Pergamon

Tetrahedron: Asymmetry Vol. 6, No. 7, pp. 1539-1542, 1995
Elsevier Science Ltd
Printed in Great Britain
0957-4166/95 $9.50+0.00

0957-4166(95)00193-X

Enantioselective Synthesis of Hydroxyethyloxiranecarboxylic Acid Derivatives by Epoxidation of 5-Ylidene-1,3-dioxane-4-ones

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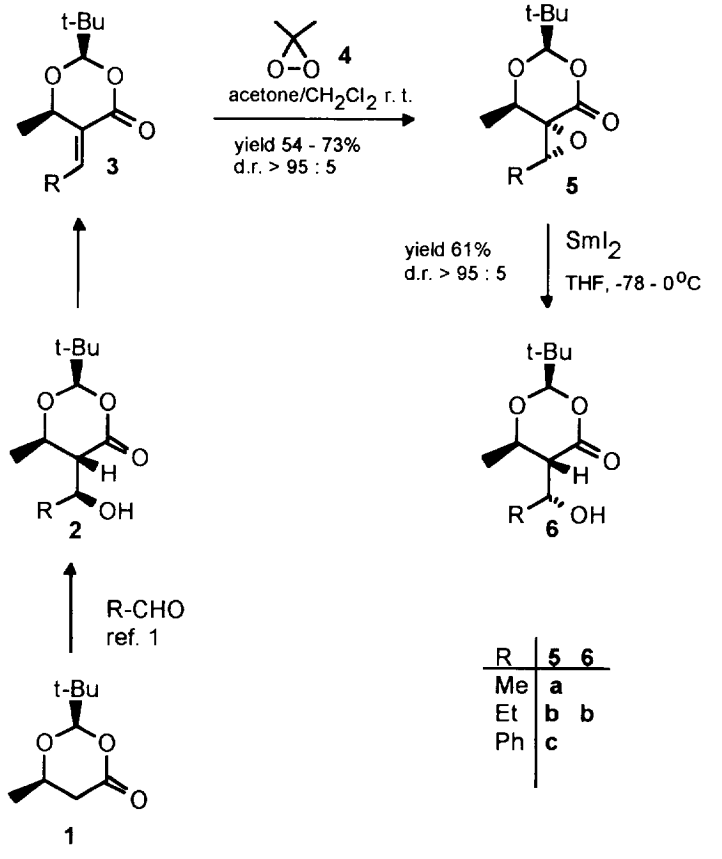
Abstract: Epoxidation of the 5-ylidene-1,3-dioxane-4-ones **3** with dimethyldioxirane (**4**) affords enantiomerically pure oxiranes **5** in satisfactory yields. These products **5** are novel hydroxyethyloxiranecarboxylic acid derivatives and can be reduced to enantiomerically pure 5-(α-hydroxyalkyl)-1,3-dioxane-4-ones **6**.

Homochiral 5-ylidene-1,3-dioxane-4-ones **3** are easily available from naturally occurring (R)-poly-3-hydroxy-butanoic acid via the 1,3-dioxan-4-one **1**.[1] Aldol reaction of **1** with aldehydes gives hydroxyalkyl derivatives **2** that are easily dehyrated to the 5-ylidene-1,3-dioxane-4-ones **3**. These α,ß-unsaturated ester derivatives **3** have been found to undergo highly stereoselective addition reactions to the C-C double bond, e. g. with organocuprates [1,2] or alkyl radicals[3]. Recently we found an effective access to enantiomerically pure hydroxyethylcyclopropane carboxylic acid derivatives by cycloaddition of diazomethane to 5-ylidene-1,3-dioxane-4-ones **3** and subsequent elimination of N_2.[4] In this paper we report on the epoxidation of 5-ylidene-1,3-dioxane-4-ones **3**, making use of 2,2-dimethyldioxirane (**4**), which already served as an effective epoxidizing reagent of other α,ß-unsaturated carbonyl compounds.[5,6] Interaction of reactants **3** and **4** in acetone at room temperature clearly formed hydroxyethyloxirane-carboxylic acid derivatives **6**. All products **6**[7] were enantiomerically pure according to NMR spectroscopy. The configuration of the oxiranes **5** was proved by X-ray crystal analysis of compound **5c** (see Fig. 1), revealing an attack of the dioxirane from the re-face of **2**. Surprisingly the epoxidation occurs from the opposite side from the dipolar cycloaddition of diazomethane to 5-ylidene-1,3-dioxanones **3**.[4] To obtain further evidence for the stereo-chemistry found by AMBERG and SEEBACH[1] in the aldol reaction of the dioxanone **1** with aldehydes affording **2** as the major stereoisomer (e. g. 7 : 1 diastereomeric mixture in case of R = Et) the oxirane **5b** was reduced with SmI_2.[8] The hydroxyethyldioxanone **6b** was obtained as the only stereoisomer. Its structure was confirmed by X-ray

