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SYNTHESES OF ENANTIOMERS OF 2-[6-(4-CHLOROPHENOXY)HEXYL]-OXIRANE-2-CARBOXYLIC ACID

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Summary: The title compounds were prepared by an efficient route featuring novel reductions of an acid chloride and the Sharpless epoxidation of an allylic alcohol.

The coenzyme A (CoA) esters of substituted oxirane-2-carboxylic acids such as 2-tetradecyloxirane-2-carboxylic acid (tetradecylglycidate) have been found to be powerfully hypoglycaemic in animals of several species,[1] including man.[2] This is associated with the inhibition of carnitine palmitoyltransferase A (CPT1), which is required for the oxidation of long-chain acyl CoA esters. (*Rac.*)-2-[6-(4-chlorophenoxy)hexyl]-oxirane-2-carboxylic acid [(1), generic name Etomoxir for the corresponding ethyl ester], as its CoA ester, acts as a strong inhibitor of mitochondrial CPT1 and is a candidate anti-diabetic drug.[3] This activity is likely to be associated with one enantiomer due to an enantioselective active-site directed irreversible inhibition of the enzyme by covalent bond formation.[4] To investigate this hypothesis, a synthetic method for obtaining (**1a**) (*R*-isomer) and (**1b**) (*S*-isomer) enantiospecifically was devised (Scheme 1).

The routes to the enantiomers (**1a**) and (**1b**) and their esters involve Sharpless epoxidations[5] of the allylic alcohol (**2**), which was obtained from the α,β-unsaturated ester (**3**).[6] Efficient reductions of α,β-unsaturated esters to allylic alcohols are not well reported. Carbonyl compounds have been reduced by sodium borohydride absorbed onto alumina[7] or silica.[8] We have found that $NaBH_4$ on silica is suitable for the chemoselective reduction of the acid chloride (**4**)[9] [prepared by base hydrolysis of ester (**3**) to give acid (**5**),[10] that was treated with thionyl chloride] to allylic alcohol (**2**).[11] Alternatively, reduction of ester (**3**) with aluminium trihydride in diethyl ether[12] gave allylic alcohol (**2**) directly in high yield and with complete chemoselectivity. The alcohol (**2**) was treated with *t*-butylhydroperoxide, titanium isopropoxide and diethyl L-(+)-tartrate in a modified Sharpless epoxidation[5] to give the enantiomerically pure (*S*)-(-)-epoxycarbinol (**6a**)[13] (concerning the configuration of **6a** see below). Oxidation

of the epoxycarbinol (**6a**) to oxiranecarboxylic acid (**1a**) was not trivial and a variety of reagents was tried before it was found that ruthenium(III)-catalysed oxidation ($RuCl_3$-$NaIO_4$)[14] gave a product mixture containing mainly (**1a**) but accompanied by acid (**7**) derived from oxidation of the oxirane methylene.[15] Although the required acid (**1a**) could be obtained from the mixture by recrystallisation, isolated yields were low (15–20%) and it was more efficient to esterify the crude mixture of acids and separate the esters by column chromatography or distillation. Thus, diazomethane esterification gave the ester (**8a**)[16] (purified by column chromatography). Esterification with diethyl sulphate gave ester (**9**)[17], purified by distillation, which could be hydrolysed to crystalline (*R*)-(+)-oxiranecarboxylic acid (**1a**).[18]

The above sequence was repeated on the allylic alcohol (**2**) using diethyl D-(-)-tartrate, *t*-butylhydroperoxide and $Ti(O^iPr)_4$ to give the (*R*)-(+)-epoxycarbinol (**6b**) (49%), which was treated with $RuCl_3$-$NaIO_4$[14] to give the (*S*)-(+)-oxiranecarboxylic acid (**1b**) (80%). Esterification of (**1b**) with diazomethane and column chromatography gave the ester (**8b**) (69%).[19]

