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Tetrahedron 60 (2004) 1353–1358
Tetrahedron

Synthesis of an enantiomerically pure 2,2,4-trisubstituted cyclobutanone building block by zirconocene-promoted deoxygenative ring contraction of structurally modified 4-vinylfuranosides

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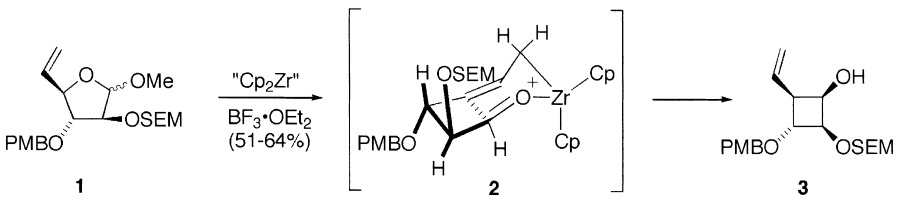
Received 24 January 2003; revised 15 July 2003; accepted 15 July 2003

Abstract—A route to an enantiopure trisubstituted cyclobutanone has been devised. The pursuit of this building block begins with D-glucose and features a zirconocene-promoted ring contraction.

The Taguchi/Hanzawa team[1] and our own group[2] have previously reported several studies dealing with diastereoselectivity control in the zirconocene-mediated ring contraction of 4-vinylfuranosides to enantiopure cyclobutanes. Multiply functionalized four-membered ring products are formed with the absolute configuration at each constituent carbon being fully definable under normal circumstances.[2] The potential importance of this process to natural products synthesis[2] and to the elaboration of useful organic scaffolds[3] has been recognized. The initial work with readily accessible modified carbohydrates has shown that transition state models typified by **2** can play a useful role in the concise rationalization of the stereochemical outcome of the deoxygenative transformations.[2] The predictability is thought to be associated with the interplay of nonbonded steric interactions during intramolecular cyclization within the allylzirconocene–aldehyde complex (Scheme 1).

In the course of another investigation, the need arose to prepare the 2,2,4-trisubstituted cyclobutanone of generic formula **4** having the (2*S*,4*R*) configuration as depicted. This scenario led us to consider the possibility that one or both of the diastereomers **5** and **6** might qualify as a suitable precursor. At least two major concerns surfaced immediately. Despite the fact that no prior attention had yet been accorded to 4,4-disubstituted systems of this type, we speculated that reaction with the zirconocene reagent[4] would materialize, particularly at more elevated temperatures, and lead to an intermediate such as **2**. Less certain was the issue of whether the additional substituent on the nucleophilic carbon would serve to retard formation of the C–C cyclobutane bond and to what degree. Also, in light of available precedent, the lack of substitution at C-3 was likely to present itself as a deterrent to high-level diastereoselectivity (Scheme 2).[2]

Our path to the targeted cyclobutanone commenced with the known D-glucose-derived tosylate **7**.[5,6] In order to facilitate elimination of the sulfonate ester, **7** was stirred in acidic methanol at rt to produce regioselectively the side chain diol,[7] oxidative cleavage of which with sodium periodate proceeded well, giving rise to the aldehyde. When the direct



1 2 3

Scheme 1.

Keywords: Zirconocene; Cyclobutanes; Diastereoselectivity; D-Glucose; Ring contraction.
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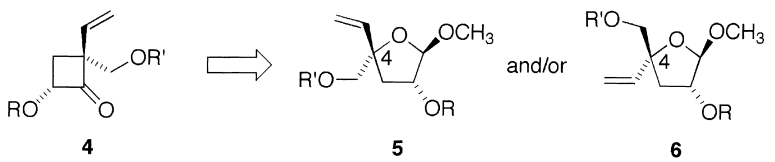
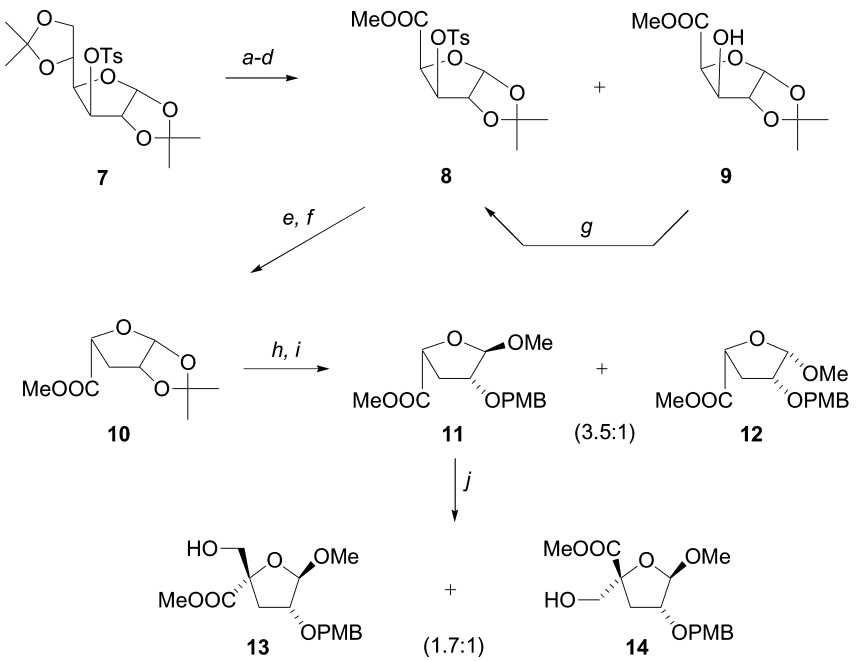
doi:10.1016/j.tet.2003.07.012



