A Novel Method for the Synthesis of Bicyclo[4.2.1]nonanes by Acid-Catalyzed Rearrangement of 6-Substituted Bicyclo[4.2.0]octanones

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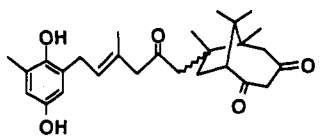
Summary: A novel and highly-efficient method for the synthesis of the bicyclo[4.2.1]nonane ring system by acid-catalyzed rearrangement of 6-substituted bicyclo-[4.2.0]octan-2-ones was developed.

The bicyclo[4.2.1]nonane ring system is a key structure of several terpenoids and their metabolites, such as the mediterraneols 1 and longicamphoric acid (2).[1] While several methods are available for the construction of the bicyclo[4.2.1]nonane skeleton, most of them utilize cycloaddition reactions.[2] We wish to report here a novel approach for the construction of the bicyclo[4.2.1]nonane framework which is based on acid-catalyzed rearrangement of 6-substituted bicyclo[4.2.0]octanones.



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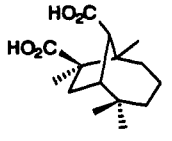

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Recently, we reported a new method for the construction of the bicyclo[3.3.0]octane 7 by acid-catalyzed rearrangement of 5,6-disubstituted bicyclo[4.2.0]octanones 3. The reaction is initiated by fission of the central cyclobutane bond to generate the eight-membered-ring cation 4, and subsequent 1,2-hydride shift (path a) followed by transannular cyclization of cation 5 furnishes the bicyclo-[3.3.0]octanones 7 (Scheme I).[3a] We envisaged, based on this mechanism, that a novel and efficient method for the synthesis of the bicyclo[4.2.1]nonane (bridged) ring system 8 could be developed by acid-catalyzed rearrangement of 6-substituted bicyclo[4.2.0]octanones 3 which do not possess an alkyl substituent at C(5) (R^4 = H). Namely, migration of R^3 located on the C(6) substituent to the adjacent cationic center of intermediate 4 would afford cation 6 (path b), and subsequent cyclization of cation 6 would give the bridged bicycles 8.[4] From this point of view, we have investigated the acid-catalyzed rearrangement of 6-substituted bicyclo[4.2.0]octanones **3a–g**, **12**, **13**, **16**, and **17** and found that the expected bicyclo[4.2.1]nonanones were obtained efficiently from those substrates with a tertiary or a secondary alkyl substituent.

Scheme I

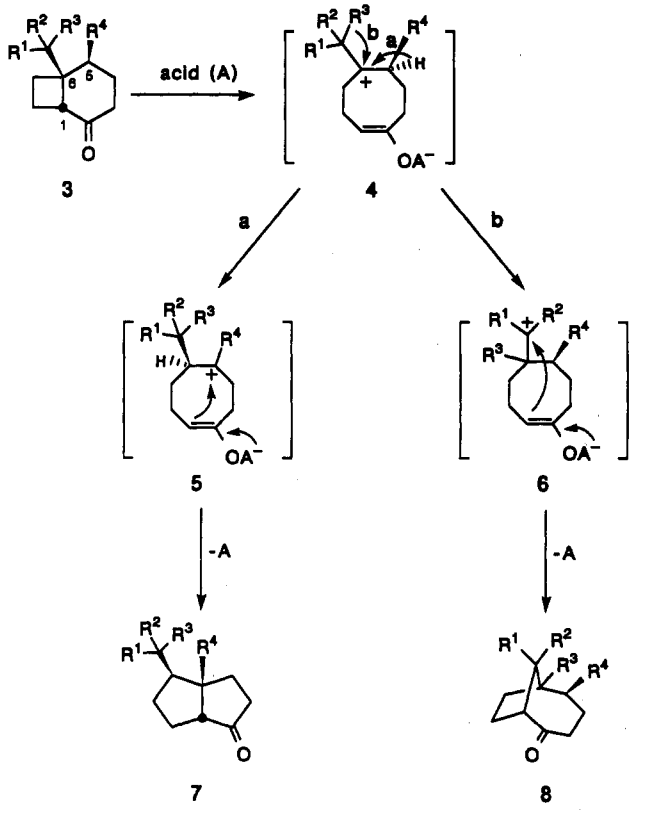

Table I. Acid-Catalyzed Rearrangement of 3a–g with $AlCl_3$[a]

