Synthesis of PAF Antagonist MK-287

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The synthesis of PAF antagonist MK-287 is described. Our route utilizes a 5-aryl-substituted butyrolactone as the key optically active intermediate, which is constructed in four steps from commercially available 5-iodovanillin. Asymmetry is introduced using β-chlorodiisopinocampheylborane to reduce a prochiral ketone. The second asymmetric center is installed relative to the existing stereocenter with stereocontrol exceeding 50:1. This step utilizes a copper-catalyzed Grignard displacement of an α-bromo ether. The α-bromo ether was generated using trimethylsilyl bromide activation of a silylated hemiacetal. The details leading to our development of the silyl acetal method for anomeric activation are also described.

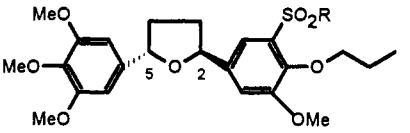
Introduction

Platelet-activating factor (PAF) is an optically active unsymmetrically substituted D-glycerol derivative.[1,2] Prior to structure elucidation, PAF was first discovered as a powerful platelet-stimulating agent which caused platelet aggregation and release of histamine.[3] This unknown substance was termed platelet-activating factor. Investigations into the pharmacology of PAF accelerated when synthetic preparations became available.[2] Systemic effects of iv injections of PAF vary according to species and include bronchoconstriction (guinea pigs), increased vascular permeability (rats and guinea pigs), and pulmonary hypertension (rabbits).[1]

Binding of PAF to its specific receptor is thought to be the first step necessary to display its biological functions.[4] Hence, the design of specific PAF receptor antagonists could lead to a mechanism-based therapy for asthma, inflammation, acute allergy, ischemia, and toxic shock.

Lignans of the 2,5-diaryltetrahydrofuran series were identified as competitive PAF-receptor antagonists.[5] The most potent compound in the initial series possessed a 2,5-*trans*-diaryl stereochemical relationship. Further structure activity studies indicated that more potent PAF antagonists contained an electron-withdrawing group on one *but not* both aromatic rings. These features are incorporated in L-659,989 in which a metabolically stable methyl sulfone serves as the electron-withdrawing functional unit and a trimethoxyaryl ring is appended at C-5.[6-8] Structural modification of the methyl sulfone leads to a more polar and highly potent PAF antagonist, MK-287.[9]

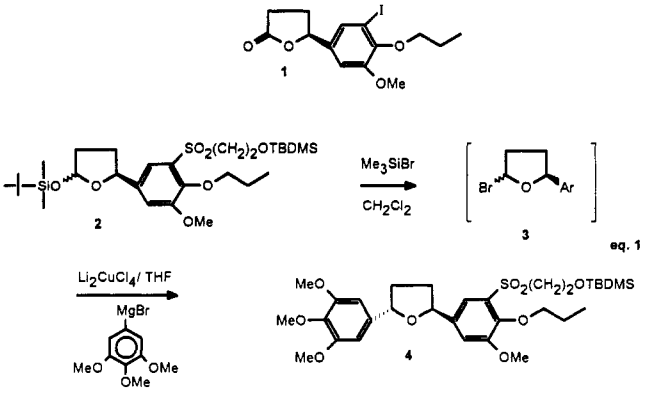
The (−) enantiomer of MK-287 (i.e. the *S,S*-enantiomer, as drawn) is 20-fold more potent than the (+) enantiomer. In this paper we describe the full details for the synthesis of our lead candidate MK-287.



L-659,989 R=CH_3

MK-287 R=$(CH_2)_2OH$

The existing MK-287 synthesis[9] provided the target compound with high enantiomeric excess (>98% ee); however, control of the relative stereochemistry was moderate. The desired trans isomer was produced along with the cis isomer in a ratio of 4:1, respectively. Isolation of the pure trans isomer required preparative HPLC. In this paper we describe a practical synthesis of PAF antagonist MK-287. Our synthesis provides MK-287 with high enantiomeric excess (99% ee) *and also controls the relative stereochemistry* (>50:1 trans:cis). Our approach employs lactone 1 as a key intermediate which is readily available in optically active form.[8b] Functional group modifications convert lactone 1 into silyl acetal 2. Acetal 2 is then readily converted into bromide 3 followed by a highly stereoselective copper-catalyzed Grignard displacement which affords *trans*-diaryltetrahydrofuran 4, eq 1. Control of stereochemistry was anticipated based



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(8) (a) For the first synthesis of the 2*S*,5*S* enantiomer of L-659,989 see: Ponpipom, M. M.; Bugianesi, R. L.; Chabala, J. C. *Tetrahedron Lett.* **1988**, *29*, 6211. (b) For an enantioselective synthesis using iodide 1 as well as silyl acetyl activation, see: Thompson, A. S.; Tschaen, D. M.; Simpson, P.; McSwine, D. J.; Russ, W.; Little, E. D.; Verhoeven, T. R.; Shinkai, I. *Tetrahedron Lett.* **1990**, *31*, 6953.
(9) Sahoo, S. P.; Graham, D. W.; Acton, J.; Biftu, T.; Bugianesi, R. L.; Girotra, N. N.; Kuo, C.-H.; Ponpipom, M. M.; Doebber, T. W.; Wu, M. S.; Hwang, S.-B.; Lam, M.-H.; MacIntyre, D. E.; Bach, T. J.; Luell, S.; Meurer, R.; Davies, P.; Alberts, A. A.; Chabala, J. C. *Bioorg. Med. Chem. Lett.* **1991**, *1*, 327.

