[(tmeda)$PdCl_2$] as the precursor showed that a reduction of palladium(II) chlorides by [InCp*] and [GaCp*] leading to formation of [Cp*ECl_2] is in principle possible, but these reactions are less selective and yields are lower.

In summary, our results confirm the opening quotation that [InCp*] and [GaCp*] exhibit interesting potential as novel ligands for transition metals which exceeds the analogy to CO ligands and phosphanes. In this context, it is worth mentioning that photolysis of a solution of **1** in C_6D_6 (25 °C, 2 h, 150 W) results in selective cleavage of the Cp* shell of the Pd_3In_8 in the form of decamethylfulvalene, and we are currently investigating the metallic precipitate formed. The results are indicative of a link to the current field of mixed-metal nanoparticles and colloids.

Experimental Section

1: A solution of [(tmeda)$Pd(CH_3)_2$] (0.100 g, 0.396 mmol) in hexane (4 mL) was treated with four equivalents of [InCp*] (0.396 g, 1.584 mmol) in hexane (10 mL). The reaction mixture was warmed to 60 °C for 1 h, whereupon a red crystalline precipitate was formed. After recrystallization from benzene, the crystals were isolated by removal of the mother liquor by using a cannula, washed twice with a small amount of cold hexane, and dried in vacuo. Yield: 0.275 g, 90 %. M.p. 81 °C (decomp); ^{1}H NMR (C_6D_6, 250 MHz, 25 °C): $\delta = 2.12$ ppm (s, 120 H); ^{13}C NMR (C_6D_6, 250 MHz, 25 °C): $\delta = 113.7$, 11.2 ppm; elemental analysis: calcd for $C_{80}H_{120}In_8Pd_3 \cdot C_6D_6$: C 42.97; H 5.53, found: 42.79, 5.64.

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[11] Crystal structure analysis of **1**·C_6D_6: crystal size: $0.35 \times 0.28 \times 0.20$ mm, triclinic, $P\bar{1}$, $a = 12.826(3)$, $b = 16.146(4)$, $c = 25.215(6)$ Å, $\alpha = 97.595(4)$, $\beta = 101.316(4)$, $\gamma = 111.313(4)°$, $V = 4650.0(18)$ Å^3, $Z = 2$, $\rho_{calcd} = 1.657$ mg m^{-3}, $2\Theta_{max.} = 50.160$, $\lambda(Mo_{K\alpha}) = 0.71073$ Å, $T = 213(3)$ K. A total of 23 924 reflections (16 005 unique) were collected on a Bruker-axs SMART diffractometer (R(int) = 0.0322). The structure solution and refinement was performed by using the programs SHELXS-86 and SHELXL-97. The final values for $R1$ and $wR2(F^2)$ were 0.0705 and 0.2253, respectively. The reason for the unusually high value for $wR2(F^2)$ is not yet clear and is currently under investigation. The Cp* rings at In2 and In8 were isotropically refined and the interatomic distances and angles in all of the Cp* rings were fixed. The Cp* rings are disordered. The unit cell contains other atoms, which probably belong to benzene molecules, but cannot be accurately assigned and refined. As the molecular structure of **1** clearly shows, the high steric demand of the Cp* units excludes the formation of higher [Pd(InCp*)$_2$] oligomers. The key for the synthesis of [Pd(InCp*)$_2$]$_n$ ($n > 3$) is the design of new, sterically less hindered, yet soluble ligands of the type In(CpR) (R = alkyl). CCDC-187560 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: (+44) 1223-336-033; or deposit@ccdc.cam.ac.uk).

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[20] Identification of the Ga^{III} and In^{III} side products by ^{1}H and ^{13}C NMR spectroscopy (C_6D_6, 250 MHz, 25 °C). [Cp*Ga$(CH_3)_2$]: ^{1}H NMR: $\delta = -0.15$ ppm; ^{13}C NMR: $\delta = -7.8$ ppm. [Cp*In$(CH_3)_2$]: ^{1}H NMR: $\delta = -0.11$ ppm; ^{13}C NMR: $\delta = -6.9$ ppm.

