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A Catalytic Enantioselective Hetero Diels–Alder Approach to the C20–C32 Segment of the Phorboxazoles

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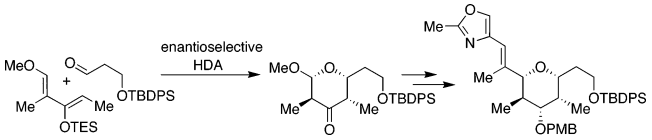

An efficient synthesis of the C20–C32 segment of the phorboxazoles has been achieved using an enantioselective hetero Diels–Alder reaction catalyzed by Jacobsen's Cr(III) amino indanol Schiff base catalyst.

Since the discovery of the cytotoxic macrolide phorboxazoles (Figure 1) by Molinski in 1995,[1] considerable effort has been directed toward their synthesis. In 1998, the first total synthesis of phorboxazole A was completed by Forsyth;[2] the subsequent total syntheses were performed by Evans (phorboxazole B),[3] Smith,[4] Pattenden,[5] and Williams.[6] The phorboxazoles have been the focus of numerous other efforts,[7] including our own recent approach to the C1–C17 segment of phorboxazole B.[8] Phorboxazole A and its C13 epimer, phorboxazole B, exhibit exceptional cytostatic activity; they have shown a mean GI_{50} value of $<1.6 \times 10^{-9}$ M in vitro against the NCI panel of 60 tumor cell lines.[9] In addition, the

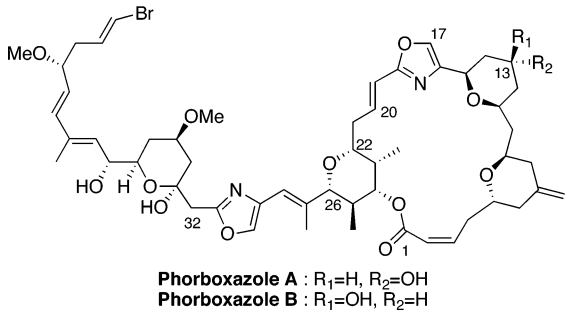

FIGURE 1. Phorboxazoles.

phorboxazoles are believed to operate by a unique mode of action: phorboxazole A induces S-phase arrest in Burkitt lymphoma cells yet shows no inhibition of tubulin polymerization or interference with microtubular stability.[9] From a synthetic standpoint, the phorboxazoles present an attractive challenge. They contain a number of interesting structural features, including 15 asymmetric centers, a 21-membered macrolactone, four diversely substituted tetrahydropyran rings, two oxazoles, and a vinyl bromide.

The most widely studied region of the phorboxazoles is the C22–C26 tetrahydropyran ring system. This highly-functionalized polypropionate segment features five contiguous asymmetric centers and has been a showcase for various methods of polypropionate and tetrahydropyan synthesis. Thus far, all approaches have been dependent on stoichiometric amounts of a chiral source which may be chiral starting materials, auxiliaries, or reagents. Our retrosynthetic analysis for a catalytic enantioselective approach to this region is shown in Scheme 1. Disconnection at the C27–C28 olefin in **1** is a strategy first used by Pattenden[5b] and most recently employed by Zhou.[7a] We noted that the stereochemistry at C26 in **2** could be ignored initially because the acidity of the C26 proton should allow for base-catalyzed epimerization to the more stable desired equatorial methyl ketone.[10] Therefore, it was hoped that

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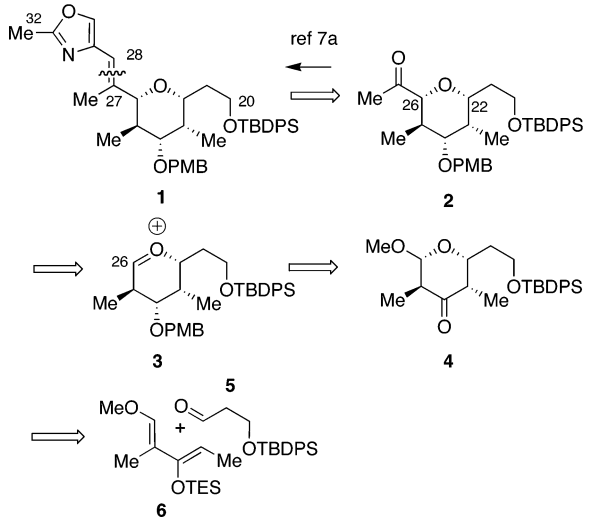
SCHEME 1. C20−C32 Retrosynthesis



