A Practical Route to a Complex Bis-Steroidal Diene Intermediate Using a Microwave Assisted Heck-Reaction

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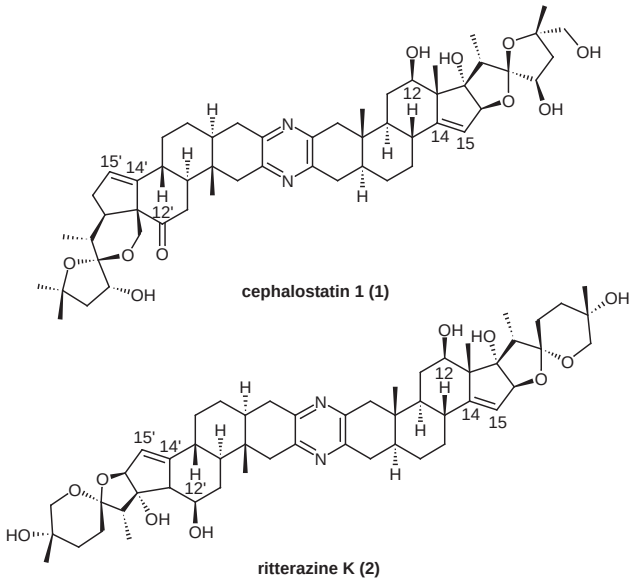
Abstract: A very special set of Heck-conditions led reliably to a non-symmetric bis-steroidal diene which underwent regioselective high-pressure Diels–Alder cycloadditions with non-symmetric electron poor acetylenes. The cyclohexadienes thus obtained were aromatized to the corresponding benzene derivatives.

Key words: natural products, Heck reaction, microwave conditions, Diels−Alder reactions, regioselectivity

Along with our efforts to identify functional groups and sub-structures essential for the biological activity of the tumor inhibiting cephalostatin- (e.g. **1**)[1–4] and ritterazine-type (e.g. **2**) marine natural products (Scheme 1), we became interested in the significance of the pyrazine-ring connecting two steroidal moieties.



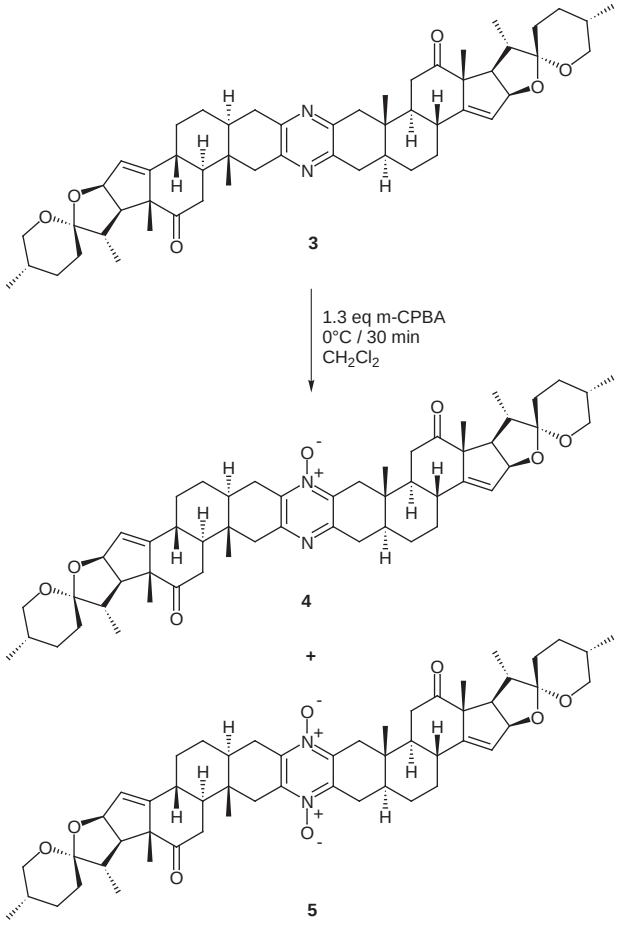
Scheme 1

As pyrazine formation is biogenetically certainly the most simple way to link two steroids with an aromatic system, one may speculate that any 6π-system, maybe even a simple benzene ring, could be in its place.

On the other hand, there is no doubt that the pyrazine ring represents an electron-poor heteroaromatic system. Compared to benzene, electrophilic substitution reactions on suitably substituted pyrazines suffer from this low reactivity,[5] while *N*-oxides, for example, are easily obtained via simple oxidation reactions.

Our attempts to selectively epoxidize the steroidal D-ring double bonds in diketone **3** for instance, employing peracids and hydroperoxides, simply afforded a mixture of the quite polar mono- and bis-*N*-oxides **4** and **5** (see Scheme 2) in a fast reaction.[6]

This result proves the important role of electron pairs on nitrogen in the general chemical behaviour of these inter-



