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New Asymmetric Approach to Natural Pyrrolizidines: Synthesis of (+)-Amphorogynine A, (+)-Amphorogynine D, and (+)-Retronecine†

Caroline Roche, Katarína Kadlečíková, Amaël Veyron, Philippe Delair,* Christian Philouze, and Andrew E. Greene

Université Joseph Fourier de Grenoble, Chimie Recherche (LEDSS), 38041 Grenoble Cedex, France

David Flot‡ and Manfred Burghammer

European Synchrotron Radiation Facility (ID13 Microfocus Beamline), 38043 Grenoble Cedex, France

Philippe.Delair@ujf-grenoble.fr

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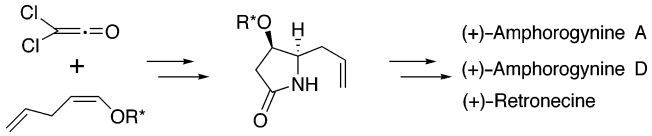

Three natural pyrrolizidines, (+)-amphorogynines A and D and (+)-retronecine, have been prepared from a common lactam intermediate. This central compound, in turn, was synthesized in diastereomerically enriched form through a highly selective [2 + 2]-cycloaddition of dichloroketene with a chiral enol ether, followed by Beckmann ring expansion and reduction. Subsequent stereocenters were then cleanly introduced through internal induction.

Introduction

Pyrrolizidine alkaloids are widespread in nature and capable of affecting a large number of biological processes.[1] Their broad spectrum of biological activities, which includes hepatotoxicity, pneumotoxicity, and nucleotoxicity (mutagenesis, carcinogenesis, antimitotic effects),[1a] and their often novel structures have made them popular synthetic targets for showcasing new synthetic methods and strategies.[2] With few exceptions,[3] however, the syntheses to date have relied on chiral pool material to produce the natural products.

Several years ago, we described an asymmetric preparation of cyclobutanones by [2 + 2]-cycloaddition of dichloroketene to chiral enol ethers[4] and have since studied the application of this chemistry for the synthesis of several types natural products, in particular alkaloids. We have demonstrated that enantiopure pyrrolidines[5] and indolizidines[6] can be readily prepared; we now show that natural pyrrolizidines are also accessible with similar efficiency.[7]

In 1998, Païs and co-workers reported the isolation and structures of four new pyrrolizidines from the New Caledonian plant *Amphorogynine spicata*.[8] These alkaloids, named amphorogynines A, B, C, and D (**1a**−**d**), represented an unknown class of pyrrolizidines, characterized by substitution at C-1 and C-6 (Figure 1).

The main pyrrolizidine class, however, is comprised of azabicycles, such as (+)-retronecine (**2**), having at C-1 a

† This paper is dedicated to our friend and colleague, Prof. André Rassat, deceased July 16, 2005.

‡ To whom inquires concerning the X-ray structure determination should be addressed.

(1) (a) *Naturally Occurring Pyrrolizidine Alkaloids*; Rizk, A.-F. M., Ed.; CRC Press: Boston, 1991. (b) Hartmann, T.; Witte, L. In *Alkaloids: Chemical and Biological Perspectives*; Pelletier, S. W., Ed.; Elsevier Science, Ltd.: Oxford, 1995; Vol. 9, Chapter 4. (c) *Pyrrolizidine Alkaloids*; World Health Organization: Geneva, 1988. (d) Roeder, E. *Curr. Org. Chem.* **1999**, *3*, 557−576. (e) Asano, N.; Nash, R. J.; Molyneux, R. J.; Fleet, G. W. J. *Tetrahedron: Asymmetry* **2000**, *11*, 1645−1680.

(2) Broggini, G.; Zecchi, G. *Synthesis* **1999**, 905−917. Liddell, J. R. *Nat. Prod. Rep.* **1998**, *15*, 363−370. Liddell, J. R. *Nat. Prod. Rep.* **1999**, *16*, 499−507. Liddell, J. R. *Nat. Prod. Rep.* **2000**, *17*, 455−462. Liddell, J. R. *Nat. Prod. Rep.* **2001**, *18*, 441−447. Liddell, J. R. *Nat. Prod. Rep.* **2002**, *19*, 773−781.

(3) See, for example: Denmark, S. E.; Hurd, A. R. *J. Org. Chem.* **2000**, *67*, 2875−2886. Denmark, S. E.; Cottell, J. J. *J. Org. Chem.* **2001**, *66*, 4276−4284.

(4) Greene, A. E.; Charbonnier, F. *Tetrahedron Lett.* **1985**, *26*, 5525−5528.

(5) Kanazawa, A.; Gillet, S.; Delair, P.; Greene, A. E. *J. Org. Chem.* **1998**, *63*, 4660−4663. Delair, P.; Brot, E.; Kanazawa, A.; Greene, A. E. *J. Org. Chem.* **1999**, *64*, 1383−1386.

(6) (a) Pourashraf, M.; Delair, P.; Rasmussen, M.; Greene, A. E. *J. Org. Chem.* **2000**, *65*, 6966−6972. (b) Rasmussen, M.; Delair, P.; Greene, A. E. *J. Org. Chem.* **2001**, *66*, 5438−5443.

(7) For a preliminary account of a portion of this work, see: Roche, C.; Delair, P.; Greene, A. E. *Org. Lett.* **2003**, *5*, 1741−1744.

(8) Huong, D. T. T.; Martin, M.-T.; Litaudon, M.; Sévenet, T.; Païs, M. *J. Nat. Prod.* **1998**, *61*, 1444−1446.

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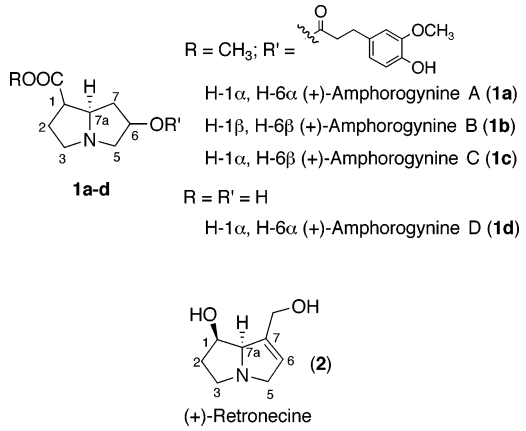


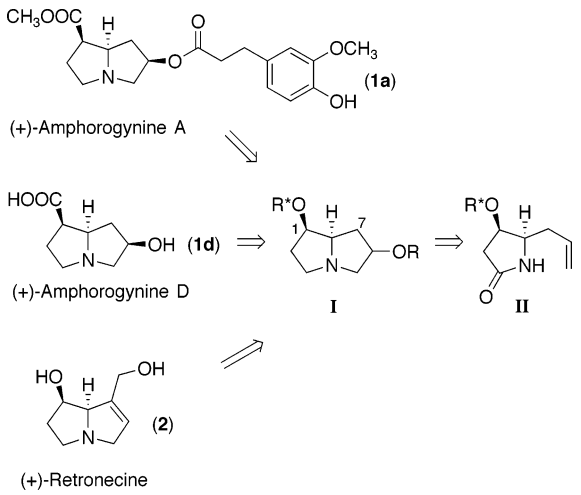
FIGURE 1. Structures of (+)-amphorogynines A−D and (+)-retronecine.

hydroxyl and at C-7 a hydroxymethyl, or functional group derivatives. (+)-Retronecine, the most common of the necine bases, has been isolated from species of *Senecio* and *Crotalaria*[1b] and is found in a variety of alkaloids, such as monocrotaline, senecionine, and retrorsine. Since the first synthesis of racemic retronecine by Geissman and Waiss in 1962,[9] several additional preparations have been carried out.[10] In addition, natural retronecine has been prepared from the chiral pool[11] and the ent-form of the natural product has formally been synthesized through enzymatic resolution.[12] Detailed below are the first reported asymmetric total syntheses of natural (+)-amphorogynine A, (+)-amphorogynine D, and (+)-retronecine.

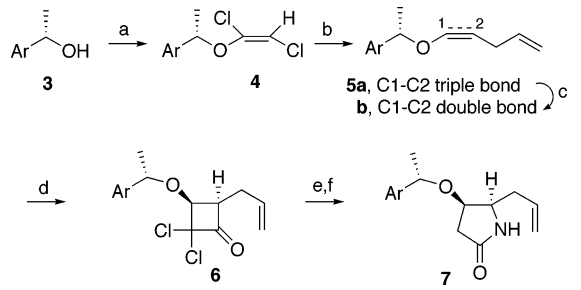
Results and Discussion

Retrosynthetic analysis indicated that intermediate **I** might serve as a common precursor of (+)-amphorogynine A, (+)-amphorogynine D, and (+)-retronecine (Chart 1). Amphorogynines A and D could be derived by methoxycarbonylation at C-1, followed by simple transformations,

CHART 1



SCHEME 1[a]



[a] Reagents: (a) KH, THF; $Cl_2C{=}CHCl$, 79%. (b) C_4H_9Li, THF; $CH_2{=}CHCH_2I$, HMPA. (c) Pd/$BaSO_4$, H_2, $NH_2C_2H_4NH_2$, DMF. (d) Cl_3CCOCl, Zn−Cu, $(C_2H_5)_2O$. (e) $NH_2OSO_2C_6H_2(CH_3)_3$, CH_2Cl_2; Al_2O_3, CH_3OH. (f) Zn−Cu, NH_4Cl, CH_3OH, 72% from **4** (94%/step). Ar = 2,4,6-triisopropylphenyl.

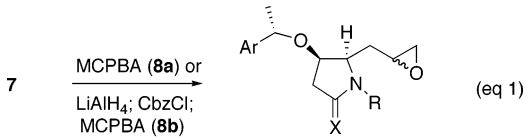
whereas (+)-retronecine might issue from the same azabicycle by introduction of a hydroxymethyl equivalent at C-7, followed by elimination and then precedented transformations. Intermediate **I** could result from oxidation, cyclization, and reduction of pyrrolidone **II**, which appeared might easily be secured through asymmetric dichloroketene−chiral enol ether cycloaddition, followed by Beckmann ring expansion and dechlorination.

On the basis of precedent[13] and molecular modeling studies of the derived enol ether,[7] the *S* enantiomer of 1-(2,4,6-triisopropylphenyl)ethanol (**3**), a readily available[14] and effective chiral controller, was used as the starting material in this work (Scheme 1). Treatment of the chiral alcohol with potassium hydride, followed by trichloroethylene, led in 79% yield to the expected dichloroenol ether (**4**), which was converted into the fragile ynol ether **5a** by reaction with 2.1 equiv of *n*-butyllithium and excess allyl iodide.[15] Careful partial hydrogenation of **5a** with palladium on barium sulfate in the presence of ethylenediamine[16] delivered the corresponding enol ether **5b**, which was contaminated with ca. 8% of the dihydro

(9) Geissman, T. A.; Waiss, A. C. *J. Org. Chem.* **1962**, *27*, 139−142.
(10) Keck, G. E.; Nickel, D. G. *J. Am. Chem. Soc.* **1980**, *102*, 3632−3634. Vedejs, E.; Martinez, G. R. *J. Am. Chem. Soc.* **1980**, *102*, 7993−7994. Tufariello, J. J.; Lee, G. E. *J. Am. Chem. Soc.* **1980**, *102*, 373−374. Niwa, H.; Kuroda, A.; Yamada, K. *Chem. Lett.* **1983**, 125−126. Ohsawa, T.; Ihara, M.; Fukumoto, K.; Kametani, T. *J. Org. Chem.* **1983**, *48*, 3644−3648. Narasaka, K.; Sakakura, T.; Uchimaru, T.; Guédin-Vuong, D. *J. Am. Chem. Soc.* **1984**, *106*, 2954−2961. Vedejs, E.; Larsen, S.; West, G. W. *J. Org. Chem.* **1985**, *50*, 2170−2174.
(11) (a) Rüeger, H.; Benn, M. *Heterocycles* **1983**, *20*, 1331−1334. (b) Buchanan, J. G.; Singh, G.; Wightman, R. H. *J. Chem. Soc., Chem. Commun.* **1984**, 1299−1300. (c) Chamberlin, A. R.; Chung, J. Y. L. *J. Org. Chem.* **1985**, *50*, 4425−4431. (d) Nishimura, Y.; Kondo, S.; Umezawa, H. *J. Org. Chem.* **1985**, *50*, 5210−5214. (e) Niwa, H.; Miyachi, Y.; Okamoto, O.; Uosaki, Y.; Yamada, K. *Tetrahedron Lett.* **1986**, *27*, 4605−4608. (f) Buchanan, J. G.; Jigajinni, V. B.; Singh, G.; Wightman, R. H. *J. Chem. Soc., Perkin Trans. 1* **1987**, 2377−2384. (g) Niwa, H.; Okamoto, O.; Miyachi, Y.; Uosaki, Y.; Yamada, K. *J. Org. Chem.* **1987**, *52*, 2941−2943. (h) Shishido, K.; Sukegawa, Y.; Fukumoto, K.; Kametani, T. *J. Chem. Soc., Perkin Trans. 1* **1987**, 993−1002. (i) Kametani, T.; Yukawa, H.; Honda, T. *J. Chem. Soc., Chem. Commun.* **1988**, 685−686. (j) Niwa, H.; Miyachi, Y.; Okamoto, O.; Uosaki, Y.; Kuroda, A.; Ishiwata, H.; Yamada, K. *Tetrahedron* **1992**, *48*, 393−412. (k) Pandey, G.; Lakshmaiah, G. *Synlett* **1994**, 277−278. (l) For a synthesis of the ent-form, see: Huang, J.-M. H.; Hong, S.-H.; Wu, K.-L.; Tsai, Y.-M. *Tetrahedron Lett.* **2004**, *45*, 3047−3050. (m) For an asymmetric formal synthesis, see: Nagao, Y.; Dai, W.-M.; Ochiai, M.; Shiro, M. *J. Org. Chem.* **1989**, *54*, 5211−5217.
(12) Cooper, J.; Gallagher, P. T.; Knight, D. W. *J. Chem. Soc., Chem. Commun.* **1988**, 509−510.
(13) B. M. de Azevedo, M.; Greene, A. E. *J. Org. Chem.* **1995**, *60*, 4940−4942. Nebois, P.; Greene, A. E. *J. Org. Chem.* **1996**, *61*, 5210−5211. Kanazawa, A.; Delair, P.; Pourashraf, M.; Greene, A. E. *J. Chem. Soc., Perkin Trans. 1* **1997**, 1911−1912.
(14) Delair, P.; Kanazawa, A.; B. M. de Azevedo, M.; Greene, A. E. *Tetrahedron: Asymmetry* **1996**, *7*, 2707−2710.
(15) Kann, N.; Bernardes, V.; Greene, A. E. *Org. Synth.* **1997**, *74*, 13−22.

enol ether. As expected, this crude material underwent highly face selective cycloaddition in the presence of in situ generated dichloroketene[17] to give the desired cyclobutanone **6** as the major diastereomer (93:7 mixture). Ring expansion with Tamura's Beckmann reagent,[18] followed by dechlorination[19] with Zn−Cu couple in methanol saturated with ammonium chloride, provided the key pyrrolidinone intermediate **7** in 72% yield overall yield from **4** (94%/step).

