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A NEW STEREOSPECIFIC SYNTHESIS OF [3.1.0] BICYCLIC CYCLOPROPANO ANALOG OF 2',3'-DIDEOXYURIDINE

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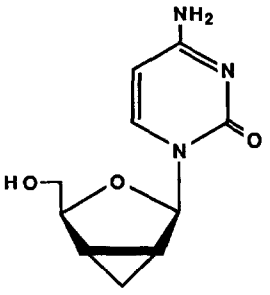
Summary: A new stereospecific synthesis of 2',3-α-methylene-2',3'-dideoxyuridine **13** *is reported from 5'-O-(4-monomethoxytrityl)-α,β-ene-3'-phenylselenone* **2** *[2 → 11 → 12 → 13].*

Several 2',3'-dideoxynucleosides such as 3'-azidothymidine, 3'-fluorothymidine, 2',3'-dideoxyinosine, 2',3'-dideoxydidehydrothymidine specifically inhibit the HIV-specific reverse transcriptase[1-20]. These dideoxynucleoside analogs have been subsequently found to be chemotherapeutically useful against HIV, and are undergoing different phases of clinical trial. Recently, a eight-step synthesis of the fused [3.1.0]-bicyclic ring-system of 2',3'-α-methylene-2',3'-dideoxycytidine **1** from tri-O-acetyl-D-glucal has been reported[21] as a promising category of HIV-specific reverse transcriptase inhibitor which has prompted us to record herein our new facile three-step synthesis of the uracil analogue **13** *directly* from an easily accessible β-D-ribonucleoside precursor **2**.

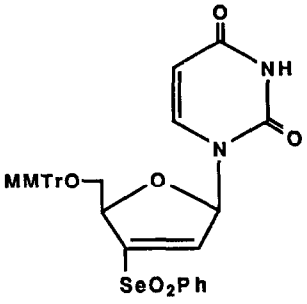
As a part of our program concerned with the discovery of new types of dideoxynucleosides as specific inhibitor of HIV-reverse transcriptase, we have shown[22] that an appropriately 5'-protected α,β-ene-3'-phenylselenone **2** is indeed a synthetic equivalent of a dication CH_2^+ - CH_2^+ **3**. It has been demonstrated that **2** acts as a Michael acceptor in the conjugate addition reactions at C-2', the adduct then undergoes a neighbouring S_N2 type nucleophilic ring-closure reaction at C-3' with both ammonia and primary amines to give α-fused-[3.1.0]-aziridines[22]. Carbon nucleophiles such as sodium malonate, and conjugate bases of nitromethane and acetophenone, upon reaction with **2**, gave also a convenient access to derivatives of 2',3'-deoxy-2',3'-α-methylene-[3.1.0]-nucleosides **4** - **6** [22].

The anion of methylene bis-diethylphosphate adds to **2** in a concerted manner to give **7a** in 42% yield which can be easily deprotected to give the corresponding 5'-hydroxy derivative **7b** in a high yield. It is also interesting to note that whereas the reaction of **2** with the conjugate base of methylacetoacetate gave an unusual 2',3'-fused furano [3.3.0] system **9a** [22], the anion of isobutylcyanoacetate, under identical conditions, gave the [3.1.0]-fused α-methylene derivative **8a** (67%), which was conveniently deprotected to give **8b** (94%) (experimental).

Our repeated attempts to cleave the carbon-nitrogen bond in the aliphatic nitro derivative **5a** by radical promoted reductive cleavage reaction[23] to obtain **13** turned out to be unsuccessful. Similarly, attempts to introduce the



1



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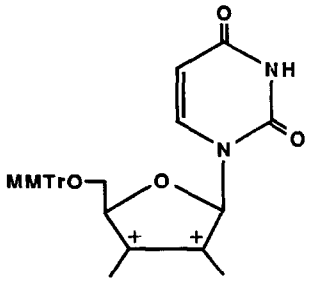

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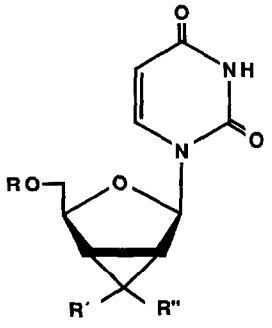
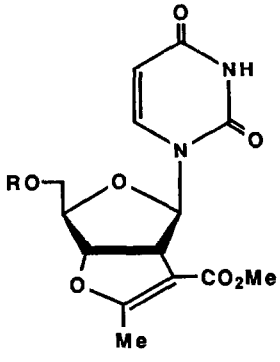
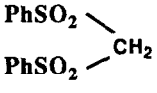




