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Enantioselective synthesis of the C-14 to C-5 cyclopentane segment of jatrophane diterpenes

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Abstract—The enantioselective synthesis of the C-14 to C-5 cyclopentane segment of jatrophane diterpenes is reported. An Evans aldol addition, a Horner–Wadsworth–Emmons olefination and a thermal intramolecular carbonyl ene reaction of an α-keto ester served as key C/C-connecting transformations.

The milky latex of plants belonging to the genus *Euphorbia* (family *Euphorbiaceae*) is a rich source of jatrophane diterpenes featuring the bicyclo[10.3.0]pentadecane framework **1** (Fig. 1).

Jatrophanes are being isolated from *Euphorbia* species with remarkable diversity with respect to hydroxylation and/or acyloxylation of the carbon skeleton. Recent studies of the biological activities of jatrophane diterpenes revealed promising results. For instance, jatrophane **2** from *E. pubescens* showed a cell type selective growth inhibitory effect on the cancer cell line NCI-H460 (nonsmall cell lung cancer).[1] Jatrophane **3** from *E. semiperfoliata* exhibited microtubule-interacting properties and influenced p53 expression and Raf-1/Bcl-2 activation.[2] Jatrophane **4** from *E. dendroides* inhibited the P-glycoprotein-mediated efflux of daunomycin from human K562/R7 leukaemia cells.[3]

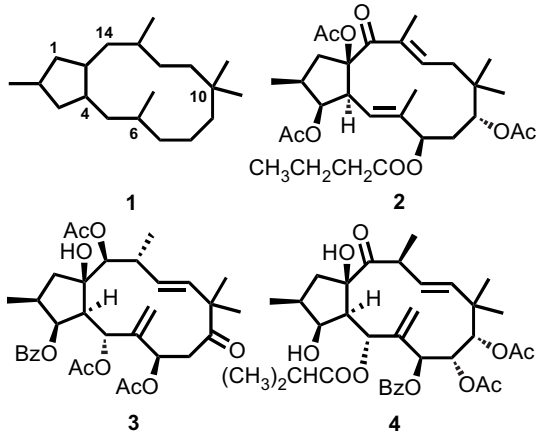

Figure 1. Jatrophane framework **1** and selected jatrophanes from *Euphorbia pubescens* **2**, *E. semiperfoliata* **3**, *E. dendroides* **4**.

The validated biological activities and structural diversity of jatrophanes qualifies them as privileged structures for drug discovery.[4] A diversity-oriented synthetic approach towards natural and nonnatural jatrophanes requires a highly convergent retrosynthetic analysis. Our synthetic plan considers the C-14 to C-5 cyclopentane fragment **5** as a building block of central importance for an efficient synthetic access to jatrophane diterpenes.

We envisioned that a thermal intramolecular carbonyl ene reaction could convert the easily accessible acyclic α-keto ester **6** to a highly substituted 1-hydroxycyclopentane carboxylic acid ester **5** (Fig. 2).[5] Based on a simple qualitative analysis of the concerted transition state geometry for the ene reaction, we expected that the absolute configuration of C-3 of the α-keto ester **6** (jatrophane numbering is used throughout this letter) would be decisive for the substrate-induced diastereoselectivity of the ene reaction (see Fig. 3).

Therefore, we decided to utilize the (3*R*)-configured α-keto ester **6** as substrate for the ene reaction and to

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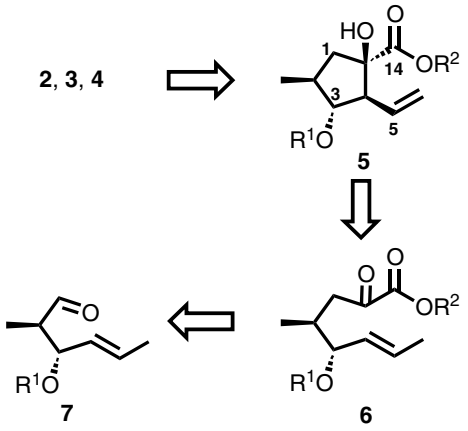


