Asymmetric Synthesis of Benzoquinolizidines: A Formal Synthesis of (-)-Emetine

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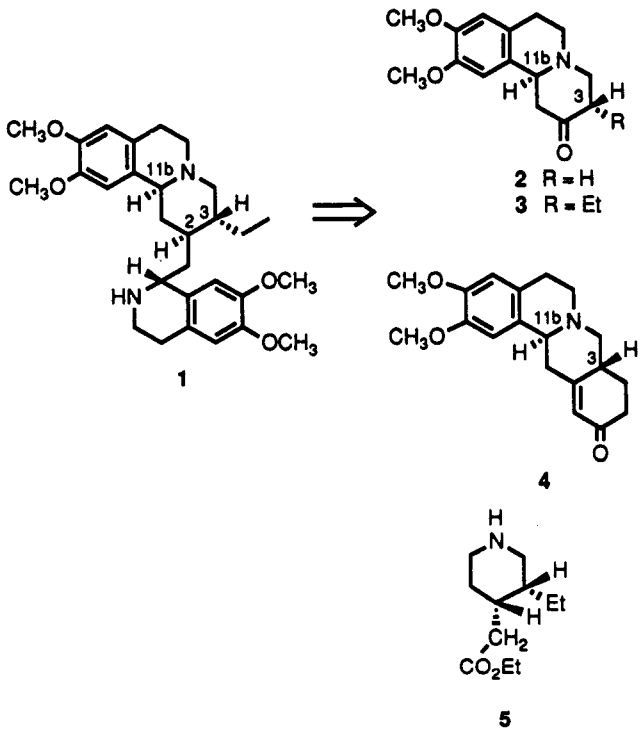
Chiral formamidines affixed to tetrahydroisoquinoline derivatives affords the appropriate precursor **9** to various benzo[*a*]quinolizidines **2** and **3** and dibenzo[*a*,*g*]quinolizidines **4** in modest to high optical purity. Both **3** and **4** have been utilized in total syntheses of natural emetine **1**, thus the route herein constitutes a formal total synthesis of **1**. Furthermore, Mannich cyclizations of 1-alkylisoquinolines **18a-c** proceeded with or without loss of absolute stereochemistry at the C-1 position. Explanation for this behavior is based upon whether a [3,3] rearrangement or a Mannich reaction takes place. The former results in virtually complete racemization of **18**, whereas the latter totally conserves the chirality in **18**. Finally, 1-alkynylisoquinolines of high optical purity were transformed, via the Overman protocol, to alkylidine benzo[*a*]quinolizidines **24** in good yield and to our knowledge, high enantiomeric excess.

Introduction

"Ipecac Root", the root of *Cephaelis ipecacuanha* and certain other plants of the same species, has been used for centuries as an emetic, and was subsequently found to be of greater importance because of its antiamebic activity.[1,2] The principal alkaloid found in the root, to which it owes its pharmacological importance, is emetine, **1**. More than a dozen syntheses of emetine have been described[1] which showcase many elegant and important transformations. Several common synthetic intermediates in the preparation of emetine and other related ipecac alkaloids are the benzo[*a*]quinolizidines **2-4**. The ketone **3** is a key intermediate in which two of the four stereocenters (e.g. 11b, 3) of emetine are contained. The configurations about these centers in the benzo[*a*]quinolizidine ring system are found, as expected, to have the most sterically demanding group at each center in an equatorial position.[3]



Several approaches to **3** have appeared,[4-6] which constitute the synthesis of emetine in a formal sense. However, all approaches with the exception of two,[5,6] have been concerned with the synthesis of racemic ketone **3**. Openshaw and Whittaker[5] developed a commercially viable synthesis of emetine in which (-)-**3** was obtained in a highly efficient manner through the resolution of a racemic mixture. Fujii and co-workers[6a] have also demonstrated a novel enantioselective route to ipecac alkaloids in which they utilized ethyl cincholoiponate (+)-**5**, a degradation product of cinchonine. From the ability of the well-known chiral formamidine methodology to generate stereocenters α to nitrogen in virtually optically pure form,[7] it was our contention that the benzo[*a*]quinolizidine ring systems could be accessed. Herein we describe the use of these formamidines to construct emetine in an asymmetric manner through the synthesis of the benzoquinolizidine intermediates **2-4**.

Results and Discussion

A. Synthesis of Dibenzo[*a*,*g*]quinolizidine, 4. In a previously described asymmetric synthesis of (-)-yohimbone[8] it was found that Mannich cyclization of enantiomerically enriched (99% ee) intermediate **6** resulted in fully *racemic* product **8**. Fortunately, a trivial modification of Winterfeldt's original procedure[9] solved the apparent racemization via the [3,3] sigmatropic rearrangement of this sequence (vide infra). Reduction of the keto group of **6** to the alcohol **7** allows the ring closure to yohimbenone **8** (after oxidation) to proceed with complete conservation of enantiomeric purity. This latter process, employed for the asymmetric synthesis of (-)-yohimbone, was therefore examined with the intention of affording the same margin of enantioselectivity in the preparation of emetine via enone **4**. The latter was originally prepared in racemic form by Brossi and co-workers[10] which allowed access to

(1) *The Isoquinoline Alkaloids: Chemistry and Pharmacology.* Shamma, M., Blomquist, A. T., Wasserman, H., Eds.; Academic Press: New York, 1972; p 25. Fuji, T.; Ohba, M. *The Alkaloids* **1983**, *22*, 1. For a recent asymmetric synthesis of emetine, see: Ihara, M.; Yasui, K.; Taniguchi, N.; Fukumoto, K. *J. Chem. Soc., Perkin Trans. 1* **1990**, 1469.

(2) *The Isoquinoline Alkaloids*; Bentley, K. W., Ed.; Pergamon Press: New York, 1965.

(3) Battersby, A. R.; Binks, R.; Davidson, D.; Davidson, G. C.; Edwards, T. P. *Chem. Ind.* **1957**, 982. Brossi, A.; Lindlar, H.; Walter, M.; Schnider, O. *Helv. Chim. Acta* **1958**, *41*, 119.

(4) Bosch, J.; Balet, A.; Diez, A.; Rubiralta, M. *Tetrahedron* **1987**, *43*(13), 3021.

(5) Openshaw, H. T.; Whitaker, N. *J. Chem. Soc., London* **1963**, 1449 and 1461.

(6) Fujii, T.; Yoshifuji, S. *Tetrahedron* **1980**, *36*(11), 1539. Fujii, T.; Akiyama, S.; Ohba, M. *Heterocycles* **1984**, *22*(1), 159.

(7) (a) Meyers, A. I. *Aldrichimica Acta* **1985**, *18*, 59. (b) For a recent example see: Meyers, A. I.; Guiles, J. *Heterocycles* **1989**, *28*(1), 295.

(8) Meyers, A. I.; White, F. H.; Miller, D. B. *J. Am. Chem. Soc.* **1988**, *110*, 4778.

(9) Benson, W.; Winterfeldt, E. *Chem. Ber.* **1979**, *112*, 1913.