Total Synthesis of Amphidinolide T4**

Alois Fürstner,* Christophe Aïssa, Ricardo Riveiros, and Jacques Ragot

Marine dinoflagellates of the genus *Amphidinium* sp. living in symbiosis with the Okinawan (Japanese) flatworm *Amphiscolops* sp. are exceedingly rich sources of bioactive macrolides.[1] Though structurally quite diverse, all "amphidinolides" known to date exhibit pronounced cytotoxicity against various cancer cell lines, with some members reaching potencies which rank them amongst the most cytotoxic compounds that are presently known.[2] In contrast to macrolide antibiotics derived from terrestrial microorganisms, the majority of amphidinolides feature an odd-numbered macrolide ring, which raises questions concerning the biosynthesis of these structurally unique secondary metabolites.

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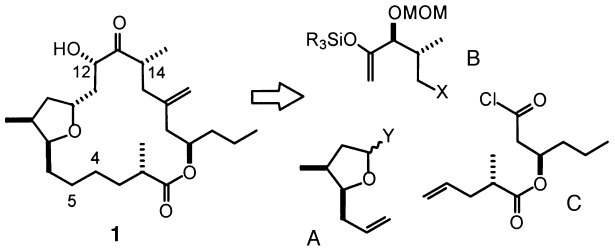
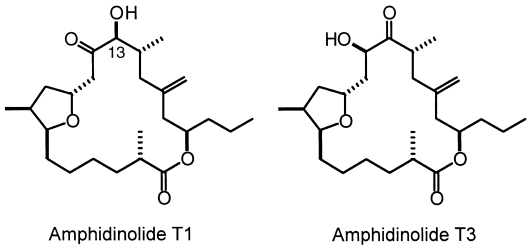
Described below is the first total synthesis of amphidinolide T4 (**1**; Scheme 1), a prototype member of this series containing a 19-membered lactone core.[3,4] Because its



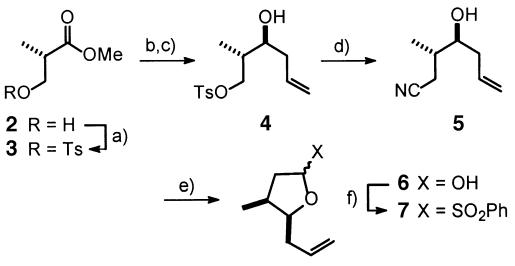
Scheme 1. Structure and retrosynthetic analysis of amphidinolide T4 (**1**).

congeners T1 and T3 differ from **1** only in the oxygenation pattern of the C-12/C-14 region,[3,5] the synthesis is planned such that it can later be adapted to the preparation of these compounds as well.



For the sake of convergency, it was envisaged to assemble this target from three building blocks of similar size and complexity (**A**–**C**) by means of a stereoselective Lewis acid mediated alkylation of a silyl enol ether with a lactol-derived oxocarbenium cation,[6] a palladium-catalyzed acylation of an organozinc reagent with an enantiomerically pure acid chloride,[7] as well as a ring-closing metathesis (RCM) reaction for the formation of the macrocyclic ring (Scheme 1).[8] In this maneuver, the C-4/C-5 bond is targeted for efficiency reasons as the required precursors seem to be particularly easily accessible.

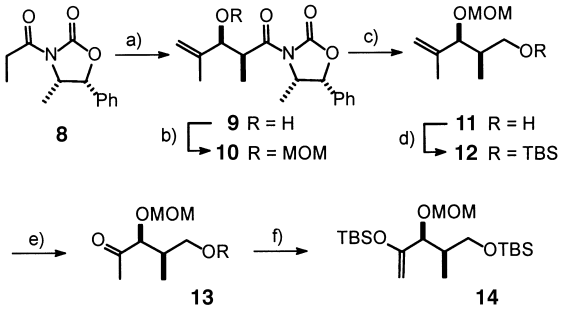
This aspect is evident from Scheme 2, which shows the preparation of compound **7** as the synthetic equivalent of **A**. Compound **7** is readily available from the commercial hydroxyester **2** which is tosylated prior to reduction with



Scheme 2. Synthesis of segment **A**: a) TsCl, Et_3N, DMAP, CH_2Cl_2, 94%; b) Dibal-H, toluene, −95°C; c) (−)-Ipc_2B-allyl, Et_2O, −100°C, 70% (over both steps); d) KCN, DMSO, 99%; e) Dibal-H, CH_2Cl_2, −78°C, 91%; f) $PhSO_2H$, $CaCl_2$, CH_2Cl_2, 0°C, 87%. DMAP = 4-dimethylaminopyridine, Ts = tosyl, Dibal-H = diisobutylaluminum hydride, Ipc_2B-allyl = allyldiisopinocamphanylborane.

