Chiral Formamidines. The Total Asymmetric Synthesis of (-)-8-Azaestrone and Related (-)-8-Aza-12-oxo-17-desoxoestrone†

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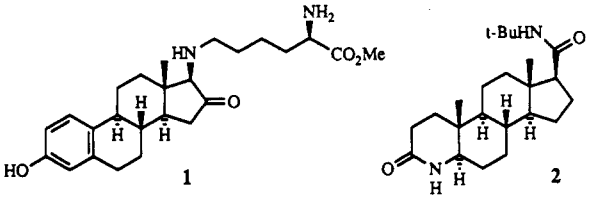
Attachment of the chiral formamidine moiety to 6-methoxy-1,2,3,4-tetrahydroisoquinoline afforded the key chiral, nonracemic precursor **8**, upon which the azasteroid skeleton was constructed. Asymmetric alkylation with α-halo esters or β-halo ethers gave **15** and **22**, respectively, in high ee's. Cyclization, following enamine formation with cyclopentanedione or cyclopentanone, led to the chiral steroidal skeletons **6** and **5**, respectively. The final stereocenters, leading to 8-azaestrone **4** with unnatural absolute configuration (antipodal), were accomplished by intramolecular alkylation of (+)-**6b** and subsequent reduction and ether cleavage. For the 12-oxosteroid **3**, the methyl at C-13 was inserted by initial conjugate reduction of the enone **5** with a copper hydride reagent (Stryker method) requiring the presence of a silyl chloride affording **21**. The addition of methyl iodide to C-13 occurred after transforming the triethylsilyl enol ether, **21**, to its lithium enolate. Stereochemical assignments for both azasteroids **3** and **4** were confirmed by spectroscopic means including circular dichroism curves.

The steroids continue to be actively studied, particularly with regard to modulating gene expressions.[1] Azasteroids such as **1** have been utilized to evaluate oncogenic events



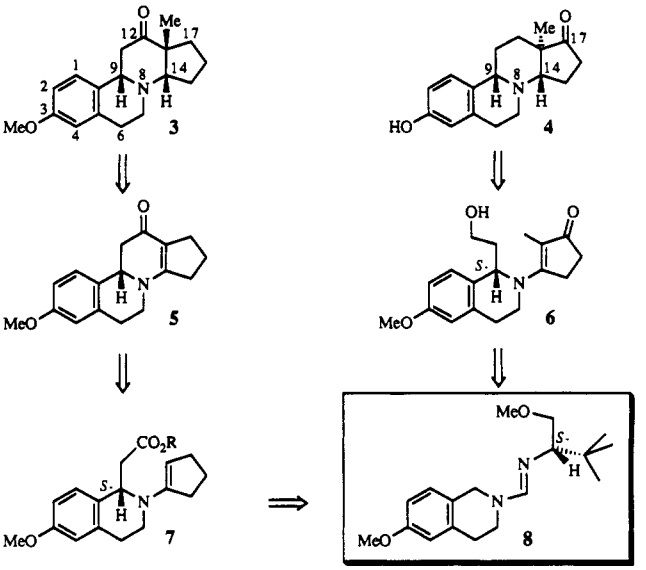
in breast tissue,[2] whereas **2** has been identified as an inhibitor of 5α-reductase and holds promise as an agent against benign prostatic hyperplasia.[3] Although the placement of the nitrogen atoms in **1** and **2** is rather different, these substances share the common feature of being semisynthetic.

In the continuing program wherein a number of complex natural products are accessed using chiral formamidines[4] it was envisioned that several azasteroids (e.g, **3**, **4**) could be viable targets (Scheme I). Furthermore, it was felt that a single chiral formamidine **8** would be suitable for reaching either azasteroidal system. Noting that both azasteroids **3** and **4** have "unnatural" configurations from their carbocyclic analogs (e.g., C-8, 9, 13, 14) due to the fact that the starting chiral auxiliary **8** possesses the *S*-configuration, we still proceeded as planned. Reversal of the configuration in **8** would lead to **3** and **4** in "natural" steroid configuration, but the acquisition of a particular enantiomeric form did not seem, at this point, to be an issue of substance.

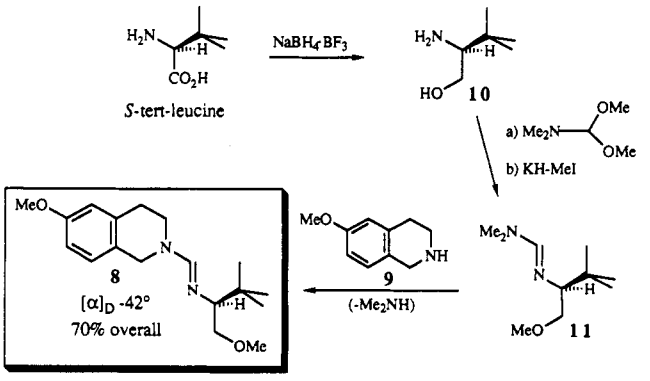
The route to the targets required that the isoquinoline **8** be metalated and alkylated with suitably functionalized electrophiles (i.e., α-halo ester or β-haloethanol) to furnish **6** or **7**. These materials would, in accord with earlier observations,[4] lead to products with *S*-configuration at the newly formed asymmetric carbon. If these were successfully reached, the synthetic route to the *N*-cyclopentenyl moieties (**5**, **6**) would next be implemented in a manner resembling our earlier efforts in this field.[5]

Synthesis of the key divergent intermediate isoquinoline **8** (Scheme II) was accomplished in 85–90% yield by formamidine exchange between the methoxytetrahydroisoquinoline **9**[6] and the dimethylamino derivative, **11**. The

Scheme I



Scheme II



latter was efficiently prepared by reduction of *S*-*tert*-leucine to the carbinol **10** using sodium borohydride–BF_3

†This paper is dedicated to Professor Charles W. Rees for his decades of contribution to organic chemistry and to commemorate his retirement in 1992.

(1) (a) Power, R. F.; Mani, S. K.; Codina, J.; Conneely, O. M.; O'Malley, B. W. *Science* **1991**, *254*, 1636. (b) Swaneck, G. E.; Fishman, *J. Proc. Natl. Acad. Sci. U.S.A.* **1988**, *85*, 7831. (c) Spelsberg, T. C.; Ruh, T.; Ruh, M.; Goldberg, A.; Horton, M.; Hora, J.; Singh, R. *J. Steroid Biochem.* **1988**, *31*, 579.

(2) Miyairi, S.; Ichikawa, T.; Nambara, T. *Tetrahedron Lett.* **1991**, *32*, 1213.

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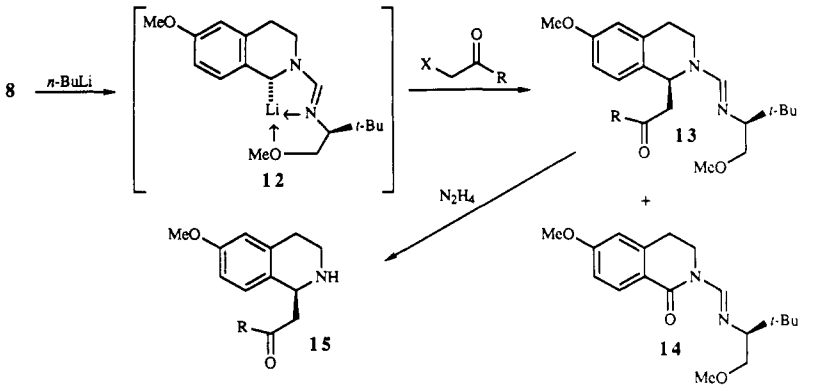
Table I. Metalation–Alkylation of 8 to 13 and 14 and Hydrolysis to 15



entry	X	R	ratio alkyn 13:Oxidn 14	yield (%) of 13	yield (%) of 15	ee (%)
1	Cl	Ot-Bu	2:1[a]	45[b]	98	93
2	Cl	Oi-Pr	15:1[a]	60–70	88	91
3	Cl	OEt	35:1[a]		*d*	
4	Cl	NEt_2	43:1	93[b]	97	39
5			0:1[c]			

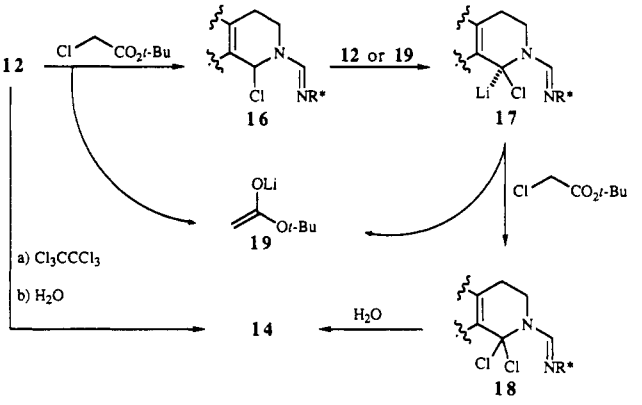
Cl_3C–CCl_3

[a] A solution of 12, at −78 °C, was added to a solution of the electrophile at −110 °C. [b] A suspension of 1.2 equiv of KH was present during the addition of 12 to the α-halo ester. [c] An equal mixture of 8 and 14 was obtained. [d] R = $NHNH_2$ was the only product.

in THF.[7] This was followed by treatment with dimethylformamide–dimethyl acetal to afford the (dimethylamino)formamidine alcohol (crude yield, quantitative) and its subsequent transformation to 11 with potassium hydride and methyl iodide. The overall transformation from *tert*-leucine to 11 was performed in 81–89% yield.

The next task en route to reaching the azasteroids was the acetylmethylation of 8. To this end, a series of α-halo esters and amides were examined by introducing them to the 1-lithio formamidine 12. The latter was generated from 8 using *n*-butyllithium in THF at −78 °C after 30 min. Of concern at this juncture of the study was the acidity of the α-proton which would appear in the product, 13. To avoid the detrimental possibility that the acidic α-position would quench the anion 12, potassium hydride was introduced into the solution of 12 prior to addition of the *tert*-butyl 2-chloroacetate. The results of this experiment are given in entry 1 of Table I. In addition to a 45% yield of the alkylated material 13, there was also present (~15–20%) an unexpected lactam, 14. Spectral (NMR, IR, MS) studies were in complete accord with the structure of 14. It was subsequently found that KH was readily not necessary to perform the reaction satisfactorily so this was omitted and other chloro esters were examined. Attempts were now focused on maximizing the alkylation yields of 13 and minimizing the formation of the lactam 14. The

Scheme III



origin of the latter will be considered below. From Table I it is immediately clear that the *tert*-butyl ester gave the poorest ratio of alkylation to oxidation (to lactam 14). The use of isopropyl and ethyl esters (entries 2, 3) gave vastly superior ratios of alkylation to oxidation, and the diethylamide (entry 4) was the most favorable electrophile in this regard. As good as the alkylation oxidation ratios appeared, each (entries 2–4) had some disadvantage in subsequent steps in the synthetic scheme. Since the chiral auxiliary was no longer required, its removal was effected using aqueous alcoholic acetic acid containing hydrazine. For the ethyl ester 13 (entry 3), only acyl hydrazide was formed, thus rendering it useless for further work. For the diethylamide 13 (entry 4) the formamidine removal was very efficient giving 15 in essentially quantitative yield; however, the percent enantiomeric excess was only 39% (chiral stationary-phase LC). The severe loss of enantiomeric purity when diethylamide was employed is probably due to the disruption of the chelate in 12. Previous studies from this laboratory have shown[4b] that strong ligands such as DMF, HMPA, etc. tend to reduce the stereoselectivity of the alkylation step. This has been attributed to the association of the ligand with the lithium cation and ultimately to breaking up the chelate such that

(3) (a) Rasmusson, G. H.; Reynolds; Utne, T.; Jobson, R. B.; Primka, R. L.; Berman, C.; Brooks, J. R. *J. Med. Chem.* **1984**, *27*, 1690. (b) Rasmusson, G. H.; Reynolds, G. F.; Steinberg, N. G.; Walton, E.; Patel, G. F.; Liang, T.; Cascieri, M. A.; Cheug, A. H.; Brooks, J. R.; Berman, C. *Ibid.* **1986**, *29*, 2298.