crystal analysis (see Fig. 2). Hence either stereoisomers **2** or **6** can now be synthesized efficiently either by aldol reaction or by reduction of the oxirane **5** respectively.



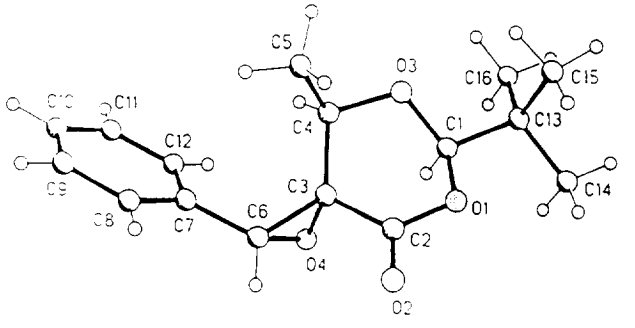


Fig. 1: X-ray crystal analysis of oxirane **5c**[10]

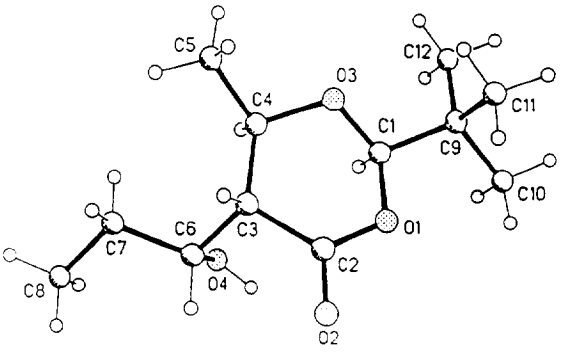


Fig. 2: X-ray crystal analysis of hydroxyethyldioxanone **6b** [11]

Chiral epoxides in general have gained wide interest as building blocks in organic synthesis, and in particular of enantiomerically pure bioactive compounds.[9] The novel oxiranes **5** represent interesting derivatives of chiral 2-(α-hydroxyethyl)-oxirane-2-carboxylic acids and can serve as versatile starting materials for various open-chained chiral hydroxycarboxylic acids. These investigations are currently underway.

Acknowledgement

We thank Zeneca Biopolymers for donation of polyhydroxybutyrate and Shell AG for a generous gift of pivalaldehyde. We gratefully acknowledge financial support from Deutsche Forschungsgemeinschaft and from Fonds der Chemischen Industrie.

