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A New Synthetic Route to Nucleosides: Dissymmetric Construction of a Cyclopentene System by Double [3,3]-Sigmatropic Rearrangement and Double Ring-Closing Metathesis

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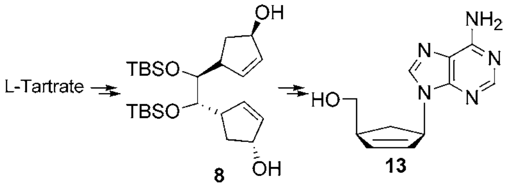
ABSTRACT



The dissymmetric synthesis of a carbocyclic nucleoside was achieved by a novel double [3,3]-sigmatropic rearrangement/double ring-closing metathesis strategy with a high stereoselectivity.

Classical one-directional methods such as linear synthesis and convergent synthesis are the approaches most frequently observed in the literature for the preparation of nucleosides.[1,2] Another strategy, a two-directional synthesis by simultaneous homologation, has received considerable attention recently. When applied to the appropriate target molecules, namely, those with a significant element of symmetry, this strategy offers a highly efficient synthetic route for preparing stereochemically pure products in relatively few steps compared with the one-directional strategy.[3] Although several synthetic procedures for nucleosides have been developed on the basis of one-directional strategy, no attempt has been made to prepare nucleosides using a more efficient two-directional strategy.

During our studies directed toward the synthesis of novel carbocyclic nucleosides based upon sequential [3,3]-sigmatropic rearrangement and ring-closing metathesis (RCM),[4] we accidentally discovered double [3,3]-sigmatropic rearrangement and double RCM, which led us to develop an efficient and unprecedented synthetic method for nucleosides. Herein, we would like to report a novel two-directional synthesis route to carbocyclic nucleoside via simultaneous homologation starting from a C_2-symmetric chiral template “L-tartrate”.

As depicted in Scheme 1, the initial efforts were focused on preparing a C_2-symmetric bis(divinyl), **7**. The axially dissymmetric ester, **2**, was readily obtained starting from the commercially available diisopropyl L-tartrate with use of the reported reaction procedure.[5] The axially dissymmetric ester,

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[1] (a) Shealy, Y. F.; Clayton, J. D. *J. Am. Chem. Soc.* **1966**, *88*, 3885. (b) Kusaka, T.; Yamamoto, H.; Shibata, M.; Murai, M.; Kishi, T.; Mizuno, K. *J. Antibiot.* **1968**, *21*, 255. (c) Arita, M.; Dachi, K.; Ito, Y.; Sawai, H.; Ohno, M. *J. Am. Chem. Soc.* **1983**, *105*, 4049. (d) Vince, R.; Hua, M. *J. Med. Chem.* **1990**, *33*, 17.

[2] Recent reviews: (a) Borthwick, A. D.; Biggadike, K. *Tetrahedron* **1992**, *48*, 571. (b) Agrofoglio, L.; Suhas, E.; Farese, A.; Condom, R.; Challand, S.; Earl, R. A.; Guedj, R. *Tetrahedron* **1994**, *50*, 10611. (c) Crimmins, M. T. *Tetrahedron* **1998**, *54*, 9229.

[3] For the selected reviews, see: (a) Poss, C. S.; Schreiber, S. L. *Acc. Chem. Res.* **1994**, *27*, 9. (b) Magnuson, S. R. *Tetrahedron* **1995**, *51*, 2167.

[4] Hong, J. H.; Oh, C. H.; Cho, J. H. *Tetrahedron* **2003**, *59*, 6103.

[5] Saito, S.; Narahara, O.; Ishikawa, T.; Asahara, M.; Moriwake, T. *J. Org. Chem.* **1993**, *58*, 6292.

