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ASYMMETRIC SYNTHESIS *VIA* ACETAL TEMPLATES. 12.[1] HIGHLY DIASTEREOSELECTIVE COUPLING REACTIONS WITH A KETENE ACETAL. AN EFFICIENT, ASYMMETRIC SYNTHESIS OF R-(+)-α-LIPOIC ACID

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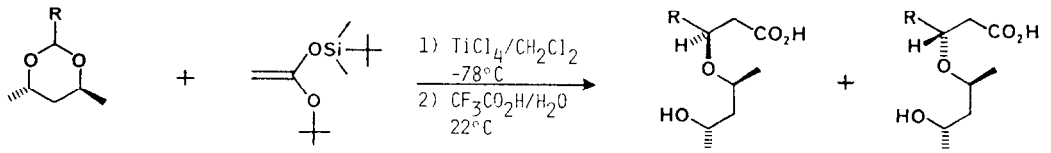
Abstract: $TiCl_4$ catalyzes the essentially quantitative coupling of chiral acetals 1 with 1-t-butoxy-1-t-butyldimethylsilyloxyethene 2 to generate β-alkoxycarboxylates in which the new asymmetric center is formed with excellent diastereoselection. β-Hydroxycarboxylic acids of high ee result from removal of the chiral auxiliary. The procedure has been applied to the synthesis of R-(+)-α-lipoic acid 10.

Recent work[2] has delineated the high diastereoselection realized in the $TiCl_4$-catalyzed aldol-type coupling of chiral acetals such as 1 with various enol silanes. We now describe the extension of this work to the use of the ketene acetal nucleophile 2,[3] which is easily prepared in multigram quantities from t-butyl acetate by well established procedures.[4] The outcome of $TiCl_4$-promoted coupling reactions between 2 and three representative acetals is summarized in Table 1.

In all cases, excellent isolated yields and high diastereoselectivities were best obtained by a concurrent addition of the acetal and ca. 2 (for 1a and 1b) or 3 (for 1c) mol equiv of $TiCl_4$ to a solution of ca. 4 mol equiv of the ketene acetal 2 in CH_2Cl_2 at -78°C.[5] The immediate coupling products -- mixtures of silyl and t-butyl esters, rich in the former -- were hydrolyzed by aqueous trifluoroacetic acid to the diastereomeric carboxylic acids 3/4.

SCHEME 1



1 2 3 4

a R = cyclohexyl
b R = n-octyl
c R = $(CH_2)_4CO_2$i-Pr

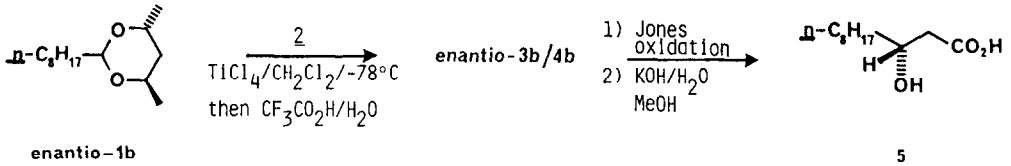
TABLE 1: Results of Transformations Shown in Scheme 1*

Entry	Acetal	Coupling Product	% Yield	Ratio 3:4[7]
1	1a	3a/4a[6a]	98	97:3
2	1b	3b/4b[6a]	98	98:2
3	1c	3c/4c[6a,b]	90-93	98:2

*The results reported herein were obtained from studies made with racemic acetals, i.e., 1 + enantio-1, derived from the readily available (±)-2,4-pentanediol.[15a] Thus the products were also racemic, i.e., 3 + enantio-3 and 4 + enantio-4. This expedient gives complete information regarding the stereoselectivity of the coupling reaction.

Evidence for the stereochemical course of the process depicted in Scheme 1 was obtained by the transformation shown in Scheme 2. Enantio-3b, derived from R,R-acetal enantio-1b[2] was converted, by the well established oxidation/β-elimination method[8] (76%), into 3R-3-hydroxyundecanoic acid 5[6a] ($[\alpha]_D^{25}$ -17°, c = 1, $CHCl_3$). This product differed from naturally-occurring 3S-5,[9] of established absolute configuration, only in the sign of its optical rotation. Thus, mechanistically, the stereochemical outcome of the reactions in Table 1 is consistent with the S_N2-like transition state model proposed in an earlier communication.[10]

