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Paclitaxel synthetic studies. A Diels–Alder approach to the A-ring†

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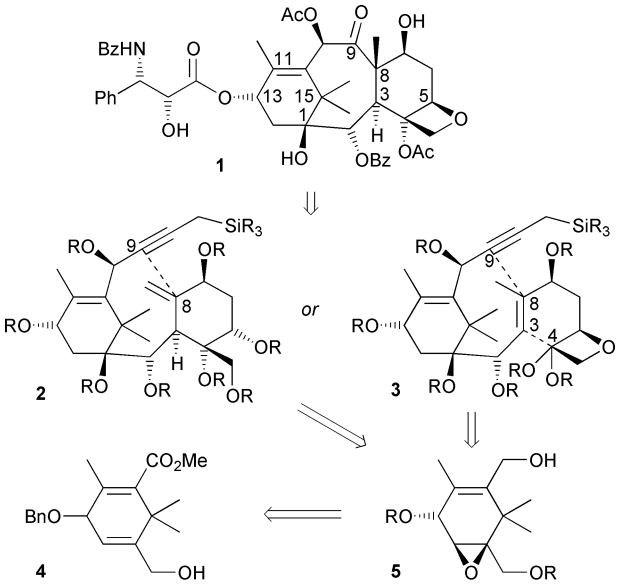
Highly substituted cyclohexenes corresponding to the A-ring of the anti-cancer diterpene natural product paclitaxel are synthesised using a Diels–Alder reaction and decarboxylative elimination as the key steps.

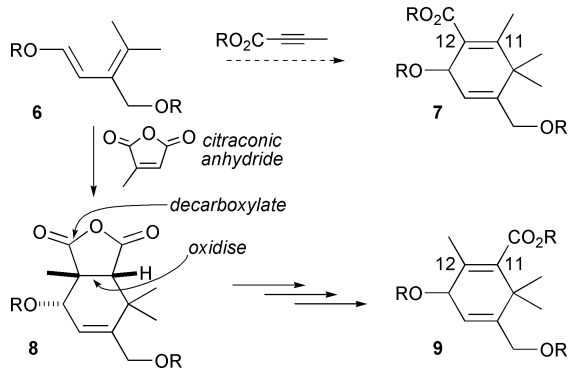
The paclitaxel family of molecules, exemplified by the parent paclitaxel (Taxol®) **1**[1] has commanded the attention of a significant number of organic chemistry research teams worldwide.[2] The strategies we are pursuing for the assembly of paclitaxel involve late-stage formation of the eight-membered B-ring by the joining together of C-9 and C-8 using radical- or carbocation-mediated cyclisation of a substrate **2**; in one of the approaches we intend to form the C-ring in the same step using a Lewis acid-induced carbocation-mediated cascade process starting from **3** in which the C-3–C-4 bond is formed as well. Both these sequences require a pre-formed A-ring fragment such as **5**, and this Communication reports the synthesis of key precursor **4** (Scheme 1).

In our synthetic plan for **4** we were keen to incorporate the required C-13 oxygenation directly using the Diels–Alder reaction rather than introducing it later by oxidation of C-13.[2a] This choice posed a strategic problem concerning Diels–Alder regiochemistry, in that [4+2] cycloaddition of **6** and a simple alkyne-containing dienophile such as a but-2-ynoate ester was likely to give a cycloadduct **7** bearing a C-12 rather than a C-11 ester substituent. Therefore it was decided to use citraconic anhydride as the dienophile,[3] since it was anticipated that the regiochemical orientation of the Diels–Alder reaction would be controlled by steric repulsion between the fully-substituted



Scheme 1

† Experimental details for **4**, **13**, **16**, **17**, **19**–**21** are available as supplementary data. For direct electronic access see http://www.rsc.org/suppdata/cc/b0/b005533f/

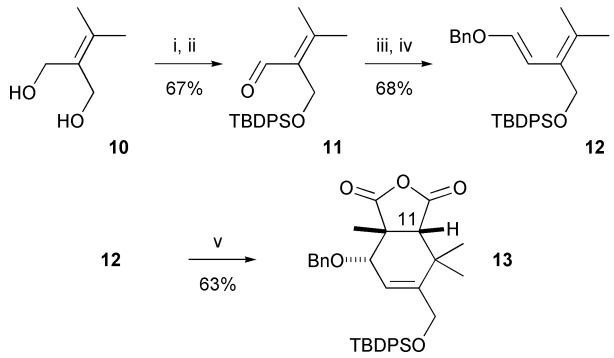


Scheme 2

diene and dienophile termini; subsequent selective decarboxylation and oxidation of adduct **8** would deliver the required C-11–C-12 unsaturation, as in **9** (Scheme 2).

