Mild Aryl Ether Formation in the Semisynthesis of the Novel Macrolide Immunosuppressant L-732,531

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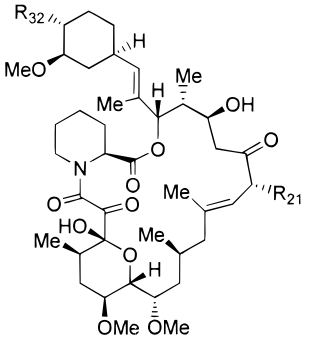
Received March 10, 1998

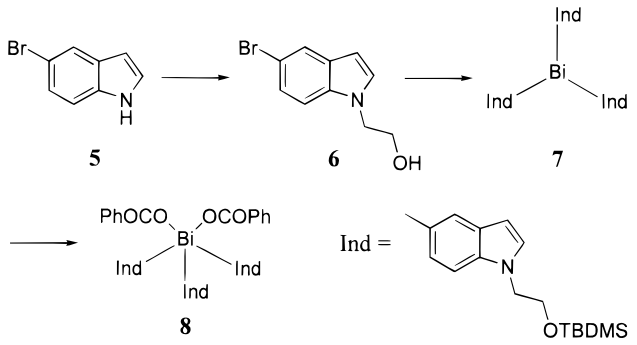
The macrolide FK-506 (**1**) which was first isolated and characterized at Fujisawa in 1987[1] has elicited great interest among medicinal chemists.[2] In an effort to reduce undesired side effects associated with the clinical use of FK-506,[3] many derivatives of FK-506 have been prepared and evaluated.[4] Recently, we needed a large quantity of arylated macrolide **3**, which has demonstrated a particularly promising biological profile.



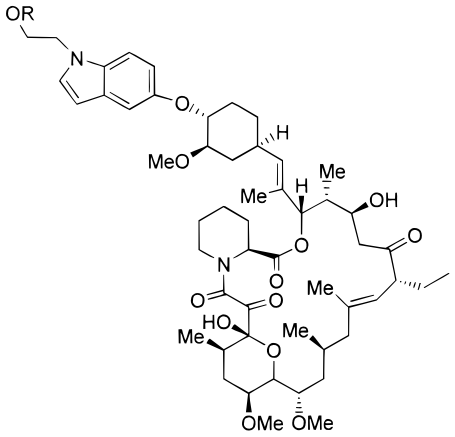
	R_{21}	R_{32}
1 FK-506	allyl	OH
2 Ascomycin	ethyl	OH
3 L-732,531	ethyl	[1-(2-hydroxyethyl-1*H*-indol-5-yl)oxy]

Few methods have been identified that allow the preparation of highly functionalized aryl alkyl ethers under mild conditions. A copper-mediated arylation of alcohols using pentavalent organobismuth reagents has been described for relatively simple substrates.[5] These reactions showed an unexpected and synthetically useful regioselectivity in the arylation of 1,2-diols.[6] Recently, this chemistry was used at Merck to prepare various O-32 arylated derivatives of ascomycin (FK-520; **2**).[7] This paper describes a practical synthesis of bismuthane **8** as well as its coupling with the macrolide alcohol **2** to yield the interesting immunosuppressant **3** after deprotection.

Scheme 1



A *tert*-butyldimethylsilyl protecting group was found to provide the optimal balance between ease of introduction in bismuthane **7** and ease of removal from the sensitive macrolide **14**. A two-step preparation of **7** starting from 5-bromoindole (**5**) was targeted to proceed via **6** (Scheme 1), a compound known to be crystalline.[8] Temporary protection of 2-bromoethanol (**9**) was achieved by adding an equimolar amount of 2-methoxypropene (**10**). Presumably, residual HBr in **9** catalyzed this exothermic reaction (Scheme 2). According to ^{13}C NMR a statistical mixture of **11**/**12**/**13** (2/1/1 ratio, respectively) was obtained in quantitative yield. The use of a mixture is inconsequential since the corresponding alkylated products will be hydrolyzed to a single product following



	R
14	TBDMS
3	H

(1) (a) Kino, T.; Hatanaka, H.; Hashimoto, M.; Nishiyama, M.; Goto, T.; Okuhara, M.; Koshaka, M.; Aoki, H.; Iminaka, H. *J. Antibiot.* **1987**, *40*, 1249−1255. (b) Kino, T.; Hatanaka, H.; Miyata, S.; Inamura, N.; Nishiyama, M.; Yajima, T.; Goto, T.; Okuhara, M.; Koshaka, M.; Aoki, H.; Ochiai, T. *J. Antibiot.* **1987**, *40*, 1256−1265. (c) Tanaka, H.; Kuroda, A.; Murasawa, H.; Hatanaka, H.; Kino, T.; Goto, T.; Hashimoto, M.; Taga, T. *J. Am. Chem. Soc.* **1987**, *109*, 5031−5033.

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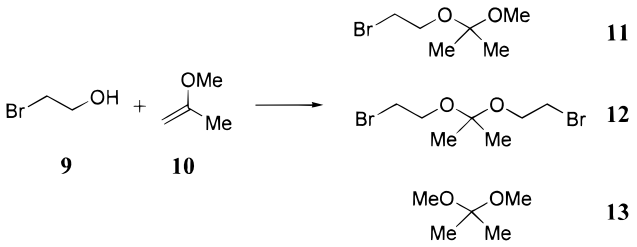
(6) (a) David, S.; Thieffry, A. *Tetrahedron Lett.* **1981**, *22*, 5063−5066. (b) David, S.; Thieffry, A. *J. Org. Chem.* **1983**, *48*, 441−447. (c) Barton, D. H. R.; Finet, J.-P.; Pichon, C. *J. Chem. Soc. Chem. Commun.* **1986**, 65−66.

