ORGANIC LETTERS

2006
Vol. 8, No. 8
1573−1576

Synthesis of the Norjatrophane Diterpene (−)-15-Acetyl-3-propionyl-17-norcharaciol

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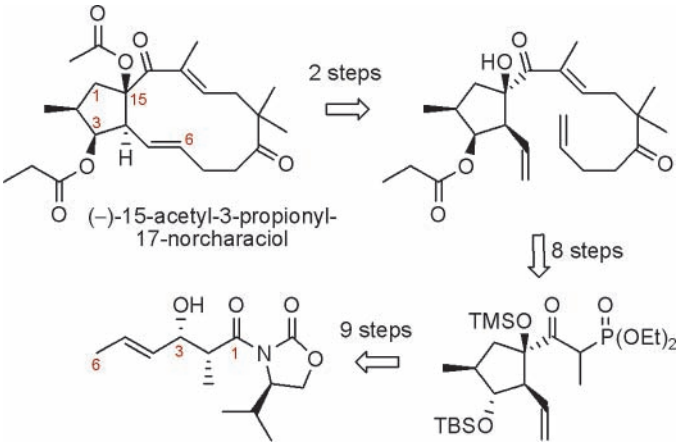
Received January 15, 2006

ABSTRACT



A scalable enantioselective synthesis of the nonnatural 17-norjatrophane diterpene 3-propionyl-15-acetyl-17-norcharaciol is described. Key C/C-connecting transformations are an Evans aldol reaction, an intramolecular carbonyl ene reaction, a Horner–Wadsworth–Emmons olefination, and a ring-closing metathesis for the formation of a 12-membered carbacycle.

Plants of the genus *Euphorbia* are a rich source of biologically active bi- and polycyclic diterpenes.[1] Besides daphnanes, tiglianes, ingenanes, and others, diterpenes featuring the jatrophane framework **1** are being isolated in tremendous structural diversity.[2−4] Jatrophanes possess a variety of different biological activities. Most notably, they are inhibitors of the P-glycoprotein (Pgp),[5] a membrane protein whose major function is the active transport of amphiphatic xenotoxins out of the cytoplasm.[6] It is assumed that the overexpression of the multidrug resistance protein 1 (MDR1) gene that encodes for Pgp contributes to the resistance of cancer cells against a broad spectrum of antineoplastic drugs.[7]

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(1) (a) Singla, A. K.; Pathak, K. *Fitoterapia* **1990**, *61*, 483−516. (b) Evans, F. J.; Taylor, S. E. *Fortschr. Chem. Org. Naturst.* **1983**, *44*, 1−99.

(2) The first diterpene featuring the jatrophane skeleton was isolated from *Jatropha gossypiifolia*; see: (a) 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*, 4476−4477. (b) Kupchan, S. M.; Sigel, C. W.; Matz, M. J.; Gilmore, C. J.; Bryan, R. F. *J. Am. Chem. Soc.* **1976**, *98*, 2295−2300. (c) Taylor, M. D.; Smith, A. B.; Furst, G. T.; Gunasekara, S. P.; Bevelle, C. A.; Cordell, G. A.; Farnsworth, N. R.; Kupchan, S. M.; Uchida, H.; Branfman, A. R.; Dailey, R. G.; Sneden, A. T. *J. Am. Chem. Soc.* **1983**, *105*, 3177−3183.

(3) For recent reports on the isolation and the pharmacological properties of jatrophanes from *Euphorbia*, see: (a) Corea, G.; Fattorusso, C.; Fattorusso, E.; Lanzotti, V. *Tetrahedron* **2005**, *61*, 4485−4494. (b) Zhang, W.; Guo, Y.-W. *Planta Med.* **2005**, *71*, 283−286. (c) Pan, Q.; Ip, F. C. F.; Ip, N. Y.; Zhu, H.-X.; Min, Z.-D. *J. Nat. Prod.* **2004**, *67*, 1548−1551. (d) Valente, C.; Pedro, M.; Duarte, A.; Nascimento, M. S. J.; Abreu, P. M.; Ferreira, M.-J. U. *J. Nat. Prod.* **2004**, *67*, 902−904. (e) Valente, C.; Pedro, M.; Ascenso, J. R.; Abreu, P. M.; Nascimento, M. S. J.; Ferreira, M.-J. U. *Planta Med.* **2004**, *70*, 244−249.

(4) To the best of our knowledge, 17-norjatrophanes have not yet been isolated as natural products.

(5) Hohmann, J.; Molnar, J.; Redei, D.; Evanics, F.; Forgo, P.; Kalman, A.; Argay, G.; Szabo, P. *J. Med. Chem.* **2002**, *45*, 2425−2431.

