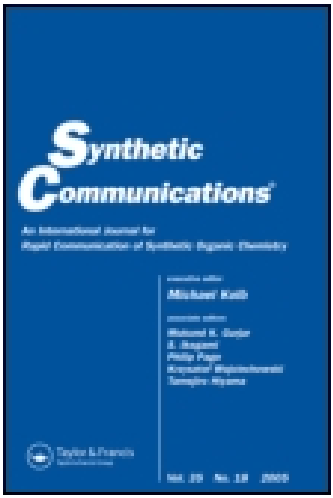

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Preparation and Reactions of Optically Active 4-Hydroxy-1,3-dioxolanes: 2-Hydroxy Aldehyde Equivalents

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PREPARATION AND REACTIONS OF OPTICALLY ACTIVE 4-HYDROXY-1,3-DIOXOLANES: 2-HYDROXY ALDEHYDE EQUIVALENTS

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Abstract: The preparation and reactions of optically and chemically stable (S)-4-hydroxy-1,3-dioxolane **3** as a 2-hydroxy aldehyde equivalent were explored. Hydroxydioxolane **3** was prepared by reduction of ketodioxolane **2** which was obtained from (S)-2-hydroxycarboxylic acid **1**. The reactions of **3** with triethyl phosphonoacetate and organometallic reagents were carried out. These and other conversions gave synthetically and biologically useful products in moderate to good chemical and moderate stereochemical yields.

α-Hydroxy aldehydes are of considerable interest because of their synthetic and biological utilities.[1] Since α-hydroxy aldehydes can consist of two or three consecutive functional groups as well as well-defined α-carbon stereocenters, synthetically a great deal of attention has been paid to this class of compound. Indeed, extensive studies[1] have focused on the reactions of α-hydroxy aldehydes with a variety of reagents including the addition of organometallic nucleophiles to the aldehyde carbonyl, [4+2] heterocyclic Diels-Alder reactions, aldol condensation reactions, and Horner-Wadsworth-Emmons olefination reactions. However, even though there exists great synthetic utility for optically active α-hydroxy aldehydes (or α-protected hydroxy aldehydes) as chiral buiiding blocks,

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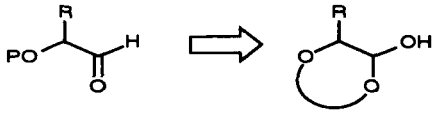
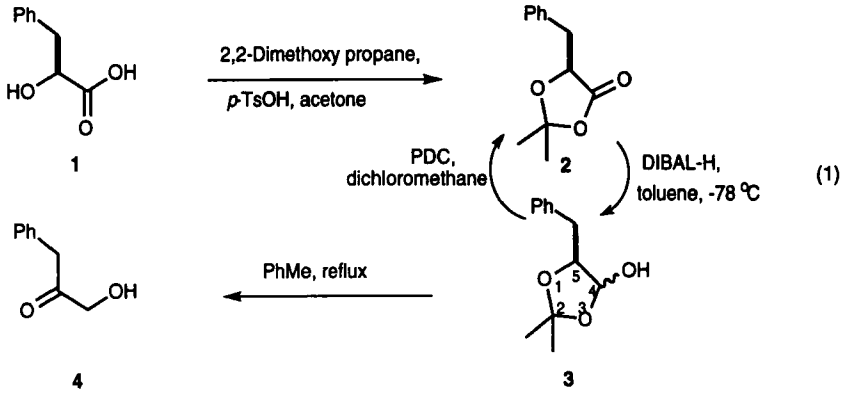
the effective synthesis of protected a-hydroxy aldehydes from simple starting materials is still cumbersome. For instance, protection-deprotection steps for the hydroxyl group are necessary to manipulate the aldehyde group. Furthermore, it is likely that their optical and chemical stabilities are also problematic, as for their counterpart α-amino aldehydes.[2] These considerations have led us to explore a new type of α-hydroxy aldehyde equivalent which is 1) readily available from simple starting materials; 2) optically and chemically stable; and 3) reactive toward nucleophilic reagents. To satisfy these requirements, we thought that a cyclic hemiketal would be an excellent candidate because it has the same oxidation state as an aldehyde and its reactions have been well studied.[3] Moreover, the newly created chiral center would be defined very clearly because of its conformational restraint. Herein, we report a versatile synthesis and reactions of a new type of optically and chemically stable α-hydroxy aldehyde equivalent.



