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An Approach to the A/B Substructure of 11(15→1)-Abeotaxanes. A Formal Synthesis of Compressanolide.

Gordon L. Lange* and Alexandru Merica

Guelph-Waterloo Centre for Graduate Work in Chemistry
Department of Chemistry and Biochemistry
University of Guelph, Guelph, Ontario N1G 2W1 Canada

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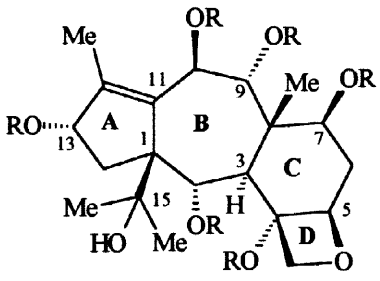
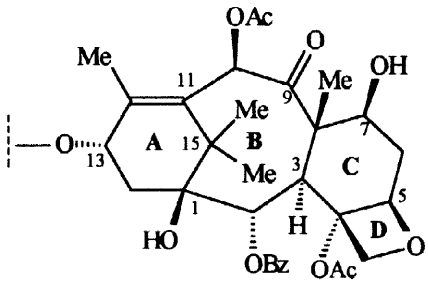
Abstract: Preparation of highly functionalized **16** constitutes one of the first attempts at the synthesis of the A/B carbon skeleton of the 11(15→1)-abeotaxanes. Further transformations of labile **16** give enedione **17**, an important relay compound in the synthesis of guaianolide compressanolide.

In 1991 brevifoliol was isolated from a *taxus* species[1] and later shown to have a rearranged 5/7/6 abeotaxane skeleton **1**.[2] In the past six years many other examples of abeotaxanes have been reported[3] and some have been shown to be active in the microtubule disassembly assay.[4] The very promising antitumor agent paclitaxel **2** (Taxol®)[5] also exhibits this activity. Although numerous approaches to the partial[6] or total synthesis of **2** have been reported,[7] synthetic approaches to the abeotaxanes have thus far been restricted to the conversion of paclitaxel derivatives to these rearranged systems by chemical[4,8] or enzymatic means.[9] In this letter we describe an approach to the synthesis of the carbon skeleton of the A/B substructure of the 11(15→1)-abeotaxanes. As an extension of this study we also report an efficient formal synthesis of the guaianolide compressanolide **3**.



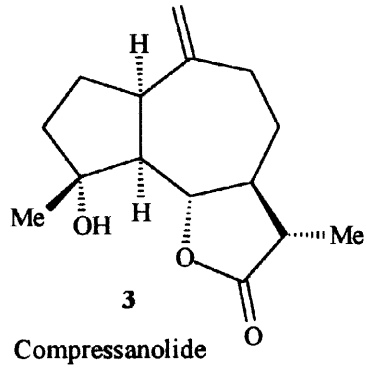
1

Abeotaxanes
R = H, Ac, Bz, etc.



2

Paclitaxel



3

Compressanolide

Some years ago we reported that solvolysis of photoadduct derivative **4** gave the bridged product **5** plus a linear triquinane.[10] In a more recent unpublished study we found that tertiary alcohol **6** very readily rearranged to **7**[11]

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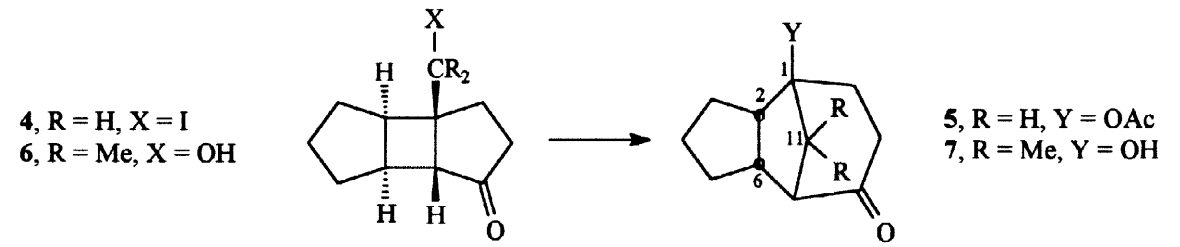
(Scheme 1). If methodology could be developed to cleave the C-2-C-6 bond in **7**, the bicyclo[5.3.1]undecane system present in the A/B substructure of paclitaxel **2** would be obtained with the dimethylated bridge at C-11 and the bridgehead hydroxyl at C-1. Below we describe an investigation into this general approach in which the A/B skeleton of the 11(15→1)-abeotaxanes rather than the anticipated A/B taxane skeleton was obtained.