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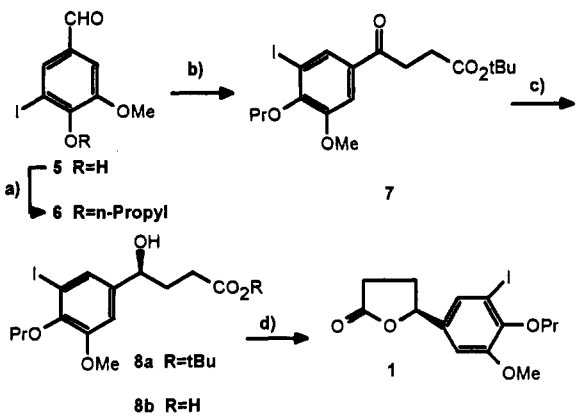
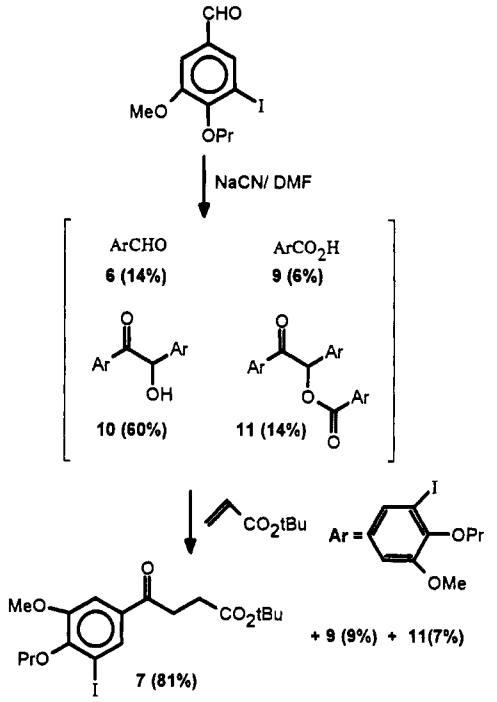
Scheme I



[a] (a) *n*-Propyl bromide/K_2CO_3/DMF/70 °C; (b) *tert*-butyl acrylate/NaCN; (c) β-chlorodiisopinocampheylborane/THF then NaOH; (d) pyridinium *p*-toluenesulfonate.

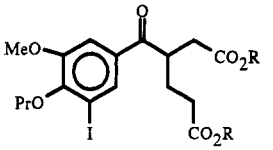
Scheme II



upon the pioneering results of Corey[10] who demonstrated trans:cis ratios of greater than 10:1 for this type of displacement. Successful implementation of this strategy relies upon the use of our silyl acetal method[8b] to generate bromide **3**.

Synthesis of Iodide 1. The synthesis of iodide **1** is shown in Scheme I. Commercially available 5-iodovanillin was alkylated with *n*-propyl bromide in dimethylformamide (DMF) at 70 °C, affording propyl ether **6** in >95% yield. Production of γ-keto ester **7**, containing the carbon backbone of the THF ring, was achieved in one step (83% yield) using conditions described by Stetter.[11] Thus, aldehyde **6** was reacted with 25 mol % of sodium cyanide in DMF. To this mixture was added a solution of *tert*-butyl acrylate in DMF. After 30 min at 23 °C the product was isolated using an aqueous workup. The simplicity of this procedure masks a complex reaction mechanism in which many species are in equilibrium. Monitoring the reaction by HPLC revealed the existence of several intermediates, which were isolated and identified. Upon addition of sodium cyanide to aldehyde **6** in DMF, the HPLC area percent revealed a reaction mixture consisting of the starting aldehyde (14%), acid **9** (6%), benzoin adduct **10** (60%), and benzoin ester **11** (14%), Scheme II. Once the *tert*-butyl acrylate is added, the composition of the reaction mixture changes to γ-keto ester **7** (81%), carboxylic acid **9** (9%), and benzoin ester **11** (7%). The composition of all reactive species decreases upon addition of the acrylate. Thus, each species, except **9**, is in equilibrium with the reactive species which we assume to be a cyanohydrin anion.

Several additional features are worth noting. Aldehyde **6** is relatively stable in DMF; however, as much as 20% of the oxidation product **9** can be generated once sodium cyanide has been added. Increased amounts of **9** lead to increased amounts of **11**, both of which decrease the yield of γ-keto ester **7**. To avoid this the DMF solution should be thoroughly deoxygenated prior to addition of NaCN. Use of the hindered *tert*-butyl acrylate minimizes production of the overaddition product **12**. With ethyl



acrylate, approximately 10% of **12** (R = Et) is generated, while the use of *tert*-butyl acrylate minimizes the overaddition product to <1%. Lastly, the use of cyanide catalysis was essential since the thiazolium catalysts[11] do not afford γ-keto ester **7**. An aqueous workup and bicarbonate wash are used to remove DMF and acid **9** from the product mixture. The γ-keto ester is suitable for the next step without further purification.

