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

by **Hari Babu Mereyala**[1]) and **Bruno Frei**[2])*

Laboratorium für Organische Chemie der Eidgenössischen Technischen Hochschule, Universitätstrasse 16, ETH-Zentrum, CH-8092 Zürich

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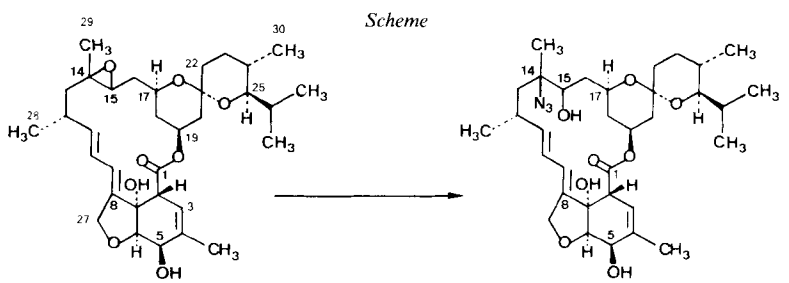
A novel, mild, and highly stereoselective transformation of epoxides to azidohydrins by treatment with Et_3Al/HN_3 in toluene is described. As an example for the versatility of the reaction, a polyfunctional compound, 14,15-epoxy-14,15-dihydromilbemycin D (**1**), was transformed to 14-azido-14,15-dihydro-15-hydroxymilbemycin 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

Scheme



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[1]) New address: National Chemical Laboratory, Pune-411008, India.

[2]) New address: *Ciba-Geigy Ltd.*, Agricultural Division, CH-4002 Basle.

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

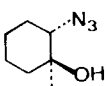
(Scheme). Since reaction of the polyfunctional epoxide **1** with NaN_3 led to decomposition of the starting material, and no azidohydrin could be detected, it was necessary to develop a new, milder process. Several years ago, *Nagata et al.* had introduced Et_3Al/HCN and Et_2AlCN as reagents for the smooth cleavage of epoxides to give β-cyanohydrins [17] [18]. Therefore, we selected the corresponding azide reagents Et_3Al/HN_3 or Et_2AlN_3 [19] [20] as the reagents of choice[4]).

2. Results and Discussion. – Indeed, the reaction of the epoxide **1** with Et_3Al/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 Et_3Al/HN_3 as a mild and efficient reagent for the transformation epoxide→azidohydrin is further illustrated by 6 representative examples given in the *Table*.

Table. *Reactions of the Epoxides* **3**–**8** *with* Et_3Al/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 (SiO_2) *60* (*Merck;* 0.040–0.063 mm, 230–400 mesh ASTM). ^{1}H-NMR spectra: *Varian EM-390* instrument (90 MHz) or *Bruker WP-80/CW* (80 MHz); $CDCl_3$ solns. or, exceptionally (as indicated below) CCl_4 solns.

1. *Et_3Al/HN_3 Reagent.* To dry toluene (8 ml) was added neat Et_3Al (1.36 ml, 10 mmol) at 0° under Ar with efficient stirring. A soln. of HN_3 [27] (dried over Na_2SO_4; 6.1 ml, 7.05% in C_6H_6, 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 epoxide[5]) (5 mmol) in dry toluene (4 ml) under Ar at −70° was slowly added, by means of a cannula, the Et_3Al/HN_3 reagent. After completion of the reaction (TLC), Et_2O (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 Et_2O layer was worked up to yield the azidohydrin which was purified by CC (SiO_2; Et_2O/hexane gradients).

