Asymmetric Total Synthesis of the Caribbean Fruit Fly Pheromone (+)-Epianastrephin

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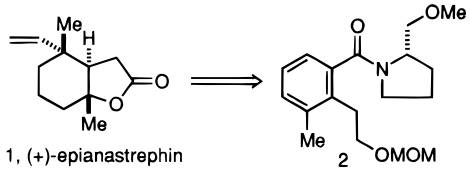
An asymmetric total synthesis of (+)-epianastrephin (**1**) from the chiral benzamide **2** (15 steps, 9.5% overall yield) is described. Birch reduction−alkylation of **2** with methyl iodide gave **3** in 91% yield as a single diastereomer. Cyclohexadiene **3** was converted to olefinic carboxylic acid **6b**, and a tandem iodolactonization−radical reduction sequence provided lactone **8** with three contiguous stereogenic centers. Chiral HPLC comparison of diol **12b**, the immediate precursor to (+)-epianastrephin (**1**), with **12b** prepared from racemic epianastrephin demonstrated that **1** had been prepared with >98% ee.

The Tephritidae (true fruit fly) family contains about 4000 species organized into 500 genera and represents one of the largest families of Diptera (true flies). Within the subfamily Trypetinae, the genus *Anastrepha* contains about 180 species of tropical and subtropical flies. Two such species, the Caribbean fruit fly, *Anastrepha suspensa* (Loew) and the Mexican fruit fly, *Anastrepha ludens* (Loew) are responsible for substantial loss of citrus, tropical fruits, and nuts in the Caribbean, Florida, Mexico, and the Southwestern United States. With the growing pressure to eliminate the use of often effective but indiscriminate insecticides, significant research efforts have been directed toward the use of the insect's own signaling agents (pheromones) for monitoring and controlling their numbers and distribution.[1]

Nation reported the isolation of a mixture of four biologically active components from whole male *A. suspensa*.[2,3] This blend consists of two alcohols and two lactones and was found to be more attractive to female flies than any of the four individual components. Further studies identified the alcohols as (*Z*)-3-nonen-1-ol and (*Z*,*Z*)-3,6-nonadien-1-ol and the lactones as anastrephin and epianastrephin (**1**). The structures of the two lactones were determined by X-ray crystallographic analysis[4] and synthesis.[5,6] It is noteworthy that both anastrephin and epianastrephin obtained from natural sources are 55:45 mixtures of enantiomers. Herein, we report the asymmetric synthesis of (+)-epianastrephin (**1**) via Birch reduction−alkylation of the chiral benzamide **2**.



Results and Discussion

The chiral benzamide **2** was prepared in two steps from 3,4-dihydro-5-methyl-2(1*H*)-benzopyran-1-one[7] as described in the Experimental Section. The conversion of **2** to (+)-epianastrephin (**1**) is shown in Scheme 1. Birch reduction−alkylation of **2** with methyl iodide gave the 1,4-cyclohexadiene **3** in 91% yield as what appeared to be a single diastereomer by ^{1}H NMR analysis. It is significant that Birch reduction−methylation of related chiral 2-alkylbenzamides provided diastereoselectivities ranging from 18:1 to >99:1 with the same sense of diastereoselection as that resulting from the 2,3-dialkylbenzamide **2**.[8,9] Hydrogenation of 1,4-cyclohexadiene **3** gave the 1-cyclohexene **4** in 95% yield.

Protiolactonization or iodolactonization[10] of **4** was expected to provide an opportunity to introduce the remaining two stereogenic centers required for preparation of **1**; however, the tetrasubstituted double bond in **4** resisted such electrophilic addition reactions. The chiral auxiliary was removed by an internal transesterifica-

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(4) Stokes, J. B.; Uebel, E. C.; Warthen, J. D., Jr.; Jacobsen, M.; Flippen-Anderson, J. L.; Gilardi, R.; Spishakoff, L. M.; Wilzer, K. R. *J. Agric. Food Chem.* **1983**, *31*, 1162−1167.

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(7) (a) 3,4-Dihydro-5-methyl-2(1*H*)-benzopyran-1-one has been prepared in 77% overall yield from o-tolylacetic acid; see: Schultz, A. G.; Kirincich, S. J. *J. Org. Chem.* **1996**, *61*, 5631−5634. (b) For the first preparation of 3,4-Dihydro-5-methyl-2(1*H*)-benzopyran-1-one, see: Bhide, B. H.; Shah, K. K. *Ind. J. Chem.* **1980**, *19b*, 9−12.

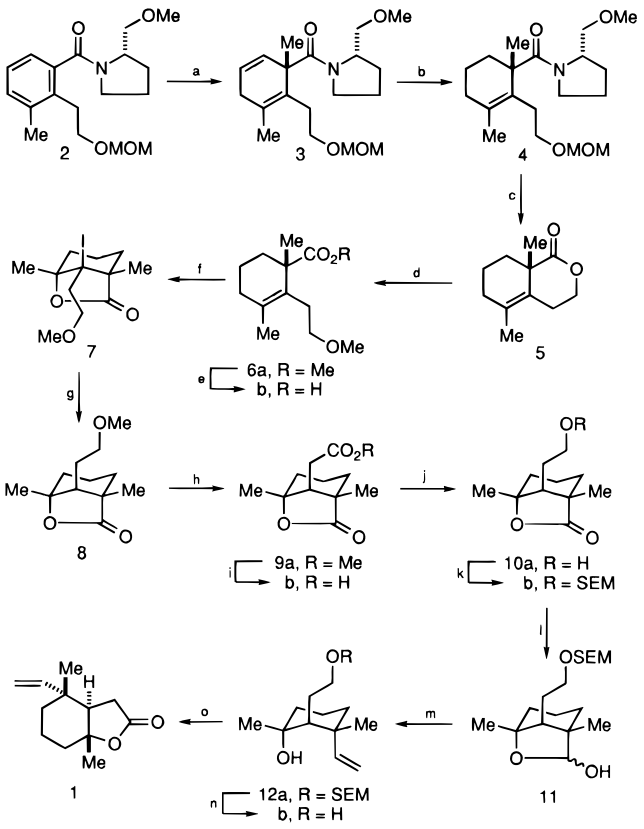
(8) Schultz, A. G.; Green, N. J. *J. Am. Chem. Soc.* **1991**, *113*, 4931−4936.