(10) Brossi, A.; Bruderer, H.; Rachlin, A. I.; Teitel, S. *Tetrahedron* **1968**, *24*, 4277.

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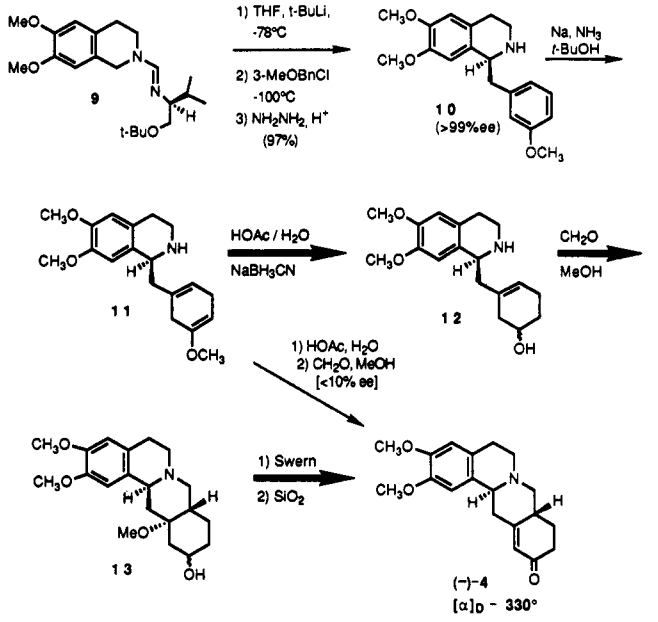
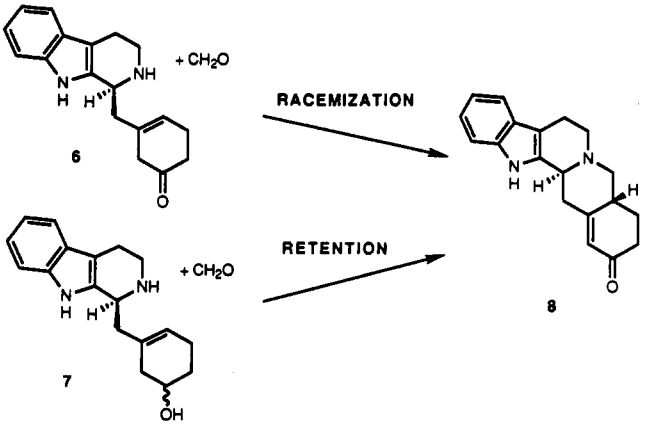
Scheme I



2,3,11-trisubstituted berberines. Subsequently, Takano and co-workers[11] prepared racemic enone 4, which was the key intermediate in their formal synthesis of (±)-emetine.



Proceeding in a manner related to the earlier preparation of yohimbone,[8] the formamidine **9** was metalated[12] with *t*-BuLi (THF, −78 °C), and the subsequent lithio species was alkylated with 3-methoxybenzyl chloride (6 h, −100 °C). Without isolation, the chiral auxiliary was removed under hydrazinolysis (NH_2NH_2–EtOH–H_2O, HOAc) to afford the benzylisoquinoline **10** in 97% yield for the three-step sequence (Scheme I). The enantiomeric purity of **10** was determined to be >99% by chiral HPLC stationary-phase analysis of its 1-naphthamide[15] when compared to the racemic naphthamide. Dissolving metal reduction (Na, NH_3, *t*-BuOH) of the amine **10** generated enol ether **11**. Mild hydrolysis of the enol ether followed by treatment of the β,γ-unsaturated ketone with methanolic formaldehyde furnished the *racemic* (<10% ee) enone **4**,

Scheme II

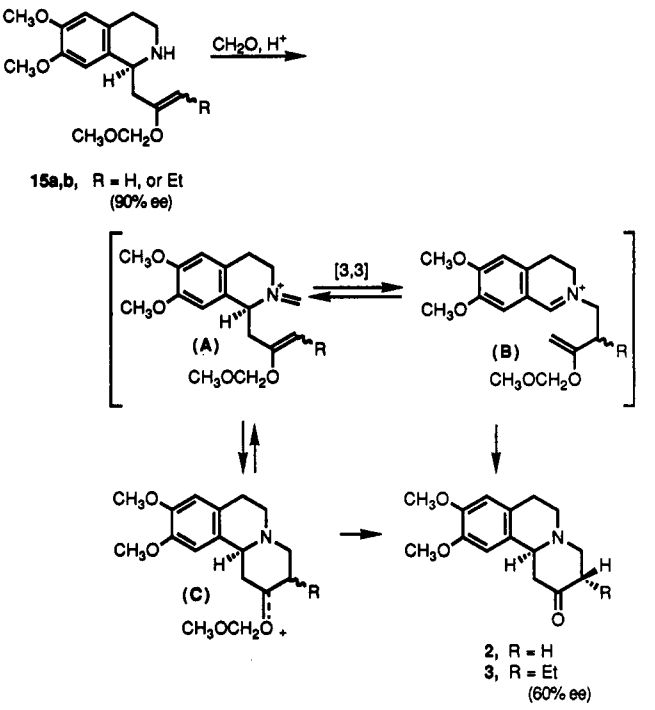


Table I. Alkylation of 9 with Allylic Chlorides 16

product	X	R	% yield	% ee
15a	OCH_2OMe	H	91	90
15b	OCH_2OMe	Et	92[a]	90
15c	CH_2SiMe_3	H	68[b]	97

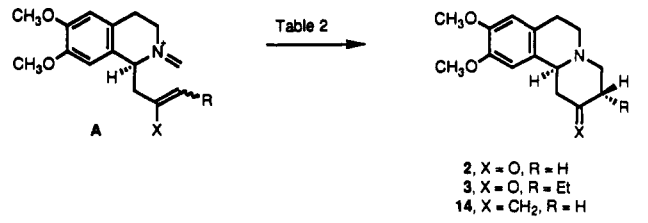
[a] *E*, *Z* mixture. [b] 92% based upon recovered starting material.

in >90% overall yield. This disappointing result was reminiscent of the behavior during the Mannich cyclization observed in the yohimbone[8] synthesis. Following the modifications employed in the (−)-yohimbone synthesis, the optically active enone (−)-**4** was eventually produced in a series of three steps from enol ether **11** (bold arrow pathway). Thus, hydrolysis of enol ether **11** with moist acetic acid and concomitant reduction of the keto group with sodium cyanoborohydride afforded amino alcohol **12** as a mixture of epimeric alcohols (1:1) that were inseparable by silica gel chromatography. The separation, however, was of no consequence since the carbinols were ultimately to be transformed to the single enone. Treatment of a methanol solution of **12** with excess formaldehyde generated tetracyclic alcohol **13** as a mixture of epimeric alcohols that were also inseparable by silica gel chromatography. Swern oxidation[13] of this mixture, followed by silica gel chromatography, yielded a single optically active enone (−)-**4**. The enantiomeric purity of (−)-**4** was assessed by complexation of racemic versus optically enriched enone **4** with (*R*)-Mosher acid according to the method of Villani and co-workers.[14] ^1H NMR analysis of these species indicated a >99:1 ratio of enantiomers in which the minor enantiomer present was below the limits of detection.

