

Synthesis of a Highly Functionalized AB Taxane Ring System Using 1,4-Dioxene

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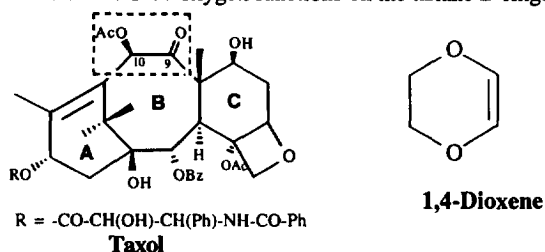
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Abstract: A short synthesis of a highly functionalized AB taxane ring system is described which features the introduction of the C-9 and C-10 oxygen functions on the eight-membered B ring using 1,4-dioxene.

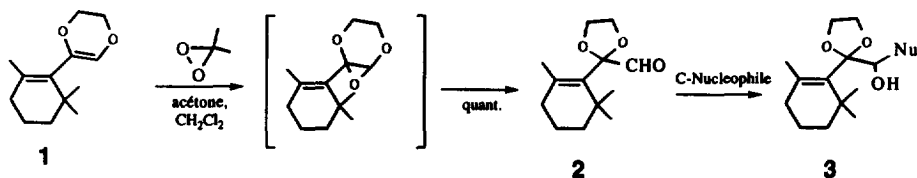
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Taxane diterpenoids continue to stimulate enormous synthetic activity due to their considerable therapeutic potential and their highly challenging structure. Presently, three different routes culminated in the successful total synthesis of the anti-tumor agent Taxol[®] (paclitaxel).¹⁻³ The crucial problem in the synthesis of taxane derivatives is obviously the construction of the sterically congested eight-membered B ring, and several approaches have been reported.⁴

Studies from this laboratory have illustrated the utility of 1,4-dioxene (2,3-dihydro-1,4-dioxin) in the formation of carbon-carbon bonds with rapid elaboration of useful functional groups.^{5,6} We have thus recently demonstrated that this synthon was effective for the early introduction of the C-6 and C-7 oxygenated groups in the A,B ring system of forskolin.^{5a,b} With this precedent, we were interested in the possibility of using dioxene for the introduction of the C-9 and C-10 oxygen functions on the taxane B-ring.



This work was stimulated by our recent reports concerning the introduction of a second C-C bond with simultaneous cleavage of the dioxene ring.⁷ For instance, oxidation of alkyldioxenes such as **1** with dimethyldioxirane gave the corresponding epoxide rearrangement products, α -ketal aldehydes **2**, which react with various carbon nucleophiles to afford **3** (scheme 1). Application of the intramolecular version of this transformation was envisioned for the construction of a highly functionalized AB taxane ring system as indicated in scheme 2.



Scheme 1

The synthesis began by the introduction of dioxene ring into the known A-ring precursor **4** (scheme 3). Thus, the enol triflate, readily prepared from **4**, underwent a palladium-mediated cross coupling reaction⁸ with dioxenylntri-*n*-butylstannane⁹ affording after acid hydrolysis **5** in good overall yield (70% from **4**). Addition of 1-methoxyallenyllithium¹⁰, generated from 1-methoxyallene and *n*-butyllithium in THF at -70°C , to **5** followed by acid hydrolysis of the resulting methyl enol ether gave hydroxyenone **6** in 88% yield. Michael addition of thiophenol to **6** in the presence of catalytic amount of triethylamine¹¹ cleanly furnished phenyl sulfide **7**. Reduction of the hydroxyenone portion of **7** with $\text{NaBH}_4 \cdot \text{CeCl}_3 \cdot 7\text{H}_2\text{O}$ in methanol (Luche's reagent)¹² at -70°C was highly stereoselective and afforded only one diastereomer in quantitative yield. This high stereoselectivity is probably to be the consequence of metal chelation of the vicinal hydroxyl group, and resulted in the formation of the desired "anti-Cram" reduction product.¹² This 1,2-diol was then protected as acetonide (dimethoxypropane, camphorsulfonic acid, CH_2Cl_2) leading to **8** (80-90% yield from **6**). This transformation served two purposes in that it introduced a protecting group and, importantly, restricted the conformation of the acyclic precursor thus facilitating the ring closure reaction.

