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Towards the Total Synthesis of Jerangolids - Synthesis of an Advanced Intermediate for the Pharmacophore Substructure

Julian Lenhof,[a] Michael Hutter,[b] Volker Huch[c] and Johann Jauch*[a]

Dedicated to Prof. Dr. Volker Schurig on the occasion of his 80.th birthday

Abstract: The jerangolids are a class of natural products with a skipped diene substructure isolated from *Sorangium cellulosum*. Here, we present a new strategy for the total synthesis of these compounds based on a skipped diyne as central building block and a suitably substituted epoxy aldehyde as bulding block for the dihydropyran substructure. So far, we reached an advanced intermediate which is related to the pharmacophore subunit of the jerangolids as well as of the ambruticins. A key step is a Shi epoxidation with high e.r. to form the epoxy aldehyde. Both building blocks are coupled in a Carreira alkynylation, where additional mechanistic studies based on DFT calculation were realized. The alkynylation is followed by a nucleophilic 6-endo-tet epoxide opening to form the pyrane structure and a Nicholas reduction to remove a propargylic OH group.

Introduction

The first jerangolids[1] were isolated by Gerth, Höfle and coworkers in 1995 from the myxobacterium *Sorangium cellulosum So ce 307* (Fig. 1).

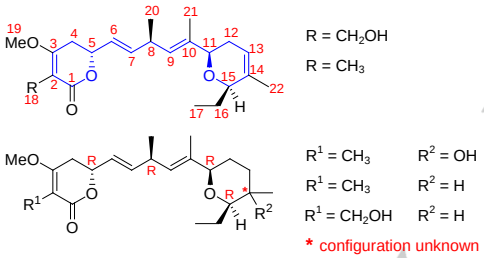


Figure 1. Structures of the so far known jerangolids.

The jerangolids are structurally related to the ambruticins[2] (Fig. 2) which were isolated from *Polyangium cellulosum var. fulvum*[2a, b] and *Sorangium cellulosum So ce 10*.[2c, d] Since both, the jerangolids and the ambruticins, show potent antifungal activity,[1, 2] it was assumed[3] that the common substructure of both natural compounds (C6-C17 and C20-C22 jerangolide numbering) is the pharmacophore responsible for the fungicidal effect.

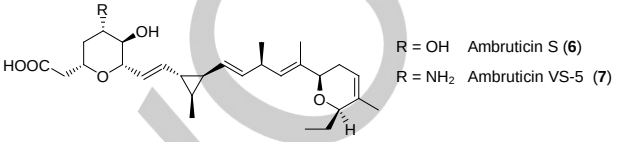
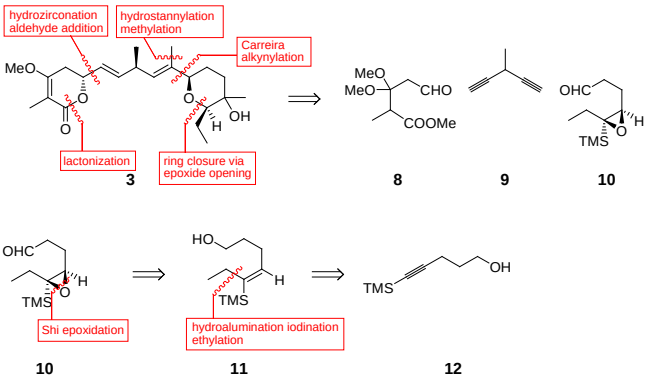


Figure 2. Structures of selected ambruticins.

Due to the interesting structure and the pharmacological activity of the jerangolids total syntheses were developed for these substances. Whereas Marko et al.[4] synthesized jerangolid D (**2**), Hanessian and coworkers[5] synthesized jerangolid A (**1**) and Hahn et al. very recently developed a total synthesis for jerangolid E (**4**). Besides these complete syntheses, also synthetic approaches for substructures of the jerangolids appeared in the literature.[7]

We became interested in the jerangolids because of their cryptical symmetric structure (Fig 1, blue structure) and their promising pharmacological activity. Here we would like to present preliminary results of our synthetic efforts to develop a synthetic strategy for jerangolid B (**3**), which should be adaptable also for the synthesis of all other jerangolids. Therefore we here focus on the synthesis of an advanced intermediate related to the C6-C17 substructure (closely related to the pharmacophore of jerangolids and ambruticins).

Results and Discussion



Scheme 1. Retrosynthetic disconnections into small building blocks.

Retrosynthetically, we envisioned removing the methyl group C21 and disconnecting the C10-C11 bond as well as the C5-C6 bond as shown in Scheme 1. Ring closure to the hydroxy-tetrahydropyran ring is effected through nucleophilic epoxide opening of the corresponding epoxy aldehyde **10** after Carreira

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alkynylation of the prochiral 3-methyl-1,4-pentadiyne **9**. The idea behind this disconnection was if it would be possible to construct the stereogenic center C11 with the correct configuration in a Carreira alkynylation *and* concomitantly desymmetrisize[8] the diyne **9** to get the correct configuration at C8. Diyne **9** is a known compound[9] and epoxy-aldehyde **10** can be traced back to trimethylsilylpentynol **12**. The TMS group in **10** is needed to directly open the epoxide to the tetrahydropyran ring (6-endo-tet cyclization) rather than to the tetrahydrofuran ring (5-exo-tet cyclization).[10]

Our synthesis started with the preparation of diyne **9** according to Verkruisse et al.,[9] but we used TMS-acetylene instead of acetylene as starting material (see lit.[9e]), so that in the last step the TMS groups have to be removed (Scheme 2).

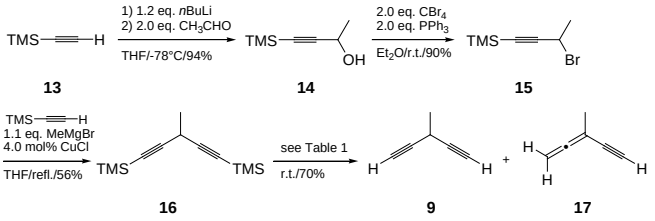


Table 1. Desilylation of **16**.

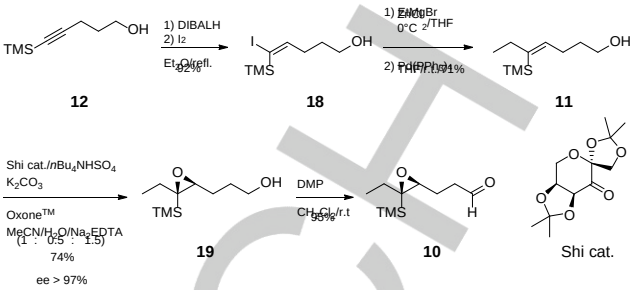
reactants	solvent	diyne **9** [%][a]	allenyne **17** [%][a]
TBAF	THF	1	99
TBAF/AcOH	THF	99[b]	1

[a]ratios were determined with ^{1}H-NMR-spectroscopy; [b]isolated yield 70% of **9** in THF solution.

Scheme 2. Synthesis of 3-methyl-1,4-pentadiyne **9**.

