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# Synthesis of the Cannabisativine Skeleton via an Intramolecular Allylsilane–Nitrone Cycloaddition

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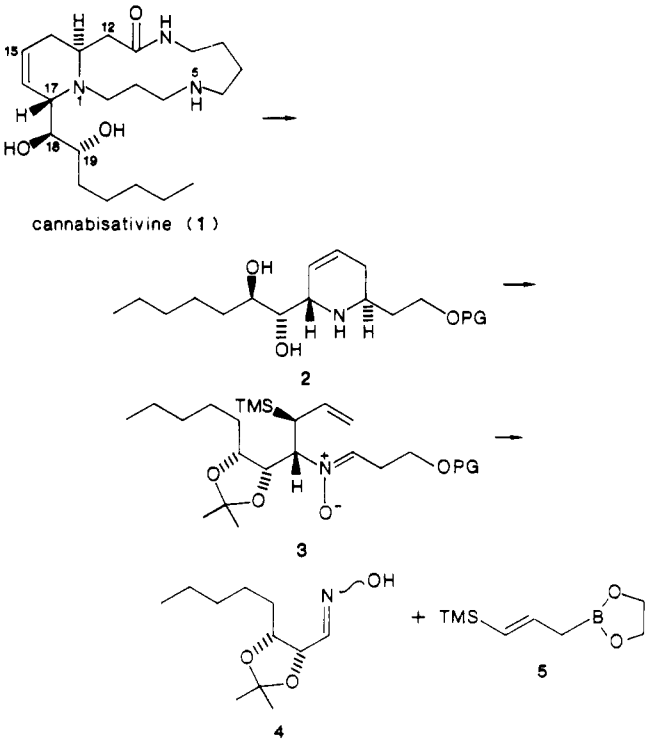
A synthesis of the carbon skeleton of cannabisativine (1) is described. The relative stereochemistry of the stereogenic centers at carbons 17, 18, and 19 was secured by the addition of [γ-(trimethylsilyl)allyl]boronate **5** to the oxime **4**. The major hydroxylamine **13** of the 1.7:1 mixture was condensed with 3-(benzyloxy)propanal to form nitrone **15**, which cyclized to the *trans*-tetrahydropyridine **18** upon treatment with TMSOTf at −40 °C. Deprotection and reduction of the hydroxylamine **18** affords the carbon skeleton of cannabisativine. Stereochemical differences between the thermally induced cyclization of nitrone **15** and the TMSOTf-promoted cyclization are discussed.

Cannabisativine (1) is an unusual macrocyclic spermidine alkaloid isolated from the roots and leaves of the common marijuana plant, *Cannabis sativa* L., whose structure was established by single-crystal X-ray analysis.[2] The skeleton of cannabisativine contains a 13-membered lactam ring annelated to a 2,6-trans-disubstituted tetrahydropyridine ring. Natsume and co-workers were the first to report a synthesis of this intriguing molecule in 1984.[3] Their work was followed in 1985 by Wasserman's synthesis.[4] The Natsume approach relied on building up the skeleton by functionalizing a tetrahydropyridine ring and then appending the 13-membered ring lactam. In contrast, Wasserman chose to build up the spermidine ring followed by tetrahydropyridine ring annelation.

Our goal in carrying out a synthesis of cannabisativine was viewed primarily as a problem in construction of the acyclic carbon backbone with its associated stereochemistry followed by a cyclization to form the *trans*-2,6-tetrahydropyridine **2** (Scheme I). The 13-membered spermidine ring could then be appended by using known technology.[4,5,6] Our synthetic design involved allylboronate

**Scheme I**




methodology to establish the relative chirality at carbons 17, 18, and 19 (cannabisativine numbering). α-Asymmetric induction in the addition of the allylboronate **5** to oxime **4** may produce two possible diastereomers due to syn or anti addition with respect to the alkoxy substituent. The

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(2) (a) Elsohly, M. A.; Turner, C. E.; Phoebe, C. H., Knapp, J. E.; Schiff, P. L.; Slatkin, D. J. *J. Pharm. Sci.* **1978**, *67*, 124. (b) Slatkin, D. J.; Knapp, J. E.; Schiff, P. L.; Turner, C. E.; Mole, M. L. *Photochemistry* **1975**, *14*, 580. (c) Lotter, H. L.; Abraham, D. J.; Turner, C. E. *Tetrahedron Lett.* **1975**, 2815. (d) Turner, C, E.; Hsu, M. H.; Knapp, J. E.; Schiff, P. L.; Slakin, D. J. *J. Pharm. Sci.* **1976**, *65*, 1084.

(3) Ogawa, M.; Kuriya, N.; Natsume, M. *Tetrahedron Lett.* **1984**, *25*, 969.

(4) Wasserman, H. H.; Leadbetter, M. R. *Tetrahedron Lett.* **1985**, *26*, 2241.

(5) Ogawa, M.; Nakajima, J.; Natsume, M. *Heterocycles* **1982**, *19*, 1247.

(6) Bailey, T. R.; Garigipati, R. S.; Morton, J. A.; Weinreb, S. H. *J. Am. Chem. Soc.* **1984**, *106*, 3240.

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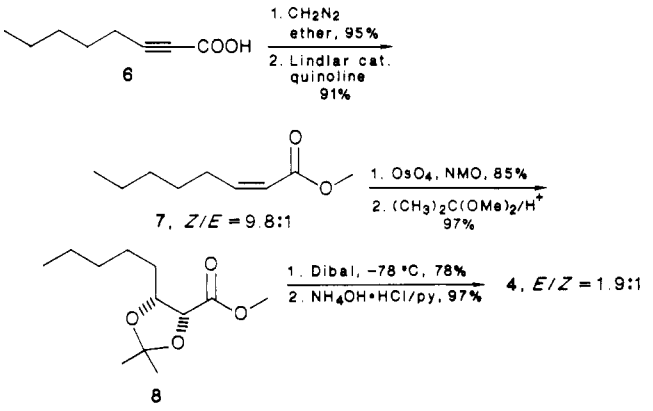
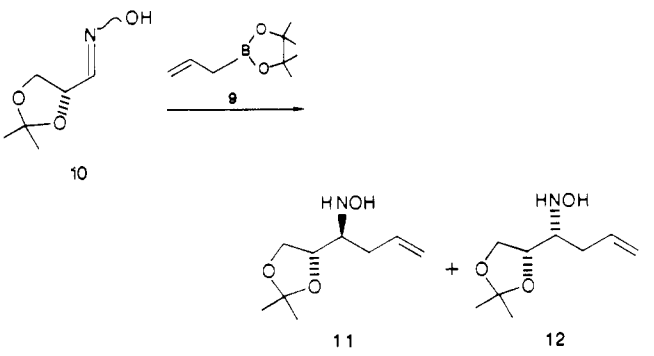
**Scheme II**




