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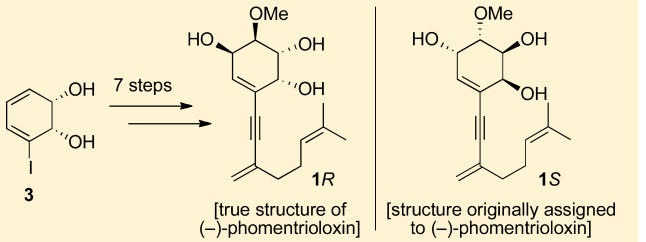
Chemoenzymatic Total Synthesis of the Phytotoxic Geranylcyclohexentriol (−)-Phomentrioloxin

Xinghua Ma, Martin G. Banwell,* and Anthony C. Willis

Research School of Chemistry, Institute of Advanced Studies, The Australian National University, Canberra ACT 0200, Australia

Supporting Information

ABSTRACT: The enantiomeric form, **1***R*, of the structure (**1***S*) assigned to the phytotoxic natural product phomentrioloxin has been synthesized in seven steps from the homochiral *cis*-1,2-dihydrocatechol **3**. These studies reveal that the true structure of phomentrioloxin is represented by **1***R* and not by **1***S*.



The rapidly increasing resistance of weeds and related pests to those herbicides currently used for crop protection is a source of great concern and has prompted the search for new lead compounds.[1,2] Natural products continue to offer considerable potential in this regard.[3] Various studies have shown that species of the genus *Phomopsis* produce phytotoxic metabolites.[4] Furthermore, it has been suggested that a form of this fungal pathogen found associated with symptomatic saffron thistle (*Carthamus lanatus*) could be a useful source of mycoherbicides for the biocontrol of this noxious weed which causes economically significant crop and pasture losses in Australia.[5,6] On that basis, Evidente and co-workers recently reported[6] the isolation of the phytotoxic agent phomentrioloxin (**1***S*, Figure 1) from liquid cultures of a *Phomopsis* sp. and

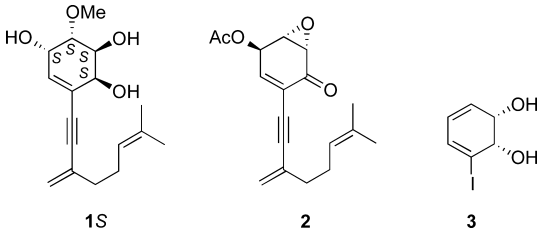


Figure 1. Structures of compounds **1***S*, **2**, and **3**.

established its structure, including relative stereochemistry, using a combination of spectroscopic techniques, most notably single-crystal X-ray analysis. They also showed that the compound was readily converted into the corresponding acetonide and that the remaining free hydroxy group could then be derivatized as the corresponding (+)- or (−)-Mosher ester. Analysis of the differences in chemical shifts between relevant resonances in the ^{1}H NMR spectra of these diastereomeric esters resulted in the illustrated absolute configuration being assigned to the natural product. Curiously, however, the other enantiomeric form (**1***R*) of the compound is shown in the ORTEP derived from the above-mentioned X-ray analysis.[6]

Various biological evaluations of phomentrioloxin (**1**) revealed[6] that on application (at a concentration of 6.85 mM) to the leaves of both host and nonhost plants it causes necrotic spots, inhibition of tomato rootlet elongation, ca. 90% reduction of chlorophyll content, and a 50% reduction in the fresh weight of the fronds of *Lemna minor* (common duckweed), a potentially invasive species. In addition it was shown that the compound was inactive as an antifungal or antibacterial agent and nontoxic to brine shrimp larvae. The above mentioned Mosher esters were similarly inactive. These features, coupled with the observed variation in biological activity as a function of structural modification,[6] suggest that phomentrioloxin (**1**) represents a useful lead for the development of new, natural, and environmentally acceptable herbicides.

The biological features of phomentrioloxin (**1**) prompted us to establish an analogue development program using modifications of the protocols we employed in our recently completed synthesis of the structurally related epoxyquinol tricholomenyn A (**2**).[7] The starting material used for this purpose was the *cis*-1,2-dihydrocatechol **3**, a compound obtained in enantiomerically pure and stereochemically well-defined form through the whole-cell biotransformation of iodobenzene.[8] Herein we report the conversion of this same metabolite into compound **1***R*, thereby establishing the absolute stereochemistry of the title natural product.