Scheme 2

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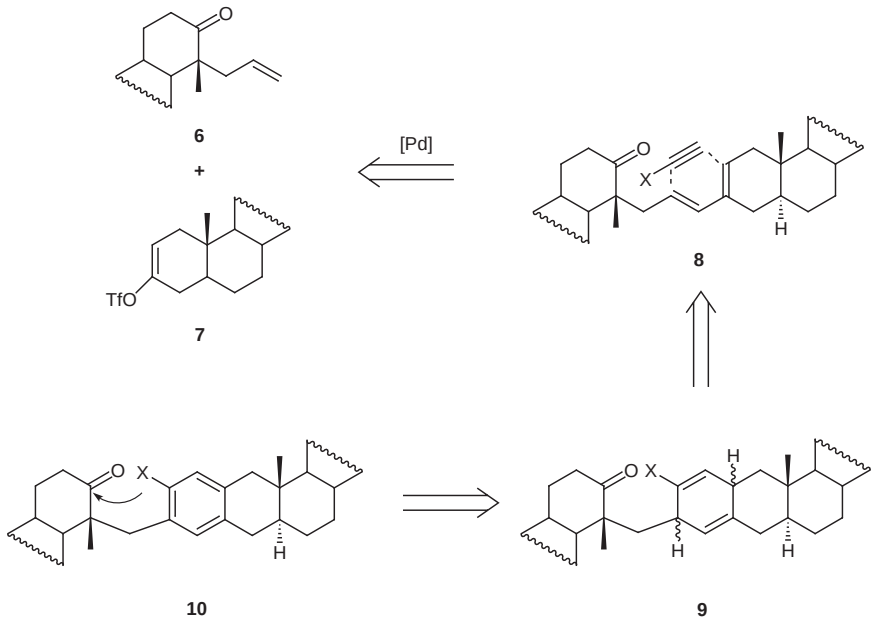
esting molecules. It seemed worthwhile to elaborate a procedure which would allow the replacement of the heterocycle by other 6π-systems in order to obtain a deeper insight into the pharmacological relevance of this moiety.

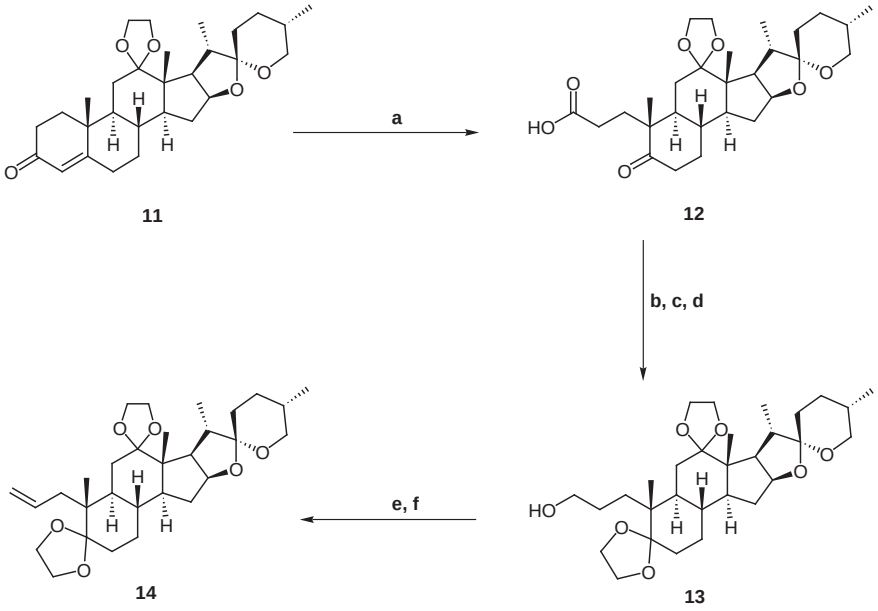
As the Diels–Alder cycloaddition employing acetylenes represents a highly flexible route to cyclohexadienes[7] (see Scheme 3), which themselves are ideal precursors for benzene derivatives, we decided on an intermediate like **8** as the diene of choice for this project.

Although the general idea looks simple there were a few important details to worry about.

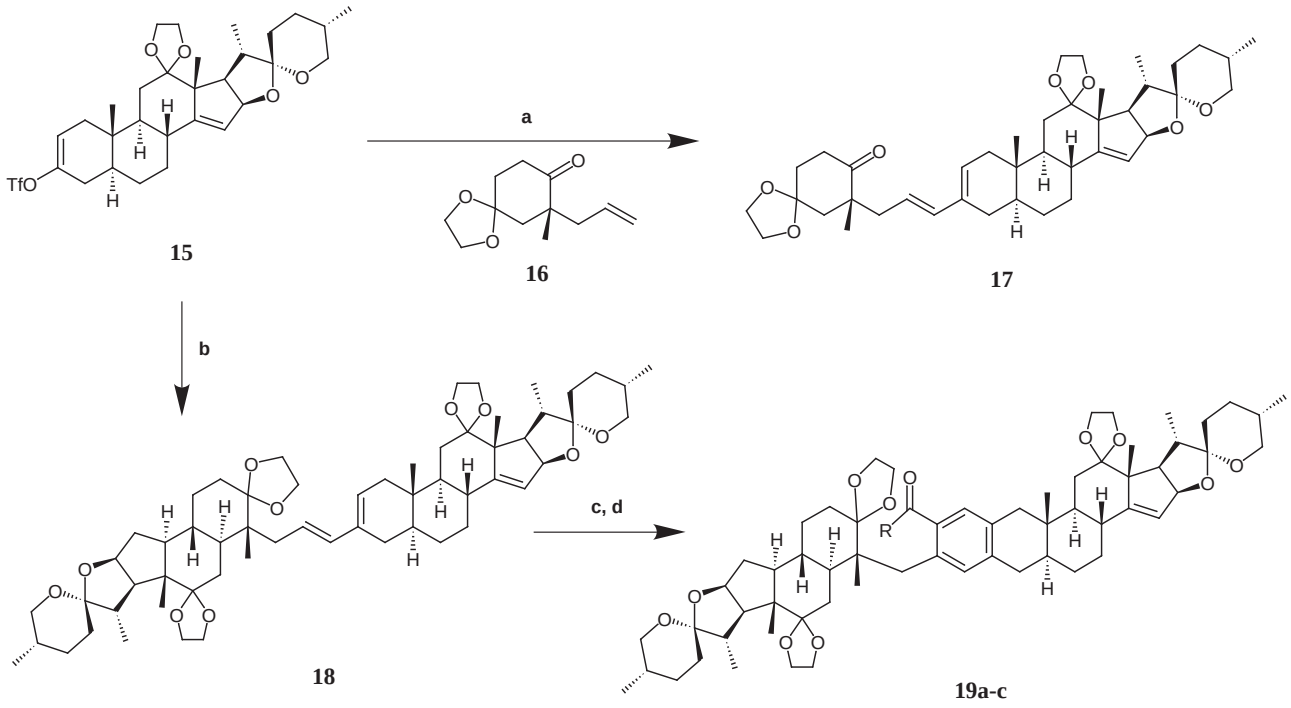
First of all a reliable and efficient approach to ring-A-opened steroids of type **6** had to be identified.[8,9] Furthermore, one had to find proper conditions for the Heck-reaction[10] of a non-activated terminal alkene and the problem of regioselectivity with a non-symmetric dienophile had to be taken into account[11] in the cycloaddition process. The regioselectivity was by no means easy to predict even if an electronic preference for the orientation given in **8** appeared likely.



