

# The asymmetric Birch reduction and reduction–alkylation strategies for synthesis of natural products

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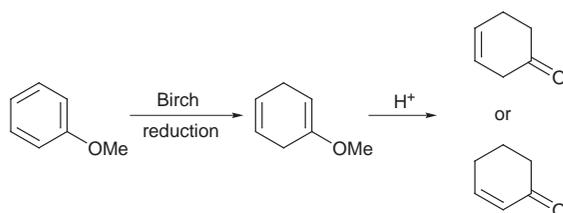
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Synthetic applications of the asymmetric Birch reduction and reduction–alkylation are reported. Synthetically useful chiral intermediates have been obtained from chiral 2-alkoxy-, 2-alkyl-, 2-aryl- and 2-trialkylsilyl-benzamides **I** and the pyrrolobenzodiazepine-5,11-diones **II**. The availability of a wide range of substituents on the precursor benzoic acid derivative, the uniformly high degree of diastereoselection in the chiral enolate alkylation step, and the opportunity for further development of stereogenic centers by way of olefin addition reactions make this method unusually versatile for the asymmetric synthesis of natural products and related materials.

## Introduction

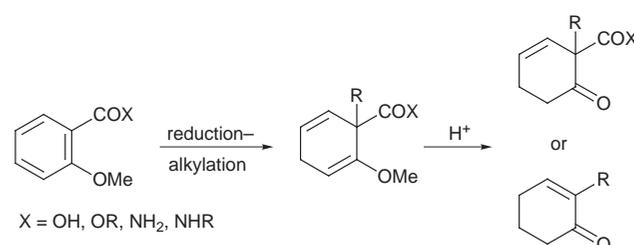
The Birch reduction has been used by several generations of synthetic organic chemists for the conversion of readily available aromatic compounds to alicyclic synthetic intermediates.<sup>1</sup> Birch reductions are carried out with an alkali metal in liquid NH<sub>3</sub> solution usually with a co-solvent such as THF and always with an alcohol or related acid to protonate intermediate radical anions or related species. One of the most important applications of the Birch reduction is the conversion of aryl alkyl ethers to 1-alkoxycyclohexa-1,4-dienes. These extremely valuable dienol ethers provide cyclohex-3-en-1-ones by mild acid hydrolysis or cyclohex-2-en-1-ones when stronger acids are used (Scheme 1).



Scheme 1

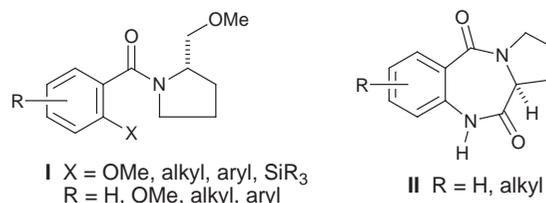
The Birch reduction of derivatives of 2-methoxybenzoic acid followed by alkylation of the intermediate enolate is of even greater strategic value. The resulting chiral cyclohexa-

1,4-dienes are converted to 2,2-disubstituted cyclohex-3-en-1-ones by hydrolysis of the enol ether. If the carboxylic acid is used in the reduction step, then treatment of the intermediate cyclohexa-1,4-diene with acid results in hydrolysis–decarboxylation to give 2-substituted cyclohex-2-en-1-ones (Scheme 2).



Scheme 2

Against this backdrop of prior investigation, we initiated a program directed at the development of an asymmetric version of the Birch reduction and reduction–alkylation of derivatives of benzoic acid.<sup>2</sup> We opted to make use of a chiral auxiliary covalently bound to the carboxylic acid group and after a brief screening of possible candidates were delighted to find that the inexpensive amino acid (*S*)-proline and its product of reduction by LiAlH<sub>4</sub>, (*S*)-pyrrolidine-2-methanol, served beyond all reasonable expectation. It has been demonstrated that 2-alkoxy-, 2-alkyl-, 2-aryl- and 2-trialkylsilyl-benzamides of general structure **I** can be effectively utilized in asymmetric organic synthesis of a wide range of synthetic targets. It was necessary to develop a different protocol for the anthranilic acids; the pyrrolobenzodiazepine-5,11-diones **II**, obtained by condensation of 1 equiv. of (*S*)-proline with the corresponding isoatoic anhydride, provided a remarkably flexible solution to the incorporation of nitrogen substitution on the derived cyclohexane ring.

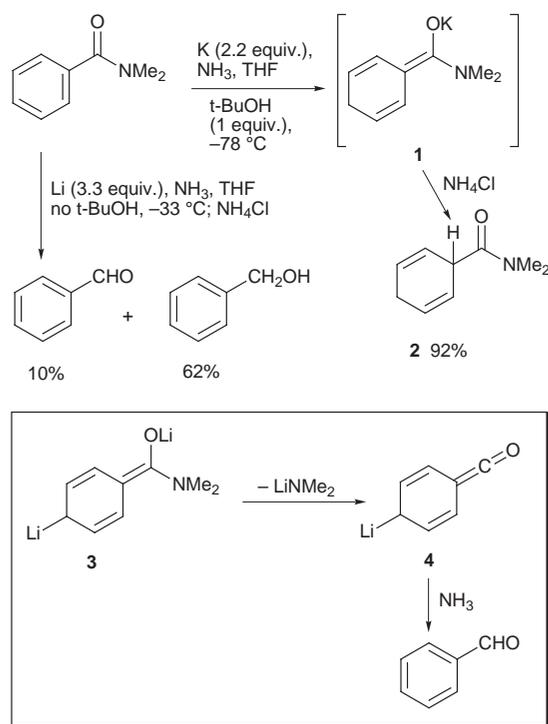


Much of the characterization of reactivity of **I** (X = OMe) and some of the early applications of **I** and **II** to asymmetric organic synthesis were reviewed in 1990.<sup>3</sup> The focus of this feature article is on recent developments with greatly expanded sets of substrates corresponding to the generalized structures **I** and **II**. Particular attention is devoted to the utilization of these substrates for the asymmetric synthesis of natural products and related materials.

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## Tools for asymmetric synthesis

At the outset of our studies of the reactivity of **I** and **II**, it was necessary to investigate claims that tertiary benzamides were inappropriate substrates for the Birch reduction. It had been reported that reduction of *N,N*-dimethylbenzamide with sodium in  $\text{NH}_3$  in the presence of *tert*-butyl alcohol gave benzaldehyde and a benzaldehyde–ammonia adduct. We found that the competition between reduction of the amide group and the aromatic ring was strongly dependent on reaction variables, such as the alkali metal (type and quantity), the availability of a proton source more acidic than  $\text{NH}_3$ , and reaction temperature. Reduction with potassium in  $\text{NH}_3$ –THF solution at  $-78^\circ\text{C}$  in the presence of 1 equiv. of *tert*-butyl alcohol gave the cyclohexa-1,4-diene **2** in 92% isolated yield (Scheme 3). At the other extreme, reduction with lithium in  $\text{NH}_3$ –THF at  $-33^\circ\text{C}$  in the absence of *tert*-butyl alcohol gave benzaldehyde and benzyl alcohol as major reaction products.<sup>4</sup>



Scheme 3

Reduction of the aromatic nucleus in *N,N*-dimethylbenzamide occurs by an initial single electron transfer to give a radical anion. Protonation of the radical anion generates a radical and a second electron transfer gives the amide enolate **1**. Protonation of the cross-conjugated trienolate moiety in **1** occurs  $\alpha$  to the incipient carbonyl group to give the cyclohexa-1,4-diene **2**.<sup>1</sup>

Amide group reduction probably occurs by the mechanism shown in Scheme 3. Two-electron transfer without protonation would give dianion **3**. Elimination of  $\text{LiNMe}_2$  from **3** would give **4** (an acyl anion equivalent) and protonation of **4** at the carbonyl group would give benzaldehyde.