The synthetic sequence leading to target **1***R* is shown in Scheme 1 and begins with the conversion of diol **3** into the corresponding and previously reported[9] acetonide **4** (100%) through treatment of the former compound with 2,2-dimethoxypropane (2,2-DMP) in the presence of *p*-toluenesulfonic acid (*p*-TsOH) at 18 °C for 1 h. Dihydroxylation of the

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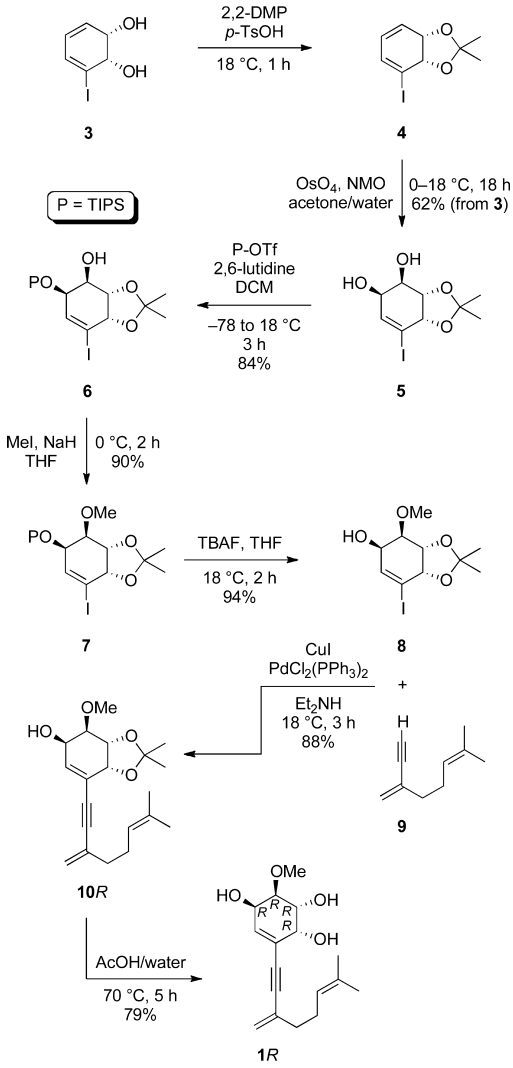
Scheme 1. Synthesis of (−)-Phomentrioloxin (1*R*) from the *cis*-1,2-Dihydrocatechol 3



nonhalogenated and more electron-rich double bond within diene **4** using the Upjohn protocol [involving OsO_4 and *N*-methylmorpholine *N*-oxide (NMO)] proceeded in a diastereoselective fashion to give the previously reported[9] diol **5** (62%), the allylic hydroxyl group of which could be selectively protected as the corresponding triisopropylsilyl (TIPS) ether upon reaction with TIPSOTf and 2,6-lutidine in dichloromethane (DCM) between −78 and 18 °C. The ether **6** (84%) so-formed was treated with methyl iodide in the presence of sodium hydride at 0 °C, thereby generating the desired and crystalline bis-ether **7** in 90% yield. In order to ensure that the required arrangement of ether residues had been established in the course of the conversion **5** → **6** → **7**, we undertook a single-crystal X-ray analysis of the last compound.[10] The derived ORTEP is shown in Figure 2, and this served to confirm the illustrated structure, including absolute stereochemistry, for compound **7**.

Treatment of bis-ether **7** with tetra-*n*-butylammonium fluoride in THF at 18 °C for 2 h resulted in cleavage of the TIPS group and the formation of the allylic alcohol **8** in 94% yield. Subjection of the latter compound to Sonogashira cross-coupling[7,11] with the readily accessible terminal alkyne **9**[12] using copper(I) iodide in the presence of $PdCl_2(Ph_3P)_2$ and

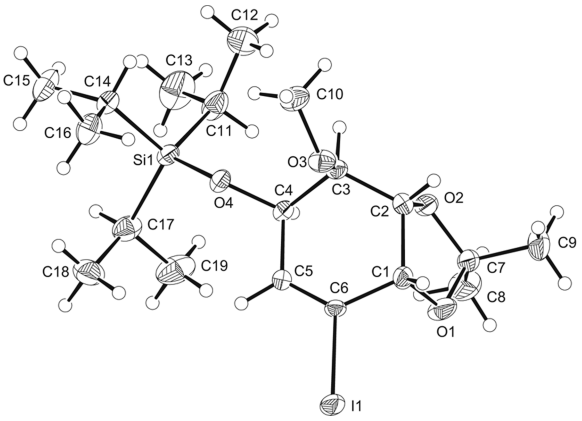
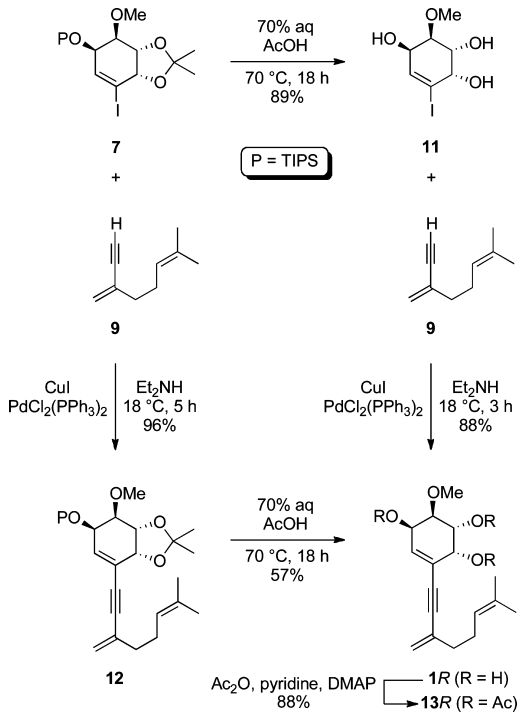


