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Total Synthesis of (±)-Inophyllum B

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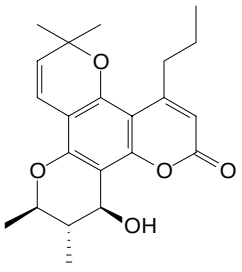
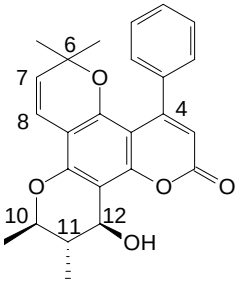
Abstract: (±)-Inophyllum B has been synthesized for the first time by a five-step approach from phloroglucinol, including the Pechmann reaction, Friedel-Crafts acylation, cyclization, chromenylation and Luche reduction

Keywords: (±)-Inophyllum B, anti-HIV-1 activity.

(+)-Calanolide A, isolated from tropical plants of the genus *Calophyllum ianigerum* in 1992[1], is a potent non-nucleoside inhibitor of reverse transcriptase from human immunodeficiency virus type 1(HIV-1 RT). In addition, (+)-Calanolide A is also active against strains of HIV-1, which are resistant to diverse kinds of non-nucleosides(*e.g.* nevirapin, TIBO) as well as nucleosides such as AZT. (+)-Calanolide A is undergoing phase Ⅰ B clinical trial. (±)-Calanolide A has been synthesized by us[2] and found that it inhibit the accumulation of HIV-1 P_{24} antigen in human PBMC cell with an IC_{50} of 0.83 μ mol/L. (+)-Inophyllum B, isolated from the *Calophyllum inophyllum* in 1972[3], has a similiar structure of (+)-calanolide A with a phenyl group at the 4-position instead of the n-propyl group (**Figue 1**). Up to now, there is no report about the synthesis of inophyllum B in literatures. Thus, we interested to synthesize (±)-inophyllum B for testing its anti-HIV-1 activity.



Calanolide A



Inophyllum B

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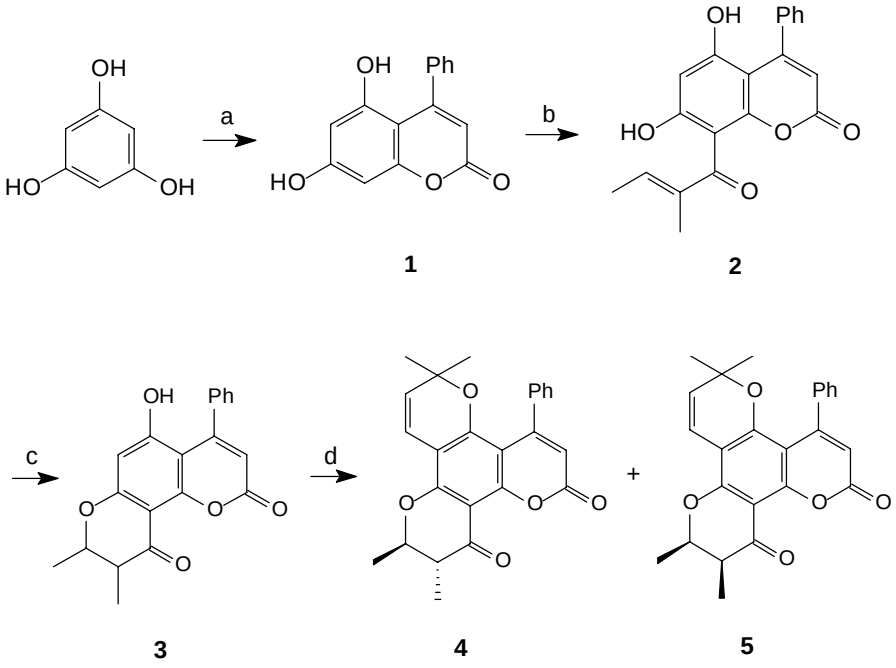
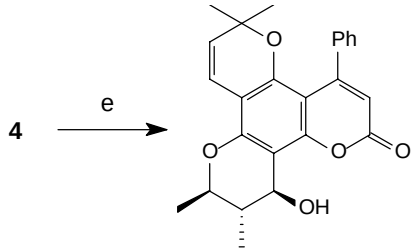
Inophyllum B has three heterocyclic rings, B, C and D constructed from a phloroglucinol core (A). Our synthetic approach is as follows (**Scheme** 1). Phloroglucinol was as starting material to construct the coumarin skeleton followed by construction of the chromanone ring. The chromene ring was built at last. Finally Luche reduction of the chromanone gave the target product (±)-inophyllum B which was fully characterized by ^{1}H-NMR, IR, MS and elemental analysis.