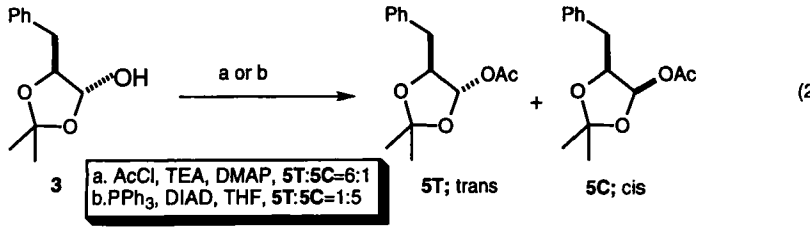
To prepare 4-oxo-1,3-dioxolane **2** which was a key intermediate for the desired 4-hydroxy-1,3-dioxolane **3**, the readily available 2-hydroxycarboxylic acid **14** was used (Eq. 1). Indeed, when (S)-2-hydroxy-3-phenylpropanoic acid (**1**), prepared from L-phenylalanine by diazotization, was treated with 2,2-dimethoxypropane in the presence of catalytic amounts of *p*-TsOH, 4-oxo-5-benzyl-2,2-dimethyl-1,3-dioxolane, (**2**) ($[\alpha]_D^{20}$ - 51.7), was furnished in 95% yield. Subsequent reduction of **2** by DIBAL-H provided the corresponding 4-hydroxy-5-benzyl-2,2-dimethyl-1,3-dioxolane (**3**) in 81% yield after purification by silica gel chromatography. Stereochemistry at the newly produced C-4 position was tentatively assigned as the S configuration, since it is likely that a bulky reducing

agent would approach from the less hindered face of the carbonyl group preferentially. However, this was not the case (*vide infra*).



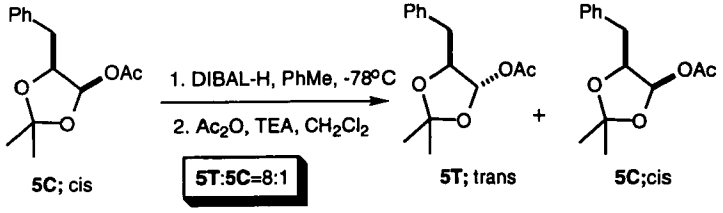
(1)

At this point, we determined the stereochemical integrity at the C-5 center of hydroxy compound **3**. Hydroxydioxolane **3** was oxidized back to oxodioxolane **2** ($[\alpha]_D^{20}$ - 52.1) by pyridinium dichromate (PDC) in 87% yield (Eq. 1). Comparison of the optical rotation showed that there was no detectable evidence of epimerization at the C-5 center during this process, which included chromatographic purification. Moreover, compound **3** remained chemically unchanged even after storage at 0°C for several weeks. However, hydroxydioxolane **3** was cleanly converted to ketopropanol **4** in toluene at reflux, probably via an enolization process from the α-hydroxy aldehyde following loss of acetone, or by hydride migration, either during or after the loss of acetone.



(2)

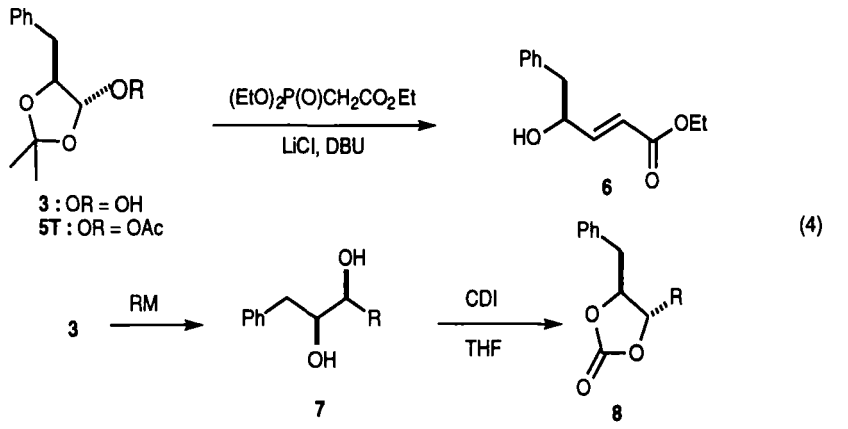
Stereochemical assignment of the C-4 position was determined by acetylation of the hydroxyl group. Treatment of hydroxydioxolane **3** with acetyl chloride in the presence of triethylamine furnished acetoxydioxolane **5** in a 6:1 diastereomeric ratio (Eq. 2). To our surprise, however, the major isomer of acetoxydioxolane **5** was the (4S,5S) isomer (**5T**; trans) rather than the expected (4R,5S) isomer (**5C**; cis) as determined by an NOE experiment.[6] Mitsunobu inversion of **3** provided acetoxydioxolane **5** in a 1:5 (5T:5C) diastereomeric ratio,[7] as revealed



(3)

by an NOE experiment.[6] Also, treatment of **5C** with DIBAL-H followed by acetylation gave **5T** as the major product (Eq. 3). Thus, it was concluded that thermodynamic control gave the more stable **3** as a (4S,5S) configuration (trans) from **2** following DIBAL-H reduction.

