Stereoselective Synthesis of β,γ-Unsaturated- and β,γ-Epoxy Glycerol Derivatives starting with Glyceraldehyde and their Use in the Synthesis of Alditols

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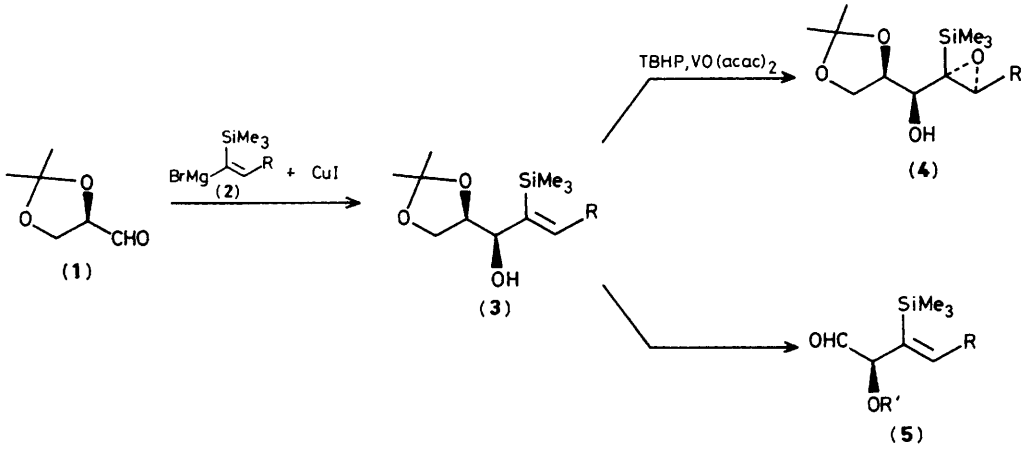
Highly stereoselective addition of vinylcopper and vinylcuprate compounds to glyceraldehyde acetonide affords both *syn*- and *anti*-β,γ-unsaturated glycerol derivatives, respectively, which can readily be converted into all the possible steric isomers of the β,γ-epoxy glycerol derivatives, which are useful intermediates in the synthesis of alditols.

Recently we reported that the reaction of D-glyceraldehyde acetonide (**1**) with 1-trimethylsilylvinylcopper compounds, prepared *in situ* from CuI and 1-trimethylsilylvinyl Grignard reagents (**2**), proceeds highly stereoselectively (>98%) affording *syn* addition products (**3**) in excellent yields.[1] The compounds (**3**) thus prepared are versatile intermediates in organic synthesis. For example, as shown in Scheme 1, epoxidation of (**3**) with TBHP/VO(acac)$_2$ (TBHP = t-butylhydroperoxide, Hacac = pentane-2,4-dione) gives *syn* epoxy alcohols (**4**) exclusively,[1] which are useful precursors for the

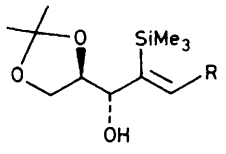


Scheme 1. **a**; R = H, **b**; R = n-C_5H_{11}.

Table 1. Metal hydride reduction of the ketones derived from (7) or (4).

	Substrate[a]	Reducing agent	Solvent	Temp. (°C)	Ratio[b] (9):(7)	Ratio[b] (10):(4)	Yield (%)[c]
(11)	**a**; R = H	$NaBH_4$	MeOH	−78	4:1		94
		L-Selectride	THF	−78	>99:1		93
	b; R = n-C_5H_{11}	$NaBH_4$	MeOH	−10	>99:1[d]		99
		L-Selectride	THF	−78	1.4:1		88
(12)	**a**; R = H	DIBAL	THF	−78		3.9:1	62
		$NaBH_4$	MeOH	−10		1:19	85
	b; R = n-C_5H_{11}	DIBAL	THF	−78		5.3:1	89
		$NaBH_4$	MeOH	−10		1:4.3	92

[a] Prepared by Swern oxidation of (7) or (4) in >85% yield. [b] Determined by h.p.l.c. [c] Isolated yield. [d] The trimethylsilyl group in the ketone is indispensable for high stereoselectivity. Without the trimethylsilyl group the stereoselectivity was 2:1.



