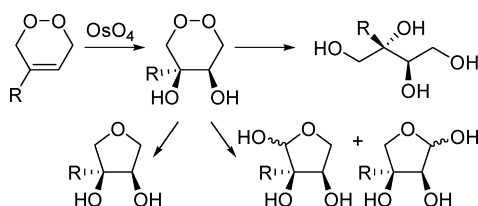## Dihydroxylation of 4-Substituted 1,2-Dioxines: A Concise Route to Branched Erythro Sugars

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The synthesis of 2-*C*-branched erythritol derivatives, including the plant sugar (±)-2-*C*-methylerythritol **2**, was achieved through a dihydroxylation/reduction sequence on a series of 4-substituted 1,2-dioxines **3**. The asymmetric dihydroxylation of 1,2-dioxines was examined, providing access to optically enriched dihydroxy 1,2-dioxanes **4**. The synthesized 1,2-dioxanes were converted to other erythro sugar analogues and tetrahydrofurans through controlled cleavage of the endoperoxide linkage.

Branched-chain sugars represent a rare class of naturally occurring carbohydrates found in plants and antibiotics.[1] The first and probably best-known example is apiose **1** (Figure 1), which was initially isolated from parsley[2] and is found in many plants as a structural component of glycosides, such as apiin.[3] Subsequently, numerous other examples of branched carbohydrates have been isolated from natural sources, and many nonnatural compounds have been synthesized.[4] Of recent interest
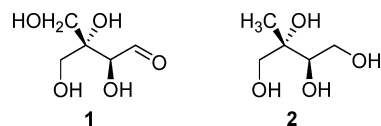

FIGURE 1. Apiose **1** and 2-*C*-methylerythritol (ME) **2**.

is the branched plant sugar 2-*C*-methylerythritol (ME, **2**), which has been implicated in the biosynthesis of isoprenoids via the mevalonate independent methylerythritol phosphate (MEP) pathway.[5]

Free ME has also been isolated from many plants, such as *Convolvulus glomeratus*.[6] In addition, an important study by Claeys et al. found significant quantities of methylerythritol and its diastereomer methylthreitol in the atmosphere above the Amazonian rainforest.[7] It has been postulated that the tetrols are formed from photooxidation of isoprene (emitted from the forest) and are now considered significant secondary organic aerosols worldwide.[8]

The recent discoveries of the role ME plays in nature has provoked the development of several synthetic routes to both racemic and enantiopure 2-*C*-methylerythritol, as well as various phosphate derivatives.[9] Given that animals lack the MEP pathway, it seems an obvious target for the development of herbicides and antibacterial agents.[10] To this end efforts toward the synthesis of other ME analogues have begun with the recent reporting of trifluoromethyl[11] and amino analogues.[12] However, to the best of our knowledge no general route to 2-*C*-branched erythritol derivatives has been reported, which is vital for providing access to a diverse range of compounds necessary for further biochemical studies and biological testing.

It was proposed that a general and concise synthesis of 2-*C*-branched erythritol derivatives, including ME, could be ac-

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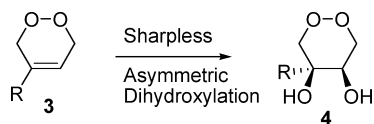
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SCHEME 1

TABLE 1. Asymmetric Dihydroxylation of 4-Substituted 1,2-Dioxines 3

entry[a]	R	ligand	product (yield)	ee
1	Ph	(DHQD)$_2$PHAL[b]	**4a** (33)	87
2	Ph	(DHQD)$_2$PHAL	**4a** (70)	93
3	Ph	(DHQD)$_2$PHAL[c]	**4a** (40)	89
4	Ph	(DHQ)$_2$PHAL	**4a** (68)	85
5	c-C$_6$H$_{11}$	(DHQD)$_2$PHAL	**4b** (90)	85
6	c-C$_6$H$_{11}$	(DHQD)$_2$AQN	**4b** (99)	70
7	c-C$_6$H$_{11}$	(DHQD)$_2$PYR	**4b** (75)	89
8	1-Ad	(DHQD)$_2$PHAL	**4c** (91)	80
9	Me	(DHQD)$_2$PHAL	**4d** (63)	10
10	Bn	(DHQD)$_2$PHAL	**4e** (65)	40
11	n-C$_6$H$_{13}$	(DHQD)$_2$PHAL	**4f** (83)	93

