Angewandte Chemie

Natural Product Synthesis

# Chasing a Phantom by Total Synthesis: The Butylcycloheptylprodigiosin Case[**]

*Alois Fürstner,[*] Karin Radkowski, and Hartwig Peters*

The deeply red-colored tripyrrole alkaloids of the "prodigiosin" series exert pronounced immunosuppressive activities at doses that are not cytotoxic.[1] Most notably, in vivo studies have shown that these pigments produced by various *Serratia* and *Streptomyces* strains act synergistically with cyclosporine A, FK 506, or rapamycin, which are presently the dominating drugs in clinical immunosuppressive regimens.[2,3] Since the availability of agents that can act at different stages along the T-cell activation pathway may improve therapeutic results, the prodigiosins constitute important new lead compounds in the search for supplementary drugs to prevent allograft rejection. These findings have rejuvenated interest in this class of pyrrole alkaloids, as evident from many recent studies mapping their biological profiles in great detail.[1]

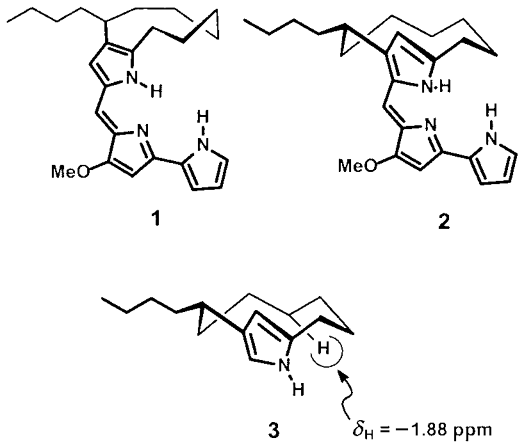
During our program aimed at the total synthesis[4–7] and biochemical validation of various pyrrolic natural products,[8] our attention was drawn to a secondary metabolite called "butylcycloheptylprodigiosin".[9] It was originally isolated from *Streptomyces* sp. Y-42 and *Streptomyces abikoensis* (formerly, *Streptoverticillium rubrireticuli*). Gerber and Stahly assigned structure **1** to this then novel member of the prodigiosin family (Scheme 1).[10] Floss and co-workers later attributed the same structure to the "pink pigment" obtained from a culture broth of *Streptomyces coelicolor* mutants.[11]

---

[*] Prof. A. Fürstner, K. Radkowski, Dr. H. Peters
Max-Planck-Institut für Kohlenforschung
45470 Mülheim/Ruhr (Germany)
Fax: (+49) 208-306-2994
E-mail: fuerstner@mpi-muelheim.mpg.de

[**] Generous financial support from the Deutsche Forschungsgemeinschaft (Leibniz award program), the Fonds der Chemischen Industrie, and the Merck Research Council is gratefully acknowledged. We thank Dr. R. Mynott and C. Wirtz for their invaluable help with numerous NMR analyses and Prof. H. Floss for providing a copy of the $^1$H NMR spectrum of his "pink pigment" for comparison.

DOI: 10.1002/ange.200462215

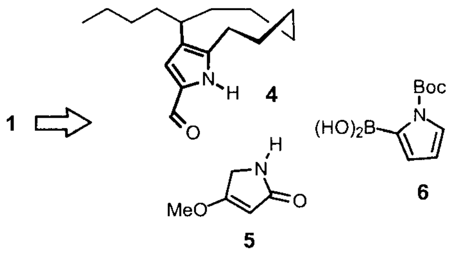


*Scheme 1.* The structures of butylcycloheptylprodigiosin (**1**) and its *meta*-bridged isomer streptorubin B (**2**); an illustration of the characteristic spectral fingerprint of *meta*-pyrrolophane **3**.

However, these assignments were questioned by Weyland and co-workers, who showed that their sample isolated from the actinomycete strain B 4358 was the *meta*-bridged isomer streptorubin B (**2**) rather than the *ortho*-annelated compound **1**, thus suggesting that the structure of the latter needed to be revised.[12] As these three research groups were investigating samples derived from different bacterial strains, it appeared to us that this conclusion might have been premature and that the available data deserved more scrupulous consideration.

