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ASYMMETRIC SYNTHESIS OF 2-ALKYL-2,3-DIHYDROXYPROPIONATES FROM GLYCEROL

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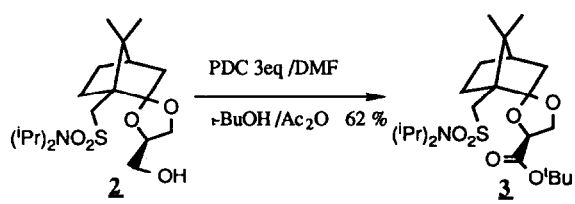
Abstract: The preparation of optically active 2-substituted 2,3-dihydroxypropionates from glycerol is described.

Optically active 2,3-dihydroxypropionates are an important class of chiral building blocks for the synthesis of enantiomercally pure natural products,[1] and are present as a portion of many natural products.[2] The preparation of these materials usually requires many steps.[1,3] Herein we report a general method for the preparation of optically active 2-substituted 2,3-dihydroxypropionates from glycerol.

We have previously reported an efficient method for the preparation of optically active (S)-(-)-1,2-O-alkylidene-*sn*-glycerol **2** from asymmetric ketalization of glycerol and (D)-N,N-diisopropyl-10-camphorsulfonamide **1**.[4] Further elaboration of the free hydroxyl functionality of alcohol **2** to the corresponding *t*-butyl ester **3**[5] could be achieved by an one pot direct oxidation of alcohol **2** employing Corey's procedure (pyridinium chlorochromate/ acetic anhydride/ *t*-butyl alcohol)[6] in 62% yield.



t-Butyl ester **3** was treated with 2 equivalents of base, lithium diisopropylamide (LDA) at -78°C to form the corresponding enolate, and the resulted enolate was then treated with alkylating agent. Treatment of the resulting enolate with a variety of alkylating agents (Table 1: entry 1-4) gave α-substituted adducts **4** and **5**, but with only a maximum d.e. of 33%. Addition of 2 equivalents of hexamethylphosphoramide (HMPA) (Table 1: entry 5) gave only a slight increase to 50% d.e. Interestingly, when 6 equivalents of HMPA were added to the reaction mixture, before the addition of the alkylating agent, some remarkable changes in the experimental results were noticed: a completely opposite diastereoselectivity and an enhancement of asymmetric induction up to >87% for the allylations were observed. (Table 1: entry 6 and 7) In the early stages of these experiments the yields were found to be low. The decrease in yield was presumably due to the metal ion being solvated by HMPA and the bare enolate ion becoming less stable, for example a β-elimination of the β-alkoxy group might occurr, and decomposing to other products. This could be realized by the recovery of ketosulfonamide **1**, one of the β-elimination product, after workup of the alkylation reaction. To avoid poor yield arose from a β-

elimination of the bare enolate ion, alkylating agent was added immediately after the addition of HMPA. Not only the yield of the alkylation product was improved to 70-88%, but also the degree of asymmetric induction was upgraded to >87% except for benzylation. (Table 1: entry 8-11) Alkylation of the zinc enolate of *t*-butyl ester **3** gave a similar trend in asymmetric induction to the lithium enolate, however the degree of asymmetric induction was much higher. (Table 1: entry 12-15)

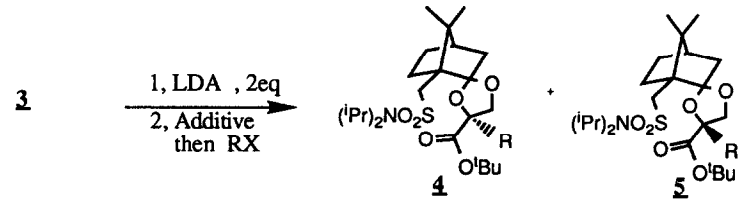


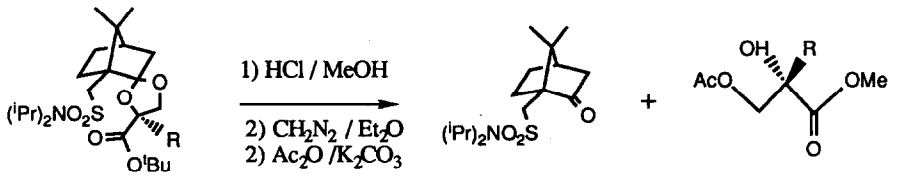
Table 1 Results on the Alkylation of The Enolate of **3**

