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Asymmetric Total Synthesis of (-) Podophyllotoxin

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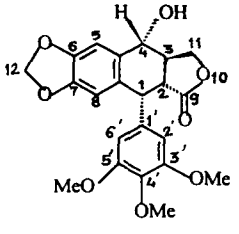
Abstract : Asymmetric synthesis of podophyllotoxin is achieved through tandem conjugate addition of S (-) benzyl phenyl sulfoxide to but-2-en-4-olide. Copyright © 1996 Elsevier Science Ltd

Podophyllotoxin **1**, the major constituent of several plant species of the Podophyllum family, occupies a unique and significant place among lignan natural products. It is a potent inhibitor of microtubule assembly and is a key intermediate for clinical antitumour agents[1] etoposide **2** and teniposide **3**. The challenge of the synthesis lies in the formation of four contiguous stereocenters and the presence of a base sensitive *trans* lactone.



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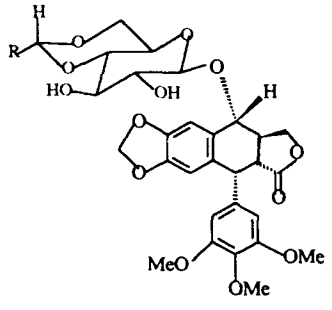

2 R = CH_3

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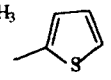
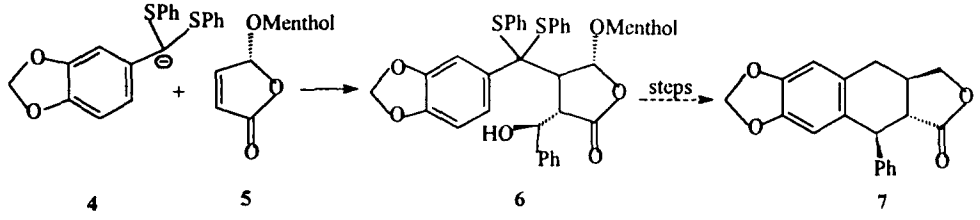


Four general approaches to the synthesis of podophyllotoxin derivatives[2] have so far been developed although several variations and innovations have been introduced within each of these overall schemes; namely i) the oxoester route,[3] ii) dihydroxy acid route,[4] iii) Diels - Alder approach,[5] iv) tandem conjugate addition.[6]

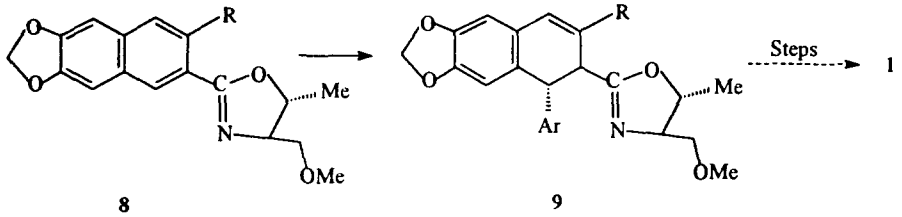
Only five approaches to the asymmetric synthesis of podophyllotoxin or analogues have been achieved using asymmetric conjugate addition or Diels-Alder reactions. The key step in the first route (Scheme 1) reported by Ward et al.[6b] involves asymmetric conjugate addition of anion 4 to chiral butenolide 5 to yield adduct 6 which has been further elaborated to (-) deoxy-iso-podophyllotoxin.



4 5 6 7

Scheme 1

Meyers et al[7] achieved asymmetric synthesis of (-) podophyllotoxin in 24 steps (Scheme 2). The key step in the synthesis is asymmetric conjugate addition of a trimethoxyphenyl anion to chiral oxazoline 8 to yield chiral adduct 9.