(9) Birch reduction−methylation of the 2,3-dimethylbenzamide corresponding to **2** gave little if any diastereoselectivity (unpublished observations of S. J. Kirincich); the same process with the 2-methylbenzamide gave a diastereomer distribution >99:1. Aggregation effects may play a significant role in the stereoselectivity of these and related alkylations as noted earlier: Schultz, A. G.; Macielag, M.; Sundararaman, P.; Taveras, A. G.; Welch, M. *J. Am. Chem. Soc.* **1988**, *110*, 7828−7841.

(10) Schultz, A. G.; Holoboski, M. A.; Smyth, M. S. *J. Am. Chem. Soc.* **1993**, *115*, 7904−7905.

S0022-3263(96)00568-3 CCC: $12.00

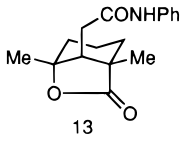
Scheme 1[a]



[a] Reaction conditions: (a) K, NH_3, THF, *t*-BuOH (1 equiv) −78 °C; piperylene; MeI (3 equiv) −78 to 25 °C; (b) 10% Pd/C, H_2, EtOAc; (c) H_2SO_4, MeOH, H_2O, reflux; (d) $HC(OMe)_3$, MeOH, H_2SO_4, 50 °C; (e) KOH, MeOH, H_2O, reflux; (f) $NaHCO_3$, H_2O, THF, I_2, KI; (g) AIBN, Bu_3SnH, PhH, reflux; (h) RuO_4, $NaIO_4$, CCl_4, MeCN, H_2O; (i) KOH, MeOH, H_2O, reflux; (j) $(COCl)_2$, PhH, reflux; Li(*t*-BuO)$_3$AlH, THF, 0 °C; (k) SEMCl, DIPEA; (l) DIBAL, CH_2Cl_2, −78 °C; (m) $Ph_3P{=}CH_2$, DMSO, 70 °C; (n) HOAc, MeOH, MeCN; (o) TPAP, NMO, CH_2Cl_2, MeCN.

tion,[11] realized by treatment of **4** with aqueous acid at reflux to give lactone **5** (84%). To avoid the occurrence of competing cycloetherification reactions in a subsequent iodolactonization, **5** was directly converted to methyl ester−methyl ether **6a** by utilization of King's procedure for alcoholysis of lactones.[12] Saponification of **6a** gave carboxylic acid **6b** in 86% overall yield from **5**.

Iodolactonization of **6b** occurred slowly but efficiently to give **7** in 85% yield. Reduction of the tertiary iodide in **7** with AIBN and Bu_3SnH in benzene gave **8** in 94% yield. The stereoselectivity for this reaction was established by an X-ray determination of structure for the anilide derivative **13**.[13] The exclusive equatorial delivery of a hydrogen atom from Bu_3SnH to the tertiary radical generated from **7** is remarkable but is not without precedent in the literature of radical substitution reactions of bridged halocyclohexanes.[14] Various factors have been considered in attempts to explain the observed stereoselectivities.[14,15] With regard to the conversion of **7** to **8**, it is clear that an axial approach of Bu_3SnH to the C(8) radical derived from oxabicyclo[3.2.1]octan-7-one **7** would encounter 1,3-interactions with the axial hydrogen atoms at C(2) and C(4); the equatorial approach of Bu_3SnH appears to be relatively unobstructed.



Cleavage of the methyl ether group in **8** was found to be problematic. Consequently, **8** was oxidized to methyl ester **9a**, and **9a** was saponified to give carboxylic acid **9b** in 83% overall yield. Reduction of the acid chloride prepared from **9b** with Li(*t*-BuO)$_3$AlH gave alcohol **10a**, which was converted to the more labile SEM derivative **10b**. Reduction of **10b** with diisobutylaluminum hydride (DIBAL) provided lactol **11** in 70% overall yield from **9b**.

Wittig olefination of **11** using conventional reaction conditions failed to give **12a**. However, addition of a solution of methylenetriphenylphosphorane in DMSO prepared by the method of Corey and co-workers[16] to lactol **11** in DMSO followed by heating this mixture in a sealed tube under an argon atmosphere at 70 °C for 23 h gave the desired olefin **12a** in 85% yield. Cleavage of the SEM ether gave **12b**, and oxidation of **12b** with tetrapropylammonium perruthenate(VII)[17] gave (+)-epianastrephin (**1**).

The ^1H NMR and ^{13}C NMR spectra, TLC, and $[\alpha]_D$ obtained from synthetic **1** compared favorably with data reported in the literature. In addition, a sample of racemic epianastrephin, obtained from Professor James Nation to determine the enantiomeric purity of synthetic **1**, was reduced to diol **12b**, and chiral HPLC comparison of this material to synthetic **12b** demonstrated that (+)-epianastrephin had been prepared with an enantiomeric excess of >98%.

