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REARRANGEMENT APPROACH TO THE FORMAL DISPLACEMENT OF THE BRIDGEHEAD METHOXYL GROUP OF BICYCLO[3.2.2]NON-6-EN-2-ONES WITH ALKYL, ALKENYL, AND ARYL GROUPS

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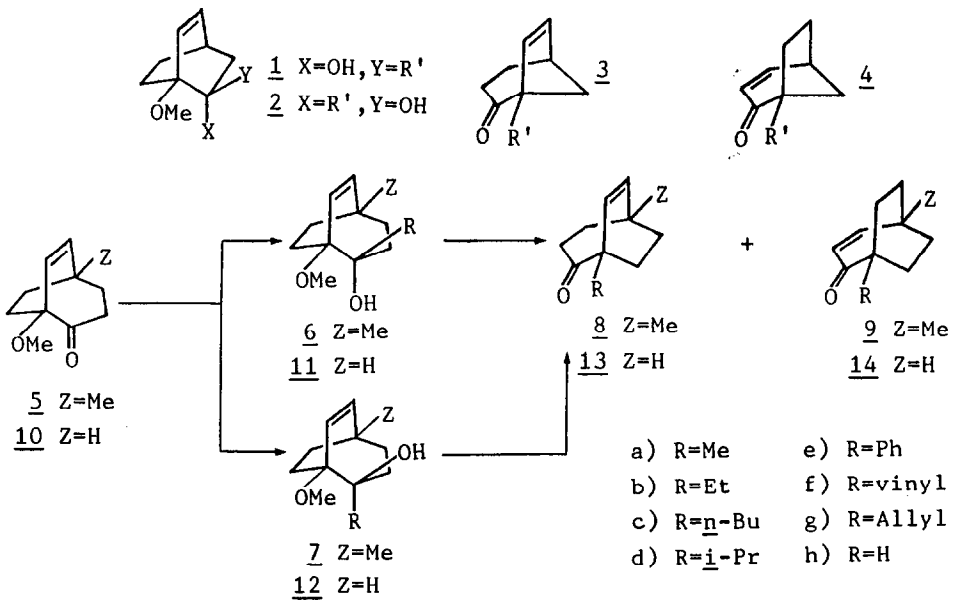
Summary: A *preferential transformation of the C_2-substituted 1-methoxybicyclo[3.2.2]non-6-en-2-ols, derived from 1-methoxybicyclo[3.2.2]non-6-en-2-ones, into the C_1-substituted bicyclo[3.2.2]non-6-en-2-ones was accomplished by utilizing TsOH in toluene (85 °C) or boiling benzene.*

There are few practical methods for the C-C bond formation at a bridgehead position of bicyclo[l.m.n] systems, because those cannot include nucleophilic substitutions at that position. In connection with our program to develop methods for stereoselective syntheses of natural products containing [m-n] fused-ring systems from bridged bicyclic compounds,[1-3] we examined a strategy for the formal C-C bond formation at the C_1-bridgehead of bicyclo[3.2.2]non-6-en-2-ones.

The pinacol-type rearrangement of 1-methoxybicyclo[2.2.2]oct-5-en-2-ols (such as 1 and 2) is known to give bicyclo[3.2.1]octenones (3 and 4): Treatment of the anti-alcohols (1) with an acid yields only the β,γ-unsaturated ketones (3), whereas that of syn-alcohols 2 affords a mixture of ketones 3 and 4.[4]



One of the expected products (i.e., 8) to this type of conversion of the higher homologs (such as 6 and 7), derived from the ketone (5), corresponds to the enantiomer which is formally substituted at the bridgehead position of 5. Herein we report the facile transformation of 5 into 8 and the remarkable regioselectivity of the pinacol-type rearrangement of 1-methoxybicyclo[3.2.2]-non-6-en-2-ols (6 and 7) and the related alcohols.

The anti- and syn-homoallylic alcohols (6a, 6c-d, and 6e and 7a-d, 7f, and 7g, respectively)[5] were derived from 5[2] as the major products by treatment with organolithium compounds and Grignard reagents, respectively, although the stereoselectivity was not high enough.[6] The stereochemical assignments to both the alcohols were performed by lanthanoid-induced shift (LIS) studies on their proton-NMR spectra.[7]

When the anti-alcohol (6a) was heated with TsOH (1 equiv.) in 50% acetic acid at 60 °C, a mixture of ketones 8a and 9a (ca. 1:1) was obtained in 68% yield. The portion of 8a increased up to 75% by treating with 0.1-0.2 equiv. of TsOH in toluene at 85 °C (listed in Table 1).[8] Under similar conditions, all the syn-alcohols (7a-g) gave only the desired ketones (8a-g, respectively). These remarkable regioselectivities are very different from those of the lower homologs (1 and 2).[4]

