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DIASTEREOSELECTIVE ELABORATION OF THE CARBON SKELETON OF β-HYDROXYESTERS FROM YEAST REDUCTIONS
Preparation of (2S)-2-Hydroxy-cyclohexane Carboxylic Acids with Three Contiguous Stereogenic Centers

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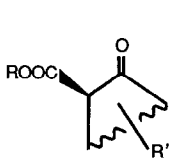
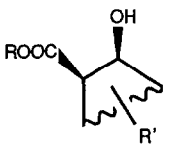
Abstract: The dioxanone-type acetal **2** from (1*R* ,2*S*)-2-hydroxy-cyclo-hexane carboxylic acid (**1**) and pivalaldehyde is dehydrogenated to a derivative **3** of 6-hydroxy-cyclohexene carboxylic acid. Highly selective *Michael* additions and trapping of the resulting enolates with electrophiles give single diastereomers **4** and **5** which can be hydrolized to 6-substituted 2-hydroxy-cyclohexane carboxylic acids of type **C** and **D**.

Yeast reductions of α-substituted β-ketoesters (equilibrating mixtures of enantiomers) furnish β-hydroxyesters derived from the *(R)* -precursor (**A** → **B**); open-chain, five- and six-ring, carbocyclic, bicyclic, and heterocyclic substrates have been employed)[2,3)], thus providing a host of enantiomerically pure starting materials for syntheses. Using the (1*R* ,2*S*)-hydroxyacid from 2-cyclohexanone carboxylate[3)], we demonstrate here a methodology for stereoselective mono- and dialkylation to give products of type **C** and **D**, respectively.



A



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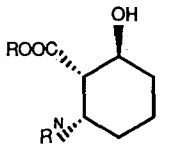
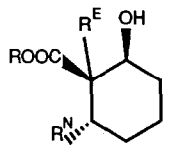
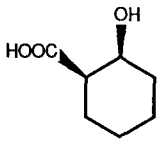


C

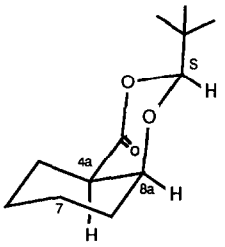


D

The hydroxyacid[4a)] **1** was condensed[4b)] with pivalaldehyde to the bicyclic dioxanone **2** in 90% yield and >50:1 selectivity[5)]. Introduction of the double bond by selenation and oxidative elimination[4c)] gave the two possible α.β-unsaturated carbonyl compounds (6:1), the major product **3** was separated by crystallization[5)] (65% yield from **2**; 25 mmol scale).



1



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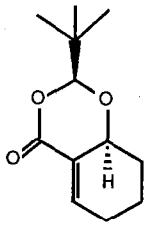

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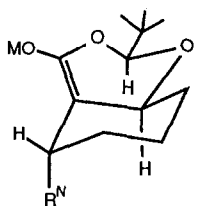
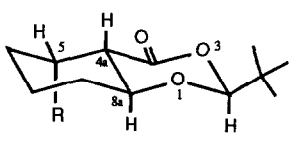
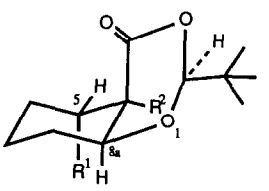


E

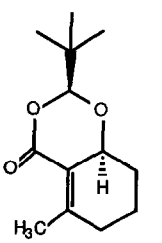
As evident from the content of *Table 1,* compound **3** turned out to be an excellent *Michael* acceptor for cuprates[4d]. The products **4a** - **4g** are formed[5] with high selectivity and have all the same configuration as evident from the 300 MHz ^{1}H-NMR spectra: the bridgehead hydrogens H-4a (δ 2.31-2.42 ppm, *dd* , 11 and 4 Hz) and H-8a (δ 3.75-4.00[7], *td* , 11 and 4 Hz) are antiperiplanar (*trans* -fusion of the rings), and the hydrogens on the new stereogenic centers (C-4a and C-5) are synclinal. While the configuration at C-5 is the result of kinetic control (axial attack), that at the α-carbonyl position may be not[4e,8]: enolate trapping with electrophiles other than protons (see *Table 1*) leads selectively to products which are tentatively assigned the *cis* -fused structure **5**, with a boat conformation of the dioxanone ring (positive NOE between H_3C-4a and H-2, H-5, and H-8a of **5a**, see also data in footnote[5]). If this assignment is correct, the alkylation has taken place from the *(Si)* -face of the intermediate enolate **E**, the same steric course (rel. topicity *lk* -1.2 and *lk* -1.4) observed with the corresponding monocyclic enolate[9,10]. [As compared to the latter one[9], the bicyclic enolates of type **E** are much more stable towards β-elimination (-60 *vs.* 0°C)].



