REARRANGEMENT OF A SUBSTITUTED EPOXYTETRAHYDROPYRAN TO THE CORRESPONDING TETRAHYDROFURANCARBALDEHYDE

Urs Séquin[*] and Andreas Schneider[‡]

Institut für Organische Chemie der Universität, St. Johanns-Ring 19, CH-4056 Basel, Switzerland

Abstract - The aluminum chloride catalyzed reaction of a substituted 3,4-epoxytetrahydropyran with N,N-dimethyl-trimethylsilylamine did not lead to the expected silylated β-aminoalcohol but rather to a tetrahydrofurancarbaldehyde.

The acid catalyzed rearrangements of epoxycyclohexane derivatives to either cyclohexanones or with ring contraction to cyclopentanecarbaldehydes are well known.[2 - 5] We now wish to report on a similar ring contraction in the epoxy-tetrahydropyran series, which to our knowledge has not been described hitherto.
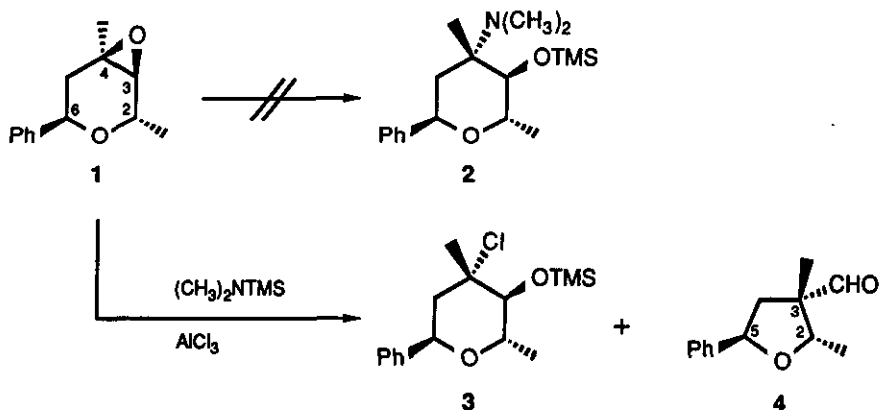
In the course of our synthetic efforts towards model compounds resembling ring F of the pluramycin type antibiotics[6] we wanted to open the epoxide 1[7] with N,N-dimethyl-trimethylsilylamine in order to introduce the dimethylamino func-

---

[‡] Taken in part from the dissertation of A. S..[1]

tion at C(4). The procedure for opening oxiran rings by means of the corresponding diethyl derivative of trimethylsilylamine had recently been described by Taddei and coworkers.[8] The reaction involves catalysis with anhydrous aluminum chloride and proceeds usually in 2 to 20 h. With mono-substituted oxiranes this reaction proved to be rather regioselective; poly-substituted starting material led, however, to mixtures of regioisomers. We tested the reaction with 1,2-epoxy-1-methylcylohexane (5), a trisubstituted substrate resembling to a certain extent our epoxide 1. The reaction was followed by GC and proved to be much slower than stated by Taddei and coworkers.
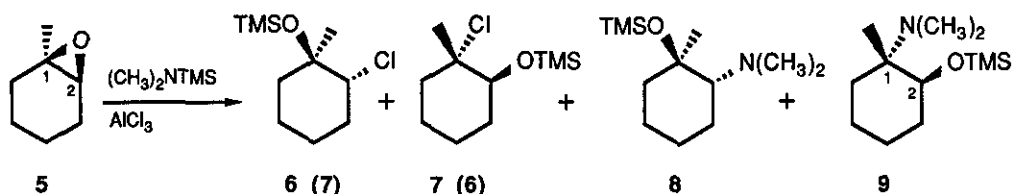
After 8 days at room temperature, four products (6 - 9) were obtained in yields of 11, 10, 15, and 52%, respectively. Preliminary information about their constitutions came from a GC/MS run. The two minor products 6 and 7 (the constitutions shown in the scheme may be interchanged) were apparently trimethylsilylated chlorohydrins, whereas 8 and 9 contained both the dimethylamino and the trimethylsilyloxy groups. They were therefore the expected regioisomers. These findings were corroborated for the main product of the reaction, 9, by its ^{1}H- and ^{13}C-nmr spectra. Furthermore, the ^{13}C-nmr resonances of C(1) and C(2) (43.3 and 71.7 ppm, respectively) indicated that 9 was indeed the desired isomer, in which the dimethylamino group was at the carbon atom bearing the methyl group.

