

## Synthesis of Podophyllotoxin

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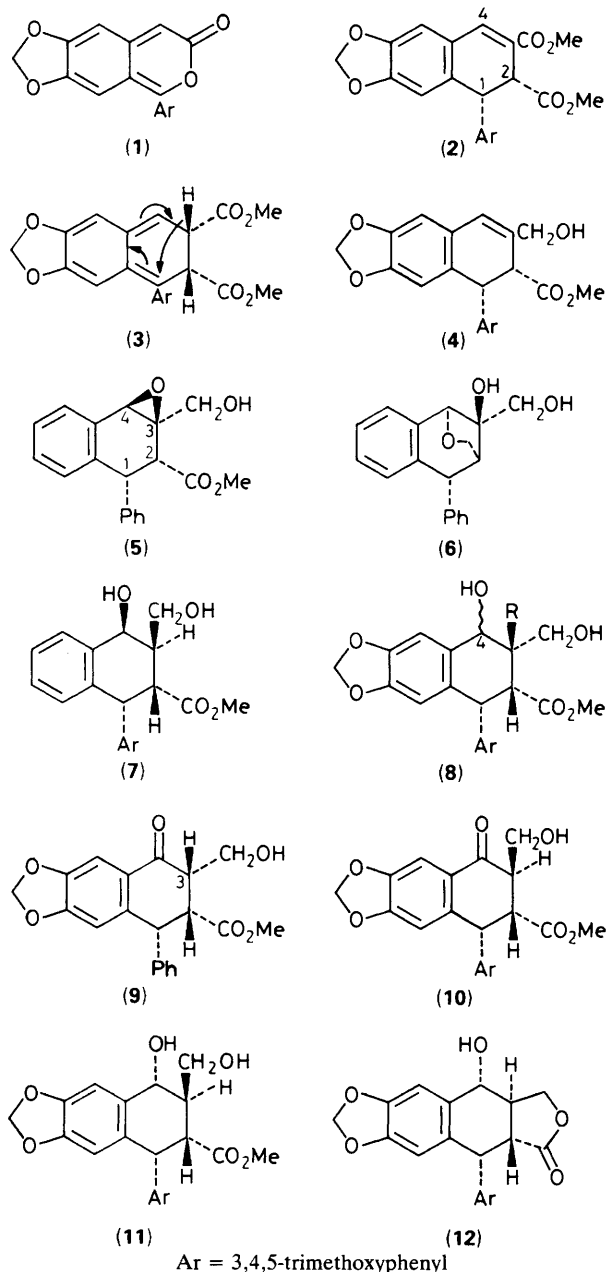
The alkene (**2**) obtained directly from the reaction of dimethyl maleate with the pyrone (**1**) is converted into ( $\pm$ )-podophyllotoxin (**12**) in seven steps and 24% overall yield; novel steps include the epimerisation of (**9**) at C-3 using 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) and selective oxidation of (**8**) to (**9**) using  $(\text{Bu}^n_3\text{Sn})_2\text{O}-\text{I}_2$ .

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Reaction of the isolable *o*-quinonoid pyrone (**1**)<sup>1</sup> with dimethyl maleate at 140 °C gives the dihydronaphthalene (**2**) in 71% yield.<sup>2†</sup> We have earlier suggested the use of (**2**) as an intermediate in lignan synthesis.<sup>2</sup> Herein we describe the conversion of (**2**) into ( $\pm$ )-podophyllotoxin.

† It is likely that formation of (**2**) involves decarboxylation of an initial pyrone-maleate adduct to give (**3**) which undergoes the indicated (3-arrows) 1,5-hydrogen shift selectively.

Selective reduction of the less hindered methoxycarbonyl group at C-3 of (**2**) was achieved with lithium triethylborohydride in tetrahydrofuran (THF) at -70 °C (3 h) to give (**4**) in high but somewhat variable yield (64–76%). The similarly prepared model for (**4**) lacking methylenedioxy and methoxy groups on the aromatic rings was readily epoxidised (*m*-chloroperbenzoic acid,  $\text{CH}_2\text{Cl}_2$ , 0  $\rightarrow$  20 °C) to give mainly the  $\beta$ -epoxide (**5**). However, reduction of (**5**) with sodium bis(2-methoxyethoxy) aluminium hydride (Red-Al) gave the



ether (6) rather than the model (7) for methyl epipodophyllate. The latter had been the expected product since epoxides of allylic alcohols are known to be reduced with Red-Al to 1,3-diols with inversion at C-2.<sup>3</sup>

Accordingly the following revised strategy for the conversion of (4) into podophyllotoxin was adopted. Reaction of (4) with *N*-bromosuccinimide in Me<sub>2</sub>SO-H<sub>2</sub>O gave the stereoisomeric bromohydrins (8; R = Br) (72%, 4 $\alpha$ -OH: 4 $\beta$ -OH ratio 4:1). Debromination of the mixture [Bu<sup>n</sup><sub>3</sub>SnH, C<sub>6</sub>H<sub>6</sub>, azoisobutyronitrile (AIBN), *h* $\nu$ ] gave a mixture of the diols (8; R = H) in 96% yield. Initial attempts to effect selective oxidation of the benzylic alcohol site in (8; R = H) with MnO<sub>2</sub>, and with 2,3-dichloro-5,6-dicyanobenzoquinone gave the ketone (9) in poor yield. However, we have found that a mixture of iodine and bis(tri-*n*-butyltin) oxide in CH<sub>2</sub>Cl<sub>2</sub> (20°C) is an extremely effective and selective oxidant for this conversion; the 4 $\alpha$ -OH epimer gave (9) in 72% recrystallised yield and the 4 $\beta$ -OH epimer gave (9) in 60% recrystallised yield.<sup>‡</sup>

Selective inversion at C-3 of (9) was achieved in quantitative yield by treatment with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in THF (7 h, 20°C). The high yield observed for this process favours a deprotonation-reprotonation mechanism rather than one involving reverse aldolisation. Reduction of (10) with lithium triethylborohydride gave methyl podophyllate (11) (89%). This was lactonised to podophyllotoxin (12) in 75% yield using our 4 Å molecular sieves-ZnCl<sub>2</sub>-THF procedure.<sup>1</sup>

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## References

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<sup>‡</sup> The selective oxidation of both secondary and benzylic alcohols with (Bu<sup>n</sup><sub>3</sub>Sn)<sub>2</sub>O-Br<sub>2</sub> is well known.<sup>4</sup> We uncovered the (Bu<sup>n</sup><sub>3</sub>Sn)<sub>2</sub>O-I<sub>2</sub> reactions in attempting to remove tin residues, after the debromination of (8; R = Br), by stirring with I<sub>2</sub>-NaF; (9) was obtained in 52% yield.