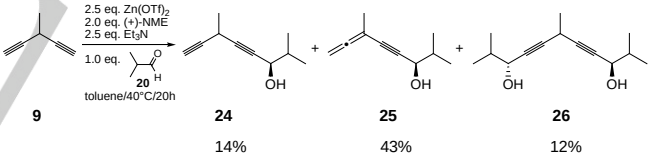
Desilylation of **16** to **9** is a crucial step. TBAF in THF, CH_2Cl_2 or toluene gave allenyne **17** as sole product, also pyridine-HF complex resulted in **17**, probably due to isomerization of diyne under basic conditions. For successful desilylation without isomerization of **9** to **17** it is necessary to add 2.0 eq. of HOAc prior to the addition of TBAF. Purification of **9** is very difficult due to high volatility and instability at room temperature. Since the planned Carreira alkynylation with **9** runs best in toluene as solvent, we isolated **9** as a solution in toluene, which can be stored without decomposition in a freezer at -30°C. The concentration of this solution was determined by ^{1}H-NMR spectroscopy.

Next, we synthesized building block **10** (Scheme 3). Starting from commercially available 5-trimethylsilyl-pent-4-yn-1-ol **12**, hydroalumination with DIBALH and iodination with I_2 led to vinyliodide **18.**[11] Negishi coupling[12] with ethylzinc bromide gave unsaturated alcohol **11**, which was converted to epoxy alcohol **19** through Shi epoxidation[13] with er = 98.5:1.5.[14] Finally, Dess-Martin oxidation resulted in epoxy aldehyde **10** in 46% yield over four steps.



Scheme 3. Synthesis of the building block **10** for the tetrahydropyrane substructure of the jerangolids.

Now, the stage was set for the planned Carreira alkynylation.[15] Prior to the coupling of skipped diyne **9** with epoxy aldehyde **10**, we studied the alkynylation of **9** with isobutyraldehyde (**20**), 3-phenyl-propionaldehyde (**21**) and with benzaldehyde (**22**) to find suitable reaction conditions. Astonishingly, no reaction occurred at room temperature, in contrast to Carreira´s standard conditions.[15] As control experiments, we pursued alkynylations with 1-octyne (**23**) and aldehyde **20** under standard conditions in toluene and in methylene chloride as solvents. These control experiments worked quite well, so the skipped diyne **9** must have a lower intrinsic reactivity than simple alkynes.[16] After extensive experimentation with **9** and isobutyraldehyde (**20**) we found that a Carreira alkynylation takes place at 40 °C and requires 2.5 eq. of $Zn(OTf)_2$, 2.5 eq. N-methyl ephedrine and 2.0 eq. of Et_3N. To prevent excessive formation of **26**, aldehyde **20** had to be added very slowly (best with a syringe pump over several hours) to the reaction mixture (Scheme 4).



Scheme 4. Optimized conditions for Carreira alkynylation of **9** with **20**.

Unfortunately, we did not only get the expected diynol **24** in rather low yield, but the allenynol **25** as main product together with the diyndiol **26**. Up to now, we were unable to find conditions to obtain **24** as main product. 1,4-pentadiynes with an active C-H bond in 3-position always showed isomerization to the corresponding allenynols alongside the alkynylation.

Obviously, isomerization of **9** to **17** occurs during alkynylation of the aldehyde. To gain more insight into isomerization during the Carreira reaction with **9**, DFT calculations were performed.[17] Allenyne **17** was computed to be 11,5 kcal/mol more stable than the diyne **9**, indicating that the allenyne is thermodynamically preferred. We also calculated various possible Zn complexes[18] from **9** and **17** (Fig. 3).

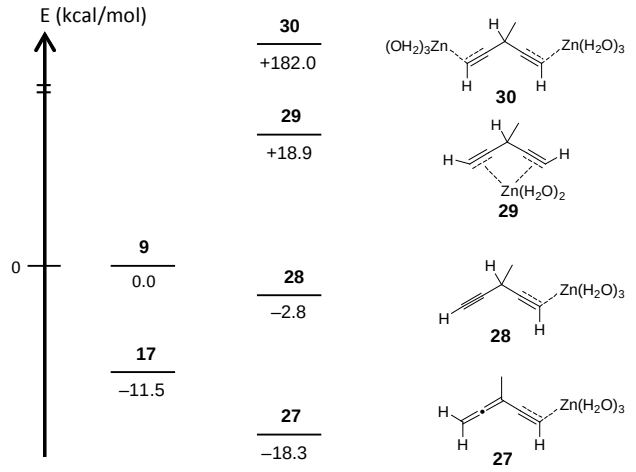
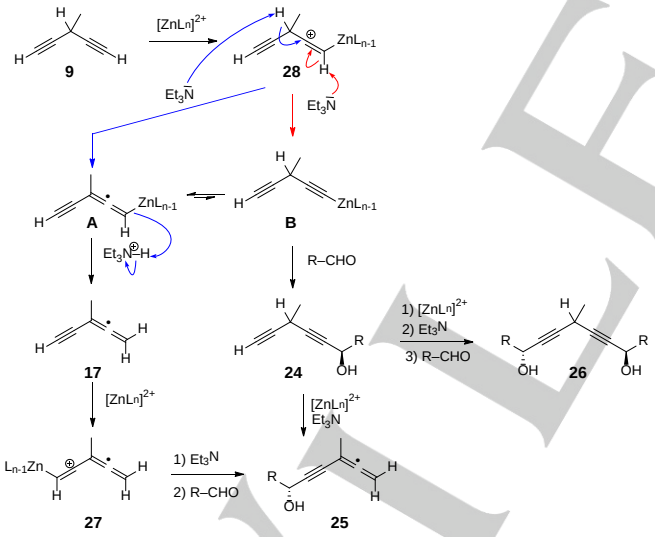


Figure 3. Structures and relative energies of **9**, **17**, and Zn complexes **27**, **28**, **29** and **30**.

For additional information of the Zn complexes **27**-**30** (bond distances, bond angles) see SI.

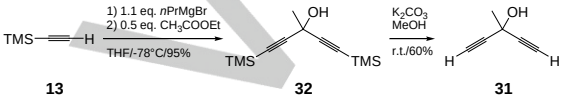
Until now, there is no further information in literature about the exact alkynylation mechanism of skipped diynes. Therefore we present our suggested mechanism for the alkynylation and occurring isomerization based on the results of the DFT calculations in scheme 4.



Scheme 5. Possible mechanism to explain products **24**, **25** and **26**. The blue reaction path must be fast compared to the red reaction path to explain the relative amounts of the products.

