of a variety of sluggishly reactive and/or sparsely soluble hypervalent iodine reagents in water under neutral conditions. Further studies on the application of this system are now in progress.

Experimental Section

Method A (for primary alcohols): PhI=O (0.44 mmol; Tokyo Chemical Industry Co., Ltd.) was added at room temperature to a stirred mixture of **1** (0.20 mmol) and KBr (0.04 mmol) in water (1.0 mL), and the mixture was stirred for 2 h. The resulting mixture was extracted with AcOEt, washed with brine, dried over Na_2SO_4, evaporated in vacuo, and the residue was purified by column chromatography (EtOAc/*n*-hexane) to give pure **2**. Intermolecular esterification through nucleophilic attack on the initially formed aldehyde also proceeds under the conditions of Method B.

Method B (for secondary alcohols): Water (2.0 mmol) was added dropwise to a stirred mixture of **1** (0.2 mmol), PhI=O (0.22 mmol), and KBr (0.2 mmol). The mixture was stirred or sonicated for several hours while checking the reaction progress by gas or thin-layer chromatography. After completion, *n*-hexane was added to the mixture, and then filtered. Evaporation of the solvent under vacuum afforded a crude product that was further purified by column chromatography (Et_2O/*n*-hexane) to give pure **2**.

Method C (for the oxidation with PSDIB): PSDIB (22 mmol), used without any pretreatment, was added at room temperature to a stirred suspension of **1** (20 mmol) and KBr (14 mmol) in water (40 mL), and the mixture was then sonicated for several hours. The resulting mixture was filtered and the residue containing **2** was washed with water to remove KBr, then extracted with *n*-hexane or MeOH, and the filtrate was evaporated to give **2**. The product was purified by column chromatography, when necessary.

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[14] PSDIB was prepared from polystyrene standard ($M_w = 44000$) (Aldrich) via poly(iodostyrene) (78% iodinated) following known procedures. Elemental analysis (C 45.86, H 3.93, I 37.41) revealed the resin loading to be 2.0 mmol g^{-1}, which indicated that 68% of the iodophenyl rings in the resin was converted into (diacetoxyiodo)-phenyl rings: Y. Yamada, M. Okawara, *Makromol. Chem.* **1972**, *152*, 153 – 162.

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[16] Intermolecular homoesterification mainly proceeds to give $Ph(CH_2)_3OCO(CH_2)_2Ph$ (51%) in the absence of $NaHCO_3$ (**2k**: 38%).

[17] Even after stirring PSDIB in water for 4 d, the addition of **1e** and KBr to this suspension gave **2e** in 68% yield.

[18] **2e** was obtained only in 8% yield, when the reaction was performed with PSDIB in CH_2Cl_2 (containing 4-Å molecular sieves) in the presence of 20 mol% NEt_4Br as a bromide ion source. However, addition of a catalytic amount of water to the above mentioned mixture enhanced the yield of **2e** to 51%.

Total Synthesis of (+)-Concanamycin F**

Ian Paterson,* Victoria A. Doughty, Malcolm D. McLeod, and Thomas Trieselmann

The concanamycin group of macrolides, first isolated from a culture of *Streptomyces diastatochromogenes* Sp. S45 by Kinashi and co-workers and typified by concanamycin A (**1**, Figure 1)[1a–d] and its aglycone, concanamycin F **2**),[1e,f] exhibit potent inhibition of vacuolar (H^+) ATPase activity.[2] The

