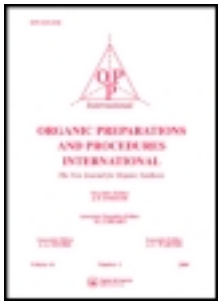

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Ming Huo [a], Yun-Yan Kuang [a] & Fen-Er Chen [a]

[a] Department of Chemistry, Fudan University, Shanghai, 200433, P R CHINA

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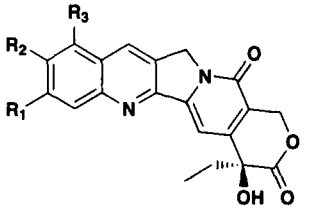
PRACTICAL ROUTE TO A β-KETOPHOSPHONATE, A KEY INTERMEDIATE FOR THE TOTAL SYNTHESIS OF 20(S)-CPT AND RELATED ANALOGUES

Ming Huo, Yun-Yan Kuang and Fen-Er Chen*

Department of Chemistry, Fudan University
Shanghai, 200433, P. R. CHINA

As part of a program for the total synthesis of pentacyclic alkaloids, we were interested in the 20(S)-camptothecin series, such as 20(S)-camptothecin (**A**), 20(S)-9-nitrocamptothecin (**B**) and 20(S)-10-hydroxycamptothecin (**C**)[1], in which the β-ketophosphonate (**8**) had been established as a key intermediate in the synthesis of these compounds. Ciufolini and Roschanger obtained this compound from propionanilide in 43% overall yield,[2] while Boger and Hong has prepared it from *o*-amino-benzaldehyde in 47% overall yield.[3] Although both yields are

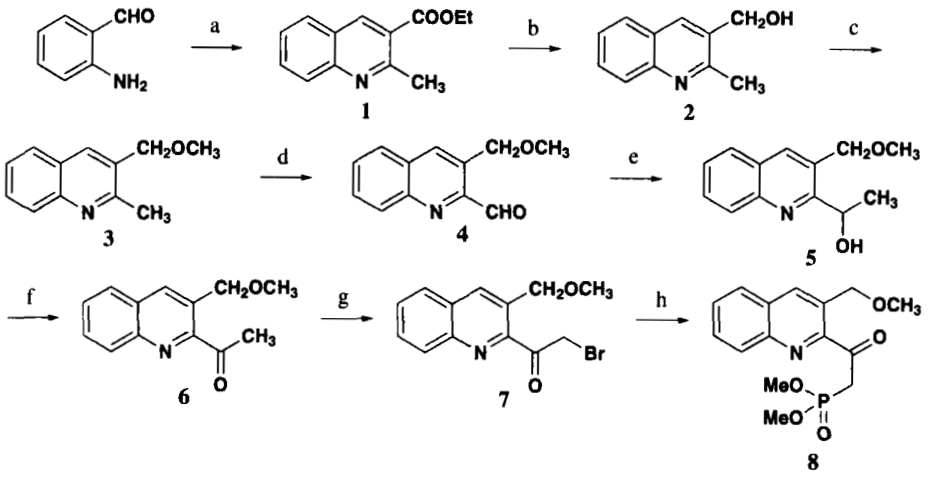


A. $R_1 = R_2 = R_3 = H$, 20(S)-CPY
B. $R_1 = R_2 = H$, $R_3 = NO_2$, 9-NO_2-CPT
C. $R_1 = R_3 = H$, $R_2 = OH$, 10-OH-CPT

moderate, the use of chromatographic separation, expensive catalyst ($Pd(dppp)_2Cl_2$) and low temperatures (-78°C) makes these routes difficult for large-scale preparations. We now describe a new and efficient procedure for the synthesis of **8** from commercially available *o*-aminobenzaldehyde (*Scheme 1*).

Compound **8** was obtained as follows. The Friedlander condensation of *o*-aminobenzaldehyde with ethyl acetoacetate and subsequent reduction of the crude ester **1** with $NaBH_4/CaCl_2$/EtOH provided alcohol **2** in 70% yield. Treatment of **2** with MeI in DMSO led smoothly to the formation of the corresponding ether derivatives **3** in nearly quantitative yield. Oxidation of **3** with SeO_2 in dioxane at 80-85°C for 3 hrs afforded the aldehyde **4** in 92% yield. Addition of MeMgI to **4**, followed by the oxidation of the resulting crude alcohol **5** with CrO_3/AcOH furnished ethyl ketone **6** in 64% yield, which was easily converted to compound **7**

