

# A NEW APPROACH TO THE SYNTHESIS OF OPTICALLY ACTIVE CYCLOHEXANE ANALOGS OF NUCLEOSIDE USING A MICHAEL-TYPE ADDITION REACTION TO NITRO-CYCLOHEXENES AS A KEY REACTION

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Using as a key reaction a Michael-type addition reaction to nitro-cyclohexene derivatives, two optically active cyclohexane analogs of nucleoside, (-)-9-pseudo- $\beta$ -D-glucopyranosyladenine (**8**) and (-)-9-pseudo- $\beta$ -L-idopyranosyladenine (**16**), were synthesized from adenine and D-glucose.

**KEYWORDS** (-)-9-pseudo- $\beta$ -D-glucopyranosyladenine; (-)-9-pseudo- $\beta$ -L-idopyranosyladenine; carbocyclic nucleoside; pseudo-glycoside; nucleoside cyclohexane analog optically active; Michael-type addition reaction; nitro-cyclohexene; D-glucose

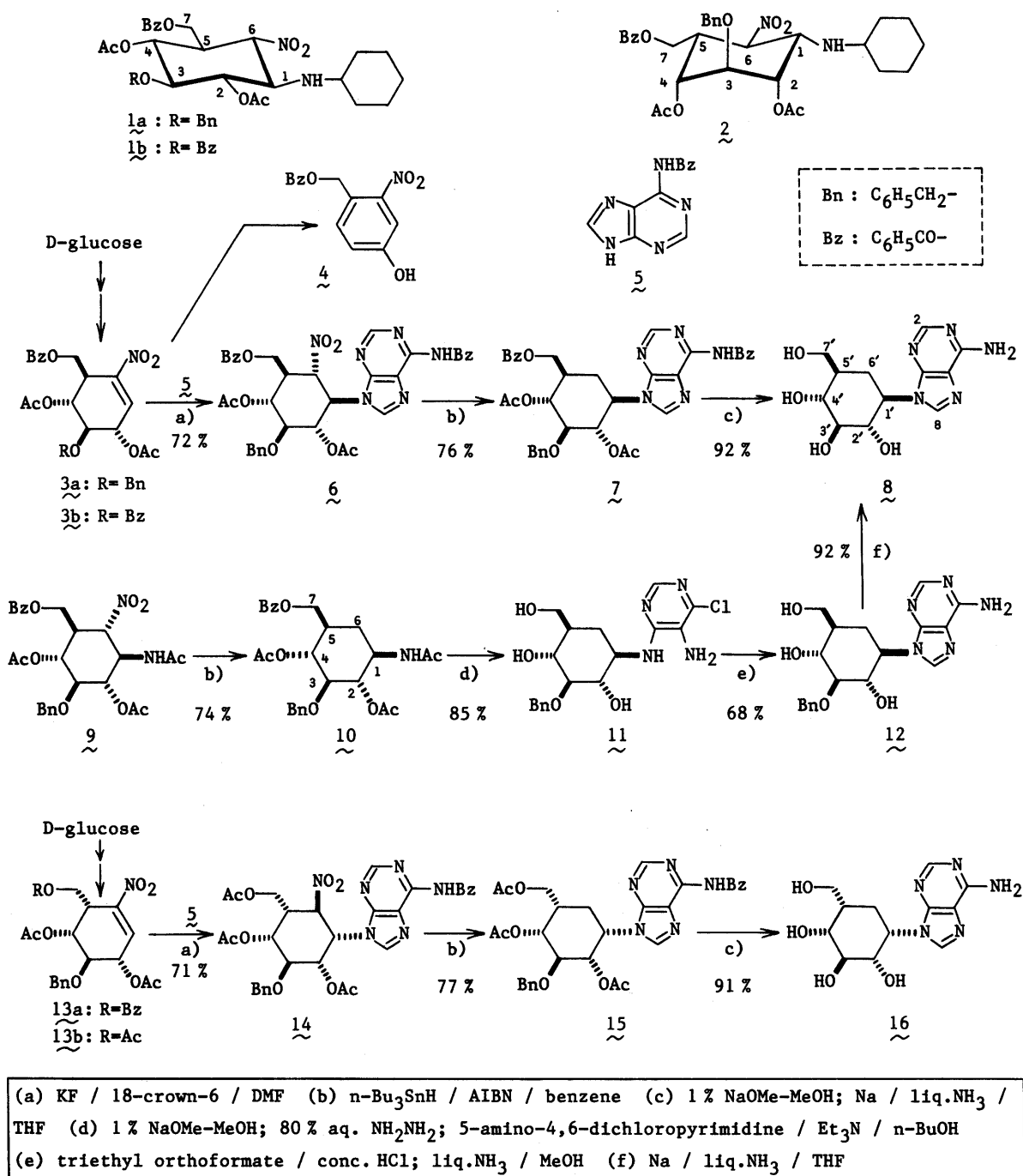
Carbocyclic nucleosides, which are nucleoside analogs having a carbocyclic ring in place of the carbohydrate moiety, exhibit interesting biological activities such as antiviral, antitumor, and antibacterial properties. These facts have made carbocyclic nucleosides attractive synthesis targets.<sup>1)</sup>

