Highly Diastereoselective Cyclopentane Construction: Enantioselective Synthesis of the Dendrobatid Alkaloid 251F

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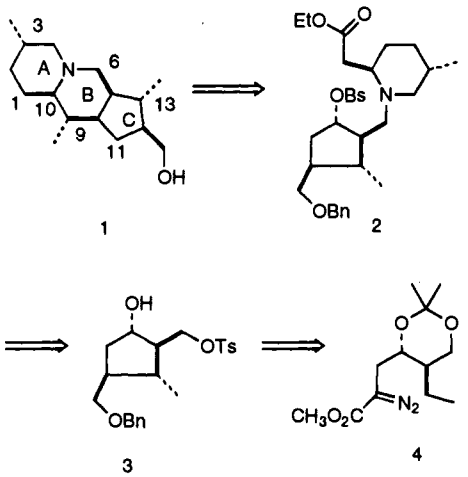
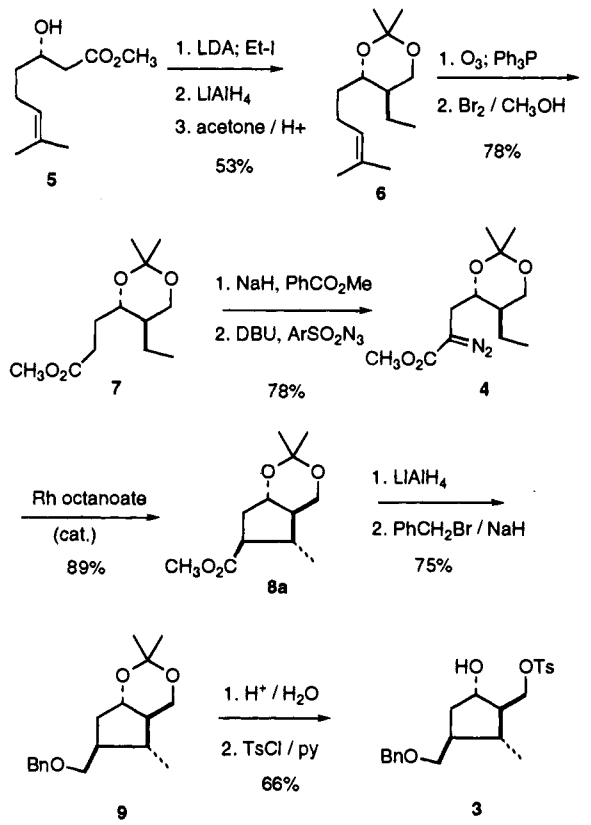
Abstract: We report the first total synthesis, and thus structural confirmation, of the dendrobatid alkaloid **251F** (**1**), based on the retrosynthetic analysis illustrated (**1** ← ← **4**). Key observations in this synthesis are that both the Rh-mediated cyclization of **4** and the anionic cyclization of **2** proceed with excellent diastereoselectivity.

In 1992 Daly and Spande reported[1] the isolation and structural elucidation, primarily by high field ^1H and ^{13}C NMR and mass spectrometry, of alkaloid **251F** (**1**) from the skin exudate of the dendrobatid poison frog *Minyobates bombetes* of Colombia. Unlike most of the dendrobatid alkaloids, which are apparently acetogenins, **1** is clearly terpene-derived. We report the first total synthesis, and thus structural confirmation, of **1**, based on the retrosynthetic analysis illustrated. The most critical observations in this synthesis are that both the Rh-mediated cyclization of **4** and the anionic cyclization of **2** can be effected with excellent diastereoselectivity.



Preparation of the C Ring. For the proposed convergent assembly to succeed, it was necessary to prepare both the carbocyclic **C** ring and the piperidine **A** ring in high enantiomeric purity. While a variety of approaches to enantiomerically pure cyclopentanes have been developed,[2] none of these is readily applicable to the preparation of such a highly substituted cyclopentane as **3**. We therefore investigated the Rh-mediated cyclization[3,4] of diazoester **4** (Scheme 1).

Scheme 1



We were attracted to this approach by the our already-established preparation[5] of the enantiomerically pure β-hydroxy ester **5** (two steps from the inexpensive 6-methyl-5-heptene-2-

[⊗] Abstract published in *Advance ACS Abstracts,* May 15, 1995.

(1) Spande, T. F.; Garraffo, H. M.; Yeh, H. J. C.; Pu, Q. L.; Pannell, L. K.; Daly, J.W. *J. Nat. Prod.* **1992**, *55*, 822.

(2) For alternative methods for the enantioselective construction of highly substituted cyclopentanes, see: (a) Allan, R. D.; Johnston, G. A. R.; Twitchin, B. *Aust. J. Chem.* **1979**, *32*, 2517. (b) Colombo, L.; Gennari, C.; Resnati, G.; Scolastico, C. *Synthesis*, **1981**, 74. (c) Klunder, A. J. H.; Huizinga, W. B.; Sessnik, P. J. M.; Zwanenburg, B. *Tetrahedron Lett.* **1987**, *28*, 357. (d) Trigalo, F.; Buisson, D.; Azerad, R. *Tetrahedron Lett.* **1988**, *29*, 6109. (e) Henly, R.; Elie, C. J. J.; Buser, H. P.; Ramos, G.; Moser, H. E. *Tetrahedron Lett.* **1993**, *34*, 2923.

(3) For the first observation of the efficient cyclization of simple α-diazo esters, see: Taber, D. F.; Hennessy, M. J.; Louey, J. P. *J. Org. Chem.* **1992**, *57*, 436.

(4) For leading references to Rh-mediated intramolecular C–H insertion, see: (a) Doyle, M. P.; Dyatkin, A. B.; Roos, G. H. P.; Canas, F.; Pierson, D. A.; van Basten, A.; Müller, P.; Polleux, P. *J. Am. Chem. Soc.* **1994**, *116*, 4507. (b) Wang, P.; Adams, J. *J. Am. Chem. Soc.* **1994**, *116*, 3296. (c) Doyle, M. P. In *Homogeneous Transition Metal Catalysts in Organic Synthesis*; Moser, W. R., Slocum, D. W., Eds.; ACS Advanced Chemistry Series 230; American Chemical Society: Washington, DC, 1992; Chapter 30. (d) Taber, D. F. *Comprehensive Organic Synthesis, V. 3*; Pattenden, G., Ed.; Pergamon Press: Oxford, 1991; p 1045.

(5) Taber, D. F.; Silverberg, L. J.; Robinson, E. D. *J. Am. Chem. Soc.* **1991**, *113*, 6639.

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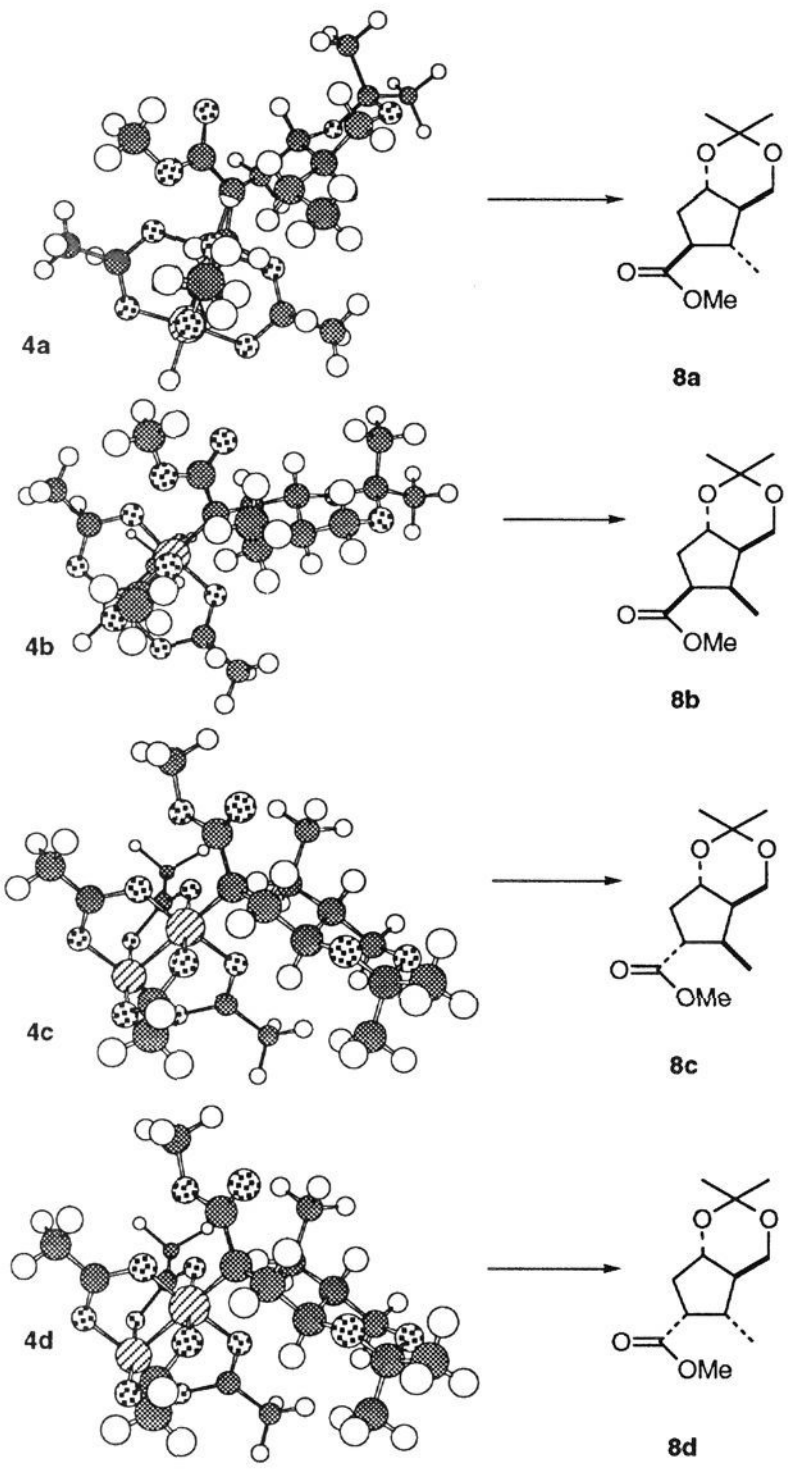
Scheme 2