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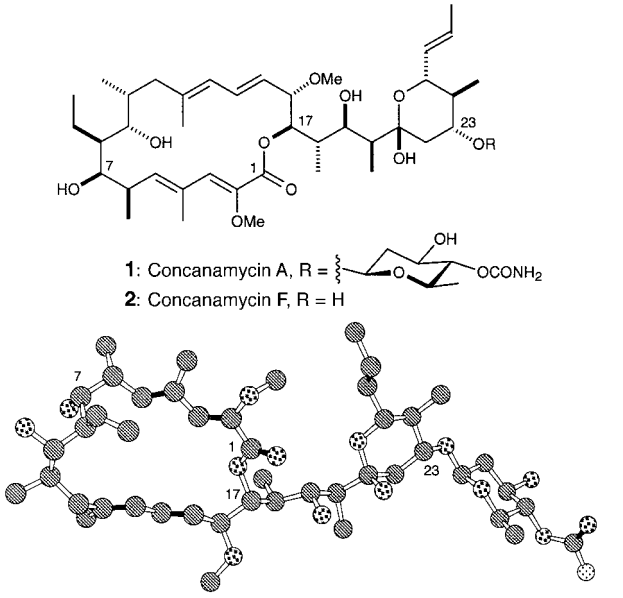
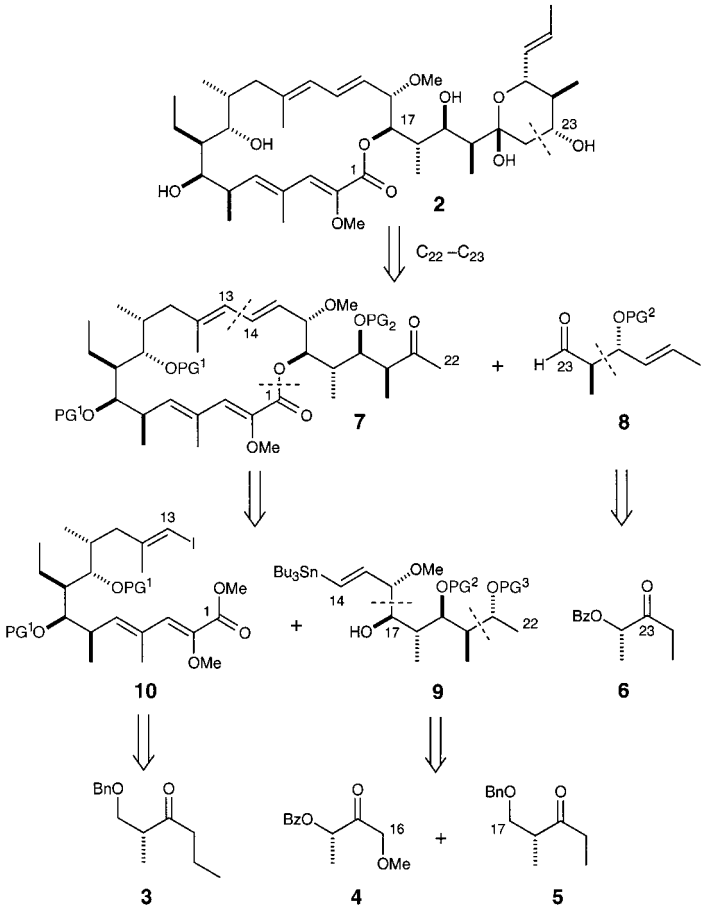


Figure 1. Structures of concanamycins A and F (concanolide A).

(ability of the concanamycins to disrupt cellular acidification leads to a diverse range of biological activity, including antiviral[3a] and immunosuppressant activity[3b] as well as the attenuation of resistance in MDR tumor cell lines.[3c] Recently, this general class of bioactive macrolides, which include the bafilomycins, has served as a template for the design of novel therapeutic agents for the treatment of osteoporosis by selectively targeting the proton ATPase responsible for bone resorption.[3d,e]

The concanamycins are characterized by a densely functionalized 18-membered macrolactone incorporating a polyoxygenated side chain at C_{17}. The side chain itself contains a six-membered hemiacetal which is both acid- and base-labile. The structural complexity of these macrolides and their significant biological activity have attracted considerable synthetic attention. A total synthesis of concanamycin F (**2**) has been described recently by the Toshima group,[4a,b] and syntheses of the simpler 16-membered macrolides bafilomycin A_1[5a–c] and hygrolidin[5d] have also been achieved. We now report an expedient, highly stereocontrolled synthesis[6] of concanamycin F (26 steps, 5.3% overall yield) by the application of *anti*-selective aldol reactions of chiral ketones **3**–**6** (Scheme 1) developed in our laboratory,[7] and by employing a $C_{22}-C_{23}$ coupling strategy for introducing the side chain. The careful selection of protecting groups proved imperative both for achieving macrocyclization and facilitating the use of mild deprotection conditions, thus enabling the survival of the sensitive side chain.

