Pergamon

Tetrahedron Letters 40 (1999) 2921–2924

TETRAHEDRON LETTERS

Bisepoxides as Biselectrophiles in the Silicon-Induced Domino Synthesis of Highly Functionalized Carbocycles

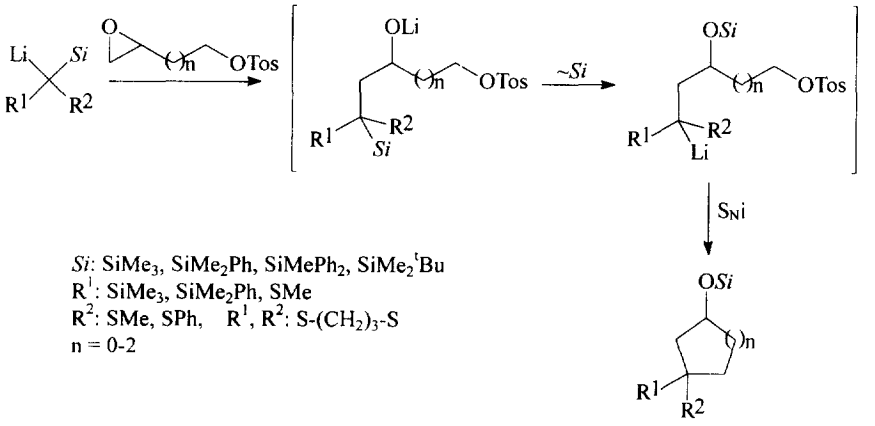
Nico Bräuer, Sylvia Dreeßen, Ernst Schaumann*

Institut für Organische Chemie, Technische Universität Clausthal, Leibnizstraße 6, D-38678 Clausthal-Zellerfeld, Germany

Received 2 February 1999; accepted 12 February 1999

Abstract: The reaction of silylated thioacetals **2a, b** with different bisepoxides **1, 4, 5** is investigated. The silicon-induced domino reaction opens a short route from D-mannitol to the highly functionalized carbocycles **7-10**. Using this cascade, 4-*epi*-validatol **(12)** is synthesized. © 1999 Elsevier Science Ltd. All rights reserved.

Recently, we have reported the one-pot synthesis of 1,3-difunctionalized cyclopentanes, -hexanes and -heptanes by a silicon-induced domino reaction.[1] This reaction proceeds via a 1,4-shift of the silyl group from carbon to oxygen[2] after nucleophilic attack of a silyl-substituted sulfur-stabilized carbanion on an epoxyalkyl tosylate, followed by intramolecular displacement of the tosylate group (Scheme 1).

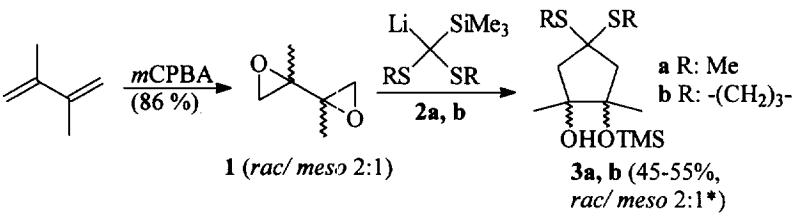


Scheme 1

Though a competition between the oxirane and the tosylate units as electrophilic centers might be anticipated, the nucleophilic attack of the carbanions on the epoxyalkyl tosylates occurs chemo- and regioselectively on the unsubstituted carbon of the epoxide; an analogous selectivity was shown by chlorohydrines.[3] Thus, the reaction leads to carbocycles as only products. However, the use of bisepoxides with two nearly identical oxiranes as biselectrophiles would lead to a mixture of cyclization products due to comparable reactivity towards carbanions. Only *meso* or C_2-symmetrical bisepoxides should prevent formation of different regioisomers.