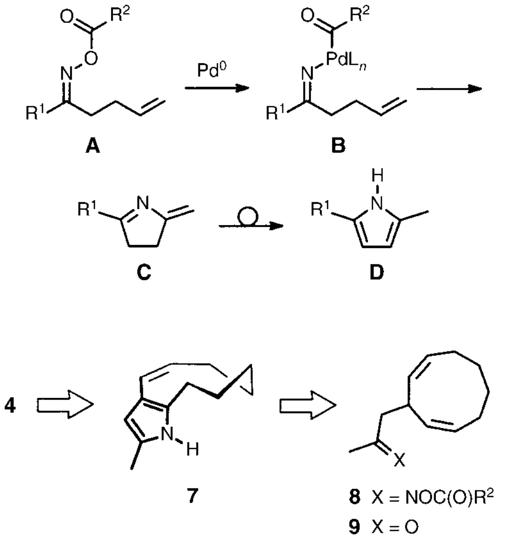
A previous synthesis campaign by our research group had opened a concise route to product **2** and its congeners by a platinum-catalyzed cycloisomerization reaction.[4,13] All the *meta*-pyrrolophanes prepared showed a very characteristic "fingerprint" in their $^1$H NMR spectra. Specifically, the rigidity of the bridging 10-membered ring forces one of the protons of the *ansa* chain to reside within the anisotropy cone of the aromatic pyrrole nucleus, thus causing a significant upfield shift of the corresponding signal to $\delta = -1.55$ ppm in **2** and $\delta = -1.88$ ppm in its core segment **3** (see Scheme 1).[4,12,14] Although the reported spectral data of the "pink pigment" isolated by the groups of Gerber and Floss are incomplete,[10,11] no such signal is documented. As it appears unlikely to us that such a conspicuous detail would have escaped the attention of two independent groups, we suspected that butylcycloheptylprodigiosin (**1**) is in fact a natural product distinct from **2** rather than a phantom. It was only through synthesis, however, that this open question could be answered.

To this end, the assembly of the pyrrolopyrromethane chromophore of **1** from building blocks **4**–**6** by successive condensation and cross-coupling reactions was envisaged (Scheme 2).[5,15] Since **5** and **6** are commercially available, the success of the project hinged on the efficient preparation of aldehyde **4**. Bearing in mind that (the ground-state as well as the transition-state) strain energy reaches its maximum with nine-membered cycles,[16] we preferred a strategy based on the annelation of the pyrrole nucleus to a *preexisting* cyclononane template over a late-stage cyclization of the medium-sized carbocycle.



*Scheme 2.* Retrosynthetic analysis of **1**.

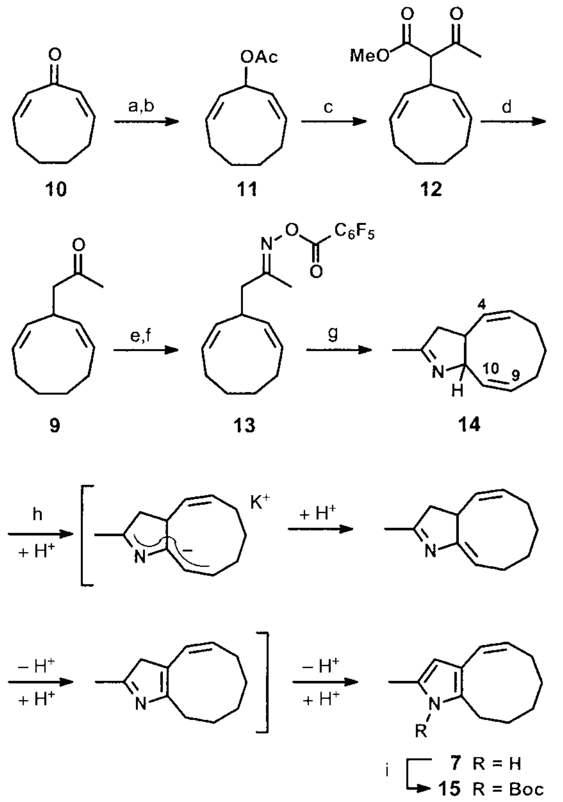
Intramolecular Heck-type reactions of unsaturated oxime esters pioneered by Narasaka and co-workers might serve this purpose well (Scheme 3).[17] In this rather unconventional transfomation, the Pd$^0$ catalyst inserts into a suitable oxime derivative **A** to give an iminopalladium intermediate **B**, which reacts with a suitably located olefin to give a pyrrole derivative **D** after isomerization of the methylenedihydropyrrole **C** initially formed. This reaction, however, is known to be very sensitive to seemingly minor changes in substrate and can be plagued by competing side reactions, such as Beckmann rearrangements, hydrolysis, or fragmentation.[17] To the best of our knowledge, no application to a total synthesis has been reported to date.