As we expected, treatment of **8** with an excess dimethyldioxirane (0.05-0.09 M solution in acetone)¹³ at -20 to 0°C first converted the sulfide into a sulfone and then oxidized the dioxene ring into an α -ketaldehyde to afford **9**¹⁵ in 85% yield. It is worthy of note that the selective oxidation of the sulfide moiety may be accomplished by carrying out the reaction with only two equivalents of the oxidant at low temperature.

Having the sulfone aldehyde **9** in hand, the eight-membered ring closure was next attempted.¹⁴ Slow addition of 0.25 M solution of LiHMDS in THF (4 equiv.) to a 7.10^{-3} M solution of **9** in THF at 0°C followed by oxidation of the crude product with Dess-Martin's periodinane reagent furnished **10**¹⁵ in 40% overall yield. The structure of this compound was assigned on the basis of spectroscopic data and further confirmed by X-ray crystallographic analysis¹⁶ (Figure 1).

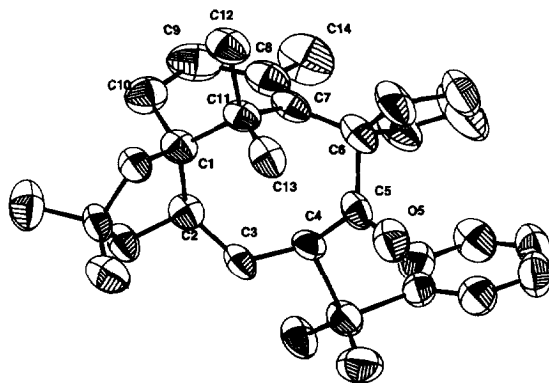
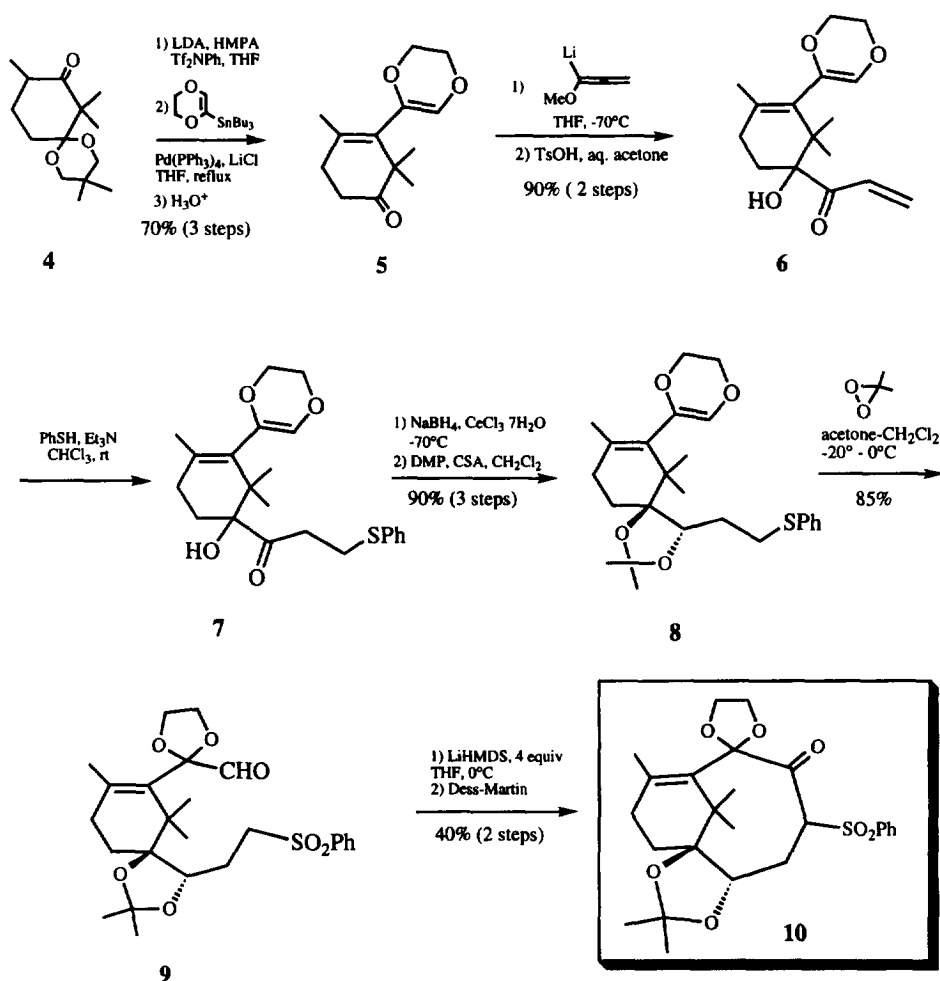
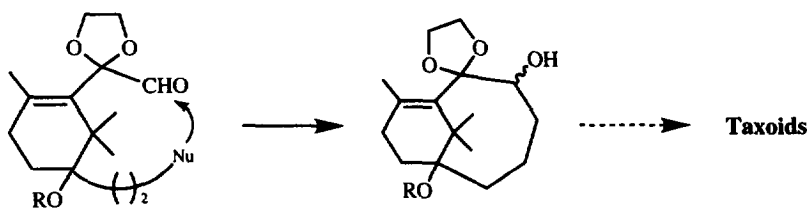


