

Short Communications

The Stereochemistry of Some Asymmetric Reformatsky Reactions

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We report here that the stereochemical outcome of five asymmetric Reformatsky reactions (1–5 in Table 1) is opposite to that predicted by the application of Prelog's generalization.¹ Thus, for the menthyl derivatives a preponderance of the L-hydroxy acids is expected (Fig. 1) but the D-isomers were found to be the main products.

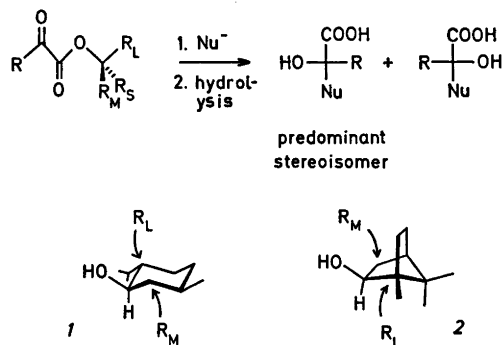


Fig. 1. Prelog's generalization applied to (–)-menthyl (1) and (+)-borneol (2). L, large; M, medium; S, small.

(–)-Menthol (1) and (+)-borneol (2) have different chiral orders of the groups R_L , R_M , and R_S at the carbinol carbons and the different stereochemical results obtained from (–)-menthyl pyruvate and (+)-borneol pyruvate are therefore expected.

Unlike the reactions which originally formed the basis of Prelog's generalization, the addition of a Reformatsky reagent to a ketone has under certain conditions been shown to be reversible.² However, for reactions 1 and 2 (Table 1) we have been unable to demonstrate any such reversibility and hence the stereo-

chemical results obtained should only be due to steric factors in the transition states leading to the Reformatsky adducts.

When THF was substituted by benzene the stereochemical result of reaction 1 was unaffected. In contrast, results according to Prelog's generalization were obtained when DMF was used as solvent and for reaction 2 when it was carried out in refluxing dimethoxymethane (two-step procedure)³ or in DMSO, and also when it was run with the corresponding lithium⁴ or chloromagnesium⁵ reagents (8.0, 7.5, 3.7, 3.2 and 1.7% enantiomeric excess of the *S* isomer respectively). The latter results thus show that the anomalous enantiomeric compositions obtained should be ascribed to the particular use of zinc rather than to the aldol-type condensation nature of the reactions. The influence of the metal ion on the steric courses of the reactions could possibly be discussed in terms of different tendencies of the ions ($Zn > Mg > Li$) to give chelate-like transition states involving both carbonyl groups of the α -keto esters. The results obtained in the more polar solvents (dimethoxymethane, DMF and DMSO) are consistent with this view since these solvents should compete with the carbonyl groups in bonding to zinc atoms, and the stereochemical outcome should then be similar to that of the corresponding lithium and magnesium reactions.

A few reactions that do not follow Prelog's generalization have been described.^{13,14} The Reformatsky reactions described here are the first reported anomalous asymmetric syntheses with the frequently used substrates (–)-menthyl pyruvate and (+)-borneol pyruvate.

Experimental. Granular zinc (Baker, 30 mesh) was purified before use.⁶ Tetrahydrofuran was distilled over lithium aluminium hydride, and dimethoxymethane was repeatedly distilled over sodium. (–)-Menthyl pyruvate showed $[\alpha]_{578}^{24} - 85.4^\circ$ (c 2.0, ethanol); lit.⁷ value: $[\alpha]_D - 84.1^\circ$ (c 1.9, ethanol). (–)-Menthyl phenylglyoxylate was prepared from phenylglyoxylic acid⁸ and (–)-menthol by the same procedure as described for (–)-menthyl pyruvate.⁷ It showed m.p. 73–74°C and $[\alpha]_{578}^{25} - 54^\circ$ (c 3.4, chloroform); lit. values: m.p. 73–74°C,⁹ $[\alpha]_{578} - 54^\circ$ (c 3.0, chloroform).¹⁰ (+)-Borneol pyruvate was prepared in the same way as the other esters and showed $[\alpha]_{578}^{24} + 50^\circ$ (c 3.5, benzene); lit.¹¹ value: $[\alpha]_{578}^{25} + 49^\circ$ (c 3.0, benzene). In all the syntheses 1–5 the reagents were used in approximately

