Enantiospecific Synthesis of the Proposed Structure of the Antitubercular Marine Diterpenoid Pseudopteroxazole: Revision of Stereochemistry

Ted W. Johnson and E. J. Corey*

Contribution from the Department of Chemistry and Chemical Biology, Harvard University, Cambridge, Massachusetts, 02138

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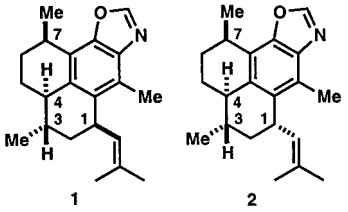
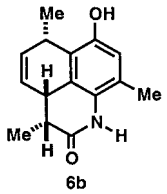
Abstract: An enantiospecific synthesis of structure **1**, previously assigned to the antitubercular marine natural product pseudopteroxazole, has been accomplished as outlined in Scheme 1. Coupling of diene acid **3** and amino phenol **4** produced the amide **5**, which was subjected to a novel oxidative intramolecular Diels−Alder reaction to generate the tricyclic lactam **6a** stereoselectively. This product was transformed via intermediates **7**−**11** into the diene **13**. Cationic cyclization of **13** afforded two diastereomeric tricyclic amphilectanes which were separated and transformed by parallel four-step sequences into **1** and **2**, respectively. Neither **1** nor **2** were identical with pseudopteroxazole, indicating a need for revision of the structure, probably to **16**.

Since the pioneering work of W. Fenical and his group on the isolation, structure, and bioactivity of the pseudopterosins,[1,2] a number of other members of this family of marine natural products, the amphilectane group, have been discovered,[3] including pseudopteroxazole (assigned structure **1**), which was found to be a potent inhibitor of *Mycobacterium tuberculosis* H37Rv.[4] The unexpected antitubercular activity of pseudopteroxazole and its novel structure prompted us to undertake a total synthesis using a stereocontrolled, biomimetic cyclization process that was previously developed for the total synthesis of pseudopterosins.[5,6] Because this synthetic approach also allows variation of configuration at C(1) in the final stages of synthesis, it also offered a route to **2**, the C(1)-diastereomer of



1. We report herein the total synthesis of **1** and **2** and the demonstration that each of these structures is different from natural pseudopteroxazole, thus necessitating structural revision of the latter. These results and previous studies leading to the revision of the stereochemistry of pseudopterosins G−J and helioporin E[7] have allowed a reassignment of structure to pseudopteroxazole.

The synthetic pathway to **1** and **2** is outlined in Scheme 1. Coupling of the (*R*)-carboxylic acid **3**[8] with the amino phenol **4** (Aldrich) using dicyclohexylcarbodiimide and 1-hydroxybenzotriazole as reagents provided diene amide **5** cleanly. Treatment of **5** with 2 equiv of lead tetraacetate in ethyl acetate at room temperature generated the corresponding quinone monoimide[9] that underwent internal Diels−Alder addition as it was formed to give the endo adduct **6a** in 69% isolated yield along with a small amount of the diastereomeric adduct **6b** (ratio **6a**: **6b** =



8:1) after silica gel chromatography with a flash column. The

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(3) (a) Tanaka, J.-i.; Ogawa, N.; Liang, J.; Higa, T.; Gravalos, D. G. *Tetrahedron* **1993**, *49*, 811. (b) Geller, T.; Schmalz, H.-G.; Bats, J. W. *Tetrahedron Lett.* **1998**, *39*, 1537. (c) Hörstermann, D.; Schmalz, H.-G.; Kociok-Köhn, G. *Tetrahedron* **1999**, *55*, 6905. (d) Rodríguez, A. D.; González, E.; Huang, S. D. *J. Org. Chem.* **1998**, *63*, 7083.

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(7) Lazerwith, S. E.; Johnson, T. W.; Corey, E. J. *Org. Lett.* **2000**, *2*, 2389.