2.2. *14,15-Epoxy-14,15-dihydromilbemycin D* (**1**; 500 mg, 0.88 mmol) in toluene (5 ml) was treated with Et_3Al/HN_3 (17.4 ml) first at 0°, then at r.t. for 2 h. Workup by the addition of Et_2O (200 ml), a 1:1 mixture of $Na_2SO_4 \cdot 10\ H_2O$/*Celite* (6 g), and MeOH (1 ml), filtration, and CC (CH_2Cl_2/acetone 25:1) gave *14-azido-14,15-dihydro-15-hydroxymilbemycin D* (**2**; 328 mg, 61%). M.p. 183° (MeOH). IR ($CHCl_3$): 3620*w*, 3560*w*, 3450*w*, 2950*s*, 2920*s*, 2860*m*, 2100*s*, 1700*m*, 1445*m*, 1430*m*, 1375*m*, 1335*m*, 1310*m*, 1290*m*, 1260*m*, 1180*m*, 1160*m*, 1145*m*, 1110*m*, 1070*m* (br.), 1030*m*, 1005*s*, 975*m*, 965*m*, 905*w*, 885*w*, 860*m*. ^{1}H-NMR (300 MHz, characteristic signals): 0.79, 0.82, 0.99, 1.01 (4*d*, J = 7, CH_3–C(12), CH_3–C(24), $(CH_3)_2$CH–C(25)); 1.22 (*s*, CH_3–C(14)); 1.86 (*m*, $w_{1/2}$ = 6, CH_3–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)). ^{13}C-NMR (75 MHz): 14.2, 17.3, 18.7, 19.8, 20.8, 23.6 (6*q*, 6 CH_3); 28.0, 35.7, 36.7, 37.1, 40.3, 43.7 (6*t*, C(13), C(16), C(18), C(20), C(22), C(23)); 28.3, 31.5, 34.8, 45.0 (4*d*, C(2), C(12), C(24), $(CH_3)_2CH$); 64.7 (*d*, C(15)); 65.9 (*s*, C(14)); 67.7, 67.7, 69.4, 78.3, 78.5 (5*d*, 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 (4*d*, C(3), C(9), C(10), C(11)); 137.9, 140.8 (2*s*, C(4), C(8)); 175.0 (*s*, C(1)). Anal. calc. for $C_{33}H_{49}N_3O_8$ (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-Epoxycyclohexane* (**3**; 500 mg, 5.1 mmol) in toluene (4 ml) was treated with Et_3Al/HN_3 (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 Et_3Al/HN_3 (1.5 ml) at −70° for 25 min yielding *(1RS,2RS)-2-azido-2-methylcyclohexanol* (**10**; oil; 47 mg, 68%). IR: 3570*w* (br.), 3420*w* (br.), 2980*w* (sh), 2940*s*, 2860*m*, 2100*s*, 1460*w* (sh), 1445*w*, 1430*w* (sh), 1230*w* (br.), 1200*w* (br.), 1150*w*, 1105*m*, 1075*m*, 1050*m* (sh), 1040*m* (sh), 1025*w* (sh), 980*w*, 840*w*. ^{1}H-NMR (90 MHz): 1.60 (*s*, CH_3–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 Et_3Al/HN_3 (1.5 ml) at r.t. for 25 min affording *(1'-azidocyclohexyl)methanol* (**11**; oil; 62 mg, 90%). IR: 3600*w* (sh), 3580*w*, 3440*w* (br.), 3300*w* (br.), 2920*s*, 2840*m*, 2100*s*, 1440*m*, 1375*w*, 1355*w*, 1300*m* (sh), 1290*m*, 1270*m*, 1250*m*, 1215*w*, 1175*w*, 1155*w*, 1120*m*, 1090*w*, 965*w*, 910*w*, 870*w*. ^{1}H-NMR (90 MHz, CCl_4): 1.00–2.20 (*m*, 11 H); 3.20–3.80 (*m*, CH_2OH).

2.6. *1,2-Epoxycyclooctane* (**6**; 270 mg, 2.14 mmol) in toluene (2 ml) was treated with Et_3Al/HN_3 (7 ml) at r.t. for 2.5 h yielding *(1RS,2RS)-2-azidocyclooctanol* (**12**; oil; 300 mg, 83%). IR: 3610*w* (sh), 3580*w*, 3450*w* (br.), 3320*w* (br.), 2920*s*, 2850*m*, 2100*s*, 1600*w* (br.), 1470*w* (sh), 1460*w*, 1440*w*, 1430*w* (sh), 1380*w*, 1350*w* (br.), 1310*w* (sh), 1290*w* (sh), 1270*w* (sh), 1250*m*, 1210*w* (sh), 1140*w*, 1110*w*, 1080*w*, 1050*w*, 1000*w*, 975*w*, 905*w*. ^{1}H-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-Epoxycyclododecane* (**7**; 140 mg, 0.77 mmol) in toluene (2 ml) was treated with Et_3Al/HN_3 (5 ml) at r.t. for 3 h yielding *(1RS,2RS)-2-azidocyclododecanol* (**13**; oil; 118 mg, 68%). IR: 3580*w*, 3400*w*, 2925*s*, 2860*s*, 2100*s*, 1460*m*, 1440*m*, 1390*w* (sh), 1370*m*, 1325*m*, 1300*w*, 1270*m* (sh), 1265*m* (sh), 1250*m*, 1190*w*, 1150*w*, 1140*w*, 1120*w*, 1090*w*, 1070*w*, 1040*m*, 1030*m*, 1010*w*, 950*w*, 910*w*, 870*w*. ^{1}H-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 Et_3Al/HN_3 (15 ml) at −70° for 15 min yielding *2-azido-2-phenylethanol* (**14**; oil; 732 mg, 90%). IR: 3625*w* (sh), 3600*w*, 3450*w* (br.), 3320*w* (br.),

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

3060*w*, 3020*w*, 2960*w*, 2920*w*, 2870*w*, 2100*s*, 1600*w* (br.), 1490*w*, 1450*w*, 1380*w*, 1370*w*, 1340*w*, 1300*w*, 1270*w*, 1240*m*, 1205*w*, 1170*w*, 1080*w* (sh), 1060*w* (sh), 1045*m*, 1030*w* (sh), 1000*w* (sh), 905*m*, 870*w*. ^{1}H-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*, C_6H_5).

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