Selective Synthesis of Bissteroidal Compounds by Multifold Heck Reactions

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Abstract: Multifold Heck reactions of a hexahydro-1*H*-indene and a dibromoterephthalaldehyde derivative are used for the synthesis of bissteroidal compounds with a common ring A as simplified analogs of cephalostatins.

Key words: cephalostatin, marine natural products, Heck reaction, palladium, steroids

In 1988, Petit et al. isolated the unusual dimeric steroid derivative cephalostatin 1 **1** from the marine worm *Cephalodosicus Gilchristi*.[1] It shows a remarkably high cytostatic activity with a GI_{50}-value of about $2.20 \cdot 10^{-9}$ M in an in vitro screening against the NCI 60 human cancer cell line panel. In view of this, synthesis of cephalostatins has been the focus of a number of recent studies.[2] In 1998, Fuchs et al. have reported the first total synthesis of **1**.[3]

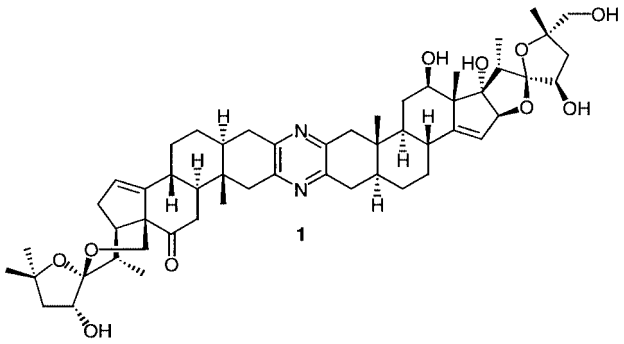
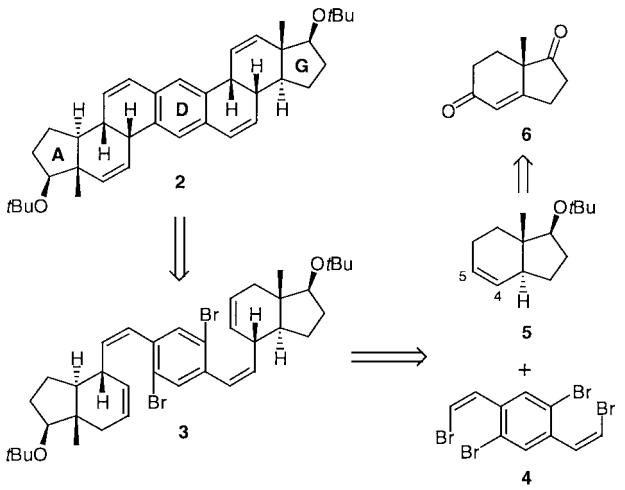


Figure 1

Considering its biological activity and its unusual bissteroidal structure as well as the lack of knowledge of its mode of action, we became interested in the synthesis of **1** and its analogs. Toward this end, we now report a facile convergent strategy by which a simplified analog of **1**, in which the central octahydrophenazine moiety is replaced by a benzene ring, can be readily constructed through twofold intramolecular Heck reaction[4] of the diindenylethenylbenzene **3** (Scheme 1). Retrosynthetic analysis of **3** led to the tetrafunctionalized benzene **4** and the hexahydro-1*H*-indene **5**, which can be obtained in a few steps from the Hajos-Wiechert-Keton **6**.[5] An intended conversion of compound **4** with **5** to give the analog **2** in a fourfold Heck reaction did not work due to the sensitivity of **4**. Therefore **9** was used as a substrate for the first Heck reaction, which was obtained from dibromoterephthalaldehyde **7a** via **8**.