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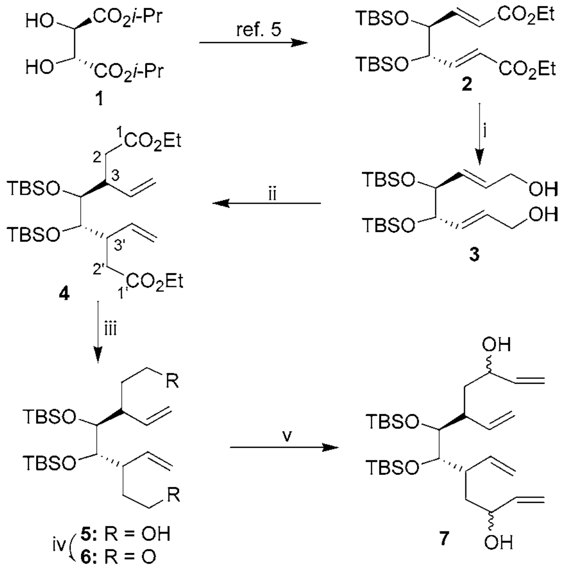
Scheme 1. Synthesis of Bis-divinyl intermediate **7**[a]



[a] Reagents: (i) DIBALH, CH_2Cl_2, −50 °C, 99%; (ii) triethylorthoacetate, propionic acid, 135 °C, overnight, 86%; (iii) DIBALH, CH_2Cl_2, −20 °C, 97%; (iv) PCC, 4 Å MS, CH_2Cl_2, rt, 5 h, 90%; (v) $CH_2{=}CHMgBr$, THF, −78 °C, 2 h, 72%.

2, was then reduced with DIBALH to afford the corresponding C_2-symmetric bis-allylic alcohol, **3**, in a quantitative yield.

The bis-allylic alcohol, **3**, was then converted to a bis-γ,δ-unsaturated ethyl ester, **4**, with the required stereochemistry at C-3 and C-3′ by the use of a double [3,3]-sigmatropic rearrangement[6] as the only product in an 86% yield. Although the stereochemistry of **4** was anticipated by invoking Saito's vicinal silyloxy group-controlled double chairlike transition state[7] (Figure 1), it was helpful for us to spectroscopically characterize the synthetic intermediates until correct stereochemistry was determined by the comparison of final compound **13** with the known antipode.

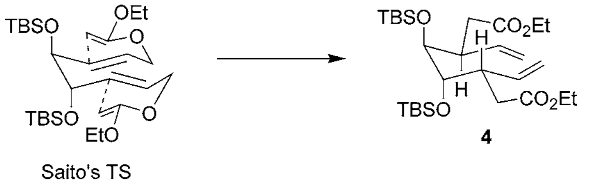
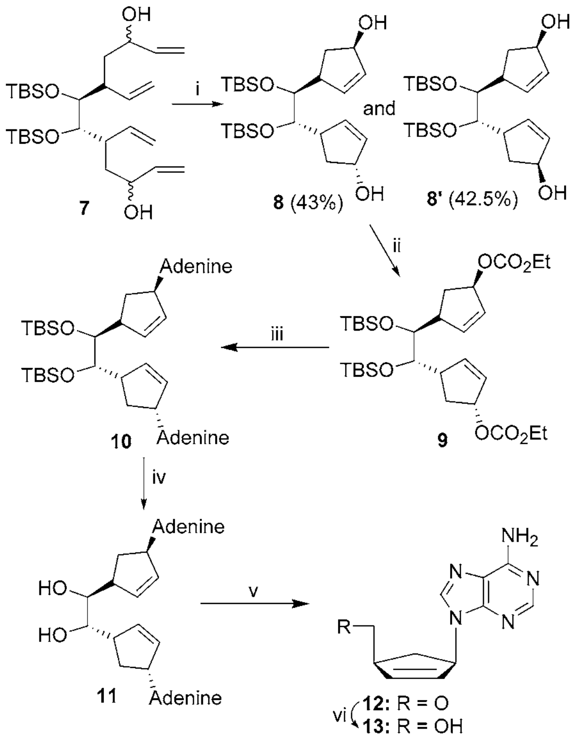


Figure 1. Transition state for **4**.

The slow addition of DIBALH to a solution of the ester in CH_2Cl_2 at −20 °C gave the bis(diol) alcohol derivative, **5**, which was subjected to PCC oxidation conditions to afford the C_2-symmetrical dialdehyde, **6**, in 87% yield for two steps. The dialdehyde was subjected to double carbonyl addition by vinylmagnesium bromide to give bis(divinyl) alcohol derivative, **7**, as a diastereomeric mixture in a 72% yield (Scheme 2). The stereochemical assignment was performed in the subsequent reaction because it was difficult to separate the mixture at this stage.

