

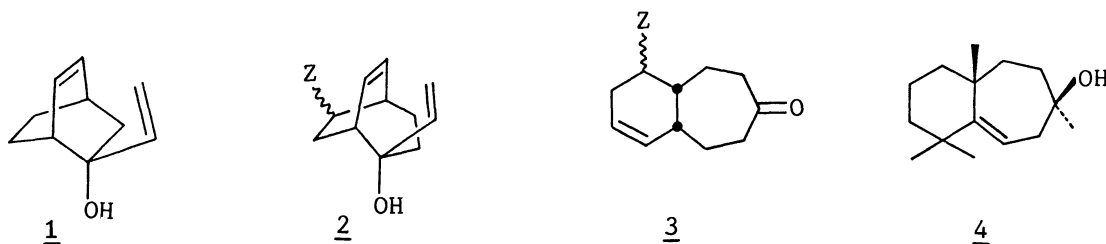
ALKOXIDE-ACCELERATED [1,3] SIGMATROPIC SHIFTS OF BICYCLO[3.2.2]NON-6-EN-2-OLS.
SUBSTITUENT EFFECTS AND TANDEM [1,3]-[3,3] SIGMATROPIC REARRANGEMENTS

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Bicyclo[3.2.2]non-6-en-2-ols are shown to undergo [1,3] sigmatropic shifts under the influence of KH and 18-crown-6. A series of the 2-endo-vinyl alcohols were transformed into the ring-expanded ketones, bicyclo[5.2.2]undec-8-en-4-ones, via the tandem [1,3]-[3,3] sigmatropic rearrangements.

The bicyclic oxy-Cope system (1) is known to undergo a [3,3] sigmatropic rearrangement at an enormously enhanced rate.¹⁾ Recently, Rigby and his co-workers have reported that the higher homolog (2) undergoes a [3,3] sigmatropic shift to give the bicyclo[5.4.0]undecane ring system (3).²⁾ In conjunction with our program to develop methods for stereoselective syntheses of [m-n] fused-ring terpenes from bicyclo[3.2.2]nonane systems,³⁾ we were interested in the anionic oxy-Cope rearrangement and found that the primary course under the reaction conditions is the alkoxide-accelerated [1,3] sigmatropic shift⁴⁾ to give the cis-bicyclo[4.3.0]-nonane system and the desired Cope rearrangement dose not proceed at all (vide infra).

A matter of concern for [1,3] sigmatropic shifts,⁵⁾ including alkoxide-accelerated reactions, is variety of their stereochemical courses which reflect the reaction mechanisms. Especially, [1,3] sigmatropic shifts in anionic oxy-Cope systems are of interest because of intricate mechanisms and synthetic utility.^{4b-f,j and l)}



According to a synthetic plan for widrrol (4),⁶⁾ the 2-endo-vinyl alcohol (6a)⁷⁾ was prepared in 66% yield along with the stereoisomer (7a, in 13% yield) from the ketone (5a)⁸⁾ on treatment with vinylmagnesium bromide at -78°C. The stereochemistry of 6a and 7a was assigned on the basis of the lanthanoid-induced shift (LIS) studies on their ¹H-NMR spectra.⁹⁾

When 6a was treated with potassium hydride and 2 equiv. of 18-crown-6 in

refluxing THF, the products were the enol ethers (8a and 9a) and the ring-expanded ketone (10a) (run 3, in Table 1). The authentic sample of 9a was derived from the hexahydroindenone (11a)¹⁰⁾ by a stereoselective addition of vinylmagnesium bromide. Alcohol 9a turned into the tricyclic acetal (12a) in a carbon tetrachloride solution.

Although 6a was treated under various conditions (runs 1-4), we could not detect even a very small amount of the expected oxy-Cope product. It was found that i) the primary course of the reactions is a suprafacial [1,3] sigmatropic shift with inversion of configuration; ii) the presence of 18-crown-6 is indispensable; and iii) the bicyclo[5.2.2]undec-8-en-4-one, 10a, would be the secondary product via the alkoxide-accelerated [3,3] sigmatropic shift of 8a. Those unexpected results prompted us to investigate the following reactions.

