Side-Chain Truncation of Apicularen A by Olefin Cross-Metathesis with Ethylene

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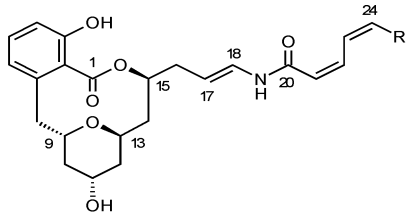
The three olefinic double bonds of natural apicularen A (**1a**) were cleaved by olefin cross-metathesis in the presence of ethylene and Hoveyda−Grubbs catalyst with concomitant *E*/*Z* isomerization of $\Delta^{17,18}$. On extended conversion, 18,-19-*seco*-apicularen A (**3**) was accumulated and isolated in pure state in 25% yield. In total synthesis, **3** is a valuable late-stage intermediate for side-chain-modified apicularens.

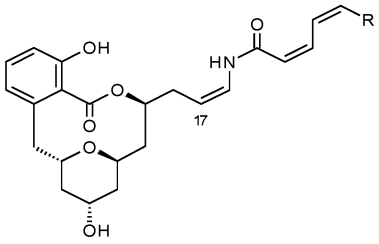
Apicularen A (**1a**) and its C-11 glycoside, apicularen B, are highly cytotoxic metabolites of the myxobacterium *Chondromyces apiculatus*.[1] From their structural features they belong to the benzolactone enamide class of mammalian V-ATPase inhibitors, which comprise salicylihalamides,[2] lobatamides,[3] and oximidines.[4] On the basis of the NCI 60-cell antitumor screen and COMPARE correlation analysis, Boyd et al.[5] predicted that apicularen A (**1a**) is also an inhibitor of V-ATPase, and, indeed, Huss et al.[6] recently demonstrated inhibition of V-ATPase from the tobacco hornworm with an IC_{50} of 20 nM. During the past 5 years a number of total syntheses of apicularen A (**1a**) and analogues were published.[7a−m] In most of these syntheses, side-chain-truncated apicularen (**3**) was a late key intermediate, which opened access to the parent compound **1a** as well as side-chain analogues.[7a−e,g−j] However, synthesis of **3** requires as many as 15−23 steps with total yields of 2−9%; thus an alternative economic access seems desirable. On the basis of the production of apicularen A (**1**) by large-scale fermentation,[1] we investigated its cleavage to **3** and related building blocks by oxidative methods[8] and olefin metathesis.[9,10] Herein we report on the olefin cross-metathesis of **1a** with ethylene, a reaction that in our hands worked well with other complex natural products, such as epothilone C,[11] spirangien A,[12] and cruentaren A.[13]

On the basis of our experiments on ethylene cross-metathesis of epothilone C[11] and cruentaren[13] with various ruthenium metathesis catalysts, we treated a solution of **1a** and ethylene with Hoveyda−Grubbs catalyst[14] and observed also a rapid conversion. On a preparative scale in the presence of 20 mol % of catalyst, the reaction mixture was analyzed by HPLC/MS after 2 h. Four major peaks were detected with the molecular masses of **1a** and **1b** (*m*/*z* 442, 414, $M + H^+$). Smaller peaks were assigned to **3** (*m*/*z* 319), a 22,23-*seco*-apicularen (*m*/*z* 387), and to a product of cross-metathesis of **1b** and **3** (*m*/*z* 703). Isolation by preparative HPLC yielded pure educt **1a** (9%), isomer **2a** (15%), **1b** (15%), and isomer **2b** (8%). As an extended reaction time did not significantly change the product mixture, in a separate experiment a second portion of 20 mol % of catalyst was added after 24 h. Workup after 48 h yielded in addition to the previously obtained compounds 25% of **3**.