Scheme 2. Dissymetric Synthesis of D-Carbocyclic Nucleoside **13**[a]



[a] Reagents: (i) $(Im)Cl_2Cy_3RuCHPh$, CH_2Cl_2, rt, overnight; (ii) $ClCO_2Et$, DMAP, pyridine, rt, overnight, 84%; (iii) adenine, $Pd_2(dba)_3.CHCl_3$, $P(O\text{-}i\text{-}Pr)_3$, NaH, THF/DMSO, reflux, overnight, 42%; (iv) TBAF, THF, rt, 3 h, 80%; (v) $NaIO_4$, $MeOH/H_2O$, 0 °C, 3 h; (vi) $NaBH_4$, C_2H_5OH, 0 °C, 2 h, 76%.

A double RCM[8] of compound **7** was effected with a 1,3-dimesityl-4,5-dihydroimidazole-2-ylidene (Imp)-substituted ruthenium-based catalyst, $(Imp)Cl_2Cy_3RuCHPh$,[9] under mild conditions (CH_2Cl_2, rt) to generate the unsaturated C_2-symmetric bis(cyclopenteneol), **8**,[10] and the less polar **8′**[11]

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(6) For selected references for nucleosides: (a) Hong, J. H.; Gao, M. Y.; Choi, Y.; Cheng, Y.-C.; Schinazi, R. F.; Chu, C. K. *Carbohydr. Res.* **2000**, *328*, 37. (b) Hong, J. H.; Gao, M. Y.; Chu, C. K. *Tetrahedron Lett.* **1999**, *40*, 231. (c) Hong, J. H.; Lee, K.; Choi, Y.; Chu, C. K. *Tetrahedron Lett.* **1998**, *39*, 3443.

(7) Saito, S.; Hirohara. Y.; Narahara, O.; Moriwake, T. *J. Am. Chem. Soc.* **1989**, *111*, 4533.

(8) For the examples of bicyclic or polycyclic compounds via double RCM reaction, see: (a) Lautens, M.; Hughes, G. *Angew. Chem., Int. Ed.* **1999**, *38*, 129. (b) Clark, J. S.; Hamelin, O. *Angew. Chem., Int. Ed.* **2000**, *39*, 372. (c) Ma, S.; Ni, B. *Org. Lett.* **2002**, *4*, 639.

(9) (a) Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953. (b) Chatterjee, A. K.; Morgan, J. P.; Scholl, M.; Grubbs, R. H. *J. Am. Chem. Soc.* **2000**, *122*, 378.

(10) Compound **8**: mp 135−138 °C; $[\alpha]^{24}_{D}$ −292° (*c* 0.65, MeOH); ^1H NMR ($CDCl_3$, 300 MHz) δ 6.10 (dd, J = 5.4, 1.8 Hz, 2H), 5.90 (m, 2H), 4.82 (br s, 2H), 3.40 (d, J = 7.2 Hz, 2H), 3.26 (m, 2H), 2.18 (quint, J = 6.3 Hz, 2H), 1.86 (quint, J = 7.2 Hz, 2H), 0.89 (s, 18H), 0.03 (s, 6H), 0.01 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 138.84, 133.53, 79.40, 46.49, 37.83, 25.85, 18.05, −3.57, −4.90. Anal. Calcd for $C_{24}H_{46}O_4Si_2$: C, 63.38; H, 10.19. Found: C, 63.59; H, 10.24.