through NBS bromination. Finally, protection of the carbonyl group of **7** with $PhSO_2NHNH_2$ to form the sulfonylhydrazone intermediate, followed by Arbukov reaction with trimethyl phosphite, and deprotection to afford the desired β-ketophosphonate **8** in 87% yield.[4]



a) $CH_3COCH_2CO_2Et$, NaOEt, EtOH, -5°C to reflux, 2 h, 80%; b) $NaBH_4$, $CaCl_2$, EtOH, r.t, 26 h, 87%; c) MeI, KOH, DMSO, r.t, 3 h, 95%; d) SeO_2, dioxane, reflux, 2 h, 92%; e) MeMgI, Et_2O, -5°C to reflux, 3 h, 85%; f) CrO_3, glacial AcOH, 45-50°C, 2 h, 75%; g) NBS, CCl_4, benzoyl peroxide, reflux, 12 h, 87%; h) $PhSO_2NHNH_2$, $P(OMe)_3$, NaOCl, THF, 20°C to reflux, 7 h, 87%

Scheme 1

In summary, an efficient synthesis of β-ketophosphonate **8** was accomplished in an overall yield of 30% from *o*-aminobenzaldehyde in eight steps. The superiority of this route stems from the fact that commercially available materials were used and that it does not require chromatographic separation, proceeds under the mild reaction conditions and avoids the use of expensive catalyst and the rigorous temperature conditions of the Ciufolini and Boger's routes.

EXPERIMENTAL SECTION

Mps were measured on a WRS-1B digital melting point apparatus and are uncorrected. Elemental analyses were performed on a Carlo-Erba 1006 elemental analyzer. ^1H NMR spectra were recorded on a Bruker DMX500 using TMS as an internal standard. Chemical shifts (δ) are expressed in ppm. GC-MS spectra were obtained on Finnigan Voyager instrument.

2-Methyl 3-quinolinecarboxylate (1).- To a stirred solution of *o*-aminobenzaldehyde (10.95 g, 90 mmol) in EtOH (12 mL) were added dropwise ethyl acetoacetate (12.5 g, 96 mmol) in EtOH (12 mL) and 10% sodium ethoxide solution (10 mL). The reaction mixture was stirred under reflux for 2 h. After removal of the solvent under vacuum, water (10 mL) was added, and the mixture was allowed to stand at 0°C overnight. The precipitate was collected and recrystallized from EtOAc-hexane to give pure **1** (15.5 g, 80%) as pale yellow needles, mp 71-72°C, *lit.*[5] 70-72°C.

^{1}H NMR (DMSO-d_6): δ 8.74 (s, 1H), 8.07-8.05 (m, 1H), 7.88-7.86 (m, 1H), 7.80-7.77 (m, 1H), 7.56-7.53 (m, 1H), 4.47-4.42 (q, 2H), 3.01 (s, 3H), 1.47-1.45 (t, 3H). GC-MS (m/z): 215(M^+), 200(M^+-Me), 186(M^+-Et), 171(186-Me), 142(M^+-CO_2Et), 127(142-Me).

Anal. Calcd for $C_{13}H_{13}NO_2$: C, 72.55; H, 6.04; N, 6.51. Found: C, 72.75; H, 6.15; N, 6.82

2-Methyl-3-hydroxymethylquinoline (2).- To a stirred solution of $NaBH_4$ (5.1 g, 138 mmol) in EtOH (20 mL) were added at 0-5°C, a solution of **1** (10.75 g, 50 mmol) in EtOH (75 mL) and a solution of anhydrous $CaCl_2$ (7.38 g, 60 mmol) in EtOH (75 mL). The reaction mixture was allowed to warm up to room temperature and stirred for 26 h. After concentration of the solution under reduced pressure to a volume of approximately 75 mL, $CHCl_3$ (200 mL) and water (300 mL) were added and the organic layer was washed with saturated aq. NaCl (100 mL x 3) and water (50 mL x 3), then dried over $MgSO_4$. The solvent was concentrated *in vacuo* to give the crude product. Recrystallization from EtOH gave the pure **2** (7.54 g, 87%) as a pale yellow crystalline powder, mp 140-142°C, *lit.*[6] 140-142°C.

