New Synthetic Approach to the Bicyclo[3.1.0]hexane Ring System from (+)-(1*R*,4*R*)-4-(Benzyloxymethyl)-4-(hydroxymethyl)cyclopent-2-enol

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A methanocarba approach to conformationally constrain the sugar ring in nucleosides and nucleotides was introduced by Marquez and co-workers.[1] Thus, a bicyclo[3.1.0]hexane system has been constrained in a North ((N), 2'-exo) or South ((S), 2'-endo) conformation, according to the pseudo-rotational cycle. In many studies of the ribose ring conformation of nucleosides and nucleotides binding to G protein-coupled receptors (GPCRs), novel (N)-ligands for adenosine receptors[2] and P2Y receptors[3] provided favorable receptor affinity and/or selectivity compared to their corresponding (S)-conformers. In addition, (N)-bicyclo[3.1.0]hexane nucleosides, -tides and oligonucleotides, including 2'-deoxy analogues, were good candidates for the development of a potent antiherpes agent,[4] as an inhibitor of (cytosine C5)-methyltransferase, for using in oligonucleotides[5] and as a mechanistic probe of base flipping by *Hhal* DNA methyltransferase.[6]

Since the biological relevance of (N)-bicyclo[3.1.0]-hexane derivatives is so high, additional effort is warranted to overcome the drawbacks of the previous synthetic pathways described in earlier publications.[7,8] Those methods involved two or three operationally demanding steps and gave unexpectedly low yields when applied to a gram-scale synthesis (Figure 1). The preparation of (N)-bicyclo[3.1.0]-hexanes in quantity is crucial to progress in the related research fields; thus, improving the yield of existing synthetic steps or developing novel synthetic pathways is desirable. In this letter we describe the conversion of (+)-(1*R*,4*R*)-4-(benzyloxymethyl)-4-(hydroxymethyl)cyclopent-2-enol into a key intermediate (+)-bicyclo[3.1.0]hexane alcohol **1**. The starting material **2** contains a quaternary carbon, which eliminates the need for harsh conditions usually associated with the construction of a quaternary carbon center. Although there remain aspects for further refinement, this work provides a novel route to obtain the crucial intermediate (+)-bicyclo[3.1.0]hexane **1**.

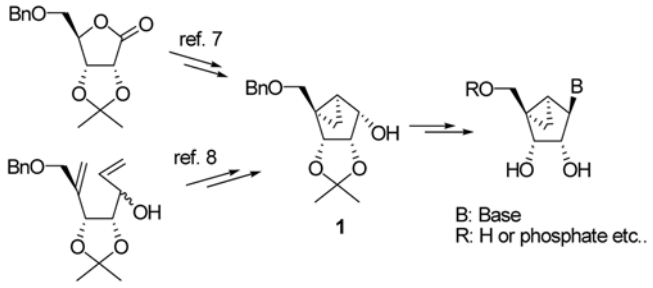
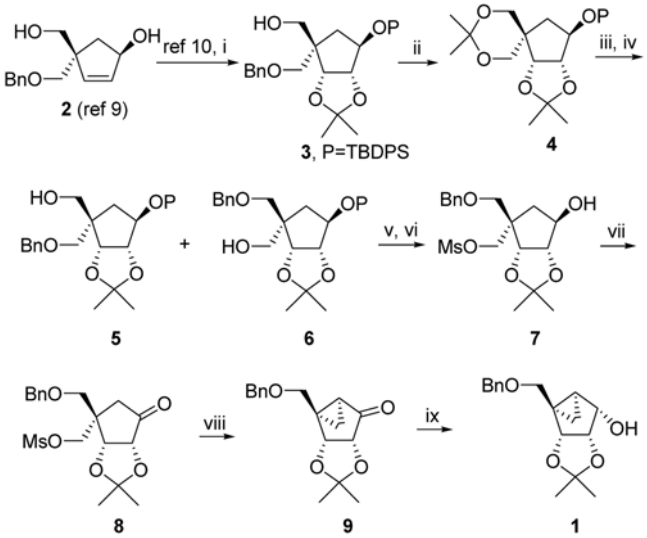


Figure 1. Two previous synthetic routes to the bicyclo[3.1.0] hexane system and its application to various nucleosides and nucleotides.