(6) Borst, P.; Elferink, R. O. *Annu. Rev. Biochem.* **2002**, *71*, 537−592.

10.1021/ol060115t CCC: $33.50
Published on Web 03/16/2006

Several recent studies have investigated the structure−activity relationship of jatrophanes as modulators of multidrug resistance.[8] However, these studies are so far restricted to naturally occurring jatrophanes. Therefore, we have initiated a research program aimed at the enantioselective de novo synthesis of the jatrophane framework.[9] We envision providing access to purposeful functionalized nonnatural jatrophanes for systematic structure−activity studies.

At the outset, we selected 15-acetyl-3-propionyl-characiol **2a** for the initial development of a reliable synthetic strategy toward the jatrophane framework (Figure 1). Originally, Seip

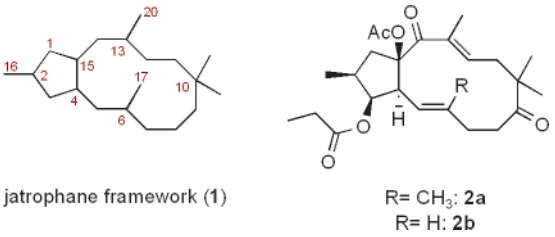
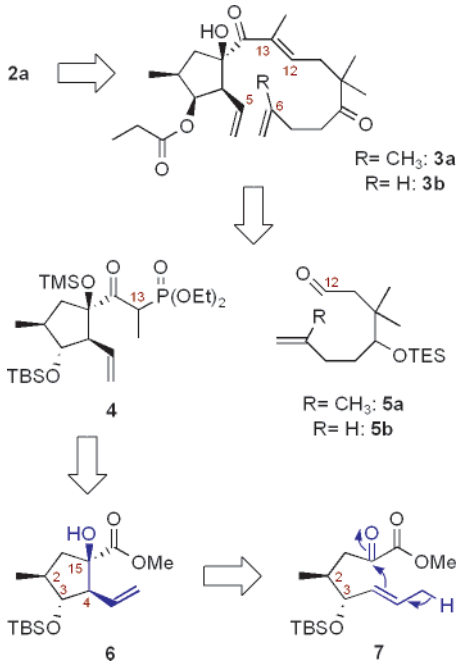


Figure 1. Jatrophane framework (**1**), 15-acetyl-3-propionyl-characiol (**2a**), and the 17-nor derivative (**2b**). The depicted numbering is used throughout the paper.

and Hecker reported the isolation of **2a** from the latex of *Euphorbia* characias.[10] The gross structure and the relative configuration of **2a** were deduced from NMR studies.

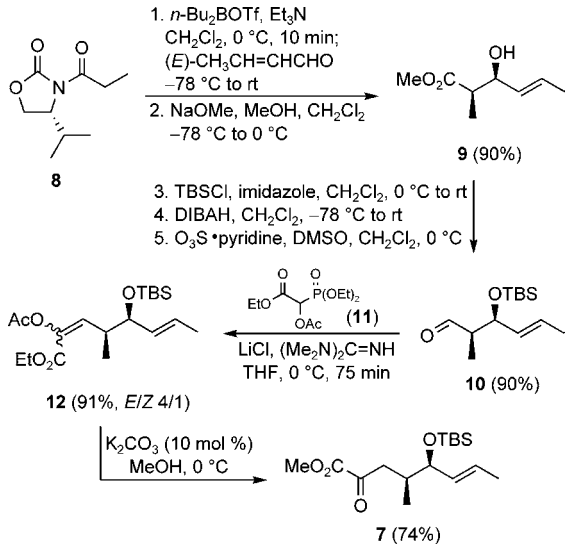
Our initial retrosynthetic analysis of 15-acetyl-3-propionyl-characiol (**2a**) utilized a ring-closing metathesis (RCM) transform to disconnect the stereogenic trisubstituted C5/C6 double bond providing the synthon **3a** (Scheme 1). Disconnection of the C12/C13 double bond of **3a** afforded the β-keto phosphonate **4** and the aldehyde **5a**. The β-keto phosphonate **4** was further simplified to the highly substituted cyclopentane building block **6**. Having identified a carbonyl ene retron in **6**, we opted for the disconnection of the C4/C5 bond by a carbonyl ene transform to provide the α-keto ester **7**. Thus, pivotal steps of the retrosynthesis are a RCM to close a 12-membered carbacycle by the formation of a trisubstituted double bond and a diastereoselective intramolecular carbonyl ene reaction for the synthesis of the highly substituted cyclopentane fragment **6**.