Although it appeared that epoxide opening by the ring nitrogen in the epoxide derived from **7** might be problematical because of difficulty in achieving the proper alignment for attack,[20] the potential directness of this approach to the desired hydroxylated pyrrolizidine overrode this concern. Lactam **7** was thus epoxidized with *m*-chloroperbenzoic acid to give in 89% yield **8a** as a mixture of diasteromeric epoxides (eq 1). This material,



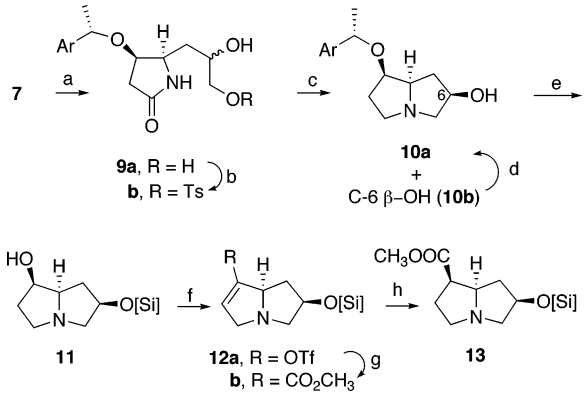
(eq 1)

8a, X = O; R = H
b, X = H,H; R = Cbz

however, did indeed resist all attempts to effect productive cyclization (C_4H_9Li or NaH, with or without Lewis acid) and provided only complex mixtures.[21] It was considered possible that the strongly basic conditions applied to **8a**, instead, were behind these failures, and thus epoxy pyrrolidine **8b** was next prepared from **7** and converted into the free amine by hydrogenolysis. This, though, also proved reluctant to cyclize, despite some precedent.[22]

In view of these unpromising but not totally unexpected results, an alternative sequence to achieve cyclization, based in part on chemistry used in our slaframine work,[6a] was next investigated (Scheme 2). Osmium tetroxide-catalyzed dihydroxylation of **7** furnished the corresponding diol **9a** (55:45 diastereomeric mixture), which could be freed now by chromatography from the small amount of accompanying contamination from the earlier overreduction (during **5a** → **5b**) and isolated in 74% yield. The primary hydroxyl group in **9a** was next selectively tosylated via the dibutylstannoxane derivative, formed in situ, to give hydroxy tosylate **9b** in 87% yield.[23] Treatment of **9b** with excess borane−dimethyl sulfide complex, followed by amine−borane decomplexation with 10% Pd/C and triethylamine in methanol,[24] provided pyrrolizidinol **10a** and its diastereomer **10b** as a readily separable ca. 1:1 mixture. The unwanted isomer **10b** could be converted into **10a** through Swern oxidation to give the corresponding (unstable) ketone, followed by the stereoselective reduction (10:1) with sodium borohydride (51% total yield of **10a** from **9b**). The microcrystalline HCl salt of this pyrrolizidinol permitted the diastereomeric purity of the intermediate to be upgraded to ≥99:1 by recrystallization and, also, its structure and relative (and thus absolute) stereochemistry to be confirmed by X-ray analysis.[25,26]

SCHEME 2[a]



[a] Reagents: (a) OsO_4, $(CH_3)_3NO$, $(CH_3)_3COH/H_2O$ (74%). (b) $(C_4H_9)_2SnO$, CH_3OH; TsCl, $(C_2H_5)_3N$ (87%). (c) $BH_3{\cdot}S(CH_3)_2$, THF; 10% Pd/C, CH_3OH. (d) $(COCl)_2$, $(CH_3)_2SO$, CH_2Cl_2; $(C_2H_5)_3N$. $NaBH_4$, C_2H_5OH (51% from **9b**). (e) TBDPSCl, imidazole, DMAP, DMF. CF_3COOH, CH_2Cl_2 (74%). (f) $(COCl)_2$, $(CH_3)_2SO$, CH_2Cl_2; $(C_2H_5)_3N$. LiHMDS, THF; Comins triflimide (68% from **11**). (g) $Pd(OCOCH_3)_2$, $(C_6H_5)_3P$, $(C_2H_5)_3N$, CO, CH_3OH−DMF (63%). (h) 10% Pd/C, H_2, CH_3OH (93%). [Si] = TBDPS.

The C-6 hydroxyl group in **10a** was now protected as its *tert*-butyldiphenylsilyl ether, which was sufficiently robust to permit selective cleavage of the C-1 ether with trifluoroacetic acid to give alcohol **11** (74%, two steps). The free C-1 hydroxyl group in **11** was next oxidized under Swern conditions to afford the corresponding unstable ketone, which could be converted selectively into enol triflate **12a** in 68% overall yield by enolization with LiHMDS, followed by enolate trapping with the Comins

(16) Campos, K. R.; Journet, M.; Cai, D.; Kowal J. J.; Lee, S.; Larsen, R. D.; Reider, P. J. *J. Org. Chem.* **2003**, *68*, 2338−2342. These conditions were more selective than those previously used.[7]

(17) Hassner, A.; Krepski, L. R. *J. Org. Chem.* **1978**, *43*, 3173−3179. Brady, W. T.; Lloyd, R. M. *J. Org. Chem.* **1979**, *44*, 2560−2564. For reviews on dichloroketene, see: Hyatt, J. A.; Raynolds, P. W. *Org. React.* **1994**, *45*, 159−646. Tidwell, T. T. *Ketenes*; Wiley: New York, 1995.

(18) Tamura, Y.; Minamikawa, J.; Ikeda, M. *Synthesis* **1977**, 1−17.

(19) Johnston, B. D.; Slessor, K. N.; Oehlschlager, A. C. *J. Org. Chem.* **1985**, *50*, 114−117.

(20) Baldwin, J. *J. Chem. Soc., Chem. Commun.* **1976**, 734−736.

(21) For related examples, see: LaLonde, R. T.; Muhammad, N.; Wong, C. F.; Sturiale, E. R. *J. Org. Chem.* **1980**, *45*, 3664−3671.

(22) Ratovelomanana, V.; Vidal, L.; Royer J.; Husson, H. P. *Heterocycles* **1991**, *32*, 879−888.

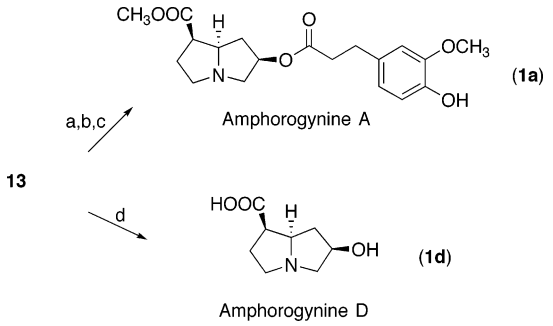
(23) For a similar conversion, see: Ley, S. V.; Brown, D. S.; Clase, J. A.; Faibanks, A. J.; Lennon, I. C.; Osborn, H. M. I.; Stokes, E. S. E.; Wadsworth, D. J. *J. Chem. Soc., Perkin Trans. 1* **1998**, 2259−2276. See also: Martinelli, M. J.; Vaidyanathan, R.; Pawlak, J. M.; Nayyar, N. K.; Dhokte, U. P.; Doecke, C. W.; Zollars, L. H. M.; Moher, E. D.; Khau, V. V.; Kosmrlj, B. *J. Am. Chem. Soc.* **2002**, *124*, 3578−3585.

(24) Couturier, M.; Tucker, J. L.; Andresen, B. M.; Dubé, P.; Negri, J. T. *Org. Lett.* **2001**, *3*, 465−467.

(25) Because of the small crystal size (0.3 × 0.04 × 0.04 mm) and its weak diffraction, this analysis could only be achieved with the high-intensity, microfocused source at the European Synchrotron Radiation Facility (ID13 Microfocus Beamline). Diffraction patterns from crystals as small as 3 × 3 × <1 μm can be recorded and refined through the use of this unique tool. See: Gaillot, A. C.; Flot, D.; Drits, V. A.; Manceau, A.; Burghammer, M.; Lanson, B. *Chem. Mater.* **2003**, *15*, 4666−4678. Zolotukhin, M. G.; Colquhoun, H. M.; Sestiaa, L. G.; Williams, D. J.; Rueda, D. R.; Flot, D. *Polymer* **2004**, *45*, 783−790.

(26) Crystal data for $C_{24}O_2N_1H_{40}Cl_1$: monoclinic, *C*2/*c*, a = 40.563(7) Å, b = 6.287(1) Å, c = 18.840(3) Å, β = 93.912(5)°, V = 4793(2) Å^3, Z = 8, d_{calcd} = 1.136 mg/m^3, $F(000)$ = 1792.0, Θ_{max} range 2.04−29.10°, 117 141 measured reflections, 5949 [R(int) = 0.089] independent reflections, refinement on F: R(1) [1 > 2σ (I)] = 0.046, wR2 [all data] = 0.075, GOF (all data) = 1.969. The Crystallographic Information File (CIF) has been deposited at the Cambridge Crystallographic Data Centre, as CCDC 271614. These data can be obtained from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, U.K.; fax, (+44) 1223-336-033; deposit@ccdc.cam.ac.uk.

SCHEME 3[a]



[a] Reagents: (a) TBAF, THF (82%). (b) *O*-TBDMS hydroferulic acid, DIC, DMAP, CH_2Cl_2 (70%). (c) TBAF, THF (77%). (d) 12 N HCl, dioxane (77%).

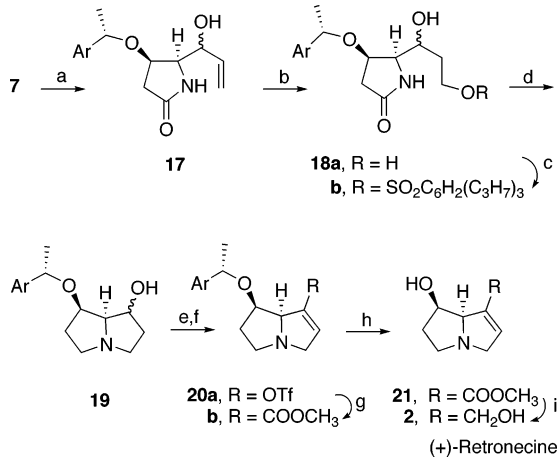
triflimide.[27] Palladium-catalyzed carbomethoxylation[28] of **12a** delivered in 63% yield the conjugated ester **12b**, which, because of its folded topography and bulky silyloxyl group on the concave face, underwent hydrogenation exclusively on the convex face to afford ester **13** in 93% yield.

From this central intermediate, the syntheses of amphorogynines A and D could readily be achieved (Scheme 3). Amphorogynine A was obtained by deprotection of the C-6 hydroxyl group in **13** with TBAF to give the free alcohol (**14**, not shown), which was esterified with *tert*-butyldimethylsilyl-protected hydroferulic acid.[29] Removal of the phenolic silyl group in the ester with TBAF in THF then cleanly afforded **1a**. The IR, ^{1}H NMR, and ^{13}C NMR spectra of synthetically derived amphorogynine A (mp 103−104 °C; $[\alpha]^{20}_D$ +42) were superimposable with those of an authentic sample of the natural product (mp 102−103 °C; $[\alpha]^{20}_D$ +44).[30]

Amphorogynine D, in turn, could be directly accessed from the silyloxy ester **13** by acid hydrolysis, followed by cation exchange chromatography. While the ^{1}H NMR spectrum of the product was not strictly concordant with the data reported[8] for the natural compound, an authentic sample, prepared by hydrolysis of natural amphorogynine A, was identical with our material. Furthermore, the methyl esters (HCl salts) and the ethyl esters derived from the synthetic and natural compounds were also indistinguishable.[31]

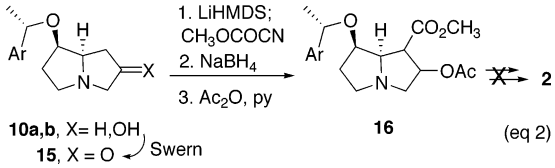
Given the central position of (+)-retronecine among the natural pyrrolizidines, we next focused on its preparation. It was hoped that the mixture of alcohols **10a**,**b** could be efficiently oxidized to the corresponding ketone (prepared earlier from pure **10b**). If this were the case, methoxycarboxylation via the probable kinetical enolate (away from the nitrogen atom[32]) would then give a keto ester, which might be an effective precursor of retronecine. To

SCHEME 4[a]



[a] Reagents: (a) SeO_2, TBHP, $ClCH_2CH_2Cl$ (62%). (b) Catechol borane, $((C_6H_5)_3P)_3RhCl$, THF; H_2O_2, H_2O (72%). (c) $(C_3H_7)_3C_6H_2SO_2Cl$, DMAP, $(C_2H_5)_3N$, DMF (75%). (d) $BH_3{\cdot}(CH_3)_2S$, THF; 10% Pd/C, CH_3OH (88%). (e) $(CH_3)_2SO$, $(COCl)_2$, CH_2Cl_2; $(C_2H_5)_3N$. (f) KHMDS, THF; Comins triflimide (50%, two steps). (g) $Pd(P(C_6H_5)_3)_4$, CH_3OH, DMF, CO (1 atm) (61%). (h) CF_3COOH, CH_2Cl_2 (100%). (i) Dibal-H, THF, −78 °C (65%).

this end, the epimeric mixture of alcohols **10a**,**b** was converted by Swern oxidation into the corresponding fragile ketone **15** (eq 2). Deprotonation of this ketone at



low temperature with LiHMDS and treatment of the enolate with Mander's reagent,[33] which minimized *O*-methoxycarboxylation, yielded regioselectively the expected keto ester. This unstable compound was immediately reduced with sodium borohydride and acetylated to give diester **16**. Unfortunately, despite considerable experimentation, the overall yield of this diester never exceeded 29% and was often much lower. This, coupled with unpromising results on attempted acetate elimination, prompted us to back up in the sequence and study the attractive alternative approach that involved functionalizing the allylic (pro C-7) position prior to cyclization (Scheme 4).

Lactam **7** was thus converted by using selenium dioxide and *tert*-butyl hydroperoxide into allylic alcohol **17**[34] (62%), which, through rhodium-catalyzed hydrobo-

(27) Comins, D. L.; Dehghani, A. *Tetrahedron Lett.* **1992**, *33*, 6299−6302.

(28) Cacchi, S.; Morera, E.; Ortar, G. *Tetrahedron Lett.* **1985**, *26*, 1109−1112.

(29) Solladié, G.; Gressot-Kempf, L. *Tetrahedron: Asymmetry* **1996**, *7*, 2371−2379. Hydroferulic acid is available from Lancaster Synthesis, Bischheim, Strasbourg, France.

(30) A chiral-pool synthesis of amphorogynine A appeared contemporaneously with our preliminary report.[7] See: Yoda, H.; Egawa, T.; Takabe, K. *Tetrahedron Lett.* **2003**, *44*, 1643−1646.

(31) The ^{1}H NMR spectrum of the ethyl ester was in full agreement with the data reported by Robins and Sakdarat. See: Robins, D. J.; Sakdarat, S. *J. Chem. Soc., Perkin Trans. 1* **1981**, 909−911.

(32) See, for example: Garst, M. E.; Bonfiglio, J. N.; Grudoski, D. A.; Marks, M. *J. Org. Chem.* **1980**, *45*, 2307−2315. Giles, M.; Hadley, M. S.; Gallagher, T. *J. Chem. Soc., Chem. Commun.* **1990**, 1047−1048. Sharma, R.; Lubell, W. D. *J. Org. Chem.* **1996**, *61*, 202−209. Boumendjel, A.; Roberts, J. C.; Hu, E.; Pallai, P. V. *J. Org. Chem.* **1996**, *61*, 4434−4438. Blanco, M.-J.; Paleo, M. R.; Penide, C.; Sardina, F. J. *J. Org. Chem.* **1999**, *64*, 8786−8793.

(33) Mander, L. N.; Sethi, S. P. *Tetrahedron Lett.* **1983**, *24*, 5425−5428. Crabtree, S. R.; Mander, L. N. *Org. Synth.* **1991**, *70*, 256−264.

