Unexpected Hydrolysis of a C(7)-Oxo-Substituted 2-Oxonorborn-1-yl Triflate: Norbornane-Ring Expansion versus Norbornane-Ring Contraction

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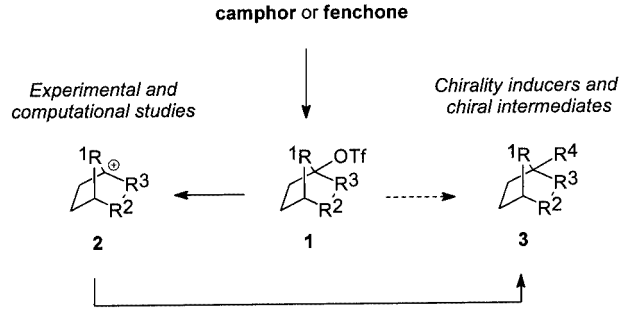
Camphor-derived 3,3-dimethyl-2,7-dioxonorborn-1-yl triflate, a new C(7)-substituted 2-oxonorborn-1-yl triflate, reacts readily with water to give an interesting bicyclo[2.2.2]octane-derived lactone, which results from an expansion of the norbornane ring by the methano bridge. This unusual reactivity constitutes the first example in which a 2-oxonorborn-1-yl triflate undergoes hydrolysis with norbornane-ring expansion instead of the expected norbornane-ring contraction (formation of a bicyclo[2.1.1]hexane-1-carboxylic acid). Mechanistically the process takes place through a stereocontrolled tandem bicycle-ring opening–bicycle-ring closing, which is activated by the oxo group located at the C(7)-norbornane position.

Introduction

1-Norbornyl triflates (e.g. **1** in Scheme 1) are an important class of bicyclic derivatives that have allowed the study of the amazing bridgehead (non-planar) 1-norbornyl carbocations (e.g. **2** in Scheme 1), as well as the preparation of other interesting bridgehead-substituted norbornanes (e.g. **3** in Scheme 1).[1−3]



Scheme 1

During the last few years, our research group has extensively contributed to this research field by: (a) the development of straightforward enantiospecific synthetic routes to new interesting 1-norbornyl triflates from readily available enantiopure 2-norbornanones [e.g. natural (+)-camphor or natural (−)-fenchone],[1] (b) the experimental and theoretical study of the stability and structure of the 1-norbornyl carbocations generated from such obtained 1-norbornyl triflates,[2] and (c) the use of some of those enantiopure 1-norbornyl triflates for the preparation of interesting norbornane-derived chiral inducers (e.g. chiral catalysts for asymmetric synthesis) as well as key chiral synthetic intermediates for the preparation of valuable molecules (e.g. jasmonoids, prostaglandins and other natural cyclopentanoids)[3] (Scheme 1).

The present communication reports the preparation of a new enantiopure C(7)-substituted (7-oxo) 2-oxonorbon-1-yl triflate from the chiral pool (natural camphor). The developed synthetic route to this 1-norbornyl triflate is a model procedure for the enantiospecific preparation of other interesting C(1)/C(2)/C(7)-trisubstituted norbornanes (e.g. valuable tridentate ligands). The obtained 2,7-dioxonorborn-1-yl triflate, in contrast to other 2-oxonorborn-1-yl triflates, undergoes an easy stereocontrolled hydrolysis to produce a 2-oxabicyclo[2.2.2]octane derivative. This unexpected hydrolysis, which takes place with norbornane-ring expansion, is activated by the strained oxo group located at the C(7)-norbornane position. The substituent effect (oxo effect) at the C(7)-norbornane position could be used as a synthetic strategy for the easy C(1)−C(7) cleavage of other substituted 2,7-dioxonorbon-1-yl triflates, allowing the stereocontrolled preparation of valuable substituted cyclohexanoids.

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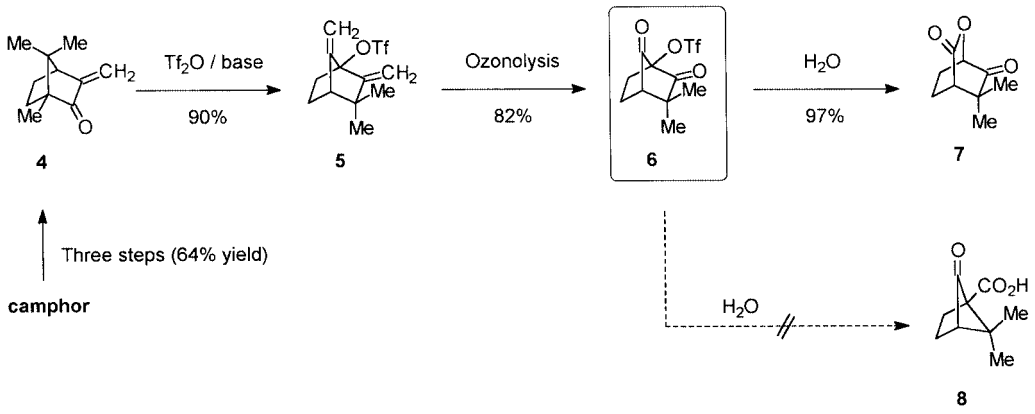