[a] Reactions were typically performed using 0.3 mmol of olefin in H$_2$O (1.5 mL) and t-BuOH (1.5 mL), with K$_2$CO$_3$ (0.9 mmol), K$_3$Fe(CN)$_6$ (0.9 mmol), MeSO$_2$NH$_2$ (0.3 mmol), K$_2$OsO$_4$ (2 mol %), and chiral ligand (5 mol %) at 25 °C unless otherwise stated. [b] Only 1 mol % ligand and 0.4 mol % K$_2$OsO$_4$·2H$_2$O were used. [c] Reaction was perfomed at 0 °C until complete by TLC.

complished by application of the photooxidation, dihydroxylation, and reduction strategy, previously reported by us, to 1,3-butadienes.[13] The Sharpless asymmetric dihydroxylation has previously been utilized for the de novo synthesis of carbohydrates.[14] Application of this reaction to achiral 1,2-dioxines should also provide access to optically enriched erythritols. Moreover, cleavage of the endoperoxide bond can be controlled under suitable conditions, which should provide access to other branched erythro sugars from the common dihydroxy 1,2-dioxane **4** starting material.

We now wish to report the first examples of the asymmetric dihydroxylation of 1,2-dioxines and the conversion of the dihydroxy 1,2-dioxanes to various branched erythro sugars and tetrahydrofurans, including the plant sugar (±)-2-C-methyl-erythritol **2**.

A series of known 4-substituted 1,2-dioxines **3** were conveniently prepared by photo-oxidation of the requisite 1,3-butadienes. The racemic dihydroxylation of these endoperoxides was then performed using the modified Upjohn conditions described by Sharpless[15] and previously reported by us[13] (see Supporting Information for yields). Logically we then examined the asymmetric dihydroxylation of 1,2-dioxines, which has not previously been reported (Scheme 1).

Phenyl-substituted 1,2-dioxine **3a** was chosen as the model substrate. We began with the conditions reported by Sharpless[16] (Table 1, entry 1). Although high asymmetric induction was achieved, the reaction was sluggish and the yield was low (33%), mainly due to competing base-catalyzed decomposition of the

SCHEME 2

		Yield
5a	R = Ph	71%
5b	R = c-C$_6$H$_{11}$	80%
5c	R = 1-Ad	84%
2	R = Me	73%
5e	R = Bn	74%
5f	R = n-C$_6$H$_{13}$	78%
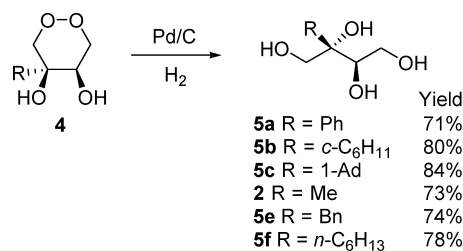
1,2-dioxine caused by the presence of K$_2$CO$_3$.[17] This was somewhat surprising as trisubstituted olefins are considered "standard" substrates in the Sharpless asymmetric dihydroxylation and usually go to completion in under 24 h at 0 °C.[16]

To suppress decomposition, we decided to increase the reaction rate by employing a "super" AD-mix (entry 2).[18] As anticipated the use of a super AD-mix consisting of 2 mol % K$_2$OsO$_4$ and 5 mol % phthalazine (PHAL) ligand gave a significant increase in reaction rate and hence an increased yield as well as a slight increase in ee, thus becoming the preferred conditions for the asymmetric dihydroxylation of 4-substituted 1,2-dioxines. The use of other readily available quinidine-based ligands produced slight variations in yield and ee (entries 6 and 7).