In order to obtain informations about the comformations (of the three carbon bridge) of the alcohols, less substituted alcohols 11a and 12a were prepared from ketone 10.[2,3] The NMR spectrum of 12a (400MHz) shows three characteristic couplings (a long-range coupling between C_2-Me and H_{3s} (J<1 Hz), a large vicinal coupling between H_{3s} and H_{4a} (J=13.7 Hz), and a very small coupling between H_{4a} and H_5 (J<0.5 Hz)) which are consistent with conformer 15. This means the other conformer (16) has the large steric hindrance between H_{3a}, H_{8a}, and H_{9a}. The stable conformer (15) must have also the steric repulsion between the substituent (CH_3), H_{4a}, and H_{8a}. Thus, the isomer (11a) seems to have a similar conformation to that of 12a (i.e., 17).[9]

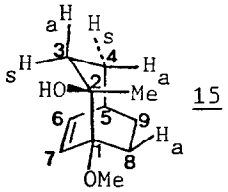
The similarity between the conformations of 12a and 7 receives supports from the long-range coupling (7a) and/or the resemblance between their LIS values.[7] Thus, the stable conformations of these syn-alcohols are those like 15. The preferential formation of the desired ketone (8) from 7 suggests that this pinacol-type rearrangement involves the carbonium ion (19) in which the axis of the empty p-orbital lies nearly parallel to the C_1-C_7 bond and the p-orbital can interact with the C_6-C_7 pi-orbital. However, the double bond of 7 can not participate stereoelectronically in the ionization stage. It is a rational explanation that ketones 8 are formed via the thermodynamically more stable carbonium ion intermediates (19, rather than 20). Releasing of that steric repulsion seems to assist the stereochemical change to give 19.

In the case of anti-alcohols, the reaction pathway through the isomeric ion (20) competes with that via 19. Although exact kinetic studies are lacking, we noticed that the anti-alcohols are less reactive than the syn-alcohols, respectively. Thus, the C_6-C_7 pi-electrons of 6 do not contribute

Table 1. Pinacol-type rearrangement of 1-methoxybicyclo[3.2.2]non-6-en-2-ols.[a)]

anti-Alcohol	Products	(ratio)[b)]	Yield %	syn-Alcohol	product	yield %
6a	8a, 9a	(3 : 1)	72	7a	8a	91
6b	----------		--	7b[c)]	8b	90
6c	8c, 9c	(9 : 1)	88	7c	8c	90
6d	8d, 9d	(24 : 1)	86	7d	8d	91
6e	8e, 9e	(21 : 1)	81	7e	8e	99
6f[c)]	8f, 9f	(22 : 1)	83	7f[c)]	8f	83
6g	----------		--	7g[c)]	8g	84
11a[d)]	13a, 14a	(1.3: 1)[e)]	72	12a[d)]	13a	52

a) Carried out in toluene with TsOH (0.1-0.2 equiv.) at 85 °C unless otherwise mentioned. The anti- and syn-alcohols were consumed within 1-12 h and 0.5-1 h, respectively. b) Estimated from their proton-NMR spectra. c) Treated with TsOH (1 equiv.) in boiling benzene. d) Heated at 60 °C with TsOH (1 equiv.) in 50% acetic acid. e) Calculated from the isolated yields.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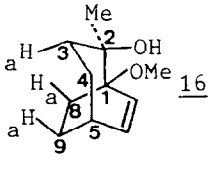
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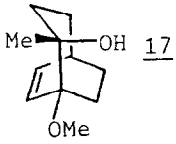
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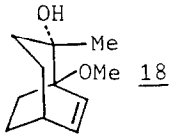
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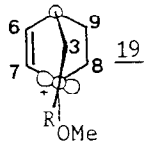
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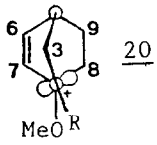
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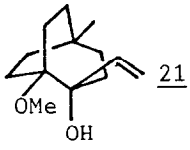
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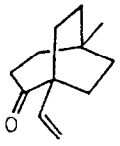
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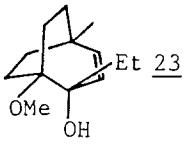
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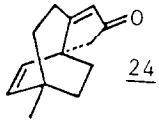
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to the acid-catalyzed carbonium ion formation. This correponds with that the presumable conformers of those alcohols are not similar ones to 18, but 17. The substituent effect on the product composition seems to correspond to the ease of the stereochemical change to give 19 by increasing the size of the substituent (R). When R is a large group, the flapping of the three carbon bridge to give 19 is preferable rather than the mortion of R to lead 20 with the change of the hybridization.

This pinacol-type transformation is applicable to the secondary syn-alcohol (7h).[10] Treatment of 7h with an equivalent of TsOH in boiling benzene for 1 h gave the β,γ-unsaturated ketone (8h) in 81% yield. Thus we can replace the bridgehead methoxyl group of 5 with hydrogen. An unfavourable result was obtained from the reaction of the anti-isomer (6h) under similar conditions. However, the α,β-unsaturated ketone (9h) was derived in 53% yield from the methanesulfonate of 6h by treating under the same conditions.[11]

During preparation of the authentic specimen of 9f, it was found that the reaction of alcohol (21)[12] with TsOH (1 equiv.) in boiling benzene gives a 4 : 1 mixture of 8b and 22 in 86% yield. This unique tandem [allyl cation migration]-[pinacol-type rearrangement] receives a support from the preferential

formation of 8b from 23[13] under the same conditions (for 30 min, 83% yield).

