Enyne Metathesis Approach towards the Cyclopentane Motif of Jatrophane Diterpenes

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Received: 30.07.2013; Accepted after revision: 09.09.2013

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 spurges, as members of this 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 jatrophone in 1970 by Kupchan and co-workers,[2] considerable effort has been devoted to the isolation and structure elucidation of bioactive constituents of spurges. 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 (oxygenation 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]

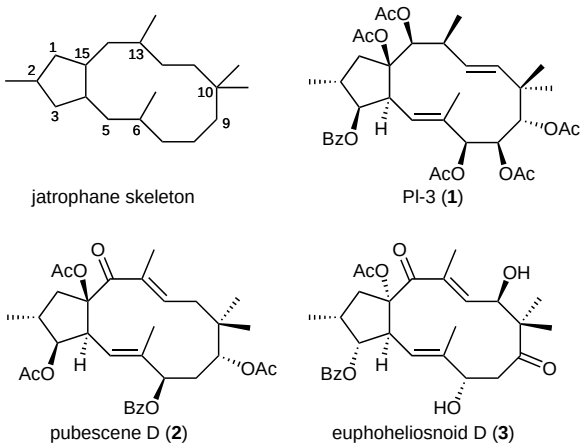


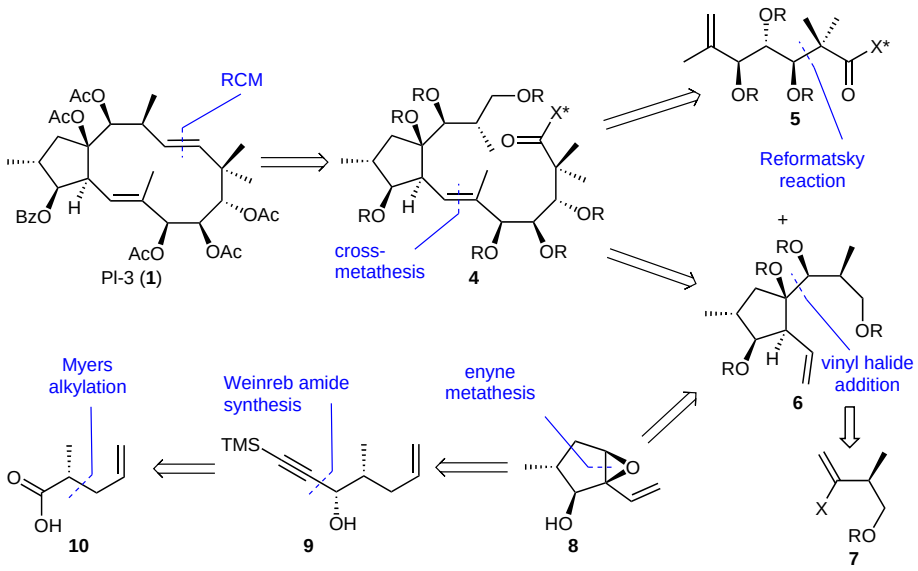
Figure 1 Jatrophane diterpenes

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

SYNLETT 2013, 24, 000A–000F
Advanced online publication: 28.10.2013
DOI: 10.1055/s-0033-1339923; Art ID: ST-2013-B0718-L

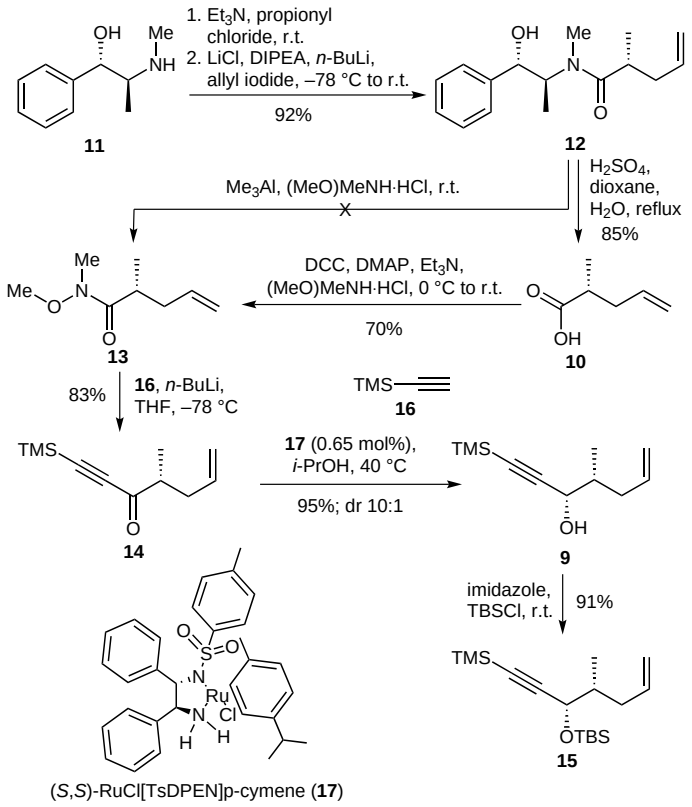


Scheme 1 Retrosynthetic analysis of Pl-3.

