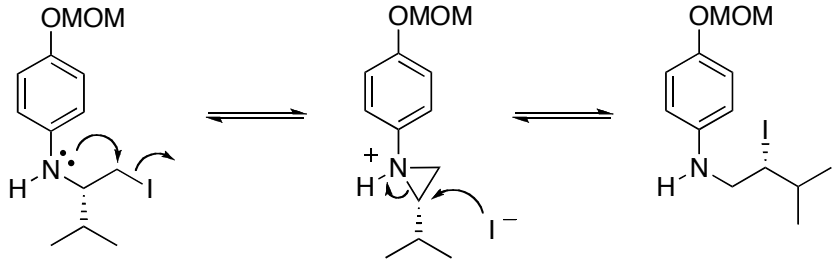
For formation of the isopropyl-substituted dihydroindole **86.4**, optically pure amino alcohol **83.2** derived from valine was first coupled to protected *p*-iodophenol (**62.1**) in good yield (71%), using the standard procedure. Protection of the nitrogen of the resulting **83.3**, using PhOCOCl, was only marginally successful. It produced a low yield (*ca.* 42%) of material that was contaminated with starting alcohol **83.3**. Careful flash chromatography of the impure **83.4** failed to resolve the two constituents, regardless of the solvent system used.



*Could not be separated from **83.4**
(*ca.* 10% of product)

Scheme 83

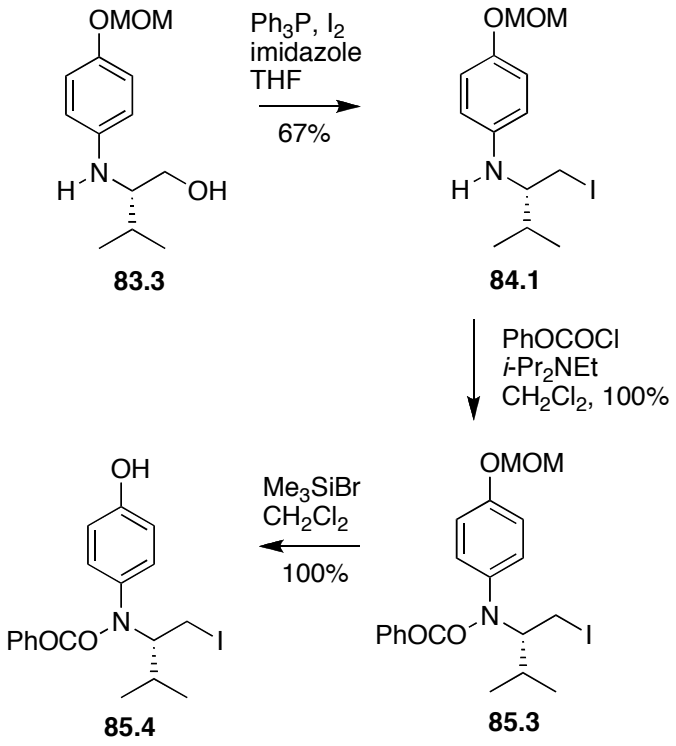
In order to access pure **83.4**, it was decided to make the unprotected iodoamine **84.1** first and then protect its nitrogen to make the desired carbamate **83.4**. However, it was possible that there would be some undesired rearrangement as summarized in Scheme 84. The formation of rearrangement product **84.3** would result in the unintended formation of a β-substituted dihydroindole. Fortunately, the rearrangement product was not observed, likely due to the immediate use of **84.1** after its formation (see Scheme 85). It was also possible that, if transition product **84.2** did form, nucleophilic attack of iodide at the undesired position would be inhibited by the bulky isopropyl group.



84.1 **84.2** **84.3**

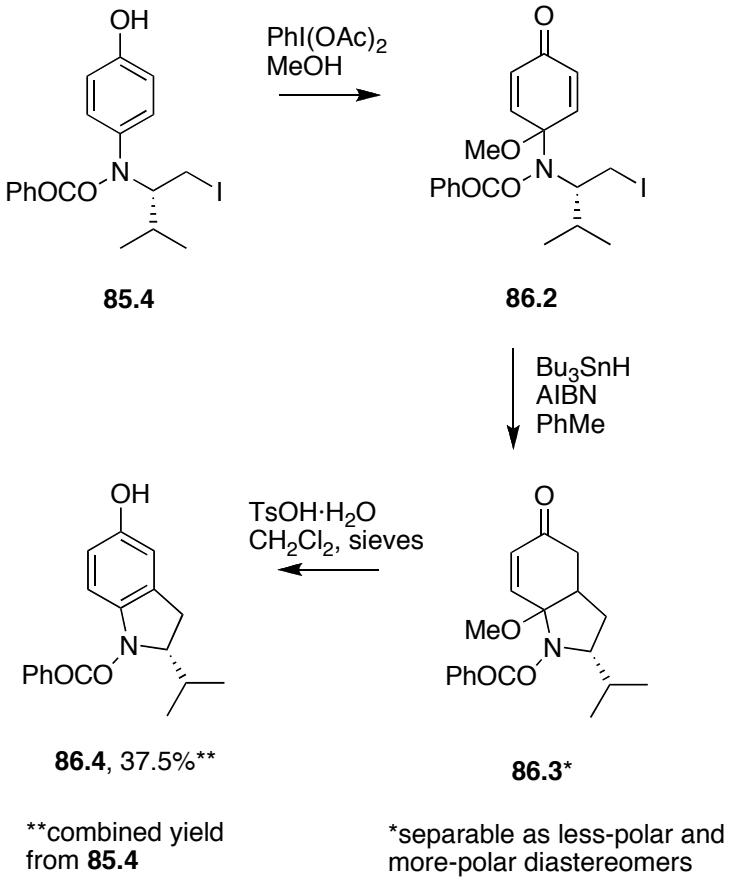
Scheme 84

Immediately after iodide **84.1** was formed using the standard method (67**%**), it was purified and treated with PhOCOCl and Hünig's base to form **85.3** in quantitative yield (Scheme 85). Deprotection of **85.3** proceeded quantitatively to provide phenol **85.4**.



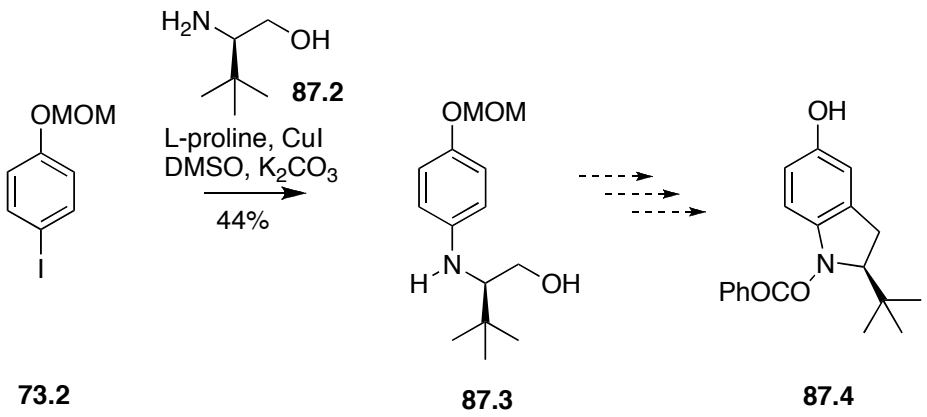
Scheme 85

Phenol **85.4** was then oxidized to **86.2**, which was purified and then immediately used (without concentration of its solutions) in the following radical cyclization step. Radical cyclization product **86.3** was comprised of easily separable, partially aromatized diastereomers that were then separately subjected to acidic conditions to form the desired phenol **86.4** in 37.5% combined yield (over three steps). It was not possible to establish the separate yields for each diastereomer in the aromatization step, as their exact masses were unknown due to the aromatization of a significant portion of **86.3** into **86.4**.



Scheme 86

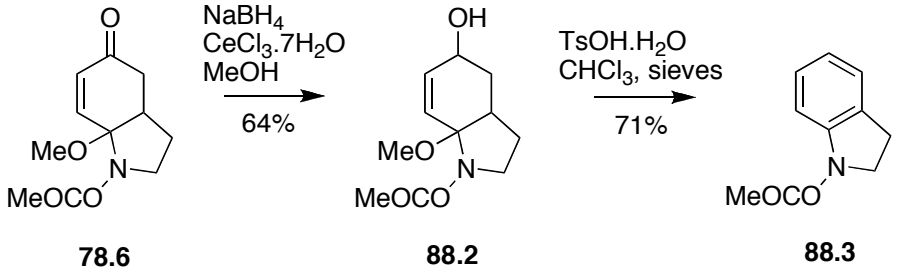
The synthesis of *tert*-butyl-substituted dihydroindole **87.3** was attempted, beginning with the coupling of amino alcohol **87.2** and protected *p*-iodophenol (**62.1**). Over a prolonged period (40 h) at high temperature (80 °C), yields remained unacceptably low (44%).



Scheme 87

2.6 *Manipulation before Aromatization*

It is possible to intercept enone intermediates and modify them before aromatization (Scheme 88). Enone intermediate **78.6** was converted into the alcohol **88.2** in moderate yield (64%) upon exposure to Luche conditions. Subsequent exposure of **88.2** to acidic conditions generated dihydroindole **88.3**, lacking the hydroxyl functionality.



Scheme 88

3 CONCLUSIONS

The formation of benzo-fused 5-membered *N*-heterocycles reported in Section 2 was extended and several of the earlier experiments were improved,[1d] so as to demonstrate a reliable and general approach to the oxidative radical cyclization onto benzenes to generate benzo-fused nitrogen heterocycles.

The method has been shown, through my examples, to support the formation of 5-membered, nitrogen heterocyclic rings. It has also been demonstrated by other members of this group that 6- and 7-membered *N*-heterocycles are accessible. The formation of non-phenolic species has also been demonstrated here, as has the introduction of various alkyl substituents on the aromatic ring by other contributors.[1d]

The method appears to be a very powerful and flexible tool in the formation of benzo-fused nitrogen heterocycles. It can also be used to make enantiomerically pure substituted dihydroindoles by use of easily accessed amino alcohols.

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 35 cm) of BASF catalyst and then through a similar column of Drierite. Glassware was dried in an oven for at least 3 h before use (135 °C) and either cooled in a dessicator over Drierite, or assembled quickly, sealed with rubber septa, and allowed to cool under a slight static pressure of Ar or N_2. All solvents for reactions were dried, as described below. Reaction mixtures were stirred by Teflon-coated magnetic stirring bars.

Hexane and EtOAc used for chromatography were distilled before use.

Microliter syringes were washed with water, acetone and ether, using the plunger to drive the solvents through. Air was drawn through the syringes which were then stored for at least one day in a desicator before use. Cannula transfers were always carried out under slight pressure (Ar or N_2) and not by suction.

Commercial thin layer chromatography (TLC) plates (silica gel, Merck 60F–254) were used. Spots were detected either by spraying the plate with a solution of phosphomolybdic acid, followed by charring with a heat gun, or by examination of the plate 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 K_2CO_3.

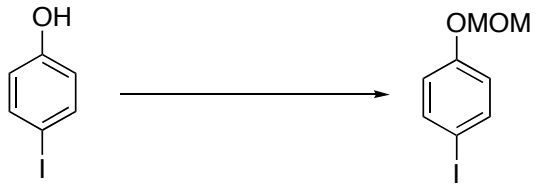
FT-IR measurements were made from the specified solvent using KBr plates.

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. The use of "br" indicates that the signal is broad.

Mass spectra were recorded with AEI Models MS-12, MS-50, MS9 (modified), or Kratos MS50 (modified) mass spectrometers.

Cu-catalyzed coupling reactions should be done at a concentration greater than 1 M. When the reaction is scaled up (> 1 g) the concentration should be lower (0.5-0.75 M).

4-(Methoxymethoxy)phenyl Iodide (62.1).

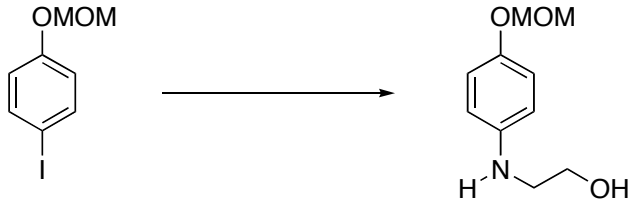


66.1 **62.1**

Into a nitrogen-flushed, long-necked round bottom flask was placed **66.1** (1.990 g, 9.045 mmol), followed by dry CH_2Cl_2 (9.25 mL) and then *i*-Pr_2NEt (1.65 mL, 9.50 mmol). The reaction vessel was then cooled to -78 °C (acetone-

dry ice) and MOMCl (0.728 g, 9.05 mmol) was added in portions over 5 min. After 10 min, the cold bath was removed and stirring was continued for 2 h 20 min. The mixture was quenched with water (2 mL) and the aqueous layer was extracted with $CHCl_3$ (3 x 5 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (3.0 x 25 cm), using EtOAc-hexane mixtures from 0% to 25% EtOAc, gave the **62.1** (1.765 g, 84%): FTIR (CH_2Cl_2, cast) 2954, 2900, 1586, 1485, 1235 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 3.44 (s, 3 H), 5.12 (s, 2 H), 6.80 (apparent d, J = 8.3 Hz, 2 H), 7.55 (apparent d, J = 9.0 Hz, 2 H); exact mass *m/z* calcd for $C_8H_9O_2I$ 263.9647, found 263.9652.

2-[[4-(Methoxymethoxy)phenyl]amino]ethanol (75.3).

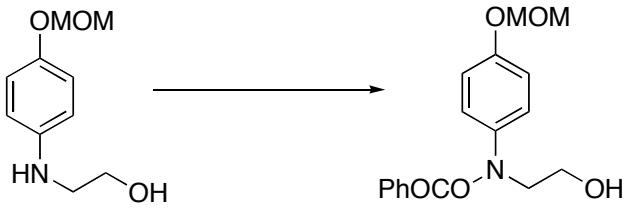


62.1 **75.3**

Into an oven-dried, nitrogen-flushed, one-piece round bottom flask and reflux condenser assembly was placed **62.1** (0.535 g, 2.03 mmol). CuI (0.0770 g, 0.405 mmol), 2-ethanolamine (0.611 mL, 10.1 mmol), L-proline (0.0930 g, 0.810 mmol), and oven-dried K_2CO_3 (0.560 g, 4.05 mmol) where then added consecutively. Dry DMSO was then added (1.90 mL) and the mixture was

lowered into an oil bath preset at 80 °C and stirring was continued for 6 h. The mixture was cooled to room temperature and partitioned between water and $CHCl_3$. The aqueous layer was extracted three times with $CHCl_3$ and the combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (3 x 22 cm), using EtOAc-hexane mixtures from 0% to 100% EtOAc, gave **75.3** (355 mg, 88%): FTIR (CH_2Cl_2, cast) 3384, 2947, 2894, 2826, 1616, 1513, 1464 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 2.95-3.15 (br s, 2 H), 3.23 (t, *J* = 5.4 Hz, 2 H), 3.48 (s, 3H), 3.78 (t, *J* = 5.1 Hz, 2 H), 5.07 (s, 2 H), 6.60 (apparent d, *J* = 8.9 Hz, 2 H), 6.91 (apparent d, 8.9 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 46.9 (t), 55.8 (q), 61.2 (t), 95.6 (t), 114.4 (d), 118.0 (d), 143.4 (s), 149.8 (s); exact mass *m/z* calcd for $C_{10}H_{15}NO_3$ 197.1052, found 197.1051.

(2-Hydroxyethyl)[4-(methoxymethoxy)phenyl]carbamic Acid Phenyl Ester (75.4).

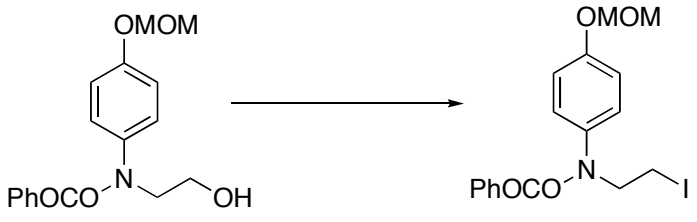


75.3 **75.4**

PhOCOCl (0.213 mL, 1.70 mmol) was injected rapidly into stirred and cooled (-30 °C, acetone-dry ice) solution of **75.3** (299 mg, 1.51 mmol) and *i*-

Pr_2NEt (0.295 mL, 1.70 mmol) in dry CH_2Cl_2 (10 mL). After 30 min, the cold bath was removed and stirring was continued for an additional 1.5 h. The reaction was quenched with saturated aqueous $NaHCO_3$ (20 mL) and the aqueous layer was extracted three times with $CHCl_3$. The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2.5 x 18 cm), using EtOAc-hexane mixtures from 10% to 50% EtOAc, gave **75.4** (480 mg, 100%) as an oil: FTIR ($CDCl_3$ cast) 3468, 2950, 1720, 1592 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) d 2.5-2.7 (br s, 1 H), 3.49 (s, 3 H), 3.86 [dd (one appears as a broad signal), J = 4.5 Hz, 4 H], 5.18 (s, 2 H), 7.06-7.07 (m, 4 H), 7.18 (t, J = 7 Hz, 1 H), 7.26-7.28 (m, 2 H), 7.33 (t, J = 7.5 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 125 MHz) d 53.6 (t), 56.1 (q), 61.0 (t), 94.5 (t), 116.8 (d), 121.5 (d), 125.4 (d), 128.5 (d), 129.2 (d), 135.5 (q), 151.3 (q), 156.3 (q); exact mass *m*/*z* calcd for $C_{17}H_{19}NO_5$ 317.3416, found 317.1264.

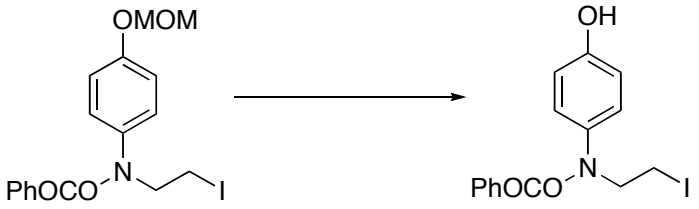
(2-Iodoethyl)[4-(methoxymethoxy)phenyl]carbamic Acid Phenyl Ester (75.5).



75.4 **75.5**

To a stirred and cooled (0 °C) solution of **75.4** (324 mg, 1.02 mmol) in dry THF (20 mL) was added imidazole (264 mg, 3.88 mmol), Ph_3P (723.0 mg, 2.757 mmol) and I_2 (674.0 mg, 2.655 mmol), in that order. After 1 h, the cold bath was removed and stirring was continued for 12 h. The mixture was quenched with a solution of saturated aqueous $Na_2S_2O_3$ (12 mL) and brine (12 mL). The aqueous layer was extracted three times with $CHCl_3$ and the combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (3 x 18 cm), using EtOAc-hexane mixtures from 2% to 20% EtOAc, gave **75.5** (410 mg, 94%): FTIR ($CDCl_3$ cast) 2954, 1720, 1592 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 3.30 (t, *J* = 7.3 Hz, 2 H), 3.49 (s, 3 H), 3.98-4.26 (br m, 2 H), 5.18 (s, 2 H), 7.08 (apparent d, *J* = 8.9 Hz, 3.5 H), 7.13-7.24 (br s, 1.3 H), 7.27 (apparent d, *J* = 8.9 Hz, 2.2 H), 7.30-7.40 (br s, 2 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 0.8 (t), 52.9 (t), 56.1 (q), 94.5 (t), 116.9 (d), 121.5 (d), 125.4 (d), 128.5 (d), 129.2 (d), 134.4 (s), 151.2 (s), 156.5 (s), 153.9 (s), 156.5 (s); exact mass *m*/*z* calcd for $C_{17}H_{18}INO_4$ 427.0281, found 427.0281.

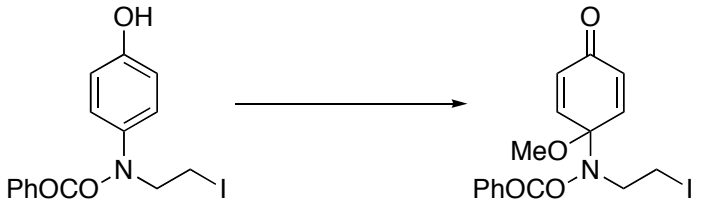
(4-Hydroxyphenyl)(2-iodoethyl)carbamic Acid Phenyl Ester (75.6).



75.5 **75.6**

Me_3SiBr (1.07 mL, 8.09 mmol) was injected at a fast, dropwise rate into a stirred solution of **75.5** (288 mg, 0.674 mmol) in dry CH_2Cl_2 (23 mL). After 22 h, the reaction mixture was quenched with water (30 mL), and then partitioned between water and $CHCl_3$. The aqueous layer was extracted four times with $CHCl_3$, and the combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (3 x 17 cm), using EtOAc-hexane mixtures from 2% to 25% EtOAc, gave the **75.6** as a white solid (253 mg, 98%): Spectral data previously reported.[56]

(2-Iodoethyl)(1-methoxy-4-oxocyclohexa-2,5-dienyl)carbamic Acid Phenyl Ester (76.2).

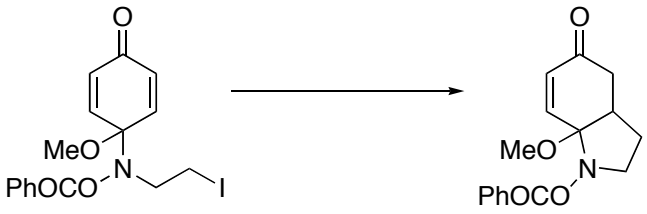


75.6 **76.2**

$PhI(OAc)_2$ (163 mg, 0.496 mmol) was added to a stirred and cooled (0 °C) solution of **75.6** (152 mg, 0.397 mmol) in dry MeOH (26 mL). After 20 min the cold bath was removed and stirring was continued for 4.5 h, at which point it was quenched with a solution of 1 M aqueous $Na_2S_2O_3$ (35 mL) and saturated aqueous $NaHCO_3$ (35 mL). The aqueous layer was extracted three times with $CHCl_3$, dried (Na_2SO_4), and evaporated. Flash chromatography of the residue over silica

gel (2 x 18 cm), using EtOAc-hexane mixtures from 2% to 20% EtOAc, gave **76.2** (unknown mass and yield as unable to concentrate without decomposition): FTIR (microscope) 3044, 2937, 2850, 2835, 1726, 1673, 1633, 1494, 1455, 1385 cm^{-1}; unable to concentrate to acquire adequate ^{1}H and ^{13}C NMR; exact mass *m*/*z* calcd for $C_{16}H_{16}INO_4$ 413.0119, found 413.0118.

7a-Methoxy-5-oxo-2,3,3a,4,5,7a-hexahydroindole-1-carboxylic Acid Phenyl Ester (76.3).

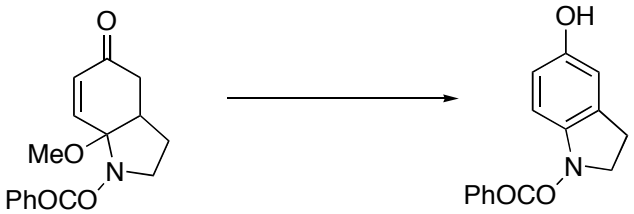


76.2 **76.3**

A solution of Bu_3SnH (0.158 mL, 0.595 mmol) and AIBN (43.0 mg, 0.262 mmol) in dry PhMe (10 ml) was added over 2.5 h by syringe pump to a stirred and heated (85 °C) solution of **76.2** (163 mg, 0.396 mmol, assuming previous reaction was quantitative) in dry PhMe (34 mL). Heating at 85 °C was continued for an additional 14.5 h, at which point the reaction mixture was cooled and evaporated. Flash chromatography of the residue over 10% finely ground KF/90% silica gel (2 x 20 cm), using EtOAc-hexane mixtures from 2% to 50% EtOAc, gave **76.3** (unknown mass and yield as unable to obtain without partial decomposition into aromatic final product): FTIR (microscope) 3066, 2955,

2901, 2833, 1726, 1687, 1493, 1456, 1370 cm^{-1}; unable to acquire adequate ^{1}H and ^{13}C NMR as both spectra were very complicated due to presence of aromatic, final product; exact mass *m*/*z* calcd for $C_{16}H_{17}NO_4$ 287.1158, found 287.1159.

5-Hydroxy-2,3-dihydroindole-1-carboxylic Acid Phenyl Ester (76.4).

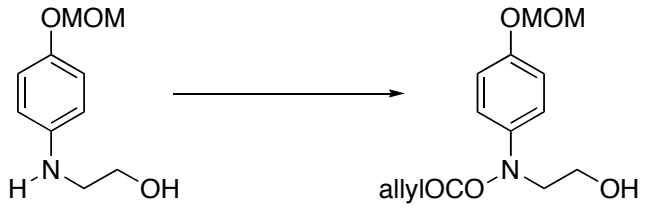


76.3 **76.4**

$TsOH.H_2O$ (60.0 mg, 0.315 mmol) was added to a stirred mixture of **76.3** (113 mg, 0.393 mmol, assuming quantitative yields for the last two steps) and 4Å molecular sieves (10 pieces) in $CHCl_3$ (20 mL, not dried). Stirring was continued for 2.5 h, and the mixture was filtered and evaporated. Flash chromatography of the residue over silica gel (2 x 16 cm), using EtOAc-hexane mixtures from 0% to 50% EtOAc, gave **76.4** (57.4 mg, 57% over three-steps): FTIR (microscope) 3390, 2923, 1693, 1601, 1490, 1416, 1336 cm^{-1}; ^{1}H NMR (500 MHz, CD_3OD) δ 3.13 (t, *J* = 8.2 Hz, 3 H), 3.96-4.12 (apparent s, 0.5 H), 4.19 (t, *J* = 8.2 Hz, 1.5 H), 6.60 (d, *J* = 8.0 Hz, 1.0 H), 6.68 (s, 0.9 H), 6.79-6.85 (m, 0.1 H), 6.95-7.08 (apparent s, 0.1 H), 7.18 (d, *J* = 7.6 Hz, 2 H), 7.23 (t, *J* = 7.1 Hz, 1 H), 7.39 (t, *J* = 7.6 Hz, 2.2 H), 7.56 (d, *J* = 8.5 Hz, 0.7 H); ^{13}C NMR (125 MHz, CD_3OD) δ 28.7 (t), 48.9 (t), 113.3 (d), 114.6 (d), 116.5 (d), 123.0 (d), 126.8 (d),

130.4 (d), 134.4 (s), 135.7 (s), 152.4 (s), 152.9 (s), 155.1 (s); exact mass *m/z* calcd for $C_{15}H_{13}NO_3$ 255.0895, found 255.0894.

(2-Hydroxyethyl)[4-(methoxymethoxy)phenyl]carbamic Acid Allyl Ester (68.2).

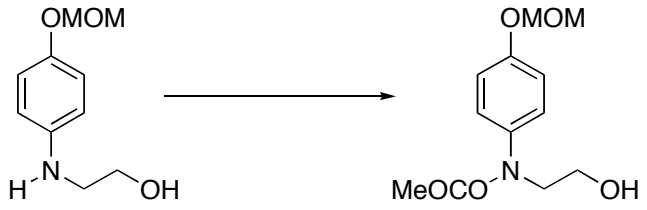


75.3 **68.2**

Allyl chloroformate (0.052 mL, 0.49 mmol) was injected rapidly into a stirred and cooled (-30 °C, acetone-dry ice) solution of **75.3** (160 mg, 0.811 mmol) in dry CH_2Cl_2 (8.0 mL). After 5 min, the ice bath was removed and after an additonal 7 min *i*-Pr_2NEt (0.085 mL, 0.49 mmol) was added. After 2 min, the cold bath (-30 °C) was replaced and a second portion of allyl chloroformate (0.052 mL, 0.4867 mmol) was injected rapidly. After 5 min, the cold bath was removed, and stirring was continued for 15 min, at which point the mixture was quenched with water (5 mL). The aqueous layer was extracted three times with $CHCl_3$ and the combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (3 x 35 cm), using EtOAc-hexane mixtures from 0% to 100% EtOAc, gave **68.2** (205 mg, 87%) as an oil: FTIR (CH_2Cl_2, cast) 3457, 2948, 2827, 1701, 1511, 1445, 1402 cm^{-1}; ^1H NMR

($CDCl_3$, 500 MHz) δ 2.30-2.90 (br s, 1 H), 3.48 (s, 3 H), 3.74-3.83 (br m, 2 H), 4.58 (apparent d, J = 3.3 Hz, 2 H), 7.02 (apparent d, J = 9.0 Hz, 2 H), 7.14 (d, J = 8.5 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 53.4 (t), 56.0 (q), 61.3 (t), 66.4 (t), 94.5 (t), 116.7 (d), 117.2 (s), 128.5 (d), 132.6 (d), 135.8 (s), 156.0 (s); exact mass *m/z* calcd for $C_{14}H_{19}NO_5$ 281.1263, found 281.1261.

(2-Hydroxyethyl)[4-(methoxymethoxy)phenyl]carbamic Acid Methyl Ester (77.3).

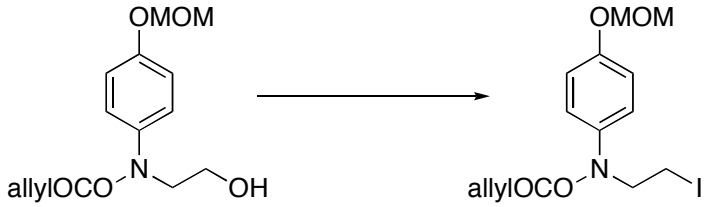


75.3 **77.3**

MeOCOCl (0.039 mL, 0.42 mmol) was injected rapidly into stirred and cooled (-30 °C, acetone-dry ice) solution of **75.3** (136 mg, 0.692 mmol) in dry CH_3CN (10 mL). After 5 min, the ice bath was removed and after an additional 7 min *i*-Pr_2NEt (0.072 mL, 0.42 mmol) was added. After 2 min, the cold bath (-30 °C) was replaced and a second portion of MeOCOCl (0.039 mL, 0.42 mmol) was injected rapidly. After 5 min, the cold bath was removed, and stirring was continued for 5 h, at which point the mixture was quenched with brine (10 mL). The aqueous layer was extracted three times with $CHCl_3$ and the combined organic extracts were dried (Na_2SO_4) and evaporated. Flash chromatography of

the residue over silica gel (1.8 x 19 cm), using EtOAc-hexane mixtures from 2% to 80% EtOAc, gave **77.3** (177 mg**,** 100%) as an oil: FTIR ($CHCl_3$, cast) 3455, 2954, 1703, 1511, 1455, 1387 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 2.20-3.00 (br s, 1 H), 3.48 (s, 3 H), 3.67 (s, 3 H), 3.74-3.81 (m, 4 H), 5.18 (s, 2 H), 7.02 (apparent d, *J* = 8.8 Hz, 2 H), 7.13 (d, *J* = 8.6 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 53.2 (q), 53.4 (t), 56.1 (q), 61.2 (t), 94.5 (t), 116.8 (d), 128.5 (d), 135.8 (s), 156.1 (s), 157.6 (s); exact mass *m/z* calcd for $C_{12}H_{17}NO_5$ 255.1107, found 255.1010.

(2-Iodoethyl)[4-(methoxymethoxy)phenyl]carbamic Acid Allyl Ester (77.4).

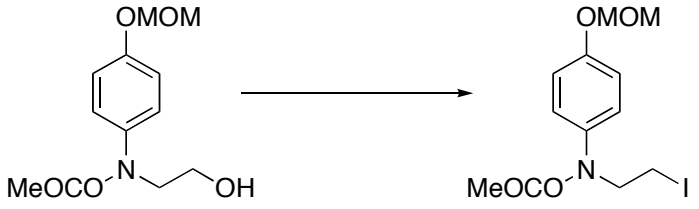


68.2 **77.4**

To a stirred and cooled (0 °C) solution of **68.2** (174.8 mg, 0.6214 mmol) in dry THF (14 mL) was added imidazole (160.7 mg, 2.361 mmol), Ph_3P (440.1 mg, 1.678 mmol) and I_2 (410.1 mg, 1.616 mmol), in that order. After 1 h, the cold bath was removed and stirring was continued for 11 h. The mixture was diluted with $CHCl_3$ and partitioned between a 1:1:1:4 mixture of brine, saturated aqueous $NaHCO_3$, 1 M aqueous $Na_2S_2O_3$ and water. The aqueous layer was extracted

three times with $CHCl_3$ and the combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2.7 x 21 cm), using EtOAc-hexane mixtures from 2% to 50% EtOAc, gave **77.4** (214 mg, 88%): FTIR (CH_2Cl_2, cast) 2952, 2897, 1705, 1511, 1396 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 3.22 (t, *J* = 8.0 Hz, 2 H), 3.49 (s, 3 H), 3.99 (t, *J* = 7.3 Hz, 2 H), 4.45-4.75 (apparent br s, 2 H), 5.05-5.32 (apparent br s, 4 H), 5.65-6.10 (br s, 1 H), 7.03 (apparent d, *J* = 9.0 Hz, 2 H), 7.14 (apparent d, *J* = 8.6 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 60 °C, 100 MHz) δ 0.9 (t), 45.8 (t), 53.0 (t), 56.0 (q), 61.2 (t), 66.4 (t), 94.8 (t), 95.0 (t), 117.0 (d), 117.1 (d), 117.4 (s), 120.3 (d), 128.6 (d), 132.7 (d), 135.1 (s), 155.2 (s), 156.4 (s); exact mass *m/z* calcd for $C_{14}H_{18}NO_4I$ 391.0281, found 391.0272.

(2-Iodoethyl)[4-(methoxymethoxy)phenyl]carbamic Acid Methyl Ester (77.5).

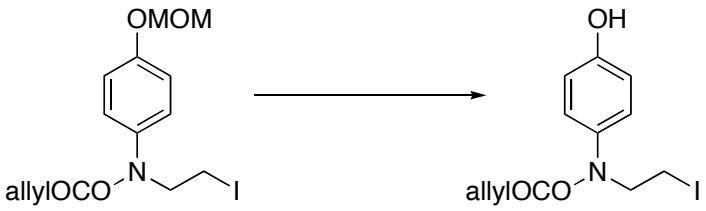


77.3 **77.5**

To a stirred and cooled (0 °C) solution of **77.3** (139.9 mg, 0.5481 mmol) in dry THF (12.2 mL) was added imidazole (0.142 mg, 2.08 mmol), Ph_3P (0.388 mg, 1.48 mmol) and I_2 (0.362 mg, 1.43 mmol), in that order. After 1 h, the cold

bath was removed and stirring was continued for 19 h. The mixture was quenched with a solution of saturated aqueous $Na_2S_2O_3$ (7 mL) and brine (7 mL). The aqueous layer was extracted three times with $CHCl_3$ and the combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2.7 x 21 cm), using EtOAc-hexane mixtures from 2% to 25% EtOAc, gave **77.5** (165 mg, 83%): FTIR (CH_2Cl_2, cast) 2953, 2899, 1709, 1511, 1449, 1381 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 3.20 (t, *J* = 7.9 Hz, 2 H), 3.46 (s, 3 H), 3.56-3.80 (br s, 3 H), 3.96 (t, *J* = 7.3 Hz, 2 H), 5.16 (s, 2 H), 7.02 (apparent d, *J* = 9.0 Hz, 2 H), 7.11 (apparent d, *J* = 8.6 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 1.2 (t), 52.8 (t), 53.1 (q), 56.1 (q), 94.5 (t), 116.8 (d), 128.6 (d), 134.7 (s), 155.9 (s), 156.2 (s); exact mass *m/z* calcd for $C_{12}H_{16}NO_4I$ 365.0124, found 365.0131.

(4-Hydroxyphenyl)(2-iodoethyl)carbamic Acid Allyl Ester (68.3).

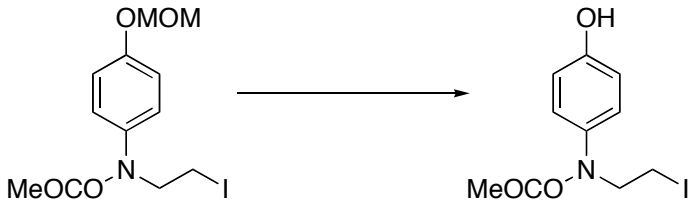


77.4 **68.3**

Me_3SiBr (0.444 mL, 3.36 mmol) was injected at a fast, dropwise rate into a stirred solution of **77.4** (137 mg, 0.336 mmol) in dry CH_2Cl_2 (11.5 mL). After 18.5 h, the reaction mixture was quenched with water (10 mL), and partitioned

between water and $CHCl_3$. The aqueous layer was extracted four times with $CHCl_3$, and the combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1.8 x 22 cm), using EtOAc-hexane mixtures from 2% to 25% EtOAc, gave **68.3** (89.3 mg, 74%): FTIR (CH_2Cl_2, cast) 3340, 2947, 1674, 1647, 1515, 1450, 1408 cm^{-1}; ^1H NMR (CD_3OD, 500 MHz) δ 3.21 (t, *J* = 7.1 Hz, 2 H), 3.89-3.98 (br t, *J* = 5.9 Hz, 2 H), 4.42-4.73 (br m, 2 H), 5.00-5.45 (br m, 2 H), 5.73-6.10 (br m, 1 H), 6.78 (d, *J* = 8.5 Hz, 2 H), 7.08 (d, *J* = 7.8 Hz, 2 H); ^{13}C NMR (CD_3OD, 100 MHz) δ 1.6 (t), 47.5 (t), 53.8 (t), 63.2 (t), 67.2 (t), 116.5 (d), 116.7 (d), 117.3 (t), 122.6 (d), 129.9 (d), 131.6 (s), 133.4 (s), 133.8 (d), 155.8 (s), 157.2 (s), 157.9 (s), 158.4 (s); exact mass *m/z* calcd for $C_{12}H_{14}NO_3I$ 347.0018, found 347.0015.

(4-Hydroxyphenyl)(2-iodoethyl)carbamic Acid Methyl Ester (70.3).

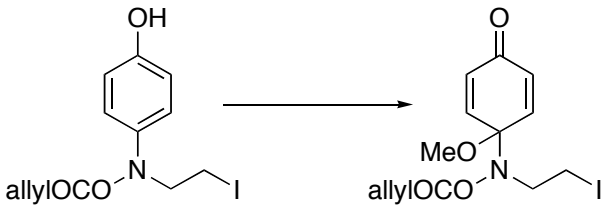


77.5 **70.3**

Me_3SiBr (0.668 mL, 5.06 mmol) was injected at a fast, dropwise rate into a stirred solution of **77.5** (0.154 mg, 0.422 mmol) in dry CH_2Cl_2 (14.4 mL). After 18.5 h, the reaction mixture was quenched with water (15 mL), and partitioned between water and $CHCl_3$. The aqueous layer was extracted four times with

$CHCl_3$, and the combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1.5 x 25 cm), using EtOAc-hexane mixtures from 2% to 25% EtOAc, gave **70.3** as solid (126 mg, 93%): FTIR (CH_2Cl_2, cast) 3331, 2954, 1675, 1515, 1457, 1389 cm^{-1}; ^1H NMR (CD_3OD, 400 MHz) δ 3.20 (t, *J* = 7.5 Hz, 2 H), 3.46-3.84 (br m, 3 H), 3.90 (t, *J* = 7.3 Hz, 2 H), 6.77 (d, *J* = 8.7 Hz, 2 H), 7.05 (d, *J* = 7.6 Hz, 2 H); ^{13}C NMR (CD_3OD, 100 MHz) δ 1.7 (t), 53.6 (q), 53.9 (t), 116.8 (d), 130.0 (d), 133.5 (s), 157.9 (s), 158.1 (s); exact mass *m/z* calcd for $C_{10}H_{12}NO_3I$ 320.9862, found 320.9859.

(2-Iodoethyl)(1-methoxy-4-oxocyclohexa-2,5-dienyl)carbamic Acid Allyl Ester (69.1).

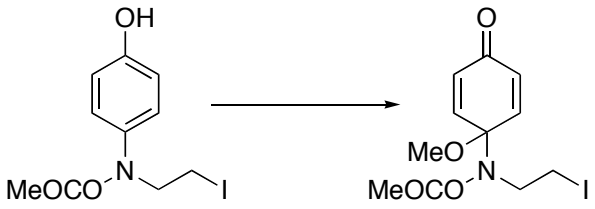


68.3 **69.1**

$PhI(OAc)_2$ (86.5 mg, 0.269 mmol) was added to a stirred and cooled (0 °C) solution of **68.3** (74.6 mg, 0.215 mmol) in dry MeOH (18.5 mL). After 20 min the cold bath was removed and stirring was continued for 2.5 h, at which point the mixture was quenched with a mixed solution of 1 M aqueous $Na_2S_2O_3$ (15 mL) and saturated aqueous $NaHCO_3$ (15 mL). The aqueous layer was extracted three times with $CHCl_3$, dried (Na_2SO_4), and evaporated. Flash

chromatography of the residue over silica gel (1.9 x 19 cm), using EtOAc-hexane mixtures from 2% to 25% EtOAc, gave **69.1** (unknown mass and yield as unable to concentrate without decomposition): FTIR (CH_2Cl_2, cast) 3046, 2938, 2833, 1709, 1673, 1633, 1395 cm^{-1}; unable to concentrate to acquire adequate ^1H and ^{13}C NMR; exact mass *m/z* calcd for $C_{13}H_{16}NO_4I$ 377.01242, found unable to concentrate to acquire adequate ^1H and ^{13}C 377.0118.

(2-Iodoethyl)(1-methoxy-4-oxocyclohexa-2,5-dienyl)carbamic Acid Methyl Ester (70.4).

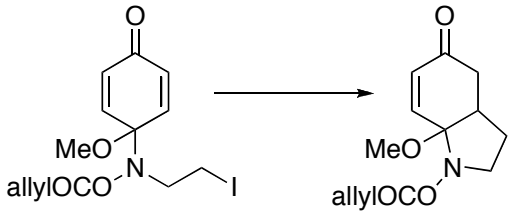


70.3 **70.4**

$PhI(OAc)_2$ (63.2 mg, 0.196 mmol) was added to a stirred and cooled (0 °C) solution of **70.3** (50.4 mg, 0.157 mmol) in dry MeOH (13.5 mL). After 30 min the cold bath was removed and stirring was continued for 2 h, at which point the reaction mixture was cooled (0 °C) and another portion of $PhI(OAc)_2$ was added (63.2 mg, 0.1962 mmol). After 30 min, the cold bath was removed and stirring was continued for 20 h. The mixture was cooled (0 °C) and a further portion of $PhI(OAc)_2$ (126.4 mg, 0.3924 mmol) was added. After 30 min the cooling bath was removed and the reaction mixture was quenched with a mixed

solution of 1 M aqueous $Na_2S_2O_3$ (30 mL) and saturated aqueous $NaHCO_3$ (30 mL). The aqueous layer was extracted three times with $CHCl_3$, and the combined organic extracts were dried (Na_2SO_4), and evaporated. Flash chromatography of the residue over silica gel (1.5 x 20 cm), using EtOAc-hexane mixtures from 10% to 25% EtOAc, gave **70.4** (unknown mass and yield as unable to concentrate without decomposition): IR and MS spectral data previously reported[56]; unable to concentrate solutions to acquire adequate ^1H and ^{13}C NMR.

