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TOTAL SYNTHESIS OF (±) PODOPHYLLOTOXIN

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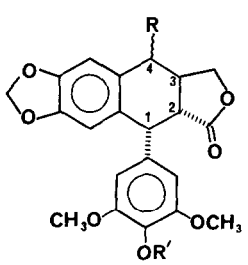
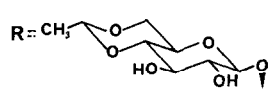
Abstract: A straightforward approach to podophyllotoxin was developed using silyl enol ether 5.

Podophyllotoxin (1) is a lignan isolated from Podophyllum peltatum and P. emodi[1]. It is a potent inhibitor of microtubule assembly and a key intermediate of an antitumor agent, etoposide (2)[2]. Although there have been several elegant syntheses of this compound or its C4 epimer (epipodophyllotoxin)[3], we sought an operationally simpler route, which is the subject of this letter.

The challenge of the synthesis lies in the formation of four contiguous stereocenters and the presence of a base-sensitive trans lactone. Two of the published syntheses involve conversion of a cis lactone (picropodophyllotoxin) to a trans lactone by a kinetic protonation of the lactone enolate.[3a,b] This produces a mixture of isomers in which the desired trans lactone is the minor component. Another problem is that bis-alkylation is observed to be the major course of action in the base-catalyzed hydroxymethylation of tetralone 3.[4]



1 R = HO, R' = CH_3

2 R = 

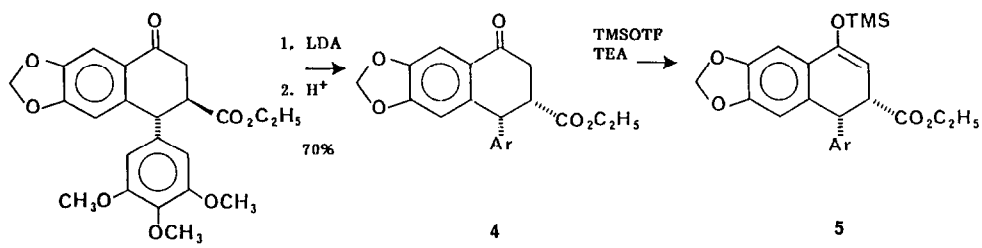
, R' = H

To circumvent these problems we planned to establish the stereochemistry of the C2 center early in the synthesis. The possible use of cis ester 4 was suggested by a considerable amount (approximately 16%) of 4 in the equilibrium mixture resulting from treatment of trans ester (3) with EtONa in EtOH at 21°C. We reasoned, furthermore, that under mild conditions 4 could be converted to a silyl enol ether without epimerization at C2, and then alkylation would take place from the β-face since the α-face is shielded by a pendant aromatic ring and the ethoxycarbonyl group[5] and that use of the silyl enol ether should also eliminate the problem of bisalkylation.

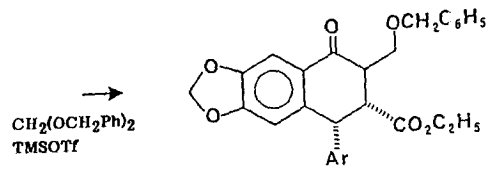
The starting material in our synthesis (Scheme) was readily available by the published route.[3e,4b] Cis ester 4 was obtained by treatment of 3 with 4 eq. of LDA followed by an aqueous HCl quence at -40°C. After one recrystallization from EtOH the desired cis ester was obtained in 70% yield.[6] This keto ester was treated with TMSOTf in the presence of triethylamine at 3°C to give silyl enol ether.5[7] Under these conditions, the stereochemistry at C2 was maintained as the dihedral angle between the C1 and C2 protons was calculated to be approximately 21° from their coupling constant (7.1Hz).[8] The silyl enol ether thus prepared was allowed to react with dibenzyloxymethane in the presence of a catalytic amount of TMSOTf to give compound 6.[9,12] The yield for the two steps was 70-74%, and as expected, only the β-isomer was obtained. The benzyloxymethyl group could also be introduced using benzyloxymethyl chloride and $TiCl_4$.[10]