Figure 2. ORTEP derived from the single-crystal X-ray analysis of compound **7** with labeling of selected atoms. Anisotropic displacement ellipsoids display 30% probability levels. Hydrogen atoms are drawn as circles with small radii.

diethylamine resulted in the formation of the desired trienyne **10**, which was obtained as a viscous, light yellow oil in 88% yield. Finally, treatment of compound **10***R* with 4:1 v/v acetic acid−water at 70 °C for 5 h resulted in hydrolytic cleavage of the acetonide group and formation of phomentrioloxin (**1***R*), which was obtained in 79% yield as a white, crystalline solid.[13] A single-crystal X-ray analysis of this material revealed that it was the same, in terms of structure (including relative stereochemistry), as that reported by Evidente.[6,10]

Interestingly, the specific ordering of the steps associated with the closing stages of the synthesis was not critical to success. So, for example, if the cleavage of the acetonide group within compound **8** was carried out first (Scheme 2), then the resulting triol **11** (89%) could be engaged in a Sonogashira cross-coupling reaction with terminal alkyne **9** to give target **1***R*

Scheme 2. Alternate Coupling Regimes for Obtaining (−)-Phomentrioloxin (1*R*)



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in 88% yield. Similarly, Sonogashira cross-coupling reaction of the fully protected cyclohexene-tetraol **7** with terminal alkyne **9** gave the anticipated product **12** (96%), which upon treatment with 70% v/v aqueous acetic acid afforded triol **1***R* in 57% yield. For the purposes of comparison with the previously reported[6] derivative, compound **1***R* was converted into the corresponding triacetate **13** (88%) under standard conditions.

The ^{1}H and ^{13}C NMR spectroscopic data obtained on compound **1***R* were completely consistent with the assigned structure. They also proved to be a good match with those reported[6] for the natural product apart from a minor discrepancy in the ^{13}C NMR data set (Table 1). In particular, and as highlighted in entry 2 of Table 1, the chemical shift difference between the signals due to C5 is much larger than the rest. The origins of this discrepancy remain unclear.

Table 1. Comparison of the ^{13}C NMR Data Recorded for Synthetically Derived Compound 1*R* with Those Reported for the Natural Product Phomentrioloxin

		δ_C		
entry	carbon no.[a]	synthetically derived compound **1***R*[b]	naturally derived phomentrioloxin[c]	$\Delta\delta$
1	6	134.7	135.4	−0.7
2	**5**	**132.3**	**135.3**	**−3.0**
3	3′	130.9	131.5	−0.6
4	6′	123.9	124.4	−0.5
5	8′	123.1	123.8	−0.7
6	7′	122.1	123.1	−1.0
7	2′	91.5	92.4	−0.9
8	1′	86.8	87.3	−0.5
9	3	78.5	79.1	−0.6
10	1	68.4	69.1	−0.5
11	2	67.4	67.9	−0.5
12	4	64.0	64.8	−0.8
13	OMe	58.5	59.3	−0.8
14	4′	37.2	37.9	−0.7
15	9′	26.7	27.4	−0.7
16	10′	25.6	26.4	−0.8
17	5′	17.7	18.4	−0.7

[a]Assignments from ref 6. [b]Recorded in $CDCl_3$ at 100 MHz and referenced against the central peak of the "triplet" due to solvent (δ_C 77.0). [c]Recorded in $CDCl_3$ at 100 MHz and referenced against TMS (δ_C 0.0).

The specific rotations recorded on our samples of diol **1***R*, the precursor acetonide **10***R*, and the derived triacetate **13***R* are presented in Table 2 and compared with those reported[6] for their enantiomers. Clearly, each pair of compounds has the same sign, and given that the chirality of the starting material **3** is well-defined, these results suggest that the absolute configuration of the natural product phomentrioloxin was incorrectly assigned. Accordingly, we deduce that the true structure of phomentrioloxin is represented by **1***R* (and not by **1***S*). The discrepancy in the magnitudes of the two sets of specific rotations shown in Table 2 remains unclear. The possibility that naturally derived phomentrioloxin is a mixture of *R* and *S* enantiomers (with the former predominating) cannot be discounted at the present time.

