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Oxepanes from an Unusual Acetal Cleavage of 6,8-Dioxabicyclo[3.2.1]octanes

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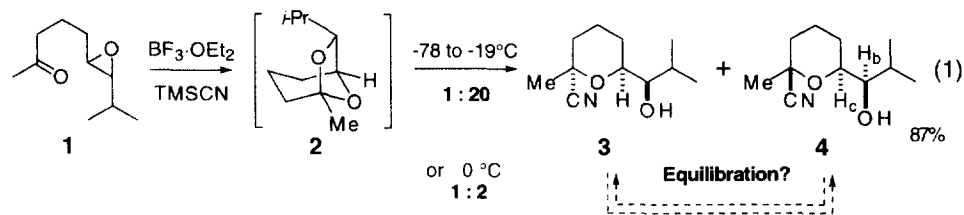
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Abstract.: On treatment with $\text{BF}_3 \cdot \text{OEt}_2$ and TMSCN, epoxy ketone **1** cyclized to the bicyclic acetal **2**, which then cleaved to give primarily the oxepane **5** as a single stereoisomer. Reductive decyanation of **5** led to the oxepane **7**, a structural unit present in the brevetoxin family of natural products. The scope and limitations of this reaction sequence were investigated.

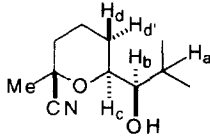
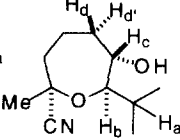
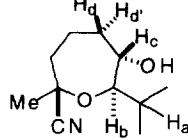
Several years ago Fotsch and Chamberlin² reported the cyclization and cleavage of epoxy ketone **1** with TMSCN and $\text{BF}_3 \cdot \text{OEt}_2$ to give the trans cyano tetrahydropyran **4** accompanied by the cis cyano tetrahydropyran **3**, eq 1. The product ratio varied from 20:1 to 2:1 as a function of the reaction temperature, and this variability was taken as evidence that the reaction was reversible. This report attracted our attention because we had attempted to equilibrate cyanohydrin adducts to no avail, and we decided to reinvestigate the system. On careful examination, the reported spectral data for compound **4** appeared to be inconsistent with its assigned structure (Table 1): the coupling constants between H_c (C2) and H_d and H_d (C3) were reported as 10 and 7.5 Hz, and these are very unusual vicinal coupling constants in a six-membered ring. Another possible mode of cleavage would lead to the seven-membered rings **5** or **6**. Conformational searches were carried out on **4**, **5** and **6** using the MM2* force field in MacroModel 4.5,³ and the calculated coupling constants⁴ are reported in Table 1, along with the experimental values. The experimental data is consistent with the seven-membered ring structures **5** or **6**, but inconsistent with the six-membered ring product **4**. This conclusion was confirmed by the experiments reported below.

Literature Report:²



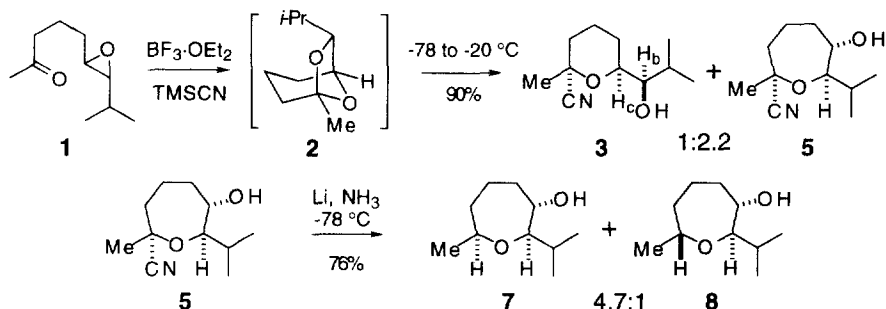
Epoxy ketone **1** was prepared by a new route,⁵ and cyclized using the literature procedure.² Using $\text{BF}_3 \cdot \text{OEt}_2$ and TMSCN from -78 to -20 °C, a 2.2:1 ratio of two products were isolated that matched the reported spectral data for **4** and **3**, respectively. Acetylation of the compound reported as **4**

Table 1. Calculated Coupling Constants for 4–6, and Experimental Values (Hz)

				Observed <i>J</i> Values: Lit. (This work)
	4	5	6	
J_{a-b}	8.9	2.2	1.6	3 (2.7)
J_{b-c}	2.9	7.9	8.7	8.5 (8.7)
J_{c-d}	2.4	4.9	5.2	7.5 (5.0)
$J_{c-d'}$	11.6	9.3	10.7	10 (8.6)