SCHEME 2



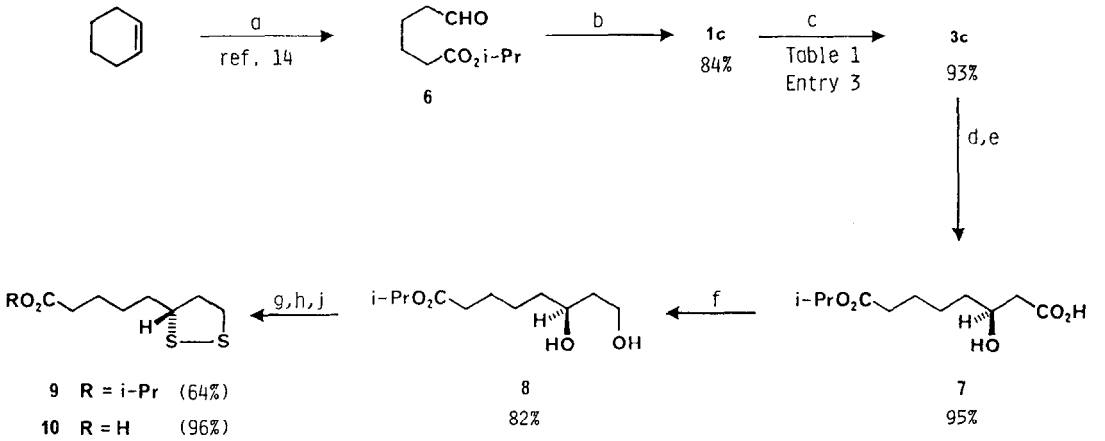
enantio-1b

5

The availability of essentially optically pure β-hydroxycarboxylic acids by this method prompted us to apply the technique to the synthesis of R-(+)-α-lipoic acid 10, the coenzyme associated with α-ketoacid dehydrogenases.[11] The R-configuration of 10 has recently been confirmed by Golding[12] *via a synthesis of the unnatural antipode enantio-10 from S-malic* acid. Existing syntheses of (+)-α-lipoic acid have invariably relied upon resolution of an appropriate racemic precursor,[13] hence the route delineated in Scheme 3 represents the first asymmetric synthesis. Requisite S,S-acetal 1c[6a,b] was obtained *via* aldehyde 6 in two steps from cyclohexene using the ozonolytic procedure of Schreiber[14] followed by acetalization with S,S-2,4-pentanediol[15b] (84% overall). Selection of the carboxyl protecting group was governed by a desire to avoid competitive ester hydrolysis during basic treatment at a later stage in the synthesis.

$TiCl_4$ mediated coupling of 1c and 2 afforded 3c[6a,b] (93% yield, 98:2 diastereoselectivity[7]). Oxidation of the secondary alcohol was effected by Jones' reagent (98%) but, in contrast to the earlier example, freshly prepared piperidinium acetate in boiling benzene[2]

SCHEME 3



[a] O_3/i-PrOH/-78°C then Ac_2O/Et_3N; [b] (2S,4S)-pentan-2,4-diol/p-toluenesulphonic acid/C_6H_6, [c] $TiCl_4/CH_2Cl_2$/ketene acetal 2/-78°C then TFA/H_2O; [d] Jones' oxidation; [e] piperidinium acetate/C_6H_6/reflux; [f] BH_3·THF, then 4M-aqueous KOH; [g] $MeSO_2Cl/Et_3N$/0°C; [h] to give 9: Na_2S/S/DMF/-79°C; [j] to give 10: K_2CO_3/MeOH/H_2O.

proved to be the most facile method of β-elimination. Thus, S-7[6a] was isolated in 97% yield. Reduction of 7 to 1,3-diol 8 was achieved (82%)[6a] by BH_3·THF complex[16] (2 equiv in THF, 22°C, 1.5 h), using aqueous KOH (4 M, 2.5 equiv, 22°C, 2 h) to hydrolyze the intermediate cyclic borate ester. No competitive saponification of the isopropyl ester was detected. Straightforward completion of the synthesis followed essentially the same route as Golding's.[12] Mesylation of 8,[17] followed by disulfide displacement (Na_2S/S/DMF, 20 h at 70°C)[18] gave (+)-isopropyl lipoate 9 in 65% yield.[6a,b,19,20] Hydrolysis of 9 (K_2CO_3/MeOH/H_2O, 22°C, 40 h) and crystallization left R-(+)-α-lipoic acid 10[6a] (96%), m.p. 43-45°C, $[\alpha]_D^{23}$ +102° (c = 0.91, C_6H_6), reported[11] m.p. 46-48°C, $[\alpha]_D^{23}$ +104° (c = 0.88, C_6H_6). The foregoing sequence proceeded in 37% overall yield based on S,S-2,4-pentanediol.