Fig. 1 ORTEP drawing of 10

Thus, starting from the keto 1,3-diene **5**, easily prepared from the known ketone **4** and 1,4-dioxene, we have achieved an efficient construction of a highly functionalized AB taxane ring system.



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15. All new compounds are fully characterized by their spectroscopic and analytical data. **10**: mp 208-210°C (MeOH)IR (CCl₄) : ν_{\max} 1738 cm⁻¹. ¹H NMR (400MHz, CDCl₃): δ 7.96 (d, J=8 Hz, 2H), 7.64-7.69 (m, 1H), 7.52-7.57 (m, 2H), 4.22 (d, J=11 Hz, 1H, H-4), 4.09 (q, J=7 Hz, 1H), 3.92-4.00 (m, 2H, H-2 and 1H ethylene ketal), 3.71 (q, J=7 Hz, 1H), 2.87 (q, J=7 Hz, 1H), 2.70 (dd, J=15 and 4 Hz, 1H, H-3), 2.57 (dd, J=21 and 10 Hz, 1H, H-9), 2.34-2.44 (m, 1H, H-3), 2.15-2.28 (m, 1H, H-9), 1.90-2.04 (m, 2H, H-10), 1.89 (s, 3H), 1.41 (s, 3H), 1.35 (s, 3H), 1.15 (s, 3H), 1.09 (s, 3H). ¹³C NMR (100.6 MHz, CDCl₃): δ 197.7 (C-5), 137.8 (C-7*), 137.6 (C-8*), 133.9 (CH), 130.0 (2CH), 128.8 (2CH), 110.4 (C-6), 108.8 (C-17), 87.6 (C-1), 85.7 (CH, C-12), 68.7 (CH, C-4), 66.0 (CH₂, C-15*), 63.1 (CH₂, C-16*), 39.0 (C-11), 33.0 (CH₂-C-3), 32.1 (CH₂, C-9*), 31.6 (CH₂, C-10*), 30.0 (CH₃), 29.8 (CH₃), 29.6 (CH₃), 21.3 (CH₃), 20.5 (CH₃). MS (EI): m/z (%) 476 (M⁺), 307 (63), 249 (100), 179 (46), 165 (56). MS (CI, NH₃): m/z (%) 494 (M+NH₄)⁺ (100).
16. X-Ray crystal data of **10**: Colourless crystals, triclinic, space group P1, cell parameters: a=14.35(1), b=16.497(2), c=10.99(1) Å, α =89.9(1)°, β =112.47(9)°, γ =89.5(1)° and Z=4 (V =2406 Å³, $F(000)$ =1016 and μ =1.557 cm⁻¹). 7215 reflections were measured on a PHILIPS PW1100 four-circle diffractometer up to $2\theta=132^\circ$, using the CuK α radiation monochromated by graphite. They were reduced to a set of 3764 unique reflections after merging ($R_{\text{sym}}=4.3\%$). The structure was solved by direct methods and refined anisotropically to R=6.8% (on F, 596 parameters, 3722 observed reflections above the 2σ background level) and $R_w=19.8\%$ (on intensities) with the SHELX93 program. Hydrogen atoms were introduced at their theoretical places with a fixed isotropic thermal factor $U=0.05$. The full description of the X-ray structure of **10** has been deposited with the Cambridge Crystallography Data Centre, UK. A copy of the standard CIF output file can be obtained from the authors at the e-mail address: prange@lure.u-psud.fr

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