9a : R = MMTr
9b : R = H



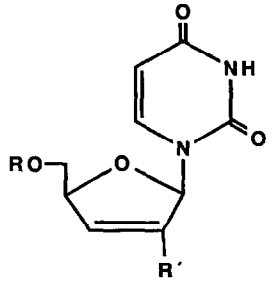
10

4a : R = MMTr, R′ = R" = CO_2Me
4b : R = H, R′ = R" = CO_2Me
5a : R = MMTr, R′ = H, R" = NO_2
5b : R = H, R′ = H, R" = NO_2
6 : R = MMTr, R′ = H, R" = COPh

7a : R = MMTr, R′ = R" = $PO(OEt)_2$
7b : R = H, R′ = R" = $PO(OEt)_2$
8a : R = MMTr, R′ = CN, R" = CO_2iBu
8b : R = H, R′ = CN, R" = CO_2iBu

11 : R = MMTr, R′ = R" = SO_2Ph
12 : R = MMTr, R′ = R" = H

13 : R = R′ = R′′ = H



14 : R = MMTr, R′ = $CH(PhSO_2)_2$
15 : R = MMTr, R′ = CH_3
16 : R = H, R′ = CH_3

2',3'-fused-α-methylene system stereoselectively in **2** by Simmon-Smith condition (Et_2Zn + CH_2I_2)[24] was also unsuccessful and gave only the reduced product: 5′-O-MMTr-α,β-ene-3′-phenylselenide derivative of uridine.

Finally, we chose to employ the conjugate base of methylene bis-phenylsulfone **10** for a conjugate addition to the α,β-ene-3'-phenylselenone **2**. The anion of **10** reacted first at C-2' of **2** which was followed by an intramolecular S_N2 cyclization reaction in the adduct to give **11** in 35 % yield along with **14** (21 %). Clearly, 2′,3′-vinyl-2′-*C*-alkane **14** was formed by the *cis*-elimination of phenylselenic acid in the adduct[27]. Previously, it has been shown that the anion of methylene bis-alkylsulfones conjugatively adds to the vinylsulfonium salts to give cyclopropanes[25,26], but to our knowledge, this is the first example of the facile conjugate addition of an anion of bis-arylsulfone to a α,β-ene-3'-phenylselenone to give a cyclopropane derivative such as **11**. Subsequently, a reductive desulfonation (Mg-MeOH)[26] of the cyclopropane derivative **11** gave the 5'-O-MMTr-2',3'-α-methylene-2',3'-dideoxyuridine **12** in 58 % yield. A standard deprotection of 5'-O-MMTr group[22] from **12** with the help of 80 % aqueous acetic acid gave the desired [3.1.0] bicyclic nucleoside **13** in 83 % yield.

We have also reductively desulfonated substituted β-ene-alkane **14** by the treatment of Mg in methanol to obtain the hitherto unreported, novel 1-[(5'-O-MMTr)-2',3'-dideoxy-2'-methyl-β-D-*glycero*pent-2'-enofuranosyl]uracil **15** in 46 % yield which was also deprotected with 80 % aqueous acetic acid[22] to give the fully deprotected α,β-ene-2′-*C*-alkane **16** in 89 % yield.

The new stereospecific synthesis of bicyclic-[3.1.0]-cyclopropyl nucleoside **13** and 2′,3′-dideoxy-2′,3′-ene-2′-methyl nucleoside **14** directly from a β-D-nucleoside precursor should provide an efficient and convenient route to a variety of cyclopropane and 2′-*C*-alkane substituted-α,β-ene-analogues of dideoxynucleosides.

Experimental.

^{1}H-NMR spectra were recorded (in δ scale) with Jeol 90Q spectrometer at 90 MHz, using TMS (0.0 ppm). ^{13}C-NMR were recorded at 22.5 MHz using both ^{1}H-coupled and ^{1}H-decoupled or INEPT modes. ^{31}P-NMR were recorded at 36 MHz in the same solvent mixture as for ^{1}H-NMR using 85% H_3PO_4 as external standard (0.0 ppm). UV absorption spectra were recorded with Varian-Cary 2200 instrument. Jeol DX 303 instrument was used for recording high resolution mass spectra. TLC was carried out using Merck pre-coated silica gel F_{254} plates. The column chromatographic separations were carried out using Merck G60 silica gel.

