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Synthetic Studies toward Jatrophane Diterpenes from *Euphorbia characias*. Enantioselective Synthesis of (−)-15-*O*-Acetyl-3-*O*-propionyl-17-norcharaciol[†]

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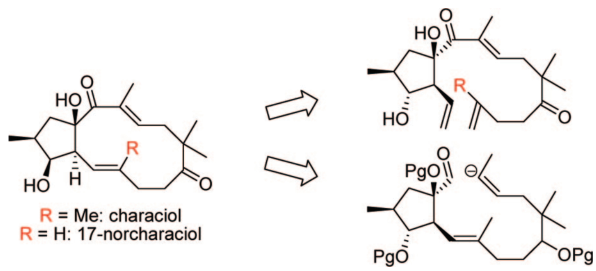
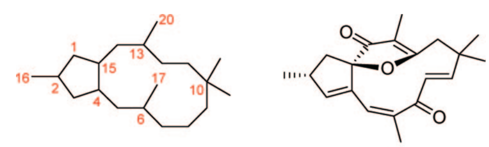


The enantioselective synthesis of (+)-17-norcharaciol is described. An uncatalyzed intramolecular carbonyl−ene reaction and a ring-closing metathesis were used as key C/C-connecting transformations to assemble the *trans*-bicyclo[10.3.0]pentadecane norditerpenoid core. We also report the evolution of our synthetic strategy toward the fully substituted characiol skeleton and the experiences from this venture.

Introduction

Euphorbia (Euphorbiaceae, spurge family) represents a genus of about 2000 species.[1] The majority of these *Euphorbia* species are herbaceous with a worldwide distribution in temperate and tropical zones.[2] Tree, shrubby, and succulent *Euphorbia* species are found almost exclusively in the tropics and subtropics. An often caustic milky latex is abundant in all parts of the plants. *Euphorbia* species are a prolific source for polycyclic diterpenes.[3] The plants have found widespread application in traditional folk medicine as well as gained the attention of the pharmaceutical industry.[4]

Jatrophanes, the dominant bicylic diterpenes from *Euphorbia* sp., are characterized by a bicyclo[10.3.0]pentadecane core (**1**, Figure 1). In 1970, Kupchan and co-workers reported the isolation and structural elucidation of jatrophone (**2**), the first member within this diverse diterpene family, from the roots of *Jatropha gossypiifolia*.[5,6]



1 **2**

FIGURE 1. Jatrophane basic framework (**1**) and jatrophone (**2**) from *Jatropha gossypiifolia*.

Euphoria characias, an evergreen perennial with a bushy habit, is widely distributed in the Mediterranean region. In 1984, Seip and Hecker reported the isolation and structural elucidation of eight jatrophane diterpenes (**3b−i**) from the latex and roots

[†] Dedicated to the memory of Prof. Wolfgang Kreiser.

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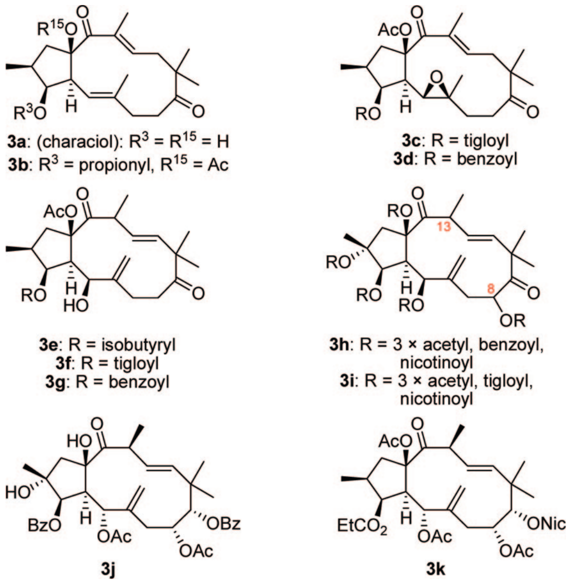
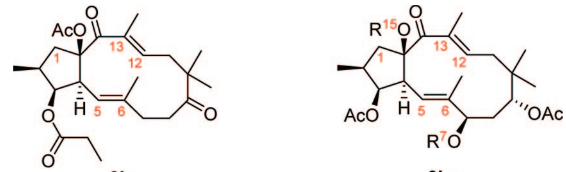


FIGURE 2. Jatrophane diterpenes from *E. characias*.



3b (*E. characias*)

3l-n (*E. pubescens*)

cmpd.	R^7	R^{15}
3l	benzoyl	Ac
3m	butyryl	Ac
3n	benzoyl	H

FIGURE 3. $\Delta^{5,6}\Delta^{12,13}$-Jatrophanes containing an *all-cis*-configured cyclopentane fragment.

of *E. characias* (Figure 2).[7] Essentially, they assigned the relative and absolute configuration of the jatrophanes **3b**−**i** by analogy to related lathyrane diterpenes for which the structure had been unambiguously assigned by X-ray single crystal diffraction.[8] The positioning of the acyl groups was based on NMR data, transesterification experiments, or simply, by analogy. For the jatrophanes **3h**,**i**, the exact positioning of the acyl substituents and the configuration of the stereogenic carbon atoms C8 and C13 was not rigorously verified. Hence, the unambiguous assignment of the gross structure and configuration of these jatrophanes awaits further investigations. Twenty years after the study of Seip and Hecker, Lanzotti and co-workers reported the isolation of 12 jatrophane diterpenes, named euphocharacins A−L (E_{A-L}), from *E. characias*.[9] It was found that the euphocharacins **3j** and **3k** (Figure 2) are stronger inhibitors of the cellular P-glycoprotein-mediated daunomycin efflux than cyclosporine A, a compound which was advanced to clinical trials as a multidrug-resistance reversal agent.[10]

A variety of different biological activities have been reported for jatrophane diterpenes: inhibitory activity on the mammalian mitochondrial respiratory chain,[11] cell cleavage arrest,[12] cytotoxicity against various human cancer cell lines,[13] antiviral activity,[14] antiplasmodial activity,[15] microtubule interaction,[16] multidrug resistance modulating activity,[17] and inhibition of the P-glycoprotein.[18] These findings coupled with intriguing structure of the densely functionalized bicyclic jatrophane core have prompted synthetic efforts by the groups of Mulzer[19] and Uemura,[20] as well as our group.[21]

In this paper, we report in detail the results from a research program that is aimed at the total synthesis of jatrophane diterpenes that are characterized by a C5/C6 and C12/13 double bond as well as an *all-cis*-configured cyclopentane segment. The diester **3b** is the structurally most simple jatrophane within this diterpene family (Figure 3). The structurally related jatrophanes **3l**−**n** have been isolated from *Euphorbia pubescens* (Figure 3).[22] A moderate cell type selective growth inhibitory effect on the nonsmall cell lung cancer cell line (NCI-H460) has been reported for **3l**−**n**.

Results and Discussion

Synthesis of the Cyclopentane Building Block. Our original initiative focused on the development of a synthetic access to characiol (**3a**) as a relay compound for a subsequent synthesis of the jatrophanes **3b**−**d** (Figure 4).

In the synthesis of the bicyclic jatrophane core, the major obstacle was anticipated to be the *trans*-anulation of the 12-membered ring, containing 6 sp^2-hybrized carbon atoms in the relatively short tether, onto the highly substituted 5-membered ring. Nevertheless, we opted for a retrosynthesis that disconnects the C13/C14 bond and provides the vinyl anion synthon **4**, which should be accessible from a vinyl iodide under appropriate halogen−metal exchange conditions (Figure 4). This disconnection mode was selected on the basis of the ample literature evidence for the utility of the Nozaki−Hiyama−Kishi (NHK)

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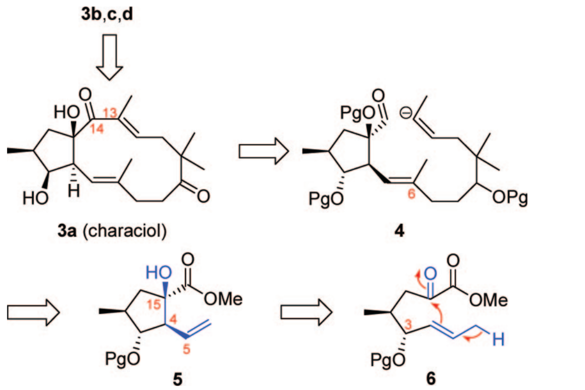


FIGURE 4. Initial retrosynthetic analysis.

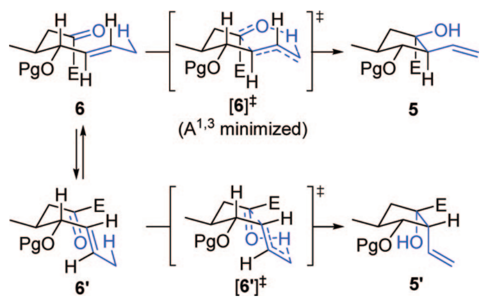
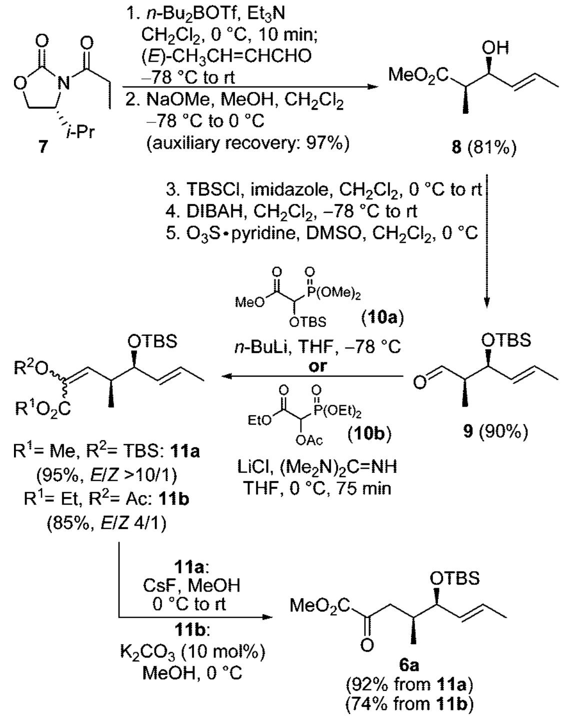