*Scheme 3.* The conversion of unsaturated oxime esters into pyrrole derivatives by a Narasaka–Heck reaction. Application of this transform to the preparation of the core segment of **1**.

In the present context, this method might open a convenient entry to the core segment **4** of the butylcycloheptylprodigiosin skeleton. Cyclononadienylacetone (**9**) was considered to be the optimal substrate for this reaction because 1) the presence of two double bonds should increase the number of reactive encounters during the Narasaka–Heck cyclization of the derived oxime ester **8** and, hence, increase the yield; 2) the remaining double bond in the expected product **7** provides a handle for the introduction of the butyl side chain of the target; and 3) the symmetrical structure of **9** should facilitate the large-scale preparation of this strained compound.

Our synthesis started from (*Z*,*Z*)-cyclononadienone (**10**).[18] 1,2-Reduction of the ketone group with diisobutylaluminum hydride (DIBAL-H) followed by acetylation of the resulting alcohol gave acetate **11** in almost quantitative yield (Scheme 4). Exposure of **11** to methyl acetoacetate in the presence of NaH and catalytic amounts of $[Pd(PPh_3)_4]$ afforded product **12** in 74% yield. This outcome is remarkable for various reasons: although one might expect that oxidative insertion of a $Pd^0$ center into the bisallylic acetate **11** engenders the formation of a pentadienylpalladium intermediate that then reacts with the nucleophile to give a conjugated diene product,[19] the double bonds are site-isolated in the major isomer **12**. Moreover, it is noteworthy that both of them are *Z* configured, although nine-membered rings are large enough to embody *E* alkenes without difficulty, and palladium catalysis is known to isomerize allylic systems effectively. This regio- and stereochemical outcome therefore advocates the notion that the two "allylic" sites in **11** remain uncoupled during the course of the Tsuji–Trost reaction as a result of the conformational peculiarities of the medium ring.[20]



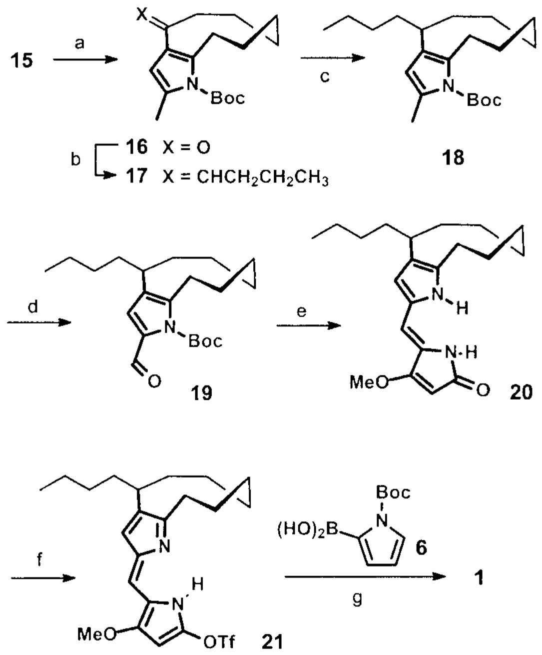
***Scheme 4.*** Synthesis of the *ortho*-pyrrolophane core structure: a) DIBAL-H, $CH_2Cl_2$, 0°C, 97%; b) $Ac_2O$, $Et_3N$, DMAP (0.5 mol%), $CH_2Cl_2$, 97%; c) methyl acetoacetate, NaH, $[Pd(PPh_3)_4]$ (5 mol%), THF, 55°C, 74%; d) aq DMSO, 180°C, 99%; e) $H_2NOH{\cdot}HCl$, NaOAc, aq EtOH, 100°C, 97%; f) pentafluorobenzoyl chloride, $Et_3N$, $Et_2O$, −78°C→RT, 97%; g) $Pd(OAc)_2$ (12 mol%), $[P(o\text{-tolyl})_3]$ (12 mol%), $Et_3N$, DMF, 110°C, 54%; h) KH, 1,3-diaminopropane, 65%; i) $Boc_2O$, DMAP (10 mol%), MeCN, 50°C, 69%. DMAP = 4-dimethylaminopyridine, DMSO = dimethyl sulfoxide.