Recently, using a stereoselective deacetoxylation reaction and a cyclitol formation reaction for nitro-furanose derivatives at the key steps, we have developed versatile methods for converting carbohydrates to optically active pseudo-hexopyranoses and pseudo-pentofuranoses.<sup>2,3)</sup> During studies of the chemical behavior of the pseudo-nitrohexopyranoses, a method was developed for synthesizing optically active pseudo-aminosugar. By this method, validamine, epi-validamine, and valienamine have been synthesized from D-glucose.<sup>4a)</sup>

As an extension of these synthesis studies of pseudo-sugar, we have found that pseudo-glycosides such as carbocyclic nucleosides are successfully synthesized using a Michael-type addition reaction of a nucleic acid base to nitro-cyclohexene derivatives. In this paper, we report the synthesis of two new optically active cyclohexane analogs of nucleoside, (-)-9-pseudo- $\beta$ -D-glucopyranosyladenine {(-)-9-[(1'R,2'S,3'S,4'R,5'R)-2',3',4'-trihydroxy-5'-(hydroxymethyl)cyclohexyl]adenine, **8**} and (-)-9-pseudo- $\beta$ -L-idopyranosyladenine {(-)-9-[(1'S,2'S,3'S,4'R,5'S)-2',3',4'-trihydroxy-5'-(hydroxymethyl)cyclohexyl]adenine, **16**}, from adenine and nitro-cyclohexenes prepared from D-glucose.<sup>4)</sup>

Treatment of **3a**<sup>4a)</sup> or **3b**<sup>4b)</sup> with cyclohexylamine in THF in the presence of KF and 18-crown-6 (2°C, 2 h) yielded **1a** (75 %),<sup>5a)</sup> colorless oil,  $[\alpha]_D^{20} +16^\circ$  (CHCl<sub>3</sub>), C<sub>31</sub>H<sub>38</sub>N<sub>2</sub>O<sub>9</sub><sup>6)</sup> or **1b** (74 %),<sup>5b)</sup> colorless oil,  $[\alpha]_D^{20} +37^\circ$  (CHCl<sub>3</sub>), C<sub>31</sub>H<sub>36</sub>N<sub>2</sub>O<sub>10</sub>. By a similar procedure, **2** (75 %),<sup>5c)</sup> colorless oil,  $[\alpha]_D^{20} +7^\circ$  (CHCl<sub>3</sub>), C<sub>31</sub>H<sub>38</sub>N<sub>2</sub>O<sub>9</sub> was prepared from **13a**.<sup>4a)</sup> Thus, we found that the Michael-type addition reactions to these nitro-cyclohexenes provided thermodynamically stable products having an equatorial amino group at the 1-position.<sup>7)</sup> When **3a** was treated with N<sup>6</sup>-benzoyladenine (**5**) in DMF in the presence of KF and 18-crown-6 (2°C, 1 h), **6** (72 %),<sup>5d)</sup> a white powder,  $[\alpha]_D^{22} -5^\circ$  (CHCl<sub>3</sub>), C<sub>37</sub>H<sub>34</sub>N<sub>6</sub>O<sub>10</sub>, was obtained. But when **3b** was treated under the same conditions as for **3a**, an aromatic compound **4**, a white powder, C<sub>14</sub>H<sub>11</sub>NO<sub>5</sub>, was readily formed. Reductive elimination of the nitro group in **6** with n-Bu<sub>3</sub>SnH in benzene in the presence of  $\alpha,\alpha'$ -azobis-iso-butyronitrile (AIBN) (80°C, 3 h), furnished **7** (76 %),<sup>5e)</sup> a white powder,  $[\alpha]_D^{22} -12^\circ$  (CHCl<sub>3</sub>), C<sub>37</sub>H<sub>35</sub>N<sub>5</sub>O<sub>8</sub>. After removal of the acetyl groups and the benzoyl groups in **7** with 1% NaOMe-MeOH (23°C, 8 h), the product was subjected to debenzoylation (Na, liq. NH<sub>3</sub>, THF, -78°C, 30 min) to provide (-)-9-pseudo- $\beta$ -D-glucopyranosyladenine (**8**, 92 %),<sup>5f)</sup> a white powder,  $[\alpha]_D^{20} -7^\circ$  (MeOH), C<sub>12</sub>H<sub>17</sub>N<sub>5</sub>O<sub>4</sub>. The structure **8** was further verified by the following synthesis from a pseudo-aminosugar **9**.<sup>4a)</sup>