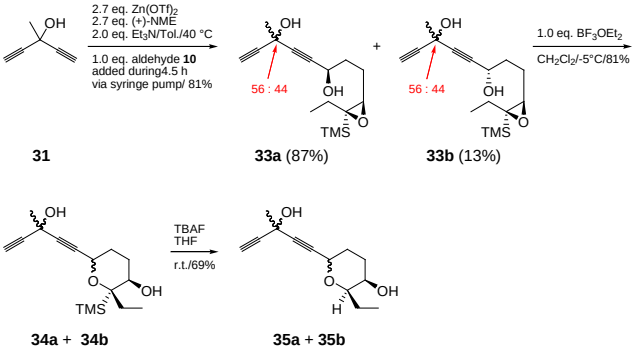
The complexation of **9** with zinc generates the vinylic cation **28**. Thereby the acidity of position three and five increases significantly and after deprotonation with triethylamine, the allenylzinc **A** or zincacetylide **B** are formed. Following this, the zincacetylide **B** reacts with the aldehyde to the particular propargylic alcohol **24**, whereas the reactivity of the allenylzinc species is too low for further reactions and is consequently protonated by the ammonium ion. The allenyne **17** undergoes the same complexation to form the most stable zinc complex **27** and further reacts to the propargylic alcohol **25**. Based on the DFT calculations, the blue reaction pathway is favored leading to the formation of the energetically lower allenyne **17** and the zinc complex **27**, assuming thermodynamic control of the mechanism after formation of intermediate **A**.

To circumvent the allene formation, the central building block **9** had to be replaced by a less volatile and more stable diyne, which can not isomerize to an allenyne like **17** or **25**. Therefore, we used the tertiary alcohol **31** as a substitute for **9**. **31** is a stable, less volatile compound, the OH-group can in principle be removed by the Nicholas reaction[19] and it is easily accesssible[20] (Scheme 6). We got crystals of **31** suitable for X-ray analysis. Details thereof can be found in the SI.



Scheme 6. Synthesis of the new central building block **31**.

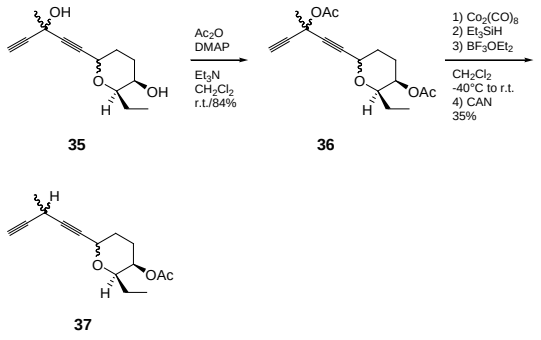
With **31** in hand, the Carreira alkynylation with aldehyde **10** could be performed. Applying the conditions for diyne **9**, we obtained the desired secondary alcohol **33** as a mixture of diastereomers (Scheme 7). Regarding the expected de-symmetrization of the enantiotopic triple bonds in **31**, the diastereoselectivity is very small (56:44), whereas the selectivity of the Carreira alkynylation is acceptable (87:13) (Scheme 7).[21] The mixture of diastereomers **33a** and **33b** was cyclized to tetrahydropyranes **34a** and **34b** through BF_3-induced epoxide opening in 81% yield and high 6-endo-tet selectivity (same composition as **33a** and **33b**, but now, the diastereomers could be separated via flash chromatography). The regioselectivity is controlled by the silyl-group, which favors a nucleophilic attack at the α-carbon center.[10i,22] The TMS group attached to C15 could be removed in 69% yield with TBAF in THF to give the advanced intermediate **35**. Here, the diastereomers also could be separated with flash chromatography.



Scheme 7. Carreira alkynylation of **31** and epoxy aldehyde **10**, cyclization and deprotection.

At this stage we studied the racemic deoxygenation of the tertiary alcohol via Nicholas reaction.[19] A stereoselective

method was published by Kann.[23] To remove the OH group it has to be converted into an acetate, since acetates work better in Nicholas reactions than free OH groups.[19] Thus, treatment of **35** with acetic anhydride and DMAP gave acetate **36**, which was subjected to deoxygenation with $Co_2(CO)_8$, Et_3SiH and $BF_3{\cdot}OEt_2$ to give the skipped diyne **37** after oxidative regeneration of the triple bond with ceric ammonium nitrate in 35% (Scheme 8).



35 **36** **37**

Scheme 8. Deoxygenation under Nicholas conditions.

Conclusions

In summary, we could synthesize compound **37**, which is an advanced intermediate in our total synthesis of the jerangolids, in 11 steps and 7% yield, with the longest linear sequence of 7 steps. This intermediate permits the completion of the synthesis of the natural products as well as the synthesis of analogues for pharmacological testing. Key steps are a Carreira alkynylation with a skipped diyne, a TMS directed 6-endo-tet epoxide opening and a Nicholas reaction with Et_3SiH for the deoxygenation of a tertiary alcohol. The strategy is highly flexible, which opens the possibility to synthesize many structural analogues for pharmaceutical evaluation. Currently, we work on the completion of the synthesis of jerangolid B and the optimization of the Nicholas reaction. This work will be published in due course.

Experimental Section

General: All reactions were run under a N_2 atmosphere in dried (heat gun) glass ware. All solvents used in reactions were purchased in HPLC grade quality and were additionally freshly distilled under N_2. THF and toluene were destilled from sodium/benzophenone and dichloromethane was distilled from CaH_2. Solvents for flash chromatography and for the extraction of aqueous phases were distilled under laboratory atmosphere with a rotavap. Petrol ether refers to a mixture of hexanes with a boiling range from 45-65°C. All other chemicals were used as purchased without additional purification. Silica gel for flash chromatography was from Merck, Darmstadt, Germany (Silica 60, particle size 40-63 μm). TLC plates for reaction monitoring were from Merck, Darmstadt, Germany ($Si60_{254}$ glass plates 50x100 mm). NMR spectra were recorded with a BRUKER AV 400 NMR spectrometer at 400 MHz (^1H) and 100 MHz (^{13}C) respectively. HRMS spectra were recorded on a Bruker SolariX 7T FTICR-MS.

4-(Trimethylsilyl)but-3-yn-2-ol (14). Trimethylsilylacetylene (**13**) (21.9 mL, 153 mmol) is dissolved in dry THF (200 mL) and cooled to –78°C. *n*BuLi (72 mL of a 2.5 M solution in hexane, 180 mmol) is added over 15 min. The resulting yellow solution is stirred for 1.5 h at –78°C prior to slow addition of acetaldehyde (25.3 mL, 450 mmol) over 30 min. Stirring is continued at –78°C for three hours. Then, the reaction is quenched by adding sat. NH_4Cl solution. The phases are separated and the aqueous phase is extracted with diethyl ether. The combined organic phases are washed with brine and dried over $MgSO_4$. Filtration and evaporation of the solvent yields the product as slightly yellow oil (13.3 g, 95.5 mmol, 62 %), which is used without further purification. ^1H-NMR (400 MHz, $CDCl_3$, 20°C): δ = 0.18 (s, 9 H, TMS), 1.45 (d, J = 7.0 Hz, 3 H, H1), 4.52 (q, J = 7.0 Hz, 1H, H2) ppm. ^{13}C-NMR (100 MHz, $CDCl_3$, 20°C) δ = –0.16 ($H_3\underline{C}$-Si), 24.2 (C1), 58.7 (C2), 88.4 (C4), 107.7 (C3) ppm.