trapping of a C26 oxonium ion **3** with an acyl anion equivalent would give the desired tetrahydropyran **2**. The oxonium ion **3** would arise from the methyl glycoside **4**, available from a catalytic enantioselective hetero Diels−Alder reaction between aldehyde **5**[11] and Danishefsky diene **6**.[12]

Our forward synthesis of the C20−C27 subunit of the phorboxazoles is shown in Scheme 2. The combination of the high enantioselectivity of Jacobsen's chromium(III) Schiff base catalyst **7a**[13] (Figure 2) with the reactivity of Danishefsky's siloxy diene **6** produced the intermediate cyclic silyl enol ether **8** in less than 3 h using 5 mol % **7a**; normal catalyst loadings of 2 mol % **7a** were typically allowed to stir overnight to ensure complete reaction. Although the tenuously stable vinylogous ortho ester **8** can be isolated and purified by silica gel chromatography, we found it advantageous to directly affect axial protonation of the enol ether[12,14] setting the C25 methyl group equatorial and producing ketone **4** in a 77% yield. Chiral HPLC analysis indicated that ketone **4** obtained with catalyst **7a** had an enantiomeric excess of 91%.[15] Our attempts at improving the enantiomeric excess at this stage met with no success: lowering the temperature to 0 °C produced an identical ee, as did the use of catalyst **7b** which contains the SbF_6^- counterion.

However, after the ketone was reduced to equatorial alcohol **9** using sodium borohydride, the product could be recrystallized from boiling hexanes to produce crystalline **9** in a 98.5% ee.[15] This material was protected as the PMB ether **10** and carried on to the key C26 carbon−carbon bond-forming event. After considerable experimentation, we were able to install a C26 nitrile by

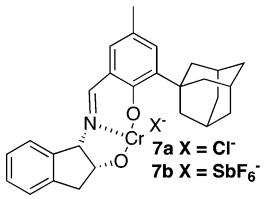
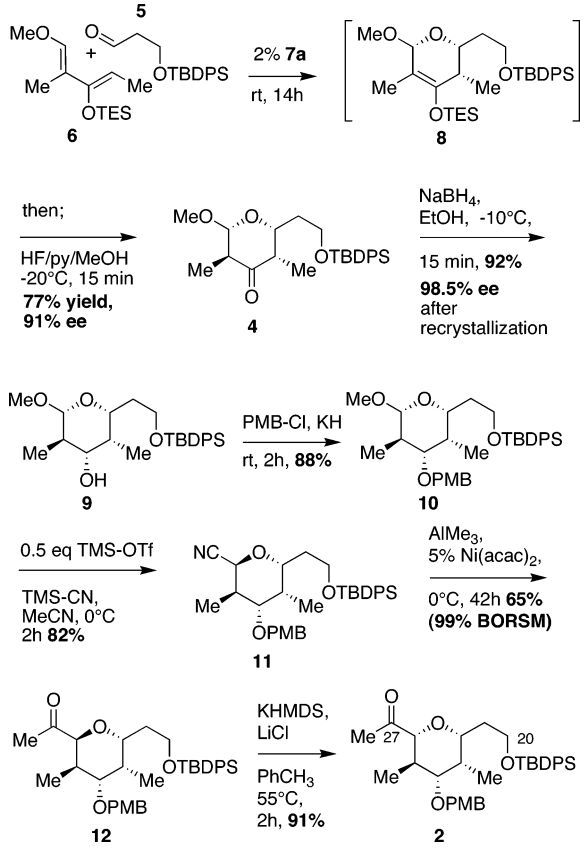


FIGURE 2. Jacobsen hetero Diels−Alder catalysts.

