Tetrahedron Letters,Vol.27,No.31,pp 3591-3594,1986 0040-4039/86 $3.00 + .00
Printed in Great Britain Pergamon Journals Ltd.

HIGHLY DIASTEREOSELECTIVE SYNTHESIS OF 1,2-EPOXY-4-HYDROXYALKYL CARBAMATES. MASKED AND ACTIVATED α,γ-DIHYDROXY-ALKANALS AND -ALKANONES

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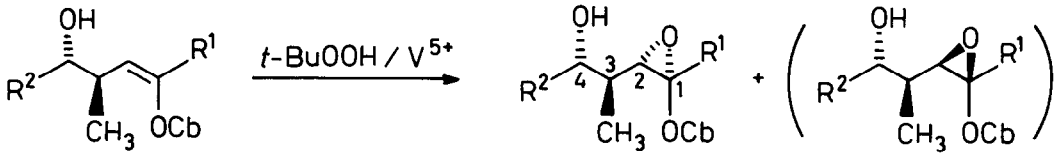
Summary: (Z)-anti-4-Hydroxy-1-alkenylcarbamates **1** yield, with essentially complete diastereoselectivity, the epoxides **2** with (1Z)-2,3-anti-3,4-anti-configuration on treatment with tert.-butylhydroperoxide/vanadylbis(acetoacetonate).

Diastereomerically pure 4-hydroxy-1-alkenyl N,N-diisopropylcarbamates[1] **1** having the relative configuration (Z)-anti[2] are easily prepared from metallated 2-alkenylcarbamates and carbonyl compounds via a titanium-mediated homoaldol reaction[3]. They represent protected γ-hydroxy-alkanals (for R^1 = H) or -alkanones (for R^1 = alkyl); on Hg^{2+}-catalyzed methanolysis from the enol carbamates **1** and by subsequent oxidation, trans-disubstituted γ-lactones[3b] are formed.



1 **2** **3**

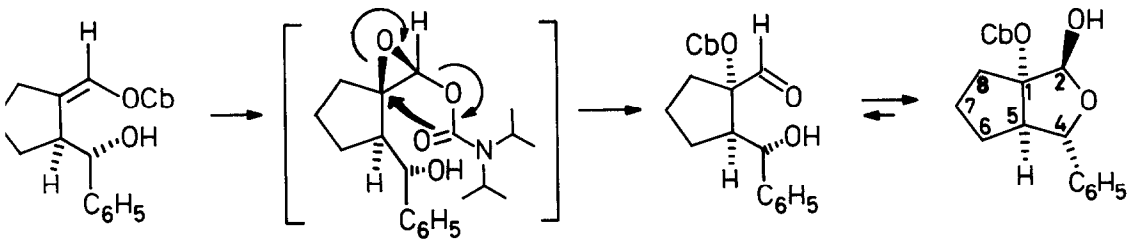
OCb = O-C(=O)-N(*i*Pr)$_2$ R^1,R^2 : see Table

Here the bonus of consistent double bond configuration is not utilized. The hydroxyl-directed epoxidation to form the oxiranes **2** is expected to proceed with high diastereofacial selection, as was found for appropriate homoallylic alcohols[4] (**1**, alkyl replaces OCb). Although 2-oxy-oxiranes have rarely proved of value in organic synthesis[5], we reasoned that in **2** the regio- and stereoselectivity of nucleophilic ring opening might be more facile and more easily controllable because of the hydroxy group.

On treatment of the enol carbamate **1a** with m-chloroperbenzoic acid (CH_2Cl_2 0°C), two diastereomeric[2] epoxides **2a** and **3a** were obtained in a ratio 85 : 15, yield 86%. Employing the Sharpless method[4b] using tert.-butylhydroperoxide/vanadylbis(acetoacetonate), only a single product **2a** was detected (^1H and ^{13}C NMR). The carbamates **1b-f** gave similar results (Table 1).

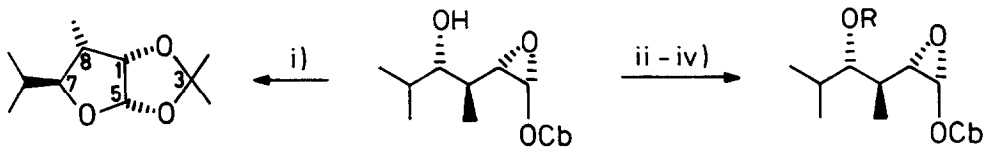
The epoxide[6] **2a** (m.p. 96°C) was subjected to X-ray crystal structure analysis[7] (Figure 1) which proved its (1R*,2S*,3S*,4S*)-configuration.

