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A concise stereocontrolled formal total synthesis of (±)-podophyllotoxin using sulfoxide chemistry†

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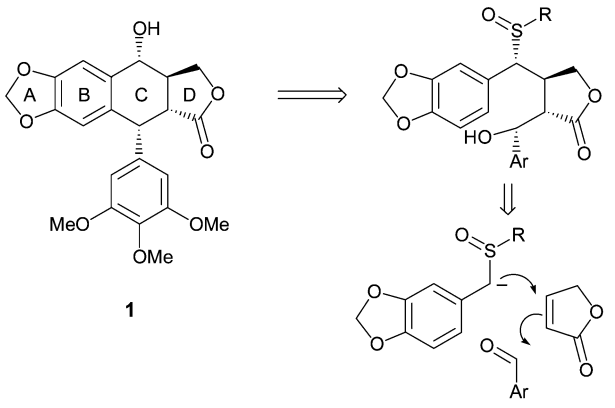
A short stereoselective formal total synthesis of (±)-podophyllotoxin has been carried out from a sulfoxide, using a one-pot tandem conjugate addition/aldol/electrophilic aromatic substitution reaction to form a tetralin, which was converted into picropodophyllin in two steps.

The natural product podophyllotoxin **1** possesses significant antitumour activity, and is in clinical use as an antiviral agent.[1] However, its most important use is as the precursor for the anticancer agents etoposide, etopophos, and teniposide.[1] Such is the success of these drugs that the wild plant populations from which podophyllotoxin is harvested are declining,[2] and there is much interest in exploring alternative sources. Chemical synthesis is one option, but although several total syntheses have been reported,[3] and new approaches continue to appear,[4] there is still a need for more efficient routes.

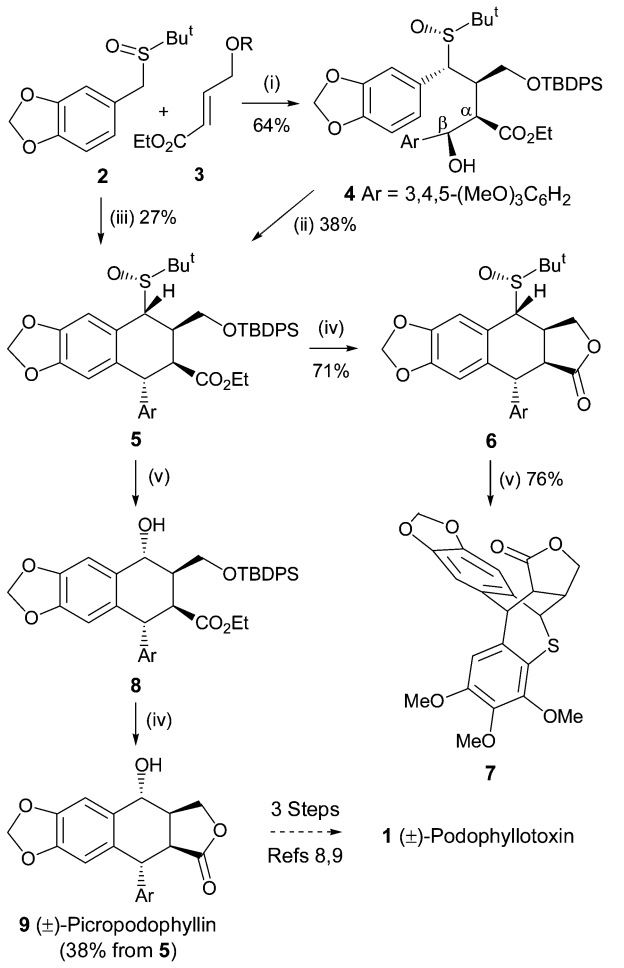
Synthetic strategies involving conjugate addition of acyl anion equivalents to butenolides, followed by aldol condensation, and tetralin formation provide particularly flexible and concise routes to podophyllotoxin and analogues.[3] The use of a sulfoxide-stabilised anion as the nucleophile in the conjugate addition was attractive because of the potential to use an enantiomerically pure sulfoxide to carry out an asymmetric synthesis (Scheme 1). However, although excellent asymmetric induction can indeed be obtained in conjugate additions of sulfoxide-stabilised anions,[5] we and others found that cyclic electrophiles could not be used.[5,6] The report of an exceptionally short asymmetric synthesis of podophyllotoxin, that relied on conjugate addition of a sulfoxide to butenolide,[7] ran counter to these observations. We attempted to repeat the published procedure, but did not obtain the reported addition product. We therefore proceeded with an alternative route that utilised an acyclic unsaturated ester as the precursor for the D ring of podophyllotoxin, and now report the results of the first phase in the development of this route, which culminated in a particularly short synthesis of (±)-picropodophyllin **9**, a known precursor for podophyllotoxin.[8,9]



Scheme 1

Addition of racemic *tert*-butyl sulfoxide **2** to ethyl γ-(*t*-butyldiphenylsilyloxy)crotonate **3**,‡ and addition of 3,4,5-trimethoxybenzaldehyde to the intermediate enolate, afforded diastereomerically pure adduct **4** in 64% yield (Scheme 2), along with a second diastereomer (4%) and some untrapped conjugate adduct. The relative stereochemistry of the four new centres formed in this step was assigned on the basis of earlier results,[5] and the NMR data for the carbinol proton (δ 4.88 ppm, $J_{\alpha\beta}$ 3.7 Hz).[10] The *syn*/*anti* diastereoselectivity of the aldol reaction was higher than found in related systems,[3] indicating that some remote asymmetric induction enhanced the usually weak *syn* selectivity.

