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DIASTEREOSELECTIVE SYNTHESIS OF 2,3,4-TRISUBSTITUTED γ-LACTOLS AND γ-LACTONES VIA REGIO- AND STEREOCONTROLLED OPENING OF A 1,2-EPOXY-4-HYDROXYALKYL CARBAMATE WITH HETERO-NUCLEOPHILES

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Summary: The acid-catalyzed ring opening of the title epoxide **1** takes place at the C-1 atom with retention of configuration at C-2 to form 2,3-cis-2-hydroxy-substituted γ-lactol derivatives **3**. In basic media, nucleophiles attack the C-2 atom with inversion of configuration yielding 2,3-trans-lactols **5**. Oxidation furnishes corresponding γ-lactones **6**, **11** or **13**.

Diastereomerically pure 1,2-epoxy-4-hydroxyalkyl carbamates of type **1** are readily prepared from 2-alkenyl carbamates and aldehydes[1)], with formation of the C-3 - C-4 bond. Since both synthetic steps (titanium-mediated homoaldol reaction[2)] and hydroxyl-directed epoxidation) proceed with essentially complete diastereoselectivities, no isomer separations are necessary. The oxy-substituted oxirane ring in **1** constitutes an activated α-hydroxy carbonyl moiety. Among the few synthetic applications of 2-oxy-oxiranes[3)], those providing information on the configurative course of their ring opening are very scarce[3a,b,c)]. Therefore, with the epoxide[4)] **1** as a representative example, we explored the reaction of the novel class of compounds with nucleophiles.

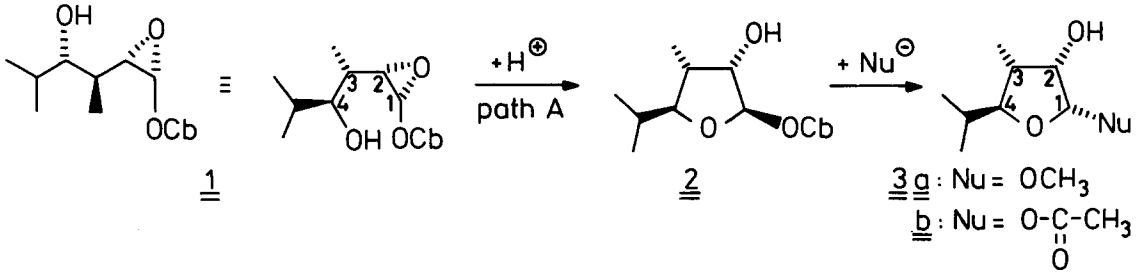
Under the influence of an acidic catalyst[5)], reaction path A is expected to occur, beginning with a rapid attack of the 4-OH group at C-1 and with formation of an intermediate 2-hydroxy-lactol carbamate[6)] **2**. In the presence of equimolar amounts of acid, with loss of diisopropyl amine and carbon dioxide from **2**, the nucleophile Nu should enter the 1-position to form **3** (presumable epimers at C-1). Retention of configuration at C-2 is the stereochemical result. However, without catalyst, a strong nucleophile Nu is expected to attack the less electron deficient[7)] C-2 atom with inversion of configuration (path B). After elimination of N,N-diisopropylcarbamate anion from the hemi-acetal **4**, the lactol **5** should be the first isolable product.

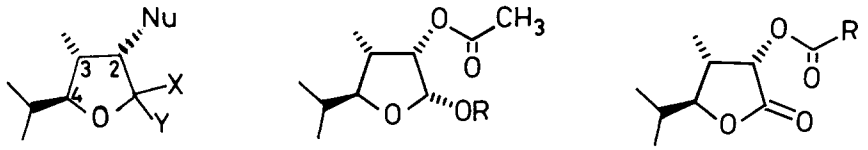
When stirring **1** with 1.0 equiv. of methane sulfonic acid in excess methanol at -78°C, a single lactol ether **3a** was isolated with 83% yield. Its configuration was determined from the single crystal X-ray analysis[8)] of the p-chlorophenyl urethane[9)] **9b** (m.p. 105°C), Figure 1. Under the same conditions, but with 10 equiv. of acetic acid, the acetates **10** and **11** were obtained with 60% and 24% yield, respectively. From the NMR spectra of lactone **13**, obtained from **10**, and comparison with its 2-epimer **6a**, it is evident that no inversion at C-2 had occurred. Obviously, the primarily formed 1-acetate **3b** suffers from rapid trans-acetylations.

