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Bromohydrin reactions of Grieco's bicyclic lactone

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ABSTRACT

The bromohydrin reaction in Grieco's bicyclic lactone **1** was reinvestigated. Two regioisomeric bromohydrins were obtained (**2** and **8**), and their configurations were unambiguously determined by X-ray diffraction analyses.

Grieco's bicyclic lactone (**1**) has been a valuable starting material for the syntheses of prostaglandins,[1] monoterpenes,[2] the antibiotic lactone brefeldin A,[3] and also δ-valerolactones.[4] The microbial synthesis of this lactone has been reported recently, in a 200-L scale.[5] Recently, Ghosh and Takayama reported an efficient synthesis of a cyclopentyltetrahydrofuran HIV-1 protease inhibitor from this versatile synthon.[6] It was reported that addition of *N*-bromosuccinimide to Grieco's bicyclic lactone yielded a mixture of two regioisomeric products **2** and **3** in different ratios under a variety of reaction conditions, Figure 1.

We initially investigated the stereoselective hydroxylation of Grieco's bicyclic lactone during our efforts to prepare the C1–C9 fragment of the aurisides, Figure 2.[4c] The aurisides are marine glycosylated macrolactones isolated in minute amounts from *Dolabella auricularia* by Yamada.[7]

One of the reactions we investigated was the formation of bromohydrins in the dimethylated lactone **4**, Scheme 1. We envisioned that a bromonium ion would be formed preferentially on the *exo*-side of the lactone. To our surprise, we found that the major product of the reaction was bromohydrin **5** that possessed an

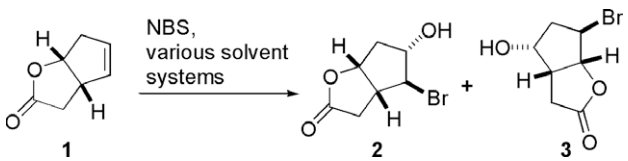

Figure 1. Bromohydrin reaction.

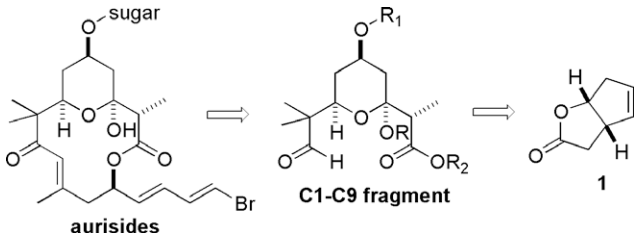

Figure 2. Retrosynthetic analysis of aurisides.

endo-bromine atom and an *exo*-hydroxyl group.[8] The structural assignment of bromohydrin **5** was unambiguously determined by X-ray analysis.[9] The two other products were assigned as shown in Scheme 1.

Gratifyingly, oxymercuration–demercuration of lactone **4** gave the desired *endo*-hydroxyl, which was required for the synthesis of the C1–C9 fragment of aurisides.[4c] Therefore, we decided to abandon the bromohydrin route. Interestingly, we did not observe the regioisomer type (**3**) assigned by Ghosh and Takayama. Based on these results, we decided to reinvestigate the stereochemical outcome of the bromohydrin reaction with bicyclic lactone **1**.

Addition of NBS to bicyclic lactone **1** in a mixture of acetone-water (4:1) delivered a 58:42 mixture of bromohydrins **8** and **2** in 52% combined yield, Scheme 2.[10] These two bromohydrins were chromatographically separated, and their structures unambiguously assigned by single crystal X-ray analyses.[9] In this case, we observed again that the major bromohydrin had an *endo*-bromine atom and the minor bromohydrin had an *exo*-bromine atom. Both products resulted from formation of bromonium ion on both faces of the olefin and regioselective nucleophilic opening of the bromonium ion by water on the more accessible carbon.

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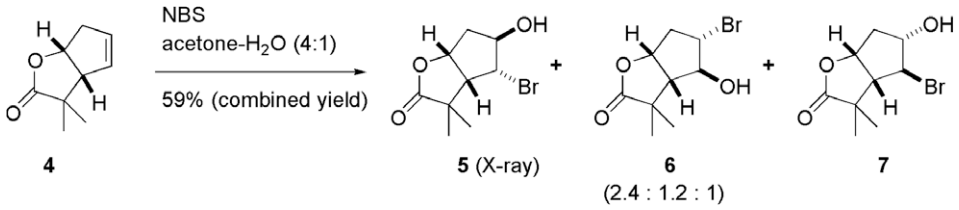
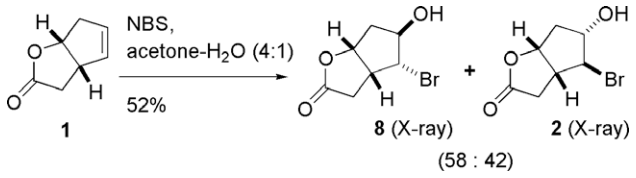


Scheme 1. Bromohydrin reaction of dimethylated lactone.