7a-Methoxy-5-oxo-2,3,3a,4,5,7a-hexahydroindole-1-carboxylic Acid Methyl Ester (78.5).

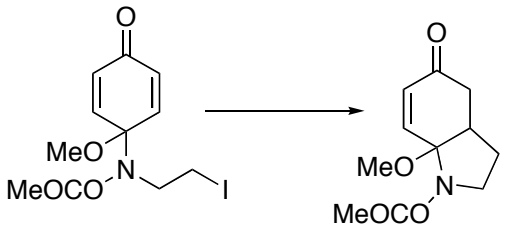


69.1 **78.5**

A solution of Bu_3SnH (0.080 mL, 0.30 mmol) and AIBN (23.3 mg, 0.142 mmol) in dry PhMe (8.3 ml) was added over 2.5 h by syringe pump to a stirred and heated (85 °C) solution of **69.1** (81.1 mg, 0.215 mmol, assuming previous reaction was quantitative) in dry PhMe (16.7 mL). Heating at 85 °C was continued for an additional 7.5 h, at which point the reaction mixture was cooled and evaporated. Flash chromatography of the residue over 10% finely ground KF/90% silica gel (1.5 x 22 cm), using EtOAc-hexane mixtures from 2% to 25%

EtOAc, gave **78.5** (unknown mass and yield as unable to obtain without partial decomposition into aromatic, final product): FTIR (CH_2Cl_2, cast) 3365, 2940, 1700, 1497, 1398 cm^{-1}; unable to acquire adequate ^1H and ^{13}C NMR as both spectra were very complicated due to presence of aromatic, final product; exact mass *m/z* calcd for $C_{13}H_{17}NO_4$ 251.1158, found 251.1159.

7a-Methoxy-5-oxo-2,3,3a,4,5,7a-hexahydroindole-1-carboxylic Acid Methyl Ester (78.6).

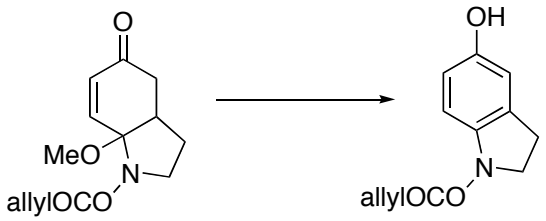


70.4 **78.6**

A solution of Bu_3SnH (0.0520 mL, 0.196 mmol) and AIBN (11.0 mg, 0.0669 mmol) in dry PhMe (6 ml) was added over 2 h by syringe pump to a stirred and heated (85 °C) solution of **70.4** (54.8 mg, 0.157 mmol, assuming previous reaction was quantitative) in dry PhMe (12 mL). Heating at 85 °C was continued for an additional 12 h, at which point the reaction mixture was cooled and evaporated. Flash chromatography of the residue over 10% finely ground KF/90% silica gel (1.1 x 18 cm), using EtOAc-hexane mixtures from 25% to 50% EtOAc, gave **78.6** (unknown mass and yield as unable to obtain without partial decomposition into aromatic, final product): FTIR (CH_2Cl_2, cast) 2955, 1704,

1445, 1368 cm^{-1}; unable to acquire adequate ^{1}H and ^{13}C NMR as both spectra were very complicated due to presence of aromatic, final product; exact mass *m/z* calcd for $C_{11}H_{15}NO_4$ 225.1001, found 225.1003.

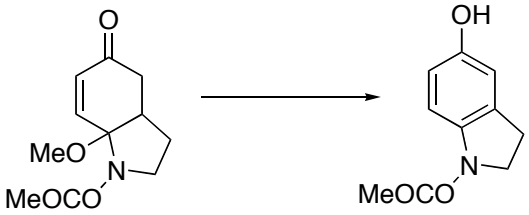
5-Hydroxy-2,3-dihydroindole-1-carboxylic Acid Allyl Ester (78.7).



78.5 **78.7**

$TsOH{\cdot}H_2O$ (11.0 mg, 0.0573 mmol) was added to a stirred mixture of **78.5** (18.0 mg, 0.0716 mmol, assuming quantitative yields for the last two steps) and 4Å molecular sieves (15 pieces) in $CHCl_3$ (10 mL, not dried). Stirring was continued for 2.5 h, and the mixture was filtered and evaporated. Flash chromatography of the residue over silica gel (1 x 17 cm), using EtOAc-hexane mixtures from 2% to 50% EtOAc, gave **78.7** (10.3 mg, 22% over three steps): IR and MS spectral data previously reported[56]; ^{1}H NMR (400 MHz, CD_3OD) δ 3.05 (t, *J* = 9.0 Hz, 2 H), 3.98 (t, *J* = Hz, 2 H), 4.78 (s, 2 H), 5.23 (dd, 1.0, 11.0 Hz, 1 H), 5.35 (dd, *J* = 1.5, 17.0 Hz, 1 H), 6.01 (ddd, *J* = 5.5, 11.0, 27.5 Hz, 1 H); ^{13}C NMR (125 MHz, CD_3OD) δ 28.5 (t), 67.0 (t), 113.2 (d), 114.5 (d), 116.3 (d), 116.7 (d) 118.0 (s), 129.8 (s), 134.2 (d), 154.6 (s).

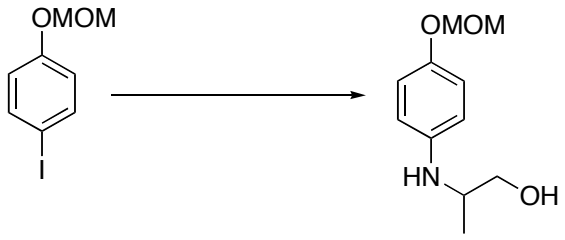
5-Hydroxy-2,3-dihydroindole-1-carboxylic Acid Methyl Ester (78.8).



78.6 **78.8**

$TsOH \cdot H_2O$ (23.9 mg, 0.126 mmol) was added to a stirred mixture of **78.6** (35.4 mg, 0.157 mmol, assuming quantitative yields for the last two steps) and 4Å molecular sieves (10 pieces) in $CHCl_3$ (10 mL, not dried). Stirring was continued for 15 min, and the mixture was filtered and evaporated. Flash chromatography of the residue over silica gel (1 x 18 cm), using EtOAc-hexane mixtures from 5% to 50% EtOAc, gave **78.8** (18.0 mg, 59% over three steps): FTIR (CH_2Cl_2, cast) 3313, 2921, 1675, 1497, 1456, 1405 cm^{-1}; ^1H NMR (400 MHz, CD_3OD) δ 3.04 (t, J = 8.6 Hz, 2 H), 3.68-3.90 (br s, 3 H), 3.95 (t, J = 8.1 Hz, 2 H), 6.56 (apparent dd, J = 2.6, 8.7 Hz, 0.9 H), 6.64 (m, 0.9 H), 6.76 (apparent d, J = 8.9 Hz, 0.1 H), 6.98 (apparent d, 9.0 Hz, 0.1 H), 7.15-7.42 (br s, 0.3 H), 7.42-7.70 (br s, 0.7 H); ^{13}C NMR (100 MHz, CD_3OD) δ 28.5 (t), 49.0 (t), 52.9 (q), 113.1 (d), 114.3 (d), 116.1 (d), 134.0 (s), 136.2 (s), 154.5 (s), 155.2 (s); exact mass *m/z* calcd for $C_{10}H_{11}NO_3$ 193.0739, found 193.0735.

2-[[4-(Methoxymethoxy)phenyl]amino]propan-1-ol (79.2).

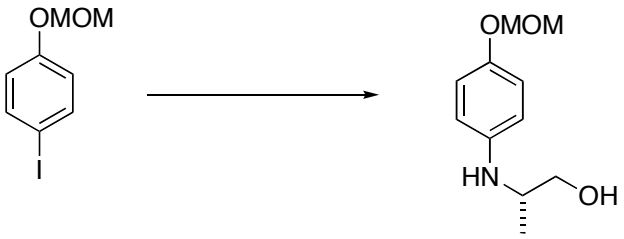


62.1 **79.2**

Into an oven-dried, nitrogen-flushed, one-piece round bottom flask and reflux condenser assembly was placed **62.1** (0.892 g, 3.38 mmol). Copper(I) iodide (0.129 g, 0.675 mmol), 2-amino-1-propanol (1.089 g, 14.49 mmol), L-proline (0.156 g, 1.35 mmol), and oven-dried K_2CO_3 (0.934 g, 6.75 mmol) where then added consecutively. Dry DMSO was then added (3.2 mL) and the mixture was lowered into an oil bath preset at 80 °C and stirring was continued for 18 h. The mixture was cooled to room temperature and partitioned between water and $CHCl_3$. The aqueous layer was extracted three times with $CHCl_3$ and the combined extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2.0 x 24 cm), using EtOAc-hexane mixtures from 0% to 50% EtOAc, gave **79.2** (523.8 mg, 73%): FTIR (CH_2Cl_2, cast) 3383, 2961, 2825, 1614, 1512, 1451, 1406 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.17 (d, J = 6.4 Hz, 3 H), 2.45-3.05 (br s, 2 H), 3.44-3.51 (m, 4 H), 3.55 (apparent ddq, J = 4.0, 6.4, 12.7 Hz, 1 H), 3.71 (dd, J = 4.0, 10.6 Hz, 1 H), 6.65 (apparent d, J = 8.9 Hz, 2 H), 6.92 (apparent d, J = 8.9 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 17.4 (q),

52.0 (d), 55.8 (q), 66.1 (t), 95.5 (t), 115.6 (d), 117.9 (d), 142.2 (s), 150.2 (s); exact mass *m/z* calcd for $C_{11}H_{17}NO_3$ 211.1209, found 211.1209.

(2*S*)-2-[[4-(Methoxymethoxy)phenyl]amino]propan-1-ol [(*S*)-79.2].

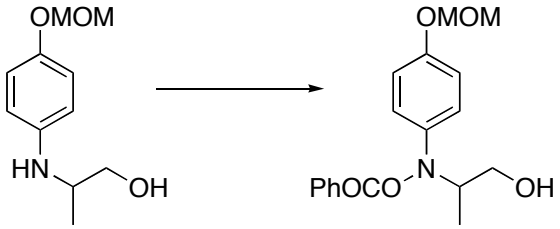


62.1 **(*S*)-79.2**

Into an oven-dried, nitrogen-flushed, one-piece round bottom flask and reflux condenser assembly was placed **62.1** (0.283 g, 1.07 mmol). Copper(I) iodide (0.0410 g, 0.214 mmol), optically pure 2-amino-1-propanol (*S*)-**79.6** (0.322 g, 4.29 mmol), L-proline (0.0492 g, 0.427 mmol), and oven-dried K_2CO_3 (0.296 g, 0.536 mmol) where then added consecutively. Dry DMSO was then added (1 mL) and the mixture was lowered into an oil bath preset at 80 °C and stirring was continued for 17 h. The mixture was cooled to room temperature and partitioned between water and $CHCl_3$. The aqueous layer was extracted three times with $CHCl_3$ and the combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2.0 x 28 cm), using EtOAc-hexane mixtures from 0% to 50% EtOAc, gave (*S*)-**79.2** (186 mg, 82%): FTIR (CH_2Cl_2, cast) 3380, 2932, 1511, 1227, 1196 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.13 (d, *J* = 6.4 Hz, 3 H), 2.70-2.91 (br s, 2 H), 3.43 (apparent t, *J* = 6.2

Hz, 1 H), 3.45 (s, 3 H), 3.50 (dt, *J* = 4.1, 6.2 Hz, 1 H), 3.65 (dd, *J* = 4.0, 10.3 Hz, 1H),1 H), 5.04 (s, 2 H), 6.59 (apparent d, *J* = 8.9 Hz, 2 H), 6.88 (apparent d, *J* = 9.0, 2 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 17.4 (q), 51.7 (d), 55.8 (q), 66.1 (t), 95.5 (t), 115.3 (d), 118.0 (d), 142.6 (s), 149.9 (s); exact mass *m/z* calcd for $C_{11}H_{17}NO_3$ 211.1209, found 211.1210.

(2-Hydroxy-1-methylethyl)[4-(methoxymethoxy)phenyl]carbamic Acid Phenyl Ester (79.3).

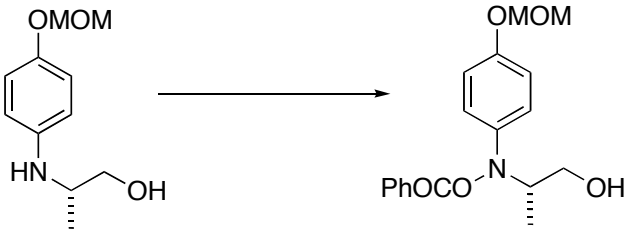


79.2 **79.3**

PhOCOCl (0.186 mL, 1.48 mmol) was injected rapidly into a stirred and cooled (-30 °C, acetone-dry ice) solution of **79.2** (0.280 g, 1.33 mmol) and *i*-Pr_2NEt (0.268 mL, 1.48 mmol) in dry CH_2Cl_2 (6.8 mL). After 30 min, the cold bath was removed and stirring was continued for an additional 4.5 h. The reaction mixture was quenched with saturated aqueous $NaHCO_3$ (15 mL) and the aqueous layer was extracted three times with $CHCl_3$. The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1.8 x 20 cm), using EtOAc-hexane mixtures from 0% to 50% EtOAc, gave **79.3** (337 mg, 77%) as a solid: mp 94.5-97.5 °C; FTIR (CH_2Cl_2, cast) 3468,

3044, 2935, 2826, 1720, 1593, 1511, 1400 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.13 (d, *J* = 6.9, 3 H), 1.80-2.42 (br s, 1 H), 3.50 (s, 3 H), 3.58 (dd, *J* = 9.4, 11.5 Hz, 1 H), 3.70 (dd, *J* = 4.1, 11.5 Hz, 1 H), 5.19 (s, 2 H), 7.07 (apparent d, *J* = 8.9 Hz, 3.8 H), 7.16 (t, *J* = 7.4 Hz, 1 H), 7.24 (apparent d, *J* = 8.9 Hz, 2.1 H), 7.31 (t, *J* = 7.8 Hz, 2.1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 15.2 (q), 56.0 (d), 56.1 (q), 94.5 (t), 116.5 (d), 121.6 (d), 125.2 (d), 129.1 (d), 130.5 (d), 131.8 (s), 151.4 (s), 155.5 (s), 156.7 (s); exact mass *m/z* calcd for $C_{18}H_{21}NO_5$ 331.1420, found 331.1424.

(*S*)-(2-Hydroxy-1-methylethyl)[4-(methoxymethoxy)phenyl]carbamic Acid Phenyl Ester [(*S*)-79.3].

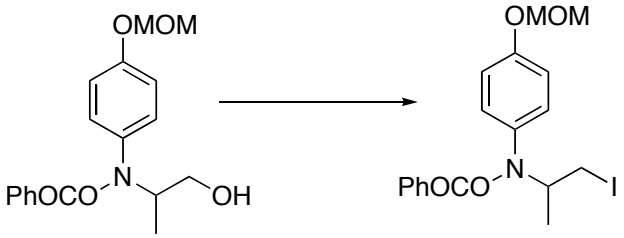


(*S*)-79.2 **(*S*)-79.3**

PhOCOCl (0.510 mL, 4.06 mmol) was injected rapidly into a stirred and cooled (-30 °C, acetone-dry ice) solution of (*S*)-**79.2** (0.7661 g, 3.626 mmol) and *i*-Pr_2NEt (0.708 mL, 4.06 mmol) in CH_2Cl_2 (18.5 mL). After 30 min, the cold bath was removed and stirring was continued for an additional 3.5 h. The reaction mixture was quenched with saturated aqueous $NaHCO_3$ (50 mL) and the aqueous layer was extracted three times with $CHCl_3$. The combined organic extracts were

dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (3 x 20 cm), using EtOAc-hexane mixtures from 10% to 50% EtOAc, gave (*S*)-**79.3** (1.14 g, 95%) as an oil: FTIR (CH_2Cl_2, cast) 3468, 2935, 1718, 1593, 1511, 1456, 1400 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ1.18 (d, *J* = 7.0 Hz, 3 H), 2.97 (br s, 1 H), 3.50 (s, 3 H), 3.56 (apparent dd, *J* = 9.5, 11.3 Hz, 1 H), 3.68 (apparent dd, *J* = 4.1, 11.6 Hz, 1 H), 4.49-4.59 (m, 1 H), 5.18 (s, 2 H), 7.06 (apparent d, *J* = 8.9 Hz, 3 H), 7.14 (t, *J* = 7.4 Hz, 1 H), 7.24 (apparent d, *J* = 8.9 Hz, 2 H), 7.30 (t, *J* = 7.8, 3 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ15.2 (q), 56.0 (q), 56.1 (d), 64.5 (t), 94.5 (t), 116.5 (d), 121.7 (d), 125.2 (d), 129.1 (d), 130.6 (d), 131.7 (s), 151.4 (s), 155.4 (s), 156.7 (s); exact mass *m/z* calcd for $C_{18}H_{21}NO_5$ 331.1420, found 331.1414.

(2-Iodo-1-methylethyl)[4-(methoxymethoxy)phenyl]carbamic Acid Phenyl Ester (79.4).

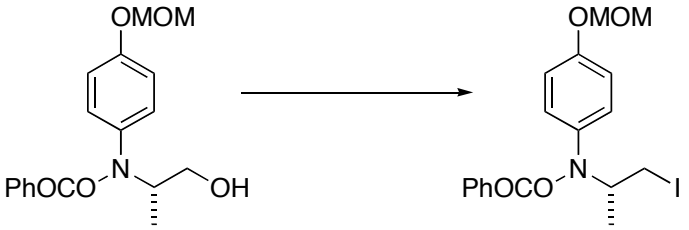


79.3 **79.4**

To a stirred and cooled (0 °C) solution of **79.3** (178 mg, 0.537 mmol) in dry THF (12 mL) was added imidazole (139 mg, 2.04 mmol), Ph_3P (380 mg, 1.45 mmol) and I_2 (355 mg, 1.397 mmol), in that order. After 1 h, the cold bath was

removed and stirring was continued for 1 h. The reaction mixture was quenched with a solution of saturated aqueous $Na_2S_2O_3$ (6 mL) and brine (6 mL). The aqueous layer was extracted four times with $CHCl_3$ and the combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1.8 x 24 cm), using EtOAc-hexane mixtures from 0% to 50% EtOAc, gave **79.4** (220 mg, 93%): FTIR (CH_2Cl_2, cast) 2956, 2899, 1720, 1511, 1313 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.37 (d, *J* = 6.8 Hz, 3 H), 3.26 (apparent dd, *J* = 6.3, 10.1 Hz, 1 H), 3.32-3.42 (br t, *J* = 8.6, 1 H), 3.50 (s, 3 H), 4.55-4.79 (br s, 1 H), 5.20 (s, 2 H), 7.08 (apparent d, *J* = 9.0, 4 H), 7.16 (t, *J* = 7.3, 1 H), 7.26-7.36 (apparent d, *J* = 9.0 Hz, 4 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 8.5 (t), 14.2 (q), 56.1 (q), 56.2 (d), 94.5 (t), 116.6 (d), 121.6 (d), 125.3 (d), 129.1 (d), 130.5 (d), 131.6 (s), 151.3 (s), 154.0 (s), 156.9 (s); exact mass *m/z* calcd for $C_{18}H_{20}NO_4I$ 441.0437, found 441.0436.

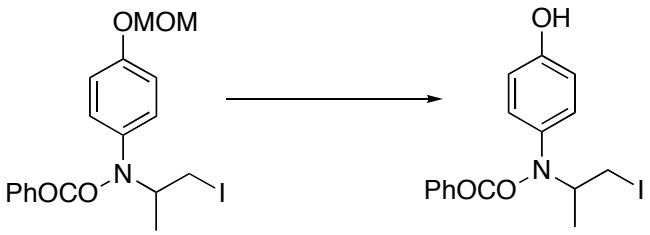
(*S*)-(2-Iodo-1-methylethyl)[4-(methoxymethoxy)phenyl]carbamic Acid Phenyl Ester [(*S*)-79.4].



(*S*)-79.3 **(*S*)-79.4**

To a stirred and cooled (0 °C) solution of (*S*)-**79.3** (392.0 mg, 1.183 mmol) in dry THF (24 mL) was added imidazole (306.0 mg, 4.495 mmol), Ph_3P (838.0 mg, 3.194 mmol) and I_2 (781.0 mg, 3.076 mmol), in that order. After 1 h, the cold bath was removed and stirring was continued for an additional 3 h. The reaction mixture was quenched with a solution of saturated aqueous $Na_2S_2O_3$ (15 mL) and brine (15 mL). The aqueous layer was extracted four times with $CHCl_3$ and the combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2.5 x 22 cm), using EtOAc-hexane mixtures from 2% to 10% EtOAc, gave (*S*)-**79.4** (512 mg, 98%): FTIR (CH_2Cl_2, cast) 2956, 1720, 1593, 1511, 1495, 1455, 1394, 1313 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ1.37 (d, *J* = 6.8 Hz, 3 H), 3.26 (apparent dd, *J* = 6.3, 10.1 Hz, 1 H), 3.38 (apparent t, *J* = 9.5 Hz, 1 H), 3.50 (s, 3 H), 4.55-4.75 (apparent br s, 1 H), 5.20 (s, 2 H), 7.01-7.11 (m, 3 H), 7.16 (apparent t, *J* = 8.8 Hz, 1 H), 7.27-7.37 (m, 5 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ8.6 (t), 18.9 (q), 56.1 (q), 56.1 (d), 94.5 (d), 116.6 (d), 121.6 (d), 125.3 (d), 129.1 (d), 130.3 (d), 131.6 (s), 151.3 (s), 154.0 (s), 156.9 (s); exact mass *m/z* calcd for $C_{18}H_{20}NO_4I$ 441.0437, found 441.0435.

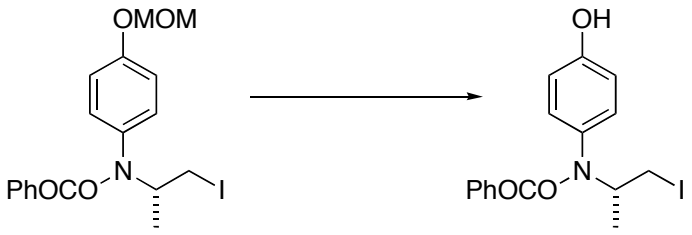
(4-Hydroxyphenyl)(2-iodo-1-methylethyl)carbamic Acid Phenyl Ester (79.5).



79.4 **79.5**

Me_3SiBr (0.230 mL, 1.75 mmol) was injected at a fast, dropwise rate into a stirred solution of **79.4** (79.0 mg, 0.175 mmol) in dry CH_2Cl_2 (6 mL). After 14 h, the reaction mixture was quenched with water (10 mL), and then partitioned between water and $CHCl_3$. The aqueous layer was extracted four times with $CHCl_3$, and the combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2.0 x 20 cm), using EtOAc-hexane mixtures from 2% to 25% EtOAc, gave **79.5** as a yellow semi-solid (67.2 mg, 95%): FTIR (CH_2Cl_2, cast) 3361, 2976, 1717, 1685, 1514, 1399 cm^{-1}; ^1H NMR (CD_3OD, 400 MHz) δ 1.28 (d, *J* = 6.7 Hz, 3 H), 3.10-3.44 (m, 2 H), 4.52-4.84 (br m, 1 H), 6.83 (apparent d, *J* = 8.9 Hz, 2 H), 7.00 (apparent d, *J* = 8.9 Hz, 1.5 H), 7.08-7.44 (m, 5.5 H); ^{13}C NMR (CD_3OD, 100 MHz) δ 8.8 (t), 19.1 (q), 57.4 (d), 116.7 (d), 122.7 (d), 126.5 (d), 130.1 (s), 130.3 (d), 152.8 (s), 156.2 (s), 158.7 (s); exact mass *m/z* calcd for $C_{16}H_{16}NO_3I$ 397.0175, found 397.0174.

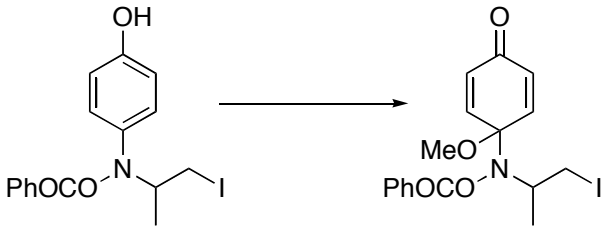
(*S*)-(4-Hydroxyphenyl)(2-iodo-1-methylethyl)carbamic Acid Phenyl Ester [(*S*)-79.5].



(*S*)-79.4 **(*S*)-79.5**

Me_3SiBr (0.930 mL, 7.05 mmol) was injected at a fast, dropwise rate into a stirred solution of (*S*)-**79.4** (311.0 mg, 0.7048 mmol) in dry CH_2Cl_2 (24 mL). After 9 h, the reaction mixture was quenched with water (40 mL), and then partitioned between water and $CHCl_3$. The aqueous layer was extracted four times with $CHCl_3$, and the combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1.8 x 23 cm), using EtOAc-hexane mixtures from 2% to 25% EtOAc, gave (*S*)-**79.5** as a yellow solid (270 mg, 96%): FTIR (CH_2Cl_2, cast) 3359, 2977, 1717, 1689, 1611, 1594, 1514, 1494, 1446, 1399, 1336 cm^{-1}; ^1H NMR (CD_3OD, 400 MHz) δ1.29 (d, *J* = 6.5 Hz, 3 H), 3.20-3.40 (br m, 2 H), 4.50-4.82 (br m, 1 H), 6.84 (apparent d, *J* = 8.9 Hz, 3 H), 6.94-7.07 (br m, 1.2 H), 7.10-7.43 (br m, 4.8 H); ^{13}C NMR (100 MHz, CD_3OD) δ8.7 (t), 19.1 (q), 57.5 (d), 116.7 (d), 122.7 (d), 126.5 (d), 130.1 (s), 130.3 (d), 131.7 (d), 152.8 (s), 156.2 (s), 158.7 (s); exact mass *m/z* calcd for $C_{16}H_{16}NO_3I$ 397.0175, found 397.0178.

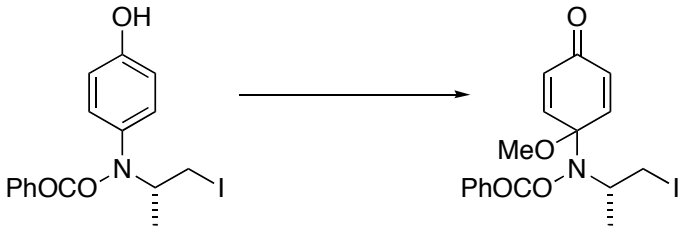
(2-Iodo-1-methylethyl)(1-methoxy-4-oxocyclohexa-2,5-dienyl)carbamic Acid Phenyl Ester (80.2).



79.5 **80.2**

$PhI(OAc)_2$ (71.0 mg, 0.220 mmol) was added to a stirred and cooled (0 °C) solution of **79.5** (70.0 mg, 0.176 mmol) in dry MeOH (15 mL). After 20 min the cold bath was removed and stirring was continued for 1 h 40 min, at which point the mixture was quenched with a mixed solution of 1 M aqueous $Na_2S_2O_3$ (12 mL) and saturated aqueous $NaHCO_3$ (12 mL). The aqueous layer was extracted three times with $CHCl_3$, dried (Na_2SO_4), and evaporated. Flash chromatography of the residue over silica gel (1.5 x 25 cm), using EtOAc-hexane mixtures from 0% to 25% EtOAc, gave the **80.2** (unknown mass and yield as unable to concentrate without decomposition): FTIR ($CHCl_3$, cast) 3335, 2974, 2937, 1717, 1670, 1507 cm^{-1}; unable to concentrate to acquire adequate ^1H and ^{13}C NMR; exact mass *m/z* calcd for $C_{17}H_{18}NO_4I$ 427.0281, found 427.0279.

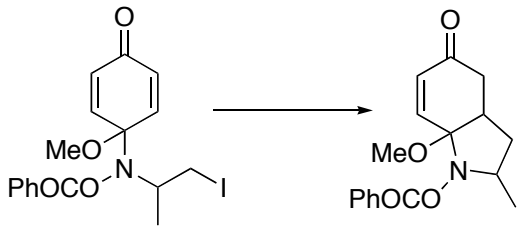
(*S*)-(2-Iodo-1-methylethyl)(1-methoxy-4-oxocyclohexa-2,5-dienyl)-carbamic Acid Phenyl Ester [(*S*)-80.2].



(*S*)-79.5 **(*S*)-80.2**

$PhI(OAc)_2$ (87.0 mg, 0.271 mmol) was added to a stirred and cooled (0 °C) solution of (*S*)-**79.5** (86.0 mg, 0.217 mmol) in dry MeOH (18.6 mL). After 20 min the cold bath was removed and stirring was continued for 1 h 30 min, at which point the mixture was quenched with a mixed solution of 1 M aqueous $Na_2S_2O_3$ (15 mL) and saturated aqueous $NaHCO_3$ (15 mL). The aqueous layer was extracted three times with $CHCl_3$, dried (Na_2SO_4), and evaporated. Flash chromatography of the residue on silica gel (1.5 x 29 cm), using EtOAc-hexane mixtures from 0% to 20% EtOAc, gave (*S*)-**80.2** (unknown mass and yield as unable to concentrate without decomposition): FTIR ($CHCl_3$, cast) 3337, 2973, 2834, 1721, 1625, 1594, 1493, 1453 cm^{-1}; unable to concentrate to acquire adequate ^1H and ^{13}C NMR; exact mass *m/z* calcd for $C_{17}H_{18}NO_4I$+Na 450.0173, found 450.0170.

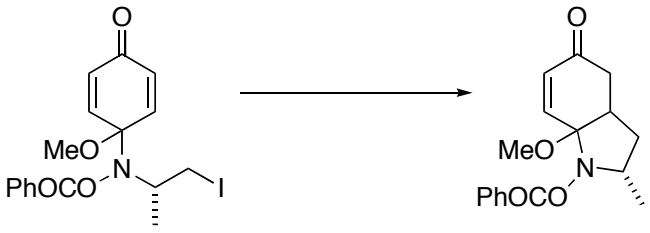
7a-Methoxy-2-methyl-5-oxo-2,3,3a,4,5,7a-hexahydroindole-1-carboxylic Acid Phenyl Ester (80.3).



80.2 **80.3**

A solution of Bu_3SnH (0.065 mL, 0.25 mmol) and AIBN (15.3 mg, 0.0930 mmol) in dry PhMe (6.8 mL) was added over 2 h by syringe pump to a stirred and heated (85 °C) solution of **80.2** (75.3 mg, 0.176 mmol, assuming previous reaction was quantitative) in dry PhMe (13.7 mL). Heating at 85 °C was continued for an additional 10 h, at which point the reaction mixture was cooled and evaporated. Flash chromatography of the residue over 10% finely ground KF/90% silica gel (1.5 x 22 cm), using EtOAc-hexane mixtures from 2% to 50% EtOAc, gave **80.3** (unknown mass and yield as unable to obtain without partial decomposition into aromatic, final product): FTIR (CH_2Cl_2, cast) 2965, 1719, 1684, 1506, 1494 cm^{-1}; unable to acquire adequate ^1H and ^{13}C NMR as both spectra were very complicated due to presence of aromatic final product; exact mass *m/z* calcd for $C_{17}H_{19}NO_4$ 301.1314, found 301.1317.

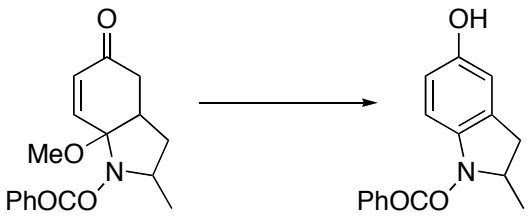
(2*S*)-7a-Methoxy-2-methyl-5-oxo-2,3,3a,4,5,7a-hexahydroindole-1-carboxylic Acid Phenyl Ester [(2*S*)-80.3].



(*S*)-80.2 **(2*S*)-80.3**

A solution of Bu_3SnH (0.080 mL, 0.30 mmol) and AIBN (19.0 mg, 0.116 mmol) in dry PhMe (8.4 mL) was added over 2 h by syringe pump to a stirred and heated (85 °C) solution of (*S*)-**80.2** (92.5 mg, 0.217 mmol, assuming previous reaction was quantitative) in dry PhMe (16.8 mL). Heating at 85 °C was continued for an additional 10 h, at which point the reaction mixture was cooled and evaporated. Flash chromatography of the residue over 10% finely ground KF/90% silica gel (1.5 x 25 cm), using EtOAc-hexane mixtures from 2% to 50% EtOAc, gave (2*S*)-**80.3** (unknown mass and yield as unable to obtain without partial decomposition into aromatic, final product): FTIR (CH_2Cl_2, cast) 3400, 2965, 2832, 1721, 1686, 1594, 1511, 1494, 1456, 1366 cm^{-1}; unable to acquire adequate ^1H and ^{13}C NMR as both spectra were very complicated due to presence of aromatic, final product; exact mass *m/z* calcd for $C_{17}H_{19}NO_4$ 301.1314, found 301.1315.

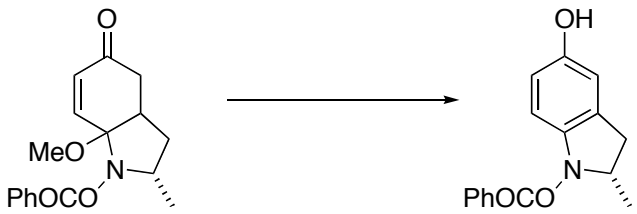
5-Hydroxy-2-methyl-2,3-dihydroindole-1-carboxylic Acid Phenyl Ester (80.4).



80.3 **80.4**

$TsOH{\cdot}H_2O$ (17.0 mg, 0.0895 mmol) was added to a stirred mixture of **80.3** (53.1 mg, 0.176 mmol, assuming quantitative yields for the last two steps) and 4Å molecular sieves (10 pieces) in $CHCl_3$ (6 mL, not dried). Stirring was continued for 45 min, and the mixture was filtered and evaporated. Flash chromatography of the residue over silica gel (1 x 25 cm), using EtOAc-hexane mixtures from 0% to 50% EtOAc, gave **80.4** (24.3 mg, 51% three-steps): FTIR (CH_2Cl_2, cast) 3370, 2973, 1689, 1490, 1408 cm^{-1}; ^1H NMR (DMSO-d6, 400 MHz, 80 °C) δ 1.33 (d, *J* = 6.4 Hz, 3 H), 2.62 (dd, *J* = 2.2, 16.0 Hz, 1 H), 3.37 (dd, *J* = 9.8, 16.6 Hz, 1 H), 4.58 (m, 1 H), 6.58 (dd, *J* = 2.8, 8.9 Hz, 1 H), 6.68 (apparent d, *J* = 2.8 Hz, 1 H), 7.18-7.26 (m, 3 H), 7.37-7.45 (m, 3 H), 8.85 (s, 1H); ^{13}C NMR (CD_3OD, 125 MHz) δ 21.6 (q), 37.0 (t), 57.4 (d), 113.5 (d), 114.6 (d), 116.5 (d), 117.2 (d), 122.9 (d), 126.7 (d), 130.5 (d), 131.9 (d), 133.3 (s), 134.6 (s), 152.4 (s), 155.2 (s); exact mass *m/z* calcd for $C_{16}H_{15}NO_3$ 269.1052, found 269.1053.

(2*S*)-5-Hydroxy-2-methyl-2,3-dihydroindole-1-carboxylic Acid Phenyl Ester [(*S*)-80.4].

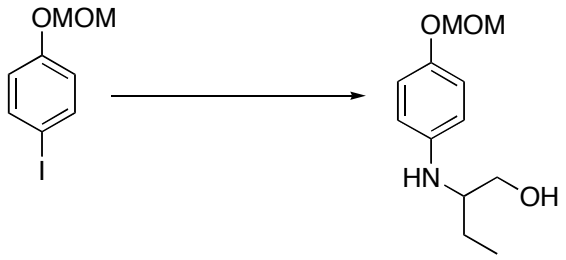


(2*S*)-80.3 **(*S*)-80.4**

$TsOH{\cdot}H_2O$ (18.0 mg, 0.0955 mmol) was added to a stirred mixture of (2*S*)-**80.3** (36.0 mg, 0.119 mmol, assuming quantitative yields for the last two steps) and 4Å molecular sieves (10 pieces) in $CHCl_3$ (5 mL, not dried). Stirring was continued for 30 min, and the mixture was filtered and evaporated. Flash chromatography of the residue over silica gel (1 x 27 cm), using EtOAc-hexane mixtures from 0% to 50% EtOAc, gave (*S*)-**80.4** (32.4 mg, 56% three-steps): FTIR (CH_2Cl_2, cast) 3387, 1716, 1694, 1652, 1605, 1490, 1456, 1409 cm^{-1}; ^1H NMR (400 MHz, CD_3OD) δ1.40 (apparent d, *J* = 5.5 Hz, 3 H), 2.66 (apparent d, *J* = 16.1 Hz, 1 H), 3.40 (apparent dd, *J* = 8.0, 16.0 Hz, 1 H), 4.45-4.81 (br m, 1 H), 6.61 (apparent d, *J* = 8.5 Hz, 1 H), 6.67-6.71 (m, 0.9 H), 6.82 (apparent d, *J* = 8.7 Hz, 0.1 H), 6.87-7.02 (br m, 0.1 H), 7.07 (apparent d, *J* = 8.7 Hz, 0.1 H), 7.18 (d, *J* = 7.8 Hz, 2 H), 7.24 (t, *J* = 7.5 Hz, 1.0 H), 7.40 (apparent t, *J* = 7.8 Hz, 2.2 H), 7.49-7.59 (br d, *J* = 8.2 Hz, 0.6 H); ^{13}C NMR (100 MHz, CD_3OD) δ 21.6 (q), 37.0 (t), 57.4 (d), 113.5 (d), 113.6 (d), 117.1 (d), 122.9 (d), 126.7 (d), 130.5 (d), 133.3

(s), 134.6 (s), 152.4 (s), 152.7 (s), 155.3 (s); exact mass *m/z* calcd for $C_{15}H_{15}NO_3$ 269.1052, found 269.1053.

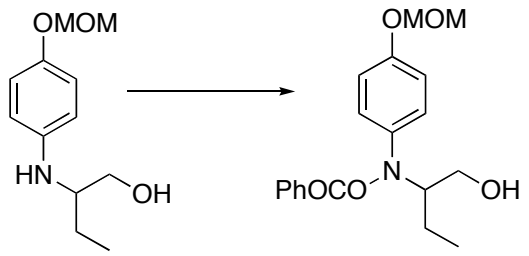
2-[[4-(Methoxymethoxy)phenyl]amino]butan-1-ol (81.2).



62.1 **81.2**

Into an oven-dried, nitrogen-flushed, one-piece round bottom flask and reflux condenser assembly was placed **62.1** (1.756 g, 5.735 mmol). Copper(I) iodide (0.218 g, 1.42 mmol), 2-amino-1-butanol (2.045 g, 22.94 mmol), L-proline (0.264 g, 2.29 mmol), and oven-dried K_2CO_3 (1.585 g, 11.47 mmol) where then added consecutively. Dry DMSO was then added (5.35 mL) and the mixture was lowered into an oil bath preset at 80 °C and stirring was continued for 12 h. The mixture was cooled to room temperature and partitioned between water and $CHCl_3$. The aqueous layer was extracted three times with $CHCl_3$ and the combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2.5 x 35 cm), using EtOAc-hexane mixtures from 0% to 50% EtOAc, gave the **81.2** (1.18 g, 79%): Spectral data previously reported.[56]

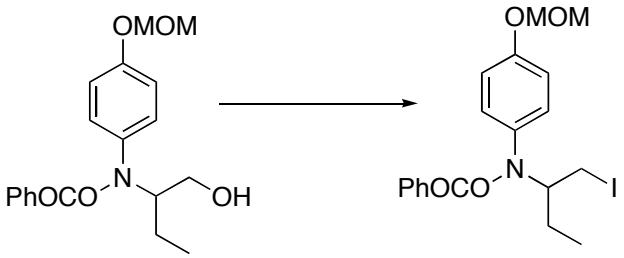
[(1-Hydroxymethyl)propyl][4-(methoxymethoxy)phenyl]carbamic Acid Phenyl Ester (81.3).



81.2 **81.3**

PhOCOCl (0.552 mL, 4.40 mmol) was injected rapidly into a stirred and cooled (-30 °C, acetone-dry ice) solution of **81.2** (0.830 g, 3.93 mmol) and *i*-Pr_2NEt (0.766 mL, 4.40 mmol) in dry CH_2Cl_2 (20 mL). After 30 min, the cold bath was removed and stirring was continued for an additional 11.5 h. The reaction mixture was quenched with saturated aqueous $NaHCO_3$ (25 mL) and the aqueous layer was extracted three times with $CHCl_3$. The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2.5 x 23 cm), using EtOAc-hexane mixtures from 0% to 50% EtOAc, gave **81.3** (1.15 g, 94%) as yellow oil: Spectral data previously reported.[56]

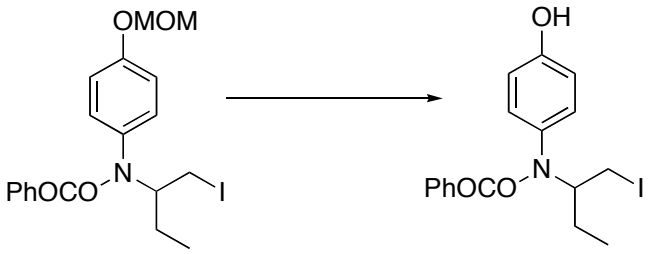
[(1-Iodomethyl)propyl][4-(methoxymethoxy)phenyl]carbamic Acid Phenyl Ester (81.4).



81.3 **81.4**

To a stirred and cooled (0 °C) solution of **81.3** (386 mg, 1.11 mmol) in dry THF (30 mL) was added imidazole (286 mg, 4.20 mmol), Ph_3P (783 mg, 2.98 mmol) and I_2 (729 mg, 2.87 mmol), in that order. After 1 h, the cold bath was removed and stirring was continued for 12 h. The reaction mixture was quenched with a solution of saturated aqueous $Na_2S_2O_3$ (13 mL) and brine (13 mL). The aqueous layer was extracted four times with $CHCl_3$ and the combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2.8 x 27 cm), using EtOAc-hexane mixtures from 2% to 20% EtOAc, gave **81.4** (510 mg, 96%): Spectral data previously reported.[56]

(4-Hydroxyphenyl)[(1-iodomethyl)propyl]carbamic Acid Phenyl Ester (81.5).