Table 2. Comparison of the Specific Rotations Recorded for Synthetically Derived Compounds 1*R*, 10*R*, and 13*R* with Those Reported for Their Naturally Derived Counterparts[a]

compound	$[\alpha]_D$[b,c]	compound	$[\alpha]_D$[d,e]
1*R*	−65 (*c* 0.5)	**1***S*[f]	−23 (*c* 0.4)
10*R*	+34 (*c* 0.5)	**10***S*[f]	+21 (*c* 0.2)
13*R*	−236 (*c* 0.2)	**13***S*[f]	−132 (*c* 0.3)

[a]All optical rotations recorded in $CHCl_3$. [b]This work. [c]Recorded at 20 °C. [d]Obtained from ref 6. [e]Recorded at 25 °C. [f]Stereochemistry as originally reported in ref 6.

The work reported here serves to further emphasize the utility of enzymatically derived and stereochemically well-defined *cis*-1,2-dihydrocatechols as starting materials in the unambiguous total synthesis of various chiral, nonracemic natural products.[14,15]

EXPERIMENTAL SECTION

General Experimental Procedures. Unless otherwise specified, proton (^{1}H) and carbon (^{13}C) NMR spectra were recorded at 18 °C in base-filtered $CDCl_3$ on a Varian spectrometer operating at 400 MHz for proton and 100 MHz for carbon nuclei. For ^{1}H NMR spectra, signals arising from the residual protio-forms of the solvent were used as the internal standards. ^{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. 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. Infrared spectra (ν_{max}) were recorded on a Perkin−Elmer 1800 Series FTIR spectrometer. Samples were analyzed as thin films on KBr plates. Low-resolution ESI mass spectra were recorded on a Micromass LC-ZMD single quadrupole liquid chromatograph−mass spectrometer, while high-resolution measurements were conducted on an LCT Premier time-of-flight instrument. Low- and high-resolution EI mass spectra were recorded on an Autospec Premier Micromass magnetic-sector machine. Optical rotations were recorded in $CHCl_3$ at 20 °C on a Perkin−Elmer model 343 polarimeter. Melting points were measured on an Optimelt 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 as supplied by Merck. 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.[16] 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 available from Sigma−Aldrich, Merck, TCI, Strem, or Lancaster chemical companies and were used as supplied. Drying agents and other inorganic salts were purchased from the AJAX, BDH, or Unilab chemical companies. Tetrahydrofuran (THF), methanol, and dichloromethane were dried using a Glass Contour solvent purification system that is based upon a technology originally described by Grubbs et al.[17] Where necessary, reactions were performed under an argon atmosphere.

Compound **5**. A magnetically stirred solution of diol **3**[18] (2.00 g, 8.40 mmol) in 2,2-dimethoxypropane (25 mL) was treated with *p*-toluenesulfonic acid (40 mg, 0.21 mmol). After stirring at 18 °C for 1 h, the reaction mixture was quenched with triethylamine (1 mL) and then concentrated under reduced pressure. The residue thus obtained was dissolved in CH_2Cl_2 (25 mL), and the resulting solution treated with NH_4Cl (50 mL of a saturated aqueous solution). The separated aqueous phase was extracted with CH_2Cl_2 (1 × 10 mL), and the combined organic phases were washed with $NaHCO_3$ (1 × 50 mL of a saturated aqueous solution) before being dried ($MgSO_4$), filtered, and then concentrated under reduced pressure. The residue so-formed, and presumed to contain acetonide **4**,[9] was dissolved in acetone−water

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(48 mL of an 83:17 v/v mixture), and the ensuing solution cooled to 0 °C and then treated with *N*-methylmorpholine *N*-oxide (NMO) (2.50 g, 21.34 mmol) and osmium tetroxide (21 mg, 0.08 mmol).[19] Stirring was continued for 18 h, during which time the reaction mixture was allowed to warm to 18 °C and then treated with sodium metabisulfite (5 mL of a saturated aqueous solution). After being allowed to stir at 18 °C for 1 h NH_4Cl (80 mL of a saturated aqueous solution) was added to the reaction mixture. The separated aqueous phase was extracted with ethyl acetate (4 × 40 mL), and the combined organic phases were then dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Subjection of the light yellow oil thus obtained to flash chromatography (silica, 1:50:50 v/v/v methanol−ethyl acetate−hexane elution) and concentration of the appropriate fractions (R_f = 0.3 in 8:2.5:5.5 v/v/v ethyl acetate−CH_2Cl_2−hexane) afforded the title compound **5**[9] (1.63 g, 62% over two steps) as a white, crystalline solid: mp 139−142 °C (lit.[9] mp 139−141 °C); $[\alpha]_D$ +25 (*c* 0.5, $CHCl_3$) {lit.[9] $[\alpha]_D$ +28 (*c* 0.62, $CHCl_3$)}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.43 (m, 1H), 4.64 (d, *J* = 5.3 Hz, 1H), 4.40 (t, *J* = 5.3 Hz, 1H), 4.33 (m, 1H), 4.23 (m, 1H), 2.47 (m, 2H), 1.43 (s, 3H), 1.40 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 139.0, 110.0, 100.5, 78.3, 76.1, 69.3, 67.8, 27.6, 26.3; IR ν_{max} 3503, 3380, 2984, 2923, 2884, 1633, 1447, 1369, 1233, 1156, 1131, 1079, 1052, 1025, 943, 895, 855 cm^{-1}; MS (EI, 70 eV) *m*/*z* 312 ($M^{+\bullet}$, 14%), 297 (50), 254 (40), 110 (65), 101 (100); HRMS $M^{+\bullet}$ calcd for $C_9H_{13}IO_4$ 311.9859, found 311.9859.

