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DIASTEREOSELECTIVE NUCLEOPHILIC ADDITION TO CHIRAL OPEN-CHAIN α-KETOACETALS: SYNTHESIS OF (R)- AND (S)-MEVALOLACTONE

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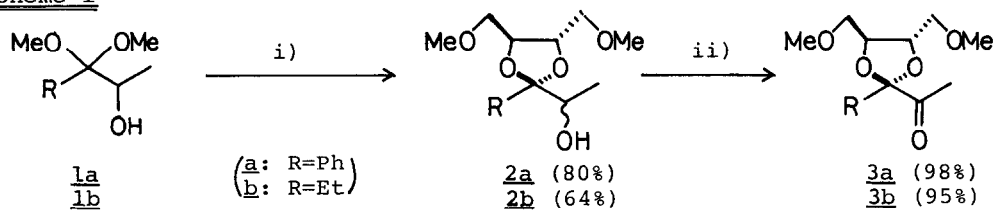
Summary: Highly stereoselective addition of Grignard reagents to chiral open-chain α-ketoacetals(3a,3b) has been attained. Application of the reaction to syntheses of the key intermediates(6,8) for (R)- and (S)-mevalolactone is also described.

Much attention has been focused on the highly stereocontrolled addition of organometallic reagents to open-chain ketones having chiral centers next to carbonyl function.[1] Eliel and Mukaiyama have attained such asymmetric nucleophilic addition by using chiral open-chain α-ketoaldehyde derivatives(α-keto-1,3-oxathiane[2] and α-ketoaminal[3]) which have chiral auxiliaries as aldehyde equivalents. However, there is no example using open-chain α-ketoacetal system. The present communication describes the highly diastereoselective addition of Grignard reagents to the chiral open-chain α-ketoacetals(3a,3b) derived from (-)-(2S,3S)-1,4-dimethoxy-2,3-butanediol,[4] whose utility in asymmetric synthesis has been recognized recently,[5] and its application to the synthesis of (R)- and (S)-mevalolactone.[6]

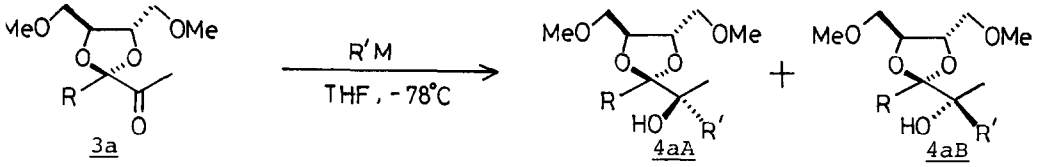
The ketoacetals(3a,3b)[7] were readily prepared as shown in Scheme 1 from the corresponding α-hydroxydimethylacetals(1a,1b)[8] by transacetalization with 1.2 eq.

Scheme 1



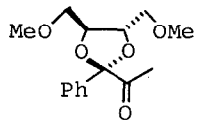
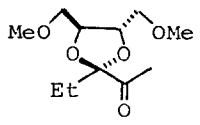
i) 1.2 eq. chiral diol/cat. camphor sulfonic acid/neat/reduced pressure(0.5mmHg)/r.t.
ii) $(COCl)_2$/DMSO/Et_3N/CH_2Cl_2/-78°C

of (-)-(2S,3S)-1,4-dimethoxy-2,3-butanediol followed by Swern oxidation.[9] [3a: $[\alpha]_D$ +65°(c 0.97, $CHCl_3$); 3b: $[\alpha]_D$ -6.1°(c 1.50, $CHCl_3$)] The reactions of the acetals(3a,3b) with organometallic reagents(5 eq) were held in tetrahydrofuran at -78°C. As shown in Table 1, the Grignard reagents gave extremely high diastereoselectivity(94-100%) providing the predominant products 4aA and 4bA (entries 1-4 and 7-10). The relatively poor stereoselectivity was obtained in the reactions with lithium reagents(entries 5,6,11, and 12).



