*Tetrahedron: Asymmetry* Vol. 3, No. 2, pp. 255-260, 1992
Printed in Great Britain

0957-4166/92 $3.00+.00
Pergamon Press plc

# SYNTHESIS, RESOLUTION AND ASSIGNMENT OF ABSOLUTE CONFIGURATION OF 2-(α-HYDROXY)ARYL ACRYLATE ESTERS

**Siegfried E. Drewes*, Neville D. Emslie, John S. Field, Abdullah A. Khan and Niyum Ramesar**

**Department of Chemistry, University of Natal Pietermaritzburg 3201, South Africa**

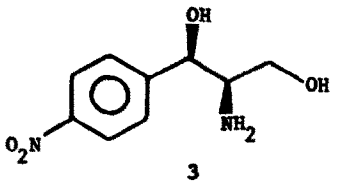
(*Received* 25 *November* 1991)

**Abstract:** (-)(R,R)-2-Amino-1-(4-nitrophenyl)propan-1,3-diol **3** has been used to resolve racemic 3-hydroxy-2-methylene-3-phenylpropanoic acid **1a**. Conversion of the laevorotatory enantiomer into *anti* and *syn* methyl 3-hydroxy-2-methyl-3-phenylpropanoate, **2a** and **2b** respectively, was achieved with $Pd/H_2$. Correlation of the specific rotations of **2a** and **2b** with isomers of known configuration established the absolute configuration of **4a** as R. This was confirmed independently by X-ray crystallography.

2-(α-Hydroxy)alkyl and aryl acrylates, prepared by the Baylis-Hillman Reaction[1] have been used by numerous researchers as synthetic intermedates[1-6]. In its simplest form the Baylis-Hillman Reaction involves the reaction of methyl acrylate with an aldehyde, most often benzaldehyde, in the presence of DABCO[7], to afford **1b**. The hydroxyacrylates prepared in this way are obviously racemates and generally they have been used in this form for further elaboration. Various authors have, however, attempted to induce chirality in the reaction product. We ourselves have used a masked acrylate coupled to a chiral auxiliary[8] for this purpose, and Basavaiah[9] has achieved some success by employing (-)-menthyl acrylate to induce chirality. However, in no instance has it been possible to designate the configuration of the major stereoisomer, and this has presented a real obstacle to further progress.

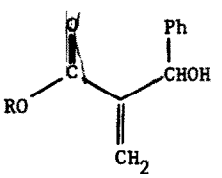
We have now solved the problem by the following series of interconversions: Racemic **1a**, obtained by mild hydrolysis of **1b**, readily formed a salt with (-)(R,R)-2-amino-1-(4-nitrophenyl)propan-1,3-diol **3**. From the mixture predominantly one

diastereomer **5** crystallized on cooling. This was filtered off, and recrystallized (acetone/$CHCl_3$) to constant m.p. 99°C and $[\alpha]_D^{25}$ = -23.5 (c1.05, MeOH). The usual work-

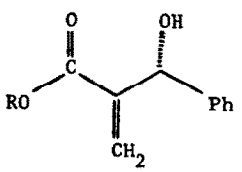


**3**

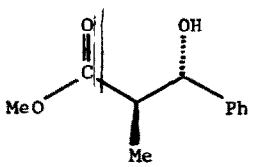
up afforded homochiral acid **4a**, m.p. 79°C, $[\alpha]_D^{25}$ = -23.2 (c1.05, $CHCl_3$). Methylation under mild conditions to prevent racemisation (dicyclohexylcarbodiimide, dimethylaminopyridine, MeOH)[14] gave **4b** $[\alpha]_D^{26}$ = -111.1 (c1.11, MeOH). This was subsequently hydrogenated ($Pd/H_2$)[16] to give a diastereomeric mixture from which **2a**, $[\alpha]_D^{21}$ = -57.9 (c1.1, $CHCl_3$), and **2b**, $[\alpha]_D^{23}$= -22.8 (c1.2, $CHCl_3$) could be separated by flash chromatography. In a recent series of papers Oppolzer[10,11] lists the rotation for **2a** (2S,3R) as +58.9 ($CHCl_3$) and also quotes for **2b** (2S,3S) a rotation of -20.8 ($CHCl_3$). A value of +23.5 is given for the enatiomer of **2b**. Specific rotation values very similar to ours for **2a** have also been obtained by Brown[12]. He quotes -21.89 for a substance of e.e. 46% isolated by kinetic resolution of racemic **1b** and to which he assigns a (2R,3S) absolute configuration [13].