SCHEME 2. Synthesis of the C20−C27 Subunit



treatment of methyl glycoside **10** with TMS-CN/TMS-OTf at 0 °C in MeCN to produce axial nitrile **11**. We were encouraged at this stage because the two steps needed to complete our synthesis of **2**, namely, conversion of nitrile **11** to axial methyl ketone **12** and epimerization to **2**, have precedents, set by Hoffmann,[10] in a closely related system. Unfortunately, both of these steps proved to be problematic in our case. Hoffman's conditions for the methylation of the nitrile (MeMgBr/sonication/15 h) did produce **12** but in a low yield (∼30%) with significant decomposition and unreacted starting material. $AlMe_3$ and catalytic $Ni(acac)_2$[16] proved to be superior for our substrate, providing a 65% yield of **12** after 48 h. Although the reaction was difficult to force to completion, these conditions provided a near-quantitative recovery of the unreacted **11** to give a 99% yield of **12**; the yield was based on recovered starting material (BORSM). The axial methyl ketone **12** proved surprisingly resistant to epimerization under mildly basic conditions, including Hoffmann's method (DBU/CH_2Cl_2/reflux/48 h), triethyl-

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(15) The enantiomeric excess of **4** and **9** was determined by synthesis of *ent*-**4** and *ent*-**9** from catalyst *ent*-**7a** and injection against a standardized mixture of the enantiomers on a Chiralcel OD HPLC column.
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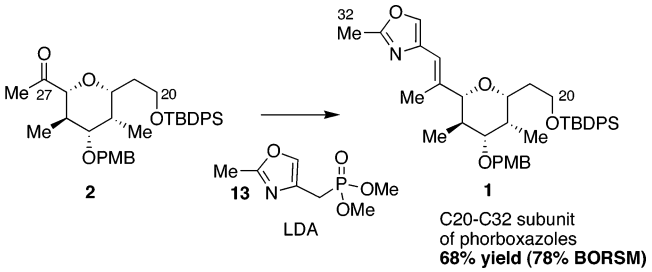
SCHEME 3. Synthesis of the C20−C32 Subunit



amine (EtOH/rt/48 h), and LDA (THF/0 °C/4 h), none of which produced any epimerization that could be detected by ^{1}H NMR analysis. Epimerization to **2** was ultimately accomplished in a 91% yield using LiCl and substoichiometric amounts of KHMDS in toluene at 55 °C. With equatorial methyl ketone **2** in hand, we intersected a known intermediate in Zhou's efforts toward the synthesis of the phorboxazoles.[7a] Installation of the oxazole moiety (Scheme 3) according to the method of Pattenden,[5a,b] as applied by Zhou,[7a] produced the fully elaborated C20−C32 subunit **1** in a 68% yield (78% BORSM) as expected. A comparison of the published ^{1}H and ^{13}C NMR spectra for **1** and **2** confirmed our structure assignments, and the identical signs of the optical rotation indicated that we had made the same enantiomers of these products, although the magnitudes of the specific rotations differed slightly (+31.4 vs +38[7a] for **1**, +72.3 vs +53.6[7a] for **2**).[17]

In summary, the synthesis of the C20−C32 phorboxazole subunit **1** was completed in 7 steps with a 20% overall yield (36% BORSM) from readily available starting materials which compares favorably to Zhou's synthesis of **1** [15 steps, 3.8% overall yield (4.8% BORSM)].[7a,c] Efficient introduction of the five contiguous asymmetric centers and requisite functionality of the C20−C32 subunit via a catalytic enantioselective hetero Diels−Alder reaction[13] was demonstrated, adding to the growing application of Jacobsen's catalyst to construct the phorboxazoles[7e,f] and other tetrahydropyran-containing natural products.