After this promising result with the model compound 5, the epoxide 1 was treated in the same way with N,N-dimethyl-trimethylsilylamine. However, the desired silylated β-aminoalcohol 2 was not formed. After 10 days at room temperature 13% of the silylated chlorohydrin 3 were obtained according to GC together with 10% of the aldehyde 4; 50% of the starting material was recovered unchanged. The aldehyde 4 was obtained as the main product (74%, GC) when the reaction was carried out at 41°C for 5 days. The constitutions of 4 and 3 were determined mainly from their spectral data.

The mass spectrum of $\underline{4}$, which had the molecular ion at m/z 204, indicated that $\underline{4}$ was an isomer of the starting material $\underline{1}$. From the prominent singlet at 9.79 ppm in the proton nmr spectrum the conclusion was drawn that $\underline{4}$ was an aldehyde. Additional resonances were observed for a methyl group (singlet), for a CH_3-CH- fragment and for a CH_2-CH- fragment; they all were reminiscent of similar groups in the starting material $\underline{1}$ and thus led to the constitution shown in formula $\underline{4}$. The ^{13}C-nmr spectrum was fully consistent with these findings.

The configurations at C(2) and C(5) of the aldehyde $\underline{4}$ were assumed to be the same as in the starting material. NOE experiments were carried out to corroborate this and for the determination of the configuration at C(3). Irradiation of the aldehyde proton gave an NOE for H-C(5) and both protons at C(4) but not for H-C(2). On the other hand, when H-C(5) was irradiated, an NOE was detected for the aldehyde proton and for the low-field proton at C(4). When in a third experiment H-C(2) was saturated, signal enhancements were observed for the high-field proton at C(4), for the two methyl groups but not for the aldehyde proton. These experiments clearly show that the relative configurations in $\underline{4}$ are such that the two methyl groups are trans to each other and that in addition the aldehyde function and the phenyl group are also trans to each other.

The mass spectrum of $\underline{3}$ had the signal for M^+ at m/z 312/314 indicating that one atom of chlorine was in the molecule and that formally $\underline{3}$ was derived from $\underline{1}$ by the addition of trimethylchlorosilane. The presence of the TMS group was further indicated by a signal at m/z 73. The proton NMR spectrum of $\underline{3}$ showed similar features as did the corresponding spectrum of the starting epoxide $\underline{1}$: a singlet resonance for a methyl group, the resonances for a $CH_3-CH-CH-$ fragment as well as for a CH_2-CH- group and the phenyl resonance. The chemical shift of H-C(3) (ca. 3.8 ppm) indicated that the oxygen function was probably at C(3) and the chlorine atom at C(4). The proof for this was obtained when $\underline{3}$ was treated with sodium azide and $ZnCl_2$ in an attempt to substitute the tertiary chlorine atom by a nitrogen function.[9] The corresponding azide was not formed. Instead – apparently as the result of a $ZnCl_2$ mediated abstraction of the chlorine atom and subsequent ring contraction – the already known aldehyde $\underline{4}$ was obtained.

This aldehyde would not have been formed, had the chlorine atom been attached to C(3) of **3**; the methyl ketone **10** would rather have been obtained.

10
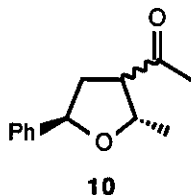
We assume that due to the polysubstituted nature of the epoxide **1** the expected attack of the N,N-dimethyl-trimethylsilylamine which would have given the desired product **2** did not take place. During the very long reaction time the small amount of aluminum chloride added was then able to mediate the ring contraction reaction to the aldehyde **4**. The formation of the silylated chlorohydrin **3**, on the other hand, may have been caused by traces of HCl present in the aluminum chloride.[8]