Scheme 2. Bromohydrin reaction of Grieco's lactone.

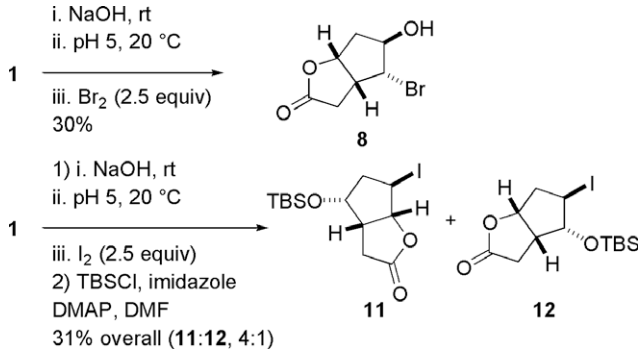
Corey's group reported that a single bicyclic bromohydrin was obtained when the bromohydrin addition was carried out on the corresponding bicyclic ketone, followed by Baeyer–Villiger oxidation, Scheme 3.[3] Indeed, only one bromohydrin **10** was obtained when bicyclic ketone **9** was treated with NBS in acetone–water. Baeyer–Villiger oxidation of bicyclic ketone **10** delivered bromohydrin lactone **2**.

Based on previous work by Corey,[11] a one-pot strategy consisting of hydrolysis of the bicyclic lactone **1** and treatment with molecular bromine was attempted to prepare bromohydrin **3**, Scheme 4. To our surprise, only bromohydrin **8** could be isolated in low yield. In contrast, the reported iodolactonization reaction proceeded uneventfully, and in accordance to Gulácsi et al.[12]

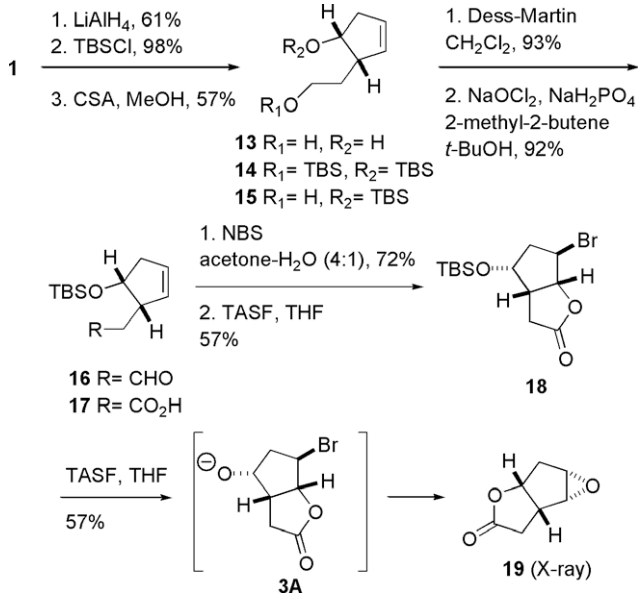
A different approach was then taken for the synthesis of bromohydrin **3**, Scheme 5. Reduction of bicyclic lactone **1** with lithium aluminum hydride gave diol **13**. Double protection of diol **13** as the TBS ether **14** was followed by selective cleavage of the primary TBS group to deliver alcohol **15**. Two-step oxidation of alcohol **15** to the carboxylic acid **17** was accomplished by treatment with Dess Martin reagent[13] to furnish aldehyde **16**, followed by Lindgren–Pinnick oxidation.[14] The crude carboxylic acid **17** was submitted to our bromination conditions to afford silyl ether **18**.

Unfortunately, cleavage of the silyl protecting group even under mild and neutral conditions, using TASF, did not afford the desired bromohydrin **3**, but the *endo*-epoxide **19**.[15,16] The stereochemistry of the epoxide **19** was confirmed by X-ray analysis.[9] Apparently, *endo*-epoxide **19** is formed via trans-lactonization followed by HBr elimination.

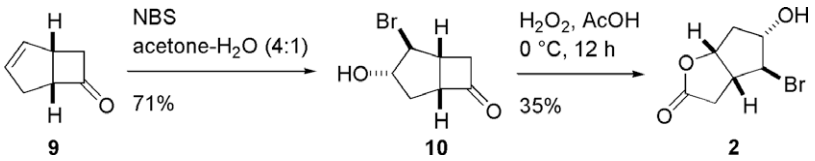
In summary, we have shown the correct regio- and stereochemistry of the bromohydrin reaction in Grieco's bicyclic lactone **1**. The stereochemistry of bromohydrins **2** and **8**, and epoxide **19** was unambiguously determined by X-ray analyses. Comparison of the ^{1}H and ^{13}C NMR spectra of the bromohydrins obtained by Ghosh and Takayama showed that they correspond to bromohydrins **2** and **8**.



