

49. Preparation of Vicinal Azidohydrins by Reaction of Oxiranes with Triethylaluminium/Hydrogen Azide

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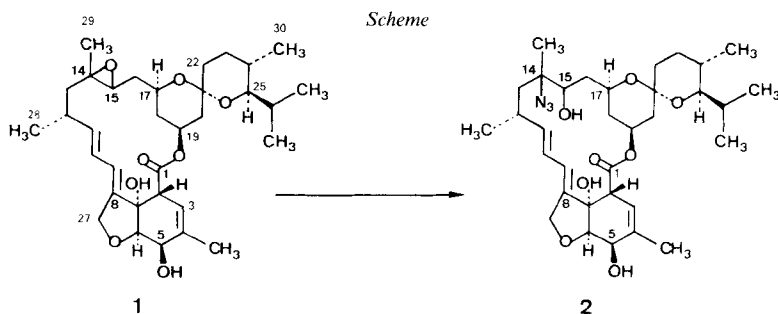
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A novel, mild, and highly stereoselective transformation of epoxides to azidohydrins by treatment with $\text{Et}_3\text{Al}/\text{HN}_3$ in toluene is described. As an example for the versatility of the reaction, a polyfunctional compound, 14,15-epoxy-14,15-dihydromilbemycin D (**1**), was transformed to 14-azido-14,15-dihydro-15-hydroxymilbemycin D (**2**) in 61 % yield.

1. Introduction. – Vicinal azidohydrins are generally obtained from oxiranes by a reaction with alkali azide in a suitable solvent [1–12]. Phase-transfer reagents are also used for the same transformations [13]. The reactions are often carried out under either alkaline or acidic conditions, and they usually require high temperatures and/or long reaction times. As side reactions, isomerizations, epimerization, and rearrangements may be induced by the alkaline conditions of the reactions with alkali azides. To the best of our knowledge, there is no report on the cleavage of epoxides derived from medium- to large-ring olefins by any of these methods. Medium rings with epoxy functions are known to be highly resistant to nucleophilic reagents, or they give rise to transannular-reaction products [14]. Thus, it is our opinion that most methods known to date for the preparation of azidohydrins are limited to open-chain epoxides, small-ring epoxides, and epoxides activated by neighboring groups.

As part of a program on chemical modifications of milbemycin D [15], we planned to transform 14,15-epoxy-14,15-dihydromilbemycin D (**1**) [16]³⁾ into a vicinal azidohydrin



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³⁾ Numbering of the milbemycin molecule according to [15].

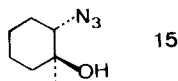
(Scheme). Since reaction of the polyfunctional epoxide **1** with NaN_3 led to decomposition of the starting material, and no azidohydrin could be detected, it was necessary to develop a new, milder process. Several years ago, Nagata *et al.* had introduced $\text{Et}_3\text{Al}/\text{HCN}$ and Et_3AlCN as reagents for the smooth cleavage of epoxides to give β -cyanohydrins [17] [18]. Therefore, we selected the corresponding azide reagents $\text{Et}_3\text{Al}/\text{HN}_3$ or Et_2AlN_3 [19] [20] as the reagents of choice⁴).

2. Results and Discussion. – Indeed, the reaction of the epoxide **1** with $\text{Et}_3\text{Al}/\text{HN}_3$ in toluene was a highly selective process and gave 14-azido-14,15-dihydro-15-hydroxymilbemycin D (**2**) in 61 % yield. The versatility of $\text{Et}_3\text{Al}/\text{HN}_3$ as a mild and efficient reagent for the transformation epoxide $\rightarrow$ azidohydrin is further illustrated by 6 representative examples given in the Table.

Table. Reactions of the Epoxides **3–8** with $\text{Et}_3\text{Al}/\text{HN}_3$ in Toluene

Entry	Epoxide	Temperature	Reaction Time	Azidohydrin	Yield
1	 3	-70°	15 min	 9	72%
2	 4	-70°	25 min	 10	68%
3	 5	r.t.	25 min	 11	90%
4	 6	r.t.	2.5 h	 12	83%
5	 7	r.t.	3 h	 13	68%
6	 8	-70°	15 min	 14	90%

A general procedure is described: the reagent is prepared *in situ* by reaction of equimolar quantities of Et_3Al with HN_3 in a non-polar solvent (*e.g.* toluene or benzene). The results in the Table indicate that the transformation of medium- and large-ring epoxides require higher temperatures and longer reaction times (*entries 4, 5*) than that of the epoxycyclohexanes **3** and **4**. A high regioselectivity was observed to yield tertiary azides (*entries 2, 3*), and *trans*-azidohydrins are the products. It is noteworthy that the reaction of the epoxide **4** with NaN_3 was less selective, leading to the expected secondary azide **15** as the major product, in addition to the azidohydrin **10** (ratio *ca.* 2:1) [25].



