JOC The Journal of Organic Chemistry

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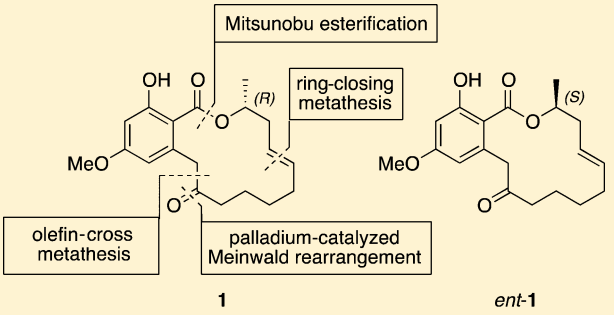
Total Syntheses of the Resorcylic Acid Lactone Neocosmosin A and Its Enantiomer

Yiwen Zhang, Michael Dlugosch, Martin Jübermann, Martin G. Banwell,* and Jas S. Ward

Research School of Chemistry, Institute of Advanced Studies, The Australian National University, Canberra, ACT 2601, Australia

Supporting Information

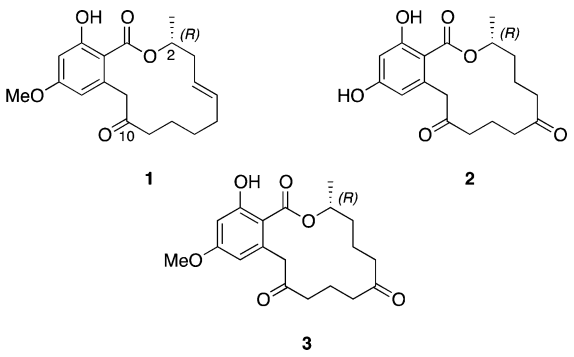
ABSTRACT: A total synthesis of the structure, **1**, assigned to the recently reported resorcylic acid lactone (RAL) neocosmosin A has been established. Olefin-cross metathesis, ring-closing metathesis, palladium-catalyzed Meinwald rearrangement, and Mitsunobu esterification reactions were used as key steps. A late-stage and simple modification to the reaction sequence also provided compound *ent*-**1** that, in fact, represents the true structure of the natural product.



The polyketide-derived resorcylic acid lactones (RALs) have been isolated from a wide range of organisms and are produced *in vivo* from malonate and acetate units.[1] A significant number of the members of this large class of natural product display a fascinating array of biological properties, including antifungal, antimalarial, mycotoxic, antibacterial, and/or anticancer activities. Indeed, some of them have inspired the development of analogues that now seem poised to enter the clinic for, *inter alia*, the treatment of melanoma and small-cell lung cancers.[1] This situation, coupled with their fascinating molecular architectures, has prompted extensive studies directed toward the total synthesis of RALs, and an impressive array of methods for achieving such ends have emerged.[1]

In early 2013, Cutler and co-workers reported[2] the isolation of three known and three new RALs from a fungus, *Neocosmospora* sp. (UM-0351509), found in the Southern U.S. The new compounds were named neocosmosins A−C and assigned structures **1**−**3**,[2b] respectively (Chart 1). Certain of these compounds displayed good *in vitro* binding affinity for human opioid and cannabinoid receptors, thus suggesting, for the first time, that some RALs may be useful for modulating pain. Prompted by such observations, the new structures of the neocosmosins, and our previous work[3] on the assembly of RALs, we commenced synthetic studies in the area. Our initial focus was the preparation of the structure, **1**, assigned to neocosmosin A. Herein, we detail total syntheses of compound **1** and its enantiomer (*ent*-**1**), thereby establishing, in fact, that it is the latter structure that corresponds to the natural product neocosmosin A. During the course of the studies detailed here, Das and co-workers reported[4] a distinct synthesis of compound *ent*-**1**.

Chart 1



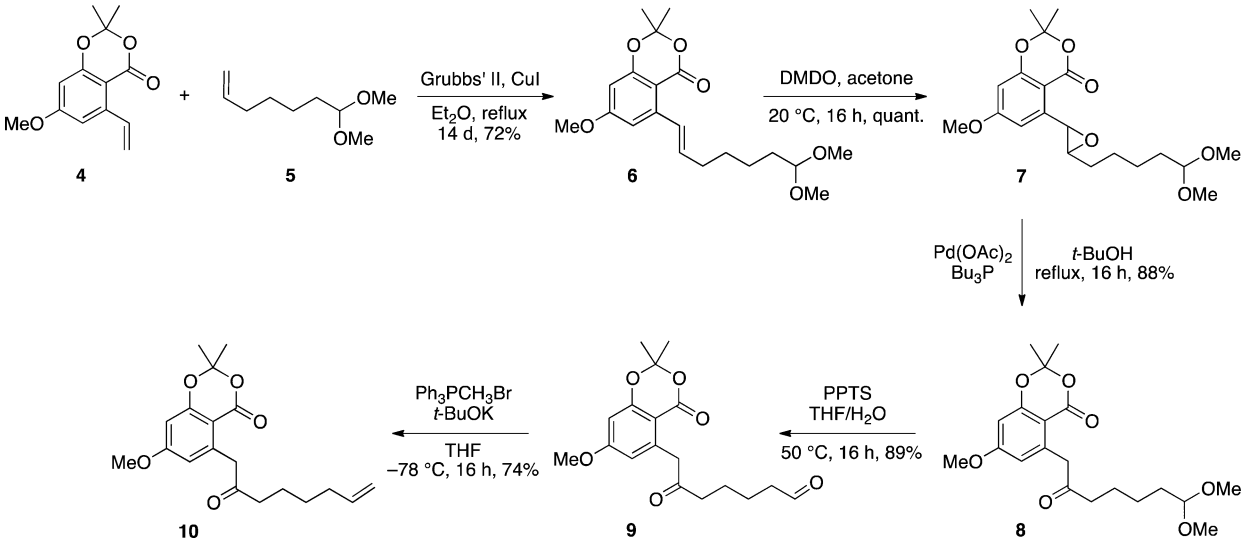
The proven effectiveness of ring-closing metatheses (RCMs) as a means for assembling the 14-membered macrolide of the RALs[3b,5] prompted us to pursue this approach to targets **1** and *ent*-**1**. We also sought to use some of the same building blocks as employed in our earlier studies.[3] A further consideration was the desire to delay as long as possible the establishment of the single stereogenic center (C2) associated with the target compounds in order that the syntheses (of the two enantiomers) would only diverge at a very late stage.