Introduction of optical activity utilizes an asymmetric ketone reduction. Several practical reagents have been reported recently which can be applied to our substrate.[10,12,13] The most convenient reagent was diisopinylcampheylchloroborane introduced by Brown.[12] The advantages of this reagent are commercial availability, ready source of either enantiomer of α-pinene, and its operational simplicity. Furthermore, we have developed a convenient one-pot preparation of this reagent using pinene which is of only 83% ee. Results using chloroborane **15** prepared from 83% pinene rival results using **15** prepared from 98% ee pinene, vide infra.

Reaction of a THF solution of γ-keto ester **7** at 0 °C with chloroborane **15** affords alcohol **8a** in 85–90% yield, Scheme I. The optical purity of **8a** was determined to be 90% ee using a Mosher ester derivative.[14] Typically, ester **8a** was not isolated, but rather, the *tert*-butyl ester was hydrolyzed in methanolic sodium hydroxide. The resulting carboxylic acid sodium salt was then readily separated from neutral pinene and other chloroborane byproducts. Upon acidification to pH = 2, acid **8b** was isolated using a toluene extraction and was free of any pinene residues. Lactonization of acid **8b** can then be achieved in toluene

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(13) Ohkuma, T.; Kitamura, M.; Noyori, R. *Tetrahedron Lett.* **1990**, *31*, 5509.

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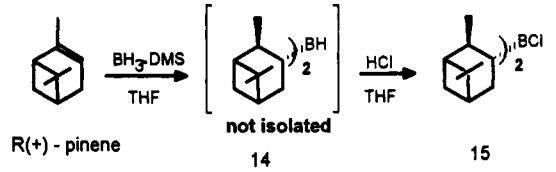
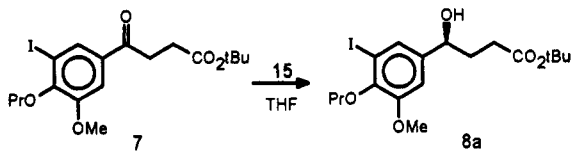
Scheme III. In Situ Preparation of Diisopinocampheylchloroborane





R(+) - pinene (ee)	ee of alcohol 8a
98%	90%
91	89
83	87
75	82

using mildly acidic conditions with azeotropic removal of water. Lactone 1 produced in this manner has an optical purity of 90% as determined by HPLC on a chiral support (see the Experimental Section). One recrystallization from hexane/toluene affords iodide 1 which was >99% ee. The overall yield of optically pure lactone 1 from γ-keto ester 7 was 65%.

In Situ Preparation of Diisopinocamphenylchloroborane. The literature procedure[12] for the chloroborane preparation requires isolation of diisopinocampheylborane 14, Scheme III. The isolation step removes unreacted pinene which is of low enantiomeric excess (ee). Conversion of pure 14 into crystalline chloroborane utilizes HCl in diethyl ether. Since 14 is extremely air-sensitive we investigated whether the isolation step was essential. Thus, pinene (91% ee) was first reacted with borane methyl sulfide (0.45 equiv) and *without isolation* the mixture containing 14 and the unreacted *S*-enantiomer of pinene[12d] was converted into chloroborane 15. Material produced in this manner is as effective in asymmetric ketone reductions as is material derived from optically pure (98% ee) pinene,[15] Scheme III. Pinene of low optical purity was prepared by mixing known quantities of pure enantiomers. As can be readily seen from the table in Scheme III, use of low ee pinene for the in situ chloroborane preparation indicates that pinene as low as 83% ee is nearly as effective as the more expensive optically pure pinene. Thus the presence of the unreacted *S*-enantiomer of pinene has virtually no bearing on the quality of the reducing agent. The ability to procure either enantiomer of pinene coupled with a simple reagent preparation make the chloroborane 15 attractive synthetic reagent.

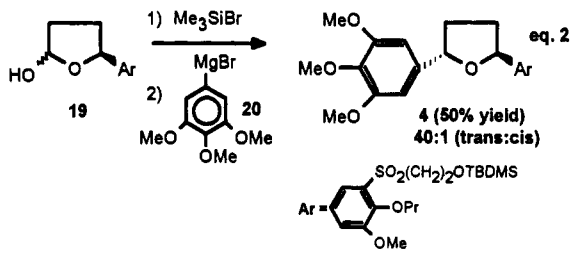
Installation of the Trimethoxyphenyl Ring. Lactone 1 is an excellent precursor for installing the trimethoxyphenyl ring. The lactone carbonyl can be reduced and converted into a suitable leaving group which is then displaced to afford the requisite 2,5-diaryltetrahydrofuran. Several methods have been reported which install an aromatic ring at an anomeric center. For an efficient PAF synthesis we require high trans:cis selectivity. The most direct methods employ the free hydroxyl (lactol). Reaction of a five-membered ring lactol with diphenylzinc in the presence of boron trifluoride etherate is reported to be moderately trans selective (2:1).[16] The lactol hydroxyl can be converted into a halide and then displaced using a Grignard reagent[10,17] or a cuprate.[18] The Grignard displacement reported by Corey is highly trans selective (>10:1).

