Enyne Metathesis Approach towards the Cyclopentane Motif of Jatrophane Diterpenes

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Abstract: A short and efficient synthesis of the cyclopentane moiety of the jatrophane diterpene Pl-3 has been developed. The route features an enyne metathesis reaction, and a stereoselective palladium-catalyzed reductive epoxide opening as key steps.

Key words: metathesis, palladium, natural products, stereoselective synthesis, terpenoids

With more than 2000 known species, the Euphorbiaceae family is one of the largest and most diverse of all genera. Many species of the widely distributed spurge family are commonly referred to, have been extensively used in traditional herbal folk medicine to cure various health conditions, such as skin diseases, gonorrhea, migraine, intestinal parasites, and warts.1

Since the isolation of jatrophane in 1970 by Kupchan and co-workers,2 considerable effort has been devoted to the isolation and structure elucidation of bioactive constituents of spurge. As a result of this intensive study, a vast number of structurally complex isoprenoid constituents have been obtained, some of which revealed highly interesting biological properties ranging from antiproliferative to pronounced multi-drug-resistance (MDR) reversal activity.3,4

While it is well established that most macrocyclic diterpenoids are biosynthesized from an isomer of geranylgeranyl diphosphate,5 the exact process leading to the different core frameworks of jatrophane diterpenes and related natural products remains unknown. Despite the differences in the twelve-membered macrocycle of jatrophane diterpenes (oxxygenation pattern, double bond geometry, stereochemistry of substituents), structural features in the cyclopentane moiety are essentially identical in many of these fascinating natural products. Some examples of recently isolated biologically interesting jatrophane diterpenes are shown in Figure 1.6–8

We have been interested in the active ingredients of the Euphorbiaceae family for some time, partly due to their intriguing biological properties but also because of the fascinating synthetic challenge presented by this class of natural products. Additionally, only a few routes to jatrophane diterpenes have been reported so far.9–23

As a result of our ongoing efforts towards Euphorbiaceae diterpenes, we have devised a route towards Pl-3 (1).19 This bicyclic natural product was isolated from an Hungarian sample of the annual herbaceous plant Euphorbia platyphyllos by Hohmann and co-workers in 2003 and has been shown to possess remarkable MDR reversal activity.6

The synthetic strategy, outlined in Scheme 1, is based on the late stage connection of three building blocks (5–7). The final operation in the preparation of the jatrophane diterpene is a metathesis reaction to close the macrocycle. Building block 5 becomes available from D-ribose via a samarium diiodide mediated diastereoselective Reformatsky reaction as key step as recently reported.19 Advanced intermediate 6 should be accessible via selective reductive opening of epoxide 8, followed by oxidation of the secondary alcohol and addition of the corresponding lithiated vinyl halide. Epoxide 8 was envisaged to be prepared from the corresponding diene, the product of the key enyne metathesis reaction of alkyne 9. As suitable starting material for the sequence we decided to utilize chiral carboxylic acid 10,24 available on multigram scale via the Myers asymmetric alkylation protocol.25 Vinyl halide 7 will be prepared from commercially available Roche ester. The route to both synthetic intermediates 5 and 6 is highly flexible and allows the preparation of structurally related intermediates for the synthesis of other jatrophane diterpenes.

As outlined in Scheme 2, the sequence started with the preparation of chiral carboxylic acid 10.24 Thus, reaction of pseudoephedrine (11) with propionyl chloride afforded...
the precursor for the diastereoselective Myers alkylation with allyl iodide and amide 12 was obtained in excellent yield as single diastereomer.\(^2\)

Next, amide 12 had to be converted to the corresponding Weinreb amide to facilitate the nucleophilic attack of deprotonated ethynyl trimethylsilane (16). Unfortunately, the trimethyl aluminum catalyzed reaction of amide 12 with N-methylhydroxylamine hydrochloride did not afford the desired product\(^2\) and Weinreb amide 13 had to be accessed in a two-step procedure via initial acid hydrolysis of 12 and subsequent exposure of the carboxylic acid (10) to N-methylhydroxylamine hydrochloride, DCC, Et\(_3\)N, and a catalytic amount of DMAP. Reaction of Weinreb amide 13 with deprotonated ethynyltrimethylsilane then afforded enyne 14 in high yield.

With 14 in hand, the stereoselective reduction of the carbonyl moiety could be attempted. Initial experiments with the CBS reagent\(^2\) or Alpine borane\(^2\) delivered the de-

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**Scheme 1** Retrosynthetic analysis of Pl-3.