A pathway for the formation of 10a was proven by the independent reaction and the control (runs 7 and 8, respectively). The 2-*exo*-vinyl alcohol (7a), the stereoisomer of 6a, did isomerize yielding 8a, 9a, and 10a (runs 5-6). In this case, the [1,3] shift with retention of the configuration (a forbidden pericyclic reaction) competes clearly with the shift with inversion.

The reaction modes of 6b⁹⁾ and 7b,⁹⁾ prepared from 5b,¹¹⁾ are very similar to those of 6a and 7a, respectively (runs 9-11).

In order to determine the effect of the substituent on the migrating carbon, the tertiary alcohols (13,¹²⁾ 14,¹²⁾ and 15¹³⁾) were prepared from 5a. When the potassium alkoxide of 13 was heated under reflux in dioxane (bath temp, 140 °C) with 2 equiv. of 18-crown-6 for 6.5 h, 54% of 13 was consumed and the inversion product (16) was obtained in 21% yield. The same reaction of the alkoxide of 14

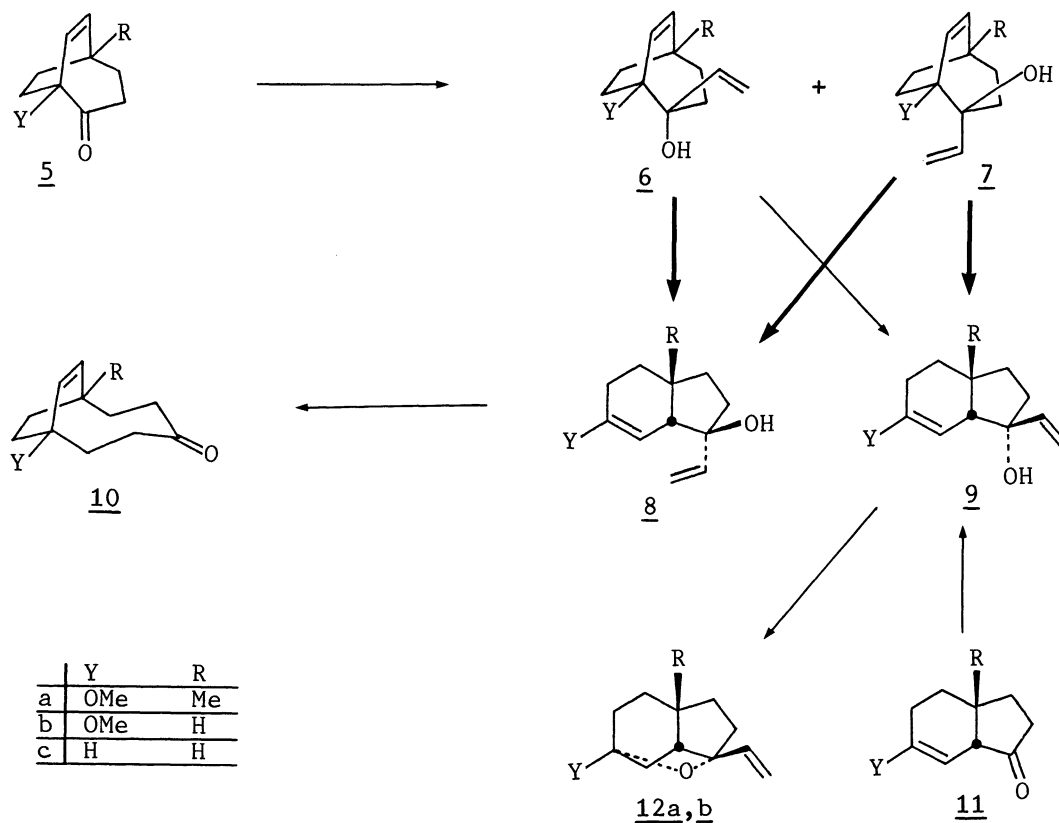
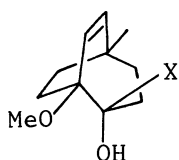


