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Total Syntheses of the Telomerase Inhibitors Dictyodendrin B, C, and E

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Abstract: Concise and flexible total syntheses of the pyrrolo[2,3-*c*]carbazole alkaloids dictyodendrin B (**2**), C (**3**), and E (**5**) are described. These polycyclic telomerase inhibitors of marine origin derive from the common intermediate **18** which was prepared on a multigram scale by a sequence comprising a TosMIC cycloaddition with formation of the pyrrole A-ring, a titanium-induced reductive oxoamide coupling reaction to generate an adjacent indole nucleus, and a photochemical 6π-electrocyclization/aromatization tandem to forge the pyrrolocarbazole core. Conversion of **18** into dictyodendrin C required selective manipulations of the lateral protecting groups and oxidation with peroxoimidic acid to form the vinylogous benzoquinone core of the target. Zinc-induced reductive cleavage of the trichloroethyl sulfate ester then completed the first total synthesis of **3**. Its relatives **2** and **5** also originate from compound **18** by a selective bromination of the pyrrole entity followed by elaboration of the resulting bromide **27** via metal−halogen exchange or cross-coupling chemistry, respectively. Particularly noteworthy in this context is the generation of the very labile *p*-quinomethide motif of dictyodendrin E by a palladium-catalyzed benzyl cross-coupling reaction followed by vinylogous oxidation of the resulting product **41** with DDQ. The Suzuki step could only be achieved with the aid of the borate complex **40** formed in situ from *p*-methoxybenzylmagnesium chloride and 9-MeO-9-BBN, whereas alternative methods employing benzylic boronates, -trifluoroborates, or -stannanes met with failure.

Introduction

Eukaryotic chromosomes are terminated by nonencoding, single-stranded telomeric ends, which play essential roles in chromosome protection, positioning, and cell division. Most notably, they are progressively shortened by ca. 50−200 nucleotides in each successive round of replication; once a critical length is reached, a signaling pathway is triggered leading to apoptotic cell death to prevent further aging. The telomeres hence constitute a decisive mitotic clock that is ultimately responsible for the finite lifespan of somatic cells.[1]

More than 85% of malignant tumors are reprogrammed to circumvent this protective mechanism by upregulation of human telomerase. This ribonucleoprotein with reverse-transcriptase properties is capable of adding TTAGGG repeats to the 3′-ends of telomers which thereby keep a certain length, escape from apoptosis, and hence gain cellular immortality as the characteristic trait of cancer.[2,3] Therefore, it comes as no surprise that inhibition of telomerase activity might be considered as cancer's "Achilles heel" and considerable efforts are presently directed to exploit this cancer-specific vulnerability in the quest for more selective chemotherapeutic agents and/or the development of adjuvant clinical regimens.[4,5]

Small molecule telomerase inhibitors, however, are still rare.[6,7] Thereby, it is particularly striking that telomerase inhibitors of marine origin are largely unknown even though the sea has yielded a huge number of novel bioactive metabolites including some of the most promising leads for the development of anticancer drugs during the past decades.[8] In view of this conspicuous lack of inhibitors, a recent publication from Fusetani et al. deserves particular attention, disclosing a new

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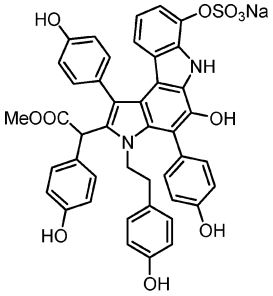
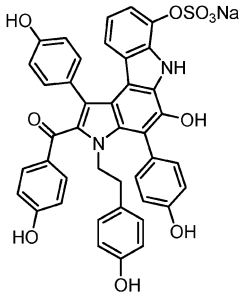
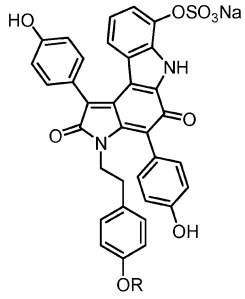


Dictyodendrin A (**1**)

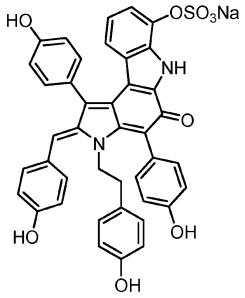


Dictyodendrin B (**2**)

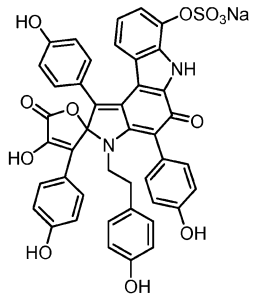


Dictyodendrin C (**3**, R = H)

Dictyodendrin D (**4**, R = SO_3Na)



Dictyodendrin E (**5**)



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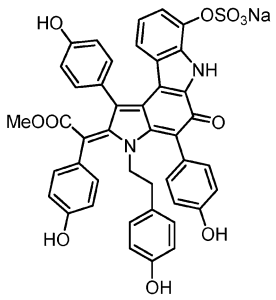

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family of alkaloids isolated from the sponge *Dictyodendrilla verongiformis* collected off the South Japanese coast.[9] The dictyodendrins **1**−**5** were claimed to be the first marine natural products with telomerase inhibitory properties (100% inhibition at 50 μg/mL concentration), although no further details or biochemical profiling has been reported. They are closely related to the aldose reductase inhibitors **6** and **7** previously isolated from a *Dictyodendrilla* sp.[10] Collectively, these tyramine-derived alkaloids feature a characteristic and unique pyrrolo[2,3-*c*]-carbazole moiety that is decorated with electron-rich arene rings and carries at least one sulfate group in the periphery. As such, the dictyodendrins are distantly related to a series of other marine pyrrole alkaloids such as the lamellarins, lukianol, ningalin, storniamide, polycitone, purpurone, or halitulin, many of which are also potent anticancer agents.[11−13] Overall, the scarcity of the dictyodendrins, the as of yet incomplete understanding of their physiological properties, the promise of efficient telomerase inhibition, and their compact and demanding structural characteristics render these marine natural products formidable targets for a synthesis-driven investigation at the chemistry/biology interface. As the initial step of this endeavor, we now present the first total synthesis of three prototype members of this family, which is concise and efficient, maps the pertinent chemical behavior of these compounds, and is also flexible by design to allow for substantial variations at a later stage.[14,15]