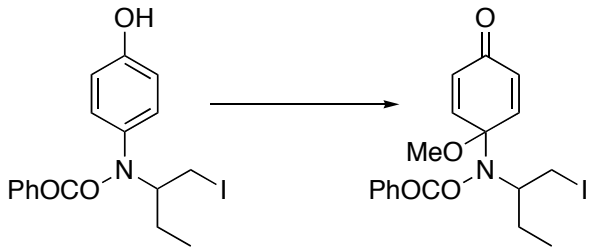


81.4 **81.5**

Me_3SiBr (0.308 mL, 2.33 mmol) was injected at a fast, dropwise rate into a stirred solution of **81.4** (128.5 mg, 0.2912 mmol) in dry CH_2Cl_2 (11 mL). After 28 h, an additional portion of Me_3SiBr (0.096 mL, 0.73 mmol) was added, and stirring was continued for a further 1.5 h. The mixture was quenched with water (15 mL), and then partitioned between water and $CHCl_3$. The aqueous layer was extracted three times with $CHCl_3$, and the combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1.7 x 23 cm), using EtOAc-hexane mixtures from 0% to 50% EtOAc, gave **81.5** as a colourless solid (94.2 mg, 83%): FTIR (CH_2Cl_2, cast) 3366, 2967, 2934, 2877, 1719, 1690, 1515, 1400 cm^{-1}; ^1H NMR (CD_3OD, 500 MHz) δ 1.02-1.20 (apparent br t, J = 7.0 Hz, 3 H), 1.50-1.73 (m, 2 H), 3.09 (t, J = 10.0 Hz, 1 H), 3.40 (apparent dd, J = 4.1, 10.5 Hz, 0.9 H), 3.54 (dd, J = 4.1, 11.0 Hz, 0.1 H), 4.38-4.69 (br m, 1 H), 6.84 (d, J = 8.9 Hz, 2.1 H), 7.00 (d, J = 7.6 Hz, 1.5 H), 7.10-7.22 (apparent br t, J = 7.2 Hz, 1.8 H), 7.22-7.42 (m, 3.6 H); ^{13}C NMR

(CD_3OD, 100 MHz) δ 7.6 (t), 12.0 (q), 27.0 (t), 63.7 (d), 116.7 (d), 122.6 (d), 126.4 (d), 129.7 (s), 130.3 (d), 131.6 (d), 152.9 (s), 157.0 (s), 158.7 (s); exact mass *m/z* calcd for $C_{17}H_{18}NO_3I$ 411.0331, found 411.0337.

[1-(Iodomethyl)propyl](1-methoxy-4-oxocyclohexa-2,5-dienyl)carbamic Acid Phenyl Ester (82.2).

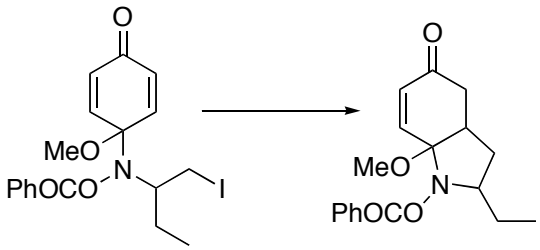


81.5 **82.2**

$PhI(OAc)_2$ (48.1 mg, 0.149 mmol) was added to a stirred and cooled (0 °C) solution of **81.5** (49.4 mg, 0.120 mmol) in dry MeOH (10.2 mL). After 20 min the cold bath was removed and stirring was continued for 3 h, at which point the mixture was quenched with a mixed solution of 1 M aqueous $Na_2S_2O_3$ (6 mL) and saturated aqueous $NaHCO_3$ (6 mL). The aqueous layer was extracted three times with $CHCl_3$, dried (Na_2SO_4), and evaporated. Flash chromatography of the residue over silica gel (1.5 x 17 cm), using EtOAc-hexane mixtures from 0% to 20% EtOAc, gave **82.2** (unknown mass and yield as unable to concentrate without decomposition): FTIR (CH_2Cl_2, cast) 3370, 2967, 2936, 1722, 1690, 1672, 1631,

1593 cm^{-1}; unable to concentrate to acquire adequate ^{1}H and ^{13}C NMR; exact mass *m/z* calcd for $C_{18}H_{20}NO_4I$ 441.0437, found 441.0432.

2-Ethyl-7a-methoxy-5-oxo-2,3,3a,4,5,7a-hexahydroindole-1-carboxylic Acid Phenyl Ester (82.3).

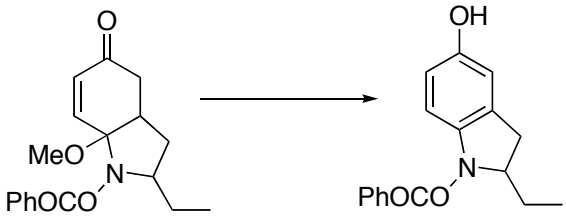


82.2 **82.3**

A solution of Bu_3SnH (0.044 mL, 0.17 mmol) and AIBN (10.4 mg, 0.0634 mmol) in dry PhMe (5.7 ml) was added over 2 h by syringe pump to a stirred and heated (85 °C) solution of **82.2** (52.8 mg, 0.120 mmol, assuming previous reaction was quantitative) in dry PhMe (13 mL). Heating at 85 °C was continued for an additional 9 h, at which point the reaction mixture was cooled and evaporated. Flash chromatography of the residue over 10% finely ground KF/90% silica gel (1.5 x 14 cm), using EtOAc-hexane mixtures from 2% to 50% EtOAc, gave **82.3** (unknown mass and yield as unable to obtain without partial decomposition into aromatic, final product): FTIR (CH_2Cl_2, cast) 3407, 2965, 2877, 1720, 1686, 1512, 1494, 1456 cm^{-1}; unable to acquire adequate ^{1}H and ^{13}C

NMR as both spectra were very complicated due to presence of aromatic, final product; exact mass *m/z* calcd for $C_{18}H_{21}NO_4$ 315.1471, found 315.1466.

2-Ethyl-5-hydroxy-2,3-dihydroindole-1-carboxylic Acid Phenyl Ester (82.4).

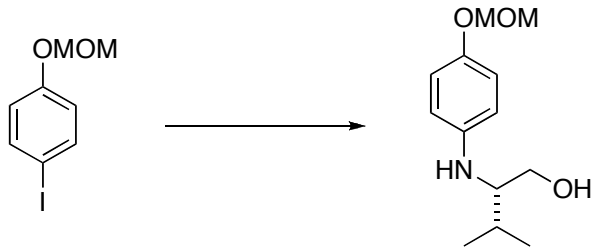


82.3 **82.4**

$TsOH{\cdot}H_2O$ (11.0 mg, 0.0563 mmol) was added to a stirred mixture of **82.3** (22.2 mg, 0.0704 mmol, assuming quantitative yields for the last two steps) and 4Å molecular sieves (10 pieces) in $CHCl_3$ (6 mL, not dried). Stirring was continued for 45 min, and the mixture was filtered and evaporated. Flash chromatography of the residue twice over silica gel (1 x 25 cm), using EtOAc-hexane mixtures from 2% to 50% EtOAc, gave **82.4** (18.6 mg, 55% over three-steps): FTIR (microscope) 3413, 3041, 2966, 2877, 1694, 1606, 1477, 1411 cm^{-1}; ^1H NMR (CD_3OD, 500 MHz) δ 0.93 (apparent br s, 3 H), 1.55-1.95 (apparent br m, 2 H), 2.79 (d, *J* = 15.7 Hz, 1 H), 3.29-3.38 (br m, 1 H), 4.38-4.68 (br m, 1 H), 6.56-6.63 (m, 0.9 H), 6.68 (s, 0.9 H), 6.71-6.75 (m, 0.1 H), 6.77-6.88 (m, 0.1 H), 6.90-7.05 (m, 0.2 H), 7.10-7.20 (m, 1.9 H), 7.20-7.27 (m, 1 H), 7.30-7.45 (m, 2.2 H), 7.45-7.60 (s, 0.7 H); ^{13}C NMR (CD_3OD, Hz) δ 9.4 (q), 28.9 (t), 34.2 (t), 62.5

(d), 113.1 (d), 114.4 (d), 116.9 (d), 122.8 (d), 126.6 (d), 130.4 (d), 133.6 (s), 135.3 (s), 152.2 (s), 152.8 (s), 155.1 (s); exact mass *m/z* calcd for $C_{17}H_{17}NO_3$ 283.1209, found 283.1213.

(*S*)-2-(4-(Methoxymethoxy)phenylamino)-3-methylbutan-1-ol (83.3).

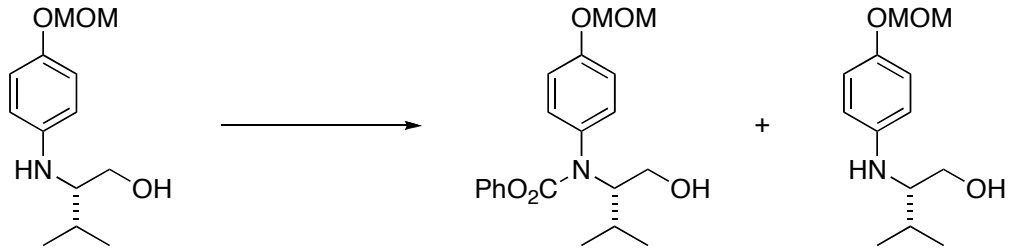


62.1 **83.3**

Into an oven-dried, nitrogen-flushed, one-piece round bottom flask and reflux condenser assembly was placed **62.1** (0.216 g, 0.757 mmol). Copper(I) iodide (0.0291 g, 0.152 mmol), amino alcohol **83.2** (0.346 g, 3.03 mmol), L-proline (0.0350 g, 0.303 mmol), and oven-dried K_2CO_3 (0.209 g, 1.52 mmol) were then added consecutively. Dry DMSO was then added (0.83 mL) and the mixture was lowered into an oil bath preset at 80 °C and stirring was continued for 24.5 h. The mixture was cooled to room temperature and partitioned between water and $CHCl_3$. The aqueous layer was extracted three times with $CHCl_3$ and the combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2.0 x 23 cm), using EtOAc-hexane mixtures from 0% to 50% EtOAc, gave **83.3** (139 mg, 71%): FTIR (CH_2Cl_2 cast)

3387, 2957, 2825, 1616 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.97 (d, *J* = 6.8 Hz, 3 H), 0.99 (d, *J* = 6.9 (, H;Hz, 3 H), 1.88 (apparent octet, *J* = 6.5 Hz, 1 H), 3.2 (ddd, *J* = 9.1, 9.1, 4.3 Hz), 3.47 (s, 3 H), 3.47-3.54 (m, 1 H), 3.77 (dd, *J* = 10.9, 4.2 Hz, 1 H), 5.15 (s, 2 H), 6.63 (apparent d, *J* = 9.0 Hz, 2 H), 6.89 (apparent d, *J* = 8.9 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 18.9 (q), 19.2 (q), 30.2 (d), 55.8 (d), 62.2 (d), 62.5 (t), 95.5 (t), 115.2 (d), 118.0 (d), 143.4 (s), 149.9 (s); exact mass *m*/*z* calcd for CH_, found .$C_{13}H_{21}NO_3$ 239.1522, found 239.1521.

(*S*)-Phenyl 1-Hydroxy-3-methylbutan-2-yl(4-(methoxymethoxy)-phenyl)carbamate (83.4).

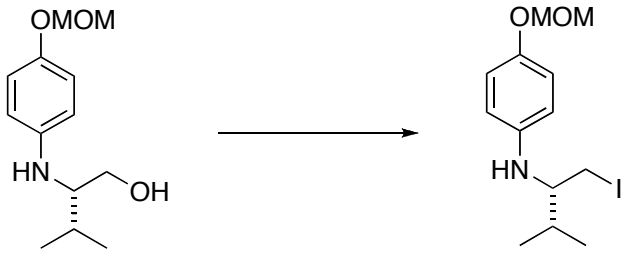


83.3 **83.4** **83.3**

PhOCOCl (0.050 mL, 0.40 mmol) was injected rapidly into a stirred and cooled (-30 °C, acetone-dry ice) solution of **83.3** (0.160 g, 0.669 mmol) in CH_2Cl_2 (5 mL). After 25 min, *i*-Pr_2NEt (0.070 mL, 0.40 mmol) was added and the cold bath was removed. After a further 20 min, the cold bath was replaced and additional PhOCOCl (0.050 mL, 0.40 mmol) was injected rapidly. The cold bath was removed and stirring was continued for 14 h. The reaction mixture was

quenched with saturated aqueous $NaHCO_3$ (15 mL) and the aqueous layer was extracted three times with $CHCl_3$. The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1.8 x 22 cm), using EtOAc-hexane mixtures from 0% to 30% EtOAc, gave **83.4** (99.7 mg, *ca.* 42%) as an oil that could not be separated from a minor component (**83.3**) comprising < 10% of the mixture. Satisfactory spectral data of pure **83.4** was not obtained.

(*S*)-*N*-(1-Iodo-3-methylbutan-2-yl)-4-(methoxymethoxy)aniline (84.1).

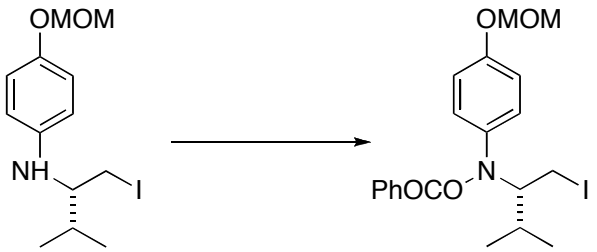


83.3 **84.1**

To a stirred and cooled (0 °C) solution of **83.3** (61.8 mg, 0.258 mmol) in dry THF (5 mL) was added imidazole (66.8 mg, 0.982 mmol), Ph_3P (182.9 mg, 0.6974 mmol) and I_2 (166.4 mg, 0.6556 mmol), in that order. After 1 h, the cold bath was removed and stirring was continued for 13.5 h. The reaction mixture was quenched with a solution of saturated aqueous $Na_2S_2O_3$ (3 mL) and brine (3 mL). The aqueous layer was extracted four times with $CHCl_3$ and the combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of

the residue over silica gel (1 x 26 cm), using EtOAc-hexane mixtures from 0% to 10% EtOAc, gave **84.1** (60.8 mg, 67%): FTIR (CH_2Cl_2 cast) 3385, 2960, 1734, 1615, 1511 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.00 (d, J = 6.5, 3 H), 1.03 (d, J = 6.8 Hz, 3 H), 1.40-1.49 (m, 1 H), 3.39 (dd, J = 14.4, 5.0 Hz, 1 H), 3.42-3.53 (m, 4 H), 3.77-3.90 (br s, 1 H), 4.38-4.42 (m, 1 H), 5.08 (s, 2 H), 6.59 (apparent d, J = 8.7 Hz, 2 H), 6.93 (apparent d, J = 8.7 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 20.3 (q), 23.0 (q), 32.4 (d), 50.2 (d), 51.4 (t), 55.8 (q), 95.5 (t), 114.5 (d), 118.0 (d), 142.1 (s), 150.0 (s); exact mass *m*/*z* calcd for $C_{13}H_{20}O_2NI$ 349.0539, found 349.0540.

[(*S*)-1-Iodo-3-methylbut-2-yl][4-(methoxymethoxy)phenyl]carbamic Acid Phenyl Ester (85.3).

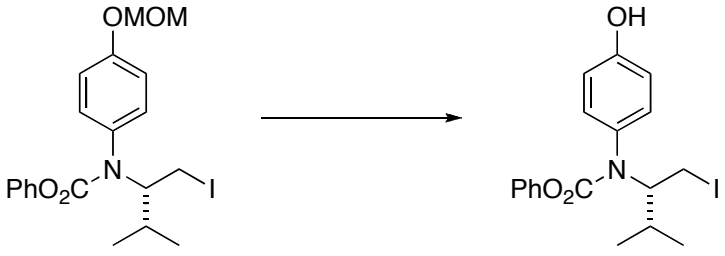


84.1 **85.3**

PhOCOCl (0.016 mL, 0.13 mmol) was injected rapidly into a stirred and cooled (-30 °C, acetone-dry ice) solution of **84.1** (0.040 g, 0.12 mmol) in CH_2Cl_2 (9.5 mL). After 15 min, *i*-Pr_2NEt (0.022 mL, 0.126 mmol) was added and the cold bath was removed. After an additional 2 h, the reaction was quenched with

saturated aqueous $NaHCO_3$ (5 mL) and the aqueous layer was extracted three times with $CHCl_3$. The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1.6 x 21 cm), using EtOAc-hexane mixtures from 0% to 10% EtOAc, gave **85.3** (53.8 mg, 100%): FTIR (CH_2Cl_2 cast) 2962, 1723, 1593, 1511 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.20 (d, *J* = 6.6 Hz, 3 H), 1.18-1.37 (m, 3 H), 1.86-2.04 (m, 1 H), 2.92-3.20 (m, 1 H), 3.49 (s, 3 H), 3.60-3.74 (m, 1 H), 4.22-4.45 (m, 1 H), 5.20 (s, 2 H), 7.07 (d, *J* = 9.2 Hz, 3 H), 7.10-7.26 (m, 2 H), 7.26-7.42 (m, 2 H), 7.42-7.51 (m 2 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 6.5 (d), 20.1 (q), 21.4 (q), 31.9 (d), 56.1 (q), 94.5 (t), 116.5 (d), 121.6 (d), 125.2 (d), 129.1 (d), 130.1 (d), 151.4 (s), 154.8 (s), 156.7 (s); exact mass *m*/*z* calcd for $C_{20}H_{24}O_4NI$ 469.0750, found 469.0755.

(*S*)-Phenyl 4-Hydroxyphenyl(1-iodo-3-methylbutan-2-yl)carbamate (85.4).

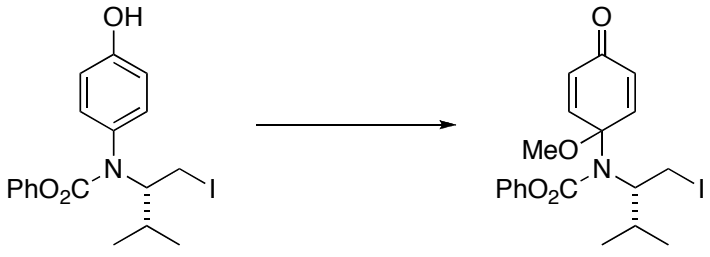


85.3 **85.4**

Me_3SiBr (0.196 mL, 1.49 mmol) was injected at a fast, dropwise rate into a stirred solution of **85.3** (0.0872 mg, 0.186 mmol) in dry CH_2Cl_2 (6.8 mL). After

7 h, the reaction mixture was quenched with water (20 mL) and then partitioned between water and $CHCl_3$. The aqueous layer was extracted four times with $CHCl_3$, and the combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1.8 x 25 cm), using EtOAc-hexane mixtures from 0% to 20% EtOAc, gave **85.4** as a yellow solid (79.0 mg, 100%): FTIR (CH_2Cl_2 cast) 3152, 2964, 1720, 1593, 1516 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.95-1.03 (m, 3 H), 1.20-1.34 (m, 3 H), 1.78-1.95 (m, 1 H), 2.82-3.10 (m, 1 H), 3.60-3.69 (m, 1 H), 4.24-4.48 (m, 1 H), 6.18 (s, 1 H), 6.56-6.79 (m, 2 H), 7.06 (d, J = 7.9 Hz, 1 H), 7.14 (t, J = 7.3 Hz, 1 H), 7.16-7.42 (m, 5 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 6.5 (t), 7.0 (t), 20.0 (q), 20.1 (q), 21.3 (q), 21.5 (q), 66.98 (d), 66.99 (d), 115.8 (d), 116.4 (d), 121.6 (d), 121.8 (d), 121.9 (d), 125.3 (d), 125.7 (d), 129.2 (d), 129.3 (d), 129.4 (d), 130.1 (d), 151.1 (s), 151.4 (s), 155.4 (s), 155.7 (s), 156.20 (s), 156.24 (s) [duplicate signals dues to rotamers]; exact mass m/z calcd for $C_{18}H_{20}O_3NI$ 425.0488, found 425.0495.

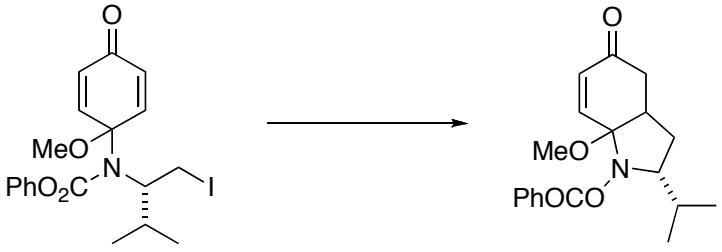
(*S*)-Phenyl 1-Iodo-3-methylbutan-2-yl(1-methoxy-4-oxocyclohexa-2,5-dienyl)carbamate (86.2).



85.4 **86.2**

$PhI(OAc)_2$ (76.0 mg, 0.232 mmol) was added to a stirred and cooled (0 °C) solution of **85.4** (79.0 mg, 0.186 mmol) in dry MeOH (16 mL). After 20 min the cold bath was removed and stirring was continued for 4.5 h, at which point the mixture was quenched with a mixed solution of 1 M aqueous $Na_2S_2O_3$ (8 mL) and saturated aqueous $NaHCO_3$ (8 mL). The aqueous layer was extracted three times with $CHCl_3$ and the combined organic extracts were dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (1.5 x 22 cm), using EtOAc-hexane mixtures from 0% to 20% EtOAc, gave **86.2** (unknown mass and yield as unable to concentrate without decomposition): FTIR ($CHCl_3$, cast) 3368, 3044, 2965, 2873, 2833, 1722, 1674, 1632, 1592 cm^{-1}; unable to concentrate to acquire adequate ^1H and ^{13}C NMR; exact mass *m/z* calcd for $C_{19}H_{22}NO_4I$ 455.0594, found 455.0599.

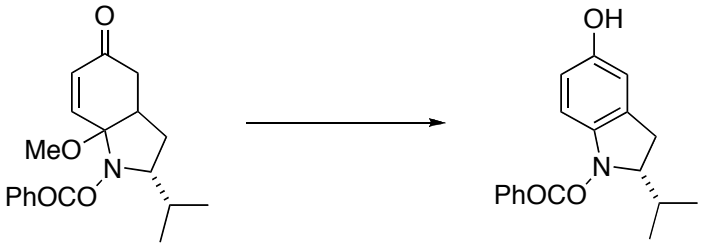
(2*R*)-2-Isopropyl-7a-methoxy-5-oxo-2,3,3a,4,5,7a-hexahydro-1*H*-indol-1-yl Benzoate (86.3).



86.2 **86.3**

A solution of Bu_3SnH (0.069 mL, 0.26 mmol) and AIBN (20.1 mg, 0.123 mmol) in dry PhMe (20 mL) was added over 2.5 h by syringe pump to a stirred and heated (85 °C) solution of **86.2** (84.6 mg, 0.186 mmol, assuming previous reaction was quantitative) in dry PhMe (9 mL). Heating at 85 °C was continued for an additional 11 h, at which point the reaction mixture was cooled and evaporated. Flash chromatography of the residue over 10% finely ground KF/90% silica gel (1.5 x 22 cm), using EtOAc-hexane mixtures from 0% to 50% EtOAc, gave **86.3** (unknown mass and yield of desired product as unable to obtain without partial decomposition into aromatic, final product) as two separable diastereomers (less-polar partially aromatized diastereomer: 15.5 mg; more-polar partially aromatized diastereomer: 25.5 mg): FTIR (CH_2Cl_2, cast) 3405, 2962, 1718, 1595, 1511 cm-1; unable to acquire adequate ^1H and ^{13}C NMR as both spectra were very complicated due to presence of aromatic, final product; exact mass *m/z* calcd for $C_{19}H_{23}NO_4$ 329.1627, found 329.1626.

(*R*)-5-Hydroxy-2-isopropylindolin-1-yl Benzoate (86.4).

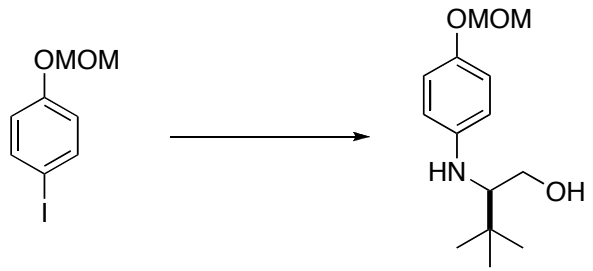


86.3 **86.4**

$TsOH \cdot H_2O$ (7.0 mg, 0.037 mmol) was added to a stirred mixture of **86.3** (less-polar fraction, 13.5 mg, 0.0410 mmol, assuming pure) and 4Å molecular sieves (10 pieces) in $CHCl_3$ (10 mL, not dried). Stirring was continued for 5.5 h, and the mixture was filtered and evaporated. Flash chromatography of the residue over silica gel (1 x 24 cm), using EtOAc-hexane mixtures from 0% to 20% EtOAc, gave **86.4** (9.4 mg, *ca.* 77%). (three-step yield from iodophenol **85.4**, including yield of more polar reacted fractions **86.3** below: 53%): FTIR (CH_2Cl_2 cast) 3379, 2962, 2874, 1717, 1685, 1653, 1606 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.79 (d, J = 6.9 Hz, 3 H), 0.90-1.03 (m, 3 H), 1.28 (apparent s, 1 H), 2.20-2.40 (br s, 1 H), 2.80-2.95 (m, 1 H), 4.40-4.67 (m, 1 H), 6.56-6.63 (m, 1 H), 6.67-6.70 (m, 1 H), 7.16 (d, J = 8.0 Hz, 2 H), 7.24 (t, J = 7.4 Hz, 1 H), 7.37-7.45 (m, 2 H), 7.45-7.56 (m, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 16.0 (q), 18.8 (q), 30.4 (t), 33.0 (t), 66.1 (d), 112.6 (d) 114.3 (d), 116.5 (d), 122.5 (d), 126.5 (d), 130.1 (d), 131.1 (s), 134.2 (s), 135.9 (s), 152.1 (s), 153.0 (s), 155.0 (s); exact mass m/z calcd for $C_{18}H_{19}NO_3$ 297.1365, found 297.1362.

$TsOH \cdot H_2O$ (13.0 mg, 0.0683 mmol) was added to a stirred mixture of **86.3** (more-polar fraction, 24.5 mg, 0.0744 mmol, assuming pure) and 4Å molecular sieves (10 pieces) in $CHCl_3$ (15 mL, not dried). Stirring was continued for 3 h, and the mixture was filtered and evaporated. Flash chromatography of the residue over silica gel (1 x 24 cm), using EtOAc-hexane mixtures from 0% to 20% EtOAc, gave **86.4** (11.3 mg, *ca.* 51%). (three-step yield from iodophenol **85.4**, including above **86.4**: 53%).

(*R*)-2-[4-(Methoxymethoxy)phenylamino]-3,3-dimethylbutan-1-ol (87.3).

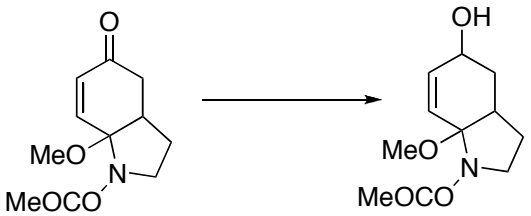


62.1 **87.3**

Into an oven-dried, nitrogen-flushed, one-piece round bottom flask and reflux condenser assembly was placed **62.1** (0.1000 g, 0.3787 mmol). Copper(I) iodide (0.0144 g, 0.0757 mmol), amino alcohol **87.2** (0.2219 g, 1.894 mmol), L-proline (0.0174 g, 0.152 mmol), and oven-dried K_2CO_3 (0.1047 g, 0.7574 mmol) where then added consecutively. Dry DMSO was then added (0.36 mL) and the mixture was lowered into an oil bath preset at 80 °C and stirring was continued for 40 h. The mixture was cooled to room temperature and partitioned between water and $CHCl_3$. The aqueous layer was extracted three times with $CHCl_3$ and the combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2.0 x 20 cm), using EtOAc-hexane mixtures from 10% to 100% EtOAc, gave **87.3** (43.1 mg, 45%): FTIR (CH_2Cl_2 cast) 3389, 2961, 2826, 1613, 1512, 1463 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.98 (s, 9 H), 2.00-3.05 (br s, 1 H), 3.17-3.29 (br s, 1 H), 3.40-3.47 (m, 1 H), 3.48 (s, 3 H), 3.78-3.90 (br s, 1 H), 5.07 (s, 2 H), 6.50-6.83 (br s, 2 H), 6.89 (d, *J* = 8.7

Hz, 2 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 27.1 (q), 35.0 (d), 55.8 (q), 62.1 (t), 65.5 (d), 95.5 (t), 114.8 (d), 118.0 (d), 114.8 (s), 149.6 (s); exact mass *m*/*z* calcd for $C_{14}H_{23}NO_3$ 253.1678, found 253.1675.

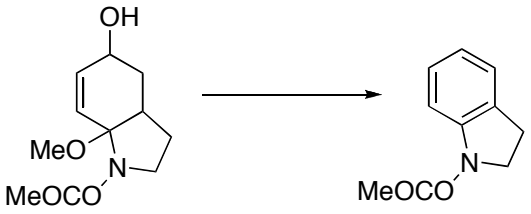
5-Hydroxy-2,3-dihydroindole-1-carboxylic Acid Methyl Ester (88.2).



78.6 **88.2**

$CeCl_3 \cdot 7H_2O$ (194.3 mg, 0.5214 mmol) was added to a stirred and cooled (-78 °C) (acetone-dry ice) solution of **78.6** (53.4 mg, 0.237 mmol) in dry MeOH (5 mL). $NaBH_4$ (9.9 mg, 0.26 mmol) was then added and the cold bath was removed. After 5 min the reaction mixtire was quenched with water (5 mL) and the aqueous layer was extracted four times with Et_2O. The combined organic extracts were washed with brine, dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (1.1 x 22 cm), using EtOAc-hexane mixtures from 50% to 100% EtOAc (which contained approximately 0.5% Et_3N), gave **88.2** (24.8 mg, 46% three steps): FTIR (microscope) 3436, 2928, 1717, 1447, 1390 cm^{-1}; unable to acquire adequate ^{1}H and ^{13}C NMR as both spectra were very complicated due to presence of diastereomers and partially aromatized product; exact mass *m/z* calcd for $C_{11}H_{17}NO_4$ 227.1158, found 227.1155.

2,3-Dihydroindole-1-carboxylic Acid Methyl Ester (88.3).



88.2 **88.3**

$TsOH{\cdot}H_2O$ (18.2 mg, 0.0958 mmol) was added to a stirred mixture of **88.2** (24.8 mg, 0.109 mmol) and 4Å molecular sieves (10 pieces) in $CHCl_3$ (5 mL, not dried). After 20 min, an additional portion of $TsOH.H_2O$ (18.2 mg, 0.0958 mmol) was added and stirring was continued for 15 min, at which point the mixture was filtered and evaporated. Flash chromatography of the residue over silica gel (0.9 x 15 cm), using EtOAc-hexane mixtures from 5% to 25% EtOAc, gave **88.3** (13.7 mg, 71%): FTIR (microscope) 2918, 2850, 1716, 1489, 1444, 1396 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 3.13 (t, *J* = 8.7 Hz, 2 H), 3.85 (s, 3 H), 4.02 (apparent t, *J* = 8.3 Hz), 6.96 (dt, *J* = 1.0, 7.5 Hz, 1 H), 7.12-7.22 (m, 2 H), 7.30-7.74 (br m, 0.35 H), 7.74-8.02 (br s, 0.65 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 27.6 (t), 47.4 (t), 52.5 (q), 114.7 (d), 122.5 (d), 124.7 (d), 127.5 (d), 130.8 (s), 142.6 (s), 153.6 (s); exact mass *m/z* calcd for $C_{10}H_{11}NO_2$ 177.0790, found 177.0786.

4 *References and footnotes*

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CHAPTER 2

SYNTHESIS OF REGIOSELECTIVELY SUBSTITUTED BENZENE RINGS

1 INTRODUCTION

1.1 *General*

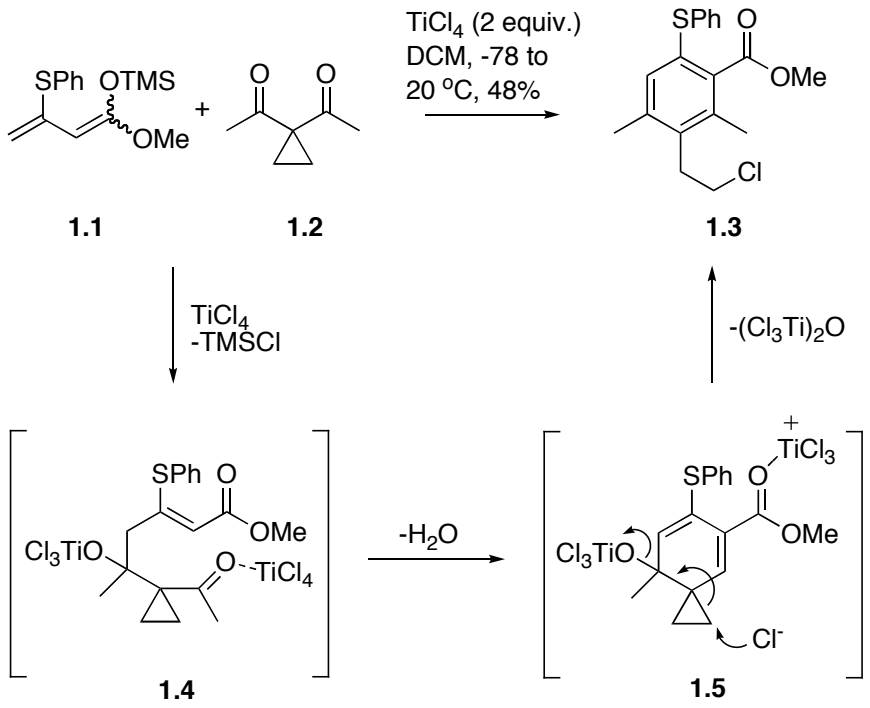
The formation of regioselectively substituted benzenes and other aromatic ring systems is a common challenge in organic synthesis. Despite being a field of general interest for over a century, there still exist challenges in the accomplishment of this task. Standard electrophilic aromatic substitution (e.g. Friedel-Crafts-based methodologies) and the less widely employed nucleophilic aromatic substitution are not always effective. In these cases, one can be aided and/or restricted by the presence of directing substituents that can activate or deactivate, based on resonance and inductive effects, positions for substitution on the aromatic ring. Consequently, synthetic plans are often limited by the initial placement of substituents on the aromatic system that is to be further elaborated.

Recently, there has been some progress in the preparation of regioselectively substituted benzene rings using non-aromatic starting materials. The general objective is to form the substituted framework of the aromatic system before effecting aromatization. By innovative use of Diels-Alder cyclization and other pericyclic reactions, ring closing metathesis strategies, linear approaches and other indirect methods, the synthesis of regioselectively substituted arenes has been developed.

1.2 *Formation of Substituted Aromatic Rings using Silyl Enol Ethers*

Langer *et al.* have successfully formed a variety of substituted aromatic rings using various silyl enol ethers as building blocks in many methodology studies.[1-6] They have devised domino, one-pot reactions that generate densely-

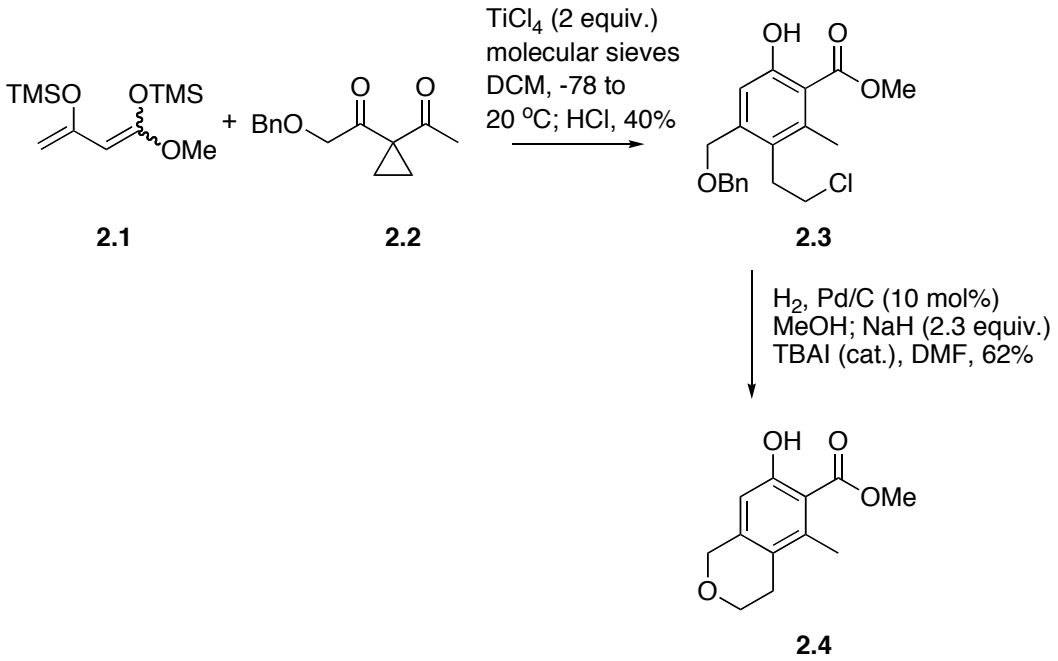
substituted aromatic systems. For example, 1-trimethylsilyloxy-3-arylthio-1,3-butadienes **1.1** have been reacted with 1,1-diacylcyclopropanes **1.2** in order to generate various 2-(phenylthio)benzoates (Scheme 1).[1] The reaction occurs in the presence of $TiCl_4$ (or $TiBr_4$, in some cases) where $TiCl_4$-mediated attack of the terminal carbon of **1.1** onto **1.2** gives intermediate **1.4**. Cyclization then occurs to form intermediate **1.5**, and then $TiCl_4$-assisted cleavage of the spirocyclopropane and spontaneous aromatization provides polysubstituted 2-(phenylthio)benzoate **1.3** in moderate yield (48%). It was observed that an excess of $TiCl_4$ (2.0 equiv.) was required to achieve these yields; when only 1.0 equiv. of the Lewis acid was used, the yield decreased considerably.



Scheme 1

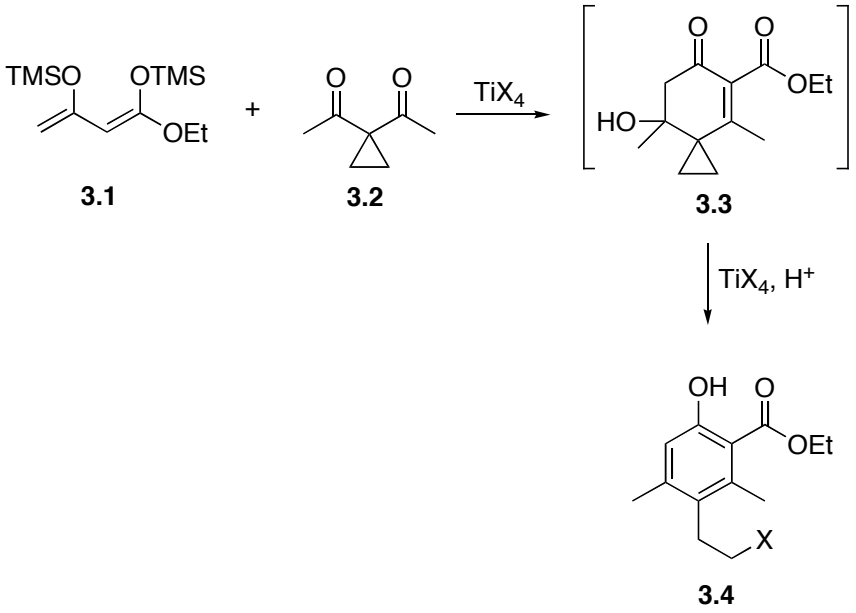
Langer *et al.* have also used 1,1-diacylcyclopropanes (**2.2**) in conjunction with 1,3-bis(trimethylsilyloxy)-1,3-butadienes (**2.1**) in substrate-directed domino "[3+3] cyclization/homo-Michael" reactions to generate highly functionalized

phenols.[2] The $TiCl_4$-mediated attack of the terminal carbon of **2.1** onto cyclopropane **2.2** afforded the desired 5-chloroethyl-4-(methoxymethyl)salicylate **2.3** after cyclization, Lewis acid-assisted cleavage of the spirocyclopropane and subsequent aromatization. This domino reaction provided **2.3** in moderate yield (40%), and the compound could then be transformed into tetrahydrobenzopyran **2.4** by removal of the benzyl group and Williamson annulation, in moderate yield (62% over the three steps).



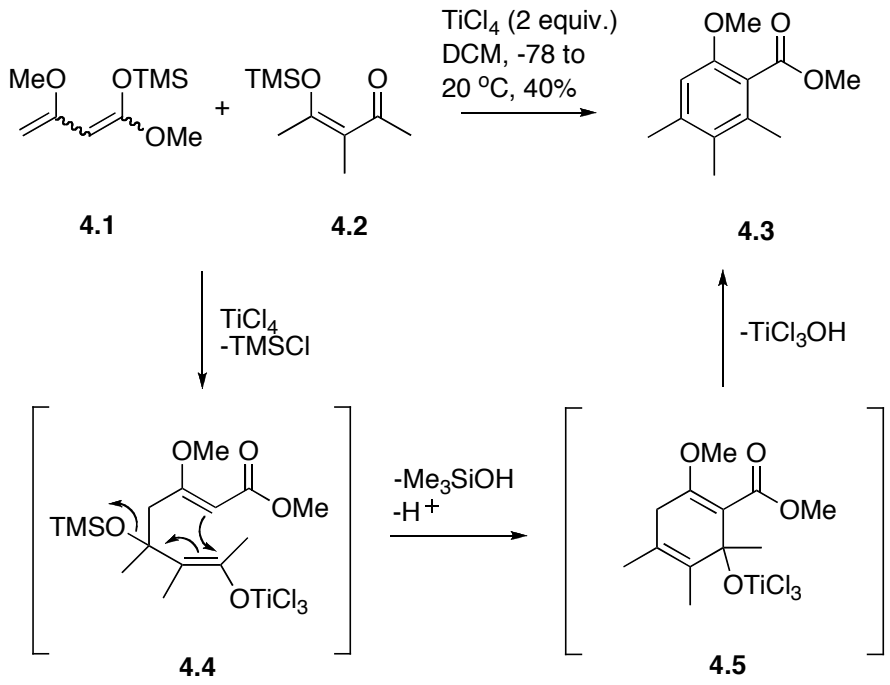
Scheme 2

When silyl enol ether **3.1** is cyclized onto 1,1-diacetylcyclopropane (**3.2**) with $TiCl_4$ as catalyst, the substituted salicylic ester **3.4** is generated in good yield (82%, X = Cl).[3] Comparable yields are observed when $TiBr_4$ is used, in which case the bromo-substituted variant of **3.4** (80%, X = Br) is formed.