Central to our synthetic planning[6a, 8] was the late installation of the C_{17} side chain by the stereocontrolled aldol coupling of methyl ketone **7** with aldehyde **8**, thus affording a protected version of concanamycin F and potentially providing access to novel glycoside analogues. The majority of the stereochemistry and oxygenation in the two components selected for construction of the macrocyclic ketone **7**, that is the stannane **9** and the iodide **10**, would then be introduced using boron-mediated aldol reactions.[8] Previously, we had



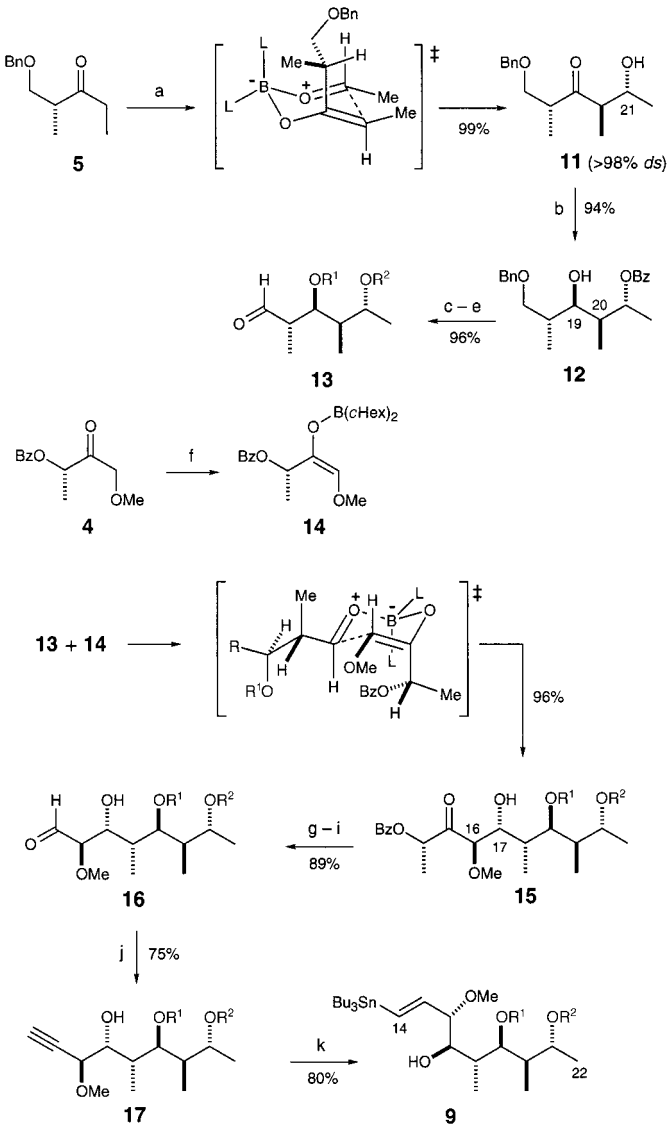
Scheme 1. Retrosynthetic analysis. Bn = benzyl, Bz = benzoyl, PG = protecting group.

shown that an *anti*-aldol reaction between ketone **3** and methacrolein and in situ reduction of the intermediate boron aldolate gave access to a key intermediate which was elaborated into iodide **10**.[6b]

A synthesis of the vinylstannane partner **9**, which contains six contiguous stereocenters, was now required. Achieving efficient macrocyclization (by lactonization or intramolecular sp^2-sp^2 coupling), followed by $C_{22}-C_{23}$ aldol coupling (**7** + **8**) and global deprotection, were identified as further critical issues for completion of the total synthesis.