Scheme 3



Scheme 4 *Reactions and conditions*: (a) K_2CO_3 (3 equiv), $NaIO_4$ (4.7 equiv), $KMnO_4$ (0.4 equiv), *t*-BuOH–H_2O (1:1), 30 min, 25 °C, 94%; (b) CH_2N_2, CH_2Cl_2, 25 °C, >99%; (c) HO-$(CH_2)_2$-OH–CH_2Cl_2 (1:1), PTSA (2.1 equiv), 96 h, 25 °C, 91%; (d) $LiAlH_4$ (2.5 equiv), THF, 10 min, 25 °C, >99%; (e) *o*-NO_2PhSeCN (1.2 equiv), PBu_3 (1.2 equiv), THF, 3 H, 25 °C, 82%;[13] (f) H_2O_2 (35%), THF, 24 h, 25 °C, 90%.



Scheme 5 **19a**: R = OCH_3; **19b**: R = CH_3; 19c: R = H
Reactions and conditions: (a) $Pd(OAc)_2$ (11 mol%), n-Bu_4NCl (1.4 equiv), K_2CO_3 (2.9 equiv), DMF, 65 h, 70 °C, 69%; (b) **14**, *n*-Bu_4NCl (1 equiv), Cs_2CO_3 (1.5 equiv), $Pd(OAc)_2$ (1.1 equiv), microwave (20 min), 77%; (c) **19a**: methyl propiolate (10 equiv), $ZnCl_2$ (0.5 equiv), CH_2Cl_2, 14 kbar, 3 d, 67%; **19b**: butynone (10 equiv), 14 kbar, 3 d, 59% yield, 82% de; **19c**: propargylic aldehyde (10 equiv), 8 kbar, 3 d, 80%; d) DDQ (2 equiv), dioxane (2.5 ml), 3 H, 90 °C, 67% (**19a**), 96% (**19b**), 80% (**19c**).

For the preparation of the ring-open steroid **13** we could rely on the well established Lemieux-Rudloff-oxidation[12] which performed best as compared to various other protocols and generated keto-acid **12** in 94% yield starting from the unsatured ketone **11** (Scheme 4). This in turn was easily available from hecogenin.

The $\Delta^{2,3}$-enoltriflate **15** needed for the Heck-coupling was easily obtained from the corresponding 3-keto-precursor, which had been prepared in our laboratory in connection with investigations on the significance of the $\Delta^{14,15}$ double bond in the steroidal D-ring.[1,2,18]

As suspected, the subsequent Heck-reaction affording diene **18** turned out to be not trivial at all (Scheme 5). Although model compound **16** uneventfully afforded a 69% yield of diene **17** under Jeffery's conditions[14], the straightforward transfer of this technique to the steroidal derivative **14** only led to a meager 45% yield of the desired coupling product **18**. A significant improvement of the yield up to 62% could be achieved by changing the base from potassium carbonate to cesium carbonate[15]. When this reaction was finally run under single mode microwave conditions[16a,b] a reliable yield of 77% was obtained. The beneficial effect of microwave addition on the Heck-reaction in general had been reported at this stage already,[16a,b] but only while we were investigating the formation of diene **18**, did A. Hallberg and his colleagues[17] apply this technique to a very similar coupling process. Having access to diene **18** in multigram amounts, the stage was set for cycloaddition experiments.

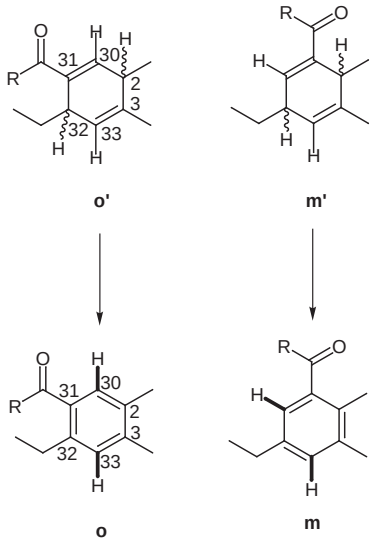
To finally arrive at a tetrasubstituted cyclohexadiene (see **9**, Scheme 3), the dienophiles chosen were methyl propiolate (R = OCH_3), butynone (R = CH_3) and propargylic aldehyde (R = H), but even with this generally most reactive aldehydes[18] no cycloaddition was observed under thermal conditions or with the help of catalysts.

Finally, however, high pressure conditions gave rise to a 3:1 mixture of isomers in the case of propargylic aldehyde. The isomers were shown to be diastereoisomers, since subsequent dehydrogenation converted all the material into a single product.