(8) The (*R*)-acid **3** was synthesized starting with (*R*)-2-methyl-3-*tert*-butylsilyloxypropionaldehyde (see: Burke, S. D.; Cobb, J. E.; Takeuchi, K. *J. Org. Chem.* **1990**, *55*, 2138) by the following sequence: (1) Wittig coupling with lithio (*E*)-2-butenyldiphenylphosphine oxide (Binns, M. R.; Haynes, R. K.; Katsifis, A. G.; Schober, P. A.; Vonwiller, S. C. *J. Am. Chem. Soc.* **1988**, *110*, 5411) by the method of Lythgoe et al. (Lythgoe, B.; Moran, T. A.; Nambudiry, M. E. N.; Ruston, S. *J. Chem. Soc., Perkin Trans. 1* **1976**, 2386) to form the (*E,E*)-diene; (2) TBS cleavage with $Bu_4N^+F^-$ in THF at 23 °C; and (3) Jones oxidation with chromic acid and sulfuric acid in acetone.

(9) Fernando, C. R.; Calder, I. C.; Ham, K. N. *J. Med. Chem.* **1980**, *23*, 1153.

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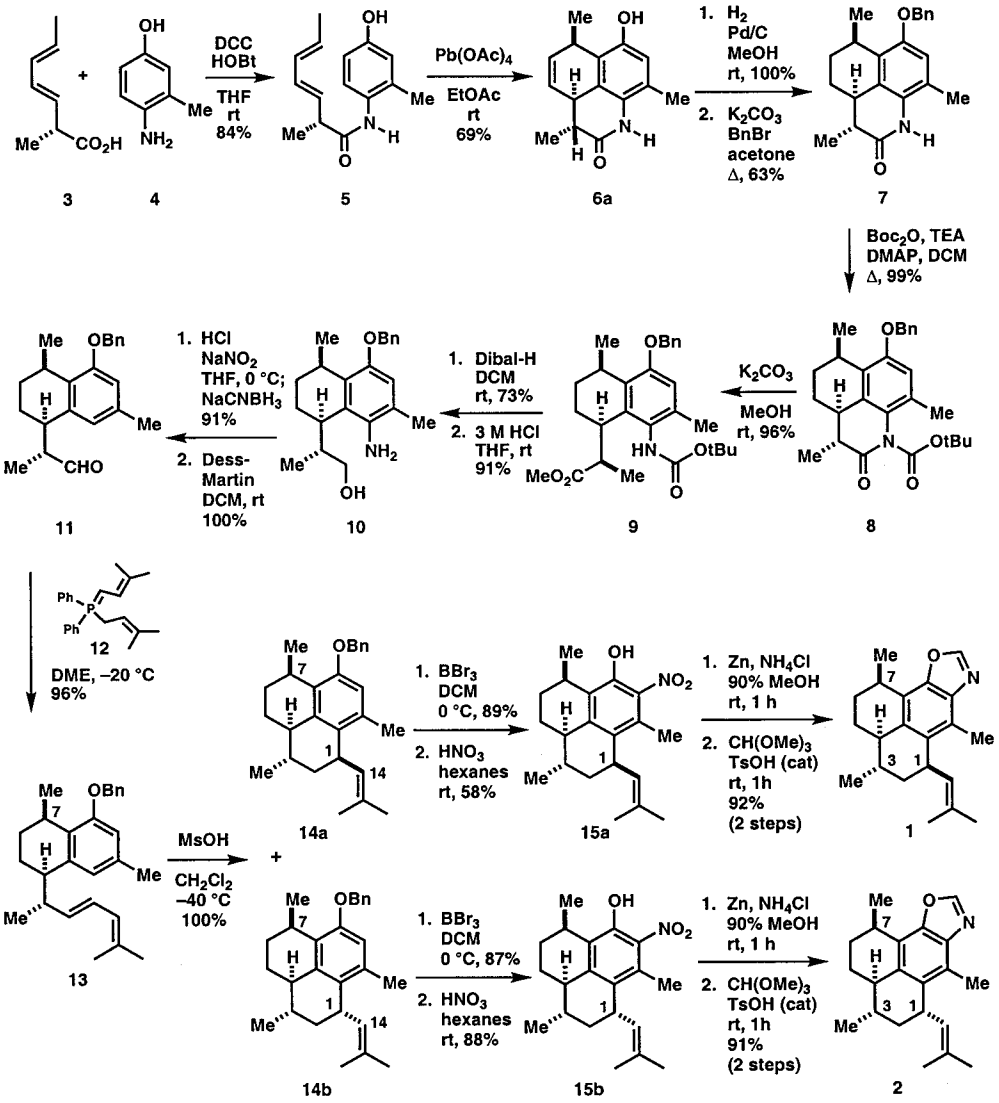
Scheme 1



