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RESOLUTION OF 1,3-ALKANEDIOLS VIA CHIRAL SPIROKETALS DERIVED FROM ℓ-MENTHONE

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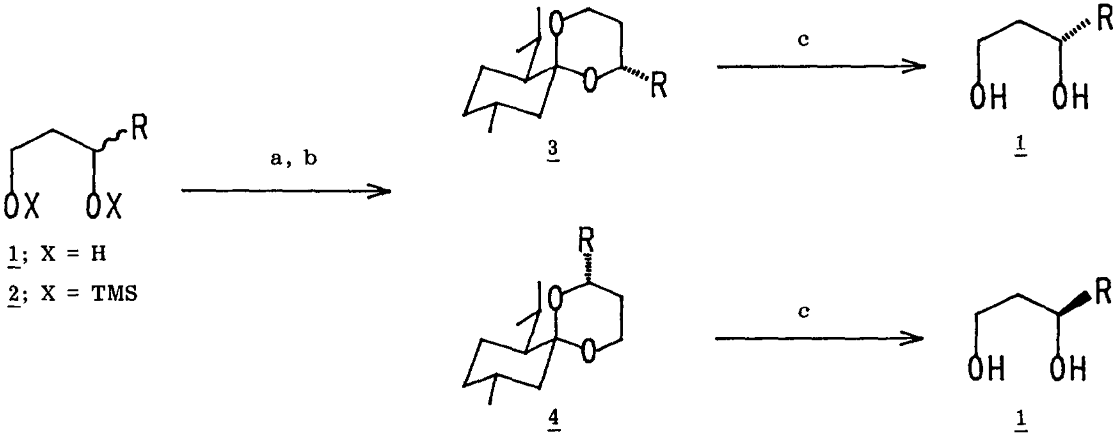
Summary: Ketalization reaction of racemic 1,3-alkanediols with ℓ-menthone gave a mixture of diastereomeric spiroketals that was easily separated by silica gel column chromatography and converted into enantiomerically pure diols by acid-catalyzed hydrolysis.

Enantiomerically pure 1,2- and 1,3-alkanediols are useful building blocks in asymmetric synthesis.[1] One of the most promising approaches for the resolution of these diols is their conversion by use of a chiral ketone into diastereomeric ketals.[2] In 1983 Meyers reported a ketalization reaction of 1,2-alkanediols with enantiomerically pure (S)-2-propylcyclohexanone for the determination of enantiomeric composition.[3] However, above derivatization gave rise to the formation of a new chiral center at the dioxocarbon atom producing four diastereomers whose ratios can only be analyzed by ^{13}C NMR or HPLC. In connection with our ongoing studies on enantiodifferentiating functionalization of prochiral diols via chiral spiroketals,[4] we examined the ketalization of racemic 1,3-alkanediols 1 with ℓ-menthone and found that (i) among four possible diastereomers, spiroketals 3 and 4 are selectively formed and (ii) separation

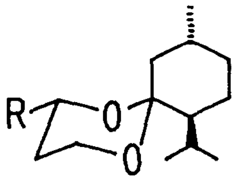


a) $(TMS)_2NH$, TMSOTf, THF, 0 °C; b) ℓ-menthone, TMSOTf, CH_2Cl_2, -40 °C; c) concd. HCl, MeOH, r. t..

of 3 and 4 are readily achieved by flash chromatography on silica gel. Thus, this method affords an efficient method for the resolution of 1,3-alkanediols.