^{1}H NMR ($CDCl_3$): δ 8.11 (s, 1H), 8.04-8.01 (m, 1H), 7.78-7.74 (m, 1H), 7.67-7.66 (m, 1H), 7.51-7.46 (m, 1H), 4.87 (s, 2H), 2.71 (s, 3H), 2.50 (bs, 1H). GC-MS (m/z): 173(M^+), 156(M^+-OH), 142(156-CH_2), 127(142-CH_2)

Anal. Calcd for $C_{11}H_{11}NO$: C, 76.30; H, 6.35; N, 8.09. Found: C, 76.53; H, 6.22; N, 8.21

2-Methyl-3-methoxymethylquinoline (3).- To a stirred suspension of KOH (4.48 g, 40 mmol) in anhydrous DMSO (50 mL) were added **2** (3.46 g, 20 mmol) and MeI (5.68 g, 40 mmol). The reaction mixture was stirred at room temperature for 3 h. Water (60 mL) was added, and the mixture was extracted with CH_2Cl_2 (40 mL x 4). The combined organic extracts were washed with water (30 mL x 5), dried over $MgSO_4$, The solvent was concentrated to dryness under *vacuo.* The crude product was purified over silica gel [PE(60-90°C), Rf 0.48] to gave pure **3** as a viscous yellow oil (3.55 g, 95%).

^{1}H NMR ($CDCl_3$): δ 8.04-8.01 (m, 2H), 7.78-7.74 (m, 1H), 7.66-7.63 (m, 1H), 7.49-7.44 (m, 1H), 4.58 (s, 2H), 3.47 (s, 3H), 2.70 (s, 3H). MS (m/e): 187(M^+), 172(M^+-CH_3), 156(M^+-OCH_3), 141(156-CH_3).

Anal. Calcd for $C_{12}H_{13}NO$: C, 77.00; H, 6.95; N, 7.49. Found: C, 77.12; H, 6.89; N, 7.53

2-Formyl-3-methoxymethylquinoline (4).- To a stirred suspension of SeO_2 (3.33 g, 30 mmol) in dioxane (150 mL) was added at 50-55°C, a solution of **3** (2.91 g, 16.8 mmol) in dioxane (50 mL). The reaction mixture was stirred at 80-85°C for 3 h, and cooled to room temperature. The reaction mixture was filtered through the Celite, and the solvent was concentrated under *vacuo.* CH_2Cl_2 (120 mL) and Water (80 mL) was added to the reaction mixture. The organic layer was washed with saturated aq. NaCl (100 mL x 3) and water (50 mL x3), then dried over $MgSO_4$. The solvent was concentrated under *vacuo* to a crude solid which was recrystallized from EtOAc to afford **4** (3.04 g, 92%) as yellow crystals, mp. 80-81°C

^{1}H NMR (DMSO-d_6): δ 10.29 (s, 1H), 8.48 (s, 1H), 8.23-8.21 (m, 1H), 7.91-7.89 (m, 1H), 7.80-7.77 (m, 1H), 7.70-7.67 (m, 1H), 5.05 (s, 2H), 3.60 (s, 3H). GC-MS (m/z): 201(M^+), 186(M^+-

CH_3), 172(M^+-CHO), 170(M^+-OCH_3), 141(172-OCH_3)

Anal. Calcd for $C_{12}H_{11}NO_2$: C, 71.64; H, 5.47; N, 6.96. Found: C, 71.78; H, 5.35, N, 7.04.

2-(α-Hydroxyethyl)-3-methoxymethylquinoline (5).- To a stirred solution of Grignard reagent [prepared from CH_3I (3.98 g, 28 mmol) and Mg (0.68 g, 28 mmol) in anhydrous. Et_2O (20 mL) with stirring at reflux for 30 minutes under nitrogen] at 0°C, was added a solution of **4** (2.01 g, 10 mmol) in Et_2O (30 mL). The reaction mixture was stirred under reflux for 4 h, and cooled to room temperature. After addition of saturated aq. NH_4Cl (7.5 mL) and 2N HCl (20 mL), the mixture was extracted with $CHCl_3$ (75 mL). The organic layer was washed with saturated aq. $NaHCO_3$ (50 mL x3) and water (50 mL x 3), then dried over Na_2SO_4. The solvent was concentrated under *vacuo* and the oily residue was chromatographed on silica gel (AcOEt:cyclohexane, 2:5) to give the pure **5** (1.85 g, 85.2%) as a pale yellow oil.

^{1}H NMR (DMSO-d_6): δ 8.18 (s, 1H), 8.07-8.05 (m, 1H), 7.83-7.82 (m, 1H), 7.72-7.69 (m, 1H), 7.55-7.52 (m, 1H), 5.17-5.13 (q, 1H), 4.95 (bs, 1H), 4.66-4.60 (s, 2H), 3.49 (s, 3H), 1.52-1.50 (d, 3H). GC-MS (m/z): 217(M^+), 202(M^+-CH_3), 199(M^+-OH), 186(M^+-OCH_3), 184(199-CH_3), 172(186-CH_2), 141(184-OCH_3)

Anal. Calcd for $C_{13}H_{15}NO_2$: C, 71.89; H, 6.91; N, 6.45. Found: C, 71.99; H, 6.84; N, 6.38.