Scheme 1. Retrosynthetic Analysis of **2a**



The synthesis of the α-keto ester **7** began with an asymmetric aldol addition utilizing the N-acylated Evans auxiliary **8** (Scheme 2).[11] The removal[12] of the auxiliary

Scheme 2. Synthesis of the α-Keto Ester **7**



provided the β-hydroxy ester **9** that was protected, reduced to the primary alcohol, and subsequently oxidized[13] to afford

(7) Robert, J.; Jarry, C. *J. Med. Chem.* **2003**, *46*, 4805−4817.

(8) (a) Corea, G.; Fattorusso, E.; Lanzotti, V.; Taglialatela-Scafati, O.; Appendino, G.; Ballero, M.; Simon, P.-N.; Dumontet, C.; Di Pietro, A. *J. Med. Chem.* **2003**, *46*, 3395−3402. (b) Valente, C.; Ferreira, M. J. U.; Abreu, P. M.; Gyemant, N.; Ugocsai, K.; Hohmann, J.; Molnar, J. *Planta Med.* **2004**, *70*, 81−84. (c) Corea, G.; Fattorusso, E.; Lanzotti, V.; Motti, R.; Simon, P.-N.; Dumontet, C.; Di Pietro, A. *J. Med. Chem.* **2004**, *47*, 988−992. (d) Corea, G.; Fattorusso, E.; Lanzotti, V.; Motti, R.; Simon, P.-N.; Dumontet, C.; Pietroio, A. D. *Planta Med.* **2004**, *70*, 657−665.

(9) For a preliminary communication, see: Helmboldt, H.; Rehbein, J.; Hiersemann, M. *Tetrahedron Lett.* **2004**, *45*, 289−292. For other synthetic approaches toward jatrophane diterpenes from *Euphorbia*, see: (a) Gilbert, M. W.; Galkina, A.; Mulzer, J. *Synlett* **2004**, 2558−2562. (b) Mulzer, J.; Giester, G.; Gilbert, M. *Helv. Chim. Acta* **2005**, *88*, 1560−1579. For the total synthesis of jatrophone, a jatrophane diterpene from *Jatropha gossypiifolia*, see: (c) Smith, A. B.; Lupo, A. T.; Ohba, M.; Chen, K. *J. Am. Chem. Soc.* **1989**, *111*, 6648−6656. (d) Gyorkos, A. C.; Stille, J. K.; Hegedus, L. S. *J. Am. Chem. Soc.* **1990**, *112*, 8465−8472. (e) Han, Q.; Wiemer, D. F. *J. Am. Chem. Soc.* **1992**, *114*, 7692−7697.

(10) Seip, E. H.; Hecker, E. *Phytochemistry* **1984**, *23*, 1689−1694.

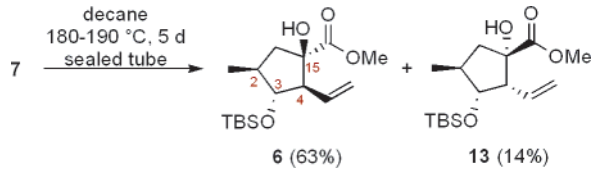
(11) Evans, D. A.; Bartroli, J.; Shih, T. L. *J. Am. Chem. Soc.* **1981**, *103*, 2127−2129.

(12) See ref 11. However, addition of NaOMe at −78 °C was mandatory for optimal yields. The auxiliary was recovered in 97% yield under these conditions.

the aldehyde **10** as a single diastereomer. To convert the aldehyde to the desired α-keto ester **7**, a two-step sequence was established consisting of a Horner−Wadsworth−Emmons olefination utilizing the phosphonate **11**[14] and a subsequent transesterification to provide the α-keto ester **7**.[15]

The pivotal thermal intramolecular carbonyl ene reaction was studied next (Scheme 3). Heating the α-keto ester **7** in

