An Asymmetric Route to the Conanine BCDE Ring System. A Formal Total Synthesis of (+)-Conessine

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Abstract: The first enantioselective synthesis of the known (+)-conessine precursor (+)-benzohydrindan **23** from the chiral nonracemic bicyclic lactam **1** is described. The key transformation was the highly diastereoselective (3 + 2) cycloaddition of azomethine ylide **11a** to lactam **7** in order to construct the pyrrolidine E ring system at any early stage in the synthesis. The requisite pyrrolidine methyl group at C-21 was stereoselectively installed late in the synthesis by lithiation of *N*-Boc-pyrrolidine intermediate **20** with *sec*-BuLi/TMEDA followed by quenching at −90 °C with iodomethane, furnishing the tetracyclic pyrrolidine **21**. Reduction of *t*-Boc **21** with lithium aluminum hydride affords (+)-*N*-methyl tetracycle **23** in a concise 13-step synthesis from **1**.

Introduction

Stereoselective pyrrolidine syntheses have attracted the attention of synthetic organic chemists for many years since pyrrolidine rings are found in many alkaloid natural products including (+)-conessine and regholarrhenine A and C which are members of the *Hollarhena* class of Kurchi alkaloids (Figure 1).[1] Isolated from the bark of *Holarhena antidysenterica*, these steroidal alkaloids have been shown to possess significant biological activity.[2] The best known of these steroidal alkaloids is (+)-conessine which has been used in the treatment of dysentery.

Synthetic efforts to reach conessine were quite extensive in the 1960s when Stork,[3] Nagata,[4] and Johnson[5] all reported successful total syntheses of the racemic steroidal alkaloid. Stork,[3] Mukharji,[6a] and Mukherjee[6b] also completed syntheses of the racemic advanced intermediate **B** from accessible steroidal precursors **A**. The transformation of **B** to conessine was also made more attractive by Velluz[7] who demonstrated that the AB ring could be readily obtained in six steps, a significant improvement over earlier routes.[8]

The intended asymmetric route to conessine, *via* the tetracyclic pyrrolidine **B**, appeared to be an attractive one, particularly in view of the lengthy sequence employed earlier.[6,7] Furthermore, the frequent low yielding steps, and the incomplete characterization of **B**,[7] provided the incentive to seek not only a more efficient route but also one in which the appropriate enantiomer of **B** could be acquired.

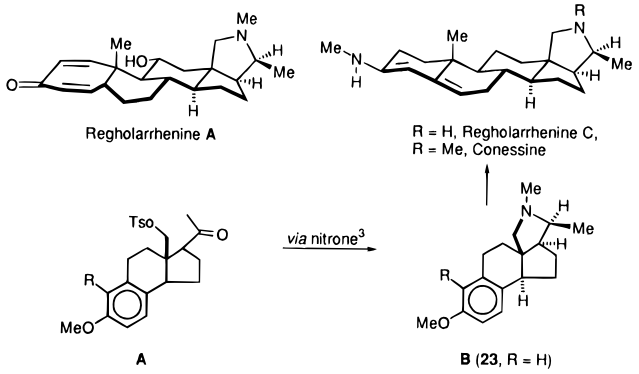

Figure 1.

From previous work dealing with the synthesis of chiral cyclopentenones[9] and 3,4-disubstituted pyrrolidines[10] derived from chiral bicyclic lactams, it was felt that a potentially efficient route to the tetracyclic ring system **B** of (+)-conessine could be accessed. Thus, a synthetic plan was devised (Scheme 1) which would utilize a (3 + 2) azomethine ylide addition to the suitably substituted chiral, nonracemic lactam **7**. The resulting cycloadduct **9** would then be induced to undergo an intramolecular aryllithium addition to the lactam carbonyl, affording the carbinolamine **13**. The latter, upon acidic hydrolysis, should provide the spiro dicarbonyl derivative **14** which would be cyclized, in an aldol manner, to the tetracyclic cyclopentenone **15**. Precedence for this cyclization paradigm was presented in a recent report[9] to generate chiral, nonracemic benzohydrindenones **C**.

Results and Discussion

The synthetic sequence which ultimately led to the enantiopure conanine BCDE system **23** began by initially constructing the requisite chiral bicyclic lactam **7** (Scheme 2). The tethered arylethyl side chain to be affixed to lactam **1** was prepared routinely from commercially available 3-methoxyphenylacetic acid. Reduction to the alcohol **2**, followed by

[⊗] Abstract published in *Advance ACS Abstracts,* October 1, 1996.

(1) Jeger, O.; Prelog, V. In *The Alkaloids: Chemistry and Physiology;* Manske, R. H. F., Ed.; Academic Press: New York, 1960; Vol. VII, p 319.

(2) (a) Siddiqui, B. S.; Usmani, S. B.; Begum, S.; Siddiqui, S.; Aftab, K.; Gilani, A. *Heterocycles* **1995**, *41*, 267 and references cited within. (b) Bhutani, K. K.; Ali, M.; Sharma, S. R.; Vaid, R. M.; Gupta, D. K. *Phytochemistry* **1988**, *27*, 925. (c) Bhutani, K. K.; Vaid, R. M.; Ali, M.; Kapoor, R.; Soodan, S. R.; Kumar, D. *Phytochemistry* 1**990**, *27*, 925.

(3) Stork, G.; Darling, S. D.; Harrison, I. T.; Wharton, P. S. *J. Am Chem Soc.* **1962**, *84*, 2018.

(4) Nagata, W.; Terasawa, T.; Aoki, T. *Tetrahedron Lett.* **1963**, 869.

(5) Marshall, J. A.; Johnson, W. S. *J. Am. Chem. Soc.* **1962**, *84*, 1484.

(6) (a) Mukharji, P. C.; Sircar, J. C.; Devasthale, V. V. *Indian J. Chem.* **1971**, *9*, 515. (b) Mukherjee, M.; Mukherjee, L. M. *Indian J. Chem.* **1980**, *19B*, 185. (c) Mukherjee, M.; Mukherjee, L. M. *Indian J. Chem.* **1981**, *20B*, 1019.

(7) Velluz, L.; Mathieu, G.; Monine, G. *Tetrahedron Suppl.* **1966**, *8*, 495.

(8) Stork, G.; Loewenthal, H. J. E.; Mukharji, P. C. *J. Am. Chem. Soc.* **1956**, *78*, 501.

(9) Snyder, L.; Meyers, A. I. *J. Org. Chem.* **1993**, *58*, 7507.

(10) (a) Fray, A. H.; Meyers, A. I. *Tetrahedron Lett.* **1992**, *33*, 3575. (b) Fray, A. H.; Meyers, A. I.; *J. Org. Chem.* **1996**, *61*, 3362.

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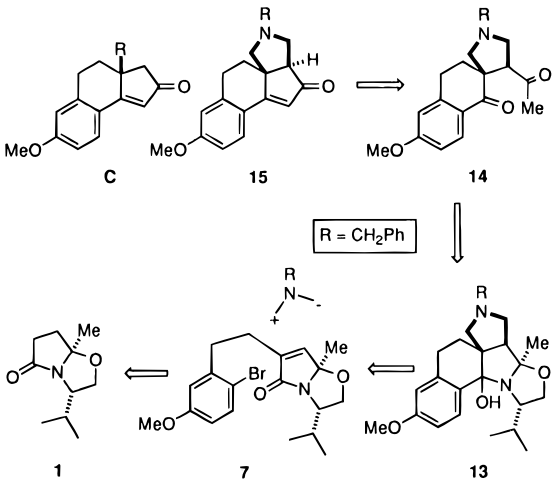
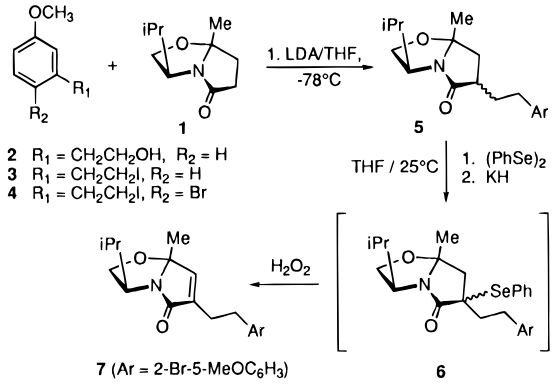
Scheme 1. Retrosynthetic Route to the Conanine BCDE Ring System



Scheme 2



transformation to the iodide **3** with triphenylphosphine and iodine,[11] gave the necessary precursor for aromatic bromination. The latter took place using bromine in CH_2Cl_2 at −10 °C and produced the aryl bromide **4** in 95% yield.

