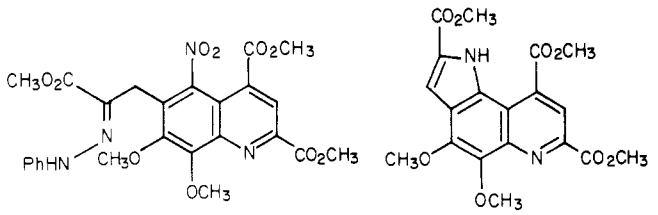

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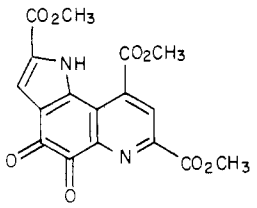

16

(75%). Since a sample of 1 was not available to us, and since there is only scant spectral data reported[4] for the natural coenzyme, our synthetic material was characterized by clean conversion to acetone adduct 2 (acetone/H_2O/NH_4OH, room temperature, 0.5 h), which was identical in UV, ^1H NMR, and TLC with an authentic sample.[11,20]

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Registry No. 1, 72909-34-3; 2, 73030-04-3; 3, 77869-39-7; 4, 78891-29-9; 5, 78891-30-2; 6, 78891-31-3; 7, 78891-32-4; 8, 78891-33-5; 9, 78891-34-6; 11, 78891-35-7; 12, 78891-36-8; 13, 78891-37-9; 14, 78891-38-0; 15, 78891-39-1; 16, 74447-88-4; 2,3-dimethoxytoluene, 4463-33-6; pyruvic acid, 127-17-3; methyl acetoacetate, 105-45-3.

(20) We are extremely grateful to Drs. H. S. Forrest and S. A. Salisbury for spectra and a sample of acetone adduct 2, and for their cooperation during the course of this research.

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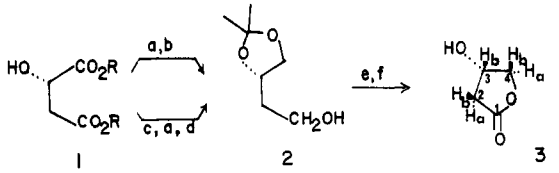
Stereoselective Alkylation and Aldol Reactions of (*S*)-(−)-β-Hydroxy-γ-butyrolactone Dianion

Summary: The dianion of 3 reacts with alkyl halides to give exclusively *trans*-2-alkyl-3-hydroxy lactones and with aldehydes to give 2,3-*trans*-disubstituted lactones which exhibit erythro selectivity in the newly formed aldol moiety.

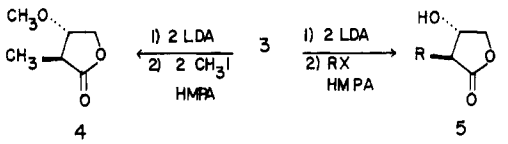
Sir: The dianions of β-hydroxy esters can be alkylated[1] with better than 90% stereoselectivity[2,3] to give threo-type[4] products. We have extended this reaction to include the dianion of a cyclic analogue, (*S*)-(−)-3,4-dihydroxybutanoic acid 1,4-lactone (3), and we report herein that the alkylations proceed with virtually complete threo (trans to O^-) selectivity[5] at C-2 (relative asymmetric induction[6]). Furthermore, both relative and internal asymmetric induction are observed during aldol reactions of this chiral dianion with aldehydes, giving predominately erythro aldols. Variation of the erythro/threo ratios can be rationalized in terms of acyclic vs. cyclic transition-state models.

Scheme I. Synthesis of Hydroxylactone 3[a]

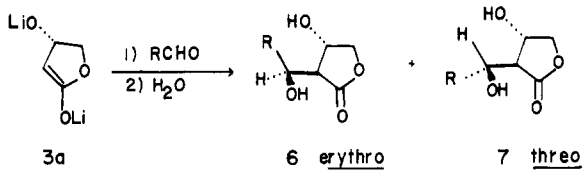


[a] Reagents: (a) $LiAlH_4$, THF; ^-OH; (b) acetone, $ZnCl_2$ or *p*-TsOH; (c) 2-methoxypropene, $POCl_3$; (d) $BF_3{\cdot}Et_2O$; (e) Jones oxidation; (f) H_2O, H_2SO_4.

