with sterically demanding *tert*-butyl and neopentyl substituents crystallize readily (type A).

Another property listed in Tables 1 and 2 is the very intense photoluminescence exhibited by some of the dyes in the solid state. This finding was surprising to us as solutions of **3**–**6** do not fluoresce. For many fluorophores the opposite behavior is typical, that is despite intensive fluorescence in solution, radiationless deactivation takes place in the crystalline state. Evidently, these properties are also influenced considerably by packing effects, which have a decisive influence on the relaxation paths for the excitation energy. Many of the nonluminescent dyes listed in Table 1 are planar molecules whose bronze or green colors in the solid state indicate strong $\pi-\pi$ interactions in the crystal. The dyes with sterically demanding substituents, on the other hand, form red crystals that shine intensively in numerous cases.[15, 16]

The dye library obtained through a highly efficient multicomponent synthesis led us to colorants with glass-forming and solid-state photoluminescent properties. Sterically demanding substituents proved crucial to both properties by determining the packing of the functional π systems, thus paving the way for the exploitation of these interesting dyes in new materials.

Experimental Section

Typical procedure for the synthesis of the merocyanine dyes **3** and **4**: A thiazole **8** (0.05 mol) or a methylene base **9** (0.05 mol), respectively, a hydroxypyridone **7** (0.05 mol), and dimethylformamide (0.075 mol, 5.5 g) were heated to 90 °C in acetic anhydride (20–30 mL) for about 3 h. The solid which precipitated upon cooling to room temperature was filtered off, washed thoroughly with 2-propanol and/or aqueous ethanol until the color of the filtrate changed from violet to red, and subsequently dried in a vacuum-drying cabinet at 50 °C.

For the physical characterization, the dyes were recrystallized from acetic anhydride, toluene, or toluene/hexane mixtures.

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[11] In numerous reactions, starting materials with purities (NMR, GC) $<80\,\%$ were used and nevertheless very good yields were obtained and pure products isolated. Difficulties were encountered with the most readily soluble dyes when these did not crystallize from the reaction mixtures in the presence of solubility-promoting impurities or when greater amounts of 2-propanol, which became necessary in the washing procedure, led to losses in yield.
[12] Because of the high influence of the purity on the investigated properties (see Tables 1 and 2), the dyes were recrystallized once more.
[13] H. K. Cammenga, M. Epple, *Angew. Chem.* **1995**, *107*, 1284–1301, *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 1171.
[14] Although the glassy state is regarded as a typical feature of polymeric substances, great progress was recently achieved by using low molecular weight organic glasses in the development of photoconductive and electroluminescent materials: a) K.-Y. Law, *Chem. Rev.* **1993**, *93*, 449–486; b) J. Salbeck, *Ber. Bunsen-Ges. Phys. Chem.* **1996**, *100*, 1667–1677.
[15] Compounds of the structural types **4**–**6** also show intensive luminescence in solid solutions, that is in textile dyeing on polyester. A detailed discussion of the competition between radiationless deactivation and photoluminescence, which is evidently strongly dependent on the rigidity of the matrix, should become possible based on the emission spectra of solid samples and dyed textile fibers as well as on crystal structure analyses.
[16] As extremely small concentrations of impurities already function as traps in the solid state, the data given in Tables 1 and 2 should not be overinterpreted. Especially the substances marked (+) could show better emission properties given a higher purity.

Total Synthesis of (−)-Bafilomycin A_1: Application of Diastereoselective Crotylboration and Methyl Ketone Aldol Reactions**

Karl A. Scheidt, Akihiro Tasaka, Thomas D. Bannister, Michael D. Wendt, and William R. Roush*

Bafilomycin A_1 (**1**), a member of the hygrolide family of macrolide antibiotics that includes the concanamycins[1] and the hygrolidins,[2] is a potent vacuolar ATPase inhibitor that displays broad antibiotic activity.[3] First isolated in 1983 by Werner et al. from a culture of *Streptomyces griseus* sp. *sulphurus*,[4] the stereochemistry of the bafilomycins was proposed based on NMR data[5] and was subsequently verified