Table 1. Optical yields obtained in five asymmetric Reformatsky reactions.^a

$$\begin{array}{c}
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 \parallel \\
 \text{R}-\text{C}-\text{COOR}^* + \text{BrCH}_2\text{COOR}' \xrightarrow[2. \text{hydrolysis}]{1. \text{Zn}} \begin{array}{c} \text{COOH} \\ | \\ \text{HO}-\text{C}-\text{R} \\ | \\ \text{H}-\text{C}-\text{H} \\ | \\ \text{COOH} \\ \text{L} \end{array} + \begin{array}{c} \text{COOH} \\ | \\ \text{R}-\text{C}-\text{OH} \\ | \\ \text{H}-\text{C}-\text{H} \\ | \\ \text{COOH} \\ \text{D} \end{array}
 \end{array}$$

	R	R*	R'	Optical yields (%)	Configuration of hydroxy acid
1	CH ₃	(-)-Menthyl	Et	2.2, 3.5, 1.5	R (D)
2	CH ₃	(-)-Menthyl	<i>t</i> -Bu	3.7, 2.5	R (D)
3	C ₆ H ₅	(-)-Menthyl	Et	~8	S (D)
4	CH ₃	(+)-Bornyl	Et	2.8	S (L)
5	CH ₃	(+)-Bornyl	<i>t</i> -Bu	2.0	S (L)

^a All reactions were performed in refluxing THF.

20 % excess over the keto ester. The latter was used in 5 g quantities dissolved in 10 ml of THF. All reagents were mixed under nitrogen and the reactions were started by gentle heating; the spontaneous reflux was controlled by cooling with water but ceased after about 5 min. The mixtures were subsequently heated under reflux for 3–4 h (by which time all the zinc had been consumed) and then poured into dilute hydrochloric acid-ice and extracted three times with diethyl ether. The combined organic layers were dried (Na₂SO₄) and concentrated. Yields were estimated by NMR with piperonal as internal standard and found to be 50–85 %. Analytical and preparative GLC, measurements of optical rotations (in chloroform) and transformation of crude mixed esters to diethyl citramalate were performed as previously described.⁴ The purity of the diethyl citramalate was checked by both NMR and analytical GLC and no menthol or borneol could be detected. Optically pure (*S*)-diethyl citramalate shows $[\alpha]_{D}^{25} +20.1^\circ$ (*c* 2.2).⁴ The optical yield in reaction 3 was determined as follows. The mixed ester was hydrolysed with 1 M NaOH and after acidification the diacid was extracted with diethyl ether and esterified with diazomethane. The resulting ester was hydrogenated in methanol, using 5 % rhodium on alumina as catalyst, to yield dimethyl 2-cyclohexylmalate. After preparative GLC and hydrolysis the CD curve of the molybdate complex of the 2-cyclohexylmalic acid was compared with that of the complex of (*S*)-2-isopropylmalic acid (erroneously denoted *R* in the previous paper¹²). The optical yield was estimated assuming that these acids in optically pure forms show the same molecular ellipticities.

Attempted epimerisations. The crude mixed ester from reaction 2 was purified by removal of volatile components under reduced pressure

and was then dissolved in hexamethylphosphorotriamide. An equimolar amount of lithium hydride was added and the mixture was stirred for 24 h (23 °C) and worked up as usual. A 100 % recovery of mixed ester was obtained (GLC, phenanthrene as internal standard). Routine hydrolysis and esterification gave (*R*)-diethyl citramalate in an optical yield of 2.3 %. When this experiment was performed at 60 °C (24 h) the recovery was again quantitative and (*R*)-diethyl citramalate was obtained in an optical yield of 1.9 %.