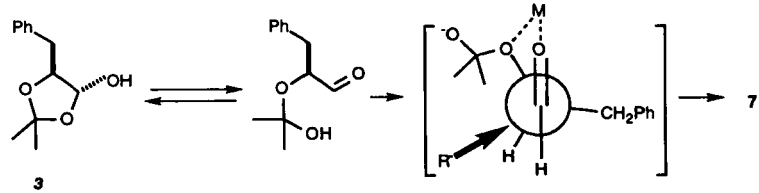
With a desired optically and chemically stable hydroxydioxolane **3** in hand, we turned our attention to the reactivity of this hydroxy aldehyde equivalent. A Horner-Wadsworth-Emmons olefination reaction was performed on **3** by treatment with triethyl phosphonoacetate in the presence of LiCl and DBU (Eq. 4).[8] Indeed, only *trans*-ethyl hydroxypentenoate **6** was obtained in 53% yield. Also, acetoxydioxolane **5** (**5T**:**5C**=6:1 mixture) was similarly converted to the same product in 44% yield. It is worthwhile to note that the synthetic and biological importance of optically active γ-hydroxy-α,β-unsaturated carbonyl compounds has been demonstrated.[9]



(4)

Nucleophilic addition reactions of organometallic reagents to O-protected hydroxy aldehydes is well-documented.[10] Thus, we have evaluated the reactivity of hydroxydioxolane **3** toward organometallic reagents (Eq. 4). When compound **3** was treated with a variety of different organometallics with or without Lewis acid, the desired diols **7** were isolated in moderate to good yields (Table). The diastereomeric ratios for the product mixtures were assigned by ^{1}H NMR and/or GC-MS of the crude diols. To determine the stereochemistry of the newly created carbon center (C-4), compounds **7** were treated with 1,1'-carbonyldiimidazole to provide 2-oxodioxolanes **8** for NOE experiments.

Stereochemistry at the newly created carbinol carbon for the major isomers was assigned as the S configuration (Eq. 5). This stereoselectivity probably arises from chelation-controlled addition of the nucleophile to the aldehyde (or an oxonium ion).



(5)

Table. Reaction of Dioxolane 3 with Organometallics.

Entry	RM	Equiv.	Additive/Solvent	Yield(%)[a]	Ratio of **7** (syn:anti)[d]
1.	CH_3MgBr	6.0	none/THF:PhMe(2:1)	70[b, 11]	1.6:1
2.	VinylMgBr	6.0	none/THF	78[b]	1.5:1
3.	PhMgBr	6.0	none/THF	79[b]	3.2:1
4.	$AllylSnBu_3$	1.0	$SnCl_4/CH_2Cl_2$	38(72)[c]	syn only
5.	2-lithiopyridine	3.0	THF	38(85)[c]	syn only

[a]Isolated yields after flash chromatography. All new compounds have been fully characterized by ^1H NMR, ^{13}C NMR, IR, MS, elemental analysis, and/or HRMS. [b]Two step yields. [c]Yields for diols was determined with ^1H NMR and/or GC-MS. Parenthetic yield refers to cyclic carbonates.[d] Ratio of crude diols was determined with ^1H NMR and/or GC-MS.

In summary, even though further synthetic and mechanistic studies remain to be done to establish the scope and limitations of this 4-hydroxydioxolane as an α-hydroxy aldehyde equivalent, we believe that this versatile synthetic equivalent can be used for the synthesis of biologically useful, complex molecules.

EXPERIMENTAL SECTION

GENERAL. Melting points are uncorrected. THF was distilled from sodium benzophone ketyl prior to use. ^1H and ^{13}C NMR were obtained with a Gemini 300 spectrometer.

(S)-5-Benzyl-2,2-dimethyl-4-oxo-1,3-dioxolane (2). A mixture of (S)-2-hydroxy-3-phenylpropanoic acid (10.0 g, 60 mmol) and *p*-$TsOH{\cdot}H_2O$ (500 mg) in 2,2-dimethoxypropane (30 mL) and acetone (100 mL) was stirred at room

temperature for 22 h. After concentration by rotary evaporation, the resulting residue was dissolved in ethyl acetate (150 mL), washed with sat. $NaHCO_3$ (100 mL), brine (100 mL), dried ($MgSO_4$), passed through a short pad of silica gel, and concentrated to provide a white solid (11.7 g, 95%): mp 56 - 58°C; $[\alpha]_D^{20}$ - 51.74 (c 0.97, $CHCl_3$; ^1H NMR ($CDCl_3$) δ 1.35 (s, 3H, $C(CH_3)_2$), 1.49 (s 3H, $C(CH_3)_2$), 3.12 (ABq, 2H, CH_2Ph), 4.65 (two d, 1H, $CHCH_2Ph$), 7.26 (m, 5H, phenyl); ^{13}C NMR ($CDCl_3$) δ 26.16, 26.93, 37.65, 75.04, 110.84, 127.03, 128.38, 129.81, 135.79, 172.49; IR (neat) 3032, 2993, 1793, 1387, 1242 cm^{-1}; MS m/z 206 (M^+), 191, 148. Anal calcd for $C_{12}H_{14}O_3$: C, 69.89; H, 6.84. Found: C, 69.83, 6.89.