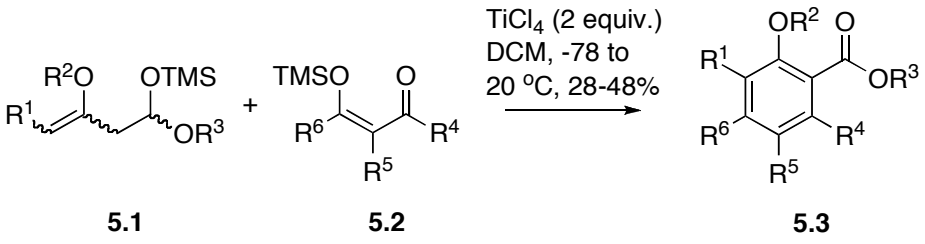
Scheme 3

The synthesis of functionalized arylalkyl and diaryl ethers by [3+3] cyclization has also been reported (Scheme 4).[4] These studies provide convenient access to arylalkyl and diaryl ethers that have an ester functionality next to the ether linkage. Langer has achieved this by the reaction of 3-alkoxy- and 3-aryloxy-1-silyloxy-1,3-butadienes (**4.1**) with 3-(silyloxy)alk-2-en-1-ones (**4.2**). Cyclization occurs in the presence of $TiCl_4$ to first form intermediate **4.4** by conjugate addition of the terminal double bond of **4.1** onto the enone functionality of **4.2**, followed by cyclization (**4.4→4.5**) and then aromatization (**4.5→4.3**) to form the desired arylalkyl ether in moderate yield (40%).



Scheme 4

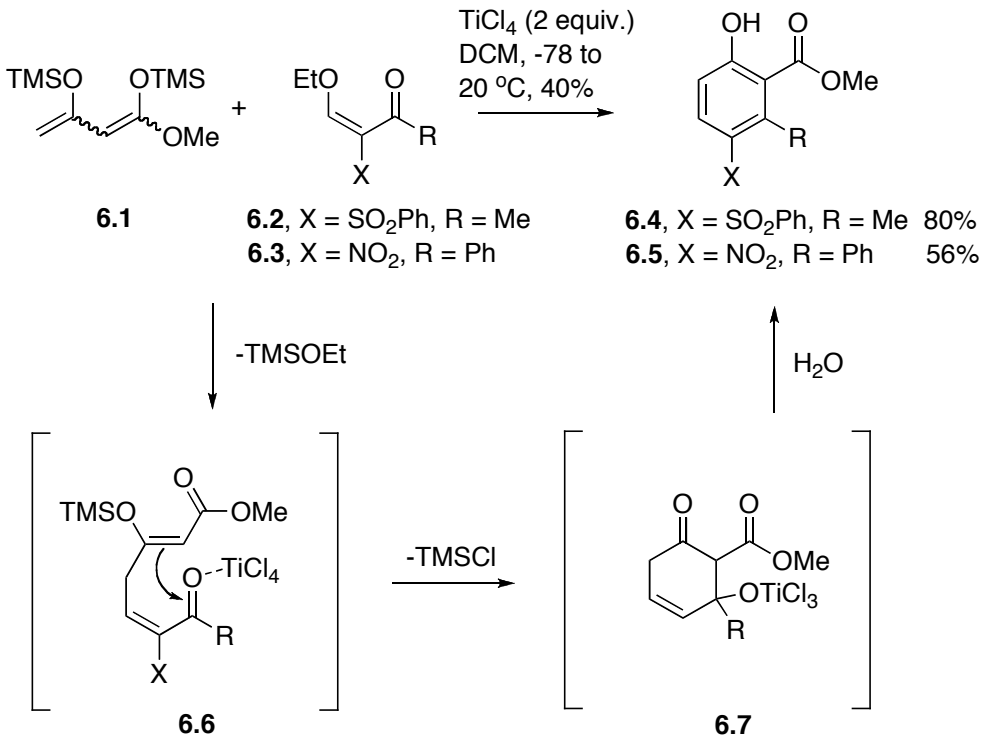
Despite low overall yields, the above methodology is clearly of use in the formation of polysubstituted arylalkyl ethers. The versatile nature of this diversity-amenable approach is highlighted in Scheme 5. Various starting materials **5.1** and **5.2** with simple alkyl and aryl substituents (Me, Et, Ph) were reacted as shown in Schemes 4 and 5, and resulted in low to moderate yields of the alkylaryl ether products **5.3**.



Scheme 5

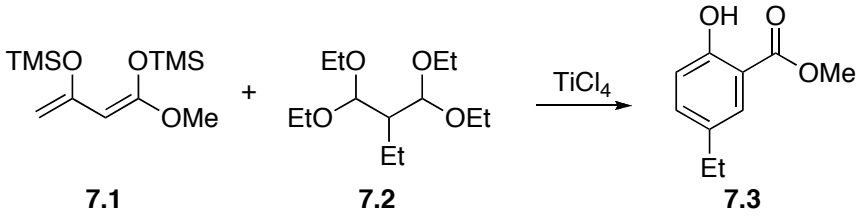
Langer has also reported the first synthesis of 4-(arylsulfonyl)phenols[5] as well as 4-nitrophenols[6] by regioselective [3+3] cyclocondensations involving 1,3-bis(silyloxy)-1,3-butadienes and 2-arylsulfonyl-3-ethoxy-2-en-1-ones or 3-ethoxy-2-nitro-2-en-1-ones, respectively (Scheme 6). 4-(Arylsulfonyl)phenols are of considerable relevance pharmacologically, and exhibit antibacterial activity,[7] inhibition of phospholipase A_2,[8] as well as being cytotoxic against HeLa cells and the antipicorna virus[9] and exhibiting anti-HIV activity.[10] 4-Nitrophenols also show pharmacological activity as antiandrogenetic agents,[11] vasodilators[12] and estrogenically active agents.[13]

These species are both generated by $TiCl_4$-mediated attack of the terminal double bond of **6.1** onto sulfonyl- or nitro-bearing vinylogous esters **6.2** and **6.3**, respectively, to provide **6.6**. Cyclization and then aromatization gives the trisubstituted sulfonyl- or nitrophenols **6.4** and **6.5**, respectively. The formation of sulfonyl-bearing species **6.4** appears to work in much better yields (i.e. 80%) than for the formation of nitro-bearing species **6.5** (56%).



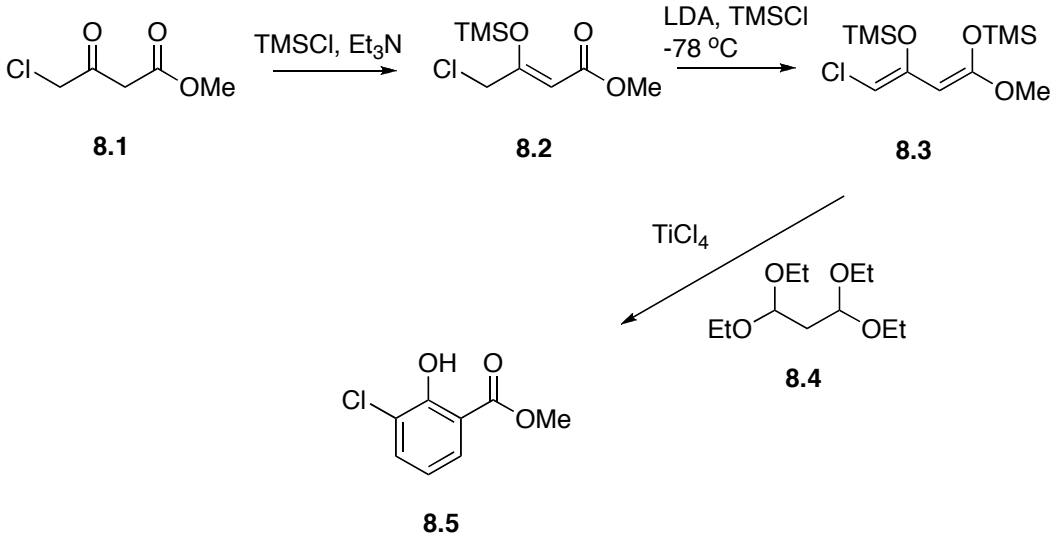
Scheme 6

A related methodology has been reported by Langer *et al.* where 2-alkyl-1,1,3,3-tetraethoxypropanes are cyclized with 1,3-bis(silyl enol ethers).[14] This method has allowed the formation of phenols that have *para*-alkyl substitutions. Bis(acetal) **7.2** appears to be activated with $TiCl_4$ to generate an oxonium ion, which is then attacked by the terminal carbon of **7.1** with the loss of Me_3SiCl. Cyclization and then acidic workup provides the final product **7.3** in moderate yield (51%). The use of Me_3SiOTf instead of $TiCl_4$ was unsuccessful in these studies.



Scheme 7

Langer has also reported one-pot, regioselective cyclizations of chlorinated 1,3-bis(silyoxy)-1,3-butadiene species to generate substituted chlorinated aromatics when reacted with bis(acetal) **8.4** (Scheme 8).[15] For instance, compound **8.1** was first silylated with Me_3SiCl to give **8.2**, which was then converted to diene **8.3** by deprotonation with LDA and subsequent addition of Me_3SiCl. Cyclization of **8.3** with **8.4**, using $TiCl_4$, then gave the substituted phenol **8.5**.

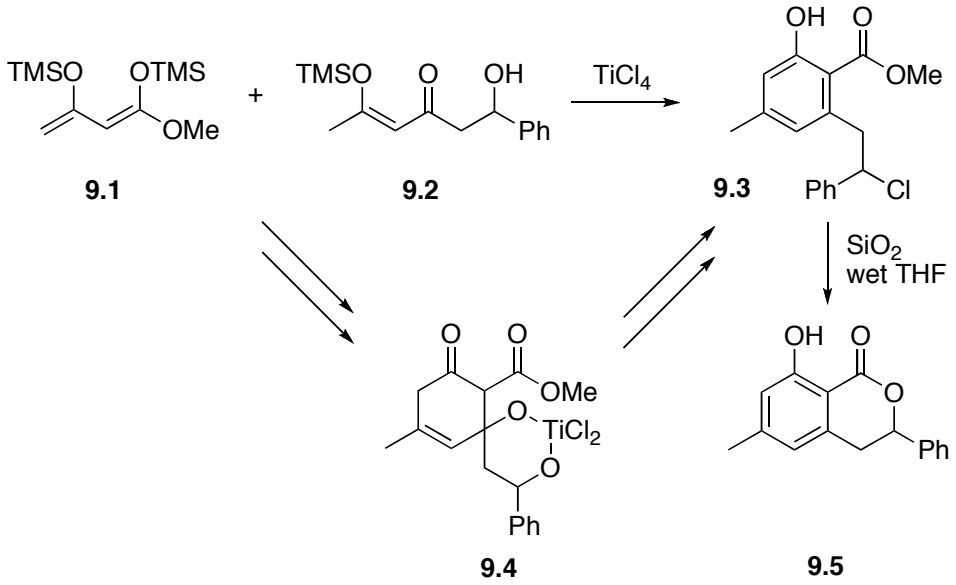


8.1 **8.2** **8.3** **8.4** **8.5**

Scheme 8

Langer[16] also described domino [3+3] cyclization/lactonization reactions of 1,3-bis(silyloxy)-1,3-butadiene **9.1** with the 1-hydroxy-5-silyloxy-4-en-3-one **9.2** mediated by $TiCl_4$. Compound **9.2** underwent [3+3] cyclization with 1,3-bis(silyl enol ether) **9.1** to afford **9.3**, the reaction proceeding with very good regioselectivity. Formation of **9.3** can be explained by reaction of $TiCl_4$ with **9.2** to eventually give, upon cyclization, intermediate **9.4**, which is then converted into **9.3** on the addition of hydrochloric acid and the loss of titanium during

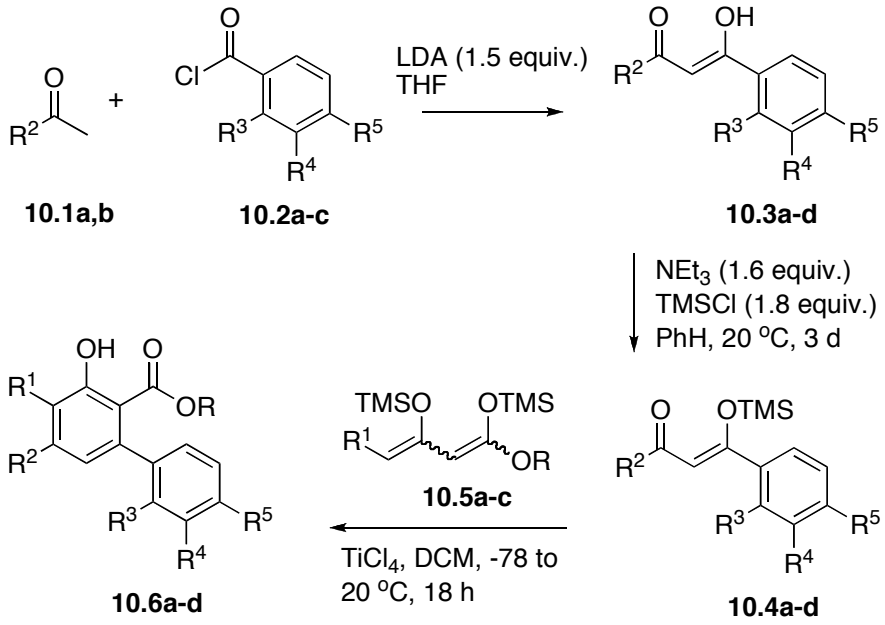
aqueous workup. It was observed that the free hydroxyl of **9.2** is necessary for the formation of a single product. When this hydroxyl is replaced by a methoxy group, a mixture of regioisomers results. Phenol **9.3** was then lactonized to **9.5** using silica.



Scheme 9

Langer has also devised a way to form functionalized 6(5*H*)-phenanthrinidones, using a [3+3]-cyclocondensation/lactamization strategy.[17] 6(5*H*)-Phenanthrinidones are molecules of pharmacological interest (e.g. they have anticoagulant, antiparasitic and antileukemia activities) and also occur as substructures of many natural products. The LDA-mediated condensation of the methyl ketones **10.1a** and pentan-2-one (**10.1b**) with benzoyl chlorides **10.2a-c** allowed access to benzoyl ketones with nitro-substitutions (**10.3a-d**). These were then transformed into 1-aryl-1-silyloxy-1-en-3-ones **10.4a-d** using a standard method. These silyl-protected enols were then reacted with 1,3-bis(trimethylsilyloxy)-1,3-butadienes **10.5a-c** in the presence of $TiCl_4$ to provide

novel biaryl species with nitro-substituents (**10.6a-d**) in moderate yields (36-48%). In order for these cyclization reactions to provide good regioselectivity, it was noted by the authors that the reactions needed to be carried out in highly concentrated solutions.

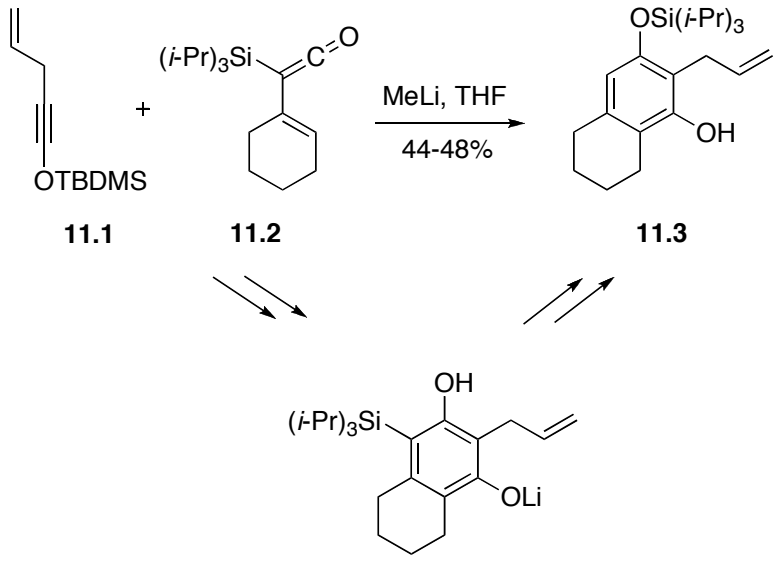


10.1	**10.2**	**10.3**(%)	**10.4**(%)	**10.5**	**10.6**(%)	R	R^1	R^2	R^3	R^4	R^5
a	a	a(54)	a(91)	a	a(36)	Me	H	Me	NO_2	H	H
b	a	b(45)	b(88)	a	b(48)	Me	H	*n*Pr	NO_2	H	H
a	b	c(34)	c(90)	c	c(37)	Et	Et	Me	H	NO_2	H
a	c	d(43)	d(92)	b	d(46)	Me	Me	Me	H	H	NO_2

Scheme 10

To synthesize highly-substituted phenols and other heteroaromatic compounds, Austin *et al.* have designed a benzannulation strategy that involves reaction of lithium ynolates with vinyl ketenes.[18] The reaction of **11.1** with MeLi and then with **11.2** gave substituted phenol **11.3** in moderate yield (*ca.* 46%). It is assumed that intermediate **11.4** forms as the result of the addition of the lithium ynolate derived from **11.1** to the ketene **11.2**, and then tautomerization to the

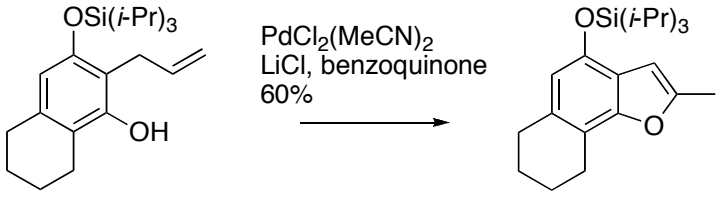
phenol occurs. Irreversible migration of the silyl group of **11.4** to the adjacent free phenol then provides **11.3**.



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

Scheme 11

If phenol **11.3** is exposed to $PdCl_2(MeCN)_2$ in the presence of benzoquinone and LiCl, it can be transformed to the benzo-fused oxygen heterocycle **12.2** in moderate yield (60%) (Scheme 12).

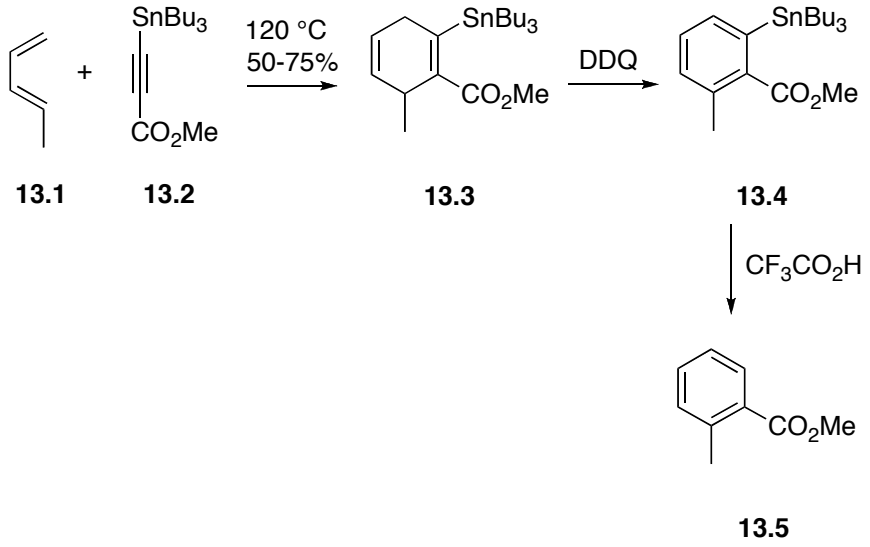


11.3 **12.2**

Scheme 12

1.3 *Formation of Substituted Aromatic Rings by Diels-Alder Reaction*

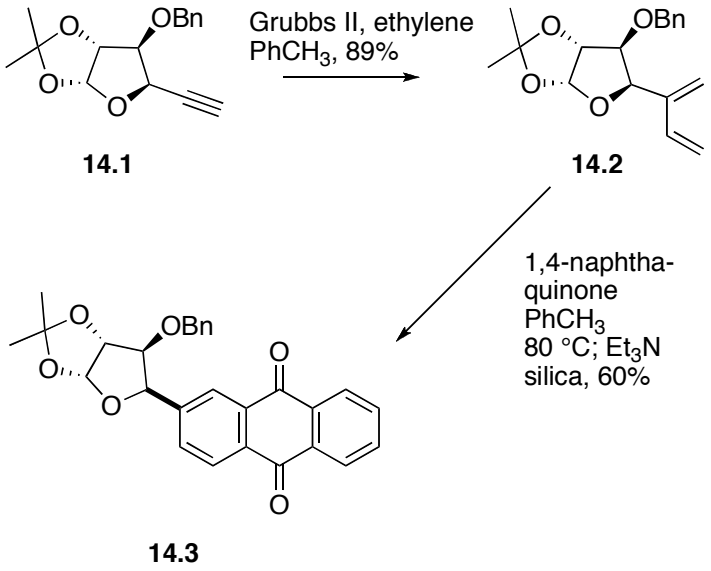
Jousseaume and Villeneuve have carried out regiospecific [4+2] cycloadditions of various substituted 1,3-butadienes with functionalized alkynyltins.[19] Diene **13.1** (2.0 equiv.) and alkyne **13.2** (1.0 equiv.) were reacted neat at 120 °C for 48 h and provided a single regioisomer. The resulting 1,4-diene **13.3** was then treated with DDQ to form aromatic species **13.4**, which was destannylated using TfOH to give the desired 1,2-disubstituted benzene **13.5**.



Scheme 13

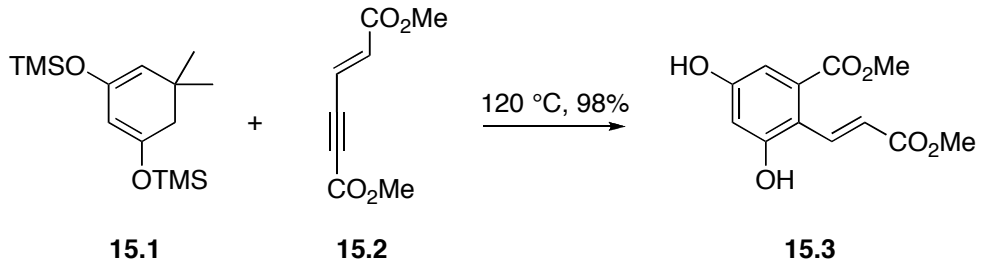
Kaliappan and Subrahmanyam[20] have used enyne metathesis to make dienes (e.g. **14.2**), which undergo Diels-Alder reactions with quinones and then aromatization (**14.2→14.3**) to provide *C*-aryl glycosides (**14.3**). *C*-Alkynyl glycoside **14.1** (prepared from D-glucose in 7 steps, 50% overall yield) underwent enyne metathesis in the presence of ethylene and second generation Grubbs catalyst (5 mol%) to form diene **14.2** in 89% yield. The cycloaddition product

was then reacted with 1,4-naphthaquinone in the presence of Et_3N and silica gel to provide the aromatized final product **14.3** in 60% yield.



Scheme 14

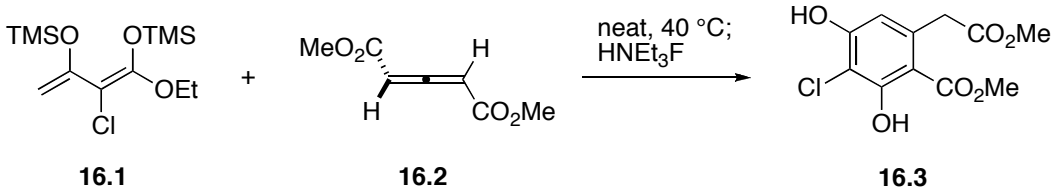
Using unsymmetrical dienes and enynes, Dai *et al*. have synthesized polysubstituted aromatic compounds and substituted biaryl compounds by means of highly selective Diels-Alder reactions.[21] They have observed that deactivated alkenes are less reactive than deactivated alkynes when treated with asymmetric nucleophilic dienes in [4+2] cycloaddition reactions. Enyne **15.2** was heated at 120 °C for 12 h with diene **15.1** (derived from dimedone). The styrenyl ester **15.3** was the only product observed. Based on monitoring of the progress of the reaction by proton NMR measurements, the authors noted that this outcome is the product of kinetic and not thermodynamic control.



15.1 **15.2** **15.3**

Scheme 15

Langer has reported the synthesis of 2-chloro-1,3-bis(trimethylsilyloxy)-1,3-butadienes (**16.1**) and their pericyclic reaction with various dieneophiles.[22] The formation of chlorinated phenol **16.3** by the [4+2] cycloaddition of diene **16.1** and allene **16.2** gave a reasonable yield (64%) and very good regioselectivity.

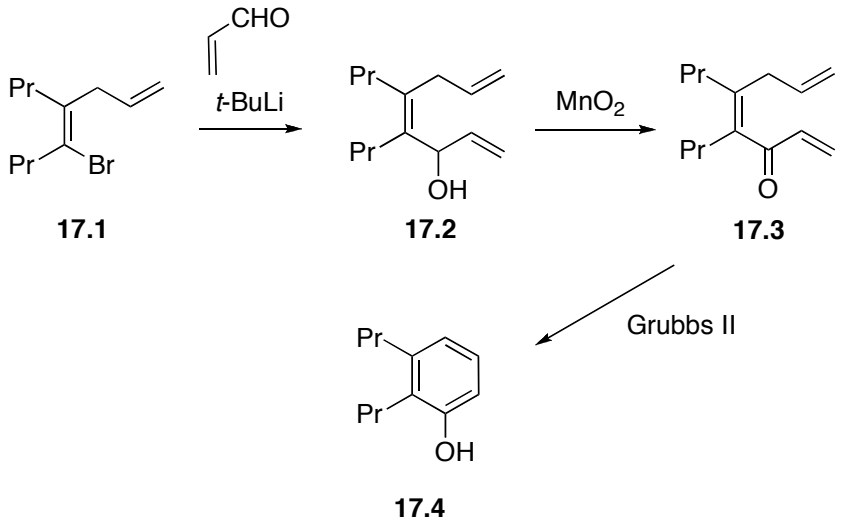


16.1 **16.2** **16.3**

Scheme 16

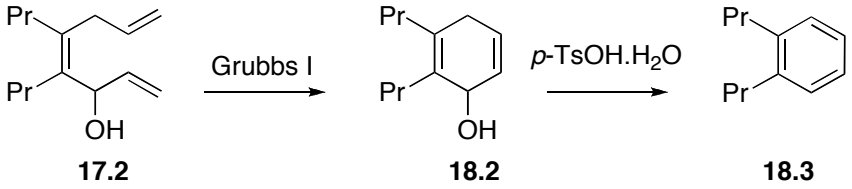
1.4 Formation of Substituted Aromatic Rings by a Linear Approach

Various phenol derivatives have been made by Yoshida and Imamoto from linear precursors that are amenable to ring closing metathesis (RCM) that generates an arene framework.[23] Phenol **17.4** is formed by Michael addition of the Li/Br exchange product derived from **17.1** to acrolein to produce **17.2**. Enol **17.2** was then oxidized with MnO_2 to give **17.3**, which undergoes RCM in the presence of Grubbs II catalyst (7.5 mol%) resulting in a very good yield of phenol **17.4** (93%).



Scheme 17

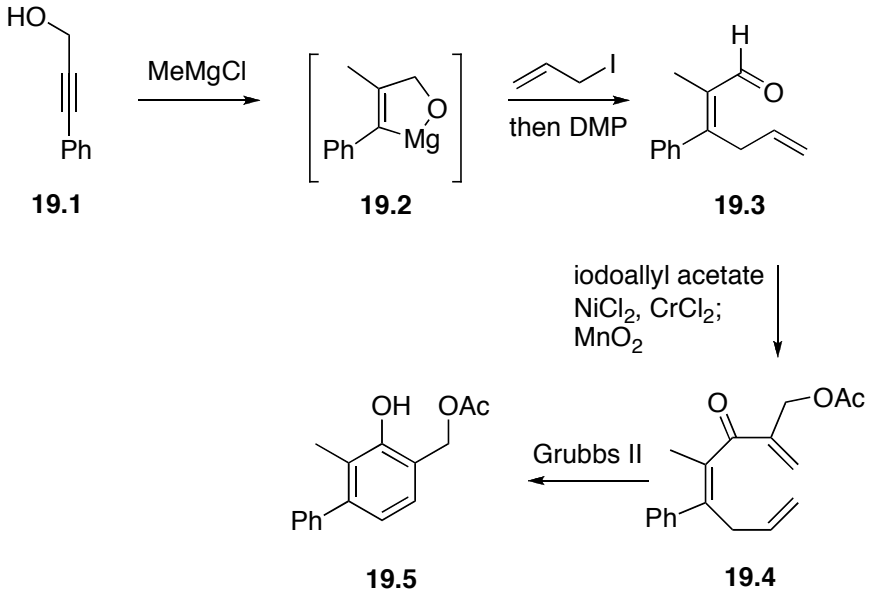
Yoshida and Imamoto also devised a straightforward methodology for the synthesis of benzenes by using tandem RCM and dehydration reactions (Scheme 18).[24] Starting with the substrate **17.2**, the first generation Grubbs catalyst was used to form dienol **18.2**, which was aromatized to **18.3** by a dehydration process involving *p*-TsOH·H_2O to give **18.3** in near-quantitative yield (from **17.2**).



Scheme 18

A route to aromatic compounds using RCM and dehydration or tautomerization was also developed.[25] Intermediate **19.2** was prepared using stereoselective carbometallation of a propargyl alcohol and was then allylated and oxidized to **19.3**. Compound **19.3** was treated with 2-iodoallyl acetate in a

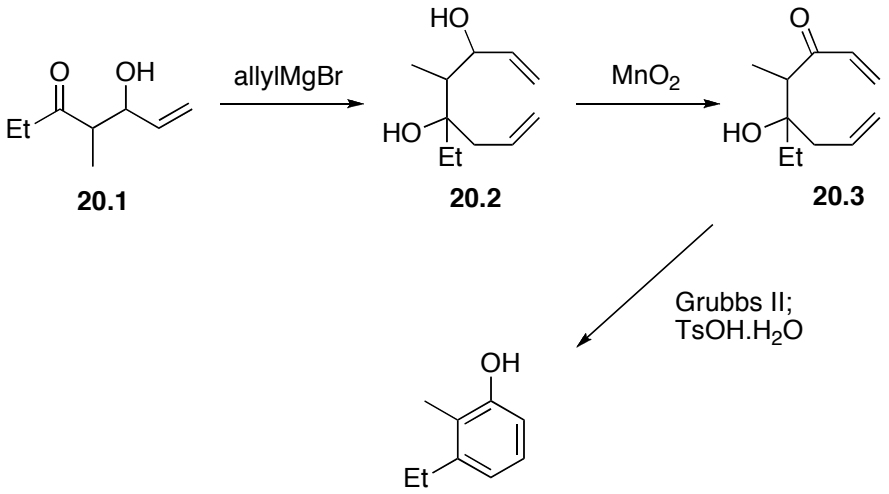
Nozaki-Hiyama-Kishi reaction and was then oxidized using MnO_2 to produce **19.4.** This was treated with the second generation Grubbs catalyst to form tetrasubstituted phenol **19.5** after tautomerization (87%).



19.1 **19.2** **19.3** **19.5** **19.4**

Scheme 19

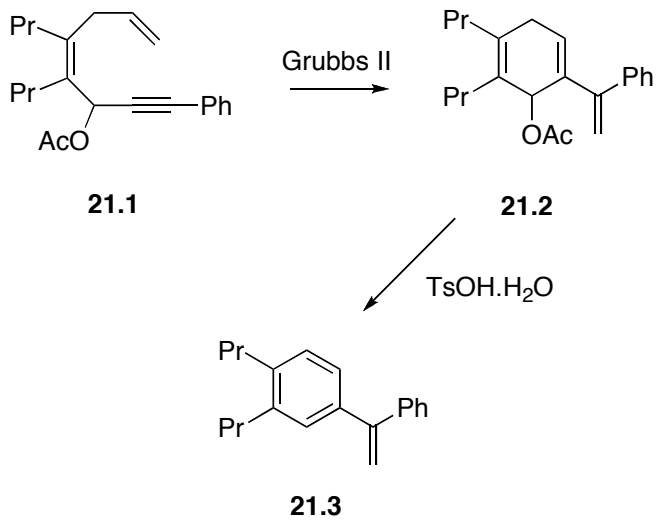
Yoshida and Imamoto also reported that phenols can be synthesized using a method that involves the formation of diene diols that undergo RCM (Scheme 20).[26] Ketone **20.1** was reacted with allylmagnesium bromide to produce the diene diol **20.2**, which was then oxidized to **20.3** with MnO_2. When reacted with second generation Grubbs catalyst, **20.3** was converted into **20.4** in 85% yield after *p*-TsOH·H_2O-promoted dehydration/aromatization.



20.1 **20.2** **20.3** **20.4**

Scheme 20

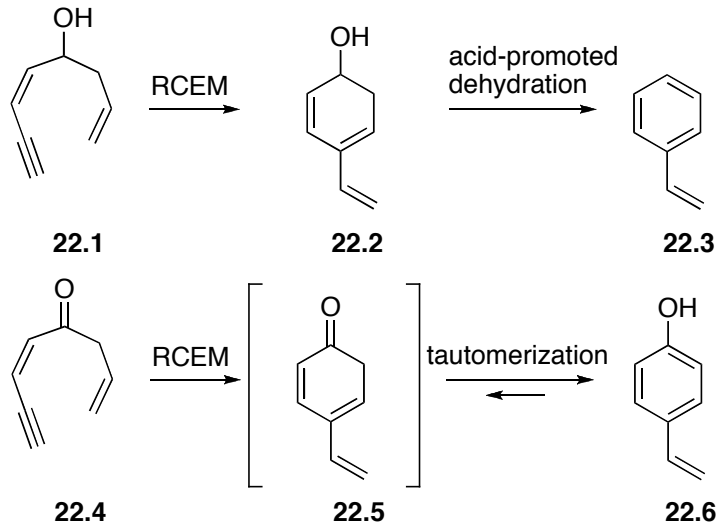
The formation of styrenes by ring closing enyne metathesis (RCEM) with second generation Grubbs catalyst has also been reported.[27] Substituted styrenes offer considerable utility as intermediates in organic chemistry and are well-known building blocks for pharmaceuticals[28] and polymer-supported catalysts.[29] When the protected alcohol **21.1** was treated with Grubbs II catalyst at 80 °C, styrene precursor **21.2** was formed via RCEM. Its acetate group was then eliminated, providing the styrene **21.3** in a 92% yield.



21.1 **21.2** **21.3**

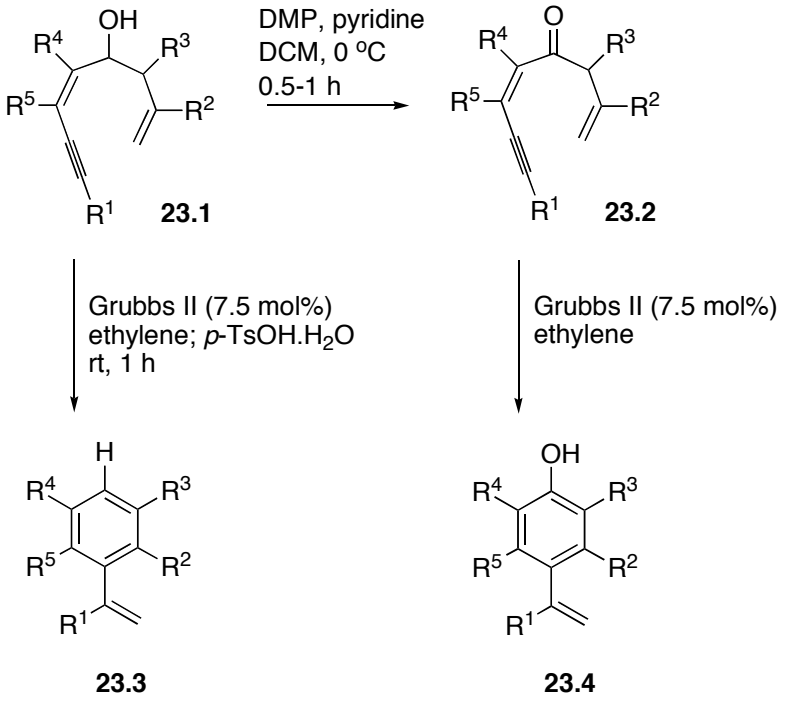
Scheme 21

Yoshida has reported a similar method for the synthesis of carbocyclic aromatic compounds, which also makes use of ruthenium-catalyzed RCEM.[30] 1-Octadien-7-yn-4-ol **22.1** can be subjected to RCEM conditions to form styrene **22.3** by dehydration of dihydrophenol **22.2**, as seen in Scheme 22 (*cf.* Scheme 21). Analogously, 1,5-octadien-7-yn-4-one **22.4** can be subjected to RCEM to form unstable intermediate **22.5** that tautomerize to the phenolic styrene **22.6**.



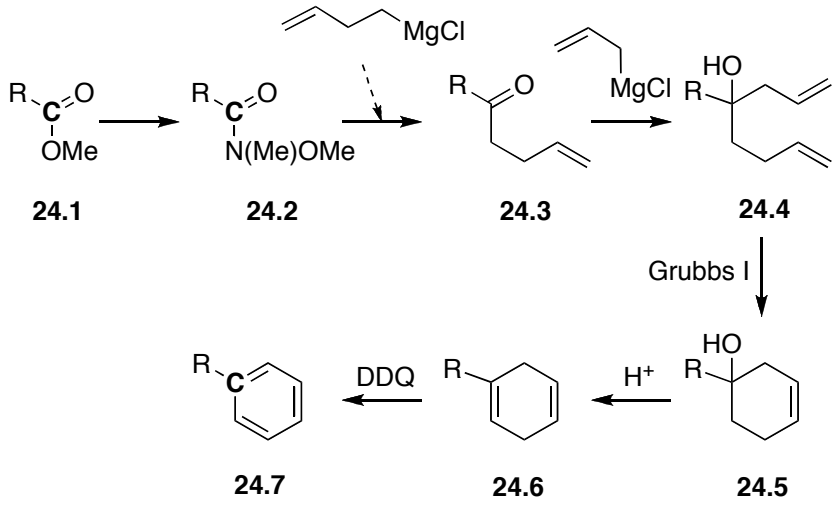
Scheme 22

1,5-Octadien-7-yn-4-ols **23.1** were converted into 1,5-octadien-7-yn-4-ones **23.2** by oxidation with Dess-Martin periodinane.[30] Both alcohols **23.1** and ketones **23.2** feature a great degree of substitution patterns (alkyl substituents R^1 through R^5), allowing for densely substituted styrenes **23.3** and phenolic styrenes **23.4** to be generated. These are formed in good to excellent yields by RCEM of **23.1** and **23.2** using second generation Grubbs catalyst, followed by acid-assisted dehydration or spontaneous tautomerization to the desired aromatic styrenes, respectively.



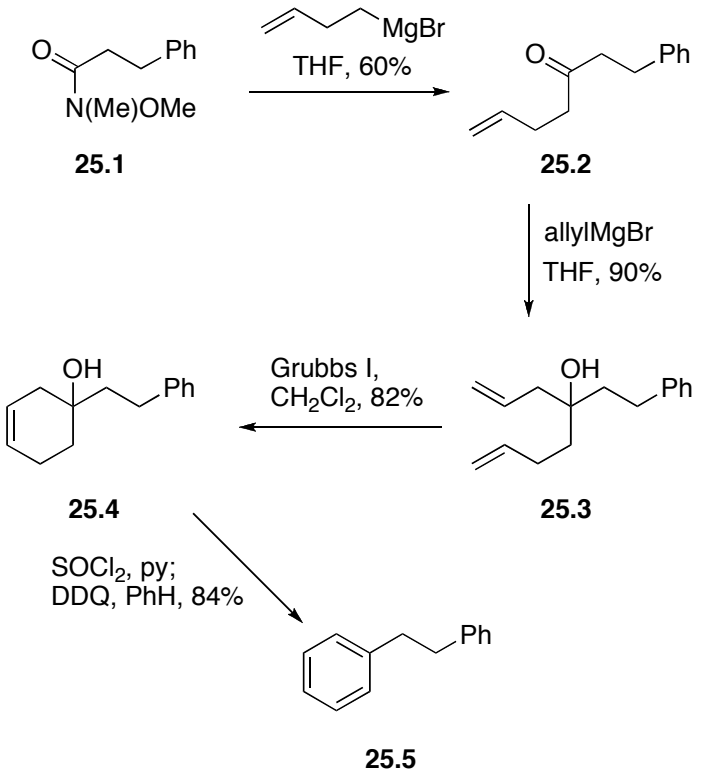
Scheme 23

The Clive group has published work in the area of linear arene synthesis through research carried out by M. Pham.[31,32] This work was prompted by a need in this laboratory to convert a methyl ester into a benzene ring that incorporated the ester carbonyl carbon. This problem was solved along the lines summarized in Scheme 24.



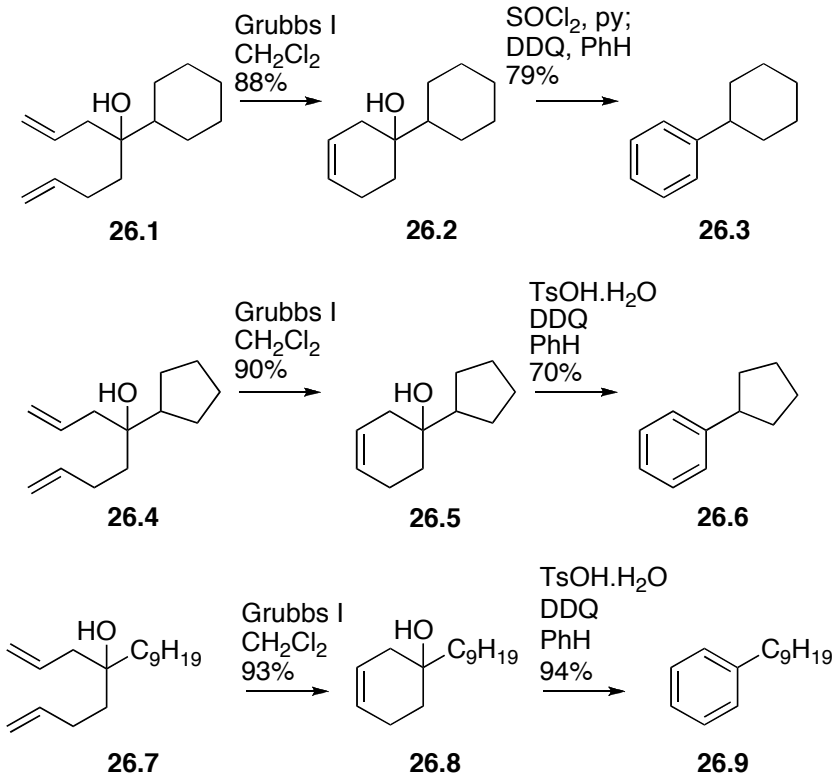
Scheme 24

In an early study,[32] following the outline of Scheme 24, 3-butenylmagneium bromide was added to Weinreb amide **25.1** to give the desired ketone **25.2** in moderate yield. The following reaction with allylmagnesium bromide provided tertiary alcohol **25.3** in high yield. Ring closing metathesis of **25.3** using first generation Grubbs catalyst provided cyclic alkene **25.4** (84%), which was then aromatized in two steps using thionyl chloride in pyridine at 0 °C, followed by DDQ in benzene at 80 °C to provide 1,2-diphenylethane in 84% yield.