The alkylation of the bicyclic lactam **1**[12] was performed using LDA at −78 °C to form the enolate which was treated with the aryl iodide **4**, affording the monoalkylated lactam **5** in 92% yield as a 2:1 mixture of diastereomers. In order to achieve this yield, it was necessary to utilize 2.0 equiv of LDA and 3.0 equiv of the aryl iodide. Interestingly, no double alkylation occurred with the use of excessive base and electrophile. Presumably this was the result of steric crowding about the tertiary proton as well as a slower rate of electrophilic alkylation.

Introduction of the unsaturated linkage into **5** was performed using either of the following two methods. Initially the use of $KN(SiMe_3)_2$[9,13,14] to generate the enolate of **5** at −78 °C followed by diphenyl diselenide to give **6** was investigated. Oxidation of the latter with hydrogen peroxide gave the unsaturated lactam **7** in 72% yield. It was noted during the course of optimizing the selenylation−oxidation sequence that KH (2.0 equiv) also efficiently generated the enolate and after selenylation−oxidation produced the unsaturated lactam in 75% yield. The use of KH in place of $KN(SiMe_3)_2$ was somewhat fortunate since the cost of the latter base is exceedingly high.

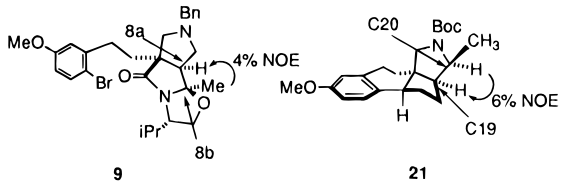
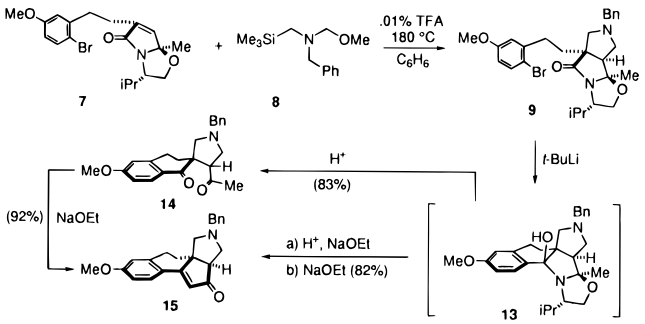


Figure 2.

Scheme 3



With the unsaturated chiral lactam **7** in hand, the azomethine ylide cycloaddition was next investigated. Treatment of **7** with the known[15−17] azomethine precursor **8** under a variety of acid-catalyzed and pressurized conditions ultimately gave the cycloadduct **9** in 86−90% yield and as a 15:1 mixture of *anti*−*syn* products (Scheme 3).

The need for high pressure to induce the cycloaddition of **8** to **7** is not without precedent. High pressures[18] have proven effective in 1,3-dipolar cycloaddition reactions of azides,[19] nitrones,[20] nitronates,[21] and diazomethane.[22] Therefore, it seemed reasonable that the (3 + 2) cycloaddition might be achieved under conditions of higher pressure and temperature. Accordingly, the crucial (3 + 2) cycloaddition was first achieved in reasonable yield (50−60%) under conditions of medium pressure by combining unsaturated lactam **7**, azomethine ylide precursor **8**, and catalytic trifluoroacetic acid (10−30 mol %) in benzene in a sealed Ace pressure tube at 240 °C.[23] In this manner, (3 + 2) cycloaddition occurs, affording pyrrolidine **9** as a 15:1 ratio of diastereomers, and separation of these diastereomers was readily accomplished by flash chromatography.[24] The major cycloadduct is assigned so the pyrrolidine ring exhibits β face fusion based on a 4% NOE enhancement (*anti* product, Figure 2) between angular methyl 8b (1.52 ppm) and the 8a methine hydrogen resonance (2.49 ppm). In addition, the ^{13}C NMR chemical shift of the angular methyl group at 8b (28.2 ppm) further suggests that the major cycloadduct has the

(11) Collins, D. J.; Fallon, G. D.; Skene, C. E. *Aust. J. Chem.* **1992**, *45*, 71.

(12) Bicyclic lactam **1** was derived from (*S*)-valinol and levulinic acid and is commercially available from Ultrafine Chemicals, Manchester, U.K.

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(14) Williams, R. M.; Im, M. N. *J. Am. Chem. Soc.* **1991**, *113*, 9276.

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(17) Vedejs, E.; Martinez, G. R. *J. Am. Chem. Soc.* **1979**, *101*, 6453.

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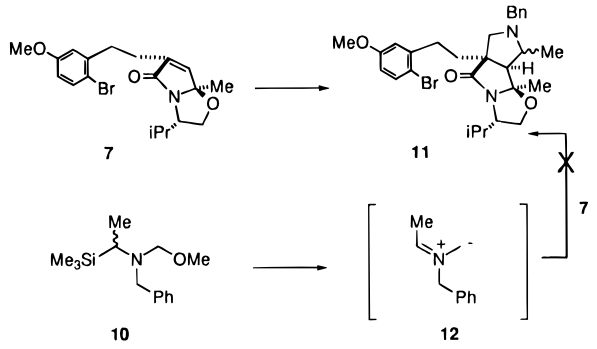
(22) Desuray, H.; Weiler, J. *Tetrahedron Lett.* **1974**, 2209.

(23) Vapor pressures of benzene at selected temperatures: 10 atm (178.8 °C), 20 atm (221.5 °C), and 40 atm (272.3 °C) *CRC Handbook of Chemistry and Physics*, 56th ed.; Weast, R. C., Ed.; CRC Press: Cleveland, OH, 1976; p 6.

(24) The ratio of diastereomers was determined by integration of pertinent resonances corresponding to *anti* and *syn* isomers.

Scheme 4



pyrrolidine forming *anti* to the angular methyl group.[25] Also, the ^{13}C NMR chemical shift of the angular methyl group 8b (21.2 ppm) in the minor isomer is consistent with its being *syn* to the pyrrolidine ring.[25]

Since the (3 + 2) cycloaddition was found to proceed with "truly catalytic" amounts of TFA,[26] it was thought that the protonated pyrrolidine in the product might serve as the active catalyst for this reaction. In order to test this hypothesis, a solution of unsaturated lactam **7**, dipole precursor **8**, and protonated pyrrolidine **9** (1%) as a TFA salt were combined in a sealed tube. Under these conditions a rate acceleration to 6 h was observed as compared to 24 h in the absence of protonated product.[27] Optimized conditions utilized a benzene or benzene−chloroform solvent containing 0.01 mol % trifluoroacetic acid and 2.0 equiv of **8**. The mixture was then heated to 180−190 °C in a glass (Ace) pressure vessel for 6 h.

Due to the successful construction of the E ring system in **9** by (3 + 2) cycloaddition, the possibility to stereoselectively install the C21 methyl group in conessine by use of a methyl-substituted azomethine ylide, **12**, was considered (Scheme 4). Accordingly, the procedure of Padwa[15] was used to construct dipole precursor **10** in a manner analogous to the synthesis of **8**. However, it has been observed by Padwa[15] that reactions of azomethine ylide **12** with unsymmetrical dipolarophiles afford products with regiochemistry resulting from attachment of the less substituted carbon terminus of the azomethine ylide to the least substituted terminus of the dipolarophile. Thus, if this precedent held, the (3 + 2) cycloaddition of **10** to unsaturated lactam **7** would proceed with the wrong regiochemistry. Nevertheless, it was hoped that the phenethyl side chain present in **7** might direct the regiochemistry to the desired regioisomer. Unfortunately, under optimal conditions for the synthesis of **9** as well as using a variety of Lewis acids, decomposition of the parent azomethine ylide was the only event observed. At this stage it was decided to postpone installation of the C21 methyl group until later in the synthesis.

The C ring of (+)-conessine was next constructed by addition of excess *t*-BuLi (2 equiv) to a THF solution of pyrrolidine cycloadduct **9** over KH. The expected metal−halogen exchange rapidly occurred, providing a transient alkyllithium species that spontaneously cyclized to carbinolamine **13**. Without further manipulation, the carbinolamine was directly hydrolyzed as previously described.[9] It was found that direct hydrolysis of the THF solution containing carbinolamine using excess tetrabutylammonium dihydrogen phosphate buffer led to poor yields of spirodiketone **14**. However, when the crude reaction mixture containing carbinolamine **13** was diluted with an equal volume of CH_2Cl_2 and then treated with excess phosphate buffer solution[28] (15−30 equiv), good yields of spirodiketone **14** were obtained after refluxing the biphasic mixture for 24−48 h.[29] Spirodiketone **14** did not spontaneously cyclize to form benzohydrindenone **15**, but upon treatment with sodium ethoxide in ethanol, cyclization readily occurs to afford **15**, thereby completing construction of the conanine BCDE ring system. Additionally, it was found to be expedient to convert pyrrolidine **9** to benzohydrindenone **15** in two pots without intervening purification. By this approach, crude spirodiketone **14** was submitted directly to base-catalyzed aldol conditions to afford benzohydrindenone **15** in 82% yield for the three-step sequence from pyrrolidine **9**.