The opening phase of the syntheses are shown in Scheme 1 and involved an olefin-cross metathesis (OCM) of the previously reported and readily accessible resorcylic acid derivative **4**[3c] with the known[6] unsaturated acetal **5** that is readily generated from cyclohexene, as detailed in the Experimental Section. The almost exclusively *E*-configured alkene **6** (72%) formed by such means was treated with freshly prepared dimethyldioxirane[7] to give epoxide **7** (quant.) that, upon exposure to $Pd(OAc)_2$ and *n*-Bu_3P, engaged in a Meinwald-type rearrangement reaction[8] to give ketone **8** (88%). Hydrolysis of the acetal residue within the last compound was achieved by treating its THF/water solution

Received: March 16, 2015
Published: April 1, 2015

DOI: 10.1021/acs.joc.5b00590
J. Org. Chem. 2015, 80, 4828−4833

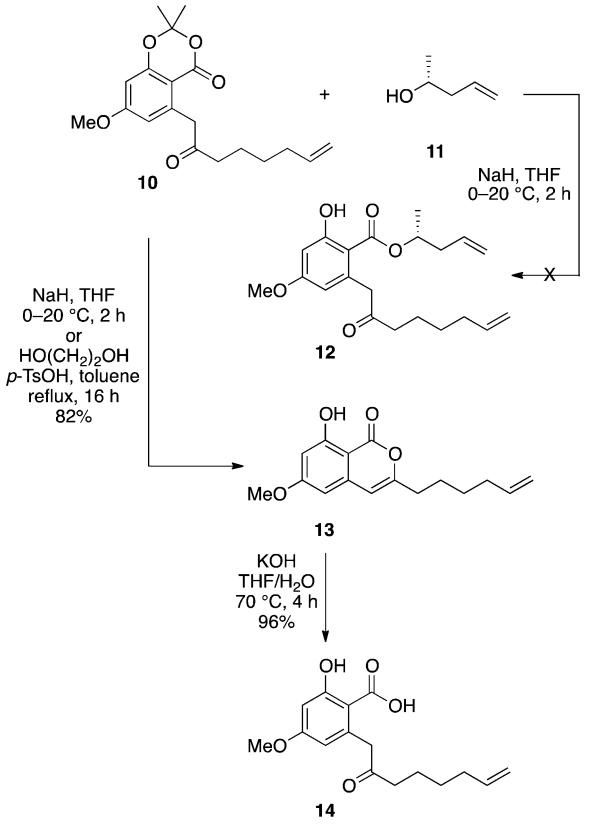
Scheme 1



with pyridium *p*-toluenesulfonate (PPTS) at 50 °C for 16 h. The resulting keto-aldehyde **9** (89%) could be selectively methylenated using 1.2 mol equivalents of the Wittig reagent and so affording the terminal olefin **10** in 74% yield.

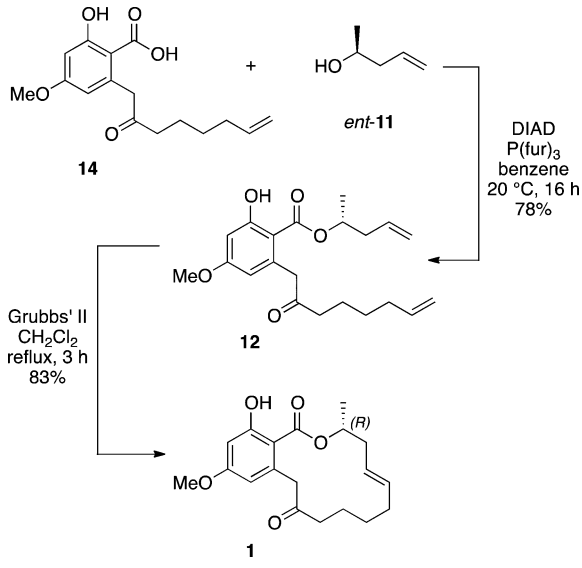
On the basis of our earlier work,[3c] we anticipated (Scheme 2) that reaction of compound **10** with the *R*-configured and commercially available unsaturated alcohol **11** in the presence sodium hydride would deliver diene **12**, the substrate required for the foreshadowed RCM reaction that should complete the synthesis of target **1**. In the event, however, a facile lactonization of compound **10** took place instead. Thus, when a mixture of compounds **10** and **11** was treated with sodium hydride and subjected to an acidic work up, then a chromatographically separable mixture of lactone **13** (15%) and the corresponding hydrolysis product **14** (35%) was obtained. When compound **10** alone was treated with ethylene glycol and catalytic quantities of *p*-toluenesulfonic acid (*p*-TsOH) in refluxing toluene, then lactone **13** could be obtained as the exclusive product of the reaction in 82% yield. Furthermore, treatment of the latter compound with potassium hydroxide in THF/water afforded, after an acidic workup, the benzoic acid **14** (96%).