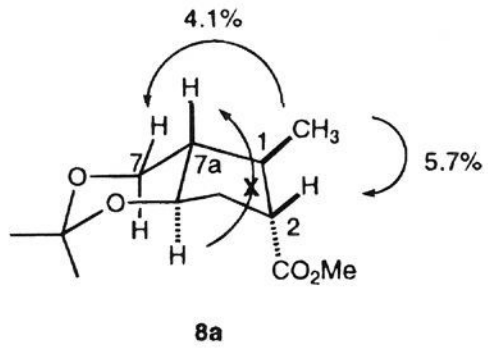
one, 90% overall yield and 97% ee, by Ru BINAP hydrogenation[6] of the intermediate β-ketoester). Alkylation[7] of the dianion proceeded to give the expected anti product, which was reduced and protected to afford **6**. Ozonolysis of the alkene **6** followed by oxidation[8] gave the ester **7**.

Evans reported traces of diazo transfer on reaction of 4-nitrobenzenesulfonylazide with an ester enolate.[9] We have found that initial benzoylation of the ester enolate substantially increases the yield of the subsequent diazo transfer. This is the first practical procedure for direct diazo transfer to an ester.[10]

Cyclization of **4** could proceed to a give a mixture of one or more of the diastereomers **8a−8d** (Scheme 2). There are four corresponding diastereomeric transition states, **4a−4d,** leading to cyclization. Previous work on Rh-mediated intramolecular C−H insertion[3,4]supports the concept that initial complexation of the intermediate Rh carbene with the target C−H bond is rapid and reversible. We reasoned that bridging the 1,3-diol with the acetonide protecting group could provide a rigidity to these transition states.

Considering each of the diastereomeric transition states in turn, **4a** seemed the most favorable. Transition state **4b** looks very much like **4a**, with, however, an additional destabilizing buttressing interaction between the methyl group and the ester. In transition state **4c**, the Rh dimer, swung out of the way in **4a** and **4b**, is tucked up in a sterically more congested area under the ring. Transition state **4d** has the same problem, and also adds the buttressing between the methyl group and the ester seen in **4b**.[11]

In fact, the cyclization of **4** proceeded smoothly, to give **8a** as the only (^{13}C NMR) diastereomer observed. The relative configuration of **8a** was assigned by a combination of COESY and NOE techniques. The most significant observations were a 4.1% NOE between the methyl group and the equatorial H at C-7 and a 5.7% NOE between the methyl group and the H at C-2. The lack of an NOE between the ring fusion H's confirmed the trans ring fusion. Given the rigid nature of the chair conformation of the six-membered ring, these observations then secure the relative configuration of **8a**.



8a

Reduction of the ester and subsequent protection led to **9**. Monotosylation of the derived diol then gave **3**, in 12 steps and 14% overall yield from **5**. Using this approach, we have routinely prepared gram quantities of enantiomerically pure **3**.

Preparation of the Piperidine A Ring. To pursue the proposed convergent assembly of **1**, we also needed gram quantities of the enantiomerically pure piperidine **14** (Scheme 3). This was conveniently available starting with the Sharpless asymmetric epoxidation[12] of geraniol **10**. Reduction of the epoxide (92% ee) following the Hutchins procedure[13] proceeded cleanly to give the 2-hydroxycitronellol **11**,[14] which on periodate cleavage[15] followed by reductive workup gave norcitronellol **12**. We have found this assembly of **12** to be much more convenient than alternative chiral auxiliary-based methods.

(6) (a) Noyori, R.; Ohkuma, T.; Kitamura, M.; Takaya, H.; Sayo, N.; Kumobayashi, H.; Akutagawa, A. *J. Am. Chem. Soc.* **1987**, *109*, 5856. (b) Kitamura, M.; Ohkuma, T.; Inoue, S.; Sayo, N.; Kumobayashi, H.; Akutagawa, A.; Ohta, T.; Takaya, H.; Noyori, R. *J. Am. Chem.Soc.* **1988**, *110*, 629. (c) Kitamura, M.; Ohkuma, T.; Takaya, H.; Noyori, R. *Tetrahedron Lett.* **1988**, *29*, 1555. (d) Nishi, T.; Kitamura, M.; Ohkuma, T.; Noyori, R. *Tetrahedron Lett.* **1988**, *29*, 6327. (e) Schreiber, S. L.; Kelly, S. E.; Porco, J. A.; Sammakia, T.; Suh, E. M. *J. Am. Chem. Soc.* **1988**, *110*, 6210. (f) Noyori, R.; Ikeda, T.; Ohkuma, T.; Widhalm, M.; Kitamura, M.; Takaya, H.; Akutagawa, S.; Sayo, N.; Saito, T.; Taketomi, T.; Kumobayashi, H. *J. Am. Chem. Soc.* **1989**, *111*, 9134. (g) Jones, B. A.; Yamaguchi, M.; Patten, A.; Danishefsky, S. J.; Ragan, J.A.; Smith, D. B.; Schreiber, S. L. *J. Org. Chem.* **1989**, *54*, 17. (h) Oppolzer, W.; Wills, M.; Starkmann, C.; Bernardinelli, G. *Tetrahedron Lett.* **1990**, *31*, 4117.

(7) A 95:5 ratio is reported for the alkylation of an analogous β-alkoxy ester enolate: Frater, G. *Helv. Chim. Acta* **1979**, *62*, 2825. We have not yet been able to isolate or characterize the very minor diastereomer of **7**. The yield reported for **7** is for diastereomerically pure (^{13}C) material.

(8) Williams, D. R.; Klingler, F. D.; Allen, E. E.; Lichtenthaler, F. W. *Tetrahedron Lett.* **1988**, *29*, 5087.

(9) Evans, D. A.; Britton, T. C.; Ellman, J. A.; Dorow, R. L. *J. Am. Chem. Soc.* **1990**, *112*, 4011.

(10) For an overview of diazo transfer chemistry, see: (a) Regitz, M.; Maas, G. *Diazo Compounds: Properties and Synthesis*; Academic Press: Orlando, 1986. (b) Askani, R; Taber, D. F. *Comprehensive Organic Synthesis, Vol. 6*; Winterfeldt, E., Ed.; Pergamon: Oxford, 1991; p 103.

(11) We have developed a computational approach that rationalizes both the highly diastereoselective cyclization of **4** and the similarly diastereoselective cyclization of other substituted α-diazo esters. We will describe these results separately.

(12) (a) Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 5974. (b) Hanson, R. M.; Sharpless, K. B. *J. Org. Chem.* **1986**, *51*, 1922.

