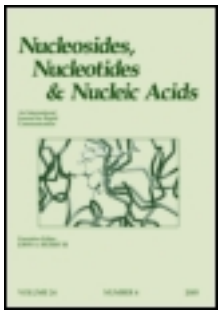

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Microwave-Assisted Synthesis of Acyclic C-Nucleosides from 1,2- and 1,3-Diketones

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MICROWAVE-ASSISTED SYNTHESIS OF ACYCLIC *C*-NUCLEOSIDES FROM 1,2- AND 1,3-DIKETONES

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□ *A simple, rapid and regioselective approach for the synthesis of C-acyclic nucleosides* ***3***, ***4***, ***6***, *and* ***9*** *of dihydropyrimidine, imidazole and indeno[1,2-b]pyridine-9-one derived from 1,2- and 1,3-diketones was performed. By using DMF or pyridine as solvent or bentonite clay as a support, in the presence of TMSTf, $ZnCl_2$, NH_4OAc, or NH_4NO_3, all the desired products were obtained within 5–25 minutes under microwave irradiation (MWI). Acid hydrolysis of* ***6*** *and* ***9*** *afforded the free acyclic C-nucleosides* ***7*** *and* ***10***, *respectively. Upon treatment with NaOMe under MWI,* ***3*** *and* ***14*** *rearranged to the C-nucleoside* ***4*** *and* ***16***.

Keywords Acyclic *C*-nucleosides; Beginelli reaction; ß-diketones; microwave-assisted synthesis; pyrimidinones

INTRODUCTION

Recent work has demonstrated the feasibility of using acyclic nucleoside analogues as antiviral chemotherapeutic agents. The acyclic purine derivatives have been the most widely studied.[1–4] For instance, (*S*)-9-(2,3-dihydroxypropyl)adenine ((*S*)-DHPA),[5] the potent antiherpetic drug[6,7] acyclovir (ACV, Zovirax),[8,9] 9-(2-phosphonylmethoxyethyl)adenine (PMEA), (*S*)-1-(3-hydroxy-2-phosphonylmethoxypropyl) adenine (HPMPA),[10] (*RS*)-9-[4-hydroxy-2-(hydroxymethyl) butyl]guanine (HBG), and 9-[(1,3-dihydroxy-2-propoxy)methyl] guanine (DHPG),[11,12] are examples of such potent antiviral agents against a number of DNA and

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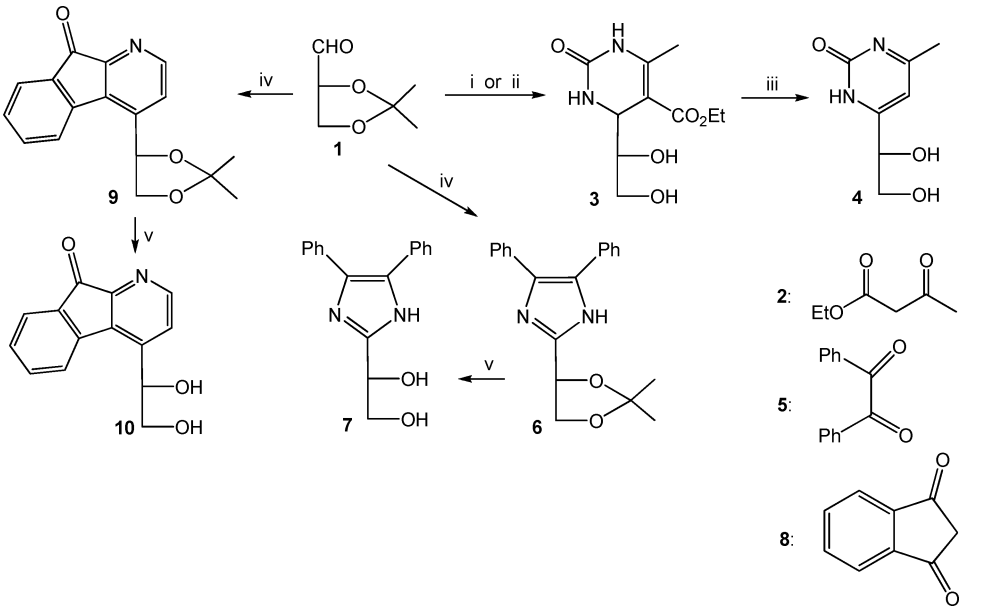
RNA viruses. Structure-activity relationship studies have shown that the side chains of acyclonucleosides play a crucial role in the interaction of the acyclonucleosides with their antiviral target enzymes.[13] In order to expand our research on the modification of acyclic nucleosides[14–19] and to obtain these building blocks in higher yields with shorter reaction times and under milder reaction conditions, we turned our attention to microwave irradiation (MWI). Herein, we report a rapid, facile, and practical protocol for the formation of acyclic *C*-nucleosides of dihydropyrimidine, imidazole, and pyridine bases derived from 1,2- and 1,3-diketones.