Scheme 3. Thermal Intramolecular Carbonyl Ene Reaction



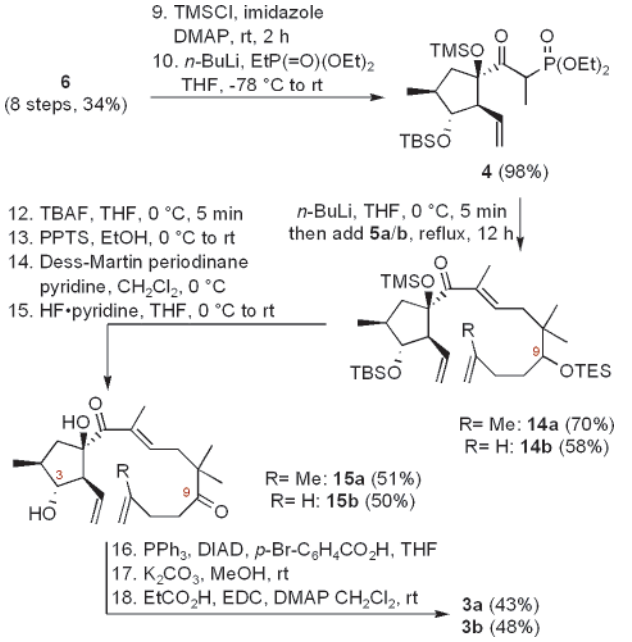
a sealed tube for several days to 185 °C afforded a mixture of the two diastereomeric cyclopentanes **6** and **13** which were separable by flash chromatography.[16] The relative configuration of **6** and **13** was deduced from NOESY studies and later confirmed for **6** by an X-ray crystal structure analysis of a derivative.[17]

Under the thermal reaction conditions, the stereochemical outcome of the ene reaction is thermodynamically controlled. Subjecting pure **6** or **13** to the identical thermal conditions afforded the same ratio of diastereomers as that originally observed from **7**. Therefore, recycling of the undesired diastereomer **13** is possible and increases the overall efficiency of the ene reaction. Thus, the cyclopentane building block **6** is conveniently accessible in an eight-step scalable sequence with an overall yield of 34%. To obtain the required absolute configuration at C4 and C15 from the ene reaction, it was mandatory to utilize the α-keto ester **7** that features the nonnatural absolute configuration at C3.

The synthesis was continued by protecting the tertiary hydroxyl group of **6** as a trimethylsilyl (TMS) ether that was sufficiently stable for the ensuing transformations (Scheme 4).

A Claisen-type condensation with diethyl ethylphosphonate provided the *β*-keto ester **4** which was subsequently deprotonated and treated with the aldehyde **5a**[18] to afford the α,*β*-unsaturated ketone **14a** as a single double-bond

Scheme 4. Synthesis of the Substrates for the RCM



isomer. Our original plan was to perform the RCM as late as possible in the synthesis. Therefore, the TMS and the triethylsilyl (TES) protecting group were removed and the secondary hydroxyl group at C9 was oxidized employing the Dess−Martin periodinane.[19] The *tert*-butyldimethylsilyl (TBS) ether was then cleaved to afford the diol **15a** featuring the undesired absolute configuration at C3. As expected, the configuration at C3 could be inverted by a Mitsunobu reaction[20] to provide the corresponding benzoate which was transesterificated to afford the C3 alcohol. Finally, regioselective acylation of the secondary hydroxyl group in the presence of 1-[3-(dimethylamino)propyl]-3-ethyl-carbodiimide hydrochloride[21] (EDC) afforded the ester **3a**.

With the triene **3a** in hand, we attempted the crucial RCM[22] to establish the 12-membered carbacycle.[23] However, the employment of the first[24] or second generation[25] Grubbs catalyst or the Hoveyda catalyst[26] for this purpose was

(13) Parikh, J. R.; Doering, W. v. E. *J. Am. Chem. Soc.* **1967**, *89*, 5505−5507.

(14) Schmidt, U.; Langner, J.; Kirschbaum, B.; Brau, C. *Synthesis* **1994**, 1138−1140. However, a modified procedure for the preparation of **11** was utilized. See the Supporting Information for details.

(15) We thank Dr. Michael Harre, Schering AG Berlin, for bringing the phosphonate **11** to our attention and for providing a procedure for its large-scale preparation and application.

(16) Microwave irradiation and the application of ionic liquids are currently under investigation. Lewis acid based protocols have been reported for the intramolecular carbonyl ene reaction of α-keto esters; see: (a) Kaden, S.; Hiersemann, M. *Synlett* **2002**, 1999−2002. (b) Yang, D.; Yang, M.; Zhu, N. *Org. Lett.* **2003**, *5*, 3749−3752. However, attempts to utilize these protocols were unsuccessful. Initial attempts to employ the anti-(3*S*,4*R*)-configured α-keto ester **7** as the substrate for the ene reaction failed. However, further studies are ongoing and the results will be reported as part of a full paper.

(17) See the Supporting Information for details.

(18) See the Supporting Information for details of the synthesis of **5a**,**b**.

(19) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155−4156.

(20) (a) Mitsunobu, O.; Yamada, M. *Bull. Chem. Soc. Jpn.* **1967**, *40*, 2380−2382. (b) Mitsunobu, O. *Synthesis* **1981**, 1−28.