4



5



6

In three cases (**4a**, **4e**, **5a**), we have cleaved the acetals[4f], esterified the acid groups (CH_2N_2) and isolated the cyclohexanes **C** (R = CH_3, R^N = CH_3 and $CH{=}CH_2$, respectively, 75-90% overall yield)[5] and **D** (R = R^E = R^N = CH_3)[5]. Also, the dehydrogenation procedure[4c] applied to **4a** gives[4g,5] the methylated analogue **6** which we now test as *Michael* acceptor[11].

Table 1. - *Michael Additions of Cuprates to the C,C Double Bond of* **3.**

The products **4** were obtained by treatment with cuprates (3 R_2CuM/ether/ 0^oC) and aqueous workup. Compound **5c** was isolated after sequential treatment of **4b** with BuLi (-70°C/THF) and MeI/DMPU[6], while **5a** and **5b** result from direct enolate trapping (cuprate as above, then BuLi/ -70°C, DMPU/-70°C, and iodomethane or allyl bromide/-70 to +20°C). The yields are those of purified products, they have not been optimized and were determined from 1mmol-scale reactions. The selectivities were determined by ^{1}H-NMR analysis of the crude products. Some characteristic data of **4** and **5** are given in footnote[5].

Nucleophile added to **3**	R (R^1)	Electro-phile	R^2	No	Product % yield	Selectivity
$(CH_3)_2CuLi$	CH_3	H_2O/NH_4Cl		**4a**	75	50:4:1
$(C_4H_9)_2CuLi$	C_4H_9	H_2O/NH_4Cl		**4b**	79	20:1
$(s\text{-}C_4H_9)_2CuLi$	$s\text{-}C_4H_9$	H_2O/NH_4Cl		**4c**	54	9:1
$(t\text{-}C_4H_9)_2CuLi$	$t\text{-}C_4H_9$	H_2O/NH_4Cl		**4d**	43	4:1
$(C_2H_3)_2CuMgBr$	$CH_2{=}CH$	H_2O/NH_4Cl		**4e**	75	10:1:1
$(C_3H_5)_2CuLi$	$CH_2{=}CH\text{-}CH_2$	H_2O/NH_4Cl		**4f**	81	20:1
$(PhMe_2Si)_2CuLi$	$PhMe_2Si$	H_2O/NH_4Cl		**4g**	76	
$(CH_3)_2CuLi$	CH_3	CH_3I	CH_3	**5a**	60	>20:1
$(CH_3)_2CuLi$	CH_3	allyl-Br	C_3H_5	**5b**	75	>20:1
	C_4H_9	CH_3I	CH_3	**5c**	70	>20:1