RESULTS AND DISCUSSION

The synthesis of dihydropyrimidinones has been presented in recent years, because of their diverse pharmacological activities (such as antiviral, antibacterial, and antihypertensive activity) as well as their efficacy as calcium channel blockers and α-antagonists.[20,21] By following recent reported work[22,23] on dihydropyrimidinones based on the Biginelli reaction, we developed and present here a convenient and efficient one-pot synthesis of the acyclic *C*-nucleosides having dihydropyrimidinone, imidazole, and indene-1,3-dione bases. Thus, treatment of (±)-2,2-dimethyl-[1,3]dioxolan-4-carbaldehyde (**1**)[24] with ethyl acetoacetate (**2**) and urea using the triflate catalyst (TMSTMf) under MWI at 65°C afforded (*R* and *S*)-**3** (41%) resulting from the formation of the stereocenter at C-4 of the DHPM ring. Alternatively, **3** was prepared in a better yield (36%) under the same conditions but using natural phosphate doped with $ZnCl_2$ instead of the triflate catalyst. The structure of **3** was assigned by NMR and its mass spectrum [m/z: $C_{10}H_{16}N_2O_5$ (244.24) 245 ($M+H^+$)]. ^{1}H NMR of **3** showed a doublet of doublets at δ 6.95 ppm ($J_{1',4} = 3.0$ Hz, $J_{NH,4} = 3.1$ Hz) that was attributed to H-4, since H-1′, H-2′a and H-2′b were oriented as multiplets at the region δ 3.89–3.52 ppm. In the ^{13}C NMR of **3**, a signal at δ 55.8 ppm was assigned to C-4.

Interestingly, treatment of **3** with NaOMe in MeOH under MWI at 100°C for 5 minutes furnished a product that was tentatively identified as 6-(1,2-dihydroxyethyl)-pyrimidin-2-one (**4**) (45%). The structure of **4** was assigned by HBMC NMR experiment, where C-6 at δ 147.1 ppm showed a $^2J_{C,H}$ coupling with H-5 at δ 6.46 ppm and H-1′ at δ 3.95 ppm. The spectrum was also characterized by elimination of the CO_2Et group at C-5 of **3**, indicative of H-4 abstraction by action of methoxide ion and simultaneous loss of water, leading to the formation of **4**.

Kidwai et al.[25] had recently synthesized the trisubstituted imidazole derivatives from condensation of benzil with aldehydes in excess of NH_4OH under MWI. In our hands, compound **1** has also turned out to be a useful intermediate for the preparation of other model of *C*-acyclic nucleoside,