To reach the intended tetracycle **23**, it was necessary to reduce the enone **15** in a 1,2 or 1,4 manner with appropriate stereochemical control. The tetracyclic enone **15** was found to be resistant to a variety of reducing conditions including highly reactive magnesium[30] or zinc metals.[31ab] In addition, attempts to reduce **15** with $NaBH_4$ gave only starting material.

A number of homoannular enones have been efficiently deoxygenated to the corresponding olefins with $AlCl_3$ and $LiAlH_4$. Accordingly, when **15** was charged into a mixture of $AlCl_3/LiAlH_4$, deoxygenation readily occurred without double bond migration to afford **16** as a crystalline solid in 92% yield (Scheme 5).

The next requirement toward the synthesis of **23** was α addition of hydrogen to saturate the olefin at C14. It was anticipated that hydrogenation of **16** would occur from the α face on the basis of well-documented reductions in systems analogous to 13β-substituted-$\Delta^{14,15}$-steroids.[7a,8,33] The hydrogenation of **16** was attempted in the presence of $PdCl_2$ in ethanol, which after a few hours, produced a 3:1 mixture of **20** and *epi*-**20** (R = H). ^1H NMR examination was unable to distinguish whether the major product was a result of α or β addition. An X-ray structure of one of the isolated epimers would be necessary to clarify this point; however, this mixture of amines proved to be inseparable by standard chromatography techniques. The mixture was then carried on to the next step with the hope of later evaluating the stereochemical outcome of the C14-hydrogenation. Treatment of the mixture of amines in **20** (R = H) with Boc-ON and KH resulted in rapid formation

(25) This gamma gauche (γg) substituent effect is greatest in conformationally rigid systems whenever two protons bearing carbons are at dihedral angles of 60° or less. See: Wehrli, F. W.; Wirthlin, T. *Interpretation of Carbon-13 NMR Spectra*; Heydon & Son, Ltd: Chichester, U.K., pp 27−28, 37. For bicyclic lactams, with few exceptions, the chemical shift for the angular methyl group in the *anti* isomers **9** (27−29 ppm) is considerably downfield from that of the *syn* isomers (19−23 ppm).

(26) Complete decomposition of unsaturated lactam **7** occurs upon use of $BF_3{\cdot}OEt_2$ and $TiCl_4$ at higher temperatures than 0 °C.

(27) In a separate experiment 1 mol % pyrrolidine **9** was added to a solution of dipole precursor **8** and unsaturated lactam **7** followed by trace TFA (~0.01%). After heating, the (3 + 2) cycloaddition proceeded to completion within 6 h at 190 °C.

(28) Owing to the high cost of 1 M tetrabutylammonium dihydrogen phosphate buffer solution ($90 for 500 mL of 1 M solution, Aldrich), a buffer recovery protocol was implemented. Upon completion of hydrolysis of carbinolamine **13**, the biphasic mixture was allowed to separate and the aqueous phase was saved and reused 3−4 times in subsequent syntheses to afford **15** in better than 80% yield each time.

(29) In some instances ^1H NMR of the crude spirodiketone **14** revealed considerable quantities of unhydrolyzed carbinolamine **13**. In these cases the crude material was redissolved in CH_2Cl_2 and treated with fresh phosphate buffer solution and hydrolysis continued at reflux temperatures until complete consumption of carbinolamine was observed.

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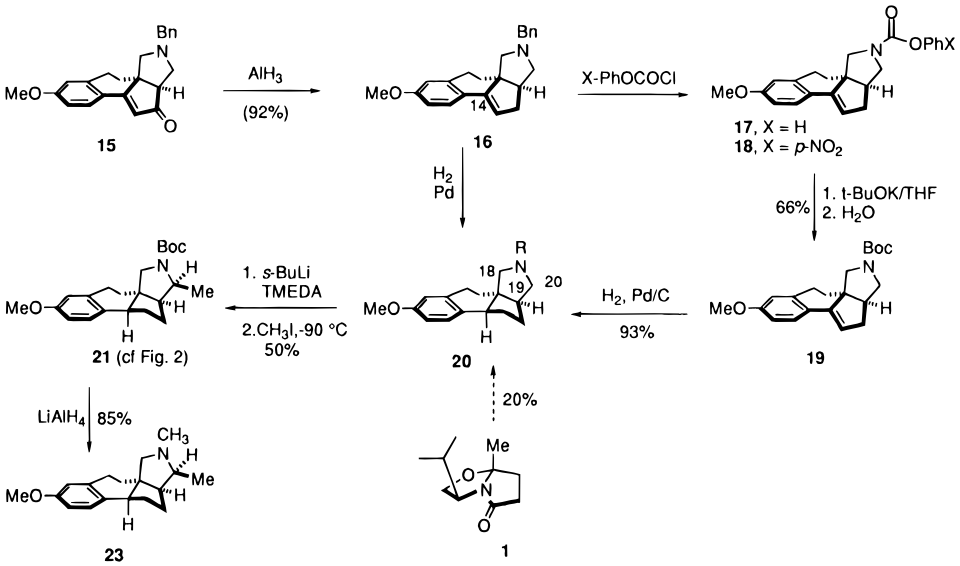
(33) (a) Platner, P. A.; Ruzicka, L.; Heuser, H.; Angliker, E. *Helv. Chim. Acta* **1947**, *30*, 395. (b) Banerjee, D. K.; Chatterjee, S.; Pillai, C. N.; Bhatt, M. V. *J. Am. Chem. Soc.* **1956**, *78*, 3769.

Scheme 5



of *tert*-butyl carbamate **20** (R = Boc), also as a 3:1 ratio of epimers, but separable. The configuration of the minor isomer of *N*-Boc-pyrrolidine **20** (R = Boc) was determined by X-ray crystallography to have *S*-configuration (α-H) at C14; thus, the required epimer **20** was unfortunately the minor product from the reduction. Apparently, hydrogenolysis of the *N*-benzyl group in **16** occurred before C=C hydrogenation, which allowed competitive hydrogenation from the β face. Consequently, it was necessary to devise an alternative route to **20** that would provide predominantly α addition of hydrogen at C14.

It was decided to replace the *N*-benzyl group of **16** with a bulky group that would remain intact under the usual hydrogenolytic conditions. In this regard, replacement of the *N*-benzyl group with a carbamate could possibly serve two purposes: (a) direct the hydrogenation at C14 from the α face; (b) serve as an activating group for stereoselective carbanionic installation of the C21 methyl group to reach the final product **23**. It was, therefore, anticipated that *N*-Boc-pyrrolidine **19** could be ideally suited for these purposes.

In order to form **19**, it was necessary to convert the *N*-benzylolefin **16** into a phenyl carbamate which might eject the phenoxy group with *tert*-butoxide in direct analogy to the method described by Comins.[34] Accordingly, the *N*-benzyl derivative **16** was heated with phenyl chloroformate (X = H), furnishing the phenyl carbamate **17**. However, when KH was added to a solution of **17** in refluxing *tert*-butyl alcohol, cleavage of the phenyl carbamate group occurred without *tert*-butoxide incorporation, producing only the free NH derivative. After azeotropic removal of *t*-BuOH the residue was treated with Boc-ON in ethanol, furnishing the desired *N*-Boc-olefin **19** in low yield (30%). Exposure of *N*-Boc-olefin **19** to an atmosphere of H_2 over activated palladium on carbon afforded, exclusively, the desired benzhydrindan **20**[35] in near quantitative yield as a result of hydrogen delivery to the less hindered α face. The *S* (α-H) configuration at C14 was compared to the X-ray data taken earlier, and both showed identical stereochemistry.

After confirmation of the correct stereochemistry in the hydrogenation of *N*-Boc-pyrrolidine **20**, improvements in the sequence from benzohydrindene **16** were sought since the three-step yield from **16** to **20** was only 30%. It was believed that use of a more reactive phenyl carbamate might allow for direct displacement of phenoxide with *tert*-butoxide as originally observed by Comins.[34] To this end, **16** was treated with *p*-nitrophenyl chloroformate and immediately formed phenyl carbamate **18** (X = NO_2). Addition of the crude carbamate to a mixture of stirring *t*-BuOK (5 equiv) in THF followed by the immediate addition of 1.0 equiv of H_2O provided clean displacement of *p*-nitrophenol and incorporation of *tert*-butoxide, furnishing *N*-Boc-pyrrolidine **19** in 66% yield. In summary, at this stage, the benzohydrindan **20** was prepared in 65% yield by a three-pot process from the *N*-benzylpyrrolidine **16** with purification necessary only for the final product. This procedure also precluded the use of the Boc-ON reagent. It is noteworthy that **20** (R = Boc) was prepared in 20% overall yield from commercially available **1**.