Compound ***6***. Triisopropylsilyl trifluoromethanesulfonate (1.60 mL, 5.95 mmol) was added, dropwise, to a magnetically stirred solution of compound **5** (982 mg, 3.15 mmol) and 2,6-lutidine (1.5 mL, 12.90 mmol) in CH_2Cl_2 (30 mL) maintained at −78 °C under a nitrogen atmosphere. The ensuing mixture was allowed to warm to 18 °C over 3 h, then treated with NH_4Cl (60 mL of a saturated aqueous solution). The separated aqueous phase was extracted with CH_2Cl_2 (1 × 20 mL), and the combined organic phases were dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The resulting light yellow oil was subjected to flash chromatography (silica, 3:100 v/v ethyl acetate−hexane elution) to give, after concentration of the appropriate fractions (R_f = 0.3 in 0.5:2.5:5.5 v/v/v ethyl acetate−CH_2Cl_2−hexane), compound **6** (1.24 g, 84%) as a white, crystalline solid: mp 77−78 °C; $[\alpha]_D$ −24 (*c* 0.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.28 (t, *J* = 1.7 Hz, 1H), 4.61 (m, 1H), 4.46−4.40 (complex m, 2H), 4.27 (m, 1H), 2.67 (br s, 1H), 1.40 (s, 3H), 1.38 (s, 3H), 1.19−1.03 (complex m, 21H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 138.8, 109.7, 100.7, 77.8, 75.7, 69.1, 68.7, 27.5, 26.3, 17.9, 12.3, 12.1; IR ν_{max} 3561, 2943, 2893, 2867, 1631, 1463, 1381, 1370, 1235, 1079, 1053, 947, 882, 862, 836 cm^{-1}; MS (EI, 70 eV) *m*/*z* 453 [$(M - CH_3\cdot)^+$, 4%], 367 (62), 240 (100), 131 (47); HRMS $(M - CH_3\cdot)^+$ calcd for $C_{18}H_{33}IO_4Si$ 453.0958, found 453.0959.

Compound ***7***. Sodium hydride (300 mg of a 60% dispersion in mineral oil, 7.5 mmol) was added to a magnetically stirred solution of compound **6** (1.16 g, 2.48 mmol) and iodomethane (460 μL, 7.39 mmol) in dry THF (25 mL) maintained at 0 °C under a nitrogen atmosphere. Stirring was continued for 2 h at 0 °C then the reaction mixture was treated with ice−water (60 mL). The separated aqueous phase was extracted with ethyl acetate (1 × 25 mL), and the combined organic phases were then dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The ensuing light yellow oil was subjected to flash chromatography (silica, 1:50 v/v ethyl acetate−hexane elution) to give, after concentration of the appropriate fractions (R_f = 0.4 in 0.5:2.5:5.5 v/v/v ethyl acetate−CH_2Cl_2−hexane), compound **7** (1.07 g, 90%) as a white, crystalline solid: mp 81−83 °C; $[\alpha]_D$ −36 (*c* 0.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.43 (d, *J* = 3.0 Hz, 1H), 4.62 (dd, *J* = 1.2 and 5.3 Hz, 1H), 4.53 (ddd, *J* = 1.2, 2.9, and 4.1 Hz, 1H), 4.39 (m, 1H), 3.73 (m, 1H), 3.53 (s, 3H), 1.40 (s, 3H), 1.38 (s, 3H), 1.15−1.05 (complex m, 21H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 141.1, 109.5, 98.9, 80.2, 79.0, 75.0, 68.8, 59.7, 27.5, 26.0, 18.0, 12.2; IR ν_{max} 2940, 2888, 2865, 1635, 1461, 1382, 1335, 1240, 1221, 1197, 1138, 1122, 1081, 954, 880, 858, 681 cm^{-1}; MS (EI, 70 eV) *m*/*z* 467 [$(M - CH_3^{\bullet})^+$, 2%], 439 (55), 254 (100), 222 (44), 145 (63); HRMS $(M - CH_3^{\bullet})^+$ calcd for $C_{19}H_{35}IO_4Si$ 467.1115, found 467.1116.