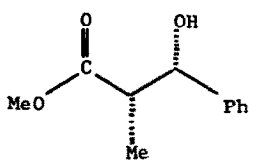
**1a** R = H
**1b** R = Me



**4a** R = H
**4b** R = Me
**4c** R = $^t$Bu



**2a**



**2b**

The homochiral acid **4a** was also converted to the tertiary butyl ester **4c** $[\alpha]_D^{26}$ = -93.2 (c1.09, MeOH) using the isobutylene method.[15] The $[\alpha]_D^t$ values are summarised in Table 1.

These results allow us to designate the absolute configurations of **2a** and **2b** as (2R,3S) and (2S,3S) respectively, and accordingly the 2-(α-hydroxy)phenyl acrylates **4a** **4b** and **4c** possess the 3R configuration for the laevorotatory isomer. It seems reasonable to assume that stereoisomers in which phenyl is replaced by other substituted phenyl moeities (e.g. 4-methoxy- or 4-chlorophenyl) will have the same stereochemistry.

TABLE 1: Summary of $[\alpha]_D^t$ values.

| Compound | $[\alpha]_D^t$ |
|---|---|
| **4a** | $[\alpha]_D^{26}$ = -23.2 (c1.05, $CHCl_3$) |
| **4b** | $[\alpha]_D^{25}$ = -111.1 (c1.11, MeOH) |
| **4c** | $[\alpha]_D^{26}$ = -93.2 (c1.09, MeOH) |
| **2a** | $[\alpha]_D^{21}$ = -57.9 (c1.1, $CHCl_3$) |
| **2b** | $[\alpha]_D^{23}$ = -22.8 (c1.2, $CHCl_3$) |
| **5** | $[\alpha]_D^{25}$ = -23.5 (c1.05, MeOH) |

The homochiral diastereomeric salt m.p. 99° obtained by reacting **1a** with the chiral amine **3**, was also examined by X-ray crystallography[14] (Figure 2) and this confirmed the configuration at C(3) in **4a** as R.