Results and Discussion

Retrosynthetic Considerations and Preparation of a Common Synthesis Platform. The individual dictyodendrins **1**−**5** differ only with regard to their oxidation pattern and the substituents attached to the C.2 position of the pyrrole A-ring. Therefore, it seemed possible to access the entire family by suitable manipulations of a common synthetic intermediate of type **9** (Scheme 1). Any such attempt, however, must consider the lability of the conspicuous sulfate decorating compounds **1**−**5**. Most likely, it is advantageous to introduce this group at a very late stage of the synthesis, thus making a suitable and orthogonal protection of the phenolic position at C.10 necessary; the presence of the intact sulfate group, however, was reported to be essential for telomerase inhibitory activity.[9]

Moreover, it is known that the individual dictyodendrins undergo rapid fragmentation in aqueous acidic media by which they lose their C.2 substituents as well as the sulfate groups and converge to compound **8** as the common "degradation" product.[9] This information suggests that the vinylogous quinone in **8** represents a thermodynamic sink that benefits from additional stabilization by the lone pairs of the flanking N-atoms. In recognition of this chemical bias, we envisaged the generation of this characteristic structural motif in the projected synthesis of dictyodendrin C (**3**) directly from compound **9**, provided that an oxidant can be found that selectively attacks the C.14 OH group and the electronically coupled C−H bond at the remote C.2 position. Although such a transformation should ultimately open access to dictyodendrin C (**3**) as the most stable compound of this series, its higher congeners would also derive from the same precursor **9** via suitable acylation or alkylation/oxidation of the pyrrole A-ring.

The preparation of a suitably functionalized surrogate of the common synthesis platform **9** commenced with readily available

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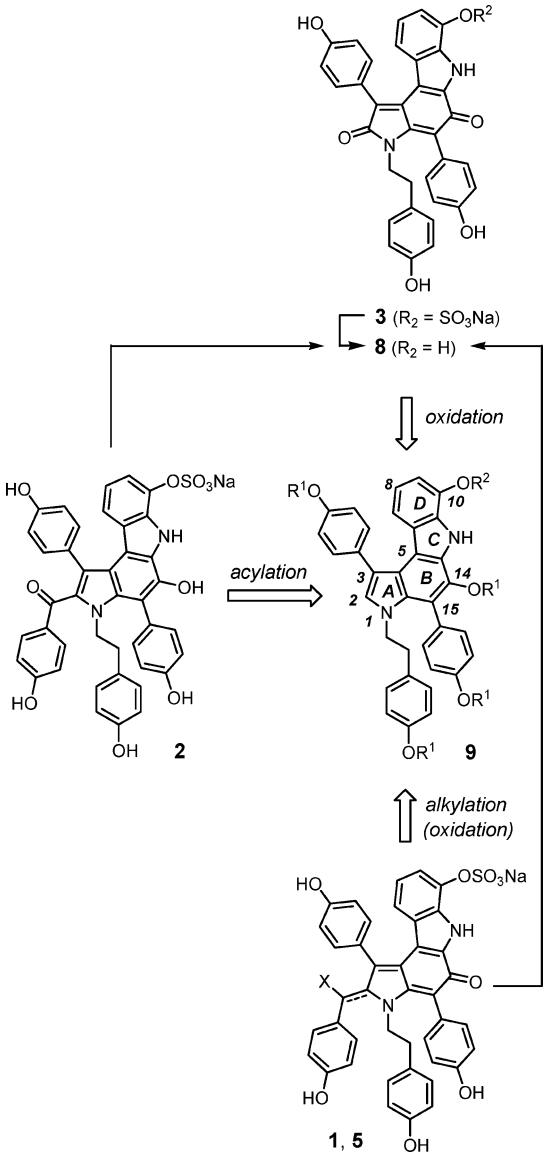
Scheme 1. Envisaged Generation of the Individual Dictyodendrins from a Common Precursor **9** and Their Known Degradation, Converging to Compound **8**[a]



[a] Numbering scheme used throughout this paper.

acetophenone **10**,[16] which was converted into isopropyl ether **11** prior to base-induced condensation with *p*-methoxybenzaldehyde (Scheme 2). The resulting chalcone **12** cleanly reacted with toluenesulfonylmethyl isocyanide (TosMIC) in the presence of NaH at low temperature[17] to give a pyrrole which was N-alkylated in situ with *p*-$MeOC_6H_4(CH_2)_2Br$. Reduction of the nitro group in the resulting product **13** with Fe/HCl furnished aniline **14** in excellent yield on a multigram scale, which was condensed with acid chloride **15**[18] under standard conditions to give amide **16** without incident.

Previous investigations from this laboratory had shown that ketoamides, on treatment with "low-valent" titanium, convert to indole derivatives even in the presence of other reducible sites.[19,20] This reaction is best performed with titanium on graphite prepared from $TiCl_3$ and KC_8 (2 equiv)[21] as the reagent, although other sources of low-valent titanium also provide good to excellent results in many cases.[22] Such intramolecular reductive coupling reactions are distinguished by an exceptional driving force and a remarkable chemoselectivity profile,[23] which allows for applications even to fairly elaborate cases.[19−24]

This notion was confirmed by the application of this protocol to ketoamide **16** which afforded the desired indole **17** in up to 93% isolated yield on exposure to titanium−graphite in refluxing DME. Thereby, it was necessary to buffer the slightly Lewis-acidic reaction medium with pyridine to prevent partial cleavage of the labile enol ether moiety of the substrate. During the synthesis campaign described herein, this transformation was carried out repeatedly on different scales and has provided multigram amounts of indole **17**, thus attesting to the robustness and reliability of this methodology for reductive heterocycle synthesis.

Indole **17** thus formed is set up for subsequent closure of the dictyodendrin core by a 6π-electrocyclization. This pivotal transformation proceeded smoothly upon irradiation with UV light (Hanovia Hg lamp, 250 W) in MeCN; addition of Pd/C and nitrobenzene to the reaction medium causes concomitant aromatization of the product initially formed,[25] thus giving rise to the desired pyrrolocarbazole **18** in 81% yield in a single operation.[26] Since **18** represents a fully functional intermediate for the preparation of all individual members of the dictyodendrin family, a very short, convenient, and scaleable gambit of our total synthesis project has been secured employing only inexpensive starting materials (seven steps, ca. 40% overall yield). Moreover, the chosen route should allow for substantial variations as desirable for a synthesis-driven exploration of pertinent structure/activity relationships of this series of alkaloids at a later stage.