Conversion of the lactol hydroxyl to a fluoro[19] or benzenesulfonyl group[20] followed by displacement has also been used to install an aromatic ring. However, these methods were only moderately trans selective (2–4:1) when applied to our system. Lastly, reports by Daves[21] and Larock[22] describe a palladium-catalyzed Heck type arylation of a glycal, which is reported to be highly trans selective (>99:1). However, moderate yields were reported by Larock for installing a *trimethoxyphenyl* ring using the Heck arylation chemistry. In terms of brevity, the method of choice proved to be conversion of the lactol to a halide followed by displacement. The issue which had a major impact on the synthetic route was to find a suitable method to activate the lactol hydroxyl. Our observations and results in this regard are discussed below.

Lactol Activation and Grignard Coupling. Synthesis of the lactol 19 was achieved in four steps from iodo lactone 1, Scheme IV. Conversion of iodide 1 to a sulfide utilized an Ullmann type cross-coupling employing 2-hydroxyethyl disulfide (Aldrich).

The sulfide was cleanly oxidized to a sulfone using an aqueous acetonitrile solution of magnesium monoperoxyphthalate (MMPP).[23] It was necessary to warm the mixture to 50 °C to ensure complete conversion to the sulfone. The primary alcohol was then protected as the corresponding *tert*-butyldimethylsilyl ether under standard conditions.[24] The three-step conversion of iodide 1 into sulfone 18 proceeded in 77–81% overall yield. Reduction with diisobutylaluminum hydride in toluene produced lactol 19 (97%) as a 1:1 mixture of trans and cis isomers. To complete the synthesis all that remained was to install the second aryl ring *in high chemical yield* and to deprotect the primary alcohol.

Reaction of 19 in methylene chloride at −80 °C with trimethylsilyl bromide (TMSBr) was followed by addition of a THF solution of (3,4,5-trimethoxyphenyl)magnesium bromide, eq 2. This afforded MK-287 silyl ether 4 in ca.



50% yield with a 40:1 trans:cis selectivity.

(15) Simpson, P.; Tschaen, D.; Verhoeven, T. R. *Synth. Commun.* **1991**, *21*, 1705.

(16) Tomooka, K.; Matsuzawa, K.; Suzuki, K.; Tsuchihashi, G.-I. *Tetrahedron Lett.* **1987**, *28*, 6339.

(17) Corey, E. J.; Chen, C.-P.; Parry, M. J. *Tetrahedron Lett.* **1988**, *29*, 2899.

(18) Bihovsky, R.; Selick, C.; Giusti, I. *J. Org. Chem.* **1988**, *53*, 4026.

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(20) (a) Brown, D. S.; Ley, S. V. *Tetrahedron Lett.* **1988**, *29*, 4869. (b) Brown, D. S.; Bruno, M.; Davenport, R. J.; Ley, S. V. *Tetrahedron* **1989**, *45*, 4293.

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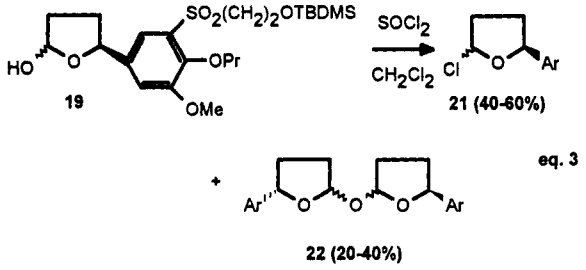
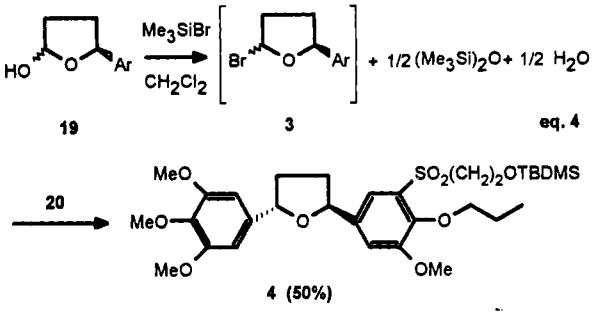
(25) The optical purity of iodide 1 was determined by ^{1}H NMR using 2,2,2-trifluoro-1-(9-anthryl)ethanol as a chiral solvating agent.