relative stereochemistry of the diastereomers **6a** and **6b** at the carbons α and β to the lactam carbonyl was apparent from the ^{1}H NMR spectra. The trans diaxial arrangement of H_α and H_β in **6a** was indicated by a 14 Hz coupling constant as compared to a value $J_{\alpha\beta}$ = ca. 5 Hz for diastereomer **6b**. Sequential hydrogenation of **6a** at 1 atm of H_2 in MeOH at 23 °C and benzylation (K_2CO_3 and BnBr in acetone at reflux) produced benzyl ether **7** in 63% overall yield. Conversion of **7** to the *N-tert*-butoxycarbonyl derivative **8** and methanolysis of the resulting δ-lactam subunit afforded the methyl ester **9** in high yield. Reduction of the ester function of **9** with diisobutylaluminum hydride in dichloromethane and subsequent cleavage of the *tert*-butoxycarbonyl group provided the amino alcohol **10** in good yield.

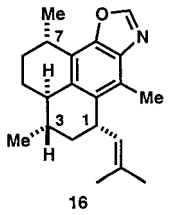
Replacement of the amino group in **10** by hydrogen, the next synthetic objective of the plan summarized in Scheme 1, proved to be problematic using conventional methodology. However, it was discovered that conversion of **10** to the corresponding diazonium salt followed by reduction with sodium cyanoborohydride at 0 °C effected the required reductive deamination in very good yield. Sodium cyanoborohydride can be recommended for such deaminations. Oxidation of the resulting primary alcohol with the Dess−Martin periodinane reagent afforded aldehyde **11** quantitatively. Wittig coupling of **11** with phosphonium ylide **12**[10,11] was stereospecific and gave the (*E*)-conjugated diene **13** in 96% yield. Cationic cyclization of **13** was effected using methanesulfonic acid as catalyst in CH_2Cl_2 at −40 °C, a process applied earlier to the synthesis of pseudopterosins.[5] From previous results it had been expected that the cyclization of the allylic cation from **13** would proceed by the Ar-1,6 pathway to form the (1*R*)-diastereomer **14a**.[5] In fact, although the cyclization proceeded quantitatively, the product was a mixture of diastereomers **14a** and **14b** in a ratio of about 1:2 (for discussion, see below). The mixture was separated chromatographically on a Chiralcel OD column and the individual diastereomers were converted by parallel processes to the isomeric pseudopteroxazole structures **1** and **2**. The assignment of configuration to the C(1)-diastereomers **14a** and **14b** was made from the ^{1}H NMR spectra by comparison with the corresponding C(1)-diastereomers of the pseudopterosins[5] and using the detailed analysis recently published.[7] In the case of **14a**, the vinyl proton attached to C(14) appeared at δ 5.13 as a broadened doublet, J = 9.2 Hz. In the case of **14b**, the vinyl proton attached to C(14) appeared further upfield at δ 5.00 as a broadened doublet, J = 9.2 Hz. For **14a**, the allylic proton attached to C(1) appeared at δ 3.64 as a broadened doublet, J = 9.2 Hz, due to coupling with the vicinal vinyl proton and broadening from small couplings to the C(2)

(10) Cristau, H.-J.; Ribeill, Y. *Synthesis* **1988**, 911.
(11) Vedejs, E.; Fang, H. W. *J. Org. Chem.* **1984**, *49*, 210.

methylene protons. For **14b** the C(1) allylic proton showed up at δ 3.79 as a doublet of doublets of doublets, $J = 9.2, 9.2, 9.2$ Hz, from coupling to the vicinal vinyl proton ($J = 9.2$ Hz) and the vicinal protons at C(2). These data for **14a** and **14b** are remarkably similar to those for A type pseudopterosin structures on one hand and their C(1)-diastereomers on the other.[5,7]