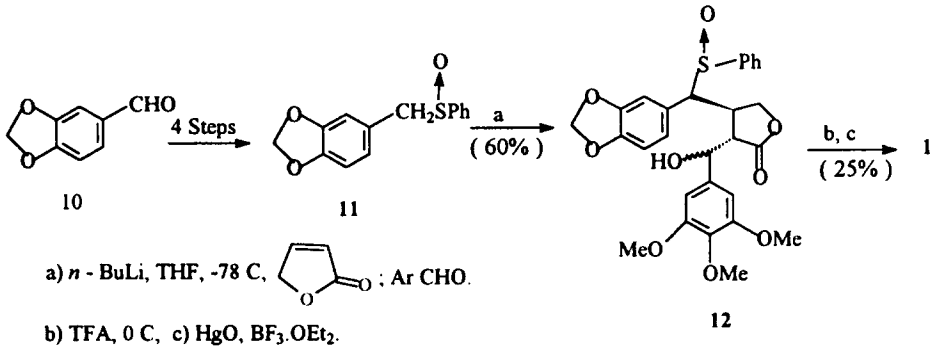
8 9

Scheme 2

Recently Bush and Jones[8] reported the synthesis of (-) 1 in 8 steps with 15% overall yield, based on Diels - Alder addition of the o-quinonoid pyrone to the chiral dienophile 5. Subsequently Pelter et al.[9] have achieved the synthesis of (-) isopodophyllotoxin through similar Diels - Alder reaction between an aryl isobenzofuran and the dienophile 5. Bogucki and Charlton[10] have synthesized (-) deoxy-podophyllotoxin through the Diels-Alder cycloaddition between the fumarate of methyl (S)-mandelate and α - hydroxy-α-aryl-o-quinodimethane.

We report herein a short and convenient synthesis of (-) podophyllotoxin through asymmetric tandem conjugate addition of *S* (-)-piperonyl phenyl sulfoxide anion to butenolide and 3,4,5-trimethoxy benzaldehyde, followed by acid catalyzed cyclization and Pummerrer type elimination of sulfoxide **(Scheme3)**

The sulfoxide **11** was prepared from piperonal in four steps which include sodium borohydride reduction to piperonol, conversion to piperonyl bromide by treatment with aqueous HBr, the condensation with sodium thiophenolate to obtain piperonyl phenyl sulfide followed by chiral sulfoxidation through modified Sharpless method reported by Kagan et al,[11] using titanium tetra-isopropoxide, R,R (-) diethyl tartarate, t-butyl hydroperoxide (TBHP) and water. The chiral sulfoxide **11**, a colourless solid (mp.82-83° C, ethyl acetate / petroleum ether) has [α]$_D^{25}$ = - 75.5° (c, 2 %, acetone). The tandem conjugate addition of the chiral piperonyl phenyl sulfoxide anion was carried out according to the procedure described by Ward et al.[6b]



Scheme 3

A mixture of (-) piperonyl phenyl sulfoxide (10 mmol) and n-butyl lithium (10 mmol) in THF (100 ml) was stirred at - 78°C for 1h, a solution of but-2-en-4-olide (10 mmol) was added and after 1h stirring a solution of 3,4,5-trimethoxybenzaldehyde (10 mmol) in THF was introduced and stirring was continued for 2h. Usual workup and purification by column chromatography over silica gel yielded the adduct **12** (viscous oil , 60%). The adduct **12** on reaction with trifloroacetic acid for 3h yielded a cyclized tetrahydronaphthalene derivative, which on further treatment with HgO and BF_3. OEt_2[6b] for 28 h, yielded (-) podophyllotoxin, mp 176 -178°C, (methanol / chloroform), [α]$_D^{25}$ = -104.3° (c, 0.4 % $CHCl_3$). The spectral properties of our synthetic compound[12] are identical with natural **1** isolated from *Podophyllum emodi*.

Thus the present report constitutes short and convenient synthesis of (-) podophyllotoxin.

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12 **IR** : υ_{max} ($CHCl_3$) : 3473, 3030, 2898, 1775,1586, 1505, 1498, 1424, 1370, 1250, 1220, 1115, 1005, 950, 900 cm^{-1} ; **^{1}H NMR** (500 MHz,$CDCl_3$) : δ 7.11 (1H, s, H-5), 6.50 (1H, s, H-8), 6.37 (2H, s, H-12), 5.99 (1H, d, J=1.28 Hz, H-2'), 5.93 (1H, d, J=1.28 Hz, H 6'),4.75 (1H,d,J=8.6 Hz, H-4), 4.61 (1H, dd, J=2.1, 9.7 Hz, H-11α), 4.59 (1H, d, J=2.7 Hz, H-1), 4.07 (1H, t, J=9.7 Hz,H - 11β),3.80 (3H, s, -OMe at 4'), 3.75 (6H, s, 2x-OMe, H3' & H5'), 2.83 (1H, dd, J=2.7, 8.5,H-2); 2.76 (1H, m, H-3).; ^{13}C NMR (125 MHz $CDCl_3$) : δ 174.69 (s), 152.82 (s), 148.02 (s), 137.44 (s), 135.67 (s), 133.39 (s), 131.38 (s), 130.92 (s), 110.01 (d), 108.63 (d), 106.53(d); 101.69 (t), 73.01 (d), 71.58 (t), 61.00 (q), 56.51 (q), 45.54 (d), 44.32 (d), 40.98 (d) ; Mass : m / z 414 (M^+) ; Analysis : C, 63.68 ; H, 5.42 ; $C_{22}H_{22}O_8$ requires C, 63.75 ; H, 5.35.

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