(7) (a) Sinclair, P. J.; Wong, F.; Wyvratt, M.; Staruch, M. J.; Dumont, F. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 1035−1038. (b) Sinclair, P. J.; Wong, F.; Staruch, M. J.; Wiederrecht, G.; Parsons, W. H.; Dumont, F.; Wyvratt, M. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 2193-2196.

(8) We thank Dr. P. J. Sinclair of these laboratories for this observation. The corresponding TBDMS ether is *not* a crystalline compound.

S0022-3263(98)00451-4 CCC: $15.00
Published on Web 08/22/1998

Scheme 2



indole alkylation without isolation. Often sodium hydride in DMF is used for deprotonation. However, these conditions are considered a safety hazard on large scale.[9] Therefore, the more practical powdered potassium hydroxide[10] was used as the base for the alkylation in a solution of DMSO in THF. Only 10 vol % of DMSO was found to suffice to ensure regioselective N vs C-3 alkylation of **5**. Upon completion of the alkylation, water was added to the reaction mixture. The salt load effected a phase separation between a THF layer containing the product and a solution of DMSO in water. Treatment of the THF solution of crude alkylated products with aqueous acid followed by workup and crystallization yielded the crystalline **6** (84% overall isolated yield from **5**). A one-pot silylation, halogen−metal exchange, and quench with bismuth(III) chloride was developed for the conversion of **6** to **7**. Treatment of **6** under standard silylating conditions in THF (TBDMSCl, Et_3N, DMAP) led to complete conversion to the corresponding silyl ether. The crystalline triethylamine hydrochloride was filtered under nitrogen, and the resulting clear THF solution was directly used for halogen−metal exchange with *n*-butyllithium between −75 and −70 °C.[11] The resulting indolyllithium derivative was then directly quenched with a solution of $BiCl_3$ in THF yielding **7** in 80% yield after crystallization.

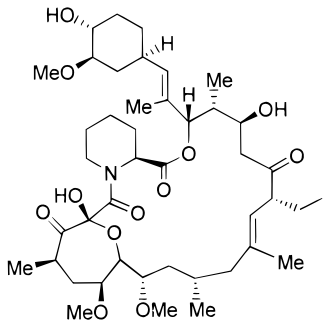
Various protocols were evaluated for the conversion of **7** to a pentavalent bismuthane required for coupling with **2**. Most literature methods were deemed inefficient since they require the isolation of intermediates.[12] After evaluating various more direct protocols, oxidation of **7** with an equimolar quantity of benzoyl peroxide (a stable and safe crystalline peroxide) was selected as the best method.[13] The procedure yielded **8** in excellent yields. Although **8** could be isolated as a crystalline solid, direct use for the arylation reaction in the same pot was preferred. In such a direct protocol benzoyl peroxide was slightly undercharged with respect to **7** (0.95 mol equiv) in order to minimize the formation of an analogue of **8** in which one of the indole ligands had been benzoyloxygenated, presumably at the 3′ position.[14]

Table 1. Solvent Effects in the Reaction of 2 with 8[a]

entry	solvent[b]	equiv of **8**	**2** in %	**14** in %	**15** in %
1	MeOH	1.25	86	<1	ND
2	NMP	1.26	95	ND	ND
3	IPA	1.22	87	8	ND
4	MeCN	1.14	79	17	<1
5	EtOAc	1.06	45	53	2
6	MTBE	1.23	37	57	4
7	DMF	1.24	62	57	8
8	$MeNO_2$	1.29	22	62	6
9	DCM	1.18	16	70	5
10	THF	1.24	36	72	2
11	acetone	1.25	20	78	5
12	toluene	1.21	12	80	7
13	MEK	1.11	17	78	5
14	MEK	1.26	9	83	8
15	MEK	1.47	3	86	12
16	MEK	1.80	1	80	21

[a] All reactions were run using isolated **8** at rt under ambient atmosphere for 16 h in the presence of 0.2−0.3 equiv of $Cu(OAc)_2$ using dodecahydrotriphenylene as an internal standard. Yields were determined by HPLC (ND = not detected). [b] All solvents were used as commercially obtained without further purification and/or drying. The following less common abbreviations are used: NMP, *N*-methyl-2-pyrrolidinone; IPA, 2-propanol; MTBE, methyl *tert*-butyl ether; DCM, dichloromethane; MEK, 2-butanone.

Analysis of ascomycin (**2**) and its reaction products was quite complicated due to the fact that (in analogy to FK-506) this compound has been demonstrated to form a mixture of a major (with structure **2**) and two minor tautomers (one of which has been identified as **4**) in



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solution. Each of these isomers can exist in cis and trans amide rotamers due to restricted rotation around the N7−C8 bond (rotamers not only obscure NMR spectra but also necessitate HPLC analysis at 55 °C at which temperature they convert to a single species).[15,16] The ascomycin available to us typically contained upon dissolution **2**, **4**, and the third unidentified tautomer in a ratio of 95/4/1. An additional complicating factor is the fact that **2**, obtained via fermentation from *Streptomyces hygroscopicus* va. *ascomyceticus*, is contaminated with a lower and a higher methylene homologue (**2**; R_{21} = methyl and 1-propyl, respectively) which are typically present at <1% each. As expected, any reaction of this mixture of starting materials will give a corresponding mixture of products. To simplify the following discussion our starting material is presented as consisting solely of **2**.

The key coupling step between **2** and pentavalent organobismuth **8** catalyzed by copper salts gave numer-

(9) DeWall, G. *Chem. Eng. News* **1982**, *60(37)*, 5, 43.