(34) Allylic alcohol **17** had recently been prepared in our laboratory in conjunction with another project. See: Ceccon, J.; Poisson, J.-F.; Greene, A. E. *Synlett* **2005**, 1413−1416. Several alternative methods were unsuccessful: Andrus, M. B.; Lashley, J. C. *Tetrahedron* **2002**, *58*, 845−866. Gokhale, A. B.; Minidis, A. E. B.; Pfaltz, A. *Tetrahedron Lett.* **1997**, *36*, 1831−1836. Chen, M. S.; White, M. C. *J. Am. Chem. Soc.* **2004**, *126*, 1346−1347.

ration and oxidation,[35] yielded the desired 1,3-diol **18a** as a ca. 1:1 mixture of diastereomers in 72% yield. Selective activation of the primary alcohol, in preparation for cyclization, was best achieved by using bulky triisopropylbenzenesulfonyl chloride, which furnished sulfonate **18b** in 75% yield. The cyclization step was conducted with excess borane−dimethyl sulfide complex in THF, as before, to give pyrrolizidinol **19** in excellent yield (1:1 mixture of diastereoisomers). Carefully controlled Swern oxidation of **19** afforded the corresponding unstable ketone, which could be converted into enol triflate **20a** with KHMDS and the Comins reagent (50% yield, two steps). Palladium-catalyzed methoxycarbonylation[28] of this derivative next produced in 61% yield the corresponding unsaturated ester **20b**, which showed only trace amounts of diastereomeric impurities (≤2%) in its 500-MHz ^{1}H NMR spectrum. The C-1 hydroxyl group was now liberated in quantitative yield with 10% trifluoroacetic acid in methylene chloride to provide hydroxy ester **21**, an intermediate common to several syntheses of the natural product. The synthesis was completed by treatment of the hydroxy ester with Dibal-H at −78 °C, as previously described,[11k] to furnish (+)-retronecine, indistinguishable from an authentic sample of the natural product obtained by hydrolysis of natural monocrotaline.[36]

Conclusion

In summary, three natural pyrrolizidines, (+)-amphorogynines A and D and (+)-retronecine, have been prepared from a common intermediate, lactam **7**. This central intermediate, in turn, was synthesized in diastereomerically enriched form through a highly selective [2 + 2]-cycloaddition of dichloroketene with a chiral enol ether, followed by Beckmann ring expansion and reduction. Subsequent stereocenters were then cleanly introduced through internal induction. The high degree of stereocontrol and flexibility inherent in this approach should allow access to several other types of pyrrolizidines.

Experimental Section[37]

2-[(*S*)-1-(*E*)-1,2-Dichlorovinyloxyethyl]-1,3,5-triisopropylbenzene (4). A suspension of 11.2 g (0.084 mol) of 30% KH in mineral oil was placed in an argon-flushed flask and washed three times with pentane. A solution of 10.0 g (0.040 mol) of (*S*)-(−)-1-(2,4,6-triisopropylphenyl)ethanol in 140 mL of THF was then added dropwise. The mixture was stirred until hydrogen evolution was complete (ca. 2 h), cooled to −50 °C, and treated dropwise over 30 min with 4.00 mL (0.045 mol) of trichloroethylene. The reaction mixture was then allowed to warm to 20 °C over 2 h and treated carefully with methanol until the end of the effervescence. The mixture was diluted with pentane, which was then washed with saturated aqueous NH_4Cl, dried over Na_2SO_4, and filtered. The crude product obtained on concentration of the filtrate was purified by filtration through silica gel (triethylamine-deactivated) with pentane to afford 11.0 g (79%) of dichloro enol ether **4**: mp 38−41 °C (pentane); $[\alpha]^{20}_D$ +16.0 (*c* 1.0, chloroform); IR 3086, 1623, 1609, 1078, 1040 cm^{-1}; ^{1}H NMR (300 MHz) δ 1.20−1.35 (m, 18 H), 1.70 (d, J = 6.9 Hz, 3 H), 2.90 (sept, J = 6.9 Hz, 1 H), 3.15−3.75 (m, 2 H), 5.60 (s, 1 H), 6.00 (q, J = 6.8 Hz, 1 H), 7.05 (s, 2 H); ^{13}C NMR (75.5 MHz) δ 20.3 (CH_3), 23.9 (CH_3), 24.5 (CH_3), 24.7 (CH_3), 29.4 (CH), 34.1 (CH), 76.4 (CH), 98.3 (CH), 122.1 (CH), 131.2 (C), 142.9 (C), 148.5 (C); MS (EI) *m/z* 343 and 341 (M^+), 248, 231 (100). Anal. Calcd for $C_{19}H_{28}Cl_2O$: C, 66.47; H, 8.22. Found: C, 66.63; H, 8.36.

2-[(*S*)-1-(Pent-4-en-1-ynyloxy)ethyl]-1,3,5-triisopropylbenzene (5a). To a solution of 15.25 g (44.42 mmol) of dichloro enol ether **4** in 350 mL of THF at −90 °C was added dropwise 46.2 mL (115.5 mmol) of a 2.5 M solution of *n*-butyllithium in hexanes. The reaction mixture was allowed to warm to −40 °C and treated dropwise with 12.2 mL (133.1 mmol) of allyl iodide (filtered over basic alumina) and then with 33 mL of HMPA. The resulting solution was allowed to warm to 0 °C over 2 h and then poured into cold saturated NH_4Cl. The aqueous layer was extracted three times with cold pentane. The combined organic phase was washed with water, dried over Na_2SO_4, filtered, and concentrated to give 15.19 g of acetylenic enol ether **5a** as a yellow oil, which was used immediately without purification: IR (film) 3005, 2960, 2930, 2869, 2269, 1608, 1460, 1230 cm^{-1}; ^{1}H NMR (300 MHz) δ 1.15−1.35 (m, 18 H), 1.72 (d, J = 6.9 Hz, 3 H), 2.75−2.95 (m, 3 H), 3.15−3.45 (m, 2 H), 4.85−5.05 (m, 2 H), 5.65−5.80 (m, 2 H), 7.00 (s, 2 H); ^{13}C NMR (75.5 MHz) δ 21.6 (CH_3), 23.9 (CH), 23.9 (CH_3), 24.5 (CH_3), 29.3 (CH), 34.1 (CH_2), 83.0 (CH), 91.7 (C), 114.8 (CH_2), 119.3 (CH), 120.4 (CH), 122.0 (C), 130.9 (C), 134.1 (CH), 148.5 (C).

2-[(*S*)-1-((*Z*)-Penta-1,4-dienyloxy)-ethyl]-1,3,5-triisopropylbenzene (5b). To a solution of 15.19 g of crude ynol ether **5a** in 82 mL of DMF at 0 °C were added 1.8 g of 10% palladium on barium sulfate and 2.00 mL (29.9 mmol) of ethylenediamine. The mixture was vigorously stirred at 0 °C under a hydrogen atmosphere for 10 min, after which 17.1 mL of 1-hexene was added dropwise. After being stirred for 9 h (the reaction was followed by IR), the mixture was diluted with pentane and filtered over Celite. The filtrate was thoroughly washed with cold water and brine, dried over Na_2SO_4, filtered, and concentrated at 0 °C under reduced pressure to provide 14.19 g of enol ether **5b** as a yellow oil, which was used without further purification: IR (film) 2961, 2935, 2867, 1667, 1612, 1464, 1384 cm^{-1}; ^{1}H NMR (300 MHz) δ 1.20−1.35 (m, 18 H), 1.63 (d, J = 6.9 Hz, 3 H), 2.80−3.00 (m, 2 H), 3.30−3.70 (m, 2 H), 4.31 (m: dddd, J = 7.3, 7.3, 6.3, 1.1 Hz, 1 H), 4.95 (br d, J = 10.0 Hz, 1 H), 5.05 (br d, J = 17.2 Hz, 1 H), 5.37 (q, J = 6.9 Hz, 1 H), 5.85 (m: ddddd, J = 17.2, 10.0, 6.2, 6.2, 1.1 Hz, 1 H), 6.03 (m: dddd, J = 6.3, 1.4, 1.4, 1.4 Hz, 1 H), 7.03 (s, 2 H); ^{13}C NMR (75.5 MHz) δ 22.5 (CH_3), 23.9 (CH_3), 24.5 (CH_3), 28.5 (CH_2), 29.1 (CH), 34.0 (CH), 75.4 (CH), 103.3 (CH), 113.9 (CH_2), 121.9 (CH), 133.0 (C), 137.7 (CH), 144.5 (CH), 147.7 (C).

(3*S*,4*R*)-4-Allyl-2,2-dichloro-3-[(*S*)-1-(2,4,6-triisopropylphenyl)ethoxy]cyclobutanone (6). To a stirred suspension of 14.14 g of crude enol ether **5b** and 14.7 g (224.8 mmol) of Zn−Cu couple in 420 mL of ether was added over 25 min a solution of 6.00 mL (53.8 mmol) of freshly distilled trichloroacetyl chloride in 105 mL of ether. The mixture was vigorously stirred for an additional 1 h at 20 °C, after which the ethereal mixture was filtered over Celite and diluted with a large volume of pentane. The resulting mixture was partially concentrated under reduced pressure, filtered over Celite, and diluted with pentane again. These steps were repeated until the removal of the zinc chloride was complete. The filtrate was then washed with saturated aqueous $NaHCO_3$, dried over Na_2SO_4, and concentrated to give 17.97 g of cyclobutanone **6** as yellow solid, which was used below without further purification: IR (film) 2965, 2931, 2871, 1806, 1608, 1458, 1382 cm^{-1};

(35) Rao, A. V. R.; Mysorekar, S. V.; Yadav, J. S. *Synth. Commun.* **1987**, *17*, 1339−1347. Uncatalyzed hydroboration with disiamylborane, borane−dimethyl sulfide, dihexylborane, or 9-BBN gave a low yield and/or unsatisfactory regioselectivity.

(36) Donohoe, T. J.; Guillermin, J.-B.; Walter, D. S. *J. Chem. Soc., Perkin Trans. 1* **2002**, 1369−1375.

(37) Complex multiplets (m) have been analyzed, when possible, by using the method of Hoye and co-workers: Hoye, T. R.; Hanson, P. R.; Vyvyan, J. R. *J. Org. Chem.* **1994**, *59*, 4096−4103. Hoye, T. R.; Zhao, H. *J. Org. Chem.* **2002**, *67*, 4014−4016.

^{1}H NMR (300 MHz) δ 1.10−1.40 (m, 18 H), 1.66 (d, J = 6.9 Hz, 3 H), 2.45−2.65 (m, 2 H), 2.87 (sept, J = 6.9 Hz, 1 H), 3.29 (sept, J = 6.9 Hz, 1 H), 3.52 (m: ddd, J = 9.4, 9.4, 6.3 Hz, 1 H), 3.83 (sept, J = 6.9 Hz, 1 H), 4.33 (d, J = 9.4 Hz, 1 H), 5.02−5.18 (m, 2 H), 5.45 (q, J = 6.9 Hz, 1 H), 5.86 (m: dddd, J = 17.0, 10.1, 6.9, 6.9 Hz, 1 H), 7.00 (d, J = 2.0 Hz, 1 H), 7.07 (d, J = 2.0 Hz, 1 H); ^{13}C NMR (75.5 MHz) δ 22.5 (CH_3), 23.9 (CH_3), 24.9 (CH_3), 25.4 (CH_3), 28.2 (CH), 29.2 (CH), 29.7 (CH_2), 34.0 (CH), 58.5 (CH), 73.4 (CH), 77.2 (CH), 88.3 (C), 117,1 (CH_2), 120.8 (CH), 123.4 (CH), 134.5 (CH), 147.1 (C), 148.3 (C), 148.9 (C), 195.8 (C); MS (DCI, NH_3 + isobutane) *m/z* 444, 429, 427, 425 (MH^+), 232, 231 (100), 230.

(4*R*,5*R*)-5-Allyl-4-[(*S*)-1-(2,4,6-triisopropylphenyl)ethoxy]-pyrrolidin-2-one (7). A solution of 18.31 g of crude cyclobutanone **6** in 460 mL of dichloromethane at 20 °C was treated with 13.9 g of *O*-mesitylenesulfonylhydroxylamine and a small amount of Na_2SO_4 and stirred for 9 h. Additional 1.0-g portions of *O*-mesitylenesulfonylhydroxylamine were added after 4, 6, and 7 h. After filtration of the mixture over Celite, the solvent was removed under reduced pressure and the resulting residue was dissolved in 200 mL of toluene and placed on a column of 650 mL of basic alumina, which was eluted with methanol. The fractions were combined and concentrated under reduced pressure, and the resulting residue was triturated with dichloromethane, and the mixture was filtered over Celite. Evaporation of the solvent left 17.46 g of dichloro lactam (4*R*,5*R*)-5-allyl-3,3-dichloro-4-[(*S*)-1-(2,4,6-triisopropylphenyl)-ethoxy]pyrrolidin-2-one as a yellow solid: mp 112−116 °C (pentane); IR (film) 3248, 2964, 2924, 2864, 1735, 1610, 1462 cm^{-1}; ^{1}H NMR (300 MHz) δ 1.12−1.40 (m, 18 H), 1.72 (d, J = 6.8 Hz, 3 H), 2.15−2.40 (m, 1 H), 2.55−2.65 (m, 1 H), 2.84 (sept, J = 6.9 Hz, 1 H), 3.34 (sept, J = 6.8 Hz, 1 H), 3.55−3.64 (m, 1 H), 3.89 (sept, J = 6.8 Hz, 1 H), 4.44 (d, J = 7.0 Hz, 1 H), 5.08−5.18 (m, 2 H), 5.60−5.80 (m, 2 H), 6.10 (br s, 1H), 6.96 (d, J = 1.8 Hz, 1 H), 7.04 (d, J = 1.8 Hz, 1 H); ^{13}C NMR (75.5 MHz) δ 23.0 (CH_3), 23.9 (CH_3), 25.0 (CH_3), 25.5 (CH_3), 28.3 (CH), 28.9 (CH), 33.9 (CH), 34.4 (CH_2), 55.0 (CH), 73.6 (CH), 81.8 (CH), 82.5 (C), 119.0 (CH_2), 120.9 (CH), 123.4 (CH), 133.5 (CH), 146.5 (C), 148.1 (C), 148.8 (C), 167.5 (C); MS (DCI, NH_3 + isobutane) *m/z* 461, 459, 457, 444, 442, 440 (MH^+, 100), 406, 231, 230. Anal. Calcd for $C_{24}H_{35}Cl_2NO_2$: C, 65.45; H, 8.01; N, 3.18; Cl, 16.10. Found: C, 65.43; H, 8.12; N, 3.15; Cl, 16.18.

A suspension of 17.46 g of the above crude dichloro lactam and 6.77 g (103.5 mmol) of Zn−Cu couple in 380 mL of methanol saturated with NH_4Cl was stirred at 20 °C under argon for 15 h and then filtered over Celite. The filtrate was concentrated under reduced pressure and the residue dissolved in dichloromethane, which was washed with water and brine, dried over Na_2SO_4, and filtered. Evaporation of the solvent left the crude product, which was filtered over silica gel with 0−2% methanol in dichloromethane to provide 12.40 g of lactam **7** containing some monochloro lactam. The mixture was resubjected to the above conditions to afforded 12.05 g of lactam **7** (72% overall yield from **4**): mp 102−104 °C (pentane); IR (film) 3213, 2955, 2927, 2867, 1703, 1107, 1080 cm^{-1}; ^{1}H NMR (300 MHz) δ 1.10−1.30 (m, 18 H), 1.52 (d, J = 6.8 Hz, 3 H), 2.10−2.30 (m, 1 H), 2.45−2.55 (m, 3 H), 2.83 (sept, J = 6.9 Hz, 1 H), 3.13 (sept, J = 6.8 Hz, 1 H), 3.62 (m: ddd, J = 10.2, 7.0, 2.8 Hz, 1 H), 3.85 (sept, J = 6.8 Hz, 1 H), 4.14 (m: ddd, J = 7.0, 7.0, 7.0 Hz, 1 H), 5.00−5.15 (m, 3 H), 5.74 (m: dddd, J = 17.8, 9.7, 8.2, 6.1 Hz, 1 H), 6.1 (s, 1 H), 6.93 (s, 1 H), 7.03 (s, 1 H); ^{13}C NMR (75.5 MHz) δ 23.0 (CH_3), 23.8 (CH_3), 24.8 (CH_3), 27.9 (CH), 29.0 (CH), 33.8 (CH), 34.6 (CH_2), 36.5 (CH_2), 57.2 (CH), 71.1 (CH), 72.2 (CH), 118.0 (CH_2), 120.4 (CH), 123.1 (CH), 131.9 (C), 134.5 (CH), 145.7 (C), 147.5 (C), 148.6 (C), 175.1 (C); MS (DCI, NH_3 + isobutane) *m/z* 372 (MH^+, 100), 371, 231. Anal. Calcd for $C_{24}H_{37}NO_2$: C, 77.58; H, 10.04; N, 3.77. Found: C, 77.61; H, 10.10; N, 3.62.