The synthesis of the $C_{14}-C_{22}$ stannane subunit **9** (Scheme 2) started out with a $(c\text{Hex})_2\text{BCl}$-mediated boron aldol reaction[7a,b] of ethyl ketone **5** with acetaldehyde, which gave the *anti*-adduct **11** in 99% yield (>98% *ds*). The temporary introduction of the C_{21}-hydroxy group enabled access to the desired $C_{19}-C_{20}$ *syn* relationship by employing a 1,3-*anti* hydroxy-directed reduction. Thus, an Evans–Tishchenko reduction[9] of **11** (SmI_2, PhCHO) generated the ester **12** as the sole product (94%). A three-step sequence of: 1) silylation to generate the diethylisopropylsilyl (DEIPS) ether; 2) hydrogenolysis of the benzyl ether ($Pd(OH)_2$); and 3) Swern oxidation gave **13** in 96% overall yield.

The novel (*S*)-lactate-derived ketone **4**[10] was employed for the chain extension of **13** and introduction of the oxygen-bearing stereocenters at C_{16} and C_{17}. Enolization of **4** ($(c\text{Hex})_2\text{BCl}$, Et_3N, Et_2O) generated the (*E*)-enol borinate



Scheme 2. Synthesis of the $C_{14}-C_{22}$ subunit (**9**). a) $(c\text{Hex})_2BCl$, Et_3N, Et_2O, 0 °C, 2 h; MeCHO, Et_2O, $-78 \rightarrow -20$ °C, 16 h; H_2O_2, MeOH, pH 7 buffer, 0 °C, 1 h; b) PhCHO, SmI_2, THF, −10 °C, 1 h; c) DEIPSCl, imidazole, DMF, 20 °C, 16 h; d) $Pd(OH)_2$, H_2, 20 °C, 3 h; e) DMSO, $(COCl)_2$, CH_2Cl_2; Et_3N, $-78 \rightarrow 0$ °C, 30 min; f) $(c\text{Hex})_2BCl$, Et_3N, Et_2O, 0 °C, 3 h; **13**, Et_2O, $-78 \rightarrow -20$ °C, 16 h; H_2O_2, MeOH, pH 7 buffer, 0 °C, 1 h; g) $NaBH_4$, MeOH, 20 °C, 30 min; h) K_2CO_3, MeOH, 20 °C, 30 min; i) $Pb(OAc)_4$, Na_2CO_3, CH_2Cl_2, 20 °C, 10 min; j) $MeCOC(=N_2)PO(OMe)_2$, K_2CO_3, MeOH, 20 °C, 16 h; k) $[PdCl_2(PPh_3)_2]$, Bu_3SnH, CH_2Cl_2, 20 °C, 10 min. R^1 = DEIPS (≡ PG^2 in Scheme 1), R^2 = Bz (≡ PG^3 in scheme 1). *c*Hex = cyclohexyl, DEIPSCl = diethylisopropylsilyl chloride, DMSO = dimethyl sulfoxide.

14 which on addition to aldehyde **13** gave solely the *anti*-α-methoxy-β-hydroxy ketone **15** (96%), where the dominant enolate π-facial bias is matched with the (weak) Felkin–Anh preference of the aldehyde component.[7c] Compound **15** was then transformed into the β-hydroxy aldehyde **16** in 89% overall yield by: 1) ketone reduction ($NaBH_4$); 2) chemoselective hydrolysis (K_2CO_3, MeOH) of the benzoate proximate to the C_{15}-OH; and 3) glycol cleavage ($Pb(OAc)_4$).

Elaboration into the (*E*)-alkenylstannane **9** was then addressed. After obtaining unsatisfactory yields for Takai olefination[11] on this sensitive, highly oxygenated aldehyde, the desired transformation was achieved by using the Ohira–Bestmann alkynation protocol[12] (75%) and subsequent Pd-catalyzed *syn*-hydrostannation[13] of the terminal alkyne **17** to give **9** in 80% yield. This efficient 11-step sequence provided the $C_{14}-C_{22}$ subunit **9** in 46% yield with essentially complete control in the introduction of the six stereogenic centers.