Denitrohydrogenation of **9** with n-Bu<sub>3</sub>SnH and AIBN (benzene, 80°C, 2.5 h) yielded **10** (74 %),<sup>5g)</sup> a white powder,  $[\alpha]_D^{26} +18^\circ$  (CHCl<sub>3</sub>), C<sub>27</sub>H<sub>31</sub>NO<sub>8</sub>. After removal of the acetyl and benzoyl groups in **10** with 1% NaOMe-



MeOH followed by de-N-acetylation with 80% aq.  $\text{NH}_2\text{NH}_2$  in a sealed tube ( $100^\circ\text{C}$ , 60 h), the product was subsequently subjected to treatment with 5-amino-4,6-dichloropyrimidine in  $n\text{-BuOH}$  in the presence of  $\text{Et}_3\text{N}$  to provide 11 (85%),<sup>5h</sup> a white powder,  $[\alpha]_D^{28} -6^\circ$  (MeOH),  $\text{C}_{18}\text{H}_{23}\text{N}_4\text{O}_4\text{Cl}$ . Following treatment of 11 with triethyl orthoformate in the presence of conc. HCl ( $25^\circ\text{C}$ , 3 h), the product was ammonolyzed with liq.  $\text{NH}_3$  in a sealed tube ( $60^\circ\text{C}$ , 2 h) to yield 12 (68%),<sup>5i</sup> a white powder,  $[\alpha]_D^{20} -3^\circ$  (MeOH),  $\text{C}_{19}\text{H}_{23}\text{N}_5\text{O}_4$ . Debenzylation of 12 with liq.  $\text{NH}_3$ -Na in THF ( $-78^\circ\text{C}$ , 30 min) furnished 8 (92%), identical with the product synthesized via 6.

On the other hand, treatment of 13b<sup>4b</sup> with 5 as described above for 3a yielded 14 (71%),<sup>5j</sup> colorless oil,  $[\alpha]_D^{20} -15^\circ$  ( $\text{CHCl}_3$ ),  $\text{C}_{32}\text{H}_{32}\text{N}_6\text{O}_{10}$ . Denitrohydrogenation of 14 yielded 15 (77%),<sup>5k</sup> a white powder,  $[\alpha]_D^{22} -8^\circ$  ( $\text{CHCl}_3$ ),  $\text{C}_{32}\text{H}_{33}\text{N}_5\text{O}_8$ , which was subjected to deacetylation and debenzoylation as described above for 7.

to provide (-)-9-pseudo- $\beta$ -L-idopyranosyladenine (16, 91%),<sup>5m</sup> a white powder,  $[\alpha]_D^{20}$  -47° (MeOH), C<sub>12</sub>H<sub>17</sub>N<sub>5</sub>O<sub>4</sub>.