(4*R*,5*R*)-5-(2,3-Dihydroxypropyl)-4-[(*S*)-1-(2,4,6-triisopropylphenyl)ethoxy]pyrrolidin-2-one (9a). To a solution of 5.70 g (15.36 mmol) of lactam **7** (containing 15−20% of dihydro derivative[7]) in 50 mL of *tert*-butyl alcohol and 14.5 mL of water were added 1.75 g (15.75 mmol) of trimethylamine oxide dihydrate and 8.0 mL (0.64 mmol) of a 2.5% solution of osmium tetroxide in *tert*-butyl alcohol. The reaction mixture was refluxed and additional trimethylamine oxide dihydrate (0.80 g, 7.20 mmol) was added at 1-h intervals over the first 3 h. After being refluxed for 12 h, the reaction mixture was allowed to cool to 20 °C, treated with 150 mL of 0.75 M aqueous $NaHSO_3$, and stirred for 30 min. The crude product was isolated with ethyl acetate in the usual manner and purified by dry silica gel chromatography with 2−30% methanol in dichloromethane to provide 4.60 g (74%) of diol **9a** as a mixture of diastereomers. Less polar diastereomer: mp 145−147 °C; ^{1}H NMR (300 MHz) δ 1.10−1.30 (m, 18 H), 1.51 (d, J = 6.8 Hz, 3 H), 1.52−1.80 (m, 2 H), 2.45 (d, J = 6.8 Hz, 2 H), 2.82 (sept, J = 6.9 Hz, 1 H), 3.04−3.18 (m, 2 H), 3.35−3.45 (m, 1 H), 3.50−3.60 (m, 1 H), 3.68−3.90 (m, 4 H), 4.07 (m: ddd, J = 6.8, 6.8, 6.8 Hz, 1 H), 5.05 (q, J = 6.8 Hz, 1 H), 6.87 (br s, 1 H), 6.93 (s, 1 H), 7.01 (s, 1 H); ^{13}C NMR (75.5 MHz) δ 23.10 (CH_3), 23.14 (CH_3), 25.0 (CH_3), 28.0 (CH), 29.2 (CH), 30.9 (CH), 32.5 (CH_2), 33.9 (CH_2), 36.6 (CH_2), 57.9 (CH), 67.0 (CH_2), 70.9 (CH), 72.2 (CH), 72.6 (CH), 120.7 (CH), 123.2 (CH), 131.8 (C), 146.0 (C), 147.8 (C), 148.7 (C), 175.3 (C). More polar diastereomer: mp 161−162 °C; IR (film) 3292, 3052, 2960, 2929, 2874, 1675, 1607, 1467, 1423, 1265, 1166, 1064, 740 cm^{-1}; ^{1}H NMR (300 MHz) δ 1.10−1.30 (m, 18 H), 1.50 (d, J = 6.8 Hz, 3 H), 1.60−1.70 (m, 2 H), 2.46 (d, J = 6.8 Hz, 2 H), 2.83 (sept, J = 6.9 Hz, 1 H), 3.04−3.18 (m, 1 H), 3.34−3.48 (m, 1 H), 3.50−3.60 (m, 1 H), 3.70−3.94 (m, 4 H), 4.00−4.08 (m, 1 H), 4.11 (m: ddd, J = 6.8, 6.8, 6.8 Hz, 1 H), 5.03 (q, J = 6.8 Hz, 1 H), 6.93 (s, 1 H), 7.01 (s, 1 H), 7.41 (s, 1 H); ^{13}C NMR (75.5 MHz) δ 23.1 (CH_3), 23.9 (CH_3), 25.0 (CH_3), 28.0 (CH), 29.1 (CH), 32.4 (CH_2), 34.0 (CH), 36.6 (CH_2), 57.6 (CH), 67.0 (CH_2), 69.0 (CH), 71.1 (CH), 72.5 (CH), 120.6 (CH), 123.2 (CH), 131.9 (C), 145.9 (C), 147.7 (C), 148.8 (C), 176.0 (C); MS (DCI, NH_3 + isobutane) *m/z* 406 (MH^+, 100), 231, 175. Anal. Calcd for $C_{24}H_{39}NO_4$: C, 71.07; H, 9.69; N, 3.45. Found: C, 71.02; H, 9.78; N, 3.42.

2,4,6-Triisopropylbenzensulfonic Acid 3-Hydroxy-3-{(2*R*,3*R*)-5-oxo-3-[(*S*)-1-(2,4,6-triisopropylphenyl)ethoxy]-pyrrolidin-2-yl}propyl Ester (9b). To a solution of 2.00 g (4.90 mmol) of diol **9a** in 30 mL of methanol was added 1.20 g (4.82 mmol) of dibutyltin oxide. After being refluxed for 3 h, the reaction mixture was cooled to 0 °C and treated with 2.50 mL (17.94 mmol) of triethylamine and 2.75 g (14.42 mmol) of freshly recrystallized *p*-toluenesulfonyl chloride. After being stirred for 1 h at 0 °C and 1 h at 20 °C, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ and diluted with dichloromethane. The organic layer was washed with water and brine, dried over sodium sulfate, and filtered over Celite. Evaporation of solvents under reduced pressure left 4.45 g of crude product, which was purified by silica gel chromatography (0−5% methanol in dichloromethane) to yield 2.40 g (87%) of tosylate **9b** as a mixture of diastereomers: mp 98−100 °C (pentane); IR (film) 3416, 3053, 2965, 2929, 2870, 1693, 1608, 1362, 1265 cm^{-1}; ^{1}H NMR (300 MHz) δ 1.08−1.28 (m, 18 H), 1.50 (d, J = 6.8 Hz, 3 H), 1.52−1.90 (m, 2 H), 2.40 (s, 3 H), 2.42−2.50 (m, 2 H), 2.83 (sept, J = 2.3 Hz, 1 H), 3.13 (sept, J = 6.6 Hz, 1 H), 3.68−4.02 (m, 5 H), 4.02−4.17 (m, 1 H), 4.40 (s, 1 H), 4.96−5.14 (m, 1 H), 6.94 (s, 1 H), 7.02 (s, 1 H), 7.30 (d, J = 8.3 Hz, 2 H), 7.43 (s, 1 H), 7.76 (d, J = 8.3 Hz, 2 H); ^{13}C NMR (75.5 MHz) δ 22.9 (CH_3), 22.9 (CH_3), 23.7 (CH_3), 24.8 (CH_3), 27.8 (CH), 28.9 (CH), 32.0 (CH_2), 32.3 (CH_2), 33.8 (CH), 36.3 (CH_2), 53.8 (CH), 57.3 (CH), 65.5 (CH), 68.7 (CH), 70.7 (CH), 70.9 (CH), 72.2 (CH), 72.5 (CH), 73.5 (CH_2), 73.9 (CH_2), 120.4 (CH), 120.5 (CH), 123.0 (CH), 127.8 (CH), 129.7 (CH), 131.6 (C), 131.8 (C), 132.4 (C), 132.5 (C), 144.7 (C), 144.7 (C), 145.7 (C), 145.8 (C), 147.4 (C), 147.6 (C), 148.5 (C), 148.5 (C), 175.0 (C), 175.5 (C); MS (DCI, NH_3 + isobutane) *m/z* 560 (MH^+), 388, 231 (100). Anal. Calcd for $C_{31}H_{45}NO_6S\cdot{}^1/_2H_2O$: C, 65.46; H, 8.15; N, 2.46; S, 5.64. Found: C, 65.65; H, 8.15; N, 2.46; S, 6.01.

(1*R*,7a*R*)-[(*S*)-1-(2,4,6-Triisopropylphenyl)ethoxy]hexahydropyrrolizin-6-ol (10a). From 9b. A solution of 3.00 g

(5.37 mmol) of tosylate **9b** in 48 mL of THF was treated with 7.7 mL (77 mmol) of borane−dimethyl sulfide complex and then refluxed for 5.5 h. After being cooled to 0 °C, the reaction mixture was carefully treated with 20 mL of methanol until the end of the effervescence and then concentrated under reduced pressure. The residue was diluted with 22 mL of methanol, cooled to 0 °C, and treated with 2.3 mL of triethylamine and 0.585 g of 10% palladium on carbon. The mixture was stirred overnight at 20 °C and then filtered over Celite. The filtrate was concentrated under reduced pressure and the residue was dissolved in dichloromethane. The organic layer was washed with water, 1 N HCl, 10% NaOH, and brine. After being dried over Na_2SO_4 and filtered, the solvent was evaporated to give a crude mixture of diastereomers **10a** and **10b**. Purification of this material by silica gel (triethylamine-deactivated) chromatography with methanol saturated with ammonia in dichloromethane, followed by a 10% NaOH wash (necessary because of partial protonatation during chromatography), yielded 0.740 g of pure diastereomer **10a** and 0.672 g of diastereomer **10b**, slightly contaminated with **10a** (71% combined yield). Less polar diastereomer **10a**: mp 95−97 °C (pentane); $[\alpha]^{26}_D$ −62.5 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz) δ 1.08−1.33 (m, 18 H), 1.54 (d, J = 6.7 Hz, 3 H), 1.65−1.78 (m, 1 H), 1.86−1.98 (m, 1 H), 2.11−2.26 (m, 2 H), 2.75−2.88 (m, 2 H), 2.91−3.06 (m, 2 H), 3.13−3.30 (m, 2 H), 3.53−3.63 (m, 1 H), 3.71−3.80 (m, 1 H), 3.84 (sept, J = 6.8 Hz, 1 H), 4.15−4.25 (m, 1 H), 4.74 (br s), 5.31 (q, J = 6.7 Hz, 1 H), 6.93 (s, 1 H), 7.02 (s, 1 H); ^{13}C NMR (75.5 MHz) δ 23.0 (CH_3), 23.8 (CH_3), 23.8 (CH_3), 24.1 (CH_3), 24.9 (CH_3), 25.1 (CH_3), 25.5 (CH_3), 27.8 (CH), 29.0 (CH), 31.2 (CH_2), 33.7 (CH_2), 33.9 (CH), 53.4 (CH_2), 62.8 (CH_2), 68.0 (CH), 69.2 (CH), 73.3 (CH), 75.7 (CH), 120.8 (CH), 123.2 (CH), 130.7 (C), 146.4 (C), 147.8 (C), 148.7 (C); MS (DCI, NH_3 + isobutane) *m/z* 408, 375, 374 (MH^+, 100), 231, 144. Anal. Calcd for $C_{24}H_{39}NO_2 \cdot {}^2/_3H_2O$: C, 74.76; H, 10.54; N, 3.63. Found: C, 74.75; H, 10.34; N, 3.67. More polar diastereomer **10b:** IR 3442, 2962, 2929, 2868, 1609, 1460, 1362, 1075 cm^{-1}; ^{1}H NMR (300 MHz) δ 1.10−1.30 (m, 18 H), 1.47 (d, J = 6.7 Hz, 3 H), 1.58−1.69 (m, 1 H), 1.75−1.90 (m, 1 H), 2.10−2.30 (m, 2 H), 2.52−2.64 (m, 2 H), 2.82 (sept, J = 6.7 Hz, 1 H), 2.96−3.08 (m, 2 H), 3.20 (sept, J = 6.7 Hz, 1 H), 3.60−3.68 (m, 1 H), 3.70−3.75 (m, 1 H), 3.88 (sept, J = 6.7 Hz, 1 H), 4.39−4.47 (m, 1 H), 5.10 (q, J = 6.7 Hz, 1 H), 5.58 (br s, 1 H), 6.92 (s, 1 H), 7.00 (s, 1 H); ^{13}C NMR (75.5 MHz) δ 23.2 (CH_3), 23.7 (CH_3), 24.2 (CH_3), 24.7 (CH_3), 25.0 (CH_3), 25.1 (CH_3), 27.8 (CH), 28.9 (CH), 32.8 (CH_2), 33.2 (CH_2), 33.7 (CH), 51.8 (CH_2), 63.2 (CH_2), 66.8 (CH), 69.9 (CH), 74.5 (CH), 75.4 (CH), 120.3 (CH), 122.9 (CH), 132.5 (C), 145.6 (C), 147.1 (C), 148.6 (C).

From 10b. To a solution of 0.350 mL (4.01 mmol) of freshly distilled oxalyl chloride in 9.2 mL of dichloromethane at −60 °C was added 0.565 mL (7.96 mmol) of dimethyl sulfoxide. After being stirred for 10 min at −60 °C, the solution was treated dropwise with a solution of 0.565 g (1.51 mmol) of pyrrolizidine **10b** in 9.2 mL of dichloromethane. The reaction mixture was stirred for 1.5 h, while the temperature was allowed to rise to −40 °C, and then treated with 2.0 mL (14.3 mmol) of triethylamine. After 15 min at −40 °C, the reaction mixture was allowed to warm to 20 °C and was then diluted with dichloromethane. The organic layer was washed with saturated aqueous NH_4Cl, water, 10% aqueous NaOH, water, and brine, dried over Na_2SO_4, filtered, and concentrated to give 0.600 g of crude (1*R*,7a*R*)-[(*S*)-1-(2,4,6-triisopropylphenyl)-ethoxy]tetrahydropyrrolizin-6-one as a brown oil, which was used below without further purification: IR (film) 2959, 2933, 2869, 1756, 1608, 1459 cm^{-1}; ^{1}H NMR (300 MHz) δ 1.10−1.35 (m, 18 H), 1.47 (d, J = 6.8 Hz, 3 H), 1.80−1.95 (m, 1 H), 2.15−2.45 (m, 2 H), 2.75−2.92 (m, 3 H), 3.09 (A of AB J = 17.8 Hz, 1 H), 3.12−3.30 (m, 2 H), 3.41 (B of AB J = 17.8 Hz, 1 H), 3.60−3.68 (m, 1 H), 3.80 (sept, J = 6.8 Hz, 1 H), 3.85−3.92 (m, 1 H), 5.13 (q, J = 6.8 Hz, 1 H), 6.93 (s, 1 H), 7.01 (s, 1 H); ^{13}C NMR (75.5 MHz) δ 23.3 (CH_3), 23.7 (CH_3), 24.0 (CH_3), 24.8 (CH_3), 25.2 (CH_3), 27.7 (CH), 28.9 (CH), 31.3 (CH_2), 33.7 (CH), 36.3 (CH_2), 52.8 (CH_2), 62.0 (CH_2), 65.4 (CH), 69.6 (CH), 76.3 (CH), 120.4 (CH), 122.9 (CH), 131.8 (C), 145.3 (C), 147.3 (C), 148.6 (C), 216.7 (C); MS (DCI, NH_3 + isobutane) *m/z* 372 (MH^+, 41), 231 (100). To a solution of 0.670 g of crude pyrrolizidinone in 25 mL of ethanol at 0 °C was added 0.425 g (11.23 mmol) of sodium borohydride. After being stirred at 0 °C for 4 h, the reaction mixture was treated with water and diluted with dichloromethane. The aqueous layer was extracted with dichloromethane and the combined organic layers were then washed with 10% aqueous NaOH and water. The crude product was isolated in the usual manner and purified by silica gel (triethylamine-deactivated) chromatography with 2−50% methanol saturated with ammonia in dichloromethane to give an additional 0.266 g of diastereomer **10a** (51% combined yield).