Scheme 2



The lack of success forming diene **12** by the pathway detailed above could be circumvented by subjecting commercially available (*S*)-(+)-4-penten-2-ol (*ent*-**11**) (Scheme 3) to a Mitsunobu reaction using acid **14** as nucleophile together with a combination of di-isopropyl azodicarboxylate (DIAD) and tri(2-furyl)phosphine [P(fur)$_3$][9] for activating the alcohol. By such means, the target diene ester **12** was obtained in 78% yield. This product is assumed to possess the *R*-configuration at

Scheme 3

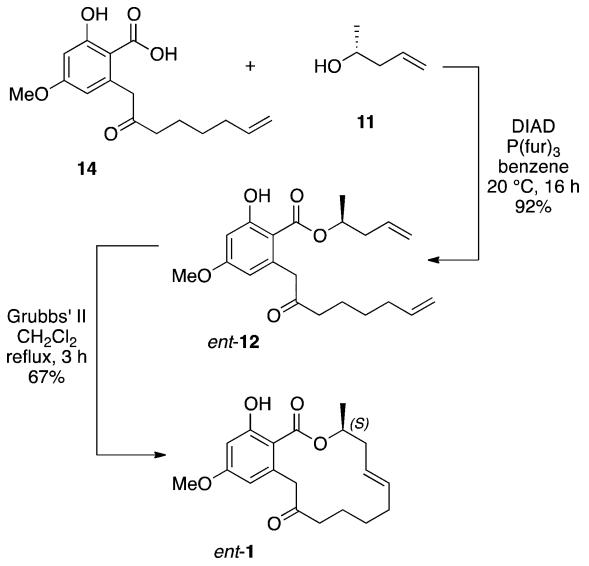


DOI: 10.1021/acs.joc.5b00590
J. Org. Chem. 2015, 80, 4828–4833

C2 (RAL numbering) by virtue of the operation of the usual S_N2 pathway in the Mitsunobu reaction.[10] The pivotal RCM reaction of compound **12** could be effected using the Grubbs' second generation (Grubbs' II) catalyst[11] in refluxing dichloromethane, thereby producing crystalline RAL **1** in 83% yield. The NMR, IR, and MS spectral data obtained on this material matched those reported[2a] for neocosmosin A. However, while the specific rotation of compound **1** was of a similar magnitude to that reported for the natural product, it was of the opposite sign, thus suggesting that the absolute configuration (*R*) assigned[2b] to this RAL is incorrect. Accordingly, the synthesis of compound *ent*-**1** was pursued.

The synthesis of the macrolide *ent*-**1** was readily achieved by the pathway shown in Scheme 4. This pathway represents a

Scheme 4



minor modification of the one used to prepare enantiomer **1**. Thus, ester *ent*-**12** was obtained in 92% yield by engaging (*R*)-(+)-4-penten-2-ol (**11**) in a Mitsunobu esterification reaction with benzoic acid **14**. The ester was then converted, in 67% yield, into target *ent*-**1** on exposure to the Grubbs' II catalyst. The assigned structure was in full accord with the derived spectral data, but final confirmation of this (including the illustrated absolute configuration) followed from a single-crystal X-ray analysis, the details of which are provided in the Experimental Section and Supporting Information. As revealed in Table 1, a comparison of the ^{13}C and ^{1}H NMR spectral data derived from compound *ent*-**1** with those reported for neocosmosin A revealed an excellent match. Equally significantly, the specific rotation of the synthetically derived material compared very favorably, in terms of both magnitude and sign, with that reported for the natural product $\{[\alpha]_D^{20}$ −42 (*c* 0.6, $CHCl_3$) for *ent*-**1** vs $[\alpha]_D^{25}$ −43 (*c* 0.6, $CHCl_3$) reported[2a] for neocosmosin A}.

The studies detailed above have clearly established that the true structure of the RAL neocosmosin A is represented by *ent*-**1** and not **1** as suggested by Cutler et al.[2b,12] The synthetic strategy employed here should be readily adapted to the synthesis of neocosmosins B and C as well as a number of related RALs, allowing for detailed studies of the capacity of such compounds to act at human opioid and cannabinoid receptors and thereby enhancing the possibility of identifying new agents for managing pain in mammalian systems.

EXPERIMENTAL SECTION

General Protocols. Unless otherwise specified, proton (^{1}H) and carbon (^{13}C) NMR spectra were recorded at room temperature in base-filtered $CDCl_3$ on a spectrometer operating at 400 MHz for proton and 100 MHz for carbon nuclei. The signal due to residual $CHCl_3$ appearing at δ_H 7.26 and the central resonance of the $CDCl_3$ "triplet" appearing at δ_C 77.0 were used to reference ^{1}H and ^{13}C NMR spectra, respectively. ^{1}H NMR data are recorded as follows: chemical shift (δ) [multiplicity, coupling constant(s) *J* (Hz), relative integral], where multiplicity is defined as s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, or combinations of the above. Samples were analyzed by infrared spectroscopy (ν_{max}) as thin films on KBr plates. Low-resolution ESI mass spectra were recorded on a single quadrupole liquid chromatograph−mass spectrometer, whereas high-resolution measurements were conducted on a time-of-flight instrument. Low- and high-resolution EI mass spectra were recorded on a magnetic-sector machine. Melting points were measured on an automated melting point system and are uncorrected. Analytical thin-layer chromatography (TLC) was performed on aluminum-backed 0.2 mm thick silica gel 60 F_{254} plates. Eluted plates were visualized using a 254 nm UV lamp and/or by treatment with a suitable dip followed by heating. These dips included phosphomolybdic acid/ceric sulfate/sulfuric acid (conc.)/water (37.5 g:7.5 g:37.5 g:720 mL) or potassium permanganate/potassium carbonate/5% sodium hydroxide aqueous solution/water (3 g:20 g:5 mL:300 mL). Flash chromatographic separations were carried out following protocols defined by Still et al.[13] with silica gel 60 (40−63 μm) as the stationary phase and using the AR- or HPLC-grade solvents indicated. Starting materials and reagents were generally commercially available and were used as supplied. Drying agents and other inorganic salts were purchased from commercial suppliers. Tetrahydrofuran (THF), methanol, and dichloromethane were dried using a solvent purification system that is based upon a technology originally described by Grubbs et al.[14] Where necessary, reactions were performed under a nitrogen or argon atmosphere.