3-(Bromobut-1-ynyl)trimethylsilane (15). Tetrabromomethane (33.2 g, 100 mmol) is dissolved in dry diethyl ether (slightly orange solution). To this solution a solution of **14** (12.0 g, 50 mmol) in diethyl ether (5.0 mL) is added at once with stirring at room temperature. Next, triphenylphosphine (26.2 g, 100 mmol) is devided into four portions and these portions are added at intervals of 15 min. while stirring the reaction mixture. After ca. 60 min (TLC control, petrol ether/diethyl ether 3:1 v/v) the reaction is finished and the reaction mixture is filtered through celite and purified by flash chromatography (petrol ether/diethyl ether 3:1 v/v) to give the product as colourless oil (11.1 g, 49.5 mmol, 99%). ^1H-NMR (400 MHz, $CDCl_3$, 20°C): δ = 0.19 (s, 9 H, TMS), 1.92 (d, J = 7.0 Hz, 3 H, H4), 4.62 (q, J = 7.0 Hz, 1H, H3) ppm. ^{13}C-NMR (100 MHz, $CDCl_3$, 20°C) δ = –0.29 ($H_3\underline{C}$-Si), 27.3 (C4), 31.3 (C3), 91.0 (C1), 105.0 (C2) ppm.

3-Methyl-1,5-bis(trimethylsilyl)penta-1,4-diyne (16). A solution of MeMgBr (3.0 M, 19.0 mL, 57 mmol) in diethyl ether is diluted by THF (60 mL) prior to dropwise addition of Trimethylsilylacetylene (**13**) (9.5 mL, 67 mmol) during 15 min. so that the reaction mixture is gently boiling. After cooling to room temperature, dry CuCl (180 mg, 3.6 mmol) is added and the reaction mixture is heated to reflux for 1.5 hours. After cooling to room temperature, a solution of **15** (11.1 g, 50 mmol) in THF (8.5 mL) is added dropwise during 30 min. The black solution is heated and stirred for further 2.5 hours at reflux. After cooling to room temperature, the reaction mixture is added carefully to a mixture of 1 M HCl (50 mL) and ice. The mixture is extracted with diethyl ether and the combined organic extracts are washed with sat. $NaHCO_3$ solution and brine successively. Drying with $MgSO_4$, filtration and evaporation of the solvent gives the crude product which is purified by distillation (Kugelrohr) at 5 torr at 85-90°C. Yield: colourless oil (6.83 g, 31 mmol, 62%). ^1H-NMR (400 MHz, $CDCl_3$, 20°C): δ = 0.17 (s, 18 H, TMS), 1.44 (d, J = 7.0 Hz, 3 H, H6), 3.51 (q, J = 7.0 Hz, 1H, H3) ppm. ^{13}C-NMR (100 MHz, $CDCl_3$, 20°C) δ = –0.06 ($H_3\underline{C}$-Si), 19.7 (C6), 22.4 (C3), 84.5 (C2/C4), 105.2 (C1/C5) ppm.

3-Methylpenta-1,4-diyne (9). 3-Methyl-1,5-bis(trimethylsilyl)-penta-1,4-diyne (**16**) (441 mg, 2 mmol) is dissolved in toluene at room temperature. Next, acetic acid (230 μL, 4 mmol) is added with stirring and a solution of TBAF (1.24 g, 4 mmol) in toluene (4 mL) is added very slowly dropwise during 1 hour. Stirring at room temperature is continued until **16** is consumed completely (ca. 60 hours, judged by ^1H-NMR spectroscopy). Sat. $NaHCO_3$ solution is added and the organic phase is washed twice with water. The combined aqueous phases are re-extracted once

with toluene (4 mL). The combined organic phases are dried with $MgSO_4$. After filtering the $MgSO_4$, the yield and concentration of the product in toluene is determined by ^{1}H-NMR spectroscopy and the solution is used for the Carreira reaction. Yield: 1.26 mmol of **9** (63%) in 10 mL of toluene (c = 0.126 mmol/mL). ^{1}H-NMR (400 MHz, $CDCl_3$, 20°C): δ = 1.48 (d, J = 7.0 Hz, 3H, H6), 2.17 (d, J = 2.5 Hz, 2H, H1 and H5), 3.45 (qt, J = 7.0, 2.5 Hz, 1H, H3) ppm. ^{13}C-NMR (100 MHz, $CDCl_3$, 20°C): δ = 17.4 (C6), 21.9 (C3), 68.7 (C1 and C5), 83.0 (C2 and C4).

(*E*)-5-Iodo-5-(trimethylsilyl)pent-4-en-1-ol (18). 1-(Trimethylsilyl)pent-4-yn-1-ol (**12**) (5.47 g, 35 mmol) are dissolved in diethyl ether (80 mL) and cooled to 0°C. At this temperature, a solution of DIBALH in toluene (1.2 M, 71.5 mL, 85.8 mmol) is slowly added dropwise. After all DIBALH has been added, the reaction mixture is heated to reflux for 24 hours. After cooling to room temperature the mixture is cooled to –78°C and a solution of iodine (35.5 g, 140 mmol) in diethyl ether (75 mL) is carefully added dropwise whereupon the reaction mixture turns dark brown. After two hours at –78°C, the reaction mixture is allowed to reach room temperature (remove the cooling bath; stirring and warming over night reduces the yield dramatically!) and is quenched with 1 M HCl (ca. 150 mL). The phases are separated and the aqueous phase is extracted with diethyl ether. The combined organic phases are washed successively with sat. $Na_2S_2O_3$ solution and brine and are dried with Na_2SO_4. After filtration and evaporation the crude product is purified via flash chromatography (petrol ether/acetone 3:1 v/v). Yield: colourless oil (9.12 g, 32 mmol, 92%). ^{1}H-NMR (400 MHz, $CDCl_3$, 20°C): δ = 7.18 (t, J = 7.8 Hz, 1 H, H4), 3.66 (t, J = 6.5 Hz, 2 H, H1), 2.19 (dt, J = 7.3, 7.8 Hz, 2H, H3), 1.66 (tt, J = 6.5, 7.5 Hz, 2H, H2), 1.43 (br s, 1H, OH), 0.28 (s, 9H, TMS) ppm. ^{13}C-NMR (100 MHz, $CDCl_3$, 20°C) δ = 155.5 (C4), 107.3 (C5), 61.9 (C1), 31.9 (C3), 31.4 (C2), 1.1 (TMS) ppm. HRMS (ESI+): calc. for $C_8H_{18}IOSi$ ($[M+1]^+$): m/z = 285.01662; found: m/z = 285.01670.