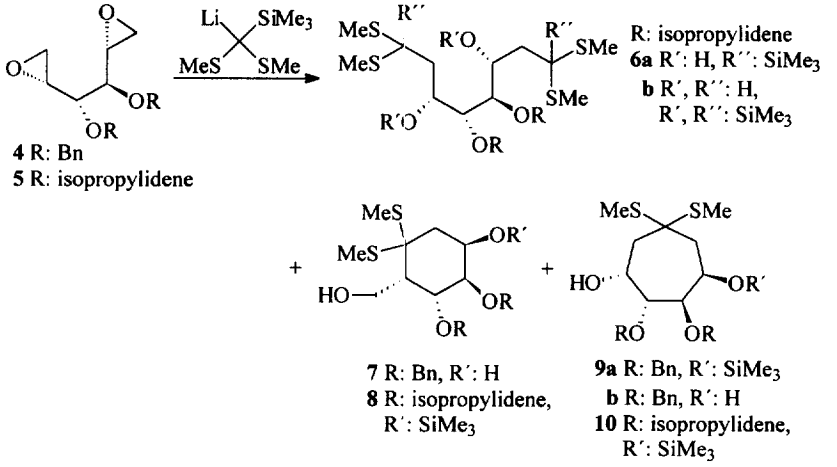
To investigate the general suitability of bisepoxides in the silicon-induced domino reaction 2,3-dimethyl-1,2-3,4-diepoxy butane **(1)**, obtained from the corresponding butadiene by epoxidation,[4] was chosen as a simple biselectrophile. Reaction with the lithiated silylthioacetals **2a, b** yielded the cyclopentanediols **3a, b** (Scheme 2).[5]

PII: S0040-4039(99)00386-X



Scheme 2

The carbohydrate-based C_2-symmetrical bisepoxides **4, 5**[6a, b] are other interesting biselectrophiles for this domino reaction. In analogy to the cyclization of **4, 5** with amines to give piperidines and azepanes,[6b,c] we expected two different cyclization products. In fact, reaction of **4, 5** with C_1 bisanion equivalent **2a** yielded the cyclohexanes **7, 8** as well as cycloheptanes **9, 10** along with acyclic by-products **6** (Scheme 3, Table 1).[7]



Scheme 3

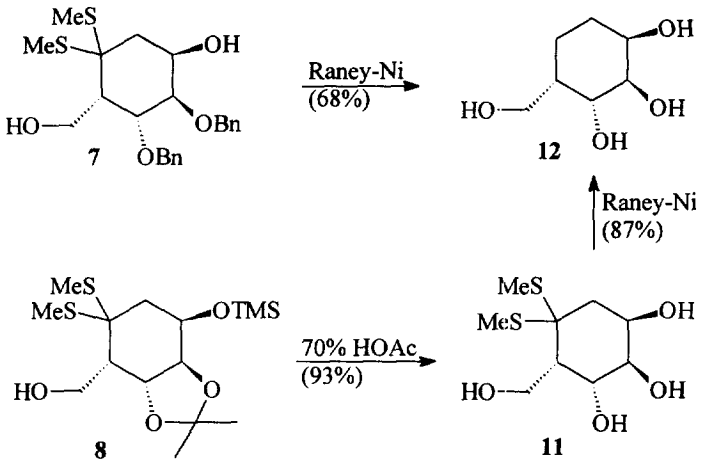
Table 1. Yields of Cyclization Products and Reaction Conditions

Entry	Bisepoxide	Reaction Conditions	Cyclohexane	Cycloheptane	acyclic Product
1	**4**	-40°C- -20°C, 1 day	**7** (23 %)	**9a** (29 %) **9b** (11 %)	---
2	**4**	-80°C- -20°C, 1 day	**7** (29 %)	**9a** (20 %) **9b** (10%)	---
3	**4**	-80°C, 1 day	**7** (30 %)	**9a** (16 %)	---
4	**5**	-80°C- -20°C, 1 day	**8** (21 %)	**10** (10 %)	**6a** (11 %) **6b** (3 %)
5	**5**	-80°C, 1 day	**8** (19 %)	**10** (16 %)	**6a** (12 %)

Cyclohexanes **7, 8** are results of a 6-exo-*tet*-cyclization while cycloheptanes **9, 10** arise from an equally favored[8] 7-endo-*tet* ring closure. Unfortunately, the selectivity with regard to 6-exo-*tet*-/ 6-endo-*tet*-cyclization is not very pronounced. It varies between nearly 2:1 (Table 1, entries 3 and 4) and 0.6:1 (Table 1, entry 1). There is some effect of the reaction temperature on the ratio of carbocycles, but in contrast to similar problems

known in the literature,[6b-d,9] variation of the protective groups failed to give a more chemoselective reaction. Thioacetal **2b** as bisanion equivalent turned out to be less reactive than **2a** and gave no satisfactory results.