Scheme 25

The ring closing metathesis of **26.1**, **26.4**, and **26.7**, which were generated using corresponding Weinreb amides (*cf.* Scheme 25), was carried out with first generation Grubbs catalyst in dichloromethane at reflux (Scheme 26).[32] The resulting cyclized enols **26.2**, **26.5**, and **26.8** were obtained in high yields. Compound **26.2** was dehydrated with thionyl chloride in pyridine and then dehydrogenated with DDQ in benzene, using the regular procedure, to generate aromatic species **26.3** in 79% yield. Intermediates **26.5** and **26.8**, were aromatized using the method indicated in Scheme 24. Each was dehydrated and dehydrogenated in a one-pot procedure using *p*-TsOH·H_2O and DDQ in benzene at reflux to provide the benzene derivatives **26.6** and **26.9** in good yields (70% and 94%, respectively).

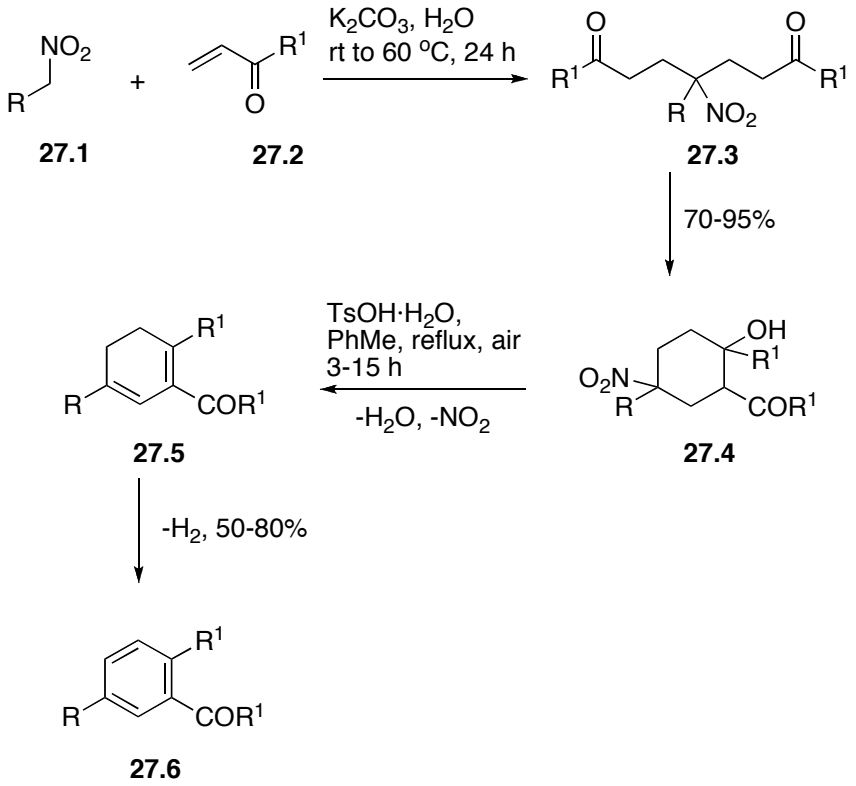


Scheme 26

1.5 Other Methods of Substituted Aromatic Ring Construction

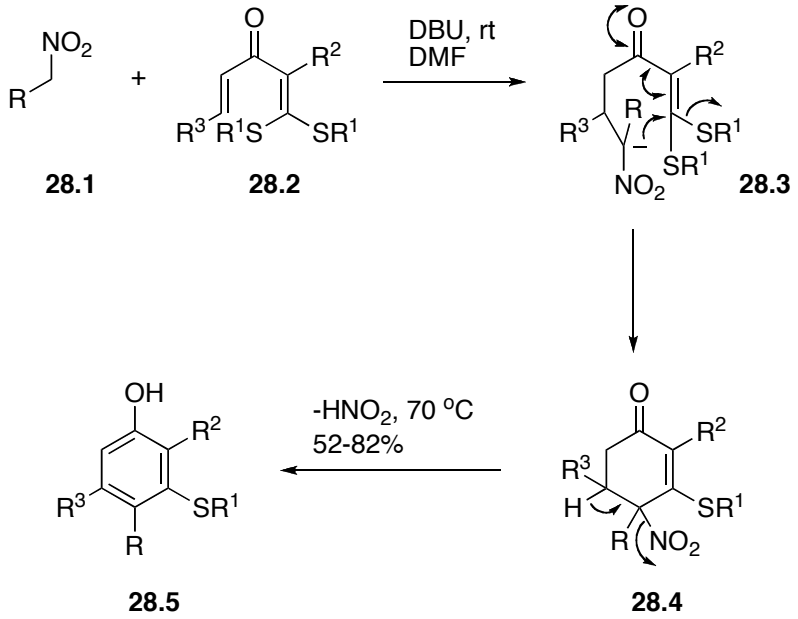
Ballini has reported the use of nitroalkanes as useful precursors in the synthesis of a variety of benzene derivatives.[33] In the simplest example, a 1-acyl-2,5-dialkylbenzene was formed via double Michael addition of primary nitroalkane **27.1** to enones **27.2**. This was followed by *in situ* intramolecular aldol condensation of the resulting adducts **27.3** to form cyclohexanols **27.4**. These species were formed in moderate to good yields and were diastereomeric mixtures. The cyclohexanols were treated with a stoichiometric amount of *p*-TsOH·H_2O (Dean-Stark apparatus with simultaneous purging with air) to provide the corresponding aromatic products **27.6** from cyclohexadiene intermediates **27.5** (50-80% yield from the starting cyclic alcohols **27.4**). This procedure allows for the formation of substituted aromatic compounds **27.6** in satisfactory to good

yields. It is important to note the nitro group is used as both a means to form two C-C bonds, and then as a good leaving group to generate diene intermediates **27.5**.



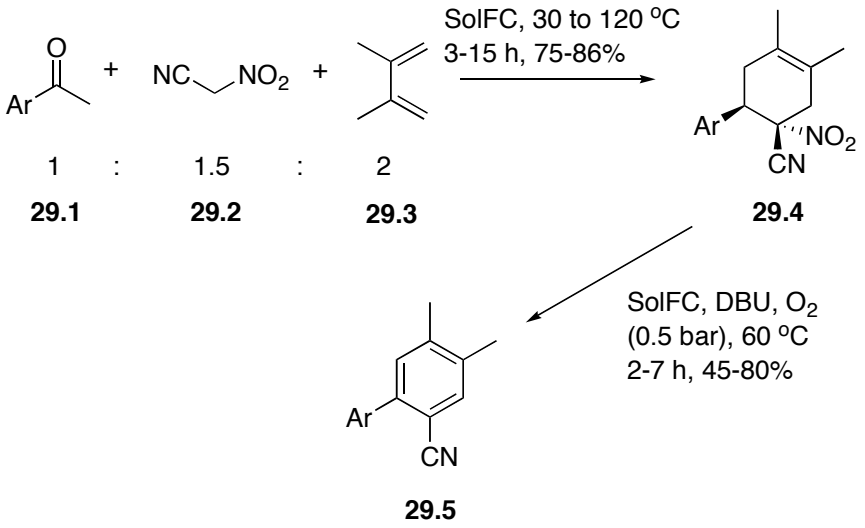
Scheme 27

Ballini also used α-alkenoyl ketenedithioacetals **28.2** in double addition reactions with primary nitroalkanes **28.1** (Scheme 28).[33] Compounds such as **28.2** are interesting, due to 1) their 1,5-biselectrophilic nature, 2) their dense and easily diversified substitution patterns, and 3) the presence of an alkylthio leaving group that is amenable to nucleophilic vinylic substitution reactions (S_NV).[34] The combination of **28.1** and **28.2** in the presence of DBU (1.5 equiv.) in DMF at room temperature, provided phenols **28.5** in 52-82% yield, upon expulsion of the nitro group.



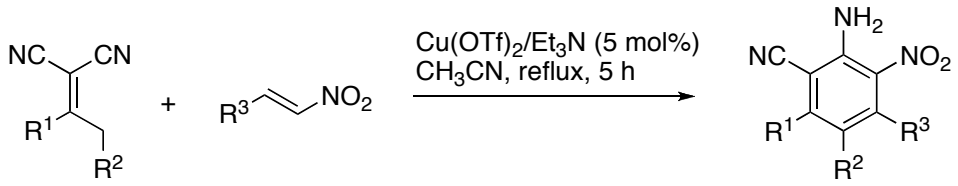
Scheme 28

Biphenyl-2-carbonitriles **29.5** have been formed by Ballini in a multicomponent synthesis involving nitroacetonitrile (**29.2**).[33] Under solvent-free conditions (SolFC), acetyl arenes **29.1** (Ar = Ph and other simple, multiply substituted benzenes), 2-methylbutadiene (**29.3**) and nitroacetonitrile (**29.2**) were converted to biphenyl-2-carbonitriles **29.5** by three sequential processes: 1) nitro-aldol condensation and then 2) Diels-Alder cyclization of the newly-formed electron-poor alkene (conjugated nitro-alkene), followed by 3) aromatization, driven by the highly favored nitrous acid expulsion. The final biphenyls **29.5** are formed in moderate to good yields (45-80%).



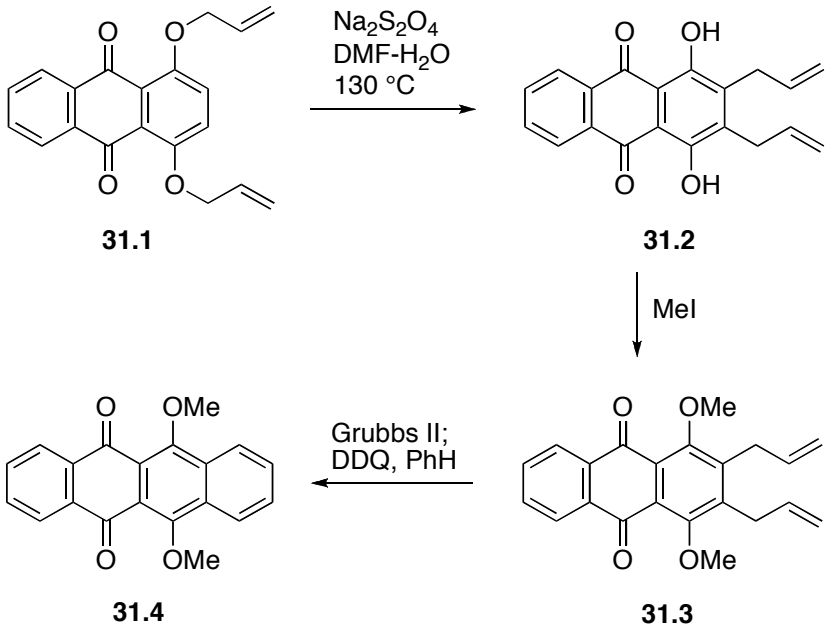
Scheme 29

Su has reported the one-pot synthesis of polyfunctionalized benzenes by condensations of nitroolefins **30.2** and activated α-methylene alkenes **30.1**, which is mediated by a new catalytic system involving $Cu(OTf)_2$ and Et_3N.[35] In these examples, the nitro group of **30.2** remains intact throughout the course of the reaction and becomes one of several functional groups of the hexasubstituted final products **30.3**. Yields are generally high (67-86%) for this convergent method of constructing densely-substituted benzenes. It should be noted that Su *et al.* did extensive optimization studies of the catalytic conditions used in these cyclocondensation reactions. Zinc-, magnesium- and scandium triflates were also paired with Et_3N but gave poorer results. The specific loading of 5 mol% Lewis acid and amine base also provided the best yields.



Scheme 30

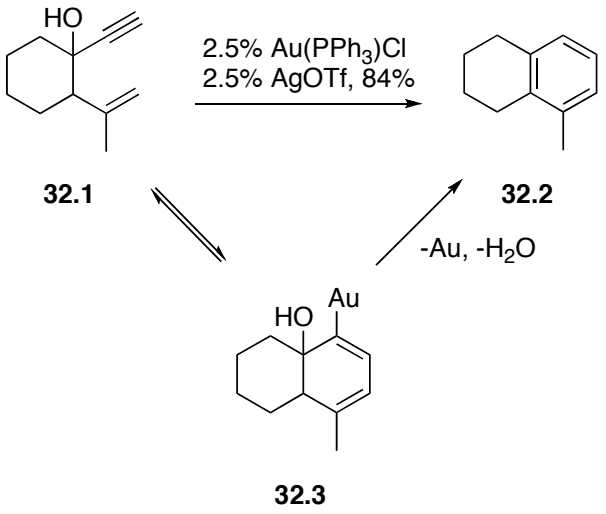
A straightforward procedure to form aromatic systems by annulation has been reported.[36] The first step involves the Claisen rearrangement of *bis*-allyloxy anthraquinone **31.1**, which undergoes rearrangement when subjected to sodium dithionite and NaOH with heating for 1 h, to generate bis(phenol) **31.2**. The free phenolic groups are then protected to form **31.3** and subsequent RCM (using Grubbs II catalyst) and DDQ oxidation gives the benzannulated product **31.4** in good overall yield (49%).



Scheme 31

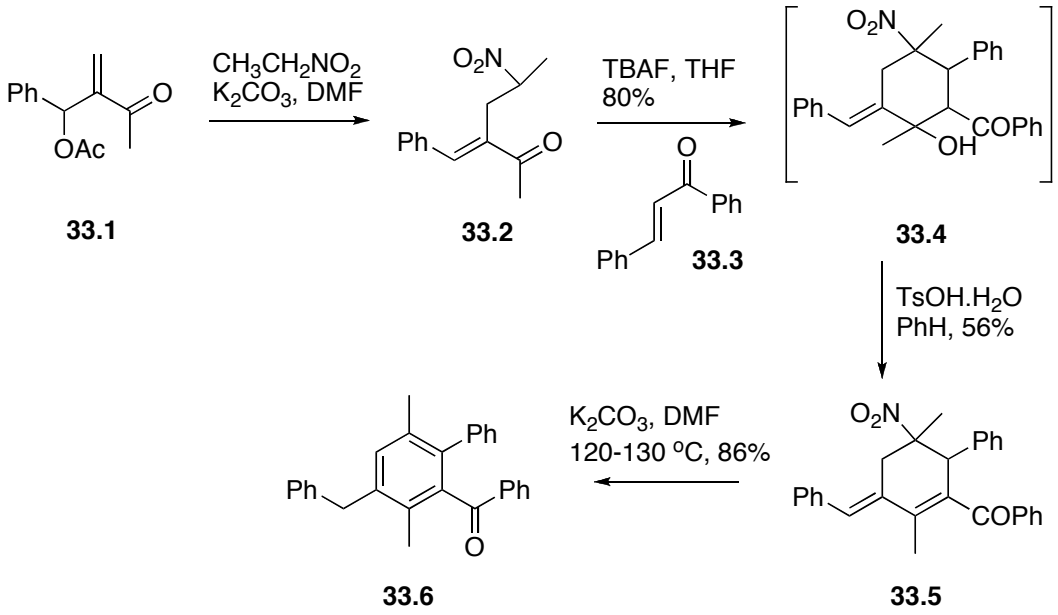
Grisé and Barriault have also carried out benzannulation studies in which 3-hydroxy-1,5-enynes are formed using gold catalysis (Scheme 32).[37] A number of gold catalysts were examined and it was observed that a combination of $Au(PPh_3)Cl$ and AgOTf made for the best catalyst system. Cyclization to Au(I)-complexed **32.1** has been proposed to occur in a 6-*endo-dig* fashion to provide

32.3. Dehydration and protonolysis of **32.3** then produces aromatic compound **32.2**.



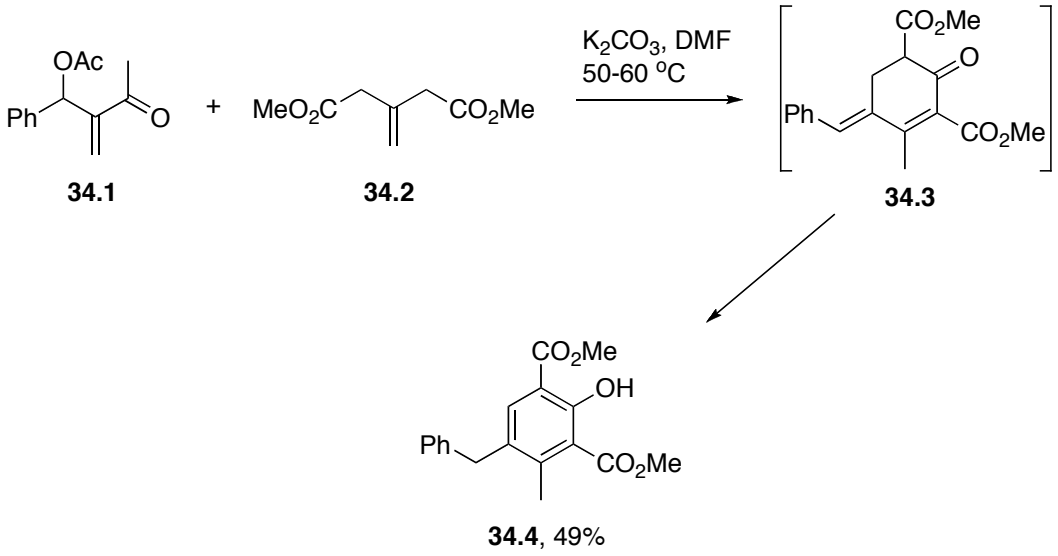
Scheme 32

Kim *et al*. have described a procedure for the synthesis of densely functionalized pentasubstituted benzenes (Scheme 33).[38] The reaction of nitro-compound **33.2** and β-substituted Michael acceptor **33.3** occurred in the presence of TBAF to form annulation product **33.4** as a diastereomeric mixture. Treatment of **33.4** with *p*-TsOH·H_2O in refluxing benzene gave **33.5** as a mixture of isomers about the external double bond. When **33.5** was reacted with base at high temperature, the polysubstituted benzene **33.6** resulted in good yield (86%).



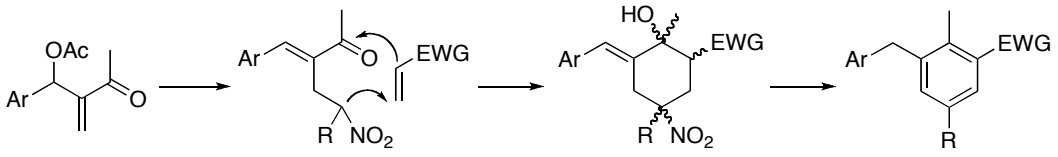
Scheme 33

Kim has also made polysubstituted phenols via a [3+3] annulation strategy using 1,3-dinucleophilic reagents.[39] Baylis-Hillman acetate **34.1** was reacted with dimethyl 1,3-acetonedicarboxylate (**34.2**) in the presence of base to provide phenol **34.4** in moderate yield. This represents a simple method for the one-pot synthesis of polysubstituted phenols, despite low reported yields.



Scheme 34

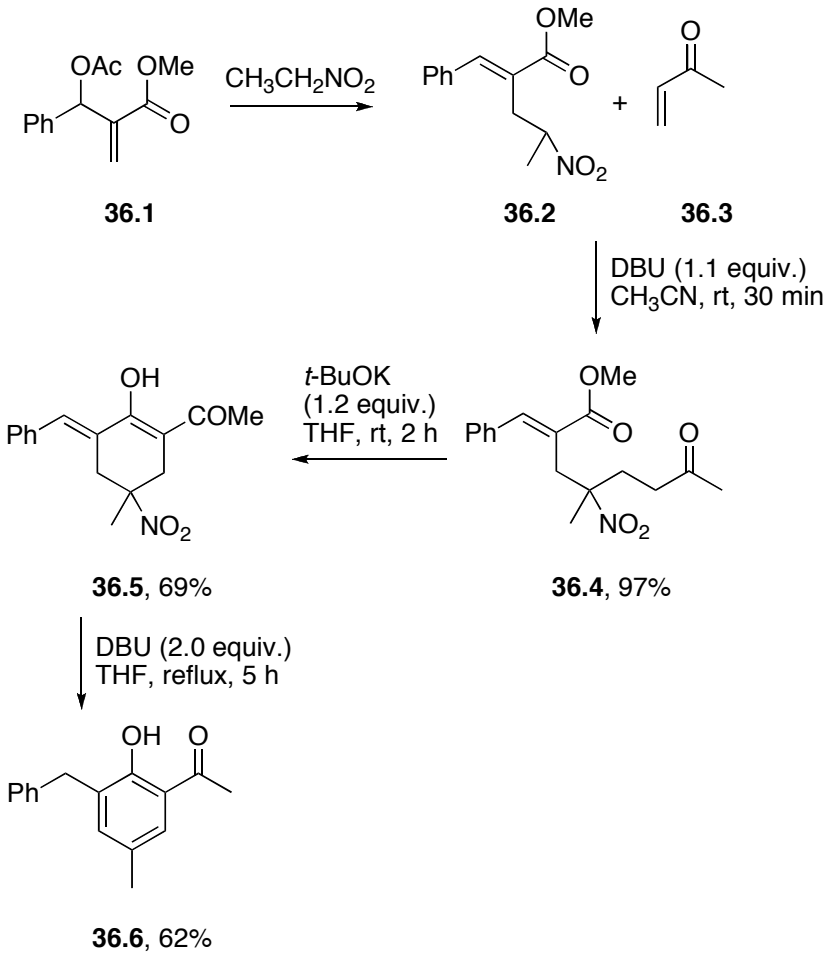
Kim has also reported the regioselective construction of highly-substituted phenols that are generated from Baylis-Hillman adducts by a formal [4+2] annulation strategy.[40] This procedure is detailed in Scheme 35, where Baylis-Hillman acetates are reacted in an S_N2' process with a nitroalkane, followed by Michael addition, aldol condensation, elimination of HNO_2 and ultimate aromatization to form the desired aromatic product.



Scheme 35

In practice, the Baylis-Hillman acetate **36.1** from methyl acrylate was reacted with nitroethane to form α,β-unsaturated methyl ester **36.2**. This was

condensed in a Michael reaction with methyl vinyl ketone in the presence of DBU in excellent two-step yield (97%). Unfortunately, DBU was not an effective base for the following aldol-type cyclization (**36.4→36.5**), and potassium *tert*-butoxide in THF was required to form the cyclized product **36.5** (69% yield) by aldol-type cyclization and subsequent enolization. The penultimate formal 1,3-hydrogen shift and then elimination of HNO_2 was affected with DBU to generate the polysubstituted phenol **36.6** in 62% yield.

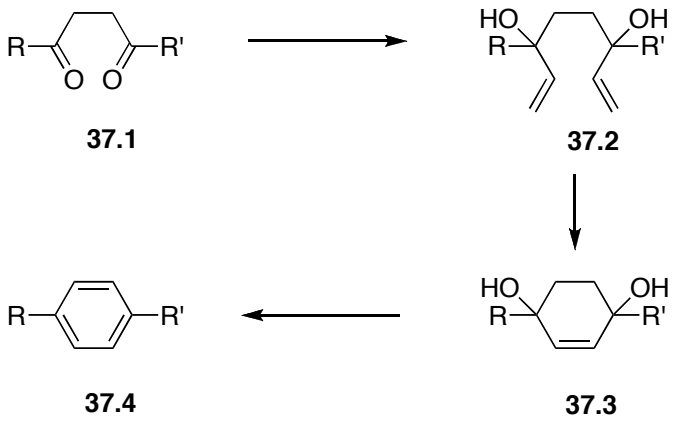


Scheme 36

2 RESULTS AND DISCUSSION

2.1 Objectives

In addition to studies carried out in the Clive group by M. Pham,[31,32] a linear method for synthesis of regioselectively-substituted aromatic rings has been developed and is described here.[41] In this procedure, 1,4-dicarbonyl compounds (**37.1**) were converted by reaction with vinyllithium, into diols (**37.2**), which were then subjected to ring closing metathesis and dehydration, producing, in the simplest case, *p*-disubstituted benzenes (**37.4**) (Scheme 37).

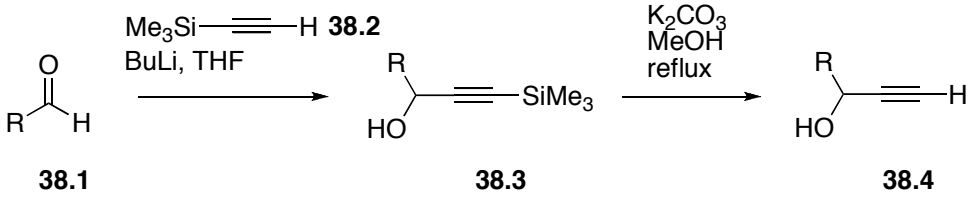


Scheme 37

2.2 General Procedures and Preparation of Starting Materials: Overview

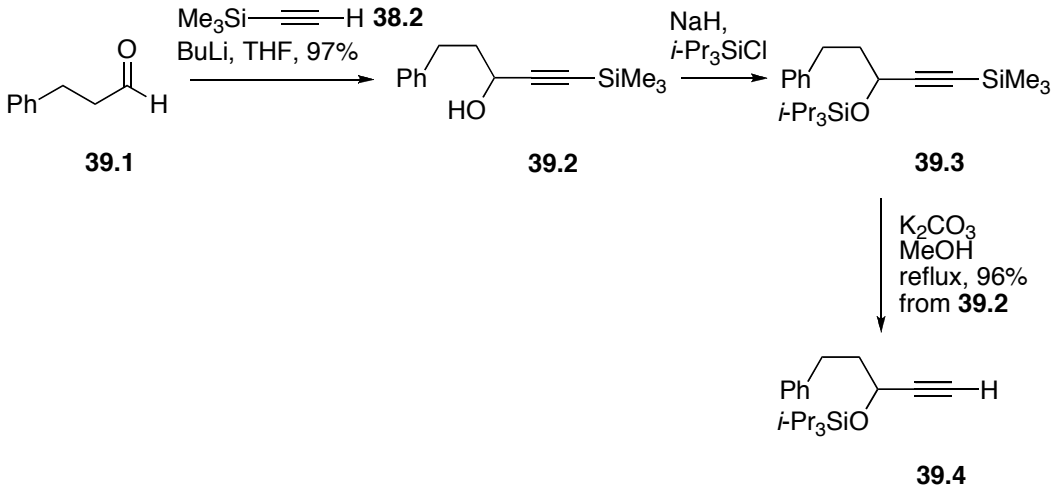
The key materials for our approach are 1,4-diketones. A number of routes to such compounds are, of course, available,[42] and we selected the use of acetylenes as representing a straightforward and versatile method. To this end, various acetylenic alcohols (**38.4**) were prepared by the standard process of acetylide addition to an aldehyde **38.1** (R = 2-phenylethyl, *n*-pentyl, cyclohexyl/cycloheptyl, adamantyl) (Scheme 38). We generally used

trimethylsilylacetylene as a convenient acetylide synthon, and then removed the silicon group with K_2CO_3 in MeOH.



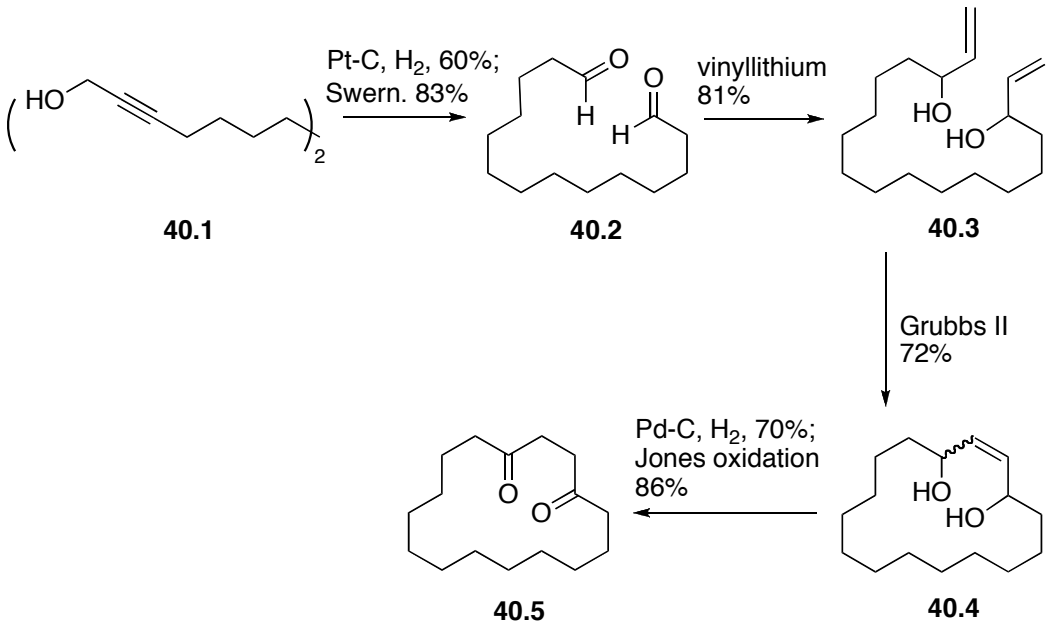
Scheme 38

Small, but conventional, modifications of this route were applied to make acetylene **39.4** (Scheme 39). In this case, the initial adduct from dihydrocinnamaldehyde and lithium trimethylsilylacetylide was silylated with *i*-Pr_3SiCl and, after this step, removal of the Me_3Si group gave acetylene **39.4**. The remaining triisopropylsilyl-protected oxygen was left in place so that a second unprotected alcohol, introduced later, could be manipulated independently (see Scheme 45).



Scheme 39

The sequence **40.2→40.5** is also different from the others as it is based on an α,ω-dialdehyde that is converted into a 16-membered cyclic 1,4-diketone (**40.5**) by way of ring closing metathesis (**40.3→40.4**), rather than by acetylide addition to two carbonyls (Scheme 40). The cyclic diketone **40.5** was prepared by ring closing metathesis of **40.3**, mediated by the second generation Grubbs catalyst[43] at high dilution;[44] the resulting olefinic diol **40.4** was a mixture of stereoisomers, but this is of no consequence as the following steps of double bond hydrogenation and hydroxyl oxidation (**40.4→40.5**) remove all centers of stereogenicity. The starting α,ω-dialdehyde[45] (**40.1→40.2**) was assembled by the reduction of a bis(propargylalcohol) chain, as shown in Scheme 40.

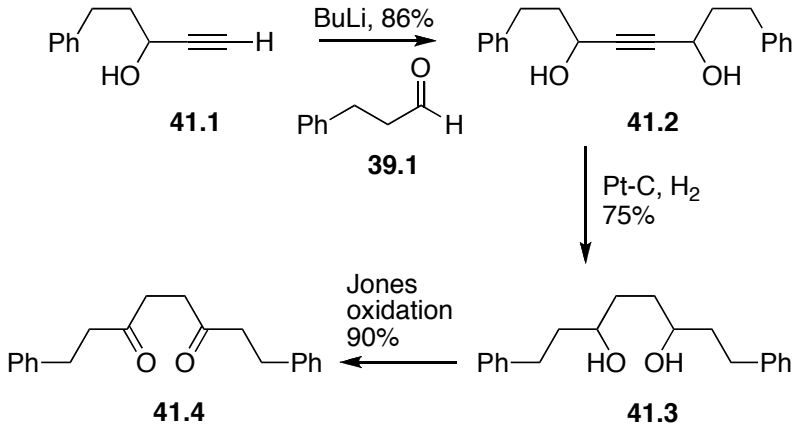


40.1 **40.2** **40.3** **40.4** **40.5**

Scheme 40

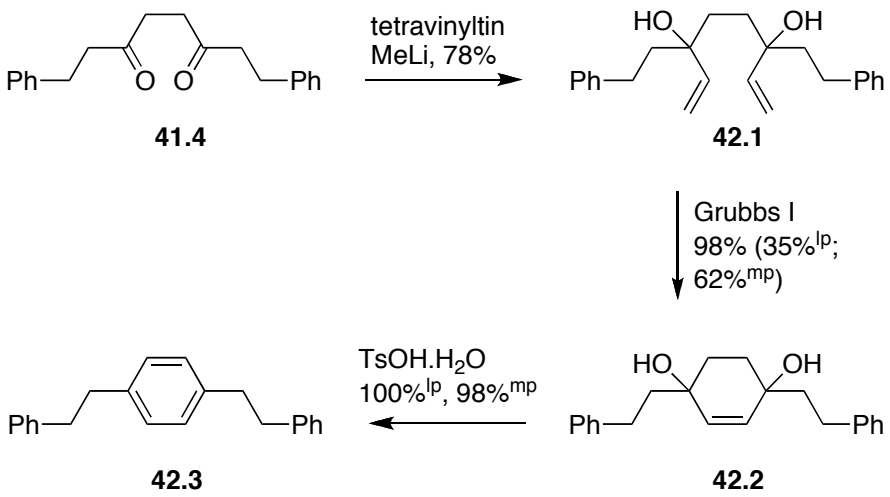
2.3 Preparation of p-Disubstituted Benzenes

In the first example, acetylene **41.1** was added to dihydrocinnamaldehyde (**39.1**) using *n*-BuLi as base. The resulting alkyne diol **41.2** was reduced to the corresponding 1,4-diol **41.3** with Pt-C under H_2 in acceptable yield (75%). Jones oxidation of **41.3** in acetone at 0 °C provided 1,4-diketone **41.4** in good yield (90%).



Scheme 41

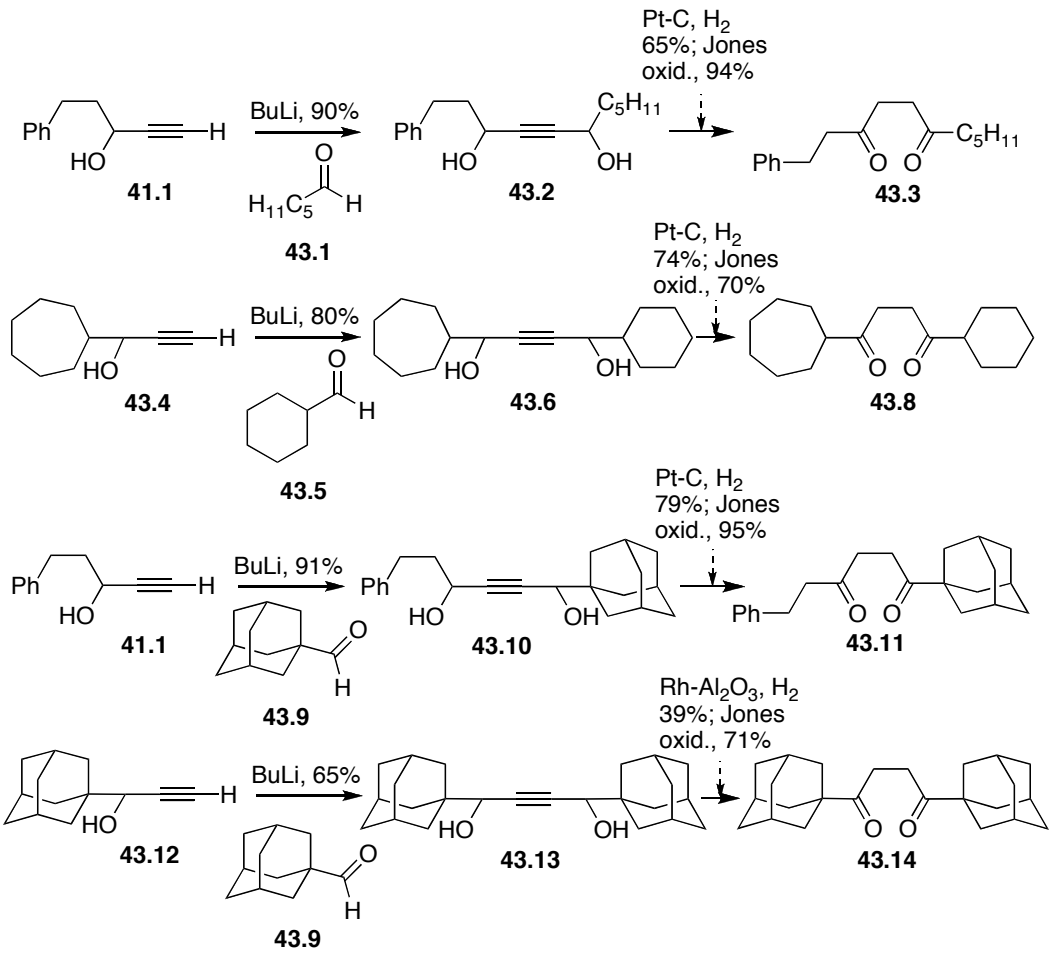
1,4-Diketone **41.4** was then treated with an excess of vinyllithium (generated from tetravinyltin and MeLi) to give terminal diene **42.1** in good yield. Diene **42.1** was cyclized by RCM using first generation Grubbs catalyst, providing two easily separable diastereomers of **42.2** in excellent yield [35% less-polar (lp) diastereoisomer; 62% more polar (mp)]. The resulting diols were then independently subjected to acidic conditions, which readily led to the corresponding aromatic product **42.3** by double-dehydration in 100% and 98% yields, respectively.



Scheme 42

The above methodology (Scheme 42) was generally applied to four other examples, leading to the formation of a variety of *p*-disubstituted benzenes. 1,4-Diketones **43.3**, **43.8**, **43.11** and **43.14** were formed in good to excellent overall yields by the standard procedure, starting from the propargylic alcohols shown in Scheme 43. Internal alkyne diols **43.2**, **43.6**, **43.10** and **43.13** were generated in moderate to good yields from propargylic alcohols **41.1**, **43.4** and **43.12** by reaction with the indicated aldehydes **43.1**, **43.5** and **43.9**, repectively, in the presence of BuLi. The following conversion of the alkyne diols to the alkane diols required the use of different hydrogenation catalysts in some cases. Pt-C under H_2 were generally used to perform this task (see Scheme 41, **41.2→41.3**); it was observed in some examples that Pd/C under H_2 provided low yields, presumably due to formation of side-products due to hydrogenolysis. For examples **43.3**, **43.8** and **43.11**, yields using Pt-C were moderated to good (70% to 95%). Due to the reluctance of **43.13** to undergo reduction using either Pt-C, Pd/C or diimide (where starting material was recovered in all three cases), Rh-

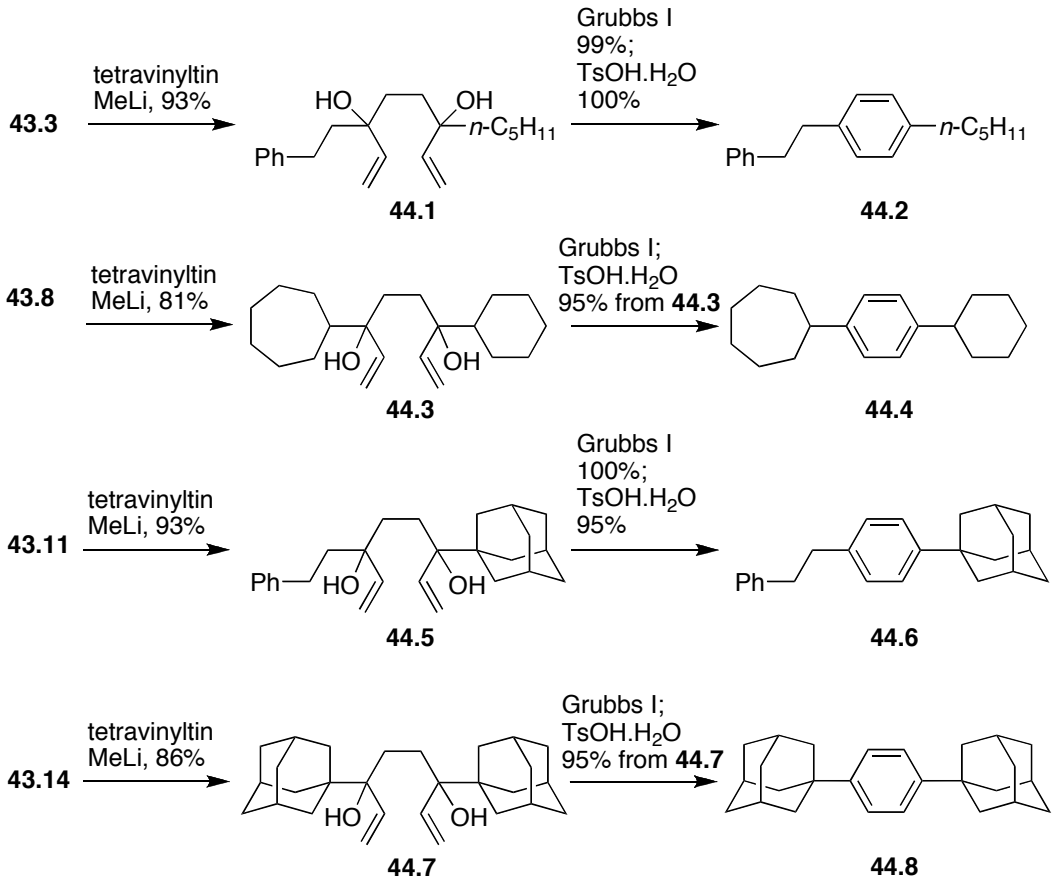
Al_2O_3 was used to provide reduced product in low yield (39%). Jones oxidation of the resulting diols proceeded without difficulty to provide the desired 1,4-diketones.



Scheme 43

The various 1,4-diketones **43.3**, **43.8**, **43.11** and **43.14** shown in Scheme 43 were then treated with vinyllithium (generated from tetravinyltin and MeLi) to generate 1,7-diene-3,6-diols **44.1**, **44.3**, **44.5** and **44.7** in good yields (81-93%). These diols were then cyclized using first generation Grubbs catalyst and readily provided the cyclohexene diol intermediates (*cf.* Scheme 42, **42.2**) in very good

yield. These intermediate diols were then purified and exposed to acidic conditions to provide aromatized products **44.2**, **44.4**, **44.6** and **44.8** in very good yields.

