Synthesis and Stereochemistry of (3α)-6β,7β-Dihydroxy- and 6β-Hydroxy-8-alkyl-8-azabicyclo[3.2.1]octane-3-spiro-5′-imidazoline-2′,4′-diones

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The synthesis of 6β-hydroxy- and 6β,7β-dihydroxy-8-alkyl-8-azabicyclo[3.2.1]octane-3-spiro-5′-hydantoins was stereoselectively achieved by Bucherer-Bergs reaction of the corresponding ketones. An α configuration on C_3 was proposed for all hydantoins on the basis of spectral data.

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Introduction.

Several tropane and nortropane-3-spiro-5′-hydantoins [1] have shown interesting pharmacological properties as anticolinergic, anticonvulsant and antiinflamatory agents [2-4]. This property was particularly interesting since the activity of some derivatives was superior to that of phenylbutazone, and comparable to that of indometacine. In an attempt to achieve efficient antiinflamatory agents devoid of CNS depressant activity, the preparation of more polar derivatives was planned, in order to avoid passage through the blood-brain barrier. With this aim, the synthesis of 6-hydroxy and 6,7-dihydroxy derivatives of the tropane-3-spiro-5′-hydantoin moiety **1** was proposed.

Results and Discussion.

Synthesis.

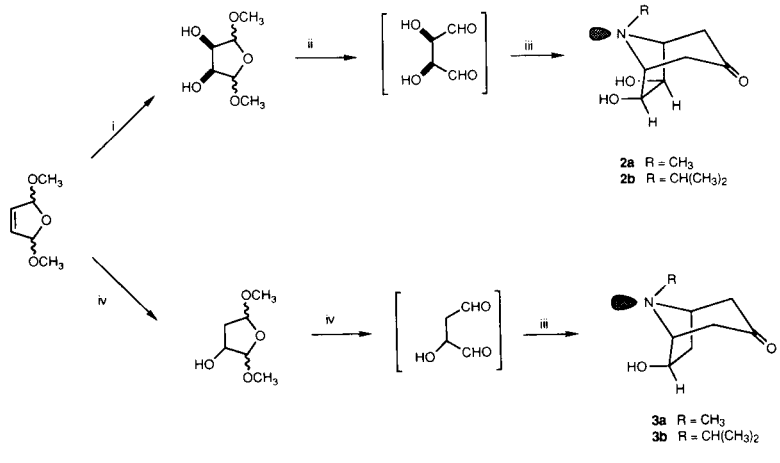
Ketones **2a,b** and **3a,b** were prepared (Scheme 1) by Robinson-Schöpf synthesis starting from commercially available 2,5-dimethoxy-2,5-dihydrofuran, which was transformed into the suitable succinaldehyde derivative by dihydroxylation with dilute potassium permanganate followed by acid hydrolysis (compounds **2**), or by direct acid hydrolysis (compounds **3**). Compound **2a** had been prepared by a similar method, albeit in a lower yield, by Sheehan and Bloom [5]. Change of the molar ratio between oxidizing agent and 2,5-dimethoxy-2,5-dihydrofuran allowed us to increase the yield of **2a** to 58% of pure, isolated product. Our synthesis of compound **3a** is a minor modification of that described by Dewar and co-workers [6]. Hydantoins **1** were obtained by Bucherer-Bergs reaction on ketones **2** and **3**. This reaction was completely stereoselective, yielding exclusively the isomer with an α configuration at the spiro atom C_3 (Scheme 2).

Stereochemistry.

Structural study of compounds **1** requires the following features to be established: a) Stereochemistry of carbon atoms bearing the hydroxyl functions (C_6, C_7); b) relative configuration of the spiro atom C_3, and c) orientation of the alkyl chain at N_8. These studies were carried out by examination of the ^{1}H-nmr and ^{13}C-nmr data of compounds **1**, which can be found in the Experimental.