The transformation of **14a** into **1** was then accomplished by a sequence of four steps, as shown in Scheme 1. The tricyclic benzyl ether **14a** was subjected to benzyl ether cleavage (BBr_3 in CH_2Cl_2 at 0 °C) and then nitrated (HNO_3 in hexanes[12]) to form the nitro phenol **15a**. Treatment of **15a** with Zn dust and NH_4Cl in CH_3OH at 23 °C for 1 h[13] effected conversion to the corresponding amino phenol which upon reaction with methyl orthoformate and a catalytic amount of 4-toluenesulfonic acid at 23 °C for 1 h[14] gave the desired tetracyclic oxazole **1** in 92% yield over the two steps. In a parallel series of experiments starting with benzyl ether **14b** the tetracyclic oxazole **2** was produced (see Supporting Information).

Comparison of the spectral data for pseudopteroxazole[4,15] with those for synthetic **1** and **2** showed that all these compounds differ. It is clear that the stereochemistry of pseudopteroxazole must be revised from that assigned **1**,[4] as we had previously surmised.[7] It now seems that pseudopteroxazole probably is best represented by structure **16**, in common with other synthetic[5]



16

and naturally occurring amphilectanes.[7] The synthesis of **16** is now in progress in our laboratories. If pseudopteroxazole is found to have structure **16**, it would then reside in the same stereochemical family with pseudopterosins G−J and helioporin E. Further, all the pseudopterosins, e.g. A−E type and G−J type, would be unified biosynthetically as originating from serrulatane (seco pseudopterosin) precursors by ring closure, which connects C(1) to the benzenoid ring.

Two aspects of the above-described synthesis of **1** and **2** deserve comment: (1) the diastereoselective intramolecular Diels−Alder reaction to form **6a** and **6b** in a ratio of 8:1 and (2) the cationic ring closure **13** → **14a** + **14b**. With regard to the former, it should be noted that the cyclization **5** → **6** appears to be the first example of this type of internal cycloaddition involving an in situ generated quinone imide. The diastereoselectivity favoring **6a** over **6b** is readily understood in terms of an endo transition state for the internal Diels−Alder process, even though the structures of the reaction products **6a** and **6b** provide no information with regard to endo vs exo pathways. The endo transition state leading to **6a** involves no adverse steric factors, whereas that leading to **6b** involves a significant repulsion between the methyl substituent on the C(3) stereocenter and the olefinic hydrogen at C(5) (pseudopterosin numbering, see Figure 1). Since the endo pathway is normally preferred for Diels−Alder reactions with quinoid dienophiles

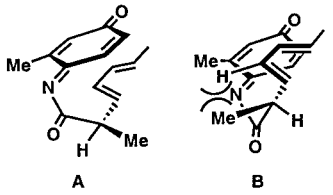


Figure 1. (A) Pre-transition state assembly (endo) leading to **6a**. (B) Pre-transition state assembly (endo) leading to **6b**.

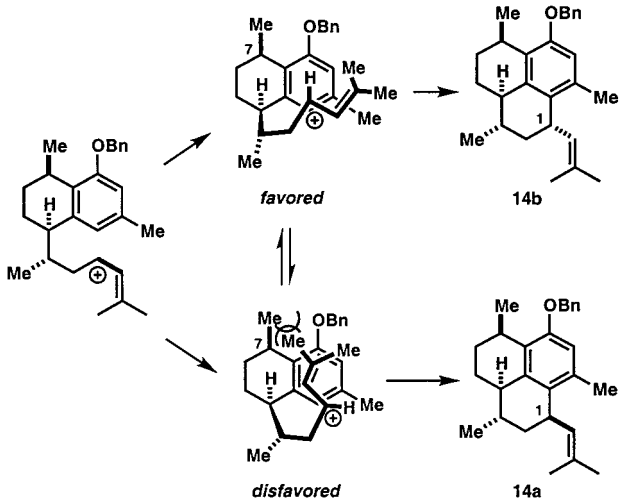
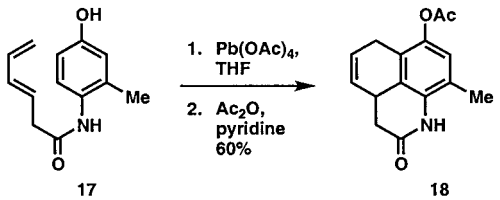


Figure 2. Steric repulsion involving the C(7)-methyl substituent disfavoring formation of **14a** relative to **14b** during the cationic cyclization of **13**.