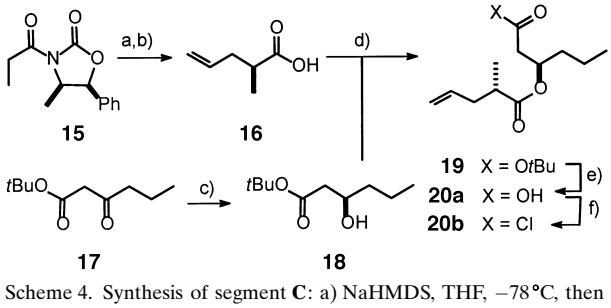
Dibal-H. Treatment of the resulting aldehyde with (−)-Ipc_2B-allyl[9] at a low temperature affords the alcohol **4** in a diastereomerically pure form on a multigram scale. While the tosylate is sufficiently stable to act as a protecting group for the primary alcohol during the hydride reduction and the allylation steps, it serves as an appropriate leaving group in the subsequent reaction with KCN. The resulting nitrile **5** is again reduced with Dibal-H to afford hemiacetal **6** after acidic work-up, which is converted into the sulfone **7** upon treatment with an excess of $PhSO_2H$ in the presence of $CaCl_2$ as the dehydrating agent.[6a]

The coupling partner needed for further elaboration is obtained from *N*-propionyl oxazolidinone **8**[10] by a sequence of high yielding steps (Scheme 3). Specifically, a boron aldol reaction with methacrolein provides the *syn*-aldol **9** on a multigram scale which is protected by a MOM group prior to reduction with $LiBH_4$. The resulting primary alcohol **11** is converted into the TBS ether **12** which is subjected to ozonolysis to provide the methyl ketone **13** in excellent overall yield.[11]



Scheme 3. Synthesis of segment **B**: a) 1. Bu_2BOTf, Et_3N; 2. methacrolein, 90%; b) MOMCl, $(iPr)_2NEt$, CH_2Cl_2, 93%; c) $LiBH_4$, Et_2O, 92%; d) TBSCl, imidazole, DMF, 90%; e) O_3, CH_2Cl_2, 86%; f) TBSOTf, Et_3N, Et_2O, 0°C→RT, 91%. MOMCl = methoxymethylchloride, TBSCl = *tert*-butyldimethylsilylchloride

The last segment is easily prepared on a large scale as shown in Scheme 4. Thus, the β-keto ester **17** is hydrogenated in the presence of $[\{(R)\text{-binap})RuCl_2\}_2]\cdot(NEt_3)$ as the catalyst to give **18** in excellent enantiomeric purity (*ee* = 98%).[12] This alcohol is then esterified with the acid **16** which is readily available from the *N*-acyl oxazolidinone **15** by a standard



Scheme 4. Synthesis of segment **C**: a) NaHMDS, THF, −78°C, then allyl bromide, 60%; b) LiOH, H_2O_2, THF/H_2O, 93%; c) cat. $[\{(R)\text{-binap})RuCl_2\}_2]\cdot NEt_3$, H_2 (10 atm), MeOH, 95°C, 84%; d) EDCI, DMAP, CH_2Cl_2, 93%; e) F_3CCOOH, Et_3SiH, CH_2Cl_2, quantitative; f) $(COCl)_2$, CH_2Cl_2/DMF cat., quantitative. NaHMDS = sodium hexamethyldisilazide, binap = 2,2′-bis(diphenylphosphanyl)-1,1′-binaphthyl, EDCI = 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride.