The last major hurdle in this synthesis was the stereoselective introduction of the C21 methyl group which is present in (+)-conessine and related systems. It is known that simple achiral *N*-Boc-pyrrolidines may be metalated α to nitrogen with *sec*-BuLi/TMEDA and then alkylated with electrophiles to form substituted pyrrolidines.[36] In addition, Beak has demonstrated that highly enantioselective alkylations[37] can be achieved for simple achiral *N*-Boc-pyrrolidines utilizing (−)-sparteine in place of TMEDA.

Due to the chiral nonracemic nature of the pyrrolidine **20** (R = Boc), it was felt that a diastereoselective alkylation at C20 might be achieved without any additional chiral components in the reaction mixture. It was further anticipated that competitive alkylation at C18 to afford the undesired regioisomer would be inhibited by hindrance imposed by the adjacent neopentyl center. Therefore, it was decided to attempt alkylation of *N*-Boc-pyrrolidine **20** using Beak's optimized conditions[36] for alkylation of simple *N*-Boc-pyrrolidines. Accordingly, a solution of *N*-Boc-pyrrolidine **20** in ether was treated with an equimolar amount of TMEDA followed by *sec*-BuLi at −78 °C. The solution was then treated with excess dimethyl sulfate and warmed to room temperature. The ^{1}H-NMR spectrum of the

(34) Comins, D. L.; Weglarz, M. A.; O'Conner, S. *Tetrahedron Lett.* **1988**, *29*, 1751.

(35) Although ^{1}H NMR for **20** showed complete disappearance of the vinyl proton resonance (5.70 ppm) present in the precursor **19**, the *N*-Boc-pyrrolidine was found to exist as a mixture of two rotamers at 25 °C. Collection of spectroscopic data at 55 °C resulted in partial resolution, but it was necessary to record the spectrum of **20** in toluene-d_8 at 100 °C to effect complete resolution of signals.

(36) (a) Beak, P.; Lee, W. K. *J. Org. Chem.* **1990**, *55*, 2578. (b) Beak, P.; Lee, W. K. *J. Org. Chem.* **1990**, *55*, 2578.

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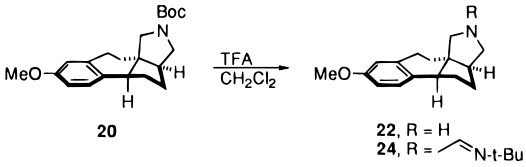
Scheme 6



20 **22**, R = H; **24**, R = N-t-Bu

crude product revealed what appeared to be an impure mixture of **21** in a 1:1 ratio of inseparable methylated diastereomers, along with starting material. Attempts to improve the ratio of methylated products by keeping the alkylation temperature below −70 °C gave only starting material. Thus, no alkylation occurred at low temperature. In fact, no alkylation of lithiated **20** took place below −25 °C, and when it did occur, the selectivity of methyl insertion was ∼1:1. It was also determined, *via* deuteration with methanol-d_1 that metalation of **20** had completely taken place (>95% D) after 8 h at −78 °C; thus, no concern was registered about the lithio anion being present during the alkylation.

With the initial attempts at deprotonation of the *N*-Boc system **20** proving to be disappointing, the formamidine group was considered to be a viable alternative. It has been shown on numerous occasions that α-aminocarbanions are readily produced when treated with organolithium reagents in the presence of chiral or achiral formamidines. Thus, the *N*-Boc and formamidine groups both activate the α-proton of an amino group but on several occasions lead to stereo- and regiochemically different results.[38d−f] Furthermore, the configurational stability of the α-lithioformamidines was found to be somewhat greater than the Boc counterparts[39] which may also play a role in the stereoselective approach to **23**. The *N*-Boc-pyrrolidine **20** was transformed into its free amine **22** using TFA−CH_2Cl_2 and then treated with *N*,*N*-dimethyl-*N*′-*tert*-butylformamidine to form the formamidine **24** in 46% unoptimized yield (Scheme 6). When the latter was metalated in THF using *sec*-BuLi−TMEDA at −78 °C, the deep red anion appeared and was alkylated with dimethyl sulfate. Workup revealed that the crude product was once again a 1:1 mixture of methyl diastereomers. This was confirmed by removing the formamidine and comparing the spectral data with the NH pyrrolidine **22** generated from the *N*-Boc analog **21**. The use of methyl iodide, in place of dimethyl sulfate, showed no change in selectivity in the methylation process although the reaction was significantly more rapid at lower temperatures. In view of the enhanced reaction rate using methyl iodide, it was felt that, by reassessing the metalation of the *N*-Boc **20** (R = Boc) and maintaining a lower alkylation temperature, a possible improvement in the stereoalkylation step may arise. In fact, this proved to be the case as the *N*-Boc **20** was metalated with *sec*-BuLi−TMEDA in ether at −90 °C and at this temperature treated with methyl iodide. The monomethyl product **21** was obtained in 50% yield as a 15:1 ratio of diastereomers. Also, a 25% yield of starting pyrrolidine **20** (R = Boc) was recovered.

The ^{1}H NMR of the major diastereomer of **21** revealed a downfield methine resonance (3.93 ppm) with a coupling constant of 6.3 Hz to the newly installed C21 methyl group (1.30 ppm) and a 6.0 Hz coupling constant with the C19 bridgehead methine (2.20 ppm). Therefore, these coupling data confirm the regiochemistry of addition at C20 and also suggest a *syn* relationship of the two methine protons at C19 and C20. For further confirmation of the stereochemistry, a 6% NOE enhancement was observed between the methine protons at C19 and C20.[40] Thus, taken together these data support the assigment of C20 in **21** as having the appropriate *S*-configuration as shown in Figure 2. It is also important to recall that the desmethyl derivative **20** (R = Boc) was assigned its structure by X-ray crystal data. Presently, it is not certain why the C20 methyl entered the β face of pyrrolidine **20**, and the reasons must await further study. However, Beak has proposed[37] on simple, monocyclic *N*-Boc-pyrrolidines that metalation and alkylation proceeds with retention. Others have proposed similar behavior[41] as well as alkylation with inversion,[42] but no hard evidence yet exists. Inspection of the X-ray structure of **20** (R = Boc) shows that either hydrogen at C20 is roughly equal with regard to accessibility to the base. Yet, the directing influence in this instance may be a consequence of the eclipsing C19 bridgehead methine which may render the α proton at C20 kinetically less accessible. It is also possible that deprotonation of the α H occurs and the β stereochemistry of the methyl product is a consequence of an inversion mechanism.[43]

Proceeding to the final target, treatment of methylpyrrolidine **21** with TFA/CH_2Cl_2 gave the corresponding NH compound in good yield (88%). This material was submitted to Eschweiler−Clarke methylation conditions to afford *N*-methylpyrrolidine **23** in 50% yield. Recrystallization produced a white crystalline solid (mp 87−8 °C),[44] with $[\alpha]_D$ +51°. The spectral data exhibited the presence of a new methyl group (2.10 ppm (^{1}H NMR), 41.0 ppm (^{13}C NMR)) consistent with N-methylation. Due to the low yield of the Eschweiler−Clarke methylation an alternate route was sought. Fortunately, it was found that reduction of **21** with $LiAlH_4$[45] cleanly furnished the desired system **23** in 85% yield.

In summary, a 13-step asymmetric synthesis of benzohydrindan **23** is described from the chiral nonracemic bicyclic lactam **1**. Significantly, the interesting pyrrolidine E ring was formed *via* an azomethine ylide cycloaddition to unsaturated lactam **7** at an early stage of the synthesis. Stereoselective introduction of the methyl group in ring E was accomplished late in the synthesis, and this intermediate was found to correspond to benzohydrindan **23**, reported earlier.[6]

Experimental Section

3-Methoxyphenethyl iodide, 3. To a 0 °C solution of triphenylphosphine (37.8 g, 144 mmol) and imidazole (9.82 g , 144 mmol) in CH_2Cl_2 (250 mL) was added iodine (36.70 g, 144.6 mmol) portionwise to form a turbid orange solution. The phenethyl alcohol **2**[46] (18.3 g, 120 mmol) over anhydrous sodium sulfate was then cannulated into the above suspension over 5 min, and the reaction was allowed to gradually warm to room temperature over 3 h while being stirred. TLC analysis revealed complete consumption of starting alcohol, and the

(38) (a) Meyers, A. I. *Aldrichim. Acta.* **1985**, *18*, 59. (b) Meyers, A. I.; Edwards, P. B.; Rieker, W. F.; Bailey, T. R. *J. Am. Chem. Soc.* **1984**, *106*, 3270. (c) Edwards, P. B.; Meyers, A. I. *Tetrahedron Lett.* **1984**, *25*, 939. (d) Meyers, A. I.; Milot, G. *J. Am. Chem. Soc.* **1993**, *115*, 6652. (e) Meyers, A. I.; Milot, G. *J. Org. Chem.* **1993**, *58*, 6538. (f) Meyers, A. I.; Nguyen, T. H. *Tetrahedron Lett.* **1995**, *36*, 5873.