**Scheme III**

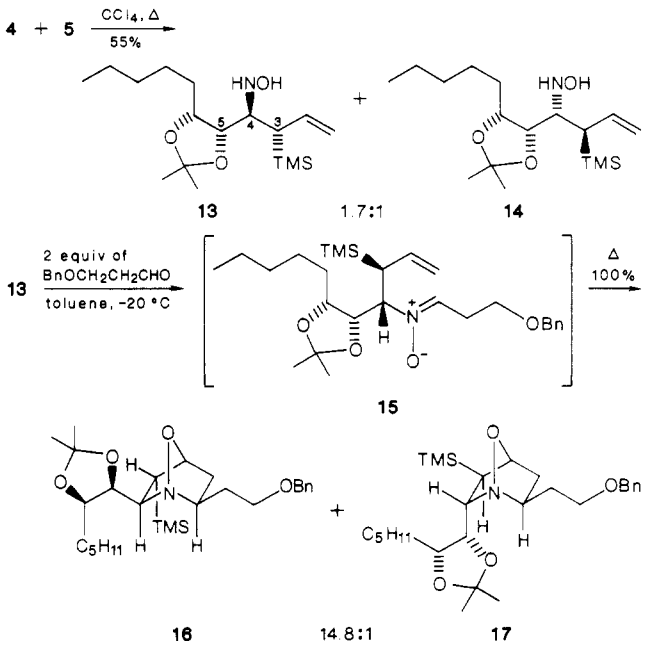



resulting hydroxylamine would then be converted to nitrone **3**, which in a key step would be cyclized to the trans-disubstituted tetrahydropyridine with the correctly placed alkene by using methodology previously developed for this purpose.[7]

The required oxime **4** for addition of the [γ-(trimethylsilyl)allyl]boronate[8] **5** was prepared in six steps from commercially available 2-octynoic acid as described in Scheme II. 2-Octynoic acid (**6**) was esterified with diazomethane in ether, followed by hydrogenation in the presence of Lindlar catalyst/quinoline to give a 9.8:1 mixture of the cis and trans unsaturated esters. The major product **7**, isolated by flash chromatography, was oxidized with osmium tetraoxide,[9] and the intermediate diol was protected as its acetonide to afford ester **8** in 83% yield. The ester **8** was reduced with diisobutylaluminum hydride[10] and treated with hydroxylamine hydrochloride in pyridine to afford an *E*/*Z* mixture (1.9:1) of oximes **4**.

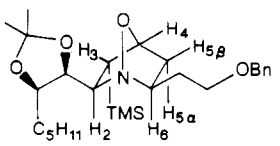
Although Hoffmann[11] had previously shown that oximes were suitable substrates for allylboronate addition reactions, we were uncertain as to the degree of α-asymmetric induction we could expect in the reaction with the trimethylsilyl-substituted allylboronate or what the influence of the oxime geometry might be since these aspects of the reaction have never been studied in detail. Hoffmann had shown that the addition of pinacol allylboronate (**9**) to 2,3-*O*-isopropylidene-D-glyceraldehyde derivative **10** affords the anti product **11** preferentially by a factor of 2–3:1 (Scheme III). We found that treatment of oxime **4** with

**Scheme IV**




[(trimethylsilyl)allyl]boronate **5** gave primarily two isomers, **13** and **14**, in a 1.7:1 ratio in 55% yield after chromatography (Scheme IV).

Two other minor isomers were formed in the reaction, but these were not isolated. The two new chiral centers at $C_4$ and $C_5$ in the major adduct **13** were assumed to be anti on the basis of Hoffmann's work. The relative stereochemistry at $C_3$ and $C_4$ was established by conversion of **13** to the rigid bicyclic isoxazolidine by thermal [3 + 2] cycloaddition. Thus a solution of nitrone **15**, which was prepared by condensation of **13** with 3-(benzyloxy)propanal at −20 °C in toluene, was refluxed for 2 h to provide the mixture of cycloadducts **16** and **17** in quantitative yield in a 14.8:1 ratio. These were inseparable by chromatography. At this point, it was crucial to identify the adducts stereochemically. The structures **16** and **17** were assigned on the basis of their 300-MHz $^1H$ NMR spectra. The major isomer **16** showed a triplet (4.8 ppm, $J_{3,4} = J_{4,5\beta}$ = 4.9 Hz, $J_{4,5\alpha}$ = 0.0 Hz) for the bridgehead proton at $C_4$, while the minor isomer **17** exhibited a doublet (4.69 ppm, $J_{4,5\beta}$ = 4.9 Hz, $J_{3,4} = J_{4,5\alpha}$ = 0.0 Hz). In the case of **16**, the relative stereochemistry between $C_2$ and $C_3$ was assigned to be anti since the value 5.6 Hz for $J_{2,3}$ falls in the typical range of anti (endo–exo) vicinal protons in the bicyclic isoxazolidines.[12,7]

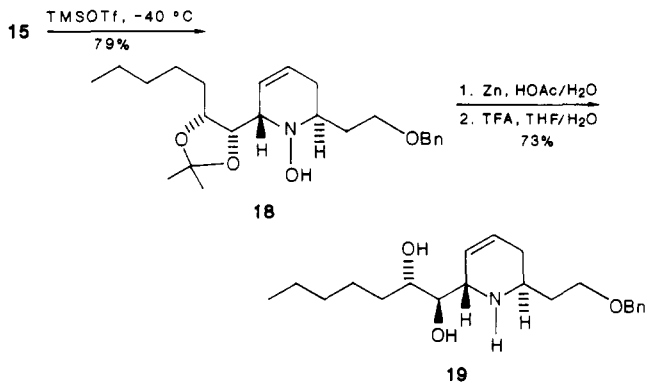



**16:** $J_{2,3}$ = 5.6 Hz, $J_{3,4} = J_{4,5\beta}$ = 4.9 Hz, $J_{5\alpha,6}$ = 7.7 Hz, $J_{4,5\alpha}$ = 0.0 Hz

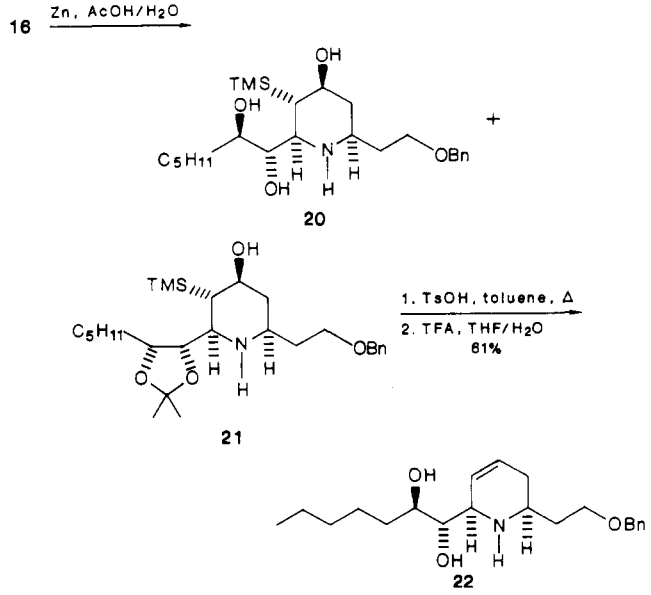
The $C_6$ stereochemistry was also assigned in the same manner. The large coupling constant ($J$ = 7.7 Hz) for $H_{5\alpha}/H_6$ indicates exo-$C_6$ stereochemistry. These spectral details then establish the cis geometry for the side-chain substituents of the latent tetrahydropyridine ring and that the diastereomeric induction in the boronate coupling did indeed proceed to give primarily the product with the hydroxylamine and the TMS groups in the anti relationship.

