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A Tandem Radical Macrocyclisation - Radical Transannulation Strategy to the Taxane Ring System

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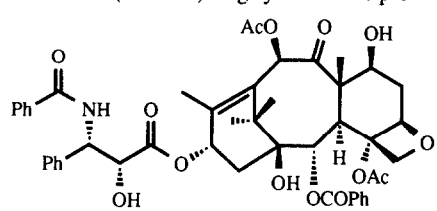
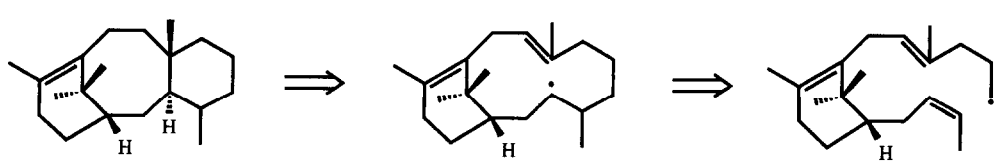
Abstract: *Treatment of the iodo-trienone (**8b**) with tri-n-butyltin hydride in the presence of AIBN is shown to produce the taxane ring system (**11**) by way of a tandem radical macrocyclisation - radical transannulation sequence, i.e. (**8b**) → (**9**) → (**11**) (cf. Scheme 1).*

Taxane alkaloids, and taxol (**1**) in particular, have rapidly established themselves as one of the most sought after families of natural products for the treatment of advanced leukaemia and cancers of the ovary and the breast.[1,2] Indeed, a recent article has reported that the National Cancer Institute has now made development of taxol an emergency priority.[3] Taxol (**1**) is obtained by extraction of the bark of the yew tree *Taxus brevifolia*.[4] A partial synthesis of the compound has also been achieved starting from the related taxane '10-deacetylbaccatin III' which can be extracted from the leaves of the European yew bush *Taxus baccata*.[5] Since these evergreens are slow growing, however, taxol is presently available only in very short supply from natural sources. This feature, together with the unusual and novel structure of taxol, have no doubt contributed greatly to what amounts to an avalanche of activity amongst synthetic organic chemists aimed at securing a viable *in vitro* route to the compound. Indeed, a plethora of ingenious synthetic designs have been described to access the basic and unique tricyclo[9.3.1.0]pentadecane ring system in the taxanes.[6] Nevertheless, only one report of a total synthesis of a taxane diterpene, *i.e.* taxasin, has been published at this time.[7] As a result of our interest in the development of cascade radical ring-forming reactions in target synthesis,[8] together with aspects of a biomimetic-type synthesis of the taxanes,[9] we have examined a new approach to the tricyclo[9.3.1.0]pentadecane ('taxane') ring system. The preliminary results of this approach,



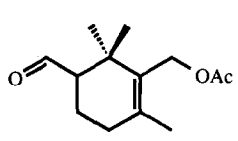
(**1**)



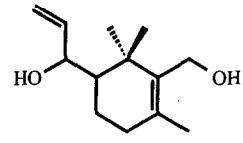
Scheme 1

which is based on a novel tandem radical macrocyclisation-radical transannulation strategy as depicted in Scheme 1, are described herein.

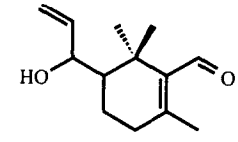
The radical precursor model compound (**8b**), incorporating two conjugated enone moieties built in to facilitate the tandem 12-*endo*, 8-*endo* cyclisation to (**11**),[10] was produced in five steps starting from the substituted cyclohexenealdehyde (**2**).[11] Thus, treatment of the aldehyde (**2**) with three equivalents of vinylmagnesium bromide first led to the allyl alcohol (**3**) (84%), which on selective oxidation using catalytic tetra(*n*-propyl)ammonium perruthenate[12] in the presence of *N*-methylmopholine oxide was then converted into the unstable hydroxy-aldehyde (**4**) in 51% yield.[13] When the aldehyde (**4**) was next treated with the vinyllithium species derived by tin-lithium exchange from the vinylstannane (**5**) (2.5 equivalents, -75°C) using butyllithium,[14] it was converted into the labile *bis*-allylic alcohol (**6**) (58%). The alcohol (**6**) was found to undergo rapid and quantitative cyclisation leading to the bridged bicyclic ether (**7**) on storage overnight, and hence it was oxidised immediately to the more stable trienedione (**8a**) (90%) using barium manganate.[15] Treatment of the bromide (**8a**) with sodium iodide in refluxing 2-butanone for 1h finally produced the radical precursor compound (**8b**).