Compound 5. *Step i.* Ozone was passed through a magnetically stirred solution of cyclohexene (15.35 mL, 150 mmol) in dry dichloromethane (300 mL) containing dry MeOH (100 mL) maintained at −78 °C (dry ice/acetone bath). Once the reaction mixture remained blue, nitrogen was bubbled through it until the color was discharged, at which point it was treated with *p*-TsOH·H_2O (2.90 g, 15 mmol) and the cooling bath was removed. With continuing stirring, the reaction mixture was allowed to warm to 20 °C (ca. 2 h) before it was treated, in portions, with Na_2CO_3 (3.28 g, 39 mmol) and, after 0.5 h, with Me_2S (24 mL, 330 mmol) that was added dropwise over 0.5 h. The resulting mixture was stirred at 20 °C for 16 h and then quenched with H_2O (200 mL). The separated aqueous phase was extracted with diethyl ether (4 × 200 mL), and the combined organic phases were dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The light-yellow oil thus obtained was purified by flash chromatography (silica, 4:1 v/v hexane/ethyl acetate elution), and after concentration of the appropriate fractions (R_f = 0.3 in 9:1 v/v hexane/ethyl acetate), 6,6-dimethoxyhexanal[6] (22.93 g, 95%) was obtained as a clear, colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.74 (s, 1H), 4.35−4.32 (complex m, 1H), 3.29 (s, 6H), 2.45−2.40 (complex m, 2H), 1.68−1.57 (complex m, 4H), 1.40−1.33 (complex m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.5, 104.4, 52.9, 43.9, 32.4, 24.3, 22.0; IR ν_{max} 3424, 2947, 2831, 2721, 1726, 1460, 1388, 1366, 1192, 1128, 1074, 1052, 958 cm^{-1}; MS (ESI, +ve) *m*/*z* 199 [$(M + K)^+$, 100%], 183 [$(M + Na)^+$, 71]; HRMS $(M + Na)^+$ calcd for $C_8H_{16}NaO_3$, 183.0997; found, 183.0997.

Step ii. A magnetically stirred suspension of $MePPh_3Br$ (61.09 g, 167.60 mmol) in dry THF (200 mL) maintained under nitrogen at 0 °C (ice bath) was treated, dropwise over 0.5 h, with *n*-BuLi (104.7 mL of a 1.6 M solution in hexanes, 167.6 mmol). The ensuing orange suspension was stirred at 0 °C for 0.5 h before a solution of 6,6-

DOI: 10.1021/acs.joc.5b00590
J. Org. Chem. 2015, 80, 4828−4833

Table 1. Comparison of the ^{13}C and ^{1}H NMR Data Recorded for Synthetically Derived Compound *ent*-1 with Those Reported for Neocosmosin A

^{13}C NMR (δ_C)		^{1}H NMR (δ_H)	
neocosmosin A[a]	compound *ent*-**1**[b]	neocosmosin A[c]	compound *ent*-**1**[d]
208.2	208.4	11.98, s, 1H	11.98, s, 1H
170.7	170.8	6.44, d, J = 2.5 Hz, 1H	6.42, d, J = 4.0 Hz, 1H
166.0	166.1	6.24, d, J = 2.5 Hz, 1H	6.21, d, J = 4.0 Hz, 1H
163.9	164.0	5.51, m, 1H	5.50−5.38, complex m, 2H
139.1	139.2	5.46, m, 1H	
135.1	135.3	5.35, m, 1H	5.32, m, 1H
124.5	124.6	4.42, d, J = 16.8 Hz, 1H	4.38, d, J = 16.7 Hz, 1H
112.1	112.2	3.82, s, 3H	3.79, s, 3H
105.7	105.8	3.51, d, J = 16.8 Hz, 1H	3.48, d, J = 16.7 Hz, 1H
100.1	100.2	2.63, m, 1H	2.59, m, 1H
72.9	73.0	2.55, m, 1H	2.52, m, 1H
55.4	55.5	2.39, m, 1H	2.36, m, 1H
50.2	50.4	2.27, m, 1H	2.25, m, 1H
40.8	40.9	2.09, m, 2H	2.14−2.00, complex m, 2H
37.7	37.8	1.65, m, 2H	1.69−1.40, complex m, 4H
32.7	32.9	1.63, m, 1H	
25.2	25.3	1.42, m, 1H	
22.1	22.2	1.40, d, J = 6.5 Hz, 3H	1.37, d, J = 6.5 Hz, 3H
18.9	19.0		

[a]Data obtained from ref 2a; recorded in $CDCl_3$ at 150 MHz. [b]Data recorded in $CDCl_3$ at 100 MHz. [c]Data obtained from ref 2a; recorded in $CDCl_3$ at 500 MHz. [d]Data recorded in $CDCl_3$ at 400 MHz.

dimethoxyhexanal (13.43 g, 83.80 mmol) in dry THF (50 mL) was added dropwise. The resulting yellow mixture was left to warm to 20 °C over 16 h and was then treated with NH_4Cl (200 mL of a saturated aqueous solution). The separated aqueous phase was extracted with diethyl ether (2 × 200 mL), and the combined organic phases were washed with brine (1 × 200 mL) before being dried ($MgSO_4$), filtered, and then concentrated under reduced pressure. The yellow oil thus obtained was subjected to flash chromatography (silica, 50:1 v/v hexane/ethyl acetate elution), and concentration of the relevant fractions (R_f = 0.5 in 9:1 v/v hexane/ethyl acetate) afforded compound **5**[6] (7.45 g, 56%) as a clear, colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.79 (m, 1H), 5.00−4.91 (complex m, 2H), 4.35 (t, J = 5.8 Hz, 1H), 3.30 (s, 6H), 2.04 (m, 2H), 1.59 (m, 2H), 1.43−1.30 (complex m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.9, 114.5, 104.6, 52.7, 33.8, 32.5, 28.9, 24.2; IR ν_{max} 3077, 2978, 2929, 2859, 2830, 1641, 1462, 1416, 1385, 1363, 1191, 1127, 1077, 1054, 910 cm^{-1}; MS (ESI, +ve) m/z 171 [$(M + Na)^+$, 100%], 159 [$(M + H)^+$, 27]; HRMS $(M + Na)^+$ calcd for $C_9H_{18}NaO_2$, 181.1204; found, 181.1205.