In contrast to the aldehyde the corresponding propargylic ester as well as butynone gave a substantially higher yield of cycloadducts under these conditions. In the case of methyl propiolate even weak Lewis acids (e. g. zinc dichloride) could be applied as catalysts without any harm. In all cases NMR data proved these compounds to be the desired tetrasubstituted benzene derivatives of type **19**.

It can be concluded from the data collected for **19a**, **19b** and **19c** that they correspond to the ortho-adduct **o′** (see Scheme 6). The most convincing arguments to prove structure **o** are the following:

First, there was no *m*-coupling visible for the two aromatic protons, as should be the case with **m**. Second, a clear coupling was observed between the carbonyl carbon and



Scheme 6

the proton at C_{33}, which should not be the case with the 1,5 orientation in **m**, and finally the long-range coupling between the proton at C_{31} and C_{33} as expected for structure **m** was completely absent. Having this very flexible and reliable microwave assisted Heck-reaction in hand, as well as the proof for a subsequent regioselective Diels–Alder process one may envisage a number of options to 'substitute' the pyrazine ring in the cephalostatins by various other 6π-systems including benzenes, pyridines or 1,2-pyrazines.

Unless otherwise noted, starting materials and solvents were obtained from commercial suppliers and used after distillation. The propargylic aldehyde[19] and tris-(triphenylphosphine)-rhodiumchloride[20] were freshly prepared before use. Silica gel 60mesh size 0.04–0.063 mm (MN) was uzsed for flash chromatogrphy.

High-pressure-reactions were carried out with the Hofer high-pressure-facility (14 kbar). The reactions under irradiation of focused microwaves were performed in Synthewave™ 402 (2.45 GHz) of Prolabo. Melting points were determined on Gallenkamp MPD 350 melting point apparatus. ^{1}H and ^{13}C NMR spectra were taken in $CDCl_3$ solns using TMS as internal reference; chemical shifts are given as δ values (ppm); the DEPT sequence was used for the ^{13}C NMR. Mass spectra were determined on a Finigan MAT 312 at an ionizing voltage of 70 eV. FAB MS were performed on a VG-Autospec in a matrix of nitrobenzyl alcohol. HRMS were measured on a VG-Autospec using the peak-matching method. IR spectra were obtained on the Perkin-Elmer FT 1710 spectrometer of Golden Gate ATR. Petroleum ether (bp 50–70 °C) has been abbreviated as PE.

11

A soln of hecogenin-12-acetal **11** (20.7 g, 43.6 mmol) and diphenyl diselenide (4.1 g, 13.09 mmol) in toluene (420 ml) was heated to reflux. Iodosobenzene (76 g, 349 mmol) was added in portions within 8 h.[21] After reflux for 24 h the reaction mixture was concentrated and adsorbed on silica gel. After column filtration (PE−EtOAc, 3:1) the crude product was purified by silica gel chromatography (PE–EtOAc, 2:1) to yield the A ring dienone (14.5 g, 31 mmol, 69%) as a white solid.

A three-necked flask with septum, three-way tap and gas inlet tube (with joint) was filled with freshly prepared tris-(triphenylphosphine)rhodiumchloride (1.13 g, 1.22 mmol) and washed for several times with hydrogen. The complex was dissolved in a mixture of anhyd toluene−anhyd EtOH (1:1, 58 ml) and prehydrogenated for 30 min. Then the A ring dienone (1.90 g, 4.05 mmol) was added as a soln in the same solvent mixture (134 ml). The reaction mixture was flushed with hydrogen for 8 h.[22] After evaporating the solvent, the catalyst was removed by column filtration (PE–EtOAc, 2:1). The brown residue was purified by column chromatography (PE–EtOAc, 2:1) to yield **11** (1.59 g, 3.37 mmol, 83%) as a white crystalline product; mp 175 °C.

IR ($CHCl_3$): 2999, 2959, 2933, 2877, 1664, 1615, 1456, 1264, 1047 cm^{-1}.

^{1}H NMR: δ = 5.74 (s, 1 H, 4-H), 4.41–4.36 (m, 1 H, 16-H), 4.03–3.99 (m, 2 H), 3.95–3.80 (m, 2 H), 3.50–3.46 (m, 1 H, 26β-H), 3.37 (t, 1 H, *J* = 10.9 Hz), 2.57–2.26 (m), 2.08–1.33 (m), 1.28–0.90 (m), 1.19 (s, 3 H, CH_3-19), 0.97 (s, 3 H, CH_3-18), 0.95 (d, 3 H, *J* = 7.0 Hz, CH_3-21), 0.79 (d, 3 H, *J* = 6.4 Hz, 27-H).

^{13}C NMR: δ = 199.3, 170.4, 124.1, 112.4, 109.4, 80.1, 66.9, 65.3, 64.3, 52.7, 51.7, 50.9, 47.9, 42.2, 38.3, 35.5, 34.5, 33.8, 32.7, 31.5, 31.4, 31.3, 30.4, 30.3, 28.8, 17.2, 17.1, 14.5, 13.8.

MS: *m*/*z* (%) = 471 (34) [M^+ + 1], 470 (100) [M^+], 384 (25), 356 (23), 347 (93), 294 (17), 138 (24), 126 (13), 99 (14).

HRMS: *m*/*z* calcd for $C_{29}H_{42}O_5$: 470.3032; found: 470.3030.

