N-Bromosuccinimide-Induced Lactonization of Bicyclo[3.2.0]hept-3-en-6-ones

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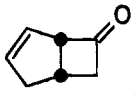
Bicyclo[3.2.0]hept-3-en-6-ones (**1**) as well as the well-known isomeric bicyclo[3.2.0]hept-2-en-6-ones (**2**) possess an appealing structure with two fused rings of different size, each functionalized in a different manner, thus allowing for regio- and stereoselective transformations, which have been exploited in the synthesis of many complex products.[1,2]



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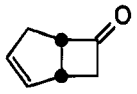

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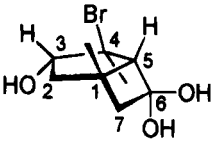
Recently, we developed a general and efficient preparation of many substituted bicyclic compounds of type **1** from the corresponding 3-hydroxy-6-heptenoic acids and found useful applications of these interesting building blocks in the synthesis of different natural products such as grandisol,[3] lineatin,[3] and filifolone.[4]

In the course of our search for synthetic utilization of compounds of type **1** we found that treatment of 1,4-dimethylbicyclo[3.2.0]hept-3-en-6-one (**3a**) with *N*-bromosuccinimide (NBS) in aqueous dimethoxyethane (DME) at 0 °C, afforded the lactone **4a**, resulting in a new method for the selective oxidation of cyclobutanone carbonyl group to the corresponding lactone (Scheme 1).

The reaction presumably involves the regio- and stereospecific formation of the halohydrin,[5] whose hydrate form **6** can undergo a fragmentation with 1,4-elimination of hydrobromic acid and opening of the four-membered ring, thus affording the sensitive hydroxy carboxylic acid **7**. This kind of acid is known to spontaneously rearrange to the corresponding bicyclic lactone in the presence of an acid or on standing.[6]

It has been shown that fragmentations take place when the compounds involved can adopt a conformation where the two breaking bonds are in an antiperiplanar alignment,[7] and indeed, this is the case of the halohydrin **6**. In fact, as can be deduced from the models, the dihedral angle between the C6–C5 and the C4–Br bonds is around 170°.[8]



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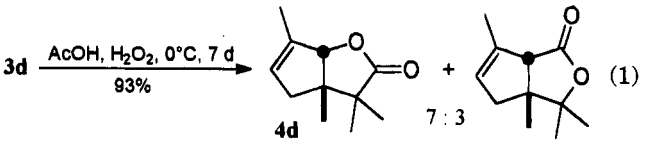
With 4-methyl-substituted bicyclo[3.2.0]hept-3-en-6-ones the fragmentation occurs spontaneously at 0 °C, since it requires the elimination of a tertiary bromine atom (Table 1).

The reaction proceeds with very good yields and in some cases may represent an interesting alternative to the existing methods for the lactonization of this kind of bicyclic ketones. For example, the hydrogen peroxide oxidation of **3d**, at 0 °C in acetic acid,[9] is complete in 7 days affording a 7:3 mixture of the two regioisomeric lactones in a 93% yield (eq 1); with NBS the same



(1)

oxidation can be achieved in 30 min at 0 °C and selectively gives only the isomer **4d** in a comparable yield.

With 4-unsubstituted substrates the intermediate halohydrin can be isolated and the corresponding lactone obtained, though in lower yields, by heating the reaction mixture at 60 °C after halohydrin formation is complete at 0 °C (Table 2).

These results suggest that the reactivity of compounds with the bicyclic structure of **1**, where the double bond and the cyclobutanone carbonyl group are joined by a bridgehead carbon atom, in some cases should not be simply regarded as the sum of the reactivities of the

(1) The chemo- and regiospecific oxidation of bicyclic ketones with the structure of **1** is an effective way for the preparation of the corresponding lactones, which are key intermediates in the synthesis of several triquinane sesquiterpenes. See: Marotta, E.; Righi, P.; Rosini, G. *Tetrahedron Lett.* **1994**, *35*, 2949–2950.

(2) Bicyclic ketones with the structure of **2** have found many applications, particularly in the synthesis of prostaglandins. For an overview, see Corey, E. J.; Cheng X.-M. *The Logic of Chemical Synthesis*; John Wiley & Sons: New York, NY, 1989, pp 249–309.

(3) Confalonieri, G.; Marotta, E.; Rama, F.; Righi, P.; Rosini, G.; Serra, R.; Venturelli, F. *Tetrahedron* **1994**, *50*, 3235–3250.