(39) Meyers, A. I.; Elworthy, T. *Tetrahedron* **1994**, 6089.

(40) Irradiation of the C20 methine shows a 3% NOE with the C21 methyl group. In addition, irradiation of the C21 methyl group shows a 3% NOE with the C20 methine and does not show any detectable NOE with the C19 bridgehead methine.

(41) (a) Hoppe, D.; Paetow, M.; Hintze, F. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 394. (b) Pearson, W. H.; Lindbeck, A. C.; Kampf, J. W. *J. Am. Chem. Soc.* **1993**, *115*, 2622. (c) Chong, J. M.; Park, S. B. *J. Org. Chem.* **1992**, *57*, 2220. (d) Gawley, R. E.; Zhang, Q. *J. Am. Chem. Soc.* **1993**, *115*, 7515.

(42) (a) Gawley, R. E.; Zhang, Q. *J. Org. Chem.* **1995**, *60*, 5767. (b) Meyers, A. I.; Dickman, D. A. *J. Am. Chem. Soc.* **1987**, *109*, 1263.

(43) We have recently studied the metalation−alkylation of **20** in greater detail and found, using D-isotope effects, that both steps proceed with retention (Kopach, M. E., Meyers, A. I. *J. Org. Chem.*, in press).

(44) The melting point for (+)-benzohydrindan **23** was slightly higher than the literature value for (±)-**23** (lit.[6a,c] mp 82 °C).

(45) Maryanoff, B.; Almond, H. *J. Org. Chem.* **1986**, *51*, 3295.

(46) Kanth, J. V. B.; Periasamy, M. *J. Org. Chem.* **1991**, *56*, 5964.

light orange suspension was then washed with saturated sodium bisulfite solution (2 × 250 mL). The resulting light yellow solution was then dried over anhydrous magnesium sulfate and concentrated to afford a light yellow residue which was applied to a silica gel column presaturated with 1:10 CH_2Cl_2/hexanes. After elution with the same solvent ratio, the resulting product fractions were then concentrated to afford 30.5 g (96.7%) of **3** as a pale yellow oil:[11] R_f = 0.59 (1:1:1 Et_2O/CH_2Cl_2/hexanes); ^{1}H NMR δ 7.22 (t, J = 7.9 Hz, 1 H), 6.77 (m, 3 H), 3.79 (s, 3 H), 3.33 (t, J = 7.7 Hz, 2 H), 3.04 (t, J = 7.7 Hz, 1 H); ^{13}C NMR δ 159.7 (C), 142.1 (C), 129.6 (CH), 120.6 (CH), 114.1 (CH), 112.1 (CH), 55.2 (CH_3), 40.4 (CH_2), 5.30 (CH_2).

2-Bromo-5-methoxyphenethyl iodide, 4. A solution of Br_2 (6.3 mL, 122.5 mmol) in CH_2Cl_2 (125 mL) was added dropwise to a solution of phenethyl iodide **3**[45] (30.5 g, 122 mmol) in CH_2Cl_2 (150 mL) at −10 °C over 2 h. The reaction mixture was then treated with a solution of saturated sodium bisulfite (200 mL), and the biphasic mixture was stirred for 15 min until the dark red color discharged. The mixture was then diluted with saturated $NaHCO_3$ (150 mL) and extracted with CH_2Cl_2 (3 × 250 mL). The combined extracts were dried over anhydrous $MgSO_4$ and concentrated to afford **4** as a pale yellow syrup (37.5 g (95%)) which was passed through basic alumina prior to use: R_f = 0.69 (1:1:1 Et_2O/CH_2Cl_2/hexanes); ^{1}H NMR δ 7.40 (t, J = 8.8 Hz, 1 H), 6.78 (d, J = 3.0 Hz, 1 H), 6.68 (dd, J = 3.0, 8.8 Hz, 1 H), 3.78 (s, 3H), 3.33 (m, 2H) 3.24 (m, 2H); ^{13}C NMR δ 159.0 (C), 140.7 (C), 133.5 (CH), 116.4 (CH), 114.4 (C), 114.2 (CH), 55.5 (CH_3), 40.8 (CH_2), 3.10 (CH_2).

Monoalkylated Lactam 5. Monoalkylation of lactam **1** was performed according to the previous method.[9] A 2.50 M solution of *n*-BuLi in hexanes (10.9 mL, 27.2 mmol) was added dropwise to diisopropylamine (2.89 g, 3.75 mL, 28.6 mmol) at −10 °C to form a thick syrup which was diluted with THF (100 mL) and cooled to −78 °C. A solution of bicyclic lactam **1** (2.49 g, 13.5 mmol) in THF (10.0 mL) was added dropwise to the LDA solution followed by a THF (5.0 mL) rinse. After 2 h at −78 °C, stirring was stopped, neat aryl iodide **4** (13.8 g, 40.5 mmol) was rapidly charged into the reaction mixture, the resulting yellow mixture was warmed immediately to 0 °C, and stirring was resumed. After an additional 6 h of stirring at 0 °C, the reaction mixture was quenched with saturated NH_4Cl (10 mL) and diluted with Et_2O (200 mL). The organic phase was separated and washed with saturated $NaHCO_3$ (2 × 150 mL), dried ($MgSO_4$), and concentrated. This was applied to a silica gel column presaturated with 1:1 CH_2Cl_2/hexanes and was eluted with the same until the less polar component (2-bromo-5-methoxystyrene) emerged. The column was then eluted with 1:1 EtOAc/hexanes to afford 4.95 g (92%) of **5** as a 2:1 ratio of diastereomers. This mixture of diastereomers was used directly in the next synthetic step. Data for **5**: GC/MS *m/z* (abundance) 397.3 (M^+ + 1), 396.3 (M^+); HRMS calcd for $C_{19}H_{26}NO_3Br$ (M^+ + 1) 396.1174, found 396.1160.

Unsaturated Bicyclic Lactam 7. To a solution of bicyclic lactam **5** (1.90 g, 4.79 mmol) and diphenyl diselenide (1.69 g, 5.41 mmol) at 25 °C in THF (50 mL) was added KH (394 mg, 9.82 mmol) portionwise over 1 h, causing mild effervescence. After 1.5 h TLC showed complete consumption of starting material and formation of higher R_f selenylated intermediates **6**. The mixture was quenched with saturated NH_4Cl (2 mL) and diluted with CH_2Cl_2 (40 mL). The flask was fitted with a reflux condenser, cold 30% H_2O_2 (30 mL, 294 mmol) was quickly added, and the biphasic mixture was stirred at rt for 12 h *(CAUTION: upon addition of H_2O_2 an exotherm occurs which maintains reflux temperature for ∼3 h).*[47] The mixture was diluted with CH_2Cl_2 (100 mL) and treated with saturated sodium bisulfite (100 mL), and the organic phase was separated and the aqueous phase extracted with CH_2Cl_2 (2 × 150 mL). The organic extracts were combined, dried ($MgSO_4$), and concentrated to afford a viscous yellow oil which was purified by column chromatography. Elution with CH_2Cl_2 afforded 1.55 g (82%) of **7** as a yellow oil: R_f = 0.70 (1:1:1 Et_2O/CH_2Cl_2/hexanes); ^{1}H NMR δ 7.38 (d, J = 8.7 Hz, 1 H), 6.72 (d, J = 3.0 Hz, 1 H), 6.60 (dd, J = 3.0, 8.8 Hz, 1 H), 6.55 (s, 1 H), 4.30 (dd, J = 7.4, 8.9 Hz, 1 H), 4.03 (dd, J = 6.3, 8.9 Hz, 1 H), 3.74 (s, 3 H), 3.48 (ddd, J = 6.5, 7.4, 10.1 Hz, 1 H), 2.91 (m, 2 H), 2.53 (m, 2 H), 1.74 (m, 1 H), 1.47 (s, 3 H), 1.08 (d, J = 6.7 Hz, 3 H), 0.90 (d, J = 6.6 Hz, 3 H); ^{13}C NMR δ 178.0 (CO), 158.9 (C), 143.5 (CH), 141.1 (C), 139.7 (C), 133.3 (CH), 115.9 (CH), 114.8 (C), 113.8 (CH), 98.7 (C), 74.0 (CH_2), 62.2 (CH), 55.4 (CH_3), 33.9 (CH_2), 33.1 (CH), 25.5 (CH_2), 22.1 (CH_3), 20.6 (CH_3), 19.2 (CH_3): IR (film) ν 1711, 1650 cm^{-1}. Anal. Calcd for $C_{19}H_{24}NO_3Br$: C, 57.88; H, 6.13; N, 3.55. Found: C, 57.70; H, 6.19; N, 3.46.

