

Synthesis of the rarely obtained *syn*-Adducts in the Reaction of Organocopper Compounds with 2,3-*O*-Isopropylidene-glyceraldehyde. Preparation of Optically Active Epoxy Alcohols

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Organocopper compounds, prepared from Grignard reagents and copper(I) iodide in tetrahydrofuran–dimethyl sulphide, react with 2,3-*O*-isopropylidene-glyceraldehyde highly stereoselectively (>10 : 1) affording the rarely obtained *syn*-addition products which can be readily converted into optically active epoxy alcohols, useful intermediates in organic synthesis.

2,3-*O*-Isopropylidene-glyceraldehyde (**1**), readily available in the (*S*)-¹ as well as the (*R*)-form,² is a synthetically useful chiral starting material for the construction of optically active organic molecules.³ There has been much recent interest in the steric course of organometallic additions to (**1**), since if the stereochemical features of this reaction could be controlled,

(**1**) would be extremely useful synthetically. Usually, organometallic compounds (R–M) such as Grignard, organolithium, or organozinc reagents afford *anti*-addition products (**3**) selectively [equation (1)].⁴ The degree of diastereoselectivity is dependent on R–M, but, with a few exceptions,^{4b–h} it is not satisfactory from a synthetic point of view.

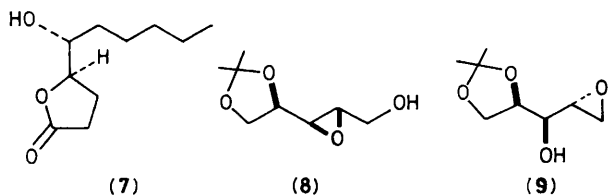
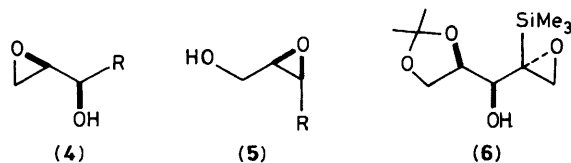
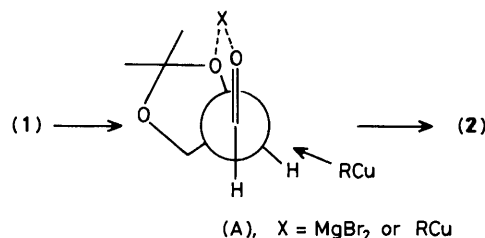
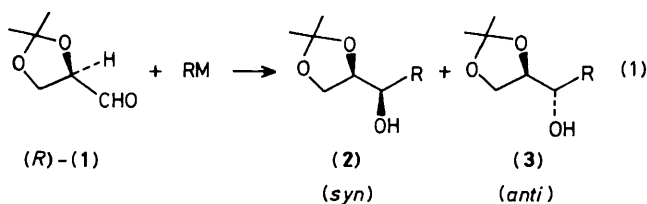
Table 1. Addition products (2) and (3) obtained by the reaction of organocopper compounds with (R)-(1).^a

Entry	Compd.	RCu ^b R	% Yield ^c (2) + (3)	Product ratio ^{d,e,f} (2) : (3)		[α] _D (c, solvent, temp./°C) of (2) ^g
1	a	Bu ⁿ	75	16:1	(1:2.4)	+19.4° (1.25, CHCl ₃ , 25)
2	b	n-C ₅ H ₁₁	74	15:1	(1:2.4)	+18.4° (1.29, CHCl ₃ , 25)
3	c	n-C ₁₀ H ₂₁	89	13:1	(1:2.2)	+13.5° (1.13, CHCl ₃ , 25)
4	d	c-C ₆ H ₁₁	75	10:1	(1:1.4)	+6.5° (1.14, CHCl ₃ , 25)
5	e	Ph	91	>99:1 ^{h,i,j}	(1.8:1)	-31.5° (3.00, MeOH, 23) ^k
6	f	<i>p</i> -MeOC ₆ H ₄	80	>99:1 ⁱ	(2.3:1)	-29.2° (1.17, CHCl ₃ , 25)
7	g	<i>p</i> -ClC ₆ H ₄	93	>99:1	(2:1)	-29.0° (1.00, CHCl ₃ , 25)
8	h	CH ₂ =C(SiMe ₃)	86	>98:2 ^h	(1:1.7)	-10.4° (1.07, CHCl ₃ , 25)

^a The reactions were carried out in THF-Me₂S at -78 °C to room temperature (2 h). ^b Prepared from RMgBr and CuI. ^c Isolated yields.