Compound ***8***. A magnetically stirred solution of compound **7** (972 mg, 2.02 mmol) in THF (10 mL) maintained at 18 °C under a nitrogen atmosphere was treated with tetra-*n*-butylammonium fluoride (3 mL of a 1.0 M solution in THF, 3.00 mmol). After 2 h the reaction mixture was concentrated under reduced pressure and the residue so-formed subjected to flash chromatography (silica, 1:2 v/v ethyl acetate−hexane elution) to provide, after concentration of the appropriate fractions (R_f = 0.4 in 4:2.5:5.5 v/v/v ethyl acetate−CH_2Cl_2−hexane), compound **8** (620 mg, 94%) as a white, crystalline solid: mp 65−66 °C; $[\alpha]_D$ +51 (*c* 0.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.42 (m, 1H), 4.57 (d, *J* = 4.9 Hz, 1H), 4.47 (t, *J* = 4.9 Hz, 1H), 4.27 (br s, 1H), 3.80 (t, *J* = 4.4 Hz, 1H), 3.53 (s, 3H), 2.72 (br s, 1H), 1.41 (s, 3H), 1.39 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 140.0, 109.9, 100.1, 78.5, 78.2, 73.6, 66.9, 59.2, 27.5, 26.3; IR ν_{max} 3455, 2985, 2933, 2830, 1631, 1456, 1380, 1372, 1230, 1108, 1076, 1039, 959, 867 cm^{-1}; MS (EI, 70 eV) *m*/*z* 326 ($M^{+\bullet}$, 7%), 311 [$(M - CH_3\cdot)^+$, 12], 223 (9), 115 (100), 43 (15); HRMS $(M - CH_3\cdot)^+$ calcd for $C_{10}H_{15}IO_4$ 310.9780, found 310.9781.

Compound ***10R***. CuI(I) (23 mg, 0.12 mmol) and $PdCl_2(Ph_3P)_2$ (56 mg, 0.08 mmol) were added to a magnetically stirred solution of compounds **8** (258 mg, 0.79 mmol) and **9**[12] (212 mg, 1.58 mmol) in diethylamine (10 mL) maintained at 18 °C under a nitrogen atmosphere. After 3 h the reaction mixture was concentrated under reduced pressure, and the residue thus obtained subjected to flash chromatography (silica, 2:5 v/v ethyl acetate−hexane elution). Concentration of the appropriate fractions (R_f = 0.5 in 4:2.5:5.5 v/v/v ethyl acetate−CH_2Cl_2−hexane) afforded compound **10*R***[6] (233 mg, 88%) as a clear, light yellow oil: $[\alpha]_D$ +34 (*c* 0.5, $CHCl_3$) {lit.[6] $[\alpha]_D$ (for **10*S***) +21 (*c* 0.2, $CHCl_3$)}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.12 (d, *J* = 3.4 Hz, 1H), 5.36 (d, *J* = 2.0 Hz, 1H), 5.26 (m, 1H), 5.11 (m, 1H), 4.58 (d, *J* = 5.8 Hz, 1H), 4.49 (m, 1H), 4.40 (dd, *J* = 3.4 and 7.3 Hz, 1H), 3.68 (t, *J* = 4.4 Hz, 1H), 3.54 (s, 3H), 2.61 (d, *J* = 8.3 Hz, 1H), 2.24−2.17 (complex m, 4H), 1.69 (s, 3H), 1.62 (s, 3H), 1.43 (s, 3H), 1.40 (s, 3H); ^{13}C NMR ($CDCl_3$−TMS, 100 MHz) δ 135.6, 132.2, 131.2, 123.4, 122.5, 121.7, 109.7, 90.6, 87.3, 79.6, 73.7, 73.1, 64.7, 58.9, 37.3, 27.6, 26.7, 26.0, 25.7, 17.7; IR ν_{max} 3456, 2984, 2932, 1632, 1605, 1453, 1379, 1232, 1107, 1076, 1039, 897, 873 cm^{-1}; MS (EI, 70 eV) *m*/*z* 317 [$(M - CH_3\cdot)^+$, 6%], 257 (10), 185 (14), 115 (100); HRMS $(M - CH_3\cdot)^+$ calcd for $C_{20}H_{28}O_4$ 317.1573, found 317.1570.