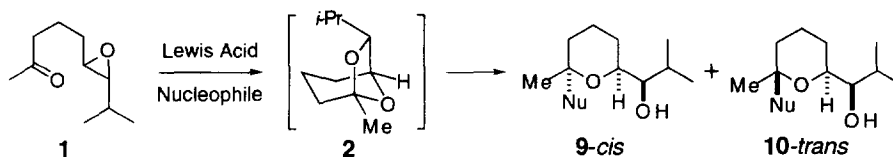
led to a downfield shift of the H_c proton (alcohol: 3.61 ppm, acetate: 4.80 ppm), consistent with the seven-membered ring structures **5** or **6**. COSY analysis confirmed the assignment of H_c proton. Only one stereoisomer of the seven-membered ring product was observed, and we believe it has the structure **5** based on an expected “axial” delivery of the nitrile, but structure **6** cannot be ruled out. Acetylation of **3** and COSY analysis are consistent with its reported structure. The ratio of six- to seven-membered ring products varied between 1:1.3 and 1:4 depending on the temperature, with the best selectivity for the seven-membered ring observed at $-40\text{ }^\circ\text{C}$.⁶ The bicyclic acetal **2** was observed as a discrete intermediate by TLC, and reaction of either the epoxy ketone **1** or the isolated bicyclic acetal **2** gave comparable results. Resubmitting **3** and **5** independently to the reaction conditions did not lead to mixtures, so the reaction is not reversible.

Scheme 1



Oxepanes rings are common to a number of natural products including the brevetoxin family of red tide toxins.⁷ Stereoselective removal of the cyano group in **5** by reductive decyanation⁸ gave oxepane **7** as the major component of a 4.7:1 mixture of stereoisomers in 76% yield. The stereochemistry of the reduction was assigned as *cis* from the observed NOE enhancement between protons at C2 and C7. Reductive decyanation of **3** gave the expected *cis* tetrahydropyran **9** ($\text{Nu} = \text{H}$). The oxepane **7** has the C2-C3 *trans* and C2-C7 *cis* stereochemical relationships found in the brevetoxin ring system, and the two-step sequence from **1** to **7** is a rapid and unusual entry into this ring structure.

Table 2. Addition of other nucleophiles to epoxy ketone 1.

Conditions

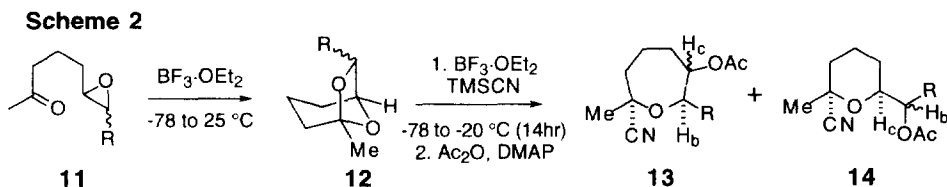
- a. Ph_3SiH , $\text{BF}_3 \cdot \text{OEt}_2$, $0\text{ }^\circ\text{C}^2$
 b. DIBAL-H, -78 to $25\text{ }^\circ\text{C}$
 c. AllylSiMe_3 , $\text{BF}_3 \cdot \text{OEt}_2$, $0\text{ }^\circ\text{C}^2$
 d. $\text{Me}_3\text{SiCCAlEt}_2$, $\text{BF}_3 \cdot \text{OEt}_2$, -78 to $-20\text{ }^\circ\text{C}$

Product (Yield)

- 9-cis**, Nu = H (83%)
10-trans, Nu = H (65%)
9-cis, Nu = allyl (76%)
9-cis, Nu = Me_3SiCC (94%)

How general is the formation of oxepanes from the cleavage of bicyclic acetal **2**?⁹ Several other nucleophile/Lewis acid combinations were investigated, and the results are shown in Table 2. In agreement with Chamberlin's original report, Ph_3SiH and allyltrimethylsilane¹⁰ both gave the axial tetrahydropyran products (entries a and c).² DIBAL-H gave the equatorial tetrahydropyran product.¹¹ Considering that the linear geometry of the TMSCN nucleophile might be significant in the formation of oxepane **5**, diethylaluminium trimethylsilylacetylide was added using $\text{BF}_3 \cdot \text{OEt}_2$ as the Lewis Acid to give only the axial tetrahydropyran adduct in 94% yield. In agreement with the report by Chamberlin,² none of the other nucleophiles investigated lead to oxepanes. The TMSCN is unique in favoring the oxepane products.