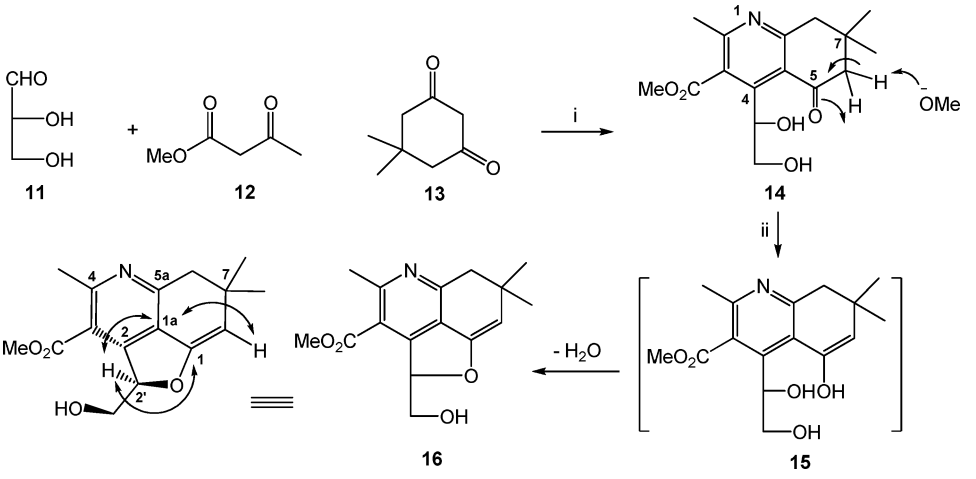
SCHEME 1 *Reagents and conditions:* (i) **2**, $CF_3SO_2SiMe_3$ (TMSTMf), MWI, 65°C, 25, min, pyridine NH_2CONH_2; (ii) $ZnCl_2$, natural phosphate (NP), MWI 45°C, DMF, NH_2CONH_2; (iii) NaOMe-MeOH, MWI, 100°C, 5 min; (iv) **5** or **8**, NH_4OH, DMF, MWI, 100°C, 10 min; (v) 80% HOAc, 80°C, 1 h

following Kidawai's method under MWI. Thus, treatment of **1** with benzil in the presence of NH_4OH at 100°C for 10 minutes afforded, after purification, **6** (87%). The ^1H NMR spectrum of **6** showed a doublet of doublets at δ 5.02 ppm was attributed to H-1′ ($J_{1',2'a} = 9.0$ Hz, $J_{1',2'b} = 3.1$ Hz), whereas the multiplet at δ 4.33–4.08 was assigned to H-2′a and H-2′b. Further, HMQC NMR study of **6** revealed a $^2J_{C,H}$ coupling between C-2′ at δ 74.6 ppm and H-1′ at δ 5.02 ppm.

An efficient and expeditious synthesis of the *C*-acyclic nucleoside of new indeno[1,2-*b*]pyridine derivative was also accomplished using MWI. Treatment of **1** with 1,3- indene-1,3-dione **8** in the presence of NH_4OAc under MWI at 100°C for 10 minutes afforded, after chromatographic purification, **9** (52%). The structure of **9** was identified by the NMR and mass spectra. In the HMQC spectrum, H-2 and H-3 appeared as two doublets at δ 8.69 and 8.01 ppm ($J_{2,3} = 9.1$ Hz), respectively, and they demonstrated $^{2/3}J_{C,H}$ correlations with C-4 at δ 145.1 ppm. Furthermore, C-4 showed a $^2J_{C,H}$ correlation with H-1′ at δ 5.12 ppm.

Acid hydrolysis of **6** and **9** by 80% HOAc in 80°C furnished the free *C*-nucleosides **7** and **10** in 76 and 81% yields, respectively. All the schematic pathways are outlined in Scheme 1.

Next, we expanded the scope of this microwave-assisted reaction to prepare a new *C*-nucleoside with a pyridine residue by following the Hantzch approach.[26] Thus, treatment of equimolar amounts of D-glyceraldehyde



SCHEME 2 *Reagents and conditions*: (i) NH_4NO_3, bentonite, MWI, 95°C, 20 min; (ii) NaOMe-MeOH, MWI, 85°C, 15 min

(**11**) with methyl acetoacetate (**2**) and dimedone (**3**) in the presence of bentonite clay as a support, NH_4NO_3 as the source of NH_3, HNO_3 as oxidant furnished, after chromatographic purification, **14** (45%). The product of this reaction was a 1,4-dihydropyridine, which could be oxidized to the corresponding pyridine derivative **15** (Scheme 2).[27] The structure of **14** was confirmed from the NMR and mass spectra. In the HMQC NMR spectrum, CH_2-6 protons at δ 2.46 ppm was identified from its $^2J_{C,H}$ correlation with C-5 at δ 198.3 ppm as well as a $^{2,3}J_{CH}$ correlation with C-8 at δ 46.9 ppm and C-4a at δ 129.0 ppm. H-1′ appeared as a multiplet at δ 4.57 ppm, whereas H-2′a, H-2′b, OMe and the hydroxyl groups were oriented as multiplets in the region at δ 4.14–3.69 ppm.