Scheme 2

Results and Discussion

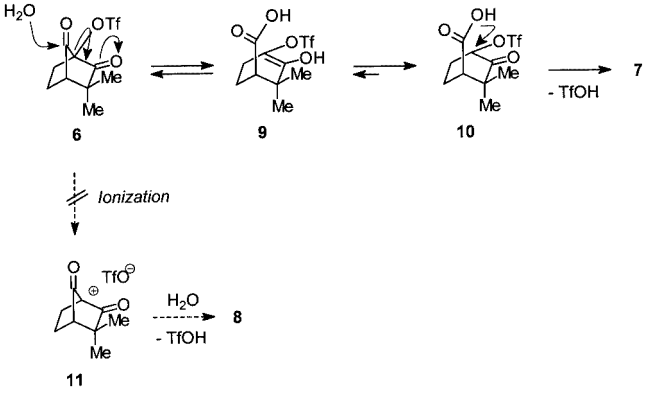
During the course of our research on the study of the reactivity and synthetic application of C(1)-substituted-norbornanes,[1−3] we were interested in the preparation of enantiopure 2,7-dioxonorborn-1-yl triflates (such as **1**, where $R^1 = R^3 = C{=}O$), which, following our established synthetic procedures, would allow the preparation of conformationally rigid tridentate (1,2,7-trisubstituted) chiral ligands [e.g. vicinal triols such as **3**, where $R^1 = R^3 =$ CH(OH) and $R^4 =$ OH].[4]

With this in mind, we have now obtained the 2,7-dioxonorborn-1-yl triflate **6** from natural (+)-camphor as shown in Scheme 2. The key step of the established synthetic procedure is a triflic-anhydride-promoted enantiospecific Wagner−Meerwein rearrangement of 3-methylenecamphor (**4**)[5] to the bridgehead triflate **5**.[6] Ozonolysis of the methylene groups of this triflate gives the desired 2,7-dioxanorborn-1-yl triflate **6**.[7]

Despite the relative stability of other 2-oxonorborn-1-yl triflates,[2b,2d] triflate **6** was found to be fairly unstable, undergoing an unusual fast hydrolysis to produce lactone **7** (Scheme 2).[8] Moreover, the formation of lactone **7** instead of the bicyclo[2.1.1]hexane-based carboxylic acid **8** (the reaction product expected from the hydrolysis of a 2-oxonorbornyl triflate),[2b,2d] is also striking (Scheme 1).

The formation of bicyclic lactone **7** can be explained according to the reaction pathway showed in Scheme 3. Thus, nucleophilic addition of water to the more strained oxo group located at the C(7)-norbornane position of **6**, probably activated by the presence of the second oxo group at C(2), takes place with fragmentation of the C(1)−C(2) norbornane bond (ring opening) to produce the cyclohexenol **9**. Cyclohexenol **9** is a tautomer of the very reactive keto-triflate **10**, which then undergoes a fast intramolecular nucleophilic attack of the carboxylic acid group (S_N2 ring closing), to give the finally detected bicyclic lactone **7**.

Therefore, the hydrolysis of triflate **6** does not takes place through the classical unimolecular mechanism (ionization) proposed for the solvolysis of other 1-norbornyl triflates, including 2-oxonorborn-1-yl triflates,[2b,2d] but through a bimolecular one (water addition to the carbonyl group).[9] The ionization of triflate **6** would give the highly unstable 2-oxonorborn-1-yl carbocation **11** due to the electron-withdrawing effect exerted by the second carbonyl group located at the C(7)-norbornane position.



Scheme 3

Conclusion

In summary, the introduction of a second α-carbonyl group [the C(7)-oxo group] in a 2-oxonorborn-1-yl triflate increases the instability of the corresponding bridgehead 1-norbornyl carbocation, making such a triflate less likely to undergo ionization (a unimolecular process giving norbornane-ring contraction products in 2-oxonorborn-1-yl triflates). In contrast, the addition of water to the carbonyl group is activated, producing the fast hydrolysis of the 2,7-dioxonorborn-1-yl triflate via a stereocontrolled tandem norbornane-ring opening/norbornane-ring closing reaction. To the best of our knowledge, the result reported herein is the first unequivocal example in which a solvent-addition mechanism is operative for the solvolysis of a 2-oxo-substituted bridgehead triflate.