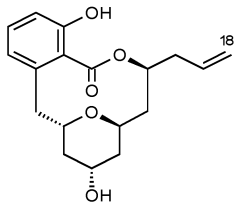
The structure of (17*Z*)-apicularen A (**2a**) followed from NMR data, exhibiting significant high-field shifts for C-16 from δ 36.4 in **1a** to 32.2, and for H-17 from δ 5.26 in **1a** to 4.82. Also the 8.9 Hz vicinal coupling of H-17/H-18 is in the expected range. Similarly, **1b** and **2b** were identified as 17*E* and 17*Z* isomers of *seco*-apicularen lacking the ethyl terminus on C-24. From the elemental composition and UV and NMR spectroscopic data, **3** was the desired compound lacking the *N*-acylamino side chain. Moreover, all physical data were in excellent agreement with those



Apicularen A (**1a**) R = Et
23,24-*seco*-Apicularen A (**1b**) R = H



(17*Z*)-Apicularen A (**2a**) R = Et
(17*Z*)-23,24-*seco*-Apicularen A (**2b**) R = H



18,19-*seco*-Apicularen A (**3**)

reported by the groups of De Brabander,[7a] Taylor,[7c,g] and Rychnovsky.[7h]

Whereas 23,24-*seco*-apicularen (**1b**) showed essentially the same cytotoxic activity as **1a** in the mouse fibroblast cell line L929, the 17*Z* isomer of apicularen A (**2a**) was by a factor of 50 less active, and truncated apicularen **3** was essentially inactive.[15]

Even if the production of apicularen A (**1a**) by fermentation and its one-step transformation are not yet optimized, this alternative route to **3** is extremely time- and labor-saving compared to the 15−23-step total syntheses. With a rich supply of **3** from fermentation[16] a variety of side-chain-modified apicularens may now be synthesized and their SAR investigated. Apart from that, it has again been demonstrated that cross-metathesis with ethylene is a very useful tool in the modification and degradation of complex natural products.

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Experimental Section

General Experimental Procedures. Optical rotations were determined on a Perkin-Elmer 241 instrument. UV spectra were recorded on a Shimadzu UV-2102 PC scanning spectrometer. IR spectra were measured with a Nicolet 20DXB FT-IR spectrometer. NMR spectra were recorded in $CDCl_3$ on a Bruker DMX-600 or DPX-300 spectrometer. EI and DCI mass spectra (reactant gas ammonia) were obtained on a Finnigan MAT 95 spectrometer, with high-resolution data acquired using peak matching (M/DM = 10000). Pure compounds were characterized by analytical HPLC on Nucleosil C_{18} (column 125 × 2 mm, 5 μm, flow 0.3 mL/min), acetonitrile/water, diode array detection. Preparative HPLC on Nucleosil (column 250 × 21 mm, 7 μm, flow 18 mL/min) used acetonitrile/water (gradients) as solvent, with UV absorption detection at 254 nm. Hoveyda−Grubbs catalyst (1,3-bis(2,4,6-trimethylphenyl)-2-imidazolidinylidene)dichloro(*o*-isopropoxyphenylmethylene)ruthenium was purchased from Aldrich.

Cross-Metathesis of Apicularen A (1a) with Ethylene. (a) Apicularen A (**1a**) (35 mg, 79μmol, 1 equiv) and Hoveyda−Grubbs catalyst (11 mg, 17 μmol, 0.2 equiv) were dissolved in absolute dichloromethane (24 mL). The solution was saturated with ethylene and stirred for 2 h. After HPLC analysis the solution was evaporated in vacuo and the dark brown residue separated by preparative HPLC (acetonitrile/50 mM ammonium acetate buffer pH 7, gradient 20:80 to 60:40 in 90 min, detection 254 nm). The major peaks were collected, acetonitrile was evaporated, and the residual water phase was extracted three times with ethyl acetate. From the organic phase, pure apicularen A (**1a**, 3.0 mg, 9%), (17*Z*)-apicularen A (**2a**, 5.3 mg, 15%), 23,24-*seco*-apicularen A (**1b**, 4.8 mg, 15%), and (17*Z*)-24,25-*seco*-apicularen A (**2b**, 2.6 mg, 8%) were obtained.