(4) (a) Highsmith, T. K.; Meyers, A. I. *Adv. Heterocyclic Natural Product Synthesis*; Pearson, W. H., Ed.; JAI Press: Greenwich, CT, 1990; Vol. 1, pp 95–135. (b) Meyers, A. I. *Tetrahedron*, in press.

(5) (a) Reine, A. H.; Meyers, A. I. *J. Org. Chem.* **1970**, *35*, 554. (b) Meyers, A. I.; Sircar, J. C. *Tetrahedron* **1967**, *23*, 785. For a structural discussion on these systems, see: Brown, R. E.; Meyers, A. I.; Trefonas, L. M.; Towns, R. L.; Brown, J. N. *J. Heterocycl. Chem.* **1971**, *8*, 279.

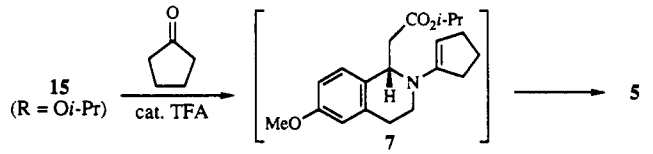
(6) Meyers, A. I.; Bos, M.; Dickman, D. A. *Org. Synth.* **1988**, *67*, 60.

(7) For earlier methods to effect this reduction, see: Dickman, D. A.; Meyers, A. I.; Smith, G. A.; Gawley, R. E. *Organic Syntheses*; Wiley: New York, 1988; Collect. Vol. VII, p 530.

the rigid topography and stable conformation in **12** can no longer effectively control the trajectory of the entering electrophile. Fortunately, when the isopropyl ester **13** (R = O-*i*-Pr, entry 2) was used, satisfactory chemical yields were achieved, and formamidine removal also gave **15** (R = O-*i*-Pr) in good yield and with satisfactory levels of enantiomeric excess (91%). Thus, the optimum conditions were based on the results of entry 2 in Table I.

Turning briefly from the synthetic route to azasteroids **3** and **4**, mention must be made regarding the lactam **14** which appeared as 33% of the product mixture during the alkylation of lithioformamidine **12** (Scheme III). From the data in Table I, the *tert*-butyl chloroacetate gave the highest ratio of lactam **14** of the various esters or amide employed (entry 1). This is considered to be a result of steric bulk in the alkylation step of **12** → **13**. The concurrent nucleophilic attack on the chlorine atom[8] to eject the enolate **19** (Scheme III) producing the α-chloro derivative **16** may be a direct consequence of the sluggish alkylation of the *tert*-butyl chloroacetate. Once **16** is formed, another deprotonation occurs (via enolate **19** or **12**) to generate anion **17** which again undergoes substitution on chlorine generating the α,α-dichloro derivative **18** and enolate **19**. Aqueous quench of the reaction mixture may be the source of the isolated lactam **14**. These chlorinations of the lithio formamidine **12** dropped off dramatically in favor of C-alkylation (to **13**) when less bulky ester or amides were employed (Table I, entries 2–4). In an effort to force the reaction toward chlorination, hexachloroethane was introduced into the THF solution of **12**. This resulted in 45% yield of the lactam **14** after hydrolytic workup. Thus, it may be reasonably assumed that the lactam (oxidation product) arose from nucleophilic attack on the chlorine atom as depicted in Scheme III.

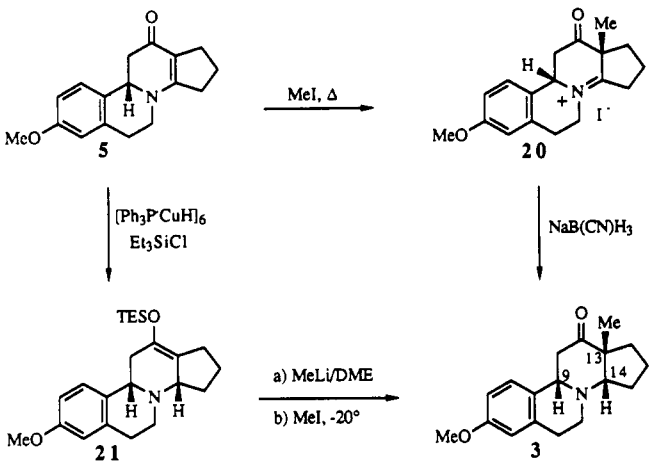
With a reasonably efficient synthetic scheme to the enantiomerically pure 2-carbopropoxymethyl isoquinoline **15** in hand, the stage was set to introduce the CD ring via the intermediate **7** (Scheme I). Heating a toluene solution



of the isoquinoline ester and cyclopentanone at reflux for 5–7 h gave, presumably, the intermediate enamine **7** (R = *i*-Pr) which spontaneously cyclized in 70% yield under the reaction conditions to the tetracyclic enamino ketone, **5**.[5] The optical rotation ($[\alpha]_D = -50°$) of the product was a reasonable omen that no racemization had occurred during the cyclization process. It is of interest to note in passing that when the *tert*-butyl ester **15** (R = O-*t*-Bu) or the *N*,*N*-diethylamide **15** (R = NEt_2) was subjected to cyclopentanone under the same conditions, little (<20%) or no tetracycle **5** appeared, once again reinforcing the fact that the isopropyl ester of **15** was indeed the precursor of choice.

To continue the scheme to the 12-oxoazasteroid **3**, it was now necessary to introduce an angular methyl group at C-13, and this was done by reducing **5** according to Stryker's use of Ph_3PCuH–Et_3SiCl.[9] The enolsilyl ether **21** was obtained in 75–79% yield as a 32:1 mixture favoring

Scheme IV



the β-H at C-14. Also, Bohlmann–Wenkert bands[10] were readily evident in the infrared spectrum of **3** further supporting the antiperiplanar position for the two protons (C-9, C-14) adjacent to the nitrogen lone pair. The enol silyl ether **21** was sufficiently robust to allow purification on silica gel and when treated with methyllithium in dimethoxyethane readily produced the lithium enolate, which when subjected, in situ, to methyl iodide gave the *C*-methyl derivative **3**. The latter was mainly the β-methyl epimer with ~20% of the α-methyl epimer of **3**. Attempts changing the ratio to favor the α-methyl system, which would, in effect produce the trans-CD ring fusion, akin to the "natural steroids", was simply not achievable after numerous attempts. The assignment of absolute and relative configurations were made by examining the CD spectrum and comparison with 8-azaestrone **4**[11] whose configuration was verified by comparison to natural estrone (see Figures 1 and 2). The fact that the 12-oxo steroid **3** possessed "unnatural" stereochemistry is readily seen in Figure 1 when compared to "unnatural" 8-azaestrone **25**. The similarities in the CD spectrum of **3** and **25** are quite satisfactory.

The synthetic effort continued with an approach to 8-azaestrone **4** and utilized the same chiral isoquinoline formamidine as before (i.e., **8**). Alkylation of the latter required a 2-carbon substituent which was introduced as 2-bromoethyl *tert*-butyldimethylsilyl ether. The alkylation (THF, −98 °C) was followed by hydrazinolysis to afford **22a**. Chiral HPLC analysis (OJ-Chiracel column) showed that the enantiomeric ratio of *S*:*R* for **22a** was 95:3. Desilylation, using HF in aqueous acetonitrile, gave the hydroxyethyl isoquinoline **22b** as a crystalline solid.[12] The D-ring moiety of **6** was inserted by azeotropic removal of water from a toluene solution of 2-methyl-1,3-cyclopentanedione and the hydroxymethyl isoquinoline **22b**. Accordingly, **6a** was produced in 65% yield from **8** and possessed properties in good agreement with the racemic version reported earlier.[5b]

Cyclization of **6a** to the tetracyclic system next required an electrophilic substituent which could be displaced by the "enamine" nature of the vinylogous amide. To this end, the hydroxyl group in **6a** was transformed into its mesylate and the latter then converted to the iodide **6b**

(8) Nucleophilic attack on halogen with displacement of enolate ions has been observed with 2-halomalonates (e.g., Meldrum's acid): (a) Marino, J. P. *J. Chem. Soc., Chem. Commun.* **1973**, 861. (b) Trost, B. M.; Melvin, L. S. *J. Am. Chem. Soc.* **1976**, *98*, 1204.

(9) Mahoney, W. S.; Brestensky, D. M.; Stryker, J. M. *J. Am. Chem. Soc.* **1988**, *110*, 291.

(10) (a) Wenkert, E.; Roychauhuri, D. K. *Ibid.* **1958**, *80*, 1613. (b) Bohlmann, F. *Chem. Ber.* **1958**, *91*, 2157. (c) Kametani, T.; Ujie, A.; Huang, S.-P.; Ihara, M.; Fukumoto, K. *J. Chem. Soc., Perkin Trans. 1* **1977**, 394.

(11) The X-ray structure of 4·HBr has been reported: Majeste, R.; Trefonas, L. M. *J. Am. Chem. Soc.* **1969**, *91*, 1508.

(12) Nelson, N. A.; Gelotte, K. O.; Tamura, Y.; Sinclair, H. B.; Schuck, J. M.; Bauer, V. J.; White, R. W. *J. Org. Chem.* **1961**, *26*, 2599.

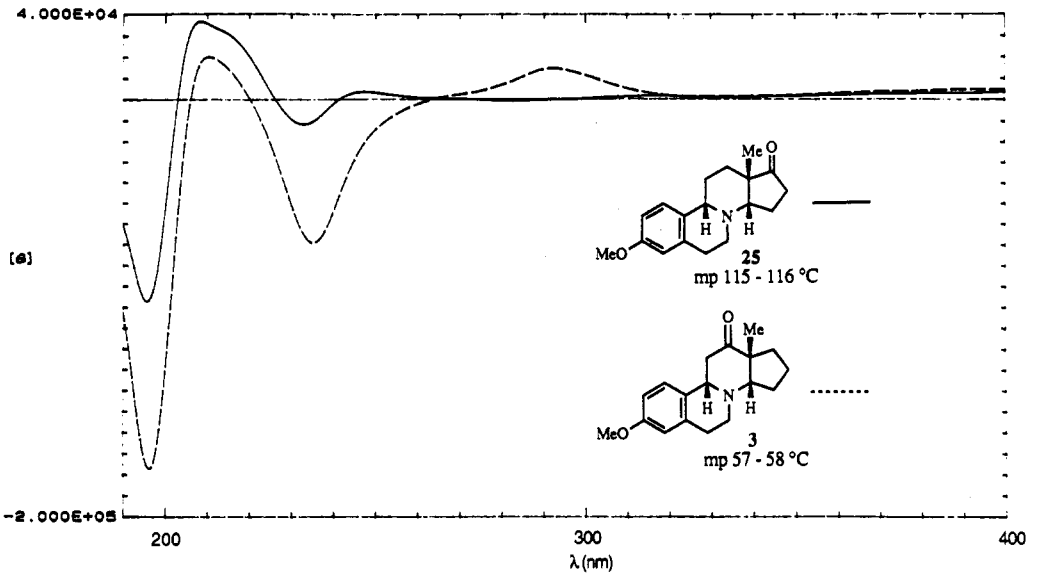


Figure 1.