The bridgehead allyl derivative (8g) has been converted into the tricyclic ketone (24) via the diketone by sequential treatment with $PdCl_2$, CuCl, and O_2[14] (71%) and t-BuOK in refluxing THF (96%). Thus, this bridgehead substitution method promises to develop new synthetic routes to natural products based on specificities of bridged polycyclic compounds.

The authors are indebted to Dr. Masanobu Suzuki and Mr. Takao Izawa, Nippon Kayaku Ltd., for obtaining of the 400 MHz NMR spectra.

References and Notes

1) T. Uyehara, J. Yamada, K. Ogata, and T. Kato, Bull. Chem. Soc. Jpn., 58, 211 (1985); T. Uyehata, J. Yamada, T.Kato, and F. Bohlmann, ibid., 58, 861 (1985); and the references cited therein.

2) T. Uyehara, K. Ohmori, Y. Kabasawa, and T. Kato, Chem. Lett., 1984, 1879.

3) T. Uyehara, Y. Kabasawa, T. Kato, and T. Furuta, Tetrahedron Lett., 26, 2343 (1985).

4) S. A. Monti, S.-C. Chen, Y.-L. Yang, S.-S. Yuan, and O. P. Bourgeois, J. Org. Chem., 43, 4062 (1978).

5) All new compounds reported here exhibit satisfactory spectral (IR and NMR) and analytical and/or mass specral characteristics.

6) Representative reagents, conditions and the résults:
A) to 5: MeLi, -78 °C: 6a, 53% and 7a, 18%; MeMgI, 0 °C: 6a, 22% and 7a, 59%; EtMgBr, -78 °C: 6b, 18% and 7b, 64%; n-BuLi, -78 °C: 6c, 52% and 7c, 18%; n-BuMgBr, 0 °C: 6c, 30% and 7c, 38%; i-PrBr, Li, sonication, 0 °C: 6d, 30% and 7d, 15%; i-PrMgBr, 0 °C: 6d, 12% and 7d, 18%; PhBr, Li, sonication, 0 °C: 6e, 51% and 7e, 14%; PhMgBr, 0 °C: 6e, 42% and 7e, 18%; CH_2=CH-CH_2MgBr, -25 °C: 6g, 23% and 7g, 64%; L-selectride: 6h, 23% and 7h, 55%.
B) to 10: MeLi, -100 °C: 11a, 57% and 12a, 25%. For 6f and 7f: see Ref. 2.

7) LIS values ($\Delta\delta$) induced by Eu(fod)$_3$ are as follows: 6a: 1.5 (H_6) and 5.1 (H_7), 7a: 4.7 (H_6) and 13.4 (H_7), 6c: 1.7 (H_6) and 6.1 (H_7), 7c: 4.7 (H_6) and 11.8 (H_7), 6d: 1.4 (H_6) and 1.8 (H_7), 7d: 3.9 (H_6) and 11.0 (H_7), 6e: 2.9 (H_6) and 9.0 (H_7), 7e: 6.4 (H_6) and 15.0 (H_7), 11a: 3.3 (H_6) and 6.4 (H_7), 12a: 7.5 (H_6) and 19.3 (H_7).

8) The authentic samples of 9a, 9c-e, and 9f were prepared independently.

9) The signals due to all the methylene protons appear within the range of 1.8-1.15 ppm.

10) The stereochemical assignments of 6h and 7h are based on the proton-NMR spectra of them (90 MHz) and their acetates (200 MHz): 6h: δ=5.75 (H_6 and H_7, s) and 3.43 (H_{2s}, t, J=5.3 Hz). The acetate of 6h: δ=5.86 (H_6 and H_7, s), 5.04 (H_{2s}, t, J=4.5 Hz), 1.98 (H_{3s}, dddd, J=14, 13, 6, and 4.2 Hz), and 1.73 (H_{3a}, m). 7h: δ=5.85 (H_6 and H_7, s), and 3.38 (H_{2a}, bdd, J=7.5 and 6 Hz). The acetate of 7h: δ=6.06 (H_7 or H_6, dd, J=9,8 and 1 Hz), 5.93 (H_6 or H_7, bd, J=9.8 Hz), 5.01 (H_{2a}, bdd, J=8.8 and 5.8 Hz), and 1.89 (H_{3a}, dq, J=14.2 and 5.8 Hz). These data also support that 6h and 7h have similar conformations to 17 and 15, respectively.

11) Details will be discussed in a full paper.

12) Derived from 5: 1) H_2, Pd-C, (94%), 2) CH_2=CH-MgBr, 0 °C (83%).

13) We found suitable conditions for Lewis-acid catalyzed rearrangement of 5 into 1-methoxy-5-methylbicyclo[3.2.2]non-3-en-2-one (25).[11] Alcohol 23 was derived from 25 by sonication with EtBr and Li in THF.

14) J. Tsuji, I. Shimizu, and K. Yamamoto, Tetrahedron Lett., 1976, 2975.

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