The predicted enantioface selectivity of the Sharpless epoxidation of (**2**) employing diethyl L-(+)-tartrate as chiral auxiliary should lead to (**6a**), *i.e.* (*S*)- configuration.[20] It follows that the configuration of (**8a**) and (**1a**) should be (*R*) which is in accord with the known[21] configuration of the similar anti-diabetic drug (*R*)-(+)-2-tetradecyloxirane-carboxylate (palmoxirate). N.m.r. experiments with a chiral shift reagent have been carried out on the (*R*)-epoxycarbinol (**6a**) and (*rac.*)-epoxycarbinol [prepared by *m*-chloroperbenzoic acid epoxidation of the allylic alcohol (**2**), 67%]. An epoxy hydrogen resonance from the racemic epoxycarbinol was split into two signals by the addition of europium(III) *tris*-3-(heptafluoropropylhydroxymethylene)-camphorate; the corresponding epoxy hydrogen signal of (**6a**) exhibited only one signal under similar conditions. A sample of racemic (**1**) gave diastereoisomeric salts with (-)-cinchonidine whose triplets for the C-6 protons could be resolved in the ^1H n.m.r. The sample of (**1a**) showed only one triplet for the C-6 protons of its (-)-cinchonidine salt.

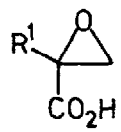
Preliminary experiments have shown that only the CoA ester of acid (**1a**) (i.e. *R*-enantiomer) inhibits CPT1 in rat liver mitochondria.[22]

Since this work was carried out, a paper by Ho *et al*[21] described the enantiospecific synthesis of methyl palmoxirate by a route that also employed the Sharpless epoxidation of an intermediate allylic alcohol.

References and notes

1. G.F. Tutwiler, R.J. Mohrbacher, and W. Ho, *Diabetes*, 1979, **28**, 242.
2. J. Verhagen, J. Leempoels, J. Burgmans, and G.F. Tutwiler, *Diabetes Suppl.*, 1984, **33**, 688.
3. *Drugs of the Future*, 1986, **11**, 1034.
4. T.C. Kiorpes, D. Hoerr, W. Ho, L.E. Weaner, M.G. Inman, and G.F. Tutwiler, *J. Biol. Chem.*, 1984, **259**, 9750.
5. R.M. Hanson and K.B. Sharpless, *J. Org. Chem.*, 1986, **51**, 1922.

