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A Rapid Entry into Podophyllotoxin Congeners: Synthesis of Justicidin B

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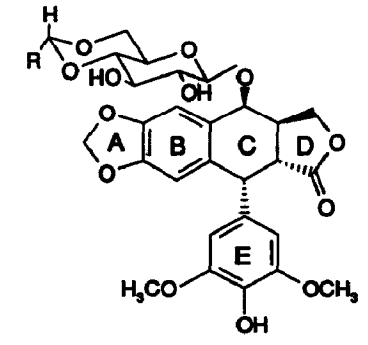
Key words: podophyllotoxin, podophyllum lignans, justicidin B, Michael Initiated Ring Closure, desulfurization, nickel-containing complex reducing agent.

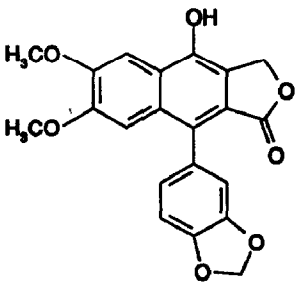
Abstract: A facile synthesis of justicidin B is described, as well as related podophyllum lignans by employing Michael Initiated Ring Closure strategy followed by desulfurization mediated by nickel-containing complex reducing agent.

The podophyllum lignans have attracted the attention of organic and medicinal chemists for several years. The development of two semisynthetic drugs, etoposide (VP-16-213-1a),[2] and tenoposide (VM-26, 1b)[3] based on the podophyllotoxin is valuable in cancer chemotherapy. The ring-A-opened lignans such as diphyllin (2) and justicidin B (7a) have been found to be much more effective against Sindbis virus than podophyllotoxin itself.[4] Diphyllin and justicidin B have been isolated from *Diphylleia grayi* and *Justicia hayatai* respectively.[5] We have been interested in the synthetic modifications on the podophyllum lignans

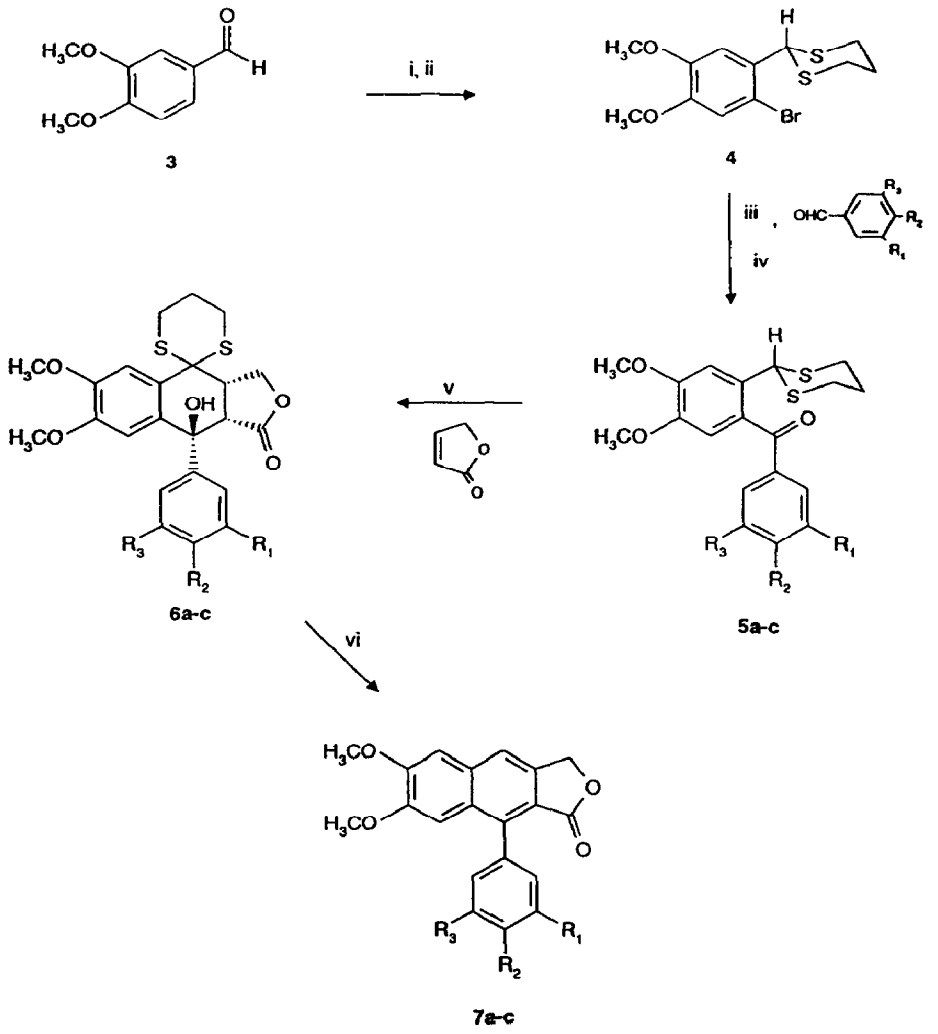


R = CH_3 , etoposide (1a)