in 43 and 42.5% yields, respectively.[12] The structural dissymmetry of **7** reasonably accounts for the outcome of compounds **8** and **8′**. Unlike **8**, which is a C_2-symmetric structure that shows only 9 peaks in the ^{13}C NMR spectrum and a 2-fold simplification of the ^{1}H NMR spectrum, **8′** exhibits 14 peaks in the ^{13}C NMR spectrum and many more proton peaks in the ^{1}H NMR spectrum than **8**. Furthermore, the absolute stereochemistries of **8** and **8′** were unambiguously confirmed by comparison of final nucleoside **13** with the known antipode.[13] The subsequent bis(ethoxycarbonylation) of compound **8** with ethyl chloroformate gave the corresponding allylic coupling substrate, **9**, in excellent yield. Pd(0)-catalyzed reactions have been the most powerful tools for the installation of functionality in the allylic position because of their reliable high fidelity of regio- and stereochemistry. This methodology was successfully adopted for the synthesis of the desired nucleosides. The adenine anion generated by NaH/DMSO in THF/DMSO at 60 °C was successfully condensed with compound **9** using a tris(dibenzylideneacetone)dipalladium(0)−chloroform adduct as a coupling catalyst to give the bis-adenine analogue, **10**, in a 42% yield.[14−15] The C_2-symmetric adenine derivative, **10**, was deprotected by a treatment with tetrabutylammonium fluoride (TBAF) to give desilylated adenine analogue, **11**, in an 80% yield, which was sequentially treated with $NaIO_4$ and $NaBH_4$ to furnish the final adenine derivative in 76% yield for two steps. The spectroscopic data (^{1}H and ^{13}C) and specific optical rotation of our synthetic nucleoside **13** ($[\alpha]^{24}_D$ −4.98° (*c* 1.12, MeOH)) was in good agreement with that of the reported antipode ($[\alpha]^{24}_D$ 4.81° (*c* 0.52, MeOH)).[13]

In conclusion, a dissymmetric synthetic route to a nucleoside was investigated using a double [3,3]-sigmatropic rearrangement and a double RCM starting from the C_2-symmetric chiral starting material L-tartrate. The scope of the present methodology and its application to the other nucleosides are under investigation in our laboratory.

Supporting Information Available: Experimental conditions for the synthesis of all compounds and their corresponding spectral and analytical data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) Compound **8′**: $[\alpha]^{24}_D$ −25.9° (*c* 2.25, MeOH); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.02 (d, $J = 3.6$ Hz, 1H), 5.93 (d, $J = 3.4$ Hz, 1H), 5.83 (d, $J = 5.4$ Hz, 1H), 5.77 (d, $J = 6.0$ Hz, 1H), 4.75 (br s, 2H), 3.44 (dd, $J = 7.2, 3.0$ Hz, 1H), 3.32 (dd, $J = 10.8, 3.0$ Hz, 1H), 3.18 (m, 1H), 2.81 (m, 1H), 2.39 (quint, $J = 7.5$ Hz, 1H), 2.08 (quint, $J = 6.6$ Hz, 1H), 1.83 (m, 1H), 1.51 (m, 1H), 0.84 (d, $J = 4.5$ Hz, 18H), 0.04 (s, 6H), 0.02 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 138.85, 136.92, 134.13, 133.47, 79.36, 79.16, 46.45, 46.10, 38.86, 37.92, 25.92, 18.06, −3.51, −4.88. Anal. Calcd for $C_{24}H_{46}O_4Si_2$: C, 63.38; H, 10.19. Found: C, 63.02; H, 9.97.

(12) This metathesis also progressed with the first-generation Grubbs' catalyst in a poor yield (57% total yield of **8** and **8′**).

(13) Wang, P.; Schinazi, R. F.; Chu, C. K. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 1585.

(14) Crimmins, M. T.; King, B. W.; Zuerch, W. J.; Choy, A. L. *J. Org. Chem.* **2000**, *65*, 8499.

(15) Compound **13**: mp 190−192 °C; $[\alpha]^{24}_D$ −4.98° (*c* 1.12, MeOH); UV (H_2O) λ_{max} 261 nm; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.15 (s, 1H), 8.09 (s, 1H), 7.24 (br s, $-NH_2$, 2H, D_2O exchangeable), 6.17 (m, 1H), 5.96−5.90 (m, 1H), 5.62−5.58 (m, 1H), 4.77 (t, $J = 5.4$ Hz, OH, D_2O exchangeable), 3.48 (m, 2H), 2.91 (m, 1H), 2.69 (dt, $J = 13.8, 8.9, 8.6$ Hz, 1H), 1.64 (dt, $J = 13.8, 5.8. 5.6$ Hz, 1H); ^{13}C NMR (DMSO-d_6) δ 154.81, 151.34, 151.30, 137.45, 128.64, 117.80, 62.84, 58.13, 46.70, 33.30. Anal. Calcd for $C_{11}H_{13}N_5O$: C, 57.13; H, 5.67; N, 30.28. Found: C, 57.44; H, 5.72; N, 30.38.