Compound 6. A magnetically stirred and degassed mixture of compound **4**[3c] (1.25 g, 5.14 mmol), compound **5** (1.02 g, 6.43 mmol), Grubbs' II catalyst (110 mg, 0.13 mmol), and CuI (30 mg, 0.15 mmol) in dry Et_2O (25 mL) was stirred at reflux under an atmosphere of argon. Grubbs' II catalyst (110 mg, 0.13 mmol) and CuI (30 mg, 0.15 mmol) were each added seven times every other day, and olefin **5** (1.02 g, 6.43 mmol) every third day and three times in total. After 14 days, the reaction mixture was concentrated under reduced pressure, and the residue thus obtained subjected to flash chromatography (silica, 8:1 v/v hexane/ethyl acetate elution) to afford compound **6** (1.35 g, 72%) as a clear, light-yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 (d, J = 15.7 Hz, 1H), 6.69 (d, J = 2.6 Hz, 1H), 6.27 (d, J = 2.6 Hz, 1H), 6.14 (dt, J = 15.7 and 6.9 Hz, 1H), 4.32 (t, J = 5.7 Hz, 1H), 3.79 (s, 3H), 3.26 (s, 6H), 2.23 (m, 2H), 1.64 (s, 6H), 1.58 (m, 2H), 1.48 (m, 2H), 1.38 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.7, 160.2, 158.7, 144.2, 135.0, 128.3, 108.1, 104.9, 104.5, 103.7, 100.1, 55.6, 52.7, 33.0, 32.4, 29.0, 25.6, 24.2; IR ν_{max} 2992, 2942, 2857, 1729, 1605, 1573, 1430, 1389, 1275, 1204, 1161, 1128, 1072, 968, 914, 855 cm^{-1}; MS (ESI, +ve) m/z 387 [$(M + Na)^+$, 100%]; HRMS $(M + Na)^+$ calcd for $C_{20}H_{28}NaO_6$, 387.1784; found, 387.1785.

Efforts to accelerate this sluggish reaction using different solvents and/or microwave irradiation conditions were all unsuccessful.

Compound 7. A magnetically stirred solution of olefin **6** (428 mg, 1.17 mmol) in acetone (3 mL) maintained at 0 °C (ice-bath) was treated with dimethyldioxirane[7] (26 mL of a 67 mM solution in acetone, 1.76 mmol). The resulting yellow solution was stirred at 20 °C for 16 h and then concentrated under reduced pressure to afford compound **7** (445 mg, quant.) as a clear, light-yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.66 (d, J = 2.6 Hz, 1H), 6.32 (d, J = 2.6 Hz, 1H), 4.40 (d, J = 2.2 Hz, 1H), 4.33 (m, 1H), 3.80 (s, 3H), 3.27 (s, 6H), 2.71 (m, 1H), 1.69 (s, 3H), 1.66 (s, 3H), 1.64−1.49 (complex m, 6H), 1.39 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.9, 160.1, 158.5, 145.0, 129.2, 106.0, 105.5, 104.5, 104.3, 100.9, 63.4, 57.1, 55.7, 52.6, 32.4, 32.3, 26.4, 25.5, 24.8, 24.5; IR ν_{max} 2944, 2862, 1726, 1670, 1612, 1582, 1442, 1378, 1283, 1203, 1160, 1131, 1068, 963, 913, 854, 751 cm^{-1}; MS (ESI, +ve) m/z 403 [$(M + Na)^+$, 100%], 381 [$(M + H)^+$, 4]; HRMS $(M + Na)^+$ calcd for $C_{20}H_{28}NaO_7$, 403.1733; found, 403.1733.

Compound 8. A magnetically stirred solution of compound **7** (1.30 g, 3.41 mmol) and $Pd(OAc)_2$ in degassed *t*-BuOH (60 mL) maintained at 20 °C under nitrogen was treated with *n*-Bu_3P (860 μL, 3.41 mmol), and the ensuing orange solution was heated at reflux for 16 h. The cooled reaction mixture was concentrated under reduced pressure, and the residue was subjected to flash chromatography (silica, 3:1 v/v hexane/ethyl acetate elution) to afford, after concentration of the appropriate fractions (R_f = 0.2 in 4:1 v/v hexane/ethyl acetate), compound **8** (1.15 g, 88%) as a clear, light-yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.36 (d, J = 2.5 Hz, 1H), 6.34 (d, J = 2.5 Hz, 1H), 4.32 (t, J = 5.7 Hz, 1H), 4.07 (s, 2H), 3.79 (s, 3H), 3.28 (s, 6H), 2.58 (t, J = 7.4 Hz, 2H), 1.67 (s, 6H), 1.64−1.55 (complex m, 4H), 1.34 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 206.9, 164.9, 160.8, 159.0, 140.8, 114.1, 105.4, 104.4, 100.2, 55.6, 52.7, 48.6, 42.7, 32.3, 25.6, 24.2, 23.4 (one signal obscured or overlapping); IR ν_{max} 2989, 2945, 2831, 1724, 1614, 1581, 1436, 1286, 1205, 1161, 1127, 1067 cm^{-1}; MS (ESI, +ve) m/z 403 [$(M + Na)^+$, 100%]; HRMS $(M + Na)^+$ calcd for $C_{20}H_{28}NaO_7$, 403.1733; found, 403.1734.