References and Notes

1) Recipient of a grant within the scientific cooperation between ETH- Zürich and C.S.I.C.- Spain
2) D. Seebach, S. Roggo, J. Zimmermann, in "Stereochemistry of Organic and Bioorganic Transformations", W. Bartmann, K.B. Sharpless (Eds.), **Workshop Conferences HOECHST**, Vol. *17*, VCH, Weinheim (1987).
3) B.S. Deol, D.D. Ridley, G.W. Simpson, **Aust. J. Chem.** *29*, 2459 (1976); G. Fráter, **Helv. Chim. Acta** *63*, 1383 (1980); D. Buisson, R. Azerad, **Tetrahedron Lett.** *27*, 2631 (1986); D. Seebach, S. Roggo, Th. Maetzke, H. Braunschweiger, J. Cercus, M. Krieger, **Helv. Chim. Acta** *70* (1987), in press.
4) a) From the ethyl ester of >99% ee and ds[3](LiOH/THF, CH_3OH, H_2O). - b) Pyridinium tosylate, benzene, *Soxhlet* with 4Å molecular sieve. - c) LDA/ THF, PhSeCl -70 → +20°C, then H_2O_2/CH_2Cl_2, pyridine. - d) Workup of the reactions with cuprates *(Table 1)* by quenching (NH_4Cl/H_2O) and warming to r.t. - e) If 4a is deprotonated with butyllithium and the enolate quenched with acetic acid at -70°C, **4a** and the *cis*- fused epimers are isolated in a 2:1 ratio! f) A solution of the acetal in ethanol was stirred with *Dowex 50 Wx8* for 15 h. Filtration and evaporation of the solvent gave a product which was reacted with diazomethane under the usual conditions. - g) Overall yield of **6** from **4a**, 59%, selectivity over other positional isomer 20:1.
5) Melting points, $[\alpha]_D^{25}$ (all c *ca.* 1, in $CHCl_3$) and some characteristic ^{1}H-NMR data of all the new compounds are: **2**, 43-44°C, +15.3, δ = 2.56 (*ddd*, 9.6, 5.7, 4.0 Hz, H-4a). **3**, from petroleum ether, 93-94°C, +31.9°. **4a**, 89-91°C, +85.3°. **4b**, 62-63°C, +60°. **4c**, 64-65°C, +41.3°. **4d**, 122-123°C, +71.5°. **4e**, 50-51°C, +60°. **4f**, 90°C, +63.7°. **4g**, b.p. 160°C/ 1 torr., +57.2°. **5a**, 124-125°, +77.5°, δ = 3.93 (*dd*, 11, 4 Hz, H-8a). **5b**, 98-99°C, +70.4°, δ = 4.00 (*dd*, 11, 5 Hz, H-8a). **5c**, 64-65°C, +48.6°, δ = 3.86 (*dd*, 11, 6 Hz, H-8a). **6**, 52-53°C, +49.6°. **C** (R = CH_3, R^N = CH_3), 56-57°C, +73°. **C** (R = CH_3, R^N = $CH{=}CH_2$), 40°C, +45.8°.
6) T. Mukhopadhyay, D. Seebach, **Helv. Chim. Acta** *65*, 385 (1982); see also **Chimia** *39*, 147 (1985).
7) H-8a of the silyl derivative **4g** appears at δ = 3.20 ppm, with the same coupling pattern.
8) Attack of the cuprate at the acetal center of **3** was not noticed as a competing reaction, see: D. Seebach, R. Imwinkelried, G. Stucky, **Angew. Chem.** *98*, 182 (1986); **Int. Ed. Engl.** *25*, 178 (1986); **Helv. Chim. Acta** *70*, 448 (1987); S.L. Schreiber, J. Reagan, **Tetrahedron Lett.** *27*, 2945 (1986).
9) D. Seebach, J. Zimmermann, **Helv. Chim. Acta** *69;* 1147 (1986).
10) For discussions of stereoselective alkylations of cyclic enolates (carbo- and heterocyclic, endo- and exocyclic double bond) see: D.A. Evans, in **"Asymmetric Synthesis"**, Vol. *3*, J.D. Morrison (Ed.), Academic Press, Inc., Orlando, 1984; D. Seebach, R. Imwinkelried, Th. Weber, in **"Modern Synthetic Methods 1986"**, R. Scheffold (Ed.), Springer-Verlag, Berlin, 1986; D. Seebach, J.D. Aebi, M. Gander-Coquoz, R. Naef, **Helv. Chim. Acta** *70* (1987), in press.
11) Our continuing studies deal with inversion of the configuration at C-2 of the hydroxyacid **1** (entry into the enantiomeric series), with providing definitive proof of the configuration of the products (including the phenylseleno-substituted intermediates), with the use of acetals derived from other aldehydes, and with the application of the methodology described here to other β-hydroxyacids[2], and to natural product synthesis.

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