Because dianion formation appears to be more important when lithium rather than potassium is used, many of the Birch reductions and reduction–alkylations of **I** and **II** that have been developed utilize potassium as the reducing metal. Piperylene is added prior to the alkylation reagent to consume any remaining metal and thereby prevent reduction of the alkylation reagent. In the event that the alkylation reagent is unstable to strong bases (e.g. homoallylic and arylolefin halides)  $\text{LiBr}$  is added to reduce the basicity of the reaction medium.

Birch reduction of the chiral benzamide **5** generates the amide enolate **6** (Scheme 4). This enolate has been characterized by NMR spectroscopy and by an extensive examination of the effects of changes in alkali metal, solvent, reaction

temperature and substituents near the reaction center on the diastereoselectivity of enolate alkylation.<sup>5</sup> These data have been reviewed before<sup>3</sup> and will not be discussed here. For this presentation it is sufficient to note that the alkylation reagent reacts with enolate **6** preferentially from the least hindered face away from the methoxymethyl group on the chiral auxiliary.

Diastereoselectivities for alkylation of enolate **6** are outstanding. Alkylation with  $\text{MeI}$  gives **7** ( $\text{R} = \text{Me}$ ) as the major product diastereomer in a ratio of 260:1 with respect to the minor diastereomer **8**. A wide range of alkylation reagents have been examined including allylic, benzylic, homoallylic, alkoxymethyl, cyanomethyl, and arylolefin halides.

It is important to perform both the Birch reduction of **5** and the alkylation of enolate **6** at  $-78^\circ\text{C}$ . Enolate **6** obtained directly from **5** at low temperatures is considered to be a ‘kinetic enolate’. A ‘thermodynamic enolate’ obtained from **6** by equilibration techniques has been shown to give an opposite sense of stereoselection on alkylation.<sup>5</sup> Although a comprehensive study of this modification has not been carried out, diastereoselectivities for formation of **8** were found to be greater than 99:1 for alkylations with  $\text{MeI}$ ,  $\text{EtI}$ , and  $\text{PhCH}_2\text{Br}$ . Thus, it should be possible to obtain both enantiomers of a target structure by utilization of a single chiral benzamide.<sup>6,7</sup>

It has been demonstrated that excellent diastereoselectivities for enolate alkylation also are obtained when alkyl substituents are positioned at C(4), C(5) or C(6) of benzamide **5**.<sup>5</sup> Aryl<sup>8</sup> and methoxy<sup>9</sup> substituents at C(5) also are compatible, but a methyl group at C(3) leads to an inversion of the diastereoselectivity of enolate alkylation. The inverted sense of stereoselection is thought to be a result of a disruption of the internal chelation shown in enolate **6** by steric effects of the neighboring methyl substituent.<sup>5</sup>

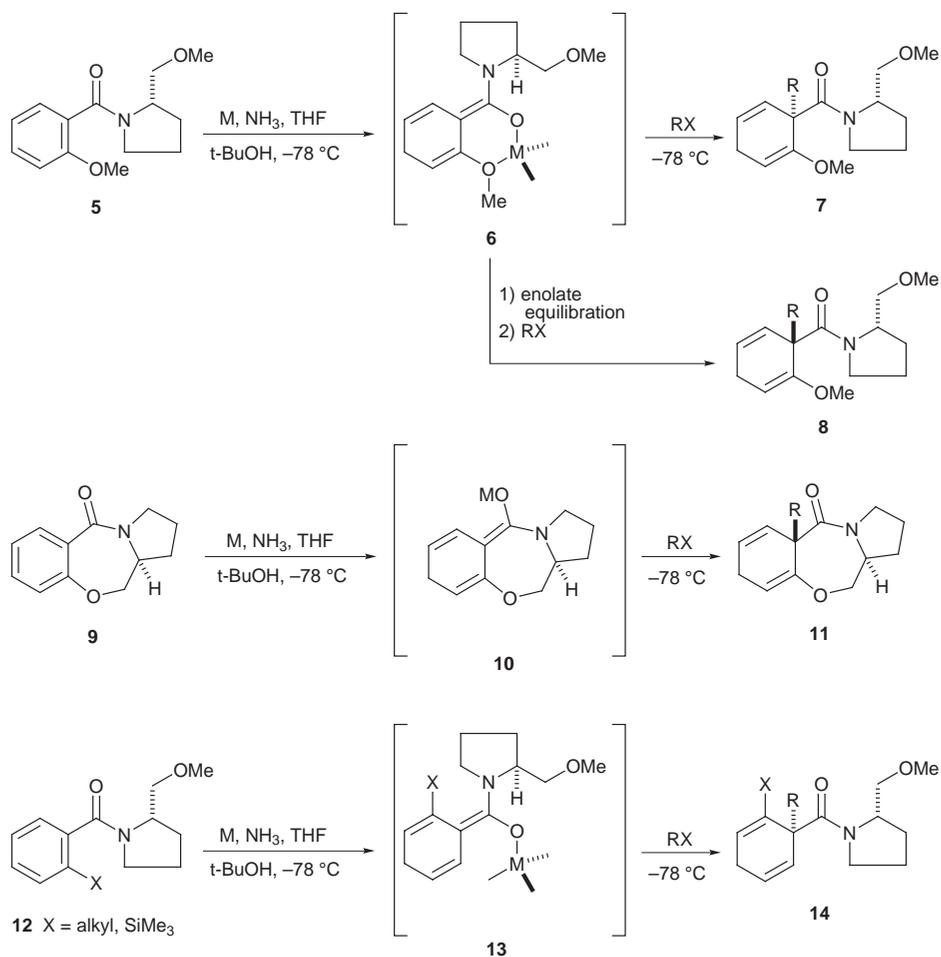
A more traveled route to the absolute configuration represented by cyclohexa-1,4-diene **8** involves Birch reduction–alkylation of benzoxazepinone **9**.<sup>2,5</sup> This heterocycle is best prepared by the base-induced cyclization of the amide obtained from 2-fluorobenzoyl chloride and (*S*)-pyrrolidine-2-methanol.<sup>10</sup> The molecular shape of enolate **10** is such that the hydrogen at the stereogenic center provides some shielding of the  $\alpha$ -face of the enolate double bond. Thus, alkylation occurs primarily at the  $\beta$ -face of **10** to give **11** as the major diastereomer. The diastereoselectivity for alkylation with methyl iodide is only 85:15, but with more sterically demanding alkyl halides such as ethyl iodide, allyl bromide, 4-bromobut-1-ene *etc.*, diastereoselectivities are greater than 98:2.