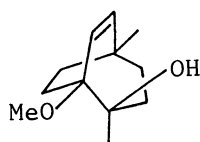
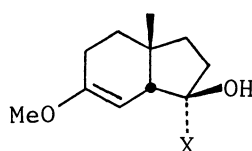
Table 1. Alkoxide-accelerated reactions of bicyclo[3.2.2]non-6-en-2-ols^{a)}

Run	Sub- strate	18-Crown-6	Temp ^{b)} °C	Time h	Products (yield/%)	Recov. %
1	<u>6a</u>	--	80	20		(91)
2	<u>6a</u>	1.0	80	17	<u>8a</u> (55)	
3	<u>6a</u>	2.0	80	3	<u>8a</u> (83), <u>9a</u> (1), <u>10a</u> (13)	
4	<u>6a</u>	2.0	120	4	<u>10a</u> (43)	
5	<u>7a</u>	2.0	80	3	<u>8a</u> (24), <u>9a</u> (44), <u>10a</u> (8)	
6	<u>7a</u>	2.0	120	5	<u>9a</u> (41), <u>10a</u> (7)	
7	<u>8a</u>	2.0	120	1	<u>10a</u> (67)	(14)
8	<u>9a</u>	2.0	120	1		(68)
9	<u>6b</u>	2.0	80	2.5	<u>8b</u> (80), <u>9b</u> (1), <u>10b</u> (15)	
10	<u>7b</u>	2.0	80	2.5	<u>8b</u> (23), <u>9b</u> (42), <u>10b</u> (20)	
11	<u>8b</u>	2.0	120	1	<u>10b</u> (45)	(42)
12	<u>6c</u>	2.0	80	3	<u>9c</u> (23), <u>10c</u> (33)	(24)
13	<u>6c</u>	2.0	120	1.5	<u>9c</u> (18), <u>10c</u> (58)	(8)
14	<u>7c</u>	2.0	80	3		(83)
15	<u>7c</u>	2.0	80	6	<u>9c</u> (1), <u>10c</u> (7)	(65)
16	<u>7c</u>	2.0	120	1.5	<u>9c</u> (1), <u>10c</u> (70)	(7)

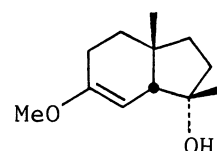
a) Carried out under Ar, using 1 mmol of a substrate in 10 ml of a solvent. The products were isolated by chromatography on silica gel. b) Temperature of the oil bath. The reactions at 80 °C and at 120 °C were carried out in THF and dioxane, respectively.



13 X=Me
15 X=Ph

14

16 X=Me
18 X=Ph

17

for 4.75 h gave 16 and the isomer (17)¹⁴⁾ in 10% and 9% yields, respectively, and 14 in 60% recovery. Compound 15 underwent the [1,3] rearrangement with inversion at 80 °C within 1.5 h and enol ether 18 was obtained quantitatively. Thus it is clear that a conjugating substituent on the migrating carbon accelerates the rate of the [1,3] sigmatropic shift.¹⁵⁾

In order to clarify the role of the C₁ substituent, the methoxyl group, we prepared the allylic alcohols (6c and 7c)¹⁶⁾ from the ketone (5c)¹⁷⁾ and examined the corresponding reactions of them (runs 12-16). The authentic sample of the [1,3] shift product (9c) was prepared from 11c.¹⁷⁾ The NMR spectrum of 10c¹⁸⁾ indicates that it is a symmetrical bicyclic compounds. Thus, again we could not detect the bicyclo[5.4.0]undecenone, the product via the anionic oxy-Cope rearrangement proposed by Rigby and his co-workers.