(because of secondary orbital interactions), and since there do not appear to be any special steric factors favoring an exo transition state,[16] the endo transition states in Figure 1 seem probable for the reaction **5** → **6**.

The cationic ring closure **13** → **14a** + **14b** is far less diastereoselective than the corresponding Ar-1,6 ring closure in the pseudopterosin A series.[5] One obvious explanation for this difference is the orientation of the methyl group attached to C(7). In the cationic cyclization of **13**, that methyl substituent disfavors formation of **14a** relative to **14b** because of steric interference with the *E*-methyl part of the isopropylidene group during ring closure to form **14a**. Such repulsions are clearly absent for the Ar-1,6 cyclization of the C(7) diastereomeric series. The two Ar-1,6-pathways leading to **14a** and **14b** are shown in Figure 2.

The oxidative intramolecular Diels−Alder reaction utilized for the construction of **6a** (Scheme 1) is potentially widely useful. We have demonstrated the prototype reaction for the synthesis of **18** from **17**. The oxidative cyclization occurs rapidly and cleanly with $Pb(OAc)_4$ in THF at 23 °C to give in good yield after acetylation the bicyclic acetate **18**. The oxidant $Pb(OAc)_4$ is superior to $C_6H_5I(OAc)_2$. A number of other oxidants were found to be unsatisfactory, including Ag_2CO_3, Ag_2O, MnO_2, and chloranil.



17 **18**

(12) Wiedenau, P.; Monse, B.; Blechert, S. *Tetrahedron* **1995**, *51*, 1167.

(13) Evans, D.; Smith, C. E.; Williamson, W. R. N. *J. Med. Chem.* **1977**, *20*, 169.

(14) (a) Katritzky, A. R.; Musgrave, R. P.; Rachwal, B.; Zaklika, C. *Heterocycles* **1995**, *41*, 345. (b) Nakahara, Y.; Fujita, A.; Beppu, K.; Ogawa, T. *Tetrahedron* **1986**, *42*, 6465.

(15) We are grateful to Prof. A. D. Rodríguez for data on pseudopteroxazole.

(16) See: Ge, M.; Stoltz, B. M.; Corey, E. J. *Org. Lett.* **2000**, *2*, 1927.

In summary, the structure previously assigned to pseudopteroxazole has been synthesized, compelling revision of structure and consideration of the alternative formulation **16**.

Experimental Section

Diels−Alder Reaction of 5. To a stirred solution of the amide **5** (0.320 g, 1.304 mmol) in ethyl acetate (10 mL) at 25 °C was added lead tetraacetate (1.157 g, 2.609 mmol) and the reaction was stirred vigorously for 5 min. Sodium bicarbonate (5%) was added and the solution was extracted with ethyl acetate (2 × 10 mL). The combined organic layers were washed again with 5% sodium bicarbonate, dried over sodium sulfate, and filtered. Nitrogen was bubbled through the solution for 5 min, and the flask was capped and left to sit for 18 h. The solution was concentrated and proton NMR spectroscopy showed an approximate 8:1 mixture of the cycloadducts **6a** and **6b**, respectively. Flash column chromatography (silica gel, 2:1:1 hexanes−ethyl acetate−chloroform then 1:1:1 hexanes−ethyl acetate−chloroform) provided the major Diels−Alder product **6a** (0.218 g, 69%), which showed a large (14.0 Hz) coupling between the protons α and β to the lactam carbonyl and the diastereomeric minor cycloadduct **6b**, which displayed only a small coupling ($J \leq 5$ Hz) between the protons α and β to the lactam carbonyl. Data for **6a**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.44 (1H, bs, N−H), 6.52 (1H, s), 5.90 (1H, m), 5.84 (1H, m), 5.19 (1H, bs, O−H), 3.52 (1H, m), 3.18 (1H, bd, $J = 14.0$ Hz), 2.29 (1H, sextet, $J = 7.2$ Hz), 2.15 (3H, s), 1.41 (3H, d, $J = 5.6$ Hz), 1.34 (3H, d, $J = 5.2$ Hz). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 174.11, 148.84, 132.72, 127.62, 123.27, 122.59, 121.20, 120.53, 115.65, 40.67, 37.43, 29.38, 22.82, 16.43, 11.62. Data for **6b**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.24 (1H, bs), 6.51 (1H, s), 5.98 (1H, m), 5.59 (1H, m), 3.77 (1H, m), 3.57 (1H, m, $J \leq 5$ Hz), 2.77 (1H, m), 2.18 (3H, s), 1.34 (1H, d, $J = 5.6$ Hz), 0.96 (3H, d, $J = 6.0$ Hz).