Treatment of **14** with NaOMe under MWI in MeOH at 85°C for 15 min resulted in the formation of a new compound with a molecular ion of m/z: $C_{16}H_{19}NO_4$ (312) $(M+Na)^+$, which was identified as methyl 2-(hydroxymethyl)-4,7,7-trimethyl-6,7-dihydro-2*H*-furo[4,3,*de*]quinoline-3-carboxylate (**16**) (45%). The possible mechanism of formation of **16** might be explained in term of the formation of intermediate **15** as a result of H-6 elimination by methoxide ion, followed by loss of H_2O under MWI at 85°C. In the HMQC NMR spectrum of **16**, H-8 at δ 4.54 ppm showed a $^3J_{C,H}$ correlation with C-1a at δ 124.9 ppm, and the latter showed the correlation with H-2′ at δ 4.85 ppm.

The formation of the furan ring was identified from the subsequent $^3J_{CH}$ correlation between H-2′ at δ 4.85 ppm and C-1 at δ 149.7 ppm. The two singlets at δ 2.53 and 3.65 ppm were assigned to C_4-Me and CH_2-6, respectively. Furthermore, the large shifts in δ values of the C=O groups at

δ 198.3 ppm (compound **14**) and C-1 at δ 149.7 ppm (compound **16**) was indicative of the formation of a furan group *via* the intermediate **15**.

EXPERIMENTAL

Microwave supported reactions were performed in a SmithSynthesizer (Personal Chemistry AB, monomode microwave cavity at 2.45 GHz, temperature control by automated adjustment of irradiation power in a range from 0 to 300 W) in Biotage microwave reaction vials (2–5 mL) with Teflon septum and an aluminum crimp top. Melting points are uncorrected and were measured on a Büchi melting point apparatus B-545 (Büchi Labortechnik AG, Switzerland). Microanalytical data were obtained with a Vario, Elementar apparatus (Shimadzu, Japan). NMR spectra were recorded on 600 MHz (^{1}H) and at 62.9 MHz (^{13}C) on spectrometers (Bruker, Germany) with TMS as internal standard and on δ scale in ppm. Heteronuclear assignments were verified by ^{1}H-^{13}C HMBC experiment. Mass spectra were recorded at 70 eV on EI and FAB mass spectra were measured on a MAT 8200 spectrometer (Finnigan MAT, USA) using 3-nitrobenzyl alcohol (NBOH) or glycerol as matrices.

Ethyl 4-((R and S)-1,2-dihydroxyethyl-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine 5-carboxylate (3)

Method A

A suspension of racemic mixture **1** (130 mg, 1.00 mmol), urea (180 mg, 3.00 mmol), ethyl acetoacetate (**2**) (130 mg, 1.00 mmol), and trimethylsilyl trifluoromethanesulphonate (TMSTf) (222 mg, 1.00 mmol) in pyridine (10 mL) was stirred under MWI at 65°C for 25 minutes. After cooling, the mixture was triturated with few drops of MeOH, then co-evaporated with toluene (4 × 20 mL) and EtOH (3 × 20 mL). The residue was co-evaporated in MeOH (5 mL) with silica gel (2 g), then poured onto a column of silica gel (5 g) using a gradient of MeOH (0–20%) and $CHCl_3$ as eluent to give (*R and S*)-**3** (100 mg, 41%), as amorphous solid. ^{1}H NMR (DMSO-d_6): δ 7.21 (s, 1H, NH); 6.95 (d, 1H, $J_{1',4}$ = 3.0 Hz, $J_{4,NH}$ = 3.1 Hz, H-4); 4.05 (q, 2H, J = 7.1 Hz, O*CH*$_2$CH$_3$); 3.89–3.52 (m, 5H, H-1′, H-2′a. H-2′b, OH); 1.12 (t, 3H, OCH$_2$*CH*$_3$). ^{13}C NMR (DMSO-d_6): δ 165.9 (*CO*OEt); 152.6 (*CO*NH); 148.9 (C-6); 95.2 (C-5); 73.9 (C-1′); 63.5 (C-2′); 60.9 (O*CH*$_2$CH$_3$); 55.8 (C-4); 17.8 (C$_6$-*Me*); 14.1 (OCH$_2$*CH*$_3$). Anal. calc, for $C_{10}H_{16}N_2O_5$ (244.24): C, 49.17; H, 6.60; N, 11.47. Found: C, 48.93; H, 6.52; N, 11.25. MS: *m/z* (FAB) 245 $(M+H)^+$.