the precursor for the diastereoselective Myers alkylation with allyl iodide and amide **12** was obtained in excellent yield as single diastereomer.[25]

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[26] 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*-methlyhydroxylamine hydrochloride, DCC, Et_3N, and a catalytic amount of DMAP. Reaction of Weinreb amide **13** with deprotonated ethynyltrimethylsilane then afforded enynone **14** in high yield.

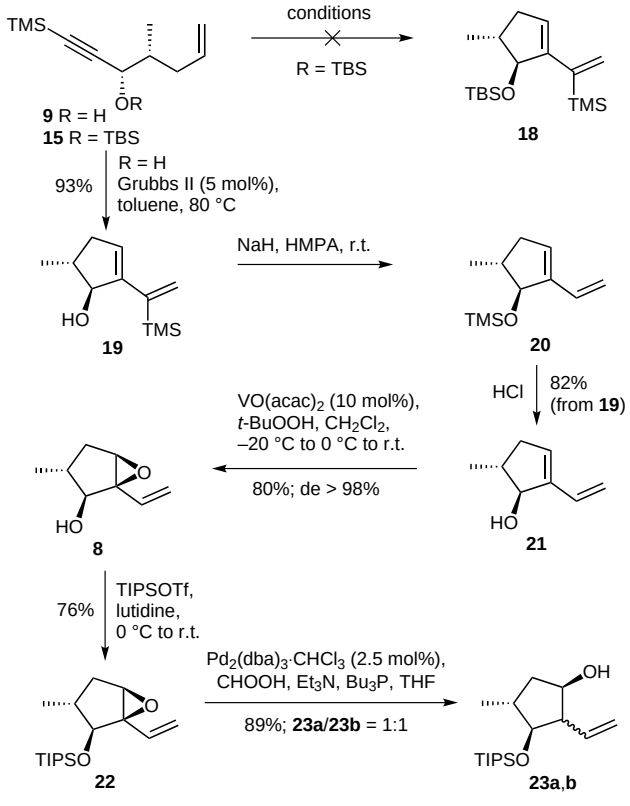
With **14** in hand, the stereoselective reduction of the carbonyl moiety could be attempted. Initial experiments with the CBS reagent[27] or Alpine borane[28] delivered the de-



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**, ynol **9** 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 CH_2Cl_2 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]



Scheme 3 Synthesis of cyclopentane **23a**,**b**

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 1 Conditions for the Cleavage of the TMS Group in **19**

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

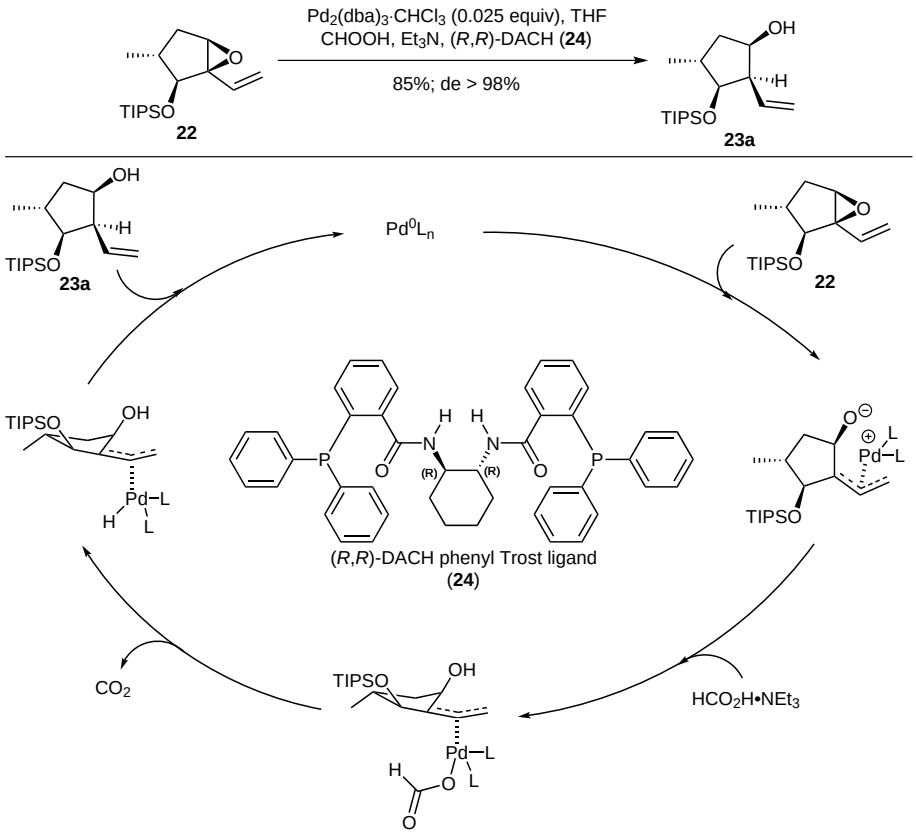
We then turned our attention to the cleavage of the silyl group via a Brook rearrangement,[32,33] taking advantage of the adjacent hydroxyl moiety. Initial experiments with NaH, LHMDS, or KHMDS proved unsuccessful, but when HMPA was added to the reaction mixture, **21** could be isolated in an excellent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