Compound ***11***. Compound **7** (208 mg, 0.43 mmol) was treated with acetic acid−water (10 mL of a 7:3 v/v mixture), and the resulting solution was heated at 70 °C for 18 h and then cooled and concentrated under reduced pressure. Subjection of the residue thus obtained to flash chromatography (silica, 1:6:3 v/v/v methanol−ethyl acetate−hexane elution) delivered, after concentration of the appropriate fractions (R_f = 0.4 in 1:7:2 v/v/v methanol−ethyl acetate−hexane), compound **11** (110 mg, 89%) as a white, crystalline solid: mp 145−147 °C; $[\alpha]_D$ −82 (*c* 0.5, $CHCl_3$); ^{1}H NMR [$(CD_3)_2SO$, 400 MHz)] δ 6.23 (d, *J* = 3.4 Hz, 1H), 5.16 (dd, *J* = 1.9 and 9.3 Hz, 1H), 4.94 (d, *J* = 4.9 Hz, 1H), 4.86 (d, *J* = 7.3 Hz, 1H), 4.19 (m, 1H), 3.92 (m, 2H), 3.42 (m, 1H), 3.36 (s, 3H); ^{13}C NMR [$(CD_3)_2SO$, 400 MHz)] δ 140.4, 105.6, 79.8, 72.3, 68.3, 66.7, 58.2; IR ν_{max} 3412, 3351, 3306, 2994, 2925, 1630, 1446, 1289, 1117, 1097, 1078, 1034, 995, 914, 822 cm^{-1}; MS (ES, 70 eV) *m*/*z* 309 [$(M + Na)^+$, 100%]; HRMS $(M + Na)^+$ calcd for $C_7H_{11}IO_4$ 308.9600, found 308.9600.

Compound ***12***. CuI(I) (9 mg, 0.05 mmol) and $PdCl_2(Ph_3P)_2$ (22 mg, 0.03 mmol) were added to a magnetically stirred solution of compounds **7** (150 mg, 0.31 mmol) and **9** (75 mg, 0.56 mmol) in diethylamine (6 mL) maintained at 18 °C under a nitrogen atmosphere. After 5 h the reaction mixture was concentrated under reduced pressure, and the residue so formed was subjected to flash chromatography (silica, 1:50 v/v ethyl acetate−hexane elution) to give, after concentration of the appropriate fractions (R_f = 0.4 in 0.5:2.5:5.5 v/v/v ethyl acetate−CH_2Cl_2−hexane), compound **12** (146 mg, 96%) as a clear, light yellow oil: $[\alpha]_D$ −46 (*c* 0.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.14 (m, 1H), 5.35 (d, *J* = 2.0 Hz, 1H), 5.24 (m, 1H), 5.13−5.09 (complex m, 1H), 4.62 (m, 2H), 4.42 (m, 1H), 3.63 (m, 1H), 3.53 (s, 3H), 2.25−2.16 (complex m, 4H), 1.68 (s, 3H), 1.62 (s, 3H), 1.41 (s, 3H), 1.38 (s, 3H), 1.20−1.04 (complex m, 21H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 137.6, 132.1, 131.3, 123.4,

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121.5, 121.4, 109.3, 90.1, 87.8, 81.3, 74.3, 74.2, 66.8, 59.4, 37.4, 27.4, 26.8, 25.7, 25.5, 18.0, 17.7, 12.3; IR ν_{max} 2942, 2867, 1629, 1605, 1463, 1380, 1369, 1235, 1137, 1080, 882, 858, 680 cm^{-1}; MS (EI, 70 eV) *m/z* 488 ($M^{+\bullet}$, 3%), 445 (17), 439 (23), 387 (44), 254 (52), 145 (83), 117 (74), 115 (100), 75 (73); HRMS $M^{+\bullet}$ calcd for $C_{29}H_{48}O_4Si$ 488.3322, found 488.3304.

Compound **1***R*. Method A: Compound **10***R* (59 mg, 0.18 mmol) was treated with acetic acid−water (5 mL of a 4:1 v/v mixture), and the solution thus obtained was heated at 70 °C for 5 h and then cooled and concentrated under reduced pressure. Subjection of the ensuing light yellow residue to flash chromatography (silica, 1:6:3 v/v/v methanol−ethyl acetate−hexane elution) delivered, after concentration of the appropriate fractions (R_f = 0.5 in 1:7:2 v/v/v methanol−ethyl acetate−hexane), compound **1***R*[6] (41 mg, 79%) as a white, crystalline solid: mp 71−73 °C; $[\alpha]_D$ −65 (*c* 0.5, $CHCl_3$) {lit.[6] $[\alpha]_D$ (for **1***S*) −23 (*c* 0.4, $CHCl_3$)}; ^1H NMR ($CDCl_3$−TMS, 400 MHz) δ 6.15 (d, *J* = 4.4 Hz, 1H), 5.38 (d, *J* = 1.4 Hz, 1H), 5.28 (s, 1H), 5.10 (m, 1H), 4.49 (m, 1H), 4.32 (d, *J* = 3.4 Hz, 1H), 4.18 (m, 1H), 3.68 (m, 1H), 3.53 (s, 3H), 2.93 (br s, 1H), 2.86 (br s, 1H), 2.65 (br s, 1H), 2.20 (s, 4H), 1.69 (s, 3H), 1.62 (s, 3H); ^{13}C NMR, see Table 1; IR ν_{max} 3402, 2965, 2915, 2191, 1671, 1632, 1604, 1444, 1377, 1244, 1106, 989, 910 cm^{-1}; MS (EI, 70 eV) *m/z* 292 ($M^{+\bullet}$, <1%), 277 (8), 259 (12), 227 (16), 199 (35), 185 (72), 175 (63), 91 (71), 69 (100); HRMS $M^{+\bullet}$ calcd for $C_{17}H_{24}O_4$ 292.1675, found 292.1673.

