A Total Synthesis of 1-Methoxycanthin-6-one: An Efficient One-Pot Synthesis of the Canthin-6-one Skeleton from β-Carboline-1-carbaldehyde

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Abstract: A total synthesis of naturally occurring 1-methoxycanthin-6-one is described. In this synthesis, we achieved one-pot conversion from β-carboline-1-carbaldehyde to the canthin-6-one skeleton by the sequential addition of lithium ketene acetal in LiHMDS solution followed by the addition of EtOH in the reaction mixture.

Key words: indoles, β-carboline, alkaloids, aldol reaction, cyclization

Recently, many 4-methoxy-β-carboline alkaloids have been isolated from Simarubaceae plants. 1-Oxygenated canthin-6-ones and 1,11-dioxygenated canthin-6-ones (Figure 1) were isolated as congeners of 1, and were also reported to have interesting biological activities, in particular, Lee et al. reported strong anti-HIV activity. Although there are some reports for the synthesis of canthin-6-one (2a), there exists only one report for the synthesis of the 1-oxygenated derivative, 1-methoxycanthin-6-one (2b).

We have developed a general synthetic method for 1 via the key compound 6b, starting from ethyl indole-2-carboxylate (4) via the C1-selective cyclization of the C2-substituent of indole 5. In this paper, we wish to report a convenient synthetic method for the canthin-6-one skeleton via the key-intermediate 6, along with the total synthesis of 1-methoxycanthin-6-one (2b). The starting aldehyde 7b was prepared in 70% yield by the careful reduction of the ester group of 6b with DIBALH (Scheme 1).

There are some reports for the synthesis of the canthin-6-one skeleton 2a from β-carboline-1-carbaldehyde (7a). However, the yields in these reports were below 40%. Giudice et al. reported that the Perkin reaction of β-carboline 3-carbomethoxy derivatives with acetic anhydride under basic condition gave methyl canthin-6-one-2-carboxylate (9) in 72% yield (Scheme 2). However, Ma et al. reported that the application of this condition to 7-methoxy-β-carboline-1-carbaldehyde gave the target 9-methoxy-5-methyl (or ethyl)-canthin-6-one in only low yields (14–17%). We also found only a trace amount of the product 2b on TLC, when we applied this condition to compound 7b (run 1 in Scheme 3).

In addition, Black et al. reported that the aldol condensation-cyclization reaction of 4,6-dimethoxy-7-formylindole (10) forms a tricycle compound 11 (Scheme 2). We applied this reaction condition to the synthesis of the can-
thin-6-one skeleton. However, no products were formed using excess of EtOAc and EtONa. Therefore, we chose t-BuOK in DMSO as a stronger basic condition. Treatment of 7b with this base in excess of EtOAc gave the target 1-methoxycanthin-6-one (2b) in 39% yield. However, an undesirable trans-olefinic compound 12b was also formed in 19% yield by dehydration (run 3 in Scheme 3).

In this reaction, the ratio of the products 2b and 12b did not change substantially by the employed reaction time. Furthermore, the isolated trans-olefinic compound (12b) could not be cyclized to the canthine skeleton 2b by treatment with EtONa in EtOH. Under this reaction condition (run 3 in the Scheme 3) the dehydration and the cyclization of the initial aldol product (14 or 15) occurred competitively as shown in Scheme 4. Black et al. reported that the cyclization of 10 was assisted by the butressing effect of the 6-methoxy group of the indole ring and the consequent relief of steric hindrance. However, the aldol product 14 has no steric effect on the vicinal group, and the reaction proceeded at higher temperature (100 °C). So the dehydration occurred from intermediate 14.