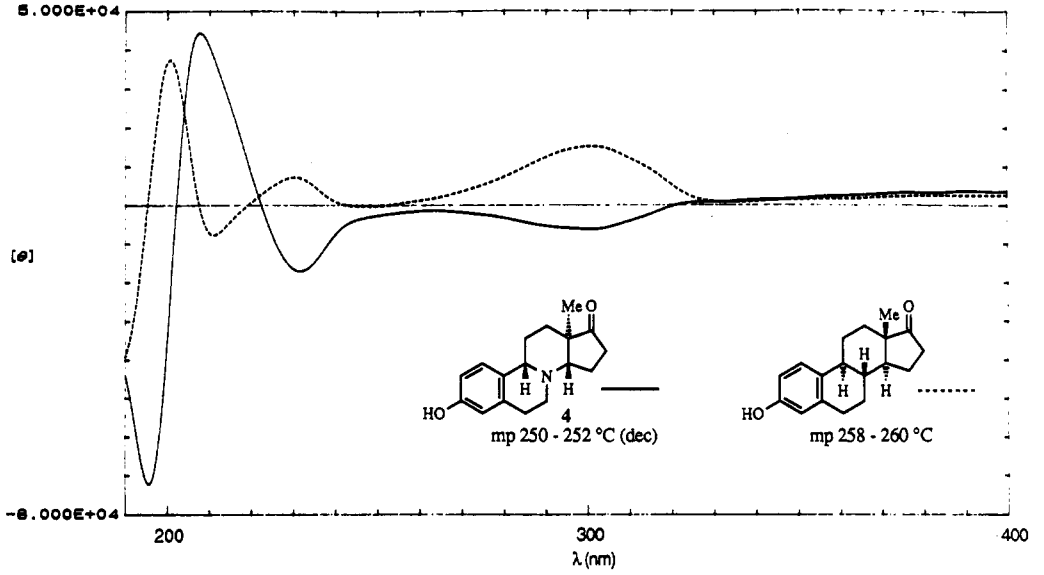
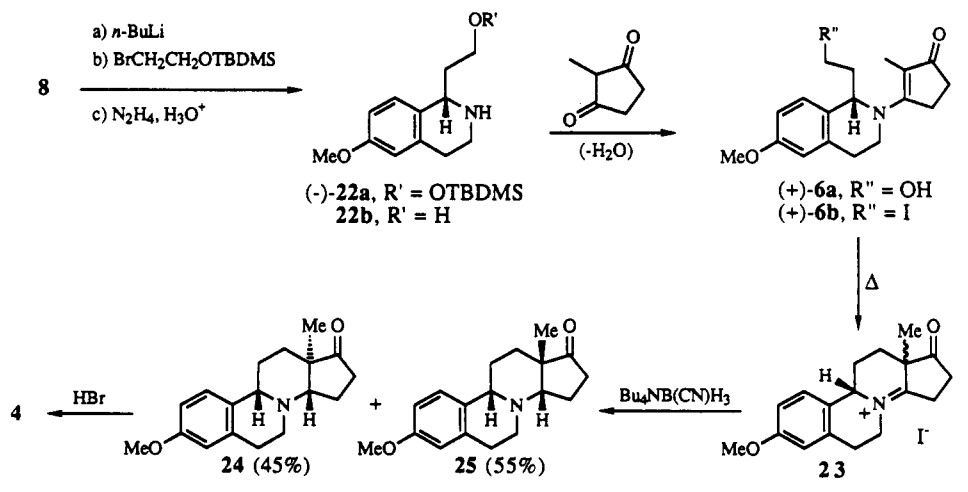


Figure 2.

Scheme V



by use of lithium iodide in dimethylformamide. The relatively unstable, light-sensitive iodide was immediately diluted with benzonitrile, and warming from 40–90 °C furnished the intermediate iminium salt **23**. This material was not isolated, but treated with tetrabutylammonium cyanoborohydride to give a mixture of the 8-azaestrone methyl ethers **24** and **25**. A small amount (~1%) of a third isomer was present, but not isolated. After separa-

tion and purification, the "unnatural" 8-azaestrone methyl ether **24** was obtained in greater than 98% epimeric purity and >99% enantiomeric purity (HPLC). Comparing the CD spectrum of **25** with the 12-oxo-8-azasteroid **3** (Figure 1) showed the rather impressive similarity in their chiroptical response and further supported the notion that **25** contained the β-oriented C-13 methyl group. On the other hand, the "unnatural" azaestrone **4** obtained by cleavage of the methyl ether with boiling 48% HBr showed clear antipodal properties when compared with natural estrone (Figure 2). Except for some shifts in the 200–240 nm region the "mirror" images were quite clear, and this supports the relative configurations of all the stereocenters.

In summary, the use of formamidines with chiral auxiliaries has allowed access to the 8-azasteroid series with high enantiomeric purity. This opens the door to a wide variety of potentially useful steroidal systems with various stereochemical characteristics.

Experimental Section

General. ^{1}H NMR spectra were recorded at 270 or 300 MHz. ^{13}C NMR spectra were recorded at 75 and at 67.5 MHz. Chemical shifts for hydrogen and carbon resonances are reported in ppm (δ) relative to deuteriobenzene or deuteriochloroform (δ = 7.15 or 7.25, respectively) and deuteriodimethyl sulfoxide or deuteriochloroform (δ = 39.5 or 77.0, respectively). Ultraviolet (UV) spectra were taken using a cell of 1.0-cm path length. Infrared (IR) spectra were recorded on a Fourier transformed instrument. Melting points are reported uncorrected. Combustion analyses were performed by Atlantic Microlab, Inc., Norcross, GA.

Thin-layer chromatography (TLC) was performed with glass plates (0.25 mm) precoated with silica gel. Reaction components were then visualized under UV light, in an iodine chamber, and/or dipped in a Dragondorf's solution [two stock solutions are prepared: (A) 1.7 g of bismuth subnitrate dissolved in 20 mL of glacial acetic acid and 80 mL of deionized water and (B) 40 g of potassium iodide dissolved in 100 mL of deionized water and then 5 mL of both A and B are diluted in 90 mL of 20% aqueous acetic acid]. Silica gel (60 Å) for flash chromatography was purchased from Amicon (200–450 mesh). Gas chromatography (GC) was performed employing helium as the carrier gas, a 30-m fused silica (SE-30) capillary column, and a flame ionization detector. Gas chromatography–mass spectrometry (GCMS) was performed with a Hewlett-Packard 5890 GC (equipped with a 12-m × 0.20-mm dimethylpolysiloxane column) linked to a Model 5970 EIMS. High-pressure liquid chromatography (HPLC) was performed at the indicated detection wavelength with a Chiralcel OJ or OD column.

Tetrahydrofuran (THF) and 1,2-dimethoxyethane (DME) were distilled from sodium benzophenone ketyl. Benzene and pentane were distilled from lithium aluminum hydride. Dichloromethane and toluene were distilled from calcium hydride. Benzonitrile and dimethyl formamide (DMF) were distilled, from phosphorous pentoxide and calcium hydride, respectively, under reduced pressure (<20 mmHg). Triethylamine was stored over potassium hydroxide.

(*S*)-(−)-*N*,*N*-Dimethyl-*N*′-[2-(3,3-dimethyl-1-methoxybutyl)]formamidine, 11, via (*S*)-(+)-*tert*-Leucinol, 10. A three-neck, flame-dried, 1-L round-bottom flask was cooled under Ar, equipped with a reflux condensor and a large magnetic stirring bar, and charged with 300 mL of freshly distilled THF and 11.6 g (0.305 mol, 2.0 equiv) of sodium borohydride. The resulting suspension was cooled to ca. 10 °C (tap water bath), and 75 mL (0.612 mol, 4.0 equiv) of BF_3·Et_2O was added over 10 min. While the temperature was maintained between 10 and 15 °C, 20.1 g (0.153 mol, 1.0 equiv) of (*S*)-*tert*-leucine was added in ca. 2-g portions via the side arm. The cooling bath was removed, and the bubbling suspension was stirred for 1 h prior to heating. The mixture was then heated to reflux. After 15 h, the white turbid solution was cooled to ambient temperature and quenched by slow addition of 120 mL of methanol and stirred for an additional 0.5 h. The volatiles were removed with a rotary evaporator, and the resulting white solids were dissolved with 120 mL of 20% aqueous NaOH and then treated with 15 g of NaOH and heated to reflux. After 1 h, the solution was allowed to cool and extracted with chloroform (3 × 100 mL). The aqueous layer was then saturated with NaCl and extracted again with ether (2 × 100 mL). The combined organic layers were washed with brine and dried (Na_2SO_4 and K_2CO_3). During removal of the volatiles in vacuo, *tert*-leucinol, **10**, crystallized as thick white needles (17.55 g, 98%): NOTE! the desired amino alcohol is a low melting solid, mp <35 °C, as well as significantly volatile, bp 65–70 °C (1.3 mmHg); $[\alpha]_D$ = +38.3° (*c* 1.5, EtOH); ^{1}H NMR (300 MHz, C_6D_6) δ 0.74 (s, 9 H), 0.90–1.80 (br s, 2 H), 2.42 (dd, *J* = 3.3, 9.6 Hz, 1 H), 3.25 (t, *J* = 10.0 Hz, 1 H), 3.71 (dd, *J* = 3.3, 10.5 Hz, 1 H), 3.90–4.70 (br s, 1 H); IR (thin film, NaCl) 3345, 3295, 2955, 2875, 1045 cm^{-1}; GCMS t_R = 5.3 min (oven temp: 50 °C for 4 min and then 20°/min to 280 °C); EI *m*/*z* (relative intensity) 86 ($M^+ - CH_2OH$, 23), 70 (8), 69 (10), 60 (base), 56 (16), 42 (54), 41 (73).