Method B

Compound **3** was prepared by following the same procedure in method a, using the catalyst $ZnCl_2$/neutral phosphate (2.0 g) instead of TMSTMf. Yield: 88 mg (36%). The NMR and other physical properties were identical to those for the compound prepared in method a.

Reaction of 3 with Sodium Methoxide

A solution of **3** (200 mg, 0.82 mmol) in 0.2 M NaOMe solution (10 mL) was stirred under MWI for 10 min at 100°C. The solution was neutralized with HOAc and then evaporated to dryness. The residue was worked up as in experiment 3 to give a compound that was identified as **4** (63 mg, 45%); m.p. 139–142°C. ^{1}H NMR (DMSO-d_6): δ 7.79 (s, 1H, NH); 6.46 (s, 1H, H-5); 3.95 (dd, 1H, $J_{1',2a'} = 8.9$ Hz, $J_{1',2b'} = 3.0$ Hz, H-1′); 3.82 (dd, 1H, $J_{2a',2b'} = 11.0$ Hz, H-2′a); 3.63 (m, 2H, H-2′b, $C_{5'}$-OH); 2.21 (s, 3H, Me). ^{13}C NMR (DMSO-d_6): δ 173.6 (C-4); 157.6 (C=O); 147.1 (C-6); 100.8 (C-5); 80.9 (C-1′); 61.0 (C-2′). 24.5 (C_4-*Me*). Anal. calc. for $C_7H_{10}N_2O_3$ (170.17): C, 49.41; H, 5.92; N, 16.46. Found: C, 49.20; H, 5.85; N, 16.20. MS: *m/z* (FAB) 171 $(M+H)^+$.

(±)-2-(2,2-Dimethyl-[1,3]dioxolan-4-yl)-4,5-diphenyl-1H-imidazole (6)

A mixture of **1** (0.65 g, 5.00 mmol) benzyl, (1.05 g, 5.00 mmol), and NH_4OAc (0.63 g, 18.00 mmol) was stirred under MWI at 100°C for 5 minutes. After cooling, the residue was worked up as in the previous experiment to give **6** (1.48 g, 87%); m.p. 141–144°C. ^{1}H NMR (DMSO-d_6): δ 12.95 (s, 1H, NH); 7.55–7.43 (m, 10H, Ar-H); 5.02 (dd, 1H, $J_{1',2'a} = 9.0$ Hz, $J_{1',2'b} = 3.1$ Hz, H-1′); 4.33–4.08 (m, 2H, H-2′a, H-2b′); 1.41 (s, 6H, 2C*Me*$_2$). ^{13}C NMR (DMSO-d_6): δ 145.9 (C-2); 136.5 (C_{arom}); 129.1, 128.5, 127.9, 127.2 (C_{arom} + C-4 + C-5); 120.8 (*C*Me$_2$); 84.5 (C-1′); 74.6 (C-2′); 26.1 (C*Me*$_2$). Anal. calc. for $C_{20}H_{20}N_2O_2$ (320.38): C, 74.98; H, 6.29; N, 8.74. Found: C, 74.71; H, 6.20; N, 8.52. MS: *m/z* (FAB) 321 $(M+H)^+$.