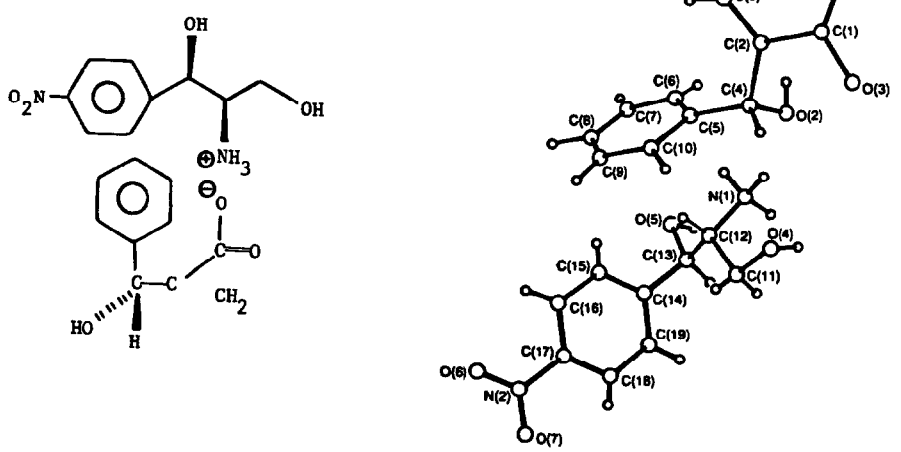



FIGURE 2

**Experimental Section**

Melting points were determined on a Kofler hot-stage apparatus and are uncorrected. Optical rotations were measured on a Perkin-Elmer 241 polarimeter. $^1$H Nmr (200 MHz) and $^{13}$C Nmr (50 MHz) spectra were recorded in the specified solvents on a Varian Gemini Spectrometer. Mass Spectra were recorded on a Hewlett Packard gas chromatographic-mass spectrometer (HP 5988). Elemental analyses were obtained using a Perkin-Elmer 240B analyser.

*(±)-3-Hydroxy-2-methylene-3-phenylpropanoic acid* (**1a**)

Methyl acrylate (10 g, 0.116 mol) and benzaldehyde (10 g, 0.094 mol) were stirred overnight in the presence of DABCO (10.57 g, 0.094 mol). The reaction mixture was diluted with ether and washed successively with HCl, $NaHCO_3$ and $H_2O$. After removing the excess methyl acrylate and solvent, the crude product **1b** (17.2 g, 95%) was used directly in the hydrolysis step. To compound **1b** (17.2 g, 0.09 mol) in ethanol (30 ml) was added potassium hydroxide (6.0 g, 0.107 mol) in $H_2O$ (150 ml). The mixture was refluxed for 3 hours, the ethanol removed, and unreacted ester extracted ($Et_2O$). The aqueous phase was acidified to pH 2 and was extracted with diethyl ether (3 x 100 ml) to give compound **1a** (12 g, 75%); m.p. 78-79°C; $^1$H Nmr ($CDCl_3$) δ 5.50 (1H, s), 5.90 (1H, m), 6.48 (1H, m), 7.228 - 7.324 (6H, m and overlapping br. s); $^{13}$C Nmr ($CDCl_3$) 171.09 (s), 141.24 (s), 140.84 (s), 128.61 (t), 128.52 (d), 128.02 (d), 126.63 (d), 72.81 (d).

M.S.: 178 (47%) $M^+$, 177 (46%), 160 (19%), 132. (48%), 105 (100%), 77 (63%), 55 (16%).

Anal. Calcd. for $C_{10}H_{10}O_3$: C, 67.42; H, 5.62.
Found: C, 67.45; H, 5.82.

Resolution of Compound **1a**

Compound **1a** (5.34 g, 0.03 mol) and (-)(R,R)-2-Amino-1-(4-nitrophenyl)propan-1,3-diol (6.36, 0.03 mol) were dissolved in a minimum amount of acetone. The mixture was refluxed for five minutes, diluted to twice the volume with chloroform, and refrigerated overnight. Filtration yielded 4.4 g of salt **5** (38%); $[\alpha]_D^{26}$ = -20 (c1.1, MeOH), m.p. 97°C. The salt was recrystallized (acetone-chloroform) to constant m.p. 99°C and $[\alpha]_D^{25}$= -23.5 (c1.05, MeOH). The yield was 3.5 g (30%).

$^1$H Nmr ($CD_3COCD_3$) 8.18 - 8.26 (2H, m), 7.19 - 7.42 (5H, m), 6.27 (1H, m), 6.01 (1H, m), 5.59 (1H, s), 4.84 (1H, d), 3.75 (2H, m), 3.16 (1H, m); $^{13}$C Nmr ($CD_3COCD_3$) 167.80 (s), 150.70 (s), 148.05 (s), 145.18 (s), 143.95 (s), 129.28 (d), 128.47 (d), 128.42 (d), 128.30 (d), 124.67 (d), 124.45 (t), 80.38 (d).

Anal. Calcd. for $C_{19}H_{22}N_2O_7$: C, 58.46; H, 5.64; N, 7.18.
Found: C, 58.48; H, 5.49; N, 7.10.

