An efficient semisynthesis of 7-deoxypaclitaxel from taxine

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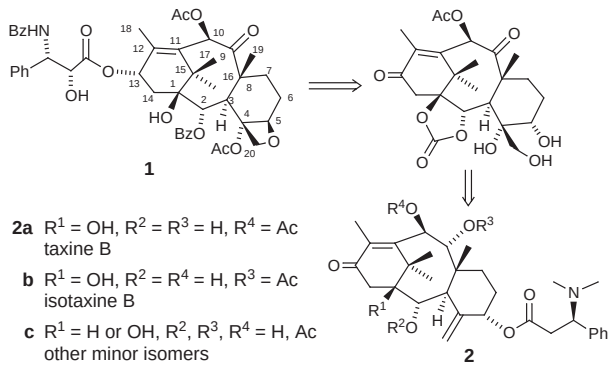
Highly cytotoxic 7-deoxypaclitaxel analogues are obtained by a semisynthesis starting from taxine—the most abundant naturally occurring taxane diterpene fraction.

Owing to its great potential in the successful treatment of many types of cancer, unusual mode of antimitotic action, and complex molecular architecture, paclitaxel has attracted enormous interest from the scientific community.[1] Paclitaxel is currently produced *via* extraction from the bark of the Pacific yew, *Taxus brevifolia*, or by semisynthesis from 10-deacetylbaccatin III, which is in turn isolated, most notably, from the leaves of the European yew, *Taxus baccata*.[2] However, 10-deacetylbaccatin III is not the most abundant secondary metabolite of the yew tree: its variable content in the needles of *Taxus baccata* ranges from 0.05 to 1 g per kg of leaves.[3] In contrast, a mixture of alkaloids collectively referred to as 'Taxine' **2** can be obtained by a simple extraction procedure in yields of 7–12 g kg^{-1},[4] the two major constituents of this fraction (*ca.* 35%) being taxine B **2a** and isotaxine B **2b**;[5] therefore, the development of the procedure that would allow for the efficient use of this starting material for the preparation of biologically active paclitaxel analogues would be of considerable interest.

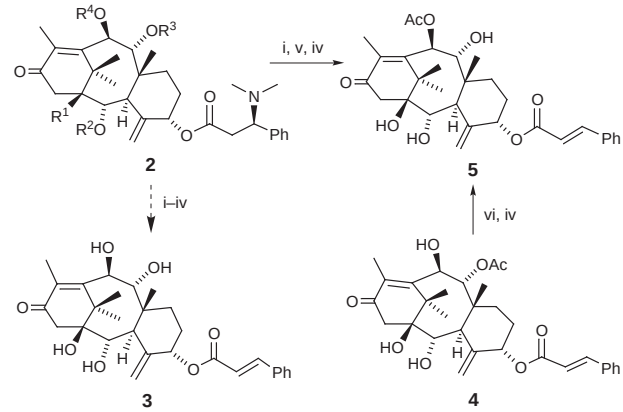
Earlier reports on 7-deoxypaclitaxel **1**, obtained by radical deoxygenation of paclitaxel, or baccatin derivative, showed this compound to be of comparable, or even superior, cytotoxic activity with respect to paclitaxel,[6] and, given the structural congruence with taxine B, indicated it as a semisynthetic target. The possibility of such a synthetic transformation was investigated by several groups.[7] As the preparative separation of taxine alkaloids is difficult, the crude taxine mixture was hydrolysed in order to obtain a well-defined starting material, *i.e.* tetraol **3**. However, the differentiation between hydroxy groups in tetraol **3** required extensive use of protective groups, leading to long synthetic sequences, and lowering considerably the overall yield.[8] We endeavoured to develop an efficient procedure for the conversion of taxine into 7-deoxypaclitaxel derivatives (Scheme 1). The accomplishment of this task was expected not only to give access to large amounts of 7-deoxypaclitaxel analogues, but also to provide additional information on the reactivity of the taxane system, as well as derivatives suitable for further SAR studies.



