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 80th 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 building 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 pyran structure and a Nicholas reduction to remove a propargylic OH group.

Introduction

The first jerangolids[1] were isolated by Gerth, Höfle and co-workers in 1995 from the myxobacterium Sorangium cellulosum So ce 307 (Figure 1).

Figure 1. Structures of the so far known jerangolids.

The jerangolids are structurally related to the ambruticins[2] (Figure 2) which were isolated from Polyanthium cellulosum var. fulvum[2a,2b] and Sorangium cellulosum So ce 10.[2c,2d] 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 co-workers[5] synthesized jerangolid A (1) and Hahn et al.[6] 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 (Figure 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

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 affected through nucleophilic epoxide opening of the corresponding epoxy aldehyde 10 after Carreira 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 desymmetrize the diyne 9 to get the correct configuration at C8. Diyne 9 is a known compound 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 tetrahydro-furan ring (6-endo-tet cyclization) rather than to the tetrahydrofuran ring (5-exo-tet cyclization).

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 I2 led to vinyl iodide 18. Negishi coupling with ethylzinc bromide gave unsaturated alcohol 11, which was converted to epoxy alcohol 19 through Shi epoxidation with $\text{[9a]}$ with $\text{er} = 98.5:1.5$. Finally, Dess–Martin oxidation resulted in epoxy aldehyde 10 in 46 % yield over four steps.

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).

Desilylation of 16 to 9 is a crucial step (Table 1). TBAF in THF, CH2Cl2 or toluene gave allenyle 17 as the 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 equiv. 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 $-30 \, ^\circ\text{C}$. The concentration of this solution was determined by $^1\text{H}$-NMR spectroscopy.

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 $^1\text{H}$-NMR spectroscopy. [b] Isolated yield 70 % of 9 in THF solution.

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-phenylpropionaldehyde (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 dichloromethane 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 equiv. of Zn(OTf)$_2$, 2.5 equiv. N-methyl ephedrine and 2.0 equiv. of Et$_3$N. 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).

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

Obviously, isomerization of 9 to 17 occurs during alkylation of the aldehyde. To gain more insight into isomerization during the Carreira reaction, 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 (Figure 3).

For additional information of the Zn complexes 27–30 (bond lengths, bond angles) see SI.

Until now, there is no further information in the literature about the exact alkylation mechanism of skipped diynes. Therefore we present our suggested mechanism for the alkylation and occurring isomerization based on the results of the DFT calculations in Scheme 5.

With 31 in hand, the Carreira alkylation 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 desymmetrization of the enantiotopic triple bonds in 31, the diastereoselectivity is very small (56:44), whereas the selectivity of the Carreira alkylation is acceptable (87:13) (Scheme 7).[21]

The mixture of diastereomers 33a and 33b was cyclized to tetrahydropyrans 34a and 34b through BF₃-induced epoxide opening in 81% yield and high 6-endo-tet selectivity (the 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.

At this stage, we studied the racemic deoxygenation of the tertiary alcohol via Nicholas reaction. A stereoselective method was published by Kann. To remove the OH group it has to be converted into an acetate since acetates work better in Nicholas reactions than free OH groups. Thus, treatment has to be converted into an acetate since acetates work better (Scheme 8).

![Scheme 8. Deoxygenation under Nicholas conditions.](image)

**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 alkylnylation with a skipped diyne, a TMS directed 6-endo-tet epoxide opening and a Nicholas reaction with Et3SiH 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 an N2 atmosphere in dried (heat gun) glassware. All solvents used in reactions were purchased in HPLC grade quality and were additionally freshly distilled under N2. THF and toluene were distilled from sodium/benzophenone and dichloromethane was distilled from CaH2. Solvents for flash chromatography (petroleum ether/diethyl ether, 3:1 v/v) to give the advanced intermediate 35. Here, the diastereomers also could be separated with flash chromatography.

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aqueous phases are re-extracted once with toluene (4 mL). The combined organic phases are dried with MgSO4. After filtering, the MgSO4 is washed with ethyl ether (80 mL) and cooled to 0 °C. 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 0 °C (argon atmosphere), the reaction mixture is allowed to reach room temperature (remove the cooling bath; stirring and warming overnight 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 dichloromethane (2 × 50 mL). The combined organic phases are washed successively with sat. Na2SO4 solution and water and are dried with Na2SO4. After filtration and evaporation the crude product is purified by flash chromatography (petroleum ether/diethyl ether, 2:1 v/v) yielding 19 as a yellowish oil (3.74 g, 18.5 mmol, 74 %).

1H-NMR (400 MHz, CDCl3, 298 °C): δ = 3.75–3.69 (m, 2 H, H1, H2), 2.73–2.69 (m, 2 H, H3), 1.99–1.90 (m, 1 H, H3), 1.84–1.74 (m, 2 H, H1), 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. 13C-NMR (100 MHz, CDCl3, 298 °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 C10H17O4Si (M−1)+: m/z = 201.1316; found m/z = 201.1315.

3-((25R,3S)-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, 11.4 mmol, 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 1 hour at room temperature and is quenched by addition of sat. NaHCO3 solution and sat. Na2SO4 solution. The phases are separated and the aqueous phase is extracted with dichloromethane. The combined organic phases are washed with brine and dried with MgSO4. 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 %).

1H-NMR (400 MHz, CDCl3, 298 °C): δ = 9.85 (br. t, J = 7.8 Hz, 1 H, H1), 2.74 (dd, J = 4.2, 8.5 Hz, 1 H, H4), 2.69–2.64 (m, 2 H, H2), 2.09–2.02 (m, 2 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. 13C-NMR (100 MHz, CDCl3, 298 °C): δ = 201.2 (C1), 62.1 (C4), 59.3 (C5), 41.4 (C3), 30.1 (C6), 23.6 (C3), 10.0 (C7), −1.2 (TMS) ppm. HRMS (ESI+): calc. for C10H18O2Si (M+1)+: m/z = 201.1361; found m/z = 201.1303.