FIGURE 5. Qualitative model for the expected stereochemical course of the carbonyl−ene reaction ($E = CO_2Me$).

reaction for the synthesis of medium to large carbocycles.[23] Further retrosynthetic simplification by the removal of the C6−C13 chain leads to the highly substituted cyclopentanoid **5**. Inspired by previous work on sequential pericyclic reactions,[24] we have identified a carbonyl−ene reaction retron in **5** (homoallylic alcohol segment in blue), and accordingly, the cyclopentanoid **5** can be deconstructed to the acyclic α-keto ester **6**. We speculated that the absolute configuration of C3 in the α-keto ester **6** in concert with the pericyclic nature of the transition state of an uncatalyzed ene reaction would channel the stereochemical course of the ene reaction in our favor (Figure 5). It was envisaged that the minimization of the 1,3-allylic strain[25] in the substrate conformer **6** and the corresponding transition structure [**6**]‡ would cause a sufficient $\Delta\Delta G^‡$ between the two geometrically possible and competing transition states [**6**]‡ and [**6′**]‡. Our qualitative stereochemical model requires an absolute configuration at C3 of the α-keto ester **6** that is opposite to the absolute configuration of C3 in characiol (**3a**). However, we were optimistic that an inversion of the configuration at C3 would be possible at an appropriate stage of the synthesis.

We began with the development of a scalable and robust enantioselective synthesis of the α-keto ester **6** (Scheme 1). Evans aldol chemistry[26] was utilized to provide, after removal

SCHEME 1. Synthesis of the α-Keto Ester 6a



of the auxiliary,[27] the β-hydroxy ester **8** which was protected,[28] reduced to the alcohol, and subsequently oxidized[29] to the corresponding aldehyde **9**.[30] We then faced the requirement of a two-carbon chain homologation with concomitant introduction of the α-keto ester moiety. A two-step sequence was utilized for this purpose. First, a Horner−Wadsworth−Emmons reaction[31] between the aldehyde **9** and methyl 2-(*tert*-butyldimethylsiloxy)-2-(dimethoxyphosphoryl)acetate (**10a**) according to Nakamura afforded the stable silyl enol ether **11a** as an *E*/*Z* = 10/1 mixture of double bond isomers.[32] Chemoselective cleavage of the silyl enol ether in the presence of the silyl alkyl ether with CsF provided the desired α-keto ester **6a** in very good overall yield.[33,34] We then studied the utility of ethyl 2-acetoxy-2-(diethyloxyphosphoryl)acetate (**10b**) as replacement for **10a**. Treatment of the aldehyde **9** with the phosphonoacetate **10b** and 1,1,3,3-tetramethylguanidine in the presence of LiCl[35] provided the vinyl acetate **11b** in slightly lower yield and decreased *E*/*Z* diastereoselectivity compared to the application of **10a**. The inseparable (*E*/*Z*)-mixture of the vinyl acetates **11b** was subsequently treated with catalytic amounts of K_2CO_3 in

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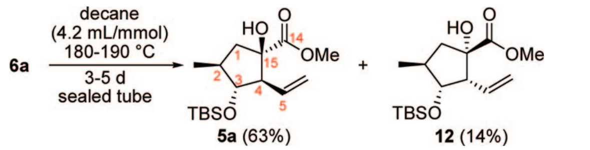
SCHEME 2. Intramolecular Carbonyl Ene Reaction



MeOH[36] to provide the desired α-keto ester **6a**, as well as the unconsumed (*Z*)-configured vinyl acetate **11b** as a mixture of the corresponding methyl and ethyl esters.[37] Attempts to force the transesterification of (*Z*)-**11b** under various conditions were unsuccessful. Nevertheless, due to its convenient preparation, application and lower cost, the phosphonoacetate **10b** is a viable alternative to the higher yielding but more expensive phosphonoacetate **10a**. The sequence depicted in Scheme 1 has been scaled to provide gram quantities of the α-keto ester **6a**.

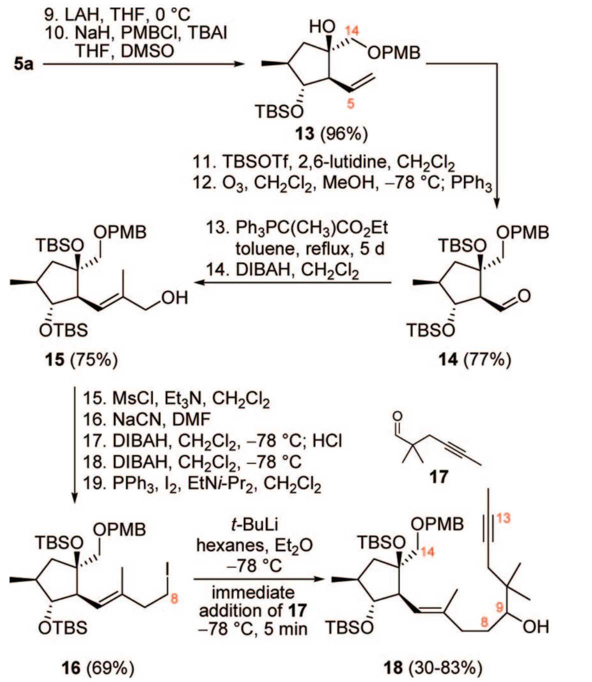
The pivotal carbonyl ene reaction was investigated in the absence of potential catalysts to ensure the concertedness of the mechanism (Scheme 2).[38] Thus, a decane solution (25 mL) of the α-keto ester **6a** (1.5 g) in a glass pressure tube was heated to 180−190 °C (bath temperature) for 3−5 days (TLC control) and afforded the two diastereomeric cyclopentanoids **5a** (63%) and **12** (14%) which are separable by chromatography. Furthermore, traces of the starting material **6a** (5%) were detected in the ^{1}H NMR spectrum of the crude product mixture. The relative configuration of the ene reaction products was initially assigned by NOE spectroscopy and later verified by a X-ray crystal structure analysis of a derivative of **5a**.[21b] In accordance with our original prediction, the major diastereomer **5a** of the ene reaction has the desired absolute configuration at C4 and C15.

In order to verify whether the product distribution of the ene reaction is kinetically or thermodynamically controlled, the separated diastereomeric ene reaction products **5a** and **12** were heated to 180 °C in decane and provided mixtures of **5a** and **12** in roughly the same ratio (**5a**/**12** = 5/1) as obtained from the original ene reaction of **6a**. This outcome clearly indicates that the product distribution of the ene reaction is thermodynamically controlled. Hence, the otherwise useless minor diastereomer **12** could be conveniently recycled to the building block **5a**. The thermodynamic preference for the major diastereomer **5a** can be attributed to a staggered arrangement of the substituents at the four stereogenic carbon atoms (Figure 5). The minor diastereomer **12** is destabilized by an eclipsed arrangement of the substituent at C3 and C4.[39]

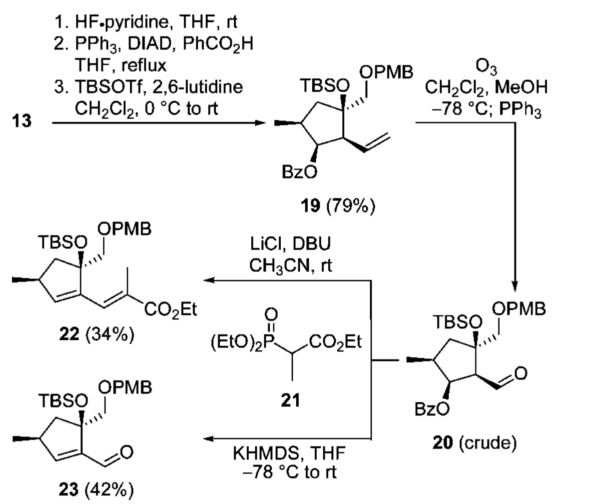
Attempted C12/C13 Ring Closure. The synthetic strategy now required elaboration of the cyclopentanoid **5a** to the alkyne **18** by chain elongation at C6 (Scheme 3). For this purpose, it was required to reduce and protect the ester functionality at C14 first. Thus, treatment of the ester **6a** with $LiAlH_4$ was followed by a Williamson ether synthesis to furnish the PMB[40] ether **13**.

At this juncture, we decided to pursue the inversion of the absolute configuration of C3 (Scheme 4). The TBS protecting

SCHEME 3. Introduction of the C6−C13 Segment



SCHEME 4. Inversion of the Absolute Configuration at C3 and Subsequent Attempts To Assemble the C5/C6 Double Bond



group in **13** was removed to unmask the hydroxyl group at C3. Mitsunobu reaction[41] and subsequent protection of the remaining free hydroxyl group as a TBS ether provided the benzoate **19** featuring the correct absolute configuration of all stereogenic carbon atoms of the cyclopentane segment.[42] Delighted by this result, we attempted to introduce the C5/C6 double bond by olefination. Ozonolysis of the double bond of the cyclopentanoid **19** afforded the aldehyde **20** which decomposed during the attempted silica gel purification. The elimination product **23** was isolated in low yield. The leaving group capacity of the benzoate group along with its *trans*-diaxial arrangement to an acidified proton is, for stereoelectronic reasons, supportive for this

(36) Attempts to use ethanol instead of methanol in combination with a variety of different inorganic bases were unsuccessful.

(37) TLC control indicates that the transesterification of (*E*)-**11b** to the corresponding methyl ester precedes the cleavage of the vinyl acetate moiety.

(38) 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.