***N*-Benzyl-*N*-(methoxymethyl)-*N*-[(trimethylsilyl)methyl]amine, 8.** Padwa's procedure[15b] was improved by adding *N*-benzyl-*N*-[(trimethylsilyl)methyl]amine (19.9 g, 103.5 mmol) *via* syringe pump to a stirred solution of 37% aqueous formaldehyde (11.1 mL, 140 mmol) at 0 °C over 3.5 h. The reaction mixture was then stirred for an additional 0.5 h and was charged with CH_3OH (10 mL) and K_2CO_3 (5 g). After stirring for 1 h at 0 °C, the reaction mixture was diluted with excess CH_3OH (100 mL) and K_2CO_3 (15 g) and the temperature reduced to −20 °C. After stirring for 17 h, excess K_2CO_3 was filtered and the mixture was concentrated to afford a pale yellow liquid. Distillation provided 20 g (88%) of pure **8** as a clear colorless liquid: bp 77−80 °C (0.1 mmHg) (lit.[15b] bp 78−80 °C (5 mmHg)); ^{1}H NMR δ 7.31 (m, 5 H), 3.99 (s, 2 H), 3.75 (s, 2 H), 3.23 (s, 3 H), 2.18 (s, 2 H), 0.04 (s, 9 H); ^{13}C NMR δ 139.7 (C), 128.7 (CH), 128.1 (CH), 126.8 (CH), 88.4(CH_2), 59.5 (CH_2), 55.4 (CH_3), 42.9 (CH_2), −1.5 $(CH_3)_3C$.

Pyrrolidine 9. A solution of unsaturated lactam **7** (2.66 g, 6.74 mmol) and dipole precursor **8** (4.1 g, 17.3 mmol) in a 10:1 benzene/$CHCl_3$ (12 mL) mixture was placed in an Ace glass pressure tube. Trifluoroacetic acid (3 mg, .03 mmol) was added and an argon blanket placed over the reaction mixture. The pressure tube was then sealed and placed in a preheated sand bath (230 °C).[48] After 36 h the reaction mixture was cooled to rt, and TLC data of the dark yellow solution revealed complete consumption of starting material **7**. The mixture was then partitioned between CH_2Cl_2 (100 mL) and saturated, aqueous $NaHCO_3$ (100 mL). The organic extracts were dried ($MgSO_4$) and concentrated to afford a light brown syrup. In a ^{1}H NMR spectrum of the crude material, integration of the resolved signals corresponding to the *anti* isomer (δ 1.52) and the *syn* isomer (δ 1.38) indicated an *anti*:*syn* ratio of 15:1 (88% de). The mixture was then purified by flash chromatography (10% EtOAc/hexanes) to afford 3.0 g (84%) of diastereomerically pure **9** as a yellow oil: R_f = 0.45 (1:1:1 Et_2O/CH_2Cl_2/hexanes); $[\alpha]_D$ = +25.1 (*c* 2.38, benzene); ^{1}H NMR δ 7.37 (d, J = 8.7 Hz, 1 H), 7.17−7.35 (m, 5 H), 6.75 (d, J = 3.0 Hz, 1 H), 6.61 (dd, J = 3.0, 8.7 Hz, 1 H), 4.16 (dd, J = 7.4, 8.1 Hz, 1 H), 3.86 (dd, J = 5.3, 8.2 Hz, 1 H), 3.74 (s, 3 H), 3.50 (ABq, J = 13.5 Hz $\Delta\upsilon$ = 59.4, 2 H), 3.35 (m, 2 H), 2.87 (td, J = 5.1, 12.5 Hz, 1 H), 2.64 (td, J = 5.9, 11.6 Hz, 1 H), 2.49 (dd, J = 1.9, 8.1 Hz, 1 H), 2.22 (apparent t, J = 8.8 Hz, 1 H), 2.12 (apparent d, J = 8.8 Hz, 1 H),1.94 (m, 2 H), 1.70 (m, 2 H), 1.52 (s, 3 H), 1.05 (d, J = 6.5 Hz, 3 H), 0.91 (d, J = 6.5 Hz, 3 H); ^{13}C NMR δ 182.2 (CO), 159.1(C), 141.8(C), 138.8 (C), 133.3 (CH), 128.2 (CH), 128.1 (CH), 126.8 (CH), 115.7 (CH), 114.6 (C), 113.7 (CH), 97.4 (C), 70.9 (CH_2), 63.1 (CH_2), 60.6 (C), 59.1 (CH_2), 55.5 (CH), 54.9(CH_2), 52.6 (CH_3), 35.3 (CH_2), 33.1 (CH), 32.9 (CH_2), 28.2 (CH_3), 20.5 (CH_3), 19.2 (CH_3); IR (film) ν 2960, 2871, 1706, 1596, cm^{-1}. Data for the minor diastereomer: R_f = 0.55 (1:1:1 Et_2O/CH_2Cl_2/hexanes); ^{1}H NMR (selected signals) δ 6.75 (d, J = 3.0 Hz, 1 H), 6.59(dd, J = 3.0, 8.7 Hz, 1H), 5.04 (dd, J = 6.9, 7.8 Hz, 1H), 4.17 (t, J = 8.2 Hz, 1H), 3.74 (s, 3 H), 3.32 (d, J = 9.2 Hz , 1 H), 3.06 (d, J = 10.2 Hz , 1 H), 2.81 (dd, J = 7.9, 11.4 Hz, 2 H), 2.70 (d, J = 6.3 Hz , 1 H), 2.36 (td, J = 5.1, 13.2 Hz, 1 H), 2.23 (dd, J = 6.6, 10.2 Hz, 1 H), 1.38 (s, 3 H), 1.13 (d, J = 6.6 Hz, 3 H), 0.89 (d, J = 6.6 Hz, 3 H); ^{13}C NMR δ 182.1 (CO), 159.0 (C), 142.2 (C), 138.7 (C), 133.2 (CH), 128.4 (CH), 128.3 (CH), 127.0 (CH), 115.5 (CH), 114.7 (C), 113.7 (CH), 99.6 (C), 69.0(CH_2), 64.1 (CH_2), 63.7 (CH), 58.7 (C), 58.2 (CH_2), 55.44 (CH_3), 55.36(CH_2), 50.4 (CH), 36.1 (CH_2), 34.4 (CH), 32.4 (CH_2), 21.0 (CH_3), 19.5 (CH_3), 19.0 (CH_3). Anal. Calcd for $C_{28}H_{35}NO_3Br$: C, 63.75; H, 6.69; N, 5.31. Found: C, 63.48; H, 6.73; N, 5.20.

Spirodiketone 14. A solution of pyrrolidine **9** (156 mg, 0.296 mmol) in THF (5 mL) was stirred over KH (22 mg) while being cooled to −78 °C to ensure water free conditions. After 40 min, a 1.9 M

(47) It is recommended that this procedure be conducted behind a blast shield in a hood.

(48) This procedure involved the use of smaller amounts of dipole precursor **8** whereas utilizing the conditions described in the discussion (6 h at 190 °C) gave the same yield of product. However, the latter conditions required the use of larger amounts of dipole precursor **8**.

solution of *t*-BuLi in pentane (0.33 mL, 0.62 mmol) was added dropwise and the resulting solution was stirred for 15 min. TLC analysis of the reaction mixture revealed disappearance of **9** (R_f = 0.49, 1:1 EtOAc/hexanes) and formation of UV active carbinol intermediate **13** (R_f = 0.39, 1:1 EtOAc/hexanes). The mixture was quenched at −78 °C with 1 M aqueous $(n\text{-Bu})_4NH_2PO_4$ (4.5 mL, 4.5 mmol). The resulting frozen mixture was allowed to warm to rt, diluted with CH_2Cl_2 (4.5 mL), and heated to reflux (40 °C) for 13 h. The reaction mixture was poured into excess saturated aqueous $NaHCO_3$ (20 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The organic extracts were dried (Na_2SO_4) and concentrated, and the oily residue was purified by radial chromatography (1:1 EtOAc/hexanes) to afford 78.6 mg (73%) of **14** as an off-white powder. An analytical sample was obtained by recrystallization from EtOH: R_f = 0.31 (EtOAc); mp 125−127 °C; $[\alpha]_D$ = −140 (*c* 1.03, benzene); ^{1}H NMR δ 7.94 (d, *J* = 8.8 Hz, 1 H), 7.20−7.35 (m, 5 H), 6.80 (dd, *J* = 2.5, 8.7 Hz, 1 H), 6.62 (d, *J* = 2.4 Hz, 1 H), 3.82 (s, 3 H), 3.67 (ABq, *J* = 12.9 Hz $\Delta\nu$ = 31.2, 2 H), 3.22 (m, 1 H), 3.06−3.14 (m, 2 H), 2.87−2.97 (m, 2 H), 2.77−2.85 (m, 1 H), 2.58−2.69 (m, 2 H), 2.16 (dt, *J* = 4.1, 13.3 Hz, 1 H), 2.09 (s, 3 H); ^{13}C NMR δ 207.4 (CO), 198.8 (CO), 163.7(C), 145.7(C), 138.7 (C), 130.6 (CH), 128.6 (CH), 128.3 (CH), 127.1 (CH), 125.7 (C), 113.4 (CH), 112.3 (CH), 61.8 (CH_2), 61.5 (CH), 60.0 (CH_2), 56.7 (CH_2), 56.2 (C), 55.4 (CH_3), 35.7 (CH_2), 29.8 (CH_3), 27.4 (CH_2); IR (film) ν 2919, 2819, 1707, 1666 cm^{-1}. Anal. Calcd for $C_{23}H_{25}NO_3$: C, 76.01; H, 6.93. Found: C, 75.89; H, 6.98.