(10) Milling of potassium hydroxide pellets to a fine powder can easily be achieved on small scale using a Waring blender.

(11) The intermediate indolyllithium derivative was found to be rather unstable under the reaction conditions mandating that the halogen metal exchange be performed as fast as possible at the lowest possible temperature. Efficient heat transfer during this exothermic addition posed particular challenges on the larger scale (up to 12 kg of **6** have been prepared using this procedure) which lowered the yield for this step by 10−15%.

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(13) (a) Challenger, F.; Wilson, V. K.; *J. Chem. Soc.* **1927**, 209−213. (b) After completion of this work catalysis of the oxidative addition of benzoyl peroxide was reported: Arnauld, T.; Barton, D. H. R.; Doris, E. *Tetrahedron Lett.* **1997**, *38*, 365−366.

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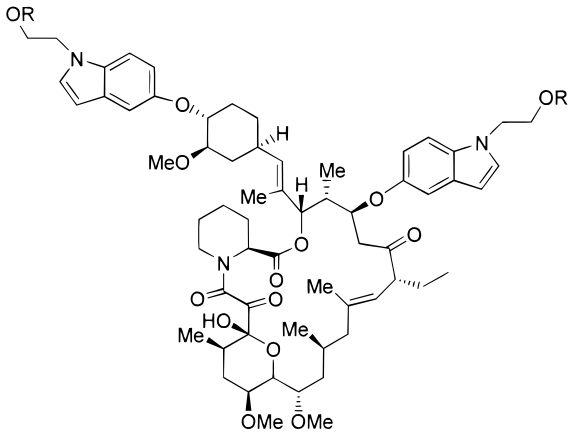
(16) Gailliot, F. P.; Natishan, T. K.; Ballard, J. M.; Reamer, R. A.; Kuczynski, D.; McManemin, G. J.; Egan, R. S.; Buckland, B. C. *J. Antibiot.* **1994**, *47*, 806−11.

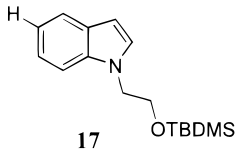
ous reaction products according to TLC and HPLC analysis. The major products of the catalyzed reaction are the desired **14**, accompanied by "bis-indolyzed" **15**,[17] benzoic acid, and indole derivatives **17** and **18**.[18] Several



R

15 TBDMS

16 H



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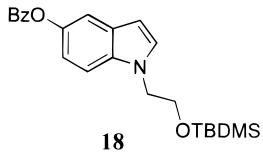

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reaction parameters were optimized to achieve the best yield with respect to the macrocycle. Table 1 shows some solvent effects on the coupling reaction in the presence of a catalytic amount of $Cu(OAc)_2$. The conversion of **2** with 1.1−1.3 equiv of the pentavalent organobismuth was incomplete in all solvents examined. Not surprisingly, in methanol none of the desired product was formed and **2** was largely recovered (entry 1). However, in the more hindered 2-propanol (present in 300-fold molar excess relative to **2**) 8% of **14** was formed (entry 3)! This result is a reflection of the activating role in the arylation by the neighboring methoxy group.[2] The data in Table 1 show little correlation between the nature of the solvent and the reaction yield. The best solvent examined was 2-butanone (methyl ethyl ketone, MEK). Attempts to drive the reaction to completion in this solvent by adding a larger excess of **8** resulted in formation of more **15** with an optimum yield for **14** at 1.4−1.5 equiv.

The effect of the catalyst was also investigated. As was observed by the pioneers in this field[19] virtually all copper(I) and copper(II) salts effect the reaction albeit with a marginally different efficiency. The less soluble CuO and Cu_2O as well as Cu powder itself show an initiation period before the reaction starts. Some other salts known to engage in what is presumably a one-electron-transfer reaction were tested with $CoCl_2$ being marginally effective while $FeCl_3$ was completely ineffective. On the basis of all data, 2-butanone and cupric acetate were selected as the best solvent and catalyst, respectively. It was found that the amount of the catalyst did not significantly effect the yield although at <10 mol % the reaction became markedly slower. Typically, 15−20 mol % relative to **2** are used in the reaction. The presence of limited amounts of water or an ambient atmosphere does not adversely effect the reaction, thus obviating scrupulous drying of solvent, substrate **2**, and catalyst. On the basis of these considerations, an optimum protocol was developed for large scale synthesis of **3**. Under the optimized conditions, the reaction is completed in about 8 h at 20−25 °C and affords the desired **14** in 80−90% assay yield. The product can be isolated from the crude reaction mixture by silica gel flash chromatography.[20] The separation of **14** from the slightly less polar **15** is difficult to achieve in this manner in a variety of solvent systems, thus substantially lowering the isolated yield for pure **14** (as compared to the crude assay yields). However, it was found that upon desilylation, the resulting **3** and the more polar **16** were more readily separated. Therefore, chromatography of the crude coupling reaction mixture over a short silica gel column was only used to effect separation of the **14**/**15** mixture from the bulk of less polar impurities (mainly **17** and **18**) and the more polar unconverted **2**.[21] The resulting partially purified mixture of **14** and **15** was then directly used in the deprotection step.