B. Synthesis of Benzo[*a*]quinolizin-2-ones. The synthetic plan for reaching these systems once again relied upon a "Mannich-type" ring closure as the key step (Scheme II). It was envisaged that generation of iminium species (**A**) would require intramolecular nucleophilic attack by a pendant group (e.g. enol ether, allyl, alkynyl) to give the desired quinolizidine species **2**, **3**, or **14**. The penultimate step involves the stereospecific creation of the stereocenter at C(1) to provide amine **15**. This was expected to arise from the metalation/alkylation sequence

(11) Takano, S.; Sasaki, M.; Kanno, H.; Shishido, K.; Ogasawara, K. *J. Org. Chem.* **1978**, *43*(21), 4169.
(12) Meyers, A. I.; Boes, M.; Dickman, D. A. *Org. Synth.* **1988**, *67*, 60.
(13) Mancuso, A. J.; Huang, S.-L.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480.
(14) Villani, F. J., Jr.; Costanzo, M. J.; Inners, R. R.; Mutter, M. S.; McClure, D. E. *J. Org. Chem.* **1986**, *51*, 3715.
(15) Pirkle, W. H.; House, D. W.; Finn, J. M. *J. Chromatogr.* **1980**, *192*, 143. Pirkle, W. H.; Welch, C. J.; Mahler, G. S.; Meyers, A. I.; Fuentes, L. M.; Boes, M. *J. Org. Chem.* **1984**, *49*, 2504.

Table II. Mannich Cyclization Conditions for A to 3

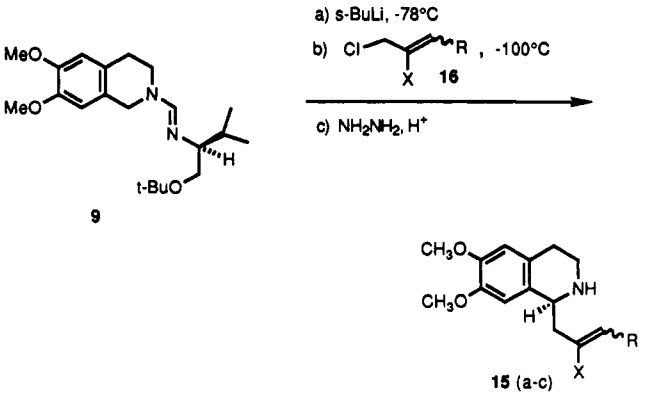


entry	solvent	temp, °C	% yield[a]	% ee[a]
1	MeOH	22	75	6
2	THF	-20	97	60
3	CH_3CN	0	95	12
4	toluene	-20	69	29
5	DMSO	22	94	32

[a] Trans isomer only.

of formamidine **9** with the appropriate three-carbon electrophile **16**.

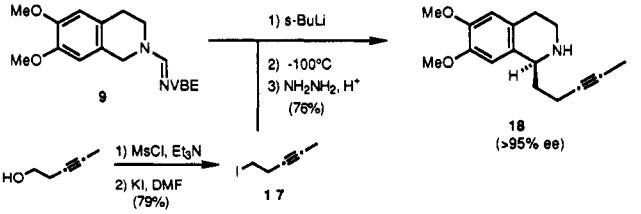
The synthesis of the requisite quinolizidine precursors **15 (a–c)** began by metalation of formamidine **9** with *t*-BuLi (THF, -78 °C) followed by reaction at -100 °C with one of a variety of electrophiles (Table I). Upon completion of the reaction, the chiral auxiliary was removed by treatment with acetic acid and hydrazine affording the alkylated isoquinolines **15a–c** in good chemical yields (>90%) for a three-step/one-pot process. The enantiomeric purity of the products was verified by the chiral stationary-phase HPLC analysis of their 1-naphthamides according to the method of Pirkle.[15] The racemic counterparts of **15a–c** necessary for the HPLC analysis were prepared from an achiral formamidine[16] in the same manner used to prepare the chiral nonracemic compounds. The analysis of both the racemic and optically enriched material indicated an enantiomeric excess (>90% ee) (Table I).



The final step in the process was based on the aminomethylation of alkenes, a variation of the Mannich reaction,[17] which has gained recent notoriety due, in part, to the elegant work of Overman and co-workers.[18] Thus, treatment of the enantiomerically enriched amines **15a–c** with formaldehyde and catalytic acid (*p*-TSA or CSA) produced the intermediate iminium ion (**A**), which readily underwent cyclization to the quinolizidines **2, 3, or 14**. A series of reaction conditions (solvent and temperature) were investigated to optimize the chemical yield and optical purity of the process. An abbreviated list of these conditions for the synthesis of the emetine precursor **3** is displayed in Table II.

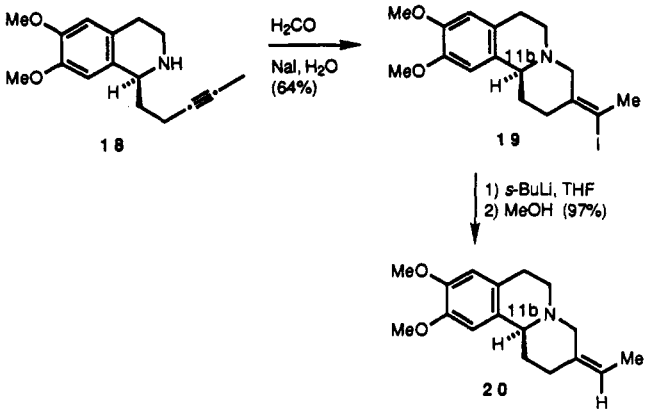
In almost all cases the reaction proceeded in good to excellent chemical yield, and appeared to be insensitive to solvent or temperature. However, upon comparison of the optical rotation of **3** (X = O, R = Et) to that obtained via the Openshaw and Whittaker procedure[5] the enantiomeric purity was found to be only 60% in the best case (entry 2). The racemization for this type of cyclization is not without precedent. At least two examples have been reported[8,19] in which Mannich cyclizations containing a center of asymmetry in conjugation with the alkene or the nitrogen suffer a precipitous loss of optical purity upon cyclization. However, it is noteworthy that any enantiomeric purity (60% ee) remained, in light of the literature reports. In order to confirm that **2** (R = H, X = O) lost its enantiomeric purity in the Mannich cyclization and not because of its inherent instability to the reaction conditions, **2** was placed under identical cyclization conditions for an extended period of time (24 h). The recovered ketone was found to have an unchanged optical rotation, thus precluding any retro-Mannich–Mannich process. That a modest amount (~30%) of optical purity was lost during the cyclization of **15** leads us to conclude that a process similar to Overman's aza [3,3] sigmatropic rearrangement is operative,[19,20] as depicted in Scheme II. A portion (40%) of iminium ion (A) undergoes rapid aza [3,3] sigmatropic rearrangement to give iminium ion (B), where the latter has now lost the stereocenter α to nitrogen. Ion B now is in a position to produce ketone **2** or **3** as a racemic mixture (1:1). The experimental observation that this does not occur completely (60% ee $\approx$ 4:1) suggests that another pathway to the ketones **2, 3** may also be operative. It is entirely plausible that 60% of iminium ion (A) cyclized to oxonium ion (C), followed by hydrolysis to the ketone. This assumes that a major portion of iminium ion (A) had not yet established equilibrium with (B), for had this occurred, a racemic mixture of cyclized ketone would have resulted. It is, therefore, unfortunate that we were unable to shut down the A to B [3,3] process which would have allowed an efficient asymmetric approach to the benzo[*a*]quinolizidines.