^d Determined by g.l.c. analysis after conversion into the corresponding methyl ethers for entries 1-4, and by ¹H n.m.r. spectroscopy for entries 5-8. ^e The ratios within parentheses were obtained by the reaction with Grignard reagents in THF. ^f Major isomers were assigned by transformation to known compounds (see text and ref. j below) except for (2d) and (2g), assignments for which rely on t.l.c. mobility comparison with the stereochemically defined other examples. ^g All the products were purified by column chromatography on silica gel except for (2e) and (2g) which were purified by recrystallization from hexane. ^h The same ratio was obtained when the reaction was carried out at -15 °C.

ⁱ The ratio decreased to 4:1 when the reaction was carried out in Et₂O-Me₂S. ^j The major products (2e) and (2f) were converted into mandelic acid derivatives by the following sequence: (i) PhCH₂Br, NaH, THF; (ii) HCl, THF, H₂O; (iii) NaIO₄, EtOH, H₂O; (iv) CrO₃-H₂SO₄, acetone; (v) H₂, Pd-C. (R)-(-)-Mandelic acid: m.p. 130-131 °C, [α]_D²⁰ -145.6° (c 0.43, EtOH); ref. 14: m.p. 132.8 °C, [α]_D²⁰ -144.7° (c 0.43, EtOH). (R)-(-)-*p*-Methoxymandelic acid: m.p. 102-104 °C, [α]_D²⁵ -136° (c 0.300, H₂O); ref. 15: m.p. 102-104 °C, [α]_D²⁵ -141° (c 0.3, H₂O). ^k Lit. [α]_D²³ -30.0° (c 3.0, MeOH); see ref. 4j.



We report here that organocopper compounds, prepared from Grignard reagents and CuI in tetrahydrofuran (THF)-Me₂S, react with (1) highly stereoselectively affording *syn*-addition products (2) in excellent yields.†

† Parts of this work were presented at the 50th Annual Meeting of the Japan Chemical Society, April 1985, Tokyo. After we finished this work, Macdonald *et al.* reported⁵ that 2,3-*O*-dibenzylglyceraldehyde reacts with [RCu]MgBr₂ in Et₂O-Me₂S highly selectively to afford *syn*-addition products. They found that (1) gave little stereoselectivity in the reaction with [RCu]MgBr₂ in Et₂O-Me₂S. We found, however, that the stereoselectivity in the reaction of (1) with RCu is highly dependent on the solvents used: see Table 1, entry 5.

The general experimental procedure is as follows. To a solution of CuI (1.7 equiv.) in THF-Me₂S (5:1) was added the Grignard reagent (1.5 equiv.) in THF at -78 °C and the mixture was stirred for 5 min at that temperature under argon. The aldehyde (R)-(1) (1 equiv.) was then added, the mixture was gradually warmed to room temperature (2 h), and usual work-up afforded the addition product. The data in Table 1 indicate that various organocopper compounds react with (1) highly selectively affording *syn*-addition products (2), which are rarely obtained as major products in reactions with other organometallic compounds. The degree of diastereoselectivity in these systems was consistently good, and thus the diastereoisomerically pure *syn*-addition products (2) were easily separated from their diastereoisomers by either column chromatography or recrystallization.

