A new synthesis method of (±)-deoxyschizandrin

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DEOXYSCHIZANDRIN 10, isolated from Schizandra chinensis baill[1], exhibits anti-hepatitis virus activity. Recently considerable interest in the synthesis of 10 has arisen from its bioactivities[2-5]. In this note a new highly efficient route to synthesize (±)-deoxyschizandrin is reported. Our synthetic strategy (outlined in scheme 1) started from gallic acid 1 in 10 steps with the overall yield of 12%, and employed I₂/NaOEt oxidative coupling reaction as a key step.

First commercially available gallic acid 1 was converted to gallic acid trimethyl ether 2. Exposure of 2 to SOCl₂ followed by treatment of sodium salt of ethyl acetoacetate gave 3. Treatment of 3 with NH₃/NH₄Cl gave β-keto ester 4. The dimer product 5 was obtained from 4 by the oxidative coupling with I₂/NaOEt (a modified Knorr method[6]) in an excellent yield. Acid-catalyzed cyclization of 5 led to furan 6, and reduction of 6 with LiAlH₄ produced 7. We found that the process from compound 7 to diarylbutane 9 could be achieved in one step by selective reduction with H₂/PdO[7]. Compound 9 was submitted to cyclization by VOF₃/CF₃COOH[8] to give (±)-deoxyschizandrin 10. Additionally, it was noted that selective removal of allylic hydroxyl group could be achieved by Pd-C (10%) (substrate: catalyst = 1:1) to yield 8, and ring-cleavage of 8 with PdO/H₂ led to 9.

Experiments

Mass spectra were recorded on a ZAB-HS spectrometer. ¹H NMR spectra were obtained on a Bruker AM-400 instrument in CDCl₃ solution with TMS as the internal standard. All compounds were purified by flash chromatography (FCG) on silica gel H (200—300 mesh) made in Qingdao Marine Chemical Factory[9].

(1) Ethyl (3, 4, 5-trimethoxybenzoyl)-acetate 4

Compound 4 was obtained by the method of ref. [10], overall yield 66%, a pale yellow solid, MS (m/z): 282 (M⁺), 267, 236, 195. ¹H NMR (CDCl₃, δ/ppm): 1.50 (t, J=7 Hz, 3 H, —CH₃), 2.50 (s, 2H, —CH₂...), 4.10 (s, 9H, 3×ArOCH₃), 4.43 (q, J=7 Hz, 2H, —CH₂Me), 7.33 (s, 2H, 2×ArH).

(2) Diethyl 2, 3-bis-(3, 4, 5-trimethoxybenzoyl)-succinate 5

After sodium metal (0.02 mol, 0.46 g) was dissolved in absolute ethanol (20 mL), an equal amount of β-keto ester 4 (0.02 mol, 5.6 g) was added at room temperature and the mixture was stirred for 2 h. The corresponding sodium salt solid, obtained by removing sol-
vent under reduced pressure, was suspended in dry ether (50 mL) and a solution of iodine (0.02 mol, 2.5 g) in dry THF (20 mL) was added dropwise with vigorous stirring. The mixture was stirred for 2 h and then concentrated, followed by purification by FCG (petroleum: ethyl acetate = 7:3) and finally afforded 5 (5.2 g, yield 92%), a pale yellow oil.

Anal. C_{28}H_{34}O_{12} calcd. %: C, 59.81; H, 6.09. found %: C, 59.75; H, 6.03. MS (m/z): 562 (M^+), 563 (M + 1), 544, 471, 367, 321, 195. 'H NMR (CDCl_3, δ/ppm): 1.13 (t, J = 7 Hz, 6H, 2 × CH_3), 3.93 (s, 18H, 6 × ArOCH_3), 4.09 (q, J = 7 Hz, 4H, 2 ×