(7) Wuts, P. G. M.; Jung, Y.-W. *J. Org. Chem.*, in press.
(8) Tsai, D. J. S.; Matteson, D. S. *Tetrahedron Lett.* **1981**, *22*, 2751.
(9) VanRheenen, V.; Kelly, R. C.; Cha, D. Y. *Tetrahedron Lett.* **1976**, 1973.
(10) Hatch, R. P.; Shringarpure, J.; Weinreb, S. M. *J. Org. Chem.* **1978**, *43*, 4172.
(11) Hoffmann, R. W.; Eichler, G.; Endesfelder, A. *Liebigs Ann. Chem.* **1983**, 2000.
(12) Wuts, P. G. M.; Jung, J.-W. *J. Org. Chem.* **1988**, *53*, 1957.

Scheme V



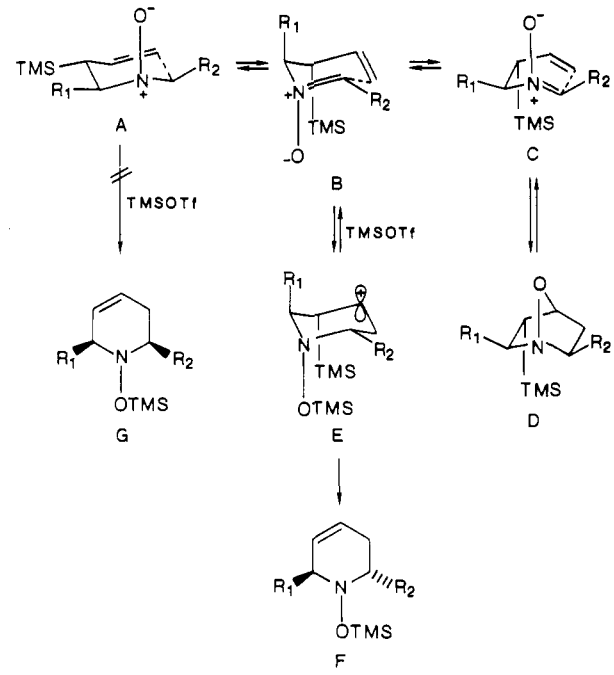

Scheme VI




We next turned our attention to the trimethylsilyl triflate (TMSOTf) catalyzed cyclization of nitrone **15** (Scheme V). Thus treatment of the nitrone with TMSOTf at −40 °C for 18 h affords only the trans-substituted tetrahydropyridine **18** in 79% yield. The stereochemistry of **18** was determined as follows: Reduction of the hydroxylamine with aqueous Zn and acetic acid followed by acetonide hydrolysis affords the diol **19**.

For comparison, the bicyclic oxazolidine **16** previously prepared from nitrone **15** was reduced with Zn/acetic acid to afford a mixture of triol **20** and acetonide **21** (Scheme VI). Treatment of this mixture with TsOH in refluxing toluene introduces the unsaturation into the ring via a Peterson olefination.[13] Acetonide hydrolysis then gives the cis 2,6-disubstituted tetrahydropyridine **22** which was spectroscopically different from compound **19** derived from the TMSOTf-catalyzed cyclization. Since the cis stereochemistry of the thermally induced cyclization was on firm ground, we felt certain that the trimethylsilyl triflate derived material gave the desired trans stereochemistry. It should be noted that attempts to effect the TMSOTf-mediated ring opening of bicyclic isoxazolidine **16** failed to afford even a trace of the desired *N*-hydroxytetrahydropyridine **23**, which may be due to competing complexation of the acetonide oxygens for TMSOTf. No attempt was made to force this reaction by using excess TMSOTf.

Scheme VII




An explanation for the stereochemical differences observed in the thermal and TMSOTf-promoted reactions may be accounted for as follows (Scheme VII): The primary energy differences between transition states A, B, and C are associated with the chair and boat forms along with an axial versus equatorial relationship for one of the side chains. In the thermally induced reaction, the geometry for cyclization requires the boat form.[14] In accord with the frontier molecular orbital (FMO) theory of 1,3-dipolar cycloadditions of nitrones to olefins, the formation of the new carbon–carbon bond is further advanced than the carbon–oxygen bond[15] and, to the extent that transition state C places any partial positive charge on the incipient bridgehead carbon, results in a preference for a pseudoaxial orientation of the TMS group because of the stereoelectronic stabilization achieved through $\sigma$–$\pi$ orbital overlap.[16] It should be noted that the [3 + 2] cycloaddition of nitrone **15** occurs slowly at room temperature, indicating that the TMS group does indeed appear to lower the transition-state energy for the reaction since normally these reactions require heating for extended periods.[17] The TMSOTf-promoted reactions, which proceeds at −40 °C, mechanistically does not require the boat form and thus assumes the chair form B with one of the side chains in an axial orientation. Again, the TMS group assumes an axial orientation as a result of the preferred parallel nature of the incipient $\pi$-orbital and the carbon–silicon $\sigma$-bond. This arrangement then leads to the observed trans product. Placing the two side chains and the TMS group equatorially as in transition state A is precluded on the grounds that it fails to manifest the strong stereoelectronic effect of disposing the TMS group axially.

(13) Peterson, D. J. *J. Org. Chem.* **1968**, *33*, 780. Hudrlik, P. F.; Peterson, D. J.; Rona, R. J. *Ibid.* **1975**, *40*, 2263. Deshong, P.; Legimus, J. M.; Lander, S. W., Jr. *Ibid.* **1986**, *51*, 574.

(14) (a) Oppolzer, W.; Siles, S.; Snowden, R. L.; Bakker, B. H. *Tetrahedron Lett.* **1979**, 4391. (b) Padwa, A., Ed. *1,3-Dipolar Cycloaddition Chemistry*; Wiley: New York, 1984.

(15) Gree, R.; Tonnard, F.; Carrie, R. *Bull. Soc. Chim. Fr.* **1975**, 1325.

(16) Lambert, J. B.; Wang, G. T.; Finzel, R. P.; Teramura, D. H. *J. Am. Chem. Soc.* **1987**, *109*, 7838.

(17) Hoffmann, R. W.; Endesfelder, A. *Liebigs Ann. Chem.* **1986**, 1823. Lau, H. H.; Schollkopf, U. *Liebigs Ann. Chem.* **1981**, 1378.

