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Total Synthesis of (±)-Cordatolide A and its Anti-HIV Activity

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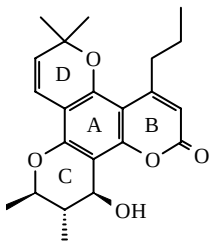
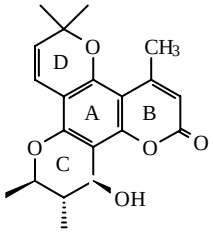
Abstract: The natural product (±)-cordatolide A has been synthesized by a four-step approach starting from phloroglucinol, including Pechmann reaction, Friedel-Crafts acylation, cyclization, chromenylation and Luche reduction.

Keywords: Total synthesis, (±)-cordatolide A.

(+)-Cordatolide A, isolated from the light petrol extract of the leaves of *C.cordatooblangum* in 1985[1], is a novel tetracyclic coumarin. Its structure is similiar to (+)-calanolide A. (+)-calanolide A, isolated from several tropical plants of the genus calophyllum in1992[2], is a potent nonnucleoside inhibitor of reverse transcriptase from human immunodeficiency virus type 1 (HIV-RT). Up to now, several research groups have reported total synthesis of (±)-calanolide A and its stereoisomers[3-5], but there was no report about the total synthesis and anti-HIV activity of the 4-position substituted derivatives of (+)-calanolide A including (+)-cordatolide A. We have reported total synthesis of (±)-calanolide A and its derivatives, with structure modification focused on the 6-position and 11-position[6-7]. In order to compare the bioactivity of different 4-substituted coumpounds, we synthesized (±)-cordatolide A and evaluated its anti-HIV activity.



(+)-calanolide A



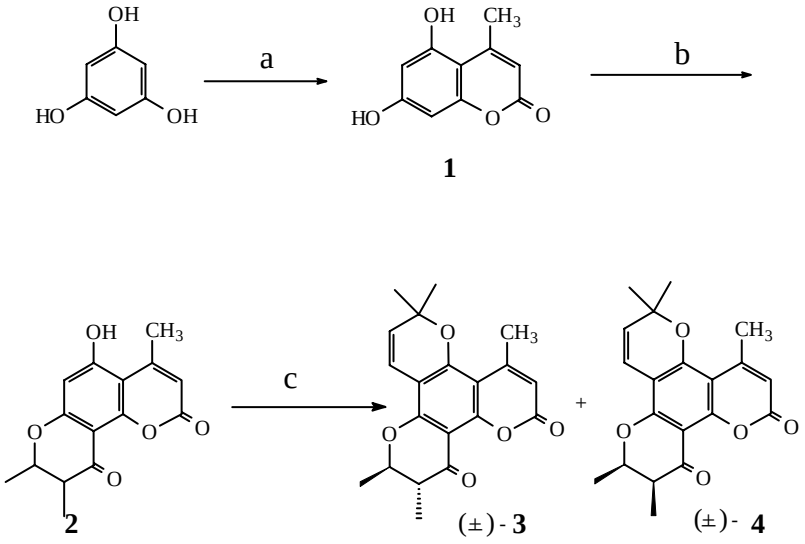
(+)-cordatolide A

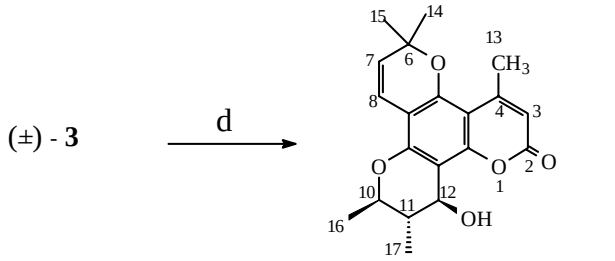
Cordatolide A has three heterocyclic rings, B, C and D constructed from a phloroglucinol core (A). According to our synthetic approach, we used phloroglucinol as a starting material and then constructed the coumarin followed by the chromanone ring. The chromene ring was built last. Finally Luche reaction reduced the chromanone (±)-**3** to give the desired product (±)-cordatolide A as shown in **scheme 1**.