(13) Hutchins, R. O.; Taffer, I. M.; Burgoyne, W. *J. Org. Chem.* **1981**, *46*, 5214.

(14) Taber, D. F.; Houze, J. B. *J. Org. Chem.* **1994**, *59*, 4004.

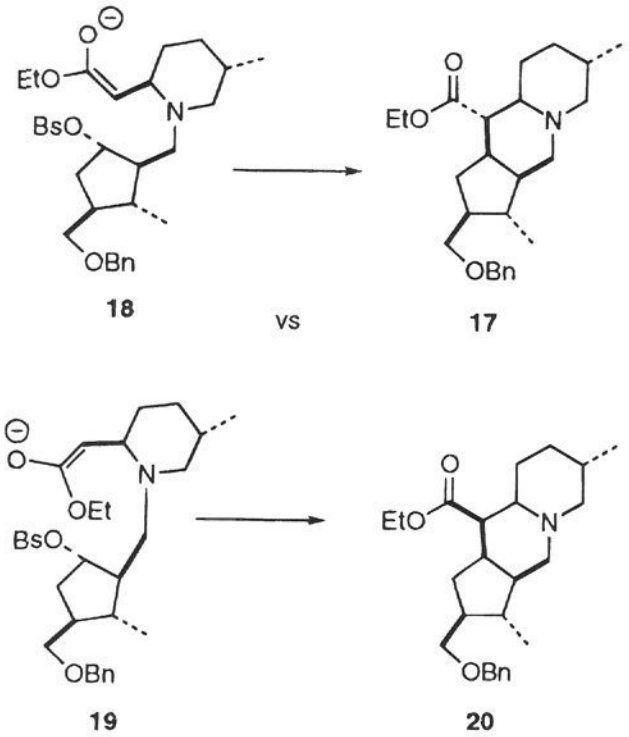
(15) Daumas, M.; Vo-Quang,Y.; Vo-Quang,L.; Le Goffic, F. *Synthesis* **1989**, 64.

Ozonolysis of the unstable azide **13** followed by phosphonate condensation and reduction of the azide[16] at −50 °C afforded **14** and **15** in a ratio of 5.6:1. Assignment of the relative configuration of **14** and **15** was made by comparison of ^{1}H NMR chemical shifts with those for known substituted piperidines.[17] At 0 °C, the same cyclization proceeded to give **14** and **15** in a ratio of 1.1:1.

Convergent Assembly of 1. Alkylation of **14** with **3** proceeded smoothly to give **16**. There were then two uncertainties to be faced in approaching the proposed intramolecular alkylation to close the **B** ring. First, it would be necessary to purify the unstable amino benzenesulfonate derived from **16**. Even if the benzenesulfonate could be sufficiently purified, the attempted enolate formation might result instead in β-elimination.

Direct formation of the cis-fused azetidinium salt was indeed a real hazard. We observed that the isolated yield of the benzenesulfonate dropped off quickly with extended reaction time. Nevertheless, rapid preparation and purification allowed the isolation of the desired benzenesulfonate.

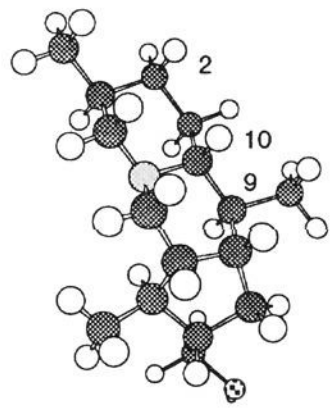
Still's demonstration[18] that it is possible to generate and alkylate the enolate of a β-amino ester made cyclization plausible. The question of the relative configuration of the newly-established stereogenic center remained. We reasoned that transition state **18** would be less congested than **19**, so **17** would be favored over **20**. While cyclization proceeded smoothly, to give **17** as a single dominant diastereomer, it is not impossible that any of ester **20** that formed could have been equilibrated to **17** under the conditions of the cyclization.



To complete the synthesis, it was necessary to convert the ester to a methyl group. Several methods[19] have been put forward for effecting this transformation. We have developed what promises to be an efficient alternative. Thus, ester **17** was reduced to the corresponding alcohol, which was then converted to the sulfide.[20] Dissolving metal reduction[21] then effected clean desulfurization as well as debenzylation to give **1**.

The amino alcohol from the reduction had a mass spectrum congruent with that reported for **1**. The identity of the synthetic amino alcohol with the natural alkaloid was confirmed by ^{1}H and ^{13}C NMR,[22] GC-MS coinjection on a capillary GC column, and GC-IR.[23]

By the method of synthesis, we are confident of the absolute configuration of the stereogenic centers at C-3, C-7, C-8, C-12, and C-13 of alkaloid **251F**. The centers at C-9 and C-10, on the other hand, are not secured by this synthesis, as ester **17** could be subject to both epimerization and β-elimination. In addition to **1**, then, structures **21**, **22**, and **23** could alternatively be possible for **251F**.



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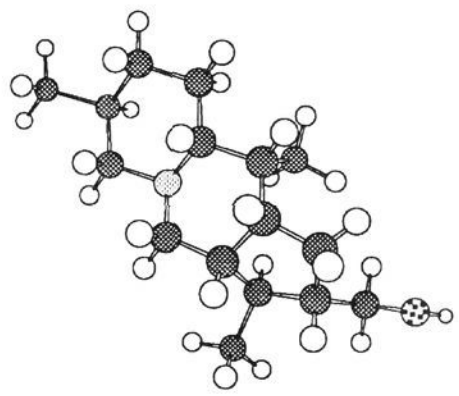
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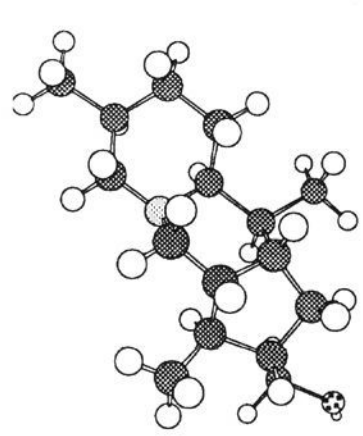
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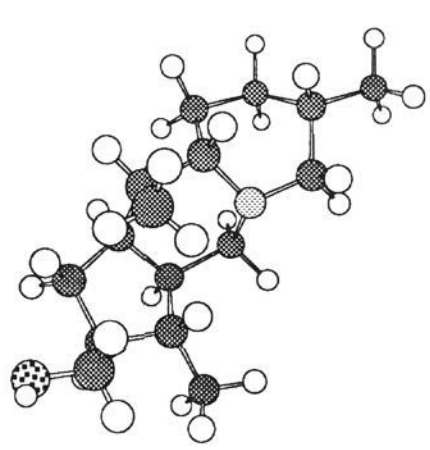

23

With five of the seven centers of **251F** established, we can return to the NOESY spectrum originally recorded for the natural product. The key NOEs for our purposes are those observed between the 2-axial H and H_{10} and between H_{10} and the 9-methyl. The former establishes that H_{10} is axial, and the latter establishes that the 9-methyl is on the same side of the ring as H_{10}. Thus, the relative configuration of **251F** is confirmed to be **1**. The absolute configuration of **1** is as yet unknown.

The isolation and structure of **1** was carried out with 300 μg of material, the total that had been purified from the *Minyobates bombetes* extract.[1] The convergent assembly of **1** outlined here, even in its initial form, has already increased the supply of the purified alkaloid by a factor of more than 100. The high

(16) Knouzi, N.; Vaultier, M.; Toupet, L.; Carrie, R. *Tetrahedron Lett.* **1987**, *28*, 1757.

(17) Cahill, R.; Crabb, T. A. *Org. Magn. Reson.* **1972**, *4*, 259.

(18) For an earlier use of a β-amino ester enolate in synthesis, see: Still, W. C.; Schneider, M. J. *J. Am. Chem. Soc.* **1977**, *99*, 948.

