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FACILE SYNTHESIS OF (2*R*,3*S*)-3-(4-METHOXYPHENYL)GLYCIDIC ESTERS *VIA* OPTICAL RESOLUTION OF THE UNISOLATED LABILE FREE ACID

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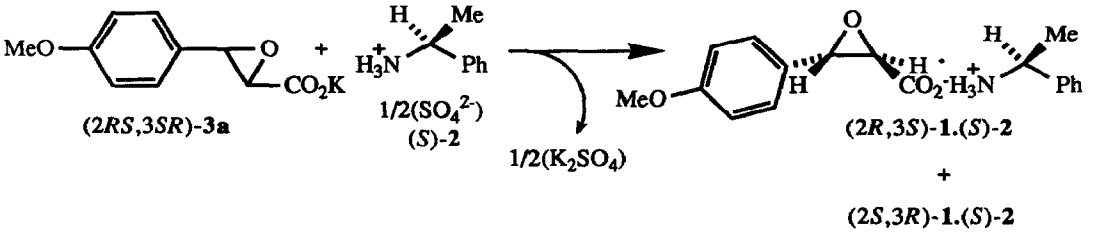
ABSTRACT: (2*R*,3*S*)-3-(4-Methoxyphenyl)glycidic esters were efficiently synthesized by the optical resolution of the racemic acid and esterification of the optically active acid thus obtained, in the form of its alkali metal salt.

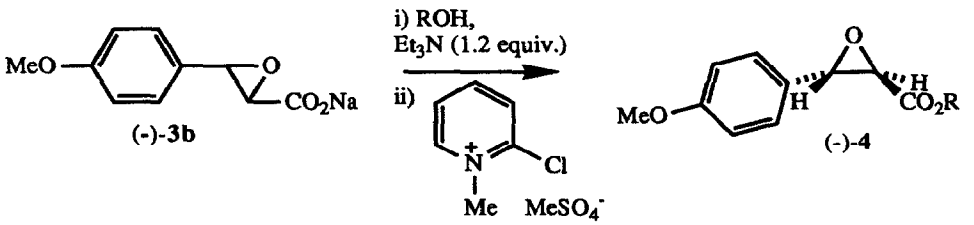
(2*RS*,3*SR*)-3-Arylglycidic esters[1] are intermediates for the synthesis of many useful compounds such as 1,5-benzothiazepines.[2] Examination of the literature revealed that very few derivatives of the arylglycidic esters have been prepared in an optically active form.[3] Optical resolution of this class of compounds is difficult since the free acids are prone to rapid decarboxylation under acidic conditions, even at low temperatures to give arylacetoaldehyde.

We wish to report here an efficient synthesis of (-)-(2*R*,3*S*)-3-(4-methoxyphenyl)glycidic ester [(-)-4],[4] a key intermediate for the synthesis of the useful coronary vasodilator diltiazem, by the optical resolution of the free acid [(±)-1] using (-)-(*S*)-1-phenethylamine sulfate without isolation but in the form of its potassium salt formed during hydrolysis of the ester, followed by esterification of the optically active sodium salt in the presence of 2-halopyridinium salt.[5] When (±)-**3a**,[6] obtained by saponification of the ester,

was reacted with (-)-(*S*)-1-phenethylamine sulfate [(-)-**2**·1/2H_2SO_4[7]] in solution (H_2O:CH_3CN=10:90), the slightly soluble diastereomeric salt [(2*R*,3*S*)-**1** · (*S*)-**2**[8]] was obtained in 77% yield based on half the amount of (±)-**3a** used after filtration of inorganic salt and crystallisation of the filtrate at -20°C.



The subsequent decomposition of the (2*R*,3*S*)-**1** · (*S*)-**2** diastereomeric salt was achieved by a salt exchange reaction using NaOMe in benzene to afford (-)-(2*R*,3*S*)-sodium 3-(4-methoxyphenyl)glycidate [(-)-**3b**][9] in 88% yield. Esterification of this salt was carried out in good yield with alcohol (ROH) by the use of 2-chloro-1-methyl-pyridinium salt[5] as a coupling reagent in the presence of 1.2 molar amounts of triethylamine under mild conditions. A typical experiment is as follows: 2-Chloro-1-methylpyridinium methylsulfate (19.8 mmol, 19.8 ml, as a 1M CH_2Cl_2-$(CH_2)_2Cl_2$ solution)[10] was added dropwise to a mixture of (-)-**3b** (3.89 g. 18.0 mmol), triethylamine (2.00 g, 19.8 mmol) and ROH (19.8 mmol) in CH_2Cl_2 (18 ml). The mixture was stirred at r.t. overnight, the solvent was evaporated, the residue extracted with ethyl acetate and washed with H_2O and brine. The ethyl acetate layer was tried (Na_2SO_4), concentrated, and the resulting residue was distilled *in vacuo* to afford (-)-**4** (Table).