Total Synthesis of Dictyodendrin C. In a first attempt, compound **18** was reacted with BBr_3 in CH_2Cl_2 at −78 °C in the presence of excess cyclohexene as an acid scavenger (Scheme 3). Although the peripheral methyl- and isopropyl ethers could not be distinguished under these conditions and were cleaved off concomitantly, we were pleased to observe that the resulting polyphenol underwent spontaneous air oxidation during the acidic/basic workup, thus furnishing compound **8** in an unoptimized 49% isolated yield. As described above, this compound represents the common degradation product of all naturally occurring dictyodendrins.[9] Its spontaneous formation also supports the notion that the vinylogous *p*-quinone motif embedded into its core constitutes a formidable thermodynamic sink, thus auguring well for the final stages of the projected total synthesis of dictyodendrin C.

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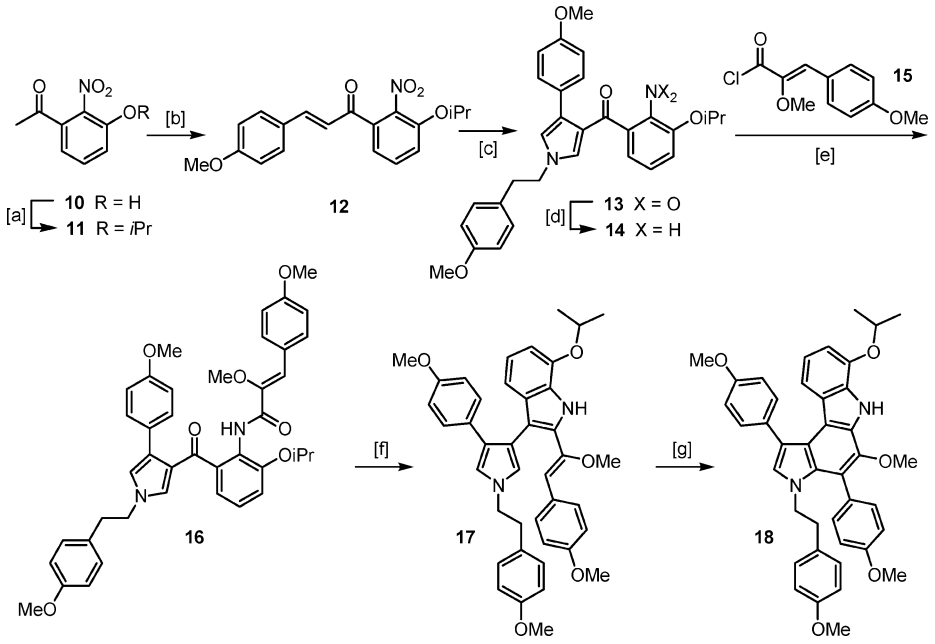
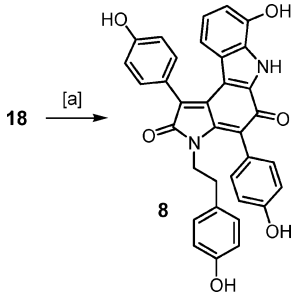
Scheme 2. Preparation of the Common Synthesis Intermediate[a]



[a] [a] 2-Bromopropane, K_2CO_3, DMF, 100 °C, 99%; [b] *p*-$MeOC_6H_4CHO$, NaOMe, MeOH, 70 °C, 74%; [c] (i) TosMIC, NaH, THF, −30 °C; (ii) *p*-$MeOC_6H_4(CH_2)_2Br$, reflux, 83%; [d] Fe powder, aq. HCl, EtOH, 96%; [e] acid chloride **15**, CH_2Cl_2, Et_3N, DMAP catalyst, 89%; [f] $TiCl_3/2KC_8$, DME, pyridine, reflux, 71−93%; [g] *hν*, MeCN, Pd/C catalyst, $C_6H_5NO_2$, 81%.

Scheme 3. Preparation of Desulfated Dictyodendrin C[a]



[a] [a] BBr_3, cyclohexene, CH_2Cl_2, −78 °C → room temperature, 49%.

In fact, a slight modification of the deprotection regime paved the way to this particular target (Scheme 4). Specifically, the selective cleavage of the isopropyl ether of **18** was achieved in 75% yield simply upon switching from BBr_3 to BCl_3 as the reagent. The resulting phenol **19** was reacted with trichloroethyl chlorosulfuric acid ester[27] to afford aryl sulfate **20** which turned out to be hydrolytically labile and had to be processed without undue delay. Gratifyingly, however, it withstood exhaustive deprotection of the remaining methyl groups with the aid of BCl_3 and tetra-*n*-butylammonium iodide in CH_2Cl_2.[28] Rather than relying on air oxidation,[29] the resulting phenol was reacted with H_2O_2 in MeCN to give quinone **21** in a superbly clean transformation; it is believed that peroxyimidic acid is the actual oxidant under these conditions.[30,31]

Compound **21** was then treated with excess zinc dust and ammonium formate in MeOH to effect reductive cleavage of the trichloroethyl ester moiety.[27] Even though partial reduction of the quinone with formation of **22** was observed, removal of the excess zinc dust followed by stirring of the crude mixture under an oxygen atmosphere resulted in the formation of a single product which was isolated in 76% yield over two steps. The analytical and spectroscopic data of this compound were in excellent agreement with those of dictyodendrin C (**3**) reported in the literature,[9] thus finishing the first total synthesis of this structurally unique marine alkaloid in the form of its ammonium salt.

Dictyodendrin B. The conversion of the relay compound **18** into dictyodendrin B (**2**) seemed straightforward, requiring acylation of the pyrrolic C.2 position[32] and suitable protecting group management only. Exploratory studies using the per-methylated compound **23**[33] as a model, however, showed that this seemingly conventional transformation is far more delicate than anticipated (Scheme 5).

Although substrate **23** was completely consumed on reaction with *p*-methoxybenzoyl chloride in the presence of $SnCl_4$, none of the expected ketone was obtained. Rather, the new product **24** formed in 64% yield had the same mass as the substrate and gave very similar NMR spectra as well, thus suggesting that an isomerization rather than the attempted Friedel−Crafts acylation had occurred under the chosen conditions. Since no incorporation of the acid part was observed, it came as no

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(29) As observed in the case of **8**, the air oxidation occurs during the acidic/basic workup. Because the sulfate group of **3**, however, is labile under these conditions, the H_2O_2/MeCN protocol had to be implemented. This method has the additional advantage that no extractive workup is necessary, thus making the isolation of the very polar final product much more efficient and convenient.