Scheme II. Alkylation of Dianion 3a



Scheme III. Aldol Condensation of Dianion 3a



The chiral hydroxy lactone 3[7] was prepared[7,8] from (*S*)-(−)-malic acid in 23% overall yield after flash chromatography (Scheme I). Proton shifts and couplings were determined by using $Eu(fod)_3$ and were confirmed by spin simulations.[9] The dianion of 3 was generated in THF at −78 °C by the addition of 2.2 equiv of lithium diisopropylamide and was unstable above −20 °C. Addition of methyl iodide to the dianion solution at −78 °C followed by warming to −45 ± 5 °C for 5 h gave only recovered starting material. However, addition of a variety of alkylating agents (Table I) in THF containing HMPA[2] (to make a 10–20% v/v solution) to the −78 °C solution followed by stirring for 5 h at −45 ± 5 °C gave moderate yields of 4 and 5 in addition to some recovered starting lactone (Scheme II). Reactions run at −45 °C for longer times gave

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(2) Frater, G. *Helv. Chim. Acta* **1979**, *62*, 2825, 2829.
(3) (a) Seebach, D.; Wasmuth, D. *Helv. Chim. Acta* **1980**, *63*, 197. (b) Züger, M.; Weller, T.; Seebach, D. *Ibid.* **1980**, *63*, 2005.
(4) We have chosen the R-group-independent convention of Heathcock[5] in naming relative configurations which conflict with Seebach's designations[3] in several cases.

(5) (a) Heathcock, C. H.; Buse, C. T.; Kleschick, W. A.; Pirrung, M. C.; Sohn, J. E.; Lampe, J. *J. Org. Chem.* **1980**, *45*, 1066. (b) Kleschick, W. A.; Buse, C. T.; Heathcock, C. H. *J. Am. Chem. Soc.* **1977**, *99*, 247.
(6) Bartlett, P. A. *Tetrahedron* **1980**, *36*, 3.
(7) From D-xylose: Machell, G.; Richards G. N. *J. Chem. Soc.* **1960**, 1924. Enantiomeric form from (*R*)-(+)-malic acid: Mori, K.; Takigawa, T.; Matsuo, T. *Tetrahedron* **1979**, *35*, 933.
(8) (a) Hayashi, H.; Nakanishi, K.; Brandon, C.; Marmur, J. *J. Am. Chem. Soc.* **1973**, *95*, 8749. (b) Corey, E. J.; Niwa, H.; Knolle, J. *Ibid.* **1978**, *100*, 1942.
(9) GLC was performed by using a Varian 3700 gas chromatograph equipped with 2 m × 2 mm i.d. glass columns packed with 3% OV-17. The 80-MHz ^1H NMR and 20-MHz ^{13}C NMR spectra were obtained in $CDCl_3$ solutions on a Varian CFT-20. 3: ^1H NMR δ 2.45 (H-2a, dd, ^2J = 18.4 Hz, $^3J_{H_2H_{2b}}$ = 1.5 Hz), 2.70 (H-2b, dd, ^2J = 18.5 Hz, $^3J_{H_2H_{2b}}$ = 5 Hz), 3.63 (OH), 4.23 (H-4a, dd, ^2J = −10.4 Hz, $J_{H_{4a}H_3}$ < 1 Hz), 4.39 (H-1b, dd, ^2J = −10.4 Hz, $^3J_{H_1H_3}$ = 4.3 Hz), 4.62 (H-3, m); ^{13}C NMR δ 177.35 (C-1), 76.35 (C-3), 67.16 (C-4), 37.62 (C-2). 5a: ^1H NMR δ 4.18 (H-3, H-4, m), 2.44 (OH, br s) 1.62 (dd, *J* = 4.3, 8.0 Hz), 1.04 (CH_2, dq, *J* = 7.2, 8.0 Hz), 0.95 (CH_3, t, *J* = 7.2 Hz); ^{13}C NMR δ 179.30 (C-1), 73.89 (C-3), 71.79 (C-4), 49.94 (C-2), 21.58 (CH_2), 11.42 (CH_3). Full experimental details for 5a–e will be published subsequently. All new compounds gave either microanalyses or high-resolution mass spectra consistent with the proposed structures.