entry	substrate	reactn time (h)	products[b] (yield (%))
1	**3a**	1	**8a** (81), **9** (11)
2	**3b**	1	**8b** (98)
3	**3c**	1	**8c** (100)
4	**3d**	50	**8d** (37), **8d′** (37)
5	**3e**	0.5	**8e** (47)
6	**3f**	0.2	**10** (82), **11** (4)
7	**3g**	120	c

[a] All reactions were carried out using 100 mg of ketone and 2 equiv of $AlCl_3$ in 5 mL of CH_2Cl_2 at room temperature. [b] Yields are for the isolated products by flash chromatography (SiO_2). [c] No rearranged product detected, see ref 3a.

The reaction of bicyclo[4.2.0]octanones **3a–g** was carried out using H_2SO_4, CF_3SO_3H, $TiCl_4$, $FeCl_3$, BCl_3, or $AlCl_3$ as acid catalyst. In most cases, $AlCl_3$ gave the most satisfactory results, which are listed in Table I.[5] The *t*-Bu,

(1) Mediterraneols A–D: (a) Francisco, C.; Banaigs, B.; Teste, J.; Cave, A. *J. Org. Chem.* **1986**, *51*, 1115. (b) Francisco, C.; Banaigs, B.; Valls, R.; Codomier, L. *Tetrahedron Lett.* **1985**, *26*, 2629. Longicamphoric acid: (c) Suryawanski, S. N.; Nayak, U. R. *Ibid.* **1977**, 2619. (d) Shitole, H. R.; Deshpande, R. P.; Nayak, U. R. *Ind. J. Chem.* **1984**, *23B*, 418. Secolongifolenediol: (e) Yadav, J. S.; Chawla, H. P. S.; Dev, S. *Ibid* **1983**, *22B*, 212. (f) Doron, F.; Arigoni, D. *Experientia* **1974**, *30*, 851. Secolongibornenal: (g) Bohlmann, F.; Zdero, C.; Jakupovic, J.; Greger, H. *Phytochemistry* **1983**, *22*, 503.

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(4) It is well-known that cyclization of 4-cyclooctenyl-1-methyl cation generated by solvolysis of the corresponding brosylate or tosylate gives bicyclo[3.3.1]nonanes as major products rather than bicyclo[4.2.1]nonanes, see: Baggaley, K. H.; Dixson, J. R.; Evans, J. M.; Graham, S. H. *Tetrahedron* **1967**, *23*, 299 and references cited therein. Note that an enolate in the cation intermediate 6 is essential to the selective ring closure to the bicyclo[4.2.1]nonane system.

(5) All results are summarized in Table SI in the supplementary material.

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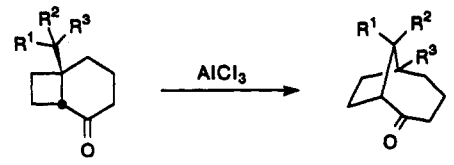
i-Pr, and cyclohexyl derivatives **3a–c** gave the corresponding bicyclo[4.2.1]nonanones **8a–c** in high yields (81–100%) (entries 1–3).[6] Although in the case of **3a**, bicyclo[4.3.0]nonane derivative **9** was obtained as a minor product, the use of other acids such as $TiCl_4$ and BCl_3 suppressed the formation of **9** and gave **8a** in yields of ca. 85%.[5] In these cases, the intermediate cation **6** formed by migration of a methyl or a hydride from **4** is tertiary. The ethyl derivative **3d** afforded the bridged bicyclic system as a 1:1 mixture of two stereoisomers **8d** and **8d′** (entry 4). The reaction, however, was more sluggish than those of **3a–c**. Similarly, the benzyl derivative **3e** yielded **8e** as a single isomer in 47% yield (entry 5).[7] On the other hand, the allyl derivative **3f** did not give the bridged products but afforded bicyclo[4.3.0]nonane derivatives **10** and **11** (entry 6).[8] The methyl derivative **3g** did not give rearranged products as described previously,[3a] because the formation of **6** as a primary carbocation would be highly unfavorable (entry 7).