Birch reduction–alkylation of 2-alkyl- and 2-trimethylsilylbenzamides corresponding to structure **12** has provided a very general route to cyclohexa-1,4-dienes of type **14**. Enolate **13** has been used to explain the alkylation diastereoselectivities for over twenty cases in which the substituent X is varied from a group as small as methyl to groups as large as  $\text{CH}_2\text{CH}_2\text{Ph}$  or  $\text{SiMe}_3$ .<sup>11,12</sup> As with enolate **5**, the alkylation reagent reacts preferentially from the less hindered face of enolate **13** to give **14**.

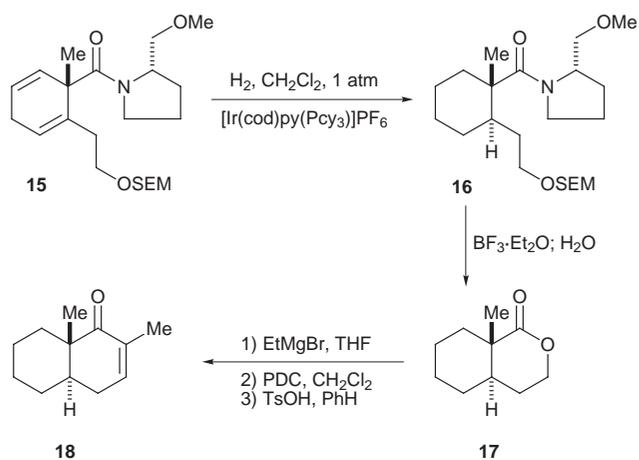
## Companion reactions that serve to expand the scope of the asymmetric Birch reduction–alkylation strategy

The development of facial selective addition reactions of cyclohexa-1,4-dienes **7** and **14** has greatly extended the value of the asymmetric Birch reduction–alkylation. For example, amide directed hydrogenation<sup>13</sup> of **15** with the Crabtree catalyst system occurs with outstanding facial selectivity *syn* to the amide carbonyl group to give **16** (Scheme 5).<sup>11</sup>

The reluctance of tertiary amides to undergo hydrolysis, especially those produced in the Birch reduction–alkylation with a quaternary center next to the carbonyl group, has inspired the development of a variety of intramolecular transacylation reactions as illustrated by the cleavage of the SEM ether in **16**



Scheme 4



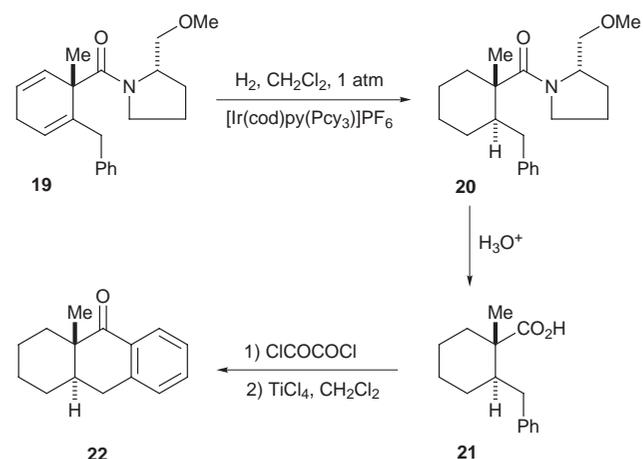
Scheme 5

and subsequent cyclization of the resulting alcohol to give lactone **17**. It is noteworthy that the chiral auxiliary can be removed at this stage by a simple partitioning of the reaction mixture between an organic solvent and aqueous acid.

Lactone **17** was converted to the *trans* fused octalone **18** by a classical Grignard-type carboannulation. Variations of the organometallic reagent used in the conversion of **17** to **18** and modifications of the substrate and alkylation reagent utilized to produce **15** afford unusually flexible options for the preparation of annulated cyclohexanes.

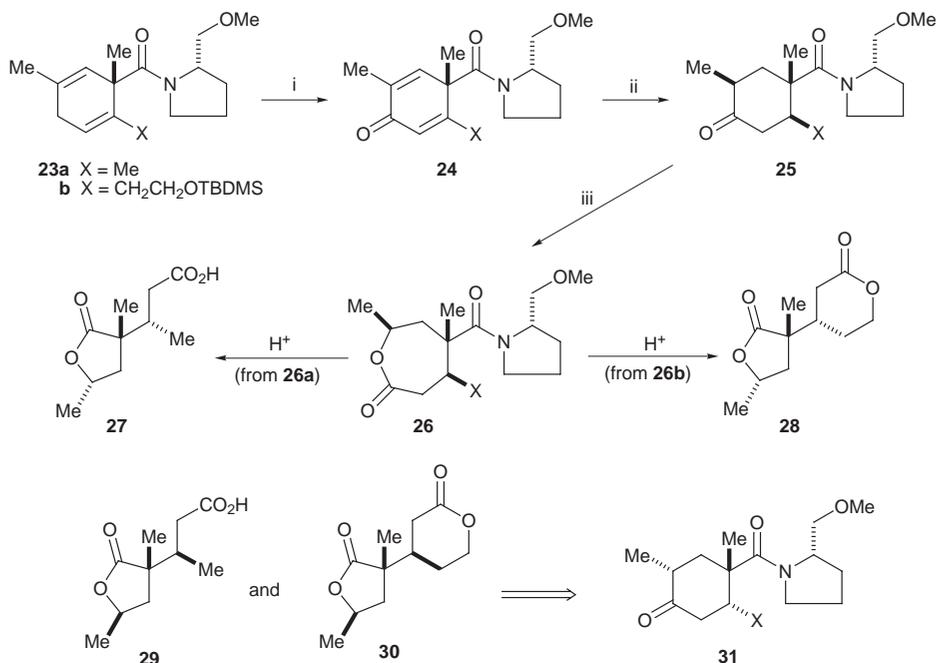
An application to the asymmetric synthesis of enantiomerically pure *trans*-hexahydroanthracen-9-ones is shown in Scheme 6. It should be possible to carry out a second stereoselective reductive alkylation of the benzoyl group in **22** as was demonstrated in the related hydrofluoren-9-one and

hydrophenanthren-9-one series.<sup>14</sup> The key to the development of synthetic strategies involving consecutive Birch reduction-alkylations will depend on sequential activations of aromatic rings toward alkali metal in ammonia reduction; carbonyl activation is illustrated by the conversion of **21** to **22** in Scheme 6.



Scheme 6

Bis-allylic oxidation of **23** and related cyclohexa-1,4-dienes provides a convenient and general preparation of cyclohexa-2,5-dien-1-ones (Scheme 7).<sup>15</sup> These cross-conjugated dienones are substrates for a variety of photochemical rearrangement and intramolecular cycloaddition reactions.<sup>16</sup> Amide-directed hydrogenations of dienones **24a** and **24b** with the homogeneous iridium catalyst afford cyclohexanones **25a** and **25b**, containing three stereogenic centers on the six-



**Scheme 7** Reagents: i, PDC, *t*-BuOOH, Celite, PhH; ii, H<sub>2</sub>, [Ir(cod)py(Pcy<sub>3</sub>)PF<sub>6</sub>, CH<sub>2</sub>Cl<sub>2</sub>, 1 atm; iii, MCPBA.