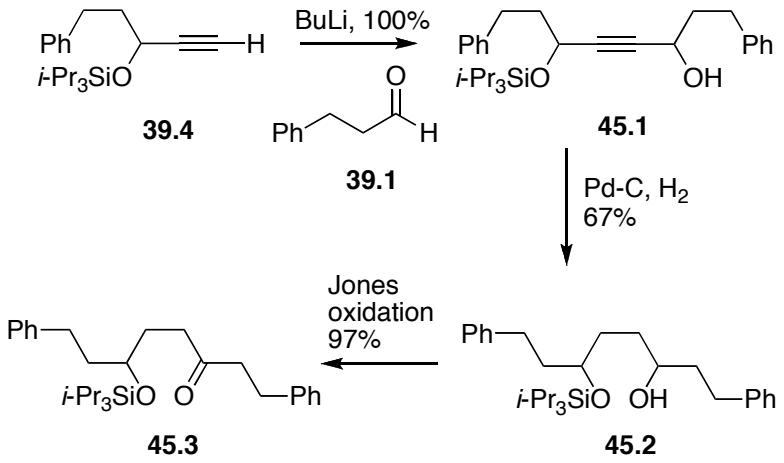


Scheme 44

2.4 Preparation of 1,2,4-Trisubstituted Benzenes

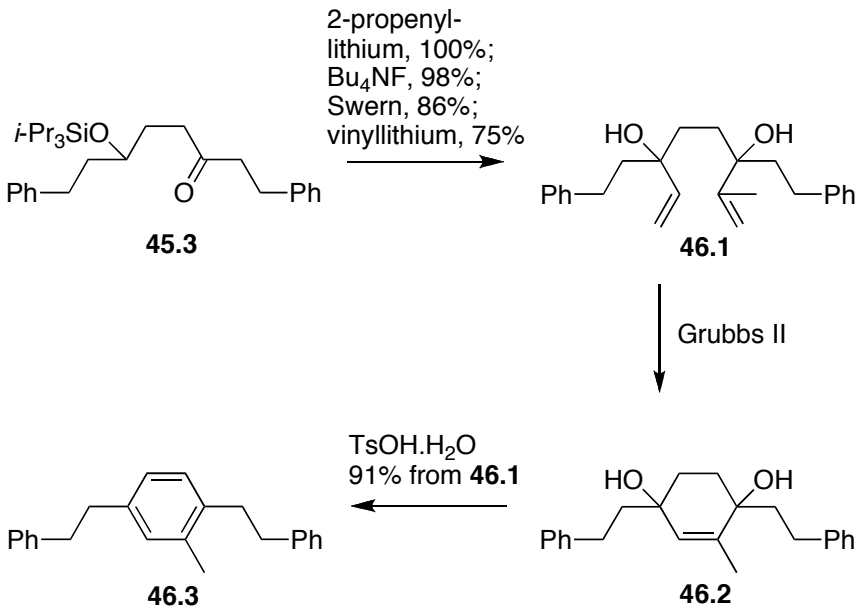
In order to form the 1,2,4-trisubstituted benzene **46.3** (see Scheme 46), triisopropylsilyl-protected propargyl alcohol **39.4** was added to aldehyde **39.1** after treatment with BuLi, providing mono-protected alkyne diol **45.1** in quantitative yield. As it is known[46] that silyl-protection of a benzylic alcohol can thwart hydrogenolysis by palladium catalysts, we assumed that the same is true of

allylic and propargylic alcohols, and so the silyl-protected compound **45.1** was reduced in the presence of Pd-C and H_2 and gave **45.2** in acceptable yield (67%). Jones oxidation of **45.2** then provided ketone **45.3** in excellent yield.



Scheme 45

Intermediate ketone **45.3** was then reacted with 2-propenyllithium to provide the corresponding 2-propenyl-substituted tertiary alcohol in quantitative yield. The triisopropyl group of this intermediate was then removed with Bu_4NF (98% yield) and the resulting hydroxyl was oxidized using Swern conditions (86% yield). Treatment with vinyllithium using the standard method provided the diene diol **46.1** in good yield (75%); this compound underwent RCM in the presence of the second generation Grubbs catalyst to form **46.2**, which was used crude in the following aromatization. Reaction under mild acidic conditions readily provided trisubstituted benzene **46.3** in 91% yield over two steps.

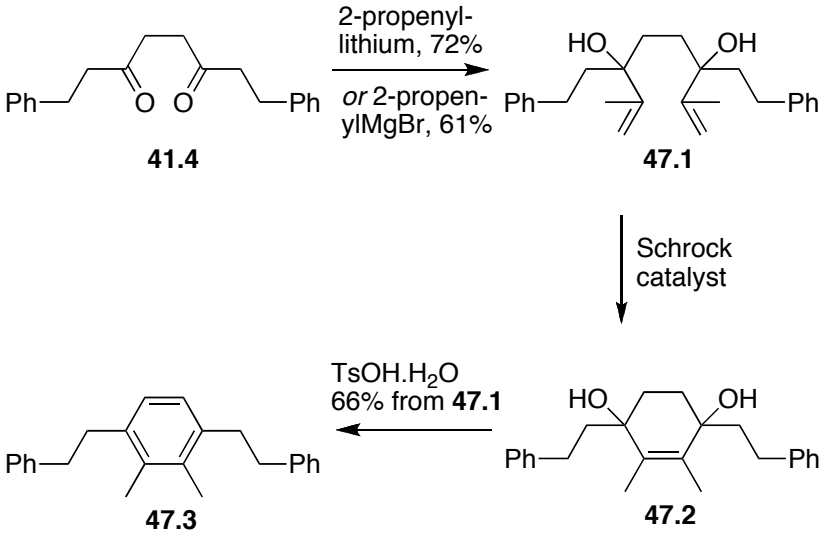


Scheme 46

2.5 Preparation of 1,2,3,4-Tetrasubstituted Benzenes

In order to form 1,2,3,4-tetrasubstituted benzene **47.3**, diketone **41.4** was reacted with an excess of 2-propenyllithium to provide bis-addition product **47.1** in good yield (71%). Isopropenylmagnesium bromide was also effective at forming **47.1**, albeit in slightly lower yield (61%). In order to effect ring closure of **47.1** by RCM, the second generation Grubbs catalyst was first used in 1,2-dichloroethane at reflux, but provided none of the desired product **47.2** or aromatized product **47.3**. The nitro variant of the Hoveyda-Grubbs catalyst was tried next, as it has been reported to form tetrasubstituted double bonds upon RCM of substituted alkenes.[47] It was used with substituted terminal diene **47.1** in 1,2-dichloroethane at reflux, but provided none of the desired product after a prolonged reaction period. The Schrock catalyst[48] was then chosen as the metathesis catalyst. Diene **47.1** was reacted with 20 mol% Schrock catalyst in

benzene in a sealed Pyrex bomb at 80 °C, but no desired product **47.2** or **47.3** was observed after heating for 2 days. It was hypothesized that the sealed bomb prevented the escape of ethylene and thus thwarted the reaction. The experiment was repeated in a Pyrex bomb and, after 2.5 days, no desired product was observed (by TLC, using a sample removed in the dry box). An additional 20 mol% catalyst was added and the reaction mixture was heated at reflux for an additional 18 h with frequent purging with nitrogen outside of the dry box over the course of the reaction, providing what appeared to be the crude product **47.2**. Exposure of this material to mild acidic conditions in benzene at reflux gave **47.3** in 66% yield (over two steps).

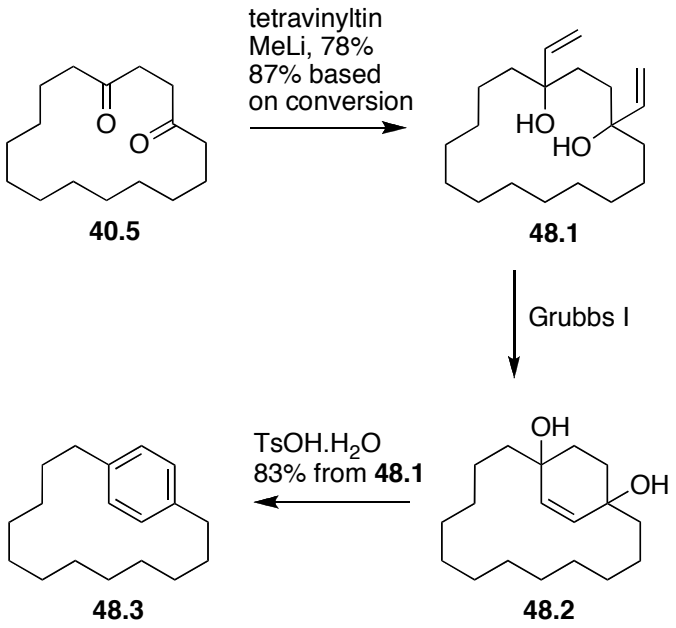


Scheme 47

2.6 Preparation of Paracyclophanes

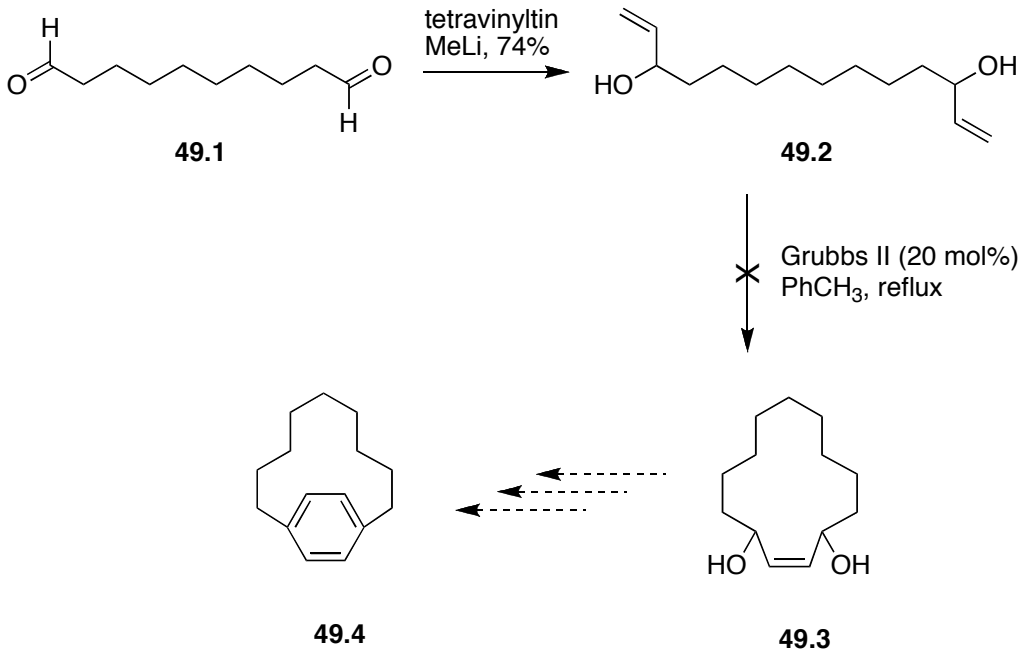
The cyclic 1,4-diketone **40.5** was used to form [12]-paracyclophane (**48.3**) by first forming the 1,7-diene-3,6-diol **48.1** by vinyl group addition using standard

conditions. This diene intermediate was then easily cyclized by RCM using the first generation Grubbs catalyst to provide cyclohexene diol **48.2** which was treated with *p*-TsOH·H_2O in benzene at reflux without purification to provide [12]-paracyclophane (**48.3**) in 83% yield (over two steps).



Scheme 48

The synthesis of [8]-paracyclophane **49.4** was also attempted in an earlier set of experiments using decanedial (**49.1**) (formed by oxidative cleavage of dodeca-1,11-diene). While tetradeca-1,13-diene-3,12-diol (**49.2**) was formed in good yield using vinyllithium, it was not possible, despite repeated experiments, to form RCM cyclized product **49.3** using the second generation Grubbs catalyst under forcing conditions (20 mol%, benzene at reflux). Further attempts at ring closure using more active RCM catalysts were not attempted.



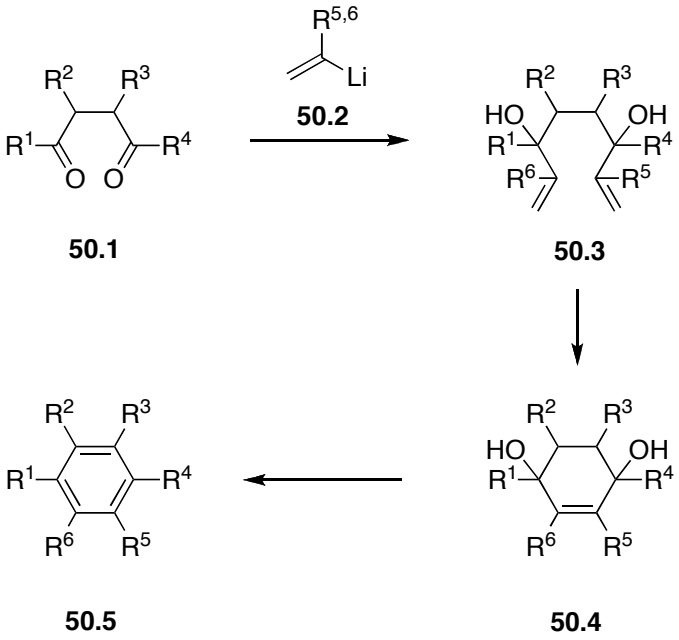
49.1 **49.2** **49.4** **49.3**

Scheme 49

3 CONCLUSIONS

The formation of regioselectively substituted benzene rings reported in Section 2 was developed and expanded to the point where it offers a useful methodology for the linear construction of various substituted aromatic rings. The method has been shown, through my examples, to support the selective formation of *p*-disubstituted benzenes, in addition to 1,2,4-trisubstituted (e.g. **46.3**) and 1,2,3,4-tetrasubstituted cases (e.g. **47.3**) in moderate to excellent yields. The methodology has, however, been shown to be of limited use in the construction of paracyclophanes of acceptable size [e.g. [12]-paracyclophane (**48.3**)].

It is possible to envisage that the above method for formation of *p*-disubstituted benzenes in also amenable to the formation of poly-substituted arene compounds **50.5** that are penta- or hexa-substituted (Scheme 50). With the reaction of elaborately substituted 1,4-diketones (**50.1**) with organometallic olefins (**50.2**), species such as **50.3** could be formed and subsequently cyclized by RCM and aromatized under acidic conditions to provide densely substituted benzenes **50.5**. It is assumed that in order to selectively alkenylate the ketones **50.1** independently, different organometallic nucleophiles **50.2** (R^5 or R^6) could either be used consecutively, with care to use no more than one equivalent of **50.2**. However, in order to achieve absolute regioselectivity, protection of one of the oxygens based on described protocols (*cf.* Scheme 39) would first have to be achieved, before deprotection, oxidation and substitution (*cf.* Scheme 45).



Scheme 50

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 35 cm) of BASF catalyst and then through a similar column of Drierite. Glassware was dried in an oven for at least 3 h before use (135 °C) 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. All solvents for reactions were dried, as described below. Reaction mixtures were stirred by Teflon-coated magnetic stirring bars.

Hexane and EtOAc used for chromatography were distilled before use.

Microliter syringes were washed with water, acetone and ether, using the plunger to drive the solvents through. Air was drawn through the syringes which were then stored for at least one day in a desiccator before use. Cannula transfers were always carried out under slight pressure (Ar or N_2) and not by suction.

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

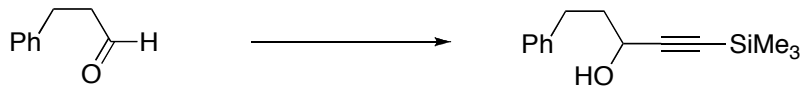
Dry solvents were prepared under an inert atmosphere and transferred by syringe or cannula. Dry THF, Et_2O, PhH, PhMe and dioxane were distilled from sodium and benzophenone ketyl. Dry CH_2Cl_2, Et_3N and *i*-Pr_2NEt were distilled from CaH_2. Dry MeOH was distilled from $Mg(OMe)_2$.

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. The use of "br" indicates that the signal is broad.

Mass spectra were recorded with AEI Models MS-12, MS-50, MS9 (modified), or Kratos MS50 (modified) mass spectrometers.

5-Phenyl-1-(trimethylsilyl)pent-1-yn-3-ol (39.2).[49]

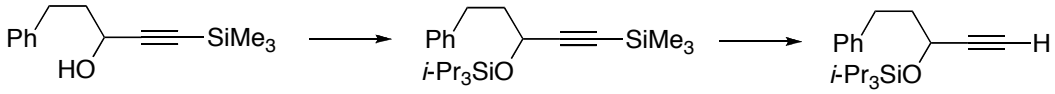


39.1 **39.2**

BuLi (2.5 M in hexane, 3.04 mL, 7.59 mmol) was added dropwise to a stirred and cooled (–78 °C) solution of trimethylsilylacetylene (1.07 mL, 7.59 mmol) in dry THF (20 mL). After 45 min, freshly distilled aldehyde **39.1** (1.00 mL, 7.59 mmol) was added dropwise. The cold bath was left in place but not recharged and stirring was continued for 15 h. The mixture was quenched with saturated aqueous NH_4Cl and extracted with EtOAc (3 x 20 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (4 x 18 cm), using EtOAc-petroleum ether mixtures from 5% to 15% EtOAc, gave **39.2** (1.71 g, 97%) as an oil: FTIR (CH_2Cl_2 cast film, microscope) 3329, 3028, 2958, 2899, 2863, 2173 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.21 (s, 9 H), 1.88-1.97 (br s, 1 H), 1.97-2.10 (m, 2 H), 2.82 (t, J = 8.1 Hz, 2 H), 4.38 (t, J = 6.6 Hz, 1 H), 7.19-7.25 (m, 3 H),

7.28-7.33 (m, 2 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ -0.1 (q), 31.4 (t), 39.2 (t), 62.2 (d), 89.9 (s), 106.5 (s), 126.0 (d), 128.4 (d), 128.5 (d), 141.3 (s); exact mass *m*/*z* calcd for $C_{14}H_{20}OSi$ 232.1283, found 232.1265.

Tris(1-methylethyl)[(5-phenylpent-1-yn-3-yl)oxy]silane (39.4).

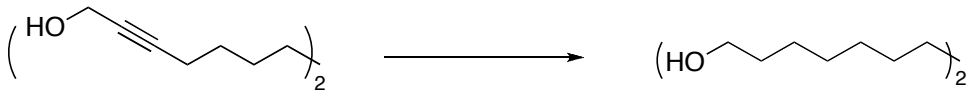


39.2 **39.3** **39.4**

NaH (0.454 g, 18.9 mmol) was quickly added to a stirred and cooled (0 °C) solution of **39.2** (1.47 g, 6.31 mmol) in dry THF (50 mL). After 15 min, *i*-Pr_3SiCl (4.05 mL, 18.9 mmol) was added dropwise. The cold bath was left in place but not recharged and stirring was continued for 12 h. The mixture was cooled to 0 °C and quenched with saturated aqueous NH_4Cl (40 mL). The aqueous phase was extracted with Et_2O and the combined organic extracts were dried (Na_2SO_4) and evaporated. The residue (**39.3**) was kept under oil pump vacuum for several h. Oven-dried K_2CO_3 (2.62 g, 18.9 mmol) was added to a stirred and cooled (0 °C) solution of crude **39.3** in dry MeOH (38 mL). The cooling bath was left in place but not recharged and stirring was continued for 17 h. The mixture was evaporated and 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 (5 x 22 cm), using EtOAc-petroleum mixtures from 1% to 5% EtOAc, gave **39.4** (1.927 g, 96% over two steps) as an oil: FTIR (CH_2Cl_2, cast microscope) 3309, 3028, 2944, 2891, 2867, 1463, 1454 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.06-1.18 (m, 21 H), 1.97-2.09 (m, 2 H), 2.44 (d, *J* = 2.1

Hz, 1 H), 2.76-2.89 (m, 2 H), 4.50 (ddd, J = 6.7, 5.6, 2.1 Hz, 1 H), 7.17-7.23 (m, 3 H), 7.27-7.31 (m, 2 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 12.2 (d), 18.0 (q), 31.1 (t), 40.5 (t), 62.3 (d), 72.5 (d), 85.3 (d), 125.8 (d), 128.4 (d), 128.5 (d), 141.8 (s); exact mass m/z calcd for $C_{20}H_{32}NaOSi$ 339.2115, found 339.2118.

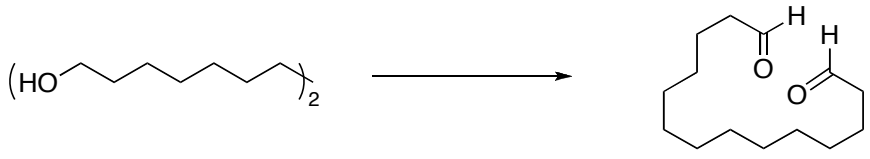
Tetradecane-1,14-diol (40.1a).[50]



40.1 **40.1a**

Pt-C (10% w/w, ca 10 mg) was added to a solution of **40.1** (0.154 g, 0.690 mmol) in MeOH (10 mL) and the mixture was stirred under H_2 (doubled balloon) for 20 h. The mixture was filtered through Celite, using EtOAc as a rinse. Evaporation of the solvent and flash chromatography of the residue over silica gel (1.8 x 19 cm), using EtOAc-petroleum ether mixtures from 40% to 80% EtOAc, gave **40.1a** (0.0959 g, 60%) as a solid.

Tetradecanedial (40.2).

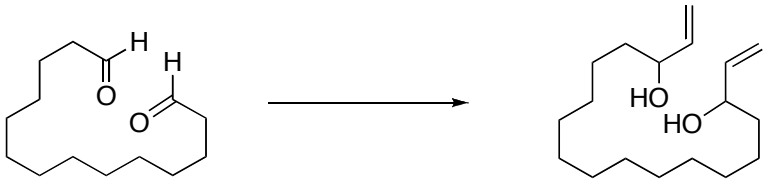


40.1a **40.2**

$(COCl)_2$ (0.356 mL, 4.08 mmol) was added dropwise to a stirred and cooled (–78 °C) solution of DMSO (0.580, 8.16 mmol) in CH_2Cl_2 (5 mL). After 15 min, a solution of **40.1a** (0.122 mL, 0.529 mmol) in CH_2Cl_2 (3 mL) was added

dropwise. After a further 45 min, Et_3N (1.47 mL, 10.6 mmol) was added dropwise and stirring was continued for 30 min. The mixture was then stored at –20 °C (freezer) for 20 h, warmed to 0 °C, and stirred at this temperature for 3 h. Water (6 mL) and CH_2Cl_2 (10 mL) were added. The aqueous phase was extracted with CH_2Cl_2 and the combined organic extracts were washed with saturated aqueous $NaHCO_3$, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1.4 x 16 cm), using EtOAc-petroleum ether mixtures from 5% to 15% EtOAc, gave **40.2** (0.0901 g, 83%) as an oil: FTIR (CH_2Cl_2, cast) 2915, 2850, 2749, 1788, 1705, 1674, 1471 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.23-1.37 (m, 16 H), 1.63 (quintet, J = 7.2 Hz, 4 H), 2.42 (td, J = 7.4, 1.9 Hz, 4 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 22.1 (t), 29.2 (t), 29.3 (t), 29.4 (t), 29.5 (t), 43.9 (t), 202.9 (d); exact mass m/z calcd for $C_{14}H_{26}NaO_2$ 249.1825, found 249.1828.

Octadeca-1,17-diene-3,16-diol (40.3).

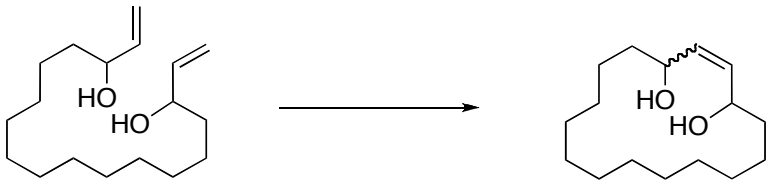


40.2 **40.3**

MeLi (1.6 M in Et_2O, 0.614 mL, 0.983 mmol) was added dropwise to a stirred and cooled (0 °C) solution of tetravinyltin (0.045 mL, 0.25 mmol) in dry Et_2O (6 mL). After 1 h, the mixture was cooled to –78 °C and **40.2** (0.014 g, 0.061 mmol) in Et_2O (2 mL plus 2 mL as a rinse) was added by cannula. The cold bath was left in place but not recharged and stirring was continued for 22 h.

The mixture was cooled to 0 °C and quenched with water (10 mL). The aqueous phase was extracted with Et_2O and the combined organic extracts were washed with brine, dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (0.7 x 15 cm), using EtOAc-petroleum mixtures from 10% to 20% EtOAc, gave **40.3** (14.1 mg, 81%) as an oil: FTIR (CH_2Cl_2, microscope) 3312, 3092, 3015, 2986, 2914, 2849, 1857, 1646, 1465 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.24-1.44 (m, 22 H), 1.48-1.58 (m, 4 H), 4.10 (apparent qt, *J* = 6.1, 1.2 Hz, 2 H), 5.11 (dt, *J* = 10.4, 1.5 Hz, 2 H), 5.22 (dt, *J* = 17.2, 1.5 Hz, 2 H), 5.87 (ddd, *J* = 17.2, 10.4, 6.2 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 25.3 (t), 29.5 (t), 29.55 (t), 29.59 (t), 37.1 (t), 73.3 (d), 114.5 (t), 141.3 (d); exact mass *m*/*z* calcd for $C_{18}H_{34}O_2$ 305.2451, found 305.2450.

Cyclohexadec-2-ene-1,4-diol (40.4).

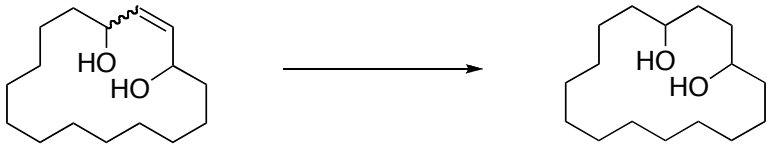


40.3 **40.4**

A solution of **40.3** (0.0107 g, 0.0379 mmol) in dry CH_2Cl_2 (10 mL) was added dropwise over 20 h to a stirred solution of Grubbs catalyst (2nd generation,[43] 0.0032 g, 0.0038 mmol) in CH_2Cl_2 (5 mL) (N_2 atmosphere). After 6 d, the mixture was evaporated and flash chromatography of the residue over silica gel (0.7 x 15 cm), using EtOAc-petroleum ether mixtures from 10% to 100% EtOAc, gave **40.4** (0.0069 g, 72%) as a solid which was a mixture of diastereoisomers: FTIR (CH_2Cl_2, cast microscope) 3357, 2925, 2855, 2680, 1956, 1660, 1633, 1460 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.15-1.42 (m, 22 H), 1.50-

1.60 (m, 2 H), 1.60-1.72 (m, 2 H), 4.10-4.15 (m, 1 H), 4.23-4.28 (m, 1 H), 5.58 (dd, J = 5.0, 2.5 Hz, 1 H), 5.71 (dd, J = 3.0, 1.3 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 23.6 (t), 24.2 (t), 25.0 (t), 25.90 (t), 25.94 (t), 27.2 (t), 27.3 (t), 27.8 (t), 28.0 (t), 36.9 (t), 37.0 (t), 72.1 (d), 73.5 (d), 133.1 (d), 135.0 (d); exact mass m/z calcd for $C_{16}H_{30}NaO_2$ 277.2138, found 277.2139.

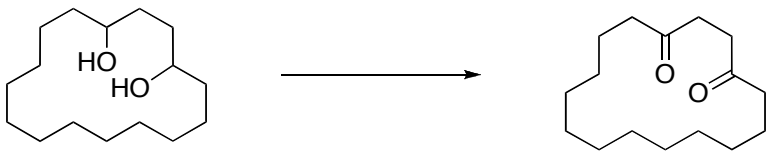
Cyclohexadecane-1,4-diol (40.4a).



40.4 **40.4a**

Pd-C (5% w/w, *ca.* 4 mg) was added to a solution of **40.4** (0.0252 g, 0.0991 mmol) in MeOH (1 mL) and the mixture was stirred under H_2 (doubled balloon) for 8 h. The mixture was filtered through Celite, using EtOAc as a rinse. Evaporation of the solvent and flash chromatography of the residue over silica gel (0.7 x 15 cm), using 2% MeOH-EtOAc, gave **40.4a** (0.0179 g, 70%) as an oil: FTIR (CH_2Cl_2, cast) 3392, 3313, 2921, 2850, 1644, 1469 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.18-1.43 (m, 26 H), 1.44-1.70 (m, 4 H), 3.72-3.82 (m, 2 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 23.1 (t), 23.6 (t), 26.47 (t), 26.51 (t), 26.56 (t), 26.64 (t), 26.7 (t), 26.8 (t), 26.9 (t), 27.0 (t), 29.7 (t), 30.9 (t), 31.3 (t), 31.4 (t), 35.18 (t), 35.24 (t), 70.2 (d), 71.0 (d); exact mass m/z calcd for $C_{16}H_{32}NaO_2$ 279.2295, found 279.2296.

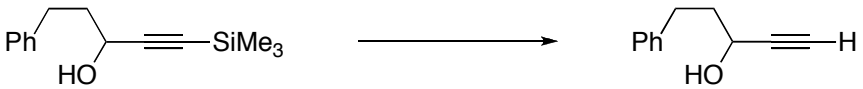
Cyclohexadecane-1,4-dione (40.5).[51]



40.4a **40.5**

Jones reagent (7.0 M in acetone, 0.025 mL, 0.176 mmol) was added dropwise to a stirred and cooled (0 °C) solution of **40.4a** (0.0150 g, 0.0585 mmol) in acetone (4 mL). After 1.5 h, the orange mixture was quenched with MeOH (3 mL) and stirring was continued for 30 min, by which time the mixture had become dark green. The organic phase was diluted with EtOAc (15 mL) and washed with water and brine, dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (0.4 x 6 cm), using a 10% EtOAc-petroleum ether mixture, gave **40.5** (0.0126 g, 86%) as an oil: FTIR (CH_2Cl_2, cast microscope) 2930, 2856, 1712, 1457, 1408 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.14-1.40 (m, 16 H), 1.58-1.66 (m, 4 H), 2.46-2.51 (m, 4 H), 2.69 (s, 4 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 23.2 (t), 25.7 (t), 26.8 (t), 26.9 (t), 27.5 (t), 36.5 (t), 42.0 (t), 210.4 (s); exact mass *m*/*z* calcd for $C_{16}H_{28}O_2$ 252.2089, found 252.2091.

5-Phenylpent-1-yn-3-ol (41.1).

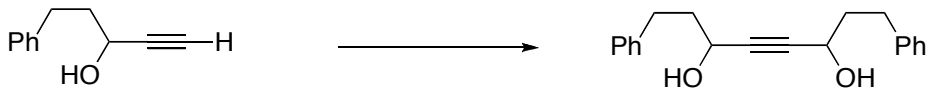


39.2 **41.1**

K_2CO_3 (1.459 g, 28.24 mmol) was added to a stirred and cooled (0 °C) solution of **39.2** (1.459 g, 6.276 mmol) in dry MeOH (60 mL). The ice bath was

left in place but not recharged and stirring was continued for 13 h. The mixture was evaporated and the residue was partitioned between water and Et_2O. The aqueous phase was extracted with Et_2O and the combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2.8 x 21 cm), using 20% EtOAc-petroleum ether, gave **41.1** (0.952 g, 94%) as an oil: FTIR (CH_2Cl_2, microscope) 3292, 3063, 3027, 2927, 2863, 2115, 1603, 1496 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.79-1.93 (br s, 1 H), 2.00-2.12 (m, 2 H), 2.50 (d, J = 2.2 Hz, 1 H), 2.82 (t, J = 7.9 Hz, 2 H), 4.38 (td, J = 12.5, 1.9 Hz, 1 H), 7.19-7.24 (m, 3 H), 7.28-7.33 (m, 2 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 31.2 (t), 39.1 (t), 61.6 (d), 73.3 (s), 84.6 (d), 126.1 (d), 128.47 (d), 128.48 (d), 141.1 (s); exact mass m/z calcd for $C_{11}H_{12}AgO$ 266.9934, found 266.9933.

1,8-Diphenyloct-4-yne-3,6-diol (41.2).[52]

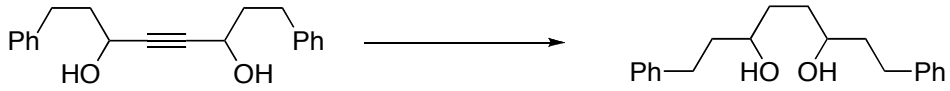


41.1 **41.2**

BuLi (2.5 M in hexane, 2.20 mL, 5.49 mmol) was added dropwise to a stirred and cooled (–78 °C) solution of **41.1** (0.4000 g, 2.497 mmol) in dry THF (20 mL). After 1.5 h, freshly distilled hydrocinnamaldehyde (0.4274 mL, 3.246 mmol) was added dropwise. The cold bath was removed and stirring was continued for 4 h. The mixture was cooled to 0 °C, quenched with dilute hydrochloric acid (1.0 N, 20 mL), and the organic solvent was evaporated. The resulting aqueous mixture was extracted with Et_2O and the combined organic extracts were dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (4 x 25 cm), using EtOAc-petroleum ether mixtures from

25% to 60% EtOAc, gave **41.2** (0.638 g, 86%) as an oil which was a mixture of diastereoisomers: FTIR ($CHCl_3$, microscope) 3331, 3062, 3026, 2948, 2927, 2862, 1947, 1871, 1804, 1603, 1496 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 2.07-2.13 (m, 6 H), 2.81 (t, J = 7.9 Hz, 4 H), 4.42 (t, J = 6.8 Hz, 2 H), 7.18-7.24 (m, 6 H), 7.28-7.32 (m, 4 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 31.41 (t), 31.42 (t), 39.1 (t), 61.7 (d), 86.08 (s), 86.09 (s), 126.1 (d), 128.47 (d), 128.50 (d), 141.1 (s); exact mass m/z calcd for $C_{20}H_{22}NaO_2$ 317.1509, found 317.1509.

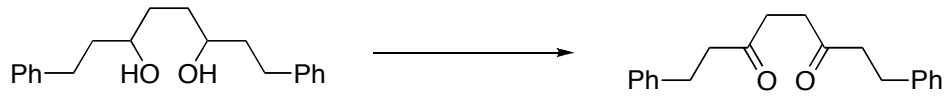
1,8-Diphenyloctane-3,6-diol (41.3).



41.2 **41.3**

Pt-C (5% w/w, *ca.* 5 mg) was added to a solution of **41.2** (0.0377 g, 0.128 mmol) in MeOH (5 mL) and the mixture was stirred under H_2 (doubled balloon) for 18 h. The mixture was filtered through Celite, using EtOAc as a rinse. Evaporation of the filtrate and flash chromatography of the residue over silica gel (0.7 x 16 cm), using EtOAc-petroleum ether mixtures from 20% to 50% EtOAc, gave **41.3** (0.029 g, 75%) as an oil: FTIR (CH_2Cl_2, microscope) 3323, 3243, 3022, 2937, 2913, 2861, 1942, 1495, 1454 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.50-1.61 (m, 2 H) 1.61-1.74 (m, 2 H), 1.75-1.84 (m, 4 H), 2.15-2.60 (br s, 2 H), 2.63-2.73 (m, 2 H), 2.74-2.84 (m, 2 H), 3.62-3.72 (m, 2 H), 7.17-7.23 (m, 6 H), 7.26-7.32 (m, 4 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 31.1 (t), 33.3 (t), 34.1 (t), 39.1 (t), 71.3 (d), 71.6 (d), 125.8 (d), 128.39 (d), 128.41 (d), 142.0 (s) (two signals missing due to overlap); exact mass m/z calcd for $C_{20}H_{26}NaO_2$ 321.1825, found 321.1821.

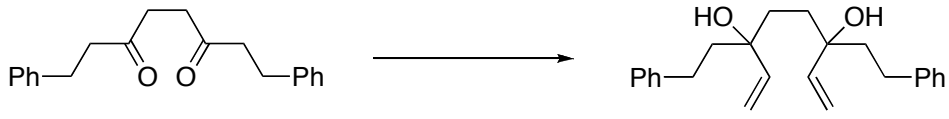
1,8-Diphenyloctane-3,6-dione (41.4).



41.3 **41.4**

Jones reagent (7.0 M in acetone, 0.54 mL, 3.8 mmol) was added dropwise to a stirred and cooled (0 °C) solution of **41.3** (0.1620 g, 0.5428 mmol) in acetone (15 mL). After 30 min, the orange mixture was quenched with MeOH (15 mL) and stirring was continued for 30 min, by which time the mixture had become dark green. The organic phase was diluted with EtOAc (30 mL) and washed with water and brine, dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (1.4 x 16 cm), using EtOAc-petroleum ether mixtures from 10% to 15% EtOAc, gave **41.4** (0.145 g, 90%) as an oil: FTIR (CH_2Cl_2, cast microscope) 3062, 3027, 2925, 1711, 1603, 1496 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 2.68 (s, 4 H), 2.81 (apparent t, J = 7.7 Hz, 4 H), 2.91 (t, J = 7.2 Hz, 4 H), 7.17-7.22 (m, 6 H), 7.27-7.31 (m, 4 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 29.8 (t), 36.2 (t), 44.3 (t), 126.1 (d), 128.3 (d), 128.5 (d), 141.0 (s), 208.4 (s); exact mass m/z calcd for $C_{20}H_{23}O_2$ 295.1693, found 295.1696.

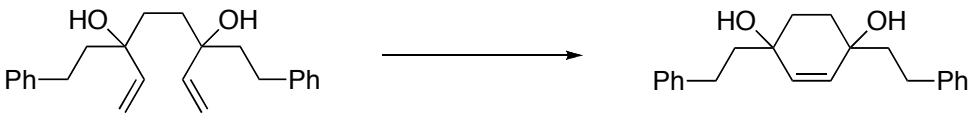
3,6-Bis(2-Phenylethyl)octa-1,7-diene-3,6-diol (42.1).



41.4 **42.1**

MeLi (1.6 M in Et_2O, 3.31 mL, 5.29 mmol) was added dropwise to a stirred and cooled (0 °C) solution of tetravinyltin (0.241 mL, 1.32 mmol) in dry Et_2O (20 mL). After 35 min, the mixture was cooled to –78 °C and **41.4** (0.1146 g, 0.3893 mmol) in Et_2O (3.5 mL plus 3.5 mL as a rinse) was added by cannula. The cold bath was left in place but not recharged and stirring was continued for 12 h. The reaction was quenched with a mixture of water (50 mL) and saturated aqueous NH_4Cl (25 mL). 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 (1.8 x 19 cm), using EtOAc-hexanes mixtures from 15% to 30% EtOAc, gave **42.1** (0.107 g, 78%) as an oil, which was a mixture of diastereoisomers: FTIR (CH_2Cl_2, cast microscope) 3416, 3085, 3062, 3026, 2946, 2863, 1945, 1867, 1744, 1642, 1603, 1497 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.55-1.70 (m, 3 H), 1.70-1.85 (m, 4 H), 1.85-1.97 (m, 3 H), 2.58-2.71 (m, 4 H), 5.18-5.24 (m, 2 H), 5.25-5.32 (m, 2 H), 5.79-5.89 (m, 2 H), 7.15-7.20 (m, 6 H), 7.25-7.30 (m, 4 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 30.0 (t), 34.3 (t), 34.4 (t), 42.7 (t), 43.3 (t), 75.2 (s), 75.3 (s), 113.3 (t), 113.5 (t), 125.78 (d), 125.79 (d), 128.36 (d), 128.41 (d), 142.36 (s), 142.38 (s), 143.2 (d), 143.5 (d); exact mass *m/z* calcd for $C_{24}H_{30}O_2$ 373.2138, found 373.2139.

1,4-Bis(2-phenylethyl)cyclohex-2-ene-1,4-diol (42.2).

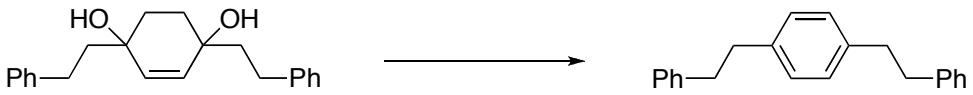


42.1 **42.2**

Grubbs catalyst (1st generation, 0.0192 g, 0.0233 mmol) was added to a stirred solution of **42.1** (0.1152 g, 0.3287 mmol) in dry CH_2Cl_2 (20 mL) (N_2 atmosphere). After 24 h, the mixture was evaporated and flash chromatography of the residue over silica gel (1.3 x 11 cm), using EtOAc-petroleum ether mixtures from 10% to 100% EtOAc, gave **42.2** [0.0376 g, 35% less polar diastereoisomer; 0.0666 g, 62% more polar diastereoisomer (98% overall)] as a solid. The more polar diastereoisomer had: FTIR (CH_2Cl_2, cast microscope) 3377, 3061, 3025, 2933, 2858, 1945, 1870, 1663, 1496 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.56-1.65 (br s, 2 H), 1.77-1.92 (m, 8 H), 2.71 (t, J = 8.7 Hz, 4 H), 5.77 (s, 2 H), 7.17-7.23 (m, 6 H), 7.26-7.30 (m, 4 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 29.9 (t), 32.9 (t), 42.8 (t), 70.3 (s), 125.9 (d), 128.3 (d), 128.5 (d), 134.4 (d), 142.2 (s); exact mass m/z calcd for $C_{22}H_{26}NaO_2$ 345.1825, found 345.1824.

The less polar diastereomer had: FTIR (CH_2Cl_2, cast microscope) 3377, 3062, 3025, 2931, 2859, 1946, 1603, 1496 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.55-1.65 (br s, 2 H), 1.77-1.94 (m, 8 H), 2.74 (t, J = 8.6 Hz, 4 H), 5.76 (s, 2 H), 7.16-7.23 (m, 6 H), 7.26-7.32 (m, 4 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 29.9 (t), 31.8 (t), 44.0 (t), 69.5 (s), 125.9 (d), 128.3 (d), 128.4 (d), 134.2 (d), 142.1 (s); exact mass m/z calcd for $C_{22}H_{26}NaO_2$ 345.1825, found 345.1823.

1,4-Bis(2-phenylethyl)benzene (42.3).[53]

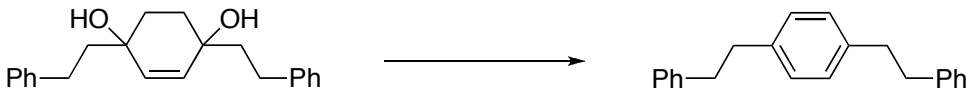


42.2 **42.3**

$TsOH.H_2O$ (0.0112 g, 0.05892 mmol) was added to a solution of the previously separated more polar diastereoisomer of **42.2** (0.0185 g, 0.0574 mmol)

in dry PhH (2 mL). The mixture was refluxed for 7 h, cooled to room temperature and partitioned between water and CH_2Cl_2. The aqueous phase was then extracted with hexane and the combined organic extracts were dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (0.7 x 18 cm), using EtOAc-petroleum ether mixtures from 0% to 2% EtOAc, gave **42.3** (0.0161 g, 98%) as an oil: FTIR (CH_2Cl_2, cast microscope) 3084, 3062, 3023, 2933, 2916, 2852, 1902, 1698, 1602, 1512, 1496, 1452 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 2.90 (s, 8 H), 7.11 (s, 4 H), 7.17-7.23 (m, 6 H), 7.26-7.31 (m, 4 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 37.5 (t), 38.0 (t), 125.9 (d), 128.3 (d), 128.38 (d), 128.44 (d), 139.3 (s), 141.9 (s); exact mass *m*/*z* calcd for $C_{22}H_{22}$ 286.1722, found 286.1723.

