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# SYNTHESIS OF ENANTIOMERICALLY ENRICHED ATROLACTIC ACID AND OTHER α-HYDROXY ACIDS

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Summary:

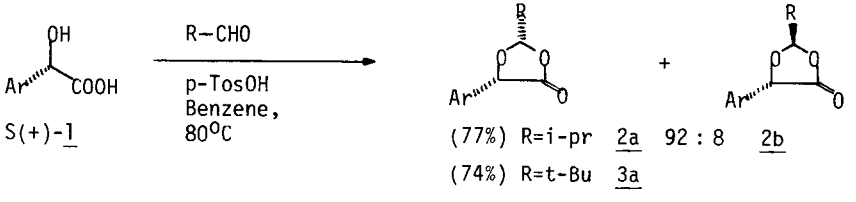
The α-anions of 2-substituted 1,3-dioxolan-4-ones derived from chiral mandelic and lactic acid (2a, 2b; 3a; 10a, 10b) were alkylated with high stereoselectivity. The products formed were hydrolysed to α-hydroxy acids with 65 - 85% e.e. ((S)(+)-5,7,9, (R)(-)-13).

Beside the classical studies on the preparation of optically active α-hydroxy acids [1][2], there are several recent reports on the same subject [3] - [6].

In connection with our work on the synthesis of optically active β-hydroxy esters through stereoselective α-alkylation of the dianions of chiral β-hydroxy esters [7], we were concerned with the problem of protecting the chirality of α-anions of α-hydroxy acids. In this report we want to communicate some of our results concerning this problem.

The 1,3-dioxolan-4-ones 2a, 2b and 3a were prepared from S(+)-mandelic acid (scheme 1). The product of the reaction with isobutyraldehyde was a ca. 92 : 8 (NMR) mixture of the cis- (2a) and the trans isomers (2b) (m.p. 54 - 56°C, $[\alpha]_D^{22}$ ($CHCl_3$, c=1)= +82,3°), whereas with pivalaldehyde only the cis-isomer 3a (m.p. 141 - 142°C, $[\alpha]_D^{22}$ ($CHCl_3$, c=1,2)= + 81,6°) was isolated [8][9][10].

Scheme 1



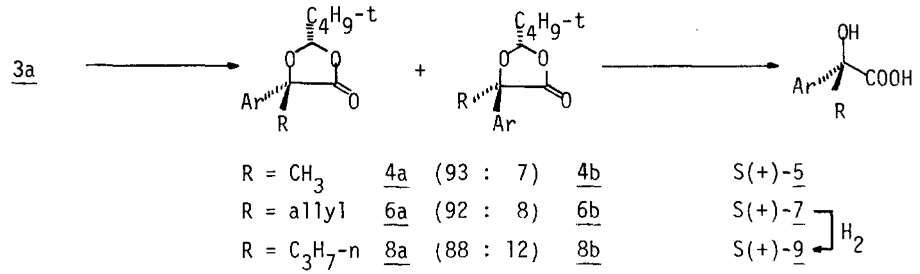
S(+)-1

(77%) R=i-pr 2a 92 : 8 2b
(74%) R=t-Bu 3a

Alkylation of 3a (1. $(i\text{-pr})_2NLi$, THF, HMPT, -70°C, 2. R-X, -70 - 0°C, 10 min.) with $CH_3J$ furnished a 93 : 7 mixture (NMR, GLC) of two products 4a and 4b in 94% yield (bp. 75 - 80°C, 0,03 Torr, $[\alpha]_D^{22}$ ($CHCl_3$, c=1,5)= +63,4°), which was hydrolysed (KOH, $H_2O$, $CH_3OH$, 10 min. at 60°C) to S(+)-atrolactic acid (S)(+)-5 ($[\alpha]_D^{22}$ ($C_2H_5OH$, c=2)= +32,1°; e.e. 85% based on $[\alpha]_D^{10,5}$ ($C_2H_5OH$, c=3,5)= +37,7° [11] (scheme 2).

Analogous alkylation of the mixture 2a, 2b gave a 91 : 9 mixture of the cis-trans isomers (90%), which after hydrolysis furnished (S)(+)-5 with 70% e.e. [12].