A 15 °C solution of **10** (11.8 g, 0.101 mol, 1.0 equiv) and 5 mL of toluene was treated with 14.6 mL (0.103 mol, 1.02 equiv) of dimethylformamide dimethyl acetal and allowed to stir at ambient temperature for 4 h, at which time the volatiles were removed with a rotary evaporator and the residue was azeotroped with toluene (2 × 20 mL) and then in vacuo (2 mmHg). The formamidino alcohol was partially characterized: IR (thin film) 3415, 3025, 2955, 2865, 1649, 1495, 1475, 1370, 1085 cm^{-1}. A 0 °C suspension of 4.3 g (0.106 mol, 1.05 equiv) of oil-free potassium hydride and 6.35 mL (0.102 mol, 1.01 equiv) of methyl iodide in 50 mL of freshly distilled THF was prepared, and the crude formamidino alcohol was added via cannula in 10 mL of THF over 5 min with vigorous stirring. The ice bath was removed, and the resulting white suspension was stirred an additional 20 min. The reaction mixture was quenched with ca. 5 g of Na_2SO_4·10·H_2O, stirred an additional 5 min, and the volatiles were removed with a rotary evaporator. The resulting residue was suspended in 30 mL ether, filtered through Celite, and the filter cake washed with ether (2 × 20 mL). The title compound **11** was distilled via a short-path apparatus at 0.6 mmHg and collected in a dry ice-cooled receiver (16.25 g, 87%) as a clear and colorless liquid: bp 56–59 °C; $[\alpha]_D$ = −103° (*c* 1.4, EtOH); ^{1}H NMR (300 MHz, C_6D_6) δ 1.06 (s, 9 H), 2.47 (br s, 6 H), 2.88 (dd, *J* = 2.7, 8.7 Hz, 1 H), 3.17 (s, 3 H), 3.37 (t, *J* = 8.7 Hz, 1 H), 3.64 (dd, *J* = 2.7, 9.0 Hz, 1 H), 7.17 (br s, 1 H); ^{13}C NMR (75 MHz, C_6D_6) δ 25.8, 27.5, 33.7, 58.6, 74.7, 75.1, 154.0; IR (thin film) 2945, 2870, 1655, 1095 cm^{-1}; GCMS t_R = 7.7 min (oven temp: 50 °C for 4 min then 20°/min to 280 °C); EIMS *m*/*z* (rel int) 186 (M^+, 10), 142 (9), 141 (base), 129 (97), 73 (34), 57 (26), 44 (base).

2-[*N*′-[(*S*)-2-(3,3-Dimethyl-1-methoxybutyl)]formamidino]-6-methoxy-1,2,3,4-tetrahydroisoquinoline, 8. A toluene (12 mL) solution of 6-(8-)methoxytetrahydroisoquinoline,[13] **9** (4.17 g, 25.6 mmol, 1.2 equiv), and *N*,*N*-dimethyl-*N*′-[(*S*)-2-(3,3-dimethyl-1-methoxybutyl)]formamidine, **11** (3.96 g, 21.3 mmol, 1.0 equiv), was heated to reflux. After 43 h, the crude reaction mixture was cooled, and the volatiles were removed with a rotary evaporator. The residue was dissolved in 30 mL of 5% Et_3N/hexanes, filtered through 6 g of silica stacked on Celite, and then washed with an additional 90 mL of 5% Et_3N/hexanes. The title compound was obtained (6.04 g, 90.5%) with 2.5% impurity of the 8-methoxy isomer as a clear/colorless oil: R_f (30% EtOAc/5% Et_3N/hexanes) 0.30; $[\alpha]_D$ = −42° (*c* 0.57, EtOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.84 (s, 9 H), 2.66 (dd, *J* = 2.7, 8.7 Hz, 1 H), 2.80 (t, *J* = 6.0 Hz, 2 H), 3.30 (t with predominant s, *J* = 9.0 Hz, 4 H), 3.39–3.61 (m, 3 H), 3.76 (s, 3 H), 4.36 (d, *J* = 16.2 Hz, 1 H), 4.50 (d, *J* = 16.5 Hz, 1 H), 6.62 (d, *J* = 2.4 Hz, 1 H), 6.72 (dd, *J* = 2.7, 8.4 Hz, 1 H), 7.01 (d, *J* = 8.4 Hz, 1 H), 7.35 (s, 1 H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 27.1, 29.4, 33.6, 43.9, 46.5, 55.2, 58.8, 74.6, 74.7, 112.4, 113.5, 126.2, 127.3, 136.0, 153.4, 157.9; IR (thin film) 2960, 2830, 1650, 1510, 1040 cm^{-1}; GCMS t_R = 10.4 min (oven temp: 50 °C for 0 min, 20°/min to 280 °C for 5 min); EIMS *m*/*z* (rel int) 304 (M^+, 19), 259 (24), 247 (25), 189 (10), 162 (base), 147 (18), 91 (10). Anal. Calcd for $C_{18}H_{28}N_2O_2$: C, 71.05; H, 9.21; N, 9.21. Found: C, 70.97; H, 9.30; N, 9.21.

The 8-methoxy isomer was identified by the presence of signals at δ 6.68 (d, *J* = 8.4 Hz) and 7.11 (t, *J* = 8.1 Hz): GCMS t_R = 9.7 min (oven temp: 50 °C for 0 min, 20°/min to 280 °C for 5

(13) Whaley, W. M.; Govindachari, T. R. *Org. React.* **1951**, *6*, 151. This procedure gave 2–5% of the 8-methoxy isomer which was removed during the purification of **3** and **6a**.

min); EIMS *m/z* (rel int) 305 (5), 304 (M^+, 18), 259 (26), 247 (28), 163 (11), 162 (base), 147 (15), 91 (7).

(*S*)-1-[(*tert*-Butoxycarbonyl)methyl]-6-methoxy-1,2,3,4-tetrahydroisoquinoline, 15 (R = O-*t*-Bu). A 100-mL round-bottom flask was charged with 8 (870 mg, 2.84 mmol, 1.0 equiv) and 60 mL of THF. The solution was cooled with a dry ice/acetone bath and degassed in vacuo for 5 min. *n*-BuLi (0.82 mL, 3.65 M in hexanes, 2.98 mmol, 1.05 equiv) was added over 5 min, giving rise to a deep orange/red solution. During the course of 30 min, a separate 200-mL round-bottom flask was charged with a large magnetic stirring bar, 60 mL of pentane, 15 mL of THF, and oil-free KH (140 mg, 3.4 mmol, 1.2 equiv). The 200-mL flask was cooled to −110 °C (liquid N_2/ether) and sequentially charged with *tert*-butyl chloroacetate (1.20 mL, 8.4 mmol, 3.0 equiv) and the lithiated formamidine added via a dry ice-wrapped Teflon cannula. The mixture was stirred an additional 5 min, quenched slowly with 20 mL of a 5:1 ether/acetic acid solution, and allowed to warm over 10 min with vigorous stirring. It was extracted with aqueous $NaHCO_3$ and ether (4 × 15 mL). Following drying (Na_2SO_4) and removal of the volatiles, the desired ester was isolated by chromatography (70 g of silica, eluted with 5% Et_3N/5% acetone/hexanes) to afford 645 mg (53%) as a clear/colorless oil that solidified to rosettes upon sitting: mp 67–68 °C; R_f (5% Et_3N/20% acetone/hexanes) 0.44; ^1H NMR (270 MHz, $CDCl_3$) δ 0.8 (s, 9 H), 1.4 (s, 9 H), 2.6–3.0 (m, 6 H), 3.2–3.4 (m with predominant s, 5 H), 3.5–3.6 (dd, 1 H), 3.7 (s, 3 H), 4.9–5.1 (br d, 1 H), 6.6–6.7 (m, 2 H), 7.0 (d, 1 H), 7.3–7.4 (m, 1 H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 27.2, 28.0, 33.6, 43.0, 43.2, 55.1, 58.6, 74.1, 74.3, 74.5, 74.7, 80.5, 112.3, 113.7, 127.6, 129.2, 136.2, 152.9, 153.0, 158.2, 170.4; IR (thin film) 2960, 2830, 1650, 1610, 1510, 1115, 1040 cm^{-1}; GCMS t_R = 12.3 min (oven temp: 50 °C for 0 min, 20°/min to 280 °C for 10 min); EIMS *m/z* (rel int) 418 (M^+, 60), 373 (base), 360 (90), 317 (35), 305 (20), 220 (45), 162 (30). Anal. Calcd for $C_{24}H_{38}N_2O_4$: C, 68.90; H, 9.09; N, 6.70. Found: C, 68.86; H, 9.13; N, 6.68.

The *tert*-butyl ester *tert*-leucinol formamidine **13** (660 mg, 1.58 mmol) was dissolved in 12 mL of an 8:1:1 (v/v/v) solution of EtOH/H_2O/HOAc, cooled to about 15 °C, and treated with N_2H_4·H_2O (0.38 mL, 7.9 mmol, 5 equiv). The solution was stirred at ambient temperature for 14 h and then treated with 3 mL of aqueous $NaHCO_3$, diluted with 20 mL of ether, salted out with K_2CO_3, and vigorously stirred while an Ar sparge was maintained through the mixture. The combined organic extract (ether, 3 × 15 mL) was dried (Na_2SO_4 and K_2CO_3). Following removal of the volatiles (rotary evaporator then at 1.5 mmHg and 80–90 °C for 15 min), amine **15** (R = O-*t*-Bu) (430 mg, 51% from **8**) was obtained as a pink oil: HPLC analysis (Chiralcel OJ, 220 nm, 0.5% *i*-PrOH/99.5% hexanes, 2.0 mL/min) t_R = 10.6 min for the *pro*-9*R*-isomer area % 3.53, t_R = 14.4 min for the *pro*-9*S*-isomer area % 96.47; R_f (5% Et_3N/40% acetone/hexanes) 0.46; $[\alpha]_D$ = −35.5° (*c* 1.0, EtOH); ^1H NMR (300 MHz, C_6D_6) δ 1.38 (s, 9 H), 2.21 (br s, 1 H), 2.40 (dt, *J* = 5.1, 15.9 Hz, 1 H), 2.55–2.77 (m, 4 H), 2.93 (dt, *J* = 5.4, 12.0 Hz, 1 H), 3.34 (s, 3 H), 4.43 (dd, *J* = 3.9, 9.0 Hz, 1 H), 6.53 (d, *J* = 2.4 Hz, 1 H), 6.66 (dd, *J* = 2.7, 8.4 Hz, 1 H), 6.79 (d, *J* = 2.7 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.1, 30.2, 41.0, 42.4, 52.5, 55.2, 80.7, 112.2, 113.8, 126.9, 130.0, 136.8, 157.8, 171.7; IR (thin film) 3330, 2970, 2920, 2835, 1725, 1155 cm^{-1}; GCMS t_R = 13.6 min (oven temp: 50 °C for 4 min, 20°/min to 280 °C); EIMS *m/z* (rel int) 277 (M^+, 12), 220 (47), 202 (8), 163 (25), 162 (base), 118 (8).

