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A ROUTE TO HOMOCHIRAL (S)-O-METHYL MANDELIC ACID AND RELATED α-ALKOXY CARBOXYLIC ACIDS FROM ISOPROPYLIDENE GLYCEROL.

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An improved synthesis of the useful ketones **7** is described. These ketones are then further modified *via* a highly stereospecific reduction. to give homochiral α-alkoxy carboxylic acids which are useful chiral auxiliaries and intermediates.

α-Alkoxy carboxylic acids are important intermediates in the synthesis of Angiotensin Converting Enzyme (ACE) inhibitors[1] and are also useful chiral auxiliaries. Here we describe a versatile route to the synthesis of these acids from the readily available homochiral isopropylidene glycerols (*R*)-**1** and (*S*)-**1**. Both (*R*)- and (*S*)-isopropylidene glycerols and the corresponding aldehydes (*R*)-**2** and (*S*)-**2** have found widespread use as chiral building blocks[2]. However, the corresponding ketones have seen little use, mainly due to their relative inaccessibility. A limited number of these ketones have been reported previously[3] but there has been some confusion concerning their

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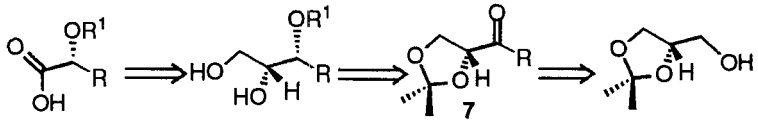
stereochemical integrity[3f,g]. Owing to the ready availability of useful quantities of both (*R*)-**1** and (*S*)-**1** and the acid (*R*)-**3** (>100 g)[4a] we have been able to explore the synthesis and chemistry of the ketones (*R*)- and (*S*)-**7**[4b].

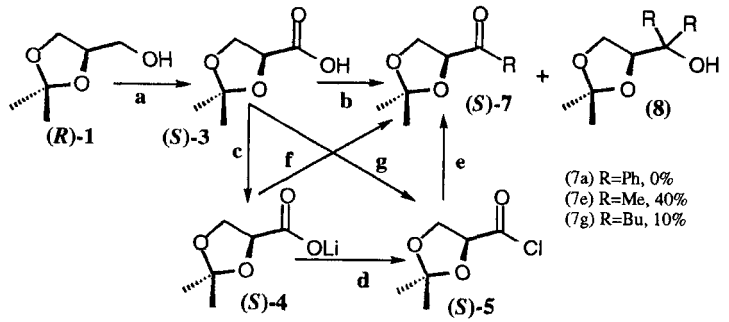
Reterosynthetic analysis of our carboxylic acids lead us to the corresponding ketones **7** as our starting material (Scheme 1). We were hopeful that stereocontrol during reduction of **7** could be achieved by extending the reported results of Chikashita[8].



Scheme 1

Thus our first concern became the synthesis of enantiomerically pure ketones in a reliable and reproducible manner. Oxidation of (*R*)-**1** with alkaline permanganate gave the acid (*S*)-**3** in good yield and without any racemization at the chiral centre[5] (Scheme 2). Alternatively catalytic oxidation of (*R*)-**1** with Pt/C and air (or oxygen) in aqueous and basic media gave excellent chemical yields of the acid (*S*)-**3**. However, the choice of base was critical in avoiding any racemization of the chiral centre [6]. Reaction of acid (*R*)-**3** or (*S*)-**3** with methyl or n-butyl lithium under a variety of conditions gave poor yields of the corresponding ketones (*R*)- or (*S*)- **7e** and (*R*)- or (*S*)-**7g** (Scheme 2).

The major product in all cases were the alcohols **8**. The addition of organometallics to acid chlorides under certain conditions has been reported to give good yields of ketones[7]. Therefore both (*S*)-**5** and (*R*)-**5** were prepared in quantitative yield by chlorination of the lithium salts (*S*)-**4** and (*R*)-**4**, since direct chlorination of (*S*)-**3** and (*R*)-**3** gave only poor yields of (*S*)-**5** and (*R*)-**5.** .However, in our hands reaction of the acid chloride (*S*)-**5** with both Grignard and organolithium reagents failed to give any of the ketones **7** (Scheme 2).