Compound 7a : To a solution of tetraethyl methylenephosphonate (0.5 ml) in tetrahydrofuran (2 ml) was added potassium tert-butyloxide (112 mg, 1 mmol) at the room temperature under nitrogen. After 15 min, **2** (200 mg, 0.3 mmol) was added and the reaction was stirred for another 20 min. The reation mixture was poured into saturated aqueous solution of ammonium chloride (100 ml), which was then extracted with ethyl acetate (3 x 40 ml). The combined extract was evaporated and the syrup was triturated with water. The residue was purified on a silica gel column to give the title compound (98 mg, 42 %). ^{1}H-NMR ($CDCl_3$): 8.96 (br, 1H) NH; 7.89 (d, $J_{5,6}$ = 8.3 Hz, 1H) H-6; 7.32-6.84 (m, 14H) arom; 6.50 (s, 1H) H-1'; 5.08 (d, 1H) H-5; 4.89 (t, $J_{4',5'}$ = 4.4 Hz, $J_{4',5''}$ = 3.7 Hz, 1H) H-4'; 4.33-4.20 (m, 8H) 4 x OCH_2; 3.80 (s, 3H) OCH_3; 3.43 (d, 2H) H-5', H-5''; 2.96-2.64 (m, 2H) H-2', H-3'; 1.36 (m, 12H) 4 x CH_3. ^{31}P-NMR ($CDCl_3$) : 21.0 (d, J_{PP} = 19.6 Hz, 1P) ; 17.6 (d, J_{PP} = 19.6 Hz, 1P). ^{13}C-NMR ($CDCl_3$) : 101.8 (d, J_{CH} = 178.6 Hz) C-5; 87.0 (s) MMTr; 85.6 (d, J_{CH} = 177.5 Hz) C-1'; 79.7 (d, J_{CH} = 153.9 Hz) C-4'; 65.0 (t, J_{CH} = 143.2 Hz) C-5'; 63.2

(m) CH_2; 55.1(q) OCH_3; 37.1, 33.5 (2 x d, J_{CH} = 180.9 Hz, J_{CH} = 178.6 Hz) C-2', C-3'; 16.3 (q) CH_3. MS (FAB$^-$): calc. for (M-H)$^-$ 767.2499, found 767.2538.

Compound 7b (yield 90 %). ^{1}H-NMR ($CDCl_3$) : 11.0 (br, 1H) NH; 8.15 (d, $J_{5,6}$ = 8.3 Hz, 1H) H-6; 6.32 (s,1H) H-1'; 5.66 (d, 1H) H-5; 4.73 (m, 1H) H-4'; 4.19 (m, 8H) OCH_2; 3.90 (s, 2H) H-5', H-5"; 2.89-2.62 (m, 2H) H-2', H-3'; 1.73 (t, 12H) 4 x CH_3. ^{31}P-NMR ($CDCl_3$) : 22.2 (d, J_{PP} = 19.4 Hz, 1P) ; 17.9 (d, J_{PP} = 19.4 Hz, 1P) ; ^{13}C-NMR ($CDCl_3$) : 101.1 (d, J_{CH} = 177.5 Hz) C-5; 86.4 (d, J_{CH} = 175.2 Hz) C-1'; 82.0 (d, J_{CH} = 152.8 Hz) C-4'; 63.5 (m) C-5', OCH_2; 37.5, 33.0 (2 x d, J_{CH} = 179.7 Hz, J_{CH} = 182.1 Hz) C-2', C-3'; 16.3 (q) CH_3. MS (FAB$^-$): calc. for (M-H)$^-$ 495.1298, found 495.1295.