An additional enantioselective route to the benzo[*a*]quinolizidines was successfully implemented and is derived from the work of Overman and Sharp.[21,22] Their chemistry, in conjunction with our chiral formamidine studies, could be quite useful as an entry into a variety of species such as isoquinoline **20**. Following standard protocol, chiral formamidine **9** was alkylated with 1-iodo-3-pentyne[23] **(17)** and, after subsequent removal of the chiral auxiliary, afforded the alkylated isoquinoline **18** in good chemical yield (76% over three steps). The optical purity of **18** was



(16) Meyers, A. I.; Du, B.; Gonzalez, M. A. *J. Org. Chem.* **1990**, *55*, 4218.
(17) For a recent review on the Mannich Reaction, see: Tramontini, M.; Angiolini, L. *Tetrahedron* **1990**, *46*(6), 1791.
(18) Doedens, R. J.; Meier, G. P.; Overman, L. E. *J. Org. Chem.* **1988**, *53*, 686 and references cited therein.
(19) Overman, L. E.; Levin, J.; Jacobsen, E. J. *J. Am. Chem. Soc.* **1988**, *110*, 4329.
(20) For a review, see: 3,3-Rearrangements of Imminium Salts. Heimgarten, H., Hansen, H. J.; Schmid, H. In *Adv. Org. Chem. Meth. Res.* (Part 2) **1979**, *9*.
(21) Overman, L. E.; Sharp, M. J. *Tetrhedron Lett.* **1988**, *29*(8), 901.
(22) Overman, L. E.; Sharp, M. J. *J. Am. Chem. Soc.* **1988**, *110*, 612.
(23) Buchi, G.; Wuest, H. *J. Org. Chem.* **1979**, *44*, 546.

established as >94% ee by ^{19}F NMR and GC analysis of the corresponding Mosher amide.[24] Sodium iodide promoted[21] cyclization of the alkyne 18 produced the vinyl iodide 19 in 64% yield. The resulting vinyl iodide 19 was next treated with s-BuLi (THF, -78 °C, 30 min) followed by methanol quench furnishing the benzoquinolizidine 20 in 97% yield. Only one regioisomer was detected by ^1H NMR (vinyl region), and this was tentatively assigned as the Z configuration.[22] Routine assays for the determination of enantiomeric purity (e.g. chiral stationary-phase analysis, NMR shift reagents) of benzoquinolizidine 20 proved less than satisfactory. However, the optical purity of 20 was assumed to be ≥94% ee (as assessed for 18), since loss in the stereochemistry at C-11b through [3,3] sigmatropic rearrangement was not considered feasible. This contention is supported by Overman's enantioselective synthesis of (+)-pumiliotoxin A.[21]



In summary, expedient methods for the asymmetric synthesis of benzoquinolizidines have been developed using processes which rely on chiral formamidine alkylations followed by a Mannich cyclization. The sequences are characterized by producing a variety of benzoquinolizidines in good overall yields and in most cases excellent enantioselectivity.

Experimental Section

(S)-(-)-(3-Methoxybenzyl)-1,2,3,4-tetrahydroisoquinoline (10). To a stirred solution of 9 (0.355 g, 0.978 mmol)[12] in tetrahydrofuran (20 mL) at -78 °C was added t-BuLi (0.63 mL of a 1.7 M solution in hexanes, 1.1 mmol), resulting in a deep red solution, which was stirred for an additional 30 min. The temperature was lowered to -98 °C, and 3-methoxybenzyl chloride (170 mg, 1.16 mmol) diluted in tetrahydrofuran (5.0 mL) was added over 30 min. After 6 h the temperature was raised to -78 °C and 20% NH_4Cl (2 mL) was added followed by normal aqueous workup. The resulting oil was not purified but immediately subjected to hydrazinolysis.[7b,12] After 12 h of stirring, a normal aqueous workup was performed. The resulting material was purified by chromatography (SiO_2) [(deactivated with 5% triethylamine, eluent: hexane (45%)-EtOAc (50%)] to give the title compound (299 mg, 97.5%) as a light yellow oil: $[\alpha]^{22}_D$ -3.2° (c 2.8, EtOH); IR (film) 3314, 2934, 2834, 1600, 1584, 1514, 1464, 1260, 1223, 1112, 1047, 858, 782, 697 cm^{-1}; ^1H NMR (300 MHz, C_6D_6) δ 2.7 (m, 1 H), 2.9 (q, J = 5.6, 9.5 Hz, 2 H), 3.1 (m, 2 H), 3.4 (dd, J = 4.0, 13.3 Hz, 1 H), 3.5 (s, 3 H), 3.63 (s, 3 H), 3.67 (s, 3 H), 4.4 (dd, J = 3.9, 9.5 Hz, 1 H), 6.64 (s, 1 H), 6.8 (s, 1 H), 6.9 (dd, J = 2.2, 5.9 Hz, 1 H), 7.05 (d, J = 7.5 Hz, 1 H), 7.3 (m, 2 H) ppm; ^{13}C NMR (300 MHz, $CDCl_3$) δ 159.7, 147.4, 146.9, 140.7, 130.5, 129.5, 127.3, 121.6, 114.9, 111.8, 111.7, 109.3, 56.7, 55.9, 55.8, 42.7, 40.7, 29.5 ppm. This amine and subsequent others were normally unstable over time precluding satisfactory combustion analyses.

(24) Dale, J. A.; Dull, D. L.; Mosher, H. S. J. Org. Chem. 1969, 34, 2543.