Pechmann reaction on phloroglucinol with 4-phenyl- acetoacetate in the presence of hydrogen chloride afforded 5,7-dihydroxy-4-phenyl coumarin **1** almost quantitatively. Then acylation of coumarin **1** using tigloyl chloride in the presence of $AlCl_3$ in $PhNO_2$ and CS_2 (v:v / 3:2) gave **2** in 70% yield. This result is differ from the case of acylation with cyclization directly for (±)-calanolide A[2] and (±)-cordatolide A[4]. Ring closure of **2** formed a key intermediate **3** in the presence of K_2CO_3 and 2-butanone in 80% yield. The chromene ring was then introduced by the pyridine-catalyzed condensation of 1,1-diethoxy-3-methyl-2-butene with **3** to give chromanone **4** and its stereoisomer **5** with a ratio of 2 : 1 in 60% yield. Compound **4** was isolated by column-chromatography with the gradient eluant (petrol.ether/ethyl acetate) in 40% yield. Luche reduction of the ketone **4** using $NaBH_4/CeCl_3{\cdot}7H_2O$ afforded **6** and purified by column-chromatography with the eluant dichloromethane/methanol(30:1). The structure was identified by ^{1}H-NMR, IR, MS spectra and elemental analysis. This five steps synthesis of (±)-inophyllum B (overall yield *ca.* 13.1%) provided a useful method for further medicinal investigation of the dipyranocoumarin class.

Scheme 1





6 , (±)-Inophyllum B

Reagents and conditions: (a) $C_6H_5COCH_2COOEt$, HCl, 25°C, 24 h, 98%; (b) Tigloyl chloride, $AlCl_3$, $PhNO_2$, CS_2, 75°C, 15 h, 70%; (c) K_2CO_3, 2-butanone, reflux, 5h, 80%; (d) Pyridine, toluene, 1,1- dimethoxy-3-methyl-2-butene, reflux, 10 h, 24%; (e) $NaBH_4$, EtOH, $CeCl_3{\cdot}7H_2O$, 0°C, 5 h, 59.7%.

Acknowledgments

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References and Notes

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5. Data for **2**: mp 115-117°C. 1H-NMR (500 MHz, DMSO-d6): δ (ppm) 10.58 and 10.34 (2s, 2H, OH-5,7), 7.32-7.37(m, 5H, Ph-4), 6.51 (q, 1H, J=5.9Hz, $CH_3CH=C(CH_3)CO$), 6.28 (s, 1H, H-6), 5.75 (s, 1H, H-3), 1.83 (s, 3H, $CH_3CH=C(CH_3)CO$), 1.82（d, 3H, J=5.9Hz, $CH_3CH=C(CH_3)CO$）.
6. Data for **4**: mp 132~134°C, ^{1}H-NMR (300 MHz, $CDCl_3$): δ (ppm) 7.2-7.38(m, 5H, Ph-4), 6.54(d, 1H, J=10.2Hz, H-8), 6.04 (s,1H, H-3), 5.40(d, 1H, J=10.2Hz, H-7), 4.30 (dq, 1H, J=9.1, 6.6Hz, H-10), 2.57 (dq, 1H, J=9.1, 7.2Hz, H-11), 1.54 (d, 3H, J=6.6Hz, CH_3-15), 1.23 (d, 3H,J=7.2Hz, CH_3-16), 0.98 and 0.94(2s, 6H, CH_3-13,14). IR (KBr): 2976, 2931, 1739, 1553, 1337, 1192, 1142, 1001, 854 cm^{-1}. Anal.Calcd.for $C_{25}H_{22}O_5 \cdot 0.33H_2O$ (%): C 73.51; H 5.59, Found: C 73.30; H 5.55
7. Data for **5**: mp 85~87°C, ^{1}H-NMR (300 MHz, $CDCl_3$): δ (ppm) 7.2-7.38(m, 5H, Ph-4), 6.54(d, 1H, J=10.2Hz, H-8), 6.03 (s,1H, H-3), 5.41(d, 1H, J=10.2Hz, H-7), 4.67 (dq, 1H, J=3.3, 6.0Hz, H-10), 2.66 (dq, 1H, J=3.6, 6.9Hz, H-11), 1.41 (d, 3H, J=6.6Hz, CH_3-15), 1.16 (d, 3H, J=6.9Hz, CH_3-16), 0.97 and 0.94(2s, 6H, CH_3-13,14).
8. Data for **6**: mp75-77°C, ^{1}H-NMR (300 MHz, $CDCl_3$):δ (ppm) 7.21-7.42(m, 5H, Ph-4), 6.50(d, 1H, J=9.9Hz, H-8), 5.95(s,1H, H-3), 5.36(d, 1H, J=9.9Hz, H-7), 4.77 (d, 1H, J=8.1Hz, H-12), 3.93 (dq, 1H, J=9.1, 6.6Hz, H-10), 1.96 (dq, 1H, J=9.1, 6.9Hz, H-11), 1.46 (d, 3H, J=6.6Hz, CH_3-16), 1.16(d, 3H, J=6.9Hz, CH_3-17), 0.96 and 0.89 (2s, 6H, CH_3-14,15). EI-MS *m/z:* 404(M^+), 389, 371, 333, 317, 134, 119, 105, 77. IR (KBr): 3458, 2972, 2929, 1712, 1581, 1422, 1359, 1153, 1057, 906, 856, cm^{-1}. Anal.Calcd.for $C_{25}H_{24}O_5 \cdot 0.5H_2O$ (%): C 72.62; H 6.10 , Found: C 72.77; H 6.11.

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