Experimental Section

Ketone 4. Jacobsen catalyst **7a**[13] (72 mg, 0.16 mmol, 0.025 equiv) and oven-dried 4 Å molecular sieves [powdered, 1.0 g (~150 mg of sieves/mmol of aldehyde)] were added with stirring to a round-bottom flask containing Danishefsky diene **6**[12] (1.70 g, 7 mmol, 1.1 equiv) and aldehyde **5**[11] (2.0 g, 6.4 mmol, 1.0 equiv). The reaction mixture was allowed to stir overnight under N_2. The intermediate silyl enol ether **8** was then diluted with dry methanol (40 mL) and transferred via cannula to a plastic reaction vessel containing 50% aq HF (2.5 mL), pyridine (38 mL), and dry MeOH (38 mL) at −15 °C. The mixture was stirred for 15 min, and then saturated $NaHCO_3$ (40 mL) was added (caution: gas evolution!) which was followed by the addition of solid $CaCO_3$ (2 g) (caution: additional gas evolution!). The mixture was filtered through Celite, and the filter cake was rinsed thoroughly with ether. H_2O (100 mL) and ether (200 mL) were added to the filtrate. The layers were separated, and the aqueous layer was extracted with ether (3 × 200 mL). The combined organic layers were washed with brine (50 mL), dried over K_2CO_3, filtered, and concentrated in vacuo to produce crude ketone **4**. Purification by column chromatography (10/1 hexanes/ether) gave 1.70 g (77.3% yield, 91% ee) of ketone **4** as a clear colorless oil. Data for **4**: HPLC (Chiracel OD-H, 0.3% 2-propanol in hexanes, flow rate 1 mL/min, observation taken at 230 nm) t_R = 7.4 min, t_R enantiomer = 8.8 min; R_f = 0.28 (9/1 hexanes/ethyl acetate); IR (thin film) 2933, 1717 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.05 (s, 9H), 1.06 (d, J = 6.8 Hz, 3H), 1.13 (d, J = 7.1 Hz, 3H), 1.70 (dddd, J = 14.1, 9.2, 5.9, 3.6 Hz, 1H), 1.92 (app ddt, J = 13.7, 9.0, 4.7 Hz, 1H), 2.36 (qd, J = 7.3, 2.7 Hz, 1H), 2.57 (dq, J = 8.6, 6.5 Hz, 1H), 3.75−3.87 (series of m, 3H), 4.01 (d, J = 8.5 Hz, 1H), 7.35−7.42 (series of m, 6H), 7.65−7.63 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 8.4 (CH_3), 11.2 (CH_3), 19.2 (C), 26.8 (CH_3), 34.3 (CH_2), 47.5 (CH), 48.5 (CH), 56.9 (CH_3), 60.0 (CH_2), 69.7 (CH), 106.6 (CH), 127.7 (CH), 129.7 (CH), 133.6 (C), 133.7 (C), 135.5 (CH), 211.3 (C); HRMS (MNa^+) calcd 463.2281, obsd 463.2283; optical rotation $[\alpha]^{21}_D$ = −6.0 (*c* 1.0, $CHCl_3$).