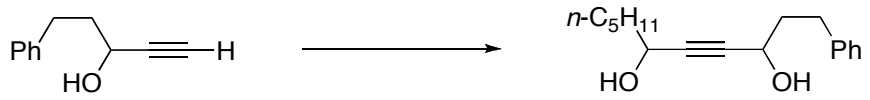
1,4-Bis(2-phenylethyl)benzene (42.3).[53]



42.2 **42.3**

TsOH.H_2O (0.0074 g, 0.039 mmol) was added to a solution of the previously separated less polar diastereomer of **42.2** (0.0126 g, 0.0391 mmol) in dry PhH (1.5 mL). The mixture was refluxed for 5 h, cooled to room temperature and partitioned between water and CH_2Cl_2. The aqueous phase was then extracted with hexane and the combined organic extracts were dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (0.7 x 15 cm), using EtOAc-petroleum ether mixtures from 0% to 2% EtOAc, gave **42.3** (0.011 g, 100%) as an oil.

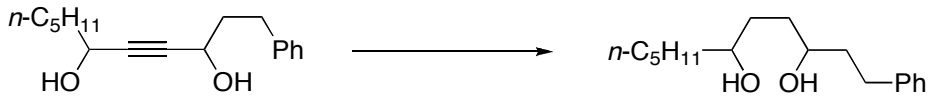
1-Phenylundec-4-yne-3,6-diol (43.2).



41.1 **43.2**

BuLi (2.5 M in hexane, 0.866 mL, 2.16 mmol) was added dropwise to a stirred and cooled (–78 °C) solution of **41.1** (0.1576 g, 0.9837 mmol) in dry THF (12 mL). After 0.5 h, freshly distilled *n*-hexanal (0.23 mL, 2.0 mmol) was added dropwise. The cold bath was removed and stirring was continued for 36 h. The mixture was cooled to 0 °C and quenched with hydrochloric acid (1.0 N, 15 mL). The organic solvent was evaporated and the resulting aqueous mixture was extracted with Et_2O. The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1.8 x 21 cm), using EtOAc-petroleum ether mixtures from 20% to 40% EtOAc, gave **43.2** (0.2321 g, 90%) as an oil: FTIR (CH_2Cl_2, cast microscope) 3322, 3027, 2953, 2931, 2860, 1943, 1873, 1803, 1745, 1604, 1496, 1455 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.90 (t, *J* = 7.0 Hz, 3 H), 1.29-1.38 (m, 4 H), 1.41-1.51 (m, 2 H), 1.63-1.78 (m, 2 H), 1.95-2.11 (m, 2 H), 2.12-2.22 (br s, 1 H), 2.22-2.36 (br s, 1 H), 2.79 (t, *J* = 7.8 Hz, 2 H), 4.41 (t, *J* = 6.1 Hz, 2 H), 7.17-7.23 (m, 3 H), 7.27-7.32 (m, 2 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.0 (q), 22.6 (t), 24.9 (t), 31.39 (t), 31.43 (t), 37.7 (t), 39.1 (t), 61.7 (d), 62.5 (d), 85.6 (s), 86.4 (s), 126.0 (d), 128.4 (d), 128.5 (d), 141.2 (s); exact mass *m*/*z* calcd for $C_{17}H_{24}NaO_2$ 283.1669, found 283.1670.

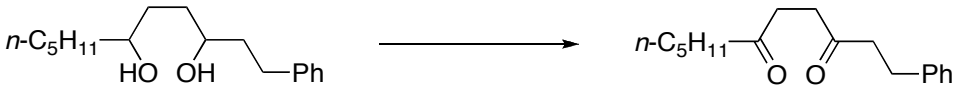
1-Phenylundecane-3,6-diol (43.2a).



43.2 **43.2a**

Pt-C (5% w/w, *ca.* 3 mg) was added to a solution of **43.2** (0.0274 g, 0.105 mmol) in MeOH (5 mL) and the mixture was stirred under H_2 (doubled balloon) for 1 h. The mixture was filtered through Celite, using EtOAc as a rinse. Evaporation of the filtrate and flash chromatography of the residue over silica gel (0.7 x 16 cm), using EtOAc-petroleum ether mixtures from 20% to 50% EtOAc, gave **43.2a** (0.0182 g, 65%) as an oil which was a mixture of diastereoisomers: FTIR (CH_2Cl_2, cast microscope) 3215, 3086, 3063, 3027, 2955, 2937, 2920, 2871, 2854, 1942, 1496, 1453 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.90 (t, J = 6.7 Hz, 3 H), 1.24-1.38 (m, 6 H), 1.38-1.60 (m, 4 H), 1.63-1.74 (m, 2 H), 1.77-1.83 (m, 2 H), 1.85-2.27 (br s, 2 H), 2.69 (apparent dt, J = 13.9, 8.1 Hz, 1 H), 2.80 (dt, J = 14.2, 7.5 Hz, 1 H), 3.59-3.73 (m, 2 H), 7.17-7.24 (3 H), 7.27-7.32 (m, 2 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 14.0 (q), 22.6 (t), 25.38 (t), 25.39 (t), 31.9 (t), 32.2 (t), 33.2 (t), 33.5 (t), 33.9 (t), 34.2 (t), 37.5 (t), 37.8 (t), 39.1 (t), 39.4 (t), 71.3 (d), 71.6 (d), 72.0 (d), 72.3 (d), 125.8 (d), 128.4 (d), 129.2 (d), 142.1 (s); exact mass *m*/*z* calcd for $C_{17}H_{28}NaO_2$ 287.1982, found 287.1985.

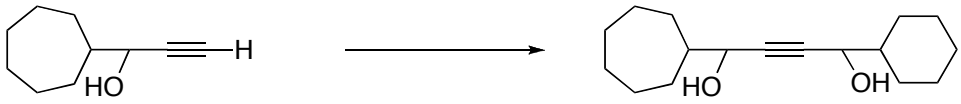
1-Phenylundecane-3,6-dione (43.3).



43.2a **43.3**

Jones reagent (7.0 M in acetone, 0.07 mL, 0.46 mmol) was added dropwise to a stirred and cooled (0 °C) solution of **43.2a** (0.0175 g, 0.0662 mmol) in acetone (5 mL). After 10 min, the orange mixture was quenched with MeOH (5 mL) and stirring was continued for 30 min, by which time the mixture had become dark green. The organic phase was diluted with EtOAc (20 mL) and washed with water and brine, dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (0.7 x 16 cm), using EtOAc-petroleum ether mixtures from 15% to 25% EtOAc, gave **43.3** (0.0162 g, 94%) as an oil: FTIR (CH_2Cl_2, cast microscope) 3028, 2956, 2931, 2872, 1712, 1604, 1454 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.90 (t, J = 7.0 Hz, 3 H), 1.23-1.37 (m, 4 H), 1.59 (quintet, J = 7.6 Hz, 2 H), 2.45 (t, J = 7.4 Hz, 2 H), 2.64-2.71 (m, 4 H), 2.80 (apparent t, J = 7.9 Hz, 2 H), 2.91 (t, J = 8.0 Hz, 2 H), 7.17-7.21 (m, 3 H), 7.26-7.30 (m, 2 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 13.9 (q), 22.4 (t), 23.5 (t), 23.5 (t), 29.7 (t), 31.4 (t), 36.0 (t), 36.2 (t), 42.8 (t), 44.3 (t), 126.1 (d), 128.3 (d), 128.5 (d), 141.0 (s), 208.5 (s), 209.7 (s); exact mass m/z calcd for $C_{17}H_{24}NaO_2$ 283.1669, found 283.1671.

1-Cycloheptyl-4-cyclohexylbut-2-yne-1,4-diol (43.6).

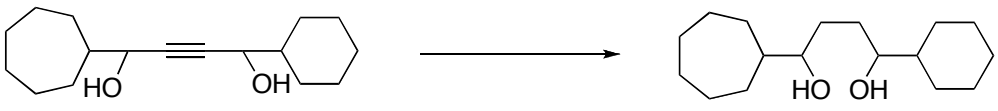


43.4 **43.6**

BuLi (2.5 M in hexane, 0.527 mL, 1.32 mmol) was added dropwise to a stirred and cooled (–78 °C) solution of **43.4** (0.0802 g, 0.527 mmol) in dry THF (10 mL). After 1 h, cyclohexanecarboxaldehyde (**43.5**) (0.096 mL, 0.79 mmol) in THF (2 mL plus 2 mL as a rinse) was added dropwise by cannula. Stirring was

continued for 45 min. The cold bath was left in place but not recharged and stirring was continued for 10.5 h. The mixture was cooled to 0 °C and quenched with hydrochloric acid (1.0 N, 10 mL). The organic solvents were evaporated, water (10 mL) was added, and the mixture was extracted with Et_2O. The combined organic extracts were dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (1.4 x 19 cm), using EtOAc-petroleum ether mixtures from 5% to 40% EtOAc, gave **43.6** (0.112 g, 80%) as an oil: FTIR (CH_2Cl_2, microscope) 3327, 2924, 2853, 2673, 1450 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.01-1.31 (m, 6 H), 1.31-1.64 (m, 8 H), 1.65-1.92 (m, 12 H), 4.20 (apparent t, J = 5.0 Hz, 1 H), 4.27 (apparent br s, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 25.8 (t), 25.9 (t), 26.4 (t), 26.70 (t), 26.74 (t), 28.0 (t), 28.1 (t), 28.28 (t), 28.33 (t), 28.34 (t), 29.5 (t), 29.97 (t), 30.00 (t), 67.2 (t), 67.5 (t), 85.29 (s), 85.31 (s), 85.91 (s), 85.94 (s); exact mass m/z calcd for $C_{17}H_{28}NaO_2$ 287.1982, found 287.1982.

1-Cycloheptyl-4-cyclohexylbutane-1,4-diol (43.6a).

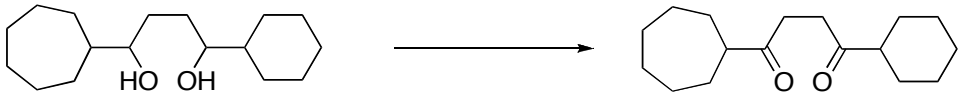


43.6 **43.6a**

Pt-C (10% w/w, *ca.* 0.020 g) was added to a solution of **43.6** (0.1015 g, 0.3839 mmol) in MeOH (6 mL) and the mixture was stirred under H_2 (thick-walled balloon) for 12 h. The mixture was filtered through Celite, using EtOAc as a rinse. Evaporation of the filtrate and flash chromatography of the residue over silica gel (1.4 x 20 cm), using EtOAc-petroleum ether mixtures from 5% to 40% EtOAc, gave **43.6a** (0.0761 g, 74%) as an oil which was a mixture of

diastereoisomers: FTIR (CH_2Cl_2, microscope) 3299, 2920, 2852, 2696, 1460, 1448 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.96-1.40 (m, 8 H), 1.40-1.63 (m, 10 H), 1.63-1.88 (m, 10 H), 2.35 (s, 2 H), 3.43-3.14 (m, 1 H), 3.45-3.58 (m, 1 H); ^{13}C NMR (acetone-d_6, 125 MHz) δ 26.97 (t), 26.99 (t), 27.1 (t), 27.3 (t), 27.67 (t), 27.69 (t), 27.97 (t), 28.00 (t), 28.70 (t), 28.72 (t), 29.1 (t), 29.3 (t), 29.4 (t), 29.6 (t), 29.7 (t), 29.8 (t), 29.9 (t), 30.0 (t), 30.2 (t), 31.15 (t), 31.20 (t), 31.9 (t), 32.0 (t), 44.7 (d), 44.9 (d), 46.2 (d), 46.3 (d), 76.0 (d), 76.1 (d), 76.7 (d), 76.8 (d); exact mass *m*/*z* calcd for $C_{17}H_{32}NaO_2$ 291.2295, found 291.2294.

1-Cycloheptyl-4-cyclohexylbutane-1,4-dione (43.8).

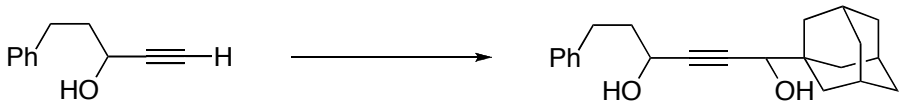


43.6a **43.8**

Jones reagent (7.0 M in acetone, 0.166 mL, 1.16 mmol) was added dropwise to a stirred and cooled (0 °C) solution of **43.6a** (0.0346 g, 0.129 mmol) in acetone (10 mL). After 1.5 h, an additional portion of Jones reagent (7.0 M in acetone, 0.100 mL, 0.700 mmol) was added and after a further 5 min the mixture was quenched with MeOH (15 mL). Stirring was continued for 30 min, by which time the mixture had become dark green. The organic phase was diluted with EtOAc (25 mL) and washed with water and brine, dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (0.7 x 16 cm), using EtOAc-petroleum ether mixtures from 5% to 15% EtOAc, gave **43.8** (0.0239 g, 70%) as an oil: FTIR (CH_2Cl_2, microscope) 2928, 2855, 2668, 1707, 1450 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.10-1.43 (m, 6 H), 1.43-1.65 (m, 6 H), 1.65-1.83 (m, 6 H), 1.83-1.94 (m, 4 H), 2.32-2.44 (m, 1 H), 2.52-2.62 (m, 1 H), 2.66-2.75 (m, 4 H);

^{13}C NMR ($CDCl_3$, 125 MHz) δ 25.7 (t), 25.9 (t), 26.7 (t), 28.3 (t), 28.5 (t), 30.0 (t), 34.1 (t), 34.2 (t), 50.8 (d), 52.4 (d), 212.8 (s), 213.1 (s); exact mass *m*/*z* calcd for $C_{17}H_{28}O_2$ 264.2089, found 264.2090.

1-(1-Adamantyl)-6-phenylhex-2-yne-1,4-diol (43.10).

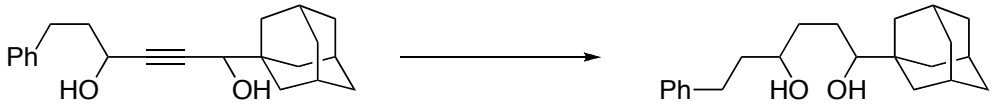


41.1 **43.10**

BuLi (2.5 M in hexane, 0.2592 mL, 0.6481 mmol) was added dropwise to a stirred and cooled (–78 °C) solution of **41.1** (0.0472 g, 0.295 mmol) in dry THF (10 mL). After 1.5 h, 1-adamantanecarboxaldehyde (0.0414 g, 0.252 mmol) in THF (2 mL plus 2 mL as a rinse) was added dropwise producing an orange solution. The cold bath was left in place but not recharged and stirring was continued for 18.5 h. The mixture was cooled to 0 °C and quenched with hydrochloric acid (1.0 N, 6 mL). The organic solvent was evaporated, water (10 mL) was added, and the mixture was extracted with Et_2O. The combined organic extracts were dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (1.4 x 15 cm), using EtOAc-petroleum ether mixtures from 20% to 40% EtOAc, gave **43.10** (0.0743 g, 91%) as a semi-solid mixture of diastereoisomers: FTIR (CH_2Cl_2, cast microscope) 3350, 3026, 2905, 2848, 1722, 1604, 1453 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.58-1.77 (m, 12 H), 1.99-2.11 (m, 5 H), 2.11-2.72 (br s, 2 H), 2.82 (t, *J* = 7.8 Hz, 2 H), 3.93 (dd, *J* = 5.9, 1.4 Hz, 1 H), 4.42-4.47 (m, 1 H), 7.19-7.25 (m, 3 H), 7.28-7.32 (m, 2 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 28.2 (d), 31.53 (s), 31.54 (s), 37.1 (t), 37.3 (t), 37.4 (t), 37.8 (t), 39.37 (t), 39.39 (t), 61.8 (d), 71.52 (d), 71.53 (d), 84.25 (s), 84.27 (s), 87.15

(s), 87.17 (s), 126.0 (d), 128.46 (d), 128.50 (d), 141.295 (s), 141.303 (s); exact mass *m*/*z* calcd for $C_{22}H_{28}NaO_2$ 347.1982, found 347.1981.

1-(1-Adamantyl)-6-phenylhexane-1,4-diol (43.10a).

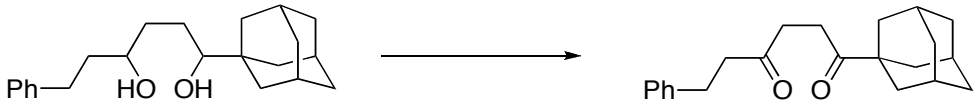


43.10 **43.10a**

Rh-Al_2O_3 (5% w/w, *ca.* 8 mg) was added to a solution of **43.10** (0.023 g, 0.071 mmol) in MeOH (3 mL) and the mixture was stirred under H_2 (thick-walled balloon) for 24 h. At this point there appeared to have been no reaction (TLC, ^{1}H NMR) and so the mixture was filtered through Celite, using EtOAc as a rinse. The solvent was evaporated and the residue was kept under oil pump vacuum. Pt-C (20% w/w, ca 6.5 mg) was added to a solution of recovered **43.10** in MeOH (3 mL) and the mixture was stirred under H_2 (balloon). After 30 min the mixture was filtered through Celite, using EtOAc as a rinse. Evaporation of the filtrate and flash chromatography of the residue over silica gel (1.4 x 15 cm), using EtOAc-petroleum ether mixtures from 20% to 40% EtOAc, gave **43.10a** (0.0184 g, 79%) as an oil: FTIR (CH_2Cl_2, cast) 3351, 3026, 2905, 2849, 2677, 1743, 1603, 1452 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.25-1.42 (m, 2 H), 1.48-1.83 (m, 16 H), 2.00 (broad s, 3 H), 2.00-2.42 (br s, 2 H), 2.64-2.74 (m, 1 H), 2.76-2.85 (m, 1 H), 3.04 (apparent d, *J* = 9 Hz, 1 H), 3.61-3.75 (m, 1 H), 7.16-7.23 (m, 3 H), 7.26-7.31 (m, 2 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 25.7 (t), 26.8 (t), 28.3 (d), 32.17 (s), 32.19 (s), 35.0 (t), 35.4 (t), 37.2 (t), 37.93 (t), 37.96 (t), 39.1 (t), 39.6 (t), 71.1 (d), 71.8 (d), 80.4 (d), 80.7 (d), 125.75 (d), 125.77 (d), 128.37 (d), 128.41

(d), 142.20 (s), 142.23 (s); exact mass *m*/*z* calcd for $C_{22}H_{32}NaO_2$ 351.2295, found 351.2297.

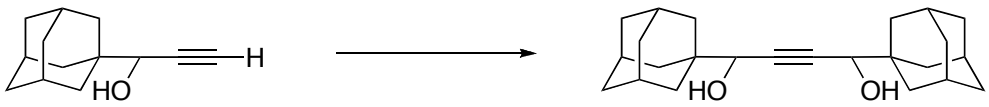
1-(1-Adamantyl)-6-phenylhexane-1,4-dione (43.11).



43.10a **43.11**

Jones reagent (7.0 M in acetone, 0.0518 mL, 0.362 mmol) was added dropwise to a stirred and cooled (0 °C) solution of **43.10a** (0.0170 g, 0.0518 mmol) in acetone (3 mL). After 20 min, the orange mixture was quenched with MeOH (3 mL) and stirring was continued for 30 min, by which time the mixture had become dark green. The organic phase was diluted with EtOAc (20 mL) and washed with water and brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (0.7 x 15 cm), using 10% EtOAc-petroleum ether, gave **43.11** (0.0161 g, 95%) as an oil: FTIR (CH_2Cl_2, cast) 3027, 2905, 2851, 1716, 1698, 1453 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.68-1.79 (m, 6 H), 1.85 (d, *J* = 2.7 Hz, 6 H), 2.05 (apparent s, 3 H), 2.64 (apparent t, *J* = 6.5 Hz, 2 H), 2.75 (apparent t, *J* = 6.1 Hz, 2 H), 2.82 (apparent t, *J* = 7.9 Hz, 2 H), 2.91 (apparent t, *J* = 7.1 Hz, 2 H), 7.17-7.21 (m, 3 H), 7.26-7.30 (m, 2 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 28.0 (d), 29.7 (t), 30.1 (t), 36.1 (t), 36.6 (t), 38.4 (s), 44.4 (t) 46.2 (t), 126.0 (d), 128.3 (d), 128.5 (d), 141.1 (s); exact mass *m*/*z* calcd for $C_{22}H_{28}NaO_2$ 347.1982, found 347.1988.

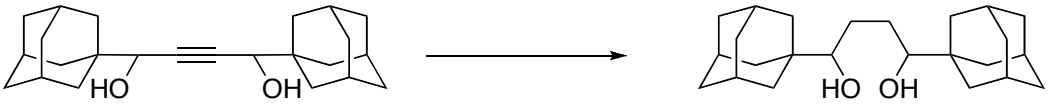
1,4-Bis-(1-adamantyl)but-2-yne-1,4-diol (43.13).



43.12 **43.13**

BuLi (2.5 M in hexane, 0.475 mL, 1.19 mmol) was added dropwise to a stirred and cooled (–78 °C) solution of **43.12** (0.1071 g, 0.5401 mmol) in dry THF (10 mL). After 1 h, aldehyde **43.9** (0.0895 g, 0.545 mmol) in THF (2 mL plus 2 mL as a rinse) was added dropwise. The cold bath was removed and stirring was continued for 18 h. The mixture was cooled to 0 °C, quenched with dilute hydrochloric acid (1.0 N, 10 mL), and the organic solvent was evaporated. The resulting aqueous mixture was extracted with Et_2O and the combined organic extracts were dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (4 x 25 cm), using EtOAc-petroleum ether mixtures from 5% to 40% EtOAc, gave **43.13** (0.1258 g, 65%) as an oil: FTIR (CH_2Cl_2, cast microscope) 3285, 2899, 2846, 2679, 2657, 1742, 1451 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.60-1.68 (m, 14 H), 1.68-1.77 (m, 12 H), 2.05 (s, 6 H), 3.93 (s, 1 H), 3.94 (s, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 28.2 (d), 37.1 (t), 37.4 (s), 37.5 (s), 37.81 (t), 37.83 (t), 71.6 (d), 71.7 (d), 85.2 (s), 85.3 (s); exact mass *m*/*z* calcd for $C_{24}H_{34}NaO_2$ 377.2451, found 377.2454.

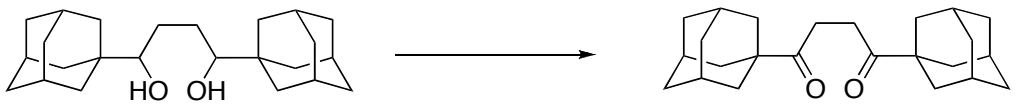
1,4-Bis-(1-adamantyl)butane-1,4-diol (43.13a).



43.13 **43.13a**

Rh-Al_2O_3 (5% w/w, 0.0100 mg) was added to a solution of **43.13** (0.0571 g, 0.161 mmol) in MeOH (5 mL) and the mixture was stirred under H_2 (doubled balloon) for 19 h. The mixture was filtered through Celite, using EtOAc as a rinse. Evaporation of the filtrate and flash chromatography of the residue over silica gel (1.4 x 15 cm), using EtOAc-petroleum ether mixtures from 5% to 20% EtOAc, gave **43.13a** (0.0106 g, 18%) and recovered starting material **43.13** (18.4 mg, 0.0519 mmol). Rh-Al_2O_3 (5% w/w, 0.0050 mg) was added to a solution of the recovered starting material in MeOH (3 mL) and the mixture was stirred under H_2 (balloon). After 14 h, more Rh-Al_2O_3 (5% w/w, *ca.* 5 mg) was added and stirring under H_2 (doubled balloon) was continued for 7 h. The mixture was filtered through Celite using EtOAc as a rinse. Evaporation of the filtrate and flash chromatography of the residue over silica gel (1.4 x 16 cm), using EtOAc-petroleum ether mixtures from 5% to 20% EtOAc, gave **43.13a** (0.0120 g, 21%), providing a combined yield of 39%: FTIR (CH_2Cl_2, microscope) 3376, 2901, 2848, 2657, 1638, 1449 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.36-1.48 (m, 2 H), 1.48-1.86 (m, 28 H), 2.00 (broad s, 6 H), 3.03 (d, J = 10.1 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 27.5 (t), 27.6 (t), 28.3 (d), 36.7 (s), 36.8 (s), 37.3 (t), 37.99 (t), 38.03 (t), 80.4 (d), 80.6 (d); exact mass m/z calcd for $C_{24}H_{38}NaO_2$ 381.2764, found 381.2758.

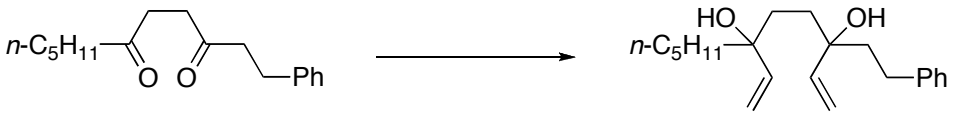
1,4-Bis-(1-adamantyl)butane-1,4-dione (43.14).[54]



43.13a **43.14**

Jones reagent (7.0 M in acetone, 0.0239 mL, 0.167 mmol) was added dropwise to a stirred and cooled (0 °C) solution of **43.13a** (0.0200 g, 0.0558 mmol) in acetone (4 mL). After 45 min, the orange mixture was quenched with MeOH (1 mL) and stirring was continued for 30 min, by which time the mixture had become dark green. The organic phase was diluted with EtOAc (20 mL) and washed with water and brine, dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (1.4 x 16 cm), using EtOAc-petroleum ether mixtures from 2% to 10% EtOAc, gave **43.14** (0.0142 g, 71%) as an oil: FTIR (CH_2Cl_2, cast microscope) 2905, 2850, 2678, 2658, 1699, 1452 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.66-1.78 (m, 12 H), 1.85 (apparent d, J = 2.8 Hz, 12 H), 2.02-2.08 (m, 6 H), 2.71 (s, 4 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 28.0 (d), 29.9 (t), 36.6 (t), 38.4 (t), 46.2 (s), 214.5 (s); exact mass m/z calcd for $C_{24}H_{34}NaO_2$ 377.2451, found 377.2452.

3-Pentyl-6-(2-phenylethyl)octa-1,7-diene-3,6-diol (44.1).

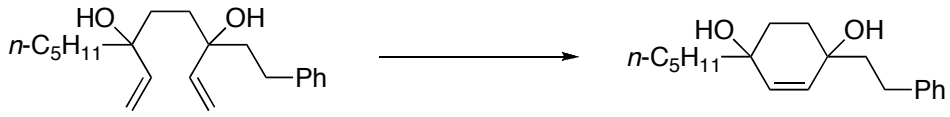


43.3 **44.1**

MeLi (1.6 M in Et_2O, 1.809 mL, 2.894 mmol) was added dropwise to a stirred and cooled (0 °C) solution of tetravinyltin (0.13 mL, 0.72 mmol) in dry Et_2O (10 mL). After 45 min, the mixture was cooled to –78 °C and **43.3** (0.0471 g, 0.181 mmol) in Et_2O (2 mL plus 2 mL as a rinse) was added by cannula. The cooling bath was left in place but not recharged and stirring was continued for 12 h. The mixture was quenched with a solution of water (25 mL) and saturated aqueous NH_4Cl (25 mL). 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 (1.4 x 16 cm), using EtOAc-hexanes mixtures from 15% to 30% EtOAc, gave **44.1** (0.0533 g, 93%) as an oil which was a mixture of diastereoisomers: FTIR (CH_2Cl_2, cast microscope) 3419, 3086, 3063, 3026, 3006, 2953, 2933, 2861, 1942, 1844, 1734, 1642, 1604, 1497, 1455 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.88 (t, J = 6.7 Hz, 3 H), 1.20-1.38 (m, 6 H), 1.44-1.72 (m, 6 H), 1.72-1.98 (m, 4 H), 2.56-2.73 (m, 2 H), 5.09-5.33 (m, 4 H), 5.72-5.90 (m, 2 H), 7.15-7.20 (m, 3 H), 7.24-7.30 (2 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.0 (q), 22.6 (t), 23.1 (t), 30.0 (t), 32.2 (t), 34.0 (t), 34.4 (t), 34.5 (t), 41.0 (t), 41.6 (t), 42.7 (t), 43.3 (t), 75.1 (s), 75.2 (s), 112.6 (t), 112.9 (t), 113.1 (t), 113.4 (t), 125.70 (d), 125.73 (d), 128.35 (d), 128.37 (d), 142.5 (s), 143.4 (d), 143.5 (d), 143.6 (d), 143.9 (d); exact mass *m*/*z* calcd for $C_{21}H_{32}NaO_2$ 339.2295, found 339.2288.

1-Pentyl-4-(2-phenylethyl)cyclohex-2-ene-1,4-diol (44.1a).



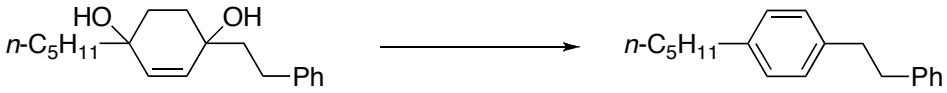
44.1 **44.1a**

Grubbs catalyst (1st generation, 0.0027 g, 0.0033 mmol) was added to a stirred solution of **44.1** (0.0523 g, 0.165 mmol) in dry CH_2Cl_2 (7 mL) (N_2 atmosphere). After 12 h, the reaction mixture was evaporated and flash chromatography of the residue over silica gel (1.4 x 14 cm), using EtOAc-petroleum ether mixtures from 10% to 40% EtOAc, gave **44.1a** [0.0306 g, 64% less polar diastereoisomer; 0.0171 g, 35% more polar diastereoisomer (99% overall)] as an oil. The more polar diastereoisomer had: FTIR (CH_2Cl_2, neat film

microscope) 3309, 3061, 3026, 2954, 2929, 2861, 1940, 1864, 1740, 1603 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.90 (t, *J* = 6.8 Hz, 3 H), 1.20-1.46 (m, 6 H), 1.47-1.65 (m, 4 H), 1.63-1.85 (m, 2 H), 1.81-2.17 (m, 4 H), 2.67-2.81 (m, 2 H), 5.70-5.74 (m, 2 H), 7.16-7.23 (m, 3 H), 7.28-7.32 (m, 2 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 14.1 (q), 22.6 (t), 23.2 (t), 29.9 (t), 32.3 (t), 32.7 (t), 32.9 (t), 41.1 (t), 42.8 (t), 70.3 (s), 70.4 (s), 125.8 (d), 128.3 (d), 128.4 (d), 134.0 (d), 134.7 (d), 142.3 (s); exact mass *m*/*z* calcd for $C_{19}H_{28}NaO_2$ 311.1982, found 311.1982.

The less polar diastereoisomer had: FTIR (CH_2Cl_2, neat film microscope) 3538, 3389, 3063, 3027, 2930, 2860, 1946, 1870, 1741, 1603, 1497, 1454 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.91 (t, *J* = 6.9 Hz, 3 H), 1.25-1.46 (m, 6 H), 1.46-1.64 (m, 4 H), 1.66-1.81 (m, 2 H), 1.83-2.20 (m, 4 H), 2.67-2.81 (m, 2 H), 5.69-5.76 (m, 2 H), 7.17-7.23 (m, 3 H), 7.26-7.32 (m, 2 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 14.1 (q), 22.6 (t), 23.2 (t), 30.0 (t), 31.7 (t), 31.9 (t), 32.3 (t), 42.2 (t), 44.0 (t), 69.5 (s), 69.6 (s), 125.8 (d), 128.3 (d), 128.4 (d), 133.8 (d), 134.7 (d), 142.2 (s); exact mass *m*/*z* calcd for $C_{19}H_{28}NaO_2$ 311.1982, found 311.1977.

1-Pentyl-4-(2-phenylethyl)benzene (44.2).[55]

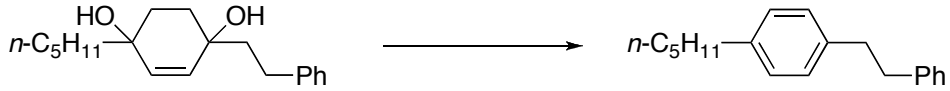


44.1a **44.2**

$TsOH.H_2O$ (0.0113 g, 0.0593 mmol) was added to a solution of the previously separated more polar diastereoisomer of **44.1a** (0.0171 g, 0.0593 mmol) in dry PhH (4 mL). The mixture was refluxed for 1 h, cooled to room temperature and partitioned between water and CH_2Cl_2. The aqueous phase was then extracted with hexane, and the combined organic extracts were dried

(Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (0.7 x 15 cm), using EtOAc-petroleum ether mixtures from 0% to 2% EtOAc, gave **44.2** (0.0150 g, 100%) as a solid: FTIR (CH_2Cl_2, neat film microscope) 3026, 2955, 2928, 2857, 1604, 1514, 1496 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.91 (t, *J* = 7.0 Hz, 3 H), 1.27-1.42 (m, 4 H), 1.63 (apparent quintet, *J* = 7.6 Hz, 2 H), 2.58 (dd, *J* = 7.7, 7.7 Hz, 2 H), 2.87-2.96 (m, 4 H), 7.14 (s, 4 H), 7.18-7.24 (m, 3 H), 7.27-7.33 (2 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.0 (q), 22.6 (t), 31.2 (t), 31.5 (t), 35.5 (t), 37.5 (t), 38.0 (t), 125.8 (d), 128.2 (d), 128.30 (d), 128.34 (d), 128.4 (d), 138.9 (s), 140.5 (s), 142.0 (s); exact mass *m*/*z* calcd for $C_{19}H_{24}$ 252.1878, found 252.1877.

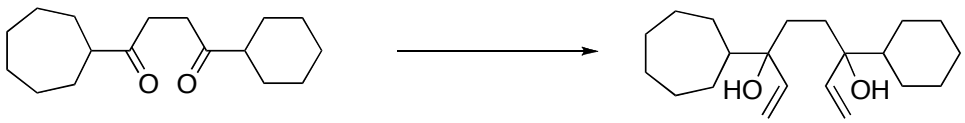
1-Pentyl-4-(2-phenylethyl)benzene (44.2).[55]



44.1a **44.2**

$TsOH.H_2O$ (0.0202 g, 0.106 mmol) was added to a solution of the previously separated less polar diastereoisomer of **44.1a** (0.0306 g, 0.106 mmol) in dry PhH (4 mL). The mixture was refluxed for 1 h, cooled to room temperature and partitioned between water and CH_2Cl_2. The aqueous phase was then extracted with hexane, and the combined organic extracts were dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (0.7 x 16 cm), using EtOAc-petroleum ether mixtures from 0% to 2% EtOAc, gave **44.2** (0.027 g, 100%) as a solid.

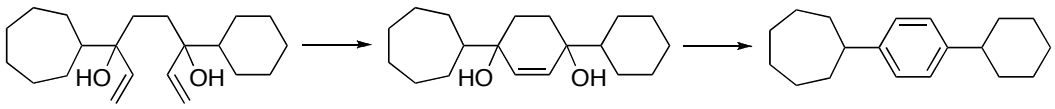
3-Cycloheptyl-6-cyclohexylocta-1,7-diene-3,6-diol (44.3).



43.8 **44.3**

MeLi (1.6 M in Et_2O, 1.160 mL, 1.856 mmol) was added dropwise to a stirred and cooled (0 °C) solution of tetravinyltin (0.0851 mL, 0.467 mmol) in dry Et_2O (8 mL). After 45 min, the mixture was cooled to –78 °C and **43.8** (0.0150 g, 0.0567 mmol) in Et_2O (2 mL plus 2 mL as a rinse) was added by cannula. The cold bath was left in place but not recharged and stirring was continued for 11.5 h. The reaction was quenched with saturated aqueous NH_4Cl (12 mL). The aqueous phase was extracted with Et_2O and the combined organic extracts were washed with brine, dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (0.7 x 17 cm), using EtOAc-hexanes mixtures from 5% to 10% EtOAc, gave **44.3** (0.0148 g, 81%) as a semi-solid, which was a mixture of diastereoisomers: FTIR ($CHCl_3$, cast microscope) 3450, 3010, 2926, 2853, 1841, 1640, 1451 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.84-1.10 (m, 2 H), 1.10-1.32 (m, 6 H), 1.32-1.62 (m, 10 H), 1.62-1.87 (m, 10 H), 1.87-2.12 (br s, 2 H), 5.10-5.24 (m, 4 H), 5.70-5.87 (m, 2 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 25.50 (t), 26.53 (t), 26.6 (t), 26.7 (t), 27.56 (t), 27.62 (t), 27.64 (t), 27.7 (t), 27.8 (t), 27.9 (t), 28.0 (t), 28.1 (t), 28.17 (t), 28.24 (t), 28.3 (t), 29.00 (t), 29.02 (t), 30.9 (t), 31.1 (t), 31.3 (t), 31.4 (t), 46.9 (d), 47.3 (d), 48.1 (d), 48.6 (d), 77.2 (s), 77.3 (s), 78.1 (s), 78.2 (s), 112.9 (t), 113.06 (t), 113.11 (t), 113.3 (t), 142.57 (d), 142.62 (d), 142.7 (d); exact mass *m*/*z* calcd for $C_{21}H_{36}NaO_2$ 343.2608, found 343.2609.

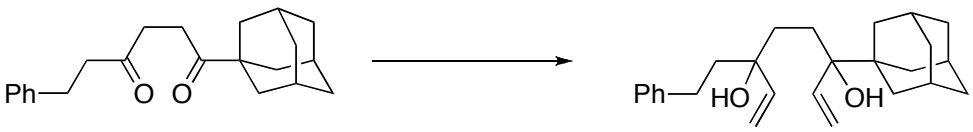
4-Cycloheptyl-1-cyclohexylbenzene (44.4).



44.3 **44.3a** **44.4**

Grubbs catalyst (1st generation, 0.0035 g, 0.0043 mmol) was added to a stirred solution of **44.3** (0.0138 g, 0.0431 mmol) in dry CH_2Cl_2 (5 mL) (N_2 atmosphere). After 18 h, the mixture was evaporated to afford a mixture of diol and aromatized product. The crude material was dissolved in PhH (4 mL) and $TsOH \cdot H_2O$ (0.0112 g, 0.05892 mmol) was added. The solution was refluxed for 1 h, cooled to room temperature and partitioned between water and CH_2Cl_2. The aqueous phase was extracted with hexane and the combined organic extracts were dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (0.7 x 16 cm), using EtOAc-petroleum ether mixtures from 0% to 2% EtOAc, gave **44.4** (0.0105 g, 95%) as a solid: FTIR (CH_2Cl_2, microscope) 3050, 3010, 2923, 2850, 2668, 1899, 1785, 1647, 1515, 1447 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.20-1.34 (m, 1 H), 1.34-1.50 (m, 4 H), 1.50-1.75 (m, 8 H), 1.75-1.97 (m, 9 H), 2.44-2.51 (m, 1 H), 2.61-2.68 (m, 1 H), 7.12 (apparent s, 4 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 26.2 (t), 27.0 (t), 27.2 (t), 28.0 (t), 34.5 (t), 36.8 (t), 44.1 (d), 46.6 (d), 126.5 (d), 126.6 (d), 145.1 (s), 147.3 (s); exact mass *m*/*z* calcd for $C_{19}H_{28}$ 256.2191, found 256.2184.

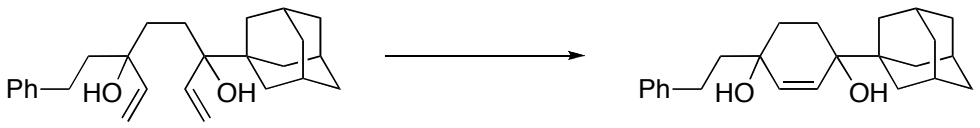
3-(1-Adamantyl)-6-(2-phenylethyl)octa-1,7-diene-3,6-diol (44.5).



43.11 **44.5**

MeLi (1.6 M in Et_2O, 0.413 mL, 0.661 mmol) was added dropwise to a stirred and cooled (0 °C) solution of tetravinyltin (0.0301 mL, 0.1652 mmol) in dry Et_2O (3 mL). After 45 min, the mixture was cooled to –78 °C and **43.11** (0.0134 g, 0.0413 mmol) in Et_2O (1 mL plus 1 mL as a rinse) was added by cannula. The cold bath was left in place but not recharged and stirring was continued for 5 h. The mixture was cooled to 0 °C and quenched with a mixture of water (50 mL) and saturated aqueous NH_4Cl (25 mL). 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 (0.7 x 15 cm), using 15% EtOAc-hexanes, gave **44.5** (0.0146 g, 93%) as a semi-solid mixture of diastereomers: FTIR (CH_2Cl_2, cast) 3433, 3085, 3025, 2905, 2849, 2679, 1742, 1667, 1497 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.44-1.53 (m, 3 H), 1.57-1.72 (m, 13 H), 1.72-1.90 (m, 3 H), 1.99 (br s, 3 H), 1.99-2.56 (br s, 1 H), 2.56-2.72 (m, 2 H), 5.12-5.32 (m, 4 H), 5.75-5.92 (m, 2 H), 7.14-7.20 (m, 3 H), 7.24-7.30 (m, 2 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 25.69 (t), 25.76 (t), 28.6 (d), 30.0 (t), 34.2 (t), 34.5 (t), 36.4 (t), 37.1 (t), 39.3 (t), 42.6 (t), 43.7 (t), 75.3 (s), 75.4 (s), 79.1 (s), 79.2 (s), 112.9 (t), 113.3 (t), 113.8 (t), 114.0 (t), 125.65 (d), 125.72 (d), 128.34 (d), 128.35 (d), 128.37 (d), 140.5 (d), 140.6 (d), 142.5 (s), 142.6 (s), 143.7 (d), 143.8 (d); exact mass *m*/*z* calcd for $C_{26}H_{36}NaO_2$ 403.2608, found 403.2608.

1-(Adamantyl)-4-(2-phenylethyl)cyclohex-2-ene-1,4-diol (44.5a).



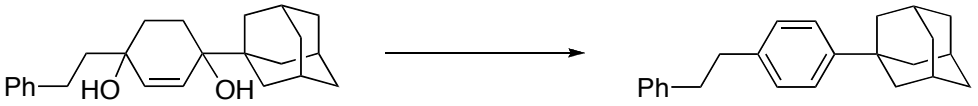
44.5 **44.5a**

Grubbs catalyst (1st generation, 0.0020 g, 0.0024 mmol) was added to a stirred solution of **44.5** (0.0146 g, 0.0384 mmol) in dry CH_2Cl_2 (2.5 mL) (N_2 atmosphere). After 3 h, the mixture was evaporated and flash chromatography of the residue over silica gel (0.7 x 16 cm), using EtOAc-petroleum ether mixtures from 10% to 100% EtOAc, gave **44.5a** [0.0091 g, 67% less polar diastereoisomer; 0.0046 g, 33% more polar diastereoisomer (100% overall)] as solids. The less polar diastereoisomer had: FTIR (CH_2Cl_2, cast) 3352, 3085, 3025, 2984, 2928, 2901, 2847, 2675, 1742, 1603, 1451 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.20-1.45 (br m, 2 H), 1.54-1.82 (m, 15 H), 1.82-2.00 (m, 3 H), 2.04 (apparent s, 3 H), 2.68-2.82 (m, 2 H), 5.83 (dd, *J* = 10.1, 1.7 Hz, 1 H), 5.95 (dd, *J* = 10.3, 1.8 Hz, 1 H), 7.16-7.23 (m, 3 H), 7.26-7.31 (m, 2 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 25.3 (t), 28.5 (d), 29.9 (t), 31.1 (t), 35.8 (t), 36.4 (s), 37.1 (t), 38.4 (t), 44.3 (t), 72.7 (s), 125.8 (d), 128.32 (d), 128.37 (d), 128.39 (d), 131.3 (d), 134.9 (d), 142.3 (s); exact mass *m*/*z* calcd for $C_{24}H_{32}NaO_2$ 375.22945. The molecular ion could not be detected as the compound readily aromatized under all conditions tried.