The reaction of the cyclopentane derivative **4** gave a rearranged product, which was elucidated as a bicyclic lactole[8] **7** by crystal structure analysis[9], (Figure 2). Obviously, in the slightly acidic reaction mixture the intermediate spiro-epoxide **5** is opened by the migrating N,N-diisopropylcarbamoyloxy group with inversion of configuration[10] to form the aldehyde **6** which is in equilibrium with its hemi-acetal **7**.



4 **5** **6** **7**

Oxiranes of type **2**, which lack a tertiary C-3 atom, are stable under the reaction conditions and also survive rapid silica gel chromatography. However, they are very reactive in the presence of Lewis acids. Thus **2a** on treatment with acetone and borontrifluoride etherate at -78°C furnished the bicyclic acetal **8** in 77% yield[11]. Although strong nucleophiles cause ring opening with inversion at C-3[12], tertiary amines are tolerated; protection of the free hydroxy group in **2** therefore causes no problems. For instance, from **2a** we obtained the acetate **9** (98%), the trimethylsilyl ether **10** (92%) and the MEM-ether **11** (71%) by the usual methods.



8 **2a**

9 R = C(=O)CH$_3$ (ii)
10 R = SiMe$_3$ (iii)
11 R = CH$_2$OCH$_2$CH$_2$OCH$_3$ (iv)

i) 1.0 equiv. $BF_3 \cdot OEt_2$/acetone -78°C. ii) Ac_2O, Et_3N, 5 mol % 4-(dimethylamino)pyridine, 15 h at -15°C. iii) Me_3SiCl, Et_3N, CH_2Cl_2, -70 - 20°C. iv) MEM-Cl, $(iPr)_2NMe$, 15 h at 40°C.

General procedure: 5.00 mmol of enolcarbamate **1** and 25 mg (2 mol-%) $VO(acac)_2$ in dry dichloromethane (40 ml) are stirred at 20°C with 7.50 mmol of a water-free solution of tert-butylhydroperoxide in 1,2-dichloroethane[13] (6 to 24 h, tlc-analysis). Then dimethyl sulfide (0.25 ml, 3.5 mmol) is added and stirring is continued for a further 30 min. For work-up, the mixture is extracted by sat. $NaHCO_3$-solution (2 x 40 ml), sat. KCl-solution (25 ml) and dried over $MgSO_4$. Evaporation of the solvent under reduced pressure, followed by silica gel chromatography (hexanes/diethyl ether 3:1) affords analytically pure **2** (see Table 1).

Table 1: (1,2-Epoxy-4-hydroxy-alkyl)carbamates **2**

educt **1**	R^1	R^2	epoxide **2**[a,b]	time(h)	yield (%)[c]
1a	H	$(CH_3)_2CH$	**2a**	6	92
1b	H	$(CH_3)_3C$	**2b**	6	86
1c	H	CH_3	**2c**	6	92
1d	H	C_6H_5	**2d**	6	90
1e	CH_3	$(CH_3)_2CH$	**2e**	24	81
1f	CH_3	C_6H_5	**2f**	24	81

(a) Epoxides **3** were not detected, diastereomeric ratio **2** : **3** > 97 : 3. (b) Satisfactory combustion analyses were obtained. (c) Yield after chromatographic purification.

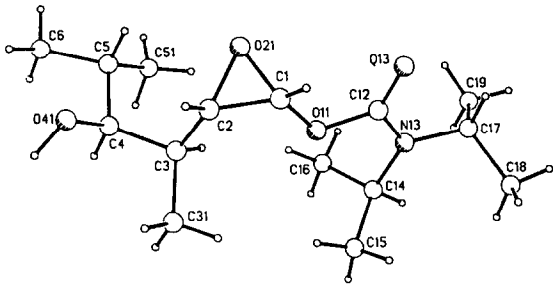


Fig. 1. One of the two independent molecules of **2a** in the crystal[7].

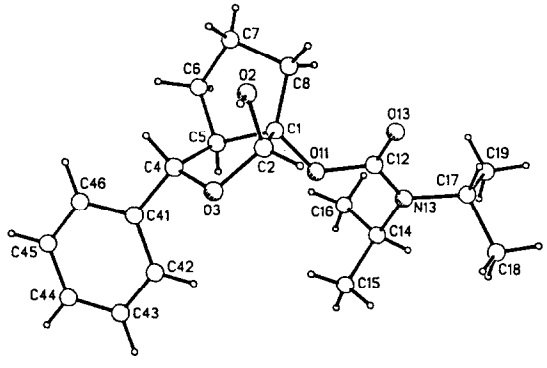


Fig. 2. The molecule of **7** in the crystal[9].