(19) For a review of methods for the deoxygenation of alcohols, see: (a) Hartwig, W. *Tetrahedron* **1983**, *39*, 2609. For additional procedures for the deoxygenation of a primary alcohol to a methyl group, see: (b) Barton, D. H. R.; Motherwell, W. B,.; Stange, A. *Synthesis* **1981**, 743. (c) Trost, B. M.; Renaut, P. *J. Am. Chem. Soc.* **1982**, *104*, 6668. (d) Grether, G.;Mitt, T.; Williams, T. H.; Uskokovic, M. R. *J. Org. Chem.* **1983**, *48*, 5309. (e) Feldman, K. S.; Wu, M.-J.; Rotella, D. P. *J. Am. Chem. Soc.* **1990**, *112*, 8490. (f) Barton. D. H. R.; Jang, D. O.; Jaszberenyi, J. C. *Tetrahedron Lett.* **1990**, *31*, 4681. (g) Barton. D. H. R.; Jang, D. O.; Jaszberenyi, J. C. *Tetrahedron Lett.* **1992**, *33*, 2311. (h) Barton. D. H. R.; Jang, D. O.; Jaszberenyi, J. C. *Tetrahedron Lett.* **1990**, *31*, 4681.

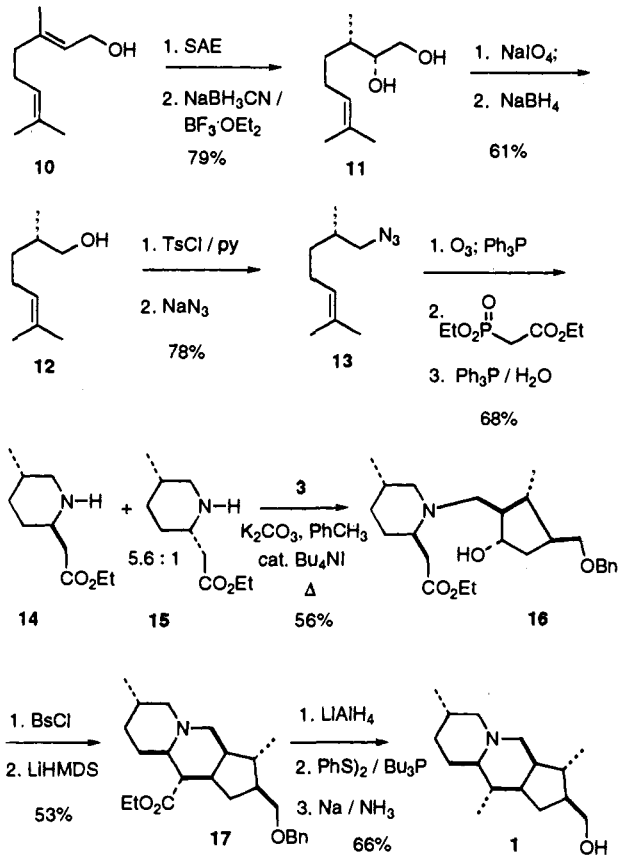
(20) Cleary, D. G. *Synth. Commun.* **1989**, *19*, 737.

(21) For the dissolving metal reduction of *secondary* phenyl alkyl thioethers to alkanes, see: (a) Haskell, T. H.; Woo, P. W. K.; Watson, D. R. *J. Org. Chem.* **1977**, *42*, 1302. (b) Masaki, Y.; Hashimoto, K.; Sakuma, K.; Kaji, K. *Tetrahedron Lett.* **1982**, *23*, 1481. (c) Suridov, A. F.; Ermolenko, M. S.; Yashunsky, D. V.; Borodkin, V. S.; Kochetkov, N. D. *Tetrahedron Lett.* **1987**, *28*, 3835.

(22) The ^{1}H and ^{13}C spectra were acquired in D_2O/DCl.

(23) We thank T. F. Spande, H. M. Garraffo, and H. C. J. Yeh, Laboratory of Bioorganic Chemistry, NIH, for making these comparisons.

Scheme 3



diastereoselectivity observed for the cyclization of **4** is especially noteworthy. Our preliminary investigations with additional α-diazo esters indicate that these substrates often cyclize with high diastereoselectivity.[11]

Experimental Section[14]

Methyl (2*S*,3*S*)-2-Ethyl-3-hydroxy-7-methyl-6-octenoate. *n*-Butyllithium (74 mL, 0.17 mol, 2.31 M in hexane) was added to a stirring solution of diisopropylamine (19 g, 0.18 mol) in THF (150 mL) at −75 °C. After warming up to −50 °C, β-hydroxyester **6** (14.4 g, 77.4 mmol) was added neat, and the temperature was raised to −30 °C. Iodoethane (8.7 mL, 0.1 mol) in HMPA (60 mL) was added, and the reaction mixture was stirred with warming to room temperature over 4 h. Saturated aqueous NH_4Cl (60 mL) was added to quench the reaction mixture. The organic layer was separated, and the aqueous layer was extracted with 30% ethyl acetate/petroleum ether. The combined extract was dried (Na_2SO_4) and concentrated. The residue was chromatographed with 8% ethyl acetate/petroleum ether to give the desired alkylated product (10.8 g, 70% yield) as a pale yellow oil: TLC R_f 0.51 (20% ethyl acetate/petroleum ether); ^1H NMR (δ) 5.10 (m, 1 H), 3.71 (s, 3 H), 3.69 (m, 1 H), 2.53 (d, J = 8.0 Hz, 1 H), 2.20 (m, 1 H), 1.76 (m, 2 H), 1.71 (s, 3 H), 1.63 (s, 3 H), 1.48 (m, 2 H), 0.92 (t, J = 7.4 Hz, 3 H); ^{13}C NMR (δ) d: 11.8, 17.6, 25.7, 51.5, 52.6, 71.6, 123.7; u: 22.7, 24.3, 35.5, 132.3, 176.0; IR (cm^{-1}) 3465, 1736, 1670, 1437, 1376, 1171; MS (*m/z*, %) 214 (M^+, 1), 196 (52), 137 (24), 136 (93), 131 (22), 125 (20), 121 (39), 113 (43), 107 (46), 102 (100); HRMS cald for $C_{12}H_{22}O_3$ 214.1569, found 214.1573; $[\alpha]_D$ = −12.0.

(4*S*,5*R*)-2,2-Dimethyl-5-ethyl-5-(4-methyl-3-pentenyl)-1,3-dioxane 6. Lithium aluminum hydride (2.3 g, 61.0 mmol) was added to a solution of the alkylated β-hydroxyester (6.1 g, 30.5 mmol) in THF (75 mL). The reaction mixture was heated to reflux for 10 h and then cooled to 0 °C. H_2O (3 mL), aqueous 10% NaOH (3 mL), and H_2O (9 mL) were added sequentially to the grayish reaction mixture over a period of 1 h. Substantial gas and heat evolution were observed, and the reaction mixture turned into a white paste. The reaction mixture was filtered, and the filtrate was concentrated to give the desired crude diol (5.6 g); ^1H NMR (δ) 5.17 (m, 1 H), 3.91 (m, 1 H), 3.69 (m, 2 H), 3.03 (br s, 1 H), 2.82 (br s, 1 H), 2.11 (m, 2 H), 1.73 (s, 3 H), 1.65 (s, 3 H), 1.60 (m, 2 H), 1.41 (m, 3 H), 0.96 (t, J = 7.4 Hz, 3 H); ^{13}C NMR (δ) d: 11.6, 17.6, 25.0, 46.0, 75.5, 123.9; u: 21.4, 24.4, 35.5, 63.6, 132.3.

p-Toluenesulfonic acid monohydrate (1.2 g, 6.1 mmol) was added to a stirring solution of the crude diol (5.6 g) in dimethoxypropane (70 mL). After 0.5 h, $NaHCO_3$ (1.3 g, 15.3 mmol) was added to neutralize the reaction mixture. The reaction mixture was filtered, and the filtrate was concentrated and chromatographed directly to give **7** (5.8 g, 53% yield from **6**) as a pale yellow oil: TLC R_f 0.89 (10% ethyl acetate/petroleum ether); ^1H NMR (δ) 5.09 (m, 1 H), 3.86 (dd, J = 5.0, 6.5 Hz, 1 H), 3.51 (m, 2 H), 2.18 (m, 2 H), 1.68 (s, 3 H), 1.61 (s, 3 H), 1.40 (d, J = 3.6 Hz, 6 H), 1.38 (m, 2 H), 1.07 (m, 2 H), 0.86 (t, J = 7.3 Hz, 3 H); ^{13}C NMR (δ) d: 10.9, 17.8, 19.3, 25.7, 29.5, 40.4, 72.5, 124.3; u: 21.0, 23.4, 33.1, 64.0, 97.9, 131.5; IR (cm^{-1}) 2926, 2859, 1457, 1379, 1264, 1199; MS (*m/z*, %) 226 (M^+, 3), 211 ($M^+ - CH_3$, 20), 168 (55), 150 (50), 135 (48), 121 (88), 111 (100), 109 (52), 107 (29); HRMS cald for $C_{14}H_{26}O_2$ 226.1934 (211.1699 loss of CH_3), found 211.1695.