Entry	Additive	RX	Ratio of **4**[7]/**5**[7]	Isolated Yield%
1	no	Benzyl bromide	1.5 : 1	70
2	no	Methyl iodide	2 : 1	95
3	no	Ethyl iodide	1.5 : 1	64
4	no	Allyl bromide	1.5 : 1	77
5	HMPA(2eq)	Benzyl bromide	3 : 1	71
6*	HMPA(6eq)	Methyl iodide	1 : 8	50
7*	HMPA(6eq)	Allyl bromide	1 : 15	21
8	HMPA(6eq)	Benzyl bromide	1 : 5	72
9	HMPA(6eq)	Methyl iodide	1 : 15	75
10	HMPA(6eq)	Ethyl iodide	1 : 15	88
11	HMPA(6eq)	Allyl bromide	1 : 15	71
12	$ZnCl_2$	Benzyl bromide	15 : 1	78
13	$ZnCl_2$	Methyl iodide	6 : 1	85
14	$ZnCl_2$	Ethyl iodide	6 : 1	81
15	$ZnCl_2$	Allyl bromide	5.5 : 1	74

*Alkylating agent was introduced 5 minutes after the addition of HMPA

In order to determine the stereochemistry on the newly formed stereogenic center, compound **4a** was hydrolyzed in methanol with concentrated HCl. The crude product was then treated with diazomethane followed by acetic anhydride in the presence of potassium carbonate at 0°C to afford (3 steps) 54% of methyl 3-acetoxy-2-hydroxy-2-methyl-propionate **6a**, with recovery of ketosulfonamide **1**, 96%. After the comparison of our measured $[\alpha]_D$ value for **6a** with literature data,[8] each of the newly formed stereogenic center at **4a** and **6a** were assigned to have an S configuration. Thus the lithium and zinc enolates underwent an alkylation from the less

hindered *si* face whereas the free enolate underwent an alkylation from the more hindered *re* face. Similarly **4b-d** were transformed to the corresponding methyl 3-acetoxy-2-hydroxy-2-alkyl-propionates **6b-d** in higher yields.(Table 2) Thus a facile entry to optically active 2,3-dihydroxypropionates from glycerol has been demonstrated.



4 **1** **6**

Table 2 Results of the Transformation of **4** to **6**

	R=	Recovery(%) of **1**	Isolated Yield(%) of **6**	$[\alpha]_D^{23}$
a	Methyl	96	54	9.30 (*c* 0.63, EtOH)
				23.40 (*c* 0.78, $CHCl_3$)
b	Ethyl	97	85	9.04 (*c* 3.01, $CHCl_3$)
c	Allyl	98	94	-9.64 (*c* 2.0, $CHCl_3$)
d	Benzyl	97	97	11.50 (*c* 2.0, $CHCl_3$)

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5. **3** : mp. 126-128°C ; IR : 1746 cm^{-1} ; ^1H NMR δ($CDCl_3$) : 4.26(dd, 1H, J= 7.7, 4.0 Hz), 4.07(dd, 1H, J=8.4, 7.7 Hz), 3.95(dd, 1H, J=8.4, 4.0 Hz), 3.73(septet, 2H, J= 6.8Hz), 3.43(d, 1H, J= 14.8 Hz), 2.95(d, 1H, J=14.8 Hz), 2.40(td, 1H, J=9.6, 4.8Hz), 2.02-2.15(m, 1H), 1.65-1.80(m,2H), 1.40(s, 9H