Krapcho decarboxylation[21] of **12** followed by conversion of the resulting cyclononadienylacetone (**9**) into the pentafluorobenzoyl oxime ester **13** under standard conditions proceeded smoothly, thus setting the stage for the envisaged Narasaka–Heck cyclization.[17] This key transformation was effected on a multigram scale by a catalyst formed in situ from $Pd(OAc)_2$ and $[P(o\text{-tolyl})_3]$ in DMF (*N*,*N*-dimethylformamide) at 110°C and delivered the unsaturated bicyclic imine **14** in 54% yield. Because of its exceptional sensitivity and unusual volatility, this compound must be treated with great care and should be elaborated without undue delay.[22]

Although Narasaka–Heck reactions of simple substrates usually deliver the corresponding pyrrole derivatives directly (see Scheme 3),[17] a method had to be found for the aromatization of product **14**. We comtemplated that deprotonation of this compound at the bridgehead position α to the nitrogen atom engenders the formation of a stabilized azapentadienyl anion that might be reprotonated to give the conjugated diene isomer preferentially, so compound **14** was treated with KAPA (potassium 3-aminopropylamide)[23] in 1,3-diaminopropane as the reaction medium at ambient temperature. In line with our expectations, the ensuing series of "thermodynamic" deprotonation/reprotonation events resulted in the *selective* shift of the 9,10-double bond in **14**, thus delivering the highly sensitive pyrrole **7**, which was immediately *N*-protected to give compound **15**.[22,24] Isomeric by-products formed under these conditions were separated after the subsequent oxidation step.

The only remaining double bond in **15** is suitably located for the introduction of the butyl side chain of the final target. However, all attempts to manipulate this olefin by means of a Wacker oxidation, a rhodium-catalyzed hydroboration, or an oxymercuration strategy were unsuccessful. Only the uncatalyzed hydroboration with $BH_3{\cdot}THF$ followed by stepwise oxidation with $H_2O_2$ (in the presence of excess $Me_3N$ to protect the alkyl borane against proto-deborylation)[25] and Dess–Martin periodinane[26] allowed us to functionalize the alkene, thus furnishing ketone **16** and its anti-Markovnikov isomer in 65% overall yield (isomer ratio ≈5:1–2.5:1; 75% based on recovered starting material; Scheme 5). The anti-Markovnikov isomer and impurities derived from isomeric olefins (see above) could be removed at this stage by routine flash column chromatography. The severe steric shielding exerted by the cyclononyl skeleton also became evident in the subsequent Wittig olefination of **16**, which required forcing conditions but delivered product **17** in good yield and excellent purity. Its trisubstituted alkene moiety was hydrogenated with $[Ir(pyridine)(cod)(PCy_3)]PF_6$[27] (cod = 1,5-cyclooctadiene, Cy = cyclohexyl) as the catalyst to give **18** without reduction of the pyrrole causing any interference.