Compound 9. A magnetically stirred solution of compound **8** (55 mg, 0.14 mmol) in THF/water (6 mL of a 2:1 v/v mixture) was treated with PPTS (18 mg, 0.07 mmol), and the ensuing mixture was stirred at 60 °C for 16 h. The cooled reaction mixture was concentrated under reduced pressure, the residue was diluted with water (50 mL), and the ensuing mixture was extracted with

DOI: 10.1021/acs.joc.5b00590
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dichloromethane (3 × 30 mL). The combined organic phases were washed with brine (1 × 50 mL) before being dried (Na_2SO_4), filtered, and then concentrated under reduced pressure. The residue was purified by flash chromatography (silica, 3:1 v/v hexane/ethyl acetate elution), and concentration of the relevant fractions (R_f = 0.4 in 1:1 v/v hexane/ethyl acetate) afforded compound **9** (41 mg, 89%) as a clear, colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.74 (s, 1H), 6.38 (d, J = 2.2 Hz, 1H), 6.36 (d, J = 2.2 Hz, 1H), 4.07 (s, 2H), 3.81 (s, 3H), 2.63 (m, 2H), 2.44 (m, 2H), 1.69 (s, 6H), 1.65 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 206.5, 202.5, 165.0, 160.8, 159.0, 140.6, 114.2, 105.5, 105.3, 100.3, 55.6, 48.7, 43.7, 42.3, 25.6, 23.0, 21.6; IR ν_{max} 2997, 2944, 2725, 1721, 1614, 1581, 1436, 1286, 1205, 1161, 1067 cm^{-1}; MS (ESI, +ve) m/z 373 [(M + K)$^+$, 96%], 357 [(M + Na)$^+$, 100], 335 [(M + H)$^+$, 52]; HRMS (M + Na)$^+$ calcd for $C_{18}H_{22}NaO_6$, 357.1314; found, 357.1306.

Compound 10. A magnetically stirred suspension of $MePPh_3Br$ (950 mg, 2.61 mmol) in dry THF (10 mL) maintained at 0 °C under nitrogen was treated with *t*-BuOK (2.5 mL of a 1.0 M solution in THF, 2.50 mmol), and the ensuing yellow suspension was stirred at 0 °C for 0.5 h and then added to a magnetically stirred solution of compound **9** (726 mg, 2.17 mmol) in dry THF (15 mL) maintained at −78 °C under a nitrogen atmosphere. The resulting yellow suspension was stirred at −78 °C for 0.5 h and then 0 °C for 5 h before being treated, successively, with NH_4Cl (10 mL of a saturated aqueous solution) and water (20 mL) and then extracted with Et_2O (3 × 30 mL). The combined organic phases were dried ($MgSO_4$), filtered, and then concentrated under reduced pressure, and the residue was subjected to flash chromatography (silica, 6:1 v/v hexane/ethyl acetate elution). Concentration of the appropriate fractions (R_f = 0.3 in 4:1 v/v hexane/ethyl acetate) gave olefin **10** (533 mg, 74%) as a clear, colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.36 (d, J = 2.5 Hz, 1H), 6.33 (d, J = 2.5 Hz, 1H), 5.76 (m, 1H), 4.99−4.88 (complex m, 2H), 4.07 (s, 2H), 3.78 (s, 3H), 2.57 (t, J = 7.4 Hz, 2H), 2.03 (m, 2H), 1.67 (s, 6H), 1.61 (m, 2H), 1.38 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 207.0, 164.9, 160.8, 159.0, 140.8, 138.6, 114.5, 114.1, 105.4, 100.2, 55.6, 48.6, 42.6, 33.6, 28.4, 25.6, 23.1 (signal due to one carbon obscured or overlapping); IR ν_{max} 2940, 1724, 1614, 1581, 1436, 1285, 1205, 1160, 1067, 911 cm^{-1}; MS (ESI, +ve) m/z 355 [(M + Na)$^+$, 100%], 333 [(M + H)$^+$, 34]; HRMS (M + Na)$^+$ calcd for $C_{19}H_{24}NaO_5$, 355.1521; found, 355.1521.

Compound 13. *Method A.* A magnetically stirred solution of compounds **10** (164 mg, 0.49 mmol) and **11** (67 mg, 0.74 mmol) in dry THF (3 mL) maintained at 0 °C under a nitrogen atmosphere was treated with NaH (43 mg of a 55% dispersion in mineral oil, 0.98 mmol). The ensuing mixture was stirred at 20 °C for 2 h and then quenched with NH_4Cl (5 mL of a saturated aqueous solution), diluted with water (20 mL), and extracted with dichloromethane (3 × 20 mL). The combined organic phases were washed with brine (1 × 50 mL) before being dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue thus obtained was subjected to flash chromatography (silica, 10:1 v/v hexane/ethyl acetate elution) to afford two fractions, A and B.

Concentration of fraction A (R_f = 0.5 in 4:1 v/v hexane/ethyl acetate) afforded compound **13** (20 mg, 15%) as a clear, colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.10 (s, 1H), 6.44 (d, J = 2.4 Hz, 1H), 6.29 (d, J = 2.4 Hz, 1H), 6.16 (s, 1H), 5.79 (m, 1H), 5.06−4.94 (complex m, 2H), 3.85 (s, 3H), 2.49 (t, J = 7.6 Hz, 2H), 2.09 (m, 2H), 1.70 (m, 2H), 1.46 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.9, 166.6, 163.8, 157.9, 139.5, 138.4, 115.0, 104.1, 101.2, 100.3, 100.1, 55.8, 33.5, 33.3, 28.3, 26.4; IR ν_{max} 3081, 2932, 2857, 1683, 1646, 1621, 1572, 1511, 1380, 1237, 1163, 1069, 846 cm^{-1}; MS (ESI, +ve) m/z 297 [(M + Na)$^+$, 100%], 275 [(M + H)$^+$, 2]; HRMS (M + H)$^+$ calcd for $C_{16}H_{19}O_4$, 275.1283; found, 275.1283.

