Diquinane Synthesis Based on Anionic [1, 3] Sigmatropic Rearrangements of an Oxy-Cope System Incorporated in the Bicyclo[3.2.1]oct-6-ene Framework

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Treatment of 2-vinylbicyclo[3.2.1]oct-6-en-2-ols with KH in toluene gave mainly [5-5] fused-ring compounds through a [1,3] sigmatropic shift.

Anionic oxy-Cope rearrangement of bridged polycyclic compounds has been noted as a synthetic strategy of a natural product.[1-3] Very recently, we have reported the alkoxide accelerated [1,3] sigmatropic rearrangement of *trans* oxy-Cope systems **1** leading to [5-6] fused-ring compounds **2**.[4] It is noteworthy that the presence of the vinylene bridge in **1** does not change the reaction course and affects only kinetically in this transformation.

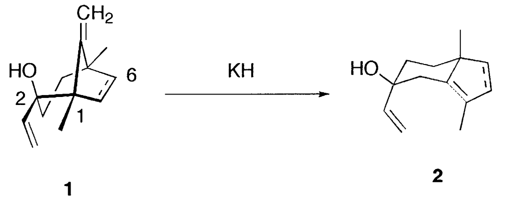
We wish to report herein a rearrangement route to [5-5] fused-ring compounds, so-called diquinanes, from the corresponding oxy-Cope systems including the etheno-bridge. For allyl alcohols **3**, we are able to expect some reaction courses such as 1) a [1,3] migration giving [5-5] fused-ring compounds **5** and **6** through cleavage of the C(1)-C(2) bond and formation of a new bond between C(2) and C(6), 2) the two-carbon ring-enlargement leading to **8** through a [1,3] migration on the vinyl group, and 3) an oxy-Cope rearrangement giving [5-7] fused-ring compounds **7**.

The precursors of the substrates **3** and **4** are the corresponding ketones derived systematically from 1-methoxybicyclo[2.2.2]oct-5-en-2-one.[5] Treatment of one of the ketones with a reagent derived from vinylmagnesium bromide and cerium trichloride in THF at -78 °C gave a mixture of allyl alcohols **3** and **4** in good yield.[6-8]

The exo alcohol **3a** was inert by treatment with KH (3 equivalents) in boiling THF for 6 h. When 18-crown-6 was employed as an additive, **3a** was consumed within 3 h in boiling THF. The reaction mixture gave small amounts of products **5a**, **6a**, and **8a**. In boiling toluene without 18-crown-6, **3a** was transformed into proper amounts of the products as listed in Table 1 (run 1). While it is not clear that an anionic [1,3] sigmatropic rearrangement is either a concerted or a stepwise process, the diquinanes **5a** and **6a** correspond to suprafacial retention and inversion products from **3a**, respectively.

The endo isomer **4a** belonging to a so-called *trans* oxy-Cope system was less reactive than **3a** under very similar conditions (run 3). Figure 1, the reaction profile of **4a** (run 4), suggests the bicyclic ketone **8a** is formed through the oxy-Cope process of the alcoholate of **6a**. By treatment with KH in boiling xylene for 2 h, 64% of **6a** was consumed and **8a** was derived in 45% yield. However, a slim possibility of the two-carbon ring-enlargement directly leading to **8a** still remains. Even trace amounts of **7a** were not detected under these reaction conditions.

The bridgehead phenyl series, **3b** and **4b**, were more reactive than the respective bridgehead methyl derivatives.[9] The exo isomer **3b**, a *cis* oxy-Cope system, was more reactive than **4b**, a *trans* oxy-Cope system. Interestingly both of them were transformed into only the [5-5] fused-ring compound **5b**.