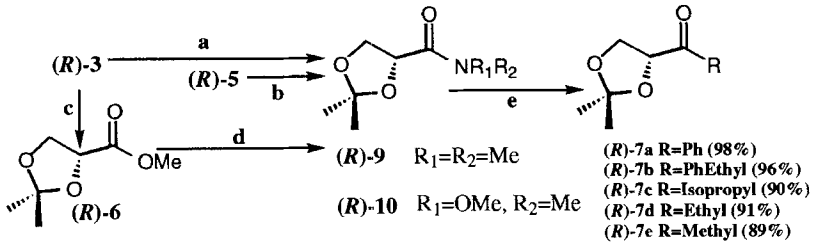
Scheme 2

Conditions; a). NaOH, $KMnO_4$, 65-70% or Pt/C, air, $NaHCO_3$, 24h, 60-65°C, 95%(97% ee); b). RLi (2equiv.), 0-40%; c). LiH, diglyme, quant.; d). $SOCl_2$, CH_2Cl_2, quant.; e), RMgX, THF, -78°C, 0%; f). RLi, (1 equiv), 0%; g). $SOCl_2$ or $(COCl)_2$, 10-20%.

It was clear that a good, simple one or two step conversion of the acid (*S*)-**3** or (*R*)-**3** to the ketones (*S*)-**7** or (*R*)-**7** was not possible.

Thus a longer route involving the Grignard reaction on the amides **9** and **10** was investigated. Our routes to the enantiomeric amides (*R*)-**9** and (*R*)-**10** are shown in scheme 3. Reaction of either (*R*)-**9** or (*R*)-**10** with a range of Grignard reagents at 0°C gave the corresponding ketones in excellent yields (Scheme 3). The optical purity of the amides (*R*)-**9** and (*R*)-**10** and the ketones (*R*)-**7a**, (*R*)-**7b**, (*R*)-**7f** were confirmed by chiral phase GC against racemic standards[5a,b]. The methyl (*R*)-**7e**, ethyl (*R*)-**7d** and isopropyl ketone (*R*)-**7c** could not be resolved but were taken to be optically pure by analogy to the other ketones[5d].

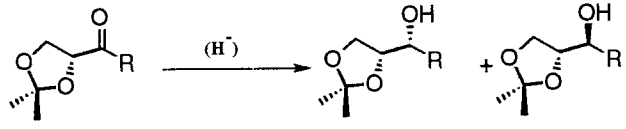
With the ketones **7** in hand we investigated the stereospecificity of reduction of the carbonyl group in greater detail than previously reported[8] The ketones (*R*)-**7a**, (*R*)-**7b**, (*R*)-**7c** and (*R*)-**7d** were chosen to represent a spread of steric bulk at the carbonyl group. The results from these reductions are listed in Table 1 and show that the major products in almost all cases were the "*syn*" alcohols (*R,R*)-**11** as predicted by the Felkin-Anh transition state (Fig.1).



Scheme 3

Conditions. a). DCC, $Me_2NH.HCl$, pyr., 80-85%; b). $R_1R_2NH.HCl$, pyr. or NEt_3, 85%; c). dimethoxypropane, cat. HCl or TsOH, MeOH, 95-100%; d). Me_2NH (2 equiv.), MeOH, 4°C, 144h, 98%; e). RMgCl or RMgBr, (1.1 equiv), THF or Et_2O, 0°C, 1h.