Compound 8a : The mixture of compound **2** (134 mg, 0.2 mmol), isobutyl cyanoacetate (142 µl, 1 mmol), potassium carbonate (148 mg, 1 mmol) in tetrahydrofuran (2 ml) was stirred at room temperature for 4 h and then poured into ethyl acetate (100 ml). The solution was washed with water (2 x 20 ml) and dried over magnesium sulfate. Solvent was removed by evaporation and the residue was separated on a silica gel column to give the title compound (85 mg, 67 %). ^{1}H-NMR ($CDCl_3$) : 8.82 (br, 1H) NH; 7.74 (d, $J_{5,6}$ = 8.1 Hz, 1H) H-6; 7.30-6.86 (m, 14 H) arom; 6.13 (s, 1H) H-1'; 5.17 (d, 1H) H-5; 4.59 (t, $J_{4',5'}$ = 4.4 Hz, $J_{4',5"}$ = 3.9 Hz, 1H) H-4'; 4.02 (d, J = 6.6 Hz, 2H) OCH_2; 3.80 (s, 3H) OCH_3; 3.49 (d, 2H) H-5',H-5"; 3.05, 2.90 (2 x d, $J_{2',3'}$ = 7.0 Hz, 2H) H-2', H-3'; 2.05 (m, 1H) CH; 1.04, 0.98 (2 x s, 6H) 2 x CH_3. ^{13}C-NMR ($CDCl_3$) : 164.8 (s) carbonyl; 102.4 (d, J_{CH} = 178.6 Hz) C-5; 87.5 (d, J_{CH} = 177.5 Hz) C-1'; 87.0 (s) MMTr; 82.0 (d, J_{CH} = 151.7 Hz) C-4'; 73.4 (t, J_{CH} = 150.0 Hz) OCH_2; 64.3 (t, J_{CH} = 142.7 Hz) C-5'; 55.1 (q) OCH_3; 39.6, 36.7 (2 x d, J_{CH} = 184.3 Hz, J_{CH} = 182.0 Hz) C-2', C-3'; 27.7 (s) CH in cyclopropane; 24.8, 18.8, $CH(CH_3)_2$.

Compound 8b (yield 94 %). ^{1}H-NMR ($CDCl_3$) : 10.1 (br, 1H) NH; 7.94 (d, $J_{5,6}$ = 8.0 Hz, 1H) H-6; 6.11 (s, 1H) H-1'; 5.79 (d, 1H) H-5; 4.47 (t, 1H) H-4'; 4.05 (2 x s, 4H) H-5', H-5", OCH_2; 3.16, 3.04 (2 x d, $J_{2',3'}$ = 7.3 Hz, 2H) H-2', H-3'; 2.05 (m, 1H) CH; 1.04 (2 x s, 6H) 2 x CH_3. ^{13}C-NMR ($CDCl_3$): 164.9 (s) carbonyl; 112.7 (s) CN; 101.9 (d, J_{CH} = 177.5 Hz) C-5; 87.4 (d, J_{CH} = 173.0 Hz) C-1'; 83.5 (d, J_{CH} = 150.2 Hz) C-4'; 73.4 (t, J_{CH} = 150.4 Hz) OCH_2; 63.1 (t, J_{CH} = 144.4 Hz) C-5'; 38.8, 37.1 (J_{CH} = 186.5 Hz, J_{CH} = 185.4 Hz) C-2', C-3'; 27.5 (s) $C(SO_2Ph)_2$ in cyclopropane; 24.5 (d) CH; 18.8 (q) CH_3. MS (FAB$^-$): calc. for (M-H)$^-$ 348.1196, found 348.1193.