(S)-1-[(5-Methoxy-1,4-cyclohexadienyl)methyl]-1,2,3,4-tetrahydroisoquinoline (11). Into a 100-mL round-bottomed three-necked flask equipped with a magnetic stirring bar, a cold finger condenser containing dry ice-acetone, and a drying tube ($CaCl_2$) was placed 10 (110 mg, 0.37 mmol). Ammonia that was passed through 1 in. × 10 in. KOH tower was condensed into the reaction vessel, maintained at -78 °C, until approximately 70 mL had been collected. Sodium (200 mg, 10 g-atoms, 30 equiv) as small chips was added until the solution was a persistent deep blue for 30 min followed by tert-butyl alcohol (0.2 mL). After 2 h total another 0.2 mL of tert-butyl alcohol was added and the blue color dissipated, the cooling bath was removed, and the ammonia was allowed to evaporate. A normal aqueous workup was performed, and after in vacuo removal of the extraction solvents, afforded 0.11 g (98% yield) of the title compound as a thick oil that was deemed suitably pure to carry through to subsequent steps without purification: IR (film) 3327, 2934, 2830, 1693, 1663, 1610, 1517, 1464, 1260, 1220, 1114, 1023, 753 cm^{-1}; ^1H NMR (300 MHz, C_6D_6) δ 2.4 (m, 2 H), 2.7 (m, 7 H), 3.2 (m, 1 H), 3.56 (s, 3 H), 3.84 (s, 6 H), 4.0 (dd, J = 4.0, 10.0 Hz, 1 H), 4.56 (s, 1 H), 4.65 (s, 1 H), 5.58 (s, 1 H), 6.59 (s, 1 H), 6.6 (s, 1 H) ppm; ^{13}C NMR (300 MHz, $CDCl_3$) δ 152.7, 147.3, 147.0, 131.5, 130.9, 127.3, 122.2, 111.8, 109.2, 90.4, 55.9, 55.8, 53.9, 52.4, 44.0, 40.5, 31.4, 29.5, 26.9 ppm.

(±)-2,3-Dimethoxy-5,6,8,8a,9,10,13,13a-octahydro-11H-dibenzo[a,g]quinolizin-11-one [(±)-4 (Approximately 10% ee)]. Enol ether 11 (110 mg, 0.37 mmol) was dissolved in acetic acid (4 mL), and water (3 mL) was added. The solution was stirred at room temperature for 1.25 h. Formalin solution (35% CH_2O in MeOH, 0.5 mL) was added to the reaction mixture, and stirring was continued for an additional 2 h. The mixture was neutralized by slow addition of solid Na_2CO_3 and diluted with water, and an aqueous workup was performed. After in vacuo removal of the extraction solvents the solid residue was purified by chromatography (SiO_2) [(deactivated with 5% triethylamine, eluent: CH_2Cl_2 (35%)-hexane (35%)-EtOAc (25%)] to give the title compound (116 mg, 97%) as a light yellow sharp melting solid: $[\alpha]_D$ -28.6° (c 1.02, CH_2Cl_2); less than 10% ee; mp 178-180 °C (lit.[10,11] mp 187-189 °C); IR ($CHCl_3$) 3444, 2936, 2834, 1736, 1667, 1611, 1514, 1467, 1371, 1331, 1230, 1210, 1147, 1009, 869, 738 cm^{-1}; ^1H NMR (300 MHz, C_6D_6) δ 1.2 (m, 1 H), 1.4 (m, 1 H), 1.7 (t, J = 11.1 Hz, 1 H), 1.9 (td, J = 5.2, 13.1 Hz, 1 H), 2.3 (m, 5 H), 2.7 (m, 3 H), 3.1 (m, 2 H), 3.42 (s, 3 H), 3.49 (s, 3 H), 5.96 (s, 1 H), 6.4 (s, 1 H), 6.5 (s, 1 H) ppm; ^{13}C NMR (300 MHz, $CDCl_3$) δ 199.4, 163.3, 147.4, 128.7, 126.5, 125.3, 111.4, 108.1, 62.3, 61.9, 56.1, 55.8, 51.3, 40.3, 36.6, 36.5, 29.1, 25.9 ppm.

(S)-(-)-2,3-Dimethoxy-5,6,8,8a,9,10,13,13a-octahydro-11H-dibenzo[a,g]quinolizin-11-one [(-)-4]. This cyclization was performed as described by Meyers, White, and Miller.[8] Enol ether 11 (75 mg, 0.239 mmol) was initially hydrolyzed in acetic acid (4 mL)-water (3 mL) at room temperature for 1.25 h, followed by reduction upon addition of $NaCNBH_3$ (31 mg, 0.48 mmol) for an additional hour. After 16 h the reaction was neutralized by slow addition of K_2CO_3. Aqueous workup afforded 0.6 g of yellow oil that corresponded to alcohol 12 by ^1H NMR. This material was not purified but carried on to the next step in the sequence. The crude alcohol was dissolved in a methanol (11 mL)-acetic acid mixture (0.6 mL) followed by addition of formalin solution (35% CH_2O in MeOH, 0.5 mL), and stirring was continued for an additional 12 h. The volatiles were removed in vacuo followed by repeated addition of benzene (3 mL) and evacuation on the rotary evaporator. This process gave 22 mg of epimeric alcohols 13 that were inseparable by chromatography (SiO_2). A flask containing CH_2Cl_2 (2 mL) and oxalyl chloride (92.4 mg, 0.73 mmol, 64 mL) was cooled to -78 °C. A solution of DMSO (114 mg, 1.46 mmol, 2 equiv) in CH_2Cl_2 was then slowly added. After the mixture was stirred for 3 min, a solution of crude alcohols 13 (22 mg, 0.067 mmol) in 2 mL of CH_2Cl_2 was added over 5 min. After the mixture was stirred for 15 min, Et_3N (300 ml) was added. Stirring was continued at -78 °C for 10 min and then warmed to room temperature. A normal aqueous workup was performed and upon removal of the extraction solvents provided 20 mg of a yellow solid. This material was purified by chromatography (SiO_2) [(deactivated with 5% triethylamine, eluent: CH_2Cl_2 (35%)-hexane (35%)-EtOAc (25%)] to give the title compound (16 mg, 76%) as a light yellow sharp melting solid. This material

exhibited identical spectroscopic and physical data (e.g. ^{1}H NMR, IR, and mp) to the racemic material;[10,11] however, the optical rotation value was significantly higher: $[\alpha]_D$ -330° (c 0.2, EtOH). The enantiomeric purity of this material was found to be >99% ee when assayed by ^{1}H NMR of its Mosher acid salt.

NMR Assay of 4. The racemic and enantiomeric material (7 mg, 0.02 mmol) were individually complexed with (*R*)-(+)-methoxy(trifluoromethyl)phenylacetic acid (5.2 mg, 0.02 mmol) in C_6D_6 (0.7 mL). The solutions were examined at 300 MHz observing the vinyl proton region: δ 5.79–5.84 (d, *J* = 10.8 Hz, 1 H), 5.84 (s, 1 H).