Methyl (4*S*,5*R*)-2,2-Dimethyl-5-ethyl-1,3-dioxanepropionate 7. A stream of ozone was passed through a solution of **6** (5.4 g, 24.1 mmol) in CH_2Cl_2 (250 mL) at −75 °C. After 20 min, the red indicator (Sudan Red) was decolorized, and the ozone was turned off. The reaction mixture was flushed with N_2, and triphenylphosphine (7.6 g, 28.9 mmol) was added. The mixture was allowed to warm to room temperature over 10 h. The reaction mixture was then concentrated, and the residue was dissolved in 1:9 H_2O/CH_3OH (60 mL). $NaHCO_3$ (40 g, 0.48 mol) and Br_2 (5 mL, 96.3 mmol, 1.95 M in 1:9 H_2O/CH_3OH) were added sequentially to the reaction mixture, turning the mixture bright orange. After stirring for 10 min, $Na_2S_2O_4{\cdot}5H_2O$ (36.0 g, 0.14 mol) was added. The orange reaction mixture decolorized instantly with evolution of gas. The reaction mixture was partitioned between ether and brine. The combined ethereal layer was dried (Na_2SO_4), concentrated, and chromatographed to give the ester **7** (4.3 g, 78% yield from **7**) as a colorless oil: TLC R_f 0.68 (20% ethyl acetate/petroleum ether), $[\alpha]_D$ = −54.4; ^1H NMR (δ) 3.88 (dd, J = 6.0, 6.5 Hz, 1 H), 3.68 (s, 3 H), 3.52 (m, 2 H), 2.43 (m, 2 H), 2.07 (m, 1 H), 1.68 (m, 1 H), 1.49 (m, 1 H), 1.36 (d, J = 6.2 Hz, 6 H), 1.09 (m, 1 H), 0.87(t, J = 7.3 Hz, 3 H); ^{13}C NMR (δ) d: 10.9, 19.3, 29.4, 40.4, 51.4, 72.4; u: 20.9, 28.3, 29.7, 63.9, 98.0, 174.3. IR (cm^{-1}) 2965, 1740, 1438, 1380, 1201, 1165, 1124, 868; MS (*m/z*, %) 215 ($M^+ - CH_3$, 45), 172 (10), 156 (7), 155 (71), 141 (52), 140 (21), 123 (100), 117 (92), 113 (29), 111 (60), 110 (25), 101(7); HRMS cald for $C_{12}H_{22}O_4$ 230.1518 (215.1284 loss of CH_3), found 215.1279. Anal. Calcd for $C_{12}H_{22}O_4$: C, 62.58, H, 9.63. Found: C, 62.89, H, 9.76.

Methyl (4*S*,5*R*)-α-Diazo-2,2-dimethyl-5-ethyl-1,3-dioxanepropionate 4. Sodium hydride (0.6 g, 15 mmol, 60% in mineral oil), methyl benzoate (1.36 g, 10.0 mmol), and 2 drops of CH_3OH were added sequentially to an ice-cold solution of ester **7** (1.15 g, 5.0 mmol) in DME (25 mL). The grayish mixture was heated to reflux for 13 h, during which time it turned dark brown. Aqueous acetate buffer (7 mL, 0.25 M, pH = 5) was added to the reaction mixture, followed by ether (15 mL). The organic layer was separated, and the aqueous layer was extracted with 30% ethyl acetate/petroleum ether (3 × 20 mL). The combined organic extract was dried ($NaSO_4$), concentrated, and chromatographed to give the benzoyl ester (1.5 g, 93% yield) as a yellow oil: TLC R_f 0.42 (20% ethyl acetate/petroleum ether); ^1H NMR (δ) 8.14−7.23 (m, 5 H), 3.86 (m, 1 H), 3.70 (d, J = 13.1 Hz, 3 H), 3.70−3.37 (m, 2 H), 2.70−2.41 (m, 1 H), 2.07−1.78 (m, 1 H), 1.48 (m, 2 H), 1.34−1.23 (dd, J = 9.8, 11.7 Hz, 6 H), 1.09 (m, 2 H), 0.91 (t, J = 7.4 Hz, 3 H).

DBU (1.3 mL, 8.6 mmol) and *p*-nitrobenzenesulfonylazide (2.0 g, 8.6 mmol) were added sequentially to a solution of the benzoyl ester (1.4 g, 4.4 mmol) in CH_2Cl_2 (20 mL) at 0 °C. After warming to room temperature (0.5 h), the reaction mixture was quenched with aqueous phosphate buffer (13 mL, 0.5 M, pH = 7). The CH_2Cl_2 layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extract was dried (Na_2SO_4), concentrated, and chromatographed to give **4** (1.4 g, 78% from **7**) as a bright yellow oil, TLC R_f 0.43 (10% ethyl acetate/petroleum ether); ^1H NMR (δ) 3.89 (dd, J = 5.1, 6.6 Hz, 1 H), 3.76 (s, 3H), 3.74 (m, 1 H), 3.56 (t, J = 11.0 Hz, 1 H), 2.68 (dd, J = 5.3, 6.1 Hz, 1 H), 2.41 (dd, J = 7.0, 8.2 Hz, 1 H), 1.56 (m, 4 H), 1.55 (d, J = 9.7 Hz, 6 H), 0.89 (t, J = 7.4

Hz, 3 H); ^{13}C NMR (δ) d: 27.6, 36.1, 46.1, 56.0, 58.6, 90.1, 144.0; u: 37.7, 43.6, 80.5, 114.9, 185.0; IR (cm^{-1}) 2960, 2078, 1699, 1437, 1221; MS (*m/z*, %) 228 (M$^+$ − N_2, 3), 213 (19), 198 (74), 197 (24), 183 (6), 140 (13), 117 (100); HRMS cald for $C_{12}H_{20}O_4N_2$ 256.1424 (228.1362 loss of N_2); found 228.1366.

Methyl [1*S*,2*S*,3a*S*,7a*R*]-1,5,5-Trimethyl-4,6-dioxa-(2,3,3a,4,5,6,7,7a)octahydroindene-2-carboxylate 8a. CH_2Cl_2 (40 mL) was passed through a pad of K_2CO_3 into the bright yellow diazo ester **4** (2.1 g, 8.2 mmol). A catalytic amount of Rh_2Oct_4 (0.9 mg, 1.16 μmol) was added to the reaction mixture. The mixture was decolorized instantly with evolution of gas. After the gas evolution had ceased (5 min), the mixture was concentrated and chromatographed directly to give a single diastereomer **8a** (1.8 g, 89% yield from **4**) as a pale yellow oil, TLC R_f 0.38 (10% ethyl acetate/petroleum ether). The absolute and relative configuration was established by NOE experiment: ^{1}H NMR (δ) 3.89 (dd, J = 5.1, 6.5 Hz, 1 H), 3.80 (m, 2 H), 3.61 (s, 3 H), 2.44 (m, 1H), 2.26 (m, 1 H), 1.81 (m, 2 H), 1.42 (d, J = 8.9 Hz, 6 H), 1.31 (m, 1 H), 1.16 (d, J = 7.6 Hz, 3 H); ^{13}C NMR (δ) d: 18.3, 19.7, 29.7, 36.9, 47.0, 49.1, 51.9, 73.8; u: 32.7, 65.5, 99.5, 176.6; IR (cm^{-1}) 2954, 1735, 1459, 1381, 1264, 1178, 1113; MS (*m/z*, %) 213 (M$^+$ − CH_3, 42), 153 (11), 139 (33), 127 (30), 121 (21), 111(49), 93 (100); HRMS cald for $C_{12}H_{20}O_4$ 228.1362 (213.1127 loss of CH_3), found 213.1132.

[1*S*,2*S*,3a*S*,7a*R*]-1,5,5-Trimethyl-2-phenylmethoxymethyl-4,6-dioxa-(2,3,3a,4,5,6,7,7a)-octahydroindene 9. Lithium aluminum hydride (0.7 g, 18.1 mmol) was added to an ice-cold solution of **8a** (1.03g, 4.5 mmol) in THF (40 mL). The reaction mixture was brought to reflux for 10 h before being chilled to 0 °C. H_2O (1.0 mL), aqueous 10% NaOH (1.0 mL), and H_2O (3.0 mL) were added sequentially over 2 h. The grayish reaction mixture was turned into a white paste. This white paste was filtered, and the filtrate was concentrated to give the crude alcohol (0.86 g): ^{1}H NMR (δ) 4.0 (dd, J = 3.8, 6.5 Hz, 1 H), 3.77−3.43 (m, 4 H), 1.89 (br s, 1 H), 1.84 (m, 3 H), 1.45 (d, J = 5.8 Hz, 6 H), 1.39 (m, 2 H), 1.08 (d, J = 6.1 Hz, 3 H).