(1*R*,6*R*,7a*R*)-6-Hydroxy-1-[(*S*)-1-(2,4,6-triisopropylphenyl)ethoxy]hexahydropyrrolizinium Chloride (10a·HCl). A solution of 1.63 g (4.36 mmol) of diastereomer **10a** in 150 mL of ether was washed with 100 mL of 2 N aqueous HCl and then concentrated under reduced pressure to give 1.63 g of the pyrrolizidine hydrochloride salt. Recrystallization of this material several times from pentane-dichloromethane afforded 1.30 g of the diastereomerically pure salt as white needles, suitable for X-ray diffraction with a high-intensity, microfocused source:[26,38] mp 183−189 °C (pentane-dichloromethane; decomposition); $[\alpha]^{26}_D$ −65.4 (*c* 1.3, $CHCl_3$); IR (film) 3322, 2958, 2931, 2868, 2575, 1459, 1264 cm^{-1}; ^{1}H NMR (300 MHz) δ 1.06−1.30 (m, 18 H), 1.59 (d, J = 6.8 Hz, 3 H), 2.02−2.20 (m, 1 H), 2.24 (m: ddd, J = 15.2, 10.2, 4.9 Hz, 1 H), 2.32−2.48 (m, 2 H), 2.83 (sept, J = 6.9 Hz, 1 H), 3.05−3.18 (m, 2 H), 3.22−3.38 (m, 1 H), 3.54 (m: dd, J = 12.5, 3.6 Hz, 1 H), 3.65 (sept, J = 6.8 Hz, 1 H), 3.89 (m: dd, J = 10.5, 7.4 Hz, 1 H), 4.04 (m: dd, J = 4.5, 4.5 Hz, 1 H), 4.34−4.46 (m, 1 H), 4.48−4.56 (m, 2 H), 5.31 (q, J = 6.8 Hz, 1 H), 6.96 (s, 1 H), 7.03 (s, 1 H), 12.5−13.0 (br s, 1 H); ^{13}C NMR (75.5 MHz) δ 22.7 (CH_3), 23.7 (CH_3), 23.8 (CH_3), 24.0 (CH_3), 24.8 (CH_3), 25.2 (CH_3), 25.5 (CH_3), 28.2 (CH), 29.3 (CH), 31.2 (CH_2), 32.2 (CH_2), 34.0 (CH), 53.3 (CH_2), 60.2 (CH_2), 68.7 (CH), 71.0 (CH), 71.9 (CH), 74.0 (CH), 121.3 (CH), 123.5 (CH), 129.0 (C), 146.5 (C), 148.4 (C), 148.8 (C); MS (DCI, NH_3 + isobutane) *m/z* 374 (MH^+, 100), 231, 141. Anal. Calcd for $C_{24}H_{40}ClNO_2$: C, 70.30; H, 9.83; N, 3.42. Found: C, 69.93; H, 9.84; N, 3.44. This salt was dissolved in dichloromethane, which was washed with saturated $NaHCO_3$ and then concentrated under reduced pressure to yield 1.08 g of pure pyrrolizidine **10a** as a white solid.

(1*R*,7a*R*,6*S*)-6-(*tert*-Butyldiphenylsilanoxy)hexahydropyrrolizin-1-ol (11). A solution of 0.740 g (1.98 mmol) of pyrrolizidine **10a** and 0.740 g (10.9 mmol) of imidazole in 25

(38) An undulator (U46) beam monochromatized by a silicon (111) double monochromator and focused on the sample by a polished ellipsoidal mirror was used with the ID13 beam-line to afford a very high flux and to guarantee a strong, yet small, incoming beam. The wavelength was set at λ = 0.721 Å. The ESRF-EMBL microdiffractometer (single horizontal φ-axis goniometer, sample rotation within a 1-μm radius sphere, semiautomatic sample alignment) was used. Perfect centering of the crystal was performed through motor-controlled φ-axis *xyz* translation stages (crucial when using a very small beam). The detector was a 2D CCD detector (MarCCD 130, 2048 × 2048 pixels; pixel size 0.06445 × 0.06445 mm^2) mounted on a translation rail, which in turn was mounted on a rotation arm. The rotation arm and φ-axis were aligned in order to be collinear. The crystal was embedded with a cryoprotectant (Paratone-N from Hampton) and then taken in a nylon loop (from Hampton Research). Several crystals were tested to select a single crystal of suitable quality for data collection. Two data sets were collected by the oscillation technique (the first, 100 frames, each with an exposure time of 2 s and 6° oscillation; the second, 100 frames, each with an exposure time of 2 s and 4° oscillation), using a two-dimensional CCD detector at 45 mm and with the cryoloop axis approximately parallel to the oscillation axis. To probe only a homogeneous part of the needle-shaped crystal, the focused beam was reduced to 30 μm in diameter by using a beam-defining aperture. The measurement was carried out at a fixed temperature of 100(2) K by using an Oxford Cryostream device. The frames were indexed and the reflections integrated using the XDS software suite (Kabsch, W. *J. Appl. Crystallogr.* **1993**, *26*, 795−800). Each reflection intensity was corrected for intensity loss due to air absorption. The two data sets were merged with XSCALE.

mL of dimethylformamide was treated with 2.10 mL (8.08 mmol) of *tert*-butyldiphenylsilyl chloride and 0.025 g (0.2 mmol) of DMAP. The reaction mixture was stirred overnight at 20 °C, treated with 5% aqueous NaOH, and then processed with dichloromethane to furnish 3.08 g of crude product. Purification of this material by silica gel (triethylamine-deactivated) chromatography with 1−10% methanol saturated with ammonia in dichloromethane afforded 1.00 g (82%) of pure (1*R*,6*S*,7a*R*)-6-(*tert*-butyldiphenylsilanoxy)-1-(2,4,6-triisopropylphenyl)ethoxy]hexahydropyrrolizine: $[\alpha]^{26}_D$ −27.9 (*c* 1.3, $CHCl_3$); IR (film) 3070, 2959, 2927, 2863, 1607, 1470, 1382, 1360, 1112, 1076 cm^{-1}; ^1H NMR (300 MHz) δ 1.03 (s, 9 H), 1.10−1.30 (m, 18 H), 1.55 (d, J = 6.8 Hz, 3 H), 1.62−1.81 (m, 2 H), 2.10−2.25 (m, 2 H), 2.52 (m: dd, J = 8.4, 8.4 Hz, 1 H), 2.73 (m: ddd, J = 9.7, 9.7, 6.0 Hz, 1 H), 2.83 (sept, J = 6.9 Hz, 1 H), 2.94−3.08 (m, 2 H), 3.15−3.29 (m, 2 H), 3.72 (m: ddd, J = 4.8, 4.8, 3.0 Hz, 1 H), 3.98 (sept, J = 7.2 Hz, 1 H), 4.41 (m: dddd, J = 8.4, 8.4, 6.6, 6.6 Hz, 1 H), 5.12 (q, J = 6.8 Hz, 1 H), 6.93 (s, 1 H), 7.02 (s, 1 H), 7.30−7.42 (m, 6 H), 7.60−7.68 (m, 4 H); ^{13}C NMR (75.5 MHz) δ 19.1 (C), 23.6 (CH_3), 23.9 (CH_3), 24.4 (CH_3), 24.8 (CH_3), 25.2 (CH_3), 25.2 (CH_3), 26.9 (CH_3), 28.0 (CH), 29.1 (CH), 32.0 (CH_2), 33.1 (CH_2), 33.9 (CH), 52.1 (CH_2), 62.1 (CH_2), 65.9 (CH), 70.4 (CH), 75.3 (CH), 76.2 (CH), 120.4 (CH), 123.1 (CH), 127.5 (CH), 127.6 (CH), 129.5 (CH), 129.6 (CH), 133.1 (C), 134.1 (C), 134.2 (C), 135.6 (CH), 135.7 (CH), 147.2 (C); MS (DCI, NH_3 + isobutane) *m/z* 612 (MH^+, 100), 611, 379, 231, 105; HRMS calcd for $C_{40}H_{58}NO_2Si$ 612.4236, found 612.4178 (MH^+). A solution of 0.960 g (1.59 mmol) of the above pyrrolizidine in 16 mL of dichloromethane was treated at 0 °C with 1.6 mL of trifluoroacetic acid. After being stirred at 20 °C for 2.5 h, the reaction mixture was treated at 0 °C with water and 5% NaOH and the organic layer was washed with 5% NaOH. The usual workup furnished the crude product, which was purified by silica gel (triethylamine-deactivated) chromatography with 2−15% methanol saturated with ammonia in dichloromethane to yield 0.540 g (90%) of pyrrolizidinol **11**: mp 113−115 °C (pentane); $[\alpha]^{26}_D$ +22.9 (*c* 1.1, $CHCl_3$); IR (film) 3432−3350, 3070, 2962, 2931, 2857, 1589, 1473, 1430, 1116 cm^{-1}; ^1H NMR (300 MHz) δ 1.06 (s, 9 H), 1.78−2.15 (m, 2 H), 2.23 (m: dddd, J = 14.3, 1.9, 1.9, 1.9 Hz, 1 H), 2.64 (m: ddd, J = 12.8, 1.9, 1.9 Hz, 1 H), 2.73 (m: dd, J = 12.8, 3.5 Hz, 1 H), 2.96−3.07 (m, 1 H), 3.20 (m: ddd, J = 7.6, 7.6, 7.6 Hz, 1 H), 3.65−3.73 (m, 1 H), 3.88−3.95 (m, 1 H), 4.08−4.16 (m, 1 H), 4.30−4.37 (m, 1 H), 7.33−7.48 (m, 6 H), 7.60−7.70 (m, 4 H); ^{13}C NMR (75.5 MHz) δ 18.9 (C), 26.8 (CH_3), 33.8 (CH_2), 37.1 (CH_2), 53.7 (CH_2), 61.5 (CH_2), 68.9 (CH), 72.5 (CH), 76.2 (CH), 127.8 (CH), 127.9 (CH), 130.0 (CH), 130.1 (CH), 132.5 (C), 132.8 (C), 135.8 (CH); MS (DCI, NH_3 + isobutane) *m/z* 383, 382 (MH^+, 100); HRMS calcd for $C_{23}H_{32}NO_2Si$ 382.2202, found 382.2226 (MH^+). Anal. Calcd for $C_{23}H_{31}NO_2Si{\cdot}2H_2O$: C, 66.15; H, 8.45; N, 3.35. Found: C, 66.33; H, 8.14; N, 3.17.

Trifluoromethanesulfonic Acid (6*S*,7a*R*)-6-(*tert*-Butyldiphenylsilanoxy)-5,6,7,7a-tetrahydro-3*H*-pyrrolizin-1-yl Ester (12a). To a solution of 0.044 mL (0.50 mmol) of freshly distilled oxalyl chloride in 0.640 mL of dichloromethane at −60 °C was added 0.075 mL (1.06 mmol) of dimethyl sulfoxide. After being stirred for 10 min at −60 °C, the solution was treated dropwise with a solution of 0.050 g (0.13 mmol) of pyrrolizidinol **11** in 0.640 mL of dichloromethane. The reaction mixture was stirred for 2 h while being allowed to warm to −40 °C and then treated with 0.195 mL (1.40 mmol) of triethylamine. After 15 min at −40 °C, the reaction mixture was allowed to warm to 20 °C and diluted with dichloromethane, and the organic layer was washed with cold 5% aqueous NaOH and cold water. The crude product was isolated in the usual manner and purified by rapid filtration through Florisil with 5% methanol saturated with ammonia in dichloromethane to give 0.050 g of (7a*R*,6*S*)-6-(*tert*-butyldiphenylsilanoxy)hexahydropyrrolizin-1-one: IR (film) 2934, 2891, 2864, 1749, 1470, 1427, 1113, 1033 cm^{-1}; ^1H NMR (300 MHz) δ 1.00 (s, 9 H), 1.93−2.10 (m, 2 H), 2.28−2.41 (m, 1 H), 2.66−2.82 (m, 2 H), 3.17 (dd, J = 12.2, 4.1 Hz, 1 H), 3.26−3.36 (m, 2 H), 3.42−3.53 (m, 1 H), 4.23−4.29 (m, 1 H), 7.30−7.45 (m, 6 H), 7.55−7.68 (m, 4 H); ^{13}C NMR (75.5 MHz) δ 18.9 (C), 26.8 (CH_3), 26.8 (CH_3), 35.5 (CH_2), 39.0 (CH_2), 50.5 (CH_2), 64.2 (CH_2), 67.5 (CH), 73.7 (CH), 127.7 (CH), 129.8 (CH), 129.9 (CH), 133.0 (CH), 133.3 (C) 135.6 (C), 135.8 (C), 218.6 (C); MS (DCI, NH_3 + isobutane) *m/z* 380 (MH^+), 274, 196, 140, 102 (100). A solution of 0.050 g (0.13 mmol) of the above ketone in 1.2 mL of THF at −90°C was treated with 0.165 mL (0.16 mmol) of a 1 M solution of LiHMDS in THF. The reaction mixture was stirred for 1.5 h while being allowed to warm to −65 °C and then a solution of 0.055 g (0.14 mmol) of *N*-(5-chloro-2-pyridyl)triflimide in 0.225 mL of THF was added at −80 °C. The reaction mixture was stirred for 2 h while being allowed to warm to −50 °C and then treated with 5% NaOH, diluted with dichloromethane, and allowed to warm to 20 °C. The organic layer was washed with 5% NaOH and the crude product was then isolated in the usual manner and purified by Florisil chromatography with 0−5% methanol saturated with ammonia in dichloromethane to provide 0.046 g (68% from **11**) of triflate **12a**: $[\alpha]^{26}_D$ −13.4 (*c* 1.1, $CHCl_3$); IR (film) 3071, 3049, 2959, 2931, 2859, 1670, 1471, 1428, 1214, 1139 cm^{-1}; ^1H NMR (300 MHz) δ 1.01 (s, 9 H), 1.83−1.90 (m, 2 H), 2.74 (A of ABX J = 11.4, 2.7 Hz, 1 H), 2.98 (B of ABX J = 11.4, 4.1 Hz, 1 H), 3.69 (m: ddd, J = 15.0, 5.2, 2.4 Hz, 1 H), 4.01 (m: ddd, J = 15.0, 3.2, 1.8 Hz, 1 H), 4.06−4.16 (m, 1 H), 4.34 (m: dddd, J = 4.0, 4.0, 4.0, 4.0 Hz, 1 H), 5.65−5.70 (m, 1 H), 7.32−7.45 (m, 6 H), 7.56−7.68 (m, 4 H); ^{13}C NMR (75.5 MHz) δ 18.9 (C), 26.7 (CH_3), 37.0 (CH_2), 59.7 (CH_2), 64.3 (CH_2), 66.5 (CH), 74.0 (CH), 112.2 (CH), 118.5 (CF_3, J = 320 Hz), 127.7 (CH), 129.80 (CH), 129.84 (CH), 133.4 (CH), 133.5 (C), 135.6 (CH), 135.7 (CH), 148.1 (C); MS (DCI, NH_3 + isobutane) *m/z* 512 (MH^+, 100); HRMS calcd for $C_{24}H_{29}F_3NO_4SSi$ 512.1538, found 512.1544 (MH^+).