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⁴) The reagent described here was prepared *in situ*, and it was not determined whether it is a complex or Et_2AlN_3 . After this work was completed [21], a method for the cleavage of oxiranes with HN_3/DMF was published [22]. Furthermore, mild syntheses of *O*-protected azidohydrins by treatment of the epoxide with Me_3SiN_3 in the presence of a Ti or V catalyst [23], or Et_2AlF [24] were described.

Experimental Part

General. See [26], except as noted below. Column chromatography (CC): silica gel (SiO₂) 60 (Merck; 0.040–0.063 mm, 230–400 mesh ASTM). ¹H-NMR spectra: Varian EM-390 instrument (90 MHz) or Bruker WP-80/CW (80 MHz); CDCl₃ solns. or, exceptionally (as indicated below) CCl₄ solns.

1. *Et₃Al/HN₃ Reagent.* To dry toluene (8 ml) was added neat Et₃Al (1.36 ml, 10 mmol) at 0° under Ar with efficient stirring. A soln. of HN₃ [27] (dried over Na₂SO₄; 6.1 ml, 7.05% in C₆H₆, 10 mmol) was added slowly maintaining the temp. between –30 and –20°, and the mixture was then brought to r.t.

2. *Transformation of the Epoxides to the Azidohydrins.* 2.1. *General Procedure.* To a soln. of the epoxide⁵⁾ (5 mmol) in dry toluene (4 ml) under Ar at –70° was slowly added, by means of a cannula, the Et₃Al/HN₃ reagent. After completion of the reaction (TLC), Et₂O (100 ml) was added, and the mixture was slowly poured into a vigorously stirred soln. of conc. HCl (10 ml) in ice-water (300 ml). The Et₂O layer was worked up to yield the azidohydrin which was purified by CC (SiO₂; Et₂O/hexane gradients).

2.2. *14,15-Epoxy-14,15-dihydromilbemycin D (1; 500 mg, 0.88 mmol)* in toluene (5 ml) was treated with Et₃Al/HN₃ (17.4 ml) first at 0°, then at r.t. for 2 h. Workup by the addition of Et₂O (200 ml), a 1:1 mixture of Na₂SO₄·10 H₂O/Celite (6 g), and MeOH (1 ml), filtration, and CC (CH₂Cl₂/acetone 25:1) gave *14-azido-14,15-dihydro-15-hydroxymilbemycin D (2; 328 mg, 61%)*. M.p. 183° (MeOH). IR (CHCl₃): 3620w, 3560w, 3450w, 2950s, 2920s, 2860m, 2100s, 1700m, 1445m, 1430m, 1375m, 1335m, 1310m, 1290m, 1260m, 1180m, 1160m, 1145m, 1110m, 1070m (br.), 1030m, 1005s, 975m, 965m, 905w, 885w, 860m. ¹H-NMR (300 MHz, characteristic signals): 0.79, 0.82, 0.99, 1.01 (4d, *J* = 7, CH₃–C(12), CH₃–C(24), (CH₃)₂CH–C(25)); 1.22 (s, CH₃–C(14)); 1.86 (m, *w*_{1/2} = 6, CH₃–C(4)); 2.31 (d, *J* = 8, OH); 3.02 (dd, *J* = 9.5, 2.0, H–C(25)); 3.28–3.34 (m with *q* character, *J* = 2.4, H–C(2)); 3.76–3.88 (m, H–C(17)); 3.92–4.02 (m, H–C(15)); 3.97 (d, *J* = 6.0, H–C(6)); 4.26–4.36 (m, H–C(5)); 4.71 (AB, *J* = 14, split into *m*, *w*_{1/2} = 3, *δ*_A = 4.66, *δ*_B = 4.76, 2 H–C(27)); 5.08 (s, OH); 5.38 (m, *w*_{1/2} = 5, H–C(3)); 5.40–5.52 (m, H–C(19)); 5.65 (dd, *J* = 12.5, 9.5, H–C(11)); 5.84–6.00 (m, H–C(9), H–C(10)). ¹³C-NMR (75 MHz): 14.2, 17.3, 18.7, 19.8, 20.8, 23.6 (6q, 6 CH₃); 28.0, 35.7, 36.7, 37.1, 40.3, 43.7 (6t, C(13), C(16), C(18), C(20), C(22), C(23)); 28.3, 31.5, 34.8, 45.0 (4d, C(2), C(12), C(24), (CH₃)₂CH); 64.7 (d, C(15)); 65.9 (s, C(14)); 67.7, 67.7, 69.4, 78.3, 78.5 (5d, C(5), C(6), C(17), C(19), C(25)); 80.5 (s, C(7)); 97.4 (s, C(21)); 117.1, 120.0, 124.1, 142.9 (4d, C(3), C(9), C(10), C(11)); 137.9, 140.8 (2s, C(4), C(8)); 175.0 (s, C(1)). Anal. calc. for C₃₃H₄₉N₃O₈ (615.74): C 64.37, H 8.02, N 6.82; found: C 64.43, H 8.10, N 6.70.