Assignment of ^{13}C-nmr spectra of hydantoins **1** was based upon signal multiplicity in proton-coupled ^{13}C-nmr spectra and examination of literature data [7-9]. Displacement of the $C_{2,4}$ signals to a higher field (*ca.* 38 ppm)

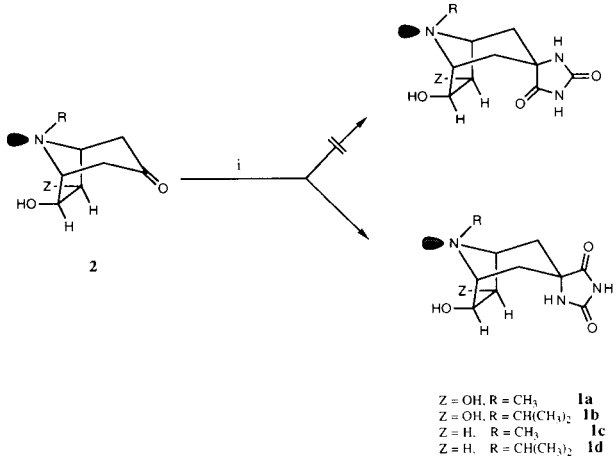
Scheme 1



Reagents and conditions: i $KMnO_4$, H_2O, 5 °C to rt, 16 h. ii 0.2 N H_2SO_4-H_2O, rt, 4 h. iii R-NH_2-HCl, 3-oxoglutaric acid, Na_2HPO_4, pH = 6-7, rt, 4 days. iv 3N HCl, rt, 16 h

than that expected from literature data for other tropane-3-spirohydantoins (*ca.* 30 ppm) can be attributed to an axial orientation of the *N*-alkyl group [6,10]. Upfield shifts of C_2 and C_4 arise from steric polarization effects on the C_2-H and C_4-H bonds and attendant expansion about the nucleus [10].

Scheme 2



Z = OH, R = CH_3 **1a**
Z = OH, R = $CH(CH_3)_2$ **1b**
Z = H, R = CH_3 **1c**
Z = H, R = $CH(CH_3)_2$ **1d**

Reagents and conditions : i KCN, $(NH_4)_2CO_3$, EtOH-H_2O, 60 °, sealed flask, 2-15 days

The *exo* disposition of the hydroxyl groups in dihydroxy derivatives **1a,b** and **2a,b** can be deduced from the fact that the signal for $C_{6,7}$-H in the ^{1}H-nmr spectra is a clean singlet. Lack of coupling with $C_{1,5}$-H can only be explained if both bonds are perpendicular, which proves the *endo* stereochemistry of $C_{6,7}$-H bonds. The same argument applies to monohydroxy derivatives **1c,d** and **2c,d** where H_6 appears as a doublet of doublets due to coupling with H_{7ax} and H_{7ec}, but no coupling with H_5 is observed. In the case of compound **1d**, coupling with the OH proton is also observed.

Finally, the α configuration for the spiro atom in compounds **1** can be deduced from ^{13}C-nmr data. Examination of a molecular model of α and β isomers of **1** reveals that in the structure with an axial configuration for $N_{1'}$ (α isomer) the carbonyl group in $C_{4'}$ is *gauche* with respect to all four C-H bonds at C_2 and C_4, while in the β isomer, that with an equatorial $N_{1'}$, it is *anti* with respect to two of them. Therefore, ^{3}J (^{13}C-H) coupling constants must be higher in the β structure. Previous studies on tropane derivatives [11] indicate that α and β isomers present half-height widths of 10 and 17 Hz, respectively, in their proton-coupled ^{13}C-nmr spectra. Therefore, the value found for this parameter in compound **1b** (11 Hz) supports the α configuration. Further evidence in favour of this structure can be found in ^{1}H-nmr data; thus, the displacement of $H_{2,4ax}$ signals to a higher field than expected [9,11] can be attributed to the anisotropic effect of the $C_{4'}$=O group, which is consistent only with the α structure.

Examination of spectral data allows, finally, to establish that the preferred conformation of the hexagonal ring in compounds **1** in solution corresponds to a flattened chair. The chair conformation is confirmed by the chemical shifts of C_2 and C_4, which would be displaced to a higher field in boat-like structures [7]. Coupling constants between $H_{2,4ax}$ and $H_{1,5}$ in compounds **1a,b** were accurately measured with the aid of HOMO decoupling experiments, and their values (J = 4 Hz) are lower than those between $H_{2,4ec}$ and $H_{1,5}$ (J = 5 Hz). Therefore, the dihedral angle $H_{2,4ec}$-C-C-$H_{1,5}$ is higher than $H_{2,4ax}$-C-C-$H_{1,5}$ and the chair is flattened. Similar conclusions can be obtained for monohydroxy derivatives **1c,d.**