Sodium hydride (0.5 g, 12.9 mmol) was added to a stirring solution of the above crude alcohol (0.86 g) in THF (20 mL). After stirring for 20 min at room temperature, benzyl bromide (0.71 g, 6.0 mmol), and tetrabutylammonium iodide (0.16 g, 0.4 mmol) were added to the reaction mixture. After 10 h at room temperature, saturated aqueous NaCl (10 mL) was added. The organic phase was separated, and the aqueous phase was extracted with 30% ethyl acetate/petroleum ether (3 × 20 mL). The combined organic extracts was dried (K_2CO_3), concentrated, and chromatographed to give **9** (0.93 g, 75% yield from **8a**) as a pale yellow oil: TLC R_f 0.64 (20% ethyl acetate/petroleum ether); ^{1}H NMR (δ) 7.33 (m, 5 H), 4.49 (s, 2 H), 3.98 (dd, J = 3.9, 6.8 Hz, 1 H), 3.71 (m, 2 H), 3.40 (m, 2 H), 1.84 (m, 3 H), 1.41 (d, J = 5.2 Hz, 6 H), 1.38 (m, 2 H), 1.16 (d, J = 6.1 Hz, 3 H); ^{13}C NMR (δ) d: 18.1, 19.7, 29.8, 35.1, 43.0, 49.4, 73.8, 127.4, 127.5, 128.3; u: 32.8, 65.8, 73.1, 73.6, 99.2, 138.6; IR (cm^{-1}) 3008, 2925, 2854, 1454, 1365, 1265, 1197, 1095, 742, 698; MS (*m/z*, %) 275 (M$^+$ − CH_3, 34), 141 (35), 125 (18), 123 (17), 111 (100), 110 (17), 109 (19), 108 (23), 107 (79), 105 (18); HRMS cald for $C_{18}H_{26}O_3$ 290.1882 (275.1647 loss of CH_3), found: 275.1643.

(1*S*,2*R*,3*R*,4*S*)-3-Methyl-2-(4-methylbenzylsulfonyloxy methyl)-4-(phenylmethoxy)cyclopentanol 3. *p*-Toluenesulfonic acid monohydrate (0.09 g, 0.46 mmol) was added to a stirring solution of **9** (1.32 g, 4.6 mmol) in CH_3OH (20 mL). After 20 min at room temperature, the reaction mixture was neutralized with $NaHCO_3$ (1.9 g, 22.9 mmol). The suspension was filtered, and the filtrate was concentrated and chromatographed to give the desired diol (1.10 g, 96% yield from **9**) as a colorless oil: TLC R_f 0.28 (5% CH_3OH/CH_2Cl_2); ^{1}H NMR (δ) 7.34 (m, 5 H), 4.51 (s, 2 H), 4.08 (q, J = 7.1 Hz, 1 H), 3.82 (dd, J = 5.1, 6.5 Hz, 1 H), 3.40 (m, 3 H), 2.43 (br s, 2 H), 2.01−1.87 (m, 3 H), 1.60 (m, 1H), 1.31 (m, 1 H), 1.14 (d, J = 6.8 Hz, 3 H); ^{13}C NMR (δ) d: 18.7, 37.2, 44.1, 57.2, 76.6, 127.5, 128.3; u: 37.1, 64.9, 73.0, 73.2, 138.5; IR (cm^{-1}) 3374 (br), 3030, 2868, 1658, 1496, 1454, 1364, 737, 698; MS (*m/z*, %) 216 (M$^+$ − 2 OH, 17), 215 (100), 197 (24), 185 (15), 144 (8), 129 (17), 155 (10); HRMS cald for $C_{15}H_{22}O_3$: 250.1569, found 250.1576.

p-Toluenesulfonyl chloride (1.0 g, 5.3 mmol) and pyridine (0.5 mL, 5.7 mmol) were added to a stirring solution of the diol (1.1 g, 4.4 mmol) in CH_2Cl_2 (20 mL). After 18 h at room temperature, aqueous 10% HCl (6 mL) followed by saturated aqueous NH_4Cl (10 mL) were added. The CH_2Cl_2 phase was separated, and the aqueous phase was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extract was dried ($NaSO_4$), concentrated, and chromatographed to give the monotosylated product **3** (1.22 g, 66% from **9**) as a colorless oil: TLC R_f 0.28 (35% ethyl acetate/petroleum ether); ^{1}H NMR (δ) 7.77 (d, J = 8.2 Hz, 2 H), 7.31 (m, 7 H), 4.48 (s, 2 H), 4.07 (m, 3 H), 3.39 (m, 2 H), 2.45 (s, 3 H), 2.17 (br, s, 1 H), 1.95 (m, 1 H), 1.75 (m, 2 H), 1.40 (m, 1 H), 1.25 (t, J = 6.1 Hz, 1 H), 0.97 (d, J = 6.5 Hz, 3 H); ^{13}C NMR (δ) d: 18.3, 21.5, 37.2, 44.0, 55.2, 73.5, 127.4, 127.8, 128.3, 129.8; u: 23.3, 70.1, 72.8, 73.0, 123.8, 138.5, 144.8; IR (cm^{-1}) 3454, 3012, 1483, 1375, 1189, 654.

(2*S*)-2,6-Dimethyl-5-hepten-1-ol 12. A solution of sodium periodate (20 g, 93.6 mmol in 104 mL of H_2O) was added to a suspension of 60−200 mesh SiO_2 (43 g) in CH_2Cl_2 (250 mL) at room temperature. After the mixture was thoroughly stirred, diol **11** (13.4 g, 77.8 mmol) was added to the SiO_2 suspension. After stirring for 5 min, the suspension was filtered, and the filtrate was added directly into a stirring solution of $NaBH_4$ (3.6 g, 93.6 mmol) in CH_3OH (200 mL) at 0 °C. After 15 min, the reaction mixture was diluted with ethyl ether (60 mL) and quenched with aqueous 10% HCl (40 mL). The organic layer was separated, and the aqueous layer was extracted with 40% ethyl acetate/petroleum ether (3 × 100 mL). The combined organic phase was dried (Na_2SO_4), concentrated, and chromatographed to give **12** (6.74 g, 61% yield from **11**) as a colorless oil: TLC R_f 0.51 (10% ethyl acetate/petroleum ether); ^{1}H NMR (δ) 5.13 (m, 1 H), 3.48 (ddd, J = 6.3, 7.1, 8.4 Hz, 2 H), 2.01 (m, 2 H), 1.69 (s, 3 H), 1.66 (m, 1 H), 1.61 (s, 3 H), 1.44 (m, 1 H), 1.17 (m, 1 H), 0.89 (d, J = 6.9 Hz, 3 H); ^{13}C NMR (δ) d: 16.5, 17.6, 25.7, 35.3, 124.5; u: 25.4, 33.2, 68.3, 131.4; IR (cm^{-1}) 3346, 2922, 1673, 1454, 1377, 1041, 826; MS (*m/z*, %) 142 (M$^+$, 23), 110 (5), 109 (48), 96 (4), 95 (39), 85 (4), 82 (79), 81 (33), 71 (25), 69 (100); HRMS cald for $C_9H_{18}O$ 142.1358, found 142.1355; $[\alpha]_D$ = −9.4.

(2*S*)-1-Azido-2,6-dimethyl-5-heptene 13. Pyridine (40 mL) and toluenesulfonyl chloride (22.5 g, 0.12 mol) were added to a stirring solution of alcohol **12** (12.9 g, 91.0 mmol) in CH_2Cl_2 (160 mL) at room temperature. After 10 h, the reaction mixture was quenched with aqueous 10% HCl (100 mL) and washed with saturated aqueous NH_4Cl (50 mL). The CH_2Cl_2 layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 150 mL). The combined CH_2Cl_2 extract was dried (Na_2SO_4), concentrated and chromatographed to give the desired tosylate (24.7 g, 92% yield) as a pale white oil: TLC R_f 0.71 (10% ethyl acetate petroleum ether); ^{1}H NMR (δ) 7.79 (d, J = 8.1 Hz, 2H), 7.36 (d, J = 8.1 Hz, 2H), 5.01 (m, 1 H), 3.86 (m, 2 H), 2.23 (s, 3 H), 1.77−1.96 (m, 3H), 1.67 (s, 3H), 1.54 (s, 3 H), 1.38 (m, 1 H), 1.12 (m, 1 H), 0.89 (d, J = 6.9 Hz, 3 H); ^{13}C NMR (δ) d: 16.3, 17.5, 21.5, 25.6, 32.3, 123.8, 127.8, 129.7; u: 24.9, 32.6, 131.8, 133.1, 144.6.