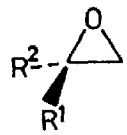
6. European Patent Application 46590.
7. E. Santaniello, F. Ponti, and A. Manzocchi, *Synthesis*, 1978, 891.
8. V. Ciurdaru and F. Hodosan, *Rev. Roum. Chim.*, 1977, **22**, 1027.
9. M.p. 47–48°C; δ_H 1.26–1.59 (6H, m, 3 x CH_2), 1.72–1.81 (2H, m, CH_2), 2.36 (2H, t, *J* 7 Hz, CH_2C=), 3.88 (2H, t, *J* 6 Hz, OCH_2), 5.78 (1H, s, C=C*H*H), 6.26 (1H, s, C=CH*H*), 6.80 (2H, d, *J* 9 Hz, H-2 and H-6) and 7.24 (2H, d, *J* 9 Hz, H-3 and H-5); υ_{max} 1 759 and 1 595 cm^{-1}; m/z 300 (M^+) and 128 (base peak, C_6H_4ClO) [Found: C, 60.1; H, 6.05. $C_{15}H_{18}Cl_2O_2$ requires C, 60.04; H, 6.05%].
10. M.p. 74.5–75.5°C [Found: C, 63.72; H, 6.77; Cl, 12.54. $C_{15}H_{19}ClO_3$ requires C, 63.65; H, 6.72; Cl, 12.55%].
11. δ_H 1.18–1.49 (6H, m, 3 x CH_2), 1.76 (2H, m, CH_2), 1.95 (1H, br s, OH), 2.06 (2H, t, *J* 7 Hz, CH_2C=), 3.89 (2H, t, *J* 6.5 Hz, OCH_2), 4.05 (2H, s, CH_2OH), 4.86 (1H, s, C=C*H*H), 5.01 (1H, s, C=CH*H*), 6.79 (2H, d, *J* 9 Hz, H-2 and H-6) and 7.20 (2H, d, *J* 9 Hz, H-3 and H-5); m/z 269 (M^+) and 128 (base peak, C_6H_4ClO).
12. *cf.* M.J. Jorgenson, *Tetrahedron Letts.*, 1962, 559.
13. M.p. 44–45°C; δ_H 1.26–1.58 (7H, m, 3 x CH_2 and OH), 1.71–1.81 (4H, m, 2 x CH_2), 2.66 (1H, d, *J* 5 Hz, C*H*HO), 2.88 (1H, d, *J* 5 Hz, CHHO), 3.62 (1H, d, *J* 12 Hz, C*H*HOH), 3.77 (1H, d, *J* 12 Hz, CHHOH), 3.92 (2H, t, *J* 6.5 Hz, OCH_2), 6.80 (2H, d, *J* 8 Hz, H-2 and H-6) and 7.21 (2H, d, *J* 8 Hz, H-3 and H-5); m/z 284 (M^+) and 128 (base peak, C_6H_4ClO,); $[\alpha]_D^{24}$ -30.7° (1% in $CHCl_3$) [Found: C, 63.46; H, 7.29. $C_{15}H_{21}ClO_3$ requires C, 63.41; H, 7.45%).
14. P.H.J. Carlsen, T. Katsuki, V.S. Martin, and K.B. Sharpless, *J. Org. Chem.*, 1981, **46**, 3936.
15. A sample of (**7**) was independently synthesised for verification of its presence as a reaction product. It was found that addition of 18-crown-6 increases both the rate of reaction and the extent of oxidation at C-1. As there was competing oxidation between the primary alcoholic and epoxy methylene functions of (**6**), we envisaged that the epoxy aldehyde (**10**) would be oxidised at C-1 at a faster rate, resulting in an increased proportion of (**1**) to (**7**). A sample of (+)-(**10**), ($[\alpha]_D^{23}$ + 21.9° (1% in $CHCl_3$)), was prepared by Swern oxidation (A.J. Mancuso, S.L. Huang, and D. Swern, *J. Org. Chem.*, 1978, **43**, 2480) of enantiomerically pure (−)-(**6a**). Ru(III)-catalysed oxidation of (+)-(**10**) gave a higher ratio of (**1**) to (**7**).
16. M.p. 32–33°C; δ_H 1.26–1.60 (6H, m, 3 x CH_2), 1.64–1.8 (2H, m, CH_2), 2.14 (2H, m, CH_2), 2.79 (1H, d, *J* 5.8 Hz, *CHHO*), 3.03 (1H, d, *J* 5.8 Hz, *CHHO*), 3.76 (3H, s, OCH_3), 3.90 (2H, t, *J* 6.4 Hz, OCH_2), 6.80 (2H, d, *J* 9 Hz, H-2 and H-6) and 7.21 (2H, d, *J* 9 Hz, H-3 and H-5); m/z 312 (M^+) and 128 (base peak, C_6H_4ClO); $[\alpha]_D$ + 7.06° (0.6% in MeOH) [Found: C, 61.15; H, 6.42. $C_{16}H_{21}ClO_4$ requires C, 61.44; H, 6.72%].
17. Oil; δ_H 1.2–2.2 (13H, m, 5 x CH_2 and CH_3), 2.90 (2H, q, CH_2O), 3.90 (2H, t, OCH_2CH_2), 4.22 (2H, m, $CO_2CH_2CH_3$), 6.80 (2H, d, H-2 and H-6) and 7.24 (2H, d, H-3 and H-5); $[\alpha]_D^{24}$ + 8.56° (1% in $CHCl_3$).
18. M.p. 53–61°C; δ_H 1.2–2.3 (10H, m, 5 x CH_2), 2.98 (2H, q, CH_2O), 3.91 (2H, t, OCH_2CH_2), 6.88 (2H, d, H-2 and H-6) and 7.22 (2H, d, H-3 and H-5); $[\alpha]_D^{24}$ + 11.0° (1% in $CHCl_3$).
19. M.p. 31–32°C; $[\alpha]_D$ -6.07° (0.6% in MeOH) for (**8b**).
20. A. Pfenniger, *Synthesis*, 1986, 89.
21. W. Ho, O. Tarhan, T.C. Kiorpes, G.F. Tutwiler, and R.J. Mohrbacher, *J. Med. Chem.*, 1987, **30**, 1094.
22. H.S.A. Sherratt and H.P.O. Wolf, unpublished results.