Pyrroles in general are known to be sensitive to oxidizing agents.[28] Therefore, the conversion of the methyl branch in **18** into the corresponding aldehyde was considered to be potentially troublesome. In fact, all classical reagents known to effect such benzylic oxidations failed in the present case. After some experimentation, however, a satisfactory solution for this problem was found by using cerium ammonium nitrate (CAN).[29] Key to success was the careful optimization of the reaction medium. Although previous reports recom-

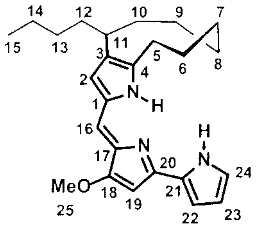


*Scheme 5.* Completion of the first total synthesis of butylcycloheptylprodigiosin (**1**): a) 1. $BH_3$·THF, THF, −10°C; 2. $H_2O_2$, $Me_3N$·THF, aq NaOH (3 M), 0°C; 3. Dess–Martin periodinane, 65% (5:1–2.5:1 isomer ratio); b) $Ph_3P{=}CHCH_2CH_2CH_3$, toluene, reflux, 75%; c) $H_2$ (1 atm), [Ir(pyridine)(cod)($PCy_3$)]$PF_6$ (10 mol%), $CH_2Cl_2$, 90%; d) CAN, $CHCl_3$/DME/$H_2O$, 60–65%; e) **5**, aq NaOH, DMSO, 60°C, 64–69%; f) $Tf_2O$, $CH_2Cl_2$, 0°C, 72–79%; g) **6**, [$Pd(PPh_3)_4$] (8 mol%), LiCl, aq $Na_2CO_3$, DME, 80°C, 70%.

mended the use of CAN in aqueous THF/HOAc,[30] compound **18** was rapidly destroyed under these conditions, likely due to uncontrolled overoxidations. In an attempt to separate the reagent from the substrate and products, the oxidations were performed in biphasic media. In fact, the use of $CHCl_3$/$H_2O$ furnished the desired aldehyde **19**, although the reaction rate was unacceptably low. Graftifyingly, the addition of small amounts of 1,2-dimethoxyethane (DME) as a "phase-transfer" agent led to a significant improvement and allowed the oxidation of **18** to proceed in only 30 minutes, thus affording the desired product **19** in respectable yields of 60–65%. The generality of this novel method for benzylic oxidations of highly sensitive electron-rich arenes is subject to further studies in this laboratory.

Now that reliable access to the key building block **19** bearing the *ortho*-annelated medium-sized ring had been secured through a sequence of rather unconventional transformations, the assembly of the final target **1** could be pursued by following established routes.[5,8,15] To this end, the base-promoted condensation of aldehyde **19** with commercial lactam **5** was accompanied by cleavage of the *N*-Boc (Boc = *tert*-butoxycarbonyl) protecting group. Treatment of the resulting product **20** with $Tf_2O$ (Tf = trifluoromethanesulfonyl) induced a reorganization of the π system and delivered triflate **21** as the substrate for the final Suzuki coupling.[31] Exposure of this compound to boronic acid **6** in the presence of catalytic amounts of [$Pd(PPh_3)_4$] and LiCl (3 equivalents) under previously optimized conditions[5a] afforded cycloheptylprodigiosin (**1**) in 70% yield as a deeply red–pink colored solid. As expected, no signal from this compound is seen upfield of trimethylsilane (TMS) in the $^1$H NMR spectrum. Although the spectrum is clearly different to that of the *meta*-bridged streptorubin B (**2**), the pattern signature is in accord with the signals reported for **1** (see Table 1 for the spectroscopic analysis).[10,11] A comparison with the spectrum of an authentic (although not entirely pure) sample of the "pink pigment" showed an excellent match. Therefore, it must be concluded that cycloheptylprodigiosin (**1**) is a natural product distinct from streptorubin B (**2**), as originally suggested by Gerber and Stahly[10] and Floss and co-workers.[11]

*Table 1:* Selected data for cycloheptylprodigiosin (**1**).[a]