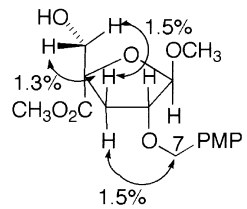
Scheme 2.



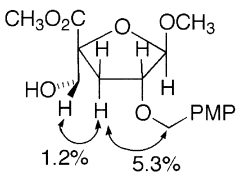
Scheme 3. (a) H^+, MeOH, rt, (b) $NaIO_4$, H_2O, THF, (c) $NaClO_2$, H_2O, CH_3CN, rt, (d) CH_2N_2, ether, (e) DBU, CH_2Cl_2, (f) H_2, 10% Pd/C, EtOH (90% for 6 steps), (g) TsCl, DMAP, Et_3N, CH_2Cl_2, rt, (h) H^+, MeOH, reflux, (i) PMB imidate, CSA, CH_2Cl_2, rt (88% for 2 steps), (j) LDA, THF, −78°C; CH_2O (93%).

oxidation of this intermediate to ester **8** with bromine in methanol[8] met with failure, recourse was made to sequential treatment with sodium chlorite[9] and diazomethane. Although these conditions were met with partial detosylation, it proved a simple matter to return from **9** to **8** (Scheme 3). At this stage, the intended E_2 elimination occurred smoothly in the presence of DBU, making possible a stereocontrolled catalytic hydrogenation to generate **10**. The six-step conversion of **7** is not demanding of chromatographic purification in its intermediary stages and delivers the saturated ester **10** in 92% overall yield.

The latter was subjected to acidic methanol at the reflux temperature to effect removal of the remaining acetonide unit and allow for protection of the C-2 hydroxyl as its *p*-methoxybenzyl ether via the trichloroacetimidate option.[10] As expected on steric grounds, methyl glycoside **11** predominated over **12** by a factor of 3.5:1 (88% yield). The major anomer was readily separated by means of silica gel chromatography and its enolate anion was condensed with formaldehyde in ether.[11] The implementation of this reaction resulted in the formation of **13** and **14**. The diastereomeric ratio of 1.7:1 indicated that π-facial discrimination for electrophilic capture by the conjugate base of **11** was not pronounced. The distinctive structural features of the aldol isomers were apparent following 1D NMR analysis and NOE studies as summarized in **A** and **B**.

