New Strategy for the Synthesis of the Taxane Diterpenes: Formation of the *A*-Ring *via* Nitro-aldol and Aldol Reactions

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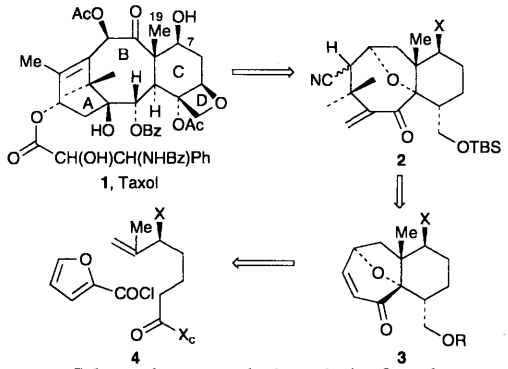
The nitro-aldehyde **6α/β** readily cyclizes to form the A-ring of taxol in quantitative yield; further elaboration of the α,β-unsaturated nitro compound **12** gave the enone **16** and the 13α alcohol **17** respectively.

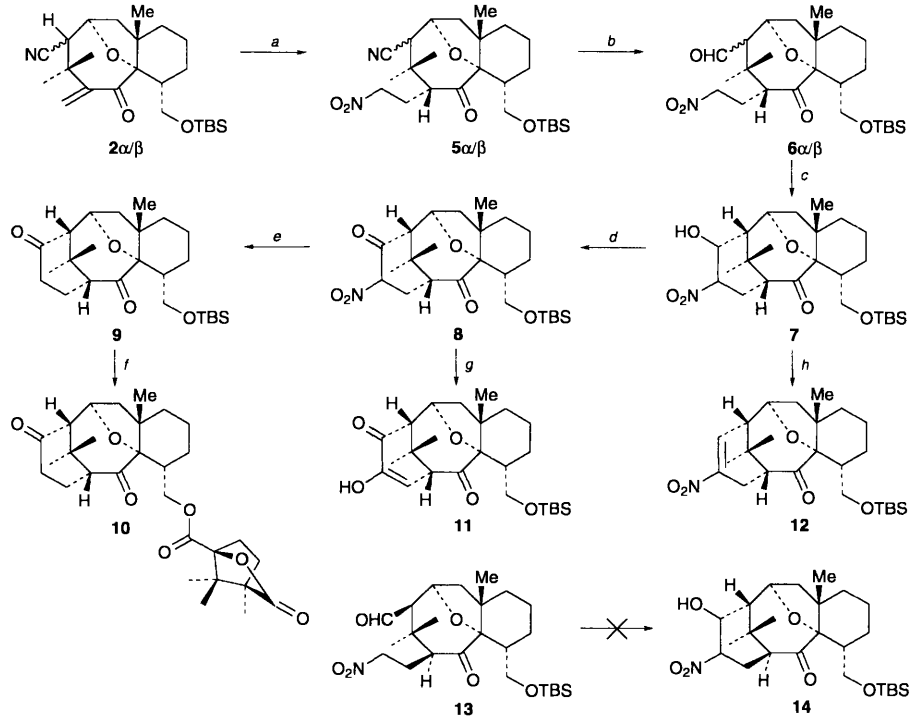
As potential precursors to the antitumour agent taxol **1**, and taxane analogues, we have converted the heptenoic acid derivative **4** (X_c = chiral auxiliary, X = OTBS or H) and furoyl chloride into the bicyclo[5.4.0]undecenone **3** (X = OTBS and X = H), which has been transformed into the *BC*-ring compound **2**, Scheme 1.[1] All that remains to complete the taxol skeleton is to construct the *A*-ring. In this paper is described a nitro-aldol (Henry reaction) and aldol approach to this problem.[2]