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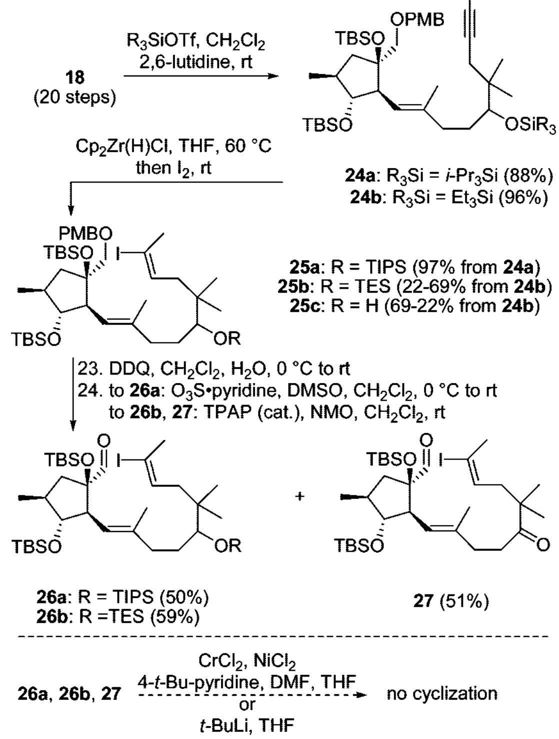
(42) The relative configuration was assigned based on NOESY experiments. See the Supporting Information for details.

undesired event. Consequently, it came to no surprise that the attempted olefination of the sensitive aldehyde **20** with the phosphonate **21** under conventional or Masamune–Roush conditions[43] led to a comparable result (Scheme 4).

In order to obviate the risk of the undesired elimination, we decided to postpone the inversion of C3 to a later point of the synthesis. Hence, we continued our synthetic efforts with the cyclopentanoid **13** as depicted in Scheme 3. Protection of the tertiary hydroxyl group as a TBS ether[44] followed by ozonolysis of the double bond afforded the aldehyde **14** which could be purified by chromatography. Because more convergent strategies failed (vide infra), we aimed for a stepwise construction of the C6 to C13 segment. Accordingly, olefination utilizing a stabilized Wittig ylide[45] and subsequent DIBAH reduction furnished the *E*-configured allylic alcohol **15**. Mesylation of the primary hydroxyl group of **15** and subsequent Kolbe nitrile synthesis provided the homologated cyanide. The cyano group was then reduced with DIBAH[46] via the aldehyde, and the resulting homoallylic alcohol was converted into the homoallylic iodide **16**. The coupling of the iodide **16** with the aldehyde **17** was investigated next. Treatment of the homoallylic iodide **16** with *tert*-BuLi (2 equiv)[47] and immediate addition of the aldehyde **17** afforded the alcohol **18** as a 1/1 mixture of diastereomers. Though initially quite successful, the coupling reaction was unreliable and yields were fluctuating between 30–83%; the dominating byproduct was the corresponding deiodinated substrate.[48]

We turned next to the elaboration of the alkyne **18** into the (*E*)-configured vinyl iodide **26** needed for the pivotal ring-closing nucleophilic addition (Scheme 5). For this purpose, the C9 hydroxyl group of **18** was protected with two different silyl protecting groups (TES, TIPS) to afford the alkynes **24a** and **24b**. The TIPS-protected alkyne **24a** was then subjected to a hydrozirconation/iodination protocol to provide **25a** as a single double-bond isomer.[49] Subjecting the TES-protected alkyne **24b** to identical reaction conditions afforded the desired vinyl iodide **25b** in inconsistent yields. The major byproduct was the alcohol **25c**; the consequence of the cleavage of the TES protecting group. Though the vinyl iodides **25b** and **25c** were isolated in fluctuating amounts, the combined yield was constant and they were separable by chromatography. The vinyl iodides **25a–c** were then treated with DDQ to remove the PMB-protecting group[50] and subsequently oxidized with TPAP/NMO[51] (**25b**,**c**) or DMSO/SO_3·pyridine[29] (**25a**) to afford the aldehydes **26a**,**b** as well as the keto aldehyde **27**. With three structurally distinct vinyl iodides available, the projected cyclization under

SCHEME 5. Toward the Substrates for the Unsuccessful Intramolecular NHK Reaction



Nozaki–Hiyama–Kishi[52] or iodine–lithium exchange[47] conditions was investigated next. Unfortunately, all efforts led only to the decomposition or reisolation of the starting material. Furthermore, the chemistry utilized for the preparation of the cyclization precursors, which were needed further exploration and optimization, was extremely cumbersome. With the intention of rendering the synthesis of the cyclization precursors more convergent, two alternative approaches toward the alkyne **30** were investigated (Scheme 6).

Attempts to alkylate the enolate derived from the ketone **29a** or the hydrazone **29b**[53] under various conditions with the allylic iodide **28** failed to provide the alkyne **30**. In a second approach to **30**, we envisioned to utilize a Claisen rearrangement[54] of the allyl vinyl ether **31**. However, in our hands, the allylic alcohol **33** was reluctant to undergo an esterification with the acid **32** under various esterification conditions.[55]

Attempted C5/C6 Ring Closure by RCM. Given the difficulties encountered in the NHK cyclization attempts and the overall length and the inefficiency of the synthetic sequence toward the cyclization precursors, an alternate retrosynthesis of characiol (**3d**) was required. Regarding convergence as key to efficiency, we proposed a strategy that rested on the availability of two larger fragments and the potential of the available

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(44) Corey, E. J.; Cho, H.; Rücker, C.; Hua, D. H. *Tetrahedron Lett.* **1981**, *22*, 3455–3458.

(45) Attempts to utilize the phosphonate **21** led to elimination.

(46) Miller, A. E. G.; Biss, J. W.; Schwartzman, L. H. *J. Org. Chem.* **1959**, *24*, 627–630.

(47) (a) Bailey, W. F.; Punzalan, E. R. *J. Org. Chem.* **1990**, *55*, 5404–5406. (b) Negishi, E.; Swanson, D. R.; Rousset, C. J. *J. Org. Chem.* **1990**, *55*, 5406–5409.

(48) Attempts to alkylate a lithiated 1,3-dithiane of the aldehyde **17** with the homoallylic alcohol **16** also delivered the corresponding protodeiodinated substrate.

(49) (a) Hart, D. W.; Schwartz, J. *J. Am. Chem. Soc.* **1974**, *96*, 8115–8116. (b) Hart, D. W.; Blackburn, T. F.; Schwartz, J. *J. Am. Chem. Soc.* **1975**, *97*, 679–680. For a review, see: (c) Wipf, P.; Jahn, H. *Tetrahedron* **1996**, *52*, 12853–12910.

(50) (a) Oikawa, Y.; Yoshioka, T.; Yonemitsu, O. *Tetrahedron Lett.* **1982**, *23*, 885–888. (b) Horita, K.; Yoshioka, T.; Tanaka, T.; Oikawa, Y.; Yonemitsu, O. *Tetrahedron* **1986**, *42*, 3021–3028.

(51) Ley, S. V.; Norman, J.; Griffith, W. P.; Marsden, S. P. *Synthesis* **1994**, 639–666.

(52) (a) Takai, K.; Kimura, K.; Kuroda, T.; Hiyama, T.; Nozaki, H. *Tetrahedron Lett.* **1983**, *24*, 5281–5284. (b) Jin, H.; Uenishi, J.; Christ, W. J.; Kishi, Y. *J. Am. Chem. Soc.* **1986**, *108*, 5644–5646. (c) Takai, K.; Tagashira, M.; Kuroda, T.; Oshima, K.; Utimoto, K.; Nozaki, H. *J. Am. Chem. Soc.* **1986**, *108*, 6048–6050. For the application of 4-*tert*-butylpyridine as an additive, see: (d) Stamos, D. P.; Sheng, X. C.; Chen, S. S.; Kishi, Y. *Tetrahedron Lett.* **1997**, *38*, 6355–6358.

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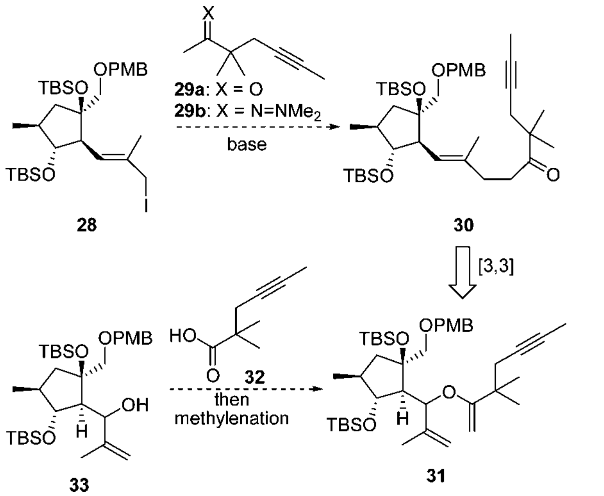
(55) (a) Montalbetti, C. A. G. N.; Falque, V. *Tetrahedron* **2005**, *61*, 10827–10852. (b) Han, S.-Y.; Kim, Y.-A. *Tetrahedron* **2004**, *60*, 2447–2467.

SCHEME 6. Unsuccessful Strategies for the Synthesis of the Building Block 30



synthetic methodology for double-bond formation. As depicted in Figure 6, we envisioned to exploit a ring-closing metathesis[56,57] (RCM) of the triene **34a** to generate the C5/C6 double bond, ideally in the absence of any protecting group. Disconnecting the C12/C13 double bond of the α,*β*-unsaturated ketone **34a** by a HWE olefination[31] transform leads to the synthons **35** and **36a**. The required synthesis of the aldehyde **36a** was no cause of concern and the already developed ene reaction could be utilized for the synthesis of the phosphonate **35**.