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Table I. Alkylation of Dianion 3a[a]

alkylating agent (RX)	temp, °C	time, h	product	yield (% isolated)	% recovd starting matl (%)
CH_3I (2 equiv)	−45 ± 5	5	4	65	
C_2H_5I (1 equiv)	−45 ± 5	5	5a	30	
$CH_3C(=CH_2)CH_2CH_2Br$	−45 ± 5	5	5b	29	
$CH_3(CH_2)_{14}CH_2OSO_2CH_3$	−45 ± 5	5	5c	33	
$CH_2=CHCH_2Br$	−78	48	5d	25	45
$C_6H_5CH_2Br$	−78	48	5e	34	20

[a] Yields are reported for isolated alkylated material after flash chromatography and are uncorrected for recovered starting material.

Table II. Aldol Condensations[a] of Dianion 3a[10]

		without $ZnCl_2$		with $ZnCl_2$		$^3J_{2,5}$, Hz	
compd	R	6/7 ratio	% yield	6/7 ratio	% yield	erythro	threo
a	C_6H_5	10:1	43	4:1	85	3.5	7.4
b	$C_6H_5CH_2$	1.3:1	45	1:1.4	89	1.0	3.1
c	$(CH_3)_3C$	>100:1	34	>100:1	48	1.8	
d	$CH_3(CH_2)_{11}CH_2$	1:1	48	1:1.2	60	2.9	3.9

[a] Yields are reported for material isolated by flash chromatography.

no increase in yield, but less starting material was recovered. Reaction at −78 °C for 48 h gave no significant improvement in yield.[3]

The alkylated product appeared as a single (>95%) isomer, as determined by TLC, by GLC, and by both ^1H and ^{13}C NMR.[9] The Eu(fod)$_3$-shifted ^1H NMR of **5a** showed that H-2a ($^3J_{H_2H_3}$ = 4.3 Hz) retained the smaller trans coupling to H-3 and that it moved faster than either the ethyl methylene or H-4b signals, confirming that alkylation had occurred with >20:1 threo selectivity[2] as in the acyclic case.[3] Indeed, alkylation of (*S*)-(−)-diethyl malate under conditions identical with those for **5a** gave a 42% isolated yield of diethyl (2*S*,3*R*)-2-hydroxy-3-ethylbutandioate ($^3J_{H_2H_3}$ = 4.0 Hz) as the exclusive alkylated product.

The aldol condensations of dianion **3a** with benzaldehyde, phenylacetaldehyde, pivaldehyde, and tetradecanal were performed under similar conditions (Scheme III). Thus, dropwise addition of an aldehyde–THF–HMPA solution to the dianion at −78 °C, stirring at −78 °C for 1 h, warming to −50 °C for 2 h, and quenching with saturated NH_4Cl solution at −50 °C led to the isolation of two diastereomeric aldol products in varying ratios. Addition of dry $ZnCl_2$[10] *increased* the total aldol yields and *reduced* the stereoselectivity. Stereoselectivity increased with the bulkiness of the aldehyde "R" group but favored the erythro product (smaller $J_{2,5}$) in each case.[11] Omission of HMPA from the reaction mixture did not change the erythro/threo ratio or the yield of aldol products. Only addition to the face of the enolate opposite to the oxyanion substituent was observed. Table II summarizes these results.

Reaction of the cyclic β-oxyanion enolate **3a** cannot be controlled by lithium coordination as suggested by Seebach[3] for the acyclic case. We favor a transition-state model in which the developing bond (and thus the electron density on C-2) must form trans to the oxyanion due to electrostatic repulsion. This model is supported by our findings that both aldol and alkylation reactions of **3a** with reagents of different steric requirements all give exclusively *trans*-2-alkyl-3-hydroxy lactones.

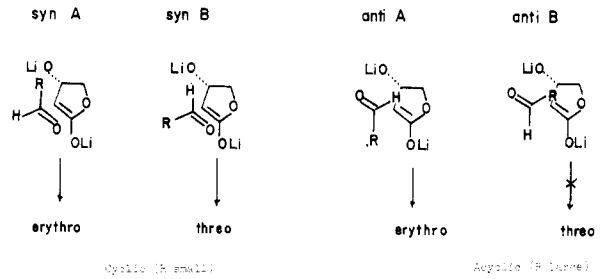

Figure 1. Proposed transition states for aldol condensation of **3a** with aldehydes.