EXPERIMENTAL

The ir spectra were recorded on a Perkin-Elmer 577 spectrophotomer, with all compounds compressed into potassium bromide pellets. The ^{1}H-nmr spectra were obtained on the following instruments: Hitachi Perkin-Elmer R-24B (60 MHz), Brucker WM-200-SY (200 MHz) and Varian VXR-300 (300 MHz). The ^{13}C-nmr spectra (75.4 MHz) were carried out on the latter instrument. Deuteriochloroform or DMSO-d_6 were used as solvents, and TMS was added in all cases as an internal standard. All chemical shifts are referred to TMS and are given in the δ scale. Only those J values that could be accurately measured are given. Elemental analyses were determined on a Carlo Erba 1104 microanalyzer. Melting points were measured in open capillary tubes, using a Büchi inmersion apparatus, and are uncorrected. All reagents were employed as received from commercial suppliers (Aldrich, Fluka, Merck, Carlo Erba, Scharlau, Probus, Panreac).

cis-3,4-Dihydroxy-2,5-dimethoxytetrahydrofuran.

A solution of 2,5-dimethoxy-2,5-dihydrofuran (59 g, 0.45 mole) in ethanol (450 ml) was placed in a five liter, round-bottomed flask equipped with a mechanical stirrer, an addition funnel and a thermometer. The reaction was cooled to −5°, and a solution of potassium permanganate (71 g, 0.45 mole) and heptahydrated magnesium sulfate (102 g, 0.41 mole) in water (1150 ml) was added over 30 minutes, with portionwise simultaneous addition of crushed ice (1500 g) in order to maintain an internal temperature of −5 to 0°. The suspension was stirred at room temperature for 4 hours, left standing overnight and filtered through a layer of silica gel. The filtrate was evaporated to 100 ml, and extracted with 1-butanol (5 x 160 ml). The extracts were dried over anhydrous sodium sulfate and evaporated, to yield the desired compound, as a pure, pale yellow oil which slowly crystallizes (41.8 g, 58%), mp, 65-67°; lit [5] 65-67°; ir (sodium chloride, film): ν O-H 3460, ν C-O 1200 cm^{-1}.

General Procedure for the Preparation of 8-Alkyl-6β,7β-dihydroxy-8-azabicyclo[3.2.1]octan-3-ones (**2**).

A solution of 3,4-dihydroxy-2,5-dimethoxytetrahydrofuran (33

g, 0.2 mole) in 0.2*N* sulfuric acid (160 ml) was magnetically stirred at room temperature for 4 hours, while treated with a stream of nitrogen. The solution was then neutralized with solid barium carbonate (16 g) and the precipitate of barium sulfate was filtered off. The filtrate was added at 10° to a solution of disodium hydrogen phosphate (142 g, 0.39 mole), 3-oxoglutaric acid (36 g, 0.25 mole) and the suitable primary amine, as an hydrochloride (0.2 mole) in water (1800 ml). *p*H of the solution was adjusted to 6-7 with 3*N* hydrochloric acid, and the reaction was left at room temperature for 4 days, neutralized with solid sodium carbonate, and divided into 250 ml portions, each of which was extracted with chloroform (2 x 150 ml). The combined chloroform extracts were dried (sodium sulfate) and evaporated, to yield a residue that was crystallized from the appropriate solvent.

6β,7β-Dihydroxy-8-methyl-8-azabicyclo[3.2.1]octan-3-one (**2a**).

This compound was obtained in 45% yield, as white crystals (ethanol) mp 190-191° (lit [5], 193-194°); ir (potassium bromide): ν O-H 3460, ν C=O 1710 cm^{-1}; ^{1}H-nmr (DMSO-d_6): 60 MHz δ 4.80 (s, 2H, exchangeable with deuterium oxide, 2 OH), 3.70 (s, 2H, $C_{1(5)}$-H), 2.60 (d, 2H, $C_{2(4)}$-H_{ax}), 2.50 (s, 3H, CH_3), 2.15 (br s, 2H, $C_{2(4)}$-H_{ec}).

Anal. Calcd. for $C_8H_{13}NO_3$: C, 56.15; H, 7.66; N, 8.19. Found: C, 56.00; H, 7.48; N, 7.96.

6β,7β-Dihydroxy-8-isopropyl-8-azabicyclo[3.2.1]octan-3-one (**2b**).