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[4] For the preparation of chiral ligands (diols and amino alcohols) from 1-norbornyl triflates see for example: [4a] A. García Martínez, E. Teso Vilar, A. García Fraile, S. de la Moya Cerero, L. R. Subramanian, *Tetrahedron: Asymmetry* **1994**, *5*, 1373−1376. [4b] A. García Martínez, E. Teso Vilar, A. García Fraile, S. de la Moya Cerero, P. Martínez Ruiz, L. R. Subramanian, *Tetrahedron: Asymmetry* **1996**, *7*, 1257−1260 and ref.[3b] For the importance of tridentate norbornane-based ligands as chiral catalysts, see for example: [4c] I. Philipova, V. Dimitrov, S. Simova, *Tetrahedron: Asymmetry* **1999**, *10*, 913−921 and 1381−1391. Restricted norbornane-based triols can be interesting intermediates for the synthesis of artificial lyposomes (see for example: [4d] A. D. Miller, *Angew. Chem. Int. Ed.* **1998**, *37*, 1768−1785), whereas restricted aminodiols can be used in the synthesis of artificial sphingosines (see for example: [4e] N. Khiar, K. Singh, M. García, M. Martín-Lomas, *Tetrahedron Lett.* **1999**, *40*, 5779−5782). On the other hand, chiral tridentate triols are interesting ligands for the preparation of transition-metal complex chiral catalysts (see for example: [4f] H. Lütjens, G. Wahl, F. Möller, P. Knöchel, J. Sundermeyer, *Organometallics* **1997**, *16*, 5869−5878).

[5] For the preparation of **4** from camphor, see: M. Gianini, A. von Zelewsky, *Synthesis* **1996**, 702−706, and references cited therein.

[6] Triflic anhydride (Tf_2O; 1.3 mol equiv.) was slowly added to a solution of **4** (0.50 g) and 1.5 mol equiv. of triisobutylamine in dry CH_2Cl_2 (10 mL). The reaction mixture was stirred at room temperature for 48 h. After standard work up (see ref.[1]) the obtained product was purified by elution chromatography (silica gel/hexane) to obtain pure (1*R*)-3,3-dimethyl-2,7-dimethylenenorborn-1-yl triflate (**5**; 0.81 g, 90% yield) as a colorless liquid. $[\alpha]_D^{20} = -17$ ($c = 0.13$, CH_2Cl_2). FTIR, MS, HRMS (a reliable elemental analysis was difficult to obtain, probably due to the high reactivity of **4**) and the ^1H and ^{13}C NMR spectra agree with the proposed structure.

[7] Triflate **5** (0.50 g) was submitted to a standard ozonolysis (ozone was passed through a CH_2Cl_2 solution at −78 °C, followed by treatment with Me_2S). After the usual work up a mixture of (1*R*)-3,3-dimethyl-2,7-dioxonorborn-1-yl triflate (**6**; 82%) and (1*S*)-3,3-dimethyl-2-methylene-7-oxonorborn-1-yl triflate (**6b**; mono-ozonolyzed product, 18%) was obtained as a colorless oil in almost quantitative yield. The FTIR, and ^1H and ^{13}C NMR spectra agreed with the two structures present in such a mixture. Dioxonorborn-1-yl triflate **6** completely decomposes to (1*R*)-5,5-dimethyl-2-oxabicyclo[2.2.2]octane-3,6-dione (**7**) when submitted to elution chromatography (silica gel or neutral alumina, hexane/CH_2Cl_2, 1:4), whereas the mono-ozonolyzed triflate remains unaltered. Lactone **7**: white solid, $[\alpha]_D^{20} = +14.7$ ($c = 2.0$, $CHCl_3$), m.p. 84.0−85.0 °C (FTIR, MS, HRMS, and ^1H and ^{13}C NMR spectra agree with the structure). A good-quality single crystal of **7** for X-ray diffraction analysis was obtained by crystallization from hexane. The X-ray-diffraction study confirmed the structure of lactone **7** unequivocally. Ketotriflate **6b**: white solid, m.p. 68−70 °C. $[\alpha]_D^{20} = -31.4$ ($c = 1.8$, $CHCl_3$). (FTIR, MS, HRMS, and ^1H and ^{13}C NMR spectra agree with the structure).

[8] A dispersion of 0.30 g of the mixture of **6** and **6b** (**6**/**6b** = 82:18, see ref.[7]) in water (5 mL) was stirred at room temperature for 1 h. After standard work-up a mixture of **7** and **6b** (**7**/**6b** = 82:18) was obtained. The mixture was separated by elution chromatography (silica gel, hexane/CH_2Cl_2, 1:4). After chromatography, pure **7** was obtained (0.13 g, 97% yield from **6**) (for characterization data see ref.[7]).

[9] Solvent addition to the carbonyl group before the triflate-group cleavage has been previously proposed, although to the best of our knowledge not totally demonstrated, for the solvolysis of some 2-oxo- and 2-thioxo-substituted bridgehead triflates. See for example: [9a] X. Creary, *Chem. Rev.* **1991**, *91*, 1625−1677. [9b] K. Takunaga, T. Ohtsu, Y. Ohga, K. Takeuchi, *J. Org. Chem.* **1998**, *63*, 2209−2217. See also ref.[2d] and the references cited therein.

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