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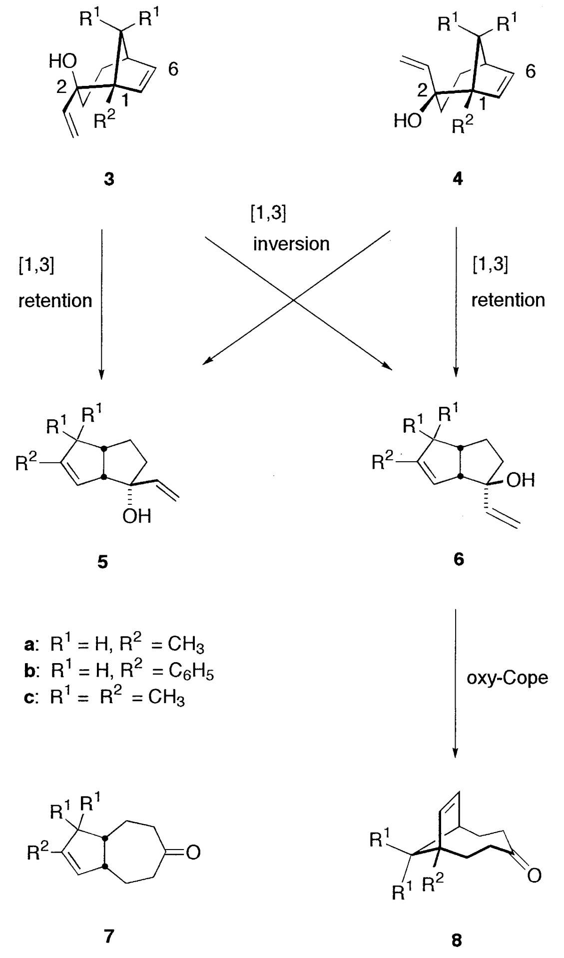
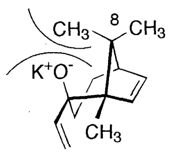


3 4 5 6 7 8

a: $R^1 = H, R^2 = CH_3$
b: $R^1 = H, R^2 = C_6H_5$
c: $R^1 = R^2 = CH_3$



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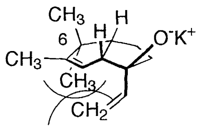

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Careful VPC monitoring of these reactions indicated that the interconversion between **3b** and **4b** did not occur under the reaction conditions. The selective transformation of both **3b** and **4b** into **5b** seems to be a key point for synthetic use of the anionic [1,3] migrations although the mechanistic reasons are uncertain.

Next, we were interested in a similar reaction of the substrate **3c** containing a dimethylmethano bridge. In comparison with **3a**, **3c** was transformed more easily into [5-5] fused-ring compounds **5c** and **6c** (run 8). This may attribute to the steric acceleration of the migration caused by the pseudo 1,3-diaxial interaction between the endo-8-methyl and the exo-2-oxide of the anionic precursor (**9**). The bridged bicyclic ketone **8c** was not detected in the reactions of **3c** (runs 8-10). The oxy-Cope process such as **6a** into **8a** is inhibited because that appropriate overlap between the C(7) and the vinyl methylene carbon seems to be difficult on the basis of the steric repulsion between the endo-6-methyl and the vinyl group in the alkoxide of **6c** (**10**). Thus, the stereochemical courses of an anionic [1,3] sigmatropic shift depend upon the structure of a substrate.[2]

In conclusion, we have successfully prepared diquinane systems from bicyclo[3.2.1]oct-6-en-2-ones through the anionic [1,3] migration of the oxy-Cope system.

Table 1. Sigmatropic rearrangement of 2-vinylbicyclo[3.2.1]oct-6-en-2-ols by treatment with KH[a]

Run	Substrate	Solvent	Temp/°C	Time/h	Products (yield/%)[b]
1	**3a**	toluene	120	3	**5a** (53), **6a** (18), **8a** (13)
2	**3a**	diglyme	120	1.5	**5a** (29), **6a** (3), **8a** (19)
3[c]	**4a**	toluene	120	20	**5a** (4), **6a** (12)
4	**4a**	xylene	145	3	**5a** (14), **6a** (4), **8a** (22)
5[d]	**3b**	toluene	20	3	**5b** (70)
6[d]	**4b**	toluene	20	50	**5b** (73)
7[d]	**4b**	toluene	50	0.5	**5b** (90)
8	**3c**	THF	80	1	**5c** (65), **6c** (26)
9	**3c**	toluene	120	3	**5c** (41), **6c** (16)
10	**3c**	xylene	145	2	**5c** (50), **6c** (20)