(*Z*)-5-(Trimethylsilyl)hept-4-en-1-ol (11). To magnesium chips (8.5 g, 350 mmol) is added a solution of bromoethane (26.1 ml, 350 mmol) in THF (120 mL) dropwise so that the Grignard reaction starts and is boiling gently throughout the addition of bromoethane. After the addition is complete, the mixture is refluxed until all Mg is consumed (Ethylmagnesiumbromide solution **A**). Next, freshly dried $ZnCl_2$ (47.7 g, 350 mmol) is dissolved in THF (430 mL) at 0°C. To this solution, 120 mL of the Grignard solution **A** prepared above is slowly added dropwise at 0°C and then the mixture is stirred at room temperature for one hour (Ethylzincchloride solution **B**). In the meantime, **18** (9.95 g, 35 mmol) is dissolved in THF (75 mL) and to this solution, $(Ph_3P)_4Pd$ (1.12 g, 1.05 mmol) is added and the mixture is stirred for 15 min. Then, solution **B** (250 mL) is added dropwise at room temperature until all **18** is consumed (TLC control, petrol ether/diethyl ether 2:1 v/v). Then excess of ethylzincchloride is destroyed by addition of a mixture of sat. NH_4Cl solution and ice. The mixture is extracted with diethyl ether snd the combined organic extracts are washed successively with water and brine. Drying with $MgSO_4$, filtration and evaporation of the solvent gives the crude product which is purified by flash chromatography (petrol ether/diethyl ether 5:1 $\rightarrow$ 2.5:1 v/v), yielding pure **11** (4.6 g, 25 mmol, 71%). ^{1}H-NMR (400 MHz, $CDCl_3$, 20°C): δ = 5.94 (t, J = 7.5 Hz, 1 H, H4), 3.67 (t, J = 6.5 Hz, 2 H, H1), 2.23-2.17 (m, 2H, H3), 2.10-2.04 (m, 2H, H6), 1.69-1.62 (m, 2H, H2), 0.96 (t, J = 7.5 Hz, 3H, H7), 0.15 (s, 9H, TMS) ppm. ^{13}C-NMR (100 MHz, $CDCl_3$, 20°C) δ = 140.6 (C4), 121.9 (C5), 62.7 (C1), 33.1 (C3), 30.9 (C2), 28.4 (C6), 15.4 (C7), 0.3 (TMS) ppm. HRMS (ESI+): calc. for $C_{10}H_{23}OSi$ ($[M+1]^+$): m/z = 197.15127; found: m/z = 187.15100.

3-((2*S*, 3*R*)-3-Ethyl-3-(trimethylsilyl)oxiran-2-yl)-propan-1-ol (19). Alken **11** (4.6 g, 25 mmol) are dissolved in acetonitrile (350 mL). To this solution a solution of Na_2EDTA ($4{\cdot}10^{-4}$ M, 250 mL) and Shi-catalyst (synthesized from *L*-sorbose; 4.5 g, 17.5 mmol) and $n Bu_4NHSO_4$ (1.02 g, 3 mmol) are added. The solution is stirred very vigorously and cooled to 0°C. At this temperature a solution of K_2CO_3 (23.0 g, 167.5 mmol) in water (180 mL) and a solution of Oxone^{TM} (24.6 g, 40 mmol $KHSO_5$) in $4{\cdot}10^{-4}$ M aqueous Na_2EDTA (180 mL) are added dropwise simultaneously. After the addition is complete, the reaction mixture is stirred vigorously for an additional hour and then quenched by addition of pentane (200 mL). The phases are separated and the aqueous phase is extracted several times with pentane and once with diethyl ether. The combined organic extracts are washed with brine and dried with $MgSO_4$. After filtration and evaporation of the solvent, the crude product is purified by flash chromatography (petrol ether/diethyl ether 5:1 $\rightarrow$ 1:1 v/v) yielding **19** as a yellowish oil (3.74 g, 18.5 mmol, 74%). ^{1}H-NMR (400 MHz, $CDCl_3$, 20°C): δ = 3.75-3.69 (m, 2 H, H1), 2.73 (dd, J = 3.8, 8.5 Hz, 1 H, H4), 1.99-1.90 (m, 1H, H3), 1.84-1.74 (m, 3 H, 2xH2 + 1xH3), 1.54-1.46 (m, 1 H, H6), 1.17-1.08 (m, 1 H, H6), 0.92 (t, J = 7.5 Hz, 3 H, H7), 0.15 (s, 9 H, TMS) ppm. ^{13}C-NMR (100 MHz, $CDCl_3$, 20°C) δ = 63.2 (C1), 62.4 (C4), 59.0 (C5), 30.3 (C6 + C3), 27.5 (C2), 10.0 (C7), –1.2 (TMS) ppm. HRMS (ESI–): calc. for $C_{10}H_{21}IO_2Si$ ($[M-1]^-$): m/z = 201.13161; found: m/z = 201.13151.

3-((2*S*,3*R*)-3-ethyl-3-(trimethylsilyl)oxiran-2-yl)propanal (10). Epoxyalcohol **19** (2.4 g, 11.8 mmol) is dissolved in dichloromethane (75 mL). Pyridine (1.12 g, 1.14 mL, 14.2 mmol) is added with stirring prior to addition of Dess-Martin periodinane (6.02 g, 14.2 mmol).The reaction mixture is stirred for one hour at room temperature and is quenched by addition of sat. $NaHCO_3$ solution and sat. $Na_2S_2O_3$ solution. The phases are separated and the aqueous phase is extracted with dichloromethane. The combined organic phases are washed with brine and dried with $MgSO_4$. After filtration, the dichloromethane is distilled off at 500-600 torr and 55°C bath temperature. The residue is purified by flash chromatography using n-pentane/diethyl ether 4:1 (v/v) as eluent. After distillation of the solvents, aldehyde **10** is obtained as colourless liquid (2.22 g, 11.1 mmol, 94%). ^{1}H-NMR (400 MHz, $CDCl_3$, 20°C): δ = 9.85 (br. t, 1 H, H1), 2.74 (dd, J = 4.2, 8.5 Hz, 1 H, H4), 2.69-2.64 (m, 2H, H2), 2.09-2.02 (m, 1 H, H3), 1.95-1.80 (m, 1 H, H3), 1.74-1.67 (m, 1 H, H6), 1.34-1-24 (m, 1 H, H6), 0.91 (t, J = 7.5 Hz, 3 H, H7), 0.15 (s, 9 H, TMS) ppm. ^{13}C-NMR (100 MHz, $CDCl_3$, 20°C) δ = 201.2 (C1), 62.1 (C4), 59.03 (C5), 41.4 (C2), 30.1 (C6), 23.6 (C3), 10.0 (C7), -1.22 (TMS) ppm. HRMS (ESI+): calc. for $C_{10}H_{21}O_2Si$ ($[M+1]^+$): m/z = 201.13161; found: m/z = 201.13031.