Conclusion

A practical asymmetric synthesis of (+)-epianastrephin (**1**) has been achieved. The synthesis of **1** required 15 steps from the readily available chiral benzamide **2** with an overall yield of 9.5%. A key step in the synthesis is the completely regio- and stereoselective functionalization of the double bond in **6b** by a tandem iodolactonization−radical reduction sequence to provide overall cis addition. The highly stereoselective Birch reduction−alkylation of the chiral 2,3-disubstituted benzamide **2** convincingly demonstrates that this substitution pattern can be utilized for the asymmetric synthesis of 1,2,6,6-tetrasubstituted 1,4-cyclohexadienes.

Experimental Section

General Procedures. Tetrahydrofuran (THF) was distilled from benzophenone sodium ketyl under nitrogen. Benzene, dimethylformamide (DMF), triethylamine, acetonitrile,

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(12) King, S. A. *J. Org. Chem.* **1994**, *59*, 2253−2256.

(13) The author has deposited atomic coordinates for this structure with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.

(14) (a) Chuang, C.-P.; Gallucci, J. C.; Hart, D. J. *J. Org. Chem.* **1988**, *53*, 3210−3218. (b) Keck, G. E.; Yates, J. B. *J. Org. Chem.* **1982**, *47*, 3590−3591. (c) Coblens, K. E.; Muralidharan, V. B.; Ganem, B. *J. Org. Chem.* **1982**, *47*, 5041−5042.

(15) It has been suggested that the stereoselectivities observed in ref 14 may be the result of a stereoelectronic effect that involves stabilization of an equatorial radical by the nonbonding orbital of the oxygen atom in the lactone bridge; see: Ramaiah, M. *Tetrahedron* **1987**, *43*, 3541−3676.

(16) Greenwald, R.; Chaykovsky, M.; Corey, E. J. *J. Org. Chem.* **1963**, *28*, 1128−1129.

(17) Ley, S. V.; Norman, J.; Griffith, W. P.; Marsden, S. P. *Synthesis* **1994**, 639−666.

and *tert*-butyl alcohol were distilled from CaH_2. Dimethyl sulfoxide (DMSO) was azeotroped with heptane and distilled from CaH_2. Solutions were concentrated by rotary evaporation. Analytical TLC was performed on 0.25 mm E. Merck silica gel (60F-254) plates using UV light and iodine as visualizing agents. Purifications by flash column chromatography used Baker silica gel (40 μm). High-resolution mass spectra were obtained from the mass spectrometry laboratory at the University of Illinois at Urbana/Champaign. Elemental analyses were performed by Quantitative Technologies, Inc., Whitehouse, NJ, and Atlantic Microlab, Inc., Norcross, GA.

(*S*)-2-[2-(Methoxymethoxy)ethyl]-1-[[2′-(methoxymethyl)pyrrolidinyl]carbonyl]-3-methylbenzene (2). A solution of triethylamine (12.7 mL, 92 mmol) in methylene chloride (50 mL) was added to a stirred slurry of aluminum chloride (1.5 g, 78 mmol) in methylene chloride (250 mL) at 0 °C. After 15 min, a solution of 3,4-dihydro-5-methyl-2(1*H*)-benzopyran-1-one[7] (10.6 g, 65 mmol) and (*S*)-prolinol methyl ether (9.8 g, 85 mmol) in methylene chloride (100 mL) was added dropwise to the cooled TEA−$AlCl_3$ mixture, and this was warmed to room temperature. After 40 h, the reaction was quenched with crushed ice and the aqueous layer was acidified with 10% aqueous HCl. The organic layer was collected, and the remaining aqueous layer was washed with methylene chloride (2 × 100 mL). The combined organic phases were dried, filtered, and evaporated to give a brown oil. Flash chromatography (100% ethyl acetate) afforded (*S*)-2-(2-hydroxyethyl)-1-[[2-(methoxymethyl)pyrrolidinyl]carbonyl]-3-methylbenzene (15.6 g, 86%) as an amber oil: ^{1}H NMR ($CDCl_3$) δ 7.17−7.20 (m, 1 H), 7.12 (overlapping dd, J = 7.6, 7.3 Hz, 1 H), 7.04 (d, J = 7.6 Hz, 1 H), 4.38−4.43 (m, 1 H), 3.81−3.87 (m, 1 H), 3.75−3.80 (m, 2 H), 3.60 (dd, J = 9.4, 2.8 Hz, 1 H), 3.41 (s, 3 H), 2.80−3.30 (m, 5 H), 2.36 and 2.37 (s, 3 H, rotamers), 1.96−2.08 (m, 2 H), 1.86−1.96 (m, 2 H), 1.57−1.76 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 137.55, 131.35, 126.18, 73.12, 72.24, 61.04, 59.07, 58.66, 57.98, 56.40, 50.05, 33.48, 33.34, 27.84, 24.51, 19.50; IR (film) 3410 (br), 2880, 1610, 1590 (shoulder), 1410 cm^{-1}; CIMS m/z (relative intensity) 278 (M^+ + 1, 100); HRMS (CI, CH_4) calcd for $C_{16}H_{24}NO_3$ (M^+ + 1) 278.1756, found 278.1752.

A solution of (*S*)-2-(2-hydroxyethyl)-1-[[2-(methoxymethyl)-pyrrolidinyl]carbonyl]-3-methylbenzene (10.0 g, 36 mmol), chloromethyl methyl ether (3.6 mL, 1.3 equiv), and *N*,*N*-diisopropylethylamine (8.2 mL, 1.3 equiv) in methylene chloride (500 mL) was stirred at room temperature for 24 h. The solution was washed with 10% hydrochloric acid, and the organic layer was dried, filtered, evaporated, and flash chromatographed (hexane/ethyl acetate, 2:1) to provide **2** (9.4 g, 81%) as a pale-yellow oil: ^{1}H NMR ($CDCl_3$) δ 7.11−7.26 (m, 2 H), 7.02−7.04 (m, 1 H), 4.59 (s, 2 H), 4.40−4.44 (m, 1 H), 3.58-3.75 (m, 4 H), 3.40 (s, 3 H), 3.31 (s, 3 H), 2.80−3.20 (bm, 4 H), 2.38 (s, 3 H), 1.88−2.05 (m, 3 H), 1.70−1.80 (m, 1 H); IR (film) 3500 (br), 2900, 1620, 1405 cm^{-1}; CIMS m/z (relative intensity) 322 (M^+ + 1, 100), 290 (20).