The exomethylene ketones **2α/β** were treated with $MeNO_2$–DBU–CH_2Cl_2 to give the conjugate addition adducts **5α/β** (85%) as a 2:1 mixture at C-11 (–CN), and a single stereoisomer at C-1. Scheme 2.† The epimeric nitriles **5α/β** were readily separated, and each reduced with DIBAL–CH_2Cl_2 at −78 °C to give the nitroaldehydes **6α** and **6β** (90%). Merely stirring a solution of **6α** in CH_2Cl_2 at 25 °C with triethylamine gave the nitro-alcohol **7** (100%) as a single (unknown) stereoisomer. The **6β**-isomer did not cyclize under these conditions (no epimerization at C-11). However, treatment of **6α/β** with tetramethylguanidine (cat.)–CH_2Cl_2 at 25 °C resulted in C-11 epimerization and cyclization to give **7** (90%).[3] In this way we can use both C-11 epimers. Oxidation of the nitro-alcohol (Dess–Martin reagent) gave the nitro-ketone **8**, which was exposed to Bu^n_3SnH/AIBN (cat.) to give the 12-oxo-taxane **9**.[4] To confirm the structure and absolute stereochemistry of **9** unambiguously, the C-20 protecting group was removed, and the camphanate ester derivative **10** prepared. Fig. 1 shows a Chem 3D representation of **10** from the X-ray coordinates. It should be noted that the C-1(β) and C-11(β) nitro-aldehyde diastereoisomer **13** does not undergo the nitro-aldol reaction, under the above conditions, to give **14** (*A*-ring on the β-face). Consequently, under thermodynamic equilibration reaction conditions, only the correct (natural) *A*-ring is formed.‡

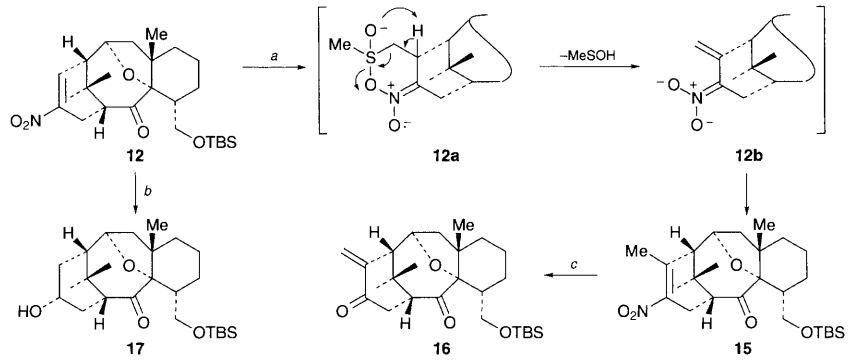
The nitro-ketone **8** undergoes an oxidative Nef-type reaction (MeONa–MeOH followed by ozone and reduction)[5] to give the α-diketone **11** which exists entirely in the depicted enolic tautomer.[6] The nitro-alcohol **7** need not be isolated, but can be directly dehydrated ($MeSO_2Cl$–DBU) to give **12**. At this stage we discovered a new and extremely useful transformation. Treatment of the α,β-unsaturated nitro compound **12** with



Scheme 1 Retrosynthetic analysis of taxol



Scheme 2 *Reagents and conditions*: *a*, $MeNO_2$ (10 equiv.), DBU (5.0 equiv.), CH_2CL_2, −15 °C (85%, α:β, 2:1); *b*, DIBAL, CH_2Cl_2, −78 °C (90%); *c*, tetramethylguanidine (10%), CH_2Cl_2, 25 °C (90%); *d*, Dess–Martin oxidation, CH_2Cl_2 (79%); *e*, Bu_3SnH (5 equiv.), AIBN, C_6H_6, reflux (60%); *f*, i, HF–pyridine, THF; ii (−)-camphanic acid chloride–Et_3N–DMAP, CH_2Cl_2 (96%); *g*, i, MeONa, MeOH; ii, O_3; iii, Me_2S (50%); *h*, i, $MeSO_2Cl$, 0 °C; ii, DBU–CH_2Cl_2, 25 °C (64% from **5**)



Scheme 3 *Reagents and conditions*: *a*, $LiCH_2S(O)Me$, THF, −78 °C (45%); *b*, i, $NaBH_4$; ii, H_2O_2 (60%); iii, DIBAL, CH_2Cl_2, −78 °C (91%); *c*, $TiCl_3$–Bu^tOK, Bu^tOH–THF