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7. **5a**: Yield 54%; colorless oil; $[\alpha]_D^{20}$ = 103.6 (c = 2.95, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$, TMS); δ / ppm: 0.93 (s, 9H) $C(CH_3)_3$; 1.27 (d, 3H, J = 6.7)C6-CH_3; 1.33 (d, 3H, J = 5.8) C1′-CH_3; 3.72 (q, 1H, J = 5.8) C1′H; 4.11 (q, 1H, J = 6.7) C6H; 5.21 (s, 1H) C2H; ^{13}C NMR (75 MHz, $CDCl_3$, TMS) δ / ppm: 14.5; 18.1; 23.9; 29.7; 55.9; 60.4; 73.7; 104.6; 167.5. **5b**: Yield 73%, colorless oil; $[\alpha]_D^{20}$ = 93.9 (c = 1.85 $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$, TMS) δ / ppm: 0.93 (s, 9H) $C(CH_3)_3$; 1.07 (t, 3H, J = 7.4) CH_2-$\underline{CH_3}$; 1.25 (d, 3H, J = 6.7) C6-CH_3; 1.33 (m, 1H) CH_2; 1.66 (m, 1H) CH_2; 3.55 (dd, 1H, J = 4.4) C1′; 4.11 (q, 1H, J = 6.7) C6H; 5.21 (s, 1H) C2H; ^{13}C NMR (75 MHz, $CDCl_3$, TMS) δ / ppm: 10.8; 18.2; 22.3; 23.9; 34.5; 60.9; 61.4; 73.8; 104.6; 167.5. **5c**: Yield 71%, m.p. 84-85°C (AcOEt); $[\alpha]_D^{20}$ = 109.9 (c = 1.76 $CHCl_3$); ^1H NMR (300MHz, $CDCl_3$, TMS) δ / ppm: 0.72 (d, 3H, J = 6.7) C6-CH_3; 0.94 (s, 9H) $C(CH_3)_3$; 4.07 (q, 1H, J = 6.7) C6H; 4.70 (s, 1H) C1′H; 5.27 (s, 1H) C2H; 7.29 (s, 5H) C_6H_5; ^{13}C NMR (75 MHz, $CDCl_3$, TMS) δ / ppm: 17.2; 23.9; 34.6; 60.0; 62.5; 73.3; 105.0; 126.1; 128.6; 132.8; 167.0.

8. The procedure of Molander, G. A.; Hahn, G. *J. Org. Chem.* **1986**, *51*, 2596 for the reduction of oxiranes was adopted yielding enantiomerically pure **6b**: Yield 61%, m. p. 93-94 °C, $[\alpha]_D^{20}$ = -12.9 (c = 2.6, EtOH); ^1H NMR (300 MHz, $CDCl_3$, TMS) δ / ppm: 0.89 (s, 9H) $C(CH_3)_3$; 0.96 (t, 3H, J = 7.3) CH_2-$\underline{CH_3}$; 1.31 (d, 3H, J = 6.2) C6-CH_3; 1.41 - 1.48 (m, 2H) $\underline{CH_2}$-CH_3; 2.57 (dd, 1H, J_1 = 3.1, J_2 = 9.4) C5H; 3.09 (m, 1H) C1′-CH; 3.91 (dq, 1H, J_1 = 6.2, J_2 = 9.4) C6H;4.90 (s, 1H) C2H; ^{13}C NMR (75 MHz, $CDCl_3$, TMS) δ / ppm: 10.69; 21.24; 23.80; 29.66; 34.99; 53.87; 71.50; 72.59; 107.88; 171.88.

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10. Crystal data for **5c**: $C_{16}H_{20}O_4$, orthorombic, $P2_12_12_1$, a = 861.22(10), b = 1070.16 (12), c = 1662.2(2) pm, Z = 4, T = -100°C. Siemens P4 diffractometer, 1735 independent reflections (MoKα radiation, $2\theta_{max}$ 52°). Structure solution: direct methods. Strukture refinement: anisotropic on F^2 (program SHELXL-93, G.M. Sheldrick, Univ. Göttingen), H atoms as rigid methyls or with riding model. Absolute configuration based on known configuration at C1 and C4. Final w$R(F^2)$ 0.090, conventional $R(F)$ 0.035, for 186 parameters.

11. Crystal datd for **6b**: monocyclinic, $P2_1$, a = 1040.9(3), b = 589.7(2), c = 1099.8(3) pm, β = 105.86(2)°, Z = 2, T = -100°C. Further details as above except: 2484 reflections, w$R(F^2)$ 0.115, R(F) 0.047, 151 parameters. Full details of both structures have been deposited at the Fachinformationszentrum Karlsruhe, Gesellschaft für Wissenschaftlich-technische Information mbH, D-76344 Eggenstein-Leopoldshafen, Germany. Any request for this material should quote a full literature citation and the reference number CSD 401750 (**5c**), 401751 (**6b**).

(Received in UK 17 May 1995; accepted 22 June 1995)