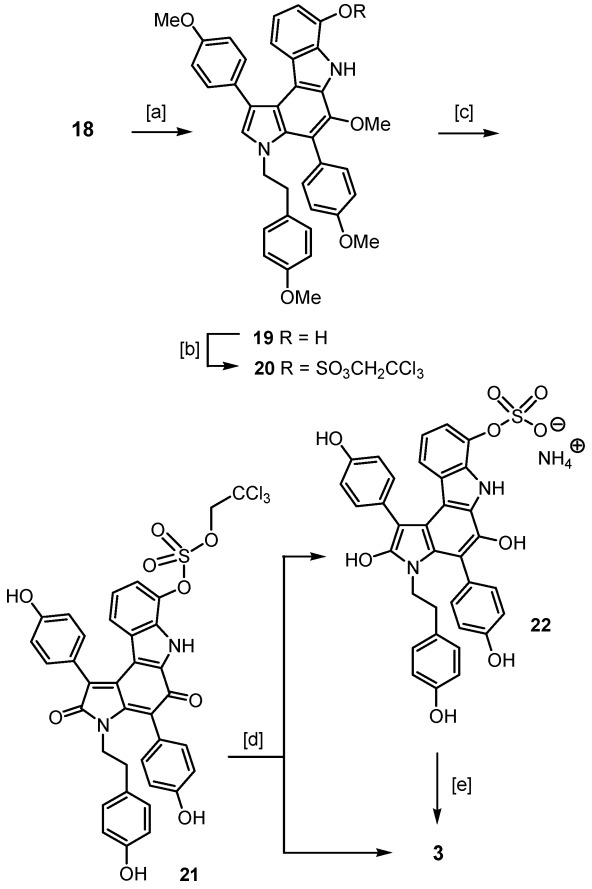
(30) For a discussion, see the following for leading references and literature cited therein: (a) Shu, L.; Shi, Y. *J. Org. Chem.* **2000**, *65*, 8807. (b) Payne, G. B.; Deming, P. H.; Williams, P. H. *J. Org. Chem.* **1961**, *26*, 659.

(31) For related oxidations of pyrroles, see: (a) Shrout, D. P.; Lightner, D. A. *Synthesis* **1990**, 1062. (b) Auerbach, J.; Franck, R. W. *J. Chem. Soc. D* **1969**, 991.

(32) For a related maneuver in the total synthesis of a complex pyrrole alkaloid, see: (a) Fürstner, A.; Weintritt, H. *J. Am. Chem. Soc.* **1998**, *120*, 2817. (b) Fürstner, A.; Weintritt, H. *J. Am. Chem. Soc.* **1997**, *119*, 2944.

(33) The preparation of compound **23** essentially follows the route described for **18**; details will be reported in a forthcoming paper describing various analogues of the naturally occurring dictyodendrins.

Scheme 4. Total Synthesis of Dictyodendrin C[a]

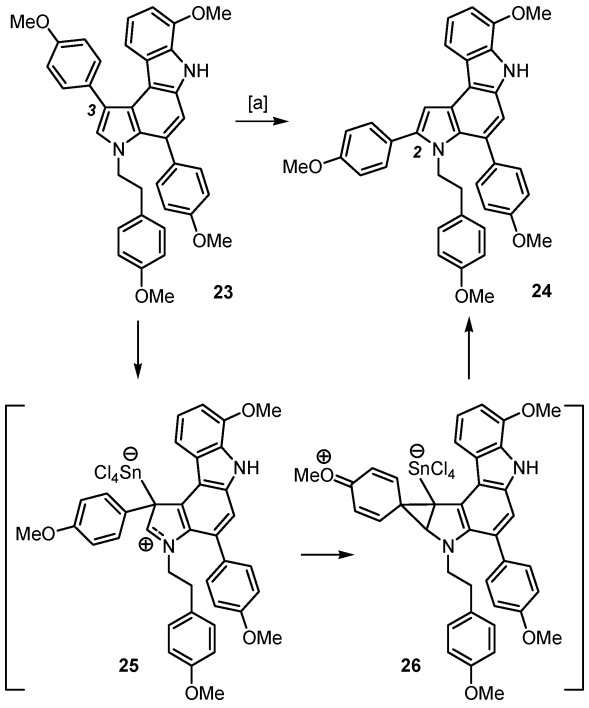


[a] [a] BCl_3, CH_2Cl_2, 0 °C, 75%; [b] $Cl_3CCH_2OSO_2Cl$, DABCO, THF, 71%; [c] (i) BCl_3, $(n\text{-Bu})_4NI$, CH_2Cl_2, 0 °C; (ii) aq. H_2O_2 (30% w/w), MeCN, 57%; [d] Zn, $HCOONH_4$, MeOH; [e] O_2 (1 atm), MeOH, 76% (combined yield).

surprise that the same product was formed in similar yield on treatment with $SnCl_4$, $TiCl_4$, or $BF_3{\cdot}Et_2O$ only. Extensive spectroscopic studies finally revealed that the *p*-methoxyphenyl ring attached to the C.3 position in **23** had migrated to the vicinal carbon atom C.2. This rearrangement presumably involves complexation of the Lewis acid at the most electron-rich C.3 carbon atom with formation of a resonance-stabilized iminium cation **25** that is prone to intramolecular electrophilic attack onto the arene moiety giving rise to the bridging Wheland complex **26**.[34] Subsequent collapse of this reactive intermediate readily explains this unusual 3→2 aryl shift.