With desilylated alkene **21** in hand, the vanadium-catalyzed directed 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 reported the influence of the double bond geometry on the stereochemical outcome of this highly useful protocol. 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 $Pd(dba)_3{\cdot}CHCl_3$ with Bu_3P as ligand, Et_3N, 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



Scheme 4 Mechanistic rationale for the selective epoxide opening and formation of alcohol **23a**

has many beautiful applications in natural product synthesis.[37,38] Trost also described the palladium-catalyzed reaction of vinylic epoxides and reported the asymmetric alkylation of vinylglycidols.[39,40] This protocol has been successfully employed in the asymmetric synthesis of (–)-malyngolide.[41] Although the palladium-catalyzed reaction has only been applied to carbon or oxygen nucleophiles, we reasoned that the DACH phenyl Trost ligand (**24**) 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.[42] 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.[43,44] 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 **22** in the presence of the chiral Trost ligand **24** afforded the desired stereoisomer of the cyclopentane building block as the only isolable product in excellent 85% yield.[45] Reaction of **22** in the presence of the enantiomer of ligand **24** resulted in low yield of the desired product, along with mainly decomposed material. The absolute configuration of **23a** 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.[36]

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.

Acknowledgment

The authors thank Dr. Hanspeter Kählig (University of Vienna) for assistance with NMR spectroscopy. The Fonds zur Förderung der wissenschaftlichen Forschung (Austrian Science Fund, FWF) is gratefully acknowledged for financial support (Project FWF-P20697-N19).