1-[(5,7-Dioxaoct-3-en-4-yl)methyl]-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (15b). Formamidine **9** (0.176 g, 0.574 mmol) was diluted with tetrahydrofuran (12 mL) and chilled to -78 °C, and *n*-BuLi (0.29 mL of a 2.2 M solution in hexane, 0.632 mmol) was added, resulting in a deep red solution which was stirred for an additional 0.5 h. The temperature was then lowered to -98 °C and **16b**[25] (0.11 g, 0.68 mmol, *E*:*Z* 2:1) was slowly added (4 min), followed by stirring till the solution was a persistent faint yellow (7 h). The reaction was quenched with NH_4Cl (saturated, 1 mL) and warmed to room temperature, and the solvent was removed under reduced pressure. General workup procedure gave an oily residue, which was immediately subjected to standard hydrazinolysis conditions[12] for removal of the auxiliary. The resulting material was purified by chromatography (SiO_2) [deactivated with (5%) triethylamine, eluent: hexane (40%)–CH_2Cl_2 (30%)–ethyl acetate (25%)] to give the title compound (172 mg, 92%); $[\alpha]^{22}_D$ +2.4° (c 1.2, EtOH); IR (neat film) 3601, 3334, 2957, 2831, 1710, 1675, 1610, 1515, 1464, 1407, 1376, 1354, 1325, 1260, 1224, 1152, 1115, 1011, 924, 858, 811 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.65 (s, 1 H), 6.64 (s, 1 H), 6.57 (s, 1 H), 6.54 (s, 1 H), 4.75 (t, *J* = 7.1 Hz, 1 H), 4.0 (m, 1 H), 3.84 (s, 3 H), 3.83 (s, 3 H), 3.5 (s, 1 H), 3.33 (s, 2 H), 3.1–3.3 (m, 1 H), 2.8–2.9 (m, 1 H), 2.7 (dd, *J* = 3.6, 4.8 Hz, 2 H), 2.3–2.6 (m, 1 H), 2.15 (t, *J* = 7.5 Hz, 1 H), 2.0 (m, 1 H), 1.6–1.69 (m, 1 H), 1.0 (m, 3 H) ppm.

(*S*)-*cis*,*trans*-3-Ethyl-9,10-dimethoxy-1,3,4,6,7,11b-hexahydro-2*H*-benzo[*a*]quinolizin-2-one (3). To a stirred solution of enol–ether **15b** (R = Et) (66 mg, 0.203 mmol) in tetrahydrofuran (2 mL) at -20 °C was sequentially added formaldehyde (175 μL, 35% v/v, 2.02 mmol, 10 equiv) and camphorsulfonic acid (2 mg, in 0.5 mL of THF). After stirring for 90 min the solution was warmed to room temperature and general workup was performed. Removal of the solvent gave an off-white oily solid that was purified by chromatography (SiO_2) [eluent: ether (66%)–chloroform (33%)] to give 21 mg (35.7%) of a sharp melting solid that corresponds to the **trans diastereomer**: mp 107–108 °C (lit.[5] mp 109–110 °C); $[\alpha]^{22}_D$ -61° (c 0.4, EtOH) [lit.[5] $[\alpha]^{22}_D$ -99° (c 1.0, EtOH)]; IR (neat film) 3019, 2962, 1704, 1611, 1518, 1465, 1360, 1216, 1021, 754, 668 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.62 (s, 1 H), 6.55 (s, 1 H), 3.85 (s, 3 H), 3.82 (s, 3 H), 3.5 (br d, *J* = 11.3 Hz, 1 H), 3.3 (dd, *J* = 5.3, 6.0 Hz, 1 H), 3.15 (m, 2 H), 2.9 (dd, 1 H, *J* = 3.0, 13.6 Hz), 2.2–2.8 (m, 5 H), 1.9 (m, 1 H), 1.15 (m, 1 H), 0.96 (t, 3 H, *J* = 7.5 Hz) ppm; ^{13}C NMR (300 MHz, $CDCl_3$) δ 209.8, 147.8, 147.4, 128.5, 126.1, 111.4, 107.8, 62.4, 60.7, 55.9, 55.8, 51.0, 50.5, 47.5, 29.4, 19.2, 11.6 ppm. Also recovered was 36 mg (61.3%) of a light yellow oil that corresponds to the **cis diastereomer**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.59 (s, 1 H), 6.56 (s, 1 H), 3.83 (s, 3 H), 3.82 (s, 1 H), 2.7–3.4 (m, 6 H) 2.4–2.6 (m, 2 H), 1.6–1.9 (m, 2 H), 0.94 (t, *J* = 7.3 Hz, 3 H) ppm; ^{13}C NMR (300 MHz, $CDCl_3$) δ 210.5, 147.9, 146.6, 127.3, 126.1, 111.6, 110.6, 64.8, 55.9, 55.7, 54.6, 51.6, 47.1, 38.6, 27.0, 22.0, 12.1 ppm.

1-[(3,5-Dioxahex-1-en-2-yl)methyl]-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (15a). To a stirred solution of **9** (687 mg, 1.89 mmol, 1.0 equiv) in tetrahydrofuran (35 mL) at -78 °C was added *t*-BuLi (1.18 mL of a 1.85 M solution in hexanes, 2.18 mmol, 1.15 equiv), resulting in a deep red solution, which was stirred for an additional 30 min. The temperature was lowered to -100 °C, and **16a**[25] (323 mg, 2.37 mmol, 1.25 equiv) was added dropwise. Subsequent stirring for 6 h resulted in a light yellow solution. The temperature was raised to -78 °C and stirred for 1 h, and then saturated NH_4Cl (1 mL) was added. General workup procedure gave an oily residue which was immediately subjected to standard hydrazinolysis[12] for removal of the auxiliary. The resulting material was purified by chromatography (SiO_2) [deactivated with 5% triethyl amine, eluent: hexane (50%)–ethyl acetate (45%)] to give the title compound (510 mg, 74 mmol, 91% overall): $[\alpha]^{22}_D$ -36.1° (c 2.6, THF); IR (neat film) 3582, 3330, 2952, 2931, 2857, 1630, 1512, 1463, 1450, 1410, 1376, 1352, 1260, 1223, 1152, 1113, 1096, 1023, 753 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 6.65 (s, 1 H), 6.58 (s, 1 H), 5.02 (s, 2 H), 4.27 (d, *J* = 2.0 Hz, 1 H), 4.14–4.18 (d, *J* = 3.5 Hz, 1 H), 4.12 (d, *J* = 1.8 Hz, 1 H), 3.85 (s, 3 H), 3.17 (m, 1 H), 2.97 (m, 1 H), 2.74 (m, 2 H), 2.63 (dd, *J* = 3.7, 14.4 Hz, 1 H), 2.45 (dd, *J* = 10.0, 14.0 Hz, 1 H), 1.9 (s, 1 H) ppm; ^{13}C NMR (270 MHz, $CDCl_3$) δ 158.1, 147.6, 147.2, 130.7, 127.3, 112.2, 110., 93.4, 86.7, 55.9, 55.7, 52.9, 42.2, 40.1, 29.3, 27.2 ppm. Anal. Calcd for $C_{16}H_{23}NO_4$: C, 65.51; H, 7.84; N, 4.78. Found: C, 65.29; H, 7.96; N, 4.80.