The same experiment was performed using the mixed ester from reaction 2 which had been carried out in two steps with dimethoxymethane as solvent. No change in sign or optical yield for diethyl citramalate was obtained either at 25 or 60 °C, but recoveries of mixed ester were only 96 % and 84 %, respectively. We have also been unable in other ways to demonstrate reversibility of reactions; for example separate experiments have been carried out, firstly in which the Reformatsky adduct was prepared in dimethoxymethane and the solvent then replaced by THF and secondly in which anhydrous zinc bromide was added to the Reformatsky adduct obtained from the above-mentioned chloromagnesium reagent.

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Improvements in the Preparation of Crystalline D-Mannose from the Doum Palm Kernel*

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D-Mannose is usually prepared¹⁻⁵ by acid hydrolysis of the D-mannan of the ivory nut, followed either by direct crystallisation of the sugar from the hydrolysate, or preparation and recrystallisation of methyl α -D-mannopyranoside,^{6,7} from which it is recovered by acid-hydrolysis.^{8,9} Like ivory nut, the kernel of the African doum palm (*Hyphaene thebaica*) has been used for the manufacture of buttons, and contains a D-mannan.¹⁰⁻¹²

In a recent publication,¹³ the doum palm kernel was described as an alternative source

of D-mannose, obtained by acid hydrolysis of the kernel shavings and direct crystallisation from glacial acetic acid, in 20% overall yield.

In the present work the method is improved by first preparing crystalline methyl α -D-mannopyranoside from the doum palm kernel shavings by methanolysis, in a good yield (50–52%). Methyl α -D-mannopyranoside is then hydrolysed with sulfuric acid to give crystalline D-mannose in 70% yield from the mannoside. The overall yield is about 34% of the doum palm kernel.

Experimental. Melting points are uncorrected. Concentrations were performed at reduced pressure below 50°C. Thin-layer chromatography (TLC) was performed on silica gel (Kiesel gel G, Merck) using butanol–pyridine–water (10:3:3) as a solvent and ceric sulfate as a spray reagent.

Methyl α -D-mannopyranoside. The doum palm kernels (500 g) were defatted with light petroleum (b.p. 60–80°C) for a week, then ground in a mill. The dry, finely-ground kernels (100 g) were added in small portions to 75% sulfuric acid (100 ml) in a mortar, at such a rate that the temperature was not allowed to exceed 30°C, and the meal was well kneaded after each addition. The meal was kept for 15 h at 25–30°C with occasional kneading until the suspension was nearly a homogeneous paste. At the end of this period, a mixture of dry, acetone-free methyl alcohol (100 ml) and concentrated hydrochloric acid (25 ml) was added under vigorous mixing, and the soft paste was transferred to a 2 l flask and diluted with absolute methyl alcohol (600 ml). The mixture was boiled under reflux for 8 h, and after addition of charcoal (15 g), it was refluxed for a further 1 h, and filtered hot. The residue was washed with hot absolute methyl alcohol (50 ml). The filtrate and washings were combined and kept at room temperature for 24 h whereupon methyl α -D-mannopyranoside crystallised in colourless cubes. After 3 days the crystals were collected, washed with absolute methyl alcohol (25 ml), dry acetone, and dried; yield, 50 g. After concentration of the mother liquor in a current of air, another 2 g was obtained. The total yield was 52% of the original meal. m.p.* 158–165°C, $[\alpha]_{D}^{20} + 72^{\circ}$ (c 2, water). This product was recrystallised from 85% ethanol with 87% recovery. It was chromatographically pure (TLC), R_F 0.48, m.p. 193°C, $[\alpha]_{D}^{20} + 82^{\circ}$ {lit. m.p. 195°C, $[\alpha]_{D}^{20} + 80^{\circ}$ (c 1, water)}.

When the unextracted meal was used, the yield of methyl α -D-mannopyranoside was 36% of the original meal, and 16–20% of unreacted meal was recovered.

D-Mannose. A solution of methyl α -D-mannopyranoside (20 g) in 2 N sulfuric acid (320 ml)

* This work was carried out in part at the Organic Chemistry Laboratories, The Norwegian Institute of Technology, University of Trondheim, Trondheim-NTH, Norway.

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* M.p. of the crude methyl α -D-mannopyranoside isolated from the ivory nut; 170°C.