Pergamon

Tetrahedron Letters 41 (2000) 3057–3060

TETRAHEDRON LETTERS

Stereoselective synthesis of a [3.3.0]-fused γ-butyrolactone. Application in the preparation of bicyclic nucleosides

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Received 24 December 1999; accepted 22 February 2000

Abstract

Stereoselective rearrangement of 6,7-epoxy-3-oxabicyclo[3.2.0]heptan-2-ones **2** and **3** in water afforded a *cis*-fused butyrolactone as a mixture of two epimers **1a**–**b**. These were used as the starting materials to prepare new bicyclonucleosides **8a**–**b**.

Keywords: cyclobutane; rearrangement; stereoselection; bicyclic nucleosides.

Modifying the sugar backbone in a nucleoside, or introducing a heteroatom, are useful strategies in search of new antiviral or antitumor agents.[1] Recently, intense efforts have been focused on the synthesis of nucleosides with a fused bicyclic ring system, either for controlling the conformational stability of the corresponding nucleotides incorporated in the DNA or for using the modified nucleosides as HIV reverse transcriptase inhibitors.[2] In this communication, we report a facile and stereoselective preparation of a [3.3.0]-fused lactone **1** from the unexpected rearrangement of 6,7-epoxy-3-oxabicyclo[3.2.0]heptan-2-ones **2** and **3** in water and its application for the synthesis of modified nucleosides (Fig. 1).

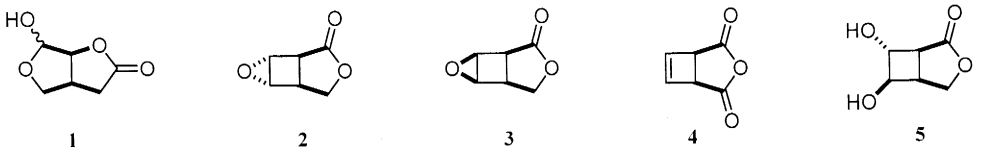

Fig. 1.

In the course of our research program concerned with the discovery of new types of bicyclic nucleosides, we subjected epoxide **2**,[3] derived from the cyclobutene anhydride **4**,[4] to the nucleophilic attack of water in different experimental conditions ($HClO_4/H_2O$/THF, Nafion-H/H_2O/THF, H_2SO_4/acetone,

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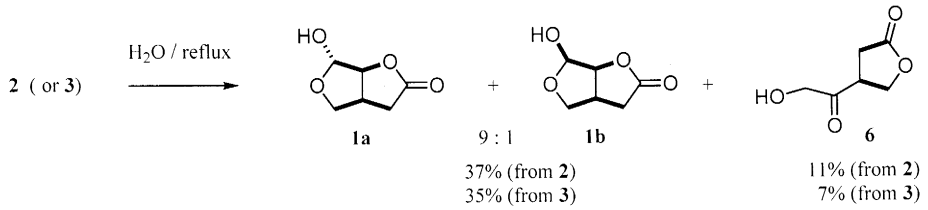
0040-4039/00/$ - see front matter
PII: S0040-4039(00)00334-8

$CF_3CO_2H/H_2O/THF$, Na_2CO_3/H_2O, etc) in order to obtain the *trans*-diol **5**. All attempts were unsuccessful and led to the recovery of the starting material or obtaining degradation products. However, when the reaction was carried out for 5 days in water alone, it yielded the unexpected *cis*-fused butyrolactone **1** in one step in a stereoselective manner, albeit in moderate yield (37%), together with a lower amount of the unstable compound **6** (11%) (Scheme 1).



Scheme 1.

The 8-hydroxy-3-oxo-2,7-dioxabicyclo[3.3.0]octane **1** was obtained as a mixture of two epimers **1a** and **1b** in a 9:1 ratio, respectively. The structures of **1a**, **1b** and **6** have been unequivocally assigned by NMR experiments (spin decoupling, NOE and HMBC) (Fig. 2).

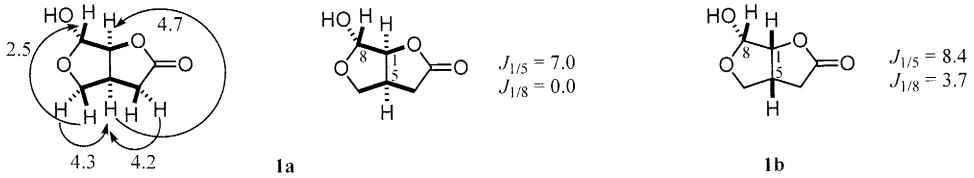
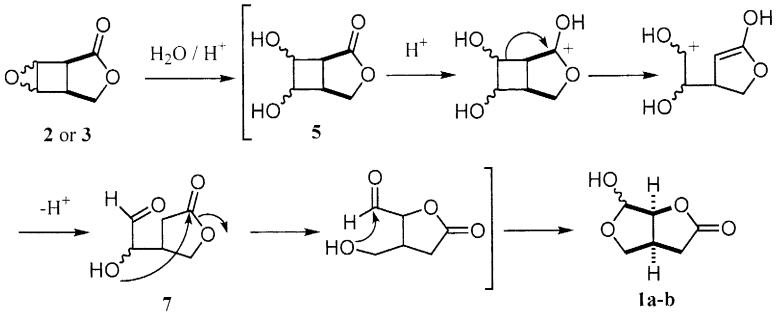