Table 1



Ketone	Reducing Agent* / Solvent (Temp.)	Ratio (11):(12) (*syn*:*anti*) [5c]	G.C. retention time *syn* & *anti* [5c]
(*R*)-(7a)	**A** (-78°C, 0, & 20°C)	3.6:1 (2.5:1 at 0°C & 20°C)	28.10' & 32.03'
R=Ph	**B** (-78°C)	30:1	at 140°C
	C (-78, 0 & 20°C)	2.2:1, (2;1 at & 1:1 at 0°c and 20°C)	
	D (-78, 0 & 20°C)	35:65 (1:1 at 0°C & 20°C)	
	E (-78°C)	1:2	
	F (-78°C)	8:1	
(*R*)-(7b)	**B** (-78°C)	18:1 (6.5:1 at 0°C & 6.3:1 at 20°C)	17.75' & 23.04'
R=Ph(CH$_2$)$_2$	**C** (-78 & 0°C)	17:1 (6.4:1 at 0°C)	at 170°C
	F (-78°C)	2.75:1	
(*R*)-(7c)	**B** (-78°C)	21:1, (8.2:1 at 20°C)	12.97' & 18.6'
R=Isopropyl	**C** (-78, 20°C)	16:1, (6.6:1 at 20°C)	at 110°C
	F (-78°C)	5.25:1	
(*R*)-(7d)	**B** (-78°C)	24.6:1 (7.3:1 at 0°C & 4:1 at 20°C	8.14' & 10.0'
R=Ethyl	**C** (-78°C)	13.5:1	at 100°C
	G (-78°C,)	13.5:1	
	F (-78°C)	3.4:1	

*A :- $Zn(BH_4)_2$/THF; **B** :- LiBH(s-Bu)$_3$/THF; **C**: - DIBAL-H/PhMe+THF(at least 1:5)

D :-DIBAL-H/PhMe; **E** :- DIBAL-H/CH_2Cl_2; **F** :- $LiAlH_4$/THF; **G** :- DIBAL-H/THF.

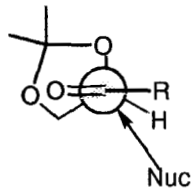
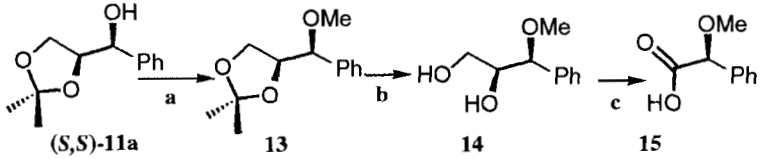


FIG. 1

Our detailed results agree well with those reported by Chikashita[8], except that in our case a small anomaly was found in the reduction of (*R*) or (*S*)-**7a**. Thus the reduction of (*R*)-**7a** with DIBAL-H in toluene at -78°C gave the *anti* alcohol (*R,S*)-**12a** as the major product (*syn*:*anti* ratio is 35:65). When the reduction is carried out at 0°C or at room temperature no selectivity is seen. Similarly DIBAL-H in dichloromethane at -78°C gave the *anti* alcohol (*R,S*)-**12a** as the major product (*syn*:*anti* ratio 1:2). However, when the toluene solution of DIBAL-H was diluted with THF (5 volumes of THF) a *syn*:*anti* ratio of 2:1 was obtained (from 2.2:1 at -78°C to 2:1 at 0°C). The exact explanation of this is not clear, although co-ordination of the (ethereal) solvent to the DIBAL-H prior to reduction may account for this result.

The proof of configuration at the new chiral centre came from the conversion of (*S,S*)-**11a** (formed from (*S*)-**7a** and separated from (*S,R*-)-**12a** by crystallisation), to the known (*S*)-O-methyl mandelic acid **15** *via* the route shown (Scheme 4).

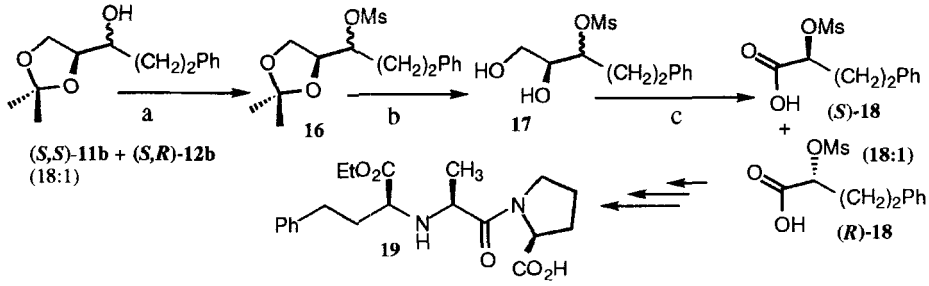


(S,S)-11a **13** **14** **15**

Scheme 4

Conditions. a). (i) NaH, THF, (ii) MeI quant.; b). H_3O^+, MeOH, quant; c). RuO_4, $NaIO_4$, 92%, ref.9; for **15** $[\alpha]_D^{20} = +148°$ (c1 in ethanol).