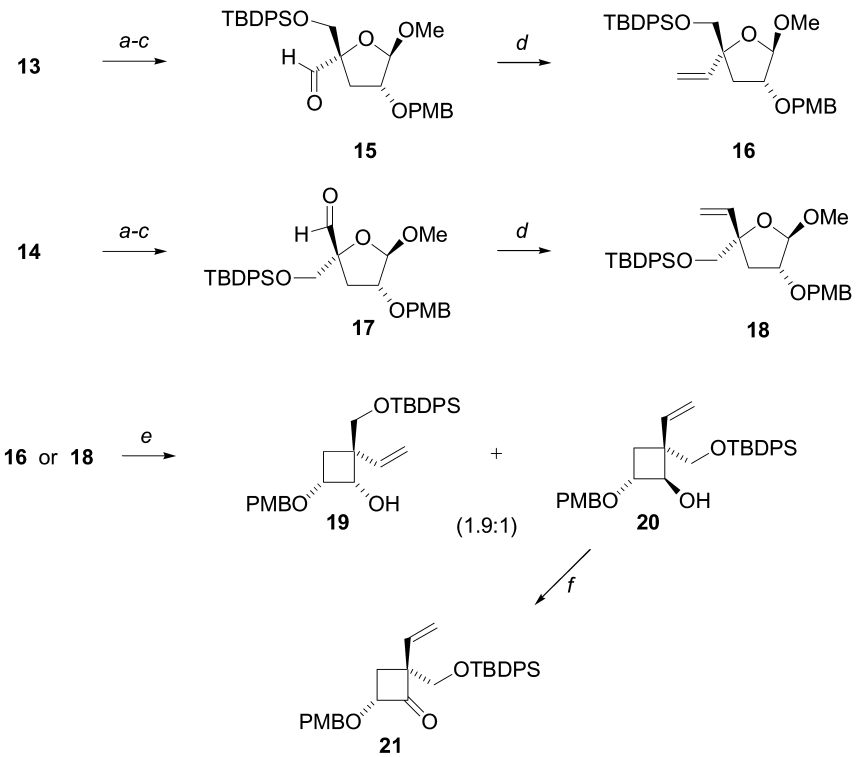


A



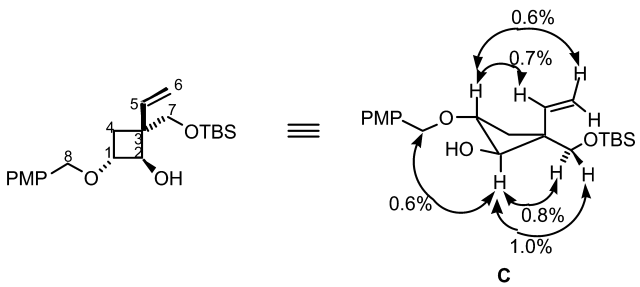
B

With these successes as a platform, the focus was next placed on chemical modification of the carbomethoxy substituent in both series. For this purpose, the primary carbinol was masked with *tert*-butyldiphenylsilyl chloride in advance of diisobutylaluminum hydride reduction to the aldehyde level and Wittig olefination (Scheme 4). It will be appreciated that the conversion of **13** to **16** and of **14** to **18** by this means is not accompanied by any concern regarding epimerization. The reactivity of both 4-vinylfuranosides toward the zirconocene reagent was independently probed and found to deliver the cyclobutanols **19** and **20** in an identical 1.9:1 ratio. The co-addition of boron trifluoride etherate as promoter gave rise to lower yields, messier reaction mixtures, and inverted product ratios. Magnesium bromide was also tested, with similar consequences. We

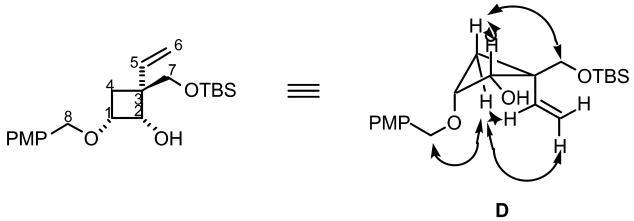


Scheme 4. (a) TBDPSCl, imid, DMF, rt (94%), (b) Dibal-H, CH_2Cl_2, −20°C, (c) Swern, (d) $Ph_3P{=}CH_2$, THF, −30°C→rt (68% for 4 steps), (e) 'Cp_2Zr', THF, 65°C (56–70%), (f) IBX, DMSO, rt (92%).[12]

offer no explanation of these effects at this time. The relative and absolute configurations of **19** and **20** were deduced by detailed NOE measurements. In particular, the observed proximity of H-2 to H-8 in **20** requires that the C-2 hydroxyl be β-oriented as shown in **C**. The α-projection of C-7 follows from the integral enhancement noted between both of its attached methylene protons and H-2. Further confirmation was derived from the interaction of H-1 with H-5 and H-6.



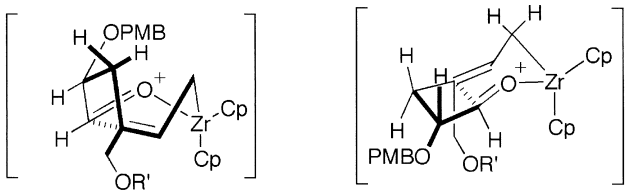
C



D

In the case of **19**, the effect observed between H-8 and H-4α in a NOESY experiment was used to differentiate the methylene pair. Following that assignment, it was possible to define the C-2 hydroxyl as α on the strength of the H-2↔H-4β interaction. The β-orientation of C-7 was similarly deciphered. The readily recognized proximity of H-4α to H-5 and H-6 provided additional compelling confirmatory evidence.

These results bring into focus several mechanistic facets of this fascinating ring contraction. The stereochemical predisposition of the OPMB substituent at C-2 in either reactant has a low-level impact on the distribution of cyclobutanols **19** and **20** as foreshadowed by less substituted congeners. The possibility that the product ratio may depend on the steric bulk of the oxygen protecting group at C-2 was not examined. Significantly, however, the π-facial selectivity of attack by the zirconocene reagent on the vinyl double bond has no major product-determining consequences. This phenomenon may be the result of a substantive kinetic bias for the subsequent ring opening that leads to the *E*-configured allylzirconocene intermediate. The possible operation of a $Z \rightleftarrows E$ isomerization cannot be ruled out, but the *cis* arrangement of the vinyl and hydroxyl groups in **19** and **20** is almost certain to stem from transition states **22** and **23**. Finally, the combined yield of **19** and **20** (56–70%) under purely thermal conditions indicates that the added $CH_2OTBDPS$ substituent is not a deterrent to four-membered ring closure, although kinetic retardation was evident relative to the ring-contracting reactions performed with similar but less crowded examples.