(6*S*,7a*R*)-6-(*tert*-Butyldiphenylsilanoxy)-5,6,7,7a-tetrahydro-3*H*-pyrrolizine-1-carboxylic Acid Methyl Ester (12b). A mixture of 0.050 g (0.10 mmol) of triflate **12a**, 0.021 g (0.08 mmol) of $P(C_6H_5)_3$, 0.006 g (0.03 mmol) of $Pd(OAc)_2$, 0.047 mL (0.34 mmol) of $(C_2H_5)_3N$, and 0.260 mL of methanol in 0.650 mL of DMF was purged with CO for 10 min and then stirred at 40 °C for 4 h under an atmosphere of CO. After being allowed to cool to 20 °C, the reaction mixture was treated with 5% NaOH, diluted with dichloromethane, and washed with 5% NaOH and water. The combined aqueous layers were extracted with dichloromethane and the combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated. The crude product was purified by Florisil chromatography with 0−10% methanol saturated with ammonia in dichloromethane to furnish 0.026 g (63%) of ester **12b**: $[\alpha]^{26}_D$ −1.1 (*c* 1.0, $CHCl_3$); IR (film) 3416, 3070, 2952, 2856, 1721, 1437, 1264, 1114 cm^{-1}; ^1H NMR (300 MHz) δ 0.99 (s, 9 H), 1.80−1.90 (m, 1 H), 2.10 (m: ddd, J = 13.0, 7.5, 4.5 Hz, 1 H), 2.68 (m: ddd, J = 10.7, 4.6, 1.2 Hz, 1 H), 3.01 (m: dd, J = 10.7, 4.4 Hz, 1 H), 3.74 (s, 3 H), 3.80 (m: ddd, J = 18.0, 5.4, 2.0 Hz, 1 H), 4.03 (m: ddd, J = 18.0, 3.6, 2.0 Hz, 1 H), 4.24−4.35 (m, 2 H), 6.72 (m: ddd, J = 2.0, 2.0, 2.0 Hz, 1 H), 7.28−7.70 (m, 10 H); ^{13}C NMR (75.5 MHz) δ 19.0 (C), 26.7 (CH_3), 39.2 (CH_2), 51.4 (CH_3), 63.5 (CH_2), 63.8 (CH_2), 69.2 (CH), 74.0 (CH), 127.6 (CH), 128.4 (CH), 128.5 (CH), 129.6 (CH), 132.0 (CH), 132.1 (CH), 133.7 (C), 133.8 (C), 135.6 (CH), 135.7 (CH), 136.8 (C), 139.0 (CH), 164.2 (C); MS (DCI, NH_3 + isobutane) *m/z* 422 (MH^+), 279; HRMS calcd for $C_{25}H_{32}NO_3Si$ 422.2151, found 422.2166 (MH^+).

(1*R*,7a*R*,6*S*)-6-(*tert*-Butyldiphenylsilanoxy)-hexahydropyrrolizine-1-carboxylic Acid Methyl Ester (13). To a solution of 0.029 g (0.069 mmol) of ester **12b** in 1.0 mL of methanol at 20 °C was added 0.010 g of 10% palladium on carbon. The mixture was vigorously stirred overnight under a hydrogen atmosphere. The reaction mixture was then filtered over Celite and the filtrate was concentrated under reduced pressure to provide 0.027 g (93%) of ester **13**: $[\alpha]^{26}_D$ +9.2 (*c* 1.0, $CHCl_3$); IR (film) 3440, 3070, 3052, 2931, 2857, 1734, 1437,

1197, 1118 cm^{-1}; ^1H NMR (300 MHz) δ 1.02 (s, 9 H), 1.46 (m: ddd, J = 17.8, 9.9, 8.0 Hz, 1 H), 1.80−1.94 (m, 2 H), 2.20−2.46 (m, 1 H), 2.58 (m: dd, J = 9.7, 7.2 Hz, 1 H), 2.90−3.12 (m, 4 H), 3.55−3.65 (m, 1 H), 3.66 (s, 3 H), 4.27−4.38 (m, 1 H), 7.30−7.70 (m, 10 H); ^{13}C NMR (75.5 MHz) δ 19.0 (C), 26.3 (CH), 26.8 (CH_3), 37.5 (CH_2), 47.5 (C), 51.6 (CH_3), 53.9 (CH_2), 61.9 (CH_2), 63.8 (CH), 73.7 (CH), 127.6 (CH), 127.7 (CH), 128.4 (CH), 128.6 (CH), 129.6 (CH), 129.7 (CH), 129.7 (CH), 131.9 (CH), 131.9 (CH), 132.0 (CH), 132.2 (CH), 133.7 (C), 133.8 (C), 135.7 (CH), 135.7 (CH), 173.5 (C); HRMS calcd for $C_{25}H_{34}NO_3Si$ 424.2308, found 424.2311 (MH^+).

(1*R*,7a*R*,6*S*)-6-Hydroxyhexahydropyrrolizine-1-carboxylic Acid Methyl Ester (14). To a stirred solution of 0.014 g (0.033 mmol) of ester **13** in 0.550 mL of THF at 20 °C was added 0.046 mL (0.046 mmol) of a 1 M solution of TBAF in THF. The reaction mixture was stirred overnight at 20 °C and then filtered over 2 mL of Florisil with 0−15% methanol saturated with ammonia in dichloromethane to provide 0.005 g (82%) of hydroxy ester **14**: $[\alpha]^{26}_D$ +40.2 (*c* 0.9, $CHCl_3$); IR (film) 3290, 3117, 2924, 2884, 1725, 1439, 1374, 1205 cm^{-1}; ^1H NMR (300 MHz) δ 1.45−1.56 (m, 1 H), 1.92−2.05 (m, 1 H), 2.15−2.39 (m, 2 H), 2.66 (m: dd, J = 10.4, 6.3 Hz, 1 H), 2.97−3.20 (m, 3 H), 3.34 (m: dd, J = 10.4, 5.6 Hz, 1 H), 3.71 (s, 3 H), 3.87 (m: ddd, J = 8.1, 8.1, 8.1 Hz, 1 H), 4.38−4.48 (m, 1 H); ^{13}C NMR (75.5 MHz) δ 27.3 (CH_2), 37.4 (CH_2), 47.4 (CH), 51.9 (CH_3), 54.1 (CH_2), 62.2 (CH_2), 64.9 (CH), 72.4 (C), 174.2 (C); MS (DCI, NH_3 + isobutane) *m/z* 186 (MH^+); HRMS calcd for $C_9H_{16}NO_3$ 186.1130, found 186.1114 (MH^+).

((1*R*,7a*R*,6*S*)-6-[4-Hydroxy-3-methoxyphenyl)propionyloxy]hexahydropyrrolizine-1-carboxylic Acid Methyl Ester ((+)-Amphorogynine A) (1a). To a solution of 0.010 g (0.054 mmol) of hydroxy ester **14**, 0.0185 g (0.059 mmol) of *tert*-butyldimethylsilyl-protected hydroferulic acid,[29] and 0.0007 g (0.006 mmol) of DMAP in 0.035 mL of dichloromethane was added 0.0125 mL (0.080 mmol) of diisopropylcarbodiimide. The reaction mixture was stirred at 20 °C for 3 h and then filtered over Celite and the filtrate was concentrated under reduced pressure. The residue was diluted with pentane and filtered over Celite. Evaporation of the solvent left the crude product, which was purified by Florisil chromatography with 0−10% methanol saturated with ammonia in dichloromethane to provide 0.018 g (70%) of (1*R*,6*S*,7a*R*)-6-{3-[4-(*tert*-butyldimethylsilanyloxy)-3-methoxyphenyl)propionyloxy]}hexahydropyrrolizine-1-carboxylic acid methyl ester: $[\alpha]^{26}_D$ +30.5 (*c* 0.9, $CHCl_3$); IR (film) 2954, 2929, 2857, 1734, 1514, 1283 cm^{-1}; ^1H NMR (300 MHz) δ 0.10 (s, 6 H), 0.96 (s, 9 H), 1.50 (m: ddd, J = 14.1, 8.4, 6.0 Hz, 1 H), 1.85−1.97 (m, 1 H), 2.18−2.32 (m, 2 H), 2.55 (t, J = 7.4 Hz 2 H), 2.73 (m: dd, J = 11.9, 4.6 Hz, 1 H), 2.77−2.88 (m, 3 H), 2.97−3.07 (m, 1 H), 3.15−3.30 (m, 2 H), 3.67 (s, 3 H), 3.75 (s, 3 H), 3.70−3.85 (m, 1 H), 5.12−5.21 (m, 1 H), 6.55−6.75 (m, 3 H); ^{13}C NMR (75.5 MHz) δ −4.7 (CH_3), 18.4 (C), 25.7 (CH_3), 26.4 (CH_2), 30.6 (CH_2), 34.4 (CH_2), 36.2 (CH_2), 47.2 (CH), 51.7 (CH_3), 53.9 (CH_2), 55.5 (CH_3), 59.4 (CH_2), 64.6 (CH), 75.4 (CH), 112.4 (CH), 120.3 (CH), 120.8 (CH), 133.8 (C), 143.5 (C), 150.8 (C), 172.6 (C), 173.4 (C); MS (DCI, NH_3 + isobutane) *m/z* 478 (MH^+); HRMS calcd for $C_{25}H_{40}NO_6Si$ 478.2625, found 478.2638 (MH^+). To a stirred solution of 0.012 g (0.025 mmol) of the above diester in 0.450 mL of THF at 20 °C was added 0.040 mL (0.040 mmol) of a 1 M solution of TBAF in THF. The reaction mixture was stirred for 1 h at 20 °C, diluted with cyclohexane, and partially concentrated under reduced pressure. The resulting solution was filtered over 1.5 mL of Florisil with 0−15% methanol saturated with ammonia in dichloromethane to give 0.007 g (77%) of amphorogynine A (**1a**): mp 103−104 °C; $[\alpha]^{26}_D$ +42 (*c* 0.9, $CHCl_3$); ^1H NMR (300 MHz) δ 1.48 (m: ddd, J = 14.0, 8.2, 5.9 Hz, 1 H), 1.83−1.97 (m, 1 H), 2.12−2.30 (m, 2 H), 2.55 (t, J = 7.8 Hz, 2 H), 2.73 (m: dd, J = 11.8, 5.9 Hz, 1 H), 2.84 (m, 3 H), 2.97−3.07 (m, 1 H), 3.13−3.23 (m, 1 H), 3.26 (m: dd, J = 11.8, 5.9 Hz, 1 H), 3.66 (s, 3 H), 3.75 (m: ddd, J = 8.2, 8.2, 8.2 Hz, 1 H), 3.85 (s, 3 H), 5.16 (m: dddd, J = 5.9, 5.9, 5.9, 5.9 Hz, 1 H), 6.60−6.70 (m, 2 H), 6.79 (d, J = 8.0 Hz, 1 H); ^{13}C NMR (75.5 MHz) δ 26.3 (CH_2), 30.6 (CH_2), 34.4 (CH_2), 36.3 (CH_2), 47.2 (CH), 51.7 (CH_3), 53.9 (CH_2), 55.9 (CH_3), 59.4 (CH_2), 64.6 (CH), 75.4 (CH), 111.0 (CH), 114.5 (CH), 120.8 (CH), 132.2 (C), 144.2 (C), 146.6 (C), 172.6 (C), 173.4 (C); MS (DCI, NH_3 + isobutane) *m/z* 364 (MH^+); HRMS calcd for $C_{19}H_{26}NO_6$ 364.1760, found 364.1778 (MH^+). This material was identical to an authentic sample of amphorogynine A.

(1*R*,6*R*,7a*R*)-6-Hydroxyhexahydro-1*H*-pyrrolizine-1-carboxylic Acid ((+)-Amphorogynine D) (1d). A solution of 0.029 g (0.068 mmol) of ester **13** in 0.100 mL of dioxane and 4 mL of 12 N HCl was stirred at 80 °C for 3.5 h. The reaction mixture was concentrated under reduced pressure and the residue was purified by cation exchange chromatography (Dowex 50 × 8−200), eluting with 2 N NH_4OH. After evaporation of solvents, the residue was dissolved in 2 N NH_4OH and washed with dichloromethane. Concentration of the aqueous layer under reduced pressure left 0.009 g (77%) of **1d**: ^1H NMR (300 MHz, D_2O) δ 1.55−1.68 (m, 1 H), 1.95−2.10 (m, 1 H), 2.18−2.43 (m, 2 H), 2.93 (dd, J = 12.0, 6.8 Hz, 1 H), 3.10−3.32 (m, 2 H), 3.34−3.48 (m, 1 H), 3.67 (dd, J = 12.0, 6.0, 1 H), 4.27 (ddd, J = 8.8, 8.8, 8.8 Hz, 1 H), 4.36 (m, 1 H); ^{13}C NMR (75.5 MHz, D_2O) δ 26.1 (CH_2), 35.7 (CH_2), 49.5 (CH), 55.5 (CH_2), 60.2 (CH_2), 67.2 (CH), 69.3 (CH), 177.4 (C). This material was the same as a sample obtained from natural amphorogynine A.

(1*R*,7a*R*,6*S*)-6-Hydroxy-1-methoxycarbonylhexahydropyrrolizinium Chloride (14·HCl). To a solution of 0.006 g (0.035 mmol) of **1d** in 1.5 mL of methanol was added 0.400 mL of 12 N HCl. The reaction mixture was stirred at 80 °C for 1 h and then concentrated under reduced pressure. The crude product was purified by Florisil chromatography to give 0.004 g (52%) of ester **14·HCl**: $[\alpha]^{26}_D$ +11.5 (*c* 0.6, CH_3OH); ^1H NMR (300 MHz, CD_3OD) δ 1.85 (m: ddd, J = 13.8, 8.2, 5.6 Hz, 1 H), 2.23−2.35 (m, 1 H), 2.49 (m: ddd, J = 14.2, 8.2, 5.6 Hz, 1 H), 2.59−2.75 (m, 1 H), 3.08 (dd, J = 12.1, 5.2 Hz, 1 H), 3.48−3.68 (m, 3 H), 3.73 (m, 1 H), 3.78 (s, 3 H), 4.46−4.56 (m, 2 H); ^{13}C NMR (75.5 MHz, CD_3OD, calibrated to the natural product derivative[8] (C-6, 54.6 ppm)) δ 25.5 (C), 35.4 (C), 45.8 (C), 51.3 (CH_3), 54.6 (C), 60.4 (C), 66.5 (C), 69.3 (C); MS (DCI, NH_3 + isobutane) *m/z* 186 (MH^+). This material was the same as a sample obtained from natural amphorogynine A. The corresponding free amine (CH_3OH, NH_3) was identical to ester **14** above.