In conclusion, we have achieved our goal of developing a route to the cannabisativine skeleton with its attendant stereochemistry. Our synthesis of tetrahydropyridines **19** and **22** demonstrated the utility of γ-(silylallyl)boronate additions to aldoximes for controlling the relative stereochemistry of three contiguous chiral centers and provides useful synthetic methodology which should have broad applications. We have also demonstrated the stereoselective formation of cis and trans 2,6-disubstituted tetrahydropyridine rings by intramolecular cycloaddition of allylsilanes to nitrones under either thermal or TMSOTf-catalyzed conditions. This work also poses the broader question of the general influence of the TMS group on the stereochemical outcome of other intramolecular dipolar cycloadditions. From our results to date it appears that the electronic effects imposed by the TMS group may in general override steric effects, allowing for greater design control in synthesis.

## Experimental Section

**Methyl 2-Octynoate.** 2-Octynoic acid (17.32 g, 12.4 mmol) was dissolved in 50 mL of diethyl ether in a 250-mL Erlenmeyer flask, and an ethereal diazomethane solution was added in small portions with swirling until the yellow color of diazomethane persisted and nitrogen gas was no longer evolved. The solution was then warmed on a steam bath to expel the excess diazomethane. After removal of solvent under reduced pressure, distillation of the resulting residue provided 17.95 g (95%) of the methyl ester as a colorless liquid; bp 115 °C, 15 Torr. This product was carried on to the next step without further purification: $^1$H NMR (300 MHz, $CDCl_3$) 3.76 (s, 3 H), 2.33 (t, $J$ = 7.1 Hz, 2 H), 1.59 (m, 2 H), 1.44–1.29 (m, 4 H), 0.90 (t, $J$ = 7.1 Hz, 3 H) ppm; $^{13}$C NMR (75.3 MHz, $CDCl_3$) 154.23, 89.77, 73.21, 52.27, 31.11, 27.43, 22.15, 18.74, 13.77 ppm; IR (neat) 2238, 1716, 1257, 1078 cm$^{-1}$.

**Methyl *cis*-2-Octenoate (7).** Methyl 2-octynoate (17.52 g, 11.4 mmol) was dissolved in 150 mL of ethyl acetate, treated with Lindler catalyst (7.0 g, 5% palladium on calcium carbonate poisoned with lead) and 10 drops of quinoline. The reaction mixture was exposed to hydrogen at atmospheric pressure until 1.02 equiv of hydrogen was absorbed. Filtration through Celite and removal of the solvent under reduced pressure provided the unsaturated ester[18] (16.10 g, 91%). $^1$H NMR showed a 9.8:1 mixture of cis/trans isomers, which were separated by chromatography, eluting with 5% ethyl acetate/hexane. For the cis isomer: $R_f$ 0.32 (95:5 hexane/ethyl acetate); $^1$H NMR (300 MHz, $CDCl_3$) 6.23 (dt, $J$ = 11.5, 7.5 Hz, 1 H), 5.76 (dt, $J$ = 11.5, 1.7 Hz, 1 H), 3.71 (s, 3 H), 2.65 (qd, $J$ = 7.4, 1.7 Hz, 2 H), 1.58–1.28 (m, 6 H), 0.89 (t, $J$ = 7.0 Hz, 3 H) ppm; $^{13}$C NMR (75.3 MHz, $CDCl_3$) 166.79, 150.53, 119.43, 50.80, 31.58, 29.09, 28.82, 22.51, 13.92 ppm; IR (neat) 3037, 3022, 1725, 1646, 1458, 1203, 1179, 817 cm$^{-1}$. For the trans isomer: $R_f$ 0.21 (95:5 hexane/ethyl acetate); $^1$H NMR (300 MHz, $CDCl_3$) 6.97 (dt, $J$ = 15.6, 7.0 Hz, 1 H), 5.82 (dt, $J$ = 15.6, 1.6 Hz, 1 H), 3.73 (s, 3 H), 2.19 (qd, $J$ = 7.1, 1.6 Hz, 2 H), 1.51–1.25 (m, 6 H), 0.89 (t, $J$ = 6.9 Hz, 3 H) ppm; $^{13}$C NMR (75.3 MHz, $CDCl_3$) 167.04, 149.45, 121.15, 51.18, 32.32, 31.43, 27.89, 22.48, 13.86 ppm; IR (neat) 1727, 1658, 1457, 1205, 1171, 988 cm$^{-1}$.

**(2*R**,3*R**)-Methyl 2,3-Dihydroxyoctanoate.** Methyl *cis*-2-octenoate (7) (4.91 g, 31.4 mmol) and *N*-methylmorpholine *N*-oxide·$H_2O$ (6.37 g, 41.7 mmol) were dissolved in acetone/water (1:1, 60 mL) in a 250-mL round-bottom flask. Osmium tetraoxide (0.59 mmol, 6 mL of a 25 mg/mL solution in *tert*-butyl alcohol) was added. The resulting solution was stirred overnight at room temperature, during which time the reaction mixture became black. Workup was accomplished by the addition of 10 g of alumina and a solution of 2.0 g of sodium hydrosulfite in 50 mL of $H_2O$, and stirring was continued for 30 min. The precipitated osmium was filtered off through Celite, washing with diethyl ether and small portions of acetone. The mixture was concentrated in vacuo, and the aqueous residue was acidified with 10% HCl to pH 2 and extracted three times with ethyl acetate. The extracts were washed with water and brine and dried over anhydrous magnesium sulfate followed by concentration. Chromatography on silica gel (eluting with 50% ethyl acetate in hexane), followed by bulb-to-bulb distillation (76–85 °C/0.02 Torr), afforded 5.04 g (85%) of pure diol: $^1$H NMR (300 MHz, $CDCl_3$) 4.23 (dd, $J$ = 5.9, 3.6 Hz, 1 H), 3.91–3.80 (m, 1 H), 3.82 (s, 3 H), 3.10 (d, $J$ = 5.9 Hz, OH), 2.25 (d, $J$ = 6.8 Hz, OH), 1.62–1.22 (m, 8 H), 0.89 (t, $J$ = 6.8 Hz, 3 H) ppm; $^{13}$C NMR (75.3 MHz, $CDCl_3$) 173.31, 74.48, 73.55, 52.32, 32.10, 31.82, 25.52, 22.58, 13.92 ppm; IR (neat) 3680–3060 (vs, br), 2955–2860, 1738, 1440, 1254, 1217, 1184, 1135, 1078 cm$^{-1}$. Anal. Calcd for $C_9H_{18}O_4$: C, 56.82; H, 9.54. Found: C, 56.69; H, 9.61.

**(4*R**,5*R**)-Methyl 2,2-Dimethyl-5-*n*-pentyl-1,3-dioxolane-4-carboxylate (8).** To a solution of diol from above (4.44 g, 23.6 mmol) in 40 mL of dry acetone were added 29.0 mL (0.24 mol) of dimethoxypropane and 30 mg of *p*-toluenesulfonic acid. After being stirred for 1.5 h at room temperature, the solution was neutralized with $CaCO_3$ (1.5 g). The mixture was filtered through Celite, concentrated, and bulb-to-bulb distilled (112–123 °C/15 Torr) to afford 5.22 g (97%) of acetonide 8: $^1$H NMR (300 MHz, $CDCl_3$) 4.57 (d, $J$ = 6.7 Hz, 1 H), 4.31 (m, 1 H), 3.75 (s, 3 H), 1.61 (s, 3 H), 1.58–1.25 (m, 11 H), 0.89 (t, $J$ = 6.9 Hz, 3 H) ppm; $^{13}$C NMR (75.3 MHz, $CDCl_3$) 170.73, 110.44, 78.14, 77.68, 51.50, 31.81, 30.36, 27.13, 26.05, 25.75, 22.54, 13.90 ppm; IR (neat) 2985–2862, 1761, 1736, 1459, 1438, 1250, 1220, 1201, 1167, 1119, 1098 cm$^{-1}$. Anal. Calcd for $C_{12}H_{22}O_4$: C, 62.58; H, 9.63. Found: C, 62.46; H, 9.70.