Lactol Activation: Alternatives to Trimethylsilyl Bromide. Our attention then focused on improving the 50% chemical yield for the coupling step. Initial attempts utilized thionyl chloride for anomeric activation. Employing an anomeric chloride for displacement showed no evidence for improvement. For example, reaction of **19** with thionyl chloride[26] afforded chloride **21**, which was stable for several hours at room temperature. Chloride **21** reacted with Grignard reagent **20** affording diaryltetrahydrofuran **4**. The yield for this reaction was also ca. 50%. More serious problems were encountered when we identified the activation byproducts. In addition to formation of chloride **21**, thionyl chloride activation produced a dimerization product identified as **22** (mixture of three diastereomers), eq 3. We attribute this to a build up of SO_2



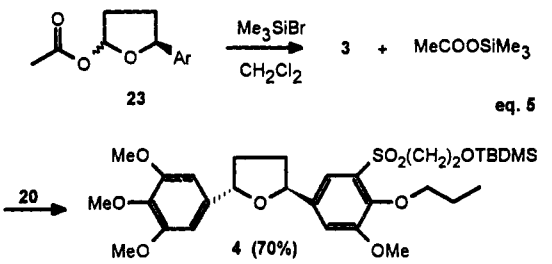
and HCl in the reaction mixture. These can then compete with thionyl chloride for the substrate. For example, reaction of lactol **19** with pure SO_2 dissolved in methylene chloride afforded a near quantitative yield of acetals **22**. Thus, although it may be possible to remove HCl as it forms (i.e., with polyvinylpyridine), removal of SO_2 would be more problematic. Use of triphenyl phosphine/CCl_4 or oxalyl chloride produced acetals **22** almost exclusively. Attempts to form a mesylate of lactol **19** using methanesulfonyl chloride afforded the glycal via elimination.[27] Since our best results were obtained using trimethylsilyl bromide, we investigated methods to improve the coupling yield using TMSBr activation.

Activation Using Trimethylsilyl Bromide and a Silyl Acetal. Further understanding of the TMSBr activation step was obtained by low-temperature NMR studies (^1H and ^{29}Si), eq 4. Lactol **19** was dissolved in



CD_2Cl_2 in an NMR tube and cooled to −80 °C. To the NMR tube was added an equivalent amount of trimethylsilyl bromide. Proton NMR at −60 °C showed rapid and complete conversion to bromide **3** as a 70:30 mixture and one major silicon byproduct. Use of ^{29}Si NMR indicated the presence of hexamethyldisiloxane. Addition of authentic hexamethyldisiloxane to the NMR reaction confirmed the major silicon byproduct of activation and allowed a balanced equation to be written for this step, eq 4. In addition to bromide **3** the presence of hexamethyldisiloxane indicates that water must also be present. The water arises from dimerization of the initially formed (but not observed) trimethylsilanol. The stoichiometry of the dimerization requires formation of 0.5 equiv of each hexamethyldisiloxane and water.

Although bromoglucose can be isolated and even recrystallized, anomeric bromide **3** (which contains no electron-withdrawing oxygen atoms) was unstable above −10 °C. The unstable nature of bromide **3** makes isolation and drying unfeasible at this stage. Thus, the Grignard reagent is added to a solution of bromide **3** which contains 0.5 equiv of water. The ensuing reactions produce coupled product **4** in 50% yield, as well as starting lactols **19** (5–10%) and bisacetals **22** (up to 20%). Simply protecting the lactol, prior to activation, should remove the proton source from the reaction and prevent water formation. This concept was tested using glycosyl acetate **23**. Formation of a glycosyl bromide from a glycosyl acetate with TMSBr is known.[28] In this case, the initially formed silicon byproduct, is trimethylsilyl acetate, eq 5. When



applied to our substrate, we found that production of bisacetals **22** and lactol **19** were completely suppressed, and the overall yield was improved to 70%. However, the reaction could not be driven to completion, and 5–10% starting acetate always remained. Furthermore, the acetate would decompose to acetals **22** on storage, presumably with production of acetic anhydride.

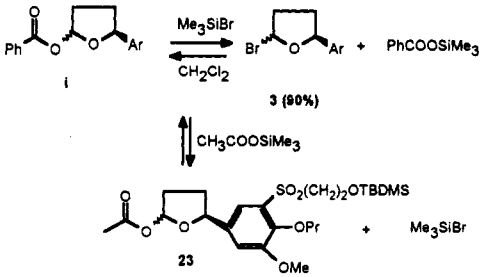
Examination of the literature procedure[28] for glycosyl acetate activation showed that 10 equiv of TMSBr were typically employed. We suspected that the TMSBr reaction may in fact be an equilibrium between starting acetate and product bromide. Strong support for this was obtained using a crossover experiment.[29] To overcome the equilibrium issue, we needed a method to drive the reaction to completion. The optimum solution was to use silylated hemiacetal **2**. Silyl acetal **2** was prepared in quantitative yield from lactol **19** under standard conditions.[24]

(26) Thionyl chloride has been used previously to synthesize glycosyl chlorides, see: (a) Smith, A. B., III; Rivero, R. A.; Hale, K. J.; Vaccaro, H. A. *J. Am. Chem. Soc.* **1991**, *113*, 2092. (b) Granata, A.; Perlin, A. S. *Carbohydr. Res.* **1980**, *86*, 305. (c) Straus, F.; Heinze, H. *Ann. Chem.* **1932**, *493*, 191.