(4R,5S)-5-Benzyl-2,2-dimethyl-4-hydroxy-1,3-dioxolane (3). To a stirred solution of ketodioxolane **2** (12.5 g, 60 mmol) in toluene (150 mL) was added DIBAL-H (100 mL of a 1M solution in toluene, 100 mmol) at -78°C. The resulting solution was stirred at the same temperature for 30 min and to this solution was added 1N HCl (100 mL) very slowly. After warming to room temperature, the solution was extracted with ethyl acetate (3 x 100 mL), passed through a short pad of silica gel, and concentrated to provide a pale yellow oil (10.2 g, 81%) after purification by flash chromatography (hexane:ethyl acetate = 95:5 to 90:10 to 80:20); $[\alpha]_D^{20}$ - 13.14 (c 1.13, ($CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.43 and 1.49 (two s, 6H, $C(CH_3)_2$ for major isomer), 1.32 and 1.55 (two s, $C(CH_3)_2$ for minor isomer), 2.90 and 3.00 (m and d, J = 7.0 Hz, CH_2Ph), 3.45 and 3.85 (br s, 1H, OH), 4.26 (m, 1H, $CHCH_2Ph$), 5.21 (m, 1H, HOC*H*), 7.28 (m, 5H, phenyl); ratio of diastereomers was approximately 2:1; IR (neat) 3423 (br), 3030, 2988, 1605, 1454, 1244, 1078 cm^{-1}; MS m/z 209 ($M+H^+$), 191, 151, 133, 121, 91. Anal calcd for $C_{12}H_{16}O_3$: C, 69.21; H, 7.73. Found: C, 69.55; H, 7.44.

Oxidation of Hydroxydioxolane 3 to Ketodioxolane 2. To a stirred solution of hydroxydioxolane **3** (420 mg, 2 mmol) in dichloromethane (20 mL) was added AcOH (30 μL), followed by powdered 3A molecular sieve (1.8 g, oven-dried overnight) and PDC (1.50 g, 4 mmol) at room temperature. The resulting suspension was stirred at the same temperature for 1 h. After addition of celite (1.8 g), the suspension was passed through a short pad of $MgSO_4$ and silica gel and concentrated to provide an oil (360 mg, 87%). A portion of the crude product was subjected to purification by preparative TLC (hexane:ethyl acetate = 95:5) to provide an analytical sample; $[\alpha]_D^{20}$ - 52.14 (c 0.78, $CHCl_3$). Spectral data were in complete agreement with the authentic sample.

(4S,5S)-5-Benzyl-2,2-dimethyl-4-acetoxy-1,3-dioxolane (5T). To a stirred solution of hydroxydioxolane **3** (2.09 g, 10 mmol), triethylamine (2.8 mL, 20 mmol) and DMAP (200 mg) in dichloromethane (80 mL) was added dropwise a solution of acetyl chloride (1.5 mL, 20 mmol) in dichloromethane (20 mL) at 0°C. The resulting solution was stirred at the same temperature for 2 h and at room temperature overnight. The solution was washed with 1N HCl (50 mL), sat. $NaHCO_3$ (50 mL), brine (50 mL), dried ($MgSO_4$), passed through a short pad of silica gel, and concentrated to provide an oil (1.41 g, 56%) after purification by flash chromatography (hexane:ethyl acetate = 95:5 to 90:10 to 80:20). Major isomer: ^{1}H NMR ($CDCl_3$) δ 1.47 and 1.49 (two s, 6H, $C(CH_3)_2$), 2.02 (s, 3H, $C(=O)CH_3$), 2.95 (d, 2H, J = 6.7 Hz, CH_2Ph), 4.42 (dq, 1H, J = 6.6, 2.7 Hz, $OC(CH_2)HCH$), 6.05 (d, 1H, J = 2.5 Hz, $CHOAc$), 7.25 (m, 5H, phenyl); diastereomeric ratio was about 6:1; ^{13}C NMR ($CDCl_3$) δ 21.12 (21.18), 26.70 (25.71), 27.69 (28.22), 39.15 (34.71), 82.62 (79.77), 98.38 (94.04), 112.52 (11.34), 126.61, 126.66, 128.42, 128.52, 128.86, 129.28, 136.56 (137.10), 170.28;

IR (neat) 3065, 2903, 1751, 1393, 1371, 1226 cm^{-1}; MS m/z 249 (M - H^+), 235, 193, 191, 161, 133, 101, 91. GC/MS showed t_R 5.12 (major) and 5.93 (minor) in an 86.7:13.3 ratio. Anal calcd for $C_{14}H_{18}O_4$: C, 67.19; H, 7.24. Found: C, 67.15; H, 7.16.