**(4*R**,5*R**)-2,2-Dimethyl-5-*n*-pentyl-1,3-dioxolane-4-carboxaldehyde.** A 250-mL flask equipped with a dropping funnel and a magnetic stirrer was charged with a solution of methyl ester 8 (5.12 g, 22.4 mmol) in dry diethyl ether (80 mL). The resulting solution was cooled to −78 °C, and diisobutylaluminum hydride (33.6 mmol, 33.6 mL of a 1.0 M solution in hexane) was then added dropwise over 40 min. The mixture was stirred for 1 h and then quenched with $H_2O$ (7 mL). The reaction mixture was allowed to warm to room temperature and stirred for an additional 1 h. The white solids were filtered and washed thoroughly with diethyl ether. The ether filtrate was dried over sodium sulfate, concentrated, and bulb-to-bulb distilled (82–91 °C/15 Torr) to provide the aldehyde (3.5 g, 78%): $^1$H NMR (300 MHz, $CDCl_3$) 9.63 (d, $J$ = 3.5 Hz, 1 H), 4.33 (m, 1 H), 4.24 (dd, $J$ = 7.1, 3.5 Hz, 1 H), 1.59–1.28 (m, 14 H), 0.87 (t, $J$ = 6.7 Hz, 3 H) ppm; $^{13}$C NMR (75.3 MHz, $CDCl_3$) 201.51, 110.50, 82.31, 78.91, 31.69, 29.84, 27.77, 26.12, 25.41, 22.48, 13.87 ppm; IR (neat) 3450, 2989-2812, 1734, 1458, 1381, 1249, 1217, 1163, 1100, 1067 cm$^{-1}$. Anal. Calcd for $C_{11}H_{20}O_3$: C, 65.97; H, 10.07. Found: C, 62.41; H, 10.28.

**(4*R**,5*R**)-2,2-Dimethyl-5-*n*-pentyl-1,3-dioxolane-4-carbaldehyde (4).** To a solution of aldehyde from above (1.23 g, 6.20 mmol) in 20 mL of dry pyridine was added hydroxylamine hydrochloride (474 mg, 6.83 mmol). After being stirred for 1 h, the mixture was diluted with diethyl ether (100 mL), washed with water (4 × 60 mL), dried over sodium sulfate, and concentrated in vacuo. The resulting residue was flash chromatographed on silica, eluting with 20% ethyl acetate in hexane to give 1.28 g (97%) of the pure aldoxime 4. $^1$H NMR analysis (300 MHz) showed a 1.9:1 $E/Z$ ratio of geometric isomers, which were inseparable by chromatography. For the E isomer (in a mixture of isomers): $^1$H NMR (300 MHz, $CDCl_3$) 7.66 (s, 1 H, OH), 7.36 (d, $J$ = 8.3 Hz, 1 H), 4.57 (dd, $J$ = 8.3, 6.1 Hz, 1 H), 4.25 (m, 1 H), 1.67–1.16 (m, 14 H), 0.89 (t, $J$ = 6.5 Hz, 3 H) ppm; $^{13}$C NMR (75.3 MHz, $CDCl_3$) 149.35, 109.26, 78.45, 76.09, 31.78, 29.91, 28.05, 25.83, 25.58, 22.49, 13.87 ppm. For the $Z$ isomer (in a mixture of isomers): $^1$H NMR (300 MHz, $CDCl_3$) 7.92 (s, 1 H, OH), 6.83 (d, $J$ = 6.7 Hz, 1 H), 5.25 (t, $J$ = 6.1 Hz, 1 H), 4.34 (m, 1 H), 1.67–1.16 (m, 14 H), 0.89 (t, $J$ = 6.5 Hz, 3 H) ppm; $^{13}$C NMR (75.3 MHz, $CDCl_3$) 151.04, 108.96, 78.15, 72.23, 31.81, 30.50, 28.21, 25.95, 25.58, 22.56, 13.92 ppm; IR (neat, as a mixture of isomers) 3376 (vs), 2988–2861, 1461, 1381, 1372, 1247, 1218, 1166, 1053, 944 cm$^{-1}$. Anal. Calcd for $C_{11}H_{21}NO_3$: C, 61.37; H. 9.83; N, 6.51. Found: C, 61.21; H, 9.88; N, 6.54.

**(1*R**,2*R**,4′*S**,5′*R**)-*N*-[1-(2′,2′-Dimethyl-5′-*n*-pentyl-1′,3′-dioxolan-4′-yl)-2-(trimethylsilyl)-3-butenyl]hydroxylamine (13) and (1*S**,2*S**,4′*S**,5′*R**)-*N*-[1-(2′,2′-Dimethyl-5′-*n*-pentyl-1′,3′-dioxolan-4′-yl)-2-(trimethylsilyl)-3-butenyl]hydroxylamine (14).** A 100-mL flask equipped with a

(18) Kennedy, J.; McCorkindale, N. J.; Raphael, R. A.; Scott, W. T.; Zwanenburg, B. *Proc. Chem. Soc., London* **1964**, 148.

