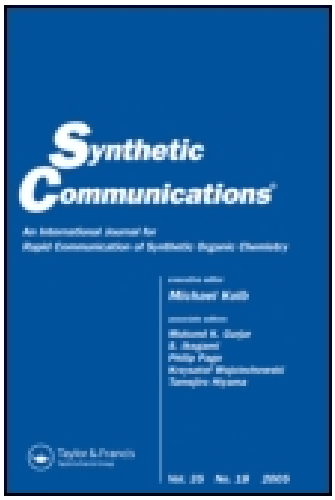

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A Straight Route Towards Glyceric Chirons

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A Straight Route Towards Glyceric Chirons

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ABSTRACT

Glycidic esters react with alcohols in the presence of a catalytic amount of magnesium perchlorate to give enantiopure 3-alkoxy-2-hydroxy esters regioselectively.

Key Words: Epoxide opening; Optically active diols.

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During the last years there has been increasing interest in the synthesis of small chiral fragments which can be incorporated into compounds of biological and synthetic importance.

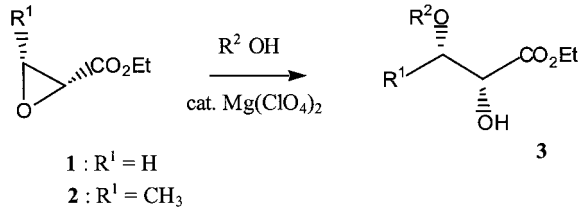
Among the polyhydroxylated synthons, one of the most popular is the acetonide derived from glyceraldehyde.[1] However, this synthon suffers from several drawbacks. Only the *R* enantiomer is readily accessible and the *S* isomer necessitates always multistep procedures.[2] Moreover it is not very stable. Compounds derived from glyceric acid are also of interest and may be prepared from D- or L-serine or D-mannitol and D-isoascorbic acid.[3] Alternatively, they may also be obtained by microbial oxidation.[4] However, due to the use of an acetonide as protecting group, in all these compounds the two hydroxyl functions cannot be differentiated.

We report here a very simple synthesis of monoprotected α,β-dihydroxy esters which allows such a differentiation by regioselective opening of ethyl epoxyesters by alcohols.

These epoxides may be prepared in bulk quantities from *R* or *S* serine.[5] Alternatively, they can be obtained by oxidation of chiral epoxyalcohols prepared by Sharpless enantioselective epoxidation of allylic alcohols.[6] However, few is known concerning the reaction of epoxides with alcohols. Some examples of epoxyalcohols opening in the presence of titane tetraisopropylate, tin phosphates or perchlorates were reported.[7,8,9] However, most of them are not applicable to epoxyesters because they promote the concurrent reaction of transesterification. To the best of our knowledge, until now, the use of a mixture $AlPO_4$–Al_2O_3 only allowed the opening of glycidic esters.[10]

In order to access to various monoprotected α,β-dihydroxyesters, we thought that it would be necessary to operate in the presence of a Lewis acid both to avoid the transesterification and to generate an electrophilic assistance. The first experiments were achieved with lithium perchlorate and benzyl alcohol and we observed with ester **1** a totally regioselective reaction at C3 position. Since the reaction was rather long, we tried then to activate the epoxide with an other metallic salt and we were pleased to observe that good results were obtained with magnesium perchlorate (Sch. 1).

The reaction was clearly more rapid than with the lithium salt and it was then possible to operate with a catalytic amount of salt (25%). This strategy was successfully extended to some other alcohols (Table 1). The same regioselectivity was observed with the 3-substituted epoxyester **2** which afforded the 2-hydroxy esters **3** exclusively (Entries 4 and 5). To achieve these reactions, the presence of a solvent was not necessary, and satisfactory yields were obtained by simply heating an equimolecular



Scheme 1.

Table 1. Synthesis of 3-alkoxyesters **3**.

Entry	Epoxide	Alcohol	Method	Yield (%)	$[\alpha]_D^{20}$ (c in CH_2Cl_2)
1	**1**	BnOH	A	75	+9.7 (3.1)
2	ent-**1**	*t*-BuOH	B	78	+2.2 (3.4)
3	**1**	3,5-$(MeO)_2$BnOH	B	74	+4.7 (3.5)
4	**2**	BnOH	A	68	+30.5 (5.4)
5	**2**	3,5-$(MeO)_2$BnOH	B	63	+21.8 (2.5)

amount of alcohol and epoxide. The target molecules were isolated in enantiomeric purities better than 98% without any racemization.

In conclusion, by using this economical and attractive method, both enantiomers of monoprotected glyceric esters now become accessible starting from readily available glycidic esters.