Anal. Calcd for $C_{18}H_{27}NO_4$: C, 67.26; H, 8.47. Found: C, 67.10; H, 8.53.

(2′*S*,6*S*)-2,6-Dimethyl-1-[2-(methoxymethoxy)ethyl]-6-[[2′-(methoxymethyl)pyrrolidinyl]carbonyl]-1,4-cyclohexadiene (3). A solution of **2** (8.9 g, 28 mmol), and *tert*-butyl alcohol (2.6 mL, 1 equiv) in THF (200 mL) was cooled to −78 °C, and ammonia (~1500 mL) was added. Potassium (2.4 g, 2.2 equiv) was added in small pieces, and after 30 min the excess metal was quenched with piperylene (1 mL) and methyl iodide (5.2 mL, 3 equiv) was added. The solution was stirred at −78 °C for 1 h, the ammonia was allowed to evaporate, and water was added. The residue was diluted with water (100 mL) and methylene chloride (100 mL) and extracted with methylene chloride (3 × 300 mL). The combined organic phases were washed with 10% aqueous sodium thiosulfate, dried, filtered, evaporated, and flash chromatographed (hexane/ethyl acetate, 2:1) to provide **3** (8.5 g, 91%) as an amber oil (single diastereomer by ^{1}H NMR): ^{1}H NMR ($CDCl_3$) δ 5.70 (dm, J = 10.1 Hz, 1 H), 5.50 (dm, J = 10.1 Hz, 1 H), 4.57 (s, 2 H), 4.24−4.29 (m, 1 H), 3.59 (dd, J = 9.2, 3.2 Hz, 1 H), 3.46−3.51 (m, 1 H), 3.34 (s, 3 H), 3.33 (s, 3 H), 3.24−3.42 (m, 4 H), 2.70 (d, J = 23.0 Hz, 1 H), 2.55 (d, J = 23.0 Hz, 1 H), 2.38−2.46 (m, 1 H), 2.25−2.31 (m, 1 H), 1.75−1.89 (m, 3 H), 1.72 (s, 3 H), 1.68−1.71 (m, 1 H), 1.30 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 172.07, 129.87, 128.27, 126.35, 122.82, 96.02, 72.14, 66.18, 58.82, 57.94, 54.97, 49.40, 46.50, 32.95, 29.30, 26.77, 26.58, 24.73, 18.96; IR (film) 2940, 2870, 1630, 1380 cm^{-1}; CIMS m/z (relative intensity) 338 (M^+ + 1, 100), 306 (19), 236 (4); HRMS (CI, CH_4) calcd for $C_{19}H_{32}NO_4$ (M^+ + 1) 338.2331, found 338.2332.

(2′*S*,6*S*)-2,6-Dimethyl-1-[2-(methoxymethoxy)ethyl]-6-[[2′-(methoxymethyl)pyrrolidinyl]carbonyl]-1-cyclohexene (4). A solution of **3** (3.0 g, 8.09 mmol) and 10% Pd/C (0.4 g) in ethyl acetate (300 mL) was shaken under a hydrogen atmosphere (60 psi, room temperature) for 72 h. The solution was filtered through Celite, evaporated, and flash chromatographed (hexane/ethyl acetate, 1:1) to provide **4** (2.89 g, 95%) as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 4.55 (s, 2 H), 4.24−4.27 (m, 1 H), 3.52 (dd, J = 9.3, 3.1 Hz, 1 H), 3.30 (s, 3 H), 3.29 (s, 3 H), 3.25−3.48 (m, 5 H), 2.45−2.48 (m, 1 H), 1.64 (s, 3 H), 1.54−1.99 (m, 11 H), 1.27 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 175.63, 131.24, 128.09, 96.15, 72.32, 66.78, 58.87, 57.72, 55.05, 49.06, 46.70, 32.87, 31.83, 31.33, 26.40, 25.21, 25.19, 19.76, 18.89; IR (film) 2940, 1620, 1380 cm^{-1}; CIMS m/z (relative intensity) 340 (M^+ + 1, 100), 308 (20), 279 (3); HRMS (CI, CH_4) calcd for $C_{19}H_{34}NO_4$ (M^+ + 1) 340.2488, found 340.2482.

(8a*S*)-5,8a-Dimethyl-3,4,6,7,8,8a-hexahydro-2(1*H*)-benzopyran-1-one (5). A solution of **4** (3.0 g, 9.0 mmol) and concd sulfuric acid (0.5 mL) in methanol (100 mL) and water (30 mL) was refluxed for 72 h. The reaction was neutralized with aqueous sodium bicarbonate and extracted with methylene chloride (3 × 100 mL). The combined organic phases were dried, filtered, evaporated, and flash chromatographed (hexane/ethyl acetate, 4:1) to give **5** (1.35 g, 84%) as a pale yellow oil: ^{1}H NMR ($CDCl_3$) δ 4.49 (ddd, J = 11.0, 6.5, 5.1 Hz, 1 H), 4.21 (ddd, J = 11.0, 7.6, 5.3 Hz, 1 H), 2.65−2.71 (m, 1 H), 2.46−2.51 (m, 1 H), 1.95−2.02 (m, 3 H), 1.68−1.79 (m, 3 H), 1.63 (s, 3 H), 1.42 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 176.94, 129.24, 125.76, 66.97, 43.26, 32.97, 31.08, 35.58, 25.17, 19.18, 17.92; IR (film) 2920, 1720, 1125, 1050 cm^{-1}; CIMS m/z (relative intensity) 181 (M^+ + 1, 100); $[\alpha]^{28}_D$ +169.55° (*c* 2.89, $CHCl_3$); HRMS (CI, CH_4) calcd for $C_{11}H_{17}O_2$ (M^+ + 1) 181.1229, found 181.1229.