Sodium azide (7.8 g, 0.12 mol) was added to a stirring solution of the tosylate (7.1 g, 24.0 mmol) in DMF (80 mL). After stirring at 60 °C for 10 h, the white orange reaction mixture was diluted with ether (30 mL) and quenched with saturated aqueous NaCl (60 mL). The mixture was partitioned between ether and brine. The combined ethereal extract was dried (K_2CO_3), concentrated, and chromatographed to give **13** (3.40 g, 78% yield from **12**) as a pinkish oil: TLC R_f 0.56 (25% CH_2Cl_2/petroleum ether); ^{1}H NMR (δ) 5.11 (m, 1 H), 3.21 (dq, J = 5.8, 10.3 Hz, 2 H), 1.98 (m, 2 H), 1.77 (m, 1 H), 1.71 (s, 3 H), 1.60 (s, 3 H), 1.44 (m, 1 H), 1.21 (m, 1 H), 0.97 (d, J = 6.6 Hz, 3 H); ^{13}C NMR (δ) d: 17.5, 17.6, 25.7, 33.1, 124.1; u: 25.2, 34.1, 57.8, 131.6; IR (cm^{-1}) 2926, 2098, 1451, 1379, 1281; MS (*m/z*, %) 139 (M$^+$ − N_2, 3), 138 (19), 125 (9), 124 (100), 111 (15), 110 (10); HRMS cald for $C_9H_{17}N_3$ 167.1424 (139.1362 loss of N_2), found 139.1386.

Ethyl (2*R*,5*S*)-5-Methyl piperidineacetate 14. A stream of ozone was passed through a solution of azide **13** (4.1 g, 24.6 mmol) in CH_2Cl_2 (240 mL) at −75 °C until the solution turned pale blue (21 min). The ozone was turned off, and the reaction mixture was flushed with N_2. Triphenylphosphine (6.4 g, 24.6 mmol) was added, and the reaction mixture was allowed to warm to room temperature over 4 h. The reaction mixture was concentrated and added to an ice-cold solution of ylide preparing from the addition of NaHMDS (29 mL, 29 mmol, 1.0 M in THF) to triethylphosphonoacetate (6.6 g, 29.5 mmol) in THF (70 mL). After stirring at room temperature for 1.5 h, the reaction mixture was chilled to −60 °C. Triphenylphosphine (6.4 g, 24.6 mmol) and H_2O (0.6 mL) were added, and the reaction mixture was allowed to warm to room temperature over 13 h. After the reaction mixture

was quenched with saturated aqueous $NaHCO_3$ (6 mL), the organic layer was separated, and the aqueous layer was extracted with ethyl acetate (3 × 40 mL). The combined organic extract was dried (K_2CO_3), concentrated and distilled bulb-to-bulb (bp $_{1.0mm}$ = 98 °C) to give a mixture of the *trans*-**14** and *cis*-**15** piperidine esters in a ratio of 5.6:1 (by ^1H NMR integration and quantitative ^{13}C) (3.09 g, 68% yield from **13**) as a yellow oil. This mixture of diastereomers was then chromatographed, eluting with 10% CH_3OH/CH_2Cl_2, to give *trans*-ester **14** (2.62 g, 58% yield from **13**) and *cis*-ester **15** (0.47 g, 10% yield from **13**) both as white crystals.

14: TLC R_f 0.37 (10% CH_3OH/CH_2Cl_2); mp = 172 °C; ^1H NMR (δ) 4.38 (br s, 1 H), 4.12 (q, J = 7.1 Hz, 2 H), 3.13 (m, 1 H), 2.93 (m, 1 H), 2.55 (m, 2 H), 2.27 (t, J = 11.5 Hz, 1 H), 1.80−1.58 (m, 3 H), 1.36 (m, 1 H), 1.23 (t, J = 7.1 Hz, 3 H), 1.19−0.99 (m, 1 H), 0.85 (d, J = 6.6 Hz, 3 H); ^{13}C NMR (δ) d: 14.1, 19.2, 30.7, 53.1; u: 31.5, 32.8, 40.4, 53.5, 60.5, 171.7; IR (cm^{-1}) 3341, 2927, 1732, 1460, 1375, 1337, 1176, 1033; MS (*m/z*, %) 185 (M^+, 2), 156 (6), 142 (2), 138 (13), 129 (22), 110 (12), 99 (27), 98 (100); HRMS cald for $C_{10}H_{19}O_2N$: 185.1416, found 185.1421; $[\alpha]_D$= −6.5.

15: TLC R_f 0.32 (10% CH_3OH/CH_2Cl_2); ^1H NMR (δ) 4.12 (q, J = 7.1 Hz, 2 H), 3.71 (s, 1 H), 3.32 (m, 2 H), 2.90 (dt, J = 6.1, 16.4 Hz, 1 H), 2.72 (m, 2 H), 2.04−1.83 (m, 3 H), 1.37 (m, 2 H), 1.29 (t, J = 7.1 Hz, 3 H), 0.94 (d, J = 6.5 Hz, 3H); ^{13}C NMR (δ) d: 14.1, 17.6, 28.6, 52.1; u: 28.0, 28.6, 39.5, 50.6, 60.5, 172.0.

Amino Alcohol 16. Tosylate **3** (0.35 g, 0.87 mmol) and Bu_4NI (0.06 g, 0.16 mmol) were added to a refluxing solution of *trans*-piperidine ester **14** (0.18 g, 0.97 mmol) and K_2CO_3 (0.19 g, 1.36 mmol) in toluene (3 mL). The reaction mixture was maintained at reflux for 3 h, before it cooled to room temperature. The reaction mixture was partitioned between ether and, sequentially, water and brine. The combined organic extract was dried (K_2CO_3) and concentrated in vacuo. The oily residue was chromatographed, eluting with 10% acetone/CH_2Cl_2, to give **16** (0.20 g, 56% yield from **3**) as a yellow oil: TLC R_f = 0.18 (10% acetone/CH_2Cl_2); ^1H NMR (δ) 7.36 (m, 5 H), 4.50 (s, 2 H), 4.15 (q, J = 7.1 Hz, 2 H), 3.84 (q, J = 8.1 Hz, 1 H), 3.34 (m, 2 H), 3.01−2.61 (m, 3 H), 2.39−2.11 (m, 3 H), 1.89 (m, 2 H), 1.81−1.29 (m, 9 H), 1.24 (t, J = 7.1 Hz, 3 H), 1.04 (m, 1 H), 1.01 (d, J = 6.4 Hz, 3 H), 0.85 (d, J = 6.4 Hz, 3 H); ^{13}C NMR (δ) d: 14.2, 18.5, 19.2, 29.2, 38.8, 43.4, 52.7, 59.8, 77.9,127.4, 128.3, 128.9; u: 29.9, 31.8, 35.4, 38.7, 57.6, 60.5, 60.9, 73.0, 73.9, 172.1; IR (cm^{-1}) 3416, 3030, 2925, 1733, 1496, 1454, 1367, 1099, 736, 698; MS (*m/z*, %) 417 (M^+, 1), 331 (22), 330 (94), 326 (3), 328 (2), 224 (11), 198 (100), 184 (13), 170 (1), 156 (3), 124 (1), 121 (10), 110 (2); HRMS cald for $C_{25}H_{39}NO_4$ 417.2879, found 417.2860; $[\alpha]_D$ = +26.7.