EXPERIMENTAL PROCEDURES

General Procedure

Products were purified by bulb to bulb distillation or by flash chromatography (Kieselgel 60 Merck: 230–400 Mesh; solvent: cyclohexane/EtOAc) and analyzed by GC (Chrompack BP5, 50 m capillary column) or by TLC (Merck silica gel 60F 254). Nuclear magnetic resonance spectra were recorded on a Bruker AC at 200 MHz for ^1H and 50 MHz for ^{13}C. $CDCl_3$ was used as solvent with TMS as internal standard. Infrared spectra were recorded on a Perkin-Elmer 599 spectrophotometer. Mass spectra were recorded on a Ribermag R10-10C instrument at 70 eV ionizing voltage; ammonia was used for chemical ionization. Optical rotations were measured on a Jasco P-1010 polarimeter.

The enantiomeric excesses were measured by GC after derivatization of the α-hydroxyester with *i*-propylisocyanate on a 25 m Chirasil-D-Val column (Chrompack)[11] or by HPLC on a 25 cm Chiracel OD using hexane-propan-2-ol (9/1) as eluent.

Method A. A mixture of epoxide (5 mmol), alcohol (10 mmol, 2 equiv.), and anhydrous $Mg(ClO_4)_2$ (1.25 mmol, 0.25 equiv.) was heated to 50°C for 48 h. Alternatively, the reaction was achieved with $LiClO_4$ (6.25 mmol, 1.25 equiv.) by heating at 60°C for three days. After cooling, the mixture was hydrolyzed with water (7 mL) and extracted with diethyl ether. After elimination of the solvent in vacuo, the excess of alcohol was removed by bulb to bulb distillation and the residue was purified by flash-chromatography.

Method B. A mixture of epoxide (5 mmol), alcohol (6 mmol) (except for Entries 3 and 5 where 4.5 mmol were used because the ester **3** and the alcohol were difficult to separate by flash-chromaography) and $Mg(ClO_4)_2$ (1 mmol, 0.25 equiv. or 2.5 mmol, 0.5 equiv. for Entry 2) was heated to 45°C for 24 h. After cooling, the mixture was hydrolyzed with water (0.4 mL). Diethyl ether (10 mL) was then added to the homogeneous mixture until the formation of two phases. The aqueous phase was extracted with 3×10 mL of diethylether. After drying ($MgSO_4$) and elimination in vacuo of the solvent, the ester **3** was purified by flash-chromatography using a solvent containing 1% of Et_3N.

Ethyl (*R*)-3-benzyloxy-2-hydroxypropanoate: $[\alpha]_D^{20} = +9.7$ (*c* 3.1, CH_2Cl_2); IR ν (cm^{-1}) 3470, 3030, 2867, 1736, 1453, 1206, 1125, 1026; ^{1}H NMR δ 1.30 (t, 3H, $J = 7.1$ Hz), 3.03 (br. s, 1H), 3.78 (d, 2H, $J = 3.4$ Hz), 4.28 (q, 2H, $J = 7.1$ Hz), 4.55 and 4.65 (2d, 2H, $J = 12.2$ Hz), 7.35 (m, 5H); ^{13}C NMR δ 13.87, 61.52, 70.54, 71.08, 73.17, 127.34, 128.09, 137.42, 172.35. MS (CI, NH_3) *m/z* (relative intensity) 242 (100, M + 18), 225 (5, M + 1), 108 (8). Anal. calcd. for $C_{12}H_{16}O_4$: C, 64.27; H, 7.19. Found: C, 64.34; H, 7.15.

Ethyl (*S*)-3-*t*-butoxy-2-hydroxypropanoate: $[\alpha]_D^{20} = +2.2$ (*c* 3.4, CH_2Cl_2); IR ν (cm^{-1}) 3470, 2975, 2936, 2875, 1746, 1365, 1233, 1194, 1124, 1095, 1022; ^{1}H NMR δ 1.16 (s, 9H), 1.24 (t, 3H, $J = 7.1$ Hz), 3.10 (d, 1H, $J = 6.7$ Hz), 3.64 (d, 2H, $J = 3.1$ Hz), 3.78 (s, 6H), 4.25 (q, 2H, $J = 7.1$ Hz); ^{13}C NMR δ 14.05, 27.15, 61.27, 63.41, 70.75, 73.19, 172.67. MS (CI, NH_3) *m/z* (relative intensity) 191 (15, M + 1), 152 (100). Anal. calcd. for $C_9H_{18}O_4$: C, 56.82; H, 9.54. Found: C, 56.75; H, 9.50.