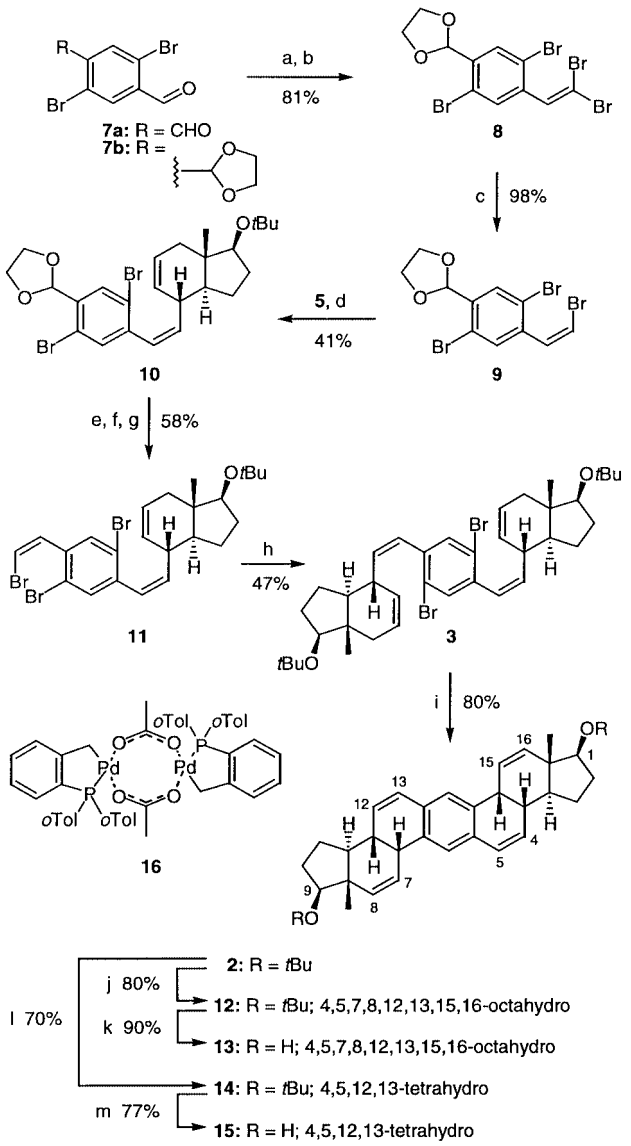
Scheme 1

This approach had the advantage that unsymmetrical analogs of **1** could also be prepared.[6]

Reaction of **7a** with ethylene glycol gave the monoacetal **7b**.[7] Corey-Fuchs reaction[8] followed by selective debromination with Bu_3SnH[9] selectively furnished the *(Z)*-2-bromoethenylbenzene **9** in 80% overall yield. Heck reaction of **9** with the hexahydro-1*H*-indene **5** afforded the indenylethenylbenzene **10** in 41% yield. The bond formation occurred exclusively at C-4 in **5** with complete facial selectivity *anti* to the angular methyl group. Neither reaction at C-5 nor formation of the homo coupled product of **9** or formation of diastereoisomers of **5** was observed.

For the introduction of a second molecule of hexahydro-1*H*-indene **5** the acetal moiety in **10** was cleaved and the obtained aldehyde was transformed into the *(Z)*-2-bromovinylbenzene derivative **11** in 59% yield again using a sequence of a Corey-Fuchs[8] reaction and selective debromination.[9] Heck reaction of compound **11** with **5** then yielded the desired diindenylethenylbenzene **3** (47%) again in a complete stereo- and regioselective way.

The following twofold intramolecular Heck reaction of **3** to give analog **2** required a precise control of the reaction time and temperature. Thus when **3** was reacted with catalytic amounts of the palladacycle **16**[10] at 130-140 °C for 1.5 hours **2** could be obtained in 80% yield. The conversion proceeded with high selectivity leading to the exclusive formation of the unusual *cis*-annelation of both the newly generated rings.



Scheme 2 [a] 2 equiv CBr_4, 4 equiv PPh_3, CH_2Cl_2, -20 °C, 0.5 h; [b] 10 equiv $HOCH_2CH_2OH$, *p*TsOH, toluene, reflux, 1.5 h, 81% (two steps); [c] 4 mol% $Pd(PPh_3)_4$, 1.1 equiv $HSnBu_3$, toluene, r.t., 1 h, 98%; [d] **9**/**5** = 4/1, 10 mol% $Pd(OAc)_2$, 20 mol% PPh_3, 8 equiv nBu_4NOAc, DMF/CH_3CN/H_2O = 1/1/0.2, 60 °C, 16 h, 41%; [e] 80% HOAc, 80 °C, 2 h, 74%; [f] 2 equiv CBr_4, 4 equiv PPh_3, CH_2Cl_2, 0 °C, 0.5 h, 90%; [g] 4 mol% $Pd(PPh_3)_4$, 1.1 equiv $HSnBu_3$, toluene, r.t., 2 h, 88%; [h] **11**/**5** = 1/2, 10 mol% $Pd(OAc)_2$, 20 mol% PPh_3, 1 equiv nBu_4NCl, 2.5 equiv K_2CO_3, DMF/CH_3CN/H_2O = 1/1/0.2, 60 °C, 5 h, 47%; [i] 5 mol% **16**, 5 equiv nBu_4NOAc, DMF/CH_3CN/H_2O = 1/1/0.2, 130-140 °C, 1.5 h, 80%; [j] 10 mol% 10% Pd/C, H_2, 3 bar, EtOAc, r.t., 16 h, 80%; [k] 2 equiv TMSI, CH_2Cl_2, r.t., 18 h, 90%; [l] 10 mol% $(PPh_3)_3RhCl$, H_2, 3 bar, EtOAc/MeOH = 1/1, r.t., 13 h, 70%; [m] 2 equiv TMSI, CH_2Cl_2, r.t., 18 h, 77%.

