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# General Synthesis of Highly Functionalized Cyclopentane Segments for the Preparation of Jatrophane Diterpenes†

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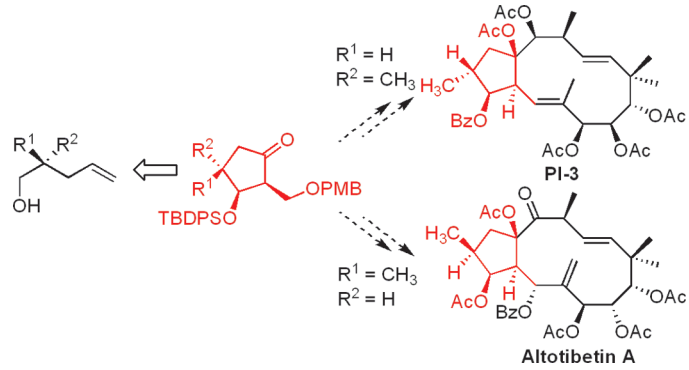
## ABSTRACT




**Short and efficient syntheses of two diastereomeric cyclopentane segments present in most jatrophane diterpenes were achieved. Key steps are a stereoselective C-2 elongation, an RCM, and a hydroboration reaction. An orthogonal protecting group methodology makes these segments useful building blocks for diterpene synthesis.**

Since the isolation of jathrophone in 1970 by Kupchan,[1] the interest in active ingredients in members of the Euphorbiaceae family is steadily increasing. The milky latices of *Euphorbia* species contain a vast number of structurally diverse diterpenes, and a considerable amount of terpenes from the tigliane, ingenane, daphnane, and jatrophane families were isolated.[2] Among the protruding biological activities of many of these natural products, antiproliferative activity[3] and multidrug resistance modulating properties[4,5] are most remarkable.

The general structure of the jatrophane skeleton, a highly functionalized *trans*-bicyclo[10.3.0]pentadecane framework, and selected examples of biologically interesting members of this class of natural products are shown in Figure 1. Despite the large number of jatrophane diterpenes isolated, the interesting synthetic challenge, and the promising biological properties, preparative work on this class of natural products can be regarded as a new field as only a few research groups are actively pursuing the synthesis of Euphorbiaceae constitutents.[6−8]

A common strucutral motif of the cyclopentane moiety of jatrophane diterpenes is the methyl group at C2 (jatrophane numbering) which can be present in either an *R* or *S* configuration as well as an oxygen functionality at C3 (Figure 1). The stereochemical pattern of this oxygen at C3 is identical in all jatrophane diterpenes with a small number

† Dedicated to Prof. Tomas Hudlicky on the occasion of his 60th birthday in recognition of his contributions to synthetic organic chemistry.

(1) Kupchan, S. M.; Sigel, C. W.; Matz, M. J.; Renauld, J. A. S.; Haltiwanger, R. C.; Bryan, R. F. *J. Am. Chem. Soc.* **1970**, *92*, 4476.
(2) Shi, Q. W.; Su, X. H.; Kiyota, H. *Chem. Rev.* **2008**, *108*, 4295.
(3) Valente, C.; Pedro, M.; Duarte, A.; Nascimento, M. S. J.; Abreu, P. M.; Ferreira, M. J. U. *J. Nat. Prod.* **2004**, *67*, 902.
(4) Hohmann, J.; Evanics, F.; Dombi, G.; Molnar, J.; Szabo, P. *Tetrahedron* **2001**, *57*, 211.
(5) Valente, C.; Ferreira, M. J. U.; Abreu, P. M.; Gyemant, N.; Ugocsai, K.; Hohmann, J.; Molnar, *J. Planta Med.* **2004**, *70*, 81.