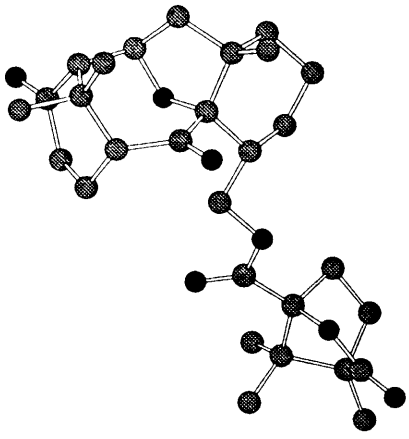
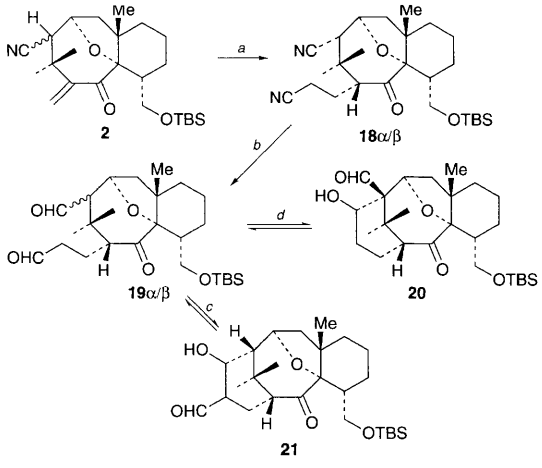


Fig. 1 Chem 3D of **10** from X-ray coordinates



Scheme 4 *Reagents and conditions*: *a*, $LiCH_2CN$, THF, −78 °C (71%; α : β 2 : 1); *b*, DIBAL–CH_2Cl_2, −78 °C; *c*, tetramethylguanidine, CH_2Cl_2–MeOH, 25 °C, 24 h (53% from **18**); *d*, neutral alumina column

dimsyllithium [$MeS(O)CH_2Li$, THF] gave, after work-up (AcOH), the new α,β-unsaturated nitro compound **15**. Presumably, this reaction proceeds through conjugate addition to give **12a** (or a non-cyclic equivalent), elimination of MeSOH to give the nitronate **12b**, and tautomerization to **15**, Scheme 3.[7]

The overall transformation converts **12** into **15** maintaining the same oxidation level. This is ideally suited for subsequent elaboration of the *A*-ring, since **15** undergoes the Nef reaction ($TiCl_3$) to give **16**. Treatment of **12** with $NaBH_4$ followed by a Nef-type reaction (H_2O_2), and DIBAL-H reduction gave the required C-13 alcohol **17** (84%) with the correct (α) stereochemistry. The stereochemistry of **17** was confirmed by single crystal X-ray analysis, and also showed that the C-13 hydroxy group forms an intramolecular hydrogen bond to the 3,10-oxido bridge.

We briefly examined the classical aldol reaction to form the taxol *A*-ring. Treatment of **2α/β** with $LiCH_2CN$ gave **18α/β** (2 : 1) which was reduced (DIBAL) to the dialdehyde **19α/β**. Purification of **19α** by chromatography over alumina resulted in cyclization to give **20**, whereas, exposure of **19α** or **19β** to $HN{=}C(NMe_2)_2$–CH_2Cl_2 resulted in the alternative aldol product **21**, Scheme 4.

These results show that the *A*-ring of the taxanes can be constructed under mild thermodynamic equilibration reaction conditions in excellent yield. Using the nitro-aldol approach the *A*-ring carbon atoms are derived from NaCN (C-12), $MeNO_2$ (C-13), CH_2O (C-14) and Me_2SO (C-18) respectively. Elaboration of the nitro-aldol adducts leads to the 13-oxo-taxane **16** and the 13α-hydroxy-taxane **17**.

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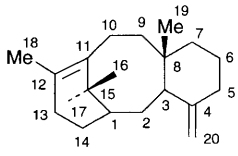
Footnotes

† 

Taxane numbering

‡ MM2 calculations indicate that the strain energy (SE) of the product resulting from closure of the *A*-ring on the top (β-) face is 4.5 SE units more strained than the observed product **6**.

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