The bissteroidal arene **2** could be further manipulated in several ways. Hydrogenation with 10% Pd on charcoal led to analog **12**, which was transformed into the diol **13** using trimethyliodosilane (TMSI). On the other hand, hydrogenation of **2** using the Wilkinson catalyst yielded analog **14**, which was again deprotected with TMSI to give diol **15**. The high chemoselectivity in the homogenous hydrogenation of **2** is probably due to a conformational effect in **2** where the angular 8a- and 16a-methyl groups shielded the α- and β-face of the $\Delta^{7,8}$- and $\Delta^{15,16}$-double bonds. The *cis*-orientation of the rings B, C and E, F in **12** was confirmed by a NOESY experiment and the structure of **14** by X-ray crystallography.[11]

The present synthesis allows a short and efficient entry to structural simplified analogs of **1**. Application of this method to different arenes and indenes should enable the preparation of symmetrical as well as unsymmetrical cephalostatin analogs, that are not accessible from natural steroids.

Typical procedure for the preparation of 2: A solution of **3** (100 mg, 1.43×10^{-4} mol), nBu_4NOAc (215 mg, 7.14×10^{-4} mol) and *trans*-di(μ-acetato)-bis[*o*-(di-*o*-tolylphosphino)benzyl]dipalladium(II)[10] **16** in DMF/CH_3CN/H_2O (1/1/0.2, 5 mL) was heated for 1.5 h at 130-140 °C in a preheated oil bath. After cooling, water (15 mL) was added and the reaction mixture was extracted with Et_2O (2 × 20 mL). The organic phase was washed with brine and dried over Na_2SO_4. Removal of the solvent and chromatographic purification (pentane/CH_2Cl_2 = 5/1) yielded **2** (60 mg, 80%) as a colourless oil. $[\alpha]_D^{20}$ = -39.0 (*c* = 0.2 in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 0.9 (s, 3H; CH_3), 1.1 (s, 9H; $OC(CH_3)_3$), 1.4 - 1.6 (m, 3H; CH_a, CH_2), 1.7 -1.9 (m, 2H; CH_b, CH_a), 2.6 -2.7 (m, 1H; CH_b), 3.5 (dd, 1H, ^3J (H,H) = 8.7 Hz, ^3J (H,H) = 6.6 Hz; CH), 3.7 (dd, 1H, ^3J (H,H) = 5.6 Hz, ^3J (H,H) = 4.4 Hz; CH), 5.8 (dd, 1H, ^3J (H,H) = 9.6 Hz, ^3J (H,H) = 5.9 Hz; CH), 6.0 (d, 1H, ^3J (H,H) = 8.7 Hz; CH), 6.1 (dd, 1H, ^3J (H,H) = 10.0 Hz, ^3J (H,H) = 4.4 Hz, CH), 6.3 (d, 1H, ^3J (H,H) = 9.6 Hz; CH), 6.9 (s, 1H, Aryl-CH); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 14.9 (CH_3), 22.8 (CH_2), 28.7 ($OC(CH_3)_3$), 31.9 (CH_2), 33.9 (CH), 37.5 (CH), 41.8 (CH), 44.7 (C), 72.3 ($OC(CH_3)_3$), 76.2 (CH), 125.0 (Aryl-CH), 125.3 (Vinyl-CH), 128.8 (Vinyl-CH), 129.2 (Vinyl-CH), 131.8 (Aryl-C), 134.6 (Aryl-C), 135.9 (Vinyl-CH); HRMS: calculated for $C_{38}H_{50}O_2$ (M^+): 538.3810, found: 538.3810.

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References and Notes

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(11) Crystallographic data for **14** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication No. CCDC-148318. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (Fax +44 1223 336 033; deposit@ccdc.cam.ac.uk).

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