The remainder of the 1,2-dioxines were dihydroxylated using the optimized super AD-mix conditions (entries 5, 8−11). While the ee was high for bulky substituents (compounds **4a,b,c**), there was poor selectivity with methyl-substituted 1,2-dioxine **4d**. This was disappointing but not unexpected. Sharpless has previously reported that for high asymmetric induction in cyclic trisubstituted olefins, the substituent must be bulky, with best results for aryl substituents.[16]

The enantioselectivities were determined by derivatization of the diols as their mono-TMS ethers, followed by ^{1}H NMR chiral shift experiments using the distinct TMS group as a reference point, which is a method favored by Warren and co-workers.[19] (see Supporting Information for conditions and characterization data).

While the preliminary results presented above are promising, some clear limitations for the asymmetric dihydroxylation of 4-substituted 1,2-dioxines are evident. The enantioselectivity of the less bulky substituents (compounds **4d,e**) was poor; therefore other ligands may need to be explored to accommodate a broader substitution pattern. Unfortunately 1,2-dioxines are inherently base-sensitive, which results in decomposition using the Sharpless AD conditions. Ideally, asymmetric dihydroxylation of 1,2-dioxines would be carried out under neutral or mildly acidic conditions; however, no adequate methodology encompassing these factors currently exists.

With the dihydroxy 1,2-dioxanes in hand, we next examined reduction of the peroxide linkage to furnish the desired 2-C-branched erythritol derivatives, Scheme 2.

For convenience the racemic diols were used. Hydrogenation over palladium on carbon returned high yields of all of the tetraols, which were readily purified by chromatography and/or recrystallization from ethyl acetate. Tetraol **2** was spectroscopically consistent with data previously reported for the plant sugar 2-C-methyl-D-erythritol.[20]

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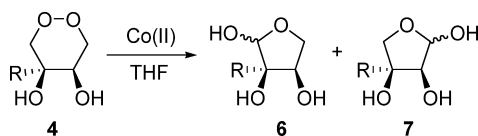
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SCHEME 3

TABLE 2. Ring Opening of Dihydroxy 1,2-Dioxanes 4 with Co(SALEN)₂

entry	R	products	yield[a]	6:7[b]
1	Ph	**6a, 7a**	92	59:41
2	c-C₆H₁₁	**6b, 7b**	91	52:48
3	1-Ad	**6c, 7c**	98	49:51
4	Me	**6d, 7d**	87	60:40
5	Bn	**6e, 7e**	89	59:41
6	n-C₆H₁₃	**6f, 7f**	87	55:45

[a] Refers to the combined isolated yield of both regio-isomers. [b] Ratio was determined by isolated mass after chromatography.

Thus starting from isoprene, the synthesis of (±)-2-*C*-methylerythritol was accomplished in three steps using a photo-oxidation/dihydroxylation/reduction sequence, with an overall yield of 25%.

The reactions of endoperoxides with transition metals such as Co(II) have been well documented.[21] Thus when the racemic dihydroxy 1,2-dioxanes **4** were treated with a catalytic quantity of Co(SALEN)₂ the 2- and 3-branched erythroses **6** and **7**, respectively, were obtained via a one-electron reduction process, Scheme 3.
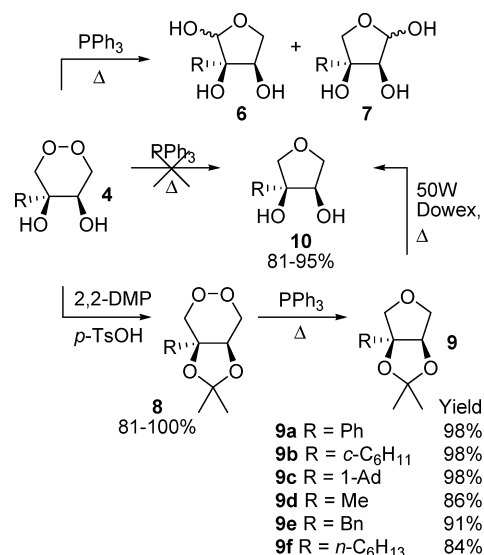
The regioisomers were readily separable by chromatography and completely stable at room temperature, providing a high combined yield for each example, Table 2. All compounds were found to exist solely in the cyclic hemiacetal form(s) both when neat and in solution, indicated by the absence of a carbonyl group in both the IR and NMR spectra, respectively.