5-Phenylpentyl-1,3-diol 1a was converted into bis-trimethylsilyl ether 2a in 91% yield by the reaction with hexamethyldisilazane in the presence of a catalytic amount of trimethylsilyl trifluoromethanesulfonate (TMSOTf) in THF at 0 °C for 15 min. To a solution of 2a (6.37 mmol) and ℓ-menthone (7.01 mmol) in CH_2Cl_2 (13 ml) was added TMSOTf (0.70 mmol) at -40 °C and the mixture was stirred for 18 h at the same temperature.[4] After the addition of 2% methanolic NaOH (5 ml), resulting mixture was stirred further for 0.5 h at a room temperature. Extractive work-up (petroleum ether, aq $NaHCO_3$) followed by the purification by flash chromatography on silica gel (4% ether in petroleum ether) gave, in the order of elution, 971 mg (48%) of spiroketal 3a[6] and 998 mg of 4a.[6] 3a (0.407 mmol) was treated in methanol (2 ml) containing a catalytic amount of concd. HCl at a room temperature for 14 h. Extractive work-up (ethyl acetate, brine) followed by flash chromatography (50-80% ethyl acetate in petroleum ether) gave 67.1 mg (92%) of (S)-1a.[7] The applicability of the present method to the resolution of 1,3-alkanediols is shown in Tables I and II.

Spiroketals derived from ℓ-menthone and 1,3-alkanediols compose a rigid conformation where the 1,3-dioxane ring prefers the less hindered chair form (eg., 3' (= 3) or 4' (= 4)) to the other chair form 5 (R^1 = R, R^2 = H or R^1 = H, R^2 = R). Thus, in the reaction of 2 with ℓ-menthone, formation of 6 (R^1 = R, R^2 = H or R^1 = H, R^2 = R) is highly disfavored due to the 1,3-diaxial interaction between substituent R and menthone ring, and therefore, (S)- and (R)-2a-c (or (R)- and (S)-2d) were converted selectively into spiroketal 3 (= 3') and 4 (= 4'), respectively.



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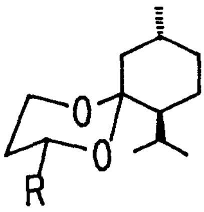

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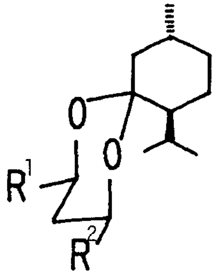

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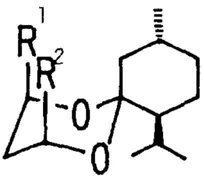

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As shown in R_f values summarized in Table II, spiroketal 3 always eluted faster than 4, thus allowing the prediction of absolute stereochemistry of the diol obtained after hydrolysis. This empirical trend is rationalized by assuming that the interaction between the less hindered equatorial (with respect to menthene ring) oxygen atom[4] and the acidic surface of silica gel governs the order of elution: in 3 the basicity of equatorial oxygen atom is sterically decreased by the neighboring alkyl substituent.

It should be noted that capillary GLC,. (OV 1, 30 m) of spiroketals 3 and 4 were base-line separated and, therefore, the present ketalization with ℓ-menthone may also be utilized for determining enantiomeric composition of 1,3-alkanediols.

Table I Preparation of Spiroketals 3 and 4

Entry	Diol		Bis-Silylation		Ketalization	
			Product	% Yield	Products	% Yield
1	1a	R = $PhCH_2CH_2$	2a	91	3a, 4a	98
2	1b	R = n-C_8H_{17}	2b	91	3b, 4b	94
3	1c	R = CH_3	2c	83	3c, 4c	77
4	1d	R = iso-C_3H_7	2d	98	3d, 4d	70

Table II Separation and Hydrolysis of Spiroketals 3 and 4

Entry	Spiroketal	R_f Value		Diol	% Yield	$[\alpha]_D$	% E.e.[c]
		A[a]	B[b]				
1	3a	0.50	0.55	(S)-1a	92	+18.6 (c 0.474, $CHCl_3$)[d]	>95
2	4a	0.31	0.46	(R)-1a	97	-18.9 (c 1.05, $CHCl_3$)[d]	>95
3	3b	0.63	0.63	(S)-1b	100	+14 (c 0.66, $CHCl_3$)[d]	92
4	4b	0.44	0.49	(R)-1b	100	+36.2 (c 0.801, MeOH)[e]	94
5	3c	0.48	0.53	(S)-1c	68	+28.9 (c 0.969, MeOH)	97
6	4c	0.40	0.46	(R)-1c	53	-31 (c 1.2, MeOH)	92
7	3d	0.57	0.58	(R)-1d	83	+37.3 (c 1.07, MeOH)	>95
8	4d	0.48	0.37	(S)-1d	88	-31.3 (c 1.41, MeOH)	98