In order to investigate the stereochemical outcome of this rearrangement, we treated 8-acetoxy-6-*tert*-butyl derivatives **12** and **13** with $AlCl_3$ (5 equiv). Bicyclo[4.2.1]nonanones **14** and **15** were obtained stereospecifically in quantitative yield from **12** and **13**, respectively.[9] This observation means that C(6) undergoes complete inversion which maintains the cis (or trans) relationship between C(6) and C(8) on the eight-membered ring of **14** (or **15**). It is, therefore, reasonable to consider that the methyl group migrates exclusively to the back side of the central C(1)–C(6) bond.

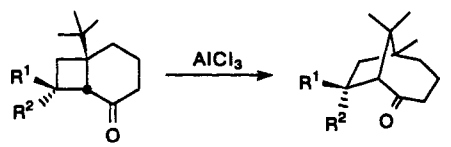


3a $R^1=R^2=R^3=Me$
3b $R^1=R^2=Me$, $R^3=H$
3c $R^1=R^2=-(CH_2)_5-$, $R^3=H$
3d $R^1=Me$, $R^2=R^3=H$
3e $R^1=Ph$, $R^2=R^3=H$
3f $R^1=vinyl$, $R^2=R^3=H$
3g $R^1=R^2=R^3=H$

8a $R^1=R^2=R^3=Me$
8b $R^1=R^2=Me$, $R^3=H$
8c $R^1=R^2=-(CH_2)_5-$, $R^3=H$
8d $R^1=Me$, $R^2=R^3=H$
8d′ $R^1=R^3=H$, $R^2=Me$
8e $R^1=Ph$, $R^2=R^3=H$
8e′ $R^1=R^3=H$, $R^2=Ph$

9

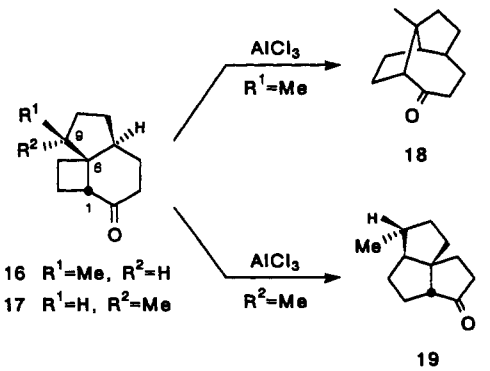
10 $\Delta^{1,6}$
11 $\Delta^{6,7}$



12 R^1=OAc, R^2=H
13 R^1=H, R^2=OAc

14 R^1=OAc, R^2=H
15 R^1=H, R^2=OAc

Both types of rearrangement, i.e., path a and path b, are, in principle, possible for substrates bearing a secondary or a tertiary alkyl group on C(6) and an alkyl group on C(5). In order to ascertain which pathway predominates and to elucidate the importance of the stereochemistry of the migrating group, we examined the acid-catalyzed reactions of tricyclic ketones **16** and **17**. Reaction of the *exo*-methyl ketone **16** with $AlCl_3$ gave tricyclic ketone **18** having a bicyclo[4.2.1]nonane nucleus in 89% yield along with a small amount of the angularly fused ketone (epimer of **19**, 3%).[10] On the other hand, similar treatment of the *endo*-methyl ketone **17** afforded only the fused ketone **19** in 90% yield as described previously.[3a] The different rearrangements of **16** and **17** may be explained by a stereoelectronic effect which is consistent with the stereochemistry of the rearrangement discussed for **12** and **13**. Thus, the endo hydrogen (R^2) on C(9) of **16** is aligned almost antiperiplanar to the central cyclobutane bond while the exo hydrogen (R^1) of **17** is not favorably situated for 1,2-hydride shift.[11]