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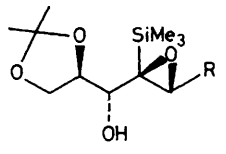

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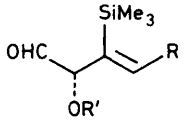

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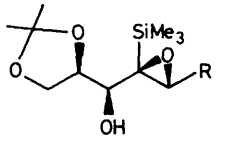

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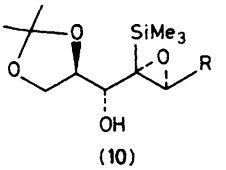

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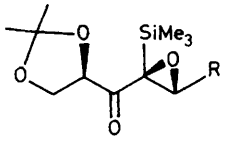

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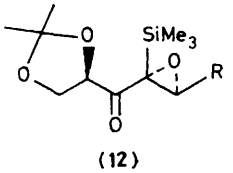
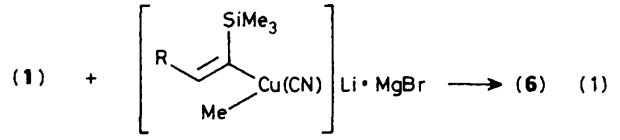


(12)

synthesis of sugars.[1,2]† Compounds (3) are also readily converted into α-alkoxy-β,γ-unsaturated aldehydes (5), which react with Grignard reagents highly stereoselectively thus allowing preparation of optically active vicinal diol derivatives.[3] The versatility of the compounds (3) in organic



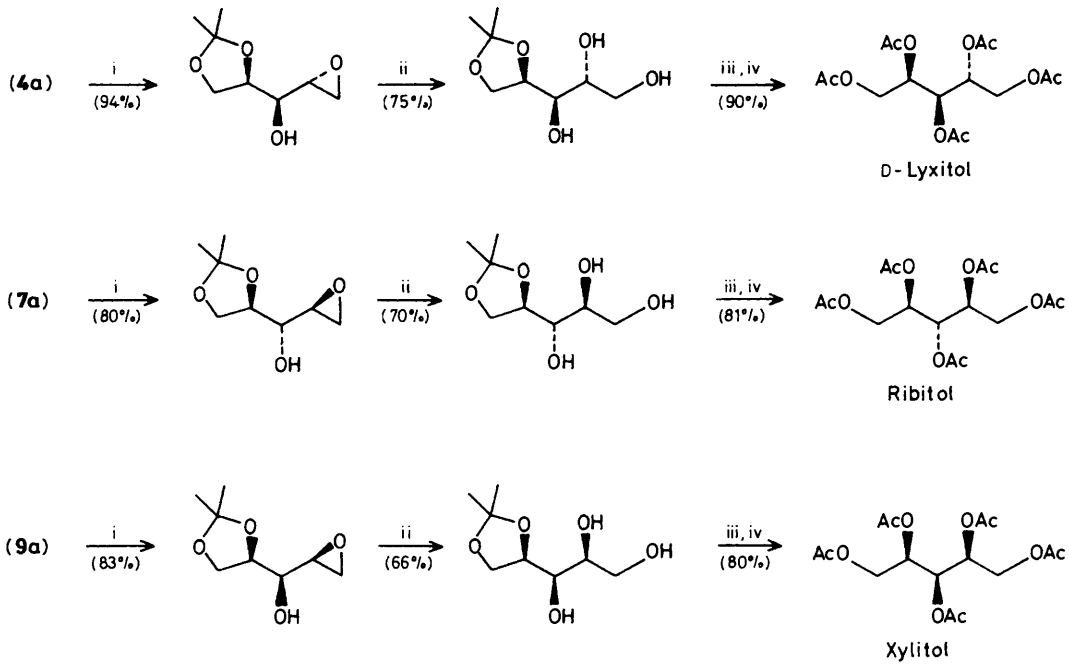
synthesis prompted us to prepare *anti* addition products (6) selectively from (1) and (2), which would make it possible to prepare (7) [a diastereoisomer of (4)] and (8) [an enantiomer of (5)]. Moreover, it would be desirable to find a convenient method for the preparation of *anti* epoxy alcohols (9) and (10). Herein we report our successful approach to these problems.