(3*R*)-2,6-dimethylocta-4,7-diyn-3-ol (24): Zinctriflate (2.42 g, 6.65 mmol) is dried under vacuum with a heat gun until a fine white powder is obtained. After cooling to room temperature and flushing with N_2, (+)-N-methyl-ephedrine (1.19 g, 6.65 mmol) is added and the flask is evacuated and flushed with N_2 three to four times. Then, dry toluene (5 mL) is added and the mixture is stirred vigorously at room temperature. After 5 min triethylamine (737 µL, 5.32 mmol) is added dropwise and the mixture is stirred at room temperature for an additional hour. To the resulting biphasic suspension a solution of 3-methyl-1,4-pentadiyne (**9**) in toluene (21.1 mL of a 0.126 molar solution; see preparation of **9** above) is added at once. Stirring is continued for 1.5 hours at room temperature prior to heating the reaction mixture to 40°C. Then, a solution of isobutyraldehyde (291 µL, 3.19 mmol) in toluene (2 mL) is added during 4.5 hours via syringe pump. After

further 30 min. at 40°C, the reaction mixture is cooled to room temperature and the reaction is quenched by addition of sat. NH_4Cl solution (ca. 10 mL). The phases are separated and the aqueous phase is extracted with diethyl ether. Use the aqueous phase later for recovering of N-methyl-ephedrine! The combined organic phases are washed with brine and dried with $MgSO_4$. After filtration and evaporation of the solvent, the crude product is purified by flash chromatography (petrol ether/acetone 6:1 v/v). Yield of **24**: 80 mg as a clear oil (0.53 mmol, 20%). Additionally, allenyne **25** (189 mg, 1.14 mmol, 43%) and **26** (71 mg, 0.32 mmol, 12%) are obtained. **25**: ^{1}H-NMR (400 MHz, $CDCl_3$, 20°C): δ = 4.89 (dq, J = 3.3, 0.9 Hz, 2H, H1); 4.28 (d, J = 5.5 Hz, 1H, H6); 1.90 (dsept, J = 6.8, 1.0 Hz, 1H, H7); 1.84 (t, J = 3.3 Hz, 3H, H10); 1.01 (d, J = 6.0 Hz, 3H, H8); 0.99 (d, J = 6.1 Hz, 3H) ppm. ^{13}C-NMR (100 MHz, $CDCl_3$, 20°C) δ = 214.1 (C2); 90.6 (C4); 84.3 (C5); 81.6 (C3); 76.1 (C1); 68.4 (C6); 34.6 (C7); 19.7 (C10); 10.1 (C8); 17.5 (C9). **24**: ^{1}H-NMR (400 MHz, $CDCl_3$, 20°C): δ = 4.16 (dt, J = 5.5, 1.3 Hz, 1H, H6); 3.53-3.46 (m, 1H, H3); 2.15 (d, J = 2.4 Hz, 1H, H1); 1.92-1.85 (m, 1H, H7); 1.47 (d, J = 6.6 Hz, 3H, H9) ppm. HRMS (ESI+): calc. for $C_{10}H_{15}O$ ($[M+1]^+$): m/z = 149.08719; found: m/z = 149.09695.

3-methyl-1,5-bis(trimethylsilyl)penta-1,4-diyn-3-ol (32): Magnesium turnings (2.67 g, 110 mmol) are placed in a dry flask. 1-bromopropane (13.53 g, 110 mmol) is dissolved in dry THF (40 mL). 5 mL of this solution is added at once to the magnesium turnings, so that the Grignard reaction starts. In case the reaction starts vigorously the reaction temperature has to be controlled by gentle cooling with cold water. Then, the rest of the bromopropane solution is carefully added dropwise at such a rate, that the reaction mixture is gently boiling. When all the bromopropane has been added, the mixture is heated to reflux until all magnesium turnings were consumed (ca. 45 min.). Then, a solution of trimethylsilylacetylene (11.79 g, 17.08 mL, 120 mmol) in THF (20 mL) is carefully added dropwise to the hot solution of *n*-PrMgBr (vigorous gas evolution!). After the addition is complete, the mixture is further refluxed for 30 min. Next, a solution of ethyl acetate (4.41 g, 4.88 mL, 50 mmol) in THF (10 mL) is slowly added dropwise while still refluxing the reaction mixture. When the addition of ethyl acetate is complete, the reaction mixture is refluxed for another 1.5 hours. After cooling to room temperature the excess of the Grignard reagent is destroyed by carefully quenching the reaction mixture with ice-cold water (30 mL; vigorous gas evolution!) and sat. NH_4Cl solution (50 mL) under vigorous stirring. The phases are separated and the aqueous phase is acidified with 1 M HCl to dissolve precipitated salts and then extracted several times with diethyl ether. The combined organic phases were washed with brine and dried with $MgSO_4$. After filtration, the solvent is evaporated and the product starts to crystallize. Yield of **32**: 11..3 g (47.5 mmol, 95%). ^{1}H-NMR (400 MHz, $CDCl_3$, 20°C): δ = 1.73 (s, 3 H, H6), 0.17 (s, 18 H, TMS) ppm. ^{13}C-NMR (100 MHz, $CDCl_3$, 20°C) δ = 106.0 (C2 + C4), 86.9 (C1 + C5), 67.9 (C3), 31.9 (C6), -0.3 (TMS) ppm.

3-methylpenta-1,4-diyn-3-ol (31): 3-methyl-1,5-bis(trimethylsilyl)penta-1,4-diyn-3-ol (**32**) (12.2 g, 51 mmol) are dissolved in methanol (180 mL). K_2CO_3 (7.05 g, 51 mmol) is added and the reaction mixture is stirred at room temperature until all starting material is consumed (TLC petrol ether/diethyl ether 1:1 v/v). Sat. NH_4Cl solution is added (ca. 50 mL), followed by diethyl ether (ca. 150 mL). The phases are separated and the aqueous phase is extracted twice with diethyl ether. The combined organic phases are washed 5-6 times with water. Drying with $MgSO_4$, filtering and evaporating the solvent at normal pressure gives the crude product, which is purified by flash chromatography (petrol ether/diethyl ether 2:1 v/v). The solvent of the combined product-containing fractions is distilled off at normal pressure at 55°C bath temperature. From the residue, the product crystallizes in the refrigerator at ca. 6°C over night to give 2.88 g of fine white needles (60%). ^{1}H-NMR (400 MHz, $CDCl_3$, 20°C): δ = 2.57 (s, 2 H, H1 + H5), 2.57 (br. s, 1 H, OH), 1.80 (s, 3H, H6) ppm. ^{13}C-NMR (100 MHz, $CDCl_3$, 20°C) δ = 84.4 (C2 + C4), 71.1 (C1 + C5), 59.5 (C3), 31.5 (C6) ppm.