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b) 3b, colorless oil,  $[\alpha]_D^{22}$  +62° (CHCl<sub>3</sub>), C<sub>25</sub>H<sub>23</sub>NO<sub>10</sub>, and 13b, colorless oil,  $[\alpha]_D^{20}$  +3° (CHCl<sub>3</sub>), C<sub>20</sub>H<sub>23</sub>NO<sub>9</sub>, were prepared from D-glucose as for 3a and 13a.<sup>4a</sup>
- 5) All new compounds were fully characterized by IR (CHCl<sub>3</sub>), <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>, with decoupling experiments), and MS spectra (unless specified otherwise):  
a) 1a; IR: 1724, 1560 cm<sup>-1</sup>, <sup>1</sup>H NMR:  $\delta$  2.66 (m, 5 $\alpha$ -H), 3.34 (dd, J=10, 10 Hz, 3 $\alpha$ -H), 3.70 (dd, J=10, 10 Hz, 1 $\alpha$ -H), 4.13 (dd, J=2, 13 Hz), 4.29 (dd, J=4, 13 Hz) (7-H<sub>2</sub>), 4.50 (dd, J=10, 10 Hz, 6 $\beta$ -H), 4.99 (dd, J=10, 10 Hz, 2 $\beta$ -H), 5.19 (dd, J=10, 12 Hz, 4 $\beta$ -H), MS (m/z): 582 (M<sup>+</sup>);  
b) 1b; IR: 1725, 1559 cm<sup>-1</sup>, <sup>1</sup>H NMR:  $\delta$  2.83 (m, 5 $\alpha$ -H), 3.53 (dd, J=10, 10 Hz, 1 $\alpha$ -H), 4.14 (dd, J=3, 12 Hz), 4.44 (dd, J=4, 12 Hz) (7-H<sub>2</sub>), 4.60 (dd, J=10, 10 Hz, 6 $\beta$ -H), 5.13 (dd, J=10, 10 Hz, 2 $\beta$ -H), 5.34 (dd, J=10, 11 Hz, 4 $\beta$ -H), 5.50 (dd, J=10, 10 Hz, 3 $\alpha$ -H), MS (m/z): 596 (M<sup>+</sup>);  
c) 2; IR: 1737, 1555 cm<sup>-1</sup>, <sup>1</sup>H NMR:  $\delta$  3.14 (m, 5 $\beta$ -H), 3.66 (dd, J=3, 11 Hz, 1 $\beta$ -H), 3.91 (dd, J=3, 3 Hz, 3 $\beta$ -H), 4.26 (dd, J=7, 12 Hz), 4.39 (dd, J=7, 12 Hz) (7-H<sub>2</sub>), 4.73 (dd, J=11, 11 Hz, 6 $\alpha$ -H), 5.20 (dd, J=3, 3 Hz, 2 $\beta$ -H), 5.25 (dd, J=3, 3 Hz, 4 $\beta$ -H), MS (m/z): 582 (M<sup>+</sup>);  
d) 6; IR: 1753, 1722, 1611, 1594 cm<sup>-1</sup>, <sup>1</sup>H NMR:  $\delta$  2.86 (m, 5' $\alpha$ -H), 3.91 (dd, J=9, 9 Hz, 3' $\alpha$ -H), 4.28 (dd, J=3, 12 Hz), 4.44 (dd, J=4, 12 Hz) (7'-H<sub>2</sub>), 5.03 (dd, J=10, 11 Hz, 1' $\alpha$ -H), 5.52 (dd, J=9, 11 Hz, 4' $\beta$ -H), 5.95 (dd, J=9, 10 Hz, 2' $\beta$ -H), 6.34 (dd, J=10, 11 Hz, 6' $\beta$ -H), 7.84, 8.82 (both s, 2,8-H), CI-MS (methane)m/z: 723 (M<sup>+</sup>+H);  
