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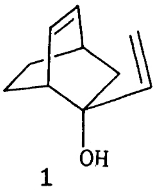
ALKOXIDE-ACCELERATED [1,3] SIGMATROPIC SHIFTS OF BICYCLO[3.2.2]NON-6-EN-2-OLS. SUBSTITUENT EFFECTS AND TANDEM [1,3]-[3,3] SIGMATROPIC REARRANGEMENTS

Tadao UYEHARA,* Kazuhiro OHMORI, Yasuhiro KABASAWA, and Tadahiro KATO
Department of Chemistry, Faculty of Science, Tohoku University,
Aramaki-Aoba, Sendai 980

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)



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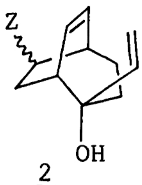

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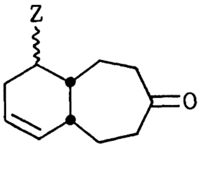

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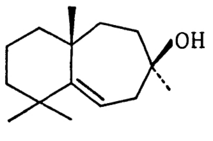

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According to a synthetic plan for widrrol (4),6) the 2-*endo*-vinyl alcohol (6a)7) was prepared in 66% yield along with the stereoisomer (7a, in 13% yield) from the ketone (5a)8) on treatment with vinylmagnesium bromide at -78°C. The stereochemistry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

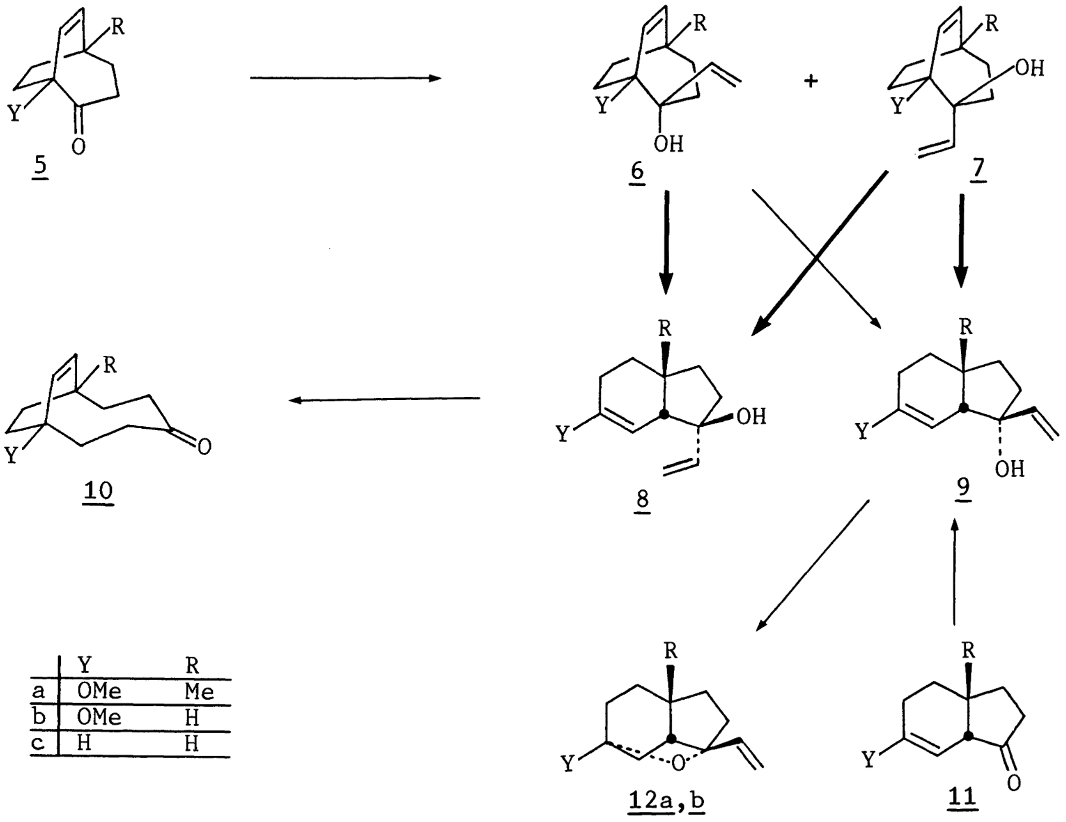
When 6a was treated with potassium hydride and 2 equiv. of 18-crown-6 in refluxing THF, the products were the enol ethers (8a and 9a) and the ring-expanded ketone (10a) (run 3, in Table 1). The authentic sample of 9a was derived from the hexahydroindenone (11a)[10] by a stereoselective addition of vinylmagnesium 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 6b[9] 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 15[13]) 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

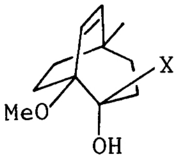


	Y	R
a	OMe	Me
b	OMe	H
c	H	H

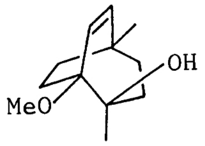
Table 1. Alkoxide-accelerated reactions of bicyclo[3.2.2]non-6-en-2-ols[a)]

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



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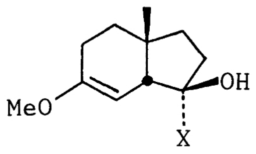
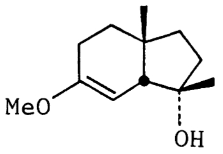


16 X=Me
18 X=Ph



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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 C_1 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 10c[18)] 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 C_1 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 C_1 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 (H_6) and 5.5 (H_7); 7a: 5.0 (H_6) and 10.7 (H_7); 6b: 2.3 (H_6) and 5.7 (H_7); 7b: 4.4 (H_6) and 10.7 (H_7).

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 (H_6) and 5.1 (H_7); 14: 4.7 (H_6) and 11.8 (H_7).

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 (H_6) and 6.6 (H_7); 7c, 4.0 (H_6) and 8.0 (H_7); 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) ^{13}C-NMR (CDCl$_3$), 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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