Alcohol 7c is less reactive than the stereoisomer (6c) and both of them are less reactive than the respective 1-methoxy derivative. Compound 8c, the stereoisomer of 9c, was not detected in all the cases. Although direct ring-enlargements of 6c and 7c to 10c cannot be denied completely,^{4b,c)} the results should be explained by a tandem [1,3]-[3,3] sigmatropic shift via 8c. When a polar substituent, such as a methoxyl group, is present at the C₁ position of the bicyclo[3.2.2]nonenol, acceleration of the reaction rate is expected for the first stage of the tandem processes but not for the second one.¹⁵⁾ It is reasonable that we could isolate 8a and 8b but not 8c.

Finally, it is noteworthy that the [1,3] shift with inversion of configuration is preferred rather than that with retention of configuration, regardless of the relative stereochemistry of the migrating carbon to the migrating framework,^{4d)} when a methoxyl group is present at the C₁ position.

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- 5) For suprafacial [1,3] sigmatropic rearrangements with retention of configuration, see; J. A. Berson, "Rearrangement in Ground and Excited States," ed by P. de Mayo, Academic Press (1980), Vol. 1, pp. 372-383; *Acc. Chem. Res.*, **5**, 406 (1972).
- 6) H. Erdtman and B. R. Thomas, *Acta Chem. Scand.*, **12**, 267 (1958).
- 7) All new compounds reported here exhibit satisfactory spectral (IR and NMR) and analytical and/or mass spectral characteristics.
- 8) Derived from 1-methoxy-4-methylbicyclo[2.2.2]oct-5-en-2-one.¹⁹⁾
- 9) LIS values (Δ , ppm), **6a**: 1.5 (H₆) and 5.5 (H₇); **7a**: 5.0 (H₆) and 10.7 (H₇); **6b**: 2.3 (H₆) and 5.7 (H₇); **7b**: 4.4 (H₆) and 10.7 (H₇).
- 10) Obtained from **5a** via a photochemical [1,3] rearrangement.
- 11) Prepared from 1-methoxybicyclo[3.2.2]nona-3,6-dien-2-one.²⁰⁾
- 12) Obtained in 72% and 18% yields, respectively, when treated with MeMgI; LIS values (Δ , ppm), **13**: 1.5 (H₆) and 5.1 (H₇); **14**: 4.7 (H₆) and 11.8 (H₇).
- 13) Yielded in 57% yield on treatment with PhMgBr at -78 °C.
- 14) Compound **17** gave the tricyclic acetal like **12** in an excellent yield.
- 15) For theoretical prediction for the effect of substituents on the rate of pericyclic reactions, see; B. K. Carpenter, *Tetrahedron*, **34**, 1877 (1978).
- 16) Isolated by preparative GLC (10% FFAP, 180 °C) from a mixture of them (55 : 45) obtained in 83% yield; LIS values (Δ , ppm), **6c**: 4.6 (H₆) and 6.6 (H₇); **7c**, 4.0 (H₆) and 8.0 (H₇); Sharpless oxidation²¹⁾ (*t*-BuOOH, VO(acac)₂, 69 h, 40 °C) of **6c** gave two kinds of monoepoxides, while that of **5c** afforded two kinds of diepoxides along with two kinds of monoepoxides.
- 17) L. A. Paquette, R. P. Henzel, R. F. Eizember, *J. Org. Chem.*, **38**, 3257 (1973); compound **5c** was prepared from bicyclo[3.2.2]nona-3,6-dien-2-one,²²⁾ and converted into **11c** photochemically.
- 18) ¹³C-NMR (CDCl₃), δ =25.26 (2C, t), 30.29 (2C, d), 31.53 (2C, t), 40.73 (2C, t), 133.04 (2C, d), and 218.55 (1C, s).
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