magnetic stirrer, a rubber septum, and a reflux condenser was charged with a solution of aldoxime **4** (1.01 g, 4.72 mmol, $E/Z$ = 1.9:1) in dry carbon tetrachloride (8 mL) under an argon atmosphere. The solution was warmed to 70 °C and slowly treated with ethylene glycol *trans*-1-(trimethylsilyl)-1-propane-3-boronate (**5**) (1.30 g, 7.08 mmol). The mixture was refluxed for 25 h and quenched by addition of anhydrous diethyl ether (50 mL) and triethanolamine (1.06 g, 7.08 mmol). After an additional 3 h of stirring, the white solid was removed by filtration and washed with diethyl ether. The filtrate was poured into a 10% solution of sodium hydroxide (20 mL) and extracted with diethyl ether (4 × 30 mL). The combined extracts were washed with water and brine, dried over sodium sulfate, and concentrated under reduced pressure to give 850 mg (55%) of a pale yellow liquid. $^1$H NMR analysis (300 MHz) of the crude product showed a 1.7:1.0 ratio of two main diastereomers. Attempts to determine the ratio of some very minor isomers by GC–MS failed due to their decomposition on the column. The diastereomers were separated by column chromatography on silica, eluting with 10:90:1 ethyl acetate/hexane/$Et_3N$, to give 521 mg of **13** and 301 mg of **14** along with a small amount of other isomers. For the major isomer **13**: $R_f$ 0.33 (90:10:1 hexane/ethyl acetate/$Et_3N$); $^1$H NMR (300 MHz, $CDCl_3$) 5.77 (ddd, $J$ = 16.2, 11.0, 10.1 Hz, 1 H), 5.21 (br, 1 H, NOH), 5.04 (dd, $J$ = 10.1, 2.4 Hz, 1 H), 5.00 (dd, $J$ = 16.2, 2.4 Hz, 1 H), 4.62 (br, 1 H, NH), 4.07 (m, 1 H), 3.97 (dd, $J$ = 9.4, 5.1 Hz, 1 H), 3.23 (dd, $J$ = 9.4, 3.8 Hz, 1 H), 2.14 (dd, $J$ = 11.0, 3.8 Hz, 1 H), 1.60–1.24 (m, 14 H), 0.89 (t, $J$ = 6.6 Hz, 3 H), 0.07 (s, 9 H) ppm; $^{13}$C NMR (75.3 MHz, $CDCl_3$) 134.82, 116.46, 106.65, 78.48, 77.79, 60.13, 36.15, 31.94, 30.11, 28.63, 26.06, 25.48, 22.73, 14.07, −1.70 ppm; IR (neat) 3450–3050 (br), 3075, 2985–2861, 1624, 1379, 1369, 1291, 1245, 1050 cm$^{-1}$. Anal. Calcd for $C_{17}H_{35}NO_3Si$: C, 61.96; H, 10.70; N, 4.25; Si, 8.52. Found: C, 61.88; H, 10.88; N, 4.13; Si, 8.40. For the minor isomer **14**: $R_f$ 0.28 (90:10:1) hexane/ethyl acetate/$Et_3N$); $^1$H NMR (300 MHz, $CDCl_3$) 5.77 (ddd, $J$ = 16.5, 11.0, 10.0 Hz, 1 H), 5.23 (br, 2 H, NOH and NH), 5.08 (dd, $J$ = 10.0, 2.2 Hz, 1 H), 5.04 (dd, $J$ = 16.5, 2.2 Hz, 1 H), 4.07 (m, 1 H), 3.81 (dd, $J$ = 10.3, 5.3 Hz, 1 H), 3.32 (dd, $J$ = 10.3, 2.1 Hz, 1 H), 2.18 (dd, $J$ = 11.0, 2.2 Hz, 1 H), 1.63–1.24 (m, 14 H), 0.90 (t, $J$ = 6.6 Hz, 3 H), 0.08 (s, 9 H) ppm; IR (neat) 3500–3050 (br), 3074, 1627, 1376, 1364, 1290, 1245, 1044 cm$^{-1}$.

**(2*S**,6*S**,4′*S**,5′*R**)-6-[2-(Benzyloxy)ethyl]-2-(2′,2′-dimethyl-5′-*n*-pentyl-1′,3′-dioxolan-4′-yl)-1,2,5,6-tetrahydro-*N*-hydroxypyridine (18).** A 25-mL flask equipped with a magnetic stirrer and a rubber septum was charged with a solution of the hydroxylamine **13** (127 mg, 0.39 mmol) in dry methylene chloride (3 mL). Finely ground anhydrous calcium chloride (216 mg, 1.00 mmol) was added, and the suspension was cooled to −20 °C. 3-(Benzyloxy)propanal (127 mg, 0.78 mmol) was added, and stirring was continued for 14 h at −20 °C. The resulting cooled suspension was quickly filtered through a Celite pad and washed with cold, dry methylene chloride (4 mL). The filtrate was cooled to −40 °C and treated with trimethylsilyl triflate (0.75 mg, 0.39 mmol). After being stirred for 18 h at −40 °C, the reaction mixture was quenched with 3.0 N aqueous HCl solution (3 mL) and stirred for an additional 1 h. The solution was neutralized with 3.0 N aqueous NaOH solution and extracted with methylene chloride (3 × 15 mL). The combined extracts were washed with brine (30 mL) and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure, and the resulting crude product was purified by flash chromatography (silica, eluted with 80:20:1 hexane/ethyl acetate/$Et_3N$) to afford the tetrahydro-*N*-hydroxypyridine **18** (126 mg, 79%) as a yellow liquid: $^1$H NMR (300 MHz, $CDCl_3$) 7.42–7.17 (m, 5 H), 5.94 (dddd, $J$ = 10.4, 4.4, 2.4, 1.4 Hz, 1 H), 5.75 (ddt, $J$ = 10.4, 3.2, 2.1 Hz, 1 H), 5.12 (br, NOH), 4.49 (AB q, $\Delta\nu$ = 11.8 Hz, $J$ = 3.5 Hz, 2 H, $PhCH_2O$), 4.10 (m, 1 H), 3.95 (br t, $J$ = 6.7 Hz, 1 H), 3.65–3.50 (m, 3 H), 3.11 (m, 1 H), 2.17 (ddd, $J$ = 17.5, 9.4, 2.4 Hz, 1 H), 1.94 (m, 2 H), 1.79–1.22 (m, 15 H), 0.90 (t, $J$ = 6.6 Hz, 3 H) ppm; $^{13}$C NMR (75.3 MHz, $CDCl_3$) 138.32, 128.37, 127.58, 126.24, 125.11, 107.77, 78.74, 78.38, 73.14, 67.67, 62.44 (br), 54.63 (br), 31.97;, 29.47, 28.03, 26.23, 25.83, 25.31, 22.68, 14.06 ppm; IR (neat) 3600–3190 (br), 3032, 2952–2859, 1655, 1605, 1454, 1378, 1367, 1049, 1029 cm$^{-1}$. Anal. Calcd for $C_{24}H_{37}NO_4$: C, 71.43; H, 9.24; N, 3.47. Found: C, 71.50; H, 9.19; N, 3.31.