[a] To a suspension of KH (0.4 mmol) in an appropriate solvent (0.5 cm^3) was added a solution of a substrate (0.12 mmol) and tetradecane (0.06 mmol, as the internal standard for VPC) in the same solvent (4 cm^3) at room temperature. The mixture was heated on a preheated oil bath under VPC monitoring. The product composition determined by the NMR spectrum of the reaction mixture obtained by the usual post-treatment was almost identical with that by the VPC analysis. [b] The yield was estimated from the VPC data. [c] Substrate **4a** was recovered in 69%. [d] The internal standard used for the VPC analysis was pentadecane.

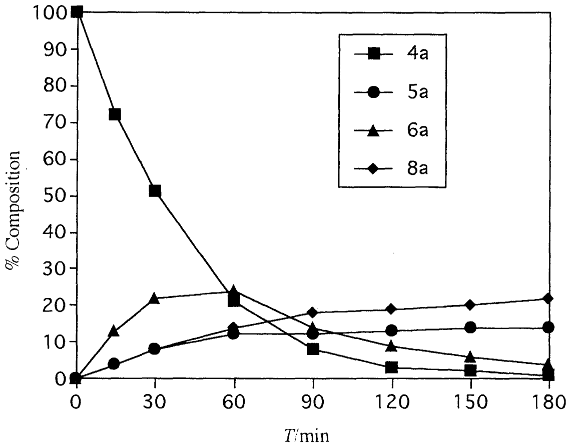

Figure 1. Conversion of **4a** under the conditions listed in Table 1 (run 4).

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References and Notes

1 For reviews, see: a) L. A. Paquette, *Synlett*, **1990**, 67. b) L. A. Paquette, *Angew. Chem., Int. Ed. Engl.*, **29**, 609 (1990).

2 For a review, see: S. R. Wilson, *Org. Reaction*, **43**, 93 (1993).

3 More recent work: a) L. A. Paquette and R. C. Thompson, *J. Org. Chem.*, **58**, 4952 (1993). b) L. A. Paquette, S. K. Huber, and R. C. Thompson, *J. Org. Chem.*, **58**, 6874 (1993). c) R. Guevel and L. A. Paquette, *J. Am. Chem. Soc.*, **116**, 1776 (1994). d) J. Doyon, W. He, and L. A. Paquette, *J. Org. Chem.*, **59**, 2033 (1994). e) J.-F. Devaux, I. Hanna, J.-Y. Lallemand, and T. Prange, *J. Org. Chem.*, **58**, 2349 (1993). f) K. Mori and Y. Matsushima, *Synthesis*, **1995**, 845.

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5 T. Uyehara, T. Inayama, T. Furuta, T. Kato, Y. Yamamoto, M. Ueno, and T. Sato, *Bull. Chem. Soc. Jpn.*, **69**, 1727 (1996), and references cited therein.

6 All new compounds reported here exhibit satisfactory spectral and analytical and/or HRMS characteristics. The stereostructures of the alcohols **3**, **4**, **5** and **6** were defined on the basis of the ^{1}H NMR studies including NOE experiments.

7 We recommend more than 30 h of stirring and then 2 h of sonication of a dry CeCl$_3$ powder in THF, see: a) T. Imamoto, N. Takiyama, K. Nakamura, T. Hatajima, and Y. Kamiya, *J. Am. Chem. Soc.*, **111**, 4392 (1989). b) N. Greeves and L. Lyford, *Tetrahedron Lett.*, **33**, 4759 (1992).

8 In the case of R^1 = H, the endo alcohol **4** was predominant (**3a**, 34%; **4a**, 56%; **3b**, 16%; **4b**, 73%). When R^1 is CH$_3$, only the exo alcohol **3c** was obtained in 98% yield.

9 An example for the substituent effect in the migrating group of an anionic [1,3] sigmatropic rearrangement, see: T. Uyehara, K. Ohmori, Y. Kabasawa, and T. Kato, *Chem. Lett.*, **1984**, 1879.