Asymmetric Total Synthesis of (−)-Podophyllotoxin

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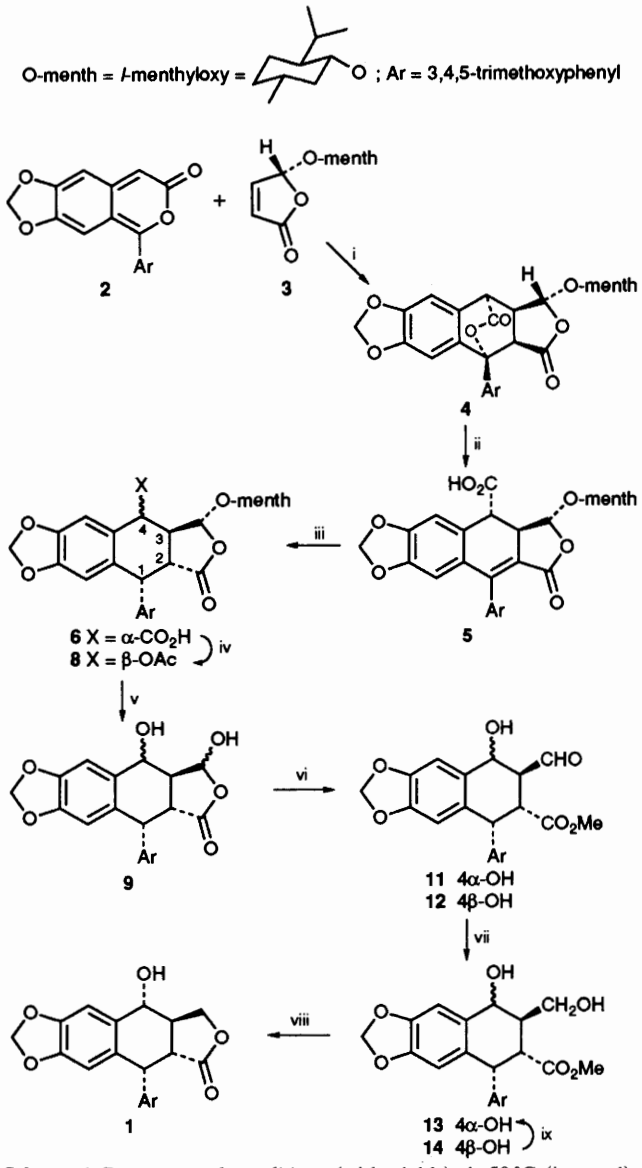
(−)-Podophyllotoxin of 98% optical purity is synthesised in eight steps and in 15% overall yield from the pyrone **2** and the chiral dienophile **3**.

Although the use of podophyllotoxin derivatives in cancer chemotherapy has prompted much synthetic work[1] there has appeared only one asymmetric total synthesis of (−)-podophyllotoxin **1**.[2] There is also a much shorter synthesis of (−)-epipodophyllotoxin (C-4 epimer of **1**)[3] which can be considered a formal synthesis of **1** in 14 steps. Both these syntheses have key steps based on carbanion chemistry. We now describe a fairly short synthesis of (−)-**1** based on Diels–Alder addition of the *o*-quinonoid pyrone **2** to the chiral dienophile **3**[4] (Scheme 1).†

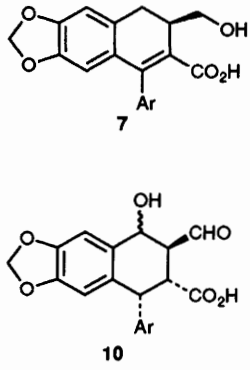
Addition of **2** to **3** at 50 °C in MeCN in base-washed glassware gave **4** as the only observed adduct in high yield. The expected high facial selectivity[4] is accompanied by very high regioselectivity, which probably arises from the aryl group of the pyrone and the carbonyl group of the dienophile; methyl acrylate adds less selectively to 2-benzopyran-3-one itself. The addition of **2** and **3** is also remarkably *endo*-selective; addition of 2(5*H*)-furanone to **2** gave both *endo* and *exo* adducts (ratio 4.2 : 1). If the Diels–Alder reaction is conducted in glassware that has not been base-washed the olefinic acid **5** accompanies the adduct **4**, and **5** can be produced from **4** in high yield merely by heating **4** in glacial acetic acid at 50 °C. The *O*-menthyl group also exerts an important influence upon the hydrogenation of **5**; addition of hydrogen to the β-face of **5** to give mostly the 2,3-*trans*-lactone **6** contrasts with almost exclusive hydrogen addition to the α-face of related lactones lacking the *O*-menthyl group. A slight preference for β-hydrogen addition is shown by the related hydroxy acids *e.g.* **7** and this has been used synthetically.[5]

The acid **6** with the correct stereochemistry at C-1, C-2 and C-3 was cleanly converted by lead tetraacetate oxidation[6] to

† A neat synthesis of (−)-neopodophyldotoxin by cycloaddition to a photoenol has been described (J. L. Charlton and K. Koh, *J. Org. Chem.*, 1992, **57**, 1514.)



Scheme 1 *Reagents and conditions* (with yields): i, 50 °C (internal), MeCN, 29 h, Ar, base-washed glassware, 79%, 1.2 g scale; ii, 49 °C (internal), HOAc, 13 h, 87%, iii, 22 °C, EtOAc, 10% Pd/C, H_2, 40 h, 71% (77% on recovered **5**); iv, 20 °C, HOAc–THF (1 : 5), $Pb(OAc)_4$, Ar, 3 h, 80%; v, 41–43 °C (internal), dioxane–0.6 mol dm^{-3} hydrochloric acid (3 : 1), 51 h, 39% 4α, 32.1% 4β; vi, CH_2N_2, Et_2O–MeOH (24 : 1), 0 °C, 86% **11**, 85% **12**; vii −78 °C, THF, Ar, $LiEt_3BH$ (2.2 equiv.), 1 h, $NaHCO_3$–H_2O quench, boil MeOH–silica gel (10 min), 84% **13**, 83% **14**; viii, 64 °C, THF, $ZnCl_2$, 4 Å molecular sieves, 2.5 h, 85%; ix, THF–4 mol dm^{-3} hydrochloric acid (1 : 1.5), 20 °C, 3.5 h, 63%, ref. 6.



the acetate **8**. The pseudoester **8** was hydrolysed under carefully controlled acidic conditions (Scheme 1) to give the epimeric lactols **9**. The absence of C*H*O resonance in the NMR spectra of these lactols show that they and not the aldehydes **10** are the predominant ring-chain tautomers. Importantly, only a minor quantity (7.5%) of the enal produced by β-elimination of water in **10** was formed under the proper hydrolysis conditions. Brief treatment of the individual lactols **9** with diazomethane in diethyl ether–methanol gave the aldehydoesters **11** and **12** which were efficiently reduced to methyl podophyllate **13** and methyl epipodophyllate **14**. The former compound was lactonised using our $ZnCl_2$-4 Å molecular sieves procedure[6] to give (−)-podophyllotoxin **1** identical with an authentic sample. Methyl epipodophyllate **14** is readily converted into methyl podophyllate (Scheme 1). Accordingly, (−)-podophyllotoxin can be prepared in 15% overall yield from the pyrone **2** with an optical yield of 98%.

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