19 20

1. Experimental[13]

1.1. General

1.1.1. Conversion of tosylate 7 to ester 10. A solution of **7**[5,6] (67.0 g, 162 mmol) in methanol (1650 mL) was treated with sulfuric acid (84 mL of 2.5 M), stirred at rt for 16 h, neutralized with concentrated sodium hydroxide, and freed of solvent. The residue was slurried with CH_2Cl_2 (1 L) and the organic phase was dried and evaporated to provide the diol. The latter was directly dissolved in THF (500 mL), cooled to 0 °C, and treated with a solution of sodium periodate (52 g, 243 mmol) in water (700 mL). The reaction mixture was stirred overnight, the THF was removed under reduced pressure, and ethyl acetate (500 mL) was introduced. The separated organic phase was washed with water (200 mL) and brine (200 mL), the aqueous layers were combined and extracted with ethyl acetate (3×200 mL), and the unified organic phases were dried and evaporated to furnish the aldehyde that was directly submitted to oxidation.

The above material dissolved in acetonitrile (440 mL) was treated sequentially with a solution of sodium dihydrogen phosphate (33.7 g, 244 mmol) in water (120 mL) and 30% hydrogen peroxide (25 mL). This mixture was cooled to 0 °C prior to the introduction of sodium chlorite (22.1 g, 244 mmol) dissolved in water (120 mL). The reaction mixture was allowed to warm to rt, stirred overnight, and freed of acetonitrile under reduced pressure. The resulting aqueous solution was extracted with ethyl acetate (2×200 mL). The aqueous layer was acidified with citric acid to pH 1–2 and extracted with ethyl acetate (2×200 mL). The combined organic phases were washed with brine (300 mL), dried, concentrated to a volume of 300 mL, and treated with an excess of diazomethane until N_2 effervescence stopped. The solvent was evaporated and the residual ester was dissolved in CH_2Cl_2 (200 mL). To this solution was added 4-(dimethylamino)pyridine (2.0 g, 16 mmol), triethylamine (3.5 mL, 25 mmol), and tosyl chloride (5.0 g, 26 mmol), and the resulting mixture was stirred overnight at rt prior to dilution with ether (500 mL), filtration, and sequential washing with saturated calcium sulfate, sodium bicarbonate, and sodium chloride solutions (200 mL of each). The organic layer was dried and evaporated to give ester **8**. The latter was directly dissolved in CH_2Cl_2 (400 mL), treated with DBU (25.2 g, 166 mmol), stirred at rt for 5 h, concentrated to a volume of 100 mL, and diluted with ethyl acetate (200 mL) prior to filtration through a pad of silica gel. Solvent evaporation furnished the unsaturated ester, which was taken up in ethanol (100 mL), and hydrogenated over 5% Pd/C (1.3 g) under an atmosphere of H_2 (40 psi). After 1 h, the reaction mixture was filtered through Celite, concentrated, and subjected to chromatography on silica gel. Elution with 3:2 hexanes/ethyl acetate afforded pure **10** as a colorless oil (29.4 g, 90% over six steps); IR (neat, cm^{-1}) 1757, 1734; ^1H NMR (300 MHz, $CDCl_3$) δ 5.78 (d, J=3.4 Hz, 1H), 4.63 (t, J=4.2 Hz, 1H), 4.55 (dd, J=0.9, 9.2 Hz, 1H), 3.69 (s, 3H), 2.59 (dd, J=0.5, 14.1 Hz, 1H), 2.23 (ddd, J=4.8, 9.2, 14.1 Hz, 1H), 1.38 (s, 3H), 1.21 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.0, 112.4, 106.8, 79.3, 76.9, 51.8, 34.8, 25.5 (2C); ES HRMS m/z $(M+Na)^+$ calcd 225.0733, obsd 225.0740; $[\alpha]_D^{20}=-63.3$ (c 1.03, $CHCl_3$).

Anal. calcd for $C_9H_{14}O_5$: C, 53.46; H, 6.98. Found: C, 53.28; H, 7.03.

1.1.2. Transformation of 10 into esters 11 and 12. A solution of **10** (5.00 g, 24.7 mmol) in methanol (100 mL) was treated with concentrated HCl (1.3 mL), refluxed for 1 h, neutralized with solid $NaHCO_3$ (5 g), and freed of methanol under reduced pressure. The residue was taken up in CH_2Cl_2 (300 mL), dried, and evaporated to leave a mixture of hydroxy methyl glycosides. This material was dissolved in CH_2Cl_2 (100 mL), treated with *p*-methoxybenzyl trichloroacetimidate (9.21 g, 32.6 mmol), and cooled to 0 °C. Camphorsulfonic acid (380 mg, 1.63 mmol) was introduced and the reaction mixture was stirred for 24 h at 0 °C and 2 days at rt, quenched with saturated $NaHCO_3$ solution, diluted with CH_2Cl_2 (300 mL), and worked up in the predescribed manner. Medium-pressure liquid chromatography on silica gel (elution with 7:3 hexanes/ethyl acetate) afforded **11** (3.88 g) and **12** (1.10 g) in 88% overall yield for 2 steps. The minor product remained contaminated with minor impurities and was not fully characterized.