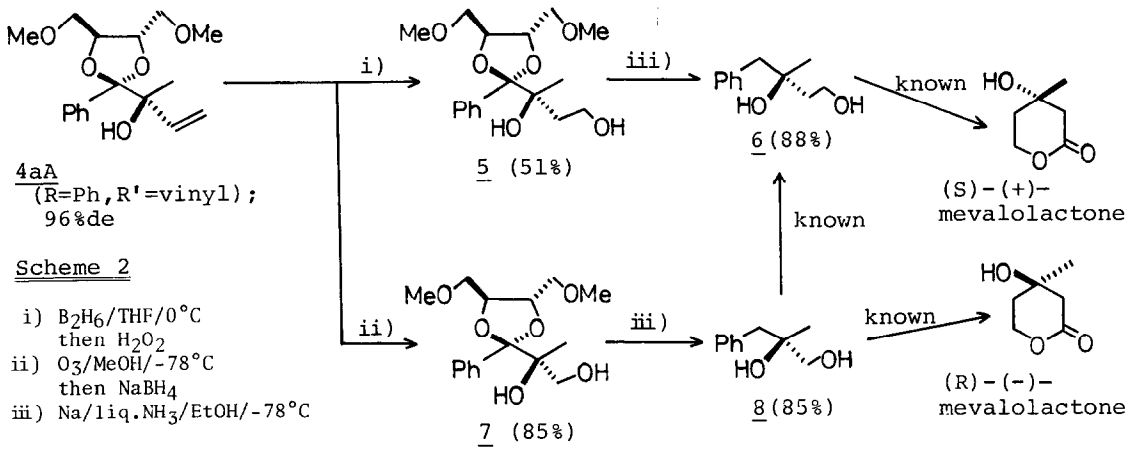
3a 3b 4aA 4bA 4aB 4bB

Table 1. Nucleophilic addition of R'M to 3a and 3b

entry	substrate	R'M[a]	yield[b]	ratio (A:B)
1		EtMgCl	98	>99 : <1[c]
2			90	98 : 2[c]
3		TMS-≡-MgCl	91	97 : 3[c]
4		PhMgBr	84	97 : 3[d]
5	3a	TMS-≡-Li	90	55 : 45[c]
6		PhLi	80	33 : 67[d]
7		EtMgCl	92	>99 : <1[e]
8			93	>99 : <1[e]
9		TMS-≡-MgCl	98	>99 : <1[e]
10		PhMgBr	81	98 : 2[f]
11	3b	TMS-≡-Li	85	80 : 20[e]
12		PhLi	80	60 : 40[f]

a) R'M (5 eq.) was added to a solution of 3 (0.1 mol). b) Purified by SiO_2 column chromatography. c) Determined by HPLC analysis: see text and ref. 10a. d) Determined by HPLC analysis: see ref. 10b. e) Determined by ^1H NMR (500 MHz, $CDCl_3$): see ref. 10c. f) Determined by ^1H NMR (90 MHz, $CDCl_3$): see ref. 10d.

The stereochemistries of the products in a series(entries 1-6) were determined as follows. The product 4aA(R=Ph, R'=vinyl; 96% de) in entry 2 was converted into the compounds(6,8) whose stereochemistries were already established.[6] Thus, hydroboration of 4aA(R=Ph, R'=vinyl) [$[\alpha]_D$ -1.1°(c 0.65, $CHCl_3$)] with B_2H_6 followed by oxidative work-up (30% H_2O_2) afforded 1,3-diol 5 [$[\alpha]_D$ +8.4° (c 1.4, $CHCl_3$)], which was deacetalized(Na/liq. NH_3/EtOH/-78°C) to give 6[$[\alpha]_D$ +1.76° (c 0.51, 95% EtOH) lit.[6] +1.77°]. Compound 4aA(R=Ph, R'=vinyl) was further converted to the diol 8[$[\alpha]_D$ +17.3°(c 0.2, 95% EtOH),

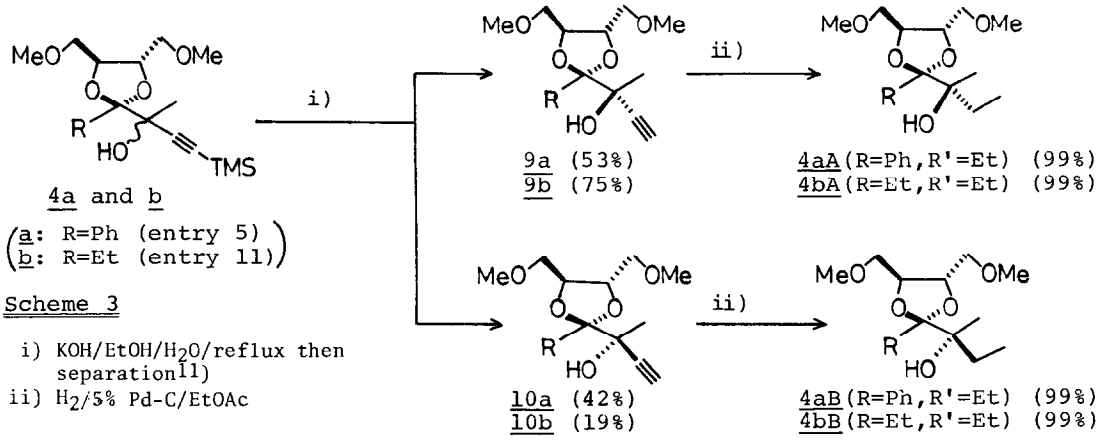


Scheme 2

i) B_2H_6/THF/0°C then H_2O_2
ii) O_3/MeOH/-78°C then $NaBH_4$
iii) Na/liq.NH_3/EtOH/-78°C