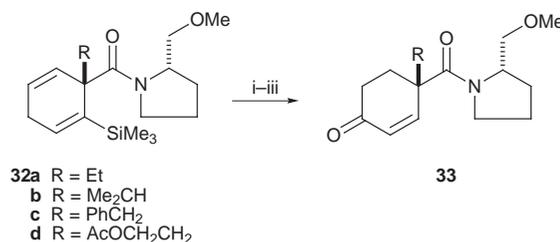
membered ring. Opposite stereoselectivity is obtained with heterogeneous catalysts such as rhodium on alumina or palladium on carbon to give cyclohexanones **31a** and **31b**.<sup>17</sup> X-Ray structural studies<sup>18</sup> demonstrate the importance of the bulky amide group in directing heterogeneous catalytic hydrogenation to the distal face of the cyclohexa-2,4-dienone ring.

We were interested in applications of the high level of stereocontrol associated with the asymmetric Birch reduction–alkylation to problems in acyclic and heterocyclic synthesis. The pivotal disconnection of the six-membered ring is accomplished by utilization of the Baeyer–Villiger oxidation (Scheme 7). Treatment of cyclohexanones **25a** and **25b** with MCPBA gave caprolactone amides **26a** and **26b** with complete regiocontrol. Acid-catalyzed transacylation gave the butyrolactone carboxylic acid **27** from **26a** and the bis-lactone **28** from **26b**; cyclohexanones **31a** and **31b** afforded the diastereomeric lactones **29** and **30**.<sup>17</sup>

Chiral butyrolactones of type **27** and **28** have substantial value in asymmetric synthesis because they contain readily differentiable difunctional group relationships (*e.g.* 1,5-dicarboxylic acid, 1,4-hydroxycarboxylic acid, 1,6-hydroxycarboxylic acid, 1,6-diol *etc.*) that would be difficult to assemble by existing asymmetric condensation and pericyclic processes. Applications of these chiral derivatives of glutaric acid to syntheses of indole, indoline and quinolinone alkaloids are illustrated in Schemes 16–18.

A structural requirement for the asymmetric Birch reduction–alkylation is that a substituent must be present at C(2) of the benzoyl moiety to desymmetrize the developing cyclohexa-1,4-diene ring (Scheme 4). However, for certain synthetic applications, it would be desirable to utilize benzoic acid itself. The chemistry of chiral benzamide **12** (X = SiMe<sub>3</sub>) was investigated to provide access to non-racemic 4,4-disubstituted cyclohex-2-en-1-ones **33** (Scheme 8).<sup>19</sup> Alkylation of the enolate obtained from the Birch reduction of **12** (X = SiMe<sub>3</sub>) gave cyclohexa-1,4-dienes **32a–d** with diastereoselectivities greater than 100:1.<sup>20</sup> These dienes were efficiently converted in three steps to the chiral cyclohexenones **33a–d**.

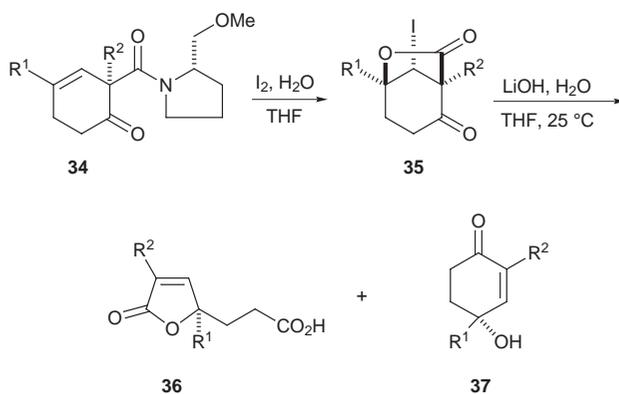
A very effective method for removal of the chiral auxiliary from cyclohexenones **34** involves treatment with I<sub>2</sub> in THF–H<sub>2</sub>O to give the iodolactones **35** (Scheme 9). These highly functionalized chiral cyclohexanones have figured prominently in the asymmetric synthesis of natural products; *e.g.* Scheme 15. Furthermore, selective cleavage of the cyclohexanone ring in **35**



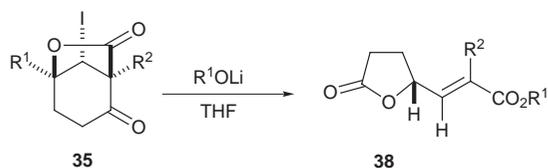
**Scheme 8** Reagents: i, PDC, *t*-BuOOH; ii, H<sub>2</sub>, Pd/C; iii, CuCl<sub>2</sub>, DMF.

with LiOH under aqueous conditions affords the butenolide carboxylic acids **36**.<sup>21</sup> A competing fragmentation process initiated by addition of hydroxide ion to the lactone carbonyl group gives the 4-hydroxycyclohexenones **37**. Yields for formation of the butenolide **36** are in the range of 80 to 90% when relatively large groups are present at C(2). On the other hand, the 4-hydroxycyclohexenone **37** is obtained in 72% yield when R<sup>1</sup> = H and R<sup>2</sup> = Me.

A different mode of fragmentation of the lactone ring in **35** occurred to give butyrolactone **38** when anhydrous lithium alkoxides were used in place of metal hydroxides under aqueous conditions (Scheme 10). It is noteworthy that **36**, **37** and **38** (R<sup>1</sup> = H) are all formed without racemization. Although we are only in the early stages of development of the chemistry of iodolactones **35**, it is already clear that there is considerable potential for utilization of the butenolides derived from **35** as scaffolds for construction of carbocyclic and heterocyclic ring



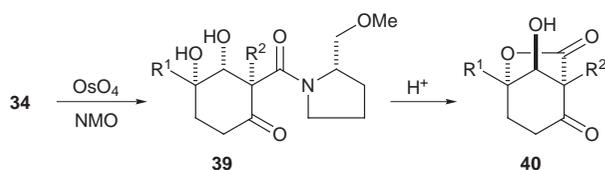
**Scheme 9**



Scheme 10

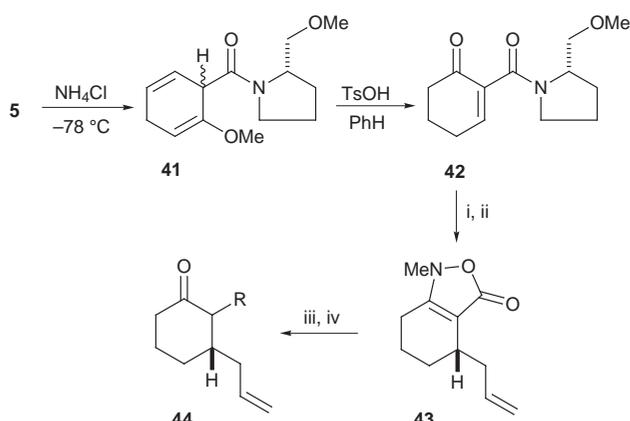
systems by way of intramolecular radical and dipolar addition reactions.<sup>21</sup>

Cyclohexenones **34** also undergo a highly diastereoselective dihydroxylation to give *cis*-diols **39** (Scheme 11).<sup>22</sup> These diol amides are converted to hydroxylactones **40** by an acid-catalyzed process involving retro aldol–realdolization prior to transacylation. The enantiomers of hydroxylactones **40** are obtained from iodolactones **35** by iodide exchange with 2,2,6,6-tetramethylpiperidin-1-yloxy free radical (TEMPO) followed by reductive cleavage of the TEMPO derivative with Zn in HOAc. The enantiomeric purity of the hydroxylactones prepared by either route is 95–98% ee.