For **11**: colorless oil; IR (neat, cm^{-1}) 1759, 1731, 1613; ^1H NMR (300 MHz, $CDCl_3$) δ 7.21 (m, 2H), 6.86 (m, 2H), 5.10 (s, 1H), 4.63 (dd, J=4.5, 9.0 Hz, 1H), 4.43 (s, 2H), 3.93 (dd, J=2.1, 5.5 Hz, 1H), 3.79 (s, 3H), 3.74 (s, 3H), 3.37 (s, 3H), 2.46 (ddd, J=5.5, 9.0, 13.5 Hz, 1H), 2.27 (ddd, J=2.1, 4.5, 13.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.4, 159.3, 129.7, 129.2, 113.8, 108.0, 81.1, 75.9, 70.8, 55.2, 55.0, 52.2, 34.0; ES HRMS m/z $(M+Na)^+$ calcd 319.1152, obsd 319.1161; $[\alpha]_D^{20}=-27.4$ (c 1.96, $CHCl_3$).

Anal. calcd for $C_{15}H_{20}O_6$: C, 60.80; H, 6.80. Found: C, 61.00; H, 6.77.

1.1.3. Hydroxymethylation of 11. *n*-Butyllithium (36.4 mL of 1.5 M in hexanes, 54.6 mmol) was added to a cold (−30 °C) solution of diisopropylamine (10.2 mL, 72.8 mmol) in dry THF (80 mL). The reaction mixture was stirred for 20 min at this temperature, then cooled to −78 °C in advance of the introduction of a solution of **11** (10.8 g, 36.4 mmol) in THF (30 mL). After 1 h of stirring, a solution of excess formaldehyde dissolved in THF was added until the color of the reaction mixture turned light brown. Subsequent

warming to −10 °C was followed by a quench with saturated NH_4Cl solution (50 mL) and subsequent dilution with ethyl acetate (500 mL) and water (200 mL). The resulting organic phase was dried and concentrated to leave a residue that was chromatograhed on silica gel. Elution with 2:3 hexanes/ethyl acetate gave **13** (7.03 g, 59%) and **14** (4.08 g, 34%).

For **13**: colorless oil; IR (neat, cm^{-1}) 3480, 1733, 1613; ^1H NMR (300 MHz, $CDCl_3$) δ 7.16 (m, 2H), 6.82 (m, 2H), 5.05 (s, 1H), 4.38 (ABq, J=11.4 Hz, $\Delta\nu$=14.2 Hz, 2H), 3.91 (d, J=4.3 Hz, 1H), 3.80 (d, J=11.4 Hz, 1H), 3.74 (s, 3H), 3.67 (s, 3H), 3.61 (d, J=11.4 Hz, 1H), 3.36 (s, 3H), 2.52 (br s, 1H), 2.43 (d, J=13.8 Hz, 1H), 2.21 (dd, J=4.9, 13.8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.9, 159.1, 129.4, 129.0, 113.6, 108.4, 88.3, 81.4, 70.4, 67.0, 55.2, 55.0, 52.4, 34.8; ES HRMS m/z $(M+Na)^+$ calcd 349.1258, obsd, 349.1249; $[\alpha]_D^{20}$=−39.1 (c 1.71, $CHCl_3$).

For **14**: colorless oil; IR (neat, cm^{-1}) 3490, 1737, 1613; ^1H NMR (300 MHz, $CDCl_3$) δ 7.22 (m, 2H), 6.86 (m, 2H), 5.01 (s, 1H), 4.44 (ABq, J=11.3 Hz, $\Delta\nu$=15.5 Hz, 2H), 3.96 (d, J=5.0 Hz, 1H), 3.80 (ABq, J=11.3 Hz, $\Delta\nu$=19.9 Hz, 2H), 3.78 (s, 3H), 3.75 (s, 3H), 3.39 (s, 3H), 2.63 (br s, 1H), 2.50 (dd, J=5.6, 14.3 Hz, 1H), 2.18 (d, J=14.3 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.3, 159.4, 129.3, 129.2, 113.9, 107.9, 87.3, 81.7, 70.9, 67.0, 55.2, 54.8, 52.3, 35.1; ES HRMS m/z $(M+Na)^+$ calcd 349.1258, obsd 349.1235.