(*S*)-9,10-Dimethoxy-1,3,4,6,7,11b-hexahydro-2*H*-benzo[*a*]quinolizin-2-one (2). To a stirred solution of enol–ether **15a** (21 mg, 0.07 mmol) in tetrahydrofuran (2 mL) at -20 °C was sequentially added formaldehyde (60 μL, 35% v/v, 0.70 mmol, 10 equiv) and camphorsulfonic acid (2 mg, in 0.5 mL of THF). After being stirred for 90 min the solution was warmed to room temperature, and general workup was performed. Removal of the solvent gave an off-white oily solid that was purified by chromatography (SiO_2) [eluent: ether (66%)–chloroform (33%)] to give the title compound as a white solid (18 mg, 0.069 mmol, 97% overall): $[\alpha]^{22}_D$ -51.3° (c 1.8, CH_2Cl_2); mp 149–150 °C (lit.[4] mp 150–151 °C); IR ($CHCl_3$) 3005, 2950, 2925, 2900, 2850–2750, 1710, 1510 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 6.62 (s, 1 H), 6.54 (s, 1 H), 3.86 (s, 3 H), 3.83 (s, 3 H), 3.5–3.49 (br d, *J* = 9.45 Hz, 1 H), 3.29–3.25 (m, 1 H), 3.1–3.16 (m, 2 H), 2.95–2.87 (m, 1 H), 2.75–2.44 (m, 6 H). Anal. Calcd for $C_{15}H_{19}NO_3$: C, 68.94; H, 7.32; N, 5.36. Found: C, 68.53; H, 6.99; N, 5.80.

(*S*)-1-[2-[(Trimethylsilyl)methyl]prop-1-en-3-yl]-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (15c). To a stirred solution of formamidine **9** (0.15 g, 414 mmol) in tetrahydrofuran (8 mL) at -78 °C was added *t*-BuLi (0.26 mL of a 1.7 M solution in hexanes, 0.46 mmol), resulting in a deep red solution, which was stirred for an additional 30 min. The temperature was lowered to -100 °C, and **16c**[26] (0.082 g, 0.48 mmol) was added dropwise with subsequent stirring for 4 h, resulting in a light yellow solution. The temperature was raised to -78 °C, and 20% NH_4Cl (1 mL) was added. Upon warming to room temperature the solvents were removed in vacuo and an aqueous workup gave an oily residue which was immediately subjected to standard hydrazinolysis conditions.[12] The resulting material was purified by chromatography (SiO_2) [deactivated with 5% triethylamine, eluent: hexane (70%)–EtOAc (25%)] to give the title compound (90 mg, 68%; 92% based on recovered starting material): $[\alpha]^{22}_D$ -18.6° (c 0.84, $CHCl_3$); IR (film) 3100, 3010, 2990, 2980, 2800, 1620, 1600, 1510, 1550, 1250, 1220, 1110, 1000, 880 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.08 (s, 9 H), 1.64 (s, 2 H), 2.45 (m, 2 H), 2.73 (m, 2 H), 2.94 (m, 1 H), 3.18 (m, 1 H), 3.84 (s, 3 H), 3.85 (s, 3 H), 4.73 (d, *J* = 3.8 Hz, 2 H), 6.58 (s, 1 H), 6.60 (s, 1 H) ppm; ^{13}C NMR (300 MHz, $CDCl_3$) δ -1.27, 26.24, 29.46, 40.2, 45.1, 52.9, 55.7, 55.84, 109.2, 110.4, 111.7, 127.3, 130.9, 144.7, 146.9, 147.2 ppm.

(*S*)-9,10-Dimethoxy-2-methylene-1,3,4,6,7,11b-hexahydro-2*H*-benzo[*a*]quinolizine (14). To a stirred solution of **15c** (11 mg, 0.034 mmol, 1.0 eq) in tetrahydrofuran (2 mL) at 20 °C was added formaldehyde (30 μL, 35% v/v, 0.34 mmol, 10 equiv) and *n*-Bu_4NF (14 μL, 0.136 mmol of 1 M hexane solution), and stirring at 20 °C was continued overnight. General workup procedure gave an oily residue which was purified by chromatography (SiO_2) [(deactivated with 5% triethylamine), eluent: hexane (70%)–EtOAc (25%)] to give the title compound (10 mg, 99%). This material exhibited no optical rotation: ^{1}H NMR (270 MHz, $CDCl_3$) δ 2.16–2.81 (m, 7 H), 2.98–3.13 (m, 4 H), 3.83 (s, 3 H), 3.86 (s, 3 H), 4.79 (d, *J* = 6.1 Hz, 2 H), 6.57 (s, 1 H), 6.67 (s, 1 H) ppm; ^{13}C NMR (300 MHz, $CDCl_3$) δ 29.23, 34.1, 40.3, 51.9, 55.8, 56.0, 57.0, 63.4, 108.0, 108.7, 111.4, 126.6, 129.8, 146.2, 147.1, 147.4 ppm. The hydrochloride was prepared: mp 163–165 °C. Anal. Calcd for $C_{16}H_{22}NO_2Cl$: C, 64.96; H, 7.49; N, 4.73. Found: C, 65.16; H, 7.47; N, 4.67.

1-(3-Pentynyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (18). Formamidine **9** (0.269 g, 0.742 mmol) was diluted

(25) Prepared according to the procedure of Okahara, M.; Gu, X.; Nishida, N.; Ikeda, I. *J. Org. Chem.* **1987**, *52*, 3192.

(26) For a recent review on the preparation and use of this reagent, see: Trost, B. M. *Angew. Chem., Int. Ed. Engl.* **1986**, *21*, 1.

with tetrahydrofuran (15 mL) and chilled to −78 °C, and s-BuLi (1.08 mL of a 0.75 M solution in hexane, 0.816 mmol) was added, resulting in a deep red solution which was stirred for an additional 30 min. The temperature was then lowered to −98 °C, and 1-iodo-3-pentyne 17 (0.16 g, 0.82 mmol) was slowly added (4 min), followed by stirring till the solution was a persistent faint yellow (7 h). The reaction was quenched with 20% NH_4Cl (1 mL) and warmed to room temperature, and the solvent was removed under reduced pressure. General workup procedure gave an oily residue which was immediately subjected to standard hydrazinolysis conditions[12] for removal of the auxiliary. The resulting material was purified by chromatography (SiO_2) [deactivated with (5%) triethylamine, eluent: hexane (50%)–ethyl acetate (45%)] to give the title compound (82 mg, 78%): hydrochloride, mp 194.5–196 °C; $[\alpha]^{22}_D$ +7.0° (c 0.56, CH_2Cl_2); IR (film) 3332, 2917, 2832, 1735, 1609, 1514, 1463, 1354, 1324, 1258, 1223, 1112, 1032, 1002, 856, 754 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.60 (s, 1 H), 6.55 (s, 1 H), 3.99 (dd, J = 3.3, 6.3 Hz, 1 H), 3.84 (s, 3 H), 3.83 (s, 1 H), 3.15 (m, 1 H), 2.95 (m, 1 H), 2.68 (q, J = 5.2, 10.5 Hz, 2 H), 2.31 (m, 2 H), 1.8–2.0 (m, 2 H), 1.79 (s, 3 H) ppm; ^{13}C NMR (300 MHz, $CDCl_3$) δ 147.2, 147.1, 131.1, 127.2, 111.7, 109.1, 78.7, 76.1, 55.9, 55.8, 54.2, 40.5, 35.5, 29.4, 15.7 ppm. Anal. Calcd for $C_{16}H_{22}NO_2Cl$: C, 64.96; H, 7.49; N, 4.73. Found: C, 64.74; H, 7.72; N, 4.73.