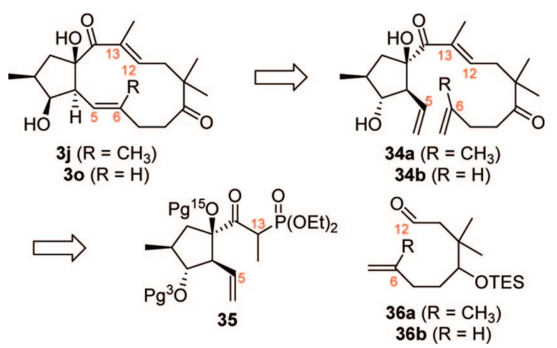
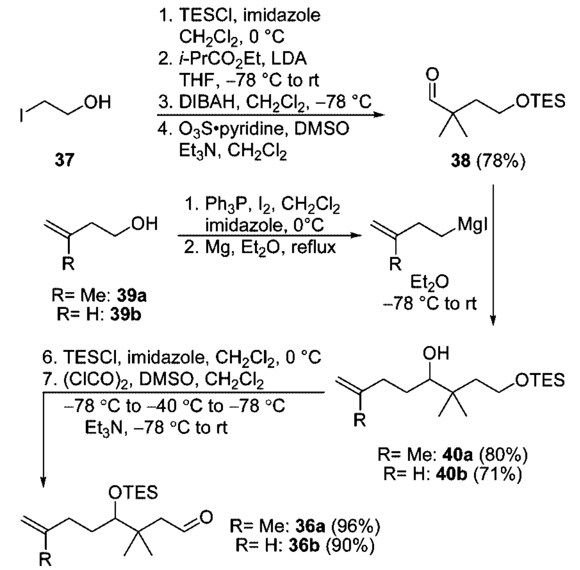


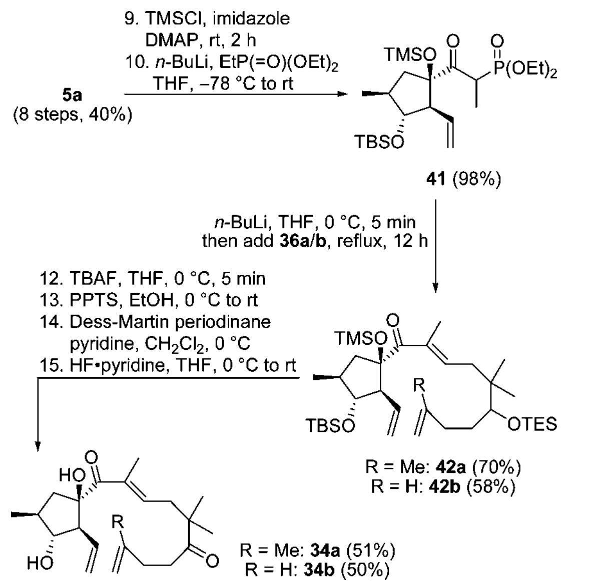
FIGURE 6. Second-generation retrosynthesis.

The synthesis of the aldehyde **36a** commenced with the protection of 2-iodoethanol (**37**) and was continued with the

SCHEME 7. Synthesis of the Aldehydes 36a,b



SCHEME 8. Preparation of the Trienes 34a,b for the RCM



alkylation of the lithium enolate of ethyl isobutyrate with TES-protected 2-iodoethanol followed by a redox sequence to provide the aldehyde **38** (Scheme 7). Exposure of the aldehyde **38** to a Grignard reagent that was prepared from the highly volatile 4-iodo-2-methyl-1-butene furnished the alcohol **40a** which was protected as a TES ether. In situ removal of the TES protecting group from the primary hydroxyl group and oxidation[58] under Swern[59] conditions provided the desired aldehyde **36a**.[60]

The synthesis of the phosphonate **41** from the major diastereomer **5a** of the ene reaction and the subsequent HWE olefination with the aldehyde **36a** was investigated next (Scheme 8). Following the protection of the tertiary hydroxyl group of **5a** as trimethylsilyl ether, a Claisen-type condensation of the

(56) For selected recent examples for the formation of medium-sized rings and macrocycles by RCM, see: (a) Toumi, M.; Couty, F.; Evano, G. *J. Org. Chem.* **2008**, *73*, 1270–1281. (b) Sun, L.; Geng, X.; Geney, R.; Li, Y.; Simmerling, C.; Li, Z.; Lauher, J. W.; Xia, S.; Horwitz, S. B.; Veith, J. M.; Pera, P.; Bernacki, R. J.; Ojima, I. *J. Org. Chem.* **2008**, *73*, 9584–9593. (c) Shu, C.; Zeng, X.; Hao, M.-H.; Wei, X.; Yee, N. K.; Busacca, C. A.; Han, Z.; Farina, V.; Senanayake, C. H. *Org. Lett.* **2008**, *10*, 1303–1306. (d) Ramana, C. V.; Khaladkar, T. P.; Chatterjee, S.; Gurjar, M. K. *J. Org. Chem.* **2008**, *73*, 3817–3822. (e) Trost, B. M.; Dong, G.; Vance, J. A. *J. Am. Chem. Soc.* **2007**, *129*, 4540–4541. (f) Trost, B. M.; Yang, H.; Thiel, O. R.; Frontier, A. J.; Brindle, C. S. *J. Am. Chem. Soc.* **2007**, *129*, 2206–2207. (g) Galletti, E.; Avramova, S. I.; Renzulli, M. L.; Corelli, F.; Botta, M. *Tetrahedron Lett.* **2007**, *48*, 751–754. (h) Smith, A. B.; Basu, K.; Bosanac, T. *J. Am. Chem. Soc.* **2007**, *129*, 14872–14874. (i) Reymond, S.; Cossy, J. *Tetrahedron* **2007**, *63*, 5918–5929. (j) Fürstner, A.; Nagano, T.; Müller, C.; Seidel, G.; Müller, O. *Chem. Eur. J.* **2007**, *13*, 1452–1462. (k) Fürstner, A.; Nevado, C.; Waser, M.; Tremblay, M.; Chevrier, C.; Teplý, F.; Aissa, C.; Moulin, E.; Müller, O. *J. Am. Chem. Soc.* **2007**, *129*, 9150–9161. (l) Larrosa, I.; Da Silva, M. I.; Gómez, P. M.; Hannen, P.; Ko, E.; Lenger, S. R.; Linke, S. R.; White, A. J. P.; Wilton, D.; Barrett, A. G. M. *J. Am. Chem. Soc.* **2006**, *128*, 14042–14043.

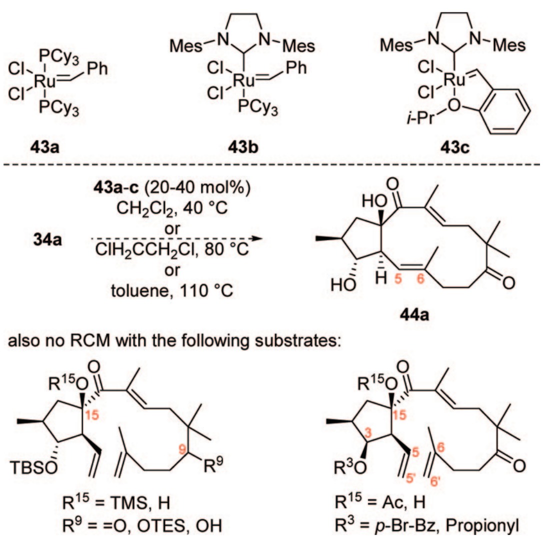
(57) For selected reviews, see: (a) Nicolaou, K. C.; Bulger, P. G.; Sarlah, D. *Angew. Chem., Int. Ed.* **2005**, *44*, 4490–4527. (b) Grubbs, R. H. *Tetrahedron* **2004**, *60*, 7117–7140. (c) Deiters, A.; Martin, S. F. *Chem. Rev.* **2004**, *104*, 2199–2238.

(58) Rodriguez, A.; Nomen, M.; Spur, B. W.; Godfroid, J. J. *Tetrahedron Lett.* **1999**, *40*, 5161–5164.

(59) (a) Mancuso, A. J.; Huang, S.-L.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480–2482. (b) Omura, K.; Swern, D. *Tetrahedron* **1978**, *34*, 1651–1660. (c) Mancuso, A. J.; Swern, D. *Synthesis* **1981**, 165–184.

(60) The sensitivity of the aldehyde **36** required buffering of the silica gel with Et_3N.

SCHEME 9. Attempted RCM



resulting ester with lithiated diethyl ethylphosphonate afforded the β-keto phosphonate **41**. Treatment of the aldehyde **36a** with the lithiated β-keto phosphonate **41** provided the α,β-unsaturated ketone **42a** as a single double-bond isomer. Successive removal of the TMS and the TES protecting group and subsequent oxidation of the secondary alcohol furnished the corresponding C9-ketone. The TBS ether was then cleaved to provide the desired diol **34a** in a longest linear sequence of 15 scalable steps from the acylated Evans auxiliary **7**.

With the requisite substrate **34a** in our hands, the RCM to the bicyclic jatrophane scaffold **44a** was explored (Scheme 9). For this purpose, the Grubbs catalysts **43a**,[61] **b**[62] and the Hoveyda catalyst **43c**[63] were utilized in different solvents at different temperatures (concentration of the substrate in the range of $(2-3) \times 10^{-3}$ mol/L). Discouragingly, not even a trace of the desired cyclization product **44a** could be identified under the reaction conditions depicted in Scheme 9. Varying amounts of the starting material were recovered. Target-aimed structural modifications at C3, C9, and C15 provided a small collection of alternative substrates for the RCM (Scheme 9). Again, all attempts to realize a RCM under various reaction conditions were futile. Depending on the substrate structure, catalyst structure, and reaction temperature, varying amounts of starting material could be isolated. Interestingly, for the substituent pattern $R^3 = H$, $R^9 = (=O)$ and $R^{15} = H$, the extent of the decomposition of the starting material was dependent on the catalyst loading (**43b**) and the reaction temperature. We speculated that in this case, the initiation of the metathesis at the sterically less encumbered C5/C5′ double bond takes place, but the subsequent productive catalytic cycle can not be completed. A possible remedy would be to direct the initiation of the catalytic cycle to the presumably less reactive C6/C6‘ double bond which would make the more reactive C5/C5′ double bond available for the subsequent ruthenacyclobutane formation.