Fig. 2. NOE enhancements (%) and coupling constants (hertz)

We also subjected the diastereomer **3** to the same experimental conditions. We noticed that this reaction proceeded in a shorter time (8 hours) and afforded, equally, a mixture of bicyclolactones **1a**–**b** and compound **6** in similar yields, 35 and 7% respectively, after purification by column chromatography. It thus seems that configurations at the epoxide moiety have only a low effect on this type of rearrangement. Recently, Font and co-worker have reported that cyclobutane lactones could be useful precursors of fused ɣ-butyrolactones of carbohydrates from stereoselective rearrangements.[5] In this case, the reaction occurred in basic medium and worked from only one of the two diastereomers. In our experiments we used distilled water (pH ≈6), and a small amount of acid might remain from the previous step involving *m*CPBA.[3] Therefore, we proposed the following mechanism, in acidic medium, for obtaining **1a**–**b** (Scheme 2). The first step would involve an acid-catalyzed attack of water providing diol **5**. Then a ring opening, facilitated by protonation at the carbonyl group, would yield the hydroxyaldehyde **7**. Subsequent nucleophilic attack of the hydroxyl group onto the carbon C-2 of the lactone would give compounds **1a**–**b** by internal translactonization followed by hemiacetalization. Furthermore, formation of the secondary unstable compound **6** is in agreement with this mechanism proposal because it may be derived from the rearrangement of intermediate **7**. Another possible mechanism might involve a cyclopropyl aldehyde, as it is known that 1,2-epoxycyclobutanes give such ring contraction products in acidic medium.[6] As a matter of fact, we have obtained the aldehydes derived from oxiranes **2** and **3** in other works;[3,7] however, when we subjected one of them to the same experimental conditions as for **2**, the reaction failed to produce **1a**–**b**, thus showing that this aldehyde is not an intermediate of the reaction.

[3.3.0]-Fused lactones of carbohydrates are known to be useful synthons for the preparation of the 2′-C and 3′-C branched-chain nucleosides through ring opening of the lactone moiety.[8] Syntheses of such bicyclolactones have already been reported involving free radical intramolecular cyclization,[9] hydrogenation of products obtained by Wittig reactions[10] or rearrangement of cyclobutane lactones in



Scheme 2.

basic medium.[5] However, these reactions always led to moderate yields. In order to increase the yield of **1a**–**b**, and to avoid formation of **6**, we modified the experimental conditions (temperature, reaction time, adding of acid), but unfortunately no improvement was observed. Nevertheless, to the best of our knowledge, it is the first time that a *cis*-fused butyrolactone has been easily prepared by this very short method. We envisaged applying it in the preparation of new bicyclic nucleosides **8**. Searching for unusual classes of nucleoside analogues, several groups have described different types of bicyclonucleosides including compounds **9** and **10**[11,12] (Fig. 3).

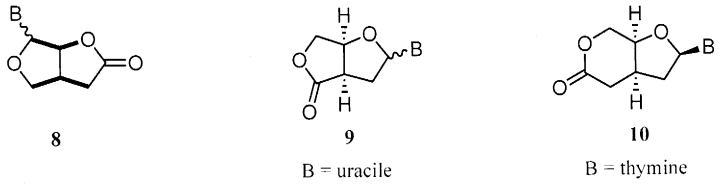
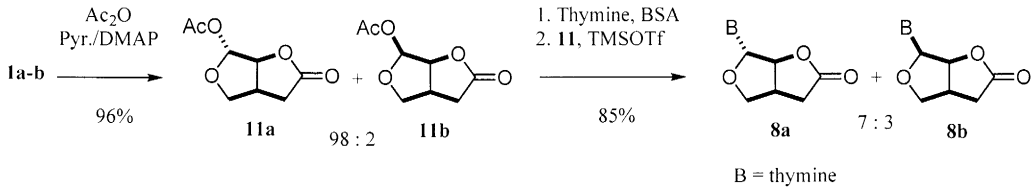


Fig. 3.