), 1.27(d, 6H, J=6.8Hz), 1.26(d, 6H, J=6.8 Hz), 1.11(s, 3H), 1.1-1.4(m,3H), 1.04(s, 3H).; ^{13}C NMR δ($CDCl_3$) : 169.60, 119.33, 81.50, 71.54, 67.56, 53.67, 51.63, 48.12, 47.94, 45.50, 43.48, 27.81, 26.46, 24.93, 22.34, 21.97, 21.54, 19.99. ; $[\alpha]_D^{23}$ -7.12 (*c* 6.6, $CHCl_3$).

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7. **4a** : mp. 131-132°C ; IR : 1733 cm^{-1} ; ^1H NMR δ($CDCl_3$) : 4.20(d, 1H, J=8.7 Hz), 3.70-3.82(septet, 2H , J=6.7 Hz), 3.69(d, 1H, J= 8.7 Hz), 3.40(d, 1H, J=14.8 Hz), 3.00(d, 1H, J=14.8 Hz), 2.43(td, 1H,J=12.3, 4.7 Hz), 1.98-2.15(m, 2H), 1.68-1.83(m, 2H), 1.45(s, 3H), 1.43(s, 9H), 2.30(d, 6H, J=6.7Hz), 1.29(d, 6H, J=6.7Hz), 1.16(s, 3H), 1.1-1.5(m, 2H), 1.08(s, 3H).; $[\alpha]_D^{23}$ -1.68 (*c* 1.1, $CHCl_3$).; **4b** : mp 163-164°C ; IR : 1725 cm^{-1} ; ^1H NMR δ($CDCl_3$) : 4.14(d, 1H, J=8.7Hz), 3.69(d, 1H, 8.7Hz), 3.72(septet, 2H, J=6.6Hz), 3.33(d, 1H, J=14.7Hz), 2.99(d, 1H, J=14.7Hz), 2.38-2.48(m, 1H), 2.07-2.16(m, 1H), 1.94-2.05(m, 1H), 1.53-1.91(m, 4H), 1.41(s, 9H), 1.28(d, 6H, J=6.6Hz), 1.26(d, 6H, J=6.6Hz), 1.1-1.5(m, 2H), 1.14(s, 3H), 1.06(s, 3H), 0.94(t, 3H, J=7.2Hz).; $[\alpha]_D^{23}$ -11.6 (*c* 1.1, $CHCl_3$).; **4c** : mp. 167-168°C ; IR : 1727 cm^{-1} ; ^1H NMR δ($CDCl_3$) : 5.7-5.9(m, 1H), 5.10(d, 2H, J=12.6Hz), 4.17(d, 1H, J=8.7Hz), 3.75 (d, 1H, J=8.7Hz), 3.73(septet, 2H, J=6.6Hz), 3.35(d, 1H, J=14.4Hz), 3.00(d, 1H, J=14.4Hz), 2.40-2.59(m, 3H), 2.07-2.16(m, 1H), 1.95-2.02(m, 1H), 1.62-1.84(m, 3H), 1.41(s,9H), 1.29(d, 6H, J=6.6Hz), 1.28(d, 6H, J=6.6Hz), 1.16(s, 3H), 1.1-1.5(m,2H), 1.07(s,3H).; $[\alpha]_D^{23}$ -19.9 (*c* 1.3, $CHCl_3$).; **4d** : mp. 170-171.5°C ; IR : 1739 cm^{-1} ; ^1H NMR δ($CDCl_3$) : 7.22-7.27(m, 5H), 4.25(d, 1H, J=9Hz), 3.85(d, 1H, J=9Hz), 3.75(septet, 2H, J=6.9Hz), 3.50(d, 1H, J=15Hz), 3.10(d, 1H, J=14.2Hz), 3.04(d, 1H, J=14.2Hz), 3.03(d, 1H, J=15Hz), 