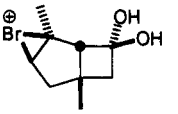
(4) Marotta, E.; Pagani, I.; Righi, P.; Rosini, G. *Tetrahedron* **1994**, *50*, 7645–7656.

(5) This selectivity could be ascribed to the preferential formation of the *exo*-bromonium ion and the subsequent attack of the nucleophile to the less hindered C3, attack at C4 from the *endo*-side being impossible, due to eclipsing interactions by the other atoms of the bicyclo system, as can be deduced by Dreiding models. See: (a) Ranganathan, S.; Ranganathan, D.; Mehrotra, A. K. *Tetrahedron Lett.* **1975**, 1215–1216. (b) Ali, S. M.; Crossalnd, N. M.; Lee, T. V.; Roberts, S. M.; Newton, R. F. *J. Chem. Soc., Perkin Trans. 1* **1979**, 122–125.

(6) (a) Grieco, P. A.; Majetich, G. F.; Ohfune, Y. *J. Am. Chem. Soc.* **1982**, *104*, 4226–4233. (b) Greene, A. E.; Le Drian, C.; Crabbé, P. *J. Am. Chem. Soc.* **1980**, *102*, 7583–7584. (c) Grieco, P. A.; Yokoyama, Y.; Withers, G. P.; Okuniewicz, F. J.; Wang, C.-L. J. *J. Org. Chem.* **1978**, *43*, 4178–4182.

(7) For an excellent review, see: Deslongchamps, P. *Stereoelectronic Effects in Organic Chemistry*; Pergamon Press: Oxford, England, 1983; pp 257–266.

(8) Two alternative pathways can be considered. The first of them is the fragmentation of the intermediate bridged bromonium ion **8**, though in this case the two breaking bonds are not in the proper alignment (dihedral angle between C6–C5 and C4–Br is around 135°) for a one-step fragmentation. A second alternative might be a two-step fragmentation from **8**, which would require, as the first step, the opening of the bridged bromonium ion, though this event is not usual for aliphatic systems (see: Carey, F. A.; Sundberg, R. J. *Advanced Organic Chemistry*; 3rd ed.; Plenum Press: New York and London, 1990; Part A: Structure and Mechanism, p 353). Both these alternative pathways would afford the bromo analog of **7** that would be expected to undergo the same rearrangement observed for **7**.



8

(9) These conditions have been employed for the Baeyer–Villiger oxidation of several bicyclo[3.2.0]hepten-6-ones. See: (a) Corey, E. J., Arnold, Z.; Hutton, J. *Tetrahedron Lett.* **1970**, 307–310. (b) Grieco, P. A. *J. Org. Chem.* **1972**, *37*, 2363. (c) Reference 1.