(4R,5S)-5-Benzyl-2,2-dimethyl-4-acetoxy-1,3-dioxolane (5C). To a stirred solution of hydroxydioxolane **3** (630 mg, 3 mmol) in THF (20 mL) was added acetic acid (0.26 mL, 4.5 mmol), followed by triphenylphosphine (1.18 g, 4.5 mmol) and diisopropyl azodicarboxylate (0.9 mL, 4.5 mmol) at room temperature. The resulting solution was stirred at the same temperature for 20 min and concentrated by rotary evaporation to provide an oil. The crude product was purified by flash chromatography (hexane:ethyl acetate = 95:5) to provide an oil (430 mg, 57%). Major isomer: ^{1}H NMR ($CDCl_3$) δ 1.37 and 1.54 (two s, 6H, $C(CH_3)_2$), 2.14 (s, 3H, $C(=O)CH_3$), 3.01 (AB of ABX, 2H, CH_2Ph), 4.37 (dt, 1H, $CHCH_2Ph$), 6.13 (d, 1H, J = 3.3 Hz, $CHOAc$), 7.23 (m, 5H). The diastereomeric ratio was 5:1.

Ethyl (S)-4-Hydroxy-5-phenyl-2-pentanoate (6). To a stirred solution of hydroxydioxolane **3** (630 mg, 3 mmol) in THF (50 mL) was added triethyl phosphonoacetate (2.24 g, 10 mmol), followed by LiCl (520 mg, 12 mmol) and DBU (1.85 mL, 12 mmol) at room temperature. The resulting solution was stirred at the same temperature overnight. After dilution with ethyl acetate (100 mL), the solution was washed with H_2O (50 mL), brine (50 mL), dried ($MgSO_4$), passed through a short pad of silica gel, and concentrated to provide an oil (350 mg, 53%) after purification by flash chromatography (hexane:ethyl acetate = 95:5 to 90:10 to 80:20): $[\alpha]_D^{20}$ - 5.47 (c 1.17, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.28 (two, t, 3H,

J = 7.1 Hz, diastereotopic CH_2CH_3), 2.15 (br s, 1H, OH), 2.78 (A of ABq, 1H, J = 8.3, 13.4 Hz, $CHCH_2Ph$), 2.92 (B of ABq, 1H, J = 5.4, 13.6 Hz, $CHCH_2Ph$), 4.19 (two q, 2H, J = 7.2 Hz, diastereotopic CH_2CH_3), 4.50 (m, 1H, HOCHCH=), 6.05 (dt, 1H, J = 15.6, 1.5 Hz, =CHCOOEt), 7.00 (ddd, 1H, J = 15.6, 4.5, 1.2 Hz, CH=CHCOOEt), 7.25 (m, 5H, phenyl); ^{13}C NMR ($CDCl_3$) δ 14.16, 43.16, 60.42, 71.68, 120.50, 126.83, 128.61, 129.40, 136.83, 148.91, 166.45; IR (neat) 3443 (br), 3028, 2982, 1716, 1306, 1277 cm^{-1}; MS m/z 221 ($M + H^+$), 203, 175, 129, 92, 91. HRMS calcd for $C_{13}H_{16}O_3$: 221.11770. Found: 221.117536.

(4SR,5R)-4-Allyl-5-benzyl-1,3-dioxolane-2-one (8). To a stirred solution of hydroxydioxolane **3** (630 mg, 3 mmol) in dichloromethane (20 mL) was added allyltributyltin (1.0 g, 3 mmol), followed by tin(IV) chloride (3 mL, 3 mmol) at -78°C under a N_2 atmosphere. After 10 min of stirring at the same temperature, the solution was warmed to room temperature and stirred overnight. After dilution with dichloromethane (100 mL), the solution was washed with sat. $NaHCO_3$ (100 mL). The aqueous phase was extracted with ethyl acetate (100 mL) and the organic extracts were combined, dried ($MgSO_4$), passed through a short pad of silica gel, and concentrated to provide an oil (200 mg, 38%) after purification by flash chromatography (hexane:ethyl acetate = 95:5 to 80:20 to 60:40): ^1H NMR ($CDCl_3$) δ 2.24 (d, 1H, J = 5.3 Hz, CHOH), 2.33 (m, 3H, OH and $CH(OH)CH_2CH=CH_2$), 2.83 (AB of ABX, 2H, CH_2Ph), 3.55 (m, 1H, CH(OH)CH(OH)), 3.70 (m, 1H, CH(OH)CH(OH)), 5.11 (m, 2H, $CH=CH_2$), 5.83 (m, 1H, $-CH=CH_2$), 7.25 (m, 5H, phenyl).