1-(4,5-Diphenyl-1H-imidazol-2-yl)ethane-1,2-diol (7)

A solution of **6** (100 mg, 0.31 mmol) in 80 HOAc (5 mL) was kept at 80°C for 1 hour. After cooling, the solution was evaporated to dryness, and the residue was co-evaporated with EtOH (4 × 10 mL). The residue was purified on a short column of silica gel (5 g) using $CHCl_3$-MeOH (9:1) as the eluent to give **7** (237 mg, 76%), as an amorphous solid. ^{1}H NMR (DMSO-d_6): 12.85 (s, 1H, NH); 7.53–7.40 (m, 10H, Ar-H); 4.50 (m, 1H, H-1′); 4.08–3.60 (m, 5H, H-2′a, H-2′b, OH). ^{13}C NMR (DMSO-d_6): δ 146.2 (C-2); 137.1 (C_{arom}); 129.3, 128.6, 127.8, 127.3 (C_{arom} + C-4 + C-5); 78.1 (C-1′); 65.2 (C-2′). Anal. calc. for $C_{17}H_{16}N_2O_2$ (280.32): C, 72.84; H, 5.75; N, 9.99. Found: C, 72.62; H, 5.62; N, 9.78. MS: *m/z* (FAB) 303 $(M+Na)^+$.

4-(2,2-Dimethyl-1,3-dioxolan-4-yl)-9H-indeno[1,2-b]pyridin-9-one (9)

This compound was prepared from **1** (0.35 g, 2.69 mmol), 1*H*-indene-1,3-dione (**8**) (0.73 g, 5.00 mmol), and NH_4OAc (0.63 g, 18.00 mmol) following the same procedure for preparation of **6**. Yield: 0.39 g (52%); m.p. 144–148°C. ^{1}H NMR (DMSO-d_6): δ 8.75 (dd, 1H, $J_{7,8} = 8.8$ Hz, $J_{6,8} = 2.9$ Hz, H-8); 8.69 (d, 1H, $J_{2,3} = 9.1$ Hz, H-2); 8.38 (dd, 1H, $J_{5,6} = 8.9$ Hz, $J_{5,7} = 2.8$ Hz, H-5); 8.01 (dd, 1H, H-3); 7.69–7.51 (m, 2H, Ar-H); 5.12 (dd, 1H, $J_{1',2a'} = 9.0$ Hz, $J_{1',2b'} = 2.9$ Hz, H-1′); 4.30–4.00 (m, 2H, H-2′, H-4a′); 1.40 (s, 6H, 2C*Me*$_2$). ^{13}C NMR (DMSO-d_6): δ 186.3 (C=O); 152.2 (C=N); 145.1 (C-4); 143.3 (C-2 + C-5a); 134.0 (C-8a); 133.0 (C-6); 130.2 (C-3), 129.2, 128.6 (C-7 + C-8); 120.5 (*C*Me$_2$); 83.9 (C-1′); 73.9 (C-2′); 26.1 (C*Me*$_2$). Anal. calc. for $C_{17}H_{15}NO_3$ (281.31): C, 72.58; H, 5.37; N, 4.98. Found: C, 72.34; H, 5.19; N, 4.73. MS *m/z* (FAB) 282 $(M+H)^+$.

4-(1,2-Dihydroxyethyl)-9H-indeno[1,2-b]pyridin-9-one (10)

This compound was prepared from **9** (120 mg, 0.43 mmol) following the same procedure for preparation of **7**. Yield: 84 mg (81%); m.p. 152–155°C. ^{1}H NMR (DMSO-d_6): δ 8.72 (dd, 1H, $J_{7,8} = 8.7$ Hz, $J_{6,8} = 2.8$ Hz, H-8); 8.69 (d, 1H, $J_{2,3} = 9.0$ Hz, H-2); 8.40 (dd, 1H, $J_{5,6} = 8.9$ Hz, $J_{5,7} = 2.8$ Hz, H-5); 8.05 (dd, 1H, H-3); 7.70–7.52 (m, 2H, Ar-H); 4.54 (m, 1H, H-1′); 4.29–3.87 (m, 4H, H-2′a, H-2b′, OH). ^{13}C NMR (DMSO-d_6): δ 186.7 (C=O); 153.1 (C=N); 143.4 (C-2 + C-5a); 134.1 (C-8a); 132.8 (C-6); 130.4 (C-3), 129.1, 128.5 (C-7 + C-8); 72.1 (C-1′); 64.9 (C-2′). Anal. calc. for $C_{14}H_{11}NO_3$ (241.24): C, 69.70; H, 4.60; N, 5.81. Found: C, 69.51; H, 5.52; N, 5.61. MS *m/z* (FAB) 264 $(M+Na)^+$.