e) 7; IR: 1741, 1712, 1611, 1592 cm<sup>-1</sup>, <sup>1</sup>H NMR:  $\delta$  2.31 (m, 5' $\alpha$ -H), 2.36 (ddd, J=10, 10, 12 Hz, 6' $\beta$ -H), 2.39 (ddd, J=6, 6, 12 Hz, 6' $\alpha$ -H), 3.82 (dd, J=10, 10 Hz, 3' $\alpha$ -H), 4.23 (dd, J=6, 11 Hz), 4.45 (dd, J=4, 11 Hz) (7'-H<sub>2</sub>), 4.77 (ddd, J=6, 10, 10 Hz, 1' $\alpha$ -H), 5.35 (dd, J=10, 10 Hz, 4' $\beta$ -H), 5.62 (dd, J=10, 10 Hz, 2' $\beta$ -H), 8.05, 8.82 (both s, 2,8-H), MS (m/z): 677 (M<sup>+</sup>);  
f) 8; UV  $\lambda_{\text{max}}^{\text{H}_2\text{O}}$  nm ( $\epsilon$ ): 261 (8400), IR (KBr): 3330, 1640, 1590 cm<sup>-1</sup>, <sup>1</sup>H NMR (CD<sub>3</sub>OD):  $\delta$  1.75 (m, 5' $\alpha$ -H), 2.10 (ddd, J=5, 5, 13 Hz, 6' $\alpha$ -H), 2.12 (ddd, J=11, 11, 13 Hz, 6' $\beta$ -H), 3.37 (dd, J=9, 9 Hz, 3' $\alpha$ -H), 3.44 (dd, J=9, 11 Hz, 4' $\beta$ -H), 3.65 (dd, J=6, 11 Hz), 3.81 (dd, J=4, 11 Hz) (7'-H<sub>2</sub>), 4.03 (dd, J=9, 11 Hz, 2' $\beta$ -H), 4.41 (ddd, J=5, 11, 11 Hz, 1' $\alpha$ -H), 8.16, 8.18 (both s, 2,8-H), <sup>13</sup>C NMR (125 MHz, D<sub>2</sub>O):  $\delta$  32.7 (6'-C), 44.3 (5'-C), 60.3 (1'-C), 64.9 (7'-C), 75.2, 76.5, 80.4 (2'-C, 3'-C, 4'-C), 121.6 (5-C), 143.9 (8-C), 152.0 (4-C), 155.2 (2-C), 158.4 (6-C), MS (m/z): 295 (M<sup>+</sup>);  
g) 10; IR: 1728, 1669, 1502 cm<sup>-1</sup>, <sup>1</sup>H NMR:  $\delta$  1.40 (ddd, J=12, 13, 13 Hz, 6 $\beta$ -H), 2.13 (m, 5 $\alpha$ -H), 2.20 (ddd, J=4, 4, 13 Hz, 6 $\alpha$ -H), 3.65 (dd, J=10, 10 Hz, 3 $\alpha$ -H), 4.09 (dddd, J=4, 8, 11, 12 Hz, 1 $\alpha$ -H), 4.15 (dd, J=6, 11 Hz), 4.32 (dd, J=3, 11 Hz) (7-H<sub>2</sub>), 4.91 (dd, J=10, 11 Hz, 2 $\beta$ -H), 5.12 (dd, J=10, 11 Hz, 4 $\beta$ -H), 5.91 (d, J=8 Hz, -NH), MS (m/z): 497 (M<sup>+</sup>);  
h) 11; IR (KBr): 3478, 2992, 1692 cm<sup>-1</sup>, <sup>1</sup>H NMR (CD<sub>3</sub>OD):  $\delta$  1.63 (ddd, J=11, 11, 13 Hz, 6' $\beta$ -H), 1.70 (m, 5' $\alpha$ -H), 2.12 (ddd, J=4, 4, 13 Hz, 6' $\alpha$ -H), 3.34 (dd, J=10, 10 Hz, 3' $\alpha$ -H), 3.43 (dd, J=10, 10 Hz, 4' $\beta$ -H), 3.53 (dd, J=10, 11 Hz, 2' $\beta$ -H), 3.63 (dd, J=6, 11 Hz), 3.76 (dd, J=4, 11 Hz) (7'-H<sub>2</sub>), 4.18 (ddd, J=4, 11, 11 Hz, 1' $\alpha$ -H), 7.79 (s, 2-H), MS (m/z): 394, 396 (3:1, M<sup>+</sup>);  
i) 12; IR (KBr): 3392, 1703, 1602, 1589 cm<sup>-1</sup>, <sup>1</sup>H NMR (CD<sub>3</sub>OD):  $\delta$  1.79 (m, 5' $\alpha$ -H), 2.10 (ddd, J=6, 6, 13 Hz, 6' $\alpha$ -H), 2.11 (ddd, J=12, 12, 13 Hz, 6' $\beta$ -H), 3.38 (dd, J=9, 9 Hz, 3' $\alpha$ -H), 3.58 (dd, J=9, 11 Hz, 4' $\beta$ -H), 3.65 (dd, J=6, 11 Hz), 3.82 (dd, J=4, 11 Hz) (7'-H<sub>2</sub>), 4.19 (dd, J=9, 11 Hz, 2' $\beta$ -H), 4.44 (ddd, J=6, 11, 12 Hz, 1' $\alpha$ -H), 8.16, 8.18 (both s, 2,8-H), MS (m/z): 385 (M<sup>+</sup>);  