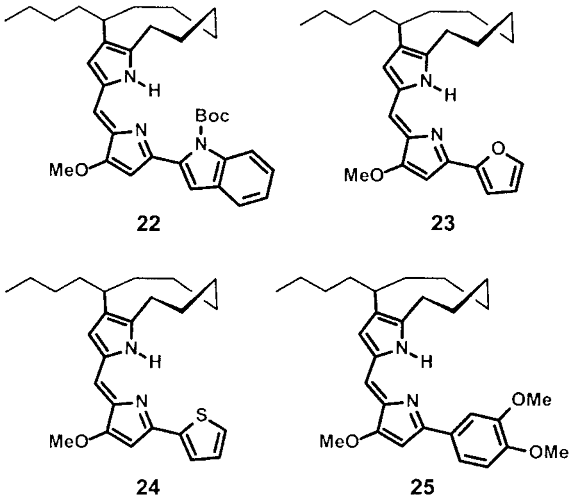
$^1$H NMR (600 MHz, $CD_2Cl_2$): $\delta$ = 6.82 (s, 1 H; 16-H), 6.72 (brs, 1 H; 24-H), 6.69 (dd, $J$ = 3.6, 1.3 Hz, 1 H, 22-H), 6.34 (s, 1 H, 2-H), 6.20 (dd, $J$ = 3.6, 2.6 Hz, 1 H, 23-H), 6.08 (s, 1 H, 19-H), 3.97 (s, 3 H, 25-H), 2.59 (m, 1 H, 11-H), 2.33 (br, 2 H, 5-H), 1.68 (m, 1 H, 6a-H), 1.62–1.50 (m, 4 H, 7a-H, 10a-H, 12-H), 1.41–1.15 (m, 9 H; 7b-H, 8-H, 9a-H, 10b-H, 13-H, 14-H), 1.00 (m, 1 H; 6b-H), 0.85 (t, $J$ = 6 Hz, 3 H; 15-H), 0.83 ppm (m, 1 H; 9b-H); $^{13}$C NMR (150 MHz, $CD_2Cl_2$): $\delta$ = 128.5 (s; C1), 118.6 (d; C2), 128.2 (s; C3), 142.9 (s; C4), 27.6 (t; C5), 27.7 (t; C6), 28.0 (t; C7), 28.1 (t; C8), 23.3 (t; C9), 38.0 (t; C10), 36.1 (d; C11), 37.1 (t; C12), 30.6 (t; C13), 23.2 (t; C14), 14.2 (q; C15), 116.2 (d; C16), 139.2 (s; C17)*, 169.2 (s; C18), 95.7 (d; C19), 159.6 (s; C20)*, 129.1 (s; C21), 112.6 (d; C22), 110.6 (d; C23), 122.3 (d; C24), 58.8 ppm (q; C25); IR (KAP): $\tilde{\nu}$ = 3322, 3103, 2921, 2852, 1738, 1618, 1577, 1552, 1449, 1361, 1333, 1285, 1221, 1148, 1116, 1086, 1057, 998, 954, 890, 767, 728 cm$^{-1}$; MS (EI) $m/z$ (%): 391 [$M^+$], (100).

[a] All assignments are unambiguous (except those marked *, which might be mutually interchanged) and are based on 1D and 2D spectra. The multiplicity of the signals in the $^{13}$C NMR spectrum refers to the geminal protons (DEPT). The insert shows the arbitrary numbering scheme.

Finally, it should be mentioned that aldehyde **19** can be used as a common building block for the preparation of a focused library of analogues by exploiting the late-stage flexibility inherent in the chosen synthetic route. A detailed mapping of the biochemical properties of the resuscitated alkaloid **1** (prepared in a 16-step sequence in approximately 1.5% overall yield from cyclononadienone) and its congeners **22–25** (Scheme 6) are underway and will be reported in due course.

Received: October 6, 2004

**Keywords:** alkaloids · cyclophanes · medium-ring compounds · palladium · pyrroles



*Scheme 6.* Analogues of **1** prepared by diversion from the total synthesis route in the final cross-coupling step.

---

[1] a) A. Fürstner, *Angew. Chem.* **2003**, *115*, 3706–3728; *Angew. Chem. Int. Ed.* **2003**, *42*, 3582–3603; b) R. A. Manderville, *Curr. Med. Chem. Anti-Cancer Agents* **2001**, *1*, 195–218; c) R. Pérez-Tomás, B. Montaner, E. Llagostera, V. Soto-Cerrato, *Biochem. Pharmacol.* **2003**, *66*, 1447–1452.