Methyl 4-(1,2-dihydroxyethyl)-2,7,7-trimethyl-5-oxo-5,6,7,8-tetrahydroquinoline-3-carboxylate (14)

A mixture of D-glyceraldehyde (**11**) (0.27 g, 3.00 mmol), methyl acetoacetate (**12**) (0.35 g, 3.00 mmol), dimedone (**13**) (0.42 g, 3.00 mmol), and NH_4NO_3 (0.24 g, 3.00 mmol) was stirred with bentonite (0.50 g) under MWI at 95°C for 20 minutes. After cooling, the mixture was co-evaporated with EtOH (4 × 10 mL), and the residue was dissolved in MeOH and co-evaporated with SiO_2 (1 g). The residue was poured onto a column of silica gel (5 g) and eluted, in gradient, with MeOH (0–20%) and $CHCl_3$ to give **14** (0.31 g, 32%), as an amorphous. ^{1}H NMR (DMSO-d_6): δ 4.57 (m, 1H, H-1′); 4.14–3.69 (m, 7H, H-2′a, H-2b′, OMe, 2xOH); 2.98 (s, 2H, CH_2-8); 2.53 (s, 3H, C_2-Me); 2.46 (m, 2H, CH_2-6); 1.28 (s, 6H, C_7-Me_2). ^{13}C NMR (DMSO-d_6): δ 198.3 (C_5=O); 169.1 (C=N); 166.8 (*C*O_2Me); 160.1 (C-2); 152.5 (C-4); 129.0 (C-4a); 120.8 (C-3); 70.1 (C-1′); 65.2 (C-2′); 52.8 (C-6); 50.9 (CO_2*Me*); 46.9 (C-8); 28.0 (C_7-*Me*$_2$); 21.7 (C_2-*Me*). Anal. calc. for $C_{16}H_{21}NO_5$ (307.34): C, 62.53, H, 6.89, N, 4.56. Found: C, 62.31, H, 6.80, N, 4.21. MS *m/z* (FAB) 308 $(M+H)^+$.

Reaction of 14 with NaOMe

A solution of **14** (100 mg, 0.31 mmol) in 0.2 M NaOMe solution (10 mL) was stirred under MWI for 15 minutes at 85°C. The solution was neutralized with HOAc and then evaporated to dryness. The residue was worked up as in experiment 3 to give compound that was identified as *methyl 2-(hydroxymethyl)-4,7,7-trimethyl-6,7-dihydro-2*H-*furo[4,3,*de*]quinoline-3-carboxylate* (**16**) (42 mg, 45%), m.p. 128–131°C. ^{1}H NMR (DMSO-d_6): δ 4.85 (m, 1H, H-2′);4.54 (s, 1H, H-8); 4.31–4.03 (m, 2H, H-3′a, H-3′b); 3.88 (s, 3H, CO_2Me); 3.62 (m, 1H, OH); 3.65 (s, 2H, CH_2_6); 2.52 (s, 3H, C_4-Me); 1.24 (s, 6H, C_7-Me_2). ^{13}C NMR (DMSO-d_6): δ 167.1 (*CO_2*Me); 164.2 (C=N); 160.7 (C-4); 149.7 (C-1 + C-2); 124.9 (C-1a); 120.8 (C-3); 106.3 (C-8); 98.4 (C-2′); 57.8 (C-3′); 52.2 (C-6); 50.3 (*CO_2Me*); 28.9 (*C_7-Me_2*); 26.8 (C-7); 21.7 (*C_4-Me*). Anal. calc. for $C_{16}H_{19}NO_4$ (289.13): C, 66.42, H, 6.62, N, 4.84. Found: C, 66.20, H, 6.54, N, 4.61. MS *m/z* (FAB) 312 $(M+Na)^+$.

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