Rationalization of the aldol stereoselectivity is less straightforward. Both cyclic and acyclic (*E*)-lithio enolates lead to threo products under kinetic control as the result of steric effects in a cyclic transition state.[5,10,12] Both the yield and the amount of the threo isomer can be increased for these cases by using divalent cations to stabilize the transition state.[10,12] Recently three groups have reported erythro-selective aldol reactions with enol silyl ethers and acetals,[13] zirconium enolates,[14a,15] and crotyltrialkyltins[14b] in which acyclic transition states account for the observed products regardless of enolate geometry. An alternative explanation[15] invokes pseudoboat transition states for (*E*)-zirconium enolates and pseudochair transition states for the *Z* isomers, leading to the same erythro product. Our results (Table II) can also be rationalized in terms of reaction via both cyclic[10] and acyclic[14b] transition states leading to threo–erythro product mixtures and erythro selectivity, respectively (Figure 1).

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(11) Full experimental details will be published separately. Ratios are based on GLC of the *n*-butyl boronates, on integration of 80-MHz ^1H NMR, and on the masses of chromatographed diastereomers. The 360-MHz ^1H NMR spectra (A. McLaughlin, Brookhaven National Laboratory) of **6a** and **7a** gave the following data (decoupling confirms shift assignments). For **6a**: δ 6.26 (Ph, s), 4.15 (H-5, d, *J* = 3.4 Hz), 3.48 (H-3, m), 3.25 (dd, *J* = 8.4, 6.5 Hz), 2.88 (dd, *J* = 8.4, 3.8 Hz), 2.15 (OH), 1.72 (dd, *J* = 3.5, 4.4 Hz). For **7a**: δ 6.25 (Ph, s), 3.88 (H-5, d, *J* = 7.4 Hz), 3.27 (H-3, m), 2.92 (dd, *J* = 8.43, 5.75 Hz), 2.80 (dd, *J* = 8.4, 5.7 Hz), 1.81 (dd, *J* = 7.4, 5.7 Hz).

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(13) Murata, S.; Suzuki, M.; Noyori, R. *J. Am. Chem. Soc.* **1980**, *102*, 3248.

(14) (a) Yamamoto, Y.; Maruyama, K. *Tetrahedron Lett.* **1980**, 4607. (b) Yamamoto, Y.; Yatagai, H.; Naruta, Y.; Maruyama, K. *J. Am. Chem. Soc.* **1980**, *102*, 7107.

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(16) Fellow of the Alfred P. Sloan Foundation (1981–1983).

The increase in "local bulkiness" at the aldehyde α-carbon going from tetradecanal to phenylacetaldehyde to benzaldehyde to pivaldehyde results in a shift from 1:1 erythro/threo to exclusively erythro products. The observed shift toward erythro selectivity can be rationalized by either the acyclic anti-A or cyclic syn-A transition states (Figure 1). However, syn-A should be unfavorable relative to syn-B for large "R", and thus anti-A best explains the shift to higher erythro/threo ratios with increasing bulkiness. An analogous anti transition state was proposed by Yamamoto[14b] to account for the erythro selectivity of the reaction of crotyltrialkyltins with aldehydes. If R is small or if a divalent cation is added, the cyclic syn transition states can become energetically more favorable than the more charge-separated acyclic anti transition states. When this occurs for R small, little selectivity will result, and erythro/threo ratios near 1:1 will be observed. To summarize, as R increases in bulk, a cyclic transition state would result in a shift to threo (syn-B) with the R group pseudoequatorial. We believe that the observed shift to erythro selectivity is best rationalized by the minimization of steric interactions and maximal separation of negative charge provided by the acyclic anti-A transition state, although a pseudoboat cyclic transition state[15] is not strictly excluded by our results. Application of these data to 1,2- and 1,3-asymmetric induction of chirality in natural products synthesis will be reported in due course.

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Registry No. 3a, 78987-06-1; **4**, 78986-53-5; **5a**, 78986-54-6; **5b**, 79005-32-6; **5c**, 78986-55-7; **5d**, 78986-56-8; **5e**, 78986-57-9; **6a**, 78986-58-0; **6b**, 78986-59-1; **6c**, 78986-60-4; **6d**, 78986-61-5; **7a**, 79081-93-9; **7b**, 79081-94-0; **7d**, 79055-74-6; benzaldehyde, 100-52-7; phenylacetaldehyde, 122-78-1; pivaldehyde, 630-19-3; tetradecanal, 124-25-4; methyl iodide, 74-88-4; ethyl iodide, 75-03-6; 3-methylbut-3-enyl bromide, 20038-12-4; 1-hexadecanol methanesulfonate, 20779-14-0; allyl bromide, 106-95-6; benzyl bromide, 100-39-0.