(1*S*)-1,3-Dimethyl-2-(2-methoxyethyl)-2-cyclohexene-1-carboxylic Acid Methyl Ester (6a). A solution of **5** (3.15 g, 18 mmol), trimethyl orthoformate (4.65 g, 2.5 equiv), and concd sulfuric acid (1 drop) in dry methanol (60 mL) was heated at 50 °C for 12 h. The reaction was diluted with water and extracted with methylene chloride (3 × 100 mL). The combined organic phases were dried, filtered, evaporated, and flash chromatographed (hexane/ethyl acetate, 4:1) to provide **6a** (3.4 g, 86%) as a clear, colorless oil: ^{1}H NMR ($CDCl_3$) δ 3.66 (s, 3 H), 3.32 (s, 3 H), 3.30−3.35 (m, 2 H), 2.44−2.50 (m, 1 H), 2.10−2.16 (m, 1 H), 1.93−2.05 (m, 3 H), 1.69 (s, 3 H), 1.51−1.67 (m, 3 H), 1.29 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 178.03, 131.98, 127.72, 71.85, 58.32, 51.74, 47.77, 35.71, 31.96, 30.99, 23.75, 20.10, 19.12; IR (film) 2920, 1730, 1430 cm^{-1}; CIMS m/z (relative intensity) 227 (M^+ + 1, 100), 195, (24), 167 (25); $[\alpha]^{27}_D$ −60.0° (*c* 1.55, $CHCl_3$).

Anal. Calcd for $C_{13}H_{22}O_3$: C, 68.99; H, 9.80. Found: C, 69.12; H, 9.85.

(1*S*)-1,3-Dimethyl-2-(2-methoxyethyl)-2-cyclohexene-1-carboxylic Acid (6b). A solution of **6a** (3.4 g, 15 mmol) and sodium hydroxide (6.0 g, 10 equiv) in methanol (100 mL) and water (10 mL) was refluxed for 48 h. The solution was acidified with 10% aqueous hydrochloric acid and extracted with methylene chloride (3 × 100 mL). The combined organic phases were dried, filtered, and evaporated to provide **6b** (3.3 g, 100%) as a yellow oil. For analytical purposes, flash chromatography (CH_2Cl_2/MeOH, 20:1) was performed on a 50 mg portion of the crude acid: ^{1}H NMR ($CDCl_3$) δ 3.34−3.43 (m, 2 H), 3.33 (s, 3 H), 2.50−2.57 (m, 1 H), 2.18−2.24 (m, 1 H), 1.92-2.06 (m, 3 H), 1.70 (s, 3 H), 1.66−1.72 (m, 1 H), 1.54−1.61 (m, 2 H), 1.31 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 183.55, 132.79, 127.24, 71.88, 58.28, 47.62, 35.95, 32.02, 30.94, 23.64, 20.15, 19.16; IR 3500−2900 (br), 1690, 1100 cm^{-1}; CIMS m/z (relative intensity) 213 (M^+ + 1, 90), 167 (100); IR 3500−2800 (br), 2940, 1690, 1100 cm^{-1}; $[\alpha]^{27}_D$ −66.84° (*c* 1.9, $CHCl_3$).

Anal. Calcd for $C_{12}H_{20}O_3$: C, 67.89; H, 9.50. Found: C, 67.99; H, 9.57.

(1*R*,5*R*,8*R*)-1,5-Dimethyl-8-iodo-8-(2-methoxyethyl)-6-oxabicyclo[3.2.1]octan-7-one (7). A solution of **6b** (3.3 g, 15 mmol), iodine (11.4 g, 3 equiv), potassium iodide (14.9 g, 6 equiv), and sodium bicarbonate (1.9 g, 1.5 equiv) in water (40 mL) and THF (40 mL) was stirred at room temperature for 10 days. The excess iodine was reduced with aqueous sodium thiosulfate, and the solution was diluted with water and then extracted with methylene chloride (3 × 100 mL). The combined organic phases were dried, filtered, evaporated, and flash chromatographed (hexane/ethyl acetate, 10:1) to provide **7** (4.33 g, 85%) as a white solid (mp 54−56 °C): ^{1}H NMR ($CDCl_3$) δ 3.45−3.50 (m, 1 H), 3.31−3.37 (m, 1 H), 3.28 (s, 3 H), 2.64−2.68 (m, 2 H), 2.50-2.57 (m, 1 H), 1.91−2.03 (m, 2 H), 1.79−1.83 (m, 1 H), 1.58−1.68 (m, 2 H), 1.50 (s, 3 H), 1.20 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 174.21, 71.15, 64.90, 58.63, 51.90, 42.37, 38.03, 35.84, 29.65, 19.93, 17.39, 16.43; IR (KBr) 2920, 1765, 1095 cm^{-1}; CIMS *m*/*z* (relative intensity) 339 (M^+ + 1, 100), 211 (80), 167 (29); $[\alpha]^{25}_D$ −72.13° (*c* 1.22, $CHCl_3$).

Anal. Calcd for $C_{12}H_{19}IO_3$: C, 42.62; H, 5.66. Found: C, 42.66; H, 5.67.