EXPERIMENTAL

Reaction of 1,2-Epoxy-1-methylcyclohexane (5) with N,N-Dimethyl-trimethyl-silylamine. - (1RS,2SR)-1,2-Epoxy-1-methylcyclohexane (**5**, 225 mg, 2 mmol, prepared by epoxidation of 1-methylcyclohexene with m-chloroperbenzoic acid) and N,N-dimethyl-trimethylsilylamine (235 mg, 2 mmol, Fluka) were dissolved in 3 ml of dichloromethane at 0°C. The solution was stirred under Ar and 27 mg (0.2 mmol) of $AlCl_3$ were added. The ice bath was removed and the mixture allowed to warm up to room temperature. After 8 days the solvent was evaporated and the residue was taken up in hexane. The yellow precipitate that formed was removed by filtration. Evaporation of the solvent from this filtrate gave 255 mg of crude product, which according to a GC/MS analysis (Hewlett Packard MSD, fused silica, methylphenylsilicone, 5 min at 100°C then temperature increase of 25°C/min) consisted mainly of four products: **6** (11%, ret. time 7.80 min), **7** (10%, 8.11 min), **8** (15%, 8.77 min), **9** (52%, 8.84 min).

MS-Data: - **6**: 207 (M^++2-CH_3, 9.5); 205 (M^+-CH_3, 28); 185 (M^+-Cl, 4.2); 137 (14); 130 (13); 129 (100); 95 (74); 93 (24); 75 (26); 73 (71); 67 (16); 55 (17).

- $\underline{7}$: 222 (M^++2, 2.2); 220 (M^+, 5.3); 207 (M^++2-CH_3, 3.0); 205 (M^+-CH_3, 7.1); 185 (M^+-Cl, 22); 144 (14); 143 (100); 130 (11); 115 (10); 95 (33); 93 (16); 75 (24); 73 (57); 67 (8.1); 55 (9.0). - $\underline{8}$: 229 (M^+, 6.2); 214 (M^+-CH_3, 5.8); 156 (M^+-Si(CH_3)$_3$, 3.8); 99 (9.9); 98 (100); 85 (84); 73 (19); 72 (33); 70 (19); 56 (12). - $\underline{9}$: 229 (M^+, 13); 214 (M^+-CH_3, 6.9); 156 (M^+-Si(CH_3)$_3$, 4.4); 102 (16); 97 (10); 84 (100); 73 (19); 71 (33); 58 (51).

By chromatography of the crude product mixture on silica gel with diethyl ether, 104 mg of (1RS,2RS)-1,N,N-trimethyl-2-(trimethylsilyloxy)cyclohexylamine ($\underline{9}$) were obtained as a colorless oil. ^{1}H-nmr (90 MHz, CDCl$_3$): 3.08 (m, 1H, H-C(2)); 2.41 (s, 6H, (CH$_3$)$_2$-N); 2.3 - 0.8 (m, 8H, H-C(3,4,5,6)); 1.29 (s, 3H, CH$_3$-C(1)); 0.14 (s, 9H, (CH$_3$)$_3$-Si). - ^{13}C-nmr (22.63 MHz, CDCl$_3$): 71.7 (d, C(2)); 44.7 (q, 2C, (CH$_3$)$_2$-N); 43.3 (s, C(1)); 29.8, 26.6, 26.2, 23.9 (4xt, C(3), C(4), C(5), C(6)); 21.9 (q, CH$_3$-C(1)); 3.1 (q, 3C, (CH$_3$)$_3$-Si).

Reaction of 3,4-Epoxy-2,4-dimethyl-6-phenyltetrahydropyran ($\underline{1}$) with N,N-Dimethyl-trimethylsilylamine.

- (2RS,3RS,4SR,6SR)-3,4-Epoxy-2,4-dimethyl-6-phenyltetrahydropyran ($\underline{1}$,[7] 150 mg, 0.73 mmol) was dissolved with exclusion of water in 10 ml of dichloromethane at 0°C. N,N-Dimethyl-trimethylsilylamine (120 μl, 90 mg, 0.76 mmol) and aluminum chloride (15 mg, 0.11 mmol) were added, and the mixture was stirred under reflux for 5 days. The products formed were according to a GC analysis $\underline{3}$ (8.2%), $\underline{4}$ (73.9%), and starting material $\underline{1}$ (6.8%). After chromatography of the crude product mixture on a silica gel column with dichloromethane/ether, pure samples of (2RS,3RS,4RS,6SR)-4-chloro-2,4-dimethyl-6-phenyl-3-(trimethylsilyloxy)tetrahydropyran ($\underline{3}$) and of (2RS,3RS,5SR)-2,3-dimethyl-5-phenyltetrahydrofuran-3-carbaldehyde ($\underline{4}$) were obtained as slightly yellowish oils.