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(30) **Preparation of Alcohol 9**: Acetylene **14** (1.0 g, 5.15 mmol, 1.0 equiv) was dissolved in freshly distilled 2-propanol (45 mL; degassed by three pump-freeze-thaw cycles prior to use). The solution was stirred at 40 °C and catalyst **17** (20 mg, 0.003 mmol, 0.0065 equiv; for preparation see Supporting Information), dissolved in 2-propanol (1 mL), was added via a syringe pump over 6 h. After consumption of the starting material the reaction was reduced in vacuo (30 °C, 40 mbar) and the residue (ca. 3 mL) was purified by flash column chromatography (hexane–EtOAc, 9:1) to afford **9** (950 mg, 95%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.77–5.87 (m, 1 H), 5.02–5.10 (m, 2 H), 4.28 (dd, *J* = 5.44, 5.44 Hz, 1 H), 2.33–2.40 (m, 1 H), 1.97–2.04 (m, 1 H), 1.78–1.86 (m, 2 H), 1.00 (s, 3 H), 0.18 (br s, 9 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 137.17 (CH), 116.65 (CH_2), 105.76 (C), 90.65 (C), 66.98 (CH), 39.40 (CH), 36.86 (CH_2), 15.08 (Me), 0.03 (Me). HRMS (ESI): *m*/*z* [M – Me]$^+$ calcd for $C_{10}H_{17}OSi$: 181.1049; found: 181.1044 ±5 ppm. $[\alpha]_D^{20}$ +3.8° (*c* = 1.630, $CHCl_3$). IR (ATR): 3351, 2960, 2352, 2171, 1640, 1376, 1249, 983, 947, 911, 838, 759, 698, 638 cm^{-1}.
(31) **Preparation of Cyclopentene 19**: Toluene (1.5 L) was degassed by an argon purge of approximately 1 h. Enyne **9** (3.00 g, 15.28 mmol, 1 equiv) was added and the solution was purged with argon for 10 min and with ethene for 10 min. Grubbs 2nd generation catalyst (0.649 g, 0.764 mmol, 0.005 equiv) was added in one portion and the solution was purged with ethene for 15 min. The mixture was heated to 80 °C for 16 h at positive pressure of ethene. After total consumption of the starting material, the mixture was reduced in vacuo (40 °C, 60 mbar) to a volume of approximately 70 mL. This volume was applied on a column and eluted with hexane (300 mL). After purification by flash column chromatography (hexane–EtOAc, 19:1), **19** (2.80 g, 93%) was isolated as a slightly brownish fluid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.92 (d, *J* = 2.80 Hz, 1 H), 5.79 (dd, *J* = 2.69, 2.69 Hz, 1 H), 5.52 (d, *J* = 2.69 Hz, 1 H), 4.54 (br s, 1 H), 2.72–2.79 (m, 1 H), 2.11–2.20 (m, 1 H), 1.90–1.96 (m, 1 H), 1.51 (br s, 1 H), 1.09 (d, *J* = 7.12 Hz, 3 H), 0.17 (s, 9 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 146.23 (C), 145.72 (C), 130.73 (CH), 125.82 (CH_2), 84.31 (CH), 41.47 (CH), 38.97 (CH_2), 19.71 (Me), –0.59 (Me). HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{11}H_{20}NaOSi$: 219.1181; found: 219.1183 ±5 ppm. $[\alpha]_D^{20}$ −89.1° (*c* = 1.030, $CHCl_3$).
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(33) **Preparation of 21**: NaH (60% dispersion in mineral oil, 0.224 g, 5.60 mmol, 2.2 equiv) was added to HMPA (1.66 mL, 9.57 mmol, 3.75 equiv) in one portion. After 5 min, a solution of **19** (0.500 g, 2.55 mmol, 1 equiv) in THF (1.66 mL) was added. After consumption of the starting material as indicated by TLC analysis (60 min) the reaction was quenched via addition of a sat. aqueous solution of NH_4Cl. The solution was acidified to pH 2 by addition of HCl (1 M) and stirred for approximately 20 min. The aqueous solution was extracted with CH_2Cl_2 (3 × 20 mL) and dried over $MgSO_4$. Silica was added and the solvent was reduced in vacuo. The crude product was purified by flash column chromatography (dry loading; pentane–Et_2O, 10:1). The solvent was carefully reduced under reduced pressure (700 mbar, 35 °C) to yield **21** (260 mg, 82%) as a colorless liquid. Note: The product is highly volatile; thus, yields vary between 40% and 82%. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.45 (dd, *J* = 17.73, 11.00 Hz, 1 H), 5.82 (dd, *J* = 2.63, 2.63 Hz, 1 H), 5.41–5.46 (m, 1 H), 5.14 (dd, *J* = 10.89, 0.84 Hz, 1 H), 4.52 (br s, 1 H), 2.71–2.78 (m, 1 H), 2.14–2.23 (m, 1 H), 1.87–1.94 (m, 1 H), 1.51 (br s, 1 H), 1.10 (d, *J* = 7.16 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 143.58 (C), 133.11 (CH), 131.87 (CH), 115.01 (CH_2), 83.20 (CH), 42.56 (CH), 38.60 (CH_2), 19.67 (Me). HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_8H_{12}NaO$: 147.0786; found: 147.0788 ±5 ppm. $[\alpha]_D^{20}$ −70° (*c* = 0.2250, $CHCl_3$). IR (ATR): 3316, 2954, 2924, 2868, 1641, 1454, 1374, 1260, 1021, 988, 905, 813 cm^{-1}.
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(45) **Preparation of 23a**: The reaction was carried out in Schlenk flasks using degassed solvents. A Schlenk flask containing $Pd_2(dba)_3 \cdot CHCl_3$ (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 CH_2Cl_2 (0.6 mL) was added. After 5 min a mixture of Et_3N (117 μL, 0.844 mmol, 5.0 equiv) and formic acid (32 μL, 0.844 mmol, 5.0 equiv) in CH_2Cl_2 (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 CH_2Cl_2 (0.1 mL). The reaction was stirred until TLC analysis showed total consumption of the starting material (3 h). A sat. aqueous solution of NH_4Cl was added and the mixture was extracted with CH_2Cl_2 (3 × 20 mL), the organic extracts were dried over $MgSO_4$, 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, $CDCl_3$): 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 (ddd, *J* = 14.42, 8.99, 0.95 Hz, 1 H), 1.51 (ddd, *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). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 135.16 (CH), 117.43 (CH_2), 85.48 (CH), 78.18 (CH), 52.81 (CH), 43.47 (CH_2), 41.40 (CH), 20.87 (Me), 18.21 (Me), 18.16 (Me), 12.37 (CH). HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{17}H_{34}NaO_2Si$: 321.2226; found: 321.2223 ±5 ppm. $[\alpha]_D^{20}$ −5° (*c* = 1.0900, $CHCl_3$). IR (ATR): 3531, 2943, 2866, 2359, 2342, 1636, 1463, 1419, 1383, 1119, 1060, 1014, 997, 912, 881, 847, 823, 729, 678 cm^{-1}.