(1*S*,5*R*,8*R*)-1,5-Dimethyl-8-(2-methoxyethyl)-6-oxabicyclo[3.2.1]octan-7-one (8). A solution of **7** (2.2 g, 6.5 mmol), tri-*n*-butyltin hydride (2.1 mL, 1.2 equiv), and azobisisobutyronitrile (0.1 g, 0.1 equiv) in benzene (100 mL) was refluxed for 2 h. The cooled solution was evaporated, and the crude oil was flash chromatographed (hexane/ethyl acetate, 3:1) to provide **8** (1.3 g, 94%) as a yellow oil that partially solidified upon standing: ^{1}H NMR ($CDCl_3$) δ 3.32−3.41 (m, 2 H), 3.33 (s, 3 H), 1.93 (t, *J* = 6.0 Hz, 1 H), 1.46−1.76 (m, 7 H), 1.39 (s, 3 H), 1.36−1.42 (m, 1 H), 1.13 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 180.19, 85.22, 71.01, 58.53, 50.91, 46.45, 27.68, 26.13, 25.10, 24.15, 19.81, 18.43; IR (film) 2940, 1770, 1120 cm^{-1}; CIMS *m*/*z* (relative intensity) 213 (M^+ + 1, 100), 167 (22); $[\alpha]^{26}_D$ −10.66° (*c* 3.66, $CHCl_3$).

Anal. Calcd for $C_{12}H_{20}O_3$: C, 67.89; H, 9.50. Found: C, 68.06; H, 9.44.

(1*S*,5*R*,8*R*)-8-[(Methoxycarbonyl)methyl]-1,5-dimethyl-6-oxabicyclo[3.2.1]octan-7-one (9a). A solution of **8** (0.50 g, 2.4 mmol), ruthenium dioxide (20 mg, 4 mol %), and sodium periodate (2.0 g, 4 equiv) in carbon tetrachloride (12 mL), acetonitrile (12 mL), and water (18 mL) was stirred at room temperature for 48 h. The reaction was quenched with methanol (5 mL), filtered through Celite, and extracted with methylene chloride (3 × 50 mL). The combined organic phases were washed with aqueous sodium thiosulfate, dried, filtered, and evaporated to provide **9a** (0.47g) as a yellow oil: ^{1}H NMR ($CDCl_3$) δ 3.70 (s, 3 H), 2.35−2.46 (m, 3 H), 1.41−1.73 (m, 6 H), 1.36 (s, 3 H), 1.10 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 179.35, 171.96, 84.52, 52.01, 50.02, 46.08, 29.81, 27.67, 26.13, 23.66, 19.24, 18.29; IR (film) 2955, 2880, 1770, 1730 cm^{-1}; CIMS *m*/*z* (relative intensity) 227 (M^+ + 1, 100) 181 (11). An acceptable elemental analysis could not be obtained.

(1*S*,5*R*,8*R*)-8-Carboxy-1,5-dimethyl-6-oxabicyclo[3.2.1]-octan-7-one (9b). A solution of **9a** (0.47 g, 2.1 mmol) and potassium hydroxide (1.3 g, 10 equiv) in methanol (10 mL) and water (10 mL) was refluxed for 10 h. The cooled solution was acidified and extracted with methylene chloride (3 × 50 mL). The combined organic layers were dried, filtered, and evaporated to provide **9b** (0.42 g, 83%, two steps) as a pale-yellow solid (mp 99−101 °C): ^{1}H NMR ($CDCl_3$) δ 2.38−2.50 (m, 3 H), 1.49−1.76 (m, 5 H), 1.43−1.48 (m, 2 H), 1.39 (s, 3 H), 1.13 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 179.36, 177.23, 84.54, 46.69, 46.15, 29.66, 27.70, 26.17, 23.69, 19.28, 18.25; IR (film) 3500−2800 (br), 1695 (br) cm^{-1}; CIMS *m*/*z* (relative intensity) 213 (M^+ + 1, 100), 195 (5), 167 (15); $[\alpha]^{26}_D$ −16.66° (*c* 1.02, $CHCl_3$).

Anal. Calcd for $C_{11}H_{16}O_4$: C, 62.25; H, 7.60. Found: C, 62.16; H, 7.63.

(1*S*,5*R*,8*R*)-1,5-Dimethyl-8-(2-hydroxyethyl)-6-oxabicyclo[3.2.1]octan-7-one (10a). A solution of **9b** (0.52 g, 2.0 mmol) and oxalyl chloride (0.44 mL, 2.5 equiv) in benzene (10 mL) was refluxed for 100 min. The solvent was evaporated, and the residue was dissolved in THF (20 mL) and cooled to 0 °C. Lithium tri-*tert*-butoxyaluminohydride (1.5 g, 3 equiv) was added, and after 45 min, the reaction was quenched with aqueous HCl. The solution was extracted with methylene chloride (3 × 50 mL), and the combined organic layers were dried, filtered, and evaporated to provide **10a** (0.39g, 82%). A sample of the crude reaction product was flash chromatographed (hexane/ethyl acetate, 1:1) to provide the alcohol as a white solid (mp 63−65 °C): ^{1}H NMR ($CDCl_3$) δ 3.66−3.74 (m, 2 H), 1.95 (overlapping dd, *J* = 6.1 Hz, 1 H), 1.48−1.78 (m, 7 H), 1.40 (s, 3 H), 1.39−1.43 (m, 1 H), 1.14 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 180.52, 85.46, 61.09, 50.56, 46.49, 27.87, 27.67, 26.14, 24.15, 19.80, 18.41; IR (KBr) 3500−3250 (br), 2940, 1755 cm^{-1}; CIMS *m*/*z* (relative intensity) 199 (M^+ + 1, 100), 181 (18), 153 (14); $[\alpha]^{25}_D$ −7.88° (*c* 3.68, $CHCl_3$).

