Pergamon

Tetrahedron Letters, Vol. 35, No. 16, pp. 2469-2472, 1994
Elsevier Science Ltd
Printed in Great Britain
0040-4039/94 $6.00+0.00

0040-4039(94)E0338-X

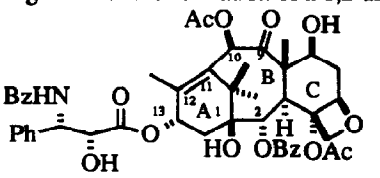
Concise Synthesis of a Taxol A-Ring Synthon: Formation of a 1,2-Alkylidene Linkage via Acetylene Chemistry

David Crich* and Joyce Z. Crich†

Department of Chemistry, University of Illinois at Chicago (M/C 111), 845 W. Taylor St., Chicago, Il 60607-7061, USA

Abstract: A taxol A ring-synthon is obtained by oxidative cyclization of homogeranic acid with mercuric triflate followed by oxidative demercuration; the Meyer-Schuster rearrangement is then employed to form the highly sterically hindered taxol 1,2-bond.

Convergent strategies for the synthesis of taxol in which A and CD-ring moieties are coupled with the formation of the B-ring require the efficient synthesis of synthons for the A and CD rings.[1,2] The challenge inherent in the CD-ring is that of assembling the dense array of functional groups around a six-membered ring with the correct relative and absolute stereochemistry and a number of elegant strategies have been documented to this end recently.[3] The problem of the A-ring synthon is more one of the construction of the highly hindered 1,2-bond suitably functionalised for eventual elaboration of the 1-hydroxy-2-benzoyloxy system of taxol.[2b,4] This problem of C-C bond formation at the highly hindered C-1 position is also inherent in any intramolecular Diels-Alder approach in which a preformed A-ring serves as a tether for formation of the B and C-rings[5], in fragmentation and rearrangement approaches to the B-ring,[1,2f,2j] and in the biomimetic approach described by Pattenden.[6] In this communication we describe an efficient entry into an A-ring synthon and the successful application of the Meyer-Schuster rearrangement to the formation of a 1,2-alkylidene bond.[7]



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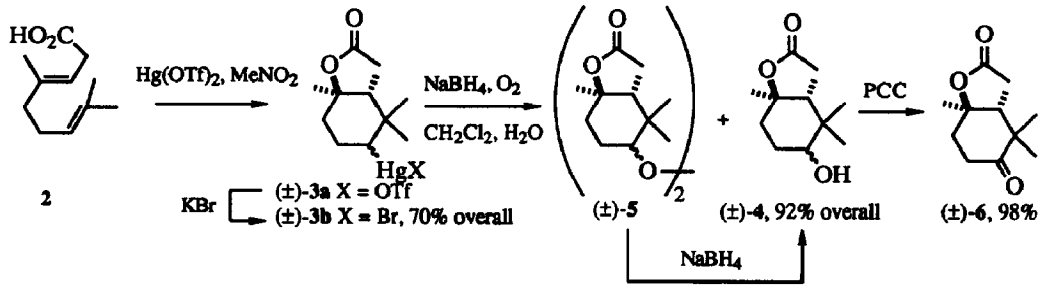
The prevalent philosophy in this laboratory has been that the formation of a suitably functionalised 13-deoxy-A-ring synthon could be most directly achieved by oxidative cyclisation of an appropriate geraniol

†: Present address: G.D. Searle, Dept. of Chemistry, 4901 Searle Parkway, Skokie, Il 60077, USA

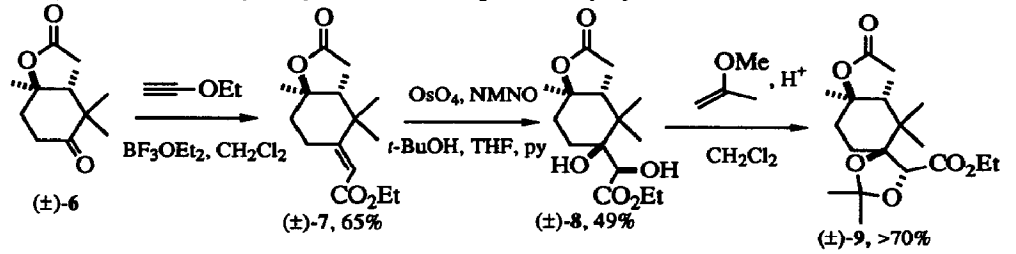
derivative. The 13-deoxy system is targeted for expediency as it removes any complications associated with that stereocenter and its protection/deprotection in latter stages of the synthesis. Moreover, it is known that allylic oxidation of the 11,12-alkene in late stage intermediates enables clean introduction of the 13-ketone and that this may be reduced with formation of the correct stereochemistry.[8] With this in mind we initially explored Lewis acid induced cyclizations of geraniol 6,7-epoxide[9] and its esters but met with little success. Frejd has shown that related cyclizations may be achieved in high yield provided that a suitable terminus is built into the system.[4c] Oxidative radical cyclisations of geranyl acetate as described by Breslow[10] were successful but unsuitable for use on a large scale due to tedious separation problems. Halogenative cyclizations of acyclic terpenoids with NBS and related species are reported to occur only in low yield[11] and so we turned to the mercuric triflate induced cyclisation of homogeranic acid **2** developed by Hoye, and were delighted to obtain excellent yields of the cyclization product **3a**, which could be converted to the crystalline bromide salt **3b** for storage.[12] We prepared **2** from geranyl bromide on a multigram scale according to the Hoye protocol however we note that it may also be prepared in one step by palladium catalysed carbonylation of geranyl acetate.[13] This oxidative cyclization approach to the taxol A-ring differs from that employed originally by Kato in his biomimetic studies[1,14] in so far as the C1 position is suitably functionalized for eventual introduction of the requisite hydroxyl group.