Concentration of fraction B (R_f = 0.2 in 4:1 v/v hexane/ethyl acetate) afforded a white, amorphous solid. Crystallization of this material (hexane/ethyl acetate) then gave compound **14** (50 mg, 35%) as a white, crystalline solid. mp 94−96 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.13 (s, 1H), 6.36 (d, J = 2.4 Hz, 1H), 6.29 (d, J = 2.4 Hz, 1H), 5.80 (m, 1H), 5.03−4.95 (complex m, 2H), 3.82 (s, 3H), 3.16 (d, J = 16.1 Hz, 1H), 3.00 (d, J = 16.1 Hz, 1H), 2.09 (m, 2H), 1.95 (m, 2H), 1.68−1.44 (complex m, 4H) (signal due to carboxylic acid group proton not observed); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.3, 166.3, 164.6, 139.1, 138.5, 115.0, 107.6, 104.6, 101.3, 99.7, 55.7, 40.8, 36.8, 33.6, 28.8, 22.9; IR ν_{max} 3377, 2933, 1645, 1629, 1584, 1505, 1439, 1362, 1307, 1205, 1160, 1064, 912 cm^{-1}; MS (ESI, +ve) m/z 315 [(M + Na)$^+$, 100%], 293 [(M + H)$^+$, 15]; HRMS (M + H)$^+$ calcd for $C_{16}H_{21}O_5$, 293.1389; found, 293.1388.

Method B. A magnetically stirred mixture of compound **10** (54 mg, 0.16 mmol), ethylene glycol (198 mg, 3.2 mmol), and *p*-TsOH·H_2O (6 mg, 0.03 mmol) in toluene (5 mL) was heated at reflux for 16 h in an apparatus fitted with a Dean−Stark trap topped by a Liebig condenser. The cooled reaction mixture was partitioned between dichloromethane (20 mL) and brine/water (20 mL of a 1:1 v/v mixture). The separated aqueous phase was extracted with dichloromethane (3 × 20 mL), and the combined organic phases were washed with brine (1 × 50 mL) before being dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue thus obtained was subjected to flash chromatography (silica, 8:1 v/v hexane/ethyl acetate elution) affording, after concentration of the appropriate fractions, compound **13** (37 mg, 82%) as a clear, colorless oil. This material was identical, in all respects, with that obtained by Method A.

Compound 14. A magnetically stirred solution of compound **10** (382 mg, 1.15 mmol) in THF/H_2O (50 mL of a 1:1 v/v mixture) was treated with KOH (322 mg, 5.75 mmol), and the ensuing yellow solution was heated at reflux for 16 h. The cooled reaction mixture was concentrated under reduced pressure, and the residue was acidified, using HCl (2 M aqueous solution), to pH 1. The suspension thus formed was diluted with brine (50 mL) and then extracted with ethyl acetate (3 × 50 mL). The combined organic phases were dried ($MgSO_4$), filtered, and concentrated under reduced pressure to give a light yellow oil. The residue so obtained was subjected to flash chromatography (silica, 2:1:0.01 v/v/v hexane/ethyl acetate/acetic acid elution) to afford, after concentration of the relevant fractions (R_f = 0.2 in 4:1 v/v hexane/ethyl acetate), compound **14** (322 mg, 96%) as a white, amorphous solid. This material was identical, in all respects, with that obtained by Method A as detailed immediately above.

Compound 12. A magnetically stirred solution of P(fur)$_3$ (164 mg, 0.70 mmol) in benzene (2 mL) was treated with DIAD (175 μL, 0.88 mmol), the ensuing yellow solution was stirred at 20 °C for 10 min, and then (*S*)-(+)-4-penten-2-ol (32 mg, 0.37 mmol) was added dropwise. The resulting mixture was stirred at 20 °C for 5 min and was then treated, dropwise, with a solution of acid **14** (103 mg, 0.35 mmol) in benzene (7 mL). The ensuing mixture was stirred at 30 °C for 16 h and then concentrated under reduced pressure. The light-yellow oil thus obtained was subjected to flash chromatography (silica, 30:1 → 15:1 v/v hexane/ethyl acetate gradient elution) to afford, after concentration of the relevant fractions (R_f = 0.6 in 4:1 v/v hexane/ethyl acetate), compound **12** (98 mg, 78%) as a clear, colorless oil. $[\alpha]_D^{20}$ −155 (c 0.6, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.72 (s, 1H), 6.40 (d, J = 2.3 Hz, 1H), 6.21 (d, J = 2.3 Hz, 1H), 5.75 (m, 2H), 5.25 (m, 1H), 5.14−5.09 (complex m, 2H), 4.99−4.91 (complex m, 2H), 4.00 (d, J = 17.2 Hz, 1H), 3.80 (d, J = 17.2 Hz, 1H), 3.76 (s, 3H), 2.47−2.30 (complex m, 4H), 2.02 (m, 2H), 1.57 (m, 2H), 1.35 (m, 2H), 1.28 (d, J = 6.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 207.4, 170.2, 165.8, 164.0, 139.0, 138.5, 133.4, 118.4, 114.7, 112.8, 105.8, 100.1, 72.2, 55.5, 51.4, 41.7, 40.2, 33.6, 28.5, 23.1, 19.5; IR ν_{max} 3077, 2978, 2935, 2853, 1716, 1646, 1616, 1578, 1430, 1356,1322, 1303, 1257, 1204, 1160, 1047, 914 cm^{-1}; MS (ESI, +ve) m/z 383 [(M + Na)$^+$, 100%], 361 [(M + H)$^+$, 16]; HRMS (M + H)$^+$ calcd for $C_{21}H_{29}O_5$, 361.2015; found, 361.2016.