It was recently reported that the reaction of monocyclic 1,2-dioxines and epoxy 1,2-dioxanes with triphenylphosphine may yield tetrahydrofurans.[22] Application of this methodology to the dihydroxy 1,2-dioxanes **4** would provide direct access to novel 3,4-dihydroxy THFs **10**, Scheme 4.

However, when subjected to the necessary conditions, only the ring-opened products **6** and **7** were observed. We have previously noted that dihydroxy 1,2-dioxanes tend to be thermally unstable;[13] however, elevated temperature is required for oxygen extrusion to be favored. We also previously observed that acetal protection of the diol unit dramatically increases the stability of the 1,2-dioxanes. Therefore, after preparation of the acetonide-protected 1,2-dioxanes **8** the reaction was repeated, this time returning the desired THFs **9** in excellent yields.

Hydrolysis of the acetonide unit was accomplished with acidic Dowex resin, furnishing the novel 3,4-dihydroxy THFs **10** in high yield. Both the protected and dihydroxy THFs **9** and **10** all gave spectral data consistent with their molecular structures. The extrusion of oxygen was confirmed by mass spectrometry and elemental analysis. In addition, the structures of **9a** and **10a** were unambiguously confirmed by X-ray analysis.

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SCHEME 4

	Yield
9a R = Ph	98%
9b R = c-C₆H₁₁	98%
9c R = 1-Ad	98%
9d R = Me	86%
9e R = Bn	91%
9f R = n-C₆H₁₃	84%

In summary, we have presented the first examples of the asymmetric dihydroxylation of 1,2-dioxines providing access to optically enriched dihydroxy 1,2-dioxanes. By chemoselective transformation of these central building blocks a general route to branched erythritol, erythrose, and tetrahydrofuran core structures was established. The efficiency of this methodology was highlighted by the three-step synthesis of (±)-2-*C*-methylerythritol.

Experimental Section

General Procedure for the Racemic Dihydroxylation of 4-Substituted 1,2-Dioxines 3 To Give Dihydroxy 1,2-Dioxanes 4. To a stirred solution of 1,2-dioxine (1 mmol) in *t*-BuOH or CH₃CN (5 mL) and water (5 mL) were added K₂OsO₄ (0.5 mol %) and citric acid (2 mmol), followed by NMO (1.1 mmol), and the bright yellow/green mixture stirred rapidly until complete by TLC. Completion of the reaction was usually accompanied by a characteristic fading of the yellow/green color. The reaction was extracted with CH₂Cl₂ or ethyl acetate (4 × 50 mL), dried (Na₂SO₄), and concentrated in vacuo, and the crude material purified by flash chromatography to furnish the pure dihydroxy 1,2-dioxanes.

(±)-(4S,5R)-4-Methyl-1,2-dioxane-4,5-diol (4d). Colorless oil (569 mg, 85%); R_f 0.33 (7:3 ethyl acetate/hexane). IR (neat): 3418, 1429, 1374, 1242, 1161, 1014, 972 cm⁻¹. ¹H NMR (300 MHz, CDCl₃ + 2 drops d_6-DMSO): δ 1.31 (s, 3H), 2.51 (br s, 2H), 3.63 (dd, J = 4.5, 8.1 Hz, 1H), 4.07–4.09 (m, 2H), 4.12 (dd, J = 8.1, 12.3 Hz, 1H), 4.24 (dd, J = 4.5, 12.3 Hz, 1H). ¹³C NMR (75 MHz, CDCl₃ + 2 drops d_6-DMSO): δ 21.3, 67.8, 69.2, 73.7, 79.2. MS *m/z* (EI): 135 (M⁺ + H, 5), 117 (16), 91 (14), 74 (82), 61 (17), 43 (100). HRMS calcd for (M⁺ + Na) C₅H₁₀O₄Na: 157.0477. Found: 157.0471.

General Method for the Reduction of Dihydroxy 1,2-Dioxanes 4 To Furnish Erythritols 2 and 5. To a stirred solution of 1,2-dioxane **4** (1 mmol) in methanol (5 mL) was added 10% w/w of 5% palladium on carbon, and the mixture was stirred overnight under an atmosphere of hydrogen. The suspension was then filtered through a small pad of kenite washing with methanol, and the solvent was removed in vacuo to give the crude polyol, which was purified by flash chromatography or recrystallized from ethyl acetate.