To a stirred solution of the above diol (220 mg, 1.15 mmol) in THF (50 mL) was added 1,1'-carbonyldiimidazole (320 mg, 2 mmol) at room temperature. The

reaction was stirred at the same temperature overnight. After the addition of additional 1,1'-carbonyldiimidazole (580 mg) and stirring for 6 h, the solution was concentrated to provide an oil, which was dissolved in ethyl acetate (60 mL). The ethyl acetate solution was washed with 1N HCl (60 mL), sat. $NaHCO_3$ (60 mL), dried ($MgSO_4$), passed through a short pad of silica gel, and concentrated to provide an oil (180 mg, 72%). A portion of the crude product was purified by preparative TLC (hexane:ethyl acetate = 95:5) to provide an analytical sample: $[\alpha]_D^{20}$ - 47.22 (c 1.18, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 2.31 (m, 2H, -CH_2CH=CH_2), 3.00 (AB of ABX, 2H, J = 14.2, 6.4 Hz, CH_2Ph), 4.40 (q, 1H, J = 6.1 Hz, BnC*H*CHAllyl), 4.52 (m, 1H, BnCHC*H*Allyl), 5.13 (m, 2H, -CH_2CH=CH_2), 5.62 (m, 1H, -CH_2C*H*=CH_2), 7.31 (m, 5H, phenyl); ^{13}C NMR ($CDCl_3$) δ 37.32, 39.32, 70.61, 80.71, 120.20, 127.36, 129.77, 129.30, 129.95, 133.94, 154.09; IR (neat) 3009, 2980, 1803, 1497, 1377, 1170, 1055 cm^{-1}. The diastereomeric ratio was 98:2.

(1SR,2S)-3-Phenyl-1-(2-pyridyl)-1,2-propanediol (7). To a stirred solution of 2-bromopyridine (1.5 mL, 15 mmol) in THF (80 mL) was added *n*-BuLi (6 mL, 2.5 M solution in hexane, 15 mmol) at -78°C under a N_2 atmosphere. After stirring at the same temperature for 30 min, a solution of hydroxydioxolane **3** (1.04 g, 5 mmol) in THF (20 mL) was added. After 10 min, the solution was warmed to room temperature and stirred overnight. After the addition of 1N HCl (80 mL), the solution was extracted with ethyl acetate (2 x 100 mL). The aqueous phase was basified with solid NaOH (pH 12) and extracted with ethyl acetate (2 x 100 mL). The combined organic extracts were washed with brine (100 mL), dried ($MgSO_4$), passed through a short pad of silica gel, and concentrated to provide a white solid (4.30 mg, 38%) after purification by flash chromatography

(hexane:ethyl acetate = 80:20 to 50:50) and recrystallization (hexane:ethyl acetate): mp 102-103°C; $[\alpha]_D^{20}$ - 28.92 (c, 1.02, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 2.93 (AB of ABX, 2H, C*H*$_2$Ph), 3.27 (br s, 1H, OH), 4.14 (m, 1H, C*H*(OH)CH(OH)), 4.35 (br s, 1H, OH), 4.59 (br s, 1H, CH(OH)C*H*(OH)), 7.28 (m, 7H, aromatic), 7.67 (dt, 1H, J = 7.6, 1.7 Hz, aromatic), 8.50 (m, 1H, aromatic); ^{13}C NMR ($CDCl_3$) δ 39.86, 73.33, 75.54, 121.57, 122.80, 126.38, 128.49, 129.44, 136.94, 138.30, 148.18, 159.83; IR (KBr) 3331 (br), 3028, 2989, 1599, 1435, 1111, 1047 cm^{-1}; MS m/z 230 ($M+H^+$), 212, 194, 138, 109. GC/MS showed the diastereomeric ratio was 96:4. Anal calcd for $C_{14}H_{15}NO_2$: C, 73.34; H, 6.59; N, 6.11. Found: C, 73.07; H, 6.59; N, 6.00.