1.1.4. Conversion of 13 to 16. To a solution of **13** (810 mg, 2.48 mmol) and imidazole (835 mg, 12.2 mmol) in DMF (10 mL) was added *tert*-butyldiphenylsilyl chloride (823 mg, 3.0 mmol). The reaction mixture was stirred at rt for 3 h before being quenched with water (30 mL) and diluted with ethyl acetate (200 mL). The separated organic layer was washed with brine, dried, and evaporated to leave a residue, chromatography of which on silica gel (elution with 7:1 hexanes/ethyl acetate) provided pure silyl ether (1.30 g, 94%) as a colorless oil; IR (neat, cm^{-1}) 1730, 1514, 1250; ^1H NMR (300 MHz, $CDCl_3$) δ 7.73–7.65 (m, 4H), 7.41 (m, 6H), 7.22 (m, 2H), 6.86 (m, 2H), 5.15 (s, 1H), 4.43 (s, 2H), 3.98 (d, J=10.1 Hz, 1H), 3.90 (d, J=4.1 Hz, 1H), 3.80 (s, 3H), 3.74 (d, J=10.1 Hz, 1H), 3.73 (s, 3H), 3.33 (s, 3H), 2.55 (d, J=13.7 Hz, 1H), 2.06 (dd, J=4.7, 13.7 Hz, 1H), 1.05 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.3, 159.2, 135.6 (2C), 133.1, 133.0, 129.8, 129.7, 129.1, 127.7, 127.6, 113.7, 108.0, 88.6, 81.1, 70.3, 69.5, 55.2, 54.8, 52.3, 35.6, 26.6, 19.2; ES HRMS m/z $(M+Na)^+$ calcd 587.2436, obsd 587.2410; $[\alpha]_D^{20}$=−13.8 (c 2.68, $CHCl_3$).

A cold (−78 °C) solution of the above ester (1.21 g, 2.14 mmol) in CH_2Cl_2 (15 mL) was treated with diisobutylaluminum hydride (6.3 mL of 1.0 M in hexanes, 6.3 mmol). The reaction mixture was warmed to −20 °C, stirred for 1 h, and quenched with sodium potassium tartrate solution (20%, 20 mL). Stirring was maintained until a clear phase separation had been achieved. The aqueous phase was extracted with CH_2Cl_2 (2×100 mL) and the combined organic phases were washed with brine (100 mL) prior to drying and evaporation. The resulting alcohol was used directly.

To CH_2Cl_2 (20 mL) containing 1.0 mL of DMSO was added oxalyl chloride (280 μL) at −78 °C. After 20 min of stirring, the alcohol from above was introduced as a solution in CH_2Cl_2 (7 mL). The reaction mixture was stirred for 1 h at −78 °C, quenched with triethylamine (3 mL), and warmed to rt before being treated with saturated $NaHCO_3$ solution (20 mL) and diluted with CH_2Cl_2 (100 mL). The separated organic phase was dried and evaporated to furnish the aldehyde that was carried forward without delay.

To a solution of methyltriphenylphosphonium bromide (1.53 g, 4.28 mmol) in THF (15 mL) was added *n*-butyllithium (2.3 mL of 1.5 M in hexanes, 3.45 mmol) at −30 °C and this mixture was stirred for 20 min before the aldehyde was introduced as a solution in THF (8 mL) and for 3 h at rt before being quenched with saturated $NaHCO_3$ solution (5 mL), diluted with ethyl acetate (300 mL) and washed with brine (100 mL). The organic phase was dried and evaporated to leave a residue that was chromatographed on silica gel. Elution with 15:1 hexanes/ethyl acetate gave **16** as a colorless oil (847 mg, 74% over three steps); IR (neat, cm^{-1}) 1613, 1588, 1514; ^1H NMR (300 MHz, $CDCl_3$) δ 7.67 (m, 4H), 7.40 (m, 6H), 7.24 (m, 2H), 6.87 (m, 2H), 6.10 (dd, J=10.8, 17.4 Hz, 1H), 6.34 (dd, J=1.6, 17.4 Hz, 1H), 6.13 (dd, J=1.6, 10.8 Hz, 1H), 5.01 (s, 1H), 4.44 (s, 2H), 3.97 (ddd, J=1.0, 2.6, 6.1 Hz, 1H), 3.80 (s, 3H), 3.62 (s, 2H), 3.28 (s, 3H), 2.35 (dd, J=6.1, 13.5 Hz, 1H), 2.01 (dd, J=2.6, 13.5 Hz, 1H), 1.07 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.2, 141.0, 135.7, 133.5, 130.1, 129.6, 129.2, 127.6, 113.8, 113.3, 108.2, 87.0, 83.2, 70.8, 69.8, 55.3, 54.7, 37.2, 26.8, 19.3; ES HRMS m/z $(M+Na)^+$ calcd 555.2537, obsd 555.2537; $[\alpha]_D^{20}$=−14.8 (c 2.04, $CHCl_3$).