Anal. Calcd for $C_{11}H_{18}O_3$: C, 66.64; H, 9.15. Found: C, 66.52; H, 9.13.

(1*S*,5*R*,8*R*)-1,5-Dimethyl-8-[2-[[2-(trimethylsilyl)ethoxy]-methoxy]ethyl]-6-oxabicyclo[3.2.1]octan-7-one (10b). A solution of **10a** (280 mg, 1.4 mmol), [2-(trimethylsilyl)ethoxy]-methyl chloride (SEMCl, 0.75 mL, 3 equiv), and *N*,*N*-diisopropylethylamine (DIPEA, 0.86 mL, 3.5 equiv) was stirred at room temperature for 5 h. The reaction was quenched with 10% aqueous HCl and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic phases were dried, filtered, evaporated, and flash chromatographed (hexane/ethyl acetate, 4:1) to provide **10b** (410 mg, 91%) as a clear, colorless oil: ^{1}H NMR ($CDCl_3$) δ 4.66 (s, 2 H), 3.59−3.63 (m, 2 H), 3.54−3.58 (m, 2 H), 1.95 (t, *J* = 6.2 Hz, 1 H), 1.46−1.79 (m, 8 H), 1.39 (s, 3 H), 1.14 (s, 3 H), 0.91−0.96 (m, 2 H), 0.02 (s, 9 H); ^{13}C NMR ($CDCl_3$) δ 180.18, 94.82, 85.19, 66.10, 65.27, 50.86, 46.46, 27.70, 26.15, 25.20, 24.22, 19.88, 18.43, 18.04, −1.49; IR (film) 2960, 1770 cm^{-1}; CIMS *m*/*z* (relative intensity) 329 (M^+ + 1, 2), 271 (100), 211 (16), 181 (7); $[\alpha]^{26}_D$ −8.30° (*c* 2.17, $CHCl_3$). An acceptable elemental analysis could not be obtained.

(1*S*,5*R*,7*R,8*R*)-1,5-Dimethyl-8-[2-[[2-(trimethylsilyl)-ethoxy]methoxy]ethyl]-7-hydroxy-6-oxabicyclo[3.2.1]-octane (11).** To a solution of **10b** (245 mg, 0.75 mmol) in CH_2Cl_2 at −78 °C was added diisobutylaluminum hydride (2.2 mL, 3 equiv, CH_2Cl_2 solution). After 1 h at −78 °C, the reaction was quenched with H_2O and warmed to room temperature. The resulting suspension was diluted with water (50 mL) and CH_2Cl_2 (50 mL), and the pH was adjusted to 4 with 10% aqueous HCl. The organic layer was removed, and the aqueous phase was reextracted with CH_2Cl_2 (30 mL). The combined organic layers were dried, filtered, evaporated, and flash chromatographed (hexane/ethyl acetate, 4:1) to provide **11** (230 mg, 93%) as a clear, colorless oil: ^{1}H NMR ($CDCl_3$) δ 5.01 (s, 1/8 × 1 H), 4.95 (s, 7/8 × 1 H), 4.67 (s, 2 H), 3.61−3.67 (m, 2 H), 3.55−3.59 (m, 2 H), 1.62−1.68 (m, 2 H), 1.27 (s, 7/8 × 3 H), 1.23 (s, 1/8 × 3 H), 1.20−1.64 (m, 8 H), 0.95 (s, 3 H), 0.90−1.02 (m, 2 H), 0.02 (s, 9 H); IR (film) 3500−3200 (br), 1250 cm^{-1}; CIMS *m*/*z* (relative intensity) 255 (M^+ −75, 90), 183 (100).

Anal. Calcd for $C_{17}H_{28}O_4$: C, 61.77; H, 10.37. Found: C, 61.61; H, 10.27.

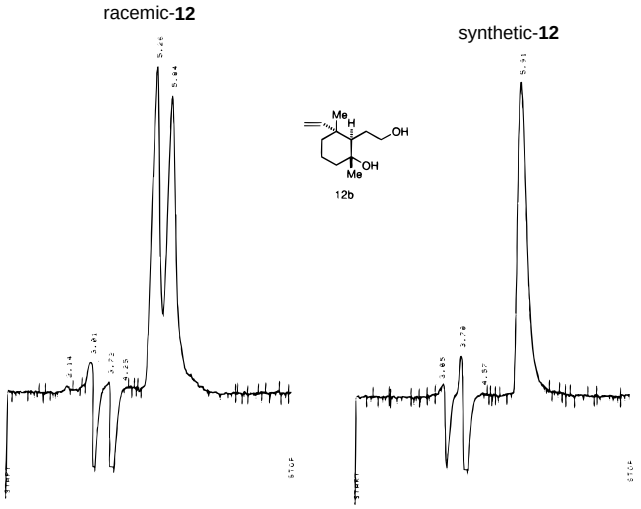
(1*R*,2*R*,3*R*)-1,3-Dimethyl-3-ethenyl-[2-[[2-(trimethylsilyl)ethoxy]methoxy]ethyl]cyclohexanol (12a). A stock solution of methylenetriphenylphosphorane in DMSO (0.66 M) was prepared according to the Corey procedure.[16] A sealed tube fitted with a rubber septum and a stir bar was flame-dried under a stream of argon. A solution of **11** (370 mg, 1.1 mmol) in DMSO (6 mL) was added via syringe to the sealed tube followed by addition of the ylide solution (8.5 mL, 5 equiv). Under an argon stream, the septum was quickly removed and replaced with the gasket and Teflon screw cap. The tube was heated at 70 °C (bath reading) for 23 h and cooled. The contents were added to a separatory funnel and diluted with water (150 mL) and CH_2Cl_2 (75 mL). The organic layer was collected, washed with water (3 × 50 mL), dried, filtered, evaporated, and flash chromatographed (hexane/ethyl acetate, 4:1) to provide **12a** (306 mg, 85%) as a clear, colorless oil: ^{1}H NMR ($CDCl_3$) δ 5.66 (dd, *J* = 17.6, 10.7 Hz, 1 H), 4.96 (dd, *J* = 10.7, 1.0 Hz, 1 H), 4.94 (dd, *J* = 17.6, 1.0 Hz, 1 H), 4.64−4.68 (m, 2 H), 3.66 (ddd, *J* = 9.6, 9.6, 4.8 Hz, 1 H), 3.60 (t, *J* = 8.3 Hz, 2 H), 3.44 (ddd, *J* = 9.6, 9.6, 4.8 Hz, 1 H), 1.80 (dm, *J* = 12.5 Hz, 1 H), 1.30−1.72 (m, 9 H), 1.22 (s, 3 H), 0.95 (s, 3 H), 0.90−0.93 (m, 1 H), −0.07 (s, 9 H); ^{13}C NMR ($CDCl_3$) δ 150.21, 111.27, 94.62, 71.69, 68.99, 65.33, 52.90, 42.01, 26.47, 24.37, 19.95, 18.03, −0.07; IR (film) 3500−3250 (br), 2930, 1250 cm^{-1}; CIMS *m*/*z* (relative intensity) 329 (M^+ + 1, 25), 255 (94),