Table

Esterification of (-)-**3b** using 2-chloro-1-methylpyridinium salt

Entry	ROH	Yield(%)	Bp°C/0.025 Torr	$[\alpha]_D^{23}$ in $CHCl_3$	E.e(%)[a]
1	MeOH	83	99-101[b]	-160 (c 0.892)	99.1
2	EtOH	83	110-111	-152 (c 1.10)	97.7

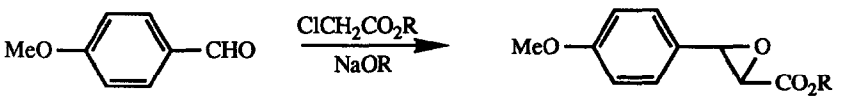
a) Determined by HPLC analyses using a chiral cellulose column: Me ester: $\alpha = 1.54$, $Rs = 5.90$, Et ester: $\alpha = 1.18$, $Rs = 1.79$[11].

b) Crystallized on standing (mp 87-88°C).

As described, the present method provides an efficient synthesis of (-)-(2*R*,3*S*)-3-(4-methoxyphenyl)glycidic esters, useful precursors of diltiazem.

References and Notes

1. The racemic starting ester was obtained by a Darzen condensation as a mixture of (2*RS*,3*SR*)-isomer and (2*RS*,3*RS*)-isomer,[12] which was enriched in the (2*RS*,3*SR*)-isomer by distillation or recrystallisation.



(2*RS*,3*SR*)-**4**

R = Me yield 57%, m.p. 66-69°C
R = Et yield 63%, b.p. 154-156°C / 1.5 Torr

2. For example, see H. Inoue, M. Konda, T. Hashiyarna, H. Otsuka, K. Takahashi, M. Gaino, T. Date, K. Aoe, M. Takeda, S. Murata, H. Narita, and T. Nagao, *J. Med. Chem.*, 1991, **34**, 675-687; and references cited therein.

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4. The absolute configuration of (-)-**1** was determined by comparison of its optical rotation with known (*S*)-(-)-ethyl 2-acetoxy-3-(4-methoxyphenyl)propionate[13], following catalytic hydrogenation and acetylation from (-)-**1**, prepared by a Darzen condensation using chiral lithium amide as base catalyst; K. Koga and H. Kawasaki, Japan Patent (JP) 1/226881 (1989) = *Chem. Abstr.* **112**, p.158034e.

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6. (±)-**3a**; mp 261-264°C(dec.), ^{1}H NMR ($(CD_3)_2CO:D_2O$ = 1:2, δ) = 3.52 (d, 1H, J = 2 Hz, epoxy H), 3.82 (s, 3H, OCH_3), 3.96 (1H, J = 2 Hz, epoxy H), 6.96 and 7.31 (d x 2, J = 8.8 Hz, 4H, Arom. H).

7. Prepared from (*S*)-(-)-1-phenethylamine ($[\alpha]_D$-39.8 (neat)) and 0.5 equivalent of 97% H_2SO_4 in cold MeOH. mp 273 - 274°C, $[\alpha]_D^{23}$ -4.1 (c 6.2, H_2O).

8. Mp 127.5 - 128.5°C (dec.), $[\alpha]_D^{23}$ -120° (c 1.02, MeOH).

9. (-)-**3b**; mp ca. 220°C (dec.), $[\alpha]_D^{23}$ -158 (c 0.697, acetone: H_2O = 1.0:1.0), ^{1}H NMR ($(CD_3)_2CO$:D2O = 1:1, δ) = 3.47 (d, 1H, J = 2 Hz, epoxy H), 3.83 (s, 3H, OCH3), 3.95 (1H, J = 2 Hz, epoxy H), 6.96 and 7.31 (d x 2, 4H, J = 8.6 Hz, Arom. H).

10. 1 M stock solution: To a refluxing solution of dimethyl sulfate (25.22 g, 200 mmol) in $(CH_2)_2Cl_2$ (30 ml) was added dropwise a solution of 2-chloropyridine (22.72 g, 200 mmol) in $(CH_2)_2Cl_2$ (30 ml), and the resulting mixture was further heated at reflux for 1 h. After cooling to r.t., the solution was diluted with CH_2Cl_2 to 200 ml.

11. The chiral column used was a 250 x 4.6 mm CHIRALCEL OD (Daicel Chemical Industries, Ltd.), and the mobile phase composed of hexane and 2-propanol in a ratio of 90 : 10 (v/v). The flow rate was maintained at 0.5 ml/min, and the procedure was carried out at ambient temperature. The effluent was monitored at 250 nm. A separation factor (α) and a resolution factor (R_s) were calculated as follows: $\alpha = k'_2/k'_1$ where k'_1 = [retention time of the first eluted isomer - dead time] / dead time, k'_2 = [retention time of the second eluted isomer - dead time] / dead time, R_s = 2 x [difference of retention times of (+) and (-) isomers] / [the bandwidths of the two peaks].

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