This compound was obtained in 39% yield as white crystals (ethanol) mp, 134-135°; ir (potassium bromide): ν O-H 3390, 3320, ν C=O 1720 cm^{-1}, ^{1}H-nmr (DMSO-d_6): 60 MHz δ 4.70 (br s, 2H, exchangeable with deuterium oxide, 2 OH), 3.70 (s, 2H, $C_{6(7)}$-H), 3.45 (m, 2H, $C_{1(5)}$-H), 3.00 (m, 1H, C*H*$(CH_3)_2$), 2.45 (d, 2H, $C_{2(4)}$-H_{ax}), 2.10 (br s, 2H, $C_{2(4)}$-H_{ec}), 1.05 (d, 6H, J = 6 Hz, CH(C*H*$_3)_2$).

Anal. Calcd. for $C_{10}H_{17}NO_3$: C, 60.30; H, 8.54; N, 7.03. Found: C, 60.66; H, 8.83; N, 6.99.

General Procedure for the Preparation of 8-Alkyl-6β-hydroxy-8-azabicyclo[3.2.1]octan-3-ones (**3**).

A solution of 2,5-dimethoxy-2,5-dihydrofuran (26 g, 0.2 mole) in 3*N* hydrochloric acid (360 ml) was stirred at room temperature for 16 hours, was then neutralized with 6*N* sodium hydroxide (*ca.* 180 ml) and was added to a solution of trihydrated sodium acetate (231.1 g, 1.69 moles), 3-oxoglutaric acid (58.4 g, 0.4 moles) and the suitable primary amine, as an hydrochloride (0.4 moles) in water (1400 ml). The *p*H was adjusted to 4-5 with 3*N* hydrochloric acid. The reaction was left at room temperature for 5 days, and was then neutralized with solid potassium carbonate. Sodium chloride (150 g) was added, the solution was divided into 250 ml portions, which were extracted with 2 x 250 ml of chloroform each. The combined chloroform extracts were dried over sodium sulfate and evaporated, and the residue was crystallized from an appropriate solvent.

6β-Hydroxy-8-methyl-8-azabicyclo[3.2.1]octan-3-one (**3a**).

This compound was obtained in 49% yield as white crystals (2-propanol) mp 108-109°; ir (potassium bromide): ν O-H 3160, ν C=O 1705 cm^{-1}; ^{1}H-nmr (deuteriochloroform): 60 MHz, δ 4.15 (dd, 1H, C_6-H), 4.00 (s, 1H, exchangeable with deuterium oxide, OH), 3.65-3.30 (2 m, 2H, $C_{1(5)}$-H), 2.8 (m, 1H, C_7-H_{endo}), 2.45 (dd, 1H, C_7-H_{exo}), 2.05 (m, 4H, $C_{2(4)}$-H), 2.40 (s, 3H, CH_3).

Anal. Calcd. for $C_8H_{13}NO_2$: C, 61.91; H, 8.44; N, 9.02. Found: C, 61.72; H, 8.37; N, 8.85.

6β-Hydroxy-8-isopropyl-8-azabicyclo[3.2.1]octan-3-one (**3b**).

This compound was obtained in 30% yield, as white crystals (petroleum ether) mp 77-79°; ir (potassium bromide): ν O-H 3180, ν C=O 1740 cm^{-1}; ^{1}H-nmr (deuteriochloroform): 60 MHz d 4.1 (dd, 1H, C_6-H), 3.20 (m, 2H, $C_{1(5)}$-H), 3.15 (s, 1H, exchangeable with deuterium oxide, OH), 3.10 (m, 1H, C*H*$(CH_3)_2$), 2.65 (m, 1H, C_7-H_{endo}), 2.40 (dd, 1H, C_7-H_{exo}), 1.95 (m, 4H, $C_{2(4)}$-H), 1.00 (d, 6H, J = 6 Hz, CH(C*H*$_3)_2$).

Anal. Calcd. for $C_{10}H_{17}NO_2$: C, 65.54; H, 9.35; N, 7.64. Found: C, 65.42; H, 9.30; N, 7.60.

General Procedure for the Preparation of 8-Alkyl-6β,6β-dihydroxy- or 6β-Hydroxy-8-azabicyclo[3.2.1]octan-3-spiro-5'-imidazolidine-2'-4'-diones **1**.

To a solution of potassium cyanide (0.5 g, 7.5 mmoles) and ammonium carbonate (1.4 g) in water (6 ml) was added the suitable tropan-3-one derivative, **2** or **3** (5 mmoles) in ethanol (2 ml). The flask was sealed and placed in an oven at 60° for 2-15 days. The solution was cooled and evaporated to two-thirds of its volume, and the precipitate was filtered to yield the desired hydantoin.