Attempted C5/C6 Ring Closure by RRCM. The relay ring-closing metathesis (RRCM) can be used to determine the initiation side of the RCM by a structural modification of the

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

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

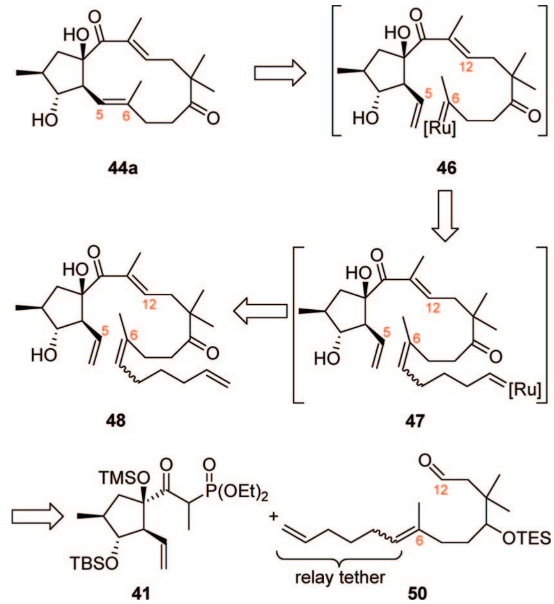
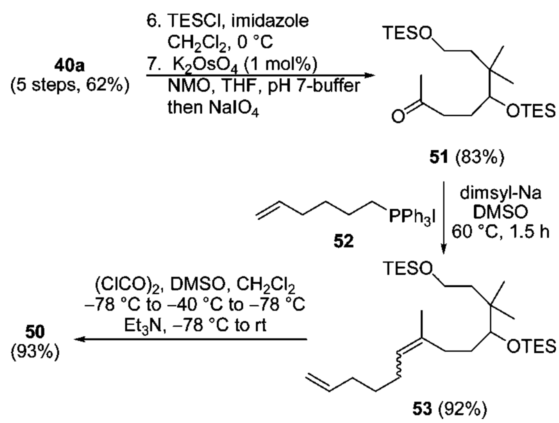


FIGURE 7. Retrosynthetic analysis based on a relay ring-closing metathesis (RRCM).

SCHEME 10. Synthesis of the Aldehyde 50 as a 2/1 Mixture of Double-Bond Isomers

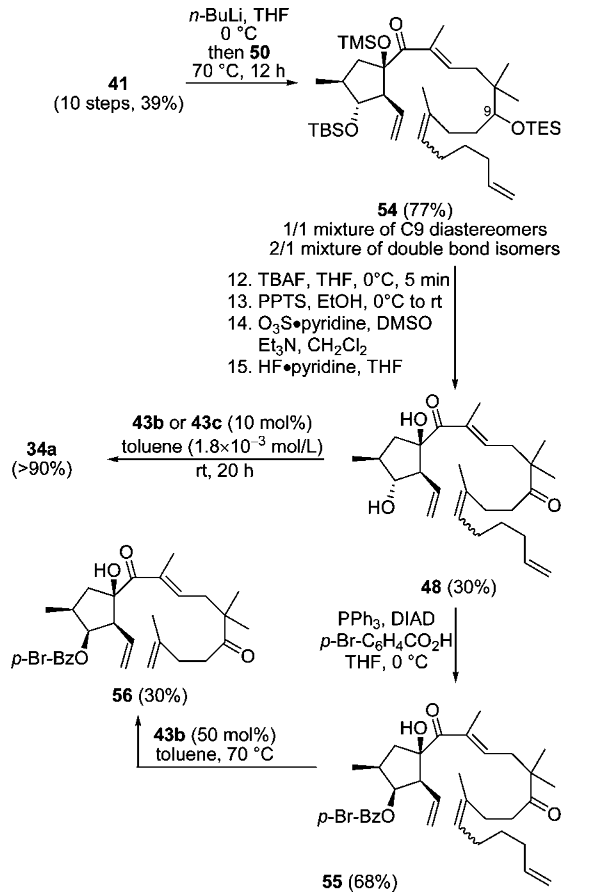


substrate.[64] In the present case, our objective was to enforce the formation of the ruthenium carbene complex **46** from the carbene complex **47** by RCM under extrusion of cyclopentene (Figure 7). Hence, the tetraene **48** would be offered as substrate to the metathesis catalyst with the expectation that the terminal double bond of the relay tether serves as the most attractive initiation site. Applying the already successful olefination transform for the retrosynthesis of the tetraene **48** furnishes the known phosphonate **41** and the aldehyde **50** which contains the required relay tether.

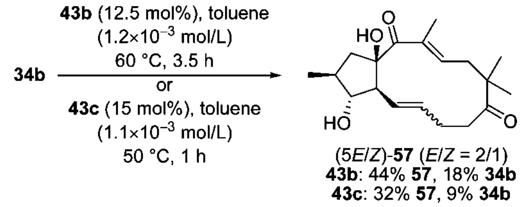
The synthesis of the aldehyde **50** was realized as depicted in Scheme 10. Starting with the already synthesized alcohol **40a** (Scheme 7), the hydroxyl group was protected and the double bond was oxidatively cleaved to provide the ketone **51**. A Wittig

(64) (a) Hoye, T. R.; Jeffrey, C. S.; Tennakoon, M. A.; Wang, J.; Zhao, H. *J. Am. Chem. Soc.* **2004**, *126*, 10210–10211. (b) Wang, X.; Bowman, E. J.; Bowman, B. J.; Porco, J. A. *Angew. Chem. Internat. Ed.* **2004**, *43*, 3601–3605. (c) Wallace, D. J. *Angew. Chem., Int. Ed.* **2005**, *44*, 1912–1915. (d) Roethle, P. A.; Chen, I. T.; Trauner, D. *J. Am. Chem. Soc.* **2007**, *129*, 8960–8961. (e) Sato, D.; Fujiwara, K.; Kawai, H.; Suzuki, T. *Tetrahedron Lett.* **2008**, *49*, 1514–1517. (f) Marvin, C. C.; Voight, E. A.; Suh, J. M.; Paradise, C. L.; Burke, S. D. *J. Org. Chem.* **2008**, *73*, 8452–8457. (g) Xie, Q.; Denton, R. W.; Parker, K. A. *Org. Lett.* **2008**, *10*, 5345–5348.

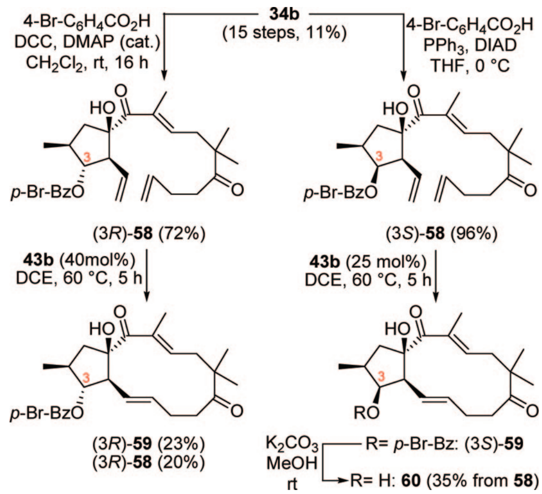
SCHEME 11. Unsuccessful RRCM Attempts



SCHEME 12. Successful RCM Provides the 17-Norjatrophane 57



SCHEME 13. Successful RCM Provides (+)-17-Norcharaciol 60



olefination afforded the diene **53** as a 2/1 mixture of double bond isomers. In situ deprotection of the primary hydroxyl group and oxidation under Swern conditions delivered the desired aldehyde **50**.[58]

With the phosphonate **41** and the aldehyde **50** in hand, we proceeded with their coupling which provided the tetraene **54** as single double bond isomer with respect to the newly generated C12/C13 double bond (Scheme 11).

Stepwise removal of the silyl protecting groups and oxidation of the C9 hydroxyl group afforded the tetraene **48** which was subjected to the RRCM conditions using either the Grubbs II (**43b**) or the Hoveyda catalyst (**43c**). Very discouragingly, not a trace of the desired RRCM product could be isolated. Instead, the relay tetherless triene **34a** was observed in almost quantitative yield,[65] apparently formed by a RCM with release of cyclopentene followed by an intermolecular cross metathesis process. We were aware from previous experiences that the result of the RCM is dependent on the structure of the substrate (vide supra). Therefore, the benzoate **55** was synthesized and treated with substoichiometric amounts of the metathesis catalyst **43b**. As a result, we observed the formation of the triene **56** and a substantial decomposition of the starting material **55**.

Initially, we attributed the failure of the RCM and RRCM to the presence of the C17 methyl group and surmised that the C17 methyl group may be responsible for the build-up of unacceptable steric strain during the metathesis process. In order to support this hypothesis, we investigated the RCM of a substrate lacking the C17 methyl group.

Total Synthesis of (+)-17-Norcharaciol (60) by RCM. The required triene **34b** (Figure 6) without the C17 methyl group was synthesized analogous to **34a** as outlined in Schemes 7 and 8. Triene **34b** underwent RCM upon exposure to the metathesis catalyst **43b** (12.5 mol%) at 60 °C to afford the 17-norjatrophane **57** as a mixture of double-bond isomers (44%, *E*/*Z* = 2/1) and some starting material (18%) (Scheme 12). Application of the metathesis catalyst **43c** led to an inferior result, although no attempts were made to optimize the reaction conditions.