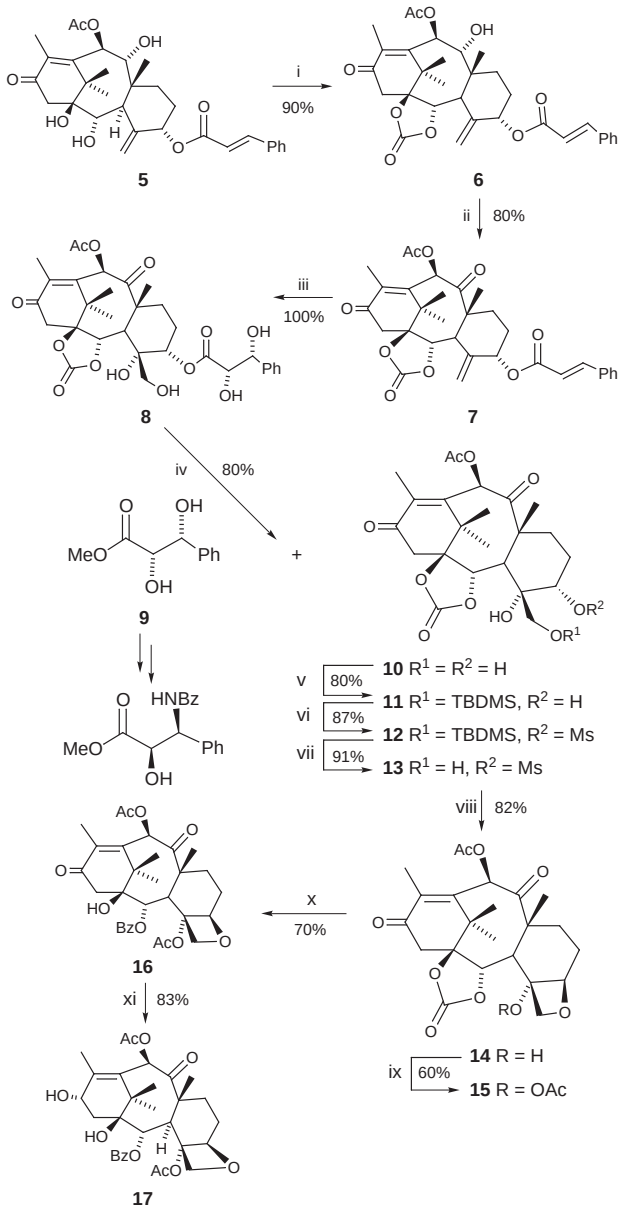
Scheme 1

We first re-examined the possibility of exploiting the favourable arrangement of functional groups in the major constituent of taxine, *i.e.* taxine B **2a** (Scheme 2). Quaternization of the crude taxine,[7a] followed by DBU induced elimination under anhydrous conditions, afforded a mixture of 9- and 10-acetyl-5-cinnamoyltaxicine I (**4** and **5**), which could be separated by a flash chromatography on a SiO_2 column, and were isolated in yields of 1 and 1.7 g kg^{-1} of needles, respectively. The former could be isomerised into the required 10-acetyl derivative **5** by treatment with methanolic KOAc (43% yield at 70% conversion, without optimisation), to afford a total of 2 g of 10-acetyl-5-cinnamoyltaxicine I **5** per 1 kg of dry leaves.

With the suitable starting compound **5** in hand, the synthesis of 7-deoxybaccatin III proceeded as displayed in Scheme 3. Treatment of **5** with phosgene, followed by hydrolytic work-up, furnished the cyclic carbonate **6** (90%), which was further oxidised to diketone **7** (Dess–Martin periodinane, 80%), thus establishing the final functionalization of the 'upper' part of the molecule. The elaboration of the oxetane ring was envisaged to proceed *via* triol **10**.[7a] For that purpose a method for selective removal of the cinnamoyl chain was needed, as the simultaneous cleavage of the C-10 acetate would require additional protective steps. To achieve this, allylic cinnamate **7** was oxidised with OsO_4/NMO, as it was anticipated that intramolecular hydrogen bonding in **8** should activate the dihydroxyphenylpropionate ester towards hydrolysis under very mild conditions. Although some concern existed about the stereochemical outcome of the osmylation, to our pleasure the reaction proceeded in quantitative yield, and with complete stereoselectivity. This structural change brought about the expected modification in the reactivity profile of **8**, as indicated by its proclivity towards spontaneous migration of the ester side chain from O-5 to O-20 on standing in solution at room temperature; treatment of **8** with K_2CO_3 or $NaHCO_3$ in MeOH–H_2O at 0 °C induced very rapid hydrolysis of the dihydroxypropanoate ester, but the hydrolysis of the C-10 acetate also



