Synthesis of Podophyllum Lignans *via* an Isolable *o*-Quinonoid Pyrone

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The 2-benzopyran-3-one (**7**) is a stable, isolable, and useful Diels–Alder diene; its adduct (**10**) formed with dimethyl fumarate is transformed in three steps into methyl epipodophyllate (**14**) which gives epipodophyllotoxin (**2**) (81%) by direct lactonisation ($ZnCl_2$–tetrahydrofuran–4 Å molecular sieves).

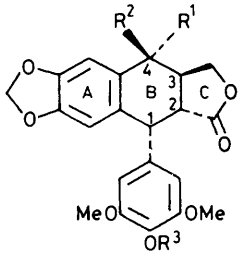
The synthesis of podophyllotoxin (**1**) and epipodophyllotoxin (**2**) is a subject of continuing interest.[1] This stems in part from the use of etoposide (VP-16) (**3**) and teniposide (VM-26) (**4**) in the treatment of bladder and lung cancer,[2] and in part from the fascinating problem of assembling efficiently, and *maintaining*, the stereocentres in ring B.

The 2-benzopyran-3-ones (**5**) and (**6**) generated as reactive intermediates by acetic anhydride dehydration of *o*-formylphenylacetic acid and 2-formyl-4-methoxyphenylacetic acid, respectively, are useful building blocks in the synthesis of aromatic steroids.[3] Accordingly, the tetrahydronaphthalene units in (**1**) and (**2**) should be accessible *via* the pyrone (**7**). Brief heating of (**8**)† in boiling acetic anhydride led to *quantitative* conversion into the pyrone (**7**); unlike (**5**), (**6**), and (**9**),[4a] compound (**7**) is isolable and has a good shelf-life. Reaction of (**7**) with dimethyl fumarate in boiling benzene gave the adducts (**10**) and (**11**) in a ratio of *ca.* 3 : 1. This ratio rose to 5 : 1 when the reaction was conducted in MeCN at 50 °C (bath temperature); (**10**) was then isolated in 76% yield by crystallisation of the adduct mixture from EtOH. Predominant formation of (**10**) in which the CO_2Me group at C-2 is *exo* and that at C-3 is *endo* agrees with the addition of dimethyl fumarate to (**9**) in boiling Ac_2O which gave adducts corresponding to (**10**) and (**11**) in a 3 : 1 ratio.[4b] This stereoselectivity agrees with the effect of α,α′-aryl substitution in promoting *exo*-addition to *o*-quinodimethanes, an effect first noted by us in 1973 and attributed to a steric effect.[4c] Accordingly, in the addition of fumarate to (**7**) or (**9**), addition to give an *endo* CO_2Me at C-2 should be suppressed as is observed.

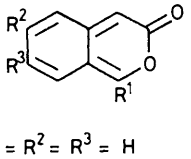
Hydrogenolysis of (**10**) over 10% Pd–C in acetic acid at 50 °C (bath temperature) proceeded with predominant inversion at C-1 to give (**12**) in 50% recrystallised yield. Oxidative decarboxylation of (**12**) [$Pb(OAc)_4$, tetrahydrofuran (THF)–HOAc (5 : 1), 20 °C] gave (**13**) (61% yield by crystallisation of the crude product from Et_2O). With lithium triethylborohydride in dry THF at −20 °C, (**13**) gave methyl epipodophyllate (**14**) (65%). Rajapaksa and Rodrigo[5] developed an interesting strategy for the conversion of (**14**) into epipodophyllotoxin (**2**). This involved conversion of (**14**) into an acetonide which unlike (**14**) did not epimerise at C-2 during alkaline hydrolysis of the methyl ester. Removal of the 'protecting' acetonide group from the resulting acid gave epipodophyllic acid (**15**) which readily lactonised to epipodophyllotoxin with dicyclohexylcarbodi-imide. Other lignan syntheses have followed this lead.[1b,6] However the protection–deprotection sequence is unnecessary as (**14**) is found to undergo rapid, clean, and efficient (81%) direct lactonisation to epipodophyllotoxin (**2**) upon heating with zinc chloride and 4 Å molecular sieves in THF. This procedure is based on the observation[7] that $ZnCl_2$–MeOH equilibrates podophyllotoxin and methyl podophyllate (60% of the former and 16% of the latter) with only minor formation of neopodophyllotoxin (8%) and picropodophyllotoxin (4%).

† Prepared from the corresponding methyl ester in turn obtained from methyl 3,4-methylenedioxyphenyl acetate, 3,4,5-trimethoxybenzoyl chloride, and either $ZnCl_2$ or $SnCl_4$.

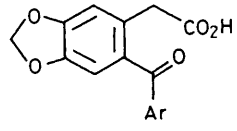
Methyl epipodophyllate (**14**) was readily epimerised at C-4 by heating in HCl–H_2O–THF to give methyl podophyllate (63%). The latter was lactonised to podophyllotoxin (**1**) (*ca.* 75%) using our $ZnCl_2$–THF–molecular sieves procedure.



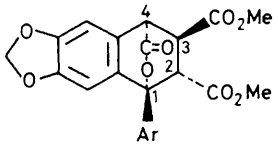
(**1**) R^1 = OH, R^2 = H, R^3 = Me
(**2**) R^1 = H, R^2 = OH, R^3 = Me
(**3**) R^1 = H, R^2 = β-D-4,6-*O*-ethylideneglucose, R^3 = H
(**4**) R^1 = H, R^2 = β-D-4,6-*O*-thienylideneglucose, R^3 = H



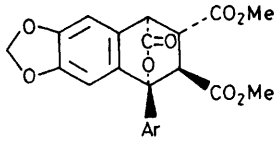
(**5**) R^1 = R^2 = R^3 = H
(**6**) R^1 = R^2 = H, R^3 = OMe
(**7**) R^1 = 3,4,5-trimethoxyphenyl; R^2,R^3 = OCH_2O
(**9**) R^1 = Ph, R^2 = R^3 = H



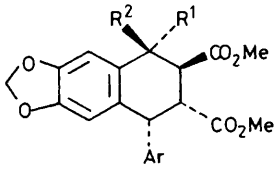
(**8**)



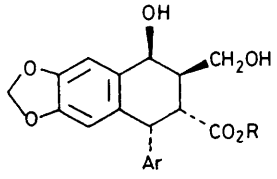
(**10**)



(**11**)



(**12**) R^1 = CO_2H, R^2 = H
(**13**) R^1 = H, R^2 = OAc



(**14**) R = Me
(**15**) R = H

Ar = 3,4,5-trimethoxyphenyl

Thus both podophyllotoxin and epipodophyllotoxin are readily prepared from the fumarate adduct (**10**) of the pyrone (**7**). The direct lactonisation of methyl podophyllate and its C-4 epimer considerably simplify existing syntheses of podophyllum lignans.

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References

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