Anal. calcd for $C_{32}H_{40}O_5Si$: C, 72.14; H, 7.57. Found: C, 71.90; H, 7.59.

1.1.5. Conversion of 14 to 18. A 763 mg (2.34 mmol) sample of **14** was reacted with *tert*-butyldiphenylsilyl chloride (820 mg, 3.00 mmol) and imidazole (820 mg, 12.0 mmol) in DMF (10 mL) as described above to give 1.21 g (92%) of the silyl ether as a colorless oil; IR (neat, cm^{-1}) 1738, 1614, 1586; ^1H NMR (300 MHz, $CDCl_3$) δ 7.65 (m, 4H), 7.37 (m, 6H), 7.13 (m, 2H), 6.82 (m, 2H), 4.96 (s, 1H), 4.37 (s, 2H), 4.03 (d, J=9.5 Hz, 1H), 3.96 (dd, J=1.4, 6.0 Hz, 1H), 3.88 (d, J=9.5 Hz, 1H), 3.80 (s, 3H), 3.75 (s, 3H), 3.36 (s, 3H), 2.72 (dd, J=6.0, 14.2 Hz, 1H), 2.11 (dd, J=1.4, 14.2 Hz, 1H), 1.04 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.2, 159.2, 135.7, 135.6, 133.4, 133.2, 129.8, 129.6, 129.1, 127.6 (2C), 113.8, 108.0, 87.2, 82.3, 70.9, 68.9, 55.3, 54.7, 52.1, 35.4, 26.7, 19.3; ES HRMS m/z $(M+Na)^+$ calcd 587.2436, obsd 587.2477; $[\alpha]_D^{20}$=−31.7 (c 3.29, $CHCl_3$).

Reduction of the above ester (1.21 g, 2.14 mmol) with diisobutylaluminum hydride (6.3 mL of 1.0 M in hexanes, 6.3 mmol) at −78 to −20 °C in the predescribed manner provided the primary alcohol that was directly oxidized by the Swern method detailed above. The resulting unpurified aldehyde **17** was treated with the ylide prepared from *n*-butyllithium (2.3 mL of 1.5 M in hexanes, 3.45 mmol) and methyltriphenylphosphonium bromide (1.53 g, 4.28 mmol). There was isolated 847 mg (74% over three steps) of **18** as a colorless oil; IR (neat, cm^{-1}) 1613, 1514, 1470; ^1H NMR (300 MHz, $CDCl_3$) δ 7.67 (m, 4H), 7.34 (m, 6H), 7.18 (m, 2H), 6.84 (m, 2H), 6.12 (dd, J=10.8, 17.4 Hz,

1H), 5.33 (dd, J=1.6, 17.4 Hz, 1H), 5.11 (dd, J=1.6, 10.8 Hz, 1H), 4.95 (d, J=1.1 Hz, 1H), 4.42 (s, 2H), 3.99 (ddd, J=1.1, 3.3, 6.1 Hz, 1H), 3.81 (s, 3H), 3.77 (d, J=9.5 Hz, 1H), 3.64 (d, J=9.5 Hz, 1H), 3.38 (s, 3H), 2.40 (dd, J=3.3, 13.5 Hz, 1H), 2.10 (dd, J=6.1, 13.5 Hz, 1H), 1.07 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.2, 141.6, 135.7 (2C), 133.6 (2C), 130.1, 129.5 (2C), 129.1, 127.5, 113.8, 113.2, 108.4, 87.0, 83.1, 71.0, 69.3, 55.3, 55.1, 36.5, 26.9, 19.4; ES HRMS m/z $(M+Na)^+$ calcd 555.2537, obsd 255.2537; $[\alpha]_D^{20}=-51.8$ (c 1.70, $CHCl_3$).

Anal. calcd for $C_{32}H_{40}O_5Si$: C, 72.14; H, 7.57. Found: C, 72.02; H, 7.56.

1.1.6. Ring contraction of 16. To a THF solution (4 mL) of zirconocene dichloride (82.4 mg, 0.282 mmol) was added *n*-butyllithium (0.38 mL of 1.5 M, 0.57 mmol) at −78 °C and the reaction mixture was stirred for 1 h prior to the introduction of **16** (100 mg, 0.188 mmol) dissolved in THF (3 mL) and warming to rt. After 9 h, the reaction temperature was raised to 55 °C and stirring was maintained overnight prior to quenching with 1N HCl (1 mL) and extraction with ethyl acetate (3×50 mL). The combined organic layers were washed with saturated $NaHCO_3$ solution (30 mL), dried, and evaporated. The residue was chromatographed on silica gel (elution with 5:1 hexanes/ethyl acetate) to deliver **19** (29 mg) and **20** (21 mg) in 70% combined yield based on 25% recovered starting material.