The silicon-induced domino reaction opens a very short way of converting sugars into highly functionalized carbocycles. Thus, cyclohexanes **7, 8** are epimeric at C-4 to validatol. In fact, following simple deprotection protocols cyclohexanes **7, 8** were converted into 4-*epi*-validatol **(12)** in one or two steps, respectively (Scheme 4).[9,10]



Scheme 4

In spite of the lack of selectively in the ring closure step, this approach represents a short and efficient route to 4-*epi*-validatol **(12)** in only 7 steps and up to 6 % overall yield.

Acknowledgements

Support of this work by the Fonds der Chemischen Industrie, Frankfurt, and by the Deutsche Forschungsgemeinschaft (Scha 231/9-1) is gratefully acknowledged.

References and Notes

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4. Bensel, N.; Klinkmüller, K.-D.; Marschall, H.; Weyerstahl, P.; *Liebigs Ann. Chem.* **1977,** 1572-1584.
5. *General Procedure for Cyclization Reactions*: A solution of the carbanion in dry THF (4 ml/mmol), prepared by deprotonation of the thioacetal with one equiv. of n-BuLi (1.6 M in hexane), was added dropwise at -80°C to a stirred solution of the bisepoxide in dry THF (4 ml/mmol). After completion of the reaction the mixture was hydrolyzed with diethyl ether/ saturated NH_4Cl solution (1:1), the aqueous phase

was extracted twice with diethyl ether, the combined organic layers were dried, solvents evaporated and the crude products were purified by column chromatography.

3a: ^{1}H NMR ($CDCl_3$, 200 MHz): 0.10, 0.14* (each s, 9H, $SiMe_3$); 1.14, 1.16*, 1.29, 1.33 (each s, 3H, CH_3); 2.00, 2.01*, 2.02, 2.05* (each s, 3H, SMe); 2.28, 2.43* (each m, 4H, CH_2); 2.93, 3.01* (each s, 1H, OH). ^{13}C NMR ($CDCl_3$, 50 MHz): 2.5, 2.6* (+, $SiMe_3$); 13.3*, 13.4*, 13.5, 13.7 (+, CH_3); 19.2, 20.3, 23.2*, 25.6* (+, SMe); 51.3, 51.6, 52.9*, 53.5* (-, CH_2); 58.1, 59.5* [o, $\underline{C}(SMe)_2$]; 80.6, 83.3, 83.4*, 85.1* [o, $\underline{C}$(Me)OH, $\underline{C}$(Me)O$SiMe_3$].

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7. **7**: ^{1}H NMR ($CDCl_3$, 200 MHz): 2.07, 2.10 (each s, 3H, SMe); 2.02- 2.22 (m, 2H, CH_2); 2.27- 2.46 (m, 1H, CH); 3.70- 3.90 (m, 3H, $C\underline{H}_2OH$, $C\underline{H}OBn$); 4.10- 4.31 (m, 2H, $C\underline{H}OBn$, $C\underline{H}OH$); 4.51- 4.76 (m, 4H, $OC\underline{H}_2Ph$); 7.22- 7.42 (m, 10H, Ph). ^{13}C NMR ($CDCl_3$, 50 MHz): 11.5, 12.7 (+, SMe); 36.4 (-, CH_2); 46.3 (+, CH), 59.1 [o, $\underline{C}(SMe)_2$]; 60.5 (-, CH_2OH); 66.6 (+, CHOH); 72.6, 73.4 (-, $O\underline{C}H_2Ph$); 76.1, 77.4 (+, $\underline{C}HOBn$); 127.7, 127.8, 127.9, 128.0, 128.4, 128.5 (+, Ph); 137.9, 138.0 (o, Ph). $[\alpha]_D^{24.5}$: +3.0° (c = 1, $CHCl_3$).