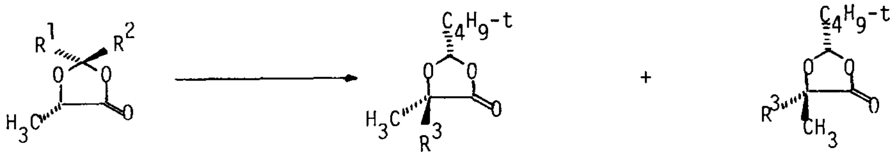
Scheme 2



(S)(+)-α-allyl-mandelic acid (7) and (S)(+)-α-propyl-mandelic acid (9) were prepared in the same way. Alkylation of 3a to the diastereomeric mixtures 6a, 6b and 8a, 8b proceeded in 94% and 88% yield, respectively. Hydrolysis of 6a, 6b furnished the crystalline acid (S)(+)-7 (m.p. (recrystallized from ether-pentane): 130°C, $[\alpha]_D^{22}$ ($CHCl_3$, c=1)= +29°). Hydrogenation on Pd, C(5%) in ethylacetate gave optically pure (S)(+)-9 (m.p. 101 - 102°C, $[\alpha]_D^{22}$ ($CHCl_3$, c=1)= +48,7°, $[\alpha]_D^{22}$ ($C_2H_5OH$, c=2)= +28,9°). On the other hand, hydrolysis of 8a, 8b gave (S)(+)-9 with 76% e.e. (m.p. 94 - 96°C, $[\alpha]_D^{22}$ ($C_2H_5OH$, c=2)= +21,9°). This sample was esterified to the methylester, in the NMR of which upon addition of $Eu(tfc)_3$, the $CH_3$-triplet resolved in two triplets in the ratio of ca. 88 : 12. (For (S)(+)-9 see ref. [6]) [13].

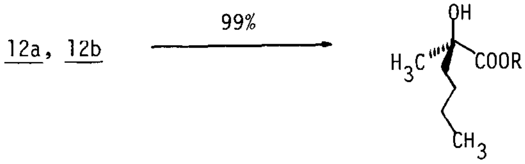
Similar work with 1,3-dioxolan-4-ones derived from S(-)-lactic acid was less satisfactory both concerning chemical and optical yield. A 85 : 15 mixture of 10a and 10b was prepared [14], but could not be separated (70% yield; b.p. 70°C at 10 Torr, $[\alpha]_D^{22}$ ($CHCl_3$, c=2,1)= +37,5°) (scheme 3). Alkylation of this mixture as above with alkylbromide and butyliodide, respectively gave each in 40% yield a 92 : 8 and 95 : 5 mixture, respectively of 11a, 11b and 12a, 12b (scheme 3) [15].

## Scheme 3



10a, $R^1$ = t-Bu, $R^2$ = H — $R^3$ = allyl 11a — 11b

10b, $R^1$ = H, $R^2$ = t-Bu — $R^3$ = n-Bu 12a — 12b



(R)(-)-13, R = H

(R)(-)-14, R = $CH_3$

12a, 12b were hydrolysed in 99% yield to (R)(-)-13 (crude m.p. 57 - 59°C, $[\alpha]_D^{22}$ ($H_2O$, c=1,6)= -6,5°; recrystallized from pentane ether, m.p. 58 - 59°C, $[\alpha]_D^{22}$ ($H_2O$, c=1,6)= -9,7°. Crude (R)(-)-13 was esterified to (R)(-)-14 which showed an enantiomeric ratio of ca. 84 : 16 (68% e.e.) in the NMR in the presence of $Eu(tfc)_3$ (see ref. [6]).

## References and Notes

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8 All compounds had correct C, H elemental analysis and were characterised with IR- and NMR-Spectra.

9 NMR (400 MHz, $CDCl_3$) 2a, 2b: 5,58 (dxd, H-2, 2b), 5,48 (dxd, H-2, 2a), 5,39 (d, H-5, 2b), 5,25 (d, H-5, 2a); 3a: 5,32 (d, H-2), 5,23 (d, H-5). J (2,5) for 2a, 2b and 3a ∿1,5 Hz.

10 For the configuration of 2,5-disubstituted-1,3-dioxolan-4-ones, see e.g. K. Pilgramm & M. Zupan, J. Heteroc.Chem. 14, 1053 (1977)

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12 It should be mentioned, that starting from a mixture like 2a, 2b, the ratio of the alkylation products (91 : 9) does not show the optical purity of the endproduct (S)(+)-5 directly. Assuming that 2a and 2b both react equally fast to a chiral anion (e.e. 84%), than each of the two enantiomers will react with $CH_3J$ with the observed selectivity (91 : 9) to two diastereomers.

13 We thank Prof. A.I. Meyers for discussing with us the problem of the slightly higher $[\alpha]$-values observed in this work for (S)(+)-9

14 NMR ($CDCl_3$) 10a, 10b: 5,3 (d, H-2, 10b), 5,15 (d, H-2, 10a), 4,48 (dxq, H-5, 10b), 4,36 (dxq, H-5, 10a); J (H-2, H-5) (10a)≈J (H-2, H-5) (10b)∿1,2 Hz.

15 For the sake of simplicity only one diastereomeric pair is shown in scheme 3 for the alkylation products (conf. Note [12]).

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