Scheme 1

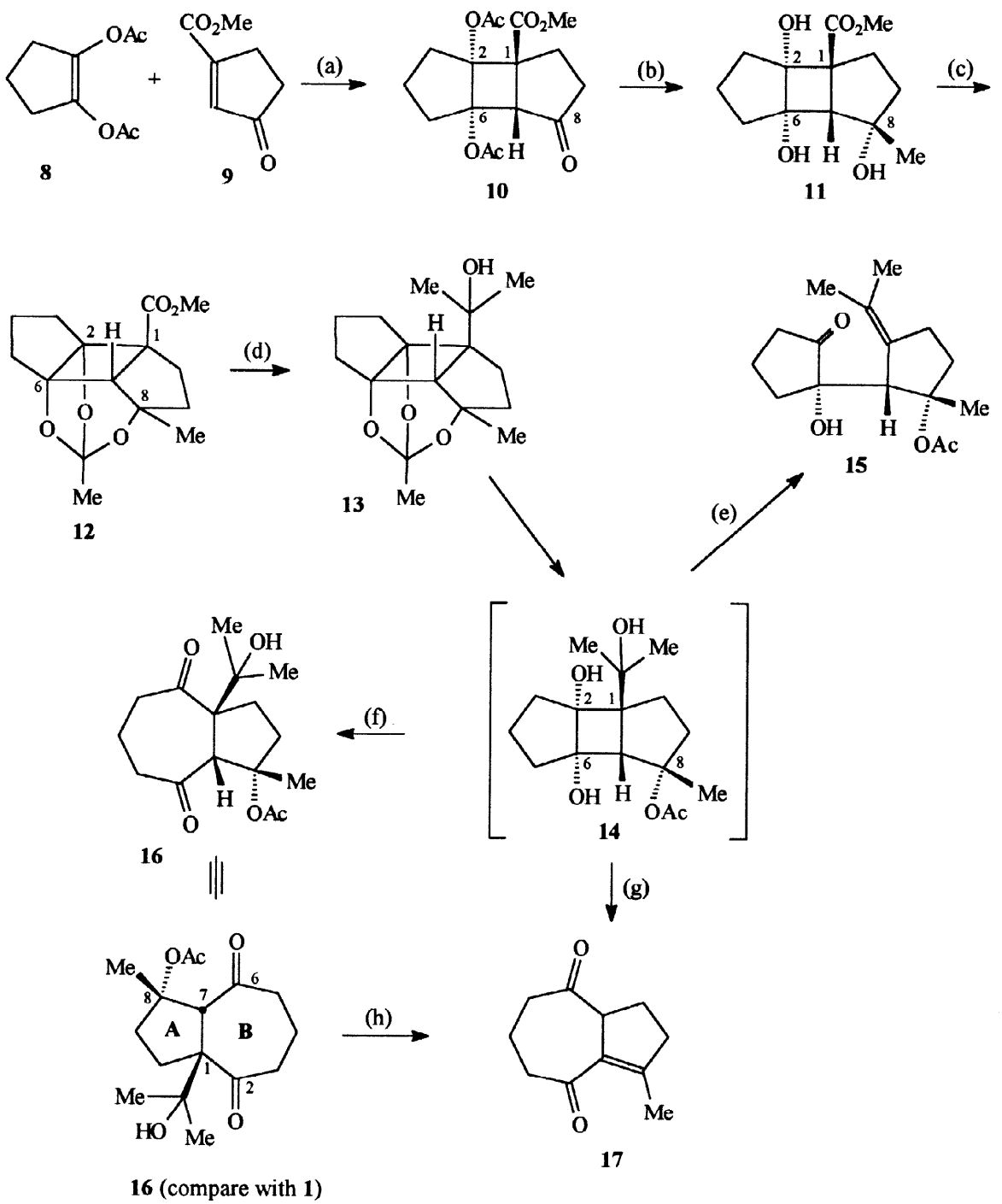


The [2+2] photoaddition of diacetoxycyclopentene **8**[12a] and enone **9**[10] gave adduct **10**[12b] (Scheme 2). Treatment of **10** with excess methyl Grignard resulted in removal of the two acetate groups and formation of methyl carbinol **11**. The hindered ester function at C-1 did not react. The highly oxygenated substrate **11** had the desired functionality at C-2 and C-6 to facilitate cleavage of the C-2-C-6 bond but was also prone to side reactions such as a retro aldol cleavage of the C-1-C-2 bond.[12c] Attempts to protect the C-2 and C-6 hydroxyl groups in **11** as a 1,2-acetonide resulted instead in protection of the C-6 and C-8 hydroxyls and formation of a 1,3-acetonide. Reaction of **11** with acidic orthoacetate gave the novel caged orthoester **12** and protection of all three hydroxyl groups. The ester group in **12** was converted to tertiary alcohol **13** with methyllithium. Attempts to convert **13** into a bridged system under acidic conditions (as in conversion of **6** to **7**) resulted in hydrolysis of the orthoester and formation of the unsaturated ketone **15** *via* a Grob-type fragmentation of the C-1-C-2 bond in intermediate **14**. After considerable experimentation it was discovered that treatment of **13** with buffered periodic acid resulted in hydrolysis of the orthoester to give **14** followed by immediate cleavage of the C-2-C-6 bond to give dione **16** in very good yield. The success of this critical reaction is dependent on periodate cleavage of the *vic*-diol in **14** before it has a chance to fragment to **15** (Scheme 2). A comparison of the structure of cleavage product **16** with **1** reveals that the former contains the carbon skeleton present in the A/B substructure of the 11(15→1)-abeotaxanes including the important dimethyl carbinol function at C-1.