(*S*)-1-[(*N*,*N*-Diethylcarboxamido)methyl]-6-methoxy-1,2,3,4-tetrahydroisoquinoline, 15 (R = NEt$_2$). According to the procedure describing the preparation of **15** (R = O-*t*-Bu), formamidine **8** (655 mg, 2.15 mmol, 1.0 equiv) was lithiated with *n*-butyllithium (0.62 mL, 3.65 M in hexanes, 1.05 equiv) and alkylated with *N*,*N*-diethyl chloroacetamide (0.44 mL, 3.2 mmol, 1.5 equiv) in the presence of oil-free potassium hydride (105 mg, 2.6 mmol, 1.2 equiv). The crude reaction mixture, following removal of the volatiles, was subjected to N_2H_4·H_2O (0.52 mL, 5 equiv) at rt in 8 mL of EtOH, 1 mL of H_2O, and HOAc (0.37 mL, 3 equiv). The title compound **15** (R = NEt_2) was isolated (12 g of silica, eluted with 5% Et_3N/5% CH_3OH/45% EtOAc/hexanes) to afford 535 mg (90%) as a clear/colorless oil: HPLC analysis (Chiralcel OJ, 220 nm, 2.0% *i*-PrOH/98% hexanes, 2.0 mL/min) t_R = 9.33 min for the *pro*-9*R*-isomer area % 30.7, t_R = 15.25 min for the *pro*-9*S*-isomer area % 69.3; R_f 0.43; ^1H NMR (300 MHz, C_6D_6) δ 0.65 (t, *J* = 7.2 Hz, 3 H), 0.99 (t, *J* = 7.2 Hz, 3 H), 1.90 (br s, 1 H), 2.50 (dd, *J* = 3.9, 9.9 Hz, 1 H), 2.58–2.85 (m, 6 H), 2.93 (dd, *J* = 4.2, 10.2 Hz, 1 H), 3.09–3.36 (m with predominant s, 5 H), 4.79 (t, *J* = 6.3 Hz, 1 H), 6.60 (d, *J* = 2.4 Hz, 1 H), 6.75 (dd, *J* = 2.7, 8.4 Hz, 1 H), 6.91 (d, *J* = 8.4 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.0, 14.1, 26.8, 28.6, 30.3, 34.9, 39.9, 40.1, 40.8, 41.8, 52.3, 55.1, 55.2, 112.0, 112.1, 113.6, 126.7, 130.1, 130.4, 137.0, 139.1, 157.6, 170.5; IR (thin film) 3480, 3320, 3110, 2970, 2925, 1660, 1635, 1040 cm^{-1}; GCMS t_R = 7.8 min (oven temp: 50 °C for 0 min, 30°/min to 280 °C for 5 min); EIMS *m/z* (rel int) 276 (M^+, 2), 247 (1), 202 (3), 176 (8), 175 (36), 163 (12), 162 (base), 118 (15), 117 (9).

Isopropyl Chloroacetate. A 3 M dichloromethane solution of 2-propanol (30 mL, 0.375 mol, 2.5 equiv) and Et_3N (25 mL, 0.18 mol, 1.2 equiv) at −10 °C (methanol/ice) was treated with chloroacetyl chloride (12 mL, 0.15 mol, 1.0 equiv) in 30 mL of dichloromethane. The dichloride was added dropwise from a pressure-equalizing addition funnel over 50 min, and the resulting slurry was stirred at 0 °C for an additional 40 min and then diluted with 200 mL of pentane. The solids were allowed to settle, and the supernatant was decanted into 50 mL of ice–water. The solids were resuspended in 100 mL of fresh pentane, allowed to resettle, and the supernatant combined with the initial extract. The combined organic layer was washed with saturated NH_4Cl (2 × 10 mL) and brine, and then dried over $MgSO_4$. Following filtration, the solution was distilled at 1 atm through a 15-cm Vigreaux column down to ca. 50 mL, and then the pressure was reduced to 3.0 mmHg. The ester was collected at 36–37 °C as a clear/colorless liquid (14.0 g, 68%): ^1H NMR (300 MHz, $CDCl_3$) δ 1.28 (dd, *J* = 0.6, 6.3 Hz, 6 H), 4.02 (d, *J* = 0.6 Hz, 2 H), 5.09 (septet, *J* = 5.4 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.6, 41.2, 70.1, 166.8; IR (thin film) 2980, 2880, 1740, 1465, 1450, 960 cm^{-1}; GCMS t_R = 2.9 min (oven temp: 50 °C for 4 min, 20°/min to 280 °C); EIMS *m/z* (rel int) 123 (M^+ with ^{37}Cl and loss of $-CH_3$, 1.5), 121 (M^+ with ^{35}Cl and loss of $-CH_3$, 4.4), 95 (3), 77 (32), 43 (base).

(*S*)-1-[(Isopropoxycarbonyl)methyl]-2-[*N*′-[(*S*)-2-(3,3-dimethyl-1-methoxybutyl)]formamidino]-6-methoxy-1,2,3,4-tetrahydroisoquinoline, 13 (R = O-*i*-Pr). A 100-mL round-bottom flask was charged with **8** (635 mg, 2.08 mmol, 1.0 equiv) and 45 mL of THF. The solution was cooled with a dry ice/acetone bath and degassed in vacuo for 5 min. *n*-BuLi (0.52 mL, 4.18 M in hexanes, 2.18 mmol, 1.05 equiv) was added over 10 min giving rise to a deep orange/red solution. During the course of 30 min, a separate 200-mL round-bottom flask was charged with a large magnetic stirrer bar, 20 mL of pentane, 7 mL of THF, and isopropyl chloroacetate (0.52 mL, 4.39 mmol, 2.1 equiv) and cooled to −110 °C (liquid N_2/ether). The lithiated formamidine was added rapidly and directly into −110 °C quench solution via a dry ice-wrapped Teflon cannula. The yellow mixture was immediately treated with 1 mL of *i*-PrOH in 20 mL of ether and allowed to warm to ca. 0 °C. It was then poured into a separatory funnel containing 5 mL of water and 5 mL of aqueous $NaHCO_3$. An aliquot was analyzed by GC and found to be (uncorrected) 5% **8**, 5% **14**, 75% **13**, and ca. 10% higher boiling components. Following extraction (EtOAc, 3 × 20 mL), drying (Na_2SO_4), and removal of the volatiles, the desired ester was isolated by chromatography (30 g of silica, rapidly eluted with 5% Et_3N/5% acetone/hexanes) to afford 589 mg (70%) as a clear/colorless oil which solidified to white rosettes: mp 63–65 °C; $[\alpha]_D$ = −38° (*c* 0.62, EtOH); R_f (5% Et_3N/10% acetone/hexanes) 0.34; ^1H NMR (300 MHz, $CDCl_3$) δ 0.86 (s, 9 H), 1.21 (d, *J* = 6.3 Hz, 6 H), 2.61–3.00 (m, 6 H), 3.20–3.32 (m with predominant s, 5 H), 3.58 (dd, *J* = 2.7, 9.1 Hz, 1 H), 3.76 (s, 3 H), 4.95–5.17 (br s with predominant septet, *J* = 6.3 Hz, 2 H), 6.63 (d, *J* = 2.4 Hz, 1 H), 6.71 (dd, *J* = 2.7, 8.7 Hz, 1 H), 7.07 (d, *J* = 8.7 Hz, 1 H), 7.35 (s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.7, 21.7, 27.1, 28.2, 33.6, 42.0, 46.2, 55.1, 58.6, 67.7, 74.1, 74.4, 112.3, 113.7, 127.6, 129.0, 136.2, 152.8, 158.2, 170.6; IR (thin film) 3065, 2950, 2870, 1730, 1650, 1610, 1040, 911 cm^{-1}; GCMS t_R = 11.6 min (oven temp: 50 °C for 0 min, 20°/min to 280 °C for 10 min); EIMS *m/z* (rel int) 405 (10), 404 (M^+, 55), 359 (base), 347 (75), 317 (15), 305 (5), 262 (35), 220 (45), 162 (95), 161 (45). Anal. Calcd for $C_{23}H_{36}N_2O_4$: C, 68.32; H, 8.91; N, 6.93. Found: C, 68.24; H, 8.97; N, 6.94.

1-Oxo-2-[*N*′-[(*S*)-2-(3,3-dimethyl-1-methoxybutyl)]formamidino]-6-methoxy-3,4-dihydroisoquinoline, 14. A 0.045 M

THF solution of 8 (134 mg, 0.44 mmol, 1.0 equiv) was cooled to −78 °C and treated with *n*-BuLi (0.13 mL, 3.65 M in hexanes, 1.05 equiv). The resulting orange/red solution was stirred for 20 min and treated with hexachloroethane (156 mg, 0.66 mmol, 1.5 equiv) in THF (2.0 mL), which gave immediate discoloration. Stirring was continued for 5 min, and then the solution was treated with 0.5 mL of methanol and poured into 10 mL ether and 3 mL of aqueous $NaHCO_3$. GCMS analysis revealed a 1:1 mixture of 8 (t_R = 10.1 min) and 14 (t_R = 11.3 min (oven temp: 50 °C for 0 min, 20°/min to 280 °C for 5 min)); EIMS *m/z* (rel int) 318 (M^+, 2), 303 (2), 273 (54), 261 (32), 219 (4), 178 (base), 160 (12), 135 (9). The title compound, 14, had been earlier isolated and characterized affording the 1(*S*)-[(isopropoxycarbonyl)methyl]- and 1(*S*)-[(*tert*-butoxycarbonyl)methyl] derivatives: R_f (5% Et_3N/10% acetone/hexanes) 0.09; ^1H NMR (300 MHz, $CDCl_3$) δ 0.89 (s, 9 H), 2.95–3.05 (m, 3 H), 3.30 (s, 3 H), 3.36 (t, *J* = 8.7 Hz, 1 H), 3.61 (dd, *J* = 2.7, 9.6 Hz, 1 H), 3.86 (s, 3 H), 3.98–4.16 (m, 2 H), 6.71 (d, *J* = 2.4 Hz, 1 H), 6.86 (dd, *J* = 2.7, 8.7 Hz, 1 H), 8.07 (d, *J* = 8.7 Hz, 1 H), 8.74 (s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 27.0, 27.8, 33.3, 40.5, 55.4, 58.6, 73.3, 74.0, 111.9, 112.8, 121.6, 130.9, 141.5, 147.0, 163.0, 164.3; IR (thin film) 3070, 2960, 2870, 1675, 1650, 1030 cm^{-1}.

(*S*)-1-[(Isopropoxycarbonyl)methyl]-6-methoxy-1,2,3,4-tetrahydroisoquinoline, 15 (R = O-*i*-Pr). The formamidine 13 (R = O-*i*-Pr) (797 mg, 1.97 mmol) was dissolved in 7 mL of *i*-PrOH and 1 mL of deionized water and cooled to 0 °C. The solution was treated with $N_2H_4 \cdot H_2O$ (1.43 mL, 29.5 mmol, 15 equiv) and HOAc (0.34 mL, 5.91 mmol, 3.0 equiv). After 4 h at 0 °C, it was neutralized with 2 mL of aqueous $NaHCO_3$, diluted with 10 mL of ether, salted-out with K_2CO_3, and vigorously stirred while an Ar sparge was maintained through the mixture. The organic layer was allowed to separate and filtered through 3 g of silica stacked on Celite. The aqueous layer was extracted (5% Et_3N/ether, 4 × 15 mL) with each extract being filtered through the silica–Celite pad. Following removal of the volatiles (rotary evaporator, then at 1 mmHg), 15 (455 mg, 88%) was obtained as a clear/colorless oil: HPLC analysis (Chiralcel OJ, 220 nm, 1.0% *i*-PrOH/99% hexanes, 1.5 mL/min) t_R = 10.8 min for the *pro*-9*R*-isomer area % 4.52, t_R = 12.3 min for the *pro*-9*S*-isomer area % 95.08; $[\alpha]_D$ = −89.6° (*c* 0.70, EtOH); ^1H NMR (300 MHz, $CDCl_3$) δ 1.21 (dd, *J* = 3.0, 6.3 Hz, 6 H), 2.29 (br s, 1 H), 2.60–2.85 (m, 4 H), 2.92–3.00 (m, 1 H), 3.16 (dt, *J* = 5.4, 12.0 Hz, 1 H), 3.77 (s, 3 H), 4.35 (dd, *J* = 3.3, 9.3 Hz, 1 H), 5.02 (septet, *J* = 6.3 Hz, 1 H), 6.59 (d, *J* = 2.7 Hz, 1 H), 6.68 (dd, *J* = 2.7, 8.7 Hz, 1 H), 6.97 (d, *J* = 8.7 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.7, 21.8, 30.1, 40.8, 41.6, 52.3, 55.1, 67.8, 112.1, 113.7, 126.8, 129.9, 136.7, 157.8, 171.8; IR (thin film) 3345, 2985, 2935, 1725, 1475, 1450, 1040 cm^{-1}; GCMS t_R = 8.9 min (oven temp: 50 °C for 0 min, 20°/min to 280 °C); EIMS *m/z* (rel int) 263 (M^+, 6), 220 (7), 202 (3), 163 (12), 162 (base), 147 (7), 118 (6).