Reductive Deamination of 10. To a stirred solution of the aniline **10** (0.058 g, 0.171 mmol) in THF (5 mL) at 0 °C was added 1.0 M aqueous HCl (0.531 mL, 0.531 mmol) followed by 1.0 M aqueous $NaNO_2$ (0.342 mL, 0.342 mmol) and the mixture was stirred at 0 °C for 40 min. A freshly prepared 1.0 M solution of sodium cyanoborohydride in water (1.709 mL, 1.709 mmol) was added dropwise and the solution was stirred for 1 h at 0 °C and then overnight at 25 °C. Water was added and the mixture was extracted with ether (3 × 5 mL). The combined organic extracts were dried over magnesium sulfate, filtered, and concentrated under reduced pressure to give the crude reduced aromatic. Flash column chromatography (silica gel, 5:1 hexanes−ethyl acetate) provided the deamination product (0.050 g, 91%) as a clear syrup. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.60−7.30 (5H, m), 6.80 (1H, s), 6.63 (1H, s), 5.12 (1H, d, $J = 11.6$ Hz), 5.05 (1H, d, $J = 11.6$ Hz), 3.75 (1H, dd, $J = 10.8$, 7.2 Hz), 3.66 (1H, dd, $J = 10.0$, 7.2 Hz), 3.30 (1H, m), 3.09 (1H, m), 2.51 (1H, m), 2.34 (3H, s), 1.90−1.50 (4H, m), 1.27 (3H, d, $J = 7.2$ Hz), 0.76 (3H, d, $J = 6.8$ Hz). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 155.93, 139.68, 137.53, 135.39, 129.47, 128.28, 127.41, 126.81, 120.03, 109.00, 69.51, 66.65, 39.08, 38.44, 28.76, 26.44, 21.78, 20.77, 17.38, 11.44. IR (thin film) 3363, 2923, 2870, 1578, 1454, 1272 cm^{-1}. High-resolution MS (EI, *m*/*z*) 324.2090, calcd for $[C_{22}H_{28}O_2]^+$ 324.2094. $[\alpha]^{20}_D$ +39.0 (*c* 0.6, $CHCl_3$).

Aldehyde 11. To a stirred solution of the reduced aromatic alcohol (0.0125 g, 0.0385 mmol) in dichloromethane at 25 °C was added Dess−Martin periodinane (0.020 g, 0.0462 mmol) and the mixture was stirred for 0.5 h. The cloudy mixture suspension was concentrated under reduced pressure and passed through a short plug of silica gel, eluting with 10:1 hexanes−ethyl acetate to provide aldehyde **11** (0.0124 g, 100%) as a clear, thick oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.87 (1H, s), 7.60−7.30 (5H, m), 6.71 (1H, s), 6.62 (1H, s), 5.10 (1H, d, $J = 12.0$ Hz), 5.03 (1H, d, $J = 12.0$ Hz), 3.51 (1H, m), 3.27 (1H, m), 3.14 (1H, m), 2.32 (3H, s), 1.90−1.60 (3H, m), 1.45 (1H, m), 1.23 (3H, d, $J = 6.8$ Hz), 0.96 (3H, d, $J = 7.2$ Hz). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 205.08, 156.18, 137.37, 137.26, 135.82, 129.82, 128.36, 127.53, 126.85, 119.40, 109.59, 69.61, 50.18, 37.91, 28.80, 26.41, 21.81, 20.77, 18.83.