**Scheme 2** Preparation of metathesis precursors 15
sired secondary alcohol in disappointingly low yield as a nearly racemic mixture. Finally, reduction of the ketone in 14 was achieved in highly diastereoselective manner following the Noyori asymmetric hydrogenation protocol. When allowed to react with significantly dried isopropyl alcohol as transfer reducing agent at elevated temperatures (40 °C) in the presence of ruthenium catalyst 17, yo19 was obtained in excellent yield and stereoselectivity.29,30 The synthesis of the enyne metathesis precursor was completed after silylation of the newly installed hydroxyl moiety (15).

The key enyne metathesis reaction proved to be more challenging than anticipated (Scheme 3). Extensive experimentation with silyl ether 15 with either the 1st or 2nd generation Grubbs metathesis catalyst in CH2Cl2 or toluene at different concentrations only led to isolation of the starting material. Only when alcohol 9 was allowed to react with Grubbs 2nd generation catalyst in carefully degassed and ethene-purged toluene, small amounts of 19 could be isolated. Careful optimization of the reaction conditions and slow addition of the metathesis catalyst over six hours via a syringe pump increased the yield of the desired material to 90%.31

Next, we intended to functionalize the endocyclic double bond in cyclopentene 19. All attempts to directly access the desired oxirane resulted in a homoallylic epoxidation of the exocyclic double bond because of the electron-donating properties of the TMS moiety. Thus, the silyl group had to be cleaved prior to the epoxidation in order to exclusively address the endocyclic double bond. As shown in Table 1, several methods were investigated to achieve the cleavage of the TMS group. Reaction of 19 with TBAF (1.0 M in THF) resulted in low and irreproducible yields of the desired product, along with decomposition of the starting material. The use of DMSO instead of THF did not improve the outcome of the reaction. When TBAF trihydrate was employed, 21 was isolated in 12% yield along with unreacted starting material.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reagents and conditions</th>
<th>Yield</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>TBAF (1.0 M, THF), THF, r.t.</td>
<td>no reaction</td>
</tr>
<tr>
<td>2</td>
<td>TBAF (1.0 M, THF), DMSO, 50 °C</td>
<td>no reaction</td>
</tr>
<tr>
<td>3</td>
<td>TBAF (1.0 M, THF), DMSO, 80 °C</td>
<td>10%; decomposition</td>
</tr>
<tr>
<td>4</td>
<td>TBAF (1.0 M, THF), DMSO, 100 °C</td>
<td>10%; decomposition</td>
</tr>
<tr>
<td>5</td>
<td>TBAF trihydrate, THF</td>
<td>12%</td>
</tr>
<tr>
<td>6</td>
<td>KHMDS, THF</td>
<td>unidentified products</td>
</tr>
<tr>
<td>7</td>
<td>LHMD, THD</td>
<td>unidentified products</td>
</tr>
<tr>
<td>8</td>
<td>NaH, THF</td>
<td>15%</td>
</tr>
<tr>
<td>9</td>
<td>NaH–HMPA, THF</td>
<td>82%</td>
</tr>
</tbody>
</table>

We then turned our attention to the cleavage of the silyl group via a Brook rearrangement,32,33 taking advantage of the adjacent hydroxyl moiety. Initial experiments with NaH, LHMDs, or KHMDS proved unsuccessful, but when HMPA was added to the reaction mixture, 21 could be isolated in an excellent yield of 84% after subsequent cleavage of the silyl ether during acidic workup.34

With desilylated alkene 21 in hand, the vanadium-catalyzed direct epoxidation with tert-butyl hydroperoxide as oxidant delivered the desired oxirane 8 as the sole isolable product. Next, the secondary hydroxyl moiety was protected as TIPS ether and oxirane 22 was obtained as substrate for the key reductive epoxide opening reaction.

Palladium-catalyzed reductive epoxide openings were described by Tsuji and Shimizu in 1986.35 A few years later, Shimizu further demonstrated that in the case of terminal alkenes 1:1 mixtures of stereoisomers were obtained because of the π-σ-π interconversion of the π-allylpalladium complex.36