(4*R*,5*S*)-5-(1-Hydroxy-2-propenyl)-4-[(*S*)-1-(2,4,6-triisopropylphenyl)ethoxy]pyrrolidin-2-one (17). Selenium dioxide (0.72 g, 6.49 mmol) in 5.20 mL (26.0 mmol) of a 5.0 M solution of *tert*-butylhydroperoxide in decane was stirred under an argon atmosphere for 1.25 h. A solution of 6.02 g (16.2 mmol) of pyrrolidinone **7** in 62 mL of dichloroethane was added and the resulting mixture was refluxed for 1 h and then allowed to cool to 20 °C and concentrated. Ethyl acetate was added and organic phase was washed with water, brine, and $NaHCO_3$, dried over Na_2SO_4, filtered, and concentrated. The resultant crude product was purified by silica gel chromatography with ethyl acetate in pentane to give 2.97 g of alcohol **17** as a ca. 1:1 mixture of diastereomers and 2.37 g of starting material, which was reused in the same reaction. The combined yield of the product was 62% after three cycles. Less polar diastereomer: mp 52−53 °C; $[\alpha]^{25}_D$ −71.7 (*c* 0.5, $CHCl_3$); IR (film, mixture of diastereomers) 3259, 3052, 2957, 2937, 2875, 1703, 1608 cm^{-1}; ^1H NMR (300 MHz) δ 1.12−1.34 (m, 18 H), 1.61 (d, J = 6.8 Hz, 3 H), 2.53 (d, J = 7.9 Hz, 2 H), 2.86 (sept, J = 6.9 Hz, 1 H), 3.15 (sept, J = 6.7 Hz, 1 H), 3.53 (m: ddd, J = 7.7, 7.7, 1.0 Hz, 1 H), 3.70 (sept, J = 6.8 Hz, 1 H), 4.30−4.44 (m, 2 H), 5.18 (q, J = 6.8 Hz, 1 H), 5.30 (m: ddd, J = 10.5, 1.5, 1.0 Hz, 1 H), 5.37 (m: ddd, J = 17.3, 1.1, 1.1 Hz, 1 H), 5.48 (br s, 1 H), 5.84 (m: ddd, J = 17.3, 10.5, 6.8 Hz, 1 H), 6.14 (br s, 1 H), 6.97 (s, 1 H), 7.06 (s, 1 H); ^{13}C NMR (75.5 MHz) δ 23.0 (CH_3), 23.8 (CH_3), 24.1 (CH_3), 25.2 (CH_3), 28.5 (CH), 29.2 (CH), 34.0 (CH), 36.1 (CH_2), 59.8 (CH), 72.5 (CH), 73.2 (CH), 118.4 (CH_2), 121.0 (CH), 123.4 (CH), 130.6 (C), 136.5 (CH), 146.1 (C), 148.2 (C), 148.7 (C), 174.2 (C); MS (DCI, NH_3

+ isobutane) *m/z* 388 (MH^+, 100), 387 (M^+), 231, 184. More polar diastereomer: ^{1}H NMR (300 MHz) δ 1.13−1.34 (m, 18 H), 1.59 (d, J = 6.8 Hz, 3 H), 2.50 (A of ABX, J = 16.6, 6.7 Hz, 1 H), 2.59 (B of ABX, J = 16.6, 8.7 Hz, 1 H), 2.86 (sept, J = 6.9 Hz, 1 H), 3.03 (br s, 1 H), 3.14 (sept, J = 6.7 Hz, 1 H), 3.63 (dd, J = 7.7, 1.7 Hz, 1 H), 3.82 (sept, J = 6.8 Hz, 1 H), 4.32 (m: ddd, J = 7.3, 7.3, 7.3 Hz, 1 H), 4.59 (d, J = 2.2 Hz, 1 H), 5.16 (q, J = 6.8 Hz, 1 H), 5.25 (m: ddd, J = 10.7, 1.6, 1.6 Hz, 1 H), 5.42 (m: ddd, J = 17.3, 1.6, 1.6 Hz, 1 H), 5.82 (m: ddd, J = 17.3, 10.7, 4.6 Hz, 1 H), 6.26 (br s, 1 H), 6.97 (s, 1 H), 7.06 (s, 1 H); ^{13}C NMR (75.5 MHz) δ 23.2 (CH_3), 23.8 (CH_3), 28.2 (CH), 29.1 (CH), 33.9 (CH), 37.4 (CH_2), 60.6 (CH), 70.5 (CH), 71.6 (CH), 72.3 (CH), 116.5 (CH_2), 120.9 (CH), 123.4 (CH), 130.8 (C), 136.4 (CH), 146.3 (C), 148.1 (C), 148.6 (C), 175.3 (C). Anal. Calcd for $C_{24}H_{35}NO_3 \cdot {}^1/_3H_2O$ (mixture of diastereomers): C, 73.24; H, 9.65; N, 3.56. Found: C, 73.32; H, 9.57; N, 3.49.

(4*R*,5*R*)-5-(1,3-Dihydroxypropyl)-4-[(*S*)-1-(2,4,6-triisopropylphenyl)ethoxy]pyrrolidin-2-one (18a). A 1 M solution of catecholborane in THF (3.25 mL, 3.25 mmol) was added dropwise to a solution of 0.250 g (0.645 mmol) of alcohol **17** and 0.060 g (0.065 mmol) of $Rh(P(C_6H_5)_3)_3Cl$ in 2.5 mL of THF. The mixture was stirred at 20 °C for 2 h, cooled to 0 °C, and carefully treated with 2 M NaOH (0.5 mL), water (1.5 mL), and 35% aqueous hydrogen peroxide (0.5 mL). The resulting mixture was stirred overnight and then extracted with ethyl acetate. The organic phase was washed with 1 M NaOH until the aqueous wash was colorless, dried over Na_2SO_4, filtered, and concentrated. The crude product was triturated with ethyl acetate to provide 0.129 g of solid diol **18a** after filtration. The filtrate was then concentrated and the residue was purified by silica gel chromatography to give an additional 0.059 g (72% combined yield) of diol **18a**. Less polar diastereomer: ^{1}H NMR (300 MHz, CD_3COCD_3) δ 1.13−1.35 (m, 18 H), 1.58 (d, J = 6.8 Hz, 3 H), 1.55−1.72 (m, 1 H), 1.80−1.92 (m, 1 H), 2.43 (A of ABX, J = 16.1, 7.9 Hz, 1 H), 2.48 (B of ABX, J = 16.1, 7.9 Hz, 1 H), 2.88 (sept, J = 6.9 Hz, 1 H), 3.23−3.41 (m, 1 H), 3.41−3.55 (m, 1 H), 3.68−3.77 (m, 3 H), 3.80−3.94 (m, 1 H), 3.98−4.10 (m, 1 H), 4.39 (m: ddd, J = 7.6, 7.6, 7.6 Hz, 1 H), 5.30 (q, J = 6.7 Hz, 1 H), 6.78 (br s, 1 H), 7.05 (s, 1 H), 7.14 (s, 1 H); ^{13}C NMR (75.5 MHz, CD_3COCD_3) δ 23.2 (CH_3), 25.3 (CH_3), 34.7 (CH), 36.3 (CH_2), 37.3 (CH_2), 60.1 (CH_2), 61.6 (CH), 70.3 (CH), 73.1 (CH), 74.8 (CH), 121.5 (CH), 123.9 (CH), 133.0 (C), 146.9 (C), 148.5 (C), 149.5 (C), 173.9 (C); MS (DCI, NH_3 + isobutane) *m/z* 406 (MH^+), 264, 231 (100), 176. More polar diastereomer: mp 200.5−201 °C (ethyl acetate); $[\alpha]^{25}_D$ −77.6 (*c* 0.4, CH_3OH); IR (KBr) 3374, 3228, 2957, 2867, 1678 cm^{-1}; ^{1}H NMR (300 MHz, CD_3COCD_3) δ 1.12−1.36 (m, 18 H), 1.53−1.66 (m, 1 H), 1.58 (d, J = 6.8 Hz, 3 H), 1.66−1.80 (m, 1 H), 2.39 (A of ABX, J = 16.0, 8.0 Hz, 1 H), 2.54 (B of ABX, J = 16.0, 7.3 Hz, 1 H), 2.87 (sept, J = 6.9 Hz, 1 H), 3.20−3.42 (m, 2 H), 3.56 (dd, J = 7.4, 2.2, 1 H), 3.61−3.71 (m, 2 H), 3.88−4.03 (m, 1 H), 4.12−4.22 (m, 1 H), 4.28 (m: ddd, J = 7.7, 7.7, 7.7 Hz, 1 H), 5.25 (q, J = 6.8 Hz, 1 H), 6.72 (br s, 1 H), 7.04 (s, 1 H), 7.13 (s, 1 H); ^{13}C NMR (75.5 MHz, CD_3OD) δ 23.5 (CH_3), 24.4 (CH_3), 25.5 (CH_3), 29.4 (CH), 30.2 (CH), 35.4 (CH), 37.4 (CH_2), 38.6 (CH_2), 59.8 (CH_2), 62.9 (CH), 67.9 (CH), 73.4 (CH), 74.2 (CH), 121.8 (CH), 124.3 (CH), 133.4 (C), 147.6 (C), 149.2 (C), 150.1 (C), 178.4 (C); MS (DCI, NH_3 + isobutane) *m/z* 406 (MH^+), 231, 176 (100). Anal. Calcd for $C_{24}H_{39}NO_4$: C 71.08, H 9.70, N 3.46. Found: C 71.11, H 9.76, N 3.35.

2,4,6-Triisopropylbenzenesulfonic Acid 3-Hydroxy-3-{(2*S*,3*R*)-5-oxo-3-[(*S*)-1-(2,4,6-triisopropylphenyl)ethoxy]-pyrrolidin-2-yl}propyl Ester (18b). To a stirred solution of 0.755 g (1.86 mmol) of diol **18a** in 9.0 mL of pyridine at 0 °C were added dropwise 1.30 mL (9.33 mmol) of triethylamine, 0.230 g (1.88 mmol) of DMAP, and 1.130 g (3.73 mmol) of 2,4,6-triisopropylbenzensulfonyl chloride. The resulting mixture was stirred at 20 °C for 7 h and then treated at 0 °C with an aqueous solution of $NaHCO_3$. After being stirred for 30 min at 0 °C, the mixture was extracted with ether. The organic phase was washed with water, 5% HCl, saturated $NaHCO_3$, and brine, dried over Na_2SO_4, filtered, and concentrated. The crude material was purified by silica gel chromatography with ethyl acetate in pentane to give 0.934 g (75%) of sulfonate **18b** as a mixture of diastereomers. Less polar diastereomer: mp 132−133 °C (pentane); $[\alpha]^{25}_D$ −51.4 (*c* 0.4, $CHCl_3$). IR 3200, 2958, 2928, 2871, 1701, 1601, 1460 cm^{-1}; ^{1}H NMR (300 MHz) δ 1.10−1.35 (m, 36 H), 1.59 (d, J = 6.7 Hz, 3 H), 1.81 (m: dddd, J = 14.0, 10.2, 5.0, 5.0 Hz, 1 H), 1.95−2.07 (m, 1 H), 2.50 (dd, J = 8.2, 1.2 Hz, 2 H), 2.85 (sept, J = 7.1 Hz, 1 H), 2.91 (sept, J = 7.1 Hz, 1 H), 3.14 (sept, J = 6.9 Hz, 1 H), 3.54 (m: ddd, J = 9.1, 9.1, 1.5 Hz, 1 H), 3.58−3.68 (m, 2 H), 4.03 (m: dddd, J = 11.1, 2.8, 2.8, 2.8 Hz, 1 H), 4.13 (sept, J = 6.8 Hz, 1 H), 4.08−4.18 (m, 1 H), 4.20−4.31 (m, 2 H), 4.36 (m: ddd, J = 8.2, 8.2, 8.2 Hz, 1 H), 5.17 (q, J = 6.7 Hz, 1 H), 5.97 (br s, 1 H), 6.97 (d, J = 1.8 Hz, 1 H), 7.05 (d, J = 1.8 Hz, 1 H), 7.18 (s, 2 H); ^{13}C NMR (75.5 MHz) δ 23.2 (CH_3), 23.7 (CH_3), 24.0 (CH_3), 24.1 (CH_3), 24.2 (CH_3), 24.9 (CH_3), 25.5 (CH_3), 29.4 (CH_3), 29.8 (CH), 34.2 (CH), 34.4 (CH), 35.7 (CH_2), 59.6 (CH), 65.9 (CH_2), 67.4 (CH), 72.6 (CH), 73.7 (CH), 121.3 (CH), 123.6 (CH), 123.9 (CH), 124.0 (CH), 129.3 (C), 130.4 (C), 146.5 (C), 148.5 (C), 148.8 (C), 151.0 (C), 153.9 (C), 173.8 (C). Anal. Calcd for $C_{39}H_{61}NO_6S$: C 69.71, H 9.15, N 2.09. Found: C 69.71, H 9.37, N 2.00. More polar diastereomer: IR 2958, 2928, 2871, 1701, 1601, 1460 cm^{-1}; ^{1}H NMR (300 MHz) δ 1.10−1.35 (m, 36 H), 1.58 (d, J = 6.8 Hz, 3 H), 1.77−1.87 (m, 2 H), 2.52 (m: ddd, J = 7.7, 7.7, 7.7 Hz, 2 H), 2.79 (d, J = 3.6 Hz, 1 H), 2.85 (sept, J = 6.9 Hz, 1 H), 2.92 (sept, J = 6.9 Hz, 1 H), 3.13 (sept, J = 6.5 Hz, 1 H), 3.54 (m: ddd, J = 7.8, 7.8, 7.8 Hz, 1 H), 3.76 (sept, J = 6.9 Hz, 1 H), 4.04−4.25 (m, 5 H), 4.31 (dd, J = 15.2, 7.6 Hz, 1 H), 5.15 (q, J = 6.8 Hz, 1 H), 6.39 (s, 1 H), 6.97 (d, J = 1.6 Hz, 1 H), 7.05 (d, J = 1.6 Hz, 1 H), 7.19 (s, 2 H); ^{13}C NMR (75.5 MHz) δ 23.4 (CH_3), 23.7 (CH_3), 24.0 (CH_3), 24.4 (CH_3), 24.9 (CH_3), 25.0 (CH_3), 28.4 (CH_3), 29.3 (CH), 34.2 (CH_2), 34.4 (CH), 37.4 (CH_2), 60.8 (CH), 66.4 (CH_2), 66.5 (CH), 71.8 (CH), 72.4 (CH), 121.1 (CH), 123.6 (CH), 124.0 (CH), 129.4 (C), 130.1 (C), 146.6 (C), 148.4 (C), 148.9 (C), 151.0 (C), 153.9 (C), 175.5 (C); MS (DCI, NH_3 + isobutane) *m/z* 672 (MH^+), 671 (M^+), 340, 267, 232, 231 (100). Anal. Calcd for $C_{39}H_{61}NO_6S \cdot H_2O$ (mixture of diastereomers): C, 67.89; H, 9.20; N, 2.03. Found: C, 67.93; H, 9.18; N, 2.00.

(1*R*,7a*R*)-7-Hydroxy-1-[(*S*)-1-(2,4,6-triisopropylphenyl)-ethoxy]pyrrolizidine (19). Borane−dimethyl sulfide complex (2.70 mL, 28.5 mmol) was added to a stirred solution of 2.15 g (3.20 mmol) of sulfonate **18b** in 29 mL of THF. The mixture was refluxed for 6 h, cooled at 0 °C, and treated carefully with methanol. The solvent was evaporated under reduced pressure and methanol was again added and evaporated (three times). The resulting crude oil was dissolved in 14 mL of methanol and stirred with 0.35 g of 10% palladium on carbon and 1.4 mL (9.8 mmol) of triethylamine for 12 h at 20 °C. The palladium was removed by filtration and the filtrate concentrated. The resulting oil was then dissolved in ether, which was washed with water, brine, and 10% NaOH, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting crude product was purified by silica gel (triethylamine-deactivated) chromatography with 0−15% methanol saturated with ammonia in dichloromethane to afford 1.05 g (88%) of alcohol **19** as a white solid. Less polar diastereomer: mp 105−106 °C (pentane); $[\alpha]^{25}_D$ −41.9 (*c* 0.5, $CHCl_3$); IR (film) 3498, 2963, 2933, 2869 cm^{-1}; ^{1}H NMR (300 MHz) δ 1.10−1.35 (m, 18 H), 1.58 (d, J = 6.9 Hz, 3 H), 1.95−2.10 (m, 3 H), 2.80−3.05 (m, 4 H), 3.10−3.25 (m, 2 H), 3.36 (dd, J = 7.7, 3.3 Hz, 1 H), 3.84 (sept, J = 6.2 Hz, 1 H), 4.23 (dd, J = 14.1, 6.4 Hz, 1 H), 4.30−4.40 (m, 2 H), 5.20 (q, J = 6.9 Hz, 1 H), 6.97 (s, 1 H), 7.06 (s, 1 H); ^{13}C NMR (75.5 MHz) δ 23.5 (CH_3), 24.0 (CH_3), 32.2 (CH_2), 34.1 (CH), 36.1 (CH_2), 52.7 (CH_2), 53.7 (CH_2), 70.5 (CH), 72.2 (CH), 73.9 (CH), 79.0 (CH), 120.9 (CH), 123.6 (CH), 131.6 (C), 148.0 (C); MS (CI) *m/z* 374 (MH^+, 100), 373 (M^+), 231. Anal. Calcd for $C_{24}H_{39}NO_2 \cdot {}^1/_2H_2O$: C, 75.35; H, 10.54; N, 3.66. Found: C, 75.04; H, 10.52; N, 3.58. More polar diastereomer: mp 115−116 °C (pentane); $[\alpha]^{25}_D$ −58.7 (*c* 0.5, $CHCl_3$); IR (film) 3361, 2962, 2961, 2868 cm^{-1}; ^{1}H NMR (300 MHz) δ

1.12−1.32 (m, 18 H), 1.52 (d, J = 6.8 Hz, 3 H), 1.70−1.85 (m, 2 H), 1.96−2.05 (m, 2 H), 2.10 (m: dddd, J = 12.7, 6.3, 6.3, 6.3 Hz, 1 H), 2.58−2.70 (m, 2 H), 2.85 (sept, J = 6.9 Hz, 1 H), 3.01 (m: ddd, J = 11.9, 6.8, 5.1 Hz, 1 H), 3.15−3.28 (m, 3 H), 3.87 (sept, J = 6.8 Hz, 1 H), 4.00 (m: ddd, J = 4.9, 4.9, 4.9 Hz, 1 H), 4.46 (m: ddd, J = 5.9, 5.9, 4.0 Hz, 1 H), 5.13 (q, J = 6.8 Hz, 1 H), 6.95 (s, 1 H), 7.04 (s, 1 H); ^{13}C NMR (75.5 MHz) δ 23.5 (CH_3), 24.0 (CH_3), 24.1 (CH_3), 24.5 (CH_3), 25.5 (CH_3), 28.5 (CH), 29.3 (CH), 31.7 (CH_2) 34.1 (CH), 35.2 (CH_2), 52.5 (CH_2), 53.5 (CH_2), 71.2 (CH), 71.8 (CH), 75.6 (CH), 77.04 (CH), 120.8 (CH), 123.4 (CH), 132.8 (C), 145.9 (C), 147.7 (C), 148.9 (C); MS (CI) *m/z* 374 (MH^+, 100), 264, 231. Anal. Calcd for $C_{24}H_{39}NO_2$: C, 77.17; H, 10.53; N, 3.75. Found: C, 77.38; H, 10.64; N, 3.82.