Scheme 11

Reaction of enolate **5** with excess  $NH_4Cl$  at  $-78\text{ }^\circ C$  gave the  $\alpha$ -protonated amide **41** as a 4 : 1 mixture of diastereomers.<sup>5</sup> This degree of stereoselectivity was considered to be unacceptable for applications in asymmetric organic synthesis. However, the chiral 2-substituted cyclohex-2-en-1-one **42**, obtained from **41** by enol ether hydrolysis along with double bond migration, undergoes conjugate addition reactions with Grignard reagents and related organometallic derivatives with moderate to good regio- and stereo-control.<sup>23</sup> Considerably more selective addition reactions of **42** occur with allyl silanes (the Sakurai reaction) and enol silyl ethers (the Mukaiyama–Michael addition).<sup>24</sup> Treatment of the conjugate adduct with *N*-methylhydroxylamine releases the chiral auxiliary to give a 1-methyltetrahydrobenzoxazolin-3-one; e.g. **43**, 96% ee. Heterocycle **43** provides 2,3-disubstituted cyclohexanones **44** by a reduction–alkylation sequence (Scheme 12).<sup>24</sup>



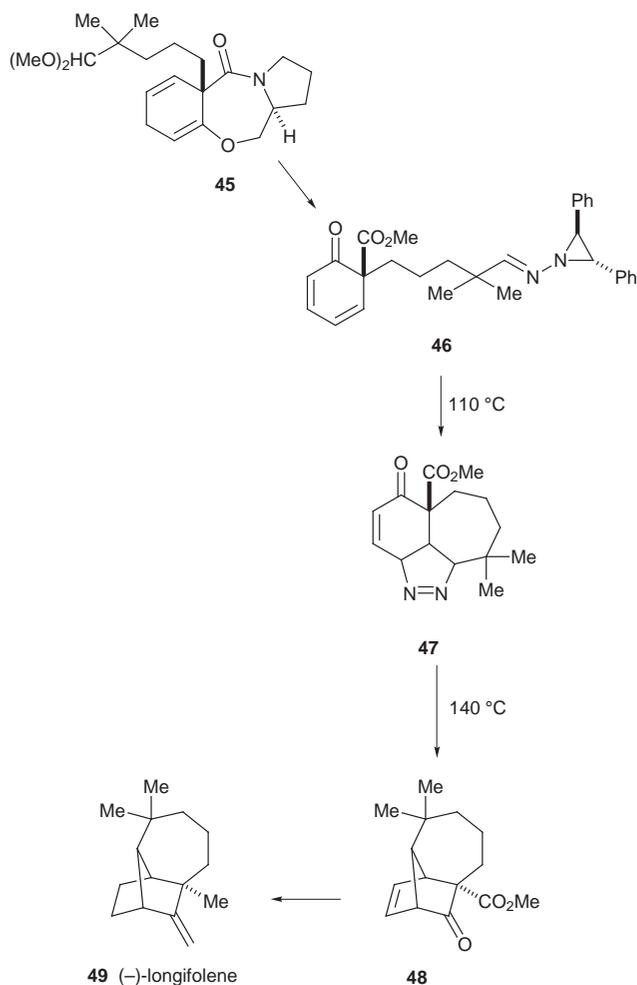
**Scheme 12** Reagents: i,  $H_2C=CHCH_2SiMe_3$ ,  $TiCl_4$ ; ii,  $MeNHOH$ ,  $H^+$ ; iii,  $Li$ ,  $NH_3-THF$ ; RX.

### Applications to the asymmetric synthesis of natural products and related materials

What truly distinguishes the asymmetric Birch reduction–alkylation protocol from other methods for preparation of non-

racemic cyclohexane derivatives is (i) the accessibility of aromatic carboxylic acids with substituents ranging from heteroatoms to alkyl and aryl groups to tethered functionality available for subsequent strategic applications, (ii) the uniformly high degree of diastereoselection in the chiral enolate alkylation step, and (iii) the opportunity for further development of stereogenic centers on the resulting chiral cyclohexa-1,4-diene ring system by facial-selective addition reactions.

The tricyclic sesquiterpene longifolene has served as a vehicle for the illustration of new strategies for organic synthesis.<sup>25</sup> Both enantiomers have been obtained from natural sources; (+)-longifolene occurs in several *Pinus* species and is commercially available while the rare (–)-longifolene has been found in certain liver mosses.<sup>26</sup> We elected to prepare (–)-longifolene **49** from the cyclohexa-1,4-diene **45**, obtained from the Birch reduction–alkylation of benzoxazepinone **9** in 96% yield with a diastereomeric excess of greater than 98% (Scheme 13).<sup>27</sup>

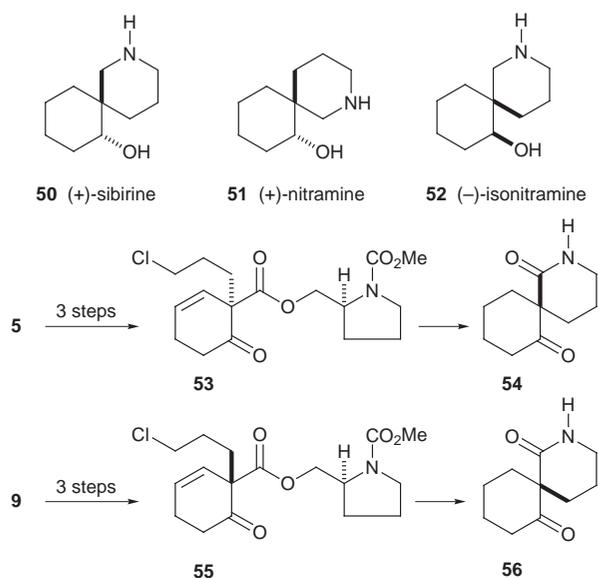


Scheme 13

Cyclohexadiene **45** was converted to **46** by what has proven to be a general method for preparation of the cyclohexa-2,4-dien-1-one ring system.<sup>28</sup> Fragmentation of the aziridinyl imine in **46** at  $110\text{ }^\circ C$  gave an intermediate diazoalkane which underwent an intramolecular 1,3-dipolar cycloaddition to give the pyrazoline **47**. At  $140\text{ }^\circ C$ , pyrazoline **47** expelled  $N_2$  and rearranged to the tricyclic ketone **48**. The development of this and related bicyclizations<sup>29</sup> illustrated a practical synthetic equivalence of an intramolecular diene–carbene 4 + 1 cycloaddition in the cyclohexa-2,4-dien-1-one series.