The ketone (*S*)-**7b** was also converted to the O-mesylated acid **18** via the above route except that owing to some difficulty in separating the epimeric alcohols the crude mixture of alcohols (*S,S*)-**11b** and (*S,R*)-**12b** (18 : 1 mixture) was carried through the synthesis (Scheme 5). The final mesylated acid (*S*)-**18** has the opposite stereochemistry to a possible precursor to the *ACE* inhibitors such as enalapril **19**[1]. Obviously using the enantiomer (*R,R*)-**11b** derived from (*R*)-**7** will give the required stereoisomer (*R*)-**18**.



Scheme 5

Conditions. a). MsCl, pyr., 24h, 0°C- RT, 70%; b). H_3O^+, MeOH, 70-80%; c). RuO_4, $NaIO_4$, 75%, ref. 9.

Thus we have shown that the ketones (*S*)-**7** and (*R*)-**7** are useful homochirons and their use for the synthesis of *ACE* inhibitors and homochiral α-amino acids is being actively pursued.

Experimental

General procedure for the synthesis of the ketones **7**

To a rapidly stirred and cooled (0°C) solution of either **9** or **10** in anhydrous THF (approximately 2.5 ml of THF per 1 mmol of amide), the Grignard reagent as a solution

in either THF or diethyl ether (1.1. equivalents) was added dropwise. The reaction was stirred for 1 h at 0°C and the quenched by pouring it rapidly into a vigorously stirred saturated solution of ammonium chloride. The mixture was stirred for 5-10 min and then extracted with dichloromethane (x 3). The extracts were dried ($MgSO_4$ or Na_2SO_4) and evaporated *in vacuo* to give the crude ketone **7**. The ketones could be further purified by careful distillation.

*e.g. (**S**)-(–)-1,2-dihydroxy-(1,2-**O**-isopropylidene)-butan-3-one **7e***

The title compound **7e** was obtained as a clear oil (89%) after distillation, b.p 130°C at 30mm Hg; $[\alpha]_D^{20}$ = -65.8°(c1 in EtOH) & $[\alpha]_D^{20}$ = - 97.78° (c0.32 in chloroform)

*(**S**)-(–)-1,2-dihydroxy-(1,2-**O**-isopropylidene)-3-phenylpropan-3-one **7a***

The title compound **7a** was obtained as a pale yellow crystalline solid (98%) from ethyl acetate / hexane, m.p. 57-59°C; $[\alpha]_D^{20}$ = -4.2° (c1 in EtOH)

General procedure for the reduction of the ketones (Table 1).

To a solution of the ketone **7** (dried by azeotroping with toluene x 2), in dry solvent (approximately 4-10 ml per mmol of ketone), at the required temperature the reducing agent in the stated solvent was added slowly. The reaction was allowed to go to completion (tlc) and then quenched by the rapid addition of a saturated aqueous solution of ammonium chloride. The aqueous phase was separated and extracted with dichloromethane (3 x 10-20 ml per mmol). The organic extracts were combined and dried (Na_2SO_4). Evaporation of the solvent in vacup gave the diastereomeric mixture of alcohols **11** & **12** in good yields (>>90%). The results are summarised in Table 1.