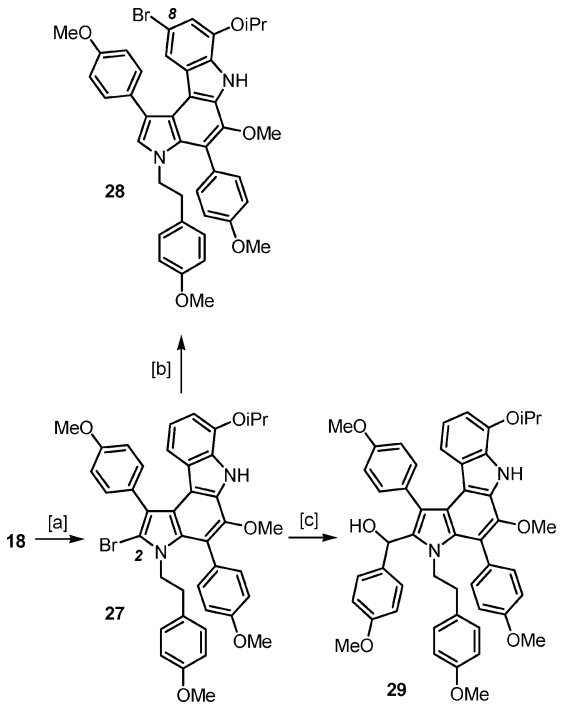
This unexpected behavior enforced a redesign of our synthesis strategy (Scheme 6). To this end, compound **18** was treated with NBS in THF at 0 °C, which resulted in selective bromination at C.2 with formation of product **27**. Although this compound can be stored for some time in the freezer in solid form, it is subject to a rapid "bromine dance" when kept in $CDCl_3$ solution at ambient temperature.[35] This vectorial process shifts the bromine substituent from the A-ring in **27** to the electron-rich

Scheme 5 [a]



[a] [a] *p*-$MeOC_6H_4COCl$, $SnCl_4$, 1,2-dichloroethane, reflux, 64%.

Scheme 6 [a]



[a] [a] NBS, THF, 0 °C, 69%; [b] $CHCl_3$, room temperature, cf. text; [c] (i) MeLi, THF, −78 °C; (ii) *n*-BuLi, −78 °C; (iii) *p*-$MeOC_6H_4CHO$, −78 °C → room temperature, 97%.

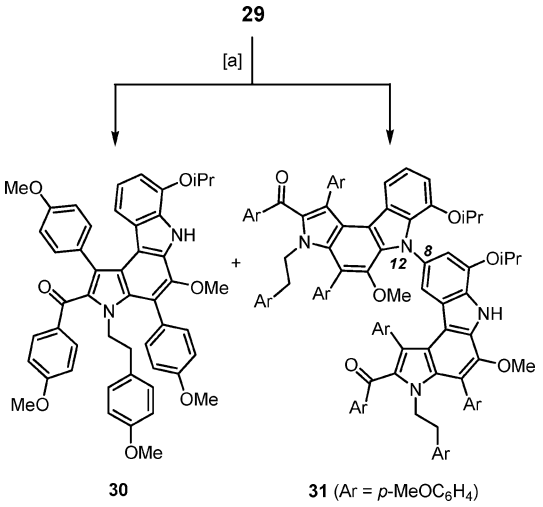
C.8 position located in the D-ring, thus furnishing the isomeric product **28**; this halide walk can be nicely followed by NMR.[36] Gratifyingly, however, the aryllithium species formed on

(34) *Carbonium Ions*; Olah, G. A., von R. Schleyer, P., Eds.; Wiley: New York, 1970; Vol. 2.

(35) Although base-induced "halogen dance" processes are well-known in (hetero)arene chemistry (cf.: Duan, X.-F.; Zhang, Z.-B. *Heterocycles* **2005**, *65*, 2005 and literature cited therein), uncatalyzed processes are less common; for a pertinent example, see: Press, J. B.; Eudy, N. H. *J. Heterocycl. Chem.* **1981**, *18*, 1261. Even though strictly neutralized $CDCl_3$ was used, it is assumed that traces of acid are generated upon reaction with the solvent that might catalyze the observed halide shift, cf. ref 36.

(36) MS analysis shows that traces of a dibrominated compound and a compound containing one bromine and one chlorine atom are formed as byproducts during this halide walk. Although incorporation of a chloride derived from the solvent might give some mechanistic hints, the exact constitution of these minor products has not been investigated any further.

Scheme 7 [a]



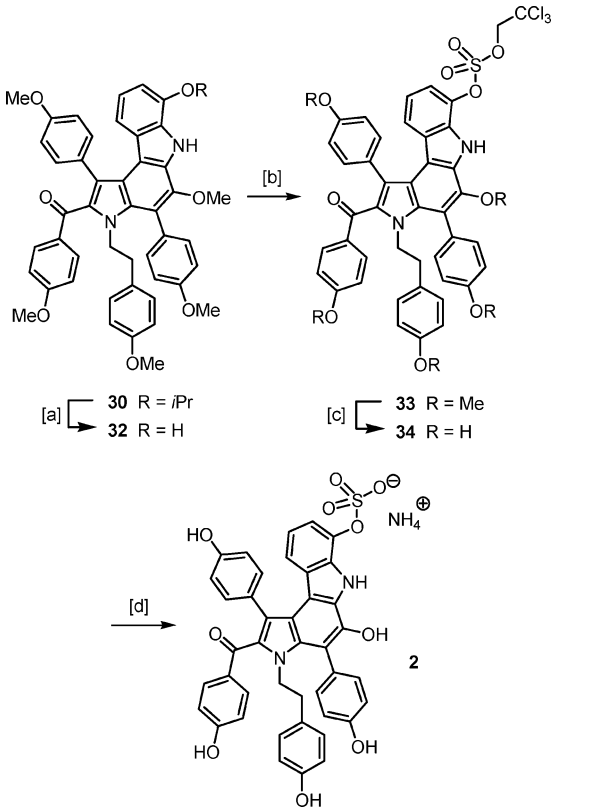
[a] TPAP (10%), NMO, MS 4Å, CH_2Cl_2 at 0.1 M concentration: 22% (**30**) + 57% (**31**); at 0.01 M concentration: 66% (**30**) + 16% (**31**).