The synthesis of (+)-(1*R*,4*R*)-4-(benzyloxymethyl)-4-(hydroxymethyl)cyclopent-2-enol **2** was done according to the previously reported method.[9] The versatility of diol **2** was demonstrated previously with the synthesis of the (N)-locked bicyclo[2.2.1]heptane system.[10] Preparation of silyl acetonide **3** from **2** followed a well-established method.[10] The published report[10] gave a synthetic method to a silyl triol, which was protected as the acetonide to afford silyl acetonide **3** (Scheme 1). Removal of the benzyl group with Pd/C in the presence of hydrogen in a variety of conditions was also accompanied by the unexpected deprotection of the silyl group. Treatment of silylated acetonide **3** with Pd black



Scheme 1. i) cat. PTSA, acetone, rt, 3 h, 95%. ii) Pd black, HCO_2H, MeOH, 60 °C, 2 h, and then cat. PTSA, acetone, rt, 5 h, 73% two steps yield. iii) cat. pyr·TsOH, MeOH, rt, 1 h, 87%. iv) BnBr, *t*BuOK, THF, 0 °C – rt, **5** (36%), **6** (43%). v) MsCl, TEA, −10 °C – rt, 30 min. vi) TBAF, THF, rt, overnight, 71% two steps yield. vii) excess PDC, CH_2Cl_2, rt, overnight, 84%. viii) *t*-BuOK, THF, –20 °C, 75%. ix) $NaBH_4$, MeOH, 0 °C, 10 min, 97%.

and formic acid[11] as a substitute for hydrogen gas accomplished the requisite debenzylation without desilylation, along with the unexpected deprotection of the acetonide group. The resulting tetraol was *in situ* protected to give the silyl diacetonide **4** in 73% yield for two steps. After the acetonide moiety on the 1,3-diol group of **4** was selectively removed in 87% yield by treatment with catalytic pyridinium *p*-toluenesulfonate[12] in methanol at room temperature, benzylation (BnBr, *t*-BuOK in THF) of the resulting 1,3-diol was attempted. Initially, it was thought that steric hindrance induced by the concave bicyclo[3.3.0]octane system would favor benzylation at the convex face over the concave. However, the resulting selectivity on benzylation was barely evident, since the ratio of **5** : **6** was found to be 1 : 1.2 based on integration of the proton NMR spectra. It is pertinent to mention here that selective benzylation or selective protection of the 1,3-diol remains a challenge for future study and is currently in progress in our lab. Fortunately, **5** and **6** were readily separated by column chromatography on silica gel. The requisite alcohol **6** was mesylated by upon treatment with methanesulfonyl chloride and TEA, followed by desilylation with TBAF to give the hydroxy mesylate **7**[13] in 71% yield for two steps. Oxidation of the hydroxyl group of **7** was accomplished using an excess of PDC in dichloromethane at room temperature to furnish the mesyl ketone **8**[14] in 84% yield, which is readily decomposed in strong basic condition or prolonged, elevated temperature. The decomposition appeared to be caused by elimination of the acetonide, which was confirmed by the disappearance of the two methyl peaks of the acetonide group in the proton NMR spectrum. However, the stability of **8** during the PDC oxidation at room temperature and the subsequent chromatography was satisfactory. Intramolecular cyclization[15] of mesyl ketone **8** was performed by treatment with exactly one equivalent of *t*-BuOK in THF at –50 °C for 10 min to furnish **9** in 75% yield.[16] The final conversion of bicyclic ketone **9** into **1** was accomplished in 97% yield by reduction of the ketone group with $NaBH_4$. The structure of **1** was confirmed by comparison with the proton NMR spectrum and optical rotation ($[\alpha] = +70.7$, c = 0.03, in chloroform, 25 °C, yellow sodium D line) of the original compound **1**[1d] ($[\alpha] = +67.3$, c = 0.27), synthesized from D-(+)-ribono-γ-lactone.[1d]

In summary, we have developed a new synthetic route to a versatile intermediate **1**, a key building block for the preparation of nucleosides and nucleotides containing the bicyclo[3.1.0]hexane system from a readily available starting material **2**. In this case, the preformed quaternary carbon center facilitated synthetic manipulation. The new procedure should allow us to make **1** in multigram scale, which in turn will facilitate the synthesis receptor probes and other biologically important bicyclo[3.1.0]hexane derivatives. Overcoming the lack of sufficient quantities of the crucial intermediate **1** should advance the biological investigation of this class of compounds. By the same token, synthetic work leading to **1** or the related 2'-deoxybicyclo[3.1.0] system is currently underway in our lab.