With the exception of Heathcock's work,[3] previous approaches to optically pure β-hydroxy carboxylic acids[21] have favored the use of chiral acetate equivalents to serve as nucleophiles, and have suffered from variable diastereoselection. The elegant valinol-derived oxazolidinones of Evans[22] serve as very effective propanoate enolate equivalents; however, relatively poor selectivities were reported with the appropriate acetate analog. The current work offers an efficient aldol-type route to optically active β-hydroxy carboxylates of predictable absolute stereochemistry from achiral aldehydes and an achiral ketene acetal.

Acknowledgement: We wish to thank the National Institutes of Health and the National Science Foundation for their support of this research. We should also like to thank Dr. S. D. Lindell (Stanford) for helpful discussions.

References and Notes

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5. The procedure for the coupling reactions listed in the Table follows: Solutions of $TiCl_4$ (0.053 ml, 0.48 mmol) and acetal 1b (0.052 g, 0.23 mmol) each in 1.5 ml of dried, distilled CH_2Cl_2 were concurrently instilled by motorized syringes over 0.5 h into a vigorously stirred solution of 0.16 g (0.7 mmol) of the ketene acetal 2 at -78°C under argon. After an additional 0.5 h, MeOH (0.2 ml) was added, then the mixture was partitioned between EtOAc and 1 M hydrochloric acid, washed with water and brine and dried ($MgSO_4$). After solvent removal, the mixture was stirred with TFA (0.4 ml) and water (0.1 ml) for 2 h. All volatiles were removed at reduced pressure, and the residue was dissolved in saturated $NaHCO_3$ and washed with ether. Acidification of the aqueous phase and extraction with EtOAc (twice) followed by washing with brine and drying ($MgSO_4$) left, after evaporation, 0.064 g (98%) of 3b/4b.[6a]
6. (a) No indication of extraneous contaminants by GC and TLC analysis. ^1H NMR and IR spectra were consistent with the assigned structure. (b) A satisfactory combustion analysis was obtained for an appropriately purified specimen.
7. Diastereomeric ratios were determined by GC (baseline separation) on a 15-m SE-54 capillary column after conversion to the corresponding methyl esters (DBU/MeI/CH_2Cl_2). See Ono, N.; Yamada, T.; Saito, T.; Tanaka, K. and Kaji, A. *Bull. Chem. Soc. Jpn.*, 1978, *51*, 2401.
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9. Tahara, S. and Mizutani, J. *Agric. Biol. Chem.*, 1978, *42*, 879. 3R-5: M.p. 61-62°C (hexane). $[\alpha]_D^{25}$ -17° (c = 1, $CHCl_3$). 3S-5: M.p. 64-65°C. $[\alpha]_D$ +17.1° (c = 1, $CHCl_3$).
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15. (a) Available as a mixture with meso-diol (Fluka AG) and purified by crystallization from ether. (b) Aldrich Chem. Co., ee 99.6% after a single recrystallization from the minimum volume of anhydrous diethyl ether. Optical purity was determined by GC analysis of the bis-MTPA ester. Johnson, W. S.; Crackett, P. H.; Elliott, J. D.; Jagodzinski, J. J.; Lindell, S. D. and (in part) Natarajan, S. *Tetrahedron Lett.*, 1984, *25*, 3951.
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19. $[\alpha]_D^{20}$ +23.4° (c = 0.4, C_6H_6). 9 was indistinguishable from a sample prepared by esterification (i-PrOH, DCC, DMAP) of commercial (±)-α-lipoic acid (NMR, IR and GC coinjection).
20. To establish rigorously the enantiomeric purity of 9, a sample was converted,[18b] by selective reductive ring opening (1 mol equiv LAH) followed by esterification with (+)-MTPA (DCC, DMAP, CH_2Cl_2, 20°C), into the diastereomeric thioesters of i-propyl octanoate-6,8-dithiol. GC analysis under conditions affording baseline separation indicated a ratio of 98:2. Similar analysis of a racemic sample derived from (±)-10[19] gave the anticipated 1:1 ratio. Thus, the 96% ee confirms the stereospecific nature of the mesylate displacement.
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