Taking these observations into consideration, we were not surprised to also isolate a 1:1 mixture of stereoisomers (23a and 23b) in 89% yield when epoxy alkene 22 was allowed to react with Pd(dba)2·CHCl3 with Bu3P as ligand, Et3N, and formic acid as reductant. The mechanistic similarity of the palladium-catalyzed reductive epoxide opening and the Tsuji–Trost allylation motivated us to further investigate this interesting reaction. The asymmetric version of the Tsuji–Trost allylation...
has many beautiful applications in natural product synthesis. Trost also described the palladium-catalyzed reaction of vinylic epoxides and reported the asymmetric alkylation of vinylglycidols. Although the palladium-catalyzed reaction has only been applied to carbon or oxygen nucleophiles, we reasoned that the DACH phenyl Trost ligand might also be suitable for the intended reductive epoxide opening. The reaction, along with the mechanistic rationale, which shows the attack of the hydride from the bottom face, is outlined in Scheme 4. Trost developed a working model which allows the prediction of the stereochemical outcome of the palladium-catalyzed allylation reaction. Among others, Lloyd-Jones contributed to this area with some interesting studies indicating that depending on concentration, temperature, and solvents, the catalytically active species might exist as monomer or oligomer. Thus, a general prediction of the exact nature of the intermediary palladium species seems extremely challenging.

We were delighted to see that the palladium-catalyzed reaction of epoxy alkene in the presence of the chiral Trost ligand afforded the desired stereoisomer of the cyclopentane building block as the only isolable product in excellent 85% yield. Reaction of in the presence of the enantiomer of ligand resulted in low yield of the desired product, along with mainly decomposed material. The absolute configuration of has been unambiguously confirmed by correlation NMR experiments (see Supporting Information).

To our knowledge, this is the first application of the DACH-phenyl Trost ligand in a reductive allylic epoxide opening reaction and constitutes an extension to the protocol described by Shimizu and co-workers for the stereoselective conversion of terminal epoxy alkenes.

Summarizing, we were able to design a short and concise synthesis of the cyclopentane motif present in Pl-3 (1). The route can also be utilized for the preparation of other structurally related jatrophanes as the five-membered rings show very similar or identical substitution patterns in many jatrophane diterpenes. Furthermore, the novel application of the DACH-phenyl Trost ligand in the stereoselective palladium-catalyzed reductive epoxide opening is a valuable extension of Shimizu’s protocol and should be of interest for the preparation of complex natural products.

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References and Notes

(45) Preparation of 23a: The reaction was carried out in Schlenk flasks using degassed solvents. A Schlenk flask containing Pd2(dba)3·CHCl3 (4.4 mg, 2.5 mol%) and (R,R)-DACH ([138517-61-0], 8.7 mg, 7.5 mol%) was purged with argon five times before CH2Cl2 (0.6 mL) was added. After 5 min a mixture of Et3N (117 μL, 0.844 mmol, 5.0 equiv) and formic acid (32 μL, 0.844 mmol, 5.0 equiv) in CH2Cl2 (0.6 mL) was added and stirring was continued for additional 5 min before epoxide 22 (50 mg, 0.169 mmol, 1.0 equiv) was added neat followed by CH2Cl2 (0.1 mL). The reaction was stirred until TLC analysis showed total consumption of the starting material (3 h). A sat. aqueous solution of NH4Cl was added and the mixture was extracted with CH2Cl2 (3 × 20 mL), the organic extracts were dried over MgSO4, filtered and reduced in vacuo. The crude product was purified by flash column chromatography (hexane–EtOAc, 40:1) delivering the desired product 23a (43 mg, 86%) as a colorless oil as sole isolable product. 

1H NMR (400 MHz, CDCl3): δ = 6.20–6.26 (m, 1 H), 5.22–5.24 (m, 1 H), 5.20 (d, J = 0.78 Hz, 1 H), 4.07–4.11 (m, 1 H), 3.98 (br d, J = 3.90 Hz, 1 H), 3.25 (d, J = 11.16 Hz, 1 H), 2.36–2.40 (m, 1 H), 2.32–2.36 (m, 1 H), 2.25 (dd, J = 14.42, 8.99, 0.95 Hz, 1 H), 1.51 (dd, J = 14.37, 5.37, 5.37 Hz, 1 H), 1.05–1.13 (m, 21 H), 0.97 (d, J = 7.32 Hz, 3 H). 13C NMR (100 MHz, CDCl3): δ = 135.16 (CH), 117.43 (CH2), 85.48 (CH), 78.18 (CH), 52.81 (CH), 43.47 (CH2), 41.40 (CH), 20.87 (Me), 18.21 (Me), 18.16 (Me), 12.37 (CH). HRMS (ESI): m/z [M + Na]+ calcd for C17H34NaO2Si: 321.2226; found: 321.2223 ±5 ppm. [α]D20 −5° (c = 1.0900, CHCl3). IR (ATR): 3531, 2943, 2866, 2359, 2342, 1636, 1463, 1419, 1383, 1199, 1060, 1014, 997, 912, 881, 847, 823, 729, 678 cm−1.