J. Chem. Research (S), 1999, 490–491†

Synthetic Studies of Dihydroagarofuran Sesquiterpene: an Improved NBS–THF–H_2O System for Stereoselective Construction of Tetrahydrofuran Moiety†

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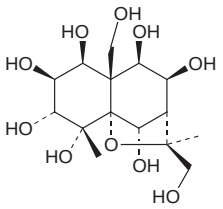
An improved aqueous NBS–THF system in a range of media has proved to be effective for stereoselective construction of the bromotetrahydrofuran moiety of dihydroagarofuran sesquiterpene polyesters from the corresponding β-hydroxyalkene.

Dihydroagarofuran sesquiterpene polyols, such as euonyminol **1** are the core of a number of sesquiterpene polyesters isolated from the Celastraceae family.[1] Because of their wide range of important biological activities,[2–4] synthetic studies on them have attracted the interest of organic chemists.[5,6] In connection with our recent synthetic work on the santonin **2**, an easily polyfunctionized and available natural source, great effort was focussed on the stereoselective construction of the tetrahydrofuran ring, and a cyclization procedure through oxymecuration of **3** with $Hg(OAc)_2$ and successive deoxymecuration with $NaBH_4$ has been successfully applied to construct this moiety.[7] In terms of overcoming over the second challenging synthetic problem, the multi-hydroxylation (*e.g.* at C-8 and C-9), such a cyclization method is not satisfactory due to the difficulty in directly accessing the 8,9-dihydroxys. Thus, it is necessary to design and develop a versatile cyclization system that could achieve both the stereoselectivity at C-7 and C-11 and the introduction of a potential group at C-7 (such as 7-bromide) for derivation of 8,9-dihydroxys.[8] Therefore, an NBS (*N*-bromosuccinimide)-promoted etherification was chosen to construct the tetrahedronfuran ring of the intermediate **3**.



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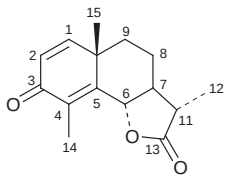

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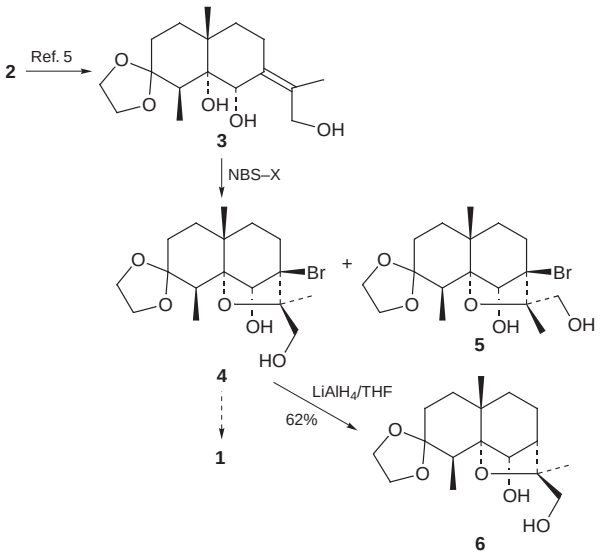
Although NBS-promoted cyclization to give the bromoether from the γ-hydroxyalkene substrates has offered a versatile means for preparing tetrahydrofuran ring,[9] it showed generally low stereoselectivity.[10] In addition, few NBS-promoted, especially aqueous NBS-promoted, cyclizations of β-hydroxyalkene substrates have been investigated,[9] and even fewer studies made on their stereoselectivity. Recently, extensive tests have revealed that an aqueous NBS–THF system in weak acidic to basic media could lead to an etheric cyclization of **3** with high diastereoselectivity at C-7 and C-11. All the experimental results are tabulated in Table 1.