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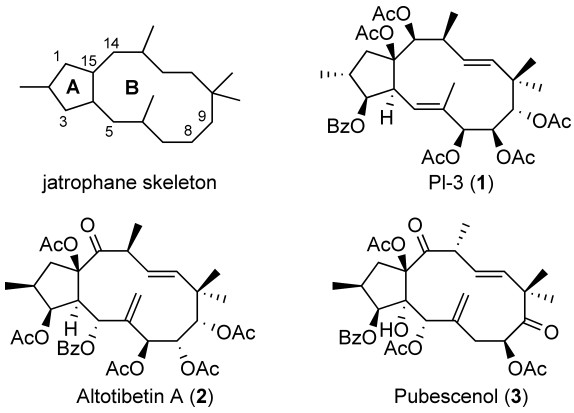



**Figure 1.** Jatrophane skeleton and selected diterpenes.

of exceptions. Although cylopentanes are common structural motifs in natural products, the syntheses of such segments are often lengthy and tedious, especially when highly functionalized.

While designing a synthesis of Pl-3 (**1**), a biologically highly active member of the jatrophane family which was first isolated by Hohmann in 2003 from *Euphorbia platyphyllos*,[9] we envisaged to devise a short and more general approach toward the five-membered ring segment to get access to various diterpenes of this family of natural products such as altotibetin A (**2**)[10] with reversed stereochemistry of the methyl group at C2. Synthetic equivalents required for preparing the corresponding natural products are shown in Figure 2.

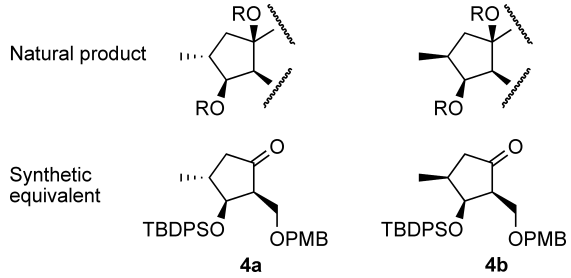
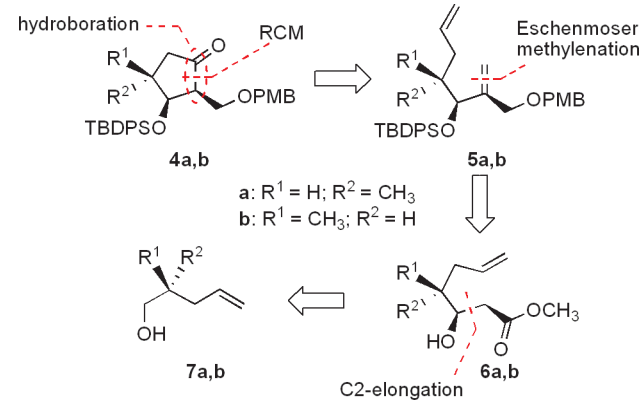



**Figure 2.** Natural product motif and synthetic equivalent.

The retrosynthetic analysis for the preparation of ketones **4a** and **4b** is outlined in Scheme 1. The key step in this sequence is a RCM reaction to establish the five-membered ring from linear precursors.

The double bond generated in this reaction can be used in a directed hydroboration/oxidation protocol to install the ketone functionality and to define the stereochemistry of the latter ring junction at C4. The precursor for the key RCM reaction was envisaged to be prepared by oxidation of alcohols **7a** and **7b**, both readily available, and stereoselective C2 elongation of the corresponding aldehydes, followed by Eschenmoser methylenation.[11]

**Scheme 1.** Retrosynthetic Analysis




Alcohols **7a** and **7b** were prepared by Myers' alkylation of the corresponding pseudoephedrine propionamide with allyl iodide and LAB reduction following a literature procedure.[12] Oxidation of alcohol **7** with IBX under standard conditions cleanly afforded aldehyde **8**. The high volatility of this material complicated the workup; however, direct distillation of the aldehyde from the reaction mixture afforded the product in good yield. The stereochemical stability of this α-chiral aldehyde, even after prolonged storage at room temperature, was demonstrated by reduction of the carbonyl group and subsequent conversion to the corresponding Mosher ester. Stereoselective C2-elongation was achieved in excellent yield using (*R*)-HYTRA (**9**) as chiral auxiliary.[13] As the determination of the diastereomeric ratio was not possible at this point, compound **10** was further transesterified to the corresponding methyl ester in quantitative yield using sodium methoxide. Interpretation of NMR spectra revealed a diastereomeric ratio of at least 10:1 for both esters **6a** and **6b**.