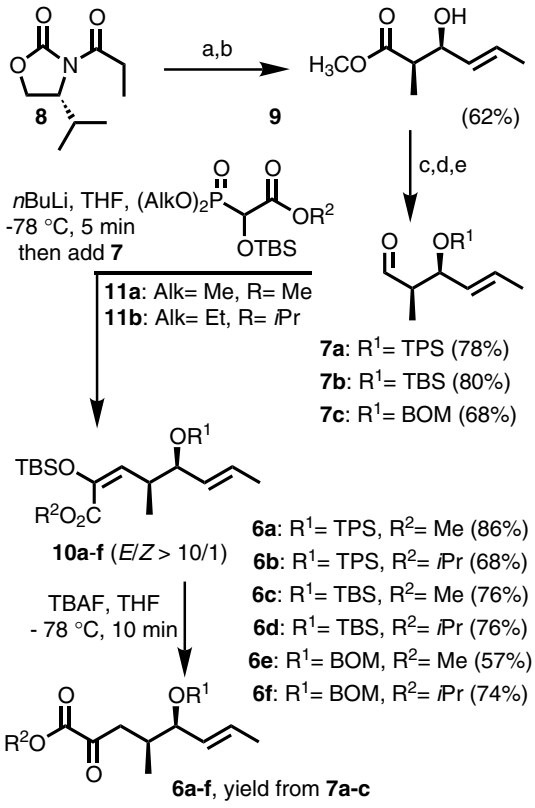
Figure 2.

subsequently invert the absolute configuration at C-3. The α-ketoester **6** should be easily obtainable from the aldehyde **7** by chain elongation. The synthesis of α-keto esters **6a**–**f** with different protecting groups R^1 and ester substituents R^2 would enable an investigation concerning the influence of steric effects of substituents on the diastereoselectivity of the critical ene reaction.

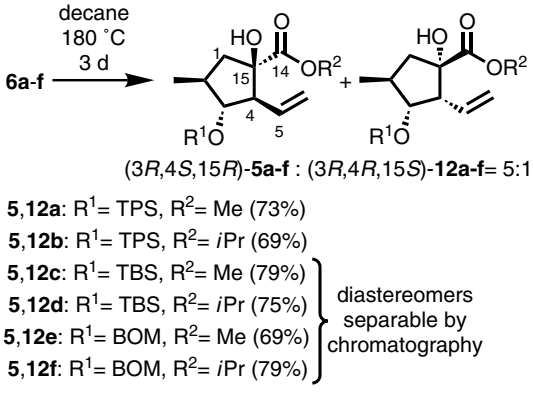
The enantioselective synthesis of the α-keto esters **6a**–**f** is outlined in Scheme 1. Evans' reliable aldol methodology followed by nucleophilic cleavage of the auxiliary afforded the diastereomerically pure ester **9**.[6,7] Protection of the C-3-hydroxyl group and subsequent redox chemistry provided the aldehydes **7a**–**c**.[8] Horner–Wadsworth–Emmons olefination of the aldehydes **7a**–**c** with the lithiated 2-(*tert*-butyldimethylsiloxy)-phosphonoacetates **11a**,**b** proceeded smoothly to afford the predominantly *E*-configured silyl enol ethers **10a**–**f**.[9,10] Desilylation of the silyl enol ethers **10a**–**f** under carefully optimized reaction conditions afforded the enantiomerically pure α-keto esters **6a**–**f**[11] in good yields.[12]

The pivotal intramolecular type I carbonyl ene reaction was performed under thermal conditions.[13] The α-keto esters **6a**–**f** were heated to 180 °C in decane in a sealed tube to provide the corresponding cyclopentanes as a mixture of the two diastereomers **5a**–**f** and **12a**–**f** (Scheme 2). We observed the exclusive formation of the 4,15-*cis* configuration. The two *cis* diastereomers were formed as a 5/1 mixture in favor of the desired (3*R*,4*S*,15*R*)-configured cyclopentanes **5a**–**f**.[14] Somewhat surprisingly, neither the nature of R^2 nor the nature of the protecting group R^1 significantly influenced the outcome of the ene reaction. A brief study of the connection between the conversion of **6c** to **5**,**12c** and the diastereoselectivity of this transformation revealed, that the 5/1 ratio of diastereomers remains virtually unchanged during the course of the reaction.[15] In order to avoid extensive decomposition, the reaction was stopped after 3 days without complete conversion of the substrate **6c**.

The 4,15-*cis*-configured diastereomers **5c**–**f** and **12c**–**f** were separable by flash chromatography and, therefore,



Scheme 1. TPS = *t*-BuPh$_2$Si, TBS = *t*-BuMe$_2$Si, BOM = PhCH$_2$OCH$_2$. Reagents and conditions: (a) *n*-Bu$_2$BOTf, Et$_3$N, CH$_2$Cl$_2$, 0 °C, 10 min; (*E*)-H$_3$CCH=CHCHO, −78 °C to rt. (b) NaOMe, MeOH, 0 °C, 20 min. (c) (i) TPSCl, imidazole, CH$_2$Cl$_2$, 0 °C to rt; (ii) TBSCl, imidazole, 0 °C to rt; (iii) BOMCl, Et*i*Pr$_2$N, TBAI, CH$_2$Cl$_2$, 0 °C to rt. (d) DIBAH, CH$_2$Cl$_2$, −78 °C, 0.5 h. (e) SO$_3$·pyridine, DMSO, CH$_2$Cl$_2$, 0 °C to rt.