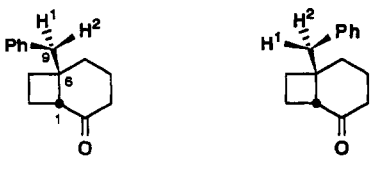
16 R^1=Me, R^2=H
17 R^1=H, R^2=Me

18

19

(6) All new compounds have been characterized spectrally, and their elemental composition was established by combustion analysis or high-resolution mass spectroscopy (see supplementary material). Starting materials **3a–e**, **12**, **13**, and **16** were prepared by the photochemical 2 + 2 addition of ethylene or vinyl acetate to the corresponding substituted cyclohexenones. Ketone **3f** was prepared as follows: (i) photocycloaddition of ethylene to 3-(3-acetoxypropyl)cyclohex-2-en-1-one, (ii) protection of the carbonyl group as a 1,3-dioxolane, (iii) hydrolysis, (iv) conversion of the alcohol to chloride, (v) dehydrochlorination, and (vi) deprotection. Details are given in the supplementary material. The structures of **8a**, **9**, **10**, and **18** were elucidated by 2D ^{13}C-INADEQATE spectra. As confirmation of the structures of **8b–d**, and **8d′**, Wolff–Kishner reductions gave the corresponding hydrocarbons having a plane of symmetry. The stereochemistry of the methyl groups of **8d** and **8d′** was assigned from ^{1}H NMR spectra in the presence of the shift reagent Eu(DPM)$_3$; the methyl protons of **8d′** exhibit greater shifts than those of **8d**. The structures of **8e**, **14**, and **15** are assigned by comparison of their ^{13}C NMR spectral data with those of other bicyclo[4.2.1]nonanones. The cis-fused ring junction of **9** was determined by the C–H COSY spectra and NOE experiments where presaturation of the methyl group on C(6) at 0.89 ppm resulted in an NOE of the methine proton on C(1) at 2.59 ppm.

(7) MM2 calculations (Allinger, N. L. *QCPE No. MM2(85)*) show that ketone **8e** obtained from the reaction of **3e** is less stable by 0.5 kcal/mol than its epimer **8e′**. In order to see whether there is a conformational preference in substrate **3e** leading either to **8e** or **8e′**, MM2 calculations for **3e** were carried out, in which the dihedral angle between the migrating hydrogen-C(9) bond and the C(1)–C(6) bond is fixed to 180°. The heat of formation of the conformer **i** which would give **8e** through migration of H^1 is −12.2 kcal/mol, while that of the conformer **ii** which would give **8e′** through migration of H^2 is −12.9 kcal/mol. Consequently, we have so far no explanation why **8e** was obtained in preference to **8e′**.



i **ii**

(8) The reason for the exceptional reactivity of **3f** is not understood.

(9) The stereochemistry of the acetoxyl group in **12–15** was assigned based on NOE experiments and the details are shown in the supplementary material.

(10) Reduction of the angularly fused ketone gave a hydrocarbon which was identical with an authentic sample prepared previously.[3a]

In summary, a novel and efficient method for the synthesis of bicyclo[4.2.1]nonane-2-ones was established. Application of the present methodology to the synthesis of the mediterraneols 1 is in progress in our laboratory.

(11) This is supported by the MM2 calculations[7] for the most stable conformers of 16 and 17 which lie within ca. 2 kcal/mol. Namely, the dihedral angle between the endo hydrogen-C(9) bond and the central cyclobutane bond is in the range of -160.5° to -70.7° for six conformers of 16, while the corresponding angle between the exo hydrogen-C(9) bond and the C(1)-C(6) bond is in the range of -33.2° to 58.2° for five conformers of 17.

Acknowledgment. Thanks are due to the Instrumental Analysis Center, Faculty of Engineering, Osaka University for assistance in obtaining NMR and mass spectra.