A crucial step in the reaction sequence was the incorporation of the exomethylene functionality. Originally, we intended to apply Eschenmoser's salt,[11] but all attempts resulted in either reisolation of the starting material when alcohol **6** was used or elimination if the

(6) (a) Gilbert, M.; Galkina, A.; Mulzer, J. *Synlett* **2005**, 2558. (b) Mulzer, J.; Giester, G.; Gilbert, M. *Helv. Chim. Acta* **2005**, *88*, 1560.

(7) Shimokawa, K.; Takamura, H.; Uemura, D. *Tetrahedron Lett.* **2007**, *48*, 5623.

(8) (a) Helmboldt, H.; Rehbein, J.; Hiersemann, M. *Tetrahedron Lett.* **2004**, *45*, 289. (b) Helmboldt, H.; Köhler, D.; Hiersemann, M. *Org. Lett.* **2006**, *8*, 1573. (c) Helmboldt, H.; Hiersemann, M. *J. Org. Chem.* **2009**, *74*, 1698. (d) Schnabel, C.; Hiersemann, M. *Org. Lett.* **2009**, *11*, 2555.

(9) Hohmann, J.; Forgo, P.; Csupor, D.; Schlosser, G. *Helv. Chim. Acta* **2003**, *86*, 3386.

(10) (a) Hohmann, J.; Redei, D.; Forgo, P.; Molnar, J.; Dombi, G.; Zorig, T. *J. Nat. Prod.* **2003**, *66*, 976. (b) Pan, L.; Zhang, X. F.; Deng, Y.; Wang, H.; Wu, D. G.; Luo, X. D. *Helv. Chim. Acta* **2003**, *86*, 2525.

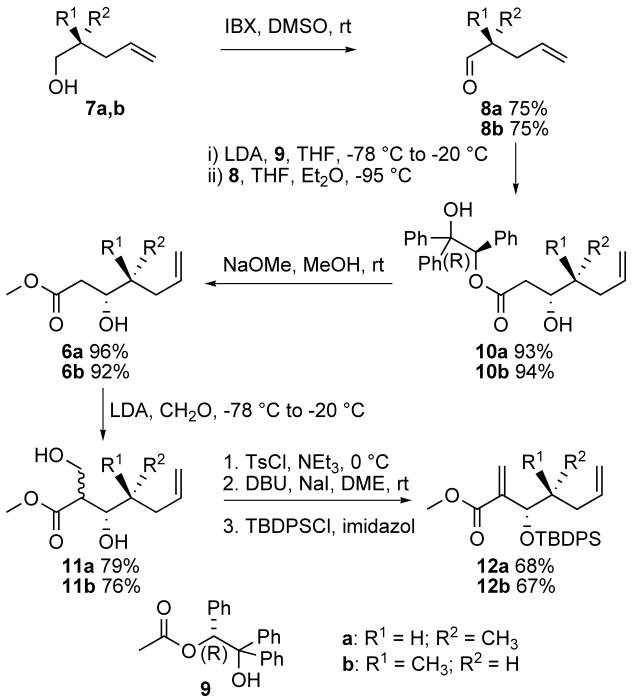
(11) Schreiber, J.; Maag, H.; Hashimoto, N.; Eschenmoser, A. *Angew. Chem., Int. Ed. Engl.* **1971**, *10*, 330.

(12) Myers, A. G.; Yang, B. H.; Chen, H.; McKinstry, L.; Kopecky, D. J.; Gleason, J. L. *J. Am. Chem. Soc.* **1997**, *119*, 6496.