Ethyl (*R*)-3-(3,5-dimethoxybenzyloxy)-2-hydroxypropanoate: $[\alpha]_D^{20} = +4.7$ (*c* 3.5, CH_2Cl_2); IR ν (cm^{-1}) 3478, 2937, 2909, 2840, 1739, 1600, 1463, 1431, 1320, 1233, 1126, 1067, 1021; ^{1}H NMR δ 1.27 (t, 3H, $J = 7.1$ Hz), 3.31 (d, 1H, $J = 6.7$ Hz), 3.75 (d, 2H, $J = 3.4$ Hz), 3.78 (s, 6H), 4.25 (q, 2H, $J = 7.1$ Hz), 4.45 and 4.55 (2d, 2H, $J = 12.4$ Hz), 6.37 (m, 1H),

6.48 (m, 2H); ^{13}C NMR δ 14.02, 55.15, 61.65, 70.73, 71.32, 73.25, 99.51, 105.20, 140.07, 160.75, 172.51. MS (CI, NH_3) m/z (relative intensity) 316 (100, M + 18), 299 (43, M + 1), 278 (3), 232 (48), 169 (81), 151 (49). Anal. calcd. for $C_{14}H_{20}O_6$: C, 59.14; H, 7.09. Found: C, 59.21; H, 7.13.

Ethyl (2*R*,3*S*)-3-benzyloxy-2-hydroxybutanoate: $[\alpha]_D^{20} = +30.5$ (c 5.4, CH_2Cl_2); IR ν (cm^{-1}) 3490, 2980, 1740, 1454, 1375, 1205, 1075; ^{1}H NMR[10] δ 1.25 (t, 3H, $J = 7.1$ Hz), 1.35 (d, 3H, $J = 6.2$ Hz), 2.96 (d, 1H, $J = 8.0$ Hz), 3.95 (dq, 1H, $J = 2.4$ and 6.4 Hz), 4.04–4.35 (m, 3H), 4.48 and 4.57 (2d, 2H, $J = 12.4$ Hz), 7.2–7.3 (m, 5H); ^{13}C NMR δ 13.90, 15.42, 61.45, 70.73, 71.32, 74.12, 127.21, 128.03, 137.07, 172.51. MS (CI, NH_3) m/z (relative intensity) 256 (100, M + 18), 239 (8, M + 1), 176 (3), 108 (34), 91 (40).

Ethyl (2*R*,3*S*)-3-(3,5-dimethoxybenzyloxy)-2-hydroxybutanoate: $[\alpha]_D^{20} = +21.8$ (c 2.5, CH_2Cl_2); IR ν (cm^{-1}) 3487, 2979, 2938, 2840, 1738, 1598, 1468, 1431, 1204, 1153, 1094, 1068; ^{1}H NMR δ 1.25 (t, 3H, $J = 7.2$ Hz), 1.33 (d, 3H, $J = 8.4$ Hz), 3.79 (s, 6H), 3.92 (dq, 1H, $J = 1.0$ and 7.2 Hz), 4.04 (m, 1H), 4.25 (m, 2H), 4.35 and 4.56 (2d, 2H, $J = 12.0$ Hz), 6.38 (m, 1H), 6.44 (m, 2H); ^{13}C NMR δ 14.00, 15.50, 55.18, 61.46, 70.69, 74.21, 75.05, 99.42, 105.34, 140.36, 160.67, 172.86. MS (CI, NH_3) m/z (relative intensity) 285 (11, M + 1), 279 (4), 222 (6), 180 (12), 169 (100), 152 (6). Anal. calcd. for $C_{15}H_{22}O_6$: C, 60.39; H, 7.43. Found: C, 60.51; H, 7.46.

REFERENCES

1. Jurczak, J.; Pikul, S.; Bauer, T. Tetrahedron **1986**, *42*, 447–488; Schmid, R.; Bryant, J.R. Organic Synthesis **1995**, *72*, 6–13.
2. Hubschwerlen, C. Synthesis **1986**, 962–964.
3. Lok, C.M.; Ward, J.P.; van Dorp, D.A. Chem. Phys. Lipids **1976**, *16*, 115–122; Hirth, G.; Walther, W. Helv. Chim. Acta **1985**, *68*, 1863–1871; Emons, C.C.H.; Kuster, B.F.M.; Vekemans, J.A.J.M.; Sheldon, R.A. Tetrahedron: Asymmetry **1991**, *2*, 359–362.
4. Berthole, M.A.; Koger, H.S.; Phillips, G.T.; Marx, A.F.; Claassen, V.P. EP 244912, 1987.
5. Petit, Y.; Larchevêque, M. Organic Synthesis **1998**, *75*, 37–43.
6. Denis, J.N.; Greene, A.E.; Serra, A.A.; Luche, M.J. J. Org. Chem. **1986**, *51*, 46–49.
7. Chong, J.M.; Sharpless, K.B. J. Org. Chem. **1985**, *50*, 1557–1560.
8. Otera, J.; Yoshinaga, Y.; Hirakawa, K. Tetrahedron Lett. **1985**, *26*, 3219–3222.
9. Chini, M.; Crotti, P.; Flippin, L.E.; Gardelli, C.; Giovani, E.; Macchia, F.; Pineschi, M. J. Org. Chem. **1993**, *58*, 1221–1227.

10. Riego, J.; Costa, A.; Saa, J.M. Chem. Lett. **1986**, 1565–1568.
11. König, W.; Benecke, I.; Sievers, S. J. Chromatograph. **1982**, *238*, 427–431.

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