12

The enone **11** (2.77 g, 5.88 mmol) was dissolved in boiling *t*-BuOH (230 ml) together with K_2CO_3 (2.44 g, 17.6 mmol). After the addition of a soln of sodium periodate (5.91 g, 27.6 mmol) and $KMnO_4$ (0.37 g, 2.35 mmol) in H_2O (230 ml) and warmed up to 60 °C, the reaction mixture was stirred for 2 h at r.t. To destroy sodium hydrogen sulfite the excess of oxidizing reagents the soln was treated with solid and acidified with dilute HCl. Extraction with Et_2O (4 × 200 mL) was followed by washing the combined organic phases with $Na_2S_2O_3$ (aq, 2 × 150 mL). After treatment with brine, drying over $MgSO_4$ and evaporation of the solvent compound **12** (94%, 5.52 mmol, 2.71 g) was isolated as a white solid; mp 125 °C.

IR ($CHCl_3$): 3690, 2960, 2931, 2877, 1705, 1603, 1457, 1230, 1048 cm^{-1}.

^{1}H NMR: δ = 4.42–4.36 (m, 1 H,), 4.02–3.80 (m, 4 H), 3.49–3.46 (m, 1 H), 3.49–3.47 (m, 1 H, 3.36 (t, 1 H, *J* = 11.1 Hz), 2.60–2.51 (m, 1 H), 2.37–1.82 (m), 1.78–1.37 (m), 1.25–0.83 (m), 1.12 (s, 3 H), 0.99 (s, 3 H), 0.95 (d, 3 H, *J* = 7.0 Hz), 0.79 (d, 3 H, *J* = 6.2 Hz).

^{13}C NMR: δ = 214.6, 179.3, 112.4, 109.8, 80.3, 67.2, 65.6, 64.6, 53.0, 51.9, 50.4, 48.2, 42.6, 38.1, 34.2, 31.8, 31.7, 31.4, 30.9, 30.6, 29.5, 29.3, 29.1, 20.7, 17.4, 14.9, 14.1.

MS: *m*/*z* (%) = 491 (46) [M^+ + 1], 490 (1) [M^+], 348 (100), 233 (15), 139 (27), 127 (15), 99 (13).

HRMS: *m*/*z* calcd for $C_{28}H_{42}O_7$: 490.2931; found: 490.2933.

13

In the first step compound **12** was esterified quantitatively using diazomethane. The methyl ester (7.90 g, 15.7 mmol) was dissolved in CH_2Cl_2 (40 ml), treated with *p*-toluenesulfonic acid (2.98 g, 15,7 mmol) and ethylene glycol (40 ml). After stirring for 24 h the layers were separated and the ethylene glycol layer was extracted three times with CH_2Cl_2 (50 mL). After evaporation the residue (40 ml) was treated again with *p*-toluenesulfonic acid (1.49, 7.83 mmol) and ethylene glycol (40 ml). The whole described procedure was repeated twice with varying amounts of *p*-toluenesulfonic acid (1.12 g, 5.87 mmol; 0.74 g, 3.91 mmol) so that after 96 h TLC monitored complete conversion of the starting material. At this point the com-

bined organic layers were washed with brine, dried over $MgSO_4$ and concentrated in vacuo. The residue was further purified by column chromatography (PE–EtOAc, 3:1) to yield the methyl ester ketal corresponding to **12** as a white powder (7.83 g, 14.26 mmol, 91%).

A suspension of $LiAlH_4$ (173 mg, 4.56 mmol) in anhyd THF (5 ml) was cooled to 0 °C and addition of a soln of the above product (1.05 g, 1.82 mmol) in anhyd THF (5 ml) followed. The reaction was monitored by TLC. At the end the reaction mixture was quenched with H_2O (173 μL), 15% NaOH soln (173 μL) and H_2O (520 μL). The product was filtered through a cotton plug, the residue was washed with CH_2Cl_2 several times (500 ml), and the combined concentrated filtrates were washed with brine and dried over $MgSO_4$. After solvent evaporation the residue was purified by column chromatography (PE–EtOAc, 1:1) over silica gel to obtain compound **13** as a white solid (0.94 g, 1.81 mmmol, >99%); mp: 179 °C.

IR ($CHCl_3$): 3625, 2958, 2932, 2879, 1456, 1379, 1241, 1148, 1048 cm^{-1}.

^1H NMR: 4.40–4.34 (m, 1 H), 4.03–3.81 (m, 8 H), 3.49–3.46 (m, 1 H), 3.37 (t, 1 H, *J* = 11.0 Hz), 2.38–2.34 (m, 1 H), 2.07–1.97 (m), 1.85–1.09 (m), 0.98 (s, 3 H), 0.94 (d, 3 H, *J* = 7.0 Hz), 0.93 (s, 3 H), 0.78 (d, 3 H, *J* = 6.4 Hz).

^{13}C NMR: δ = 113.8, 112.7, 109.5, 80.3, 66.9, 65.2, 64.4, 64.2, 64.0, 63.7, 52.7, 52.1, 48.0, 43.8, 42.9, 42.3, 33.9, 31.5, 31.4, 31.2, 30.8, 30.3, 30.3, 28.8, 28.6, 27.8, 18.3, 17.2, 14.6, 13.8.

MS: *m*/*z* (%) = 520 (42) [M^+], 334 (11), 185 (30), 99 (100).

HRMS: *m*/*z* calcd for $C_{30}H_{48}O_7$: 520.3400; found: 520.3402.

14

Compound **13** (1.88 g, 3.16 mmol) was dissolved together with *p*-nitrophenyl selenocyanate (986 mg, 4.34 mmol) in anhyd THF (15 ml). Tributyl phosphine (1.08 ml, 4.34 mmol) was added while stirring. After 3 h the solvent was removed, the residue was adsorbed on silica gel and then purified by chromatography (PE–EtOAc, 8:1) to obtain a yellow solid (1.83 g, 2.59 mmol, 82%). This phenylselenyl product (2.22 g, 3.15 mmol) was redissolved in anhyd THF (30 ml) and a H_2O_2 soln (35%; 1.24 ml) was added dropwise at r.t. After 24 h stirring the reaction mixture was diluted with H_2O, extracted with methyl-*tert*-butyl ether, washed with brine and dried over $MgSO_4$. After column filtration (PE–EtOAc, 12:1) a white crystalline product (1.42 g, 2.82 mmol, 90%) was obtained; mp 181 °C.