First, we investigated the reaction of (1) with (2) under the reaction conditions reported to give *anti* addition products predominantly from (1) and alkyl Grignard reagents. The reaction, however, was only partially successful. Thus the reaction of (1) with the titanium compound[4] prepared from $ClTi(OPr^i)_3$ and (2a) afforded (3a) and (6a) in a ratio of 1:3. The reaction of (1) and (2a) in tetrahydrofuran–hexamethylphosphoramide (THF–HMPA)[5] proceeded with a stereoselectivity of 1:3. However we found that organocuprates[6] prepared from CuCN, (2), and an alkyl-lithium react with (1) highly selectively to provide (6) [equation (1)]. A solution of 1-trimethylsilylvinylmagnesium bromide (53.1 mmol) in THF (106 ml) was added dropwise at −50 °C to a suspension of CuCN (5.25 g, 58.6 mmol) in THF (120 ml) under argon. To this solution was added methyl-lithium (53.1 mmol) in diethyl ether (31.0 ml) at −50 °C. After being stirred for 30 min at this temperature, (1) (6.19 g, 47.6 mmol) was added to this solution and the reaction mixture was stirred for 10 min at −78 °C and then for 1 h at room temperature. Usual workup followed by column chromatography on silica gel afforded (6a) and (3a) in a ratio of 95:5 (8.21 g, 75% yield).‡ Similarly, (6b) with 96% diastereoisomeric purity was obtained in 73% yield from (1) and (2b) which was prepared *via* $(\eta\text{-}C_5H_5)_2TiCl_2$-catalysed hydromagnesiation of 1-trimethylsilylhept-1-yne.[7]§ Noteworthy here is the fact that

† (3a): ^{1}H N.m.r. (CCl_4, PhH) δ 0.11 (s, 9H), 1.28 and 1.36 (2s, 6H), 2.51 (br.s, 1H), 3.53—4.14 (m, 4H), and 5.39 and 5.68 (2d, *J* 2.7 Hz, 2H); ^{13}C n.m.r. ($CDCl_3$) δ −0.43, 25.4, 26.8, 66.2, 78.3, 78.5, 109.7, 127.3, and 151.6; $[\alpha]_D^{25}$ −10.4° (*c* 1.07, $CHCl_3$). (4a): ^{1}H N.m.r. (CCl_4, PhH) δ 0.08 (s, 9H), 1.28 and 1.31 (2s, 6H), 2.43 (br.s, 1H), 2.57 and 2.65 (2d, *J* 4.9 Hz, 2H), 3.15 (d, *J* 5.1 Hz, 1H), and 3.64—4.21 (m, 3H); ^{13}C n.m.r. ($CDCl_3$) δ −2.6, 25.4, 26.4, 49.7, 51.6, 66.2, 75.4, 76.4, and 109.2; $[\alpha]_D^{25}$ −14.0° (*c* 0.96, $CHCl_3$).

‡ (6a): ^{1}H N.m.r. (CCl_4, PhH) δ 0.01 (s, 9H), 1.18 and 1.26 (2s, 6H), 2.28 (br.s, 1H), 3.66 (d, *J* 7.0 Hz, 2H), 3.98 (ddd, *J* 4.0, 6.4, 8.4 Hz, 1H), 4.23—4.44 (m, 1H), 5.37 (m, 1H), and 5.80 (m, 1H); ^{13}C n.m.r. ($CDCl_3$) δ −0.81, 25.2, 26.4, 64.3, 72.7, 77.7, 109.3, 125.5, and 150.1; $[\alpha]_D^{25}$ +11.5° (*c* 1.08, $CHCl_3$).

§ (6b): ^{1}H N.m.r. (CCl_4, PhH) δ 0.04 (s, 9H), 0.63—0.90 (m, 3H), 1.00—1.50 (m, 12H), 1.78—2.20 (m, 3H), 3.61 and 3.62 (2d, *J* 7.6, 6.0 Hz, 2H), 3.73—4.01 (m, 1H), 4.17 (d, *J* 4.0 Hz, 1H), and 6.26 (dt, *J* 1.2, 7.2 Hz, 1H); ^{13}C n.m.r. ($CDCl_3$) δ 0.32, 13.9, 22.5, 25.2, 26.4, 29.4, 31.5, 31.9, 64.1, 72.2, 78.1, 109.2, 136.5, and 143.4; $[\alpha]_D^{25}$ +16.7° (*c* 0.968, $CHCl_3$).