Acknowledgements: Financial support of this work by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie is gratefully acknowledged.

Dedicated to Professor Albert Mondon on the occasion of his 75th birthday.

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2) This paper deals with racemic compounds. Only one of the enantiomers is shown.

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6) **2a**, 100 MHz ^{1}H NMR ($CDCl_3$): δ = 0.95 (d, J = 7.0 Hz; 3-CH_3), 1.02 und 1.05 (je d, J = 7.0 Hz; $CH(CH_3)_2$), 1.25 (d, J = 7.0 Hz; $NCH(CH_3)_2$), 1.75 - 2.10 (m; 3-H, 5-H), 2.18 (d, J = 5.0 Hz; OH), 3.02 (dd, $J_{2,1}$ = 2.8 Hz, $J_{2,3}$ = 8.5 Hz; 2-H), 3.40 (ddd, J = 5.0 Hz, $J_{4,3}$ = 6.5 Hz, $J_{4,5}$ = 9.0 Hz; 4-H), 3.75 - 4.20 (m; NCH), 5.60 (d, $J_{1,2}$ = 2.8 Hz; 1-H). - 25 MHz ^{13}C NMR ($CDCl_3$): δ = 13.64 (3-CH_3), 17.06 und 19.76 (C-6, 5-CH_3), 20.12 - 21.63 ($NCHCH_3$), 30.95 (C-5), 35.07 (C-3), 45.66 - 46.99 (NCH), 57.80 (C-2), 74.62 (C-1), 80.40 (C-4), 154.29 (N-C=O).

7) Crystal data for (2a) : $P\bar{1}$, a = 10.133(3), b = 13.487(4), c = 14.051(4) Å, α = 76.59(3), β = 88.33(3), γ = 70.56(3)°, Z = 4 (two independent molecules), R = 0.066 for 3167 unique observed reflections (Mo Kα, $2\theta_{max}$ 50°).

8) **7**, m.p. 104°C (ether/hexane); in $CDCl_3$ 4:1 mixture of **7**/2-epi-**7**. ^{1}H NMR($CDCl_3$), **7**: δ = 1.20 (d) and 4.0 (m) $NCH(CH_3)_2$); 1.85 (m; 6-, 7- and 8-H_2); 2.78 (m, 5-H); 3.43 (s, OH); 4.80 (d, J = 8.5 Hz, 4-H); 5.81 (s, 2-H); 7.4 (m, C_6H_5). 2-epi-7: 4.52 (d, J = 8.5 Hz, 4-H); 5.71 (s, 2-H). - ^{13}C NMR ($CDCl_3$), **7** /2-epi-**7**/ : δ = 20.95 /20.95/ (CH_3); 26.77 /23.72/ (C-7); 27.45 /28.26/ (C-6); 34.85 /35.44/ (C-8); 45.45 (NCH); 60.04 /56.16/ (C-5); 83.84 /84.24/ (C-4); 100.58 /95.93/ (C-1); 102.02 /99.70/ (C-2); 155.33 /155.15/ (C=O).

9) Crystal data for **7** : $P2_1/c$, a = 6.948(1), b = 24.053(5), c = 11.964 (2) Å, β = 97.16(2)°, Z = 4, R = 0.058 for 2136 unique observed reflections (Mo Kα, $2\theta_{max}$ 50°). Further details of both crystal structure determinations can be obtained from the Fachinformationszentrum Energie Physik Mathematik, 7514 Eggenstein-Leopoldshafen 2, Fed. Rep. of Germany; please quote the full literature citation and reference number CSD-51622.

10) For the similar rearrangements of 2-acetoxy-oxiranes see ref. 5b).

11) **8**, oil; ^{1}H NMR ($CDCl_3$): 0.90 (d, J = 7.0 Hz, 8-CH_3); 1.8 (m), 1.01 and 1.05 (each d, J = 7.0 Hz, 7-$CH(CH_3)_2$); 1.30 and 1.49 (each s, 3-CH_3); 1.8 (m, 8-H and 7-CH); 3.59 (dd, $J_{7,7'}$ = 10.0 Hz, $J_{7,8}$ = 4.0 Hz, 7-H); 4.47 (dd, $J_{1,5}$ = 4.0 Hz, $J_{1,8}$ = 4.0 Hz, 1-H); 5.70 (d, 5-H).

12) J. Lüßmann, D. Hoppe, P. G. Jones, C. Fittschen, G. M. Sheldrick, following communication.

13) In some experiments, the commercially available solution of 80% tert.-BuOOH in (tert.-Bu)$_2O_2$ was also used without further purification and gave identical results.

(Received in Germany 29 April 1986)