(6*R*)-8-((2*R*,3*R*)-3-ethyl-3-(trimethylsilyl)oxiran-2-yl)-3-methylocta-1,4-diyne-3,6-diol (33a + 33b): Zinctriflate (7.85 g, 21.6 mmol) is dried under vacuum with a heat gun until a fine white powder is obtained. After cooling to room temperature and flushing with N_2, (+)-N-methyl-ephedrine (3.94 g, 21.6 mmol) is added and the flask is evacuated and flushed with N_2 three to four times. Then, dry toluene (21 mL) is added and the mixture is stirred vigorously at room temperature. After 5 min triethyl amine (1.62 g, 2.23 mL, 16.0 mmol) is added dropwise and the mixture is stirred at room temperature for an additional hour. To that biphasic suspension **31** (824 mg, 8.8 mmol) is added at once. Stirring is continued for 1.5 hours prior to heating the reaction mixture to 40°C. Then, a solution of epoxy aldehyde **10** (1.68 g, 8.0 mmol) in toluene (8 mL) is added during 4.5 hours via syringe pump. After further 30 min. at 40°C, the reaction mixture is cooled to room temperature and the reaction is quenched by addition of sat. NH_4Cl solution (15 mL). The phases are separated and the aqueous phase is extracted with diethyl ether (ca. 20 mL) for three times. Do **not** discard the aqueous phase! The combined organic phases are washed with brine and dried with $MgSO_4$. After filtration of the $MgSO_4$ and evaporation of the solvent the crude product is purified by flash chromatography (petrol ether/acetone 6:1 v/v). **33** is obtained as a mixture of diastereomers (1.92 g, 6.5 mmol, 81%). ^{1}H-NMR (400 MHz, $CDCl_3$, 20°C): δ = 4.53 (dt, J = 5.6, 5.0 Hz, 1H, H7), 2.77 (dd, J = 8.7, 4.2 Hz, 1H, H4), 2.53 (s, 1H, H12), 2.42-2.39 (m, 1H, OH), 1.97-1.89 (m, 3H, H5 + H6), 1.88-1.84 (m, 1H, H5), 1.76 (s, 3H, H13), 1.65-1.59 (m, 1H, H2), 1.13-1.07 (m, 1H, H2), 0.91 (t, J = 7.5 Hz, 3H, H1), 0.15 (s, 9H, TMS) ppm. ^{13}C-NMR (100 MHz, $CDCl_3$, 20°C) δ = 85.9 (C8), 84.8 (C11), 83.4 (C9), 70.8 (C12), 62.9 (C3), 61.8 (C7), 59.5 (C10), 34.9 (C4), 31.6 (C5), 30.9 (C6), 30.2 (C13), 26.5 (C2), 10.1 (C1), –1.16 (TMS) ppm. HRMS (ESI–): calc. for $C_{16}H_{25}O_3Si$ ($[M–1]^-$): m/z = 293,15784; found: m/z = 293,15812.

The aqueous phase from above is made basic by addition of NaOH solution. Extraction with diethyl ether, drying of the extract with Na_2SO_4 is a means to recover the (+)-N-methyl ephedrine for further use.

(2S,3R,6R)-2-ethyl-6-(3-hydroxy-3-methylpenta-1,4-diynyl)-2-(trimethylsilyl)-tetrahydro-2H-pyran-3-ol (34a + 34b): The mixture of diastereomers **33a** + **33b** (1.70 g, 5.7 mmol) is dissolved in dichloromethane (60 mL) and cooled to –5°C. At this temperature $BF_3{\cdot}OEt_2$ (700 µL, 5.7 mmol) is added dropwise. When all starting material has been consumed (TLC, petrol ether/acetone 3:1 v/v) the reaction mixture is quenched with sat. $NaHCO_3$ solution. The phases are separated and the aqueous phase is extracted with dichloromethane. The combined organic phases are dried with $MgSO_4$, filtered and evaporated. The resulting crude product is purified by flash chromatography (petrol ether/acetone 4:1 v/v) to yield 1.37 g **34a** and **30b** (4.6 mmol, 81%) as slightly yellow oil. ^{1}H-NMR (400 MHz, $CDCl_3$, 20°C): δ = 4.53-4.49 (m, 1H, H7), 3.73 (m, 1H, H4), 2.56 (s, 1H, H12), 2.06-1.97 (m, 1H, H2), 1.96-1.86 (m, 2H, H2 + H6), 1.78 (s, 3H, H13), 1.73-1.68 (m, 2H, H5), 1.66-1.57 (m, 1H, H2), 0.89 (t, J = 7.6 Hz, 3H, H1), 0.14 (s, 9H, TMS) ppm. ^{13}C-NMR (100 MHz, $CDCl_3$, 20°C) δ = 84.9 (C8), 84.2 (C11), 83.4 (C9), 70.7 (C12), 66.8 (C4), 59.7 (C10), 31.7 (C13), 26.2 (C6), 24.4 (C5), 23.9

(C2), 9.1 (C1), -1.47 (TMS) ppm. HRMS (ESI–): calc. for $C_{16}H_{25}O_3Si$ ($[M–1]^-$): m/z = 293,15784; found: m/z = 293,15767.

(2R,3R,6R)-2-ethyl-6-(3-hydroxy-3-methylpenta-1,4-diynyl)-tetrahydro-2H-pyran-3-ol (35a + 35b): Tetrahydro-2H-pyran **34a** + **34b** (2.60 g, 8.8 mmol) are dissolved in THF (73 mL). A solution of TBAF in THF (36.1 ml, 1 M, 36.1 mmol) are added dropwise at room temperature and the mixture is stirred for 24 h. The reaction is quenched by adding sat. NH_4Cl solution and the phases are separated. The aqueous phase is extracted with diethyl ether and the combined organic phases are washed with sat. $NaHCO_3$ solution and brine. After drying with $MgSO_4$, filtration and evaporation of the solvent, the crude product is purified by flash chromatography (petrol ether/acetone 5:1 v/v). Yield: 1.37 g of **35a** + **35b** (6.1 mmol, 69%) as a slightly orange oil. **34a**: ^{1}H-NMR (400 MHz, $CDCl_3$, 20°C): δ = 4.70 (br.d, J = 3.8 Hz, 1H, H7), 3.52 (m, 1H, H3), 3.33 (dt, J = 9.0, 4.3 Hz, 1H, H4), 2.93 (br.s, 1H, OH), 2.55 (s, 1H, H12), 1.98-1.93 (m, 1H, H2), 1.91-1.83 (m, 3H, H5 and H6), 1.61-1.74 (m, 1H, H5) 1.79 (s, 3H, H13), 1.48-1.41 (m, 1H, H2), 0.97 (t, J = 7.5 Hz, 3H, H1) ppm. ^{13}C-NMR (100 MHz, $CDCl_3$, 20°C) δ = 87.6 (C9), 84.8 (C11), 80.8 (C8), 77.7 (C3), 70.8 (C12), 69.8 (C4), 64.0 (C7), 59.6 (C10), 31.7 (C13), 29.8 (C6), 28.9 (C5), 24.4 (C2), 9.5 (C1). ppm. HRMS (ESI+): calc. for $C_{13}H_{22}O_3N$ ($[M+NH_4]^+$): m/z = 240.15942; found: m/z = 240.15885.