0022-3263/94/1959-7526$04.50/0

Scheme 1

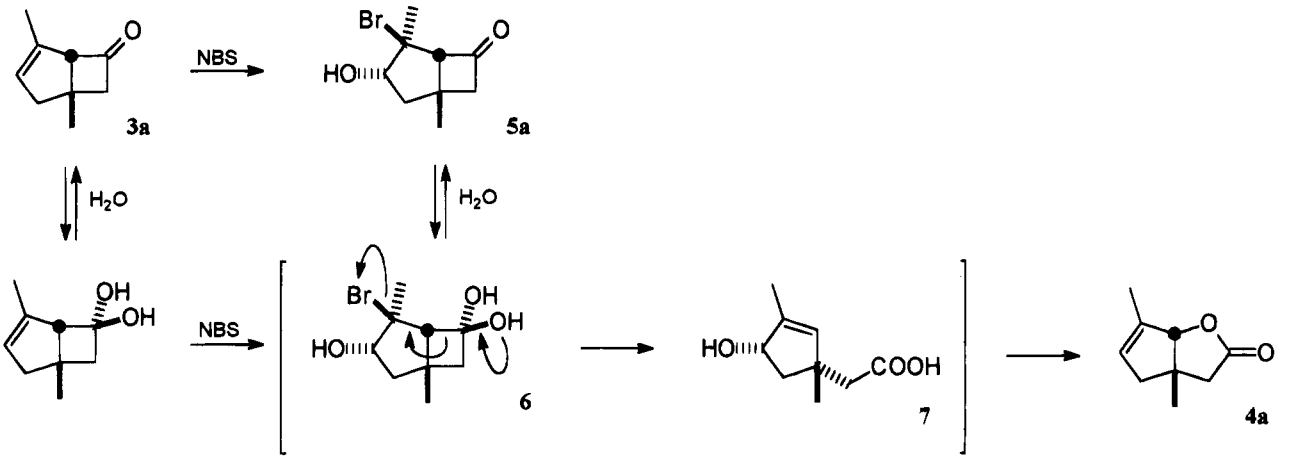


Table 1. Reaction of Several 4-Methylbicyclo[3.2.0]hept-3-en-6-ones with NBS

Substrate	Time	Product	Yield
3a	45 min	4a	84%
3b	30 min	4b	82%
3c	20 min	4c	80%
3d	30 min	4d	91%

Table 2. Reaction of 4-Unsubstituted Bicyclo[3.2.0]hept-3-en-6-ones with NBS

Substrate	Time[a]	Halohydrin	Lactone[b]
3e	3 h	not isolated	4e (72%)[c]
3f	2 h	5f (52%)	4f (61%)
3g	1.25 h	5g (72%)	4g (58%)
3h	2 h	5h (60%)	4h (66%)
3i	1.5 h	5i (81%)	4i (60%)

[a] Times refer to halohydrin formation at 0 °C. [b] Yields refer to the isolated lactone from the corresponding halohydrin. [c] From **3e**.

isolated functionalities as in systems of type **2**, but as a single moiety which arises from this peculiar disposition of the two functional groups.

Experimental Section

General. Melting points were obtained with a Büchi apparatus and are uncorrected. Yields are referred to isolated pure products. Proton and ^{13}C NMR spectra were recorded at 200 and 50 MHz, respectively, in $CDCl_3$ solvent. If not already stated, chemical shifts are expressed in ppm downfield from TMS as internal standard, and coupling constants are reported in hertz. Signal multiplicities were established by DEPT experiments. Flash chromatographic separations were performed using Merck silica gel 60 (70–230 mesh ASTM). For thin layer chromatography (TLC) analysis throughout this work, Merck precoated TLC plates (silica gel 60 GF_{254}, 0.25 mm) were used.

General Procedure for the Reaction of Bicyclo[3.2.0]-hept-3-en-6-ones with NBS. A solution of the required bicyclo-[3.2.0]hept-3-en-6-one (3.7 mmol) in a mixture of DME and water (2:1; 75 mL) was cooled to 0 °C with a bath of ice and water. NBS (660 mg; 3.7 mmol) was added to the mixture, under vigorous stirring. The course of reaction was monitored by TLC (eluant petroleum ether:diethyl ether = 1:1; R_f starting ketone ~0.9; R_f lactone ~0.4, R_f halohydrin ~0.3). After the reaction was complete the reaction mixture was extracted with diethyl ether (5 × 25 mL), and the organic phases reunited were washed with brine, dried over sodium sulfate, and finally evaporated at reduced pressure. In the case of **3e-i** the halohydrin, isolated at this point, was then heated overnight at 60 °C in a mixture of DME and water (2:1). The reaction mixture was extracted with diethyl ether (5 × 25 mL); the organics were dried over sodium sulfate and evaporated at reduced pressure to afford a crude material that was purified by flash chromatography (eluant petroleum ether:diethyl ether = 6:4; R_f ~0.3).

5,8-Dimethyl-2-oxabicyclo[3.3.0]oct-7-en-3-one (4a). The reaction was stopped after 45 min, and upon workup, compound **4a**[4] was obtained pure as a pale yellow oil (470 mg; 84% yield). Anal. Calcd for $C_9H_{12}O_2$: C, 71.02; H, 7.95. Found: C, 70.99, H, 7.81.

8-Methyl-2-oxabicyclo[3.3.0]oct-7-en-3-one (4b). After 30 min the reaction was complete, and compound **4b** was obtained upon workup. Flash chromatography of the crude product (eluant petroleum ether:diethyl ether = 1:1) afforded pure **4b**[4] as a colorless oil (420 mg; 82% yield). Anal. Calcd for $C_8H_{10}O_2$: C, 69.55; H, 7.30. Found: C, 69.49; H, 7.28.