8: ^{1}H NMR ($CDCl_3$, 200 MHz): 0.09 (s, 9H, $SiMe_3$); 1.38, 1.41 (each s, 3H, CMe_2); 1.92 (dd, J = 3.2, 15.6, CH_2); 2.02, 2.04 (each s, 3H, SMe); 2.10 (ddd, J = 1.2, 3.0, 15.6, 1H, CH_2); 2.53- 2.64 (m, 1H, CH); 3.27 (dd, J = 4.0, 8.4, 1H, OH); 3.76 (dd, J = 2.8, 10.4, 1H, CHOR); 3.87- 3.97 (m, 2H, $C\underline{H}_2OH$); 4.25 (qua, J = 3.0, 1H, $C\underline{H}OH$); 4.80 (dd, J = 4.8, 10.4, 1H, CHOR). ^{13}C NMR ($CDCl_3$, 50 MHz): 0.1 (+, $SiMe_3$); 11.3, 12.8 (+, SMe); 26.5, 27.0 (+, $C\underline{M}e_2$); 40.4 (-, CH_2); 45.7 (+, CH); 60.5 (-, CH_2OH); 60.6 [o, $\underline{C}(SMe_2)$]; 66.6 (+, CHOH); 73.7, 75.7 (+, CHOR); 109.6 (o, $\underline{C}Me_2$).

9b: ^{1}H NMR ($CDCl_3$, 200 MHz): 1.67 (d, J = 15.2, 2H, CH_2); 1.91 (s, 6H, SMe); 2.29 (dd, J = 10.4, 15.2, 2H, CH_2); 3.64 (s, 2H, CHOBn); 3.98 (d, J = 10.2, 2H, $C\underline{H}OH$); 4.44, 4.57 (each d, J = 10.2, 2H, $OC\underline{H}_2Ph$); 7.11- 7.31 (m, 10H, Ph). ^{13}C NMR ($CDCl_3$, 50 MHz): 11.9 (+, SMe); 39.7 (-, CH_2); 57.6 [o, $\underline{C}(SMe_2)$]; 66.9 (+, CHOH); 73.0 (-, $O\underline{C}H_2Ph$); 79.7 (+, $\underline{C}HOBn$); 127.8, 128.0, 137.9 (+, Ph); 127.9 (o, Ph). $[\alpha]_D^{24.5}$: -44.7° (c = 0.9, $CHCl_3$).

10: ^{1}H NMR ($CDCl_3$, 200 MHz): 0.12 (s, 9H, $SiMe_3$); 1.41 (s, 6H, CMe_2); 1.86 (m, 1H, CH_2); 2.05 (s, 6H, SMe); 2.06 (m, 1H, CH_2); 2.21 (m, 1H, CH_2); 2.59 (m, 1H, CH_2); 2.85 (s, 1H, OH); 4.10 (m, 1H); 4.17- 4.30 (m, 2H); 4.96 (m, 1H). ^{13}C NMR ($CDCl_3$, 50 MHz): 0.1 (+, $SiMe_3$); 12.0, 12.7 (+, SMe); 27.0, 27.2 (+, $C\underline{M}e_2$); 42.8, 46.1 (-, CH_2); 58.3 [o, $\underline{C}(SMe)_2$]; 64.3, 67.7 (+, CHOH, $\underline{C}HOSiMe_3$); 73.8, 76.0 (+, CHOR); 109.3 (o, $\underline{C}Me_2$). $[\alpha]_D^{23.5}$: -36.4° (c = 0.9, $CHCl_3$).

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10. **11**: ^{1}H NMR (CD_3OD, 200 MHz): 1.93- 2.06 (m, 1H, CH_2); 2.09, 2.12 (each s, 3H, SMe); 2.23- 2.37 (m, 2H, CH_2, CH); 3.84- 3.93 (m, 2H); 4.03- 4.29 (m, 3H). ^{13}C NMR (CD_3OD, 50 MHz): 12.1, 12.8 (+, SMe); 36.9 (-, CH_2); 46.4 (+, CH); 59.2 (-, CH_2OH); 59.5 [o, $\underline{C}(SMe)_2$]; 66.3, 72.1, 73.1 (+, CHOH). $[\alpha]_D^{24.5}$: +17.2° (c = 0.5, MeOH).

12: NMR spectra see ref.[9b]. $[\alpha]_D^{23}$: + 25.3° (c = 1.3, H_2O); ref.[9b]: $[\alpha]_D^{20}$: + 28° (c = 0.6, H_2O).