(4SR,5S)-5-Benzyl-4-(2-pyridyl)-1,3-dioxolane-2-one (8). A solution of diol **7** (300 mg, 1.3 mmol) and 1,1'-carbonyldiimidazole (240 mg, 1.5 mmol) in THF (50 mL) was stirred at room temperature overnight. After concentration by rotary evaporation, the resulting oily residue was purified by preparative TLC (hexane:ethyl acetate = 90:10) to provide an oil (280 mg, 85%). Major isomer: NMR ($CDCl_3$) δ 3.28 (AB of ABX, 2H, J = 14.7, 4.7, 6.7 Hz, C*H*$_2$Ph), 5.05 (m, 1H, CH_2C*H*CH-), 5.05 (m, 1H, CH_2C*H*CH-), 5.34 (d, 1H, J = 6.5 Hz, C*H*Py), 7.30 (m, 7H, aromatic), 7.73 (m, 1H, aromatic), 8.61 (m, 1H, aromatic): ^{13}C NMR ($CDCl_3$) δ 39.41 (39.89), 80.67 (73.23), 82.34 (75.55), 120.48 (121.54), 123.91 (121.83), 127.41 (126.41), 128.78 (128.52), 129.69 (129.44), 134.32, 136.97, 137.20, 138.28, 148.18, 148.90, 154.03, 155.39; IR (neat) 3030, 2924, 1805, 1574, 1440, 1165 cm^{-1}; MS m/z 256 ($M+H^+$), 214, 194, 120. The diastereomeric ratio was 86:14.

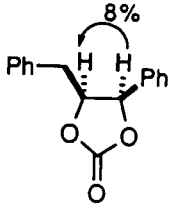
(4SR,5S)-5-Benzyl-4-phenyl-1,3-dioxolane-2-one (8). To a stirred solution of

hydroxydioxolane **3** (630 mg, 3 mmol) in THF (30 mL) was added phenylmagnesium bromide (18 mL of a 1M solution in THF, 18 mmol) at -78°C under a N_2 atmostphere. After stirring for 5 h at the same temperature, the solution was warmed to room temperature and stirred overnight. After dilution with ethyl acetate (100 mL), the solution was washed with 1N HCl (50 mL), dried ($MgSO_4$), passed through a short pad of silica gel, and concentrated to provide a pale yellow solid in quantitative yield after purification by flash chromatography (hexane:ethyl acetate = 90:10 to 80:20 to 60:40).

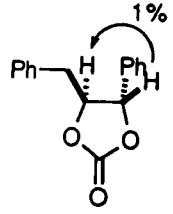
To a stirred solution of the above diol (680 mg, 3.0 mmol) in THF (60 mL) was added 1,1'-carbonyldiimidazole (650 mg, 4 mmol) at room temperature. The reaction was stirred at the same temperature overnight. After concentration, the residue was purified by flash chromatography (hexane:ethyl acetate = 95:5 to 90:10 to 80:20) to provide two fractions. First fraction (4S,5S): 330 mg as an oil; $[\alpha]_D^{20}$ - 27.32 (c 0.98, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 3.19 (AB of ABX, 2H, J = 6, 6.5, 14.5 Hz, C*H*$_2$Ph), 4.65 (m, 1H, J = 6, 6.5, 7 Hz, C*H*CH$_2$Ph), 5.23 (d, 1H, J = 7 Hz, C*H*Ph), 7.2 - 7.4 (m, 10 H, phenyl); ^{13}C NMR (75 MHz, $CDCl_3$) δ 38.95, 81.86, 84.07, 125.75, 127.57, 128.93, 129.08, 129.51, 129.55, 133.88, 135.64, 154.12; IR (neat) 3034, 2930, 1805, 1499, 1456, 1165 cm^{-1}: MS (CI) m/z 272 ($M+NH_4^+$), 193, 162, 108. Anal calcd for $C_{16}H_{14}O_3$: C, 75.58; H, 5.54. Found: C, 75.35; H, 5.52. Second fraction (4R,5S), 270 mg of white solid: $[\alpha]_D^{20}$ - 107.96 (c 0.46, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 2.50 (AB of ABX, 2H, J = 4.5, 9.5, 15 Hz, C*H*$_2$Ph), 5.15 (m, 1H, J = 4.5, 7.5, 9.5 Hz, C*H*CH$_2$Ph), 5.78 (d, 1H, J = 7.5 Hz, C*H*Ph), 7.0 - 7.5 (m, 10H, phenyl); ^{13}C NMR (75 MHz, $CDCl_3$) δ 37.00, 80.67, 81.26, 126.44, 127.05, 128.59, 128.91, 128.96, 129.51, 133.31,

135.41, 154.35; IR (KBr) 1788, 1358, 1179, 1049 cm^{-1}; MS (CI) m/z 272 ($M+NH_4^+$), 108. Anal calcd for $C_{16}H_{14}O_3$: C, 75.58; H, 5.54. Found: C, 75.60; H, 5.66.

NOE data for the two diastereomers were determined as shown.



4R,5S



4S,5S

(4SR,5S)-5-Benzyl-4-methyl-1,3-dioxolane-2-one (8). To a stirred solution of hydroxydioxolane **3** (610 mg, 3 mmol) in THF (20 mL) was added methylmagnesium bromide [12.8 mL of a 1.4M solution in toluene/THF (3:1), 18 mmol] at -78°C under a N_2 atmosphere. After stirring for 5 h at the same temperature, the solution was warmed to room temperature and stirred overnight. After addition of 1N HCl (50 mL), the solution was extracted with ethyl acetate (2 x 100 mL). The combined organic extracts were dried ($MgSO_4$), passed through a short pad of silica gel, and concentrated to provide an oil in quantitative yield after purification by flash chromatography (hexane:ethyl acetate = 80:20 to 60:40).