N-deprotonation of **27** with MeLi followed by metal−halogen exchange with *n*-BuLi[37] could be quenched with *p*-$MeOC_6H_4$-CHO to afford alcohol **29** in remarkably high yield.[38]

The seemingly trivial oxidation of this compound to the corresponding ketone again posed significant problems. Although the use of classical oxidants either resulted in no conversion (MnO_2, SO_3/pyridine) or led to rapid degradation only (PDC, PCC, Dess−Martin periodinane, TEMPO catalyst/NaOCl, Swern), the use of catalytic amounts of tetra-*n*-propylammonium perruthenate (TPAP, 10 mol %)[39] in combination with *N*-methylmorpholine-*N*-oxide (NMO) in CH_2Cl_2 (0.1 M) afforded a product mixture, of which the desired ketone **30** was the minor constituent only (22%) (Scheme 7). Mass spectrometry indicated the dimeric nature of the major product **31** (57%) formed under these conditions; however, it took considerable efforts to unambiguously elucidate its constitution. Extensive NMR investigations were necessary to show that the two subunits in **31** are joined by a C−N bond between the "indolic" nitrogen N.12 of one molecule and the electron-rich C.8 position of the second entity.[40] In recognition of this fact, we repeated the oxidation under more dilute conditions, hoping that the dimerization could be disfavored. In fact, the reaction responded well to the chosen concentration, with $c = 0.01$ M being the best compromise among product distribution, overall yield, and reaction time. Under these conditions, ketone **30** was obtained in 66% isolated yield.

The remaining protecting group manipulations proceeded uneventfully, following the successful sequence pursued in the dictyodendrin C series. Thus, cleavage of the isopropyl ether in **30** with BCl_3, attachment of the protected sulfate ester to the resulting phenol **32**, followed by exhaustive demethylation of

Scheme 8. Completion of the Total Synthesis of Dictyodendrin B[a]



[a] BCl_3, CH_2Cl_2, −20 °C, 85%; [b] $Cl_3CCH_2OSO_2Cl$, DABCO, CH_2Cl_2, 92%; [c] BCl_3, TBAI, CH_2Cl_2, 0 °C → room temperature; [d] Zn, $HCOONH_4$, MeOH, 58% (over both steps).

33, and reductive cleavage of the remaining trichloroethyl moiety in **34** with Zn/HCO_2NH_4 cleanly led to dictyodendrin B (**2**) (Scheme 8). All analytical and spectroscopic data of the synthetic samples perfectly matched those of the natural product reported in the literature.[9]

Dictyodendrin E. Dictyodendrin E (**5**) is arguably the most challenging target of this family of marine alkaloids. This is evident from the fact that this particular compound could not be isolated from the sponge in pure form but was obtained by Fusetani et al. as an inseparable mixture with a methanol adduct.[9] This information likely indicates the high reactivity of its vinylogous quinomethide core structure extending from the benzylidene substituent at C.2 to the carbonyl group at C.14.

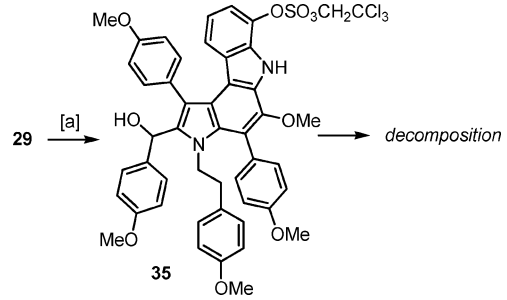
Our initial approach to **5** envisaged the vinylogous elimination of MeOH from product **35**, which in turn derives from alcohol **29** by the established protecting group regimen (Scheme 9). This strategy, however, had to be abandoned because of the exceptional lability of **35**, which decomposed on attempted purification by flash chromatography.

For a route to **5** to be viable, it was therefore essential to pass through more robust intermediates. The success of the oxidation reaction leading to the vinylogous *p*-quinone moiety of dictyodendrin C inspired such an alternative strategy, envisaging formation of the vinylogous quinomethide of **5** by a similar process. The required substrate **41** carrying a *p*-methoxybenzyl substituent at C.2 might derive from bromide **27** that had already served as the key intermediate en route to dictyodendrin B (see above).

Unfortunately, however, our initial attempts to get access to **41** by palladium-catalyzed cross-coupling of bromide **27** with

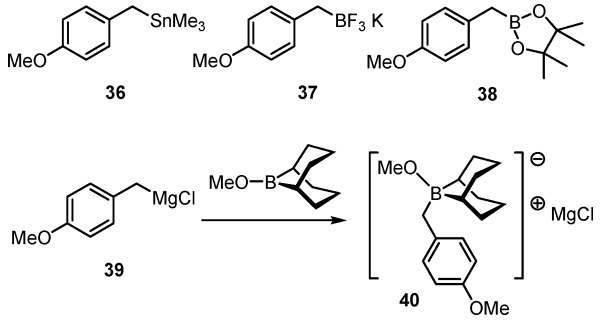
(37) The sequential use of MeLi and *n*-BuLi for a deprotonation/metal−halogen exchange tandem has precedence in the literature; for an early example and an instructive discussion, see: Kelly, T. R.; Kim, M. H. *J. Am. Chem. Soc.* **1994**, *116*, 7072.
(38) In striking contrast, however, attempts to quench the organolithium species with *p*-$MeOC_6H_4COCl$ or the corresponding Weinreb amide were by and large unsuccessful.
(39) Ley, S. V.; Norman, J.; Griffith, W. P.; Marsden, S. P. *Synthesis* **1994**, 639.
(40) A related process is reported in: Bringmann, G.; Tasler, S.; Endress, H.; Kraus, J.; Messer, K.; Wohlfarth, M.; Lobin, W. *J. Am. Chem. Soc.* **2001**, *123*, 2703.

Scheme 9 [a]



[a] [a] (i) BCl_3, CH_2Cl_2, −20 °C, 82%; (ii) $Cl_3CCH_2OSO_2Cl$, DABCO, CH_2Cl_2.

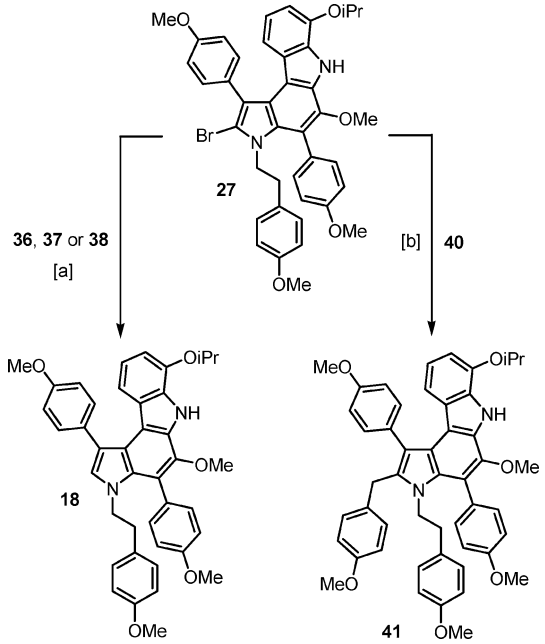
Scheme 10. Different *p*-Methoxybenzyl Donors and Preparation of a Borate Complex **40** via the 9-MeO-9-BBN Variant of the Suzuki Coupling