[2] a) A. Nakamura, J. Magae, R. F. Tsuji, M. Yamasaki, K. Nagai, *Transplantation* **1989**, *47*, 1013–1016; b) J. Magae, M. W. Miller, K. Nagai, G. M. Shearer, *J. Antibiot.* **1996**, *49*, 86–90; c) S. M. Stepkowski, Z. S. Nagy, M.-E. Wang, F. Behbod, R. Erwin-Cohen, B. D. Kahan, R. A. Kirken, *Transplant. Proc.* **2001**, *33*, 3272–3273; d) S. M. Stepkowski, R. A. Erwin-Cohen, F. Behbod, M.-E. Wang, X. Qu, N. Tejpal, Z. S. Nagy, B. D. Kahan, R. A. Kirken, *Blood* **2002**, *99*, 680–689.

[3] a) R. D'Alessio, A. Bargiotti, O. Carlini, F. Colotta, M. Ferrari, P. Gnocchi, A. Isetta, N. Mongelli, P. Motta, A. Rossi, M. Rossi, M. Tibolla, E. Vanotti, *J. Med. Chem.* **2000**, *43*, 2557–2565; b) A. Mortellaro, S. Songia, P. Gnocchi, M. Ferrari, C. Fornasiero, R. D'Alessio, A. Isetta, F. Colotta, J. Golay, *J. Immunol.* **1999**, *162*, 7102–7109.

[4] A. Fürstner, H. Szillat, B. Gabor, R. Mynott, *J. Am. Chem. Soc.* **1998**, *120*, 8305–8314.

[5] a) A. Fürstner, J. Grabowski, C. W. Lehmann, *J. Org. Chem.* **1999**, *64*, 8275–8280; b) A. Fürstner, H. Krause, *J. Org. Chem.* **1999**, *64*, 8281–8286.

[6] a) A. Fürstner, H. Weintritt, *J. Am. Chem. Soc.* **1998**, *120*, 2817–2825; b) A. Fürstner, H. Weintritt, *J. Am. Chem. Soc.* **1997**, *119*, 2944–2945; c) A. Fürstner, T. Gastner, H. Weintritt, *J. Org. Chem.* **1999**, *64*, 2361–2366.

[7] a) A. Fürstner, H. Weintritt, A. Hupperts, *J. Org. Chem.* **1995**, *60*, 6637–6641; b) A. Fürstner, H. Krause, O. R. Thiel, *Tetrahedron* **2002**, *58*, 6373–6380; c) A. Fürstner, A. Hupperts, A. Ptock, E. Janssen, *J. Org. Chem.* **1994**, *59*, 5215–5229.

[8] a) A. Fürstner, J. Grabowski, C. W. Lehmann, T. Kataoka, K. Nagai, *ChemBioChem* **2001**, *2*, 60–68; b) A. Fürstner, E. J. Grabowski, *ChemBioChem* **2001**, *2*, 706–709; c) A. Fürstner, K. Reinecke, H. Prinz, H. Waldmann, *ChemBioChem* **2004**, *5*, 1575–1579.

[9] Note that this name is not very well chosen because compound **1** is not a cycloheptyl but a cyclononyl derivative.

[10] a) N. N. Gerber, *J. Antibiot.* **1975**, *28*, 194–199; b) N. N. Gerber, D. P. Stahly, *Appl. Microbiol.* **1975**, *30*, 807–810.

[11] S.-W. Tsao, B. A. M. Rudd, X.-G. He, C.-J. Chang, H. G. Floss, *J. Antibiot.* **1985**, *38*, 128–131.

[12] H. Laatsch, M. Kellner, H. Weyland, *J. Antibiot.* **1991**, *44*, 187–191.

[13] a) A. Fürstner, H. Szillat, F. Stelzer, *J. Am. Chem. Soc.* **2000**, *122*, 6785–6786; b) A. Fürstner, F. Stelzer, H. Szillat, *J. Am. Chem. Soc.* **2001**, *123*, 11863–11869; c) M. Méndez, V. Mamane, A. Fürstner, *ChemTracts* **2003**, *16*, 397–425.