For **19**: colorless oil; IR (neat, cm^{-1}) 3544, 1612, 1514; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.65 (m, 4H), 7.41 (m, 6H), 7.27 (m, 2H), 6.89 (m, 2H), 5.95 (dd, J=10.9, 17.6 Hz, 1H), 5.26 (dd, J=1.3, 10.9 Hz, 1H), 5.09 (dd, J=1.3, 17.6 Hz, 1H), 4.46 (s, 2H), 4.41(m, 1H), 4.17 (m, 1H), 3.81 (s, 3H), 3.64 (d, J=10.1 Hz, 1H), 3.46 (d, J=10.1 Hz, 1H), 2.57 (br s, 1H), 2.27 (ddd, J=2.3, 6.8, 12.7 Hz, 1H), 2.10 (dd, J=4.9, 12.7 Hz, 1H), 1.06 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.3, 137.6, 135.6, 133.3, 133.2, 129.9, 129.7, 129.5, 127.7, 116.5, 113.8, 71.6, 71.3, 70.8, 67.9, 55.2, 49.9, 31.1, 26.8, 19.3; ES HRMS m/z $(M+Na)^+$ calcd 525.2432, obsd 525.2429; $[\alpha]_D^{20}=-25.6$ (c 1.28, $CHCl_3$).

For **20**: colorless oil; IR (neat, cm^{-1}) 3440, 1613, 1587; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.66 (m, 4H), 7.40 (m, 6H), 7.29 (m, 2H), 6.88 (m, 2H), 5.89 (dd, J=11.0, 17.7 Hz, 1H), 5.30 (dd, J=1.1, 11.0 Hz, 1H), 5.19 (dd, J=1.1, 17.7 Hz, 1H), 4.49 (s, 2H), 4.22 (d, J=6.4 Hz, 1H), 3.81 (s, 3H), 3.77 (dt, J=6.4, 8.4 Hz, 1H), 3.65 (d, J=10.2 Hz, 1H), 3.50 (d, J=10.2 Hz, 1H), 2.13 (dd, J=8.4, 11.2 Hz, 1H), 1.79 (dd, J=8.4, 11.2 Hz, 1H), 1.72 (br s, 1H), 1.09 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.1, 137.0, 135.6, 133.4, 130.4, 129.7, 129.4, 127.7, 117.1, 113.7, 78.0, 75.1, 70.5, 67.3, 55.2, 45.4, 27.7, 26.9, 19.4; ES HRMS m/z $(M+Na)^+$ calcd 525.2432, obsd 525.2423; $[\alpha]_D^{20}=+10.2$ (c 0.66, $CHCl_3$).

The entirely comparable treatment of **17** with the zirconocene reagent prepared from the same quantity of reagents resulted in the isolation of 24 mg of **19** and 18 mg of **20** (56% yield based on 19% recovered starting material).

1.1.7. Oxidation of 20 to 21. To a DMSO solution (2 mL) of **20** (241 mg, 0.479 mmol) was added 1-hydroxy-1,2-benziodoxol-3(1*H*)-one 1-oxide (IBX, 364 mg, 1.30 mmol) dissolved in DMSO (2 mL) and the reaction mixture was stirred overnight at rt prior to the introduction of ethyl acetate (4 mL) and water (4 mL), and filtration through a cotton plug. The organic phase was washed with brine, dried, and concentrated to leave a residue that was chromatographed on silica gel. Elution with 10:1 hexanes/ethyl acetate provided 220 mg (92%) of **21** as a colorless oil; IR (neat, cm^{-1}) 1782, 1613, 1514; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.68 (m, 4H), 7.41 (m, 6H), 7.30 (m, 2H), 6.89 (m, 2H), 5.73 (dd, J=10.4, 17.3 Hz, 1H), 5.16 (d, J=17.3 Hz, 1H), 5.12 (d, J=10.4 Hz, 1H), 4.79 (dd, J=8.3, 9.9 Hz, 1H), 4.74 (d, J=11.3 Hz, 1H), 4.58 (d, J=11.3 Hz, 1H), 3.96 (d, J=10.3 Hz, 1H), 3.82 (s, 3H), 3.52 (d, J=10.3 Hz, 1H), 2.62 (dd, J=8.3, 11.3 Hz, 1H), 2.40 (dd, J=9.9, 11.3 Hz, 1H), 1.06 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 207.6, 159.4, 135.7, 135.6, 134.6, 133.3, 132.9, 129.7 (2C), 129.6 (2C), 127.7, 116.4, 113.8, 84.0, 71.6, 66.3, 64.8, 55.2, 27.6, 26.7, 19.3; ES HRMS m/z $(M+Na)^+$ calcd 523.2275, obsd 523.2242; $[\alpha]_D^{20}=-2.9$ (c 1.2, $CHCl_3$).

Acknowledgements

We thank the Yamanouchi USA Foundation and the National Science Foundation for their support of our research program.

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