(S)-3-[(Z)-Propylidene]-9,10-dimethoxy-1,2,4,6,7,11b-hexahydrobenzo[a]quinolizidine (20). Following the procedure of Overman and Sharp,[21] an aqueous solution (3 mL) of the alkynylisoquinoline 18 (82 mg, 0.316 mmol) was heated (95 °C, 4 h) in the presence of NaI (10 equiv), camphorsulfonic acid (1.2 equiv), and formaldehyde (35% by wt, 10 equiv). The reaction mixture was filtered through a small pad of Celite, washing repeatedly with CH_2Cl_2. Following normal aqueous workup the solution was dried over K_2CO_3 (0.5 g) and evaporated to dryness giving 80 mg (64% yield) of a yellow solid. This solid corresponds to the [(E)-iodoethylidene]benzoquinolizidine 19. Anal. Calcd for $C_{17}H_{25}NO_3ClI$: C, 45.00; H, 5.27; N, 3.08. Found: C, 44.93; H, 4.87; N, 2.73. 19: ^1H NMR (300 MHz, $CDCl_3$) δ 6.63 (s, 1 H), 6.55 (s, 1 H), 3.93 (dd, J = 2.2, 10.6 Hz, 1 H), 3.83 (s, 3 H), 3.82 (s, 3 H), 3.2 (d, J = 9.9 Hz, 1 H), 2.95 (m, 4 H), 2.59 (s, 3 H), 2.3 (m, 1 H), 1.6 (m, 1 H) ppm; ^{13}C NMR (300 MHz, $CDCl_3$) δ 147.5, 147.1, 137.8, 129.6, 126.3, 111.3, 108.4, 102.6, 95.6, 61.9, 55.9, 55.8, 50.8, 39.9, 31.8, 29.9, 29.1 ppm. To a chilled (−78 °C) tetrahydrofuran (4 mL) solution of the benzoquinolizidine (24 mg, 0.06 mmol) was added s-BuLi (0.632 mL of a 0.75 M solution in hexane, 0.632 mmol). After 30 min the orange solution was quenched with methanol, followed by a typical aqueous workup for metalation/alkylation. The 16 mg (97.5% yield) of crude solid product was very pure by ^1H NMR. The benzoquinolizidine could be purified by crysallization of its hydrochloride salt (ether/acetone), mp 234–236 °C. Due to the hygroscopic nature of this salt, it failed to give correct combustion analysis. However, the free base could be suitably dried (KOH, 24 h, 0.1 Torr) for further analyses: $[\alpha]^{22}_D$ −86° (c 0.36, CH_2Cl_2); IR (film) 2933, 2831, 2740, 1611, 1518, 1463, 1367, 1331, 1260, 1230, 1212, 1171, 1135, 1099, 1040, 1016, 906, 855, 754 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.67 (s, 1 H), 6.56 (s, 1 H), 5.3 (q, J = 6.6, 13.5 Hz, 1 H), 3.84 (s, 3 H), 3.83 (s, 3 H), 3.76 (dd, J = 1.3, 12.4 Hz, 1 H), 3.27 (d, J = 10.7 Hz, 1 H), 3.1 (m, 2 H), 2.2–2.7 (m, 6 H), 1.66 (d, J = 6.8 Hz, 3 H), 1.5 (m, 1 H) ppm; ^{13}C NMR ($CDCl_3$) δ 147.3, 146.9, 134.1, 130.1, 126.6, 118.0, 111.3, 111.2, 108.3, 108.2, 62.9, 55.9, 55.7, 52.0, 34.7, 32.6, 29.1, 12.8 ppm. Anal. Calcd for $C_{17}H_{23}NO_2$: C, 74.69; H, 8.48; N, 5.12. Found: C, 74.97; H, 8.66; N, 4.86.

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Registry No. (-)-1, 483-18-1; **2**, 136657-36-8; *cis*-**3**, 2609-32-7; *trans*-**3**, 136657-35-7; (±)-**4**, 19778-10-0; (−)-**4**, 136657-33-5; **9**, 128778-92-7; **10**, 136657-32-4; **11**, 136587-48-9; **12** (isomer 1), 136587-49-0; **12** (isomer 2), 136587-50-3; **13** (isomer 1), 136587-51-4; **13** (isomer 2), 136657-34-6; **14**, 136587-58-1; **15a**, 136587-56-9; (*E*)-**15b**, 136587-54-7; (*Z*)-**15b**, 136587-55-8; **15c**, 136587-57-0; **16a**, 105104-40-3; (*E*)-**16b**, 136587-52-5; (*Z*)-**16b**, 136587-53-6; **16c**, 18388-03-9; **17**, 18719-28-3; **18**, 136587-59-2; **19**, 136587-61-6; **20**, 136587-60-5; **20**·HCl, 136587-62-7; 3-MeOBnCl, 824-98-6.

Nucleic Acid Related Compounds. 68. Fluorination at C5′ of Nucleoside 5′-Thioethers with DAST/Antimony(III) Chloride or Xenon Difluoride To Give 5′-*S*-Aryl-5′-fluoro-5′-thiouridines[1]

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Oxidation of 2′,3′-di-*O*-acetyl-5′-*S*-(4-methoxyphenyl)-5′-thiouridine (**2a**) with 3-chloroperoxybenzoic acid (MCPBA) gave the diastereomeric sulfoxides **4a**. Treatment of **2a** with xenon difluoride or **4a** with (diethylamino)sulfur trifluoride/antimony(III) chloride gave efficient conversions to the 2′,3′-di-*O*-acetyl-5′-fluoro-5′-*S*-(4-methoxyphenyl)-5′-thiouridine diastereomers **6a**. The stereochemistry and conformation of **6a**(5′*R*) were established by X-ray crystallography. The α-fluoro thioethers were oxidized to their sulfoxide and sulfone derivatives with MCPBA, deprotected, and characterized.

S-Adenosylmethionine (AdoMet, SAM) is the methyl donor for most enzyme-mediated methylations and produces *S*-adenosylhomocysteine (AdoHcy, SAH) as the byproduct. Since AdoHcy is a feedback inhibitor of methylation enzymes, its degradation is crucial for the continuation of biosynthesis and cell division.[2] Enzymatic decarboxylation of AdoMet gives the 5′-aminopropylsulfonium compound that serves as an aminopropyl donor for the biosynthesis of polyamines. The nucleosidic byproduct of that pathway is 5′-*S*-methyl-5′-thioadenosine (MTA).[3] Methylthioadenosine phosphorylase (MTA-Pase)[4] effects glycosyl cleavage of MTA and the resulting 5-*S*-methyl-5-thioribose 1-phosphate is converted to methionine by a salvage pathway.[5] It has been found that

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