Compound **4a**

Salt **5** (3.5 g, 8.97 mmols) was treated with 1.1 equivalent of 2N NaOH. The resolving agent was recovered by filtration and the aqueous phase was cooled to 0°C and acidified to pH 3 with 2N HCl. Extraction with diethyl ether afforded the homochiral acid **4a**. M.p. 79°C $[\alpha]_D^{25}$ = -23.2 (c1.05, $CHCl_3$). Spectral data as for **1a**.

Compound **4b**

To a stirred solution of compound **4a** (1.78 g, 10 mmol) in anhydrous $CH_2Cl_2$ (10 ml) was added 50 mg dimethylaminopyridine (DMAP) and MeOH (2 ml, 49 mmol). The mixture was cooled to 0°C and dicyclohexylcarbodiimide (DCC) (2.063 g, 10 mmol) was added in portions. The mixture was stirred at 0°C for 5 min and at 20°C for 3 hrs. Precipitated urea was filtered off and the filtrate was washed with 0.5N HCl, sat. $NaHCO_3$ and $H_2O$ and dried ($MgSO_4$). Purification by column chromatography (ether/hexane) afforded **4b** 1.44 g (75%). $[\alpha]_D^{26}$ = -111.1 (c1.11, MeOH).

$^1H$ Nmr ($CDCl_3$), 7.314 - 7.195 (5H, m), 6.26 (1H, m), 5.84 (1H, m), 5.47 (1H, br. s), 3.81 (1H, br. s), 3.58 (3H, s); $^{13}C$ Nmr ($CDCl_3$), 51.81 (q), 72.76 (d), 125.97 (t), 127.11 (d), 128.07 (d), 128.68 (d), 141.46 (s), 142.20 (s) and 166.64 (s).

M.S.: 192 (23%) $M^+$; 160 (23%), 105 (100%), 79 (44%), 77 (59%).

Compound **4c**

A stirred solution of compound **4a** (1.78 g, 10 mmol) in diethyl ether (10 ml) was treated with conc. $H_2SO_4$ (3 drops) and an excess of isobutylene[15]. Stirring was continued for 24 hrs in a pressure bottle. The bottle was chilled and the contents transferred to a separatory funnel containing ice-cold 1N NaOH. Extraction with diethyl ether afforded the crude product which was purified by column chromatography (ether/hexane). A close-running impurity had to be removed using a chromatotron (10% ether/hexane) and yielded compound **4c** (1.20 g, 51%). $[\alpha]_D^{26}$ = -93.2 (1.09, MeOH).

$^1H$ ($CDCl_3$), 7.22 - 7.34 (5H, m), 6.22 (1H, m), 5.75 (1H, m), 5.44 (1H, br. s), 3.55 (1H, br. s), 1.35 (9H, s); $^{13}C$ ($CDCl_3$), 27.94 (q), 73.54 (d), 81.66 (s), 125.34 (t), 126.53 (d), 127.66 (d), 128.33 (d), 141.59 (s), 143.37 (s), 165.45 (s).

M.S.: 234 (15%) $M^+$, 177 (54%), 132 (65%) and 105 (100%).

**Acknowlegements:**

The authors thank the Foundation for Research Development and the Natal University Research Committee for financial support.

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17. $C_{19}H_{22}N_2O_7$, M = 313.6, Monoclinic, $P2_1$: $\underline{a}$ = 10.140, $\underline{b}$ = 7.021, $\underline{c}$ = 14.400Å; $\beta$ = 99.2°; $\underline{V}$ = 1011.8 Å$^3$; $\underline{Z}$ = 2. $\underline{R}$ = 0.050 for 2612 observed reflections with $\underline{I} > 4\sigma(\underline{I})$ (Mo-$\underline{K}\alpha$ radiation) and 262 variable parameters. The correct enantiomer was determined by noting that the configuration at C(13) is fixed as $\underline{R}$.