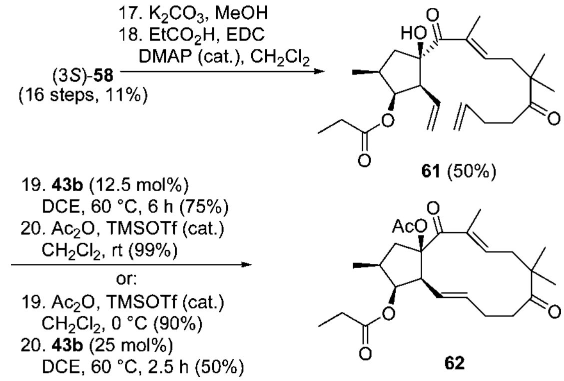
Additional experiments were performed to test the responsiveness of the *E*/*Z*-selectivity of the RCM toward structural changes at C3 (Scheme 13). Mitsunobu reaction of **34b** provided the (3*S*)-configured benzoate **58**, whereas simple esterification with 4-bromobenzoic acid made the (3*R*)-configured benzoate **58** available. Notably, when the triene (3*S*)-**58** was treated with Grubbs' second-generation metathesis catalyst **43b** (25 mol%, unoptimized conditions) at 60 °C in 1,2-dichloroethane (DCE), the norjatrophane (3*S*)-**59** was observed as single *E*-configured double bond isomer, albeit contaminated with an inseparable impurity.[66] Subsequent transesterification then provided 17-norcharaciol **60**. The beneficial effect of the benzoate group for the *E*/*Z* selectivity of the metathesis became also apparent when the diastereomeric ester (3*R*)-**58** was treated with **43b** (40 mol%, unoptimized conditions). In the event, (3*R*)-**59** was isolated as single (*E*)-configured double bond isomer, albeit in lower yield, with incomplete conversion and contaminated with inseparable impurities.

We turned next our attention to the completion of the synthesis of (−)-15-*O*-acetyl-3-*O*-propionyl-17-norcharaciol

(65) An increased reaction temperature led to a decreased yield of **34a**. Performing the RRCM in 1,2-dichlorethane at 80 °C with **43b** (10 mol %) also led to the formation of **34a** (75%).

(66) The double-bond configuration was assigned on the basis of NOESY experiments. An analogous result was obtained in toluene at 60°C.

SCHEME 14. Final Steps of Synthesis of (−)-15-*O*-Acetyl-3-*O*-propionyl-17-norcharaciol 62



(**62**), the 17-desmethyl derivative of the naturally occurring characiol diester **3b** (Scheme 14). Cleavage of the benzoate in (3*S*)-**58** by transesterification followed by 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide[67] (EDC)-mediated esterification with propionic acid provided the triene **61** in moderate overall yield (50%). Exposure of **61** to Grubbs' second-generation metathesis catalyst (**43b**, 5 × 2.5 mol %) furnished the corresponding 17-norjatrophane in very good yield (75%). The catalyst **43b** was added as a solid in five equal portions, a portion after each 1 h reaction period.[68] With the 17-norjatrophane in hand, it was straightforward to complete the synthesis of **62** by acetylation of the tertiary hydroxyl group in the presence of acetic anhydride and catalytic amounts of $(CH_3)_3SiOTf$.[69] Notably, the reversal of the last two steps—acetylation first, then RCM—led to lower yields, in particular with respect to the RCM event.

Conclusion

We have reported studies toward the total synthesis of $\Delta^{5,6}\Delta^{12,13}$ jatrophane diterpenoids. Key features of the synthesis include (i) the homologation of an α-chiral aldehyde into a γ-chiral α-keto ester, (ii) the diastereoselective uncatalyzed intramolecular carbonyl ene reaction of an δ,ε-unsaturated α-keto ester to provide a densely functionalized cyclopentane building block, and (iii) the formation of a 12-membered ring by ring closing metathesis. The work culminated in the synthesis of the non-natural 17-norjatrophane (−)-15-*O*-acetyl-3-*O*-propionyl-17-norcharaciol (**62**) in 20 steps and 4% yield along the longest linear sequence. Although our efforts toward the synthesis of the complete jatrophane core have not yet been successful, the experiences and synthetic strategies described herein should be useful for the design of alternate approaches toward the jatrophane framework. This objective is currently being pursued in our laboratory and will be reported in due course.

Experimental Section

Silyl Enol Ether (*E*)-11a. To a solution of the phosphonate **10a**[32] (4.44 g, 14.22 mmol, 1.2 equiv) in THF (56 mL) at −78 °C was added *n*-BuLi (5.55 mL, 2.35 M in hexanes, 13.03 mmol, 1.1 equiv). The reaction mixture was stirred 15 min at −78 °C. A cooled (−78 °C) solution of the aldehyde **9** (2.87 g, 11.85 mmol, 1 equiv) was then slowly added at −78 °C. After being stirred for 30 min at −78 °C, the reaction mixture was diluted with saturated aqueous NH_4Cl solution and CH_2Cl_2. The phases were separated, and the aqueous phase was extracted with CH_2Cl_2 (3×). The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. Purification of the residue by chromatography delivered the silyl enol ether **11a** (4.84 g, 13.5 mmol, 95%) as a mixture of double-bond isomers (*E*/*Z* > 10:1): R_f 0.7 (heptane/ethyl acetate 3/1); ^{1}H NMR (300 MHz, $CDCl_3$) δ −0.13 (s, 3H), −0.10 (s, 3H), 0.00 (s, 3H), 0.01 (s, 3H), 0.76 (s, 9H), 0.82 (s, 9H), 0.88 (d, *J* = 6.8 Hz, 3H), 1.53−1.58 (m, 3H), 3.02−3.15 (m, 1H), 3.63 (s, 3H), 3.78 (dd, $J_1 = J_2$ = 6.2 Hz, 1H), 5.23−5.50 (m, 2H), 5.27 (d, *J* = 10.7 Hz, 1 H), 5.84 (d, *J* = 10.1 Hz, 1H of (*Z*)-**11a**); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ −5.0, −4.9, −4.1, 16.1, 17.6, 18.2, 25.6, 25.9, 38.3, 51.3, 77.4, 126.2, 128.3, 133.0, 139.6, 165.2; IR (thin film on KBr) ν 1730, 2860−2960 cm^{-1}. Anal. Calcd for $C_{22}H_{44}O_4Si_2$: C, 61.63; H 10.34. Found: C, 61.51; H, 10.57.

TABLE 1. Selected NOESY Correlations of 15

	NOESY correlations of **15** (jatrophane numbering)		stereochemical assignment
1	1-H^{Re} (1.29 ppm)	5-CH (5.49 ppm)	*cis*: 1-H^{Re}/-CH=C(CH$_3$)−
2	4-CH (2.65 ppm)	2-CH (1.75−1.85 ppm)	*cis*: 4-H/2-H
3	4-CH (2.65 ppm)	1-H^{Si} (2.34 ppm)	*cis*: 4-H/1-H^{Si}
4	4-CH (2.65 ppm)	14-CH$_2$ (3.19 ppm)	*cis*: 4-H/14-CH$_2$
5	3-CH (3.71 ppm)	1-H^{Re} (1.29 ppm)	*cis*: 3-H/1-H^{Re}
6	5-CH (5.49 ppm)	7-CH$_2$ (4.01 ppm)	(5*E*)

Alcohol 15. To a solution of the aldeyhde **14** (803 mg, 1.54 mmol, 1 equiv) in toluene (15 mL) in a commercially available sealed tube was added (1-ethoxycarbonylethylidene)triphenylphosphorane (1.11 g, 3.07 mmol, 2 equiv). The tube was sealed with a Teflon screw-cap and placed into an oil bath at 130 °C for 5 d. The toluene was then removed at reduced pressure, the residue redissolved in a heptane/ethyl acetate 10/1, and the solution filtered through a plug of Celite. The filtrate was concentrated at reduced pressure, and the crude product was purified by chromatography (heptane to heptane/ethyl acetate 50/1) to afford the olefin contaminated with an inseparable impurity. A small purified sample for analytical purposes could be isolated: R_f 0.40 (heptane/ethyl acetat 5/1); ^{1}H NMR (300 MHz, $CDCl_3$) δ −0.16 (s, 3H), −0.07 (s, 3H), −0.05 (s, 3H), 0.00 (s, 3H), 0.76 (s, 9H), 0.81 (s, 9H), 1.00 (d, *J* = 6.8 Hz, 3H), 1.20 (t, *J* = 7.0 Hz, 3H), 1.26 (dd, J_1 = 14.1 Hz, J_2 = 8.0 Hz, 1H), 1.75 (d, *J* = 1.6 Hz, 3H), 1.70−1.89 (m, 1H), 2.31 (dd, J_1 = 13.8 Hz, J_2 = 10.2 Hz, 1H), 2.74 (dd, J_1 = 10.7 Hz, J_2 = 9.7 Hz, 1H), 3.08 (d, *J* = 8.8 Hz, 1H), 3.14 (d, *J* = 8.7 Hz, 1H), 3.74 (s, 3H), 3.77 (dd, $J_1 = J_2$ = 9.1 Hz, 1H), 4.11 (q, *J* = 7.1 Hz, 2H), 4.30 (d, *J* = 11.4 Hz, 1H), 4.35 (d, *J* = 11.7 Hz, 1H), 6.78−6.85 (m, 3H), 7.13−7.19 (m, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ −4.4, −4.2, −2.4, 12.9, 14.2, 17.9, 18.4, 18.9, 25.8, 25.9, 40.3, 42.9, 54.6, 55.2, 60.2, 73.0, 74.8, 83.0, 83.9, 113.7, 129.2, 129.6, 130.2, 141.8, 159.1, 168.0; IR (film on KBr) ν 775, 835, 1110, 1250, 1510, 1710, 2860, 2930, 2950 cm^{-1}; $[\alpha]^{25}_D$ +2.6 (c 1.55, $CHCl_3$). Anal. Calcd for $C_{33}H_{58}O_6Si_2$: C, 65.30; H, 9.63. Found: C, 65.21; H, 9.65.