Thus, we studied precisely this aldol condensation-cyclization reaction at low temperature using β-carboline-1-carbaldehyde (7a, prepared from 6a, Scheme 1) as a model compound. Lithium ketene acetate was prepared from EtOAc (2 mol equiv) with LiHMDS (3 mol equiv) and was added to a solution of 7a in THF at –78 °C. The reaction mixture was quenched by a saturated aqueous solution of NH₄Cl. The aldol compound 13a was obtained as the sole product in 61% yield (run 4 in Scheme 3). The isolated product 13a can be cyclized by treatment of 1 mol equivalent of EtONa in EtOH to form the canthin-6-one (2a) in high yield. When the aldol reaction of 7a was quenched by water instead of saturated aqueous NH₄Cl, we unexpectedly found that cyclic compound 2a was obtained as the main product in 43% yield. Due to this finding, we added EtOH instead of water to the reaction mixture at –78 °C, followed by warming to room temperature. Consequently, the yield of cyclic compound 2a was increased to 83%. Thus, we applied this condition to compound 7b and succeeded in the total synthesis of 1-methoxycanthin-6-one (2b) via one-pot reaction from 7b in good yield (88%). The synthesized compound 2b is identical to the natural product. When the cyclic product 2 forms, the cyclization precedes the dehydration of the aldol compound. On the other hand, the simple β-hydroxyester prepared from a benzaldehyde with the Li ketene acetal of EtOAc was not dehydrated to an α,β-unsaturated ester by this EtOH work-up method. We propose that the reaction mechanism is as shown in Scheme 4.

When using LiHMDS as a base, the intermediate should be Li enolate 16, so that the treatment of the intermediate 16 with acid gives only the aldol compound 13. On the other hand, on addition of H₂O or EtOH to 16, the Li ketene acetalt part of 16 should withdraw a proton from H₂O or EtOH to form an ester (17), so that 17 is cyclized to canthin-6-one 2 via 4,5-dihydro-4-hydroxycanthin-6-one (18). The cyclic β-hydroxyketone 18 is dehydrated to canthin-6-one 2 by the simultaneously formed lithium ethoxide (or hydroxide). So the dehydration of the cyclic intermediate 18 occurred more easily than that of the non-cyclic intermediate 17. In this study, we have found a new efficient one-pot synthesis of canthin-6-one 2 from β-carboline-1-carbaldehyde 7 using a lithium-based aldol condensation followed by the treatment of EtOH. We have also achieved the total synthesis of 1-methoxycanthin-6-one (2b). On the basis of our findings, the total synthesis of 1,11-dioxygenated canthin-6-one (3a–c) is now in progress.

All melting points were determined on a micro melting point hot stage apparatus (Yanagimoto) and are uncorrected. IR spectra were recorded on a JASCO FT/IR-300 spectrophotometer. ¹H NMR (400 MHz) and ¹³C NMR (100 MHz) spectra were recorded on a JEOL EX-400 and AL-400 spectrometers with tetramethylsilane as an internal reference. Mass spectra (MS) were measured on a JEOL AutoMass System II, JMS D-300 and DX-303 spectrometers with a direct inlet system. For column chromatography, Silica gel 60 (70–230 mesh ASTM, Merck) was used. For TLC, Silica gel 60F₂⁵₄ (Merck) was used. The abbreviations used are as follows: s, singlet; d, doublet; dd, double doublet; t, triplet; q, quartet; m, multiplet; br, broad.

**β-Carboline-1-carbaldehyde** (7a) Prepared from methyl β-carboline-1-carboxylate (6a) using DIABALH according to the procedure used for 4-methoxy derivative 7b as described below.
4-Methoxy-β-carboline-1-carbaldehyde (7b)

To a stirred solution of methyl 4-methoxy-β-carboline-1-carboxylate, (6b, 100 mg, 0.39 mmol) in CH₂Cl₂ (5 mL), was added DIBAL solution (1.0 M, in CH₂Cl₂, 2.34 mL, 2.34 mmol) at –40 °C under an Ar atmosphere. The mixture was stirred at –40 °C for 5 min and then quenched by the sequential addition of MeOH (0.5 mL) and 10% NaOH (0.5 mL) at –40 °C. The mixture was stirred at r.t. for an additional 0.5 h. The reaction mixture was diluted with CHCl₃, dried over anhyd MgSO₄, and then evaporated in vacuo. The residue was subjected to column chromatography using hexane–EtOAc (1:2) to give 7b (62 mg, 70%) as crystals. Recrystallization from EtOAc–hexane gave colorless prisms; mp 209–210 °C.