R =  , tenoposide (1b)



diphyllin (2)



a, R_1R_2 = -O-CH_2-O-, R_3 = H
b, $R_1 = R_2 = R_3 = OCH_3$
c, $R_1 = R_3 = OCH_3$, $R_2 = OCH_2C_6H_5$

i. Br_2, AcOH, 3h, 79%; ii. 1,3-propanedithiol, p-TsOH, C_6H_6, 90°C, 1.5 h, 97%, iii. n-BuLi, THF, -78°C, ArCHO, 88-94%, iv. MnO_2, CH_2Cl_2, 94-96%; v. LiHMDS, THF, -65°C, 2(5H)-furanone, 36-49%, vi. NiCRA, THF, 24h, 69-75%.

as DNA topoisomerase inhibitors. In this context, we developed an efficient synthetic methodology for **7a** and related ring-A-opened podophyllum lignans. Earlier preparation of **7a** has been supported[6] in connection with its structural confirmation, whereas no effort has been made for its practical synthesis.

In this report, the basic approach has been to build the lignan precursor by employing the type II Michael Initiated Ring Closure (MIRC) strategy.[7,8] While, the key feature is the versatile desulfurization accompanied by aromatization in one-pot. Thus, the first step is the bromination of veratraldehyde (**3**) followed by the protection of the aldehydic group by 1,3-propanedithiol to give dithiolane of 6-bromoveratraldehyde (**4**). This on transmetallation by n-BuLi and subsequent treatment with substituted aldehydes give the corresponding alcohols, which upon benzylic oxidation with MnO_2 yield the benzophenone intermediates (**5a-c**) as crystalline compounds. MIRC reaction between compounds **5** and 2(5H)-furanone led to the lignan precursors (**6**).

In a typical MIRC procedure; to a solution of dithiolane (**5a**, 3.7 gm, 0.01 mmol) in dry THF (150 ml) was added LiHMDS (1.0 M in THF, 10 ml) at -65° C to generate the deep purple anion. To this anion was added furanone (0.84 gm, 0.01 mol) taken in THF (5 ml), gradually maintaining the temperature at -60° C. The reaction mixture was stirred for another 2 h at this temperature and usual work up gave the single isomer of lignan precursor **6a** along with the starting material. These were separated by solubility differences in EtOAC-hexane (4:1) mixed solvent. Similarily, **6b-c** were also prepared.

The desulfurization[9,10] of the dithiolane lignans (**6**) in presence of nickel-containing complex reducing agent (NiCRA) is accompanied by aromatization to produce **7a** and other related podophyllum lignans (**7b-c**).[11] In a typical desulfurization procedure: to a stirred suspension of NaH (100 mM) and $Ni(OAc)_2$ (10 mM) in refluxing THF (20 ml) was added the activating alcohol, t-AmOH (20 mM) taken in THF (15 ml). A brownish-black colour developed. After 4 h, dithiolane lignan (10 mM) in THF (15 ml) was added and the reaction mixture was refluxed for 24 h. Upon completion the reaction medium was cooled, quenched with water (10 ml), acidified with dilute HCl, extracted with diethyl ether, and the organic phase was dried over Na_2SO_4. The crude products were purified by column chromatography (silica, chloroform-methanol, 9.8:0.2).

Mechanistically, in the desulfurization step it is observed that the dithiolane lignan (**6**) is first aromatized to open up the dithiolane ring by forming the thioether thiol lignan, which is subsequently desulfurized to yield the lignan (**7**).

In summary, this methodology offers a convenient entry towards the more demanding podophyllum lignans, via desulfurization of the dithiolane. Further investigations on the dithiolane lignan precursor are under progress for the synthesis of structurally modified podophyllum lignans.

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11. All new compounds gave satisfactory spectral and analytical data e.g. **6a** ^{1}H NMR (200 MHz, $CDCl_3$), 7.60 (1H, s, Ar), 6.79-6.95 (3H, m, Ar), 6.44 (1H, s, Ar), 5.96 (2H, s, OCH_2O), 5.69 (1H, s, OH), 4.42 (1H, m, C<u>H</u> HOCO), 4.19 (1H, m, CH <u>H</u>OCO), 3.97 (3H, s, OCH_3), 3.87 (1H, m, C<u>H</u>CH_2), 3.66 (3H, s, OCH_3), 3.30 (1H, d, J=7.3 Hz, $CHCO_2$), 3.12 (2H, m, CH_2S), 2.85 (2H, m, CH_2S), 2.18 (2H, m, $CH_2CH_2CH_2$); m/e found: M^+, 488.0979; $C_{24}H_{24}O_7S_2$ requires 488.0994. **7a** ^{1}H NMR (200 Mz, $CDCl_3$), 6.87-7.78 (6H, m, Ar), 6.11 (2H, s, OCH_2O), 5.41 (2H, CH_2OCO), 4.12 (3H, s, OCH_3), 3.82 (3H, s, OCH_3).

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