(b) Apicularen A (97 mg, 220 μmol, 1 equiv) and Hoveyda−Grubbs catalyst (30 mg, 47 μmol, 0.2 equiv) were reacted as described above. After 24 h, a second portion of catalyst (30 mg) was added and stirring continued for 24 h. Separation of the product mixture was achieved as described above applying a three-step gradient (30 min 20:80, 30 min 30:70, 30 min 40:60). Quantities of pure **1a** (8.4 mg, 9%), **1b** (8.9 mg, 10%), **2b** (6.3 mg, 7%), and **3** (17.6 mg, 25%) were obtained.

(17*Z*)-Apicularen A (2a): tan-colored oil; $[\alpha]^{20}_D$ 0 (*c* 0.5, MeOH); UV (MeOH) λ_{max} (log ϵ) 204 (4.5), 279 (4.4) nm; ^{1}H NMR (acetone-d_6, 600 MHz) δ 1.00 (1H, t, J = 7.4 Hz, H-25), 1.46−1.54 (2H, m, H-10b, H-12b), 1.59 (1H, dt, J = 14.7, 2.3 Hz, H-14b), 1.67 (1H, ddd, J = 12.7, 7.5, 5.1 Hz, H-12a), 1.84 (1H, ddd, J = 14.6, 11.1, 10.9 Hz, H-14a), 1.89−1.95 (1H, m, H-10a), 2.24−2.30 (2H, m, J = 15.2, 7.6, 7.6, 2.1 Hz, H_2-25), 2.37−2.48 (2H, m, H-8b, H_2-16), 3.36 (1H, dd, J = 14.7, 9.8 Hz, H-8a), 3.85−3.91 (1H, m, H-9), 3.95−4.01 (1H, m, H-11), 4.26 (1H, ddd, J = 17.6, 6.8, 5.1 Hz, H-13), 4.79−4.86 (1H, m, H-17), 5.45−5.52 (1H, m, J = 10.6, 7.9, 5.5, 2.5 Hz, H-15), 5.77−5.83 (1H, m, J = 10.7, 9.2, 7.7, 1.5 Hz, H-24), 5.84 (1H, d, J = 11.3 Hz, H-20), 6.70 (1H, d, J = 7.2 Hz, H-6), 6.78 (1H, d, J = 8.3 Hz, H-4), 6.84 (2H, td, J = 11.7, 1.1 Hz, H-18, H-22), 7.11 (1H, t, J = 7.9 Hz, H-5), 7.50 (1H, t, J = 11.0 Hz, H-23), 8.80 (1H, m, H-19); ^{13}C NMR (acetone-d_6, 75 MHz) δ 14.3 (C-26), 21.1 (C-25), 32.2 (C-16), 39.2 (C-14), 39.5 (C-10), 40.0 (C-12), 40.2 (C-8), 64.9 (C-11), 67.8 (C-13), 73.8 (C-9, C-15), 106.5 (C-17), 114.4 (C-4), 120.9 (C-21), 122.3 (C-6), 123.9 (C-2), 124.9 (C-18), 125.5 (C-23), 130.3 (C-5), 136.9 (C-22), 140.3 (C-7), 141.6 (C-24), 154.2 (C-3), 164.1 (C-20), 169.3 (C-1); EIMS *m*/*z* 441.2 M^+ (90); HREIMS *m*/*z* 441.2146 (calcd for $C_{25}H_{31}N_1O_6$, 441.2151).