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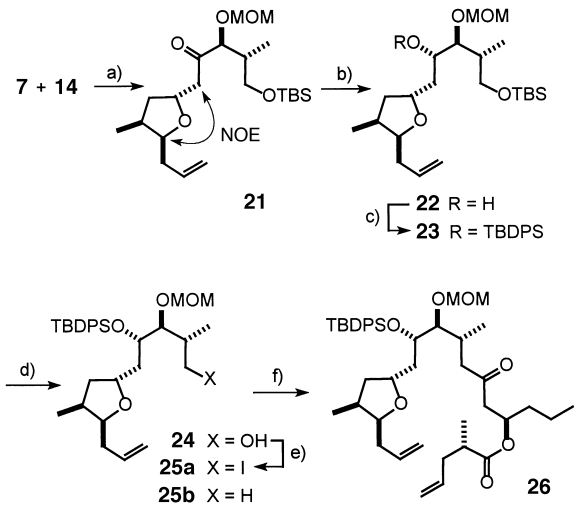
allylation reaction[13] followed by hydrolytic cleavage of the auxiliary. Deprotection of the *tert*-butyl ester in **19** with F_3CCOOH in the presence of Et_3SiH and subsequent conversion of the resulting acid **20a** into the corresponding acid chloride **20b** furnishes the missing building block **C** needed for the envisaged synthesis of amphidinolide T4.

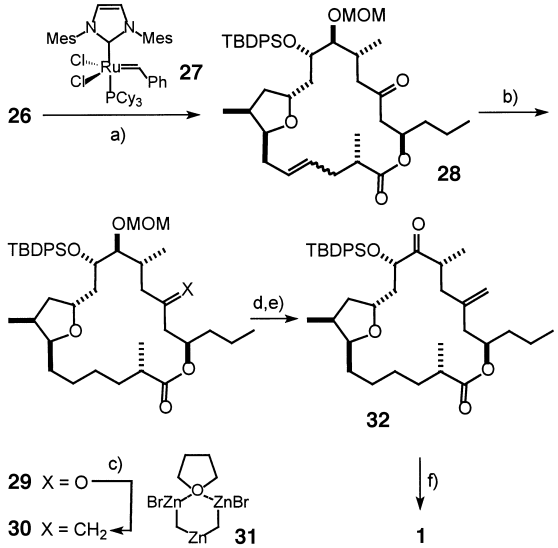
With all building blocks in hand, the assembly of the metathesis precursor was investigated. For this purpose, the ketone **13** is transformed into the *tert*-butyldimethylsilyl enol ether **14** which is stable in air and can be rigorously purified by flash chromatography.[14] While the reaction of enol ethers with tetrahydropyranyl sulfones mediated by Lewis acids has an excellent record, the corresponding tetrahydrofuranyl sulfones have the reputation of poor stereoselectivity.[6a] Gratifyingly, however, the reaction of the anomeric sulfone **7** gave very satisfactory results. After careful optimization of the individual parameters, treatment of a solution of **7** and **14** in CH_2Cl_2 at −78 °C with $SnCl_4$ afforded the desired ketone **21** in 86% yield after standard work-up. The product **21** is obtained as the desired *trans* isomer (*trans*:*cis* ≈ 26:1) as can be deduced from the strong NOE effect indicated in Scheme 5. This outcome probably reflects the shielding of the α side of the intermediate oxocarbenium cation by the methyl- and the allyl units.[6b,15] The reason why $SnCl_4$ is far superior to all other Lewis acids tested, however, is far from obvious.



Scheme 5. Fragment coupling: a) $SnCl_4$, CH_2Cl_2, −78 °C, 86%; b) L-Selectride, THF, −78 °C, 72%; c) KHMDS, TBDPSCl, THF, 77%; d) TsOH, aq. MeOH, 75%; e) I_2, PPh_3, imidazole, toluene, 80%; f) 1. Zn/Cu couple, THF; 2. **20b**, cat. $Pd_2(dba)_3$, cat. P(2-furyl)$_3$, 40–50% (**26**) + 28% (**25b**). TBDPSCl = *tert*-butyldiphenylsilylchloride, dba = dibenzylidene acetone.