(27) Sun, K. M.; Fraser-Reid, B. *Synthesis* **1982**, 28.

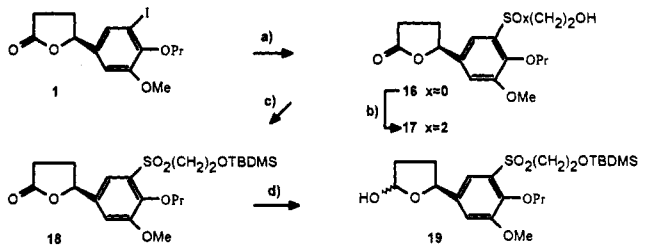
(28) Gillard, J. W.; Israel, M. *Tetrahedron Lett.* **1981**, *22*, 513.

(29) Lactol **19** was converted into benzoates **i**, which were reacted with trimethylsilyl bromide. Low-temperature ^1H NMR showed bromide **3** (90%) and starting benzoates (10%). To the mixture was added 1 equiv of trimethylsilyl acetate. The ^1H NMR showed the presence of acetates **23** (4–5%).



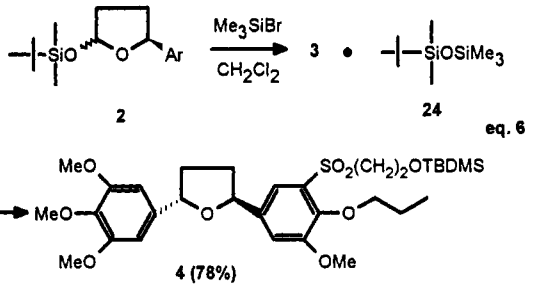
(30) Kochi, J.; Tamura, M. *Synthesis* **1971**, 303.

Scheme IV[a]



[a] (a) Hydroxyethyl disulfide/Cu^0/DMF; (b) magnesium monoperoxyphthalate/CH_3CN/H_2O; (c) *tert*-butyldimethylsilyl chloride/imidazole/DMF; (d) Dibal, toluene.

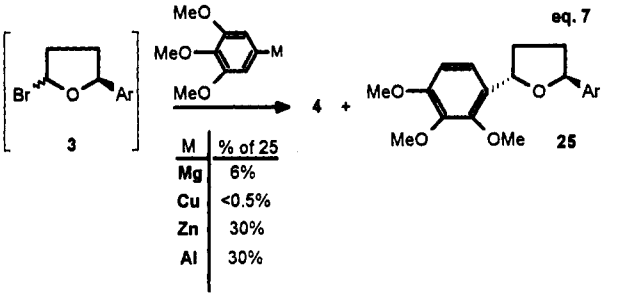
Reaction of silylated acetal **2** with TMSBr in CH_2Cl_2 at −60 °C affords bromide **3** with >99% conversion, eq 6.



Subsequent addition of a THF solution of 3,4,5-trimethoxyphenyl Grignard produces MK-287 silyl ether **4** in 78% yield. The starting silyl acetals were present at <1% (by HPLC). The high conversion of **2** into **3** is due to formation of a strong silicon oxygen bond, thus driving the reaction to the right with the formation of mixed disiloxane **24**. The reaction utilizes the initially formed silicon byproduct as a means to complete the conversion of **2** into **3**. The disiloxane has the additional value of being inert to the subsequent Grignard coupling step. Thus a true in situ method to form bromide **3** has been developed wherein the activation byproduct is an innocuous, volatile, and inert species.

Several additional points about the silyl acetal activation method should be noted. The conversion is incomplete with trimethylsilyl chloride. Solvent choice is also important since the conversion is rapid in noncoordinating solvents such as methylene chloride and incomplete in THF. Molecules containing a basic nitrogen atom do not react, even in the presence of excess trimethylsilyl bromide. The *trimethyl*silyl analog of **2** is unstable toward dimerization to form acetals **22**. Lastly, when applied to tri-*O*-benzylarabinofuranose, the activation required 2 h at 23 °C to go to completion.

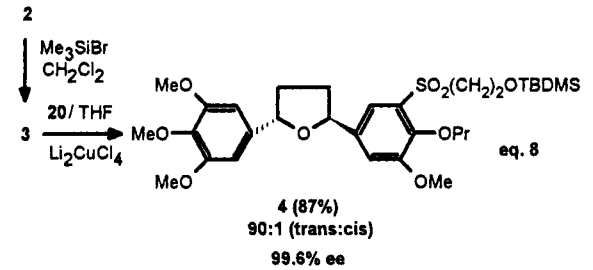
Copper-Catalyzed Grignard Coupling. With the lactol activation step now in place we investigated the Grignard coupling step more thoroughly. Our aim was to determine if magnesium was the optimum metal for bromide displacement. After examining several metals we determined that the most suitable organometallics were derived from the addition of copper salts to the Grignard reagent. Use of salts such as CuCN (0.5 equiv) or dilithium tetrachlorocuprate (1.5 mol %)[31] increased the coupling yield to 86%. Other metals were far less satisfactory. For example the organolithium and organocerium reagents failed to yield any coupled product. Transmetalation of the Grignard reagent **20** with $ZnCl_2$ (1 equiv) followed by aryl coupling resulted in a reasonable 8:1 trans:cis ratio of diaryltetrahydrofurans. However, the zinc reagent also produced ca. 30% of the ortho isomer **25** (ortho coupling pattern at δ = 6.7 and 7.15 ppm with a J = 8.6 Hz). Similar results were obtained with the aluminum reagent derived from (3,4,5-trimethoxyaryl)lithium and Me_2AlCl, eq 7.