The 2-azaspiro[5.5]undecane group of alkaloids occur in certain plants of the genus *Nitraria*. There has been some interest in the biological activity of these alkaloids because their structures are similar to the histrionicotoxins, a group of

1-azaspiro[5.5]undecane alkaloids found only in dendrobatid frogs.<sup>30</sup> The first asymmetric syntheses of (+)-sibirine **50**, (+)-nitramine **51** and (–)-isonitramine **52** from the chiral benzamide **5** and benzoxazepinone **9** established the absolute configuration of these alkaloids (Scheme 14).<sup>31</sup>



Scheme 14

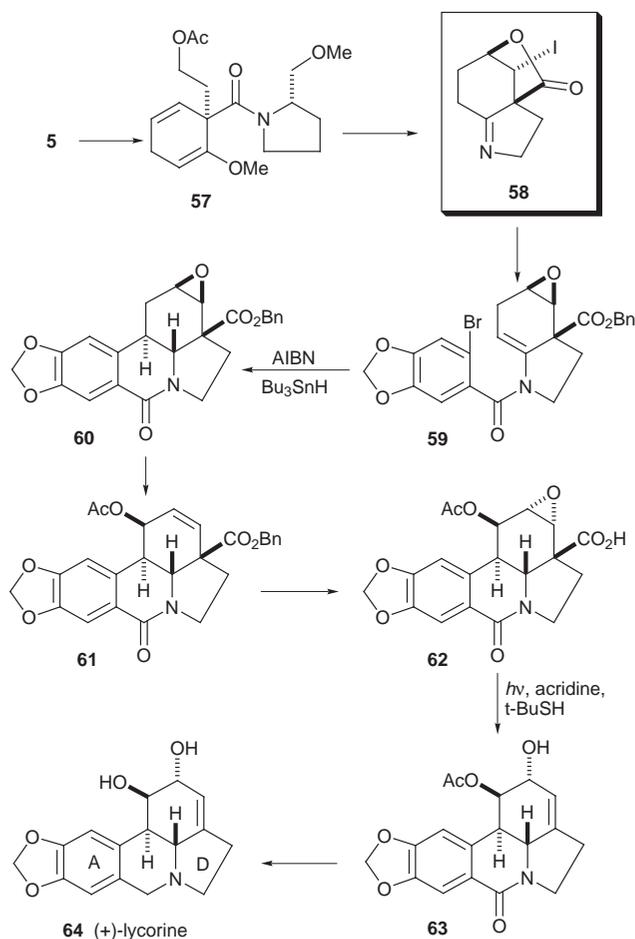
The diastereomerically related keto esters **53** and **55**, activated for removal of the chiral auxiliary, were obtained from **5** and **9**. The requisite nitrogen atom was introduced by an azide displacement of chloride and at an opportune stage of the synthesis an intramolecular aminolysis of the carboxylic ester provided the enantiomerically related keto lactams **54** and **56**. Although shorter routes to these popular synthetic targets have been reported in recent years, the conversion of **9** to (–)-isonitramine (ten steps, 50% overall yield) clearly illustrates the efficiency of the asymmetric Birch reduction–alkylation strategy for construction of the azaspiroundecane ring system.

Lycorine is the most abundant alkaloid in plants of the *Amaryllidaceae*. Several syntheses of racemic lycorine had been reported prior to our initiation of studies directed at an asymmetric synthesis of the unnatural enantiomer **64**.<sup>32</sup> A common theme in all of the syntheses of (±)-lycorine has been the utilization of either an intermolecular or intramolecular Diels–Alder construction of the key C-ring of the alkaloid. This six-membered ring presents a rather formidable synthetic challenge because of the four contiguous stereogenic centers, the *trans* 1,2-diol moiety, and the juxtaposition of the aromatic substituent and the carbon–carbon double bond.

The first asymmetric total synthesis of (+)-lycorine is outlined in Scheme 15. While our earlier applications of the Birch reduction–alkylation of chiral benzamide **5** were focused on target structures with a quaternary stereocenter derived from C(1) of the starting benzoic acid derivative, the synthesis of **64** demonstrates that the method also is applicable to the construction of chiral six-membered rings containing only tertiary and trigonal carbon atoms.<sup>33</sup>

Birch reduction–alkylation of **5** with 2-bromoethyl acetate was carried out with complete facial selectivity to give **57**. This tetrafunctional intermediate was converted to the bicyclic iodolactone **58** (>99% ee) from which the radical cyclization substrate **59** was prepared. The key radical cyclization occurred with complete regio- and facial-selectivity and subsequent stereoselective reduction of the resulting tertiary radical gave **60** with the required *trans* BC ring fusion.<sup>34</sup> The allylic alcohol unit of (+)-lycorine was obtained by a photochemical radical decarboxylation, **62** → **63**.

The eburnamine–vincamine alkaloids found in plants of the dogbane family provided a useful testing ground for application

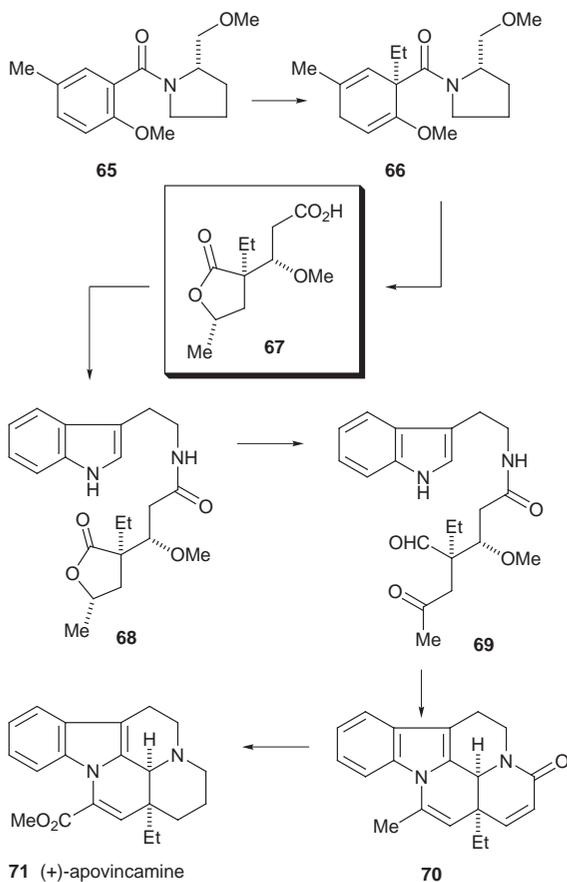


Scheme 15

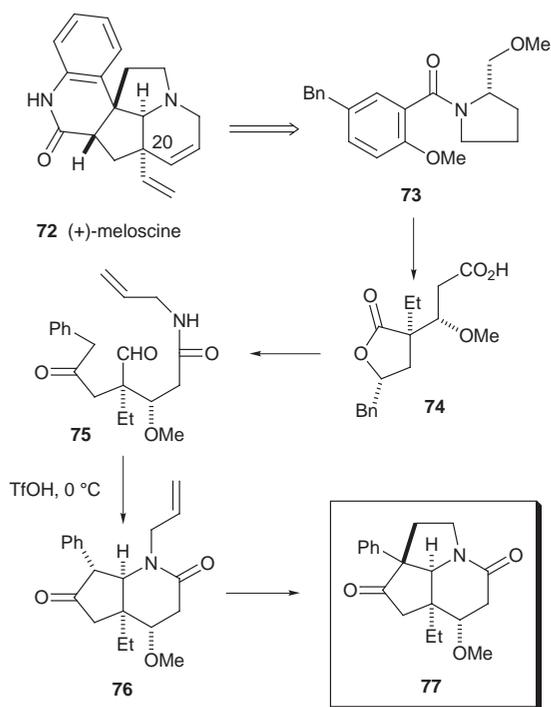
of the butyrolactone synthesis outlined in Scheme 7 to the construction of nitrogen heterocycles (Scheme 16). An asymmetric total synthesis of (+)-apovincamine **71** began with the Birch reduction–ethylation of the chiral 2-methoxy-5-methylbenzamide **65** to give **66** (diastereomer ratio > 100:1).<sup>35</sup> Tryptamine was coupled to the butyrolactone carboxylic acid **67**, and the resulting amide was converted to the keto aldehyde **69**. An acid-catalyzed cyclization of **69** followed by a base-induced elimination of MeOH provided the key *cis*-fused diene lactam **70**, which was converted to (+)-apovincamine **71** by a sequence of steps involving reduction of the ene lactam with LiAlH<sub>4</sub> and oxidation of the methyl substituent by an electrophilic dibromination.