IR ($CHCl_3$): 2957, 2931, 2883, 1457, 1379, 1241, 1180, 1149, 1126, 1049 cm^{-1}.

^1H NMR: δ = 6.13–6.02 (m, 1 H), 4.90 (m, 1 H), 4.87 (m, 1 H), 4.40–4.33 (m, 1 H), 3.96–3.81 (m, 8 H), 3.49–3.45 (m, 1 H), 3.37 (t, 1 H, *J* = 10.9 Hz), 2.93–2.87 (m, 1 H), 2.39–2.28 (m, 2 H), 2.03–1.92 (m, 2 H), 1.87–1.80 (m, 1 H), 1.69–1.14 (m), 0.99 (s, 3 H), 0.94 (d, 3 H, *J* = 7.1 Hz), 0.93 (s, 3 H), 0.78 (d, 3 H, *J* = 6.4 Hz).

^{13}C NMR: δ = 138.3, 113.7, 113.3, 112.6, 109.4, 80.3, 66.9, 65.0, 64.4, 64.1, 64.0, 52.3, 51.9, 47.9, 44.0, 44.0, 42.3, 39.8, 33.9, 31.5, 31.4, 30.4, 30.3, 30.2, 28.8, 27.8, 17.9, 17.2, 14.6, 13.8.

MS: *m*/*z* (%) = 502 (37) [M^+], 415 (11), 167 (18), 99 (100).

HRMS: *m*/*z* calcd for $C_{30}H_{46}O_6$: 502.3294; found: 502.3294.

18

In the reaction vessel **15** (768 mg, 1.27 mmol), **14** (640 mg, 1.27 mmol), Bu_4NCl (353 mg, 1.27 mmol), Cs_2CO_3 (621 mg, 1.91 mmol) palladium (II) acetate (86 mg, 0.38 mmol) and anhyd DMF (20 ml) were suspended under argon. The contents of the flask were irradiated with focused microwaves (5 min –24 W, 5 min –32 W). Further palladium (II) acetate (120 mg, 0.53 mmol) was added and the irradiation was repeated as described. After cooling, the reaction mixture was filtered over silica gel (PE–EtOAc, 1:1). The residue was concd and was purified by column chromatography (silica gel, PE–EtOAc, 5:1) to yield diene **18** (938 mg, 0.98 mmol, 77%) as a white solid.

IR: 2951, 2927, 2874, 1455, 1373, 1240, 1125, 1049, 980, 900 cm^{-1}.

^1H NMR: δ = 5.86 (d, 1 H, *J* = 15.7 Hz), 5.39 (m, 3 H), 4.84 (dd, 1 H, *J* = 8.2 Hz, 1.4 Hz), 4.36–4.29 (dd, 1 H, *J* = 9.0 , 7.8 Hz), 4.05–3.94 (m, 4 H), 3.93–3.73 (m, 8 H), 3.55–3.30 (m), 2.59 (dd, 1 H, *J* = 9.5 Hz, 8.2 Hz), 2.34 (dd, 1 H, *J* = 9.0 Hz, 7.0 Hz), 1.23 (s, 3 H), 1.16 (s, 3 H), 1.13 (m, 3 H), 0.98 (d, 3 H, *J* = 6.8 Hz), 0.96 (s, 3 H), 2.31–0.83 (m), 0.78 (d, 3 H, *J* = 6.3 Hz), 0.75 (d, 3 H, *J* = 6.3 Hz), 0.73 (s, 3 H).

^{13}C NMR: δ = 156.1, 135.1, 132.7, 126.5, 124.0, 120.0, 113.7, 113.5, 112.6, 109.4, 106.7, 85.3, 80.2, 67.1, 66.8, 65.1, 65.0, 64.7, 64.4, 64.2, 64.1, 55.4, 52.5, 51.9, 51.1, 50.8, 47.8, 44.4, 44.1, 44.0, 42.2, 41.0, 40.1, 38.9, 35.1, 33.9, 31.5, 31.4, 31.4, 30.4, 30.4, 30.3, 30.0, 29.7, 29.5, 29.2, 28.8, 28.7, 28.4, 27.7, 18.4, 18.1, 17.5, 17.1, 17.1, 14.5, 13.8, 11.7.

FAB MS: *m*/*z* (%) = 955 (100) [M^+], 893 (8), 493 (14), 462 (23), 431 (7), 345 (8), 307 (6).

19a; Typical Procedure

Diene **18** (100 mg, 0.105 mmol) was dissolved in anhyd CH_2CL_2 (1.5ml) and transfered into a teflon tube. Methyl propiolate (95 μL, 1.05 mmol) and $ZnCl_2$ (7 mg, 0.05 mmol) were added and the closed tube was pressurized at 14 kbar for 3 d. The solvent was evaporated at r.t. Finally the residue was purified by column chromatography (silica gel, PE–EtOAc, 5:1). This provided the cyclohexadiene adduct as a white foam (27 mg, 0.03 mmol, 25%). This adduct (27 mg, 0.03 mmol) and DDQ (12 mg, 0.05 mmol, 2 eq) were dissolved in anhyd dioxane (2.5 ml) and heated for 3 h at 90 °C. The reaction was monitored by TLC. After adding H_2O (1 mL) and extracting with methyl-*tert*-butyl ether (4 × 5 mL), the organic phase was washed with brine and dried over $MgSO_4$. Finally the residue was purified by column chromatography on silica gel (PE–EtOAc, 3:1) to provide **19a** (18 mg, 0.02 mmol, 67%) as a yellow foam.