163 (100); $[\alpha]^{25}_D$ −13.5° (*c* 1.63, $CHCl_3$). Acceptable elemental and high resolution mass spectrometry analyses could not be obtained.

(1*R*,2*R*,3*R*)-1,3-Dimethyl-3-ethenyl-2-(2-hydroxyethyl)-cyclohexanol (12b). A solution of **12a** (54 mg, 0.61 mmol) and acetic acid (0.5 mL) in CH_3CN (1 mL) and MeOH (1 mL) was stirred at room temperature for 36 h. The solution was neutralized with aqueous $NaHCO_3$, extracted with CH_2Cl_2 (3 × 20 mL), dried, filtered, evaporated, and flash chromatographed (hexane/ethyl acetate, 1:1) to provide **12b** (16.6 mg, 51%) as an oil that solidified upon standing (mp 85−87 °C). Chiral HPLC analysis (Chiralcel OD column, 10:1 hexane/2-propanol) indicated that the enantiomeric ratio exceeded 70:1: ^{1}H NMR ($CDCl_3$) δ 5.65 (dd, J = 17.5, 10.6 Hz, 1 H), 4.97 (dd, J = 10.8, 1.0 Hz, 1 H), 4.94 (dd, J = 17.3, 1.0 Hz, 1 H), 3.74 (ddd, J = 10.5, 4.4, 4.4 Hz, 1 H), 3.46−3.52 (m, 1 H), 3.09 (bs, 2 H), 1.83−1.86 (m, 1 H), 1.58-1.65 (m, 3 H), 1.40−1.57 (m, 3 H), 1.32−1.38 (m, 2 H), 1.29 (s, 3 H), 0.95 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 150.28, 111.45, 72.43, 63.62, 53.41, 42.84, 42.19, 39.44, 29.15, 24.19, 20.13, 16.92; IR (KBr) 3000−3400 (br), 2920 cm^{-1}; CIMS *m*/*z* (relative intensity) 199 (M^+ + 1, 7), 181 (100), 163 (31), 137 (21); $[\alpha]^{26}_D$ −18.0° (*c* 2.44, $CHCl_3$).

Anal. Calcd for $C_{12}H_{22}O_2$: C, 72.68; H, 11.18. Found: C, 72.41; H, 11.06.

(3a*R*,4*R*,7a*R*)-4,7a-Dimethyl-3a,4,5,6,7,7a-hexahydro-4-ethenylbenzofuran-2(3*H*)-one. (+)-Epianastrephin (1). Solid tetrapropylammonium perruthenate(VII) (TPAP, 3.5 mg, 10 mol %) was added to a solution of **12b** (20 mg, 0.10 mmol) and 4-methylmorpholine *N*-oxide (NMO, 31 mg, 2.5 equiv) in CH_2Cl_2 (1 mL) and CH_3CN (0.5 mL). After being stirred at room temperature for 40 min, the solvent was evaporated and the residue was flash chromatographed (hexane/ethyl acetate, 4:1) to provide (+)-epianastrephin (**1**) (13 mg, 68%) as a white solid: ^{1}H NMR ($CDCl_3$) δ 5.68 (dd, J = 17.6, 11.5 Hz, 1 H), 4.98 (dd, J = 11.5, 1.0 Hz, 1 H), 4.95 (dd, J = 17.6, 1.0 Hz, 1 H), 2.38 (dd, J = 16.4, 14.7 Hz, 1 H), 2.24 (dd, J = 16.5, 6.5 Hz, 1 H), 2.10 (dd, J = 14.9, 6.6 Hz, 1 H), 2.00−2.03 (m, 1 H),



1.81−1.87 (m, 1 H), 1.59−1.70 (m, 2 H), 1.52−1.58 (m, 1 H), 1.42−1.50 (m, 1 H), 1.38 (s, 3 H), 1.06 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 176.17, 147.76, 111.63, 86.04, 53.46, 38.46, 37.91, 37.01, 29.46, 20.88, 20.42, 16.35; $[\alpha]^{25}_D$ +69.8° (*c* 0.80, hexanes); (lit.[6e] $[\alpha]^{25}_D$ +87.9° (*c* 0.27, *n*-hexane; (lit.[6b] $[\alpha]^{25}_D$ +74.7° (*c* 4, hexanes)).

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