The butyrolactone route to alkaloids was demonstrated again with a synthesis of **77**, the core structure of the *Melodinus* alkaloid (+)-meloscine **72** (Scheme 17).<sup>36</sup> The synthetic strategy features an early incorporation of the aromatic ring in **72** as the 5-benzyl substituent in **73**. The Mannich bicyclization of **75** provides the key *cis*-pyridin-6-one **76**, from which the remaining ring in **77** is assembled by an oxidative cleavage of the *N*-allyl group and acid-catalyzed cyclization of the resulting keto aldehyde. It is expected that (+)-meloscine **72** will be prepared from a derivative of **73** containing a modified 5-benzyl substituent. The asymmetric Birch reduction–alkylation will provide a latent vinyl group to accommodate the substitution at C(20) of **72**.<sup>37</sup>

The versatile cyclohexa-1,4-diene **32a** has served as an intermediate for synthesis of (–)-eburnamonine **81** and the *Aspidosperma* alkaloid (–)-aspidospermidine **84** (Scheme 18).<sup>38</sup> Butyrolactone carboxylic acids **78** and **82** were prepared from **32** by modification of the methodology outlined in Scheme 7. The key Pictet–Spengler-type cyclization of **79** under conditions of kinetic control gave an 18:1 mixture of **80** and its C(3) β-epimer in 93% yield. Subsequent hydroboration



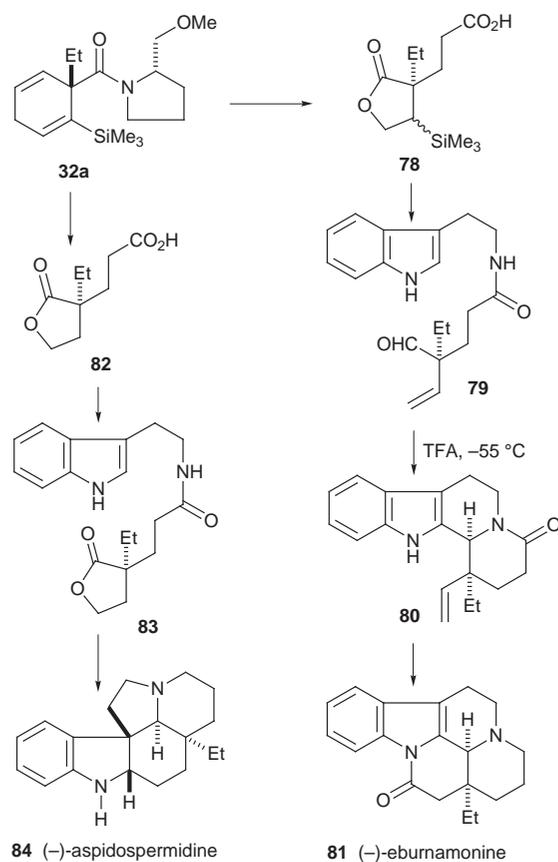
Scheme 16



Scheme 17

of **80** and oxidation of the intermediate primary alcohol gave (–)-eburnamonine **81** in a total of 12 steps from the chiral benzamide **12** (X = SiMe<sub>3</sub>) and 17% overall yield.

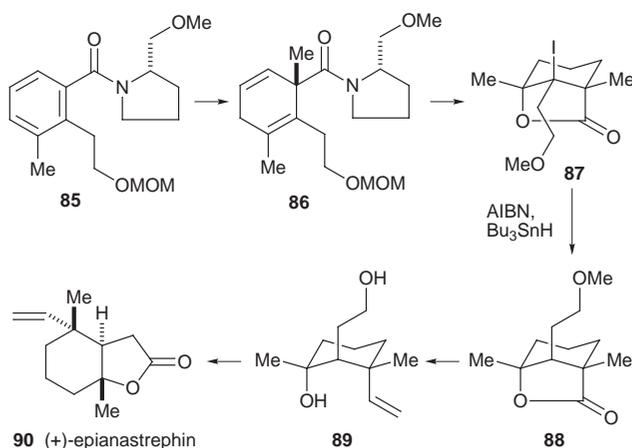
The classical Harley–Mason cyclization was utilized *en route* to (–)-aspidospermidine **84**.<sup>39</sup> The synthesis of **84** required 12 steps from the chiral benzamide **12** (X = SiMe<sub>3</sub>) and was carried out with an overall yield of 19%.