M	% of 25
Mg	6%
Cu	<0.5%
Zn	30%
Al	30%

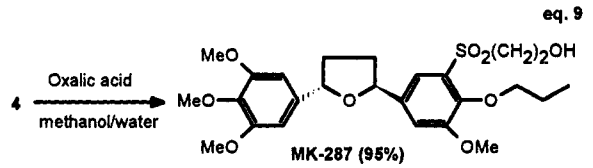
Formation of ortho isomer **25** was unexpected. Analysis by HPLC of the original Grignard coupling mixtures (without copper catalysis) showed 6–8% of ortho isomer **25**. The possibility of a regioisomeric organometallic was ruled out by deuterium quenching experiments. The Grignard reagent **20** was quenched with D_2O, and the product contained >95% deuterium at the C-5 position (by ^1H and ^{13}C NMR). We rationalize the formation of **25** as arising from a competitive Friedel–Crafts arylation of bromide **3**. Use of weaker Lewis acidic metals such as the copper reagents suppress the formation of **25** to levels below 0.5%.

The optimum conditions for the coupling reaction utilize silyl acetal **2** and dilithium tetrachlorocuprate catalysis, eq 8. Thus, a methylene chloride solution of silyl acetal



2 at −60 °C was reacted with 1.1 equiv of TMSBr. To this mixture was added a THF solution of Grignard reagent **20** which contains Li_2CuCl_4 (1–5 mol %).[31] After a 1 h reaction time, the product was isolated in 84–87% yield using an aqueous ammonium hydroxide workup. The level of cis isomer is less than 2%, and the optical purity of **4** is >99% ee. At this stage, the product was purified by filtration through a column of silica gel. This step removed byproducts from the Grignard reagent (i.e. trimethoxybenzene) and highly colored impurities.

Synthesis of MK-287. The synthesis of MK-287 was completed by desilylation of **4**, eq 9.



plished using either of two methods. The first is a standard desilylation using tetra-*n*-butylammonium fluoride in THF[24] and affords MK-287 in 98% yield. Alternatively, one can use a more economical procedure of oxalic acid in methanol/water. After 18 h at 23 °C, silyl ether **4** is converted into MK-287 in 95% yield. Acids stronger than oxalic acid were not useful since epimerization of the benzylic position adjacent to the trimethoxyphenyl ring becomes competitive with desilylation. The final product

(31) The exact charge of Li_2CuCl_2 is not critical. The reaction performs reproducibly using 0.1 mol % up to 5 mol % of the catalyst. We arbitrarily use 1.5 mol % of copper catalyst.

is purified by recrystallization from ethyl acetate/hexanes.

Conclusion

Our synthesis of MK-287 proceeds in 12 steps from commercially available 5-iodovanillin. The overall yield of the process is 27–30%. Noteworthy features include the high yield of the Stetter reaction using an acrylate as the acceptor, the in situ chloroborane synthesis using pinene of 83% ee, and the use of a silyl acetal as a substrate for anomeric activation.

Experimental Section

General Experimental. Melting points were determined on a Thomas-Hoover melt-temp and are uncorrected. Proton and ^{13}C NMR data were obtained using a Bruker AM 300 NMR spectrometer. All NMR data are reported relative to residual chloroform in the $CDCl_3$ (7.26 and 77.0 ppm). Combustion analyses were performed by Robertson Microlit Laboratories, Madison, NJ. Solvents were sieve-dried, and the water content was measured by Karl–Fisher titration. Water contents reported in this paper refer to micrograms/milliliter of solution and appear as KF values in parentheses. Yields quoted in this paper are based on HPLC assay using the external standard method. Temperatures quoted refer to the internal reaction temperature as monitored by a Teflon-coated thermocouple. All reagents were purchased from Aldrich Chemical Co. unless otherwise stated. All characterization data was performed on analytically pure samples, which were purified by recrystallization or by silica gel chromatography.[32]