In an effort to gain better understanding of this coupling reaction the structures of several side products were elucidated, and attempts were made to close the various mass balances. A balance for the indole ligands of **7** in the optimum protocol indicated that only 25 mol % of these ligands are coupled with the macrocycle (yielding **14** and **15**); approximately 70 and 5 mol % end up in **17** and **18**, respectively (a multitude of other products could be detected at <2 area% by HPLC). When substrate **2** is omitted from the reaction, complete disappearance of **8** occurs on a similar time scale! Under these conditions 50−55 mol % and approximately 10 mol % of the indole ligands are incorporated in **17** and **18**, respectively. In this case there is a more substantial discrepancy in the ligand balance albeit that, again, a multitude of minor reaction products are detected by HPLC. The structure of some of these were tentatively assigned on the basis of HPLC-MS data (**19**−**22**). In more mechanistically oriented experiments it was determined that the 5-H of **17** originated from water present during the reaction (solvent, catalyst, and substrate all contain substantial amounts of water). Performing the coupling reaction in the presence of a small amount of D_2O in dry toluene (2.4 mol equivalents relative to indole ligands) led to 80% 5-D incorporation in **17**. When the coupling reaction was carried out in the presence of a large amount of 1,1-diphenylethylene (40 equiv) as a radical trap, the yield for **14** was not significantly lowered. Therefore, it appears that free radicals are not involved in this reaction. Unfortunately, our experiments did not shed

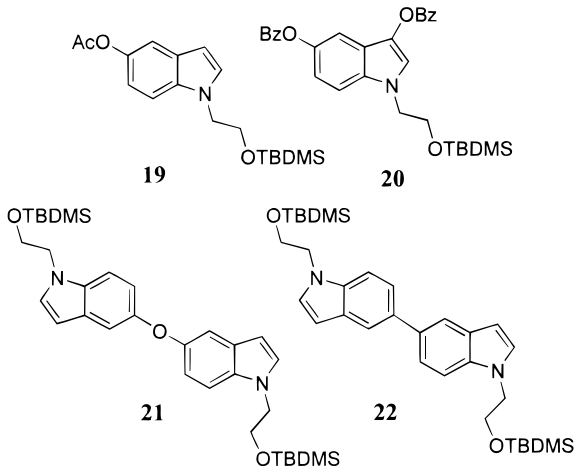
(17) A pure reference sample of this compound was obtained via silylation of **16** using TBSOTf and 2,6-di-*tert*-butylpyridine in CH_2Cl_2 followed by SiO_2 chromatography in 65% yield.

(18) Structure assignments for **17** and **18** are based on HPLC-MS analysis of the crude reaction mixture and was corroborated by NMR analysis of the chromatographically pure compounds.

(19) (a) Dodonov, V. A.; Gushin, A. V.; Brilkina, T. G. *Zh. Obshch. Khim.* **1985**, *55*, 2514−2519. (b) Barton, D. H. R.; Finet, J.-P.; Pichon, C. *J. Chem. Soc. Chem. Commun.* **1986**, 65−66.

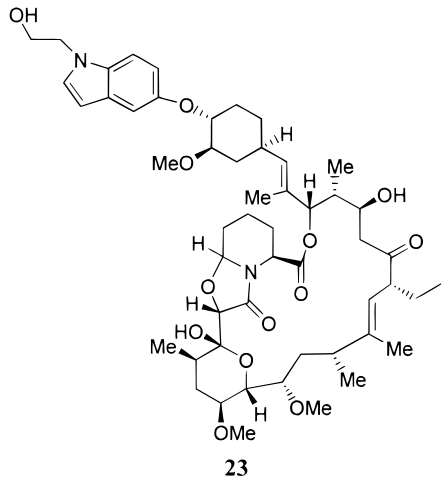
(20) Still, C. W.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *50*, 2923.

(21) The best chromatographic separation between **14** and **15** was obtained using acetone/hexanes for elution. However, acetone readily condenses with the indole moiety of these products under the desilylation conditions, thus requiring its rigorous removal. Therefore, ethyl acetate/hexanes is preferred for elution although the separation between **14** and **15** is not as good.



more light on the mechanism of these copper-catalyzed alcohol arylation reactions.[22]

In the final step **14** was deprotected under mildly acidic conditions. The crude product was purified by silica gel chromatography in which **3** was relatively easily separated from the more polar "bis-indolyzed" **16**. The overall isolated yield for the conversion of **2** into **3** via the through process was typically 55−60%. The amorphous **3** was obtained with a purity of 94 area% according to HPLC. Two equilibrium species were detected at 0.9 and 3.6 area% (tentatively assigned as the indolyzed analogue of **4**), respectively. In addition, lower and higher methylene homologues of **3** were detected at 0.5 and 0.4 area%, respectively (structure based on LC-MS). An impurity in which the indole moiety of **3** was presumably benzoyloxygenated at C-3′ (structure tentatively assigned based on LC-MS; vide supra) is typically present at 0.4 area%. Finally, it is of interest to note that **3** is not photochemically stable. Upon storing purified **3** in wet acetonitrile and exposing to light, a new product was formed according to HPLC analysis. Some of this product could be isolated via chromatography and identified on the basis of detailed NMR analysis as **23** (the stereochemistry of the aminal proton could not unambiguously be determined). This general type of photochemical reaction has been reported in the literature,[23] and a similar reaction has been reported for FK-506 by Fujisawa workers in the patent literature.[24]



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In conclusion, an efficient and practical synthesis of triindolylbismuthane **7** was developed. This reagent was then used for the two-step preparation of **3** from ascomycin (**2**) in 55−60% overall yield using an optimized copper catalyzed chemo- and regioselective arylation reaction as the key step.

Experimental Section

All commercially available materials and solvents were used as received. The quality of the benzoyl peroxide was checked by iodometric titration before use. Reaction temperatures were measured internally, unless indicated otherwise (rt = 18−23 °C). Melting points are not corrected. Merck F254 plates were used for thin-layer chromatography (UV and ceric ammonium molybdate stain were used for visualization). Preparative chromatography was performed using silica gel-60 (230−400 mesh). The macrolides exist as a mixture of amide rotamers. Therefore, selected ^{1}H and complete ^{13}C NMR data are reported for the major rotamer only.[25] HRMS data were obtained using liquid SIMS ionization.