**(2*S**,6*S**,1′*S**,2′*R**)-6-[2-(Benzyloxy)ethyl]-2-(1′,2′-dihydroxyheptyl)-1,2,5,6-tetrahydropyridine (19).** A 25-mL flask equipped with a reflux condenser and a magnetic stirrer was charged with a solution of the tetrahydro-*N*-hydroxypyridine **18** (87 mg, 0.22 mL) in glacial acetic acid (1.0 mL) and water (1.0 mL). Zinc dust (281 mg, 4.31 mmol) was added, and the suspension was heated to 80 °C for 4 h with vigorous stirring. After cooling, zinc dust was filtered off and washed with 3 mL of tetrahydrofuran. The resulting filtrate was treated with 2 mL of trifluoroacetic acid and stirred for 20 h at room temparature. After removal of the solvent under reduced pressure, the residue was dissolved in 10 mL of chloroform and the solution was washed with saturated aqueous sodium bicarbonate, dried over anhydrous sodium sulfate, and concentrated in vacuo to afford 55 mg (73%) of tetrahydropyridine **19** as an unstable brown oil. Attempted further purification by column chromatography resulted in extensive decomposition: $^1$H NMR (300 MHz, $CDCl_3$) 7.38–7.27 (m, 5 H), 6.02–5.89 (m, 2 H), 4.50 (AB q, $\Delta\nu$ = 11.7 Hz, $J$ = 3.1 Hz, 2 H, $PhCH_2O$), 3.67–3.55 (br m, 5 H), 3.49 (br d, $J$ = 8.1 Hz, 1 H), 3.38 (t, $J$ = 8.1 Hz, 1 H), 3.11 (m, 1 H), 2.16 (dt, $J$ = 17.7, 4.5 Hz, 1 H), 1.83–1.21 (m, 12 H), 0.88 (t, $J$ = 6.6 Hz, 3 H) ppm; $^{13}$C NMR (75.3 MHz, $CDCl_3$) 138.36, 128.35, 127.75, 127.58, 127.04, 126.85, 76.02, 74.13, 73.12, 67.19, 56.86, 46.45, 35.40, 33.83, 32.08, 30.44, 24.85, 22.71, 14.09 ppm; IR (neat) 3302 (br), 3113, 3083, 3063, 3033, 3005, 2952–2855, 1690, 1617, 1612, 1496, 1362, 1097, 1076, 1029 cm$^{-1}$; high-resolution MS (CI, isobutane) calcd for $C_{21}H_{34}NO_3$ 348.2539 ([M + H]$^+$), found 348.2540.

**(4′*R**,5′*R**)-*endo*-6-[2-(Benzyloxy)ethyl]-*endo*-2-(2′,2′-dimethyl-5′-*n*-pentyl-1′,3′-dioxolan-4′-yl)-*exo*-3-(trimethylsilyl)-1-aza-7-oxabicyclo[2.2.1]heptane (16).** A suspension of the hydroxylamine **13** (200 mg, 0.60 mmol) and finely ground anhydrous calcium chloride (340 mg, 3.05 mmol) in 4 mL of dry toluene was placed in a 25-mL flask, equipped with a magnetic stir bar and a reflux condenser. The suspension was cooled to −20 °C, treated with 3-(benzyloxy)propanal (495 mg, 3.05 mmol), and stirred for 8 h. The resulting nitrone solution was heated to reflux for 2 h. The suspension was cooled to room temperature, filtered, and washed with 10 mL of benzene. After removal of the solvent under reduced pressure, the residue was purified by flash chromatography (silica, eluted with 85:15 hexane/ethyl acetate) to afford 288 mg (100%) of the cycloadducts. $^1$H NMR analysis (300 MHz) showed a 14.8:1.0 mixture of **16** and **17**, which were inseparable by chromatography. For the major isomer **16** (in a mixture of isomers): $^1$H NMR (300 MHz, $CDCl_3$) 7.42–7.30 (m, 5 H), 4.80 (t, $J$ = 4.9 Hz, 1 H), 4.50 (AB q, $J$ = 12.0 Hz, $\Delta\nu$ = 16.3 Hz, 2 H, $OCH_2Ph$), 4.25 (m, 1 H), 3.85 (dd, $J$ = 10.0, 6.2 Hz, 1 H), 3.60 (m, 2 H), 2.90 (m, 1 H), 2.76 (dd, $J$ = 10.0, 5.6 Hz, 1 H), 1.87 (dd, $J$ = 11.4, 7.6 Hz, 1 H), 1.83–1.27 (m, 18 H), 0.88 (t, $J$ = 6.8 Hz, 3 H), 0.10 (s, 9 H) ppm; $^{13}$C NMR (75.3 MHz, $CDCl_3$) 138.55, 128.34, 127.58, 127.47, 107.08, 83.16, 80.54, 77.83, 72.97, 68.90, 67.92, 64.33, 38.70, 37.91, 36.85, 32.01, 30.92, 28.23, 26.16, 25.23, 22.81, 14.10, −0.81 ppm; IR (neat) 3030, 2982–2859, 1455, 1378, 1368, 1251, 1215, 1177, 1112, 1075, 1058, 1043 cm$^{-1}$. For the minor isomer **17** (in a mixture of isomers): $^1$H NMR (300 MHz, $CDCl_3$) 4.69 (d, $J$ = 4.9 Hz). The other resonances of this isomer could not be characterized due to overlap with resonances of the major isomer **16**. Anal. Calcd for $C_{27}H_{45}NO_4SI$: C, 68.17; H, 9.53; N, 2.95; Si, 5.90. Found: C, 68.08; H, 9.58; N, 2.91; Si, 5.96.

**(2*S**,6*R**,1′*S**,2′*R**)-6-[2-(Benzyloxy)ethyl]-2-(1′,2′-dihydroxyheptyl)-1,2,5,6-tetrahydropyridine (22).** To a solution of the 14.8:1 mixture of bicyclic isoxazolidine **16** and **17** (207 mg, 0.44 mmol) in glacial acetic acid (2.0 mL) and water (2.0 mL) in a 25-mL flask was added zinc dust (825 mg, 12.6 mmol). The suspension was heated to 60 °C for 4 h with vigorous stirring. The cooled reaction mixture was filtered through Celite and washed thoroughly with ethyl acetate. The combined filtrate and washings were concentrated under reduced pressure. The residue was dissolved in ethyl acetate (20 mL), and the solution was washed with saturated aqueous sodium bicarbonate solution. The organic layer was dried over anhydrous sodium sulfate and concentrated in vacuo to provide a pale yellow oil (189 mg). The resulting residue was dissolved in 10 mL of dry toluene and treated with *p*-toluenesulfonic acid·$H_2O$ (165 mg, 0.87 mmol). The reaction mixture was heated to reflux under argon for 3 h. After removal of the solvent under reduced pressure, the residue was dissolved in 5 mL of tetrahydrofuran and 2 mL of water and treated with 4 mL of trifluoroacetic acid. The reaction mixture was stirred

for 36 h, and the solvent was removed in vacuo. The residue was dissolved in chloroform, and the solution was washed with saturated sodium bicarbonate solution. After drying, the solution was concentrated to provide 92 mg (61%) of an unstable yellow liquid. Attempted purification by column chromatography resulted in decomposition. Due to the instability of this material, satisfactory C and H analysis could not be obtained: $^1$H NMR (300 MHz, $CDCl_3$) 7.38–7.26 (m, 5 H), 5.82 (br s, 2 H), 4.50 (AB q, $\Delta\nu$ = 12.1 Hz, $J$ = 1.2 Hz, 2 H, $PhCH_2O$), 3.86 (dd, $J$ = 4.0, 0.6 Hz, 1 H), 3.71 (m, 1 H), 3.61 (m, 2 H), 3.43 (dd, $J$ = 5.7, 4.0 Hz, 1 H), 3.14 (br, 2-OH), o.02 (m, 1 H), 2.05–1.30 (m, 12 H), 0.89 (t, $J$ = 6.6 Hz, 3 H) ppm; $^{13}$C NMR (75.3 MHz, $CDCl_3$) 138.27, 128.41, 127.63, 126.82, 126.08, 75.23, 74.48, 73.08, 67.88, 58.42, 51.72, 36.03, 34.23 31.93, 31.83, 25.61, 22.65, 14.04 ppm; IR (neat) 3346 (br), 3087, 3062, 3031, 3005, 2953–2859, 1695, 1635, 1623, 1616, 1496, 1454, 1430, 1378, 1362, 1270, 1085, 1028, 1012 cm$^{-1}$; high-resolution MS (CI, isobutane) calcd for $C_{21}H_{34}NO_3$ 348.2539 ([M + H]$^+$), found 348.2542.