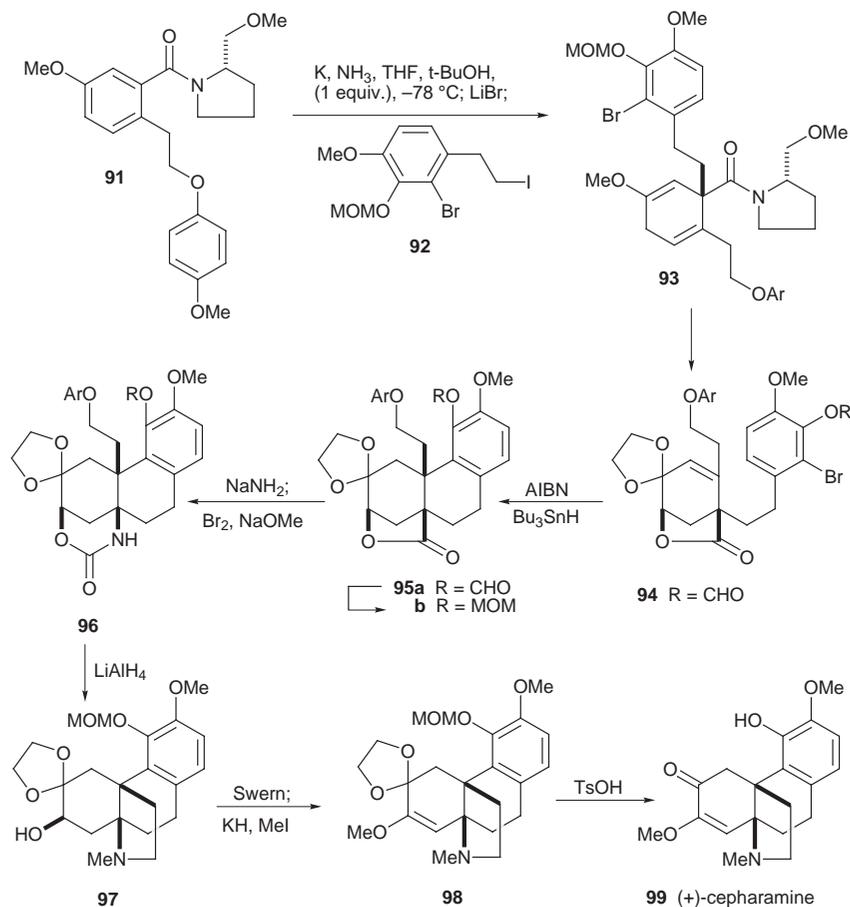
Scheme 18

Birch reduction–methylation of the 2,3-dialkyl substituted benzamide **85** (Scheme 19) provided the cyclohexa-1,4-diene **86** with diastereoselectivity comparable to that observed with the 2-alkylbenzamides illustrated in Scheme 4. Cyclohexadiene **86** was converted to iodolactone **87** and reduction of **87** with Bu<sub>3</sub>SnH occurred with exclusive equatorial delivery of hydrogen to give the axial methoxyethyl derivative **88**. Lactone **88** was converted to the Caribbean fruit fly pheromone (+)-epianastrephin **90** (> 98% ee) in 9.5% overall yield from the chiral benzamide **85**.<sup>40</sup>

The hasubanan alkaloids are of pharmacological interest because of their structural resemblance to the morphine alkaloids.<sup>41</sup> The first asymmetric synthesis of a hasubanan alkaloid, (+)-cepharamine **99**, is shown in Scheme 20.<sup>42</sup> The synthesis is highly convergent as a result of the Birch reduction of **91** and alkylation with **92** to give the cyclohexa-1,4-diene **93** in 95% yield. Conversion of **93** to **94** and radical cyclization of **94** gave the hydrophenanthrene **95a**. An exchange of protecting



Scheme 19

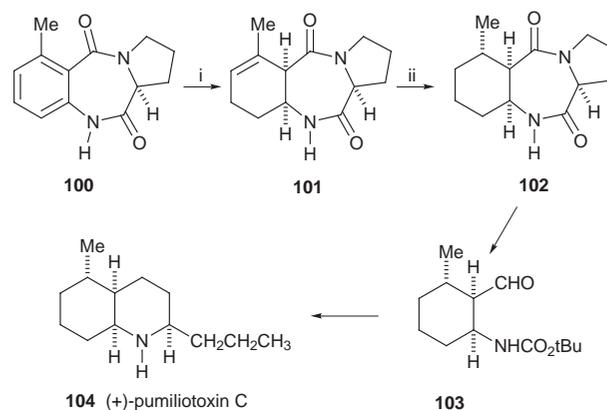


group was followed by a very efficient Hofmann-type rearrangement of **95b** with internal capture of the resulting isocyanate by the neighboring OH group to give the cyclic carbamate **96**. Formation of the *cis*-fused *N*-methylpyrrolidine ring was then carried out in one experimental operation by treatment of **96** with LiAlH<sub>4</sub> in refluxing THF. Swern oxidation of **97** to the corresponding ketone followed by *O*-alkylation of the ketone enolate afforded enol ether **98**. Acid-catalyzed ketal and MOM ether hydrolysis proceeded without disruption of the enol ether to give (+)-cepharamine **99**. The synthesis of **99** required 16 steps from the chiral benzamide **91** and was carried out with an overall yield of 12%.

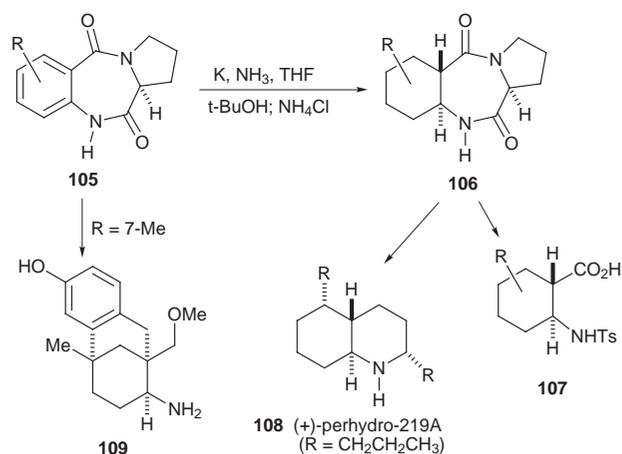
### Applications of pyrrolobenzodiazepine-5,11-diones

The pyrrolobenzodiazepine-5,11-diones **II** have been utilized in asymmetric syntheses of both the *cis*- and *trans*-decahydroquinoline alkaloids (Schemes 21 and 22). For example, reduction of **100** with 4.4 equiv. of potassium in the presence of 2 equiv. of *t*-BuOH, followed by protonation of the resulting enolate with NH<sub>4</sub>Cl at -78 °C gave the *cis*-fused tetrahydrobenzene derivative **101**.<sup>43</sup> Amide-directed hydrogenation of **101** gave the hexahydrobenzene derivative with diastereoselectivity greater than 99:1. Removal of the chiral auxiliary and adjustment of the oxidation state provided aldehyde **103** which was efficiently converted to the poison frog alkaloid (+)-pumiliotoxin C.

Reduction of all three of the double bonds in the pyrrolobenzodiazepine-5,11-dione **105** with excess potassium provides the corresponding *trans* fused hexahydrobenzene derivative **106** in high yield with complete stereochemical control. The preparation of (+)-perhydro-219A **108** from **106** has been reported<sup>13</sup> and a general method of preparation of derivatives of *trans*-2-aminocyclohexanecarboxylic acid (e.g. **107**) has recently appeared.<sup>44</sup>



**Scheme 21** Reagents: i, K (4.4 equiv.), NH<sub>3</sub>, THF, *t*-BuOH (2 equiv.); NH<sub>4</sub>Cl; ii, H<sub>2</sub> [Ir(cod)py(Pcy<sub>3</sub>)]PF<sub>6</sub>



**Scheme 22**

The enolates obtained by reduction of two of the double bonds in **105** undergo completely stereoselective alkylation to give *cis*-fused tetrahydrobenzene derivatives in excellent yield. Structural analogues of the morphine alkaloids have been prepared by way of reduction–alkylation of **105** with *p*-alkoxybenzyl halides; e.g. **109**. One of these analogues has displayed high affinity for the  $\kappa$ -opioid receptor and anti-nociceptive studies have demonstrated that this analogue is a full  $\kappa$ -agonist.<sup>45</sup>

## Conclusions and future considerations

Chiral benzamides **I** and the pyrrolobenzodiazepine-5,11-diones **II** have proven to be effective substrates for asymmetric organic synthesis. Although the scale of reaction in our studies has rarely exceeded the 50 to 60 g range, there is no reason to believe that considerably larger-scale synthesis will be impractical. Applications of the method to more complex aromatic substrates and to the potentially important domain of polymer supported synthesis are currently under study. We also are developing complementary processes that do not depend on a removable chiral auxiliary but rather utilize stereogenic centers from the chiral pool as integral stereodirectors within the substrate for Birch reduction–alkylation.<sup>46</sup>

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