[a] Elution with petroleum ether-ether-benzene (90 : 5 : 5). [b] Elution with petroleum ether-ether (90 : 10). [c] These values were determined by the capillary GLC analysis (OV 1, 30 m) of the corresponding bis-(+)-MTPA esters. [d] These values were measured after converting diols into the corresponding bis-acetates. [e] The value was measured after converting (R)-1b into (R)-γ-dodecanolactone (lit. $[\alpha]_D$ +37.7 (c 0.71, MeOH); J. P. Vineron and V. Bloy, Tetrahedron Lett., 21, 1735 (1980)) in 62% overall yield by the following reaction sequences; (1) MsCl, Et_3N, CH_2Cl_2, (ii) NaCN, DMF, (iii) aq KOH, EtOH, and (iv) aq HCl.

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References and Notes

(1) J. W. Scott in 'Asymmetric Synthesis', J. D. Morrison and J. W. Scott, ed., Academic Press, New York, 1984, vol. 4, chapter 1.

(2) (a) E. L. Eliel and K.-Y. Ko, Tetrahedron Lett., 24, 3547(1983). (b) M. K. Ellis, B. T. Golding, and W. P. Watson, J. Chem. Soc., Chem. Commun., 1600 (1984).

(3) A. I. Meyers, S. K. White, and L. M. Fuentes, Tetrahedron Lett., 24, 3551 (1983).

(4) T. Harada, T. Hayashiya, I. Wada, N. Iwa-ake, and A. Oku, J. Am. Chem. Soc., 109, 527 (1987).

(5) T. Tsunoda, M. Suzuki, and R. Noyori, Tetrahedron Lett., 21, 1357 (1980).

(6) 2a: ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.70 (1 H, dd, J = 12.4 and 13.2 Hz), 0.89 (6 H, d, J = 7.2 Hz), 0.93 (3 H, d, J = 7.4 Hz), 1.16 - 1.94 (10 H, m), 2.41 (1 H, d of hept., J = 1.8 and 7.2 Hz), 2.56 - 2.82 (3 H, m), 3.68 - 3.87 (2 H, m), 3.95 (1 H, m), 7.13 - 7.36 (5 H, m); IR (liquid film) 1160 (s), 1120 (s), 750 (s), 700 cm^{-1} (s); mass spectrum, m/z (relative intensity) 316 (M^+, 26), 231 (25), 91 (100); exact mass calcd for $C_{21}H_{32}O_2$: 316.2404, found 316.2398. 2b: ^{1}H HMR (200 MHz, $CDCl_3$) δ 0.69 (1 H, dd, J = 12.4 and 13.2 Hz), 0.89 (3 H, d, J = 6.6 Hz), 0.91 (3 H, d, J = 7.0 Hz), 0.94 (3 H, d, J = 6.7 Hz), 1.12 - 1.89 (10 H, m), 2.45 (1 H, d of hept, J = 1.8 and 7.0 Hz), 2.54 - 2.94 (3 H, m), 3.61 - 3.89 (2 H, m), 4.08 (1 H, dt, J = 3.2 and 11.6 Hz), 7.12 - 7.34 (5 H, m); IR (liquid film), 1160 (s), 1120 (s), 750 (s), 700 cm^{-1} (s); mass spectrum, m/z (relative intensity) 316 (M^+, 18), 231 (21), 91 (100); exact mass calcd for $C_{21}H_{32}O_2$ 316.2404, found 316.2399.

(7) If desired, ℓ-menthone can be recovered (70-80% yield). The recovered material should be purified for reuse by flash chromatography (2% ether in petroleum ether) to remove a small amount (10-20%) of isomenthone.

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