Method B: CuI(I) (12 mg, 0.06 mmol) and $PdCl_2(Ph_3P)_2$ (29 mg, 0.04 mmol) were added to a magnetically stirred solution of compound **11** (118 mg, 0.41 mmol) and compound **9** (163 mg, 1.21 mmol) in diethylamine (10 mL) maintained under a nitrogen atmosphere at 18 °C. After 3 h the reaction mixture was concentrated under reduced pressure, and the residue thus formed was subjected to flash chromatography (silica, 1:6:3 v/v/v methanol−ethyl acetate−hexane elution). Concentration of the appropriate fractions (R_f = 0.5 in 1:7:2 v/v/v methanol−ethyl acetate−hexane) afforded compound **1***R*[6] (107 mg, 88%) as a white, crystalline solid. This material was identical in all respects with that obtained via method A as detailed above.

Method C: Compound **12** (197 mg, 0.40 mmol) was treated with acetic acid−water (10 mL of a 7:3 v/v mixture), and the resulting solution heated at 70 °C for 18 h then cooled and concentrated under reduced pressure. Subjection of the residue thus obtained to flash chromatography (silica, 1:6:3 v/v/v methanol−ethyl acetate−hexane elution) delivered, after concentration of the appropriate fractions (R_f = 0.5 in 1:7:2 v/v/v methanol−ethyl acetate−hexane), compound **1***R*[6] (67 mg, 57%) as a white, crystalline solid. This material was identical in all respects with that obtained via method A as detailed above.

Compound **13***R*. A magnetically stirred solution of compound **1***R* (120 mg, 0.41 mmol) in pyridine (8 mL) maintained at 18 °C under a nitrogen atmosphere was treated with acetic anhydride (0.5 mL, 5.29 mmol) and 4-(*N*,*N*-dimethylamino)pyridine (11 mg, 0.09 mmol). Stirring was continued at 18 °C for 4 h then the reaction mixture was concentrated under reduced pressure. The residue thus obtained was subjected to flash chromatography (silica, 3:10 v/v ethyl acetate−hexane elution) to give, after concentration of the appropriate fractions (R_f = 0.5 in 4:2.5:5.5 v/v/v ethyl acetate−CH_2Cl_2−hexane), compound **13***R*[6] (136 mg, 88%) as a clear, colorless oil that solidified on standing: $[\alpha]_D$ −236 (*c* 0.2, $CHCl_3$) {lit.[6] $[\alpha]_D$ (for **13***S*) −132 (*c* 0.3, $CHCl_3$)}; ^1H NMR ($CDCl_3$−TMS, 400 MHz) δ 6.13 (d, *J* = 4.4 Hz, 1H), 5.79 (d, *J* = 4.4 Hz, 1H), 5.71 (m, 1H), 5.46 (m, 1H), 5.32 (m, 1H), 5.28 (m, 1H), 5.07 (br s, 1H), 3.79 (dd, *J* = 4.4 and 8.8 Hz, 1H), 3.47 (s, 3H), 2.15−2.06 (complex m, 13H), 1.68 (s, 3H), 1.61 (s, 3H); ^{13}C NMR ($CDCl_3$−TMS, 100 MHz) δ 170.4, 170.0, 169.9, 132.4, 132.0, 130.7, 123.4, 123.1, 122.7, 92.4, 85.5, 74.8, 68.0, 67.9, 66.3, 59.1, 37.1, 26.7, 25.7, 21.0, 20.9, 20.7, 17.8; IR ν_{max} 2931, 2854, 2256, 1749, 1637, 1605, 1436, 1370, 1226, 1118, 1043, 914, 733 cm^{-1}; MS (ESI) *m/z* 441 [$(M + Na)^+$, 100%]; HRMS $(M + Na)^+$ calcd for $C_{23}H_{30}O_7$ 441.1889, found 441.1890.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Data derived from the single-crystal X-ray analyses of compounds **1***R* and **7**; ^1H and ^{13}C NMR spectra of compounds **1***R*, **6**−**8**, **10***R*, **11**, **12**, and **13***R*. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*Tel: +61-2-6125-8202. Fax: +61-2-6125-8114. E-mail: mgb@rsc.anu.edu.au.

Notes

The authors declare no competing financial interest.

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