**Registry No.** 1, 57682-64-1; (±)-(*E*)-**4**, 116911-42-3; (±)-(*Z*)-**4**, 116949-70-3; (±)-**4** (aldehyde), 116949-69-0; **5**, 113999-42-1; **6**, 5663-96-7; **6** (methyl ester), 111-12-6; (*E*)-**7**, 7367-81-9; (*Z*)-**7**, 68854-59-1; (±)-**8**, 116911-40-1; (±)-**8** (glycol), 116911-41-2; (±)-**13**, 116911-43-4; (±)-**14**, 117019-43-9; (±)-**16**, 116911-46-7; (±)-**17**, 116949-71-4; (±)-**18**, 116911-44-5; (±)-**19**, 116911-45-6; (±)-**22**, 116911-47-8; $BnO(CH_2)_2CHO$, 19790-60-4.

# Oxidative Deamination of *sec*-Alkyl Primary Amines with 3,5-Di-*tert*-butyl-1,2-benzoquinone: A Second Look[1]

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Corey's oxidative deamination with 3,5-di-*tert*-butyl-1,2-benzoquinone (1) was studied with four *sec*-alkyl primary amines: cyclohexylamine (**2a**), cycloheptylamine (**2b**), 2-butanamine (**2c**), and 3-pentanamine (**2d**). The condensation products of 1 with **2a–d** were identified as the respective Schiff bases (**4a–d**) of 2-amino-4,6-di-*tert*-butylphenol (**5**) resulting from rapid, spontaneous prototropic rearrangement of the intermediate quinone imines (**3a–d**). MNDO calculations on model systems confirm that the rearrangement is thermodynamically highly favored ($\Delta\Delta H_f$ = 16.5 kcal/mol). Acidic hydrolysis of **4a–d** gave the corresponding ketones (**6a–d**) and aminophenol **5** in high yields. Aminophenol **5** was identified as the source (via oxidative coupling) of the intensely blue 2,4,6,8-tetra-*tert*-butyl-1-phenoxazinone (**12**) accompanying all aerated reactions. Attempted regeneration of 1 via air oxidation/hydrolysis of **5** instead gave **12** in high yields; electrochemical or dichromate oxidation of **5** in strongly acidic media, however, gave 1 in 64 and 56% yield, respectively. Rapid hydrolysis of the corresponding quinone iminium ion to 1 was confirmed by cyclic voltammetry of **5** in acidic media, which displayed two cathodic waves ($E_{p_c}$ = 0.409 and 0.307 V, respectively), the more negative corresponding to 1.

## Introduction

Of a limited number of synthetic reagents for oxidative deamination of primary aliphatic amines,[2] the most elegant mimic the pyridoxal/pyridoxamine interconversion for biological transamination.[3] To date, the most efficient of the "biomimetic" reagents for oxidative deamination of *sec*-alkyl primary amines is 3,5-di-*tert*-butyl-1,2-benzoquinone, "Corey's Reagent" (1) (Scheme I).[4,5] In comparison with other similar reagents,[6] oxidation occurs under unusually gentle reaction conditions (without added base), excellent yields of the respective ketones are obtained, and product isolation is convenient, without derivatization or chromatography.

**Scheme I**

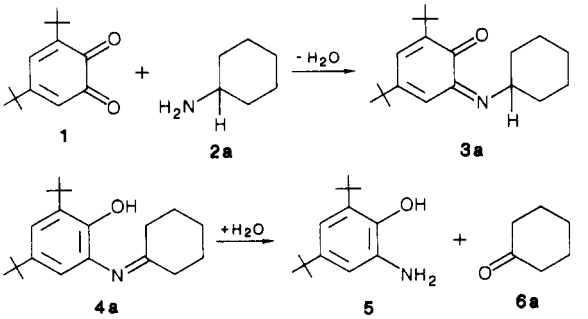


**Table I. Oxidation of *sec*-Alkyl Primary Amines 2a–d with 3,5-Di-*tert*-butyl-1,2-benzoquinone (1)**

| compound | yield ketone,[a] % |
|---|---|
| cyclohexylamine (**2a**) | 92. |
| cycloheptylamine (**2b**) | 93. |
| 2-butanamine (**2c**) | 83. |
| 3-pentanamine (**2d**) | 87. |

[a] All reactions performed with 2 g of amine, in anhydrous MeOH/THF (6:1), under $N_2$ at 25 °C; yields determined from mass of recrystallized 2,4-DNPH derivatives.

(1) Taken in part from the following: Bargas, L. M. M.S. Thesis, Georgetown University, Washington, DC 20057, April 24, 1987. Presented in part in a preliminary communication, see: Klein, R. F. X.; Bargas, L. M.; Horak, V.; Navarro, M. *Tetrahedron Lett.* **1988**, *29*, 851–2.

(2) For a review, see: (a) Baumgarten, R. J.; Curtis, V. A. In *The Chemistry of Amino, Nitroso and Nitro Compounds*; Patai, S., Ed.; Wiley: New York, 1982; Part 2, Supplement F. See also: (b) *The Chemistry of the Amino Group*; Patai, S., Ed.; Interscience: New York, 1968. (c) Baumgarten, R. J. *J. Chem. Ed.* **1966**, *43*, 398–408.

(3) (a) Dugas, H.; Penney, C. *Bioorganic Chemistry*; Springer-Verlag: New York, 1981. For a review of pyridoxal chemistry, see: (b) *Transaminases*; Christen, P., Metzler, D. E., Eds.; John Wiley and Sons: New York, 1985.

(4) Corey, E. J.; Achiwa, K. *J. Am. Chem. Soc.* **1969**, *91*, 1429–32.

(5) *o*-Quinone 1 is unsuitable for preparation of aldehydes due to preferential formation of substituted benzoxazoles. See: Corey, ref 4. In addition, α-amino acids undergo facile β-elimination to also give substituted benzoxazoles. See: Vander Zwan, M. C.; Hartner, F. W.; Reamer, R. A.; Tull, R. *J. Org. Chem.* **1978**, *43*, 509–11.

(6) (a) Buckley, T. F.; Rapoport, H. *J. Am. Chem. Soc.* **1982**, *104*, 4446–50. (b) Babler, J. H.; Invergo, B. J. *J. Org. Chem.* **1981**, *46*, 1937–8. (c) Dinizio, S. E.; Watt, D. S. *J. Am. Chem. Soc.* **1975**, *97*, 6900–1. (d) Calo, V.; Lopez, L.; Todesco, P. E. *J. Chem. Soc., Perkin Trans. 1* **1972**, 1652–3.

0022-3263/88/1953-5994$01.50/0 