Scheme 2. i, Bu^tOK, Bu^n_4NF; ii, NaOH, 70 °C; iii, HCl; iv, Ac_2O, pyridine.

the organocuprate prepared from CuI, (**2a**), and MeLi showed low stereoselectivity (*syn* : *anti* = 1 : 3) in the reaction with (**1**).

As expected, the epoxidation of (**6**) with TBHP–$VO(acac)_2$ furnished *syn* epoxy alcohols (**7**) exclusively (85% yield).[8]¶ We attempted to prepare *anti* epoxy alcohols (**9**) and (**10**) *via* oxidation of (**7**) and (**4**), followed by reduction of the resulting ketones with metal hydride reagents, respectively.[9] It can be seen from Table 1 that the sense and degree of the diastereoselectivity of the reaction vary significantly depending on both the stereochemistry of the ketones and the metal hydride used. The epoxy alcohols (**9a**) and (**9b**) were obtained exclusively by reduction of the corresponding ketones with L-Selectride and $NaBH_4$, respectively,‖ while, (**10a**) and (**10b**) were obtained with >3.9 : 1 selectivity by the diisobutylaluminium hydride (DIBAL) reduction of the corresponding ketones.

It is thus possible to prepare both (**3**) and (**6**), and all the four possible stereoisomers (**4**), (**7**), (**9**), and (**10**) starting with (**1**) as required. It should be noted that their antipodes can be obtained by starting with L-glyceraldehyde acetonide. The β,γ-epoxy glycerol derivatives (**4a**), (**7a**), and (**9a**) thus prepared were readily converted into D-lyxitol, ribitol, and xylitol respectively, according to the procedure reported by Masamune and Sharpless[2] (Scheme 2).

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¶ (**7a**): ^1H N.m.r. (CCl_4, PhH, D_2O) δ −0.03 (s, 9H), 1.15 and 1.23 (2s, 6H), 2.41 and 2.75 (2d, *J* 5.0 Hz, 2H), and 3.43—4.03 (m, 4H); ^{13}C n.m.r. ($CDCl_3$) δ −3.03, 25.2, 26.3, 46.2, 52.9, 66.8, 70.9, 75.8, and 109.0; $[\alpha]_D^{25}$ +3.2° (*c* 1.05, $CHCl_3$). (**7b**): ^1H N.m.r. (CCl_4, PhH, D_2O) δ 0.07 (s, 9H), 0.69—1.02 (m, 3H), 1.06—1.80 (m, 14H), 2.76—2.96 (m, 1H), and 3.47—4.07 (m, 4H); ^{13}C n.m.r. ($CDCl_3$) δ −0.92, 13.9, 22.6, 25.4, 26.3, 26.7, 30.0, 31.6, 57.2, 57.8, 67.9, 70.2, 77.3, and 109.3; $[\alpha]_D^{25}$ +2.3° (*c* 1.23, $CHCl_3$).

‖ (**9a**): ^1H N.m.r. (CCl_4, PhH, D_2O) δ 0.02 (s, 9H), 1.23 and 1.29 (2s, 6H), 2.41 and 2.69 (2d, *J* 4.9 Hz, 2H), and 3.40—3.96 (m, 4H); ^{13}C n.m.r. ($CDCl_3$) δ −3.03, 25.4, 26.4, 47.2, 52.3, 66.4, 74.2, 75.2, and 109.3; $[\alpha]_D^{25}$ −16.6° (*c* 0.878, $CHCl_3$). (**9b**): ^1H N.m.r. (CCl_4, PhH, D_2O) δ 0.10 (s, 9H), 0.70—1.02 (m, 3H), 1.06—1.80 (m, 14H), 2.73—2.96 (m, 1H), and 3.43—3.92 (m, 4H); ^{13}C n.m.r. ($CDCl_3$) δ −0.92, 13.9, 22.5, 25.5, 26.5, 26.7, 30.1, 31.6, 57.0, 60.4, 66.4, 74.3, 75.1, and 109.2; $[\alpha]_D^{25}$ −8.0° (*c* 0.929, $CHCl_3$).

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