(±)-2-*C*-Methylerythritol (2).[20] Colorless oil (120 mg, 73%); R_f 0.23 (1:4 MeOH/CH₂Cl₂). ¹H NMR (300 MHz, D₂O): δ 1.11 (s, 3H), 3.46 (d, J = 11.7 Hz, 1H), 3.57 (dd, J = 8.4, 11.1 Hz, 1H), 3.57 (d, J = 11.7 Hz, 1H), 3.65 (dd, J = 2.1, 8.4 Hz, 1H), 3.82

(dd, J = 2.1, 11.1 Hz, 1H). ^{13}C NMR (75 MHz, D$_2$O): δ 21.0, 64.6, 68.9, 76.8, 77.6.

General Procedure for Ring Opening Dihydroxy 1,2-Dioxanes 4 with Co(SALEN)$_2$ To Furnish Erythroses 6 and 7. To a stirred solution of *N,N'*-bis(salicylidene)ethylene diaminocobalt(II) (0.025 mmol) in THF (5 mL) at ambient temperature was added 1,2-dioxane (1 mmol), and the reaction left to stir until complete by TLC (~16 h). All volatiles were then removed in vacuo, and the product purified by flash chromatography.

(±)-2-*C*-Methyl-erythrofuranose (6d).[23] Major anomer: colorless oil (78 mg, 52%, 87% total); R_f 0.43 (1:4 MeOH/CH$_2$Cl$_2$). ^{1}H NMR (600 MHz, D$_2$O): δ 1.34 (s, 3H), 3.73 (dd, J = 6.0, 8.4 Hz, 1H), 4.22 (dd, J = 6.0, 7.2 Hz, 1H), 4.26 (dd, J = 7.2, 8.4 Hz, 1H), 5.16 (s, 1H). ^{13}C NMR (150 MHz, D$_2$O): δ 20.7, 72.6, 76.4, 80.7, 105.1. Minor anomer: ^{1}H NMR (600 MHz, D$_2$O): δ 1.33 (s, 3H), 3.93 (dd, J = 4.2, 9.6 Hz, 1H), 4.03 (dd, J = 4.2, 6.0 Hz, 1H), 4.16 (dd, J = 6.0, 9.6 Hz, 1H), 5.04 (s, 1H). ^{13}C NMR (150 MHz, D$_2$O): δ 24.0, 74.0, 76.7, 78.6, 102.9.

General Procedure for Acetonide Protection of Dihydroxy 1,2-Dioxanes. To a stirred solution of 1,2-dioxane 4 (1 mmol) in dry CH$_2$Cl$_2$ (5 mL) was added 2,2-dimethoxypropane (3 mmol) followed by *p*-toluenesulfonic acid (10 mol %), and the solution was stirred under nitrogen until complete by TLC (~1 h). The reaction was diluted with CH$_2$Cl$_2$ (20 mL), washed with saturated NaHCO$_3$ (20 mL), and dried (Na$_2$SO$_4$), and the solvent removed in vacuo. The residue was then purified by flash chromatography.

(±)-(3a*S*,7a*R*)-2,2,3a-Trimethyltetrahydro-[1,3]dioxolo[4,5-*d*][1,2]dioxine (8d). Volatile colorless oil (967 mg, 81%); R_f 0.27 (CH$_2$Cl$_2$); IR (neat) 1460, 1370, 1247, 1215, 1121, 1019 cm^{-1}. ^{1}H NMR (300 MHz, CDCl$_3$): δ 1.41 (s, 3H), 1.44 (s, 3H), 1.54 (s, 3H), 3.77 (ddd, J = 0.9, 2.4, 12.6 Hz, 1H), 3.84 (br s, 1H), 4.31 (dd, J = 0.9, 12.6 Hz, 1H), 4.40 (ddd, J = 1.5, 2.4, 14.0 Hz, 1H), 4.50 (dd, J = 1.8, 14.0 Hz, 1H). ^{13}C NMR (75 MHz, CDCl$_3$): δ 22.1, 27.1, 28.7, 71.3, 74.0, 75.7, 78.4, 109.1. MS *m/z* (EI): 174 (M$^+$, 4), 227 (100), 209 (9), 167 (15), 149 (18), 83 (24). HRMS calcd for (M$^+$ + Na) C$_8$H$_{14}$O$_4$Na: 197.0790. Found: 197.0785.