On heating **1** with 1.0 equiv. of sodium acetate, phenolate, azide, thiolates or p-toluene sulfinate, (dimethylformamide, 24h at 90°C, method A; or acetonitrile, 48h at 85°C, method B), the expected γ-lactols **5a-f**, epimeric at C-1, were obtained in good yields (Table 1). Oxidation of **5a-f** by the Sarett reagent[10] (CrO_3·2 pyridine) afforded the γ-lactones **6a-f**. The lactols **5b,d-f** and also the corresponding γ-lactones **6** are accompanied by 5 - 8% of the 2-epimers **7** or **8**, presumably formed from the tautomeric 4-hydroxy-alkanals under basic conditions.

By the same method, lactol **10** gave lactone **13** (yield 85%). Lactol ether **9a** was oxidized by the Grieco method[11] (m-chloroperbenzoic acid/ borontrifluoride etherate) to yield the urethane-protected γ-lactone **12** (84%).

2,3-trans-lactones **6** are recognized in their ^1H NMR by the coupling constant $J_{2,3}$= 10-10.5 Hz and in ^{13}C NMR by the chemical shift of C-3 between δ = 37.7 - 40.1 ppm. The 2,3-cis-isomers **12** or **13** exhibit $J_{2,3}$ = 8.0 Hz and δ(C-3) = 34.9 - 37.3 ppm, respectively[12].





7 X=H, Y=OH **10** R = H **12** R = NHC_6H_5

8 X+Y=O **11** R = $C(=O)CH_3$ **13** R = CH_3

4 – 8	a	b	c	d	e	f
Nu =	O-C-CH_3 (O)	OC_6H_5	N_3	SC_6H_5	$SCH_2C_6H_5$	SO_2-p-Tol

OCb = O-C-N(*i*Pr)$_2$ (O)

We conclude that 1,2-epoxy-4-hydroxyalkyl carbamates offer a flexible and convenient strategy for the efficient, highly stereocontrolled synthesis of complex γ-lactones and related compounds. Further studies are in progress.

Table 1: Yields of γ-lactols and γ-lactones **5** and **7**, or **6** and **8**

(M)Nu	lactol	method	yield	lactone	yield	ratio **6** : **8**
$(K)O_2CCH_3$	**5a**	A	71%	**6a**	84%	>98 : 2
$(Na)OC_6H_5$	**5b**	B	64%	**6b**	84%	95 : 5
$(Na)N_3$	**5c**	A	63%	**6c**	83%	>98 : 2
$(Na)SC_6H_5$	**5d**	B	89%	**6d**	81%	93 : 7
$(K)SCH_2C_6H_5$	**5e**	B	92%	**6e**	82%	92 : 8
$(Na)SO_2$p-Tol	**5f**	B	63%	**6f**	82%	93 : 7

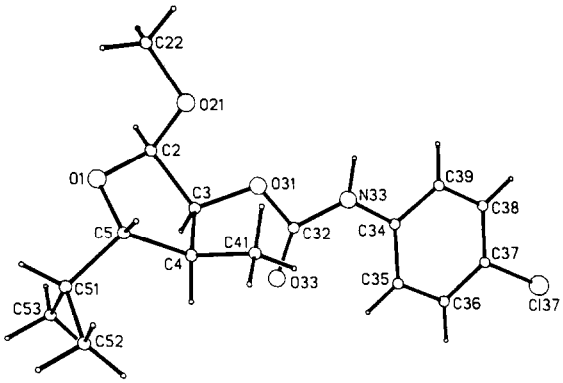
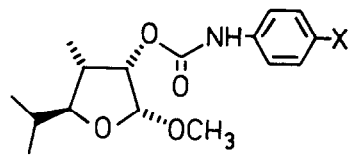


Fig. 1. The molecule of **9b** in the crystal[8)]



9 a X = H

b X = Cl

Procedures: acid-catalyzed ring-opening to **3a**: To epoxide **1** (287 mg, 1.00 mmol) in dichloromethane (3 ml) and methanol (3.0 ml) at -78°C in nitrogen atmosphere, distilled methanesulfonic acid (0.065 ml, 1.00 mmol) was added and stirring was continued for 15 h at -78°C. The reaction mixture was poured to ether/aqueous 2N HCl (14 + 4 ml), the ether solution washed with $NaHCO_3$-solution, dried over $MgSO_4$, evaporated, and the residue purified by liquid chromatography (silica gel, hexanes/ether 8 : 1); yield 144 mg (83%) **3a**.