To a stirred solution of the above diol (450 mg, 2.7 mmol) in THF (50 mL) was added 1,1'-carbonyldiimidazole (650 mg, 4 mmol) at room temperature. The reaction was stirred at the same temperature overnight. After concentration, the residue was purified by flash chromatography (hexane:ethyl acetate = 80:20 to 60:40) to provide an oil (360 mg): $[\alpha]_D^{20}$ - 41.05 (c 0.29, $CHCl_3$); ^1H NMR

($CDCl_3$) δ 1.28 (d, 2.4 H, J = 6.3 Hz, $CHCH_3$), 1.44 (d, 0.6 H, J = 6.6 Hz, $CHCH_3$), 2.8 - 3.2 (m, 2H, CH_2Ph), 4.44 (m, 1.6 H, CH), 4.90 (m, 0.4 H, CH), 7.32 (m, 5H, phenyl); IR (neat) 3032, 2984, 1800, 1497, 1454, 1377, 1213, 1180, 1017 cm^{-1}; MS (CI) m/z 193 ($M+NH_4^+$), 149, 132, 131, 91. Anal calcd for $C_{11}H_{12}O_3$: C, 68.74; H, 6.29. Found: C, 68.95; H, 6.35.

(4SR,5S)-5-Benzyl-4-vinyl-1,3-dioxolane-2-one (8). To a stirred solution of hydroxydioxolane **3** (610 mg, 3 mmol) in THF (20 mL) was added methylmagnesium bromide (18 mL of a 1 M solution in THF, 18 mmol) at -78°C under a N_2 atmosphere. After dilution with ethyl acetate (100 mL), the solution was washed with 1N HCl (50 mL), brine (50 mL), dried ($MgSO_4$), passed through a short pad of silica gel, and concentrated to provide an oil in quantitative yield after purification by flash chromatography (hexane:ethyl acetate = 80:20 to 60:40).

To a stirred solution of the above diol (510 mg, 2.8 mmol) in THF (50 mL) was added 1,1′-carbonyldiimidazole (650 mg, 4 mmol) at room temperature. The solution was stirred at the same temperature overnight. After concentration, the residue was dissolved in ethyl acetate (100 mL), washed with 1N HCl (50 mL), dried ($MgSO_4$), and purified by flash chromatography (hexane:ethyl acetate = 90:10 to 80:20) to provide an oil (220 mg of pure sample): $[\alpha]_D^{20}$ - 38.96 (c 1.3, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 3.06 (AB of ABX, 2H, CH_2Ph), 4.54 (ddd, 1H, J = 6 Hz, $CHCH_2Ph$), 4.73 (tt, 1H, $CHCH{=}CH_2$), 5.30 (m, 2H, $CH{=}CH_2$), 5.72 (m, 1H, $-CH{=}CH_2$), 7.31 (m, 5H, phenyl); ^{13}C NMR (75 MHz, $CDCl_3$) δ 38.69, 81.43, 81.78, 120.90, 127.56, 128.91, 129.44, 131.86, 133.96, 153.94; IR (neat) 3032, 2926, 1805, 1497, 1431, 1367, 1184 cm^{-1}; MS (CI) m/z 205 ($M+H^+$)

143.91. Anal calcd for $C_{12}H_{12}O_3$: C, 70.58; H, 5.92. Found: C, 70.60; H, 6.03. A second fraction was obtained (230 mg) which contained a mixture of S and R diasteromers.

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References and Notes

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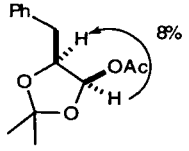
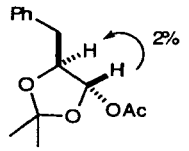
6. NOE data for **5C** and **5T**.



5C



5T

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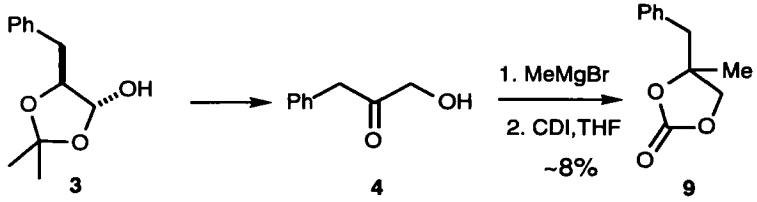
11. Compound **9** could be produced from hydroxy ketone **4** as a side product, which, in turn, could arise from **3** by rearrangement with loss of acetone.



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