At this point, it proved necessary to replace the cyclic silylene protection of the $C_{7,9}$-diol in the vinyl iodide **10** (Scheme 3) with the corresponding bis-triethylsilyl (TES) ether **18**. The $C_{13}-C_{14}$ coupling between stannane **9** and iodide **18** to give diene **19** was achieved in 89% yield under mild conditions (NMP, 20 °C, 1 h) using copper(I) thiophene-2-carboxylate (CuTC), a new Cu^I reagent introduced by Liebeskind et al.[14] to promote Stille-type coupling reactions in the absence of Pd catalysis.[15] Notably, this is the first application of this new procedure for the construction of the characteristic diene unit found in the concanamycins and bafilomycins.

Selective cleavage of the methyl ester in the presence of the benzoate was then performed by nucleophilic displacement with $KOSiMe_3$,[16] providing the secoacid derivative **20** (88%) in readiness for macrolactonization. Cyclization to the 18-membered macrolide **21** proceeded in 69% yield under modified Yamaguchi conditions ($2,4,6\text{-}Cl_3(C_6H_2)COCl$, Et_3N, 4-DMAP, PhMe).[17] The use of acyclic protecting groups was crucial to the success of this reaction.[18] We initially prepared the corresponding secoacid derivatives **20** ($R^1-R^1 = Si(t\text{Bu})_2$, R^2 = DEIPS or H, R^3 = Bz, R^4 = H)) with silylene protection of the $C_{7,9}$-diol, by a similar sequence from **10** itself. These protected derivatives could not be macrolactonized under Yamaguchi or other, more forcing, conditions, presumably due to their inability to access the required conformation. The 18-membered macrolactone could also be generated in 64% yield by an intramolecular Stille coupling performed on **22**,[18] which was obtained by hydrolysis of **18** (100%) and esterification of the derived acid **23** with **9** (67%). In contrast to the above intermolecular process, this cyclization succeeded under Pd catalysis,[19] as also shown by Toshima et al.,[5b] whereas attempted Cu^I catalysis with CuTC led to protodestannylation of **22**. Next, reductive cleavage of the benzoate in the presence of the lactone carbonyl group was achieved selectively by treatment of **21** with DIBAL, which after tetrapropylammonium perruthenate (TPAP) oxidation[20] of the resulting C_{21}-alcohol provided the macrocyclic methyl ketone **7** in 76% yield.

Introduction of the remainder of the concanamycin side chain was best achieved using a carefully optimized Mukaiyama aldol coupling,[21] which relied on Felkin–Anh induction from the aldehyde component **8** (prepared from ketone **6**[6a]). The preformed silyl enol ether from **7** (LiHMDS, Me_3SiCl, Et_3N) was combined in CH_2Cl_2 with aldehyde **8**, in the presence of CaH_2,[22] and treated with $BF_3 \cdot OEt_2$ at −100 °C for 5 min. This provided the required aldol adduct **24** as the sole isomer in 81% yield. Finally, successful removal of the silyl protecting groups necessitated stepwise treatment with TASF[23] to give the hemiacetal **25** (94%), followed by acidic hydrolysis (TsOH, aq. MeCN) of the remaining TES ethers.