2-Acetyl-3-methoxymethylquinoline (6).- To a stirred solution of **5** (2.73 g, 12.7 mmol) in glacial AcOH (10 mL) was added CrO_3 (1.0 g, 10 mmol) in portions at 45-50°C over a period of 2 h. Stirring was continued at 50°C for an additional 3 h and then after cooling to room temperature, $CHCl_3$ (75 mL) and water (50 mL) were added to the reaction mixture. The organic layer was washed with saturated aq. NaCl (15 mL x 3) and water (15 mL x 3), then dried over Na_2SO_4. The solvent was concentrated *in vacuo* to give the crude product. Recrystallization from EtOAc-hexane gave pure **6** (2.04 g, 75%) as pale yellow crystals, mp 56-57°C.

^{1}H NMR (DMSO-d_6): δ 8.40 (s, 1H), 8.13-8.11 (m, 1H), 7.83-7.81 (m, 1H), 7.72-7.70 (m, 1H), 7.61-7.59 (m, 1H), 4.93 (s, 2H), 3.55 (s, 3H), 2.84 (s, 3H). GC-MS (m/z): 215(M^+), 200(M^+-CH_3), 184(M^+-$0CH_3$), 172(200-CO), 169(184-CH_3), 141(169-CO)

Anal. Calcd for $C_{13}H_{13}NO_2$: C, 72.56; H, 6.05; N, 6.51. Found: C, 72.46; H, 5.99; N, 6.57.

2-(Bromoacetyl)-3-methoxymethylquinoline (7).- A mixture of **6** (1.08 g, 5.0 mmol), NBS (0.89 g, 5.0 mmol), benzoyl peroxide (0.1 g) and anhydrous CCl_4 (20 mL) was stirred under reflux for 12 h, and then cooled to room temperature. After removal of succinimide, the filtrate was concentrated under reduced pressure to give the crude product. Recrystallization from EtOAc-hexane gave **7** (1.27 g, 87%) as a pale yellow solid, mp 74-75°C.

^{1}H NMR (DMSO-d_6): δ 8.63 (s, 1H), 8.14-8.13 (m, 1H), 7.85-7.84 (m, 1H), 7.74-7.73 (m, 1H), 7.58-7.55 (m, 1H), 4.97 (s, 2H), 3.95 (s, 3H), 2.88 (s, 2H).GC-MS (m/z): 294(M^+), 214(M^+-Br), 200(214-CH_2), 183(214-OCH_3), 172(200-CO), 169(183-CH_2), 155(169-CH_2), 127(155-CO)

Anal. Calcd for $C_{13}H_{12}BrNO_2$: C, 53.06; H, 4.08; N, 4.76. Found: C, 53.14; H, 4.01; N, 4.89.

Dimethyl[2-[3-(Methoxymethyl)quinolin-2-yl]-2-oxoethyl]phosphonate (8).- To a stirred solution of $PhSO_2NHNH_2$ (0.55 g, 3.0 mmol) in THF (20 mL) was added **7** (0.88 g, 3.0 mmol).

The reaction mixture was stirred at room temperature for 3 h, then $(MeO)_3P$ (0.6 g, 4.8 mmol) was added and the mixture, and heated under reflux for a further 4 h with stirring. Then 5% aq. NaOCl (20 mL) was added and the mixture was stirred at room temperature for 30 min. After addition of 5% aq. $NaHSO_3$ (15 mL) and AcOEt (75 mL), the organic layer was washed with saturated aq. NaCl (100 mL x 3) and water (50 mL x 3), then dried over $MgSO_4$. The solvent was concentrated in *vacuo* to give the crude product. Recrystallization from EtOAc-hexane gave pure **8** (0.85 g, 87%) as a white solid, mp. 47-48°C, *lit.*[3] 46-47°C.

^1H NMR ($CDCl_3$): δ 8.30 (s,1H), 7.98-7.96 (m, 1H), 7.69-7.68 (m, 1H), 7.58-7.56 (m, 1H), 7.48-7.47 (m, 1H), 4.79 (s, 2H), 4.07 (d, 2H), 3.61 (d, 6H), 3.40 (s, 3H); MS (m/s): 324(M^+), 214[M^+-P(O)$(OMe)_2$], 200(214-CH_2), 183(214-OCH_3),172(200-CO)

Anal. Calcd for $C_{15}H_{18}NO_5P$: C, 55.73; H, 5.61; N, 4.33. Found: C, 55.68; H, 5.93; N, 4.05

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