As indicated in Table 1, cyclization of the β-hydroxyalkene **3** with the typical anhydrous NBS–THF system (entry 1) at 0 °C,[9] afforded mixed products of two C_{11}-epimers, **4** and **5**, in the ratio 50/50, which were hardly resolvable on a general silica gel column. Another disadvantage of this procedure was that the yield was poor and the reaction time was quite long. However, if the cyclization of **3** was conducted in weakly basic (*i.e.* $CaCO_3$, K_2CO_3, Li_2CO_3, Na_2CO_3, $NaHCO_3$, entries 2–6) aqueous solutions or suspensions, only one desired product, **4,** was obtained in good yields (65–86%). Similarly, cyclization of **3** with neutral or weakly acidic NBS–THF aqueous media also gave the exclusive product **4** in good yields (entries 7 and 8). Further experiments in stronger basic or acidic media than those in Table 1 could not afford the right product, but gave a complicated mixture (unidentified). In addition, in all examples tested (entries 2–8), we were



Scheme 1

Table 1 Cyclization of **3** with NBS in different media at 0 °C

Entry	X	Reaction time (t/h)	Products (**4**/**5**)	Isolated yield of **4** (%)
1	THF	6.0	50/50	27[a]
2	$CaCO_3-THF-H_2O$	1.5	>99/<1	86
3	$K_2CO_3-THF-H_2O$	1.5	>99/<1	82
4	$Li_2CO_3-THF-H_2O$	2.0	>99/<1	65
5	$Na_2CO_3-THF-H_2O$	2.5	>99/<1	72
6	$NaHCO_3-THF-H_2O$	2.5	>99/<1	70
7	$THF–H_2O$	1.0	>99/<1	64
8	Silica gel[b]–$THF–H_2O$	1.0	>99/<1	52

[a] The total yield of two products **4** and **5**. [b] 200–300 Mesh chromatography silica gel was applied.

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† This is a **Short Paper** as defined in the Instructions for Authors, Section 5.0 [see *J. Chem. Research (S)*, 1999, Issue 1]; there is therefore no corresponding material in *J. Chem. Research (M)*.

not able to isolate the normal adducts (*i.e.* the bromohydrin) of HOBr to the double bond.[11] For further confirmation of the stereochemistry of **4**, it was reduced with $LiAlH_4$/THF at room temperature to form **6**, which was identified as a well-known product.[7] Though we did not make a detailed investigation of the reaction mechanism, we assumed that it may incorporate the initial formation of a three-membered bromonium cation, followed by an S_N2-like addition-opening reaction to achieve the observed stereoselectivity. The improved NBS-promoted etherification procedure presented here for β-hydroxyalkenes proved to be a stereoselective and efficient etherification method, and perhaps could be applicable to other reactants.

Experimental

Synthesis of two C_{11}-Epimerized 3,3-*Ethylenedioxy*-6α,13-*dihydroxy*-7β-*bromoagarofuran* **5** *by NBS in Anhydrous THF*.–To a solution of **4** (110 mg, 0.35 mmol) in anhydrous THF (10 ml) NBS (210 mg, 1.18 mmol) was added at 0 °C under Ar gas. After stirring for 6 h at 0 °C, the mixture was diluted with EtOAc (40 ml) and washed with saturated $NaHCO_3$ solution, and then brine, and subsequently dried over Na_2SO_4. After the solvent was removed *in vacuo*, the residue was chromatographed [light petroleum (bp 60–90 °C)–acetone, 2 : 1] to afford a mixture of two isomers, **4** and **5** (70 mg, 20%). The NMR spectra showed nearly the equal amount of two isomers. ^{1}H NMR (**4** and **5**) δ_H (400 Hz, $CDCl_3$) 1.21 (d, $J = 7.5$ Hz, 3H), 1.29 (s, 3H), 1.37 (s, 3H), 1.40 (s, 2×3H), 1.41 (d, $J = 6.4$ Hz, 3H), 1.6–2.6 (m, 18H), 3.27 (d, $J = 11.2$ Hz, 1H), 3.31 (d, $J = 11.5$ Hz, 1H), 3.9–4.7(m, 12H). Compound **4**, δ_C 14.8, 17.1, 23.9, 26.4, 37.1, 38.9, 39.9, 41.2, 43.8, 65.1, 65.7, 68.1, 72.1, 78.6, 84.8, 90.5, 109.1. Compound **5**, δ_C 15.2, 17.2, 26.8, 29.6, 37.2, 43.2, 44.6, 45.8, 46.2, 51.8, 65.3, 66.4, 71.7, 79.0, 84.8, 91.4, 109.9.