(13) (a) Braun, M.; Graf, S. *Org. Synth.* **1995**, *72*, 38. (b) Braun, M.; Graf, S.; Herzog, S. *Org. Synth.* **1995**, *72*, 32.

hydroxyl group was protected as the silyl ether prior to the reaction. The problem could be solved by treatment of double-deprotonated ester **6** with freshly prepared formaldehyde solution, conversion of the primary hydroxy functionality into the corresponding tosylate, and elimination effected by exposure of this material to DBU.[14] Protection of the secondary alcohol as silyl ether afforded **12** in good yield (Scheme 2). The ester functionality in

**Scheme 2.** Preparation of Ester **12**

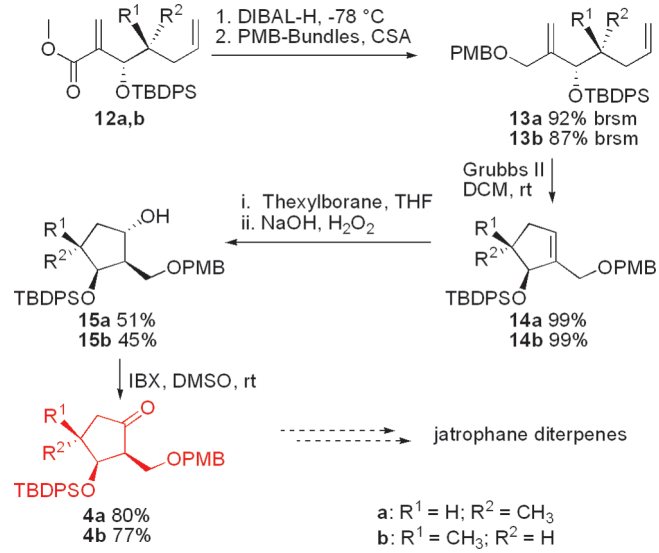



**12** was further reduced using DIBAL-H at 0 °C and converted to PMB-ether **13** using Bundle's reagent.[15] This material served as precursor for the key RCM reaction. Exposure of this material to Grubbs' second-generation catalyst[16] cleanly afforded cyclopentene derivative **14** which was used in the hydroboration reaction with thexylborane.[17] The bulkiness of the silyl ether prevented attack of the borane reagent from the top face of the molecule and selectively affords the desired stereoisomer (**15**). Oxidation of the hydroxyl functionality concludes the synthetic route and delivers ketones **4a** and **4b** in excellent yield (Scheme 3).

The stereochemical relationship of the substituents on the cyclopentyl ring was unambiguously elucidated and proven by NOE correlation experiments. The crucial cross-couplings are illustrated in Figure 3.

(14) Phukan, P.; Bauer, M.; Maier, M. E. *Synthesis* **2003**, 1324.
(15) Iversen, T.; Bundle, D. R. *J. Chem. Soc., Chem. Commun.* **1981**, 1240.
(16) Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953.
(17) Castagner, B.; Leighton, J. L. *Tetrahedron* **2007**, *63*, 5895.

**Scheme 3.** Synthesis of Cyclopentanes **4a** and **4b**




The synthesis of highly versatile cyclopentane fragments **4a** and **4b** present in most jatrophane diterpenes has been

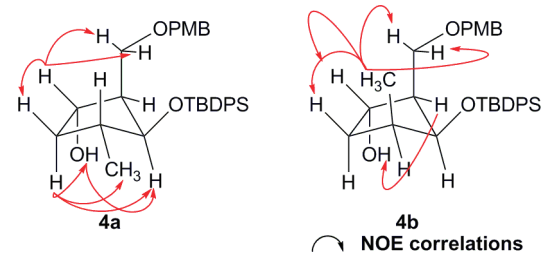



**Figure 3.** NOE correlations in cyclopentanes **15a** and **15b**.

achieved in only 12 steps and good overall yield. Further application of these highly functional five membered ring segments in the preparation of jatrophane diterpenes is currently under investigation and will be reported in due course.

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**Supporting Information Available:** Experimental procedures for all new compounds and selected NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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