2.46-2.59(td, 1H, J=12.3, 4.7 Hz), 2.15-2.24(m, 1H), 1.7-1.9(m, 2H), 1.62-1.68 (m, 1H), 1.33(s, 9H), 1.31(d, 6H, 6.9Hz), 2.9(d, 6H, J=6.9Hz), 1.19(s, 3H), 1.1-1.5(m,2H), 1.08(s, 3H).; $[\alpha]_D^{23}$ -8.97 (*c* 1.1, $CHCl_3$). ; **5a** : mp. 83-84.5°C ; IR : 1744 cm^{-1} ; ^1H NMR δ($CDCl_3$) : 4.28(d, 1H, J=7.8Hz), 3.69(septet, 2H, J=6.7Hz), 3.66(d, 1H, J=7.8Hz), 3.05(d, 1H, J=14.3 Hz), 2.78(d, 1H, J=14.3 Hz), 2.09-2.24 (m, 2H), 1.87-1.92 (m, 1H), 1.56-1.79(m, 3H), 1.45(s, 3H), 1.40(s, 9H), 1.27 (d, 12H, J=6.7Hz), 1.2-1.4(m, 1H), 0.95 (s, 6H). ; $[\alpha]_D^{23}$ -15.8 (*c* 8.3, $CHCl_3$).; **5b** : mp. 76-78°C ; IR : 1733 cm^{-1} ; ^1H NMR δ($CDCl_3$) : 4.19(d, 1H, J=8.1Hz), 3.71(septet, 2H, J=6.8Hz), 3.70(d, 1H, J=8.1Hz), 3.04(d, 1H, J=14.5Hz), 2.87(d, 1H, J=14.5Hz), 2.13-2.26(m, 2H), 1.85-1.90(m, 2H), 1.61-1.79(m, 4H), 1.45(s, 9H), 1.2-1.4(m,1H), 1.26(d, 12H, J=6.8Hz), 1.02(s, 3H), 0.99(s, 3H), 0.90 (t, 3H , J=7.2Hz).; $[\alpha]_D^{23}$ -4.06 (*c* 5.0, $CHCl_3$).; **5c** : IR : 1733 cm^{-1} ; ^1H NMR δ($CDCl_3$) : 5.70-5.84(m, 1H), 5.04-5.13(m, 2H), 4.22(d, 1H, J=8.1Hz), 3.74 (d, 1H, J=8.1Hz), 3.72(septet, 2H, J=6.7Hz), 3.06(d, 1H, J=14.4Hz), 2.83 (d, 1H, J=14.4Hz), 2.49-2.62(m, 2H), 2.11-2.23(m, 2H), 1.84-1.90(m, 1H), 1.63-1.80(m, 3H), 1.44(s, 9H), 1.28(d, 12H, J=6.7Hz), 1.1-1.5(m,1H), 0.99(s, 3H), 0.97(s, 3H).$[\alpha]_D^{23}$ 3.19 (*c* 6.2, $CHCl_3$) ; **5d** : mp. 153-154°C ; IR : 1734 cm^{-1} ; ^1H NMR δ($CDCl_3$) : 7.20-7.32(m, 5H), 4.31(d, 1H, J=8.1Hz), 3.91(d, 1H, J=8.1Hz), 3.75(septet, 2H, J=6.9Hz), 3.76(d, 1H, J=13.5Hz), 3.19(d, 1H, J=14.7Hz), 3.11(d, 1H, J=13.5Hz), 2.32-2.42(m, 1H), 2.23(td, 1H, J=12.3, 4.7 Hz), 1.88-1.95(m, 1H), 1.63-1.92(m, 4H), 1.32(d, 12H, J=6.9), 1.31(s, 9H), 1.2-1.4(m, 1H), 1.01(s, 3H), 1.00(s, 3H).; $[\alpha]_D^{23}$ 9.26 (*c* 4.1, $CHCl_3$).
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