Equatorial Alcohol 9. Ketone **4** (970 mg, 2.2 mmol) was dissolved in anhydrous EtOH (22 mL) and cooled to −10 °C. Solid $NaBH_4$ (168 mg, 4.4 mmol, 2 equiv) was added in a single portion. The mixture was stirred for 15 min, and then saturated NH_4Cl (22 mL) was added which was followed by the addition of saturated $NaHCO_3$ (44 mL) and CH_2Cl_2 (200 mL). The aqueous layer was extracted with CH_2Cl_2 (4 × 100 mL), and the combined organic extracts were dried over $MgSO_4$, filtered, and concentrated in vacuo to produce crude **9**. Purification by column chromatography (8/2 hexanes/ethyl acetate) gave 890 mg (92% yield, 91% ee) of **9** as a white solid. Recrystallization of 170 mg of **9** from 10 mL of boiling hexanes gave, after the mixture was allowed to stand at room temperature for 1 day and −15 °C for 6 h, 152 mg (89% recovery) of white crystalline **9** (ee 98.5%). Data for **9**: mp 122−124 °C; HPLC (Chiracel OD-H, 1% 2-propanol in hexanes, flow rate 1 mL/min, observation taken at 230 nm) t_R = 11.7 min, t_R enantiomer = 13.7 min; R_f = 0.30 (7/3 hexanes/ethyl acetate); IR (ATR) 3580, 2945 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.90 (d, J = 6.8 Hz, 3H), 1.03 (d, J = 6.5 Hz, 3H), 1.05 (s, 9H), 1.45 (br s, 1H), 1.55 (ddq, J = 10.7, 8.3, 6.5 Hz, 1H), 1.70 (dddd, J = 14.5, 10.0, 5.9, 4.1 Hz, 1H), 1.78 (qdd, J = 6.7, 5.2, 2.1 Hz, 1H), 1.90 (app ddt, J = 13.9, 9.2, 4.7 Hz, 1H), 3.41 (s, 3H), 3.40−3.45 (m, 1H), 3.66 (ddd, J = 8.9, 3.9, 1.8 Hz, 1H), 3.74−3.85 (m, 2H), 3.81 (d, J = 8.7 Hz, 1H), 7.35−7.45 (series of m, 6H), 7.65 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 5.7 (CH_3), 12.3 (CH_3), 19.2 (C), 26.9 (CH_3), 35.4 (CH_2), 38.4 (CH), 56.8 (CH_3), 60.4 (CH_2), 70.8 (CH), 105.5 (CH), 127.6 (CH), 129.6 (CH), 133.9 (C), 13.3.9 (C), 135.6 (CH); HRMS (MNa^+) calcd 465.2437, obsd 463.2416; optical rotation $[\alpha]^{21}_D$ = +3.5 (*c* 1.0, $CHCl_3$).

PMB-ether 10. KH (480 mg of 25 wt % suspension in mineral oil, 3 mmol, 3 equiv) was added to a solution of equatorial alcohol **9** (442 mg, 1 mmol) in dry THF (4 mL) at room temperature. The resulting slurry was allowed to stir for 30 min at room temperature, after which 4-methoxybenzyl chloride (420 μL, 3 mmol, 3 equiv) was added. The reaction was quenched after 1 h with a saturated NH_4Cl solution (5 mL) which was followed by the addition of a saturated $NaHCO_3$ solution (10 mL). The layers were separated, and the aqueous layer was extracted with ether (5 × 25 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated to an oil. Purification by column chromatography (10/0.3 hexanes/acetone) produced 497 mg (88%) of pure **10** as a clear, colorless oil. Data for **10**: R_f = 0.23 (9/1 hexanes/ethyl acetate); IR (thin film) 2956, 1513, 1248 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.94 (d, J = 6.8 Hz, 3H), 1.01 (d, J = 6.5 Hz, 3H), 1.10 (s, 9H), 1.70 (ddq, J = 10.8, 8.4, 6.3 Hz, 1H), 1.75 (m, 1H), 1.94 (app ddt, J = 13.8, 9.4, 4.7 Hz, 1H), 2.05 (m, 1H), 3.15 (dd, J = 10.8, 5 Hz, 1H), 3.42 (s, 3H), 3.62 (ddd, J = 9.0, 3.8, 1.9 Hz, 1H), 3.79−3.90 (series of m, 3H), 3.82 (s, 3H), 4.20 (1/2 ABq, J_{AB} = 11.3 Hz, 1H), 4.72 (1/2 ABq, J_{AB} = 11.3 Hz, 1H), 6.90 (m, 2H), 7.30 (m, 2H), 7.42 (m, 6H), 7.69 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 5.9 (CH_3), 12.7 (CH_3), 19.3 (C), 26.9 (CH_3), 34.1 (CH), 35.5 (CH_2), 36.9 (CH), 55.3 (CH_3), 56.7 (CH_3), 60.6 (CH_2), 69.8 (CH_2), 70.9 (CH), 82.2 (CH), 106.7 (CH), 113.8 (C), 127.6 (CH), 129.3 (CH), 129.6 (CH), 130.5 (C),

(17) We suggest that the chiral HPLC assay (see Supporting Information) of intermediate **9** (98.5% ee) provides the most reliable data supporting the optical purity of **1** and **2** prepared by the route described herein.