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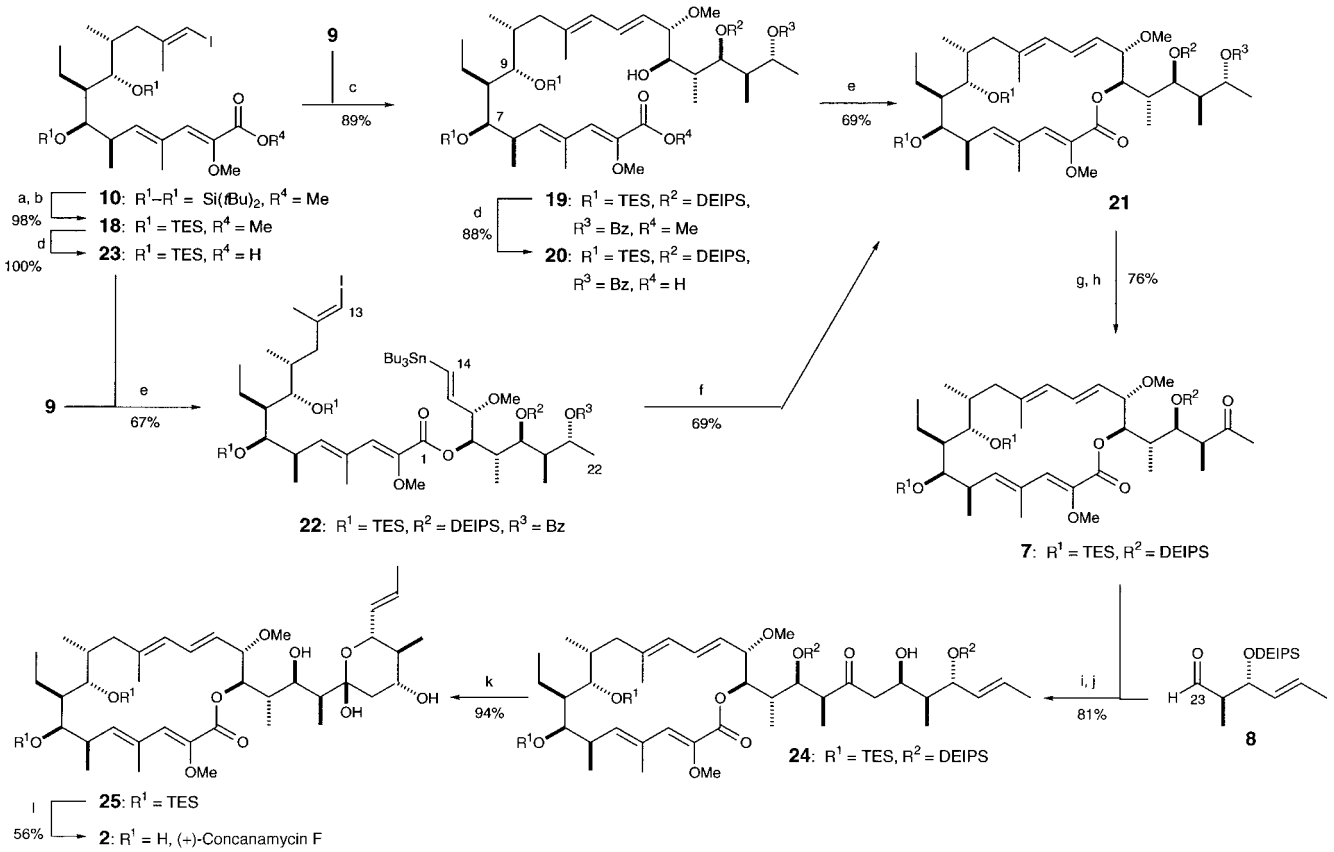

Scheme 3. Subunit coupling and total synthesis of (+)-concanamycin F (**2**). a) $HF \cdot Et_3N$, THF, 20 °C, 7 d; b) TESOTf, 2,6-lutidine, CH_2Cl_2, −78 → 0 °C, 10 min; c) CuTC, NMP, 20 °C, 1 h; d) KOTMS, Et_2O, 20 °C, 30 min; e) Et_3N, 2,4,6-$Cl_3(C_6H_2)COCl$, 4-DMAP, PhMe, 20 °C, 18 h; f) $[Pd_2(dba)_3]$, Ph_3As, iPr_2NEt, DMF, THF, 60 °C, 16 h; g) DIBAL, CH_2Cl_2, −78 °C, 1 min; h) TPAP, NMO, 4 Å mol. sieves, CH_2Cl_2, 20 °C, 2 h; i) Me_3SiCl, Et_3N, THF, −78 °C; LiHMDS, 10 min; j) $BF_3 \cdot OEt_2$, CaH_2, CH_2Cl_2, −100 °C, 5 min; k) TASF, DMF, 20 °C, 1 h; l) TsOH, MeCN, H_2O, 0 °C, 3 h. TESOTf = triethylsilyl triflate, CuTC = copper(I) thiophene-2-carboxylate, NMP = 1-methyl-2-pyrrolidinone, KOTMS = potassium trimethylsilanolate, 4-DMAP = 4-*N*,*N*-dimethylaminopyridine, dba = dibenzylideneacetone, DMF = *N*,*N*-dimethylformamide, DIBAL = diisobutylaluminum hydride, TPAP = tetrapropylammonium perruthenate, NMO = 4-methyl-morpholine-*N*-oxide, LiHMDS = lithium hexamethyldisilazide, TASF = tris(dimethylamino)sulfonium difluorotrimethylsilicate, TsOH = *para*-toluenesulfonic acid.