The more polar diastereoisomer had: FTIR (CH_2Cl_2, cast) 3397, 3085, 3062, 3026, 2904, 2849, 2677, 1742, 1603, 1452 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.42-1.60 (br m, 2 H), 1.60-1.80 (m, 15 H), 1.80-1.98 (m, 3 H), 2.02 (apparent s, 3 H), 2.68-2.84 (m, 2 H), 5.81 (dd, *J* = 10.4, 1.5 Hz, 1 H), 5.85 (dd, *J* = 10.3, 1.8 Hz, 1 H), 7.16-7.23 (m, 3 H), 7.26-7.32 (m, 2 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 27.7 (t), 28.4 (d), 29.9 (t), 33.1 (t), 35.7 (s), 35.8 (t), 37.1 (t), 41.1 (t),

71.2 (s), 72.9 (s), 125.8 (d), 128.3 (d), 128.4 (d), 128.9 (d), 137.4 (d), 142.5 (s); exact mass *m*/*z* calcd for $C_{24}H_{32}NaO_2$ 375.2295, found 375.2295.

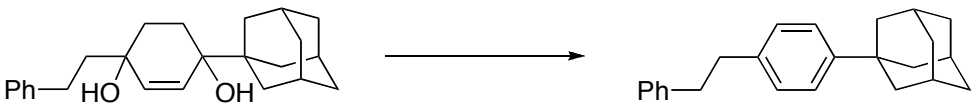
1-[4-(2-Phenylethyl)phenyl]adamantane (44.6).



44.5a **44.6**

$TsOH \cdot H_2O$ (0.0012 g, 0.0064 mmol) was added to a solution of the previously separated less polar diastereoisomer of **44.5a** (0.0075 g, 0.021 mmol) in dry PhH (4 mL). The mixture was refluxed for 2 h, cooled to room temperature and partitioned between water and CH_2Cl_2. The aqueous phase was extracted with hexane, and the combined organic extracts were dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (0.7 x 15 cm), using EtOAc-petroleum ether mixtures from 0% to 2% EtOAc, gave **44.6** (0.0064 g, 95%) as a solid: FTIR (CH_2Cl_2, cast) 3060, 3025, 2903, 2848, 2657, 1603, 1515, 1496, 1452 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.75-1.83 (m, 6 H), 1.93 (d, *J* = 2.7 Hz, 6 H), 2.10 (apparent s, 3 H), 2.87-2.96 (m, 4 H), 7.18 (apparent d, *J* = 8.4 Hz, 2 H), 7.20-7.24 (m, 3 H), 7.28-7.32 (m, 2 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 29.0 (d), 35.9 (s), 36.8 (t), 37.5 (t), 37.9 (t), 43.3 (t), 124.8 (d), 125.9 (d), 128.1 (d), 128.3 (d), 128.4 (d), 138.9 (s), 142.1 (s), 149.0 (s); exact mass *m*/*z* calcd for $C_{24}H_{28}$ 316.2191, found 316.2192.

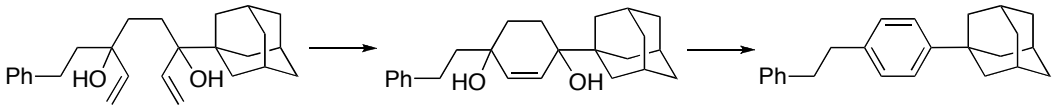
1-[4-(2-Phenylethyl)phenyl]adamantane (44.6).



44.5a **44.6**

$TsOH \cdot H_2O$ (0.0007 g, 0.004 mmol) was added to a solution of the more polar diastereoisomer of **44.5a** (0.0043 g, 0.012 mmol) in dry PhH (3 mL). The mixture was refluxed for 2 h, cooled to room temperature and partitioned between water and CH_2Cl_2. The aqueous phase was then extracted with hexane, and the combined organic extracts were dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (0.7 x 15 cm), using EtOAc-petroleum ether mixtures from 0% to 2% EtOAc, gave **44.6** (0.0035 g, 91%) as a solid.

1-[4-(2-Phenylethyl)phenyl]adamantane (44.6).

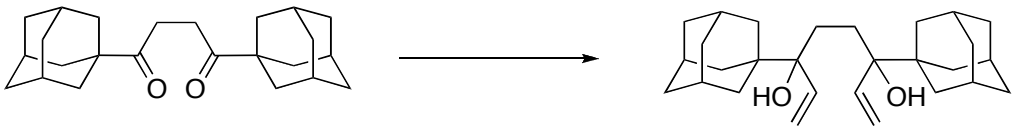


44.5 **44.5a** **44.6**

Grubbs catalyst (1st generation, 0.0041 g, 0.0049 mmol) was added to a stirred solution of **44.5** (0.0188 g, 0.0494 mmol) in dry CH_2Cl_2 (5 mL) (N_2 atmosphere). After 3 h, the mixture was evaporated, and the residue was stored for a few minutes under oil pump vacuum, and then dissolved in PhH (5 mL). $TsOH \cdot H_2O$ (0.0028 g, 0.0148 mmol) was added to the solution of crude **44.5a**. The mixture was refluxed for 30 min, cooled to room temperature and stirred for

an additional 36 h. The mixture was partitioned between water and CH_2Cl_2. The aqueous phase was extracted with hexane, and the combined organic extracts were dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (0.7 x 15 cm), using EtOAc-petroleum ether mixtures from 0% to 2% EtOAc, gave **44.6** (0.0149 g, 95%) as a solid.

3,6-Bis-(1-adamantyl)octa-1,7-diene-3,6-diol (44.7).



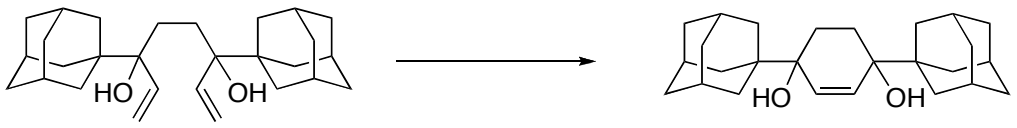
43.14 **44.7**

MeLi (1.6 M in Et_2O, 0.502 mL, 0.803 mmol) was added dropwise to a stirred and cooled (0 °C) solution of tetravinyltin (0.0366 mL, 0.2008 mmol) in dry Et_2O (5 mL). After 1 h, the mixture was cooled to –78 °C and **43.14** (0.0089 g, 0.025 mmol) in Et_2O (1 mL plus 1 mL as a rinse) was added by cannula. After 1.75 h the cold mixture was quenched with saturated aqueous NH_4Cl (6 mL) and the aqueous phase was extracted with Et_2O. The combined organic extracts were washed with brine, dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (0.7 x 12 cm), using EtOAc-hexanes mixtures from 2% to 10% EtOAc, gave **44.7** as a mixture of diastereoisomers [6.6 mg, 64% less polar diastereoisomer; 0.0023 g, 22% more polar diastereoisomer (86% overall)]: The less polar diastereoisomer had: FTIR (CH_2Cl_2, microscope) 3614, 3085, 2932, 2904, 2871, 2851, 2680, 2658, 2639, 1838, 1730, 1640, 1450, 1408 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.20-1.36 (m, 4 H), 1.36-1.50 (m, 4 H), 1.51-1.72 (m, 22 H), 1.97 (s, 6 H), 5.14 (dd, J = 17.4, 1.7 Hz, 2 H), 5.21 (dd, J = 11.0, 1.7 Hz, 2

H), 5.83 (dd, J = 17.3, 11.0 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 25.9 (t), 28.6 (d), 36.4 (t), 37.1 (t), 39.4 (s), 79.4 (s), 113.5 (t), 141.0 (d); exact mass m/z calcd for $C_{28}H_{42}NaO_2$ 433.3077, found 433.3076.

The more polar diastereoisomer had: FTIR (CH_2Cl_2, cast microscope) 3476, 2905, 2849, 1718, 1451 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.18-1.36 (m, 8 H), 1.54-1.74 (m, 22 H), 1.97 (apparent s, 6 H), 5.18 (dd, J = 17.2, 1.8 Hz, 2 H), 5.21 (dd, J = 11.0, 1.8 Hz, 2 H), 5.78 (dd, J = 17.2, 11.0 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 25.2 (t), 28.7 (d), 36.4 (t), 37.2 (t), 39.4 (s), 79.2 (s), 113.8 (t), 141.1 (d); exact mass m/z calcd for $C_{28}H_{42}NaO_2$ 433.3077, found 433.3079.

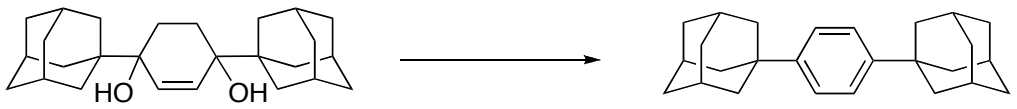
1,4-Bis-(1-adamantyl)cyclohex-2-ene-1,4-diol (44.7a).



44.7 **44.7a**

Grubbs catalyst (1st generation, 0.0033 g, 0.0039 mmol) was added to a stirred solution of **44.7** (0.0080 g, 0.019 mmol) in dry CH_2Cl_2 (1 mL) (N_2 atmosphere). After 24 h, the reaction mixture was evaporated and flash chromatography of the residue over silica gel (0.7 x 18 cm), using EtOAc-petroleum ether mixtures from 2% to 10% EtOAc, gave **44.7a** as a mixture of two impure diastereomers (ca 5.6 mg). We were unable to obtain satisfactory NMR data: exact mass m/z calcd for $C_{26}H_{38}NaO_2$ 405.27640, found 405.27677.

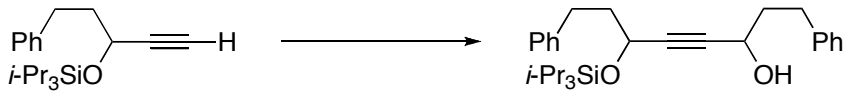
1-[4-(1-Adamantyl)phenyl]adamantane (44.8).[56]



44.7a **44.8**

$TsOH \cdot H_2O$ (0.0025 g, 0.013 mmol) was added to a solution of the above sample of **44.7a** (0.0050 g, 0.013 mmol) in dry PhH (2 mL). The mixture was refluxed for 4.5 h, cooled to room temperature and partitioned between water and CH_2Cl_2. The aqueous phase was extracted with hexane and the combined organic extracts were dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel [0.5 x 6 cm (Pasteur pipette)], using EtOAc-petroleum ether mixtures from 0% to 2% EtOAc, gave **44.8** (0.0043 g, 95%) as a solid: FTIR (CH_2Cl_2, microscope) 3085, 3047, 3027, 2907, 2849, 2657, 1507 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.72-1.82 (m, 12 H), 1.93 (d, J = 2.3 Hz, 12 H), 2.09 (apparent s, 6 H), 7.31 (s, 4 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 29.0 (d), 35.8 (s), 36.9 (t), 43.2 (t), 124.5 (d), 148.4 (s); exact mass m/z calcd for $C_{26}H_{34}$ 346.2661, found 346.2665.

6-[[Tris(1-methylethyl)silyl]oxy]-1,8-diphenyloct-4-yn-3-ol (45.1).

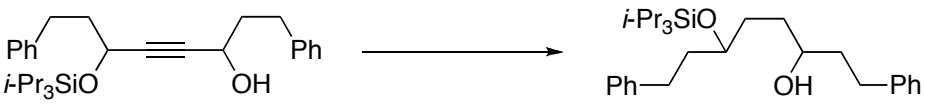


39.4 **45.1**

BuLi (2.5 M in hexane, 1.67 mL, 4.17 mmol) was added dropwise over 3 min to a stirred and cooled (–78 °C) solution of **39.4** (1.0153 g, 3.207 mmol) in

dry THF (50 mL). After 35 min, freshly distilled hydrocinnamaldehyde (0.676 mL, 5.13 mmol) was added dropwise over 3 min. The cold bath was left in place but not recharged and stirring was continued for 7.5 h. The mixture was cooled to 0 °C and quenched with hydrochloric acid (1.0 N, 50 mL). The organic solvent was evaporated and the resulting aqueous phase was extracted with Et_2O. The combined organic extracts were dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (4 x 22 cm), using EtOAc-petroleum ether mixtures from 10% to 50% EtOAc, gave **45.1** (1.4457 g, 100%) as an oil which was a mixture of diastereoisomers: FTIR (CH_2Cl_2, cast film) 3361, 3063, 3027, 2944, 2866, 1604, 1496, 1455 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.07-1.19 (m, 21 H), 1.64-1.72 (br s, 1 H), 1.98-2.11 (m, 4 H), 2.78-2.89 (m, 4 H), 4.42 (t, *J* = 6.3 Hz, 1 H), 4.58 (td, *J* = 5.8, 1.6 Hz, 1 H), 7.18-7.24 (m, 6 H), 7.28-7.33 (m, 4 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 12.3 (d), 18.1 (q), 31.27 (t), 31.29 (t), 31.39 (t), 31.41 (t), 39.18 (t), 39.23 (t), 40.46 (t), 40.49 (t), 61.9 (d), 62.5 (d), 85.06 (s), 85.08 (s), 86.86 (s), 86.88 (s), 125.8 (d), 126.0 (d), 128.4 (d), 128.45 (d), 128.47 (d), 128.48 (d), 141.3 (s), 141.8 (s); exact mass *m*/*z* calcd for $C_{29}H_{42}NaO_2Si$ 473.2846, found 473.2846.

6-[[Tris(1-methylethyl)silyl]oxy]-1,8-diphenyloctan-3-ol (45.2).

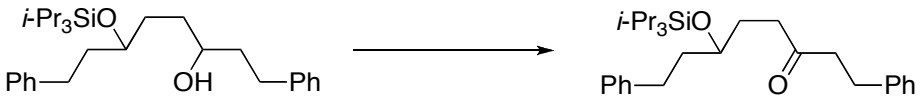


45.1 **45.2**

Pd-C (5% w/w, ca 20 mg) was added to a solution of **45.1** (0.1035 g, 0.2296 mmol) in EtOAc (4 mL) and the mixture was stirred under H_2 (thick-walled balloon) for 14 h. The mixture was filtered through Celite, using EtOAc

as a rinse. Evaporation of the solvent and flash chromatography of the residue over silica gel (1.4 x 17 cm), using EtOAc-petroleum ether mixtures from 5% to 20% EtOAc, gave **45.2** (0.0704 g, 67%) as an oil which was a mixture of diastereoisomers: FTIR (CH_2Cl_2, neat film microscope) 3370, 3086, 3063, 3027, 2943, 2891, 2866, 1941, 1869, 1801, 1604, 1496 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.06-1.08 (m, 21 H), 1.47-1.98 (m, 8 H), 2.21-2.50 (br s, 1 H), 2.55-2.73 (m, 3 H), 2.77-2.84 (m, 1 H), 3.57-3.67 (m, 1 H), 3.90-3.97 (m, 1 H), 7.16-7.23 (m, 6 H), 7.26-7.31 (m, 4 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 12.6 (d), 12.7 (d), 18.18 (q), 18.19 (q), 18.22 (q), 31.45 (t), 31.50 (t), 31.9 (t), 32.1 (t), 32.3 (t), 32.5 (t), 32.6 (t), 37.8 (t), 38.2 (t), 39.1 (t), 39.2 (t), 71.37 (d), 71.42 (d), 71.8 (d), 71.9 (d), 125.72 (d), 125.73 (d), 125.76 (d), 125.80 (d), 128.29 (d), 128.30 (d), 128.36 (d), 128.40 (d), 128.5 (d), 142.1 (s), 142.26 (s), 142.29 (s), 142.4 (s); exact mass *m*/*z* calcd for $C_{29}H_{46}NaO_2Si$ 477.3159, found 477.3161.

6-[[Tris(1-methylethyl)silyl]oxy]-1,8-diphenyloctan-3-one (45.3).

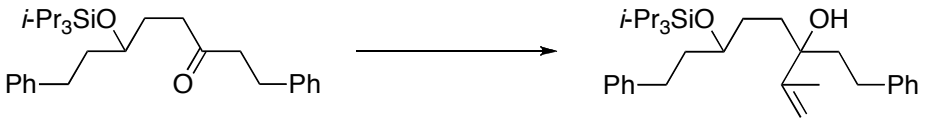


45.2 **45.3**

Jones reagent (7.0 M in acetone, 0.042 mL, 0.12 mmol) was added dropwise to a stirred and cooled (0 °C) solution of **45.2** (0.0532 g, 0.117 mmol) in acetone (4 mL). After 10 min, the orange mixture was quenched with MeOH (5 mL) and stirring was continued for 30 min, by which time the mixture had become dark green. The organic phase was diluted with EtOAc (15 mL) and washed with water and brine, dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (1.4 x 17 cm), using EtOAc-

petroleum ether mixtures from 2% to 10% EtOAc, gave **45.3** (0.0516 g, 97%) as an oil: FTIR (CH_2Cl_2, neat film microscope) 3086, 3063, 3027, 2943, 2892, 2866, 1942, 1869, 1800, 1717, 1604, 1497 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.06 (apparent s, 21 H), 1.72-1.84 (m, 3 H), 1.85-1.93 (m, 1 H), 2.45-2.57 (m, 2 H), 2.58-2.69 (m, 2 H), 2.76 (t, *J* = 7.9 Hz, 2 H), 2.92 (t, *J* = 7.4 Hz, 2 H), 3.93 (dddd, *J* = 5.4, 5.4, 5.4, 5.4 Hz, 1 H), 7.16-7.22 (m, 6 H), 7.27-7.31 (m, 4 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 12.7 (d), 18.2 (q), 29.8 (t), 29.9 (t), 31.5 (t), 38.1 (t), 38.5 (t), 44.4 (t), 70.9 (d), 125.8 (d), 126.1 (d), 128.3 (d), 128.4 (d), 128.5 (d), 141.1 (s), 142.3 (s), 210.0 (s) (two signals overlap in the aromatic region); exact mass *m*/*z* calcd for $C_{29}H_{44}NaO_2Si$ 475.3003, found 475.3009.

2-Methyl-6-[[tris(1-methylethyl)silyl]oxy]-8-phenyl-3-(2-phenylethyl)-oct-1-en-3-ol (45.3a).

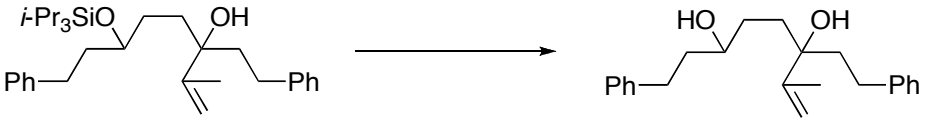


45.3 **45.3a**

t-BuLi (1.7 M in pentane, 0.462 mL, 0.785 mmol) was added dropwise to a stirred and cooled (–78 °C) solution of 2-bromopropene (0.035 mL, 0.39 mmol) in dry Et_2O (6 mL). After 45 min, **45.3** (0.0222 g, 0.0490 mmol) in Et_2O (2 mL plus 1 mL as a rinse) was added by cannula. After 15 min, the dry ice bath was replaced by an ice bath and the mixture was quenched with saturated aqueous NH_4Cl (5 mL). The aqueous phase was extracted with CH_2Cl_2 and the combined organic extracts were dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (0.7 x 18 cm), using EtOAc-hexanes mixtures from 2% to 10% EtOAc, gave **45.3a** (0.0243 g, 100%) as a semi-solid which was a mixture

of diastereoisomers: FTIR (CH_2Cl_2, cast film microscope) 3576, 3476, 3086, 3063, 3027, 2944, 2891, 2866, 1940, 1866, 1802, 1642, 1604, 1496, 1454 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.08 (apparent s, 21 H), 1.45-1.75 (m, 4 H), 1.77 (dd, *J* = 3.0, 0.7 Hz, 3 H), 1.80-1.97 (m, 4 H), 2.44-2.57 (m, 1 H), 2.58-2.76 (m, 3 H), 3.91 (dddd, *J* = 5.2, 5.2, 5.2, 5.2 Hz, 1 H), 5.01 (apparent q, *J* = 1.5, 1 H), 5.09 (apparent dq, J = 5.7, 0.7 Hz, 1 H), 7.16-7.22 (m, 6 H), 7.27-7.32 (m, 4 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 12.7 (d), 18.2 (q), 19.8 (q), 29.6 (t), 29.9 (t), 31.3 (t), 31.4 (t), 34.5 (t), 34.6 (t), 38.3 (t), 38.4 (t), 41.6 (t), 41.8 (t), 71.97 (d), 72.01 (d), 111.4 (t), 111.7 (t), 125.7 (d), 128.3 (d), 128.35 (d), 128.36 (d), 128.38 (d), 142.5 (s), 142.7 (t), 147.8 (s), 147.9 (s); exact mass *m*/*z* calcd for $C_{32}H_{51}O_2Si$ 495.36528, found 495.36512; exact mass *m*/*z* calcd for $C_{32}H_{50}NaO_2Si$ 517.3472, found 517.3471.

2-Methyl-8-phenyl-3-(2-phenylethyl)oct-1-ene-3,6-diol (45.3b).

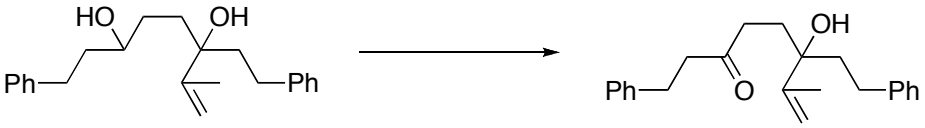


45.3a **45.3b**

Bu_4NF (1.0 M in THF, 0.1627 mL, 0.1627 mmol) was added dropwise to a stirred and cooled (0 °C) solution of **45.3a** (0.0230 g, 0.0465 mmol) in dry THF (6 mL). The cooling bath was left in place but not recharged and stirring was continued for 19 h. The mixture was quenched with water (5 mL) and extracted with EtOAc. The combined organic extracts were dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (1.4 x 15 cm), using EtOAc-petroleum ether mixtures from 20% to 100%, gave **45.3b** (0.0154 g, 98%) as an oil which was a mixture of diastereoisomers: FTIR (CH_2Cl_2,

microscope) 3381, 3085, 3062, 3026, 3001, 2943, 2861, 1946, 1870, 1805, 1707, 1643, 1604, 1584, 1496, 1454 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.35-1.74 (m, 2 H), 1.74 (dd, *J* = 1.5, 0.7 Hz, 1.8 H), 1.76 (dd, *J* = 1.5, 0.7 Hz, 1.2 H), 1.77-1.95 (m, 6 H), 2.15-2.40 (br s, 2 H), 2.46-2.56 (m, 1 H), 2.61-2.73 (m, 2 H), 2.74-2.84 (m, 1 H), 3.57-3.65 (m, 0.6 H), 3.65-3.72 (m, 0.4 H), 4.99-5.02 (m, 0.4 H), 5.02-5.04 (m, 0.6 H), 5.07-5.08 (m, 0.4 H), 5.10-5.12 (m, 0.6 H), 7.16-7.23 (m, 6 H), 7.25-7.32 (m, 4 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 19.80 (q), 19.82 (q), 29.8 (t), 29.9 (t), 31.1 (t), 31.3 (t), 32.1 (t), 32.2 (t), 35.0 (t), 36.4 (t), 38.9 (t), 39.5 (t), 41.7 (t), 41.9 (t), 71.07 (d), 72.14 (d), 77.7 (s), 77.8 (s), 111.7 (t), 112.1 (t), 125.76 (d), 125.78 (d), 125.8 (d), 125.9 (d), 128.3 (d), 128.37 (d), 128.41 (d), 141.97 (s), 142.02 (s), 142.4 (s), 142.5 (s), 147.7 (s), 147.8 (s); exact mass *m*/*z* calcd for $C_{23}H_{30}NaO_2$ 361.2138, found 361.2136.

6-Hydroxy-7-methyl-1-phenyl-6-(2-phenylethyl)oct-7-en-3-one (45.3c).

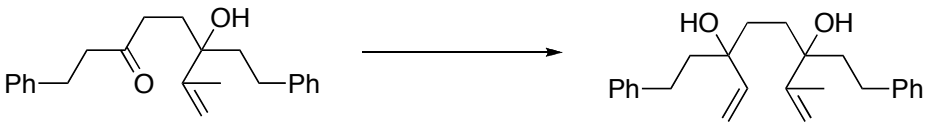


45.3b **45.3c**

$(COCl)_2$ (0.0245 mL, 0.281 mmol) was added dropwise to a stirred and cooled (–78 °C) solution of DMSO (0.0399, 0.562 mmol) in CH_2Cl_2 (3 mL). After 10 min, **45.3b** (0.0123 g, 0.0363 mmol) in CH_2Cl_2 (1 mL) was added dropwise. After a further 40 min, Et_3N (0.101 mL, 0.727 mmol) was added dropwise and stirring was continued for 10 min. The mixture was then stored at –20 °C (freezer) for 12 h. The reaction mixture was warmed to 0 °C and water (10 mL) was added. The aqueous phase was extracted with CH_2Cl_2 and the combined organic extracts were washed with saturated aqueous $NaHCO_3$, dried (Na_2SO_4)

and evaporated. Flash chromatography of the residue over silica gel (0.7 x 16 cm), using EtOAc-petroleum ether mixtures from 2% to 10% EtOAc, gave **45.3c** (0.0105 g, ca 86%) as an impure oil which was used in the next step: FTIR (CH_2Cl_2, microscope) 3464, 3085, 3062, 3026, 2949, 2867, 1944, 1871, 1804, 1709, 1644, 1604, 1496, 1454 cm^{-1}; exact mass *m*/*z* calcd for $C_{23}H_{28}NaO_2$ 359.1982, found 359.1976.

2-Methyl-3,6-bis(2-phenylethyl)octa-1,7-diene-3,6-diol (46.1).

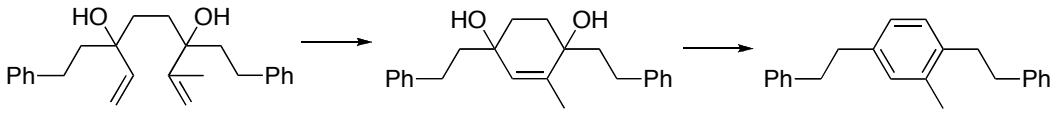


45.3c **46.1**

MeLi (1.6 M in Et_2O, 0.241 mL, 0.385 mmol) was added dropwise to a stirred and cooled (0 °C) solution of tetravinyltin (0.018 mL, 0.096 mmol) in dry Et_2O (4 mL). After 30 min, the mixture was cooled to –78 °C and **45.3c** (0.0081 g, 0.024 mmol) in Et_2O (1 mL plus 0.5 mL as a rinse) was added by cannula. The cold bath was left in place but not recharged and stirring was continued for 12 h. The mixture was cooled to 0 °C and quenched with saturated aqueous NH_4Cl (5 mL). The aqueous phase was extracted with Et_2O and the combined organic extracts were dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (1.4 x 18 cm), using EtOAc-hexanes mixtures from 2% to 20% EtOAc, gave **46.1** (0.0066 g, 75%) as an oil which was a mixture of diastereoisomers: FTIR (CH_2Cl_2, cast microscope) 3427, 3085, 3062, 3026, 3003, 2949, 2863, 1945, 1869, 1805, 1709, 1643, 1604, 1496, 1454 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.48-1.72 (m, 4 H), 1.73 (dd, *J* = 1.5, 0.7 Hz, 1.1 H), 1.75 (dd, *J* = 1.6, 0.6 Hz, 1.9 H), 1.76-1.94 (m, 6 H), 2.45-2.53 (m, 1 H), 2.57-2.71 (m,

3 H), 4.98-5.10 (m, 2 H), 5.18-5.32 (m, 2 H), 5.78-5.90 (m, 1 H), 7.15-7.20 (m, 6 H), 7.25-7.29 (m, 4 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 14.0 (q), 17.1 (q), 19.8 (t), 22.3 (t), 29.8 (t), 30.0 (t), 33.0 (t), 33.1 (t), 34.1 (t), 34.25 (t), 34.31 (t), 41.5 (t), 41.9 (t), 42.6 (t), 75.2 (s), 77.5 (s), 111.7 (t), 112.1 (t), 113.2 (t), 113.6 (t), 125.75 (d), 125.78 (d), 128.4 (d), 128.4 (d), 142.3 (s), 142.4 (s), 143.2 (s), 143.6 (s), 147.8 (s); exact mass *m*/*z* calcd for $C_{25}H_{32}NaO_2$ 387.2295, found 387.2293.

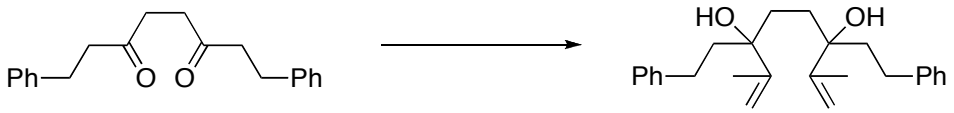
2-Methyl-1,4-bis(2-phenylethyl)benzene (46.3).



46.1 **46.2** **46.3**

Grubbs catalyst (2nd generation,[43] 0.0012 g, 0.0014 mmol) was added to a stirred solution of **46.1** (0.0020 g, 0.0055 mmol) in dry CH_2Cl_2 (2.5 mL) (N_2 atmosphere). After 15 h, the mixture was evaporated and the residue was dissolved in dry PhH (2 mL). $TsOH{\cdot}H_2O$ (0.0010 g, 0.0053 mmol) was added and the mixture was refluxed for 30 min. Evaporation of the solvent and preparative thin layer chromatography of the residue (plate 5 x 5 x 0.025 cm; 2% EtOAc-petroleum ether), gave **46.3** (0.0015 g, *ca.* 91%) containing minor impurities: FTIR (CH_2Cl_2, cast film) 3085, 3062, 3026, 2926, 2856, 1943, 1869, 1734, 1603, 1497, 1453 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.28 (s, 3 H), 2.84-2.94 (m, 8 H), 6.96-7.01 (m, 2 H), 7.06-7.11 (m, 1 H), 7.17-7.24 (6 H), 7.27-7.33 (m, 4 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 19.2 (q), 35.1 (t), 36.8 (t), 37.5 (t), 38.0 (t), 125.8 (d), 125.88 (d), 125.92 (d), 128.29 (d), 128.33 (d), 128.38 (d), 128.40 (d), 128.8 (d), 130.3 (d), 135.8 (s), 137.5 (s), 139.5 (s), 142.0 (s), 142.1 (s); exact mass *m*/*z* calcd for $C_{23}H_{24}$ 300.1878, found 300.1876.

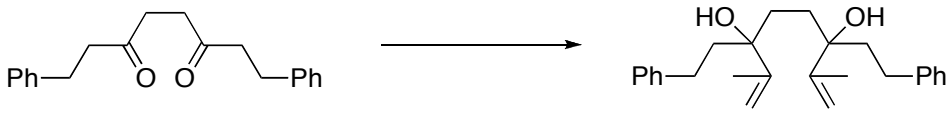
2,7-Dimethyl-3,6-bis(2-phenylethyl)octa-1,7-diene-3,6-diol (47.1).



41.4 **47.1**

Isopropenylmagnesium bromide (0.5 M in THF, 0.508 mL, 0.254 mmol) was added dropwise to a stirred and cooled (–78 °C) solution of **41.4** (0.0299 g, 0.102 mmol) in dry THF (5 mL). After 1 h, the dry ice bath was replaced by an ice bath and isopropenylmagnesium bromide (0.5 M in THF, 0.5078 mL, 0.2539 mmol) was added dropwise. The ice bath was left in place but not recharged and after 5 d the mixture was cooled (0 °C) and quenched with water (10 mL). The aqueous phase was extracted with CH_2Cl_2 and the combined organic extracts were washed with brine, dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (1.4 x 18 cm), using EtOAc-hexanes mixtures from 5% to 40% EtOAc, gave **47.1** (0.0235 g, 61%) as an oil which was a mixture of diastereoisomers: FTIR (CH_2Cl_2, microscope) 3435, 3085, 3062, 3026, 2929, 2855, 1942, 1870, 1804, 1727, 1643, 1604, 1496 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.52-1.58 (m, 1.5 H), 1.67-1.73 (m, 2.5 H), 1.75 (s, 2.5 H), 1.78 (s, 3.5 H), 1.81-1.97 (m, 6 H), 2.45-2.56 (m, 2 H), 2.62-2.72 (m, 2 H), 4.99-5.02 (m, 1.2 H), 5.03-5.06 (m, 0.8 H), 5.06-5.09 (m, 1.3 H), 5.12-5.14 (m, 0.7 H), 7.16-7.23 (m, 6 H), 7.26-7.32 (m, 4 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 19.8 (q), 29.8 (t), 29.9 (t), 32.9 (t), 33.0 (t), 41.5 (t), 42.1 (t), 111.5 (s), 112.2 (s), 125.7 (d), 125.8 (d), 128.38 (d), 128.40 (d), 128.42 (d), 142.48 (s), 142.51 (s), 147.5 (t), 148.0 (t) (one signal missing due to overlap); exact mass *m*/*z* calcd for $C_{26}H_{34}NaO_2$ 401.2451, found 401.2448.

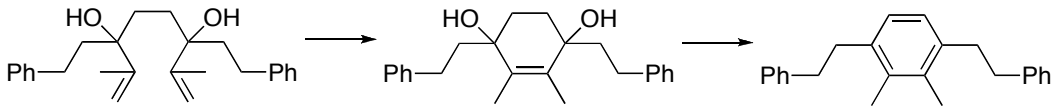
2,7-Dimethyl-3,6-bis(2-phenylethyl)octa-1,7-diene-3,6-diol (47.1).



41.4 **47.1**

t-BuLi (1.7 M in pentane, 0.279 mL, 0.474 mmol) was added dropwise to a stirred and cooled (–78 °C) solution of 2-bromopropene (0.0210 mL, 0.237 mmol) in dry Et_2O (3 mL). After 30 min, **41.4** (0.0105 g, 0.0296 mmol) in Et_2O (0.5 mL plus 0.5 mL as a rinse) was added dropwise by cannula. After 3.5 h the dry ice bath was replaced by an ice bath which was left in place but not recharged and stirring was continued for 17.5 h. The reaction mixture was cooled to 0 °C and quenched with saturated aqueous NH_4Cl (3 mL). The aqueous phase was extracted with CH_2Cl_2 and the combined organic extracts were washed with brine, dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (1.6 x 17 cm), using EtOAc-hexanes mixtures from 2% to 10% EtOAc, gave **47.1** (0.0094 g, 72%) as an oil which was a mixture of diastereoisomers.

2,3-Dimethyl-1,4-bis(2-phenylethyl)benzene (47.3).

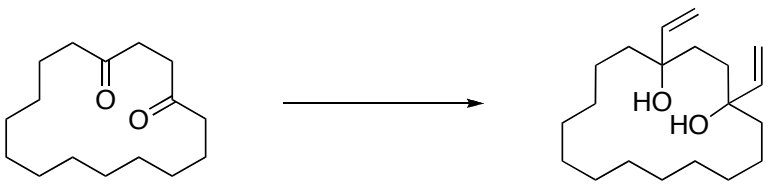


47.1 **47.2** **47.3**

Schrock catalyst[48] (0.0053 g, 0.0069 mmol) and then PhH (3 mL) were added to **47.1** (0.0131 g, 0.0346 mmol) in a Pyrex bomb (10 mL) in a glove box (N_2). The bomb was sealed, removed from the glove box, and heated (ca 80 °C)

for 2.5 days. The mixture was cooled to room temperature, reintroduced into the glove box and a sample for TLC was removed. Little conversion to **47.2** or **47.3** had occurred. The contents of the bomb were transferred to a unitary flask/reflux condenser assembly and additional Schrock catalyst[48] (0.0053 g, 0.0069 mmol) was added. The reaction vessel was removed from the glove box and the mixture was refluxed (80 °C) under N_2 with frequent purging, resulting in a color change from yellow to amber after 1 h. After a further 18 h, the solution was cooled and evaporated. Flash chromatography of the residue over silica gel (1.3 x 11 cm), using EtOAc-petroleum ether mixtures from 5% to 100% EtOAc, gave an unidentifiable mixture which was dissolved in dry PhH (3 mL). $TsOH.H_2O$ (0.0066 g, 0.035 mmol) was added. The mixture was refluxed for 3 h and then evaporated. Flash chromatography of the residue over silica gel (1.4 x 18 cm), using EtOAc-hexane mixtures from 0% to 5% EtOAc, gave several fractions containing mostly impure **47.3**. The material was purified by preparative TLC (silica, 5 x 4.5 x 0.025 cm, 3 plates; 2% EtOAc-hexanes) providing pure **47.3** (0.0072 g, 66 %) as an oil: FTIR (CH_2Cl_2, microscope) 3085, 3061, 3025, 2961, 2928, 2868, 1943, 1869, 1801, 1735, 1704, 1678, 1603, 1582, 1540, 1496, 1453 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 2.24 (s, 6 H), 2.91 (apparent s, 8 H), 7.11 (s, 2 H), 7.18-7.23 (m, 6 H), 7.27-7.34 (m, 4 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 16.6 (q), 37.3 (t), 37.8 (t), 125.7 (d), 128.09 (d), 128.13 (d), 128.17 (d), 128.24 (d), 131.8 (s), 139.1 (d), 141.7 (d); exact mass *m*/*z* calcd for $C_{24}H_{26}$ 314.2035, found 314.2031.

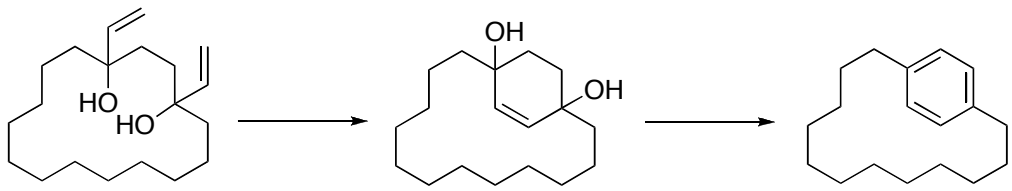
1,4-Divinylcyclohexadecane-1,4-diol (48.1).



40.5 **48.1**

MeLi (1.6 M in Et_2O, 0.967 mL, 1.55 mmol) was added dropwise to a stirred and cooled (0 °C) solution of tetravinyltin (0.0704 mL, 1.32 mmol) in dry Et_2O (6 mL). After 1.5 h, the mixture was cooled to –78 °C and **40.5** (0.0122 g, 0.0483 mmol) in Et_2O (1.5 mL plus 1.5 mL as a rinse) was added by cannula. The cold bath was left in place but not recharged and stirring was continued for 5 h. The mixture was quenched with saturated aqueous NH_4Cl (25 mL). The aqueous phase was extracted with Et_2O and the combined organic extracts were washed with brine, dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (0.7 x 12 cm), using EtOAc-hexanes mixtures from 20% to 30% EtOAc, gave **48.1** [0.0112 g, 75%; 87% corrected for recovered **40.5** (0.0017 g)] as an oil which was a mixture of diastereoisomers: FTIR (CH_2Cl_2, microscope) 3339, 3089, 3010, 2981, 2928, 2856, 1846, 1641, 1457 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.28 (s, 2 H), 1.29-1.42 (m, 20 H), 1.48-1.59 (m, 8 H), 5.08 (dd, J = 10.8, 1.2 Hz, 2 H), 5.23 (dd, J = 17.4, 1.2 Hz, 2 H), 5.95 (dd, J = 17.4, 10.8 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 22.4 (t), 22.5 (t), 26.16 (t), 26.23 (t), 26.5 (t), 26.6 (t), 26.8 (t), 26.9 (t), 27.75 (t), 27.83 (t), 32.38 (t), 32.44 (t), 38.8 (t), 39.0 (t), 74.8 (s), 74.9 (s), 112.1 (t), 144.7 (d), 144.8 (d); exact mass m/z calcd for $C_{20}H_{36}NaO_2$ 331.2608, found 331.2610.

[12]-Paracyclophane (48.3).[57]



48.1 **48.2** **48.3**

Grubbs catalyst (1st generation, 0.0027 g, 0.0032 mmol) was added to a stirred solution of **48.1** (0.0100 g, 0.0324 mmol) in dry CH_2Cl_2 (3 mL) (N_2 atmosphere). After 24 h, the reaction mixture was evaporated and dry PhH (3 mL) was added. $TsOH \cdot H_2O$ (0.0019 g, 0.0097 mmol) was added and the mixture was refluxed for 1 h, cooled and partitioned between water and CH_2Cl_2. The aqueous phase was extracted with CH_2Cl_2 and hexanes, and the combined organic extracts were dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (1.4 x 6 cm), using EtOAc-petroleum ether mixtures from 0% to 2% EtOAc, gave **48.3** (0.0066 g, 83%) as a solid: FTIR (CH_2Cl_2, neat film microscope) 3006, 2926, 2855, 1898, 1510, 1460, 1444 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.75-0.82 (m, 4 H), 0.93-1.00 (m, 4 H), 1.02-1.12 (m, 8 H), 1.55-1.62 (m, 4 H), 2.60-2.63 (m, 4 H), 7.08 (s, 4 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 25.4 (t), 26.6 (t), 27.4 (t), 27.5 (t), 29.8 (t), 35.2 (t), 128.8 (d), 140.0 (s); exact mass *m*/*z* calcd for $C_{18}H_{28}$ 244.2191, found 244.2188.

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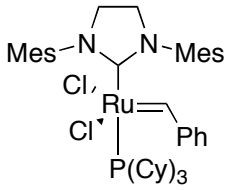
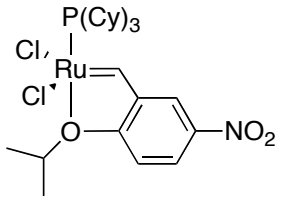
43 The IUPAC name for Grubbs 2nd generation catalyst is benzylidene[1,3-bis(2,4,6-trimethylphenyl)-2-imidazolidinylidene]dichloro(tricyclohexyl-phosphine)ruthenium.



44 [1,3-Bis(2,4,6-trimethylphenyl)-2-imidazolidinylidene]dichloro(phenyl-

methylene)(tricyclohexylphosphine)ruthenium. A solution (0.0038 M) of **40.3** was added over 20 h to a solution of the catalyst (10 mol%) in CH_2Cl_2 (7.6×10^{-4} M).



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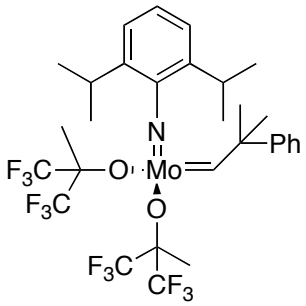
48 The IUPAC name for Schrock catalyst is 2,6 diisopropylphenylimidoneophylidene molybdenum(VI)bis(hexafluoro-*t*-butoxide)



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