To a solution of the contaminated olefin (774 mg, assumed 1.53 mmol, 1 equiv) in CH_2Cl_2 (15 mL) was added DIBAH (4.6 mL, 4.6 mmol, 1 M in CH_2Cl_2, 3 equiv) at −78 °C. The reaction mixture was stirred for 30 min at −78 °C. Saturated aqueous potassium sodium tartrate solution was then added, and the resulting mixture was stirred at ambient temperature for 1 h. The phases were separated, and the aqueous layer was extracted with CH_2Cl_2 (3×). The combined organic phases were dried ($MgSO_4$) and concentrated at reduced pressure. Chromatographic purification (heptane to heptane/ethyl acetate 20/1) delivered the allylic alcohol **15** (650 mg, 1.15 mmol, 75% from **14**) as a colorless oil: R_f 0.37 (heptan/ethyl acetate 3/1); COSY, HSQC, HMBC, and NOESY (Table 1) methods were used to confirm the NMR peak assignments on the

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basis of the jatrophane numbering; ^{1}H NMR (500 MHz, $CDCl_3$) δ −0.06 (s, TBS-CH_3, 3H), −0.01 (s, TBS-CH_3, 3H), 0.02 (s, TBS-CH_3, 3H), 0.06 (s, TBS-CH_3, 3H), 0.84 (s, TBS- 3 × CH_3, 9H), 0.86 (s, TBS- 3 × CH_3, 9H), 1.06 (d, J = 6.9 Hz, 16-CH_3, 3H), 1.29 (dd, J_1 = 14.0 Hz, J_2 = 8.0 Hz, 1-CH_2, 1H^{Re}), 1.65 (s, 17-CH_3, 3H), 1.75−1.85 (m, 2-CH, 1 H), 2.34 (dd, J_1 = 13.9 Hz, J_2 = 10.4 Hz, 1-CH_2, 1H^{Si}), 2.65 (dd, J_1 = J_2 = 9.9 Hz, 4-CH, 1H), 3.17 (d, J = 8.7 Hz, 14-CH_2, 1H), 3.20 (d, J = 8.7 Hz, 14-CH_2, 1H), 3.71 (dd, J_1 = J_2 = 8.8 Hz, 3-CH, 1 H), 3.80 (s, −OCH_3, 3 H), 4.01 (s, 7-CH_2, 2 H), 4.36 (d, J = 11.7 Hz, −OCH_2-Ar-OCH$_3$, 1 H), 4.42 (d, J = 11.5 Hz, −OCH_2-Ar-OCH$_3$, 1 H), 5.49 (d, J = 10.1 Hz, 5-CH, 1 H), 6.87 (d, J = 8.5 Hz, −OPMB, 2H), 7.23 (d, J = 8.5 Hz, −OPMB, 2H), no observable OH resonance; ^{13}C NMR (126.0 MHz, $CDCl_3$) δ −4.3 (TBS-CH$_3$), −4.0 (TBS-CH$_3$), −2.4 (2 × TBS-CH$_3$), 14.2 (17-CH$_3$), 17.9 (TBS-C), 18.4 (TBS-C), 19.0 (16-CH$_3$), 25.8 (3 × TBS-CH$_3$), 25.9 (3 × TBS-CH$_3$), 39.8 (2-CH), 42.7 (1-CH$_2$), 53.3 (4-CH), 55.2 (−Ar-OCH$_3$), 69.4 (7-CH$_2$), 72.9 (−OCH$_2$-Ar-OCH$_3$), 74.9 (14-CH$_2$), 82.4 (15-C), 84.1 (3-CH), 113.6 (−OPMB− 2 × CH═), 125.4 (5-CH═), 129.1 (−OPMB− 2 × CH═), 130.4 (−OPMB−C═), 137.0 (6-C═), 159.0 (−OPMB−C═); IR (thin film on KBr) ν 830, 1040, 1090, 1250, 1510, 2860, 2930, 2950 cm^{-1}; $[\alpha]^{30}_D$ +4.7 (c 1.6, $CHCl_3$). Anal. Calcd for $C_{31}H_{56}O_5Si_2$: C, 65.91; H, 9.99. Found: C, 66.06; H, 10.13.

Alkyne 18. To a cooled (−78 °C) solution of the iodide **16** (405 mg, 0.59 mmol, 1 equiv) in hexanes (10 mL) and Et_2O (6.5 mL) were added *t*-BuLi (0.96 mL, 1.29 mmol, 1.35 M in pentane, 2.2 equiv) and, immediately, a cooled (−78 °C) solution of the aldehyde **17** (146 mg, 1.18 mmol, 2 equiv) in hexanes (1 mL). After being stirred for 5 min at −78 °C, the reaction mixture was diluted with saturated aqueous NH_4Cl solution and CH_2Cl_2. The phases were then separated, the aqueous layer was extracted with CH_2Cl_2 (3×), the combined organic phases were dried ($MgSO_4$) and concentrated at reduced pressure, and the residue was purified by chromatography (heptane to heptane/ethyl acetate 20/1) to provide the alkyne **18** (337 mg, 0.49 mmol, 83%, 1:1 mixture of C9 epimers) and the protodeiodinated substrate (50 mg, 0.09 mmol, 15%). Alkyne **18** was obtained as a 1:1 mixture of C9 epimers: R_f 0.29 (heptane/ethyl acetate 5/1); ^{1}H NMR (300 MHz, $CDCl_3$) δ −0.04 (s, 3 + 3H), 0.00 (s, 3 + 3H), 0.03 (s, 3 + 3H), 0.05 (s, 3H), 0.06 (s, 3H), 0.85 (s, 9 + 9H), 0.88 (s, 9 + 9H), 0.93 (s, 3H), 0.94 (s, 3H), 0.96 (s, 3H), 0.97 (s, 3H), 1.06 (d, J = 6.8 Hz, 3H), 1.06 (d, J = 6.8 Hz, 3H), 1.24−1.33 (m, 1 + 1H), 1.38−1.48 (m, 1 + 1H), 1.60 (d, J = 1.0 Hz, 3H), 1.62 (d, J = 1.0 Hz, 3H), 1.63−1.80 (m, 1 + 1H), 1.80 (q, J = 2.5 Hz, 3 + 3H), 1.97−2.40 (m, 6 + 6H), 2.61 (dd, J_1 = J_2 = 9.7 Hz, 1H), 2.62 (dd, J_1 = J_2 = 9.9 Hz, 1H), 3.13−3.22 (m, 2 + 2H), 3.35−3.45 (m, 1 + 1H), 3.65−3.75 (m, 1 + 1H), 3.82 (s, 3 + 3H), 4.34−4.45 (m, 2 + 2H), 5.26 (d, J = 9.4 Hz, 1H), 5.28 (d, J = 9.4 Hz, 1H), 6.88 (d, J = 8.4 Hz, 2 + 2H), 7.22−7.27 (m, 2 + 2H), no observable OH resonance; ^{13}C NMR (75.5 MHz, $CDCl_3$) δ −4.2, −4.1, −4.0, −2.4, 3.5, 17.0, 17.1, 18.0, 18.5, 19.1, 19.2, 22.3, 22.4, 23.7, 23.8, 25.9, 26.0, 29.2, 29.4, 29.5, 29.7, 37.2, 38.0, 38.1, 39.6, 39.7, 42.5, 42.7, 53.6, 53.7, 55.3, 72.9, 75.0, 75.1, 77.5, 77.0, 77.8, 78.7, 82.5, 84.1, 84.2, 113.6, 123.5, 123.7, 129.1, 129.2, 130.5, 137.3, 137.8, 159.1; IR (film on KBr) ν 830, 1250, 1510, 2850−2950 cm^{-1}. Anal. Calcd for $C_{40}H_{70}O_5Si_2$: C, 69.92; H, 10.27. Found: C, 69.75; H, 10.27. Protodeiodinated substrate: R_f 0.55 (heptane/ethyl acetate 5/1); ^{1}H NMR (300 MHz, $CDCl_3$) δ −0.08 (s, 3H), −0.04 (s, 3H), 0.00 (s, 3H), 0.02 (s, 3H), 0.82 (s, 9H), 0.85 (s, 9H), 0.98 (t, J = 7.4 Hz, 3H), 1.03 (d, J = 6.8 Hz, 3H), 1.25 (dd, J_1 = 13.9 Hz, J_2 = 7.6 Hz, 1H), 1.56 (d, J = 1.1 Hz, 3H), 1.69−1.85 (m, 1H), 1.99 (q, J = 7.2 Hz, 2H), 2.32 (dd, J_1 = 13.9 Hz, J_2 = 10.6 Hz, 1H), 2.58 (dd, J_1 = J_2 = 9.9 Hz, 1H), 3.13 (d, J = 8.5 Hz, 1H), 3.18 (d, J = 8.5 Hz, 1H), 3.68 (dd, J_1 = 9.5 Hz, J_2 = 8.3 Hz, 1H), 3.79 (s, 3H), 4.33 (d, J = 11.7 Hz, 1H), 4.40 (d, J = 11.5 Hz, 1H), 5.18 (dd, J_1 = 10.1 Hz, J_2 = 1.2 Hz, 1H), 6.85 (d, J = 8.7 Hz, 2H), 7.21 (d, J = 8.6 Hz, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ −4.2, −4.1, −2.4, 12.4, 16.9, 18.0, 18.5, 19.3, 25.9, 26.0, 32.6, 39.6, 42.6, 53.5, 55.2, 72.9, 74.8, 82.7, 84.3, 113.6, 122.0, 129.1, 130.6, 138.8, 159.0; IR (film on KBr) ν 1100, 1250, 2850, 2900, 2950 cm^{-1}. Anal. Calcd for $C_{32}H_{58}O_4Si_2$: C, 68.27; H, 10.38. Found: C, 68.36; H, 10.31.