Tricyclic Amine 17. Pyridine (0.25 mL, 3.12 mmol) and benzenesulfonyl chloride (0.06 mL, 0.46 mmol) were added to a stirring solution of **16** (0.13 g, 0.31 mmol) in CH_2Cl_2 (2 mL). After 3 h at room temperature, the reaction mixture was partitioned between CH_2Cl_2 and, sequentially, saturated aqueous NH_4Cl and saturated aqueous $NaHCO_3$. The combined organic extract was dried (K_2CO_3) and concentrated in vacuo. The yellow residue was chromatographed, eluting with 3% acetone/CH_2Cl_2, to give the desired benzenesulfonylated product (0.12 g, 69% yield from **16**) as a pale yellow oil: TLC R_f 0.52 (4% acetone/CH_2Cl_2); ^1H NMR (δ) 7.94−7.28 (m, 10 H), 4.60 (m, 1 H), 4.47 (s, 2 H), 4.11 (q, J = 7.1 Hz, 2 H), 3.45 (dd, J = 4.1, 4.2 Hz, 1 H), 3.31 (dd, J = 5.6, 5.7 Hz, 1 H), 2.67 (m, 1 H), 2.47−2.31 (m, 3 H), 2.19−1.81 (m, 5 H), 1.73−1.42 (m, 5 H), 1.38−0.85 (m, 3 H), 1.23 (t, J = 7.1 Hz, 3 H), 1.04 (d, J = 6.6 Hz, 3 H), 0.79 (d, J = 5.8 Hz, 3 H).

Lithium bis(trimethylsilyl)amide (0.36 mL, 0.36 mmol, 1.0 M in THF) was added to a solution of the benzenesulfonylated **16** (101.0 mg, 0.18 mmol) in THF (2 mL) at −78 °C. After 2 h with warming to room temperature, the reaction mixture was quenched with brine (2 mL) and diluted ether (2 mL). The organic layer was separated, and the aqueous layer was extracted with ether (3 × 4 mL). The combined organic extract was dried (K_2CO_3), concentrated, and chromatographed to give **17** (55.7 mg, 53% yield from **16**) as a light brown oil: TLC R_f 0.67 (20% ethyl acetate/petroleum ether); ^1H NMR (δ) 7.31 (m, 5 H), 4.52 (s, 2 H), 4.15 (q, J = 7.1 Hz, 2 H), 3.54 (dd, J = 4.9, 4.2 Hz, 1 H), 3.41 (dd, J = 6.8, 2.1 Hz, 1 H), 2.80 (d, J = 12.1 Hz, 1 H), 2.65 (d, J = 10.1 Hz, 1 H), 2.26−1.46 (m, 13 H), 1.45−1.21 (m, 2 H), 1.24 (t, J = 7.1 Hz, 3 H), 1.01 (d, J = 5.9 Hz, 3 H), 0.83 (d, J = 6.0 Hz, 3 H); ^{13}C NMR (δ) d: 14.4, 18.0, 19.6, 30.8, 36.8, 40.7, 46.4, 47.2, 53.4, 62.8, 127.3, 127.4, 128.2; u: 30.9, 32.2, 32.8, 54.9, 60.1, 64.6, 73.1, 75.1, 138.9, 175.2; IR (cm^{-1}) 3029, 2929, 1728, 1454, 1375, 1098, 735, 697; MS (*m/z*, %) 398 ($M^+ - H^+$, 2), 370 (2), 354 (3), 309 (20), 308 (100), 278 (4), 264 (3), 234 (3), 206 (3), 192 (3), 164 (2), 152 (10), 150 (5), 148 (6), 136 (3), 124 (2), 111 (27), 110 (7), 107 (5); HRMS cald for $C_{25}H_{37}O_3N$ 399.2773, found 399.2742

Thiol Ether. Lithium aluminum hydride (21.1 mg, 0.56 mmol) was added to a stirring solution of **17** (52.1 mg, 0.13 mmol) in THF (1.0 mL). After stirring at 50 °C for 3 h, the reaction mixture was quenched sequentially with H_2O (0.02 mL), 10% aqueous NaOH (0.02 mL), and H_2O (0.06 mL). The grayish reaction mixture turned into a white paste. The resultant suspension was filtered, and the filtrate was concentrated to give the crude alcohol: ^1H NMR (δ) 7.34 (m, 5 H), 4.48 (s, 2 H), 3.70 (dd, J = 4.3, 5.1 Hz, 2 H), 3.54 (m, 2 H), 3.36 (m, 2 H), 2.77 (br s, 1 H), 2.24−1.16 (m, 15 H), 1.08 (d, J = 6.3 Hz, 3 H), 0.81 (d, J = 6.1 Hz, 3 H).

The crude alcohol residue was dissolved in DME (1.0 mL), and the phenyl disulfide (80.3 mg, 0.38 mmol) and *n*-tributylphosphine (81.0g, 0.38 mmol) were added. The mixture was maintained at reflux for 8 h and then cooled to room temperature. The mixture was diluted with ether (4 mL) and quenched with saturated aqueous NaCl (2 mL). After the organic phase was separated, the aqueous phase was extracted with 50% ethyl acetate/petroleum ether (2 × 4 mL). The combined organic layer was dried (K_2CO_3), concentrated, and chromatographed to give the thioether (53.2 mg, 94% yield from **17**) as a pale pink oil: TLC R_f 0.43 (20% ethyl acetate/petroleum ether); ^1H NMR (δ) 7.30 (m, 10 H), 4.49 (s, 2 H), 3.50 (dd, J = 4.2, 4.9 Hz, 1 H), 3.31 (dd, J = 1.8, 7.1 Hz, 1 H), 3.01 (dq, J = 3.6, 8.6 Hz, 2 H), 2.73 (m, 2 H), 2.22−1.01 (m, 15 H), 1.02 (d, J = 6.0 Hz, 3 H), 0.79 (d, J = 6.1 Hz, 3 H); ^{13}C NMR (δ) d: 17.8, 19.7, 30.6, 37.0, 39.9, 44.6, 46.5, 47.5, 64.0, 125.5, 127.3, 127.5, 128.3, 128.8, 128.9; u: 30.0, 33.1, 33.2, 34.8, 55.4, 65.0, 73.0, 134.0, 156.1; IR (cm^{-1}) 3008, 1453, 735, 697; MS (*m/z*, %) 449 (M^+, 2), 340 (24), 326 (11), 249 (6), 234 (32), 164 (10), 152 (22), 111 (27), 109 (100).

Alkaloid 251F 1. Ammonia (15 mL) was condensed with a cold finger condenser into a stirring solution of the thioether (50.2 mg, 0.14 mmol) in EtOH/THF (3 mL, 2:1 by volume) at −78 °C. Sodium metal (1.7 g, 73.9 mmol) was added to the reaction mixture in portions until the mixture remained dark blue. After 20 min, the reaction mixture was flushed with N_2 and allowed to warm. The residual white solid was partitioned between ethyl acetate and saturated aqueous NH_4Cl. The combined organic extract was dried (K_2CO_3), concentrated, and chromatographed to give **1** (21.0 mg, 66% yield from **17**) as a pale yellow oil: TLC R_f 0.09 (40% acetone/CH_2Cl_2); ^1H NMR in D_2O (δ) 3.55 (dd, J = 6.5, 11.0 Hz, 1 H), 3.38 (d, J = 6.5, 11.0 Hz, 1 H), 3.31 (d, J = 13.4 Hz, 1 H), 3.18 (d, J = 12.2 Hz, 1 H), 3.09 (dd, J = 4.5, 13.4 Hz, 1 H), 2.56 (td, J = 3.1, 11.3 Hz, 1 H), 2.49 (t, J = 12.4 Hz, 1 H), 2.11 (dd, J = 3.3, 14.6 Hz, 1 H), 2.0 (m, 1 H), 1.48−1.80 (m, 4 H), 1.60 (m, 1 H), 1.52 (m, 1 H), 1.30−0.98 (m, 4 H), 0.88 (d, J = 6.4 Hz, 3 H), 0.80 (d, J = 6.4 Hz, 6 H); ^{13}C NMR in D_2O (δ) d: 14.8, 15.7, 17.5, 28.4, 35.5, 37.6, 41.2, 44.3, 47.3, 67.4; u: 27.1, 30.2, 31.4, 53.2, 61.4, 64.9; IR (cm^{-1}) 3664, 2958, 2932, 2754, 1464, 1380, 1312, 1268, 1010; MS (*m/z*, %) 251 (M^+, 7), 250 (34), 236 (4), 234 (5), 222 (6), 220 (21), 194 (42), 181 (2), 164 (5), 152 (15), 112 (27), 111 (100); HRMS cald for $C_{16}H_{29}NO$ 251.2260, found: 251.2257. This material was found to be identical to the natural alkaloid by ^1H NMR, ^{13}C NMR, GC-MS (coinjection on a capillary gc column), and GC-FT/IR.

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