Following the precedent of Vandewalle,[11] it was found that tosylation of the aldol product **4** resulted in spontaneous cyclisation below room temperature to give the tetralin **5** in 38% yield.§ Moreover, *in situ* tosylation of the alkoxide formed by the conjugate addition/aldol sequence, followed by warming to room



Scheme 2 *Reagents and conditions*: (i) LDA, THF, −78 °C; **3**; 3,4,5-trimethoxybenzaldehyde; (ii) LDA, THF, −78 °C; tosyl chloride, −78 °C to rt; (iii) LDA, THF, −78 °C; ethyl γ-(*t*-butyldiphenylsilyloxy)-crotonate; 3,4,5-trimethoxybenzaldehyde; tosyl chloride, −78 °C to rt; (iv) TBAF, THF, rt; (v) Tf_2O, collidine, CH_2Cl_2, −78 to 0 °C; H_2O.

† Electronic supplementary information (ESI) available: experimental details for the preparation of compounds **2**, **4**, **5**, **6**, **7**, **8**, **9**, and **12**. See http://www.rsc.org/suppdata/cc/b3/b312245j/

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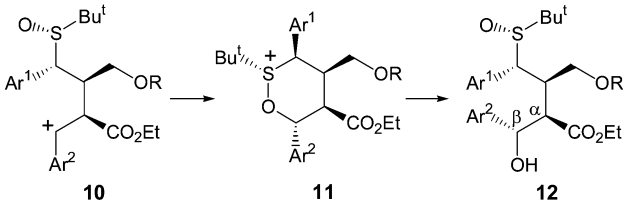
temperature, resulted in a one-pot conversion of the sulfoxide **2** into the tetralin **5**!

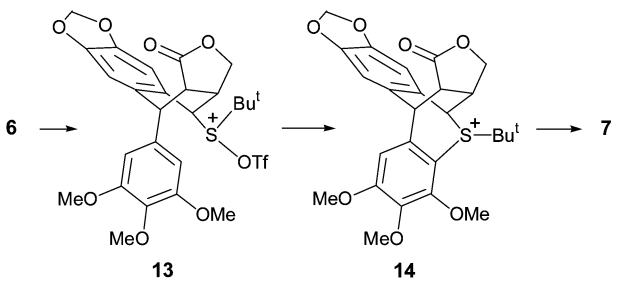
The yield of tetralin was low (27%), mainly because of competing formation of a second product in similar amounts. The side product was unstable and it could not be characterised, but it clearly was a diastereoisomer of the aldol product **4** and the $J_{\alpha\beta}$ value of 7.0 Hz indicated that it was the *anti* aldol **12** (Scheme 3). We suggest that the benzylic carbocation **10**, formed from the tosylate, undergoes two competing cyclisations, one involving nucleophilic attack by the arene to give the desired tetralin **5**, and the second involving attack by the sulfoxide to give a sulfonium salt **11**.[12,13] Assuming that the latter cyclisation occurred with the same sense of diastereoselectivity as the tetralin formation, hydrolysis of the sulfonium salt with inversion at the benzylic centre would then account for the formation of side product **12**. Use of other sulfonylating agents, solvents and conditions did not improve the yield of the tetralin **5**. Although further work clearly is required, the one-pot formation of the tetralin **5** with complete control of diastereoselectivity is a notable development.

Treatment of the silyloxy ester **5** with TBAF gave the lactone **6** in 71% yield (Scheme 2). Lactonisation appears to be greatly facilitated by the *cis* relationship of the alcohol and ester groups in the tetralin. Conversion of the C–S bond of the benzylic sulfoxide into a C–O bond was the only step remaining. Reaction of sulfoxide **6** with triflic anhydride and collidine, according to the method of Berkowitz,[14] did effect activation of the sulfoxide, but the product was the cyclic sulfide **7** rather than picropodophyllin. Presumably, the trifloxy sulfonium salt **13** underwent nucleophilic substitution by the activated arene, which was held in close proximity in the relatively rigid *cis* lactone structure, to give sulfonium salt **14**, and loss of isobutene then gave sulfide **7** (Scheme 4).

This unwanted cyclisation was avoided by changing the order of the steps (Scheme 2). Treatment of the unlactonised sulfoxide **5** with triflic anhydride, followed by water, gave the desired benzylic alcohol **8**. The potential to replace the sulfinyl group with nucleophiles to provide diverse podophyllotoxin analogues is an advantageous feature of this route.[14] Desilylation of the crude product **8** with TBAF was accompanied by spontaneous lactonisation to afford (±)-picropodophyllin **9** in 38% yield from **5**, completing the formal total synthesis of (±)-podophyllotoxin. The spectroscopic data for our product were identical to those reported for picropodophyllin.[9]



Scheme 3



Scheme 4

In conclusion, we have carried out a novel and exceptionally short synthesis of (±)-picropodophyllin. The high level of asymmetric induction by the sulfoxide, and the facile replacement of the sulfinyl group, are key features of this highly convergent and flexible route. Use of a γ-alkoxycrotonate rather than a butenolide required an extra step, *i.e.* the deprotection lactonisation. However, it provided the picropodophyllin stereochemistry directly, so that only one epimerisation is required for conversion into (±)-podophyllotoxin. Work on optimisation of the tetralin formation, and on use of an enantiopure sulfoxide,[15] is underway.

Notes and references

‡ Prepared by Wittig reaction of glycolaldehyde dimer and silylation. Use of a bulky protecting group is essential to the success of the aldol reaction, presumably because it prevents intramolecular coordination of the oxygen to the enolate counterion.

§ The *t*-butyldimethylsilyl analogue of silyloxy ester **4** was easily converted into the corresponding lactone, but attempts to form the tetralin subsequent to lactonisation were unsuccessful.

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