6β,7β-Dihydroxy-8-methyl-8-azabicyclo[3.2.1]octane-3-spiro-5'-imidazolidine-2',4'-dione (**1a**).

This compound was obtained after 15 days in 62% yield as white crystals (ethanol-water) mp 326-327°; ir (potassium bromide): ν O-H and N-H 3380, 3320, ν C=O 1760, 1710 cm^{-1}; ^{1}H-nmr (DMSO-d_6): 300 MHz δ 10.70 (s, 1H, exchangeable with deuterium oxide, $N_{3'}$-H), 8.19 (s, 1H, exchangeable with deuterium oxide, $N_{1'}$-H), 4.73 (d, 2H, J = 4 Hz, exchangeable with deuterium oxide, 2 OH), 4.16 (d, 2H, $J_{6\text{-}OH}$ = 4 Hz, $C_{6(7)}$-H), 2.93 (m, 2H, $C_{1(5)}$-H), 2.42 (s, 3H, CH_3), 2.23 (dd, 2H, J_{gem} = 14 Hz, $J_{1,3}$ = 4 Hz, $C_{2(4)}$-H_{ax}), 1.31 (d, 2H, J_{gem} = 14 Hz, $C_{2(4)}$-H_{ec}); ^{13}C-nmr (DMSO-d_6): 75.4 MHz δ 178.67 ($C_{4'}$), 156.65 ($C_{2'}$), 72.26 ($C_{6(7)}$), 64.66 ($C_{1(5)}$), 58.91 (C_3), 33.97 (CH_3), 30.18 ($C_{2(4)}$).

Anal. Calcd. for $C_{10}H_{15}N_3O_4 \cdot \frac{1}{2}H_2O$: C, 47.99; H, 6.44; N, 16.79. Found: C, 47.69; H, 6.45; N, 16.52.

6β,7β-Dihydroxy-8-isopropyl-8-azabicyclo[3.2.1]octane-3-spiro-5'-imidazolidine-2',4'-dione (**1b**).

This compound was obtained after 2 days in 72% yield (2-propanol-water) mp 317-319°; ir (potassium bromide): ν O-H and N-H 3380, 3320, ν C=O 1760, 1710 cm^{-1}; ^{1}H-nmr (DMSO-d_6): 60 MHz δ 10.50 (s, 1H, exchangeable with deuterium oxide, $N_{3'}$-H), 8.10 (s, 1H, exchangeable with deuterium oxide, $N_{1'}$-H), 5.10 (s, 2H, exchangeable deuterium oxide, 2 OH), 4.19 (s, 2H, $C_{6(7)}$-H), 3.22 (m, 2H, $C_{1(5)}$-H), 3.15 (m, 1H, C*H*$(CH_3)_2$), 2.20 (dd, 2H, J_{gem} = 14 Hz, J_{12} = 4 Hz, $C_{2(4)}$-H_{ax}), 1.25 (d, 2H, J_{gem} = 14 Hz, $C_{2(4)}$-H_{ec}), 1.15 (d, 3H, J = 6 Hz, CH(C*H*$_3)_2$), 0.95 (d, 3H, J = 6 Hz, CH(C*H*$_3)_2$); ^{13}C-nmr (DMSO-d_6): 75.4 MHz δ 179.23 ($C_{4'}$), 157.25 ($C_{2'}$), 71.64 ($C_{6(7)}$), 60.60 ($C_{1(5)}$), 59.01 (C_3), 42.64 (*C*H$(CH_3)_2$), 29.77 ($C_{2(4)}$), 21.43 (CH(*C*H$_3)_2$).

Anal. Calcd. for $C_{12}H_{19}N_3O_4$: C, 53.52; H, 7.11; N, 15.60. Found: C, 53.37; H, 7.16; N, 15.30.

6β-Hydroxy-8-methyl-8-azabicyclo[3.2.1]octane-3-spiro-5'-imidazolidine-2',4'-dione (**1c**).