1-(2-Hydroxyethyl)-5-bromoindole (6). A solution of 2-bromoethanol (35 mL; 95%, 493 mmol) in THF (230 mL) was cooled to 0−5 °C, and 2-methoxypropene (48.8 mL; 97%, 494 mmol) was added dropwise. The reaction was judged complete when a 35 ppm signal in the ^{13}C NMR spectrum of a reaction sample (0.4 mL sample diluted with 0.1 mL of pyridine-d_5) had disappeared (30 min). The resulting solution was added slowly under mechanical stirring to a mixture of 5-bromoindole (80.0 g, 408 mmol) and powdered KOH (40.0 g) in a mixture of DMSO (80 mL) and THF (480 mL) at rt. After stirring overnight at rt, water (180 mL) was added, dissolving the solids in approximately 10 min. The lower aqueous layer was separated. To the remaining orange-red layer was added a solution of 1 vol % of phosphoric acid in water (400 mL). After 4 h toluene (400 mL) was added, and the mixture was agitated for 10 min. The organic layer was washed with water (2 × 400 mL) and then partially concentrated in vacuo (110 mmHg; 35−55 °C internal temp) to a total volume of 400 mL. This solution was flushed with 400 mL of fresh toluene. Upon cooling to rt, the crystallization started. After aging for 2 h, the crystals were filtered, washed with 100 mL of 20% toluene in hexanes, and dried, yielding 80.0 g of crystalline **6** (80% yield). This material was 99.6 area% pure according to HPLC analysis (Dupont Zorbax Phenyl, 25 cm × 4.6 mm; 50/50 Water (0.1% H_3PO_4)/CH_3CN; 1.0 mL/min; 220 nm). Mp: 88 °C. ^{1}H NMR (250.1 MHz, $CDCl_3$) δ 7.75 (d, J = 1.8, 1H), 7.29 (dd, J = 8.7, 1.8, 1H), 7.22 (d, J = 8.8, 1H), 7.14 (d, J = 3.2, 1H), 6.44 (d, J = 3.3, 1H), 4.21 (t, J = 5.2, 2H), 3.88 (t, J = 5.2, 2H), 1.62 (s, 1H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 134.7, 130.2, 129.4, 124.4, 123.4, 112.8, 110.8, 101.0, 61.3, 48.7. Anal. Calcd for $C_{10}H_{10}BrNO$: C, 50.03; H, 4.20; N, 5.83. Found: C, 49.96; H, 4.05; N, 5.69.

Tris[1-(2-*tert*-Butyldimethylsilyloxyethyl)indol-5-yl]bismuthane (7). A solution of **6** (40.2 g, 167 mmol), *tert*-butyldimethylsilyl chloride (97%; 27.8 g, 184 mmol), 4-(dimethylamino)pyridine (200 mg, 1.6 mmol), and triethylamine (26.0 mL, 186 mmol) in THF (400 mL) was stirred at ambient temperature for 72 h. After cooling to 0−5 °C, the precipitate was filtered under N_2. The filter cake was washed with THF (80 mL). The combined filtrates were cooled to −72 °C, and *n*-BuLi (120 mL, 1.4 M solution in hexane, 168 mmol) was added over 5 min, maintaining the temperature below −65 °C. After the mixture was aged for an additonal 30 min at −72 °C, a solution of $BiCl_3$ (18.6 g, 59.0 mmol) in THF (100 mL) was added while maintaining the temperature below −60 °C (10 min). After warming to rt over 1 h, a slurry of 20 g of cellulose in 100

(22) Several mechanistic proposals have been made in the literature (ref 5) but none of these has been tested experimentally. Our experiments were not designed to achieve this goal.

(23) Aoyama, H.; Hasegawa, T.; Watabe, M.; Shiraishi, H.; Omote, Y. *J. Org. Chem.* **1978**, *43*, 419−422.

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mL of THF and 13 mL of water was added. The resulting suspension was stirred for 1 h and then filtered. The filter cake was washed with 200 mL of THF. The filtrates were concentrated to a total volume of 200 mL (160 mmHg, internal $T < 24$ °C). The residual solvent was displaced in vacuo with 95% ethanol (600 mL), maintaining the total volume at 200 mL. The resulting slurry was aged for 1.5 h at 20 °C and filtered. The solids were washed with 100 mL of 95% ethanol and dried under a stream of nitrogen for 15 h to give 46.6 g of **7** (80% yield). This material was 99 area% pure according to HPLC analysis (Vydac Protein C_4, 25 cm × 4.6 mm; 30/70 water (0.005 M Na_2HPO_4 and 0.005 M NaH_2PO_4)/CH_3CN; 1.5 mL/min; 276 nm). Mp: 135−136 °C. ^{1}H NMR (250.1 MHz, $CDCl_3$) δ 8.08 (s, 1H), 7.58 (dd, J = 8.3, 0.7, 1H), 7.33 (d, J = 8.2, 1H), 7.09 (d, J = 3.2, 1H), 6.37 (d, J = 2.7, 1H), 4.21 (t, J = 5.7, 2H), 3.90 (t, J = 5.7, 2H), 0.84 (s, 9H), −0.11 (s, 6H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 144.2, 135.6, 131.3, 130.6, 128.2, 111.4, 100.9, 62.3, 48.5, 25.8, 18.2, −5.7. Anal. Calcd for $C_{48}H_{72}N_3O_3Si_3Bi$: C, 55.85; H, 7.03; N, 4.07. Found: C, 55.63; H, 7.05; N, 4.10.