IR: 2951,2925, 2874, 1720, 1455, 1241, 1145, 1052, 980 899 cm^{-1}.

^1H NMR: δ = 7.36 (s, 1 H), 7.01 (s, 1 H), 5.45 (m, 1 H), 4.32 (m, 1 H), 3.81 (s, 3 H), 4.10–3.68 (m, 12 H), 3.38 (m, 1 H), 2.60 (m, 1 H), 2.39 (m, 1 H), 1.23 (s, 3 H), 1.20–1.16 (m, 3 H), 1.01 (s, 3 H), 0.99 (d, 3 H, *J* = 6.7 Hz), 0.86 (s, 3 H), 2.90–0.80 (m), 0.79 (d, 3 H, *J* = 6.3 Hz), 0.76 (d, 3 H, *J* = 6.4 Hz), 0.74 (s, 3 H)

^{13}C NMR: (100 MHz, $CDCl_3$, TMS): δ = 169.7, 155.9, 139.2, 138.1, 133.2, 132.6, 130.9, 129.5, 120.2, 113.6, 113.2, 112.6, 109.4, 106.8, 85.3, 80.2, 67.1, 66.8, 65.2, 65.1, 65.1, 64.1, 63.8, 63.1, 55.4, 51.9, 51.7, 51.1, 50.6, 47.9, 46.9, 46.2, 44.4, 42.8, 42.2, 41.4, 36.1, 35.5, 34.6, 33.8, 33.6, 31.6, 31.5, 31.4, 30.4, 30.3, 29.8, 29.7, 29.0, 29.0, 28.8, 28.7, 28.4, 27.4, 18.5, 17.2, 17.1, 16.4, 15.3, 14.6, 13.8, 13.8.

HRMS: *m*/*z* calcd for $C_{63}H_{88}O_{12}$: 1036.6276; found: 1036.6238.

19b

As described for **19a** the diene **18** (73 mg, 0.76 mmol) was treated with butynone (60 μl, 0.76 mmol, 10 eq) at 14 kbar to give butynone adduct (10:1 diastereomeres) after 3 d as a white foam (46 mg, 59%). This adduct (25 mg, 0.02 mmol) was treated with DDQ (11 mg, 0.05 mmol), worked up and purified according to the general procedure to yield the desired product **19b** as a yellow foam (24 mg, 0.02 mmol, 96%).

IR: 2952, 2926, 2874, 1724, 1681, 1453, 1124, 1056, 980, 899 cm^{-1}.

^1H NMR: δ = 7.11 (s, 1 H), 7.01 (s, 1 H), 5.40 (m, 1 H), 4.84 (dd, 1 H, *J* = 8.2, 1.9 Hz), 4.32 (m, 1 H), 4.38–3.68 (m, 12 H), 3.51–3.39 (m), 3.34 (t, 1 H, *J* = 10.9 Hz), 2.60 (m, 1 H), 2.51 (s, 3 H), 2.35 (m, 1 H), 1.23 (s, 3 H), 1.17 (s, 3 H), 1.21–1.16 (m, 3 H), 0.99 (d, 3 H,

J = 6.7 Hz), 0.86 (s, 3 H), 2.80–0.85 (m), 0.79 (d, 3 H, *J* = 6.3 Hz), 0.76 (d, 3 H, *J* = 6.4 Hz), 0.74 (s, 3 H).

^{13}C NMR: δ = 203.9, 155.9, 138.7, 137.5, 137.2 133.8, 132.4, 128.9, 120.3, 113.6, 113.3, 112.5, 109.4, 106.8, 85.3, 80.2, 67.1, 66.8, 65.8, 65.2, 65.1, 65.1, 64.1, 63.9, 63.0, 55.4, 52.6, 51.9, 51.1, 50.6, 47.9, 47.2, 46.0, 44.4, 43.0, 42.2, 41.5, 35.6, 35.3, 34.6, 33.8, 33.6, 31.5, 31.4, 30.4, 30.3, 30.3, 29.9, 29.7, 29.1, 28.8, 28.8, 28.8, 28.4, 27.4, 18.5, 17.2, 17.1, 16.6, 14.6, 13.8, 13.8, 11.4.

HRMS: *m*/*z* calcd for $C_{63}H_{88}O_{11}$: 1020.6327; found: 1020.6310.

19c

Diene **18** (100 mg, 0.105 mmol) was treated with propargylic aldehyde (57 mg, 0.105 mmol) at 8 kbar for 3 d. The reaction was monitored by TLC. The solvent was evaporated at r.t. and the residue was purified by column chromatography on silica gel (PE–EtOAc, 5:1) to provide the cycloadduct (3:1 diastereomers, ^{1}H NMR) as a white foam (40 mg, 38%). According to the general procedure the adduct (25 mg, 0.02 mmol) was treated with DDQ (11 mg, 0.05 mmol) in dioxane (2.5 ml) at 90 °C for 3 h. After work-up and purification (general procedure) resulted product **19c** was obtained as a yellow foam (20 mg, 0.02 mmol, 80%).

IR: 2951, 2926, 2874, 1680, 1454, 1123, 1050, 980, 900 cm^{-1}.