(−)-Quinolizinone, 5. The isopropyl ester amine 15 (102 mg, 0.39 mmol, 1.0 equiv) was dissolved in 5 mL of toluene, 52 μL of cyclopentanone (0.585 mmol, 1.5 equiv), and 15 μL of TFA (0.19 mmol, 0.5 equiv) and heated in a 25-mL round-bottom flask equipped with Dean-Stark trap. After 5 h at reflux, the mixture was allowed to cool and treated with 10 mL of dichloromethane and 1 mL of aqueous K_2CO_3. Following extraction (dichloromethane, 3 × 5 mL), drying (Na_2SO_4), and removal the volatiles, the residue was subjected to chromatography (10 g of silica, eluted with 5% Et_3N/25% acetone/70% hexanes). The desired compound, 5 (72 mg, 69%), solidified to an amorphous glass upon sitting: mp 179–180.5 °C (lit.[5a] mp 185–187 °C, racemate from EtOAc): R_f (5% Et_3N/45% acetone/hexanes) 0.26; $[\alpha]_D$ = −50° (*c* 0.47, EtOH); UV (EtOH) λ_{max} (ε) 328 (20 200), 222 (19 610, shoulder to 214), 214 (21 500); ^1H NMR (300 MHz, $CDCl_3$) δ 1.96 (quin, *J* = 7.5 Hz, 2 H), 2.45 (t, *J* = 16.2 Hz, 1 H), 2.62 (t, *J* = 7.8 Hz, 2 H), 2.69–2.82 (m, 4 H), 3.09 (dt, *J* = 4.8, 15.9 Hz, 1 H), 3.27 (dt, *J* = 3.0, 12.0 Hz, 1 H), 3.77–3.81 (m with predominant s, 4 H), 4.68 (dd, *J* = 4.2, 16.2 Hz, 1 H), 6.70 (d, *J* = 2.4 Hz, 1 H), 6.82 (dd, *J* = 2.4, 8.7 Hz, 1 H), 7.10 (d, *J* = 8.7 Hz, 1 H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 21.6, 27.2, 28.1, 30.3, 32.6, 44.5, 45.1, 55.2, 110.3, 113.1, 113.5, 126.9, 127.5, 134.8, 158.3, 167.6, 188.4; IR (thin film) 2945, 2910, 1695, 1630, 1040 cm^{-1}.

(9*S*,14*S*)-8-Aza-13-desmethyl-17-desoxo-12,13-didehydro-12-[(triethylsilyl)oxy]estrone Methyl Ether, 21. A benzene solution (10 mL, sparged with Ar for 5 min) of 5 (200 mg, 0.74 mmol, 1.0 equiv) was prepared at rt. In a separate flask under Ar, 745 mg (0.24 mmol, 2.3 equiv of potential hydride) of the copper(I) hydrido hexamer[9] and 0.40 mL (0.836 mmol, 3.2 equiv) of triethylsilyl chloride were dissolved in 10 mL of benzene. The brick-red solution was sparged with Ar for 5 min and added dropwise to the solution of 5. After 1.2 h at rt, the resultant brown solution was diluted with 30 mL of Et_2O and stirred vigorously for 15 min, and the solids were allowed to settle. Following decantation, the solids were resuspended in 40 mL of EtOAc with vigorous stirring, and this extraction process was repeated using EtOAc (2 × 40 mL). The combined organic extracts were washed with 5 g of ice and 10 mL of aqueous $NaHCO_3$ and then with 10 mL of brine. The combined organic extracts were filtered through Na_2SO_4 on Celite. GCMS analysis of the crude reaction mixture revealed 3% of a compound giving *m/z* of 385 (the C14 epimer of 21, ^1H NMR detected none of the $\Delta^{11,12}$ isomer) and 97% of 21. The desired enol ether, 21, was isolated (60 g of silica, eluted with 5% Et_3N/5% ether/hexanes) to afford 227 mg (79%) as a clear/colorless oil: R_f 0.32; $[\alpha]_D$ = −137.8° (*c* 0.45, EtOH); ^1H NMR (300 MHz, $CDCl_3$) δ 0.67 (q, *J* = 7.8 Hz, 6 H), 0.98 (t, *J* = 8.1 Hz, 9 H), 1.28–1.45 (m, 1 H), 1.51–1.69 (m, 1 H), 1.77–1.89 (m, 1 H), 2.07–2.69 (m, 7 H), 2.94–3.18 (m, 2 H), 3.26 (ddd, *J* = 1.5, 5.7, 10.1 Hz, 1 H), 3.54 (dd, *J* = 4.2, 10.8 Hz, 1 H), 3.77 (s, 3 H), 6.61 (d, *J* = 2.7 Hz, 1 H), 6.73 (dd, *J* = 2.7, 8.7 Hz, 1 H), 7.05 (d, *J* = 8.7 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 5.8, 6.7, 22.2, 25.5, 29.7, 32.5, 38.2, 49.2, 55.1, 60.6, 67.2, 112.3, 112.9, 118.5, 126.3, 130.5, 135.8, 140.2, 157.6; IR (thin film) 3025, 2950, 2870, 2790, 2735, 1715, 1610, 1040 cm^{-1}; GCMS t_R = 22.9 min (oven temp: 50 °C for 0 min, 10°/min to 280 °C for 5 min); EIMS *m/z* (rel int) 386 (M^+ + 1, 8), 385 (M^+, 34), 384 (11), 357 (7), 356 (12), 254 (34), 252 (19), 209 (22), 162 (base), 103 (41).

(−)-13-*epi*-Aza-17-desoxo-12-oxoestrone Methyl Ether, 3. The triethylsilylenol ether 21 (134 mg, 0.348 mmol, 1.0 equiv) was diluted with DME (3.0 mL), cooled to 0 °C, and treated with methyllithium (0.42 mL, 1.0 M in ether, 1.2 equiv). The resulting tan solution was stirred at rt for 1.5 h, cooled to −20 °C, and treated with CH_3I (27 μL, 0.44 mmol, 1.25 equiv). After being stirred for 2 h at −20 °C, the reaction was quenched with 0.5 mL of aqueous $NaHCO_3$ and diluted with 5 mL of ether. Following extraction (EtOAc, 2 × 5 mL), drying (Na_2SO_4), and removal of the volatiles, 3 was isolated (by chromatography on 20 g of silica, eluted with 5% EtOAc/20% ether/hexanes and then recrystallized from hexanes at −30 °C) as thick white needles (58 mg, 65%): mp 57–58 °C; R_f (40% EtOAc/hexanes) 0.37; $[\alpha]_D$ = −187° (*c* 0.40, CH_2Cl_2); ^1H NMR (300 MHz, C_6D_6) δ 1.05 (s, 3 H), 1.30–1.44 (m, 2 H), 1.50–1.79 (m, 3 H), 1.89 (ddd, *J* = 0.9, 3.0, 12.9 Hz, 1 H), 2.24–2.36 (m, 3 H), 2.53 (dd, *J* = 11.1, 16.5 Hz, 1 H), 2.85–2.96 (m, 3 H), 3.34 (s, 3 H), 3.56 (dd, *J* = 4.2, 11.1 Hz, 1 H), 6.53 (s, 1 H), 6.68 (d, *J* = 1.5 Hz, 2 H); ($CDCl_3$) δ 1.21 (s, 3 H, C-18*H*$_3$), 1.48–1.83 (m, 4 H), 2.06–2.23 (m, 3 H), 2.50 (dd, *J* = 11.4, 16.8 Hz, 1 H, C-11α*H*$_2$), 2.59 (br d, *J* = 4.9 Hz, 1 H, C-6β*H*$_2$), 2.64 (dd, *J* = 1.5, 15.6 Hz, 1 H, C-14*H*), 3.00 (br dd, *J* = 5.1, 16.5 Hz, 1 H, C-7β*H*$_2$), 3.06 (dd, *J* = 4.5, 16.8 Hz, 1 H, C-11β*H*$_2$), 3.21 (ddd, *J* = 1.8, 5.1, 11.4 Hz, 1 H, C-7α*H*$_2$), 3.77 (s, 3 H), 3.82 (dd, *J* = 4.5, 11.1 Hz, 1 H, C-9*H*), 6.61 (d, *J* = 2.7 Hz, 1 H, C-4*H*), 6.71 (dd, *J* = 2.4, 8.7 Hz, 1 H, C-2*H*), 6.96 (d, *J* = 8.7 Hz, 1 H, C-1*H*); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.6 (CH_2), 24.5 (CH_3), 29.9 (CH_2), 33.4 (CH_2), 36.2 (CH_2), 45.6 (CH_2), 48.6 (CH_2), 54.7 (CH), 55.2, 59.7 (CH), 75.1 (CH_3), 112.6 (CH), 112.8 (CH), 126.4 (CH), 129.9, 135.8, 157.8, 213.1; IR (thin film) 3060, 3030, 2955, 2865, 2795, 2750, 1710, 1610, 1505, 1040 cm^{-1}; GCMS t_R = 15.6 min (oven temp: 50 °C for 2 min, 15°/min to 280 °C for 5 min); EIMS *m/z* (rel int) 286 (M^+ + 1, 17), 285 (M^+, 87), 284 (base), 242 (30), 204 (16), 188 (8), 162 (34), 161 (30), 160 (47), 117 (9). Anal. Calcd for $C_{18}H_{23}NO_2$: C, 75.79; H, 8.07; N, 4.91. Found: C, 75.73; H, 8.12; N, 4.86.

(*S*)-1-(2-Hydroxyethyl)-6-methoxy-1,2,3,4-tetrahydroisoquinoline, 22b. In a 1-L round-bottom flask, 4.30 g (14.1 mmol, 1.0 equiv) of 8 was dissolved in THF (300 mL) and cooled to −78 °C. The flask was evacuated in vacuo (0.8 mmHg) for 10 min and then purged with Ar. *n*-BuLi (7.1 mL, 2.1 M in hexanes, 14.8 mmol, 1.05 equiv) was added dropwise over 10 min and the resulting orange/red solution stirred for 20 min, at which time the dry ice/acetone bath was replaced with liquid N_2/methanol bath. A 2 M THF solution of 2-bromo-1-hydroxyethyl *t*-butyldimethylsilyl ether (3.7 g, 15.5 mmol, 1.10 equiv) was added via syringe pump over 30 min, which decolorized the solution leaving

it pale yellow. The latter was quenched with 3 mL of methanol and allowed to warm to ambient temperature, and the volatiles were removed in vacuo. The efficiency of asymmetric induction was determined by GC (oven temp: 150 °C for 0 min, 5°/min to 280 °C for 5 min): t_R (for the minor *pro*-9*R*-isomer) 16.9 min area % = 1.87, t_R (for the major *pro*-9*S*-isomer) 17.3 min area % = 95.47. The alkylated material was partially characterized: IR (thin film) 2950, 2930, 2860, 1645, 1610, 1505 cm^{-1}; GCMS t_R = 13.3 min (oven temp: 50 °C for 0 min, 20°/min to 280 °C for 5 min); EIMS *m/z* (rel int) 462 (M^+, 14), 417 (23), 405 (37), 320 (24), 176 (38), 162 (base), 73 (75).