A Typical Experimental Procedure using Aqueous NBS–THF–$CaCO_3$ System.—To a well stirred solution of **3** (60 mg, 0.19 mmol) in THF–H_2O (9 : 1, 8.7 ml) at 0 °C, $CaCO_3$ powder was added (56 mg, 0.56 mmol), and, in turn, a solution of NBS (83.5 mg, 0.47 mmol) in THF (3.2 ml). The reaction mixture was stirred at 0 °C for 1.5 h, then cyclohexene was added and the system was stirred at 0 °C for a further 2 h. EtOAc was added and the organic layer was washed with brine, dried over Na_2SO_4 and purified on silica gel column [light petroleum (bp 60–90 °C)–acetone: 4 : 1] to give **4** (65 mg, 86%) as a white solid. $[\alpha]_D^{20} = +23.5°$ (*c*. 1.0, EtOH); δ_H (400 Hz, [$^2H_6$]acetone) 1.14 (d, $J = 7.5$ Hz, 3H), 1.20 (s, 3H), 1.26 (s, 3H), 1.4–2.4 (m, 9H), 3.27, 4.08 (ABq, $J = 11.5$ Hz, each 1H), 3.7–4.0 (m, 4H), 4.05 (s, 1H); the ^{13}C NMR data were the same as above. EIMS: *m/z* (%) 359[(M-CH_2OH)$^+$, 2], 361(2), 149(5), 105(3), 99(100), 87(17), 55(21); FAB-HRMS: 391.1182, calcd. for $C_{17}H_{27}O_5Br + H$: 391.1120.

Synthesis of 3,3-Ethylenedioxy-6α,13-*dihydroxyagarofuran* **6**.—To a solution of **4** (65 mg, 0.17 mmol) in THF (6 ml) was added $LiAlH_4$ (60 mg, 1.62 mmol) under Ar gas at room temperature. The reaction mixture was stirred for 60 h at room temperature. EtOAc (2 ml) and water (2 ml) were added at 0 °C, and the mixture was stirred for a further 0.5 h. The organic layer was separated off and the aqueous layer was extracted with EtOAc. The combined organic phases were washed with brine, dried and concentrated. The residue was purified by column chromatography on a silica gel column [light petroleum (bp 60–90 °C) acetone: 2 : 1] to give **6** (30 mg, 62%) as a white solid. ^{1}H NMR (400 Hz, [$^2H_6$]acetone) δ_H 1.26 (s, 3H), 1.12 (d, $J = 7.2$ Hz, 3H), 1.15 (s, 3H), 1.4–2.5 (m, 9H), 2.67 (dq, $J = 7.2$, 1.7 Hz, 1H), 3.60, 3.64 (ABq, $J = 14$ Hz, each 1H), 3.7–3.9 (m, 4H), 4.62 (s, 1H); δ_c 15.9, 20.0, 24.4, 25.6, 27.6, 35.8, 38.0, 40.5, 41.9, 48.8, 63.6, 64.6, 70.1, 78.3, 84.8, 92.9, 112.2; EIMS: *m/z* (%) 312(M$^+$, 11), 281(100), 263(25), 195(21), 177(31), 99(85); FAB-HRMS: 313.1992, calcd. for $C_{17}H_{28}O_5 + H$: 313.2015.

We are grateful for the financial support provided by the Natural Science Foundation of China (29672017). We also greatly thank Ms Wan Kai Qiu, Ms Li Yang and Mr Qi Xiu Zhu for their helpful NMR and MS measurements.

Received, 15th March 1999; Accepted, 22nd April 1999
Paper E/9/02006C

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