Compound 1. A magnetically stirred solution of diene **12** (98 mg, 0.27 mmol) in dichloromethane (150 mL, dry and degassed with argon) maintained at 20 °C under an argon atmosphere was treated, in one portion, with Grubbs' II catalyst (23 mg, 0.027 mmol). The resulting brown solution was heated at reflux for 24 h, and then another portion of the Grubbs' II catalyst (23 mg, 0.027 mmol) was added. After another 24 h, the reaction mixture was concentrated under reduced pressure, and the residue thus obtained subjected to flash chromatography (silica, 15:1 v/v hexane/ethyl acetate elution). Concentration of the relevant fractions (R_f = 0.5 in 4:1 v/v hexane/

DOI: 10.1021/acs.joc.5b00590
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ethyl acetate) gave a white solid that upon recrystallization (hexane/dichloromethane) afforded compound **1** (74 mg, 83%) as white needles. mp 102−103 °C. $[\alpha]_D^{20}$ +40 (*c* 0.6, $CHCl_3$). All of the NMR, IR, and MS spectral data recorded on this compound were essentially identical to those derived from compound *ent*-**1** (see below).

Compound *ent*-12. A magnetically stirred solution of $P(fur)_3$ (171 mg, 0.74 mmol) in benzene (3 mL) was treated, dropwise, with DIAD (182 μL, 0.91 mmol), the resulting yellow solution was stirred at 20 °C for 10 min, and then (*R*)-(−)-4-penten-2-ol (33 mg, 0.38 mmol) was added. The ensuing mixture was stirred at 20 °C for 5 min and then treated, dropwise, with a solution of acid **14** (106 mg, 0.36 mmol) in benzene (7 mL). The mixture thus obtained was stirred at 30 °C for 16 h and then concentrated under reduced pressure. The resulting light-yellow oil was subjected to flash chromatography (silica, 30:1 → 15:1 v/v hexane/ethyl acetate gradient elution) to afford, after concentration of the relevant fractions (R_f = 0.6 in 4:1 v/v hexane/ethyl acetate), diene *ent*-**12** (120 mg, 92%) as a clear, colorless oil. $[\alpha]_D^{20}$ +158 (*c* 0.6, $CHCl_3$). All of the NMR, IR, and MS spectral data recorded on this compound were identical to those derived from compound **12** (see above).

Compound *ent*-1. A magnetically stirred solution of diene *ent*-**12** (34 mg, 0.094 mmol) in dichloromethane (10 mL, dry and degassed with argon) maintained under argon was treated, in one portion, with Grubbs' II catalyst (12 mg, 0.014 mmol). The ensuing brown solution was heated at reflux for 3 h and then concentrated under reduced pressure. The brown oil thus obtained was subjected to flash chromatography (silica, 15:1 v/v hexane/ethyl acetate elution). Concentration of the relevant fractions (R_f = 0.5 in 4:1 v/v hexane/ethyl acetate) gave a white solid that upon recrystallization (hexane/dichloromethane) afforded compound *ent*-**1** (20 mg, 67%) as white needles. mp 102−103 °C (lit.[2a] mp 160−161 °C), $[\alpha]_D^{20}$ −42 (*c* 0.6, $CHCl_3$) {lit.[2a] $[\alpha]_D^{25}$ −43 (*c* 0.6, $CHCl_3$)}. ^{1}H NMR (400 MHz, $CDCl_3$) δ see Table 1; ^{13}C NMR (100 MHz, $CDCl_3$) δ see Table 1; IR ν_{max} 2975, 2934, 2848, 1709, 1646, 1614, 1577, 1381, 1355, 1305, 1257, 1220, 1203, 1161, 1112, 1042, 961 cm^{-1}; MS (ESI, +ve) *m*/*z* 355 [(M + Na)$^+$, 100%], 333 [(M + H)$^+$, 19]; HRMS (M + Na)$^+$ calcd for $C_{19}H_{24}NaO_5$, 355.1521; found, 355.1521.

Crystallographic Studies. *Crystallographic Data for Compound ent-1.* $C_{19}H_{24}O_5$, M = 332.40, *T* = 150 K, orthorhombic, space group $P2_12_12_1$, *Z* = 4, *a* = 5.1830(1), *b* = 12.7946(2), *c* = 26.0924(3) Å; *V* = 1730.30(5) Å^3, D_x = 1.276 g cm^{-3}, 3372 unique data ($2\theta_{max}$ = 144.4°), *R* = 0.033 [for 3320 reflections with $I > 2.0\sigma(I)$]; *Rw* = 0.087 (all data), *S* = 1.00.

Structure Determination. Images were measured on a CCD diffractometer (Cu Kα, mirror monochromator, λ = 1.54184 Å), and data was extracted using the CrysAlis package.[15] Structure solution was by direct methods (SIR92).[16] The structure of compound *ent*-**1** was refined using the CRYSTALS program package.[17] Atomic coordinates, bond lengths and angles, and displacement parameters for compound *ent*-**1** have been deposited at the Cambridge Crystallographic Data Centre (CCDC no. 1053186). These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

■ ASSOCIATED CONTENT

Supporting Information

Crystallographic data (CIF); anisotropic displacement ellipsoid plot derived from the single-crystal analysis of compound *ent*-**1**; ^{1}H and ^{13}C NMR spectra data for compounds **1**, *ent*-**1**, **6**−**10**, **12**, *ent*-**12**, **13**, and **14**. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: Martin.Banwell@anu.edu.au.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank the Australian Research Council and the Institute of Advanced Studies for financial support. Y.Z. is the grateful recipient of a CSC Ph.D. Scholarship provided by the Government of the People's Republic of China.

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DOI: 10.1021/acs.joc.5b00590
J. Org. Chem. 2015, 80, 4828−4833