(S)-(+)-α-methoxyphenylacteic acid **15**

Crude (*S,S*)- **13** (0.444 g, 2 mmol) was dissolved in THF (10ml) and 1N HCl (4 ml) was added. The reaction mixture was stirred rapidly for 4.5 h. Ethanol (10 ml) was added and the mixture was reduced to approximately 1/3 in volume *in vacuo*. This procedure was repeated 3-4 times until no water remained. The resultant oily solid was dried by azeotroping with toluene (2 x 10 ml) to give the diol **14** as a pale yellow solid (0.365 g, 100%). The crude diol was dissolved in acetonitrile (4 ml) and carbon tetrachloride (4 ml) was carefully added. To the stirred homogenous solution, water (6 ml) was carefully added followed by sodium periodate (1.283 g, 6 mmol) and ruthenium chloride monohydrate (0.0091 g, 0.04 mmol). The black biphasic mixture was stirred vigorously for 40 min and then diluted with dichloromethane (25 ml). The two layers were separated and the aqueous layer extracted with dichloromethane (3 x 20 ml). The combined organic extracts were dried (Na_2SO_4) and evaporated *in vacuo* to give a grey oil. This was diluted with ether (20 ml) and filtered twice through a small pad of celite. The filtrate was evaporated *in vacuo* to give crude **15** as a solid (0.348g). Recrystallisation from hexane-ether gave pure **15** (0.304 g, 91%); $[\alpha]_D^{20} = +148^0$ (c1 in EtOH).

References and Notes

1. Gravas, H., Biollaz, J., Waeber, B., Brunner, H.R., Gavras, I.and Davies, R.D., *The Lancet,* **1981**, *(ii)*, 543.

2. Jurczak, J., Pikul, S. and Bauer, T. *Tetrahedron* **1986**, *42,* 447.

3. a) Dumont, R. and Pfander, H., *Helv. Chim. Acta.*, **1983**, *66,* 814; b). Hirth, G. and Walther, W., *ibid,* **1985**, *68,* 1863; c). Hagen, S., Lawande, W., Kilaas, L.

and Anthonsen, T., *ibid*, **1980**, *36*, 1301; e). Anthonsen, T., Hage, S. and Lawande, W., *Acta Chem Scand.*,**1980** *B-34*, 41; f). Larcheveque, M. and Petit, Y., *Synthesis*, **1986**, 60; g). Tanner, D. and Somafi, P., *Syn Comm.*, **1986**, 1517.

4. a). Our main supplier of (*R*)-**1**, (*R*)-**3** and (*S*)-**3** was International Biosynthetics Ltd. Halebank; b). Sheetal Handa, J.E. Hawes and R.J. Pryce, *U.K. Patent Appl. No. 8918806.4 and E.P Appl. No. 413401 A2*

5. a). The e.e. of the acids (*R*)-**3** and (*S*)-**3** were determined by conversion to the dimethylamides (*R*)-**9** and (*S*)-**9** using conditions (a) (scheme 2) and then g.c. analysis on a WCOT fused silica capillary column coated with XE-60-S-valine-OL-phenylethylamide (50m), comparing with a racemic standard of **9**. At a He flow rate of 1.5-2.0 ml $min.^{-1}$, the retention time for (*S*)-**9** was 23.55' and or (*R*)-**9** 22.86' at a column temperature of 110°C; b). same conditions as in (a) except the column temperatures 130°C for **7a**, 140°C for **7b** and 150°C for **7f**; c). as in (a) and (b) except the column temperatures were 100°C for **11d** &**12d**, 110°C for **11c** & **12c**, 140°C for **11a** &**12a** and 170°C for **11b** &**12b;** d). thus for (*S*)-**7e**, $[\alpha]_D^{20} = -97.78^{o}$ (c0.32 in chloroform), and agrees well with that reported in reference 3g.

6. Results to be reported in due course.

7. Sato, F., Inoue, M., Oguro, K. and Sato, M., *Tet. Lett.* **1979** *20*, 4303, Eberle, M.K. and Kahle, G.G. *Tet. Lett.*, **1980**, *21*, 2303.

8 Chikashita, H., Nikaya, T., Uemura, H. and Itoh, K., *Bull. Chem. Soc. Jpn..*, **1989,** *62*, 2121.

9. Carlsen, Per H.J., Katsuki, T., Martin, V.S. and Sharpless, K.B., *J. Org. Chem.*, **1981**, *46*, 3936.

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