Direct Conversion of 9 to 15. Alternative Procedure. A solution of lactam **9** (2.0 g, 3.79 mmol) in 10:1 THF/benzene (50 mL) was stirred over KH (500 mg) while being cooled to −78 °C in the same manner as above. The organic extracts were dried ($MgSO_4$) and concentrated, and the oily residue containing **14** was dissolved in benzene (10 mL) and diluted with EtOH (100%, 135 mL). The reaction mixture was then charged with a 55% dispersion of NaH in silicone oil portionwise (5 g). The resulting solution was allowed to stir for 20 h at rt. The mixture was then neutralized by the addition of 1 N HCl (25 mL), diluted with benzene (125 mL), and concentrated under reduced pressure. The residue was partitioned between EtOAc (150 mL) and saturated $NaHCO_3$ (125 mL), and the aqueous phase was extracted thoroughly with EtOAc (3 × 150 mL). The combined extracts were dried and concentrated to give a crude residue which was purified by flash chromatography (20% EtOAc/hexanes) to afford 1.15 g (87%) of enone **15** as a yellow semisolid. In a separate experiment purified spirodiketone **14** was transformed into enone **15** in 92% yield: R_f = 0.55 (EtOAc); mp 125−127 °C; $[\alpha]_D$ = −109 (*c* 1.37, benzene); ^{1}H NMR δ 7.59 (d, *J* = 8.7 Hz, 1 H), 7.20−7.35 (m, 5 H), 6.79 (dd, *J* = 2.6, 8.7 Hz, 1 H), 6.67 (d, *J* = 2.4 Hz, 1 H), 6.29 (s, 1 H), 3.80 (s, 3 H), 3.54 (ABq, *J* = 13.5 Hz $\Delta\nu$ = 16.2, 2 H), 3.27 (d, *J* = 8.7 Hz, 1 H), 2.91 (m, 3 H), 2.41 (m, 2 H), 2.15 (m, 2 H), 2.04 (dq, *J* = 5.9, 12.6 Hz, 1 H); ^{13}C NMR δ 209.3 (CO), 175.3 (C), 161.7 (C), 140.3 (C), 138.2(C), 129.5 (CH), 128.4 (CH), 128.2 (CH), 126.8 (CH), 122.4 (C), 122.2 (CH), 113.6 (CH), 113.3 (CH), 61.7 (CH_2), 59.0 (CH_2), 56.7 (CH), 55.6 (CH_2), 55.3 (CH_3), 52.3 (C), 33.1 (CH_2), 27.1 (CH_2); IR (film) ν 1690 cm^{-1}; HRMS calcd for $C_{23}H_{23}NO_2$ (M^+ + 1) 346.1807, found 346.1809.

(1*S*,7a*S*)-4′-Methoxybenzo[4,5]hydrindeno[1,7a-*c*]-1-benzylpyrrolidine, 16. According to the procedure of Brown and White[32] a 1 M solution of $LiAlH_4$ in THF (10 mL, 10 mmol) was added to a 0 °C solution of $AlCl_3$ (3.0 g, 22.5 mmol) in Et_2O (20 mL). After stirring for 15 min, a solution of enone **15** (1.1 g, 3.18 mmol) was added and the mixture was allowed to warm to rt with stirring over 6 h. Excess EtOAc (50 mL) was slowly added dropwise to quench excess AlH_3, and 1 N NaOH (50 mL) was then slowly added. The aqueous layer was extracted with EtOAc (3 × 125 mL), and the organics were combined, dried ($MgSO_4$), and concentrated to give 1.00 g (95.2%) of **16** as an off-white semisolid judged to be pure by ^{1}H NMR. An analytical sample was prepared by recrystallization from EtOH: R_f = 0.60 (EtOAc); mp 107−9 °C; $[\alpha]_D$ = +47.5 (*c* 1.06, benzene); ^{1}H NMR δ 7.46 (d, *J* = 8.6 Hz, 1 H), 7.20−7.32 (m, 5 H), 6.71 (dd, *J* = 2.6, 8.6 Hz, 1 H), 6.61 (d, *J* = 2.6 Hz, 1 H), 5.77 (s, 1 H), 3.78 (s, 3 H), 3.58 (ABq, *J* = 13.3 Hz $\Delta\nu$ = 59.3, 2 H), 2.70−2.95 (m, 5 H, includes 2.82 (d, *J* = 9.0 Hz, 1 H)), 2.40−2.60 (m, 3 H), 2.17 (d, *J* = 9.0 Hz, 1 H), 1.94 (ddd, *J* = 2.0, 5.5, 12.4 Hz, 1 H), 1.82 (td, *J* = 5.7, 12.5 Hz, 1 H); ^{13}C NMR δ 158.6 (C), 143.6 (C), 139.2 (C), 137.1 (C), 128.6 (CH), 128.1 (CH), 126.8 (CH), 126.6 (CH), 125.4 (C), 120.1 (CH), 113.1 (CH), 112.5 (CH), 64.5 (CH_2), 60.8 (CH_2), 60.0 (CH), 57.4 (C), 55.2 (CH_3), 47.5 (CH), 40.45 (CH_2), 35.1 (CH_2), 28.1 (CH_2); IR (film) ν 3029, 2920, 1607, 1568 cm^{-1}. Anal. Calcd for $C_{23}H_{25}NO$: C, 82.84; H, 7.56. Found: C, 82.94; H, 7.61.

(1*S*,7a*S*)-4′-Methoxybenzo[4,5]hydrindeno[1,7a-*c*]-1-[[(4-nitrophenyl)oxy]carbonyl]pyrrolidine, 18. A solution of **16** (440 mg, 1.32 mmol) in CH_2Cl_2 was treated with *p*-nitrophenyl chloroformate (270 mg, 1.34 mmol) and the mixture stirred for 15 min. Evaporation of the solvent afforded a tan solid whose ^{1}H NMR showed a 1:1 ratio of benzyl chloride to **18**. The crude reaction product was then subjected to high vacuum (0.1 mmHg) for several hours to remove benzyl chloride, and the remaining material was purified by column chromatography eluting initially with CH_2Cl_2 and then 1:1:1 ether/CH_2Cl_2/hexanes to afford 347 mg (64.5%) of **18** as a tan semisolid. ^{1}H NMR data recorded at 25 °C showed the presence of two distinct rotamers, so characterization data are reported at 55 °C in $CDCl_3$: R_f = 0.58 (1:1:1 ether/CH_2Cl_2/hexanes); $[\alpha]_D$ = +42 (*c* 1.00, benzene); ^{1}H NMR (55 °C) δ 7.45 (d, *J* = 8.6 Hz, 1 H), 7.20−7.35 (m, 4 H), 6.72 (dd, *J* = 2.9, 8.6 Hz, 1 H), 6.68 (d, *J* = 2.9 Hz, 1 H), 5.79 (s, 1 H), 3.78 (s, 3 H), 3.76 (m, 2 H), 3.50 (m, 2 H), 2.75−3.01 (m, 3 H), 2.71 (br s, 1 H), 2.32 (m, 1 H), 2.05 (dd, *J* = 3.0, 12.0 Hz, 1 H), 1.70 (td, *J* = 6.0, 12.5 Hz, 1 H); ^{13}C NMR δ 159.1(C), 151.6 (C), 144.6 (C), 142.8 (C), 136.7 (C), 126.5 (CH), 126.0 (CH), 125.0 (2xCH), 124.1 (CH), 113.0 (2xCH), 55.1 (CH_3), 55.0 (CH_2), 51.5 (CH_2), 51.3 (C), 49.7 (CH), 48.7 (CH), 40.3 (CH_2), 32.9(CH_2), 28.2 (CH_2); IR (film) ν 2910, 1727, 1594, 1522 cm^{-1}.