The required diene was synthesised using the Julia procedure for the olefination step.‡ Thus, mono-protection of diol **10**[4] followed by oxidation using TPAP–NMO[5] gave enal **11**. Combination of **11** with the lithio-anion of benzyloxy(phenylsulfonyl)methane[6] and *in situ* trapping with benzoyl chloride gave a mixture of esters, which was exposed to samarium(II) iodide[7] to provide the required differentially protected diene **12**. Diels–Alder reaction of **12** with citraconic anhydride gave cycloadduct **13** as a single regio- and stereoisomer in 63% yield based on **12** (Scheme 3). The *endo* stereochemistry of **13** was inferred from the analogous reaction of **12** with maleic anhydride,[3] which had given a crystalline product amenable to X-ray structure determination.

With Diels–Alder adduct **13** in hand it was necessary to differentiate between the anhydride carbonyl groups. Treatment of **13** with dimethylamine gave an unstable§ half-amide as a



Scheme 3 *Reagents and conditions*: i, NaH (1.01 eq.), THF (0.07 M), rt, 1 h, then TBDPSCl (1 eq.), rt, 15 h; ii, TPAP (2.4 mol%), NMO (1.6 eq.), powdered 4 Å mol sieves, CH_2Cl_2 (0.5 M), rt, 1 h; iii, $BnOCH_2SO_2Ph$ (1 eq.), LDA (1 eq.), THF (0.1 M), −78 °C, 10 min, then add **11**, −78 °C, 10 min, then add BzCl (1 eq.), −78 °C→rt, 45 min; iv, SmI_2 (5 eq.), DMPU (15 eq.), THF, (0.1 M), rt, 1 h; v, citraconic anhydride (2 eq.), PhMe (3.3 M), 150 °C, 24 h.

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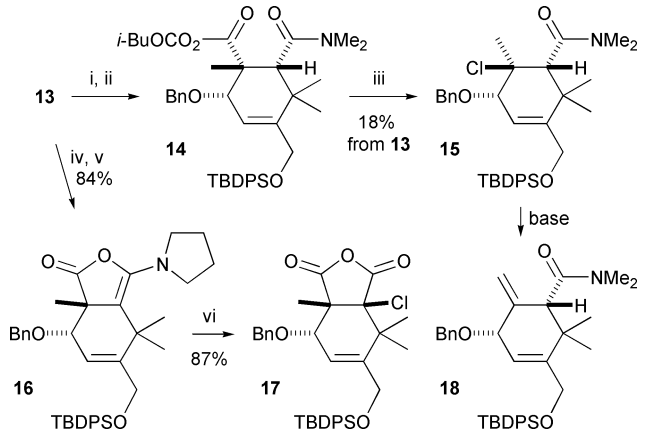
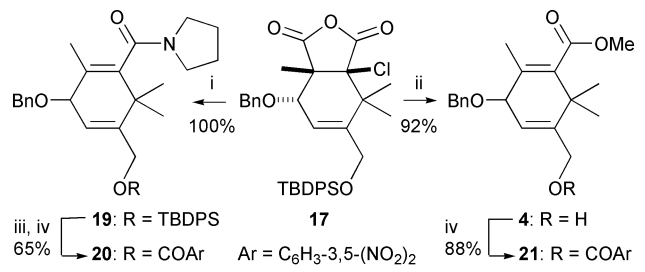


Scheme 4 *Reagents and conditions*: i, Me_2NH (5 eq.), THF (0.5 M), rt, 16 h; ii, *i*-BuOCOCl (1.1 eq.), Et_3N (1.1 eq.), CH_2Cl_2 (0.1 M), −15 °C→rt; iii, 2-mercaptopyridine *N*-oxide (1 eq.), Et_3N (1.1 eq.), CCl_3 (0.03 M), 80 °C, 2 h; iv, pyrrolidine (5 eq.), THF (0.5 M), rt, 2 h; v, *i*-BuOCOCl (1.1 eq.), Et_3N (2.5 eq.), CH_2Cl_2 (0.2 M), rt, 1 h; vi, NCS (1 eq.), Et_3N (2 eq.), H_2O (5 eq.), THF (0.1 M), rt, 2 h.