133.8 (C), 133.9 (C), 153.5 (CH), 159.2 (C); HRMS (MNa^+) calcd 585.3012, obsd 585.2994; optical rotation $[\alpha]^{21}_D = +31.0$ (c 1.0, $CHCl_3$).

Axial Nitrile 11. TMS-CN (0.34 mL, 2.56 mmol, 10 equiv) was added to a solution of methyl glycoside **10** (144 mg, 0.256 mmol) in dry acetonitrile (3.5 mL) at 0 °C. The mixture was stirred for 10 min; then TMS-OTf (23 μL, 0.128 mmol, 0.5 equiv) was added, and the reaction mixture was allowed to stir at 0−5 °C for 2 h. The reaction was quenched with a 15% Na_2CO_3 solution (10 mL), and the mixture was allowed to stir for an additional 1 h at 0−5 °C. Dichloromethane (30 mL) was added; the layers were separated, and the aqueous layer was extracted with dichloromethane (3 × 30 mL). The combined organic layers were washed with a 15% Na_2CO_3 solution (10 mL), dried over $MgSO_4$, filtered, and concentrated. Purification by column chromatography (10/0.075 benzene/ethyl acetate) produced 117 mg (82%) of **11**. Trituration with pentane produced a white solid. Data for **11**: mp 95 °C; $R_f = 0.25$ (10/0.2 benzene/ethyl acetate); IR (ATR) 2988, 2905, 2838, 1518 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.89 (d, $J = 6.9$ Hz, 3H), 1.07 (s, 9H), 1.09 (d, $J = 6.6$ Hz), 1.70 (m, 1H), 1.83 (ddt, $J = 13.7$, 8.2, 5.3 Hz), 2.10−2.20 (series of m, 2H), 3.47 (dd, $J = 10.9$, 4.4 Hz, 1H), 3.75 (m, 2H), 3.81 (s, 3H), 4.12 (ddd, $J = 7.5$, 4.8, 1.9 Hz, 1H), 4.31 (1/2 ABq, $J_{AB} = 10.9$ Hz, 1H), 4.53 (1/2 ABq, $J_{AB} = 10.9$ Hz, 1H), 4.67 (d, $J = 5.9$ Hz, 1H), 6.89 (m, 2H), 7.25 (m, 2H), 7.41 (m, 6H), 7.69 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 5.5 (CH_3), 13.1 (CH_3), 19.2 (C), 28.8 (CH_3), 32.5 (CH), 34.3 (CH), 35.4 (CH_2), 55.3 (CH_3), 60.3 (CH_2), 69.9 (CH_2), 70.5 (CH), 73.8 (CH), 79.8 (CH), 113.9 (CH), 116.3 (C), 127.7 (CH), 129.3 (CH), 129.6 (CH), 130.2 (C), 133.6 (C), 133.8 (C), 135.5 (CH), 135.6 (CH), 159.3 (C); HRMS (MNa^+) calcd 580.2859, obsd 580.2843; optical rotation $[\alpha]^{21}_D = +75.6$ (c 1.0, $CHCl_3$).