Diene 13. To a stirred solution of bis(3-methyl-2-butenyl)diphenylphosphonium bromide[9,10] (0.259 g, 0.642 mmol, azeotroped with benzene) in DME (5 mL) at 0 °C was added potassium *tert*-butoxide (0.642 mL, 0.642 mmol, 1.0 M solution in THF) and the mixture was stirred at 0 °C for 0.5 h. The solution was cooled to −20 °C and a solution of the aldehyde **11** (0.069 g, 0.214 mmol) in DME (1 mL) was added dropwise. The solution was stirred at −20 °C for 0.5 h and then quenched with saturated ammonium chloride solution and extracted with ether (3 × 5 mL). The combined organic extracts were dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The crude material was taken up in 20:1 hexanes−ethyl acetate and passed through a short plug of silica gel, eluting with 20:1 hexanes−ether to provide the pure diene **13** (0.077 g, 96%) as a clear glass. None of the cis diene was detectable in the proton NMR spectrum. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.60−7.30 (5H, m), 6.85 (1H, s), 6.62 (1H, s), 6.37 (1H, dd, $J = 15.2$, 10.8 Hz), 5.90 (1H, d, $J = 10.4$ Hz), 5.77 (1H, dd, $J = 15.6$, 7.2 Hz), 5.13 (1H, d, $J = 11.6$ Hz), 5.05 (1H, d, $J = 11.6$ Hz), 3.29 (1H, m), 3.21 (1H, m), 2.97 (1H, m), 2.36 (3H, m), 1.90−1.50 (4H, m), 1.82 (6H, s), 1.26 (3H, d, $J = 6.8$ Hz), 0.87 (3H, d, $J = 6.4$ Hz). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 156.35, 139.93, 137.97, 137.03, 135.70, 133.31, 130.01, 128.66, 127.77, 127.18, 125.62, 125.44, 120.41, 109.37, 69.86, 43.34, 39.92, 29.41, 26.92, 26.32, 22.08, 20.92, 18.67, 18.00, 13.67. IR (thin film) 2961, 2870, 1611, 1578 cm^{-1}. High-resolution MS (EI, *m*/*z*) 374.2599, calcd for $[C_{27}H_{34}O]^+$ 374.2610. $[\alpha]^{20}_D$ +1.6 (*c* 0.70, $CHCl_3$).

Cationic Cyclization of 13 to 14a and 14b. To a stirred solution of the diene **13** (0.032 g, 0.085 mmol) in dichloromethane (8 mL) at −78 °C was added a 1.0 M solution of methanesulfonic acid in dichloromethane (85 μL, 0.085 mmol). The mixture was warmed to −40 °C and stirred for 10 h. The solution was quenched with triethylamine (118 μL, 0.850 mmol) and passed through a plug of silica gel, eluting with 20:1 hexanes−ether. Concentration under reduced pressure gave the tricyclic product **14a** and the diastereomeric tricycle **14b** (0.032 g, approximate 1:2 ratio), which could be separated by preparative HPLC (Chiralcel OD column, 100% hexanes, elution times: 15 min for **14b** and 20 min for **14a**). Data for **14a**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.60−7.30 (5H, m), 6.62 (1H, s), 5.13 (1H, bd, $J = 9.2$ Hz), 5.06 (1H, d, $J = 11.6$ Hz), 5.02 (1H, d, $J = 11.6$ Hz), 3.64 (1H, bd, $J = 9.2$ Hz), 3.35 (1H, quintet, $J = 6.4$ Hz), 2.13 (3H, s), 2.10 (1H, m), 1.98 (1H, m), 1.94−1.60 (5H, m), 1.74 (3H, s), 1.66 (3H, s), 1.50 (1H, m), 1.22 (3H, d, $J = 7.2$ Hz), 1.03 (3H, d, $J = 4.8$ Hz). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 154.07, 137.89, 136.33, 134.56, 130.71, 130.27, 128.87, 128.35, 128.16, 127.43, 126.88, 111.52, 69.61, 46.51, 40.82, 35.41, 30.79, 29.60, 27.49, 25.69, 22.83, 22.43, 20.86, 19.79, 17.72. IR (thin film) 2948, 2844, 2922, 2863, 1455, 1322 cm^{-1}. High-resolution MS (EI, *m*/*z*) 392.2946, calcd for $[C_{27}H_{34}O + NH_4]^+$ 392.2952. $[\alpha]^{20}_D$ −116.6 (*c* 0.63, $CHCl_3$). Data for **14b**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.60−7.30 (5H, m), 6.63 (1H, s), 5.07 (1H, d, $J = 12.0$ Hz), 5.02 (1H, d, $J = 12.0$ Hz), 5.00 (1H, bd, $J = 9.2$ Hz), 3.79 (1H, ddd, $J = 9.2$, 9.2, 9.2 Hz), 3.31 (1H, quintet, $J = 6.4$ Hz), 2.30−2.10 (2H, m), 2.17 (3H, s), 1.98 (1H, m), 1.90−1.70 (2H, m), 1.73 (3H, s), 1.66 (3H, s), 1.50−1.30 (2H, m), 1.30−1.20 (1H, m), 1.25 (3H, d, $J = 6.4$ Hz), 1.04 (3H, d, $J = 6.4$ Hz). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 154.00, 138.32, 137.88, 134.64, 130.84, 130.67, 128.34, 128.26, 127.57, 127.42, 126.87, 111.57, 69.58, 43.46, 39.98, 35.35, 34.84, 29.57, 27.17, 25.56, 22.88, 21.51, 20.48, 20.16, 17.67. IR (thin film) 2950, 2921, 2862, 1594, 1454 cm^{-1}. High-resolution MS (EI, *m*/*z*) 392.2956, calcd for $[C_{27}H_{34}O + NH_4]^+$ 392.2952. $[\alpha]^{20}_D$ +59.3 (*c* 0.85, $CHCl_3$). For a discussion of stereochemical assignments based on the ^{1}H NMR data, see ref 7.