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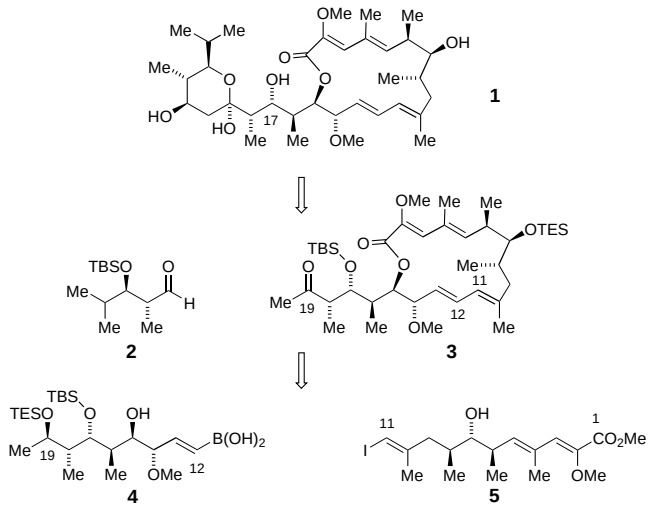
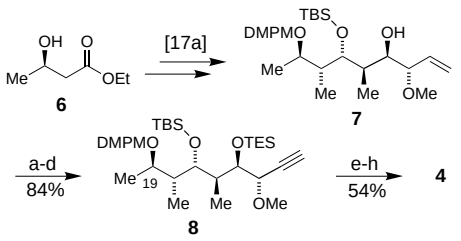
in the case of **1** by X-ray crystallography.[6] Bafilomycin A_1 contains two distinct structural features characteristic of the hygrolide macrolides: a sensitive 6-membered hemiketal that participates in a hydrogen bond network (between the C17 hydroxyl group and the carbonyl group of the 16-membered lactone) and the C2–C5 diene system that incorporates a C2 methyl enol ether. The important biological properties and interesting structural features of these molecules have stimulated considerable interest. Total syntheses of bafilomycin A_1 have been recorded by Evans and Calter[7] and Toshima et al.,[8] and syntheses of concanamycin F and hygrolidin have been accomplished by Toshima et al.[8] and Yonemitsu et al.,[9] respectively. In this communication we report a highly convergent synthesis of bafilomycin A_1 (**1**) following the strategy summarized in Scheme 1.



Scheme 1. Retrosynthetic analysis of bafilomycin A_1 (**1**). (see reference [10] for abbreviations).

We envisioned that bafilomycin could be assembled from three key fragments: the known aldehyde **2**,[11] vinylboronic acid **4**, and the vinyl iodide **5**, which in turn would be constructed utilizing highly diastereoselective aldehyde crotylboration reactions developed in our laboratory.[12] This highly convergent approach would allow for the use of a Suzuki cross-coupling reaction[13] to generate an appropriately protected macrocyclization precursor. While the Stille reaction[14] has found great utility in the assembly of natural products, including in the earlier bafilomycin syntheses,[7, 8] there are limited applications of the Suzuki reaction for late-stage union of complex intermediates, the most notable of the limited examples being recorded in the palytoxin synthesis by Kishi et al.[15] and the rutamycin synthesis by Evans et al.[16] The aldol reaction between **2** and **3**, which serves as the final C–C bond forming event in the synthesis, provides an additional opportunity to explore the factors that control the stereochemistry of fragment assembly in methyl ketone aldol reactions.[17]

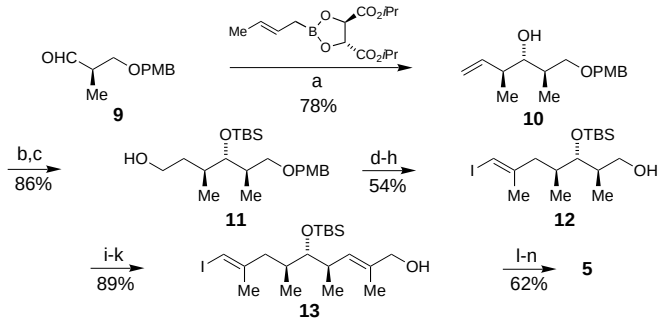
The vinylboronic acid **4** was prepared from olefin **7**, which was synthesized from commercially available ester **6** by the previously described diastereoselective allylmetalation sequence (Scheme 2).[17a] The presence of the free hydroxyl