Compound 11 and 14 : To a solution of bis(phenylsulfonyl)methane (296 mg, 1 mmol) in dimethylformamide (3 ml) was added potassium tert-butyloxide (112 mg, 1 mmol) at room temperature under nitrogen. After 15 min, compound **2** (335 mg, 0.5 mmol) was added and the reaction was stirred for another 5 h. The reaction mixture was poured into saturated aqueous solution of ammonium chloride (100 ml), which was then filtered and the solid was washed with water. The residue was purified on a silica gel column to give the title compound **11** (132 mg, 35 %) and **14** (80 mg, 21%). Compound **11** : ^{1}H-NMR ($CDCl_3$) : 9.87 (br, 1H) NH; 8.13-6.87 (m, 25 H) H-6, arom; 6.73 (s, 1H) H-1'; 5.29 (d, $J_{5,6}$ = 8.3 Hz, 1H) H-5; 4.96 (t, $J_{4',5'}$ = 3.6 Hz, $J_{4',5"}$ = 3.4 Hz, 1H) H-4'; 3.81 (s, 3H) OCH_3; 3.53-3.31 (m, 4H) H-2', H-3', H-5', H-5". ^{13}C-NMR ($CDCl_3$): 102.5 (d, J_{CH} = 178.6 Hz) C-5; 87.2 (s) MMTr; 85.9 (d, J_{CH} = 177.5 Hz) C-1'; 79.6 (d, J_{CH} = 157.3 Hz) C-4'; 67.5 (s) $C(SO_2Ph)_2$ in cyclopropane; 64.4 (t, J_{CH} = 143.8 Hz) C-5'; 55.1 (q) OCH_3; 41.2, 38.2 (2xd, J_{CH} = 182.0 Hz, J_{CH} = 180.9 Hz).C-2', C-3'. Compound **14** : ^{1}H-NMR ($CDCl_3$) : 9.57 (br, 1H) NH; 8.00-7.24 (m, 23 H) H-6, arom; 7.13 (t, $J_{1',3'}$ = 1.2 Hz, $J_{1',4'}$ = 1.4 Hz, 1H) H-1'; 6.84 (d, 2H) arom; 6.20 (dd, $J_{3',4'}$ = 3.4 Hz, 1H) H-3'; 5.45 (s, 1H) $CHSO_2Ph$; 5.11 (dd, $J_{5,6}$ = 8.2 Hz, 1H) H-5; 5.0 (m, 1H) H-4'; 3.79 (s, 3H) OCH_3; 3.48 (m, 2H) H-5', H-5". ^{13}C-NMR ($CDCl_3$) : 102.0 (d, J_{CH} = 178.0 Hz) C-5; 90.7 (d, J_{CH} = 170.8 Hz) C-1'; 87.2 (s) MMTr; 86.7 (d, J_{CH} = 159.4 Hz) C-4'; 77.8 (d, J_{CH} = 144.9 Hz) $CHSO_2Ph$; 63.6 (t, J_{CH} = 144.4 Hz) C-5'; 55.1 (q) OCH_3.

Compound 12 : To the solution of compound **11** (100 mg, 0.13 mmol) in a mixture of methanol (2 ml) and tetrahydrofuran (0.3 ml) was added activated magnesium (120 mg, 5.2 mmol) and the reaction was heated at 60 °C overnight. The mixture was poured into saturated aqueous solution of ammonium chloride (40 ml), which was extracted with ethyl acetate (4 x 30 ml). The combined extract was evaporated and the residue was purified on a silica gel column to give the title compound (38 mg, 58 %). ^{1}H-NMR ($CDCl_3$): 8.42 (br, 1H) NH; 7.89 (d, $J_{5,6}$ = 8.3 Hz, 1H) H-6; 7.34-6.84 (m, 14H) arom; 5.96 (s, 1H) H-1'; 5.16 (d, 1H) H-5; 4.32 (t, $J_{4',5'}$ = 5.0 Hz, $J_{4',5"}$ = 5.5 Hz, 1H) H-4'; 3.80 (s, 3H) OCH_3; 3.18 (m, 2H) H-5', H-5"; 1.96 (m, J_{trans} = 4.1 Hz, J_{cis} = 8.2 Hz, 2H) H-2', H-3'; 1.05 (dt, J_{gem} = 4.7 Hz, $J_{H\text{-}2'/3',\beta\text{-}H}$ = 8.2 Hz, 1H) β-H of cyclopropyl -CH_2-;

0.53 (dt, J_{gem} = 4.7 Hz, $J_{H\text{-}2'/3',\alpha\text{-}H}$ = 4.1 Hz, 1H) α-H of cyclopropyl -CH_2-. ^{13}C-NMR ($CDCl_3$) : 101.4 (d, J_{CH} = 176.4 Hz) C-5; 87.5 (d, J_{CH} = 176.3 Hz) C-1'; 86.7 (s) MMTr; 83.0 (d, J_{CH} = 149.3 Hz) C-4'; 63.5 (t, J_{CH} = 146.2 Hz) C-5'; 55.1 (q) OCH_3; 22.7, 20.4 (2xd, J_{CH} = 183.0 Hz, J_{CH} = 181.5 Hz) C-2', C-3'; 10.5 (t, J_{CH} = 161.0 Hz) CH_2. MS (FAB^-): calc. for $(M\text{-}H)^-$ 495.1920, found 495.1926.