^{1}H NMR: (400 MHz, $CDCl_3$, TMS): δ = 10.43 (s, 1 H), 7.54 (s, 1 H), 6.99 (s, 1 H), 5.46 (t, 1 H, *J* = 1.8 Hz), 4.87 (dd, 1 H, *J* = 8.3, 1.9 Hz), 4.35–4.28 (m, 1 H), 4.09–3.58 (m, 12 H), 3.52–3.20 (m), 3.33 (t, 1 H, *J* = 10.9 Hz), 2.95–2.91 (m), 2.70–2.59 (m), 2.48–2.29 (m), 2.25 (dd, 1 H, *J* = 9.0, 7.2 Hz), 1.18 (s, 3 H), 1.18 (d, 3 H, *J* = 7.0 Hz), 1.12 (s, 3 H), 0.89 (d, 3 H, *J* = 6.9 Hz), 0.87 (s, 3 H), 2.15–0.82 (m), 0.79 (d, 3 H, *J* = 6.3 Hz), 0.76 (d, 3 H, *J* = 6.2 Hz), 0.73 (s, 3 H).

^{13}C NMR: δ = 192.2, 155.9, 141.8, 141.5, 133.7, 132.9, 132.6, 128.9, 120.3, 113.6, 113.1, 112.5, 109.4, 106.8, 85.3, 80.1, 67.1, 66.8, 65.5, 65.2, 65.1, 64.2, 63.7, 63.2, 55.4, 52.8, 51.9, 51.1, 50.5, 48.0, 46.8, 45.9, 44.4, 42.8, 42.1, 41.3, 35.4, 34.9, 34.3, 33.8, 33.8, 32.4, 31.4, 31.4, 30.4, 30.3, 29.8, 29.7, 29.1, 28.9, 28.8, 28.7, 28.3, 27.1, 18.5, 17.2, 17.1, 16.9, 14.6, 13.9, 13.8, 11.4.

HRMS: *m*/*z* calcd for $C_{62}H_{86}O_{11}$: 1006.6170; found: 1006.6183.

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References

(1) Kramer, A.; Ullmann, U.; Winterfeldt, E. *J. Chem. Soc., Perkin Trans. 1* **1993**, 2865.
(2) Jautelat, R.; Müller-Fahrnow, A.; Winterfeldt, E. *J. Prakt. Chem.* **1996**, *338*, 695.
(3) Drögemüller, M.; Jautelat, R.; Winterfeldt, E. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1572; *Angew. Chem.* **1996**, *108*, 1669.
(4) Drögemüller, M.; Flessner, T.; Jautelat, R.; Scholz, U.; Winterfeldt, E. *Eur. J. Org. Chem.* **1998**, 2811.
(5) Cheeseman, G. W. H.; Cookson, R. F. In *Chemistry of Heterocyclic Compounds*, Vol. 35; Weissberger A., Taylor E. C., John Wiley & Sons: New York, **1979**, 3.
(6) Nawasreh, M. In *Stereoselective Synthesis of Cephalostatin Analogues as anti-Cancer Agents*; Dissertation: Hannover, **2000**.
(7) Behar, V.; Danishefsky, S. *J. Am. Chem. Soc.* **1993**, *115*, 7017.
(8) Hasse-Held, M.; Hatzis, M.; Mann, J. *J. Chem. Soc., Perkin Trans. 1* **1992**, 2999.
(9) Hanson, J. R.; Uyanik, C. *J. Chem. Res.* **1998**, 221; and references therein.
(10) Beletskaya, I. P.; Cheprakov, A. V. *Chem. Rev.* **2000**, *100*, 3009.
(11) Crimmins, M. T.; Al Awar, R. S.; Vallin, J. M.; Hollis, W. G. Jr.; O'Mahony, R.; Lever, J. G.; Bankaitis-Davis, D. M. *J. Am. Chem. Soc.* **1996**, *118*, 7513.
(12) Rudloff, V. *Can. J. Chem.* **1965**, *4*, 2660.
(13) (a) Grieco, P. A.; Gilman, S.; Nishizawa, N. *J. Org. Chem.* **1976**, *41*, 1485. (b) Grieco, P. A.; Yokoyama, Y. *J. Am. Chem. Soc.* **1977**, *99*, 5210.
(14) Jeffery, T. *Tetrahedron Lett.* **1985**, *26*, 2667.
(15) Flessner, T.; Doye, S. *J. Prakt. Chem.* **1999**, *341*, 186.
(16) (a) Loupry, A.; Petit, A.; Hamelin, J.; Texier-Boullet, F.; Jacquault, P.; Mathé, D. *Synthesis* **1998**, 1213. (b) Lidström, P.; Tierney, J.; Wathey, B.; Westman, J. *Tetrahedron* **2001**, *57*, 9225.
(17) (a) Vallin, K. S. A.; Larhed, M.; Hallberg, A. *J. Org. Chem.* **2001**, *66*, 4340. (b) Vallin, K. S. A.; Zhang, Q.; Curran, D. P.; Larhed, M.; Hallberg, A. *Poster displayed at Drug Discovery Technology 2001* Boston.
(18) Flessner, T. *Beiträge zur chemischen Diversität der Cephalostatine*; Dissertation: Hannover, **1999**.
(19) Sauer, J. C. *Org. Synth.* **1962**, *4*, 813.
(20) Osborn, J. A.; Wilkinson, G. *Inorg. Synth.* **1981**, *28*, 77.
(21) Barton, D. H. R.; Godfrey, C. R. A.; Morzycki, J. W.; Motherwell, W. B.; Ley, S. V. *J. Chem. Soc., Perkin Trans. 1* **1982**, 1947.
(22) (a) Birch, A. J.; Williamson, D. H. *Org. React.* **1976**, *24*, 1. (b) Djerassi, C.; Grutzwiller, J. *J. Am. Chem. Soc.* **1966**, *88*, 4537.