Scheme 2. Synthesis of the C12–C20 fragment **4**. a) TES-OTf, 2,6-lutidine, CH_2Cl_2, $-50\,^\circ C$, 1 h, 99%; b) OsO_4, NMO, THF, pH 7 buffer, 16 h; c) $Pb(OAc)_4$, EtOAc, $0\,^\circ C$, 10 min; d) $(MeO)_2P(O)CHN_2$, *t*BuOK, THF, $-78\,^\circ C \rightarrow RT$, 15 min, 85% (three steps); e) DDQ, CH_2Cl_2, pH 7 buffer, $0\,^\circ C$, 25 min, 94%; f) TFA, THF, H_2O, $0\,^\circ C$, 2.5 h, 88%; g) TES-Cl, CH_2Cl_2, pyridine, $-40\,^\circ C \rightarrow RT$, 10 h, 92%; h) catecholborane, 8 mol% 9-BBN, THF, $60\,^\circ C$, 4 h, then pH 7 buffer, RT, 1 h, 71%. (See reference [10] for abbreviations.)

group in **7** prevented direct elaboration of the olefin to the vinylboronic acid unit of **4**. In addition, removal of the DMPM ether in the presence of the C10–C13 diene at later stages of the synthesis proved to be problematic. Therefore, the hydroxyl group of **7** was protected as a TES ether, the terminal olefin was then cleaved oxidatively, and the resulting aldehyde was elaborated to acetylene **8** in 84% overall yield with the Seyferth–Gilbert reagent.[18] The DMPM and TES ethers were removed by sequential exposure of **8** to DDQ (94%) and TFA (88%), then the less hindered C19 hydroxyl group was protected as a TES ether (92%). Finally, treatment of the resulting alkynol with catecholborane and a catalytic amount of 9-BBN[19] produced the vinylboronic acid **4** after aqueous workup (71% yield).

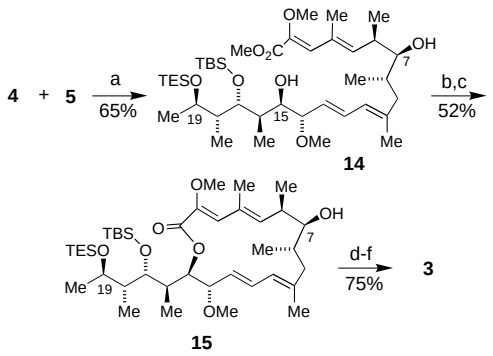
The vinyl iodide **5** was synthesized starting from the known aldehyde **9** (Scheme 3).[20] Installation of the difficult *anti*–*anti* stereotriad[21] was accomplished by our diastereoselective aldehyde crotylboration methodology[12] in the mismatched manifold.[22] Thus, the reaction of **9** and (*R*,*R*)-diisopropyl tartrate (*E*)-crotylboronate provided an 85:15 mixture of **10** and the undesired 3,4-*anti*-4,5-*syn* diastereomer (78% yield of



Scheme 3. Synthesis of the C1–C11 fragment **5**. a) Toluene, $-78\,^\circ C$, 8 h, 78%; b) TBS-OTf, 2,6-lutidine, CH_2Cl_2, $-50\,^\circ C$, 30 min, 99%; c) catecholborane, $(Ph_3P)_3RhCl$, THF, $-5\,^\circ C$, 30 min, then MeOH, 1N NaOH, H_2O_2, RT, 2 h, 87%; d) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, $-78 \rightarrow 0\,^\circ C$, 30 min, 99%; e) CBr_4, PPh_3, CH_2Cl_2, 30 min, 89%; f) *n*BuLi, THF, $-78 \rightarrow 0\,^\circ C$, 15 min, 99%; g) DDQ, CH_2Cl_2, pH 7 buffer, $0\,^\circ C$, 20 min, 96%; h) Cp_2ZrCl_2, $AlMe_3$, $Cl(CH_2)_2Cl$, $60\,^\circ C$, 14 h, then I_2 at $-30\,^\circ C$, 1 h, 65%; i) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, $-78 \rightarrow 0\,^\circ C$, 30 min; j) $Ph_3PCH(Me)CO_2Et$, toluene, $60\,^\circ C$, 15 h, 90% (two steps); k) DIBAL-H, THF, $-78\,^\circ C$, 3.5 h, 99%; l) MnO_2, CH_2Cl_2, RT, 18 h, 99%; m) KHDMS, THF, $(i\mathrm{PrO})_2P(O)CH(OMe)CO_2Me$, [18]crown-6, $0\,^\circ C \rightarrow RT$, 8 h, 85%; n) TBAF, THF, RT, 2 h, 82%. (See reference [10] for abbreviations.)