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References

1. (a) Rodriguez, J. B.: Marquez, V. E.; Nicklaus, M. C.; Mitsuya, H.; Barchi Jr., J. J. *J. Med. Chem.* **1994**, *37*, 3389. (b) Marquez, V. E.; Siddiqui, M. A.; Ezzitouni, A.; Russ, P.; Wang, J.; Wagner, R. W.; Matteucci, M. D. *J. Med. Chem.* **1996**, *39*, 3739. (c) Marquez, V. E.; Ezzitouni, A.; Russ, P.; Siddiqui, M. A.; Ford Jr., H.; Feldman, R. J.; Mitsuya, H.; George, C.; Barchi Jr., J. J. *J. Am. Chem. Soc.* **1998**, *120*, 2780. (d) Jeong, L. S.; Buenger, G. J.; McCormack, J.; Cooney, D. A.; Hao, Z.; Marquez, V. E. *J. Med. Chem.* **1998**, *41*, 2572. (e) Moon, H. R.; Kim, H. O.; Chum, M. W.; Jeong, L. S.; Marquez, V. E. *J. Org. Chem.* **1999**, *63*, 4733. (f) Joshi, B. V.; Marquez, V. E.; Fettinger, J. C.; Jacobson, K. A. *Abstracts of Papers, 227th ACS National Meeting*, Anaheim, CA, USA, 2004; MEDI-256.
2. Jacobson, K. A.; Ji, X.-D.; Li, A. H.; Melman, N.; Siddiqui, M. A.; Shin, K. J.; Marquez, V. E.; Ravi, R. G. *J. Med. Chem.* **2000**, *43*, 2196.
3. Nandanan, E.; Jang, S. Y.; Moro, S.; Kim, H. O.; Siddiqui, M. A.; Russ, P.; Marquez, V. E.; Busson, R.; Herdewijn, P.; Harden, T. K.; Boyer, J. L.; Jacobson, K. A. *J. Med. Chem.* **2000**, *43*, 829.
4. Russ, P.; Schelling, P.; Scapozza, L.; Folkers, G.; De Clercq, E.; Marquez, V. E. *J. Med. Chem.* **2003**, *46*, 5045.
5. Marquez, V. E.; Wang, P.; Nicklaus, M. C.; Maier, M.; Manoharan, M.; Christman, J. K.; Banavali, N. K.; Mackerell Jr., A. D. *Nucleosides, Nucleotides & Nucleic Acids* **2001**, *20*, 451.
6. Wang, P.; Brank, A. S.; Banavali, N. K.; Nicklaus, M. C.; Marquez, V. E.; Christman, J. K.; Mackerell Jr., A. D. *J. Am. Chem. Soc.* **2000**, *122*, 12422.
7. Marquez, V. E.; Lim, M. I.; Christopher, K. H. T.; Markovac, A.; Matthew, A. P.; Khan, M. S.; Kaskar, B. *J. Org. Chem.* **1988**, *53*, 5709.
8. Lee, K.; Cass, C.; Jacobson, K. A. *Org. Lett.* **2001**, *3*, 597.
9. Hodgson, D. M.; Gibbs, A. R.; Drew, M. G. B. *J. Chem. Soc., Perkin Trans. 1* **1999**, *24*, 3579.
10. Kim, H. S.; Jacobson, K. A. *Org. Lett.* **2003**, *5*, 1665.
11. ElAmin, B., Anantharamaiah, G. M.; Royer, P. P.; Means, G. E. *J. Org. Chem.* **1979**, *44*, 3442.
12. Van Rijsbergen, R.; Anteunis, M. J. O.; De Bruyn, A. *J. Carbohydr. Chem.* **1986**, *51*, 404.
13. Proton NMR spectrum for **7**. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26-7.40 (m, 5H), 4.57 (s, 2H), 4.50 (AB quartet, 2H, J = 4.5 Hz), 4.29 (d, 1H, J = 9.2 Hz), 4.13 (d, 1H, J = 9.2 Hz), 4.11 (m, 1H), 3.66 (d, 1H, J = 9.2 Hz), 3.57 (d, 1H, J = 9.2 Hz), 2.98 (s, 3H), 2.06 (dd, 1H, J = 6.4, 14.7 Hz), 1.69 (d, 1H, J = 14.7 Hz), 1.42 (s, 3H), 1.26 (s, 3H).
14. Proton NMR spectrum for **8**. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.18-7.37 (m, 5H), 4.57 (d, 1H, J = 4.5 Hz), 4.47 (AB quartet, 2H, J = 11.1 Hz), 4.40 (d, 1H, J = 10.0 Hz), 4.40 (m, 1H), 4.29 (d, 1H, J = 10.0 Hz), 3.66 (d, 1H, J = 9.0 Hz), 3.44 (d, 1H, J = 9.0 Hz), 2.57 (s, 3H), 2.44 (d, 1H, J = 17.5 Hz), 2.22 (d, 1H, J = 17.5 Hz), 1.42 (s, 3H), 1.32 (s, 3H).
15. Kojima, K.; Amemiya, S.; Saito, S. *Chem. Pharm. Bull.* **1987**, *35*, 948.
16. Proton NMR spectrum for **9**. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.27-7.38 (m, 5H), 5.08 (dd, 1H, J = 1.8, 8.3 Hz), 4.59 (d, 1H, J = 12.4 Hz, one of two benzylic protons), 4.53 (d, 1H, J = 12.4 Hz, one of two benzylic protons), 4.23 (dd, 1H, J = 1.4, 7.8 Hz), 3.80 (d, 1H, J = 10.5 Hz), 3.34 (d, 1H, J = 10.5 Hz), 2.04 (ddd, 1H, J = 1.8, 4.1, 10.1 Hz), 1.64 (dd, 1H, J = 4.1, 5.0 Hz), 1.53 (s, 3H), 1.31 (m, 1H), 1.30 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.85, 137.83, 128.61 (two carbons on phenyl ring), 128.00, 127.86 (two carbons on phenyl ring), 114.80, 79.53, 73.25, 71.06, 36.52, 36.15, 25.75, 24.20, 16.64.