Pechmann reaction on phloroglucinol with ethyl acetoacetate in the presence of concentrated sulfuric acid afforded 5,7-dihydroxy-4-methyl coumarin **1** almost quantitatively. Then acylation and ring closure of coumarin **1** in a one-step reaction using tigloyl chloride in the presence of $AlCl_3$ formed a key intermediate **2** in 58% yield.

The chromene ring was then introduced by the pyridine-catalyzed condensation of 1,1-diethoxy-3-methyl-2-butene. The reaction proceeded readily to give chromanone (±)-**3** and its stereoisomer (±)-**4** with a ratio of 1.5 : 1 in 72% yield. (±)-**3** was isolated by column-chromatography in 50% yield. Luche reduction of the ketone (±)-**3** using $NaBH_4/CeCl_3.7H_2O$ at ~0℃ afforded the target compound (±)-**5** in 60% yield. The spectral data including 1H-NMR, IR, MS of (±)- **5** were in agreement with the data reported for the natural product (+)-cordatolide A[1]. This four-step synthesis of (±)-cordatolide A is accomplished in about 17.4% overall yield.

Scheme 1

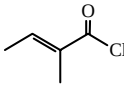


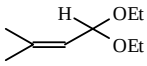


(±) - cordatolide A , (±) - **5**

Reagents and conditions:

a. CH_3COCH_2COOEt, H_2SO_4,100℃, 2h, 98%

b.  , $AlCl_3$, $PhNO_2$, CS_2, 75℃, 20h, 57%

c. Pyridine, Toluene,  , reflux, 8h, 72%

d. $NaBH_4$, EtOH, $CeCl_3 \cdot 7H_2O$, 0℃, 4h, 60%

Compound (±)-**3**: mp 203~205℃, ^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 6.63(d, J=10.0Hz, 1H, 8-H), 6.02 (s,1H, 3-H), 5.59 (d, J=10.0Hz, 1H, 7-H), 4.30 (dq, J=9.1, 6.4Hz, 1H, 10-H), 2.57 (s, 3H, 13-CH_3), 2.03 (dq, J=9.1, 6.9Hz, 1H, 10-H), 1.51 and 1.54 (2s, 6H, 14,15-2CH_3), 1.54 (d, J=6.4Hz, 3H, 16-CH_3), 1.21 (d, J=6.9Hz,3H,17-CH_3). Anal.Calcd.for $C_{20}H_{20}O_5 \cdot 0.7Et_2O$ (%): C, 69.82; H, 6.94. Found: C, 70.13; H, 7.03.

Compound (±)-**5**: mp 147~149℃(85℃[1]), ^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 6.61(d, J=10.0Hz, 1H, 8-H), 5.93 (s,1H, 3-H), 5.53 (d, J=10.0Hz, 1H, 7-H), 4.72 (d, J=7.8Hz, 1H, 12-H), 3.93 (dq, J=9.1, 6.4Hz, 1H, 10-H), 2.57 (s, 3H, 13-CH_3), 2.32 (brs, 12-OH, D_2O exchangeable), 1.92 (m, 1H, 11-H), 1.45 and 1.50 (2s, 6H, 14,15-2CH_3), 1.46 (d, J=6.4Hz, 3H, 16-CH_3), 1.15 (d, J=6.8Hz,3H,17-CH_3). EI-MS m/z (%): 342, 327, 309, 271, 243, 149, 115. IR (KBr): 3437, 2974, 2929, 1728, 1585, 1381, 1147, 1107 cm^{-1}. Anal.Calcd.for $C_{20}H_{22}O_5 \cdot 0.3H_2O$ (%): C, 68.72; H, 6.49. Found: C, 69.07; H, 6.55.

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