lit.[6] +17.3°] having larger value of optical rotation by ozonolysis (O_3/MeOH/ -78°C then $NaBH_4$ work-up) and successive deacetalization(Na/liq. NH_3/EtOH/ -78°C).(Scheme 2) The stereochemistries of the products in entries 1,3, and 5 were assigned by correlation to the ethyl compound 4aA(R=Ph, R'=Et; 96% de) obtained by hydrogenation(5% Pd-C/H_2) of the product in entry 2. That is, the product in entry 1 agreed with the ethyl compound 4aA(R=Ph, R'=Et). In the case of the products in entries 3 and 5, they were converted into the corresponding compounds 4aA(R=Ph, R'=Et) and 4aB(R=Ph, R'=Et)[10a] as shown in Scheme 3 and identified. The stereochemistries of the products in entires 4 and 6 of a series as well as those in entries 7-12 of b series were tentatively assigned from mechanistic analogy.[10]

Although the actual stereochemical course is not ascertained, the formation of 4aA and 4bA as predominant products may be reasonably explained



Scheme 3

i) KOH/EtOH/H_2O/reflux then separation[11]
ii) H_2/5% Pd-C/EtOAc

by the attack of the Grignard reagents on the si-face of the ketone in the rigid structure as shown in Figure 1. Namely, the magnesium metal is fixed by chelation between carbonyl oxygen, the methoxy oxygen atom, and the one of the acetal oxygen atoms leading to the formation of the rigid structure and then the alkyl group originated from the Grignard reagent migrates to the carbonyl carbon from the less hindered side as illustrated in the figure.

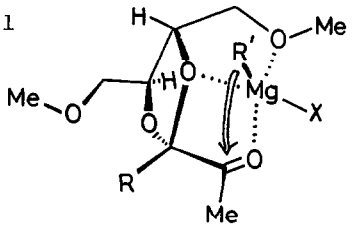


Figure 1

As shown in Scheme 2, compounds 6 and 8 are reported to be the key intermediates for (R)-(-)- and (S)-(+)-mevalolactone,[6] one of which R isomer is the biogenetic precursor of terpenoids and steroids. Therefore, this work gives a new asymmetric synthesis of (R)-(-)- and (S)-(+)-mevalolactone. It is worthy to note that in this asymmetric synthesis the chiral diol can be readily available in two enantiomers[4] and the single diastereomer is formed in the formation of the starting α-keto-acetals.

References and Notes

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4 Prepared from L-(+)-tartaric acid in four steps: (1) $MeC(OMe)_2Me$/MeOH/p-TsOH/cyclohexane/Δ (M. Carmack and C. J. Kelley, J. Org. Chem., 33, 2171 (1968); (2) $LiAlH_4/Et_2O$/reflux; (3) MeI/KOH/DMSO; (4) 95% EtOH/p-TsOH/reflux. (+)-(2R,3R)-1,4-Dimethoxy-2,3-butanediol can also be prepared from D-mannitol (A. H. Haines and C. S. P. Jenkins, J. Chem. Soc. Perkin Trans I, 1972, 273).

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7 Satisfactory spectroscopic data were obtained for all new compounds.

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10 a) Diastereomer's ratios were determined by HPLC(baseline separation) on a Chemco Pak. Nucleosil 50-5 column(eluent; hexane:ethylacetate=4:1,flow rate;0.9 ml/min) as the ethyl compounds. Retention time(Rt); 4aA(R'=Et), 40.8 min., 4aB(R'=Et), 38.6 min.
b) Ratios were determined by HPLC as the same condition as above. Rt; 4aA (R'=Ph), 23.5 min., 4aB(R'=Ph), 22.1 min.
c) The ratios of the products were determined by ^1H NMR (500 MHz, $CDCl_3$) as the ethyl compound. Compound 4bA(R'=Et), δ 0.92 (6H,t,J=7 Hz), 1.14 (3H,s), 1.2-1.8(4H,m), 3.39(3H,s), 3.41(3H,s), 3.4-4.0(4H,m), 4.15-4.56(2H,m). Compound 4bB(R'=Et), 0.92(3H,t,J=7.2 Hz), 0.95(3H,t,J=7.2 Hz), 1.15(3H,s), 1.2-1.8(4H,m), 3.38(3H,s), 3.41(3H,s), 3.44-4.0(4H,m), 4.1-4.6(2H,m).
d) The ratios were determined by ^1H NMR (90 MHz, $CDCl_3$) using the ratios of the NMR singlets due to the methoxy methyl protons[4bA(R'=Ph), δ 3.39, 3.49; 4bB(R'=Ph), 3.37, 3.43].

11 The diastereomers 9a, 10a and 9b, 10b were separated by prep. TLC respectively. (rf value; 0.37(9a), 0.26(10a), silica gel, benzene:ether=2:1 2 times development: 0.52(9b), 0.43(10b), silica gel, hexane:ether=1:1 3 times development)

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