(21) Sheehan, J.; Cruickshank, P.; Boshart, G. *J. Org. Chem.* **1961**, *26*, 2525−2528.

(22) For selected recent reviews, see: (a) Nicolaou, K. C.; Bulger, P. G.; Sarlah, D. *Angew. Chem., Int. Ed.* **2005**, *44*, 4490−4527. (b) Grubbs, R. H. *Tetrahedron* **2004**, *60*, 7117−7140. (c) Deiters, A.; Martin, S. F. *Chem. Rev.* **2004**, *104*, 2199−2238.

(23) For recent reports on the synthesis of medium rings and macrocycles via the formation of a trisubstituted double bond by RCM, see: (a) Crimmins, M. T.; Ellis, J. M. *J. Am. Chem. Soc.* **2005**, *127*, 17200−17201 (9-membered). (b) Nicolaou, K. C.; Montagnon, T.; Vassilikogiannakis, G.; Mathison, C. J. N. *J. Am. Chem. Soc.* **2005**, *127*, 8872−8888 (11-membered). (c) Smith, A. B.; Mesaros, E. F.; Meyer, E. A. *J. Am. Chem. Soc.* **2005**, *127*, 6948−6949 (16-membered).

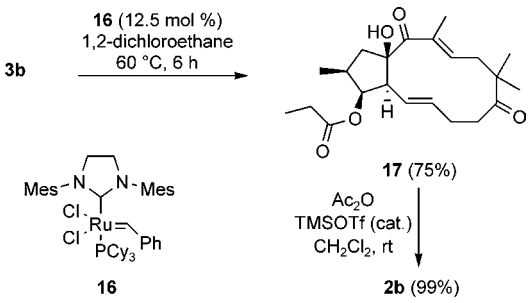
(24) Schwab, P.; Grubbs, R. H.; Ziller, J. W. *J. Am. Chem. Soc.* **1996**, *118*, 100−110.

(25) Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953−956.

(26) Garber, S. B.; Kingsbury, J. S.; Gray, B. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2000**, *122*, 8168−8179.

unsuccessful. Mainly starting material along with varying amounts of inseparable and unidentified byproducts could be isolated. The same result was obtained when other partially or fully protected intermediates of the synthetic sequence that had afforded **3a** were subjected to the RCM conditions.[27] Consequently, we reasoned that the steric requirements for the formation of the trisubstituted C5/C6 double bond are responsible for the failure of the RCM. A successful RCM of a substrate that lacks the C17 methyl group would validate this assumption. Therefore, the ester **3b** was synthesized from **4** via **14b** and **15b** utilizing the aldehyde **5b** (Scheme 4). Gratifyingly, the subsequent RCM of **3b** proceeded successfully using the second generation Grubbs catalyst (**16**) to provide the 17-norjatrophane **17** as a single *E*-configured[28] double-bond isomer (Scheme 5). Finally, the acetylation of the tertiary hydroxyl group with acetic anhydride in the presence of catalytic amounts of TMSOTf provided 15-acetyl-3-propionyl-17-norcharaciol (**2b**).[29]

Scheme 5. RCM of **3b** and Final Acetylation



In summary, attempts to generate the 12-membered carbacycle of 15-acetyl-3-propionyl-characiol (**2a**) by the formation of the trisubstituted C5/C6 double bond by RCM were futile. However, RCM of **3b** under formation of a disubstituted C5/C6 double bond was successful and provided access to the corresponding 17-norjatrophane **2b**. The enantioselective synthesis of **2b** was accomplished in a highly convergent manner, requiring a longest linear sequence of 20 steps with an overall yield of 3.5%. Modified strategies for the synthesis of jatrophane diterpenes that circumvent the encountered problem are currently under investigation in our laboratory.

Acknowledgment. Very generous financial support from the DFG and the FCI is gratefully acknowledged. We thank Prof. Bernd Schmidt for helpful discussions and advice related to ring-closing metathesis and Pia Schwab for an X-ray crystallographic analysis.

Supporting Information Available: Experimental procedures and copies of NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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(27) The relay ring-closing metathesis (RRCM, see: Hoye, T. R.; Jeffrey, C. S.; Tennakoon, M. A.; Wang, J.; Zhao, H. *J. Am. Chem. Soc.* **2004**, *126*, 10210−10211) utilizing a structurally modified substrate did not afford the desired trisubstituted double bond. Details will be published as part of a full paper.

(28) Assignment based on NOESY and ROESY studies. See the Supporting Information for details.

(29) Procopiou, P. A.; Baugh, S. P. D.; Flack, S. S.; Inglis, G. G. A. *J. Org. Chem.* **1998**, *63*, 2342−2347.