Axial Methyl Ketone 12. Nitrile **11** (30 mg, 0.054 mmol) was dissolved in dry toluene (2 mL) and cooled to 0 °C. Trimethylaluminum (2.0 M solution in hexanes, 108 μL, 0.216 mmol, 4 equiv) was added and then followed by the addition of $Ni(acac)_2$ (10 mg/mL solution in benzene, 70 μL, 0.7 mg, 0.0027 mmol, 0.05 equiv). The brown reaction mixture was allowed to stir at 0 °C for 42 h, after which 1 M HCl (2 mL) was added. The biphasic mixture was stirred at room temperature for 15 min and subsequently extracted with ether (3 × 15 mL). The combined organic extracts were dried with $MgSO_4$, filtered, and concentrated. Purification by column chromatography (10/0.15 benzene/ethyl acetate) afforded 20 mg of **12** (64.5%) as a white solid and 10.6 mg of recovered **11** (35%). Data for **12**: mp 124−126 °C; $R_f = 0.16$ (10/0.2 benzene/ethyl acetate); IR (ATR) 2921, 2858, 1710, 1506 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.88 (d, $J = 7.0$ Hz, 3H), 0.92 (d, $J = 7.1$ Hz, 3H), 1.05 (s, 9H), 1.65 (dtd, $J = 15.2$, 8.3, 3.1 Hz, 1H), 2.04 (s, 3H), 2.10−2.20 (series of m, 2H), 2.25 (m, 1H), 3.40 (br t, $J = 4$ Hz, 1H), 3.65−3.77 (series of m, 2H), 3.80 (s, 3H), 3.96 (ddd, $J = 7.8$, 4.3, 2.9 Hz, 1H), 4.09 (d, $J = 3.4$ Hz, 1H), 4.36 (1/2 ABq, $J_{AB} = 11.2$ Hz, 1H), 4.54 (1/2 ABq, $J_{AB} = 11.2$ Hz, 1H), 6.86 (m, 2H), 7.25 (m, 2H), 7.36 (m, 6H), 7.65 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 11.6 (CH_3), 19.2 (C), 26.9 (CH_3), 27.8 (CH_3), 32.3 (CH), 32.9 (CH), 55.3 (CH_3), 61.0 (CH_2), 70.9 (CH_2), 73.7 (CH), 80.7 (CH), 113.7 (CH), 127.6 (CH), 128.8 (CH), 129.5 (CH), 129.6 (CH), 131.0 (C), 133.9 (C), 133.9 (C), 135.5 (CH), 159.1 (CH), 210.5 (C); HRMS (MNa^+) calcd 597.3012, obsd 597.3007; optical rotation $[\alpha]^{21}_D = +19.9$ (c 1.0, $CHCl_3$).

Equatorial Methyl Ketone 2. LiCl (2 mg, 0.052 mmol, 1 equiv) and KHMDS (0.5 M solution in toluene, 52 μL, 0.026 mmol, 0.5 equiv) were added to a solution of **12** (30 mg, 0.052 mmol) in toluene. The resulting orange solution was heated to 55 °C for 2 h, cooled to room temperature, and diluted with 30 mL of ethyl ether. The ether layer was washed with 1 M HCl (2 × 1.5 mL) and brine (1 × 1.5 mL), dried over $MgSO_4$, filtered, and concentrated. Purification by column chromatography (10/1 hexanes/ethyl ether) yielded 27.2 mg of **2** (91%) as a clear oil. Data for **2**: $R_f = 0.23$ (9/1 hexanes/ethyl acetate); IR (thin film) 1720, 1513 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.90 (d, $J = 6.5$ Hz, 3H), 0.94 (d, $J = 7.2$ Hz, 3H), 1.06 (s, 9H), 1.70 (dddd, $J = 14.1$, 8.7, 6.1, 3.9 Hz, 1H), 1.75 (tq, $J = 10.9$, 6.6 Hz, 1H), 1.85 (ddt, $J = 13.8$, 9.3, 4.8 Hz, 1H), 2.09 (m, 1H), 2.12 (s, 3H), 3.17 (dd, $J = 10.3$, 4.7 Hz, 1H), 3.32 (d, $J = 10.6$ Hz, 1H), 3.64 (ddd, $J = 8.9$, 4.0, 1.8 Hz, 1H), 3.76 (m, 2H), 3.81 (s, 3H), 4.29 (1/2 ABq, $J_{AB} = 11.0$ Hz, 1H), 4.57 (1/2 ABq, $J_{AB} = 11.0$ Hz, 1H), 6.88 (m, 2H), 7.22 (m, 2H), 7.40 (m, 6H), 7.65 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 6.0 (CH_3), 12.9 (CH_3), 19.2 (C), 25.3 (CH_3), 26.8 (CH_3), 32.4 (CH), 34.3 (CH), 35.8 (CH_2), 55.3 (CH_3), 60.5 (CH_2), 69.7 (CH_2), 74.8 (CH), 83.0 (CH), 87.7 (CH), 113.8 (CH), 127.7 (CH), 129.3 (CH), 129.6 (CH), 130.4 (C), 133.7 (C), 133.8 (C), 135.5 (CH), 135.5 (CH), 159.2 (C), 207.4 (C); HRMS (MNa^+) calcd 597.3012, obsd 597.2991; optical rotation $[\alpha]^{21}_D = +72.3$ (c 0.5, $CHCl_3$).