10). Alcohol **10** was protected as the TBS ether (99%) and then was converted into the primary alcohol **11** (87%) through a Rh^I-catalyzed hydroboration with catecholborane.[23] Oxidation of **11** by the standard Moffatt–Swern[24] protocol provided the corresponding aldehyde that was transformed to the alkyne through the Corey–Fuchs protocol (89%).[25] The PMB group was removed with DDQ (96%), and then the alkynol intermediate was converted into vinyl iodide **12** using Negishi's carbozirconation methodology (65%).[26] The yield of **12** for this five step sequence was 54% (attempts to perform the Negishi carbometalation sequence before the PMB group was removed were largely unsuccessful). The vinyl iodide **12** was elaborated to the allylic alcohol **13** in 89% yield by a sequence of Moffatt–Swern oxidation,[24] stabilized Wittig olefination, and DIBAL-H reduction. This intermediate was oxidized to the enal by MnO_2 (99%), then the dienoate unit of **5** was introduced with greater than 95:5 (*Z*,*E*:*E*,*E*) selectivity through a Horner-Wadsworth-Emmons reaction with $(i\text{PrO})_2\text{P(O)CH(OMe)-CO}_2\text{Me}$ (85%).[27] Finally, removal of the TBS group with TBAF provided **5** (82%).

With **4** and **5** in hand, the C11–C12 bond of **14** was generated in 65% yield using Kishi's modification of the Suzuki cross-coupling reaction (Scheme 4).[28] Hydrolysis of the methyl ester and treatment of the unpurified seco acid

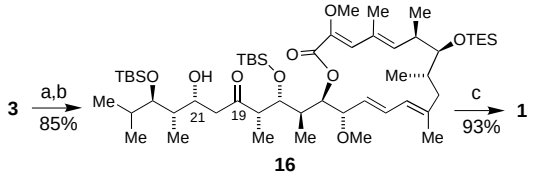


Scheme 4. Fragment assembly and synthesis of methyl ketone **3**. a) 1.0 equiv of **4** and **5**, 20 mol% $Pd(PPh_3)_4$, aq TlOH, THF, RT, 30 min, 65%; b) 1N KOH, dioxane, 80 °C, 1.5 h; c) 2,4,6-trichlorobenzoyl chloride, $i\text{Pr}_2\text{EtN}$, THF, then DMAP, toluene, reflux, 24 h, 52% (two steps); d) TES-OTf, 2,6-lutidine, CH_2Cl_2, −50 °C, 20 min, 85%; e) TFA, THF, H_2O, 5 °C, 6 h, 90%; f) Dess–Martin reagent, pyridine, CH_2Cl_2, 0 °C, 4 h, 98%. (See reference [10] for abbreviations.)

with 2,4,6-trichlorobenzoyl chloride and $i\text{Pr}_2\text{NEt}$ in THF formed the mixed anhydride; the THF was then replaced with toluene, DMAP added, and the reaction mixture heated at reflux for 24 h. This provided macrolactone **15** in 52% yield.[29] The hindered C7 hydroxyl group of **15** was protected as a TES ether (85%), then the C19 hydroxyl group was selectively deprotected (90%) and oxidized to methyl ketone **3** in 98% yield by using the Dess–Martin reagent.[30]