Trifluoromethanesulfonic Acid (7*R*,7a*S*)-7-[(*S*)-1-(2,4,6-Triisopropylphenyl)ethoxy]-5,6,7,7a-tetrahydro-*3H*-pyrrolizin-1-yl Ester (20a). To a solution of 0.805 mL (9.23 mmol) of freshly distilled oxalyl chloride in 9.3 mL of dichloromethane at −60 °C was added 1.24 mL (17.5 mmol) of dimethyl sulfoxide. After being stirred for 10 min at −60 °C, the solution was treated dropwise with a solution of 0.619 g (1.66 mmol) of pyrrolizidinol **19** in 9.3 mL of dichloromethane. The reaction mixture was stirred for 1.5 h while being allowed to warm to −40 °C and was then treated with 2.35 mL (16.9 mmol) of triethylamine. The reaction mixture was allowed to warm to −5 °C over 1.5 h and diluted with ether, and the organic layer was washed with water, brine, and 10% aqueous NaOH. The organic phase was dried over Na_2SO_4, filtered, and concentrated under reduced pressure to leave 0.617 g of crude (7*R*,7a*S*)-7-[(*S*)-1-(2,4,6-triisopropylphenyl)ethoxy]hexahydropyrrolizin-1-one, which was used immediately in the reaction below: IR (film) 2965, 2935, 2871, 1747, 1605 cm^{-1}; ^{1}H NMR (300 MHz) δ 1.12−1.27 (m, 18 H), 1.47 (d, J = 6.8 Hz, 3 H), 1.84 (m: dddd, J = 17.4, 8.7, 8.7, 4.7 Hz, 1 H), 2.22−2.33 (m, 1 H), 2.35 (m: ddd, J = 8.4, 8.4, 0.8 Hz, 1 H), 2.47 (m: ddd, J = 17.9, 8.6, 5.1 Hz, 1 H), 2.84 (sept, J = 6.9 Hz, 1 H), 3.01−3.12 (m, 2 H), 3.15−3.30 (m, 1 H), 3.22 (sept, J = 6.9 Hz, 1 H), 3.32−3.43 (m, 1 H), 3.40 (d, J = 4.8 Hz, 1 H), 3.73 (sept, J = 6.8 Hz, 1 H), 4.17 (m: ddd, J = 4.7, 4.7, 1.5 Hz, 1 H), 5.12 (q, J = 6.7 Hz, 1 H), 6.92 (d, J = 1.8 Hz, 1 H), 7.02 (d, J = 1.8 Hz, 1 H); ^{13}C NMR (75.5 MHz) δ 23.0 (CH_3), 24.0 (CH_3), 24.3 (CH_3), 25.3 (CH_3), 25.7 (CH_3), 28.2 (CH), 29.3 (CH), 32.8 (CH_2), 34.1 (CH), 38.7 (CH_2), 51.5 (CH_2), 54.0 (CH_2), 71.8 (CH), 73.6 (CH), 79.0 (CH), 120.7 (CH), 123.2 (CH), 132.2 (C), 145.7 (C), 147.4 (C), 149.2 (C), 216.9 (C); MS (DCI, NH_3 + isobutane) *m/z* 372 (MH^+, 100), 371 (M^+), 231, 142; HRMS calcd for $C_{24}H_{38}NO_2$ 372.2903, found 372.2906 (MH^+). A solution of 0.046 g of the above ketone in 0.5 mL of THF at −90 °C was treated with 0.37 mL (0.19 mmol) of a 0.5 M solution of KHMDS in THF. The reaction mixture was stirred for 10 min and then a solution of 0.097 g (0.25 mmol) of *N*-(5-chloro-2-pyridyl)-triflimide in 0.2 mL of THF was added. The reaction mixture was stirred for 1 h, while being allowed to warm to −20 °C, and then treated with aqueous NH_4Cl and ether. The organic layer was washed with water, brine, and 10% NaOH, dried over Na_2SO_4, filtered, and concentrated. The resulting crude product was purified on Florisil using 0−4% methanol saturated with ammonia in dichloromethane to afford 0.031 g (50% overall yield) of triflate **20a** as a brown oil: IR 3054, 2963, 2927, 2868, 1668, 1609, 1486 cm^{-1}; ^{1}H NMR (300 MHz) δ 1.15−1.30 (m, 18 H), 1.52 (d, J = 6.8 Hz, 1 H), 1.85 (m: dddd, J = 12.7, 8.2, 6.4, 4.4 Hz, 1 H), 1.97−2.07 (m, 1 H), 2.77 (m: ddd, J = 14.3, 8.2, 5.9 Hz, 1 H), 2.85 (sept, J = 6.9 Hz, 1 H), 3.08 (m: ddd, J = 10.1, 5.9, 5.9 Hz, 1 H), 3.22 (sept, J = 6.9 Hz, 1 H), 3.41 (m: ddd, J = 14.8, 5.8, 2.1 Hz, 1 H), 3.91 (sept, J = 6.9 Hz, 1 H), 3.97 (m: ddd, J = 14.9, 2.3, 2.3 Hz, 1 H), 4.05 (m: ddd, J = 9.6, 4.4, 4.4 Hz, 1 H), 4.11−4.18 (m, 1 H), 5.17 (q, J = 6.9 Hz, 1 H), 5.67 (m, 1 H), 6.94 (d, J = 1.9 Hz, 1 H), 7.04 (d, J = 1.9 Hz, 1 H); ^{13}C NMR (75.5 MHz) δ 23.1 (CH_3), 24.0 (CH_3), 24.1 (CH_3), 24.3 (CH_3), 25.2 (CH_3), 25.3 (CH_3), 28.1 (CH_3), 29.2 (CH_3), 32.1 (CH_2), 34.1 (CH), 54.1 (CH_2), 59.3 (CH_2), 71.6 (CH), 72.0 (CH), 77.3 (CH), 114.1 (CH), 118.7 (CF_3, J = 321 Hz), 120.8 (CH), 123.3 (CH), 132.4 (C), 144.6 (C), 145.6 (C), 147.6 (C), 149.0 (C); MS (CI) *m/z* 504 (MH^+, 100), 274, 238; HRMS calcd for $C_{25}H_{37}NO_4SF_3$ 504.2395, found 504.2406 (MH^+).

(7*R*,7a*R*)-7-[(*S*)-1-(2,4,6-Triisopropylphenyl)ethoxy]-5,6,7,7a-tetrahydro-*3H*-pyrrolizine-1-carboxylic Acid Methyl Ester (20b). A mixture of 0.202 g (0.40 mmol) of triflate **20a**, 0.116 g (0.10 mmol) of $Pd(P(C_6H_5)_3)_4$, and 2.3 mL of methanol in 2.8 mL of DMF was stirred at 45 °C for 3 h under an atmosphere of CO. After being allowed to cool to 20 °C, the reaction mixture was concentrated and 5% NaOH was added. The mixture was extracted with ether, which was washed with water, brine, and 5% NaOH, dried over Na_2SO_4, filtered, and concentrated. The crude product was purified by silica gel chromatography with methanol saturated with ammonia in dichloromethane to afford 0.102 g (61%) of ester **20b**: $[\alpha]^{25}_D$ +31.5 (*c* 0.7, $CHCl_3$); IR (film) 3059, 2964, 2930, 2870, 1720, 1462 cm^{-1}; ^{1}H NMR (300 MHz) δ 1.05−1.25 (m, 18 H), 1.51 (d, J = 6.8 Hz, 3 H), 1.95−2.1 (m, 1 H), 2.11−2.20 (m, 1 H), 2.69 (m: ddd, J = 14.3, 8.8, 5.4 Hz, 1 H), 2.82 (sept, J = 6.8 Hz, 1 H), 3.10−3.33 (m, 1 H), 3.17 (sept, J = 6.8 Hz, 1 H), 3.24 (s, 3 H), 3.48 (m: ddd, J = 17.6, 5.3, 2.2 Hz, 1 H), 3.74 (sept, J = 6.9 Hz, 1 H), 3.96 (m: ddd, J = 17.6, 3.3, 2.2 Hz, 1 H), 4.19 (m: ddd, J = 5.1, 5.1, 1.5 Hz, 1 H), 4.44−4.51 (m, 1 H), 5.02 (q, J = 6.8 Hz, 1 H), 6.49 (dd, J = 4.1, 2.0 Hz, 1 H), 6.89 (d, J = 1.9 Hz, 1 H), 6.97 (d, J = 1.8 Hz, 1 H); ^{13}C NMR (75.5 MHz) δ 23.0 (CH_3), 24.1 (CH_3), 24.2 (CH_3), 24.4 (CH_3), 24.9 (CH_3), 25.1 (CH_3), 28.9 (CH), 29.3 (CH), 34.1 (CH), 35.4 (CH_2), 51.1 (CH_3), 54.5 (CH_2), 62.2 (CH_2), 75.3 (CH), 76.1 (CH), 79.3 (CH), 120.4 (CH), 122.9 (CH), 132.6 (C), 134.6 (C), 137.9 (CH), 144.6 (C), 147.1 (C), 148.5 (C), 163.7 (C); MS (DCI, NH_3 + isobutane) *m/z* 414 (MH^+, 100), 413 (M^+), 264, 263, 184; HRMS calcd for $C_{26}H_{40}NO_3$ 414.3008, found 414.2977 (MH^+).

(7*R*,7a*R*)-7-Hydroxy-5,6,7,7a-tetrahydro-*3H*-pyrrolizine-1-carboxylic Acid Methyl Ester (21). A solution of 0.0200 g (0.048 mmol) of ester **20b** in 0.5 mL of dichloromethane at 0 °C was treated with 0.05 mL (0.65 mmol) of TFA and stirred for 3 h. The reaction mixture was concentrated under reduced pressure, methanol saturated with ammonia was added, and the mixture was again concentrated. The crude product was purified by silica gel (triethylamine-deactivated) chromatography with 10−20% methanol saturated with ammonia in dichloromethane to give 0.0089 g (100%) of hydroxy ester **21** as a white solid: mp 106−109 °C (pentane−ethyl acetate); $[\alpha]^{25}_D$ +14.0 (c 0.4, $CHCl_3$); IR 3387, 3055, 2946, 2849, 1720, 1643, 1439 cm^{-1}; ^{1}H NMR (300 MHz) δ 1.95−2.12 (m, 2 H), 2.79 (m: ddd, J = 15.6, 9.2, 6.5 Hz, 1 H), 3.37 (m: ddd, J = 8.7, 6.6, 1.7 Hz, 1 H), 3.60 (m: ddd, J = 18.2, 5.4, 2.3 Hz, 1 H), 3.79 (s, 3 H), 4.08−4.19 (m, 1 H), 4.52−4.60 (m, 1 H), 6.76−6.82 (m, 1 H); ^{13}C NMR (75.5 MHz) δ 35.6 (CH_2), 52.3 (CH_3), 54.2 (CH_2), 61.6 (CH_2), 71.0 (CH), 77.3 (CH), 131.1 (C), 139.4 (CH), 164.0 (C); MS (DCI, NH_3 + isobutane) *m/z* 184 (MH^+, 100), 152, 134; HRMS calcd for $C_9H_{14}NO_3$ 184.0974, found 184.0982 (MH^+).

(1*R*,7a*R*)-7-Hydroxymethyl-2,3,5,7a-tetrahydro-*1H*-pyrrolizin-1-ol ((+)-Retronecine) (2). To 0.47 mL (0.47 mmol) of a 1 M solution of DIBAL-H in dichloromethane at −80 °C was slowly added a solution of 0.0170 g (0.093 mmol) of hydroxy ester **21** in 0.70 mL of dichloromethane. The mixture was stirred for 3 h, while the temperature was allowed to rise slowly to −10 °C. Methanol (6 mL) and Na_2SO_4 were then added, and the mixture was stirred for 3 h at 20 °C. The resulting precipitate was removed by filtration through Celite and the filtrate was concentrated under reduced pressure. The crude product was purified by silica gel (triethylamine-deactivated) chromatography with 10−20% methanol saturated with ammonia in dichloromethane to give 0.0093 g (65%) of (+)-retronecine **2** as a white solid: mp 117−118 °C (acetone); $[\alpha]^{25}_D$ +51.3 (*c* 0.3, C_2H_5OH); IR (KBr) 3320, 3067, 2931, 2866, 1318, 1201, 1101, 1039, 1002 cm^{-1}; ^{1}H NMR (300 MHz, CD_3OD) δ 1.89−1.99 (m, 2 H), 2.68−2.79 (m, 1 H), 3.17 (m: ddd, J = 9.1, 6.7, 2.3 Hz, 1 H), 3.39 (m: dddd, J = 15.1, 5.3, 3.6,

1.8 Hz, 1 H), 3.81 (m: dddd, J = 8.0, 3.8, 1.8, 1.8 Hz, 1 H), 4.12−4.33 (m, 3 H), 4.29−4.33 (m, 1 H), 5.66−5.68 (m, 1 H); ^{13}C NMR (75.5 MHz) δ 36.7 (CH_2), 54.8 (CH_2), 59.7 (CH_2), 63.0 (CH_2), 72.0 (CH), 79.4 (CH), 125.8 (CH), 140.2 (C); MS (DCI, NH_3 + isobutane) m/z 156 (MH^+, 100), 152, 145, 124; HRMS calcd for $C_8H_{14}NO_2$ 156.1025, found 156.1033 (MH^+).

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Supporting Information Available: ^{1}H and/or ^{13}C NMR spectra of compounds **1a**, **1a** (protected), **1d**, **1d** (CH_3 ester·HCl and C_2H_5 ester), **2**, **12a**, **12b**, **13**, **14**, **20a**, **20b**, **21**. This material is available free of charge via the Internet at http://pubs.acs.org.

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