The highly functionalized **16** is itself quite labile and upon mild treatment with base it undergoes loss of acetone and β-elimination of the acetate group to give enedione **17**.[13] Even more remarkable, reaction of orthoester **13** with periodic acid followed by passage of the product through basic alumina resulted in a cascade of four reactions to give **17** directly in 88% yield (Scheme 2). **17** has been used as an important relay in the synthesis of the guaianolide compressanolide **3**[14] and thus the preparation of **17** described herein constitutes a formal synthesis of this sesquiterpenoid.

This letter reports one of the first attempts at the synthesis from simple starting materials of the carbon skeleton of the A/B ring system of abeotaxanes.[15] Previous semisyntheses of the abeotaxanes[4,8,9] involved contraction of the bicyclo[5.3.1]undecane portion of paclitaxel and derivatives to the 5/7 A/B ring system while our approach employed expansion of the 5/4/5 photoadduct structure to the desired A/B skeleton present in **1**.

Scheme 2



(a) hν, CH_2Cl_2, 0°C, 47 %; (b) MeMgBr, THF, 0°C then r.t., 60 %; (c) $MeC(OMe)_3$, PPTS, Δ, 68 %; (d) MeLi, THF, r.t., 61 %; (e) H_3O^+ or Montmorillonite K10, CH_2Cl_2, r.t., 83 %; (f) HIO_4, NaOAc, r.t., 84 %; (g) HIO_4, ether/THF; basic alumina, 88 %; (h) DBU, CH_2Cl_2, r.t., 74 %.

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12. (a) Preparation of **8** and other previously unreported 1,2-diacetoxy-1-cycloalkenes will be described elsewhere. (b) If a *bis*-trimethylsilyloxy derivative rather than **8** was used in the photoaddition, an oxetane was formed in low yield. (c) If MeLi rather than MeMgBr was used in the conversion of **10**→**11**, the retro aldol cleavage of the β-hydroxy ester moiety in **11** predominates.
13. For previous syntheses of **17** see: (a) Termont, D.; De Clercq, P. J.; De Keulekeire, D.; Vandewalle, M. *Synthesis* **1977**, 46-48. (b) Gwaltney, S. L.; Sakata, S. T.; Shea, K. J. *Tetrahedron Lett.* **1995**, *36*, 7177-7180.
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15. A search of the CAS ONLINE structure database revealed no previous syntheses of this A/B carbon skeleton from simple precursors.