Compound 15 : To the solution of compound **14** (200 mg, 0.26 mmol) in a mixture of methanol (3 ml) and tetrahydrofuran (0.5 ml) was added activated magnesium (300 mg, 13 mmol) and the reaction was heated at 60 °C for 5 h. The mixture was poured into saturated aqueous solution of ammonium chloride (40 ml), which was extracted with ethyl acetate (4 x 30 ml) . The combined extract was evaporated and the residue was purified on a silica gel column to give the title compound (60 mg, 46 %) . ^{1}H-NMR ($CDCl_3$) : 9.19 (br, 1H) NH; 7.89 (d, $J_{5,6}$ = 8.1 Hz, 1H) H-6; 7.32-6.84 (m, 15H) H-1', arom; 5.85 (m, 1H) H-3'; 5.05 (d, 1H) H-5; 4.88 (m, 1H) H-4'; 3.79 (s, 3H) OCH_3; 3.39 (d, 2H) H-5', H-5"; 1.72 (s, 3H) CH_3. ^{13}C-NMR ($CDCl_3$) : 102.5 (d, J_{CH} = 178.4 Hz) C-5; 91.0 (d, J_{CH} = 169.6 Hz) C-1'; 86.7 (s) MMTr; 85.0 (d, J_{CH} = 148.2 Hz) C-4'; 64.4 (t, J_{CH} = 143.2 Hz) C-5'; 55.1 (q) OCH_3; 11.4 (q) CH_3. MS (FAB^-): calc. for $(M\text{-}H)^-$ 495.1920, found 495.1942.

Compound 13 (yield 83 %): ^{1}H-NMR ($CDCl_3$): 7.98 (d, $J_{5,6}$ = 8.3 Hz, 1H) H-6; 5.98 (s, 1H) H-1'; 5.71 (d, 1H) H-5; 4.13 (t, $J_{4',5'}$ = 5.6 Hz, $J_{4',5"}$ = 4.6 Hz, 1H) H-4; 3.62 (2 x d, 2H) H-5', H-5"; 1.93 (dd, J_{trans} = 4.4 Hz, J_{cis} = 8.3 Hz, 2H) H-2', H-3'; 1.09 (dt, J_{gem} = 4.6 Hz, $J_{H\text{-}2'/3',\beta\text{-}H}$ = 8.3 Hz, 1H) β-H of cyclopropyl -CH_2-; 0.51 (dt, J_{gem} = 4.6 Hz, $J_{H\text{-}2'/3',\alpha\text{-}H}$ = 4.4 Hz, 1H) α-H of cyclopropyl -CH_2-. ^{13}C-NMR ($CDCl_3$) : 141.0 (d, J_{CH} = 182.0 Hz) C-6; 100.8 (d, J_{CH} = 182.7 Hz) C-5; 87.1 (2 x d, J_{CH} = 176.3 Hz, J_{CH} = 155.0 Hz) C-1', C-4'; 63.7 (t, J_{CH} = 141.0 Hz) C-5'; 21.8, 19.6 (2 x d, J_{CH} = 179.7 Hz, J_{CH} = 175.2 Hz) C-2', C-3'; ; 9.84 (t, J_{CH} = 162.9 Hz) cyclopropyl-CH_2. MS (FAB^-): calc. for $(M\text{-}H)^-$ 223.0719, found 223.0726. $[\alpha]_D^{25}$ -50.3 ° (c 0.3, methanol).

Compound 16 (yield 89 %): ^{1}H-NMR ($CDCl_3$): 9.11 (br, 1H) NH; 7.64 (d, $J_{5,6}$ = 8.3 Hz, 1H) H-6; 6.85 (m, 1H) H-1'; 5.93 (dd, $J_{1',3'}$ =1.7 Hz, $J_{1',4'}$ = 1.7 Hz, 1H) H-3'; 5.70 (d, 1H) H-5; 4.78 (m, 1H) H-4'; 3.87 (m, 2H) H-5', H-5"; 1.72 (s, 3H) CH_3. ^{13}C-NMR ($CDCl_3$): 140.9 (d, J_{CH} = 182.1 Hz) C-6; 128.1 (d, J_{CH} = 169.6 Hz) C-3'; 102.5 (d, J_{CH} = 178.6 Hz) C-5; 91.1 (d, J_{CH} = 175.2 Hz) C-1'; 86.5 (d, J_{CH} = 147.2 Hz) C-4'; 62.3 (t, J_{CH} = 142.1 Hz) C-5'; 11.2 (q) CH_3. MS (FAB^-): calc. for $(M\text{-}H)^-$ 223.0719, found 223.0716. $[\alpha]_D^{25}$ -20.5 ° (c 0.3, methanol).

Acknowledgements

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