34b: ^{1}H-NMR (400 MHz, $CDCl_3$, 20°C): δ = 4.12 (dd, J = 12.0, 2.4 Hz, 1H, H7), 3.38-3.32 (m, 1H, H3), 3.00 (dt, J = 8.7, 2.7 Hz, 1H, H4), 2.60 (br.s, 1H, OH), 2.54 (s, 1H, H12), 2.21-2.08 (m, 1H, H2), 1.98-1.93 (m, 1H, H6), 1.90-1.75 (m, 2H, H5 and H6) 1.77 (s, 3H, H13), 1.55-1.43 (m, 2H, H5 and H2), 0.97 (t, J = 7.5 Hz, 3H, H1) ppm. ^{13}C-NMR (100 MHz, $CDCl_3$, 20°C) δ = 85.0 (C9), 84.7 (C11), 83.8 (C4), 81.6 (C8); 70.9 (C12), 69.4 (C3), 67.5 (C7), 59.4 (C10), 32.7 (C5), 32.1 (C6), 31.5 (C13); 24.8 (C2), 9.5 (C1) ppm. HRMS (ESI+): calc. for $C_{13}H_{22}O_3N$ ($[M+NH_4]^+$): m/z = 240.15942; found: m/z = 240.15903.

(2R,3R,6R)-2-ethyl-6-(3-acetoxy-3-methylpenta-1,4-diynyl)-tetrahydro-3-acetoxy-2H-pyran (36a + 36b): Diol **35a** + **35b** (1.35 g, 6.1 mmol) is dissolved in dichloromethane (60 mL). Triethylamine (1.53 g, 2.11 mL, 15.2 mmol), acetic anhydride (1.87 g, 1.73 mL, 18.3 mmol) and DMAP (98.0 mg, 0.8 mmol) are added and the reaction mixture is stirred at room temperature for 17 hours. The reaction is quenched by addition of aq. HCl (1 M, 30 mL), the phases are separated and the aqueous phase is extracted with dichloromethane. The combined organic phases are washed with brine and dried with $MgSO_4$. Filtration and evaporation of the solvent gives the diacetate **36a** + **36b** as pure product (1.57 g, 5.14 mmol, 84%). ^{1}H-NMR ($CDCl_3$, 400 MHz, 20°C): δ = 4.71 (br.d, J = 4.1 Hz, 1H, H7), 4.50 (ddd, J = 2.2, 4.4, 10.0 Hz, 1H, H4), 3.73-3.67 (m, 1H, H3), 2.63 (s, 1H, H12), 2.09 (s, 3H, H14), 2.06 (s, 3H, H15), 2.04-1.97 (m, 1H, H5), 1.95-1.89 (m, 1H, H5), 1.93 (s, 3H, H13), 1.84-1.78 (m, 2H, H6), 1.67-1.59 (m, 1H, H2), 1.42-1.34 (m, 1H, H2), 0.93 (t, J = 7.3 Hz, 3H, H1) ppm. ^{13}C-NMR ($CDCl_3$, 100 MHz, 20°C): δ = 170.3 (C16), 166.4 (C17 84.5 (C8, 82.5 (C11 81.3 (C9, 74.9 (C4, 72.6 (C12 71.4 (C3), 64.1 (C7), 63.4 (C10), 30.6 (C13), 29.4 (C5), 25.5 (C6), 24.4 (C14), 21.4 (C2), 21.2 (C15), 9.4 (C1) ppm. HRMS (ESI+): calc. for $C_{17}H_{26}O_5N$ ($[M+NH_4]^+$): m/z = 324.18055; found: m/z = 324.18032.

(2R,3R,6R)-2-ethyl-6-(3-methylpenta-1,4-diynyl)-tetrahydro-3-acetoxy-2H-pyran (37a + 37b): Dicobaltoctacarbonyl (400 mg, 1.17 mmol) is dissolved in dichloromethane (15 mL) and a solution of **36a** + **36b** (306 mg, 1.00 mmol) in dichloromethane (15 mL) is added. After stirring for 1.5 h the mixture is cooled to –40°C. After 10 min. at –40°C triethylsilane (233 mg, 320 µL, 2.00 mmol) and $BF_3{\cdot}OEt_2$ (156.8 mg, 140 µL, 1.1 mmol) are added successively and the reaction mixture is stirred at –40°C for 4 hours and is allowed to reach room temperature slowly over night. The reaction is quenched by addition of sat. $NaHCO_3$ solution, the phases are separated and the aqueous phase is extracted with dichloromethane. The combined organic phases are washed with brine and dried with Na_2SO_4. After filtering and evaporation of the solvent the residue is taken up in acetone (5 mL) and cooled to 0°C. With vigorous stirring four portions of CAN (each portion: 1.1 g, 2.00 mmol) are added within 10 min. After CO evolution ceased (ca. 20 min.), the solvent is evaporated under reduced pressure and the residue is taken up in diethyl ether (10 mL) and mixed with water (10 mL). The phases are separated and the aqueous phase is extracted with diethyl ether. The combined organic phases are washed with brine and dried over Na_2SO_4. Purification of the residue by flash chromatography (petrol ether/acetone 7:1 v/v) gives pure **37a** + **37b** (86 mg, 35%). ^{1}H-NMR ($CDCl_3$, 400 MHz, 20°C): δ = 4.69-4.66 (m, 1H, H7), 5.50 (dt, J = 4.5, 9.4 Hz, 1H, H4), 3.72 (dt, J = 3.0, 8.6 Hz, 1H, H3), 3.53 (ddq, J = 1.8, 2.4, 7.0 Hz 1H, H10), 2.17 (d, J = 2.4 Hz, 1H, H12), 2.06 (s, 3H, H14), 2.04-1.97 (m, 1H, H5), 1.94-1.86 (m, 1H, H6), 1.84-1.78 (m, 2H, H5 + H6), 1.66-1.58 (m, 1H, H2), 1.50 (d, $^3J_{H,H}$ = 7.0 Hz, 3H, H13), 1.44-1.35 (m, 1H, H2), 0.93 (t, J = 7.5 Hz, 3H, H1) ppm. ^{13}C-NMR ($CDCl_3$, 100 MHz, 20°C): δ = 170.3 (C15), 85.9 (C8), 83.4 (C9), 78.1 (C11), 74.5 (C3), 71.5 (C4), 68.4 (C12), 64.1 (C7), 29.7 (C6), 25.4 (C5), 24.4 (C2), 22.2 (C13), 21.2 (C14), 17.7 (C10), 9.4 (C1) ppm. HRMS (ESI+): calc. for $C_{15}H_{21}O_3$ ($[M+H]^+$): m/z = 249.14852; found: m/z = 249.14869.

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Keywords: jerangolids • total synthesis • Carreira alkynylation • skipped diynes • Nicholas reaction

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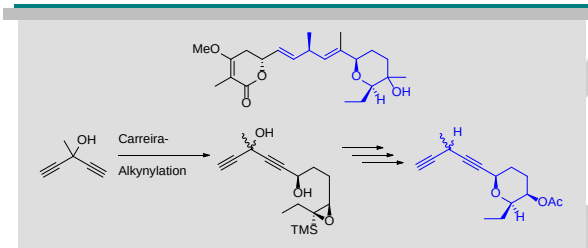

Here, we present a new strategy for the total synthesis based upon a skipped diyne as central building block. This was transformed so far into an advanced intermediate related to the pharmacophore of the jerangolids.

Jerangolids, pharmacophore

*Julian Lenhof, Michael Hutter, Volker Huch, Johann Jauch**

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Towards the Total Synthesis of Jerangolids - Synthesis of an Advanced Intermediate for the Pharmacophore Substructure