This gave a 56% yield of concanamycin F (**2**) ($[\alpha]_D^{20} = +10.6$ ($c = 0.32$, $CHCl_3$)), which had identical physical and spectroscopic data to material derived[1f] from concanamycin A ($[\alpha]_D^{20} = +11.0$ ($c = 0.3$, $CHCl_3$)).

In summary, we have completed an expedient synthesis of concanamycin F (26 steps longest linear sequence from **3** in 5.3% overall yield with >85% overall diastereoselectivity). This work demonstrates the power of substrate-based aldol stereocontrol using the ketone building blocks **3**–**6** and the utility of the Liebeskind Cu^I-promoted protocol for the Stille-type coupling of complex, polyoxygenated fragments (as in **9** + **18** → **19**). Moreover, the synthesis of novel concanamycin macrolides having modified biological activity should now be feasible.

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[22] The inclusion of CaH_2 as a drying agent was found to be essential. In its absence, the methyl ketone **7** was formed by adventitious hydrolysis with only low yields of adduct **24** isolated. The corresponding aldol reaction with the lithium enolate of **7** resulted in much poorer stereocontrol at C_{23} (ca. 3:1). For other related studies, see ref. [5c] and D. A. Evans, M. J. Dart, J. L. Duffy, M. G. Yang, *J. Am. Chem. Soc.* **1996**, *118*, 4322.

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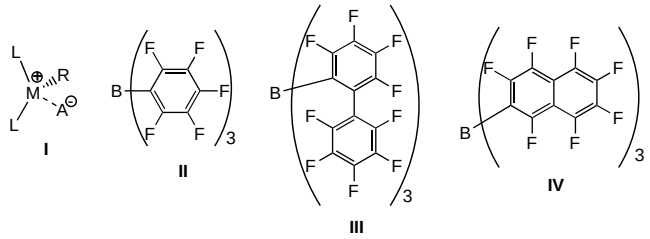
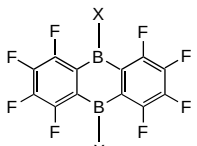
Organo-Lewis Acid Cocatalysts in Single-Site Olefin Polymerization—A Highly Acidic Perfluorodiboraanthracene**

Matthew V. Metz, David J. Schwartz, Charlotte L. Stern, Peter N. Nickias, and Tobin J. Marks*

For early transition metal single-site homogeneous olefin polymerization catalysts **I**[1], organo-Lewis acids such as alumoxanes and tris(perfluoroaryl)boranes (e.g., **II**–**IV**)[2] play a key role both in catalyst activation and in mechanistic understanding. For example, growing evidence indicates that the cation–anion pairing, as modulated by the steric and electronic characteristics of the cocatalyst/counter anion (A^- in **I**),[2, 3] can have a profound influence on polymerization and chain-transfer rates, enchainment stereochemistry, and catalyst stability.[2–4] With the goal of further modifying fluoroarylborane architecture to enhance Lewis acidity (multiple electron-deficient centers, conjugative negative-charge



I **II** **III** **IV**



Va X = Cl
Vb X = C_6F_5

delocalization, open structure), we focused on the perfluorodiboraanthracene skeleton **V**,[5] for which calculations at the B3LYP/6-31++G** level indicate **Vb** to have about 10 kcal mol^{-1} greater affinity for CH_3^- than does $B(C_6F_5)_3$.[6] We communicate here the synthesis, characterization, and unusual properties of **Vb**, including significantly enhanced Lewis acidity and cocatalytic olefin polymerization activity.[7]

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