This compound was obtained after 2 days in 60% yield as white crystals (ethanol-water) mp 335°; ir (potassium bromide): ν

O-H and N-H 3490, 3200, ν C=O, 1765, 1720 cm^{-1}; ^{1}H-nmr (DMSO-d_6): 300 MHz δ 10.62 (s, 1H, exchangeable with deuerium oxide, N_3-H), 8.09 (s, 1H, exchangeable with deuterium oxide, N_1-H), 4.33 (dd, 1H, $J_{67\ endo}$ = 7.5 Hz, $J_{67\ exo}$ = 3 Hz, C_6-H_{endo}), 3.60 (s, 1H, exchangeable with deuterium oxide, OH), 3.20 (dd, 1H, $J_{17\ exo}$ = 6 Hz, $J_{12(4)\ ax}$ = 3 Hz, C_1-H), 2.91 (m, 1H, C_5-H), 2.42 (s, 3H, CH_3), 2.35 (dd, 1H, J_{gem} = 14.1 Hz, $J_{67\ endo}$ = 7.5 Hz, C_7H_{endo}), 2.15 (dd, 2H, J_{gem} = 14 Hz, $J_{1(5)2(4)ax}$ = 3 Hz, $C_{2(4)}$-H_{ax}), 1.70 (m, 1H, J_{gem} = 14 Hz, $J_{17\ exo}$ = 6 Hz, $J_{67\ exo}$ = 3 Hz, C_7-H_{exo}), 1.36 (d, 1H, J_{gem} = 14 Hz, C_4-H_{ec}), 1.25 (d, 1H, J_{gem} = 14 Hz, C_2-H_{ec}).

Anal. Calcd. for $C_{10}H_{15}N_3O_3$: C, 53.32; H, 6.71; N, 18.65. Found: C, 53.61; H, 7.05; N, 18.55.

6β-Hydroxy-8-isopropyl-8-azabicyclo[3.2.1]octane-3-spiro-5'-imidazolidine-2',4'-dione (**1d**).

This compound was obtained after 7 days in 44% yield as white crystals (ethanol) mp 310-312°; ir (potassium bromide): ν O-H and N-H, 3580, 3320-3200, ν C=O 1775, 1730 cm^{-1}; ^{1}H-nmr (DMSO-d_6): 200 MHz δ 10.68 (s, 1H, exchangeable with deuterium oxide, N_3-H), 8.17 (s, 1H, exchangeable with deuterium oxide, N_1-H), 4.53 (d, 1H, exchangeable with deuterium oxide, J = 4.5 Hz, OH), 4.28 (m, 1H, $J_{67\ exo}$ = 2.5 Hz, $J_{67\ endo}$ = 7.5 Hz, $J_{6\text{-}OH}$ = 4.5 Hz, C_6-H_{endo}), 3.46 (dd, 1H, J_{12} = 3 Hz, $J_{17\ exo}$ = 5 Hz, C_1-H), 3.16 (m, 1H, C_5-H), 3.17 (m, 1H, C*H*$(CH_3)_2$), 2.49 (dd, 1H, J_{gem} = 14 Hz, $J_{67\ endo}$ = 7 Hz, C_7-H_{endo}), 2.11 (dd, 2H, J_{gem} = 14 Hz, $J_{1(5)2(4)\ ax}$ = 3 Hz, $C_{2(4)}$-H_{ax}), 1.63 (m, 1H, J_{gem} = 14 Hz, $J_{17\ exo}$ = 5 Hz, $J_{67\ exo}$ = 3 Hz, C_7-H_{exo}), 1.27 (d, 1H, J_{gem} = 14 Hz, C_4-H_{ec}), 1.16 (d, 1H, J_{gem} = 14 Hz, C_2-H_{ec}), 1.02 (d, 3H, J = 6 Hz, CH(C*H*$_3)_2$), 0.99 (d, 3H, J = 6Hz, CH(C*H*$_3)_2$); ^{13}C-nmr (75.4 MHz, DMSO-d_6): δ 178.90 (s, $W_{1/2}$ = 11 Hz, $C_{4'}$), 156.8 (s, $C_{2'}$), 72.42 (d, ^1J = 143.3 Hz, $C_{6(7)}$), 61.49 (d, ^1J = 134.9 Hz, C_5), 59.45 (s, C_3), 52.95 (d, ^1J = 134.4 Hz, C_1), 43.79 (d, ^1J = 130.37 Hz, *C*H$(CH_3)_2$), 33.48 (t, ^1J = 127.6 Hz, C_2), 31.96 (t, ^1J = 128.9 Hz, C_4), 21.85 (q, ^1J = 124.8 Hz, CH(*C*H$_3)_2$), 21.58 (q, ^1J = 125.0 Hz, CH(*C*H$_3)_2$).

Anal. Calcd. for $C_{12}H_{19}N_3O_3$: C, 56.90; H, 7.56; N, 16.58. Found: C, 56.68; H, 7.87; N, 16.39.

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