Supplementary Material Available: Experimental details of the acid-catalyzed reactions of **3a-g**, **12**, **13**, **16**, and **17**; spectroscopic and analytical data for **3a-f**, **8a-e**, **9-16**, and **18**; Table SI listing the results of the acid-catalyzed reactions of **3a-g** with various acids; 2D ^{13}C-INADEQUATE spectra of **8a**, **9**, **10**, and **18** (23 pages). Ordering information is given on any current masthead page.

Copper-Catalyzed Aziridination of Olefins by (*N*-(*p*-Toluenesulfonyl)imino)phenyliodinane

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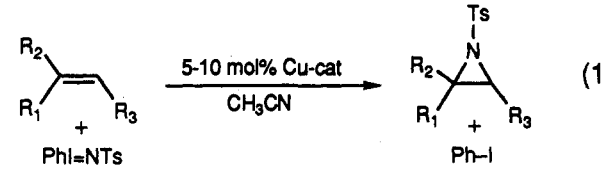
Summary: The Cu(I)- or Cu(II)-catalyzed aziridination of both electron-rich and electron-deficient olefins employing (*N*-(*p*-toluenesulfonyl)imino)phenyliodinane, PhI=NTs, as the nitrene precursor, affords *N*-tosylaziridines in yields ranging between 55%-95%.

In a seminal 1967 publication, Kwart and Kahn[1] reported the copper-bronze-catalyzed aziridination and allylic insertion reactions of benzenesulfonylazide with cyclohexene. Subsequently, Mansuy disclosed that aziridination of a number of olefins can be achieved with (*N*-(*p*-toluenesulfonyl)imino)phenyliodinane (PhI=NTs)[2] using Fe(III)- and Mn(III)-porphyrins as catlysts.[3] Other evidence for catalytic imido group transfer has appeared in the literature;[4] however, the number of olefinic substrates, nitrene precursors, and catalysts that have been evaluated in these studies has been limited. In view of the demonstrated utility of suitably functionalized aziridines in organic synthesis,[5] it is noteworthy that the scope of this reaction has not been fully developed.

Based on the proven ability of Cu(I)-based catalysts to promote olefin cyclopropanation, we have explored the scope of soluble copper catalysts in the analogous aziridination processes. In our preliminary studies concerned with the development of chiral variants of the cyclopropanation process, we have found that Cu(I) is a highly effective catalyst.[6] The purpose of the present paper is to describe the scope and optimized reactions of the Cu(MeCN)$_4$ClO$_4$[7] and Cu(acac)$_2$-catalyzed olefin aziridination using PhI=NTs as the nitrene precursor (eq 1).



(1)

Our preliminary results suggest that copper is superior to other metal complexes such as Mn(TPP)Cl, Fe(TPP)Cl, Rh$_2$(OAc)$_4$, and Co(acac)$_2$. With regard to the catalytically active oxidation state of copper, it was surprising to find that both Cu(I) and Cu(II) salts (for example, halide, triflate, and nitrate) were catalytically competent and that either Cu(MeCN)$_4$ClO$_4$ or Cu(acac)$_2$ appeared to be the catalysts of choice based on yields of olefin aziridination.

The influence of solvent polarity on the rate and efficiency of the reaction is striking. Although good yields of styrene aziridination may be achieved with a number of Cu- and Mn-based catalysts in either nonpolar or polar solvents, this substrate has proven not to be representative for either optimal solvent or metal catalyst extrapolations. A comprehensive screening of olefinic substrates and reaction solvents has led us to conclude that dipolar aprotic solvents such as MeCN and MeNO$_2$ are optimal for the reaction, and in the present study, the former solvent was shown to be the medium of choice.

The data for a representative selection of olefins with the catalyst Cu(MeCN)$_4$ClO$_4$ and Cu(acac)$_2$ is summarized in Table I along with the best results previously reported for either Mn(TPP)Cl or Fe(TPP)Cl. PhI=NTs, like its oxygen analogue PhI=O,[8] is insoluble in a variety of

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