2.3. *1,2-Epoxyoctahexane (3; 500 mg, 5.1 mmol)* in toluene (4 ml) was treated with Et₃Al/HN₃ (15 ml) at –70° for 15 min yielding *2-azidocyclohexanol [1] [2] (9; oil; 521 mg, 72%)*.

2.4. *1,2-Epoxy-1-methylcyclohexane (4; 50 mg, 0.45 mmol)* in toluene (0.5 ml) was treated with Et₃Al/HN₃ (1.5 ml) at –70° for 25 min yielding *(1RS,2RS)-2-azido-2-methylcyclohexanol (10; oil; 47 mg, 68%)*. IR: 3570w (br.), 3420w (br.), 2980w (sh), 2940s, 2860m, 2100s, 1460w (sh), 1445w, 1430w (sh), 1230w (br.), 1200w (br.), 1150w, 1105m, 1075m, 1050m (sh), 1040m (sh), 1025w (sh), 980w, 840w. ¹H-NMR (90 MHz): 1.60 (s, CH₃–C(2)); 1.00 2.20 (m, 9 H); 3.50–3.60 (m, H–C(1)).

2.5. *1-Oxaspiro[2.5]octane (5 [28]; 50 mg, 0.45 mmol)* in toluene (0.4 ml) was treated with Et₃Al/HN₃ (1.5 ml) at r.t. for 25 min affording *(1'-azidocyclohexyl)methanol (11; oil; 62 mg, 90%)*. IR: 3600w (sh), 3580w, 3440w (br.), 3300w (br.), 2920s, 2840m, 2100s, 1440m, 1375w, 1355w, 1300m (sh), 1290m, 1270m, 1250m, 1215w, 1175w, 1155w, 1120m, 1090w, 965w, 910w, 870w. ¹H-NMR (90 MHz, CCl₄): 1.00 2.20 (m, 11 H); 3.20–3.80 (m, CH₂OH).

2.6. *1,2-Epoxyoctadecane (6; 270 mg, 2.14 mmol)* in toluene (2 ml) was treated with Et₃Al/HN₃ (7 ml) at r.t. for 2.5 h yielding *(1RS,2RS)-2-azidocyclooctanol (12; oil; 300 mg, 83%)*. IR: 3610w (sh), 3580w, 3450w (br.), 3320w (br.), 2920s, 2850m, 2100s, 1600w (br.), 1470w (sh), 1460w, 1440w, 1430w (sh), 1380w, 1350w (br.), 1310w (sh), 1290w (sh), 1270w (sh), 1250m, 1210w (sh), 1140w, 1110w, 1080w, 1050w, 1000w, 975w, 905w. ¹H-NMR (80 MHz): 1.30–2.15 (m, 12 H); 2.37 (m, *w*_{1/2} = ca. 4, OH); 3.35–3.85 (m, H–C(1), H–C(2)).

2.7. *1,2-Epoxydodecane (7; 140 mg, 0.77 mmol)* in toluene (2 ml) was treated with Et₃Al/HN₃ (5 ml) at r.t. for 3 h yielding *(1RS,2RS)-2-azidocyclododecanol (13; oil; 118 mg, 68%)*. IR: 3580w, 3400w, 2925s, 2860s, 2100s, 1460m, 1440m, 1390w (sh), 1370m, 1325m, 1300w, 1270m (sh), 1265m (sh), 1250m, 1190w, 1150w, 1140w, 1120w, 1090w, 1070w, 1040m, 1030m, 1010w, 950w, 910w, 870w. ¹H-NMR (80 MHz): 1.12–1.80 (m, 21 H); 3.25–3.70 (m, H–C(2)); 3.75–4.12 (m, H–C(1)).

2.8. *Epoxystyrene (8; 600 mg, 5.0 mmol)* in toluene (4 ml) was treated with Et₃Al/HN₃ (15 ml) at –70° for 15 min yielding *2-azido-2-phenylethanol (14; oil; 732 mg, 90%)*. IR: 3625w (sh), 3600w, 3450w (br.), 3320w (br.),

⁵⁾ The epoxides **1**, **3**, **4**, and **6–8** were prepared by reaction of the corresponding olefins with *m*-chloroperbenzoic acid.

3060w, 3020w, 2960w, 2920w, 2870w, 2100s, 1600w (br.), 1490w, 1450w, 1380w, 1370w, 1340w, 1300w, 1270w, 1240m, 1205w, 1170w, 1080w (sh), 1060w (sh), 1045m, 1030w (sh), 1000w (sh), 905m, 870w. ¹H-NMR (80 MHz): 2.00 (t, *J* = 6, OH); 3.73 (dd, *J* = 7, 6, 2 H–C(1)); 4.74 (t, *J* = 7, H–C(2)); 7.35–7.60 (m, C₆H₅).

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