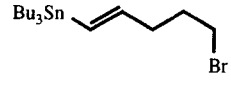
(**2**)



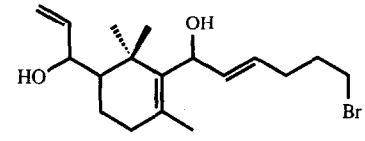
(**3**)



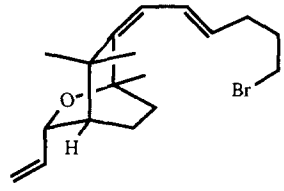
(**4**)



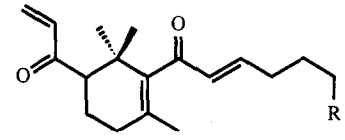
(**5**)



(**6**)

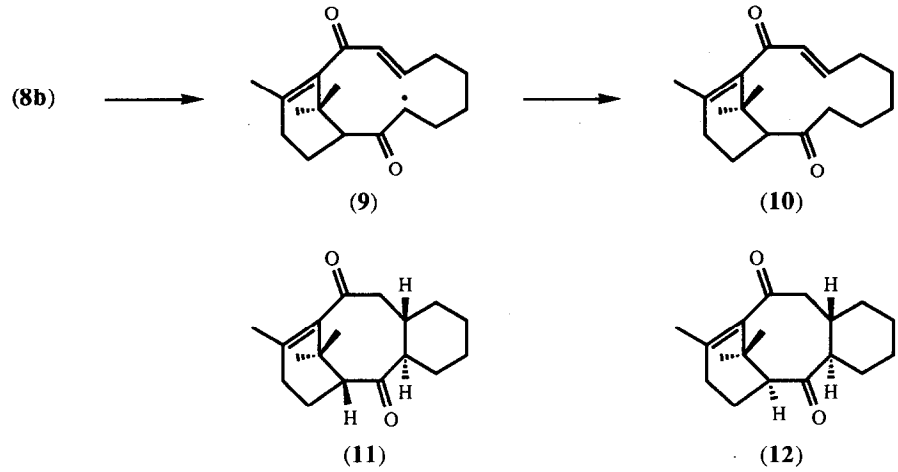


(**7**)

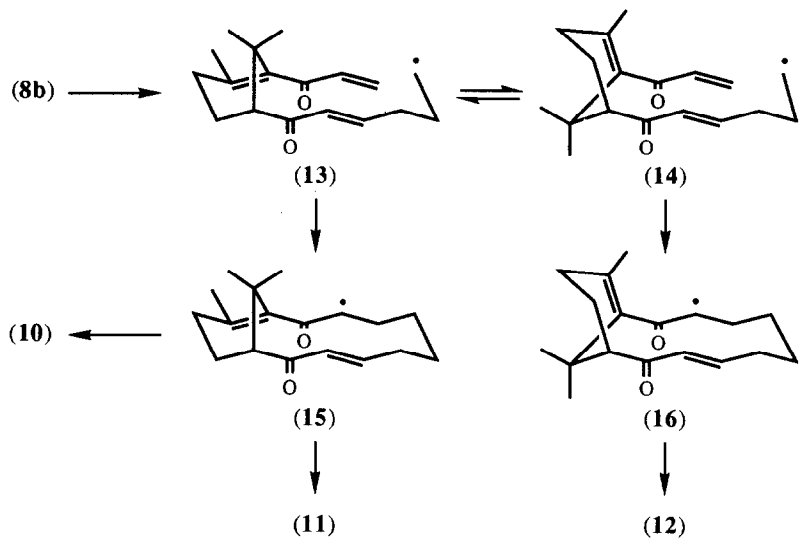


(**8**)
a R=Br; *b* R=I; *c* R=H

When a solution of the iodide (**8b**) in dry, degassed benzene was heated under reflux in the presence of tributyltin hydride and catalytic AIBN, it underwent the aforementioned tandem radical macrocyclisation-transannulation reaction (Scheme 1) and produced a 3:1 mixture of C-1 epimers of the tricyclo[9.3.1.0] pentadecanedione [(**11**) and (**12**) respectively] in approximately 25% yield. Chromatography produced a pure sample of the β-epimer (**11**), and also separated the bicyclo [9.3.1]pentadeca-dienedione (**10**; *ca* 20%), the product of 12-*endo* radical macrocyclisation of (**8b**) and *in situ* hydrogen atom quench, in addition to the reduction product (**8c**; *ca* 30%). The structures and stereochemistries of the products (**10**), (**11**) and (**12**) followed unambiguously from analysis of their n.m.r. spectroscopic data,[16] and in the cases of the epimeric tricyclic enediones (**11**) and (**12**), in conjunction with comparison of similar n.m.r. data reported for related taxane ring systems.[17]



The formation of the two epimers (**11**) and (**12**) of the taxane ring system from cyclisation of (**8b**) no doubt has its origin in 12-*endo* macrocyclisation from the two conformers, (**13**) and (**14**), of the radical precursor molecule, leading initially to (**15**) and (**16**) respectively. Subsequent 6-*exo*-trig(transannular) cyclisation from both (**15**) and (**16**), using the Beckwith transition state model,[18] then produces the *trans*-fusion about the BC ring junctions in each epimer.



Further studies are now in progress to develop and optimise this new tandem radical macrocyclisation-radical transannulation strategy to taxanes, using alternative precursor molecules and those containing additional oxygen functionality and stereochemical detail.

Acknowledgements

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