Scheme 2.

the desired (3*R*,4*S*,15*R*)-configured cyclopentanes **5c**–**f**[16] are accessible as single diastereomers, even on a larger scale.[17] Heating either the separated minor or the major diastereomer of **5c** in decane to 180 °C for several days led to the formation of a 5/1 mixture of **5c** and **12c** by a retro-ene/ene reaction. This finding indicates that the cyclopentanes **5a**–**f** are the thermodynamically more stable products of the thermal ene reactions of **6a**–**f**.[15]

The kinetic preference for the *cis*-configured cyclopentanes **5**,**12a**–**f** may be explained as depicted in Figure 3. We assume that the ene reaction proceeds through a concerted bicyclo[4.3.0]nonane-like transition state **13**. The simple diastereoselectivity is a consequence of the favourable less strained *cis*-annulated bicyclic transition state **13** (the corresponding *trans*-annulated transition states are not depicted).[15]

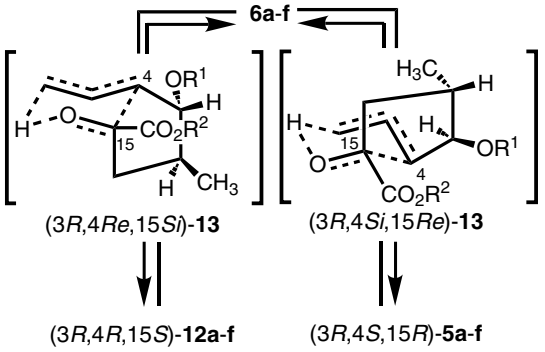
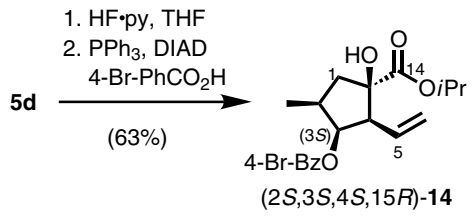


Figure 3.

As envisioned, the (3*R*)-configuration of the α-keto esters **6a**–**f** induced the required (4*R*,15*S*)-configuration of the ene reaction products **5a**–**f** (Fig. 3). However, the synthesis of the C-14 to C-5 fragment of the jatrophane diterpenes required the (3*S*)-configuration. We envisioned a Mitsunobu inversion as the method of choice for a stereospecific inversion of the configuration at C-3.[18] The plan was realized using **5d** as representative starting material (Scheme 3). The cleavage of the TBS ether on the secondary hydroxyl group proceeded uneventfully with HF in pyridine. The succeeding Mitsunobu inversion afforded the desired C-14 to C-5 segment (2*S*,3*S*,4*S*,15*R*)-**14**[19] of the jatrophane diterpenes featuring the correct absolute configuration at all four chiral carbon atoms.

In summary, the first enantioselective synthesis of the C-14 to C-5 segment **14** of the jatrophane diterpenes **2**–**4** is reported. The intramolecular carbonyl ene reaction of an α-keto ester **6** afforded the desired cyclopentane framework **5**. Thereby, the two crucial chiral centres at C-15 and C-4 were created with a complete simple (*cis*/*trans*) and an acceptable substrate-induced diastereoselectivity. Evans' reliable aldol addition secured access to the α-keto ester **6** featuring the desired absolute configuration at C-2. Work towards the completion of jatrophane total syntheses is underway in our laboratory and will be reported in due course.



Scheme 3.