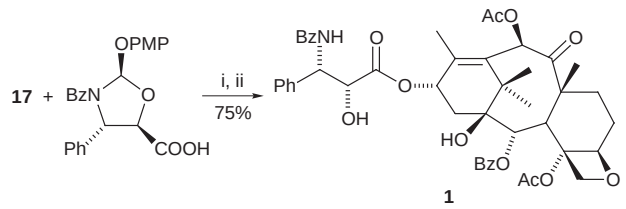
Scheme 2 *Reagents and conditions*: i, MeI, THF, room temp., 5 h; ii, K_2CO_3, H_2O, EtOH, room temp., 3 h; iii, NaOMe, MeOH, 0 °C, 16 h; iv, column chromatography on SiO_2; v, DBU, $CHCl_3$, room temp., 1.5 h; vi, 10% KOAc in MeOH, room temp., 3 h



Scheme 3 *Reagents and conditions*: i, $COCl_2$ (20 equiv.), CH_2Cl_2, 0 °C, 20 min; then Et_2O, H_2O, imidazole (cat.), 0 °C, 20 min; ii, Dess–Martin periodinane (2 equiv.), CH_2Cl_2, TFA (cat.), room temp., 12 h; iii, OsO_4 (cat.), NMO, THF, H_2O, room temp., 4 h; iv, 10% KOAc in MeOH, reflux, 30 min; v, TBDMSCl, imidazole, DMF, room temp., 3 h; vi, MsCl, Py, 0 °C to room temp., 24 h; vii, 7% HF in MeCN, room temp., 7 h; viii, Pr^i_2NEt (7 equiv.), toluene, reflux, 30 h; ix, Ac_2O (7 equiv.), DMAP (14 equiv.), CH_2Cl_2, room temp., 4 h; x, PhLi (10 equiv.), THF, −78 °C, 0.5 h; then Ac_2O, DMAP, CH_2Cl_2, room temp., 1 h; xi, $NaBH_4$ (excess), MeOH, room temp., 3 h

occurred under these conditions. Eventually, refluxing **8** with methanolic KOAc afforded the desired triol **10** in 80% yield. Optically pure (*2S*,*3R*)-(-)-methyl 2,3-dihydroxy-3-phenylpropanoate **9** was isolated as the side product of this reaction, and further converted into the paclitaxel side chain according to a previously published procedure.[9] The transformation of the key intermediate **10** into 7-deoxybaccatin III **17** was accomplished by applying a modified methodology previously developed in total syntheses of paclitaxel.[1,7a] In this way, starting from cinnamoyltaxicine I **5**, 7-deoxybaccatin III was obtained in 11.5% overall yield (unoptimized).[10]

7-Deoxybaccatin is a direct precursor of paclitaxel analogues: esterification of **17** with acid **18**,[11] followed by acidic hydrolysis (TsOH in MeOH) afforded 7-deoxypaclitaxel **1** in 75% yield (Scheme 4).[12]



Scheme 4 *Reagents and conditions*: i, DCC, DMAP (cat.), room temp., 3 h; ii, 5% TsOH in MeOH, room temp., 1 h

The described chemistry offers an efficient pathway for the preparation of new paclitaxel derivatives, and points to the naturally abundant taxane diterpene fraction—taxine—as a valuable starting material for further semisynthetic studies.

Notes and References

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10 Spectral data identical to those reported in ref. 7(*d*).

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