24,25-*seco*-Apicularen A (1b): tan-colored oil; $[\alpha]^{20}_D$ +46 (*c* 0.2, MeOH/CH_2Cl_2, 1:1); UV (MeOH) λ_{max} (log ϵ) 203 (4.3), 258 (4.2), 267 (4.1), 283 (4.1) nm; IR (KBr) ν_{max} 3347, 2922, 1714, 1679, 1643 cm^{-1}; ^{1}H NMR (acetone-d_6, 300 MHz) δ 1.43−1.54 (2H, m, H-10b, H-12b), 1.58 (1H, dt, J = 14.6, 2.3 Hz, H-14b), 1.69 (1H, ddd, J = 12.6, 7.1, 5.4 Hz, H-12a), 1.84 (1H, ddd, J = 7.2, 3.9, 3.7 Hz, H-14a), 1.88−1.96 (1H, m, H-10a), 2.34 (1H, td, J = 6.9, 1.3 Hz, H-16), 2.43 (1H, dd, J = 14.7, 1.5 Hz, H-8b), 3.34 1H, dd, J = 14.7, 9.8 Hz, H-8a), 3.75 (1H, s, OH-11), 3.81−3.92 (1H, m, H-9), 3.93−4.03 (1H, m, H-11), 4.19−4.32 (1H, m, H-13), 5.28 (1H, ddd, J = 14.5, 7.4, 7.3 Hz, H-17), 5.35−5.52 (2H, m, H-15, H_2-24), 5.78 (1H, dd, J = 11.3, 0.8 Hz, H-21), 6.49 (1H, t, J = 11.2 Hz, H-22), 6.69 (1H, dd, J = 7.5, 0.8 Hz, H-6), 6.77 (1H, dd, J = 8.2, 0.7 Hz, H-4), 6.83−6.95 (1H, m, H-18), 7.06−7.14 (1H, m, H-5), 7.80−8.00 (1H, m, J = 17.2, 11.1, 10.1, 0.9 Hz, H-23), 9.10 (1H, d, J = 10.4 Hz, H-19); ^{13}C NMR (acetone-d_6, 75 MHz) δ 36.4 (C-16), 38.9 (C-14), 39.6 (C-10), 39.9 (C-12), 40.3 (C-8), 64.9 (C-11), 68.0 (C-13), 73.7 (C-9), 74.2 (C-15), 108.4 (C-17), 114.5 (C-4), 122.0 (C-6), 122.3 (C-21), 124.5 (C-24), 126.2 (C-2, C-18), 130.2 (C-5), 134.8 (C-23), 140.2 (C-7), 142.8 (C-22), 154.3 (C-3), 163.3 (C-20), 169.3 (C-1); EIMS *m*/*z* 413.2 M^+ (17), 163.1 (78); HREIMS *m*/*z* 413.1845 (calcd for $C_{23}H_{27}N_1O_6$, 413.1838).

(17*Z*)-24,25-*seco*-Apicularen A (2b): tan-colored oil; $[\alpha]^{20}_D$ +4.0 (*c* 0.7, MeOH); UV (MeOH) λ_{max} (log ϵ) 202 (4.3), 260 (4.2), 269 (4.2), 281 (4.2) nm; IR (KBr) ν_{max} 3390, 2924, 1720, 1655 cm^{-1}; ^{1}H NMR (acetone-d_6, 600 MHz) δ 1.44−1.55 (2H, m, H-10b, H-12b), 1.59 (1H, dt, J = 14.5, 2.2 Hz, H-14b), 1.67 (1H, ddd, J = 12.8, 7.6, 5.3 Hz, H-12a), 1.84 (1H, ddd, J = 14.6, 11.1, 10.9 Hz, H-14a), 1.89−1.95 (1H, m, H-10a), 2.37−2.49 (3H, m, H-8b, H_2-16), 3.36 (1H, dd, J = 14.7, 9.8 Hz, H-8a), 3.85−3.92 (1H, m, H-9), 3.95−4.02 (1H, m, H-11), 4.23−4.31 (1H, m, H-13), 4.81−4.89 (1H, dt, J = 7.6, 9.1 Hz, H-17), 5.41 (1H, d, J = 9.8 Hz, H-15), 5.47 (2H, dd, J = 17.2, 2.1 Hz, H_2-24), 5.88 (1H, d, J = 11.3 Hz, H-21), 6.48 (1H, t, J = 11.1 Hz, H-22), 6.70 (1H, d, J = 7.2 Hz, H-6), 6.78 (1H, d, J = 8.3 Hz, H-4), 6.83 (1H, td, J = 9.3, 1.51 Hz, H-18), 7.07−7.14 (1H, m, H-5), 7.83−7.93 (1H, m, H-23), 8.84 (1H, d, J = 11.3 Hz, H-19); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 32.1 (C-16), 39.1 (C-14), 39.5 (C-10), 39.9 (C-12), 40.2 (C-8), 64.8 (C-11), 67.8 (C-13), 73.7 (C-9, C-15), 106.9 (C-17), 114.4 (C-4), 121.9 (C-21), 122.3 (C-6), 123.9 (C-24), 124.6 (C-18), 125.4 (C-2), 130.3 (C-5), 134.8 (C-23), 140.3 (C-7), 143.0 (C-21), 154.2 (C-3), 163.8 (C-20), 169.3 (C-1); EIMS *m*/*z* 413.1 M^+ (12), 163.0 (75); HREIMS *m*/*z* 413.1836 (calcd for $C_{23}H_{27}N_1O_6$, 413.1838).