Data of 3: ^{1}H-nmr (90MHz, CDCl$_3$): 7.35 (m, 5H, phenyl-H); 5.08 (t, J = 5.5, H-C(6)); 3.90 - 3.67 (m, 2H, H-C(2) and H-C(3)); 2.75 (dd, J = 13.5 and 5.5, 1H, H-C(5)); 2.48 (dd, J = 13.5 and 5.5, 1H, H-C(5)); 1.46 (d, J = 6, 3H, CH$_3$-C(2)); 1.34 (s, 3H, CH$_3$-C(4)). - MS (GC/MS, Hewlett Packard MSD, EI): 314 (M^++2, 0.5); 312 (M^+, 1.6); 166 (26); 164 (74); 151 (11); 149 (30); 144 (13); 143 (100); 131 (23); 128 (11); 120 (13); 105 (13); 93 (27); 91 (17); 77 (phenyl$^+$, 12); 75 (17); 73 ((CH$_3$)$_3$Si$^+$, 62).

<u>Data of 4:</u> [1]H-nmr (90 MHz, CDCl$_3$): 9.79 (s, 1H, H-CO); 7.32 (m, 5H, phenyl-H); 5.28 (dd, J = 7.4 and 8.5, 1H, H-C(5)); 4.08 (q, J = 6.6, 1H, H-C(2)); 2.81 (dd, J = 13 and 7.4, 1H, H-C(4) trans to the phenyl group); 1.84 (dd, J ≈ 13 and 8.5, 1H, H-C(4) cis to the phenyl group); 1.33 (d, J = 6.6, 3H, CH$_3$-C(2)); 1.18 (s, 3H, CH$_3$-C(3)). - ^{13}C-nmr (22.63 MHz, CDCl$_3$, assignments were confirmed by means of a 2D C-H-correlated spectrum): 203.9 (d, C=O); 143.8 (s, phenyl i-C); 128.5 (d, 2C, phenyl m-C); 127.3 (d, phenyl p-C); 125.2 (d, 2C, phenyl o-C); 83.2 (d, C(2)); 78.6 (d, C(5)); 56.9 (narrow d, C(3)); 43.9 (t, C(4)); 17.3 (q, CH$_3$-C(3)); 15.0 (q, CH$_3$-C(2)). - MS (GC/MS, Hewlett Packard MSD, EI): 204 (M[+], 1.5); 189 (M[+]-CH$_3$, 0.7); 176 (M[+]-CO, 3.5); 159 (10); 145 (19); 131 (18); 121 (13); 120 (100); 105 (41); 91 (23); 85 (10); 77 (phenyl[+], 17); 69 (12).

REFERENCES

1. A. Schneider, Dissertation, Basel 1986.

2. H. O. House and R. L. Wasson, <u>J. Am. Chem. Soc.</u>, 1957, <u>79</u>, 1488.

3. S. M. Naqvi, J. P. Horwitz, and R. Filler, <u>J. Am. Chem. Soc.</u>, 1957, <u>79</u>, 6283.

4. B. Rickborn and R. M. Gerkin, <u>J. Am. Chem. Soc.</u>, 1971, <u>93</u>, 1693.

5. R. Guyon and P. Villa, <u>Bull. Soc. Chim. Fr.</u>, 1975, 2593.

6. U. Séquin, <u>Prog. Chem. Org. Nat. Prod.</u>, 1986, <u>50</u>, 57.

7. A. Schneider and U. Séquin, <u>Tetrahedron</u>, 1985, <u>41</u>, 949.

8. A. Papini, A. Ricci, M. Taddei, G. Seconi, and P. Dembech, <u>J. Chem. Soc., Perkin Trans. 1</u>, 1984, 2261.

9. J. A. Miller, <u>Tetrahedron Lett.</u>, 1975, 2959.