Bis(benzoyloxy)tris[1-(2-*tert*-Butyldimethylsilyloxyethyl)indol-5-yl]bismuth (8). Bismuthane **7** (10.5 g, 10.2 mmol) was solubilized in toluene (100 mL) with heating. The mixture was filtered through cellulose (10 g). The filtrate was heated with benzoyl peroxide (3.1 g, 12.5 mmol) to 75 °C for 90 min. Hexane (200 mL) was added, and the mixture was allowed to cool to rt overnight. The crystals were filtered and dried in vacuo at 50 °C, yielding 9.0 g of **8** (69% yield). Mp: 174−176 °C; ^{1}H NMR (250.1 MHz, $CDCl_3$) δ 8.62 (d, J = 1.2, 3H), 8.28 (dd, J = 8.7, 1.3, 3H), 7.96 (dd, J = 8.2, 1.4, 4H), 7.53 (d, J = 8.8, 3H), 7.29 (m, 6H), 7.18 (d, J = 3.2, 3H), 6.51 (d, J = 3.1, 3H), 4.22 (t, J = 5.5, 6H), 3.88 (t, J = 5.5, 6H), 0.78 (s, 27H), −0.18 (s, 18H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 171.7, 151.2, 136.7, 134.4, 130.9, 130.2, 130.0, 129.6, 127.6, 127.5, 126.9, 111.6, 102.4, 62.4, 48.8, 25.8, 18.2, −5.7. Anal. Calcd for $C_{62}H_{82}N_3O_7Si_3Bi$: C, 58.43; H, 6.48; N, 3.30. Found: C, 58.28; H, 6.26; N, 3.14.

[3*S*-[3*R-[*E*(1*S**,3*S**,4*S**)],4*S**,5*R**,8*S**,9*E*,12*R**,14*R**,15*S**,16*R**,18*S**,19*S**,26a*R**]]-3-[2-[4-[[1-[2-[[1,1-Dimethylethyl)dimethylsilyl]oxy]ethyl]-1*H*-indol-5-yl]oxy]-3-methoxycyclohexyl]-1-methylethenyl]-8-ethyl-5,6,8,11,12,13,14,15,16,17,18,19,24,25,26,26a-hexadecahydro-5,19-dihydroxy-14,16-dimethoxy-4,10,12,18-tetramethyl-15,19-epoxy-3*H*-pyrido[2,1-*c*][1,4]oxazacyclotricosine-1,7,20,21(4*H*,23*H*)-tetrone (14).** A mixture of **7** (25.0 g, 24.2 mmol) and benzoyl peroxide (98 wt %; 5.5 g, 22.3 mmol) in 2-butanone (200 mL) was stirred at ambient temperature for 24 h. Then **2** (98 wt %; 12.9 g, 16.0 mmol) and copper(II) acetate (0.5 g, 2.7 mmol) were added. The mixture turned green after a few minutes and was stirred at rt for 24 h. The suspension was diluted with 600 mL of hexanes and then filtered through cellulose. The filterbed was thoroughly washed with 2-butanone (150 mL). The combined filtrates were concentrated in vacuo to yield a green syrup. The crude product was dissolved in 100 mL of a 2-butanone/hexanes 15/85 mixture and loaded onto 200 g of SiO_2-60. The column was eluted with 4 L of 10% ethyl acetate in hexanes followed by 2 L of 50% ethyl acetate in hexanes. Fractions were combined based on HPLC analyses (Dupont Zorbax Rx C_8, 250 × 4.6 mm; water (0.1% H_3PO_4)/CH_3CN gradient from 40/60 and 1.0 mL/min at 0 min to 10/90 and 1.5 mL/min at 30 min followed by isocratic at 10/90 and 1.5 mL/min until 45 min; 60 °C; 220 nm). The combined rich cut containing **14** (14.11 assay g by HPLC corresponding to 83% assay yield) and **15** (2.36 assay g by HPLC corresponding to 11% assay yield) was concentrated in vacuo to a dark foam. This mixture was used for the next step. An analytically pure sample of **14** could be obtained by careful chromatography using acetone/hexanes gradient to elute (R_f for **14** and **15** in hexanes/acetone 3/1 are 0.26 and 0.33, respectively).

14: $[\alpha]_{405} = -322°$ (c = 2; acetonitrile). ^{1}H NMR (399.9 MHz, CD_3CN) δ 7.27 (br d, J = 8.8, 1H), 7.16 (d, J = 3.2, 1H), 7.10 (d, J = 2.4, 1H), 6.81 (dd, J = 8.8, 2.4, 1H), 6.30 (dd, J = 3.2, 0.8, 1H), 5.19 (d, J = 4.4, 1H), 5.17 (d, J = 9, 1H), 4.96 (d, J = 10.0, 1H), 4.59 (br d, J = 4.8, 1H), 4.40 (d, J = 1.2, 1H), 4.30 (br d, J = 13, 1H), 4.18 (t, J = 5.2, 2H), 4.00 (m, 1H), 3.88 (t, J = 5.2, 2H), 3.60 (dd, J = 9.6, 1.2, 1H), 3.56 (m, 1H), 3.40 (s, 3H), 3.34 (s, 3H), 3.29 (s, 3H), 2.99 (d, J = 4.4, 1H), 2.89 (td, J = 13.3, 3.2, 1H), 2.74 (dd, J = 14.5, 4.8, 1H), 1.61 (d, J = 0.8, 3H), 1.59 (d, J = 1.2, 3H), 0.90 (d, J = 6.4, 3H), 0.88 (d, J = 6.4, 3H), 0.86 (d, J = 6.8, 3H), 0.82 (t, J = 7.2, 3H), 0.79 (s, 9H), −0.16 (s, 6H); ^{13}C NMR (100.6 MHz, CD_3CN) δ 212.8, 198.6, 170.4, 166.5, 153.3, 139.4, 133.0, 132.9, 132.3, 130.6, 130.1, 124.7, 114.2, 111.3, 107.4, 100.95, 98.2, 82.9, 82.8, 79.7, 76.2, 74.5, 73.9, 70.4, 63.4, 57.9, 57.5, 56.7, 55.8, 49.6, 49.6, 46.1, 41.0, 39.9, 37.4, 35.5(2C), 34.1, 33.4, 31.2, 30.6, 28.5, 27.2, 26.2, 25.5, 25.1, 22.0, 20.4, 18.8, 16.5, 16.1, 13.7, 12.0, 11.9, 10.1, −5.5. Anal. Calcd for $C_{59}H_{92}N_2O_{13}Si$: C, 66.51; H, 8.70; N, 2.63. Found: C, 66.32; H, 8.61; N, 2.77.