Acknowledgements

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10. Assignment of the double bond configuration based on the chemical shift of the vinyl ether double bond proton, see: Hiersemann, M. *Synthesis* **2000**, 1279–1290, and Ref. 9f.
11. **6d**: ^{1}H NMR (300 MHz, $CDCl_3$) δ −0.02 (s, 3H), 0.00 (s, 3H), 0.86 (s, 9H), 0.88 (d, $J = 6.8$ Hz, 3H), 1.36 (d, $J = 6.2$ Hz, 6H), 1.68 (dd, $J_1 = 6.8$ Hz, $J_2 = 0.3$ Hz, 3H), 2.15–2.29 (m, 1H), 2.48 (dd, $J_1 = 17.0$ Hz, $J_2 = 8.0$ Hz, 1H), 3.00 (dd, $J_1 = 16.9$ Hz, $J_2 = 5.5$ Hz, 1H), 3.93 (dd, $J_1 = J_2 = 6.0$ Hz, 1H), 5.11 (sept, 1H), 5.33–5.43 (m, 1H), 5.48–5.62 (m, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ −4.9, −4.2, 15.4, 17.6, 18.2, 21.6, 25.9, 36.0, 42.0, 70.4, 76.8, 127.2, 131.7, 161.1, 194.9; IR (neat) 1050, 1080, 1100, 1260, 1730, 2860, 2930, 2960, 2980 cm^{-1}; Anal. calcd for $C_{18}H_{34}O_4Si$: C, 63.11; H, 10.00. Found: C, 63.39; H, 10.36; $[\alpha]_D^{25}$ −3.4 (*c* 1.11, $CHCl_3$).
12. An increased reaction temperature or a prolonged reaction time led to inferior chemical yields.
13. Attempts to catalyze the ene reaction of **6d** with copper(II) bis(oxazolines) according to the procedure of Yang et al.[5d] did not afford the desired product **5d**.
14. The configurational assignment is based on extensive NOESY experiments.
15. The observation that the cyclopentane diastereomer **5c** was preferentially formed over **12c** even in the initial phase of the thermal ene reaction when the retro-ene reaction is slow due to the low concentration of **5c** and **12c** indicates in our opinion, that **5a**–**f** are not only the thermodynamically more stable products of the thermal ene reaction but also kinetically favored. We suppose that (3*R*,4*Re*,15*Si*)-13 (leading to **12a**–**f**) is destabilized relative to (3*R*,4*Si*,15*Re*)-13 (leading to **5a**–**f**) because the bulky substituent OR[1] at C-3 is directed toward the concave face of the bicyclo[4.3.0]nonane-like transition state (Fig. 3).
16. (2*S*,3*R*,4*S*,15*R*)-**5d**: ^{1}H NMR (500 MHz, $CDCl_3$) δ −0.05 (s, 3H), 0.00 (s, 3H), 0.86 (s, 9H), 1.10 (d, $J = 6.9$ Hz, 3H), 1.25 (dd, $J_1 = J_2 = 6.3$ Hz, 6H), 1.40 (dd, $J_1 = 14.0$ Hz, $J_2 = 8.0$ Hz, 1H), 1.91–2.02 (m, 1H), 2.53 (dd, $J_1 = 14.0$ Hz, $J_2 = 10.2$ Hz, 1H), 2.61 (dd, $J_1 = J_2 = 9.5$ Hz, 1H), 3.17 (br s, 1H), 3.74 (dd, $J_1 = 9.5$ Hz, $J_2 = 8.2$ Hz, 1H), 5.00–5.08 (m, 2H), 5.13 (dd, $J_1 = 10.1$ Hz, $J_2 = 2.2$ Hz, 1H), 5.75 (dt, $J_1 = 17.3$ Hz, $J_2 = 9.8$ Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ −4.1, −3.5, 18.0, 18.8, 21.7, 25.9, 40.0, 42.9, 61.6, 69.7, 80.1, 82.8, 119.5, 134.6, 175.6; IR (neat) 775, 835, 1100, 1250, 1720, 2860, 2930, 2960 cm^{-1}; $[\alpha]_D^{25}$ +4.8 (*c* 1.14, $CHCl_3$); Anal. calcd for $C_{18}H_{34}O_4Si$: C, 63.11; H, 10.00. Found: C, 62.95; H, 10.21.
17. The thermal intramolecular carbonyl ene reaction of **6c** has been realized on a 4 mmol scale. Up-scaling has no detrimental effect on the yield or the diastereoselectivity.
18. Mitsunobu, O. *Synthesis* **1981**, 1–28.
19. (2*S*,3*S*,4*S*,15*R*)-**14**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.02 (d, $J = 6.9$ Hz, 3H), 1.28 (dd, $J_1 = 6.3$ Hz, $J_2 = 3.8$ Hz, 6H), 1.85 (dd, $J_1 = 13.7$ Hz, $J_2 = 10.9$ Hz, 1H), 2.37–2.47 (m, 1H), 2.55 (dd, $J_1 = 13.6$ Hz, $J_2 = 8.8$ Hz, 1H), 2.98 (dd, $J_1 = 8.8$ Hz, $J_2 = 4.1$ Hz, 1H), 3.23 (br s, 1H), 5.02–5.14 (m, 3H), 5.56 (dd, $J_1 = J_2 = 3.9$ Hz, 1H), 5.79 (ddd, $J_1 = 17.3$ Hz, $J_2 = 10.4$ Hz, $J_3 = 8.8$ Hz, 1H), 7.58 (d, $J = 8.8$ Hz, 2H), 7.98 (d, $J = 8.5$ Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 14.2, 21.7, 38.2, 45.7, 57.7, 69.9, 80.9, 82.1, 119.4, 128.1, 129.0, 131.2, 131.4, 131.8, 165.4, 175.9; IR (neat) 750, 1100, 1270, 1720, 2980 cm^{-1}; Anal. calcd for $C_{19}H_{23}BrO_5$: C, 55.49; H, 5.64. Found: C, 55.66; H, 5.82; $[\alpha]_D^{25}$ +98.2 (*c* 4.50, $CHCl_3$).