Vinyl Iodide 25a. To a solution of the alkyne **24a** (103 mg, 0.122 mmol, 1 equiv) in THF (5 mL) in a commercially available glass pressure tube was added chlorobis(cyclopentadienyl)hydridozirconium(IV) (158 mg, 0.61 mmol, 5 equiv). The tube was sealed with a Teflon screw-cap, heated in an oil bath (60 °C) for 1.5 h, and then cooled to ambient temperature. To the dark purple reaction mixture was added I_2 (47 mg, 0.184 mmol, 1.5 equiv). A change of color from purple to yellow to brownish was observed. After TLC indicated the complete consumption of the zirconocene intermediate (R_f 0.4 heptane/ethyl acetate 5/1), the reaction was quenched by the addition saturated aqueous $NaHCO_3$ solution and CH_2Cl_2. The layers were separated, the organic phase was extracted with CH_2Cl_2 (3×), and the combined organic layers were dried ($MgSO_4$), concentrated at reduced pressure, and then purified by chromatography (heptane to heptane/ethyl acetate 50/1) to provide the vinyl iodide **25a** (115 mg, 0.119 mmol, 97%, 1:1 mixture of epimers at C9) as a colorless oil. **25a** as a 1:1 mixture of C9 epimers: R_f 0.5 (heptane/ethyl acetate 10/1); ^{1}H NMR (500 MHz, $CDCl_3$) δ −0.06 (s, 3 + 3H), −0.03 (s, 3 + 3H), 0.01 (s, 3 + 3H), 0.04 (s, 3 + 3H), 0.82−0.88 (m, 24 + 24H), 1.04 (d, J = 6.6 Hz, 3 + 3H), 1.09 (br.s, 21 + 21H), 1.23−1.33 (m, 1 + 1H), 1.44−1.54 (m, 1 + 1H), 1.57 (s, 3 + 3H), 1.65−1.82 (m, 2 + 2H), 1.86−1.98 (m, 1 + 1H), 1.98−2.10 (m, 1 + 1H), 2.18−2.27 (m, 1 + 1H), 2.29−2.36 (m, 1 + 1H), 2.35 (s, 3 + 3H), 2.59 (dd, J_1 = J_2 = 9.8 Hz, 1 + 1H), 3.12−3.21 (m, 2 + 2H), 3.42−3.50 (m, 1 + 1H), 3.69 (dd, J_1 = J_2 = 8.8 Hz, 1 + 1H), 3.80 (s, 3 + 3H), 4.34 (d, J = 11.4 Hz, 1 + 1H), 4.40 (d, J = 11.4 Hz, 1H), 4.41 (d, J = 11.4 Hz, 1H), 5.19 (d, J = 9.1 Hz, 1 + 1H), 6.23 (t, J = 7.7 Hz, 1 + 1 Hz), 6.86 (d, J = 8.5 Hz, 2 + 2H), 7.22 (d, J = 8.2 Hz, 2 + 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ −4.2, −4.2, −4.1, −4.0, −2.4, −2.4, 13.7, 14.1, 17.1, 17.3, 18.0, 18.5, 18.5, 19.3, 22.7, 22.8, 23.7, 25.9, 26.0, 27.7, 31.9, 32.2, 38.5, 38.9, 39.1, 39.6, 40.2, 40.3, 42.5, 53.5, 53.6, 55.2, 72.9, 74.8, 74.8, 81.1, 81.5, 82.6, 84.3, 94.5, 113.6, 123.0, 123.2, 129.1, 130.5, 137.5, 138.9, 159.0; IR (film on KBr) ν 1100, 1500, 2850−2900 cm^{-1}. Anal. Calcd for $C_{49}H_{91}IO_5Si_3$: C, 60.58; H, 9.44. Found: C, 60.27; H, 9.75.

Tetraene 54. To a THF (8 mL) solution of the phosphonate **41** (2.16 g, 4.14 mmol, 2 equiv) in a commercially available glass pressure tube at 0 °C was added *n*-BuLi (1.5 mL, 2.4 M in hexanes, 3.62 mmol, 1.75 equiv), and the reaction mixture was stirred for 5 min. A solution of the aldehyde **50** (759 mg, 2.07 mmol, 1 equiv) in THF (4 mL) was added, and the tube was sealed with a Teflon screw-cap and heated in an oil bath (70 °C) for 12 h. The reaction mixture was then diluted with saturated aqueous NH_4Cl solution and CH_2Cl_2. The layers were separated, the aqueous phase was extracted with CH_2Cl_2 (3×), and the combined organic layers were dried ($MgSO_4$) and concentrated at reduced pressure. The residue was then purified by chromatography (hexanes to hexanes/ethyl acetate 1/1) to deliver the tetraene **54** (1.17 g, 1.60 mmol, 74%, 1:1 mixture of C9 epimers and 2:1 mixture of C6 double bond isomers) as a yellow oil. The unreacted phosphonate **41** (539 mg, 1.03 mmol) was chromatographically separable and reisolated. **54**, as mixture of stereoisomers: R_f 0.93 (hexanes/ethyl acetate 10/1); ^{1}H NMR (500 MHz, $CDCl_3$), only diagnostic resonances are reported, δ −0.04 (s, 3H), 0.01 (s, 3H), 0.02−0.04 (m, 9H), 0.60−0.67 (m, 6H), 0.79−0.81 (m, 3H), 0.83 (s, 9H), 0.85−0.87 (m, 3H), 0.92−1.00 (m, 9H), 1.01−10.4 (m, 3H), 1.23−2.23 (m, 20H), 2.45−2.50 (m, 1 H), 2.68−2.75 (m, 1H), 3.21−3.32 (m, 1H), 3.45−3.50 (m, 1H), 4.90−5.02 (m, 3H), 5.08−5.15 (m, 2H), 5.75−5.92 (m, 2H), 6.80−6.86 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$), only diagnostic resonances are reported, δ −4.0, −3.3, 1.9, 1.9, 4.4, 5.7, 6.8, 7.2, 13.0, 17.9, 18.0, 22.6, 22.8, 23.5, 23.8, 25.9, 27.3, 27.4, 29.1, 29.3, 30.5, 31.5, 33.4, 37.3, 37.5, 37.9, 39.7, 39.7, 40.6, 40.6, 45.4, 45.4, 62.5, 81.2, 81.3, 81.7, 81.8, 83.7, 86.9, 86.9, 114.3, 114.4, 118.6, 118.6, 124.3, 124.9, 134.2, 134.3, 135.7, 136.3, 136.3, 138.9, 139.0, 142.4, 142.4, 204.6, 204.6; IR (film on

KBr) ν 840, 1250, 1700, 2900, 2950 cm^{-1}. Anal. Calcd for $C_{42}H_{80}O_4Si_3$: C, 68.79; H, 11.00. Found: C, 68.85; H, 11.00.

(+)-17-Norcharaciol (+)-60. A solution of the benzoate (3*S*)-**59** (17.8 mg, 0.035 mmol, 1 equiv) and finely ground K_2CO_3 (5 mg, 0.036 mmol, 1 equiv) in MeOH (3 mL) was stirred at ambient temperature for 48 h and then diluted with saturated aqueous NH_4Cl solution and CH_2Cl_2. The layers were separated, the organic phase was extracted with CH_2Cl_2 (3×), and the combined organic layers were dried ($MgSO_4$) and concentrated at reduced pressure. Chromatographic purification (hexanes/ethyl acetate 20/1 to 2/1) of the residue afforded (+)-**60** (6.8 mg, 0.021 mmol, 60%) as yellow oil: R_f 0.32 (hexanes/ethyl acetate 2/1); COSY, HSQC, HMBC, and NOESY methods were used to confirm the NMR peak assignments based on the jatrophane numbering: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.08 (d, J = 6.8 Hz, 16-CH_3, 3H), 1.15 (s, 18-CH_3 or 19-CH_3, 3H), 1.18 (s, 18-CH_3 or 19-CH_3, 3H), 1.50 (dd, J_1 = 13.9 Hz, J_2 = 11.0 Hz, 1-CH_2, 1H^{Re}), 1.72 (s, 20-CH_3, 3H), 1.98−2.09 (m, 2-CH, 1H), 2.11−2.22 (m, 4-CH, 1H and 7-CH_2, 1H and 8-CH_2, 1H), 2.44 (ddd, J_1 = 17.3 Hz, J_2 = 5.4 Hz, J_3 = 1.2 Hz, 11-CH_2, 1H), 2.52 (dd, J_1 =17.4 Hz, J_2 = 7.2 Hz, 11-CH_2, 1H), 2.70−2.77 (m, 7-CH_2, 1H and 8-CH_2, 1H), 3.04 (br s, −OH, 1H), 3.09 (dd, J_1 = 13.9 Hz, J_2 = 9.2 Hz, 1-CH_2, 1H^{Si}), 3.97 (dd, J_1 = J_2 = 3.1 Hz, 3-CH, 1H), 5.18 (ddd, J_1 = 14.9 Hz, J_2 = 9.9 Hz, J_3 = 4.7 Hz, 6-CH═, 1H), 5.81 (dd, J_1 = 15.4 Hz, J_2 = 9.9 Hz, 5-CH═, 1H), 6.91−6.95 (m, 12-CH═, 1H), only one observable OH resonance; ^{13}C NMR (126 MHz, $CDCl_3$) δ 12.9 (20-CH$_3$), 14.0 (16-CH$_3$), 24.7 (18-CH$_3$ or 19-CH$_3$), 25.3 (18-CH$_3$ or 19-CH$_3$), 27.2 (7-CH$_2$), 35.7 (8-CH$_2$), 38.9 (2-CH), 40.5 (11-CH$_2$), 48.0 (10-C), 48.1 (1-CH$_2$), 59.3 (4-CH), 81.3 (3-CH), 92.0 (15-C), 127.4 (6-CH═), 134.3 (5-CH═), 136.7 (13-C═), 144.8 (12-CH═), 202.1 (14-C═O), 215.3 (9-C═O); selected NOESY crosspeaks 20-CH_3, (1.72 ppm)/11-CH_2 (2.44 ppm and 2.52 ppm) → (12*E*), 1-H^{Si} (3.09 ppm)/3-H (3.97 ppm) → *cis*: 1-H^{Si} and 3-H, no observable NOESY crosspeak 5-H (5.81 ppm)/6-H (5.18 ppm) → (5*E*); IR (film on KBr) ν 1000, 1050, 1100, 1650, 1700, 2900, 3450 cm^{-1}; $[\alpha]^{25}_D$ +21 (c 0.3, $CHCl_3$). Anal. Calcd for $C_{19}H_{28}O_4$: C, 71.22; H, 8.81. Found: C, 70.90; H, 8.64.

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Supporting Information Available: Experimental procedures and spectral and analytical data for new compounds not given in the Experimental Section; copies of ^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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