Acetylation of the **1a**–**b** mixture with acetic anhydride, in anhydrous CH_2Cl_2, and in the presence of pyridine and DMAP, afforded acetate **11** in an excellent yield (96%) as a mixture of two diastereomers **11a** and **11b** in a 98:2 ratio, respectively (Scheme 3). This was pure enough to be used in the next step without purification. When acetate **11** was subjected to the one-pot substitution of thymine in Vorbrüggen and Bennua conditions,[13] modified by Dudycz and Wright (CH_3CN, BSA, TMSOTf),[14] the expected bicyclonucleoside **8** was obtained in a 85% isolated yield as an anomeric mixture in a ratio **8a**:**8b**=7:3. Both diastereomers **8a** and **8b** were separable by column chromatography.[15,16] Stereochemical assignments were deduced from NOE experiments.



Scheme 3.

In conclusion, a new stereoselective method for the preparation of [3.3.0]-fused γ-butyrolactones is described. An interpretation of the rearrangement is proposed. Two new bicyclic nucleosides **8a** and **8b** were afterwards synthesized from acetate **11** by substitution at the anomeric position. Their evaluation as antitumor and antiviral agents are in progress. Use of this new strategy with precursors substituted at the lactone moiety might provide useful synthons for the preparation of branched-chain nucleosides.

Acknowledgements

We thank CNRS and Région Pays de la Loire for a fellowship for C.L. and Doctor J. Salaün for useful discussions.

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15. (1*S**,5*S**,8*R**)-1-(3′-Oxo-2′,7′-dioxabicyclo[3.3.0]oct-8′-yl)thymine **8a**: mp=249–251°C (MeOH); IR (KBr, cm^{-1}): 1772, 1697, 1662, 1167; ^{1}H NMR (DMSO-d_6) δ 11.40 (br s, 1H, NH), 7.47 (d, 1H, H-6, $J_{6/CH3}$=1.0 Hz), 5.77 (d, 1H, H-8′, $J_{8'/1'}$=1.0 Hz), 5.29 (dd, 1H, H-1′, $J_{1'/5'}$=7.2, $J_{1'/8'}$=1.0 Hz), 4.37 (dd, 1H, H-6′, $J_{6'/6''}$=9.0, $J_{6'/5'}$=8.1 Hz), 3.80 (dd, 1H, H-6′′, $J_{6''/6'}$=9.0, $J_{6''/5'}$=5.8 Hz), 3.40 (m, 1H, H-5′, $J_{5'/4'}$=9.5, $J_{5'/6'}$=8.1; $J_{5'/1'}$=7.2, $J_{5'/6''}$=5.8, $J_{5'/4''}$=2.7 Hz), 2.89 (dd, 1H, H-4′, $J_{4'/4''}$=18.4, $J_{4'/5'}$=9.5 Hz), 2.51 (dd, 1H, H-4′′, $J_{4''/4'}$=18.4, $J_{4''/5'}$=2.7 Hz), 1.78 (d, 3H, CH_3, $J_{CH3/6}$=1.0 Hz); ^{13}C NMR (DMSO-d_6) δ 176.2, 164.1, 150.6, 138.0, 109.6, 92.1, 86.9, 75.4, 37.9, 33.0, 12.1; anal. calcd for $C_{11}H_{12}N_2O_5 \cdot 0.2H_2O$: C, 51.64; H, 4.88; N,10.95. Found: C, 51.59; H, 4.82; N, 10.92.
16. (1*S**,5*S**,8*S**)-1-(3′-Oxo-2′,7′-dioxabicyclo[3.3.0]oct-8′-yl)thymine **8b**: mp=256–258°C (MeOH); IR (KBr, cm^{-1}): 1784, 1709, 1660, 1284, 1157; ^{1}H NMR (DMSO-d_6) δ 11.47 (br s, 1H, NH), 7.34 (d, 1H, H-6, *J*=0.8 Hz), 5.82 (d, 1H, H-8′, *J*=3.8 Hz), 5.08 (dd, 1H, H-1′, *J*=7.2, 3.8 Hz), 3.99 (d, 2H, H-6′, *J*=5.5 Hz), 3.26 (m, 1H, H-5′), 2.92 (dd, 1H, H-4′, *J*=18.4, 10.1 Hz), 2.58 (dd, 1H, H-4′′, *J*=18.4, 3.1 Hz), 1.77 (d, 3H, CH_3, *J*=0.8 Hz); ^{13}C NMR (DMSO-d_6) δ 176.0, 163.6, 150.9, 136.1, 108.4, 85.5, 80.9, 71.6, 37.2, 33.5, 12.1; HRMS calcd for $C_{11}H_{12}N_2O_5$: 252.0746. Found: 252.0754.