18,19-*seco*-Apicularen A (3): tan-colored oil; $[\alpha]^{20}_D$ +5 (*c* 0.5, MeOH); UV (MeOH) λ_{max} (log ϵ) 205 (4.1), 282 (3.5) nm; IR (KBr) ν_{max} 3429, 292, 1712, 1641, 1609 cm^{-1}; ^{1}H NMR (acetone-d_6, 300 MHz) δ 1.48 (1H, ddd, J = 13.0, 8.4, 8,0 Hz, H-10b), 1.53 (1H, ddd, J = 13.5, 3.0, 7.5 Hz, H-12b), 1.58 (1H, ddd, J = 14.7, 2.3, 2.5 Hz, H-14b), 1.69 (1H, dddd, J = 13.0, 7.0, 5.0, 1.0, H-12a), 1.84 (1H, dt, J = 14.5, 10.8, 14a-H), 1.93 (1H, dddd, J = 13.0, 5.5, 4.5, 1.0, 10a-H), 2.31−2.40 (2H, m, H_2-16), 2.44 (1H, dd, J = 14.8, 1.6 Hz, H-8b), 3.34 (1H, dd, J = 14.7, 9.8 Hz, H-8a), 3.89 (1H, m, J = 9.8, 8.3, 4.8, 1.6 Hz, H-9), 3.99 (1H, dddd, J = 8.0, 7.0, 5.0, 3.5, H-11), 4.26 (1H, dddd, J = 10.8, 7.0, 4.9, 2.2 Hz, H-13), 5.04 (1H, ddt, J = 10.2, 2.2, 1.1 Hz, H-18b), 5.14 (1H, dq, J = 17.3, 1.6 Hz, H-18a), 5.48 (1H, dddd, J = 11.0, 7.7, 5.7, 2.5 Hz, H-15), 5.92 (1H, dddd, J = 17.1, 10.2, 7.2, 6.7 Hz, H-17), 6.69 (1H, d, J = 7.0 Hz, H-6), 6.78 (1H, d, J = 8.1 Hz, H-4), 7.10 (1H, dd, J = 8.0, 7.0, H-5); ^{13}C NMR (acetone-d_6, 75 MHz) δ 39.1 (C-14), 39.7 (C-10), 39.9 (C-12), 40.1 (C-16), 40.3 (C-8), 64.8 (C-11), 68.1 (C-13), 73.6 (C-9, C-15), 114.4 (C-4), 117.4 (C-18), 122.3 (C-6), 125.4 (C-2), 130.2 (C-5), 135.3 (C-17), 140.2 (C-7), 154.3 (C-3), 169.2 (C-1); EIMS *m*/*z* 318.0 M^+ (72) 300 (50), 134 (100); HREIMS *m*/*z* 318.1462 (calcd for $C_{18}H_{22}O_5$, 318.1467).

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(15) Made by total synthesis, **2a** was by a factor of 80−105 less active than **1a** (refs 7e,i); **3** was essentially inactive (ref 7i).

(16) *Chondromyces* producer strains may be obtained from the German Strain Collection, DSMZ, Braunschweig; contact: www.dsmz.de.

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