Reduction of the C4 carbonyl group with $LiBH_4$ at 0°C proceeded stereospecifically to give lactone 7[12] as the major product (43%) as well as alcohol 8 (25%).[12] Catalytic hydrogenation of 7 in EtOAc in the presence of 10% Pd/C gave the known[11] neopodophyllotoxin (9) in 55% yield. Following the chemistry developed by von Wartburg the C2-C4 lactone was hydrolyzed with 1N NaOH, and after acidification the diol acid (podophyllic acid) was treated with dicyclohexyl carbodiimide in THF at 0°C to give podophyllotoxin in 54% yield. Thus, this sequence gave podophyllotoxin in a straightforward manner in 5 steps from tetralone 3.

Scheme



3 4 5



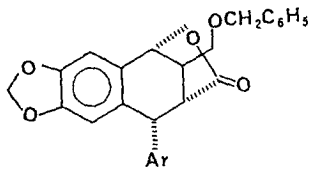
$CH_2(OCH_2Ph)_2$
TMSOTf

OR

$PhCH_2OCH_2Cl$
$TiCl_4$

6

70 - 74% for two steps

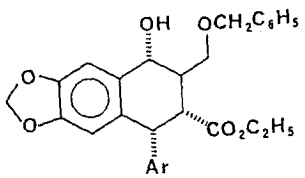


$LiBH_4$
THF

43%

7

+

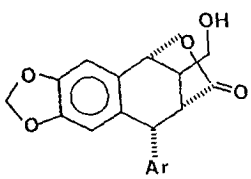


25%

8

H_2
Pd-c

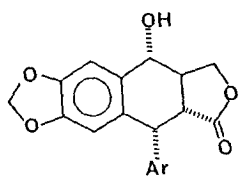
55%



9

1) OH^-
H^+

2) DCC
45%



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12. mp and NMR: 6, 107-109°C ($CDCl_3$) δ 1.19 (t,3H,J=7Hz), 2.99 (dt,1H,J=12.2,1Hz), 3.63 (dd,1H,J=9.2,3.3Hz), 3.71 (s,6H), 3.78 (s,3H), 3.83 (dd,1H,J=12.5,5.0Hz), 4.01 (m,2H), 4.30 (dd,1H,J=9.0,2.3Hz), 4.36 (d,1H,J=12.2Hz), 4.50 (d,1H,J=12.1Hz), 4.56 (d,1H,J=5.1Hz), 6.01 (s,1H), 6.02 (s,1H), 6.10 (s,2H), 6.59 (s,1H), 7.29 (m,5H): 7, 194-196°C; ($CDCl_3$) δ 2.96 (t,1H,J=4.5Hz), 3.25 (m,1H), 3.39 (dd,1H,J=7.9,7.5Hz), 3.55 (dd,1H,J=7.4,7.2Hz), 3.71 (s,6H), 3.83 (s,3H), 4.10 (d,1H,J=4.6Hz), 4.45 (s,1H), 5.16 (d,1H,J=4.8Hz), 5.96 (s,2H), 6.21 (s,2H), 6.42 (s,1H), 6.71 (s,1H), 7.29 (m,5H): 8 amorphous solid, 1.08 (t,3H,J=7.1Hz), 2.75 (m,1H), 2.99 (dd,1H,J=11.9,5.4Hz), 3.50 (t,1H,J=8.5Hz), 3.68-3.89 (m,4H), 3.75 (s,6H), 3.80 (s,3H), 4.27 (d,1H,J=5.5Hz), 4.49 (d,1H,J=12.0Hz), 4.57 (d,1H,J=12.0Hz), 4.77 (d,1H,J=7.7Hz), 5.90 (s,1H), 5.91 (s,1H), 6.23 (s,2H), 6.38 (s,1H), 7.07 (s,1H), 7.33 (m,5H).

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