3R,2S,6-Dimethylrata-4,7-diyn-3-ol (24): Zirconitride (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 N2, (+)-N-methyl-ephedrine (1.19 g, 6.65 mmol) is added and the flask is evacuated and flushed with N2 three 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-(1-methyl-1-phenylpropyl)boronic acid (100 mg, 0.41 mmol) in dry toluene (5 mL) is added dropwise. After stirring for 1 h at room temperature, the reaction mixture is cooled to 0 °C and is quenched with 1 M HCl (ca. 1.5 mL) and Na2SO4 solution (ca. 2 mL). The phases are separated and the aqueous phase is extracted with dichloromethane. The combined organic phases are washed with brine and dried with MgSO4. 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 %).
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The phases are separated and the aqueous phase is extracted twice with a 50 mL solution, followed by diethyl ether (ca. 150 mL). The substrate in THF (20 mL) is carefully added (ca. 45 min.). Then, a solution of 1-bromo-3-methyl-1,5-bis(trimethylsilyl)penta-1,4-diyn-3-ol (1.92 g, 6.5 mmol, 81 %) as a mixture of diastereomers (1.92 g, 6.5 mmol, 81 %) is added and the flask is evacuated and flushed with N2 three to four times. Then, dry toluene (21 mL) is added and the mixture is stirred vigorously at room temperature. After 5 min triethylamine (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 biphase suspension, 21 (842 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 epoxide aldehyde 10 (1.68 g, 0.80 mmol) in toluene (8 mL) is added during 4.5 hours via syringe pump. After a further 30 min. at 40 °C, the reaction mixture is cooled to room temperature and the reaction is quenched by addition of sat. NH4Cl solution (15 mL). The phases are separated and the aqueous phase is extracted with diethyl ether (ca. 20 mL) three times. Do not discard the aqueous phase! The combined organic phases are washed with brine and dried with MgSO4. After filtration of the MgSO4 and evaporation of the solvent, the crude product is purified by flash chromatography (petroleum ether/acetonitrile, 6:1 v/v). Compound 33 is obtained as a mixture of diastereomers (1.92 g, 6.5 mmol, 81 %). 1H-NMR (400 MHz, CDCl3, 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, 1H, 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. 13C-NMR (100 MHz, CDCl3, 20 °C) δ = 85.9 (C8), 84.8 (C11), 83.4 (C9), 70.2 (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–): calcld. for C16H25O3Si ([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 Na2SO4 is a means to recover the (+)-N-methyl ephedrine for further use.

3-Methyl-1,5-bis(trimethylsilyl)hexa-1,4-dien-3-ol (31): Mixture (2.67 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. After 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 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 distilled off at normal pressure gives the crude product, which is purified by flash chromatography (petroleum ether/diethyl ether, 1:1 v/v). The mixture starts to crystallize. Yield of 11.3 g (47.5 mmol, 95 %). 1H-NMR (400 MHz, CDCl3, 20 °C): δ = 1.73 (s, 3 H, H6), 0.17 (s, 18 H, TMS) ppm. 13C-NMR (100 MHz, CDCl3, 20 °C): δ = 106.0 (C2 + C4), 86.9 (C1 + C5), 67.9 (C3), 31.6 (C9), –0.3 (TMS) ppm.

3-Methyl-1,4-dien-3-ol (32): 3-Methyl-1,5-bis(trimethylsilyl)hexa-1,4-dien-3-ol (32) (12.2 g, 51 mmol) is dissolved in methanol (180 mL). K2CO3 (7.05 g, 51 mmol) is added and the reaction mixture is stirred at room temperature until all starting material is consumed (TLC petroleum ether/diethyl ether, 1:1 v/v). Sat. NH4Cl 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 MgSO4, filtering and evaporating the solvent at normal pressure gives the crude product, which is purified by flash chromatography (petroleum 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 overnight to give 2.88 g of fine white needles (60 %). 1H-NMR (400 MHz, CDCl3, 20 °C): δ = 2.57 (s, 2 H, H1 + H5), 2.57 (br. s, 1 H, OH), 1.80 (s, 3H, H6) ppm. 13C-NMR (100 MHz, CDCl3, 20 °C): δ = 84.4 (C2 + C4), 71.1 (C1 + C5), 59.3 (C5), 31.5 (C6) ppm.
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. NaHCO₃ solution and the phases are separated. The aqueous phase is extracted with diethyl ether and the combined organic phases are washed with sat. NaHCO₃ solution and brine. After drying with MgSO₄, filtration and evaporation of the solvent gives the diacetate

\[ \text{36a} \] as a slightly orange oil. (1.53 g, 2.11 mL, 15.2 mmol), acetic anhydride (1.87 g, 1.73 mL, 16.7 mmol) are added successively and \( \mu \) = 7.5 Hz, 3H), 1.91–1.83 (m, 1H, 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. \( 13 \text{C-NMR} (100 \text{ MHz, CDCl}3, 20^\circ \text{C}) \): \[ \begin{align*} & \delta = 240.15942; \text{found} \delta = 240.15885. \\
& \text{calcd. for C15H21O3 ([M + H]+): m/z = 240.15903.} \\
& \text{calcd. for C13H22O3N ([M + NH4]+): m/z = 249.14852; found m/z = 249.14869.} \\
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& \text{Acknowledgments} \\
& \text{Keywords: Alkylation} \cdot \text{Diynes} \cdot \text{Natural products} \cdot \text{Nicholas reaction} \cdot \text{Total synthesis} \\
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