[3*S*-[3*R-[*E*(1*S**,3*S**,4*S**)],4*S**,5*R**,8*S**,9*E*,12*R**,14*R**,15*S**,16*R**,18*S**,19*S**,26a*R**]]-8-Ethyl-5,6,8,11,12,13,14,15,16,17,18,19,24,25,26,26a-hexadecahydro-5,19-dihydroxy-3-[2-[4-[[1-(2-hydroxyethyl)-1*H*-indol-5-yl]oxy]-3-methoxycyclohexyl]-1-methylethenyl]-14,16-dimethoxy-4,10,12,18-tetramethyl-15,19-epoxy-3*H*-pyrido[2,1-*c*][1,4]oxazacyclotricosine-1,7,20,21(4*H*,23*H*)-tetrone (3).** To a solution of **14** and **15** (14.11 and 2.36 assay g, respectively; 13.2 and 1.8 mmol, respectively) in methanol (400 mL) was added 1.5 mL of 1.0 N hydrochloric acid. After 2 h the solution was partitioned between a solution of $NaH_2PO_4 \cdot H_2O$ (1.75 g) and Na_2HPO_4 (1.80 g) in water (500 mL) and isopropyl acetate (400 mL). The organic layer was washed with brine solution (120 g of NaCl in 400 mL of water) and then concentrated in vacuo (bath temperature 45 °C). The crude product was purified by chromatography using 150 g of SiO_2-60 eluting with a gradient of acetone in hexanes (from 25 vol % to 40 vol %). Fractions were combined based on HPLC analyses (Phenomenex CustomSil C_{18}, 250 × 4.6 mm; water (0.1% H_3PO_4)/CH_3CN gradient from 30/70 at 0 min to 5/95 at 40 min; 1.0 mL/min; 60 °C; 220 nm) and concentrated in vacuo (bath temperature <40 °C). Bis-adduct **16** can be obtained from the trailing fractions. A solution of the chromatographed **3** in acetonitrile (200 mL) was washed with hexanes (2 × 100 mL) and then evaporated to dryness to yield **3** as a slightly yellow foam (9.0 g; 72% from assayed **14**; 60% overall from **2**) after drying. The product can be obtained as an easier to handle amorphous white solid by dissolution in 6 parts of 2-propanol followed by slow addition into 60 parts of water containing 0.5 wt % of NaCl.

3: R_f = 0.40 (hexanes/acetone 1/1). $[\alpha]_{405} = -358°$ (c = 2; acetonitrile). IR (KBr) ν 3840, 3355, 1744, 1706, 1649, 1483 cm^{-1}. ^{1}H NMR (400.1 MHz, CD_3CN) δ 7.28 (d, J = 8.7, 1H), 7.18 (d, J = 3.2, 1H), 7.11 (d, J = 2.4, 1H), 6.82 (dd, J = 8.7, 2.4, 1H), 6.32 (dd, J = 3.2, 0.8, 1H), 5.18, (m, 2H), 4.95 (br d, J = 9.9, 1H), 4.52 (br m, J = 5.2, 1H), 4.41 (d, J = 1.2, 1H), 4.30 (br d, J = 13.5, 1H), 4.17 (t, J = 5.6, 2H), 4.00 (m, 1H), 3.89 (m, 1H), 3.78 (q, J = 5.6, 2H), 3.60 (dd, J = 9.5, 1.2, 1H), 3.56 (ddd, J = 11.1, 3.6, 1.2, 1H), 3.40 (s, 3H), 3.40−3.25 (m, 3H), 3.33 (s, 3H), 3.28 (s, 3H), 2.99 (d, J = 4.4, 1H), 2.89 (m, 2H), 2.74 (dd, J = 14.7, 4.8, 1H), 2.40 (m, 1H), 2.33−1.02 (m, 24H), 1.61 (d, J = 0.8, 3H), 1.59 (d, J = 1.2, 3H), 0.90 (d, J = 6.3, 3H), 0.88 (d, J = 6.7, 3H), 0.86 (d, J = 7.1, 3H), 0.82 (t, J = 7.5, 3H); ^{13}C NMR (100.6 MHz, CD_3CN) δ 212.8,198.6, 170.4, 166.4, 153.4, 139.4, 132.9, 132.9, 132.3, 130.3, 130.1, 124.7, 114.3, 111.1, 107.4, 101.1, 98.2, 83.0, 82.8, 79.7, 76.2, 74.5, 73.9, 70.4, 61.9, 57.9, 57.5, 56.7, 55.8, 49.6, 49.6, 46.1, 41.0, 39.9, 37.4, 35.5, 34.1, 33.4, 31.2, 30.7, 28.5, 27.2, 25.5, 25.1, 22.0, 20.3, 16.7, 16.1, 13.7, 12.0, 10.1. (+)-LSI−HRMS calcd for $C_{53}H_{78}N_2O_{13}$ m/z 950.5504, obsd m/z 950.5530. Anal. Calcd for $C_{53}H_{78}N_2O_{13}$: C, 66.92; H, 8.27; N, 2.95. Found: C, 66.47; H, 8.15; N, 3.02.