The addition products (2) thus obtained can be readily converted into synthetically useful optically active epoxy alcohols (4), (5), and (6) by using a simple sequence of conventional reactions.⁶ It should be noted that the antipodes of the epoxides (4), (5), and (6) can be obtained starting with (S)-(1).¹ Compound (4) can be prepared *via* a five-step sequence: (i) protection (PhCH₂Br, NaH); (ii) hydrolysis (HCl, H₂O); (iii) selective mono-tosylation of the primary hydroxy group [toluene-*p*-sulphonyl chloride (TsCl), C₂H₅N]; (iv) epoxidation (NaOH, MeOH); (v) hydrogenolysis (H₂, Pd-C). Thus, the product (4a) {[α]_D²³ -5.6° (c 0.32, CHCl₃)} was obtained from (2a) in 39% overall yield, the antipode of which {calc. rotation, [α]_D²³ +5.25° (c 1.39, CHCl₃)} is the key intermediate for the preparation of natural (-)-pentalin.⁴ⁱ The benzyl ether of (4b) obtained from (2b) (54%

yield) was transformed into the γ -lactone (7) {m.p. 40–41 °C, $[\alpha]_D^{25}$ –35.5° (c 0.374, CHCl₃)} in 73% yield by a four-step process: (i) CH₂(CO₂Me)₂, NaH, THF; (ii) K₂CO₃, MeOH, H₂O; (iii) H⁺, toluene, reflux; (iv) H₂, Pd–C. The antipode of (7) {oil, $[\alpha]_D$ +24.8° (c 0.7, CHCl₃)}⁷ was isolated from strains of *Streptomyces griseus*,⁸ and was recently synthesized from 2,3-*O*-isopropylidene-D-ribose.⁷

The epoxy alcohol (5) can also be synthesized from (2) by the sequence tosylation (TsCl, C₅H₅N), hydrolysis (HCl, H₂O), and epoxidation (NaOMe, MeOH). For example, the product (5c), which is the intermediate for the synthesis of natural (+)-disparlure, was obtained from (2c) in 78% yield {m.p. 59–61 °C, $[\alpha]_D^{20}$ –7.8° (c 1.01, EtOH)}. Previously, (5c) {m.p. 62.5–63 °C, $[\alpha]_D^{20}$ –7.8° (c 1.0, EtOH)} had been synthesized by Sharpless asymmetric epoxidation of (*Z*)-tridec-3-en-1-ol, which resulted in 91% enantiomeric excess.⁹

Sharpless epoxidation^{6a} of (2h) with Bu^tOOH and VO(a-cac)₂ (Hacac = pentane-2,4-dione) proceeded stereoselectively¹¹ to give (6) as the sole product, from which (8) {oil, $[\alpha]_D^{25}$ –16.1° (c 2.02, EtOH); ref. 10: $[\alpha]_D^{25}$ –16.6° (c 2.28, EtOH)} or (9) {oil, $[\alpha]_D^{25}$ +1.1 (c 1.12, CHCl₃)} was synthesized *via* successive protodesilylation and the Payne rearrangement¹² (NaOH, Bu^tOH) or *via* protodesilylation (Bu^tOK, Buⁿ₄NF, THF),¹³ respectively. ‡ Both (8) and (9) are useful precursors for the synthesis of sugars.^{6b,10}

The physical data (¹H and ¹³C n.m.r., $[\alpha]_D$, and/or m.p.) of all products were consistent with the assigned structures. The specific rotations of (4a), (5c), (7), and (8) confirmed that the reaction of (1) with the organocopper compounds proceeds without racemization affording *syn*-adducts (2).

Although the predominant production of *syn*-adducts (2) in the reaction of (1) with organocopper compounds does not prove the cyclic mechanism (A) in which MgBr₂ or RCu is chelated by the carbonyl and 2-oxygen of the dioxolane ring, it is consistent with such a transition state.

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‡ The optical purity of (9) was confirmed to be >95% enantiomeric excess by conversion into D-lyxitol penta-acetate {[$\alpha]_D^{22}$ +39.5° (c 1.90, EtOH); ref. 10: $[\alpha]_D^{19}$ +41.5° (c 1.88, EtOH)} according to the procedure reported by Masamune and Sharpless.¹⁰

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