The viscous residue was dissolved in 50 mL of EtOH and 3 mL of deionized water and then cooled to about 15 °C. It was then simultaneously treated with 6.8 mL (140 mmol, 10 equiv) $N_2H_4 \cdot H_2O$ and 2.4 mL (42 mmol, 3 equiv) of HOAc. The cooling bath was removed, and the solution was stirred at ambient temperature. After 3 h, the reaction was treated with 2 mL of aqueous $NaHCO_3$, diluted with 100 mL of Et_2O, and salted-out with K_2CO_3, with vigorous stirring and maintaining an Ar sparge through the mixture. The aqueous layer was extracted with ether (3 × 30 mL). The combined organic extract was dried (Na_2SO_4) and filtered through a silica–Celite plug, and the volatiles were removed with a rotary evaporator. The crude amine, **22a**, was obtained as a yellow oil: HPLC analysis (Chiralcel OJ, 220 nm, 1.0% *i*-PrOH/99% hexanes, 0.85 mL/min) t_R = 8.6 min for *pro*-9*R*-isomer area % = 3.33, t_R = 10.1 min for *pro*-9*S*-isomer area % = 95.2; $[\alpha]_D$ = −30° (*c* 1.5, EtOH); ^1H NMR (300 MHz, $CDCl_3$) δ 0.08 (d, *J* = 8.4 Hz, 6 H), 0.93 (s, 9 H), 1.86–2.12 (m, 2 H), 2.71–2.89 (m, 3 H), 2.99 (dt, *J* = 5.4, 13.2 Hz, 1 H), 3.18 (dt, *J* = 5.1, 13.2 Hz, 1 H), 3.79–3.84 (m with predominant s, 5 H), 4.17 (dd, *J* = 2.4, 9.0 Hz, 1 H), 6.62 (d, *J* = 2.7 Hz, 1 H), 6.71–6.77 (m, 1 H), 7.07 (d, *J* = 8.7 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ −5.3, 18.2, 25.9, 30.4, 38.9, 40.7, 53.2, 55.1, 60.9, 112.1, 113.7, 127.2, 131.9, 136.6, 157.5; IR (thin film) 3325, 2950, 2930, 2855, 1095 cm^{-1}; GCMS t_R = 10.3 min (oven temp: 50 °C for 0 min, 20°/min to 280 °C for 5 min); EIMS *m/z* (rel int) 321 (M^+, 4), 260 (5), 188 (4), 162 (base), 147 (5), 118 (6).

The crude silyl ether, **22a**, was dissolved in 25 mL of acetonitrile, sparged with Ar for 5 min, treated with 18 mL of 2 M HF (10% water/90% acetonitrile (v/v) 35 mmol, 2.5 equiv), and stirred at ambient temperature for 3 h. The reaction mixture was quenched with 9 mL of 5 M aqueous NaOH and diluted with 30 mL of ether. The mixture was extracted with dichloromethane (4 × 50 mL), and the combined organic layers were dried over Na_2SO_4. The volatiles were removed in vacuo and the resulting yellow viscous oil solidified to rosettes upon sitting overnight: mp 68–70 °C (lit.[12] mp 85–87 °C, racemate); ^1H NMR (300 MHz, $CDCl_3$) δ 1.86–2.11 (m, 2 H), 2.71–2.85 (m, 2 H), 3.01 (dt, *J* = 5.4, 13.2 Hz, 1 H), 3.16–3.24 (m, 1 H), 3.72–4.05 (m with predominant s, 7 H), 4.21 (dd, *J* = 2.7, 9.0 Hz, 1 H), 6.62 (d, *J* = 2.7 Hz, 1 H), 6.71–6.77 (m, 1 H), 6.97 (d, *J* = 8.7 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 29.7, 36.3, 39.7, 55.2, 56.1, 62.3, 112.5, 113.7, 127.3, 130.4, 136.2, 157.8; IR (thin film) 3300, 3225, 3055, 2940, 2830, 1605, 1035 cm^{-1}.

(+)-3-*N*-[1(*S*)-(2-Hydroxyethyl)-6-methoxy-1,2,3,4-tetrahydroisoquinolyl]-2-methylcyclopent-2-en-1-one, 6a. According to the condensation described earlier,[5b] the amino alcohol **22b** (480 mg, 2.32 mmol, 1.0 equiv) was dissolved in toluene (12 mL) and treated with 2-methyl-1,3-cyclopentanedione (312 mg, 2.78 mmol, 1.2 equiv) and *p*-tolylsulfonic acid hydrate (ca. 10 mg). The mixture was heated to reflux with constant removal of water (Dean-Stark trap) and vigorously stirred for 70 h. The mixture was allowed to cool, treated with 5 mL aqueous $NaHCO_3$, and immediately diluted with 20 mL of dichloromethane. After being stirred vigorously for 2 min, the organic layer was collected and the aqueous layer further extracted with dichloromethane (4 × 15 mL). The combined organics were dried over Na_2SO_4, and the volatiles were removed with a rotary evaporator. The desired vinylogous amide was isolated by chromatography (25 g silica, eluted with 5% Et_3N/5% MeOH/45% acetone/hexanes) to afford **6a** (451 mg, 65% from 8): mp 141–142 °C from $CHCl_3$–Et_2O (lit.[5b] mp 137–139 °C, racemate); R_f 0.22; $[\alpha]_D$ = +48.6° (*c* 0.57, EtOH); UV (EtOH) λ_{max} (ε) 292 (28600), 217 (7900), 202 (24800); ^1H NMR (300 MHz, $CDCl_3$) δ 1.91–2.14 (m with predominant s, 4 H), 2.24 (t, *J* = 4.5 Hz, 2 H, C-16H_2), 2.48 (dt, *J* = 4.8, 16.5 Hz, 1 H, C-6βH_2), 2.77 (t, *J* = 17.4 Hz, 2 H, coincidental triplets of C-6αH_2 and C-15H_2), 2.95 (ddd, *J* = 5.4, 6.0, 10.5 Hz, 1 H, C-15H_2), 3.52–3.72 (m with predominant s, 6 H), 4.20 (dd, *J* = 3.1, 9.9 Hz, 1 H, C-7αH_2), 4.44 (br s, 1 H, O*H*), 5.22 (dd, *J* = 5.1, 8.4 Hz, 1 H, C-9*H*), 6.60 (s, 1 H, C-4*H*), 6.69 (dd, *J* = 2.4, 8.4 Hz, 1 H, C-2*H*), 7.04 (d, *J* = 8.4 Hz, 1 H, C-1*H*); ^{13}C NMR (75 MHz, $CDCl_3$) δ 10.3 (*C*-18H_3), 27.1 (*C*-6H_2), 29.1 (*C*-15H_2), 32.2 (*C*-16H_2), 39.1 (*C*-11H_2), 40.6 (*C*-7H_2), 54.6 (*C*-9H), 55.1 (O*C*H_3), 57.9 (*C*-12H_2), 107.2 (*C*-13), 112.4 (*C*-2H), 113.4 (*C*-4H), 127.8 (*C*-1H), 129.6 (*C*-5 or *C*-10), 134.4 (*C*-5 or *C*-10), 158.2 (*C*-3), 172.5 (*C*-14), 204.3 (*C*-17); IR (thin film) 3345, 3000, 2930, 2870, 1645, 1610, 1535, 1035 cm^{-1}. Anal. Calcd for $C_{18}H_{23}NO_3$: C, 71.76; H, 7.64; N, 4.65. Found: C, 71.67; H, 7.70; N, 4.63.

NOTE: This procedure described the isolation of **6a** by silica gel chromatography starting from isomerically pure **8** (devoid of the 8-methoxy isomer). If the 97.5:2.5 mixture of 6-:8-methoxy isomer of **8** was used, analytically pure **6a** may be isolated in 59% yield in two crops by dissolution of the crude reaction mixture of the sequence above in hot $CHCl_3$ and trituration with Et_2O.

(+)-3-*N*-[1(*S*)-(2-Iodoethyl)-6-methoxy-1,2,3,4-tetrahydroisoquinolyl]-2-methylcyclopent-2-en-1-one, 6b. A solution of 130 mg (0.43 mmol, 1.0 equiv) of **6a** in 5 mL of CH_2Cl_2 at 0 °C was sequentially treated with Et_3N (0.12 mL, 0.86 mmol, 2.0 equiv) and mesyl chloride (37 μL, 0.47 mmol, 1.1 equiv). After 10 min, the solution was treated with 0.5 mL of water and 0.5 mL of saturated K_2CO_3 and stirred for 1 min. The mixture was extracted with dichloromethane (4 × 5 mL) and dried over Na_2SO_4, and the volatiles were removed in vacuo. The residue was dissolved in 2 mL of DMF, treated with 115 mg (0.86 mmol, 2.0 equiv) of LiI, and heated to 50 °C. After 80 min, the solution was allowed to cool and diluted with 5 mL of water and 20 mL of EtOAc. The aqueous layer was further extracted with EtOAc (2 × 10 mL), and the combined organic layers were washed with 10 mL of fresh water and brine. Following drying (Na_2SO_4) and removal of the volatiles, the primary iodide was isolated by chromatography (8 g of silica, eluted with 5% Et_3N/30% acetone/hexanes) as a clear/colorless oil (121 mg, 68%) which became pink to purple upon storage at rt and not protected from the light: R_f (5% Et_3N/5% MeOH/45% acetone/hexanes) 0.43; $[\alpha]_D$ = +55.6° (*c* 0.80, CH_3CN); ^1H NMR (300 MHz, $CDCl_3$) δ 1.92 (s, 3 H), 2.22–2.34 (m, 3 H), 2.39–2.57 (m, 2 H), 2.74 (dd, *J* = 3.9, 15.0 Hz, 2 H), 2.96 (ddd, *J* = 6.0, 10.8, 16.8 Hz, 1 H), 3.16 (t, *J* = 6.9 Hz, 2 H), 3.56 (dt, *J* = 2.7, 13.8 Hz, 1 H), 3.74 (s, 3 H), 4.17 (ddd, *J* = 2.7, 3.0, 13.8 Hz, 1 H), 5.02 (dd, *J* = 5.7, 8.4 Hz, 1 H), 6.62 (d, *J* = 2.7 Hz, 1 H), 6.72 (dd, *J* = 2.7, 8.4 Hz, 1 H), 7.00 (d, *J* = 8.4 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 1.4, 10.4, 27.3, 28.5, 32.6, 40.0, 40.8, 54.9, 57.6, 108.3, 112.4, 113.5, 127.3, 128.0, 134.5, 158.4, 171.1, 204.0; IR (thin film) 3005, 2930, 1650, 1610 cm^{-1}.