16: R_f = 0.27 (hexanes/acetone 1/1). $[\alpha]_{405} = -445°$ (c = 2; acetonitrile). ^{1}H NMR (400.1 MHz, CD_3CN) δ 7.29 (d, J = 8.7, 1H), 7.28 (d, J = 8.7, 1H), 7.19 (d, J = 3.2, 1H), 7.17 (d, J = 3.2, 1H), 7.12 (d, J = 2.4, 1H), 7.06 (d, J = 2.4, 1H), 6.81 (dd, J = 8.7, 2.4, 1H), 6.78 (dd, J = 8.7, 2.4, 1H), 6.34 (dd, J = 3.2, 0.8, 1H), 6.33 (dd, J = 3.2, 0.8, 1H), 5.20 (d, J = 7.5, 1H), 4.99 (d, J = 8.7, 1H), 4.81, dq, J = 10.3, 1.2, 1H), 4.62 (d, J = 5.2, 1H), 4.55 (d, J = 0.8, 1H), 4.49 (m, 1H), 4.32 (br d, $J \sim$ 13, 1H), 4.17 (t, J = 5.6, 2H), 4.14 (t, J = 5.6, 2H), 3.79 (m, 2H), 3.74 (m, 2H), 3.70 (dd, J = 9.5, 1.6, 1H), 3.59 (m, 1H), 3.34_1 (s, 3H), 3.33_9 (s, 3H), 3.31 (s, 3H), 2.54 (dd, J = 14.3, 4.8, 1H), 1.72 (d, J = 0.8, 3H), 1.45 (d, J = 1.2, 3H), 1.03 (d, J = 6.7, 3H), 0.91 (d, J = 6.3, 3H), 0.85 (d, J = 6.3, 3H), 0.77 (t, J = 7.5, 3H); ^{13}C NMR (100.6 MHz, CD_3CN) δ 211.2, 198.8, 170.4, 166.5, 153.3, 152.5, 139.7, 135.5, 133.1, 132.9, 132.1, 130.6, 130.4, 130.11, 130.09, 124.8, 114.2, 114.1, 111.4, 111.2, 107.3, 107.2, 101.11, 101.07, 98.5, 82.7_2, 82.6_8(2C), 77.8, 76.3, 74.4, 73.9, 61.9(2C), 57.9, 57.7, 57.2, 56.6, 56.3, 50.0, 49.5_8, 49.5_5, 45.1, 39.8, 39.6, 37.2, 35.7, 35.5,

35.3, 33.3, 30.6, 30.5, 28.8, 26.7, 25.2, 25.0, 21.6, 19.7, 16.4, 16.1, 12.4, 11.9, 11.1. Anal. Calcd for $C_{63}H_{87}N_3O_{14}$: C, 68.15; H, 7.90; N, 3.78. Found: C, 67.31; H, 7.86; N, 3.66.

Photoproduct 23: ^{1}H NMR (400.1 MHz, CD_3CN) δ 7.28 (d, J = 8.7, 1H), 7.18 (d, J = 3.2, 1H), 7.11 (d, J = 2.4, 1H), 6.82 (dd, J = 8.7, 2.4, 1H), 6.32 (dd, J = 3.2, 0.8, 1H), 5.18 (br s, 1H), 5.15 (ddd, J = 10.3, 4.4, 1.2, 1H), 4.94 (d, J = 9.1, 1H), 4.77 (d, J = 2.0, 1H), 4.61 (d, J = 6.7, 1H), 4.33 (d, J = 1.2, 1H), 4.17 (t, J = 5.6, 2H), 3.99 (m, 1H), 3.78 (q, J = 5.6, 2H), 3.60 (dd, J = 9.5, 2.2, 1H), 3.48 (m, 1H), 3.40 (s, 3H), 3.31 (s, 3H), 3.27 (s, 3H), 2.87 (t, J = 5.6, 1H), 2.65 (dd, J = 17.4, 1.6, 1H), 2.31 (dd, J = 17.4, 9.5, 1H), 1.65, (d, J = 0.8, 3H), 1.63 (d, J = 0.8, 3H), 0.92 (d, J = 6.7, 3H), 0.84 (d, $J \sim 7$, 3H), 0.83, (t, J = 7.1, 3H), 0.81 (d, J = 7.1, 3H); ^{13}C NMR (100.6 MHz, CD_3CN) δ 213.5, 171.7, 169.4, 153.4, 140.2, 132.9, 132.4, 130.4, 130.1, 129.6, 123.7, 114.3, 111.2, 107.5, 101.0, 98.7, 88.0, 83.1, 82.9, 77.1, 77.0, 76.8, 74.8, 72.5, 70.0, 58.0, 57.3, 56.6, 55.5, 53.7, 49.6, 49.2, 44.4, 40.5, 37.5, 36.0, 35.4, 33.4, 32.6, 31.8, 31.3, 30.6, 29.7, 26.6, 26.0, 25.6, 19.7, 19.2, 16.2, 15.9, 14.7, 12.1, 10.4.

Acknowledgment. We thank Dr. Larry Colwell, Jr., for collecting the HRMS data. We thank Pat Gailliot and James Corry for providing us with ascomycin.

JO980451Q