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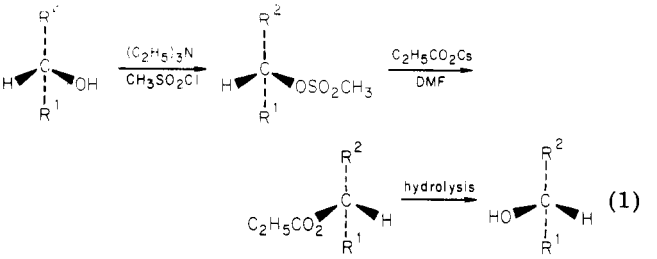
Cesium Carboxylates in Dimethylformamide. Reagents for Introduction of Hydroxyl Groups by Nucleophilic Substitution and for Inversion of Configuration of Secondary Alcohols

Summary: Cesium carboxylates, in particular the propionates, in dimethylformamide solvent give clean S_N2 substitutions on a variety of compounds.

Sir: Cesium carboxylates in dimethylformamide (DMF) are good nucleophiles.[1] In this solvent the large and polarizable cesium ion lends to the ion pair properties including nucleophilicity that lie at the heart of a recently described method for ring closure of ω-halo cesium carboxylates to macrolides.[2] We anticipated on the basis of this work that cesium carboxylates also would be useful for introduction of hydroxy substituents by intermolecular S_N2 nucleophilic substitution.

The nucleophile chosen for investigation is cesium propionate, prepared from Cs_2CO_3 and propionic acid;[3] this is a powder that can be readily dried and which is soluble (0.1 M) in DMF. Results for a variety of substitution reactions are given in Table I.

The overall scheme for alcohol inversion (entries 1-7) is given in eq 1. This approach complements two other



(1)

frequently used methods, namely, reaction of the alcohol with $RO_2CN{=}NCO_2R/(C_6H_5)_3P/RCO_2H$ to afford the inverted alcohol ester of RCO_2H[4] or treatment of the mesylate with KO_2/crown ether.[5] The inversion of (*S*)-2-octanol to the enantiomerically pure *R* enantiomer using the cesium propionate method (entry 1) proceeds in 86% overall isolated yield without detectable amounts of elimination. Inversion of (*S*)-2-octanol with $C_2H_5O_2CN{=}NCO_2C_2H_5/(C_6H_5)_3P/C_6H_5CO_2H$ is reported to afford the inverted benzoate in 20% yield[6] whereas reaction of (*S*)-2-octyl mesylate with KO_2/dibenzo-18-crown-6 gives (*R*)-2-octanol in 75% yield with 23% elimination (GLC yields).[7]

The cesium propionate method is also compatible with other functional groups as shown by the remarkably clean conversion without detectable amounts of elimination or racemization of ethyl (*S*)-lactate (entry 4) to its *R* enantiomer (isolated as propionate; hydrolysis to (*R*)-lactic acid involves loss of material owing to isolation difficulties). The problem of base-catalyzed enolization occurs, however, for ethyl (*S*)-mandelate (entry 5), the propionate of which, prepared independently, racemized completely within 24 h at 50 °C with $CsO_2CC_2H_5$/DMF. Racemization is slower for the corresponding *N,N*-dimethyl amide (entry 6), which has a lesser tendency to form an enolate. Use of the amide together with the less basic cesium benzoate (entry 7) leads to the desired *R* enantiomer in 93% optical purity.

For the cases of the mesylates of menthol and cholestanol (entries 2 and 3) some elimination occurs in competition with the desired substitution. The inversion of cholestanol using the Mitsunobu method is reported to give a quantitative yield of inverted benzoate.[8] Other leaving groups can be used with cesium propionate (entries 9-12).

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(3) The preparation of $CsO_2CC_2H_5$ is carried out by dissolving Cs_2CO_3 (5 mmol) in 40 mL of dry CH_3OH. To this solution is added dropwise propionic acid (15 mmol) in 10 mL of dry CH_3OH. An excess of propionic acid is necessary to obtain complete reaction. After 30 min the CH_3OH is removed, and the white powder remaining is washed on a filter thoroughly with $(C_2H_5)_2O$.

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