General Procedure for the Reaction of Triphenylphosphine with 1,2-Dioxanes 8 To Furnish Tetrahydrofurans 9. To a solution of 1,2-dioxane (1 mmol) dissolved in anhydrous CHCl$_3$ (5 mL) was added triphenylphosphine (1.5 mmol), and the reaction was stirred under an atmosphere of N$_2$. The reaction mixture was then heated at reflux until complete by TLC (ca. 16 h). The solvent was

removed in vacuo, and the residue was purified by flash chromatography.

(±)-(3a*S*,6a*R*)-2,2,3a-Trimethyltetrahydrofuro-[3,4-*d*][1,3]dioxole (9d). Volatile colorless oil (231 mg, 86%); R_f 0.36 (3:37 ether/CH$_2$Cl$_2$); IR (neat) 1456, 1378, 1261, 1206, 1142, 1101, 1067, 1023 cm^{-1}. ^{1}H NMR (300 MHz, CDCl$_3$): δ 1.41 (s, 3H), 1.49 (s, 6H), 3.29 (d, J = 9.9 Hz, 1H), 3.57 (dd, J = 3.3, 10.8 Hz, 1H), 3.96 (d, J = 9.9 Hz, 1H), 4.03 (d, J = 10.8 Hz, 1H), 4.37 (d, J = 3.3 Hz, 1H). ^{13}C NMR (75 MHz, CDCl$_3$): δ 22.5, 27.2, 27.4, 74.0, 79.1, 86.6, 89.1, 112.1. MS *m/z* (EI): 158 (M$^+$, 1), 143 (100), 115 (10), 97 (13), 83 (37), 55 (66), 43 (57). HRMS calcd for (M$^+$ + Na) C$_8$H$_{14}$O$_3$Na: 181.0841. Found: 181.0838.

General Procedure for the Hydrolysis of Acetonides 9 To Give Diols 10. To a solution of acetonide-protected THF 9 (1 mmol) dissolved in MeOH (10 mL) was added activated 50W Dowex X8 resin (1 g), and the mixture was stirred at 70 °C until complete by TLC (ca. 2−5 days). The reaction was allowed to cool and then filtered to remove the Dowex. The methanol was removed under reduced pressure, and the residue was purified by flash chromatography to give the pure diols.

(±)-(3*S*,4*R*)-3-Methyltetrahydrofuran-3,4-diol (10d). Colorless oil (113 mg, 82%); R_f 0.34 (ethyl acetate); IR (neat) 3400, 1462, 1379, 1103, 1042, 908 cm^{-1}. ^{1}H NMR (300 MHz, CDCl$_3$): δ 1.36 (s, 3H), 2.75 (br s, 1H), 2.86 (br s, 1H), 3.63 (d, J = 9.3 Hz, 1H), 3.73 (dd, J = 4.5, 9.9 Hz, 1H), 3.77 (d, J = 9.3 Hz, 1H), 3.91 (dd, J = 4.5, 5.7 Hz, 1H), 4.05 (dd, J = 5.7, 9.9 Hz, 1H). ^{13}C NMR (75 MHz, CDCl$_3$): δ 23.1, 73.7, 76.3, 76.7, 77.2. MS *m/z* (EI): 118 (M$^+$, 2), 75 (100), 58 (40), 55 (23), 45 (18). HRMS calcd for (M$^+$ + Na) C$_5$H$_{10}$O$_3$Na: 141.0528. Found: 141.0528.

Supporting Information Available: Experimental procedures, full characterization, ^{1}H and ^{13}C NMR spectra for all compounds, and crystallographic data and CIF files for **9a** and **10a**. This material is available free of charge via the Internet at http://pubs.acs.org.

(23) Zhao, S.; Petrus, L.; Serianni, A. S. *Org. Lett.* **2001**, *3*, 3819.

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