(1)

R^1CO_2H

(7)

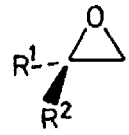


(1a) $R^2 = CO_2H$

(8a) $R^2 = CO_2Me$

(9) $R^2 = CO_2Et$

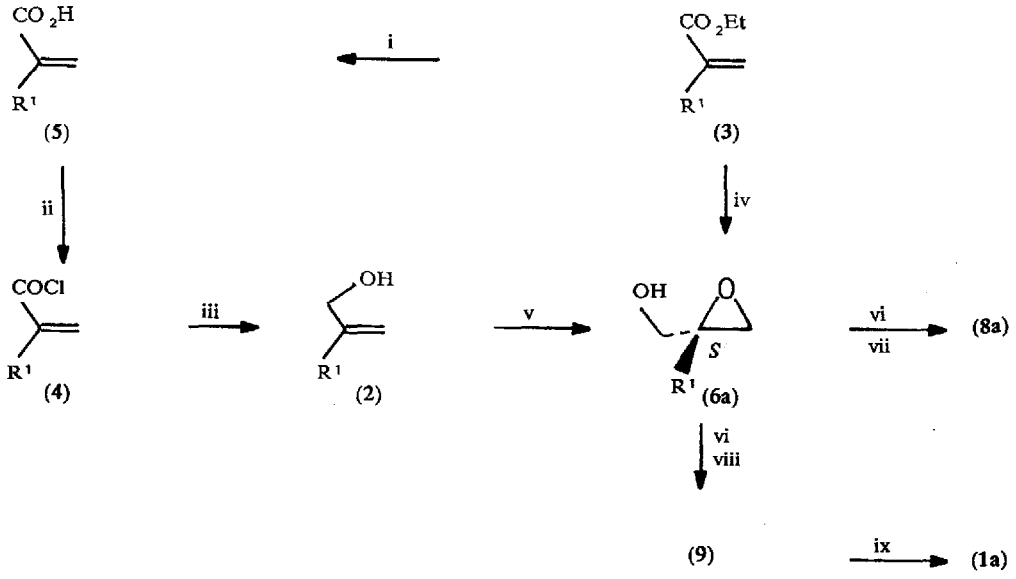
(10) $R^2 = CHO$



(1b) $R^2 = CO_2H$

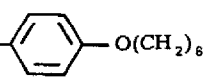
(6b) $R^2 = CH_2OH$

(8b) $R^2 = CO_2Me$



SCHEME 1

i. 25% (w/v) NaOH in MeOH , r.t., 18h, 81%
ii. $SOCl_2$ (50 mol. eq.), 0°C→ r.t. (18h), 63%
iii. $NaBH_4$–silica (10 mol. eq. of hydride), Et_2O, r.t., 18h, 60%
iv. $LiAlH_4/AlCl_3$, Et_2O, –78°C→ 0°C, 70–92%
v. Diethyl L-(+)-tartrate (0.77 mol eq.), $Ti(O^iPr)_4$ (0.51 mol eq.), *t*-BuO_2H (1.5 mol. eq.), powdered 4A sieves, –20°C (3h→ r.t. (1h)), 49%
vi. $RuCl_3$ (2.2 mol. %), $NaIO_4$ (3 mol. eq.), CCl_4–CH_3CN–H_2O, r.t., 7h, 81% *or* $RuCl_3$ (5–10 mol %), $NaIO_4$ (3 mol. eq.), 18–crown–6 (5–20 mol %), CCl_4–CH_3CN–H_2O, 0°C → r.t., 7h, 66%
vii. CH_2N_2 in Et_2O, 71%
viii. DMF, $NaHCO_3$, $(EtO)_2SO_2$, r.t., 100%
ix. NaOH in THF, r.t., 71%

NB in all the above R^1 = Cl–  –$O(CH_2)_6$

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