Application of the Whitesides oxidative demercuration reaction[15] to either **3a** or **3b** gave the C-1 alcohol **4** in excellent yield as a mixture of two diasteromers. On the 100 mg scale the reaction was fast and very clean. On the 5g scale, and despite all our efforts to the contrary , a less polar byproduct, tentatively assigned as the dialkyl peroxide **5**, is formed. Fortunately, this is not detrimental as, on stirring the reaction mixture overnight with excess borohydride, it is converted smoothly through to **4** resulting in very high overall yields. Pyridinium chlorochromate oxidation of the mixture of alcohols gave the nicely crystalline, camphoraceous ketone **6** essentially quantitatively (Scheme 1).



Scheme 1

Attention was then turned to formation of a 1,2-alkylidene bond. Somewhat predicably Wittig, Horner Emmons and Julia chemistry failed miserably. However treatment of **6** with freshly distilled ethoxyacetylene and BF_3OEt_2 according to the Vierregge modification[16] of the Meyer-Schuster reaction[17] lead directly to the isolation of the crystalline α,β-unsaturated ester **7** in excellent yield (Scheme 2). Pleasingly **7** was a single geometric isomer whose stereochemistry was assigned on the basis of a strong nuclear Overhauser enhancement of the one of the gem dimethyl groups on double irradiation of the olefinic hydrogen (Fig. 1). Reaction of **7** with a catalytic quantity of OsO_4 with *N*-methylmorpholine *N*-oxide as reoxidant according to the Van Rheenan procedure[18] provided a single diol **8** in good yield, which on treatment with either 2-methoxypropene or 2,2-dimethoxypropane and a catalytic quantity of 4-toluenesulfonic acid in dichloromethane was converted to a single crystalline acetonide **9** (Scheme 2).[19] A crystalline hydroxyketone **10** was consistently formed in moderate yields as a byproduct in the dihydroxylation reaction, presumably by overoxidation of **8**.



Scheme 2

The stereochemistry of **9** and **10**, both single crystalline diastereomers, was assigned on the basis of the indicated n.O.e. measurements (Fig. 1) and indicates that dihydroxylation occurred, atypically,[20] from the axial direction.[21]

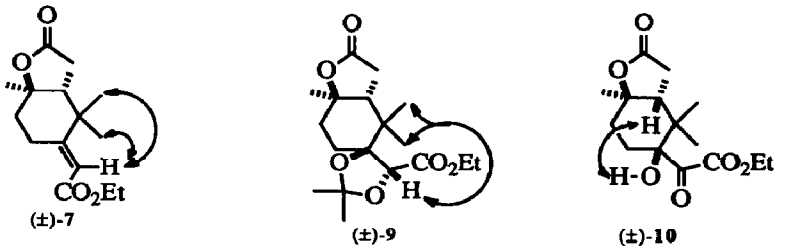


Figure 1

In summary we have described an efficient entry into an A-ring ketone and have provided methodology for the formation of the highly hindered taxol 1,2-bond and for its conversion, albeit in moderate yield at the present time, to an acetonide with proven ability[2b] to accelerate B-ring closure reactions. In this A-ring synthon the taxol 11,12-alkene is suitably protected as the versatile γ-lactone function whose carbonyl group provides a

number of opportunities for attachement of the C-ring and/or B-ring closure. Progress in this direction will be reported in due course.

Acknowledgement: We thank the Campus Research Board of the University of Illinois at Chicago for support and Mr Milan Bruncko for invaluable assistance with n.O.e. measurements.

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(*Received in USA* 2 *November* 1993; *revised* 3 *January* 1994; *accepted* 10 *February* 1994)