suitable benzyl donors (Scheme 10) met with failure. The use of the stannane **36**, the trifluoroborate **37**,[41] or the boronate **38**[42] previously recommended for benzylation reactions was not encouraging. Debromination of the substrate with formation of compound **18** was the only transformation that occurred under a variety of experimental conditions (Scheme 11). In view of this setback, we were particularly pleased to see that the 9-MeO-9-BBN variant of the Suzuki reaction previously developed by our group gave much more favorable results.[43−45] In this method, the crucial borate complex serving as the actual nucleophile in the palladium-catalyzed cross-coupling step is generated in situ from 9-MeO-9-BBN and a polar organometallic reagent, in the present case the readily available *p*-methoxybenzylmagnesium chloride (Scheme 10). In combination with $Pd(OAc)_2$ and Buchwald's sterically encumbered S−PHOS ligand,[46,47] the reactive intermediate **40** thus formed allowed for the almost quantitative benzylation of the electron-rich and rather labile bromide **27**.

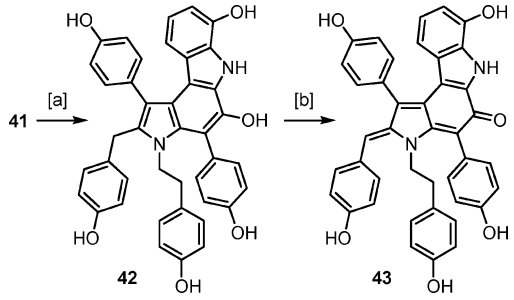
For exploratory purposes, the resulting product **41** was globally deprotected with BBr_3 to give polyphenol **42** which

Scheme 11 [a]



[a] [a] Compound **38**, $Pd(PPh_3)_4$ catalyst, CsF, THF, reflux; or compound **37**, $(dppf)PdCl_2$, Cs_2CO_3, THF/H_2O (10:1), reflux; or compound **37**, $(dppf)PdCl_2$, Et_3N, *i*PrOH; or compound **36**, $Pd(PPh_3)_4$ catalyst, copper thiophene-2-carboxylate (1.5 equiv), DMF; or compound **36**, $Pd(PPh_3)_4$ catalyst, CuCl (5 equiv), LiCl (6 equiv), DMSO; or $(PPh_3)_2PdCl_2$ catalyst, THF; [b] borate **40** (4 equiv), $Pd(OAc)_2$ (10 mol %), S−PHOS (20 mol %), DMF/THF, 90%.

Scheme 12. Preparation of Desulfated Dictyodendrin E[a]



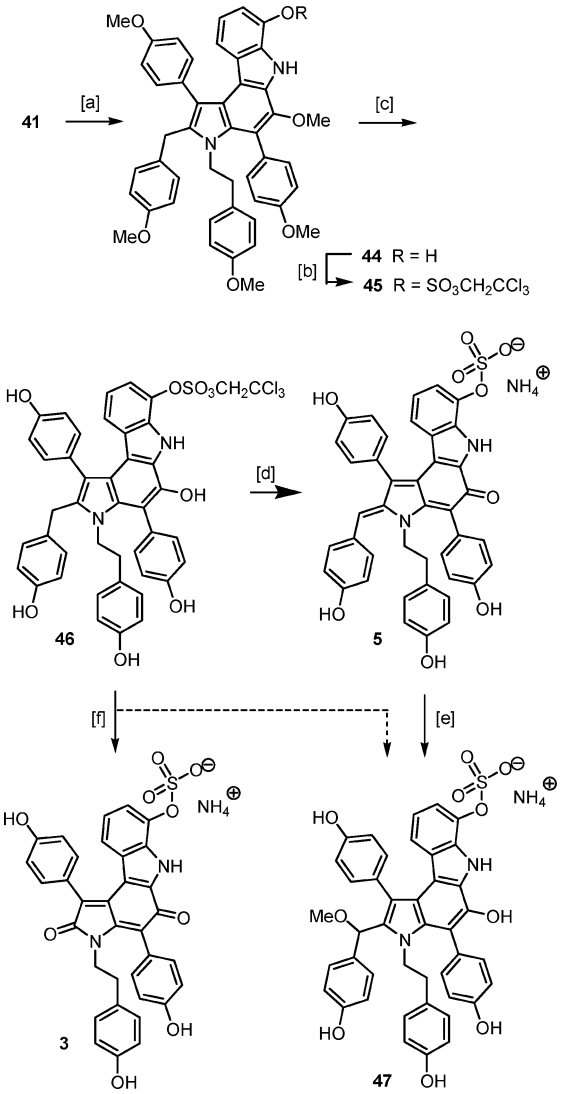
[a] [a] BBr_3, CH_2Cl_2, −78 °C → room temperature; [b] DDQ, THF, 83% (over both steps).

was processed further by DDQ oxidation in THF at ambient temperature (Scheme 12). In line with our expectations, the vinylogous quinomethide **43** was formed in 83% isolated yield over two steps, which represents desulfated dictyodendrin E. The compound was stable enough to be isolated in analytically pure form and could be unambiguously characterized. Its NMR data are in excellent accordance with those of dictyodendrin E itself, except for the protons H.7, H.8, and H.9 which are shifted to a lower field in the natural product because of their vicinity to the sulfate group residing at the adjacent O.10 position.