Very poor yields of the macrolactone were obtained when the macrolactonization was attempted on seco acids with the C7-OH group protected as TBS or TES ethers. We speculated that a silyl group on the axial C7-OH group might experience serious nonbonded interactions with the equatorial C6 and C8 methyl groups in the pre-cyclization conformation,[31] however comparable problems were not noted in the earlier bafilomycin[8] and hygrolidin[9] syntheses. Unfortunately, the attempted cyclization of a triol with the C7, C15, and C19 alcohols unprotected provided a 20-membered lactone preferentially. Moreover, attempted oxidation of the C19-hydroxyl group of macrocyclic intermediates containing an unprotected C7-OH group led to the preferential oxidation of the latter group.[32] These factors dictated the careful orchestration of protecting groups for the C7, C15, and C19 hydroxyl groups of intermediates **14**, **15**, and **3**.[33]

The completion of the synthesis required that we perform a stereoselective aldol reaction between aldehyde **2** and the methyl ketone unit of **3**. Previous studies of methyl ketone aldol reactions have revealed that the stereoselectivity is highly dependent on the metal enolate and the β-hydroxy protecting group of the aldehyde.[17a–c] In particular, a β-silyl ether in the aldehyde component leads to diminished Felkin selectivity with metal enolates. Studies by Evans et al.[11] and Paterson et al.,[34] as well as unpublished work from our laboratory,[35] demonstrated that aldehydes such as **2** undergo highly Felkin-selective aldol reactions under Mukaiyama conditions.[36] Accordingly, methyl ketone **3** was treated with a premixed solution of TMSCl and Et_3N (1:1) at −78 °C followed by LiHMDS to generate the TMS enol ether (Scheme 5).[37] Exposure of a mixture of the crude enol silane



Scheme 5. Synthesis of bafilomycin A_1. a) TMS-Cl, Et_3N, LiHMDS, CH_2Cl_2, −78 °C, 30 min; b) **2**, $BF_3\cdot OEt_2$, −78 °C, 30 min, 85%; c) TAS-F, DMF, H_2O, RT, 4 h, 93%. (See reference [10] for abbreviations.)

and aldehyde **2** in CH_2Cl_2 to $BF_3\cdot OEt_2$ for 30 min at −78 °C provided a >95:5 mixture of aldol products favoring **16** (69%; 85% based on recovered **3**). Finally, deprotection of aldol **16** with TAS-F[38] in wet DMF provided synthetic bafilomycin A_1 (**1**) that was identified by comparison with a sample of natural bafilomycin A_1 (^1H, ^{13}C NMR, and IR spectroscopy, optical rotation, and TLC mobility in several solvent systems). Use of TAS-F for this final deprotection[38b] thus solves a problem that has complicated earlier efforts in this area.[7–9]

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Keywords: aldol reactions · asymmetric synthesis · bafilomycin · total synthesis

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[10] Abbreviations: 9-BBN = 9-borabicyclo[3.3.1]nonane; DDQ = 2,3-dichloro-5,6-dicyanoquinone; DIBAL-H = diisobutylaluminum hydride; DMAP = 4-dimethylaminopyridine; DMPM = 3,4-dimethoxybenzyl; DMS = dimethyl sulfide; DMSO = dimethyl sulfoxide; HMDS = hexamethyldisilazane; NMO = 4-methylmorpholine *N*-oxide; PMB = *para*-methoxybenzyl; TAS-F = tris(dimethylamino)sulfonium difluorotrimethylsilicate; TBAF = tetrabutylammonium fluoride; TBS = *tert*-butyldimethylsilyl; TES = triethylsilyl; TFA = trifluoroacetic acid; TMS = trimethylsilyl.
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Selective Hydrovinylation of Styrene in a Membrane Reactor: Use of Carbosilane Dendrimers with Hemilabile P,O Ligands**

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Despite the numerous advantages of homogeneous catalysis, a major drawback remains in the need for efficient catalyst recovery. For many catalytic applications seen today, the finding of an elegant and convenient solution to this problem had been crucial for their commercialization. Catalyst recovery also becomes increasingly important in fine chemicals production when sophisticated ligands are used, whose cost often exceeds that of the noble metal used.

The use of dendritic materials is currently generating enormous attention in a number of areas in science and

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