4,4,8-Trimethyl-2-oxabicyclo[3.3.0]oct-7-en-3-one (4c). The reaction was stopped after 20 min, and after the usual workup, the crude material was purified by flash chromatography (eluant petroleum ether:diethyl ether = 6:4) to obtain a colorless oil (490 mg; 80% yield): IR (film) ν 1759 cm^{-1}; ^1H NMR δ 5.65 (m, 1H), 5.11 (d, 1H, J = 7.0), 2.80 (m, 1H), 2.40 (m, 2H), 1.85 (s, 3H), 1.35 (s, 3H), 1.20 (s, 3H); ^{13}C NMR δ 182.6, 138.1, 131.4, 88.64, 48.59, 42.56, 32.98, 28.08, 21.47, 14.38. Anal. Calcd for $C_{10}H_{14}O_2$: C, 72.26; H, 8.49. Found: C, 72.39; H, 8.51.

4,4,5,8-Tetramethyl-2-oxabicyclo[3.3.0]oct-7-en-3-one (4d). The reaction was stopped after 30 min, and and a pale yellow oil was obtained upon workup (610 mg; 91% yield): IR (film) ν 1770 cm^{-1}; ^1H NMR δ 5.68 (m, 1H), 4.54 (s, 1H), 2.49 (d with further fine couplings, 1H, J = 17.2), 1.97 (d with further fine couplings, 1H, J = 17.2), 1.85 (s, 3H), 1.20 (s, 3H), 1.19 (s, 3H), 1.10 (s, 3H); ^{13}C NMR δ 182.1, 137.0, 132.5, 93.86, 52.00, 45.82, 42.05, 23.46, 20.19, 19.18, 15.17. Anal. Calcd for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95. Found: C, 73.18; H, 9.01.

6,6-Dimethyl-2-oxabicyclo[3.3.0]oct-7-en-3-one (4e). After 3 h stirring at 0 °C halohydrin formation was complete (TLC, eluant petroleum ether:diethyl ether = 1:1; R_f 0.32). The reaction mixture was heated to reflux for 2 h, and upon usual workup the lactone **4e**[4] was obtained as a colorless oil (400 mg; 72% yield). Anal. Calcd for $C_9H_{12}O_2$: C, 71.02; H, 7.95. Found: C, 71.11; H, 7.94.

4-*exo*-Bromo-3-*endo*-hydroxybicyclo[3.2.0]heptan-6-one (5f). The reaction was complete after 2 h, and workup afforded a white solid (400 mg, 52% yield; mp 83–85 °C): IR (KBr) ν 3338, 1776 cm^{-1}; ^1H NMR δ 4.60 (d, 1H, J = 5.0), 4.35 (s, 1H), 3.90 (m, 1H), 3.35–2.90 (m, 4H; becomes 3H after D_2O exchange), 2.55 (ddd, 1H, J = 14.5, 8.0, 4.3), 1.95 (d, 1H, J = 14.5); ^{13}C NMR δ 208.9, 82.40, 72.70, 55.38, 53.57, 36.86, 28.92. Anal. Calcd for $C_7H_9BrO_2$: C, 41.00; H, 4.42; Br, 38.97. Found: C, 40.91; H, 4.50; Br, 39.04.

2-Oxabicyclo[3.3.0]oct-7-en-3-one (4f). Crude halohydrin **5f** was heated overnight at 60 °C in a mixture of DME:water (2:1; 40 mL). After the workup compound **4f**[4] was obtained as a pale yellow oil (150 mg; 61% yield). Anal. Calcd for $C_7H_8O_2$: C, 67.73; H, 6.50. Found: C, 67.75; H, 6.60.

4-*exo*-Bromo-3-*endo*-hydroxy-3-*exo*-methylbicyclo[3.2.0]-heptan-6-one (5g). The reaction was stopped after 1.25 h, and the usual workup afforded a white solid (590 mg, 72% yield; mp 74–76 °C): IR (KBr) ν 3452, 1768 cm^{-1}; ^1H NMR δ 4.28 (s, 1H), 3.90 (m, 1H), 2.90–3.30 (m, 4H), 2.38 (dd, 1H, J = 16.8, 7.2), 1.90 (d, 1H, J = 16.8), 1.61 (s, 3H); ^{13}C NMR δ 209.2, 85.73, 73.32, 60.07, 52.53, 41.37, 28.31, 25.02. Anal. Calcd for $C_8H_{11}BrO_2$: C, 43.86; H, 5.06; Br, 36.47. Found: C, 43.69; H, 5.11; Br, 36.55.