The proof of this concept spurred our efforts to complete the total synthesis of the sulfated natural product **5** as well (Scheme 13). Following the established protocol starting with the selective removal of the isopropyl group in **41** and subsequent introduction of the trichloroethyl sulfate moiety,[27] compound **45** was obtained; this product was highly susceptible to hydrolysis and had to be processed without delay. The cleavage of its methyl ethers with $BCl_3/(n\text{-}Bu)_4NI$,[28] however, proceeded well affording the even more sensitive compound **46** which was immediately

(41) Molander, G. A.; Ito, T. *Org. Lett.* **2001**, *3*, 393.
(42) Flaherty, A.; Trunkfield, A.; Barton, W. *Org. Lett.* **2005**, *7*, 4975.
(43) (a) Fürstner, A.; Seidel, G. *Tetrahedron* **1995**, *51*, 11165. (b) Fürstner, A.; Leitner, A. *Synlett* **2001**, 290. (c) Fürstner, A.; Nikolakis, K. *Liebigs Ann.* **1996**, 2107. (d) The method was also independently reported by: Soderquist, J. A.; Matos, K.; Rane, A.; Ramos, J. *Tetrahedron Lett.* **1995**, *36*, 2401.
(44) This method had previously allowed for very efficient allylations of aryl halides; cf.: Fürstner, A.; Seidel, G. *Synlett* **1998**, 161.
(45) For general reviews on the Suzuki reaction, see, e.g.: (a) Suzuki, A. *J. Organomet. Chem.* **1999**, *576*, 147. (b) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457.
(46) (a) Barder, T. E.; Walker, S. D.; Martinelli, J. R.; Buchwald, S. L. *J. Am. Chem. Soc.* **2005**, *127*, 4685. (b) Walker, S. D.; Barder, T. E.; Martinelli, J. R.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2004**, *43*, 1871.
(47) In this particular case, the use of $(dppf)PdCl_2$ previously recommended for Suzuki reactions according to the "9-MeO-9-BBN" protocol failed to afford the cross-coupling product. This is tentatively ascribed to the electron-rich nature of substrate **27**, which renders the use of the more electron-donating and sterically demanding S−PHOS ligand imperative for successful oxidative insertion of the Pd(0) template.

Scheme 13. Completion of the Total Synthesis of Dictyodendrin E[a]



[a] [a] BCl_3, CH_2Cl_2, −20 °C → room temperature; [b] $Cl_3CCH_2OSO_2Cl$, DABCO, THF, 83% (over both steps); [c] BCl_3, TBAI, CH_2Cl_2, 0 °C, 85%; [d] (i) Zn, $HCOONH_4$, MeOH; (ii) DDQ, THF, 75% (over both steps); [e] MeOH, cf. text; [f] (i) DDQ, THF; (ii) Zn, $HCOONH_4$, MeOH.

subjected to reductive cleavage of the trichloroethyl group followed by DDQ oxidation. Gratifyingly, this reaction sequence allowed for the isolation of dictyodendrin E (**5**) in pure form in respectable 75% yield over two steps.

For solubility reasons, however, the purification of the product had to be performed with MeOH. Any delay during this manipulation or any trace of acid in the mixture at that point causes partial addition of MeOH with formation of the inseparable adduct **47**, thus confirming Fusetani's original finding that the extended quinomethide moiety of **5** acts as an excellent Michael acceptor for external nucleophiles.[9,48] In this context, it is also worth mentioning that the order of the final steps leading from **46** to **5** is critical for success: thus, DDQ oxidation of **46** prior to reductive cleavage of the trichloroethyl sulfate ester results in an overall fragmentation with loss of the benzylidene unit at C.2, thereby giving rise mainly to dictyodendrin C **3** (Scheme 13). This finding reinforces the previous observation that all naturally occurring dictyodendrins ultimately convert to **3** or its desulfated analogue **8** as the thermodynamically most favorable compounds of this series[9] and may forecast somewhat limited structural flexibility with regard to the substitution pattern at C.2 in future SAR studies.

(48) Control experiments showed the MeOH addition to be complete after ca. 1 week at ambient temperature in the absence of external catalysts.

Conclusions

Challenged by the intriguing structures of the telomerase inhibitors belonging to the dictyodendrin family, a concise approach to these scarce alkaloids of marine origin was developed. The chosen route takes advantage of the proclivity of ketoamides to undergo reductive coupling on treatment with low-valent titanium[20] as well as of an efficient photochemical 6π-electrocyclization, which is rendered irreversible when performed in tandem with the aromatization of the cyclohexadiene derivative initially formed. The densely functionalized pyrrolo[2,3-*c*]carbazole **18** thus obtained in multigram quantities with excellent overall yield served as a common intermediate for the first total syntheses of the quinoid dictyodendrin C, its very labile quinomethide analogue dictyodendrin E, and the acylated congener dictyodendrin B. The individual end games uncover some of the unique chemical characteristics of these natural products, most notably their tendency to form extended quinoid chromophores under oxidative conditions as well as the lability of substituents at C.2. The migratory aptitude of the bromide at this position, the preference of a 1,2-aryl shift over conventional Friedel−Crafts chemistry, and the somewhat surprising tendency of such compounds to engage in dimerization at seemingly remote sites (C.8) are equally remarkable features. Finally, the success of the palladium-catalyzed benzylation by means of the 9-MeO-9-BBN variant of the Suzuki coupling is noteworthy, which might be useful in other delicate applications as well.[49] Having completed this first round of chemical explorations of this interesting class of bioactive alkaloids, we are now in the phase of redirecting the total syntheses outlined above toward the preparation of "natural productlike" analogues as well as to a study of their biochemical and biological properties. The results of these investigations will be reported shortly.

Acknowledgment. Generous financial support by the Max-Planck-Society and the Merck Research Council is gratefully acknowledged. M.M.D. and B.S. thank the Alexander-von-Humboldt Foundation and the Fonds der Chemischen Industrie, respectively, for fellowships. We also thank Prof. N. Fusetani and Prof. S. Matsunaga, Tokyo, for kindly providing samples of the dictyodendrins and copies of the original spectra for comparison as well as Dr. R. Mynott and C. Wirtz for their invaluable help with the structure assignment of several intermediates.

Supporting Information Available: Full experimental details including analytical and spectroscopic data of all new products. This material is available free of charge via the Internet at http://pubs.acs.org.

JA0617800

(49) This notion is supported by several recent applications of the 9-MeO-9-BBN variant of the Suzuki reaction which were difficult or impossible to achieve under standard conditions; cf.: (a) Fürstner, A.; Turet, L. *Angew. Chem., Int. Ed.* **2005**, *44*, 3462. (b) Lepage, O.; Kattnig, E.; Fürstner, A. *J. Am. Chem. Soc.* **2004**, *126*, 15970. (c) Yuan, Y.; Men, H.; Lee, C. *J. Am. Chem. Soc.* **2004**, *126*, 14720. (d) Marshall, J. A.; Johns, B. A. *J. Org. Chem.* **1998**, *63*, 7885. (e) Mickel, S. J. et al., *Org. Process Res. Dev.* **2004**, *8*, 113−121.