Scheme 4. Bromohydrin reaction under basic conditions.



Scheme 5. Attempts for the preparation of bromohydrin **3**.



Scheme 3. Bromohydrin reaction on bicyclic ketone.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.09.081.

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8. *Bromohydrin* **5**: white solid; mp = 136–137 °C; R_f = 0.44 (1:1, petroleum ether–ethyl acetate), 0.35 (9:1 CH_2Cl_2–ethyl acetate). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.12 (1H, m), 4.65 (1H, app. t, J = 3.5 Hz), 4.19 (1H, d, J = 4.8 Hz), 3.08 (1H, t, J = 5.5 Hz), 2.82 (1H, br s), 2.69 (1H, dt, J = 15.6, 3.6 Hz), 2.34 (1H, ddd, J = 15.6, 7.6, 1.5 Hz), 1.49 (3H, s), 1.35 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 182.0 (C), 81.3 (CH), 80.4 (CH), 55.4 (CH), 54.4 (CH), 43.7 (C), 38.3 (CH_2), 27.5 (CH_3), 19.2 (CH_3). HRMS (EI) calculated for ($C_9H_{13}BrO_3$) m/z 250.0028, found m/z 250.0039.
9. CCDC for compound **2**: 699517. CCDC for compound **5**: 699492. CCDC for compound **8**: 699544. CCDC for compound **19**: 700139. The CCDC numbers contain the supplementary crystallographic data for this Letter. These data can be obtained free of charge via http://www.ccdc.cam.ac.uk/data_request/cif, by e-mailing to data_request@ccdc.cam.ac.uk contacting the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK, fax: +44 1223 336033.
10. (a) *Bromohydrin* **2**: white solid; mp = 104–105 °C; R_f = 0.27, (3:2, petroleum ether–ethyl acetate); ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.19 (1H, obs. t, J = 6.8 Hz), 4.47 (1H, m), 4.13 (1H, m), 3.37 (1H, m), 3.31 (1H, m), 2.85 (1H, dd, J = 18.6, 11.5 Hz), 2.64 (1H, dd, J = 18.6, 3.8 Hz), 2.55 (1H, ddd, J = 11.5, 6.6, 4.6 Hz), 2.21 (1H, d, J = 15.4 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 177.4 (C), 84.5 (CH), 79.5 (CH), 58.3 (CH), 48.2 (CH), 38.5 (CH_2), 35.9 (CH_2).
(b) *Bromohydrin* **8**: white solid; mp = 49–50 °C; R_f = 0.17, (3:2, petroleum ether–ethyl acetate); ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.08 (1H, td, J = 7.2, 2.6 Hz), 4.44 (1H, ddd, J = 11.2, 5.5, 3.8 Hz), 4.20 (1H, dd, J = 7.2, 5.5 Hz), 3.35 (1H, m), 3.20 (1H, d, J = 3.7 Hz), 2.87 (1H, dd, J = 18.9, 3.7 Hz), 2.75 (1H, dd, J = 18.9, 9.9 Hz), 2.45 (1H, ddd, J = 15.0, 5.5, 2.6 Hz), 2.10 (1H, dt, J = 15.0, 6.4 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 176.8 (C), 82.6 (CH), 77.6 (CH), 58.5 (CH), 41.0 (CH), 38.4 (CH), 33.8 (CH_2).
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15. *endo*-Epoxide **19**: colorless solid; R_f = 0.34 (100% ethyl acetate); ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.99 (1H, t, J = 7.1 Hz), 3.66 (1H, br s), 3.63 (1H, br s), 3.07–3.00 (1H, m), 2.78–2.64 (2H, m), 2.49 (1H, d, J = 16.3 Hz), 2.12 (1H, ddd, J = 16.3, 7.0, 1.4 Hz), 1.64 (1 H, br s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 176.3 (C), 83.5 (CH), 60.9 (CH), 60.2 (CH), 40.2 (CH), 34.5 (CH_2), 30.3 (CH_2). HRMS (EI) calculated for ($C_7H_8O_3$) m/z 140.0473, found m/z 140.0469.
16. We epoxidized bicyclic lactone **1** with *m*-CPBA. Epoxidation of bicyclic lactone **1** furnished *endo*- and *exo*-epoxides **19** and **20** in a 2:1 ratio in 92% overall yield. These two epoxides were separated by column chromatography.