Reduction of this compound with L-Selectride affords the desired *S*-configured alcohol **22** in 72% yield,[16] which was protected as the silyl ether **23** by treatment with KHMDS and TBDPSCl. Cleavage of the orthogonal TBS group at the terminal position of **23** under acidic conditions, followed by conversion of the resulting primary alcohol **24** into the corresponding iodide **25** sets the stage for the last segment coupling. Thus, exposure of **25** to Zn/Cu couple activated with TMSCl immediately prior to use gives the corresponding organozinc reagent which reacts with the enantiomerically pure acid chloride **20b** in the presence of $[Pd_2(dba)_3]$ catalyst and tris(2-furyl)phosphane as the ligand to give the desired ketone **26** together with small amounts of the reduced product **25b**.[7] To date, attempts to improve on this result by using nucleophiles other than the organozinc reagent and/or different catalysts and ligands have been in vain. Notably, however, this reaction is one of the most advanced examples of an acyl-Negishi coupling reaction reported to date.[17]

In line with our expectations,[8,18] the subsequent formation of the macrocyclic ring by RCM of the diene **26** worked exquisitely well when carried out in the presence of the "second-generation" ruthenium carbene complex **27** as the catalyst bearing an imidazol-2-ylidene ligand (Scheme 6).[19] Hydrogenation of the resulting cycloalkene **28** (*E*:*Z* = 6:1)



Scheme 6. Completion of the total synthesis: a) catalyst **27**, CH_2Cl_2, reflux, 86%; b) H_2 (1 atm), Pd/C, EtOAc, 86%; c) Nysted's reagent **31** (excess), THF, reflux, 64%; d) TMSCl, nBu_4NBr, CH_2Cl_2, 0 °C, 85%; e) Dess–Martin periodinane, CH_2Cl_2, 83%; f) HF·pyridine, MeCN, 87%.

delivers **29** in high yield and sets the stage for the conversion of the keto group into the *exo*-methylene branch of the target. This reaction, however, turned out to be quite delicate. While $Ph_3P{=}CH_2$ was far too basic and led only to a β elimination of the aldol with concomitant opening of the macrocycle, the use of CH_2Br_2 in the presence of TiX_4/Zn (X = Cl, O*i*Pr) gave the desired olefin in somewhat variable yields.[20] The best results were obtained by applying Nysted's reagent **31**,[21] which delivers **30** in up to 64% yield.

Having secured good access to the intact carbon skeleton of **1**, removal of the MOM group in **30** by using TMSBr generated in situ followed by oxidation of the resulting alcohol on treatment with Dess–Martin periodinane[22] cleanly led to the ketone **32**. The final deprotection step was readily achieved by using HF·pyridine to give amphidinolide T4 (**1**). The analytical and spectroscopic data of the synthetic material are in excellent agreement with those published for the natural product, thus rigorously confirming the assignments previously made.[3]

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As mentioned above, the other members of the amphidinolide T family, that is, amphidinolide T1-T3, differ from T4 (**1**) mainly or exclusively in the C-12 to C-14 region of the macrocycle;[3] because the stereocenter at C-13 in **30** is appropriately set, however, the synthesis of these compounds is just a matter of a different timing of the final deprotection steps and/or simple inversion reactions. Therefore it is expected that the synthesis summarized above will give access to these valuable marine natural products as well. This and related aspects are subject to ongoing studies in our laboratory.

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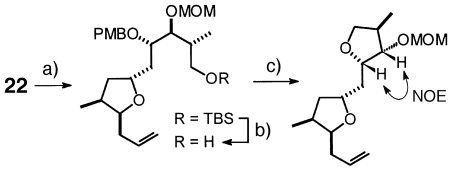

(1)

This assignment was ultimately confirmed by the conversion of **22** into **1** and comparison of the data of the synthetic sample with those of the natural product.

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Tuning PCR Specificity by Chemically Modified Primer Probes**

Michael Strerath and Andreas Marx*

Dedicated to Professor Peter Welzel on the occasion of his 65th birthday

Since the publication of the first draft of the human genome sequence in 2001, the discovery of genomic dissimilarities such as single nucleotide polymorphisms (SNPs) between different individuals has been a main focus of many research

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