single regioisomer,¶ which was converted into the mixed anhydride **14** by addition of isobutyl chloroformate. Treatment of **14** with *N*–hydroxy-2-thiopyridone in CCl_4 under reflux[8] gave in low yield the product **15** of decarboxylation–chlorination. The stereochemistry of **15** was presumed on the basis of expected attack by CCl_4 on the less hindered face of the intermediate radical.‖ All attempts to effect base-mediated elimination of the elements of HCl from **15** resulted in the formation of the β,γ-unsaturated isomer **18**. In a modified approach, treatment of cycloadduct **13** with pyrrolidine gave a half-amide adduct which was considerably more stable than the dimethylamine-derived analogue. Surprisingly, subsequent exposure of this adduct to the mixed anhydride-forming conditions resulted in cyclodehydration, giving the cyclic *O*-acylketaminal **16** in virtually quantitative yield.** The desired oxidation at C-11 was now effected by treatment of **16** with NCS–aqueous THF, giving α-chloro anhydride **17** in high yield (Scheme 4). The difference in behaviour of the dimethylamino and pyrrolidino analogues under the carbonic anhydride-forming conditions is striking; the apparent greater nucleophilicity of the amide oxygen in the latter is consistent with greater delocalisation of the amide nitrogen lone pair into the carbonyl group, which in turn inhibits the reverse reaction during ring-opening of **13** with the secondary amine nucleophile.

The final part of the synthesis involved decarboxylation and introduction of the double bond, and again this depended on initial regioselective ring-opening to give a β-chloro carboxylic acid. In the event, treatment of **17** with a large excess of pyrrolidine gave amide **19** as a single regioisomer (Scheme 5). Interestingly, **19** existed in $CDCl_3$ and d_6-DMSO solutions as mixtures of rotamers. In similar fashion, treatment of **17** with benzyltrimethylammonium methoxide in large excess gave methyl ester **4**. Mechanistically, the presumed initial ring-opened half-amide and -ester either might form β-lactone intermediates which subsequently lose CO_2,[9] or might spontaneously undergo β-elimination with concerted loss of CO_2 and chloride ion.[10] Amide **19** was converted in high yield by desilylation and esterification into the 3,5-dinitrobenzoate **20**, which yielded crystals suitable for X-ray diffraction analysis. Similar treatment of **4** gave the crystalline ester **21**.††



Scheme 5 *Reagents and conditions*: i, pyrrolidine (50 eq.), DMSO–DMPU (5:3; 0.14 M), rt , 2 h; ii, $BnMe_3N^+OMe^-$ (50 eq.), MeCN–DMPU (0.14 M), rt, 27 h; iii, TBAF (1.1 eq.), THF (0.2 M), rt, 15 min; iv, ArCOCl (1.1 eq.), Et_3N (1.5 eq.), DMAP (0.2 eq.), CH_2Cl_2 (0.2 M), rt.

In summary, we have demonstrated that a highly substituted cyclohexa-1,4-diene may be accessed using a sequential Diels–Alder–decarboxylative olefination approach to introduce the C-11–C-12 unsaturation present in the paclitaxel A-ring. Ongoing studies in our laboratory seek to identify a direct [4+2] cycloaddition entry to **17**, and to develop ways of making the cycloaddition enantioselective. The results of these and related studies will be reported in due course.

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Notes and references

‡ All yields reported herein refer to isolated, pure materials which had ^1H and ^{13}C NMR, IR and high-resolution MS characteristics in accord with the proposed structures.

§ The half-amide had a half-life in $CDCl_3$ of approximately 14 h.

¶ Treatment of this half-amide with ethyl chloroformate gave a mixed anhydride which was reduced using sodium borohydride to give a γ-lactone. The appearance of both lactone -CH_2- protons as simple doublets confirmed the absence of a vicinal proton, and therefore the complete regioselectivity of ring-opening of **13**.

‖ This assumption was later confirmed by single-crystal X-ray diffraction analysis of the product of one-pot epoxidation–debenzylation mediated by dimethyldioxirane.

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