Benzoxazole 1. To a stirred solution of the *o*-nitrophenol **15a** (0.0040 g, 0.012 mmol) in 90% methanol (2 mL) at 25 °C was added solid ammonium chloride (2 mg, 0.036 mmol) followed by zinc dust (8 mg, 0.121 mmol) and the solution was stirred for 1 h at room temperature.[13] The mixture was filtered through Celite, rinsing with methanol. The solution was concentrated under reduced pressure, water was added, and the mixture was extracted with diethyl ether (3 × 2 mL). The combined organic extracts were dried over sodium sulfate, filtered, and concentrated under reduced pressure to yield the *o*-aminophenol (0.004 g), which was used directly in the next step without further purification. The *o*-aminophenol from the previous step was dissolved in trimethyl orthoformate and one drop of a toluenesulfonic acid monohydrate solution in trimethyl orthoformate (4 mg/0.5 mL) was added and the solution was stirred at 25 °C for 1 h.[14] The solvent was removed under

reduced pressure and residual amounts of solvent were removed by azeotroping with benzene. Flash column chromatography (silica gel, 5:1 hexanes−ether) provided the pure benzoxazole **1** (0.0034 g, 92% two steps) as a clear, thick oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.97 (1H, s), 5.09 (1H, bd, J = 9.2 Hz), 3.84 (1H, bd, J = 9.2 Hz), 3.39 (1H, quintet, J = 6.4 Hz), 2.40 (3H, s), 2.19 (1H, m), 2.10 (1H, m), 1.98 (1H, m), 1.79 (3H, d, J = 1.6 Hz), 1.67 (3H, d, J = 1.6 Hz), 1.49 (1H, m), 1.36 (3H, d, J = 7.2 Hz), 1.07 (3H, d, J = 5.6 Hz), 1.90−1.58 (4H, m). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 151.14, 146.82, 137.56, 134.41, 133.37, 130.14, 129.49, 126.12, 122.74, 46.03, 40.47, 35.70, 30.28, 29.51, 28.25, 25.61, 23.18, 22.47, 20.69, 17.68, 12.60. IR (thin film) 2959, 2950, 2824, 2871, 2862, 1523, 1464, 1445, 1376, 1078, 1051 cm^{-1}. High-resolution MS (EI, m/z) 310.2157, calcd for $[C_{21}H_{27}NO + H]^+$ 310.2169. $[\alpha]^{20}_D$ −158.2 (c 0.17, $CHCl_3$).

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Supporting Information Available: Experimental procedure for the synthesis of **15b** and **2** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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