7-Methyl-2-oxabicyclo[3.3.0]oct-7-en-3-one (4g). Treatment of the crude halohydrin **5g** as described in the general procedure afforded lactone **4g**[4] as an oil (215 mg; 58% yield): IR (film) ν 1765 cm^{-1}; ^1H NMR δ 5.41 (m, 2H), 3.18–2.95 (m, 1H), 2.76 (dd, 1H, J = 18.5, 10.7 Hz), 2.59 (dd with further couplings, 1H, J = 16.7, 7.9), 2.15 (dd, 1H, J = 18.5, 5.2), 2.10 (d with further couplings, 1H, J = 16.8), 1.63 (s, 3H); ^{13}C NMR δ 178.0, 148.6, 123.7, 90.68, 43.87, 36.48, 36.11, 16.47. Anal. Calcd for $C_8H_{10}O_2$: C, 69.55; H, 7.30. Found: C, 69.61; H, 7.39.

4-*exo*-Bromo-3-*endo*-hydroxy-1-methylbicyclo[3.2.0]-heptan-6-one (5h). After 2 h of stirring at 0 °C the reaction was stopped and the usual workup furnished a white solid (490 mg; 60% yield; mp 98–100 °C): IR (KBr) ν 3384, 1776 cm^{-1}; ^1H NMR δ 4.60 (bs, 1H; becomes d after D_2O exchange, J = 5.5), 4.30 (s, 1H), 3.45 (dd, 1H, J = 4.1, 4.8), 3.27 (bs, 1H, disappears after D_2O exchange), 3.20 (dd, 1H, J = 17.2, 4.1), 2.90 (dd, 1H, J = 17.2, 4.8), 2.40 (m, 1H), 2.10 (d, 1H, J = 14.5), 1.55 (s, 3H); ^{13}C NMR δ 209.3, 82.38, 75.95, 59.73, 55.74, 43.64, 37.97, 27.26. Anal. Calcd for $C_8H_{11}BrO_2$: C, 43.86; H, 5.06; Br, 36.47. Found: C, 43.81; H, 5.14; Br, 36.50.

5-Methyl-2-oxabicyclo[3.3.0]oct-7-en-3-one (4h). Heating of the crude halohydrin **5h** overnight afforded, after chromatography, the title compound[4] as a colorless oil (205 mg; 66% yield): IR (film) ν 1765 cm^{-1}; ^1H NMR: δ 6.05 (m, 1H), 5.81 (m, 1H), 5.03 (m, 1H), 2.62–2.29 (m, 4H), 1.32 (s, 3H); ^{13}C NMR δ 177.5, 137.3, 129.4, 95.55, 46.51, 44.38, 43.30, 25.17. Anal. Calcd for $C_8H_{10}O_2$: C, 69.55; H, 7.30. Found: C, 69.48, H, 7.21.

4-*exo*-Bromo-3-*endo*-hydroxy-1,3-*exo*-dimethylbicyclo-[3.2.0]heptan-6-one (5i). The reaction was stopped after 1.5 h, and the usual workup furnished a white solid (700 mg, 81% yield; mp 86–88 °C): IR (KBr) ν 3427, 1771 cm^{-1}; ^1H NMR δ 4.22 (s, 1H), 3.42 (dd, 1H, J = 4.0, 4.2), 3.22 (dd, 1H, J = 17.2, 4.0), 2.95 (bs, 1H, disappears after D_2O exchange), 2.82 (dd, 1H, J = 17.2, 4.2), 2.24 (d, 1H, J = 14.5), 2.04 (dd, 1H, J = 14.5), 1.61 (s, 3H), 1.55 (s, 3H); ^{13}C NMR δ 208.6, 86.22, 77.05, 60.59, 59.28, 48.81, 37.53, 27.20, 25.42. Anal. Calcd for $C_9H_{13}BrO_2$: C, 46.37; H, 5.62; Br, 34.28. Found: C, 46.46; H, 5.63; Br, 34.42.

5,7-Dimethyl-2-oxabicyclo[3.3.0]oct-7-en-3-one (4i). Crude halohydrin **5i** treated as described in the general procedure affords, after chromatography, title compound[4] as a colorless oil (275 mg; 60% yield). Anal. Calcd for $C_9H_{12}O_2$: C, 71.03; H, 7.95. Found: C, 70.98; H, 7.95.

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