C20−C32 Subunit 1. Oxazole phosphonate **13**[5a] (145 mg, 0.7 mmol, 4 equiv) was dissolved in anyhydrous THF (3 mL) and cooled to −78 °C. LDA (1.0 M in THF, 0.7 mL, 0.7 mmol, 4 equiv) was added to the solution which resulted in a bright yellow solution after stirring for 30 min at −78 °C. Equatorial methyl ketone **2** (98 mg, 0.17 mmol) as a solution in THF (3 mL) was added dropwise. The resulting reaction mixture was allowed to slowly warm to room temperature overnight (~16 h). The reaction mixture was diluted with EtOAc (100 mL) and washed with a 1/1 solution of saturated NH_4Cl and water (20 mL), followed by brine (2 × 5 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification by column chromatography (9/1 hexanes/ethyl acetate) produced **1** (75.8 mg, 68% yield) and recovered **2** (13 mg, 13%, 78% BORSM yield of **1**). Data for **1**: $R_f = 0.08$ (9/1 hexanes/ethyl acetate); IR (thin film) 2929, 2855, 1247, 1111, 1035 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.83 (d, $J = 6.5$ Hz, 3H), 0.95 (d, $J = 7.0$ Hz, 3H), 1.07 (s, 9H), 1.70 (ddt, $J = 13.6$, 8.0, 5.6 Hz, 1H), 1.78−1.88 (series of m, 2H), 1.90 (s, 3H), 2.11 (qdd, $J = 6.5$, 4.7, 1.9 Hz, 1H), 3.20 (dd, $J = 10.5$, 4.7 Hz, 1H), 3.42 (d, $J = 10.2$ Hz, 1H), 3.66 (ddd, $J = 7.1$, 5.0, 1.6 Hz, 1H), 3.71−3.82 (series of m, 2H), 3.81 (s, 3H), 4.30 (1/2 ABq, $J_{AB} = 11.0$ Hz, 1H), 4.58 (1/2 ABq, $J_{AB} = 11.1$ Hz, 1H), 6.19 (br s, 1H), 7.00 (m, 2H), 7.28 (m, 2H), 7.34−7.44 (series of m, 6H), 7.49 (s, 1H), 7.68 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 6.0 (CH_3), 13.76 (CH_3), 13.82 (CH_3), 14.2 (CH_3), 19.2 (C), 26.9 (CH_3), 33.3 (CH), 34.2 (CH), 35.8 (CH_2), 55.3 (CH_3), 60.8 (CH_2), 69.6 (CH_2), 74.8 (CH), 83.5 (CH), 88.9 (CH), 113.8 (CH), 118.5 (CH), 127.6 (CH), 129.3 (CH), 129.5 (CH), 130.7 (C), 133.9 (C), 134.0 (C), 135.5 (CH), 137.9 (C), 138.2 (C), 159.1 (C), 160.5 (C); HRMS (MNa^+) calcd 676.3434, obsd 676.3463; optical rotation $[\alpha]^{24}_D = +31.4$ (c 1.0, $CHCl_3$).

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Supporting Information Available: ^1H and ^{13}C spectra for compounds **2**, **4**, and **8**−**12** and chiral HPLC traces for compounds **4** and **9**. This material is available free of charge via the Internet at http://pubs.acs.org.

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