Nucleophilic ring-opening to **5**: **1** (2.00 mmol) and the salt of the nucleophile (M)Nu (2.0 mmoles) in dry dimethylformamide (10 ml) were stirred under nitrogen at 90°C for 24 h (method A) or were stirred at 85°C in dry acetonitrile for 48 h (method B, tlc control). Work-up was accomplished as described above.

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Dedicated to Professor Rudolf Gompper on the occasion of his 60th birthday.

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8) Crystal data for **9b**: $P2_1/n$, a = 12.152(3), b = 9.322(2), c = 16.319(4) Å, ß = 110.38(2)°, Z = 4, R = 0.061 for 1452 unique observed reflections (Mo K_α, $2\theta_{max}$ 45°). Further crystallographic details can be obtained on request from the Fachinformationszentrum Energie Physik Mathematik, D-7514 Eggenstein-Leopoldshafen 2, FRG; please quote the full literature citation and the reference number CSD-51623.

9) **9a** was obtained from **3a** and p-chlorophenyl isocyanate (1.25 equiv.) with pyridine (0.15 equiv.) in refluxing dichloromethane (48 h, yield 92%, m.p. 105°C (from ether/pentane).

^{1}H NMR ($CDCl_3$) : δ = 0.95 [d, J = 6.8 Hz; $CH(CH_3)_2$], 1.05 (d, J = 7.1 Hz, 3-CH_3); 1.80 [m, $CH(CH_3)_2$]; 2.27 (m, 3-H); 3.41 (s, OCH_3); 3.59 (dd, $J_{4,3}$ = 6.1 Hz, $J_{4,4'}$ = 12.1 Hz, 4-H); 5.00 (dd, $J_{2,1}$ = 4.3 Hz, $J_{2,3}$ = 8.9 Hz, 2-H); 5.04 (d, $J_{1,2}$ = 4.3 Hz, 1-H) ppm. ^{13}C NMR ($CDCl_3$):δ = 14.32 (3-CH_3); 31.81, 17.84 and 18.28 [$CH(CH_3)_2$]; 35.52 (C-3); 54.79 (OCH_3); 75.24 (C-2); 89.11 (C-4); 102.21 (C-1); 120.07, 128.98 and 136.57 (Aryl); 153.07 (C=O) ppm.

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12) **6a** and [**8a**] ^{1}H NMR ($CDCl_3$): δ = 1.94 [1.89] (m); 1.07 [1.05] and 1.00 [1.02] [each d, $CH(CH_3)_2$]; 1.21 [1.05] (d, 3-CH_3); 2.17 [2.17] (s, O_2CCH_3); 2.39 [2.68] (ddq, $J_{3,3'}$ = 7.0 [7.0] Hz, $J_{3,4}$ = 9.5 [7.0] Hz, $J_{3,2}$ = 10.0 [8.0] Hz, 3-H); 3.90 [3.93] (dd, $J_{4,4'}$ = 4.5 [3.5] Hz, 4-H); 5.25 [5.44] (d, 2-H). - ^{13}C NMR ($CDCl_3$): δ = 15.08 [13.24] (3-CH_3); 30.55 [31.76], 16.51 [17.73], and 18.98 [18.52] [$CH(CH_3)_2$]; 20.51 [20.28] and 169.64 [169.57] (CH_3CO_2); 39.24 [35.12] (C-3); 79.14 [70.24] (C-2); 87.15 [90.60] (C-4); 171.88 [172.31] (C-1).
Selected ^{1}H and ^{13}C NMR data in $CDCl_3$ (δ, ppm): **6b** [**8b**] : $J_{2,3}$ = 10.0 [7.5] Hz, $J_{3,4}$ = 9.5 [6.5] Hz; 80.91 [75.52] (C-2); 40.13 [36.60] (C-3). - **6c**: $J_{2,3}$ = 10.5, $J_{3,4}$ = 9.5 Hz; 64.12 (C-2); 39.44 (C-3). - **6d** [**8d**]: $J_{2,3}$ = 10.0 [7.5] Hz, $J_{3,4}$ = 9.5 [6.5] Hz; 54.37 [51.58] (C-2); 38.80 [37.28] (C-3). - **6e** [**8e**]: $J_{2,3}$ = 10.0 [7.5] Hz, $J_{3,4}$ = 9.5 [6.5] Hz; 48.00 [45.22] (C-2); 39.82 [37.00] (C-3). - **6f** [**8f**]: $J_{2,3}$ = 10.0 [7.5] Hz, $J_{3,4}$ = 9.5 [6.5] Hz; 74.91 [70.76] (C-2); 37.73 [34.91] (C-3).

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