The generality of the TMSCN cleavage reaction is shown in Scheme 2. We used a standard set of reaction conditions rather than optimizing them for each substrate. The trans epoxy ketones **11a** and



Substrate	Yield	Product Ratio: 13/14	
* 11a : R = <i>n</i> -Hexyl, <i>trans</i>	87%	2.2	1.0
* 11b : R = <i>n</i> -Hexyl, <i>cis</i>	80%	1.0	9.9
† 11c : R = <i>i</i> -Pr, <i>trans</i>	96%	2.2	1.0
† 11d : R = <i>i</i> -Pr, <i>cis</i>	63%	1.0	4.9
* 11e : R = <i>t</i> -Butyl, <i>trans</i>	88%	1.0	5.3
* 11f : R = <i>t</i> -Butyl, <i>cis</i>	86%	1.0	3.5

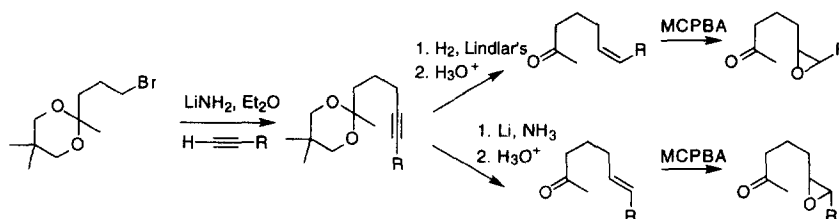
*NMR ratios; products inseparable by chromatography. †Product ratios from isolated yields.

11c favored the oxepane products **13**. The tetrahydropyran products **14** were favored with the *cis* epoxy ketones **11b** and **11d**, but both the *cis* and *trans* *t*-butyl epoxides **11e** and **11f** favored the tetrahydropyran product. The regiochemical assignment was made in each case by acetylation and COSY analysis to identify the new downfield proton as either H_c (**13**) or H_b (**14**). Both **13** and **14** were present as single stereoisomers, and the stereochemical assignments were based on analogy to **5** and **3**.

A reinvestigation of the reaction of epoxy ketone **1** with TMSCN and BF₃·OEt₂ demonstrated that the major product was the oxepane **5**. Other nucleophiles gave only tetrahydropyrans, but other epoxy ketones gave oxepane products with TMSCN and BF₃·OEt₂. Reductive decyanation of cyano oxepane **5** gave oxepane **8**, a common structural unit in the brevetoxin family of natural products.¹²

References and Footnotes

- ¹ Current Address: Department of Chemistry, University of California, Irvine, CA 92717-2025.
- ² Fotsch, C. H.; Chamberlin, A. R. *J. Org. Chem.* **1991**, *56*, 4141.
- ³ MacroModel V4.5: Mohamadi, F.; Richards, N. G. J.; Guida, W. C.; Liskamp, R.; Caufield, C.; Chang, G.; Hendrickson, T.; Still, W. C. *J. Comput. Chem.* **1990**, *11*, 440.
- ⁴ A group of conformers was identified using a Monte Carlo search, and the coupling constants were calculated using the **coplf** function, which evaluates a Boltzmann weighted average at 25 °C. Haasnoot, C. A. G.; DeLeeuw, F. A. A. M.; Altona, C. *Tetrahedron*, **1980**, *36*, 2783.
- ⁵ The epoxy ketones were prepared by the following route:



- ⁶ Reaction of bicyclic acetal **2** with TMSCN/BF₃·OEt₂ at various temperatures in CH₂Cl₂ led to the following results [ratio of **4**:**3**]: -78 °C (30 min) to 0 °C (40 hr), [1.3:1]; -78 °C (30 min) to -20 °C (40 hr), [2.1:1]; -78 °C (30 min) to -40 °C (40 hr), [4.0:1]; -78 °C (30 min) to -60 °C (40 hr), [3.3:1]. Treatment with TMSCN/TiCl₄ at -78 °C gave a ratio of 2.3:1, and TMSCN/TMSOTf at -60 °C gave a ratio of 1.8:1. MAD and *i*-Bu₃Al did not react with bicyclic acetal **2**.
- ⁷ Synthesis of brevetoxin B: (a) Nicolaou, K. C.; Theodorakis, E. A.; Rutjes, F. P. J. T.; Tiebes, J.; Sato, M.; Untersteller, E.; Xiao X.-Y. *J. Am. Chem. Soc.* **1995**, *117*, 1171. (b) Nicolaou, K. C.; Rutjes, F. P. J. T.; Theodorakis, E. A.; Tiebes, J.; Sato, M.; Untersteller, E. *J. Am. Chem. Soc.* **1995**, *117*, 1173.
- ⁸ Rychnovsky, S. D.; Zeller, S.; Skalitzky, D. J.; Griesgraber, G. *J. Org. Chem.* **1990**, *55*, 5550.
- ⁹ Reduction of 5,7-dimethyl-6,8-dioxabicyclo[3.2.1]octane with alane gave a *cis*-tetrahydropyran: Kim, Y.; Mundy, B. P. *J. Org. Chem.* **1982**, *47*, 3556. See also Kotsuki, H. *Synlett* **1992**, 97.
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- ¹¹ Mulholland, R. L.; Chamberlin, A. R. *J. Org. Chem.* **1988**, *53*, 1082.
- ¹² Support for this work was provided by the Eli Lilly Grantee program and the Alfred P. Sloan Foundation.

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