(−)-8-Azaestrone Methyl Ether and (−)-13-*epi*-8-Azaestrone Methyl Ether, 24 and 25. The alcohol **6a** (450 mg, 1.5 mmol, 1.0 equiv) was converted to its mesylate and isolated by extraction as described above. The latter was converted to the iodide, **6b**, with 220 mg (1.65 mmol, 1.1 equiv) of LiI in 5 mL of DMF. After 1.2 h at 40 °C (sand-bath temp), the solution was diluted with 20 mL of benzonitrile. The slightly yellow solution was wrapped in foil, and heating was continued for 42 h under Ar. TLC analysis showed **6b** still remaining, so the solution was heated to 80–90 °C for an additional 6 h. It was then cooled to 0 °C and treated with 550 mg (1.95 mmol, 1.3 equiv) of $Bu_4NB(CN)H_3$[14] and stirred for 1.5 h. The solution was treated with 5 mL of saturated K_2CO_3, 5 mL of water, and 25 mL of ether, stirred 5 min, and extracted with dichloromethane (3 × 15 mL). The volatiles were removed from the combined organic layers in vacuo (rotary evaporator and then short-path distillation at 0.04 mmHg). The residue was dissolved in hexanes, loaded on 20 g of silica, and washed with 20% EtOAc/hexanes. The title compounds (228 mg, 53%) were obtained as a 45:55 mixture of **24**:**25**: R_f (25% acetone/hexanes) 0.34; ^1H NMR (300 MHz, C_6D_6) δ 0.74 (s, C-18H_3 of **25**), 0.90 (s, C-18H_3 of **24**).

The desired isomer **24** was isolated by repeated recrystallization from acetone at −30 °C as white prisms: 3× gave 96% epimeric purity and 4× gave >98% epimeric purity by ^1H NMR in C_6D_6 and >99.9% enantiomeric purity by HPLC; t_R = 14.4 min, Chiralcel OD, 220 nm, 1.0% *i*-PrOH/99% hexanes, 0.50 mL/min); mp 205–206 °C (lit.[5b] mp 170–171 °C, racemate); $[\alpha]_D$ = −182°

(14) Hutchings, R. O.; Markowitz, M. *J. Org. Chem.* **1981**, *46*, 3571.

(c 1.4, CH_2Cl_2); ^1H NMR (300 MHz, C_6D_6) δ 0.90 (s, 3 H, C-18H_3), 1.25–1.56 (m, 4 H), 1.70–2.04 (m, 5 H), 2.15 (dd, J = 9.3, 18.9 Hz, 1 H, C-14H), 2.44 (dd, J = 3.0, 16.8 Hz, 1 H, C-6βH_2), 2.77 (ddd, J = 0.6, 4.8, 11.1 Hz, 1 H, C-7αH_2), 2.84 (br d, J = 10.5 Hz, 1 H, C-9H), 3.00 (dt, J = 6.0, 12.9 Hz, 1 H, C-7βH_2), 3.37 (s, 3 H), 6.61 (d, J = 2.7 Hz, 1 H, C-4H), 6.74 (dd, J = 2.7, 8.7 Hz, 1 H, C-2H), 6.95 (d, J = 8.7 Hz, 1 H, C-1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.2 (CH_3), 22.7 (CH_2), 27.2 (CH_2), 29.9 (CH_2), 30.7 (CH_2), 34.7 (CH_2), 47.2 (CH_2), 48.2, 55.1 (CH), 64.5 (CH_3), 69.0 (CH), 111.9 (CH), 113.2 (CH), 125.9 (CH), 130.3, 135.9, 157.7, 219.0; IR (thin film) 3040, 2985, 2955, 2910, 2855, 2835, 2790, 2770, 2725, 1740, 1610, 1500, 1450, 1365, 1305, 1245, 1190, 1035 cm^{-1}; GCMS t_R = 15.9 (oven temp: 50 °C for 2 min, 15°/min to 280 °C for 5 min); EIMS m/z (rel int) 285 (M^+, 32), 284 (21), 257 (14), 256 (9), 162 (13), 161 (base), 146 (11). Anal. Calcd for $C_{18}H_{23}NO_2$: C, 75.79; H, 8.07; N, 4.91. Found: C, 75.70; H, 8.14; N, 4.87.

The supernatants from above were combined and subjected to chromatography (eluted with 5% EtOAc/hexanes) to give 92 mg of **25** (>98% epimerically pure by ^1H NMR in C_6D_6) as fine white needles: mp 115–116 °C; $[\alpha]_D$ = −14.3° (c 0.42, CH_2Cl_2); ^1H NMR (300 MHz, $CDCl_3$) δ 1.02 (s, 3 H, C-18H_3), 1.12–1.26 (m, 1 H, C-11αH_2), 1.43 (dt, J = 4.2, 13.5 Hz, 1 H, C-12βH_2), 1.98–2.51 (m, 7 H), 2.61 (br d, J = 15.0 Hz, 1 H, C-6βH_2), 2.66 (d, J = 3.9 Hz, 1 H, C-14H), 2.99 (dt, J = 4.7, 14.1 Hz, 1 H, C-7αH_2), 3.18 (br d, J = 10.8 Hz, 1 H, C-9H), 3.33 (ddd, J = 1.8, 5.4, 11.4 Hz, 1 H, C-7βH_2), 3.75 (s, 3 H), 6.58 (d, J = 2.4 Hz, 1 H, C-4H), 6.69 (dd, J = 2.4, 8.7 Hz, 1 H, C-2H), 7.07 (d, J = 8.7 Hz, 1 H, C-1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.9 (CH_2), 23.7 (CH_3), 29.2 (CH_2), 30.5 (CH_2), 30.6 (CH_2), 33.5 (CH_2), 48.7 (CH_2), 50.2, 55.2 (CH), 61.8 (CH_3), 69.4 (CH), 112.0 (CH), 113.0 (CH), 126.3 (CH), 131.1, 136.4, 157.8, 222.0; IR (thin film) 2965, 2920, 2835, 2800, 2735, 1735, 1610, 1500, 1460, 1370, 1260, 1240, 1130, 1035, 780 cm^{-1}; GCMS t_R = 15.7 min for **25** (oven temp: 50 °C for 2 min, 15°/min to 280 °C for 5 min); EIMS m/z (rel int) 285 (M^+, 32), 284 (21), 257 (14), 256 (9), 162 (13), 161 (base), 146 (11).

(−)-8-Azaestrone, 4. In a 10-mL round-bottom flask equipped with a reflux condensor, 152 mg (0.53 mmol, 1.0 equiv) of (−)-8-azaestrone methyl ether was treated with 2.0 mL of 48% aqueous HBr. The solution was heated to reflux for 10 h, cooled to rt, diluted with 20 mL of dichloromethane and 10 mL of water, and *slowly* neutralized with 2.1 g of $NaHCO_3$. After being stirred for 15 min, the layers were allowed to separate and the aqueous layer was extracted with $CHCl_3$ (5 × 20 mL). Following washing with brine and drying (Na_2SO_4), silica and Celite (100 mg each) were added to the combined organic extracts and the volatiles were removed. The resulting powder was loaded onto a column (15 g, silica) and eluted with 3% MeOH/CH_2Cl_2. **4** was obtained (114 mg, 80%) as fine white needles: mp 250–252 °C dec; R_f (5:95 MeOH/CH_2Cl_2) 0.44; $[\alpha]_D$ = −182.8° (c 0.28, EtOH); ^1H NMR (300 MHz, DMSO-d_6) δ 0.86 (s, 3 H), 1.30–1.41 (m, 2 H), 1.56–1.70 (m, 2 H), 1.98–2.23 (m, 5 H), 2.42–2.59 (m, 2 H), 2.81 (t, J = 5.7 Hz, 1 H), 2.89 (dd, J = 3.3, 10.2 Hz, 1 H), 3.04 (dd, J = 5.7, 10.5 Hz, 1 H), 6.42 (d, J = 2.4 Hz, 1 H), 6.49 (dd, J = 2.4, 8.4 Hz, 1 H), 6.98 (d, J = 8.4 Hz, 1 H), 9.09 (s, 1 H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 13.8 (CH_3), 22.3 (CH_2), 26.7 (CH_2), 29.3 (CH_2), 30.4 (CH_2), 34.4 (CH_2), 46.9 (CH_2), 47.5 (C), 64.2 (CH), 68.5 (CH_3), 113.0 (CH), 114.5 (CH), 125.8 (CH), 127.5 (C), 135.4 (C), 155.3 (C), 218.0 (C); IR (0.009M in $CHCl_3$) 3315, 3010, 2810, 2750, 1735 cm^{-1}; (KBr plate) 3350, 3020, 2950, 2915, 2860, 2805, 2745, 1725, 1610, 1505, 1455, 1365, 1290, 1190, 1160, 1055, 780 cm^{-1}; GCMS t_R = 11.8 min (oven temp: 50 °C for 0 min, 20°/min to 280 °C for 5 min); EIMS m/z (rel int) 272 (M^+ + 1, 5), 271 (M^+, 27), 270 (9), 243 (13), 242 (15), 214 (6), 148 (13), 147 (base), 146 (38), 91 (10). Anal. Calcd for $C_{17}H_{21}NO_2$: C, 75.28; H, 7.75; N, 5.17. Found: C, 75.01; H, 7.86; N, 5.13.

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Supplementary Material Available: Proton and carbon magnetic resonance spectra for all compounds **3–5, 8, 11, 14, 15, 21, 22, 24,** and **25** and infrared spectra (Bohlmann–Wenkert bands) for **3, 4, 21, 24,** and **25** (37 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

Chemoenzymatic Enantiocontrolled Synthesis of (−)-Specionin†

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Specionin acetate **1a** has been synthesized from chlorobenzene in 15 steps and compared with an authentic sample. The chirality was incorporated into the synthesis by microbial dioxygenation of chlorobenzene using a mutant strain of *Pseudomonas putida*, 39D, to produce 1-chloro-2,3-dihydroxycyclohexa-4,6-diene, which was elaborated into enone **5**. Addition of the lithium dienolate derived from ethyl 4-(dimethyl-*tert*-butylsiloxy)-2-bromocrotonate to this enone provided vinylcyclopropanes **7**, which underwent a low-temperature vinylcyclopropane–cyclopentene rearrangement to tricyclic ketones **8** upon treatment with either trimethylsilyl iodide or tetrabutylammonium fluoride at −78 °C. Following the deoxygenation of the carbonyl and the convergent transformation of both C-4 isomers to a single allylic acetate **11** via either esterification or Mitsunobu inversion, the epoxidation and generation of the bisacetal was accomplished according to the known protocol. The overall yield of this synthesis was 9% for the sequence **5** to **11**. Spectral data and experimental details are provided for key compounds.

Introduction

In addition to its biological activity as an antifeedant to the spruce budworm,[1] specionin **1**, an iridoid sesquiterpene,[2] has an interesting chemical history. Its structure was incorrectly represented as **2**[3] until an unambiguous

† Dedicated to Dr. E. L. Hampton, our martial arts teacher, on the occasion of his 40th birthday.

(1) Chang, C. C.; Nakanishi, K. *J. Chem. Soc., Chem. Commun.* **1983**, 605.

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