IR (KBr): 3350, 1668 cm⁻¹.

1H NMR (DMSO-d₆): δ = 4.28 (s, 3 H, OCH₃), 7.32 (br t, J = 8.0 Hz, 1 H, C₆-H or C₇-H), 7.57 (br t, J = 8.0 Hz, 1 H, C₆-H or C₇-H), 7.79 (br d, J = 8.0 Hz, 1 H, C₅-H or C₈-H), 8.21 (br d, J = 8.0 Hz, 1 H, C₅-H or C₈-H), 8.41 (s, 1 H, C₃-H), 10.14 (s, 1 H, CHO) 12.08 (br s, 1 H, NH).

MS: m/z = 226 [M⁺, 100].

Anal. Calcd for C₁₃H₁₀N₂O₂: C, 69.02; H, 4.45; N, 12.38. Found: C, 68.78; H, 4.49; N, 12.10.

Reaction of 4-Methoxy-β-carboline-1-carbaldehyde (7b) with EtOAc Using tert-BuOK in DMSO

To a stirred solution of tert-BuOK (10 mg, 0.09 mmol) in DMSO (0.5 mL) was added a solution of 4-methoxy-β-carboline-1-carbaldehyde (7b, 10 mg, 0.04 mmol) in EtOAc (0.5 mL) and DMSO (0.1 mL) at r.t. under an Ar atmosphere. The mixture was stirred at < 100 °C for 45 min and was then quenched by ice-water (0.5 mL). The mixture was extracted with CH₂Cl₂, washed with brine, dried over anhyd MgSO₄, and then evaporated in vacuo. The residual mixture was separated to fractions Fr-A, Fr-B, and Fr-C by column chromatography using hexane–EtOAc (1:1) as a solvent.

From Fr-A, 1-methoxycanthin-6-one (2b) was obtained as pale brown crystals (4.3 mg, 39%). This compound was identical to the standard sample 2b synthesized from 7b by the direct method described below.

From Fr-B, starting material 7b was recovered (3.1 mg, 31%).

From Fr-C, ethyl 3-(4-methoxy-9H-β-carbolin-1-yl)-acrylate (12b) was obtained as a pale brown solid (2.5 mg, 19%).

Scheme 4  Mechanism for formation of 2, 12, and 13.
added to the solution and then stirred for 15 min at –78 °C. To this solution, β-carboline-1-carboxaldehyde (7a, 49.1 mg, 0.250 mmol) in THF (2 mL) was added and then stirred for 20 min at –78 °C. The whole reaction mixture was poured into aq sat. NH₄Cl (15 mL) under ice cooling, extracted with EtOAc, washed with brine, dried over anhyd MgSO₄ and evaporated in vacuo. The crude solid was purified by SiO₂ column chromatography using hexane–EtOAc to give the title compound 13a as colorless crystals (43.7 mg, 61%). Recrystallization from EtOAc–hexane gave colorless prisms; mp 121–123 °C.

IR (KBr): 3387, 1720 cm⁻¹.

1H NMR (acetone-d₆): δ = 1.60 (t, J = 7 Hz, 3 H, OCH₂CH₃), 2.89 (dd, J = 15, 9 Hz, 1 H, CHO), 3.31 (dd, J = 15, 4 Hz, 1 H, CH₂CO), 4.13 (q, J = 7 Hz, 2 H, OCH₂CH₃), 5.65 (dd, J = 9, 4 Hz, 1 H, CHO), 7.25 (br t, J = 8 Hz, 1 H, C₆-H or C₇-H), 7.54 (br t, J = 8 Hz, 1 H, C₆-H or C₇-H), 7.72 (br d, J = 8 Hz, 1 H, C₆-H or C₇-H), 8.09 (br d, J = 8 Hz, 1 H, C₆-H or C₇-H), 8.21 (br d, J = 8 Hz, 1 H, C₆-H or C₇-H), 8.28 (d, J = 5 Hz, 1 H, C₇-H or C₈-H), 10.61 (br s, 1 H, NH).