j) 14; IR: 1746, 1711, 1612, 1586 cm<sup>-1</sup>, <sup>1</sup>H NMR:  $\delta$  3.28 (m, 5' $\beta$ -H), 4.04 (dd, J=3, 3 Hz, 3' $\alpha$ -H), 4.07 (dd, J=6, 12 Hz), 4.33 (dd, J=7, 12 Hz) (7'-H<sub>2</sub>), 5.23 (dd, J=3, 3 Hz, 2' $\beta$ -H), 5.31 (dd, J=3, 3 Hz, 4' $\beta$ -H), 5.77 (dd, J=12, 12 Hz, 6' $\alpha$ -H), 5.88 (dd, J=3, 12 Hz, 1' $\beta$ -H), 8.09, 8.82 (both s, 2,8-H), CI-MS (methane)m/z: 661 (M<sup>+</sup>+H);  
k) 15; IR: 1732, 1703, 1605, 1583 cm<sup>-1</sup>, <sup>1</sup>H NMR:  $\delta$  1.93-2.02 (m, 6' $\beta$ -H), 2.51 (ddd, J=13, 13, 13 Hz, 6' $\alpha$ -H), 2.69 (m, 5' $\beta$ -H), 4.04 (dd, J=3, 3 Hz, 3' $\alpha$ -H), 4.03 (dd, J=7, 11 Hz), 4.17 (dd, J=3, 11 Hz) (7'-H<sub>2</sub>), 5.16 (dd, J=3, 3 Hz, 2' $\beta$ -H), 5.25 (br. s, 4' $\beta$ -H), 5.38 (ddd, J=3, 3, 13 Hz, 1' $\beta$ -H), 8.11, 8.82 (both s, 2,8-H), MS (m/z): 615 (M<sup>+</sup>);  
m) 16; UV  $\lambda_{\text{max}}^{\text{H}_2\text{O}}$  nm ( $\epsilon$ ): 261 (7400), IR (KBr): 3318, 1636, 1596 cm<sup>-1</sup>, <sup>1</sup>H NMR (CD<sub>3</sub>OD):  $\delta$  1.80 (ddd, J=8, 9, 14 Hz, 6' $\alpha$ -H), 2.32 (m, 5' $\beta$ -H), 2.33 (ddd, J=3, 3, 14 Hz, 6' $\beta$ -H), 3.63 (dd, J=6, 11 Hz), 3.77 (dd, J=6, 11 Hz) (7'-H<sub>2</sub>), 3.99 (br. s, 4' $\beta$ -H), 4.01 (br. s, 2' $\beta$ -H), 4.11 (dd, J=3, 3 Hz, 3' $\alpha$ -H), 5.07 (ddd, J=3, 4, 9 Hz, 1' $\beta$ -H), 8.19, 8.35 (both s, 2,8-H), <sup>13</sup>C NMR (125 MHz, D<sub>2</sub>O):  $\delta$  24.9 (6'-C), 41.1 (5'-C), 55.7 (1'-C), 65.6 (7'-C), 72.1, 73.6, 73.6 (2'-C, 3'-C, 4'-C), 121.0 (5-C), 144.3 (8-C), 151.3 (4-C), 155.0 (2-C), 158.2 (6-C), MS (m/z): 295 (M<sup>+</sup>).
- 6) The molecular composition of the compound given with the chemical formula was determined either by elemental analysis or by high resolution mass spectrometry.
- 7) When 3a or 13a was treated with aniline or cyclohexanol as described above for the treatment with cyclohexylamine, an addition product, having an equatorial substituent at the 1-position the same as in 1a, 1b, and 2a, was obtained.

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