[14] N. N. Gerber, A. G. McInnes, D. G. Smith, J. A. Walter, J. L. C. Wright, L. C. Vining, *Can. J. Chem.* **1978**, *56*, 1155–1163.

[15] R. D'Allessio, A. Rossi, *Synlett* **1996**, 513–514.

[16] C. Galli, L. Mandolini, *Eur. J. Org. Chem.* **2000**, 3117–3125.

[17] a) H. Tsutsui, M. Kitamura, K. Narasaka, *Bull. Chem. Soc. Jpn.* **2002**, *75*, 1451–1460; b) H. Tsutsui, K. Narasaka, *Chem. Lett.* **1999**, *28*, 45–46; c) S. Zaman, M. Kitamura, K. Narasaka, *Bull. Chem. Soc. Jpn.* **2003**, *76*, 1055–1062; d) H. Tsutsui, K. Narasaka, *Chem. Lett.* **2001**, *30*, 526–527; e) S. Chiba, M. Kitamura, O. Saku, K. Narasaka, *Bull. Chem. Soc. Jpn.* **2004**, *77*, 785–796.

[18] The preparation of **10** from the commercially available cyclononanone follows a literature method; an optimized procedure affording multigram quantities will be reported in a forthcoming full paper; see: a) E. W. Garbisch, Jr., *J. Org. Chem.* **1965**, *30*, 2109–2120; b) see also: R. Noyori, Y. Ohnishi, M. Katô, *Tetrahedron Lett.* **1971**, *19*, 1515–1518.

[19] For studies on metal-catalyzed alkylations of pentadienyl acetates, see: B. M. Trost, M.-H. Hung, *J. Am. Chem. Soc.* **1984**, *106*, 6837–6839.

[20] DFT optimization of the conformation of the presumed π-allylpalladium intermediate corroborate this interpretation.

[21] a) A. P. Krapcho, *Synthesis* **1982**, 805–822; b) A. P. Krapcho, *Synthesis* **1982**, 893–914.

[22] During the course of this synthesis, we noticed the exceptional volatility of many cyclononane derivatives even at fairly low temperatures, which renders the isolation of these compounds difficult and adversely affects the yields. This phenomenon is particularly pronounced in compounds **7** and **10**–**15**.

[23] C. A. Brown, P. K. Jadhav, *Org. Synth.* **1987**, *65*, 224–229.

[24] For a related aromatization reaction of a pyrrole with KAPA, see Ref.[4]

[25] M. Zaidlewicz, *J. Organomet. Chem.* **1985**, *293*, 139–146.

[26] a) D. B. Dess, J. C. Martin, *J. Org. Chem.* **1983**, *48*, 4155–4156; b) S. D. Meyer, S. L. Schreiber, *J. Org. Chem.* **1994**, *59*, 7549–7552.

[27] R. H. Crabtree, H. Felkin, T. Fillebeen-Khan, G. E. Morris, *J. Organomet. Chem.* **1979**, *168*, 183–195.

[28] A. Gossauer in *Methoden der Organischen Chemie (Houben-Weyl), Vol. E6a*, 4th ed. (Ed.: R. P. Kreher), Thieme, Stuttgart, **1994**, pp. 556–798.

[29] Reviews: a) G. A. Molander, *Chem. Rev.* **1992**, *92*, 29–68; b) T.-L. Ho, *Synthesis* **1973**, 347–354; c) for a recent study, see: A. M. Khenkin, R. Neumann, *J. Am. Chem. Soc.* **2004**, *126*, 6356–6362, and references therein.

[30] a) T. Thyrann, D. A. Lightner, *Tetrahedron Lett.* **1995**, *36*, 4345–4348; b) J. B. Paine, D. Dolphin, *Can. J. Chem.* **1976**, *54*, 411–414.

[31] a) A. Suzuki, *J. Organomet. Chem.* **1999**, *576*, 147–168; b) N. Miyaura, A. Suzuki, *Chem. Rev.* **1995**, *95*, 2457–2483.