13C NMR (acetone-d₆): δ = 36.3, 54.0, 127.7, 129.7, 141.4, 146.2, 171.5.

IR (KBr): 1671 cm⁻¹.

1H NMR (CDCl₃): δ = 1.61 (s, 3 H, OCH₃), 5.65 (dd, J = 10 Hz, 1 H, C₆-H or C₇-H), 7.53 (br t, J = 8 Hz, 1 H, C₆-H or C₇-H), 7.68 (br t, J = 8 Hz, 1 H, C₆-H or C₇-H), 7.98 (d, J = 10 Hz, 1 H, C₆-H or C₇-H), 8.24 (br d, J = 8 Hz, 1 H, C₆-H or C₇-H), 8.51 (s, 1 H, C₆-H), 8.70 (br d, J = 8 Hz, 1 H, C₆-H or C₇-H).

13C NMR (CDCl₃): δ = 56.8, 116.8, 117.1, 123.5, 124.3, 125.5, 129.4, 130.1, 130.5, 132.9, 138.2, 138.8, 151.9, 160.0.

MS: m/z = 284 [M⁺, 20], 197 (100).


67.46; H, 4.07; N, 11.08.


Canthin-6-one (2a) from Aldol Product 13a by EtONa

To a stirred solution of compound 13a (50.2 mg, 0.18 mmol) in THF (2 mL), freshly prepared EtONa solution (580 mm, 0.92 mmol) in THF (2 mL) was added and then stirred for 20 min at –78 °C. The whole reaction mixture was poured into aq sat. NH₄Cl (15 mL) and extracted with EtOAc, washed with brine, dried over anhyd MgSO₄ and evaporated in vacuo. The residual aqueous layer was extracted with CHCl₃. The organic layer was washed with brine, dried over anhyd MgSO₄ and evaporated to dryness in vacuo. The residue was subjected to column chromatography using EtOAc–hexane to give the title compound 2a as colorless crystals (35.8 mg, 92%). This compound was identical to the standard sample synthesized from 7a by the direct method described below.

Canthin-6-one (2a) (Direct Method from 7a)

To a stirred mixture of HMDS (340 mg) in EtOH (50 mL) (0.21 mmol as a EtONa) was added at –78 °C and then recooled to –78 °C. EtOAc (112 mL, 0.52 mmol) in EtOH (50 mL) (0.21 mmol as a EtONa) was added at –78 °C. Recrystallization from CHCl₃–hexane gave colorless needles; mp 258–259 °C (lit. mp 250–250.5 °C).

IR (KBr): 1671 cm⁻¹.

1H NMR (CDCl₃): δ = 4.27 (s, 3 H, OCH₃), 6.86 (d, J = 10 Hz, 1 H, C₆-H or C₇-H), 7.53 (br t, J = 8 Hz, 1 H, C₆-H or C₇-H), 7.68 (br t, J = 8 Hz, 1 H, C₆-H or C₇-H), 7.98 (d, J = 10 Hz, 1 H, C₆-H or C₇-H), 8.24 (br d, J = 8 Hz, 1 H, C₆-H or C₇-H), 8.51 (s, 1 H, C₆-H), 8.70 (br d, J = 8 Hz, 1 H, C₆-H or C₇-H).

13C NMR (CDCl₃): δ = 56.8, 116.8, 117.1, 123.5, 124.3, 125.5, 129.4, 130.1, 130.5, 132.9, 138.2, 138.8, 151.9, 160.0.

MS: m/z = 250 [M⁺, 100].


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