(1*S*,3a*S*,7a*S*)-4′-Methoxybenzo[4,5]hydrindano[1,7a-*c*]-1-(*tert*-butyloxycarbonyl)pyrrolidine, 20 (R = Boc). A solution of *N*-benzylpyrrolidine **16** (700 mg, 2.10 mmol) in CH_2Cl_2 (15 mL) was treated with *p*-nitrophenyl chloroformate (270 mg, 1.34 mmol) and the mixture stirred for 0.5 h. Evaporation of solvent afforded a tan solid, crude **18**, which was dissolved in THF (20 mL) and then added to a stirred rt solution of 1 M *t*-BuOK/THF (13.0 mL, 13.0 mmol). H_2O (72 mg, 4.0 mmol) was then added, and the dark red suspension which immediately formed was stirred for 0.5 h. The mixture was quenched with 1 N NaOH (10 mL) and diluted with EtOAc (150 mL). The aqueous layer was removed and the organic layer washed with 1 N NaOH (3 × 75 mL) to remove *p*-nitrophenol. The organic layer was dried ($MgSO_4$) and concentrated, producing a red oil which was dissolved in EtOH (20 mL) and added to a predried flask under argon containing 10% Pd/C (300 mg). The argon atmosphere was then replaced with 1 atm of hydrogen, the mixture was stirred for 17 h and filtered through Celite, and the filtercake was washed with EtOAc (20 mL). The combined rinsings were subjected to flash chromatography, giving 480 mg (66%) of **20** as a clear colorless oil which exists as two distinct *N*-Boc rotamers at rt. Recrystallization of **20** with heptane/Et_2O provided a crystalline sample. *S*-stereochemistry was confirmed by the X-ray crystal structure:[49] R_f = 0.58 (1:1:1 ether/CH_2Cl_2/hexanes); mp 114−16 °C; $[\alpha]_D$ = −66 (*c* 1.00, benzene); ^{1}H NMR (100 °C, toluene-d_8) δ 6.95 (d, *J* = 9.3 Hz, 1 H), 6.65 (m, 2 H), 3.42 (s, 3 H), 3.39 (br d, *J* = 3.1 Hz, 2 H), 3.00 (d, *J* = 12.0 Hz, 1 H), 2.91 (d, *J* = 12.3 Hz, 1 H), 2.70 (m, 2 H), 2.51 (dd, *J* = 12.0, 11.0 Hz, 1 H), 1.65−1.90 (m, 5 H), 1.61 (m, 1 H), 1.45 (m, 1 H), 1.35 (s, 9 H); ^{13}C NMR (55 °C)[50] δ 158.3 (C), 155.2 (C), 137.9 (C), 132.4 (C), 126.6 (CH), 114.0 (CH), 111.5 (CH), 79.1 (C), 55.5 (CH_3), 54.3 (CH_2), 52.3 (CH_2), 50.0 (C), 48.9 (CH), 47.0 (CH), 32.7 (CH_2), 31.9 (CH_2), 28.8 $(CH_3)_3C$, 27.6 (CH_2), 25.5 (CH_2); IR (film) ν 2928, 1693, 1610, 1399 cm^{-1}. The X-ray sample was not submitted for combustion analysis.

(1*S*,3a*S*,7a*S*)-4′-Methoxybenzo[4,5]hydrindano[1,7a-*c*]-1-(*tert*-butyloxycarbonyl)-2(*S*)-methylpyrrolidine, 21. To a stirred solution of *N*-Boc-pyrrolidine **20** (100 mg, 0.291 mmol) in ether (1 mL) over KH (15 mg) was added TMEDA (45 uL, 0.298 mmol). The reaction mixture, under dry deoxygenated argon, was stirred at rt for 15 min and then cooled to −90 °C. The mixture was charged with a 1.20 M solution of *sec*-BuLi in cyclohexane (0.75 mL, 0.90 mmol), producing

(49) The X-ray structures have been submitted to the Cambridge Crystallographic Center. The ORTEP structure for **20** is also included in the supporting information.

(50) The ^{13}C NMR spectrum, recorded at 100 °C (toluene), did not show any significant differences, in addition to solvent overlapping with the sample.

a dark red solution, and stirred for 16 h. Iodomethane (100 uL, 1.61 mmol) was added, and after 11 h at −90 °C the mixture was quenched with CH_3OH (1 mL) dropwise, warmed to rt, diluted with ether (25 mL), and washed with 1 N NaOH (2 × 20 mL). The organic layer was dried ($MgSO_4$) and concentrated to afford a yellow oil whose crude ^{1}H NMR showed a 2:1 ratio of **21**:**20**. This mixture was purified by preparative TLC, eluting with 1:1:1 ether/CH_2Cl_2/hexanes to afford 46 mg (50%) of the more polar **21** as a clear oil: R_f = 0.60 (1:1:1 ether/CH_2Cl_2/hexanes); $[\alpha]_D$ = +12° (*c* 1.10, benzene); ^{1}H NMR (300 MHz) δ 6.90 (d, *J* = 8.4 Hz, 1 H), 6.60 (m, 2 H), 3.93 (dq, *J* = 6.3, 6.0 Hz, 1 H), 3.75 (s, 3 H), 3.05 (d, *J* = 12.0 Hz, 1 H), 3.00 (m, 1 H), 2.82 (m, 1 H), 2.75 (d, 1 H, *J* = 8.8 Hz), 2.20 (m, 1 H), 1.60−2.15 (m, 7 H), 1.30 (d, *J* = 6.3 Hz, 3 H); ^{1}H NMR (500 MHz) δ 6.90 (d, *J* = 5.7 Hz, 1 H), 6.60 (m, 2H), 3.93 (dq, *J* = 3.9, 3.6 Hz, 1 H), 3.75 (s, 3 H), 3.05 (d, *J* = 7.5 Hz, 1 H), 2.90 (m, 1 H), 2.82 (m, 1 H), 2.70 (d, 1 H, *J* = 7.2 Hz), 2.20 (m, 1 H), 1.60−2.15 (m, 7 H), 1.30 (d, *J* = 3.9 Hz, 3 H); ^{13}C NMR δ 157.9 (C), 155.7 (C), 137.7 (C), 132.2 (C), 126.3 (CH), 113.7 (CH), 111.1 (CH), 79.0 (C), 55.3 (CH_3), 55.0 (CH), 52.3 (CH_2), 50.0 (C), 47.4 (2xCH), 32.3 (CH_2), 30.9 (CH_2), 28.8 ((CH_3)$_3$C), 27.4 (CH_2), 24.8 (CH_2), 15.0 (CH_3); HRMS calcd for $C_{22}H_{31}NO_3$ (M^+) 357.2304, found 357.2311.

(1*S*,3a*S*,7a*S*)-4′-Methoxybenzo[4,5]hydrindano[1,7a-*c*]-1-methyl-2(*S*)-methylpyrrolidine, 23. *N*-Boc-pyrrolidine **21** (40 mg, 0.112 mmol) was dissolved in dry ether (1.0 mL), and the mixture was charged with excess $LiAlH_4$ (1 M, 0.75 mL, 0.75 mmol) in THF and stirred at rt for 8 h. The mixture was carefully quenched with H_2O (1 mL), followed by 3 N NaOH (1 mL) and then H_2O (4 mL). The aqueous phase was thoroughly extracted with EtOAc (3 × 15 mL), and the combined extracts were dried (Na_2SO_4) and concentrated to afford a yellow oil which was subjected to preparative TLC, giving 26 mg (85%) of **23** as a light yellow oil. Recrystallization with hexanes/EtOAc provided a colorless crystalline sample: R_f = 0.40 (5% Et_3N/95% EtOAc); $[\alpha]_D$ = +51° (*c* 1.05, benzene) mp 87−8 °C; ^{1}H NMR δ 6.98 (d, *J* = 9.6 Hz, 1 H), 6.64 (m, 2 H), 3.74 (s, 3 H), 2.83−2.96 (m, 2 H), 2.73 (dd, *J* = 5.4, 12.3 Hz, 1 H), 2.65 (d, 1 H, *J* = 10.5 Hz), 2.45 (dq, *J* = 5.9, 6.3 Hz, 1 H), 2.10 (s, 3 H), 1.97−2.09 (m, 2 H), 1.75−1.95 (m, 4 H), 1.46−1.72 (m, 2 H), 1.07 (d, *J* = 6.3 Hz, 3 H); ^{13}C NMR δ 157.5 (C), 137.8 (C), 133.0 (C), 126.9 (CH), 113.6 (CH), 110.7 (CH), 64.0 (CH_2), 63.9 (CH), 55.1 (CH_3), 52.9 (CH), 50.9 (C), 50.1 (CH), 41.0 (CH_3), 35.6 (CH_2), 27.6 (CH_2), 27.4 (CH_2), 25.4 (CH_2), 14.9 (CH_3); HRMS calcd for $C_{18}H_{25}NO$ (M + 1) 272.2014, found 272.2003.

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Supporting Information Available: ^{1}H and ^{13}C NMR spectra for **1**, **5**, **7**, **9**, **14**−**16**, **20**, **21**, and **23** and an ORTEP drawing for **20** (25 pages). See any current masthead page for ordering and Internet access instructions.

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