Preparation of 4-Propyl-5-iodovanillin (6). 5-Iodovanillin (100 g, 0.36 mol) was dissolved in 250 mL of DMF (KF ≤ 160 μg/mL), and the mixture was heated at 50 °C. Anhydrous potassium carbonate (60 g, 0.43 mol) was added in one portion followed by *n*-propyl bromide (50 mL, 0.54 mol), resulting in a thick slurry which was difficult to stir. The mixture was heated to 70 °C over 15 min, and the reaction was monitored by HPLC at 0.5-h intervals until complete consumption of 5-iodovanillin (2 h). The stirred slurry was cooled to 20–25 °C, and 400 mL of H_2O was added. The pH of the mixture was adjusted from 11.3 to 7.0 by dropwise addition of 105 mL of 3 M HCl while maintaining the temperature between 20 and 25 °C and carefully controlling the effervescence of carbon dioxide gas. Ethyl acetate (250 mL) was added, and the organic layer (lower layer) was separated. The aqueous layer was extracted with an additional 250 mL of ethyl acetate, and the combined organic extracts were washed with 500 mL of 5% aqueous NaCl. The ethyl acetate extract was concentrated to half volume (250 mL), and 500 mL of DMF was added. The solution was concentrated in vacuo, keeping the temperature <50 °C, to about half volume (total volume 600 mL). The mixture at this point had a KF ≤200 μg/mL and showed no ethyl acetate by NMR. HPLC assay showed 109 g of the desired product (95% yield): HPLC conditions [C-8, CH_3CN/H_2O/phosphoric acid, 60:40:0.1, UV detection at 254 nm] 5-iodovanillin t_R = 3.5 min, propylated 5-iodovanillin t_R = 8.1 min; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.03 (t, *J* = 7.4 Hz, 3 H), 1.81 (m, 2 H), 3.84 (s, 3 H), 4.01 (t, *J* = 6.8 Hz, 2 H), 7.35 (d, *J* = 1.6 Hz, 1 H), 7.81 (d, *J* = 1.6 Hz, 1 H), 9.78 (s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 189.8, 153.7, 152.9, 134.9, 133.6, 110.9, 92.5, 75.3, 56.1, 23.6, 10.7; IR (thin film) 2950, 1680, 1575, 1550, 1450, 1405, 1375, 1265 cm^{-1}; MS [EI] *m/e* 319.9904 (319.9909 calcd for $C_{11}H_{13}O_3I$).

Preparation of Keto Ester 7. A 4-propyl-5-iodovanillin solution in DMF (15.0 g, 0.0469 mol in a 100 mL solution) (KF ≤ 800 μg/mL) was deoxygenated by bubbling N_2 through the solution for 10 min. Sodium cyanide (0.574 g, 0.0117 mol) was added in one portion, and the temperature was maintained between 25 and 30 °C. After stirring for 45 min, a solution of *tert*-butyl acrylate (6.17 mL, 5.40 g, 0.0422 mol) in deoxygenated DMF (32 mL, KF ≤ 200 μg/mL) was added over 50 min, keeping the temperature between 20 and 25 °C. The course of the reaction was monitored by HPLC. The reaction was stirred for 30 min after complete acrylate addition. Ethyl acetate (75 mL) and 15% aqueous NaCl (90 mL) were added to the reaction mixture, and the layers were separated. The aqueous phase was back extracted with ethyl acetate (75 mL). The combined organic extracts were washed with saturated aqueous $NaHCO_3$ (75 mL), followed by 2 × 75 mL of 5% aqueous NaCl. The ethyl acetate layer was concentrated in vacuo to give 17.8 g (85%) of the desired keto ester **7** by HPLC assay: HPLC conditions [Zorbax C-8, CH_3CN/H_2O/phosphoric acid, 70:30:0.1 gradient to 100:0:0.1, over 7 min; flow in 1.5 mL/min; UV detection at 254 nm] starting aldehyde t_R = 3.7 min, benzoin **10** t_R = 5.8 min, acid **9** t_R = 2.7 min, benzoin ester **11** t_R = 10.8 min, keto ester **7** t_R = 5.4 min; ^1H NMR (300 MHz, $CDCl_3$) δ 7.95 (d, *J* = 1.9 Hz, 1 H), 7.47 (d, *J* = 1.9 Hz, 1 H), 3.96 (t, *J* = 6.6 Hz, 2 H), 3.84 (s, 3 H), 3.15 (t, *J* = 6.6 Hz, 2 H), 2.63 (t, *J* = 6.6 Hz, 2 H), 1.81 (sextet, *J* = 7.1 Hz, 2 H), 1.42 (s, 9 H), 1.04 (t, *J* = 7.4 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 196.0, 172.0, 152.5, 152.3, 133.9, 131.5, 111.9, 92.3, 80.6, 75.1, 56.1, 33.2, 29.4, 28.1, 23.6, 10.7; IR (thin film) 2960, 2925, 1725, 1685, 1580, 1555, 1400, 1150 cm^{-1}; MS [EI] *m/e* 448.0781 (448.0746 calcd for $C_{18}H_{25}O_5I$).

Preparation of Diisopinocampheylchloroborane. To borane methyl sulfide (2.48 mL, 0.028 mol) and 5 mL of dry THF (KF <100 μg/mL) under N_2 at 0 °C was added (*R*)-(+)-α-pinene (9.76 mL, 0.0616 mol $[\alpha]_D$ = +43 (neat)) dropwise over 15 min. After 1 h at 0 °C, a white precipitate formed. The thick slurry was aged for 17 h at 0–5 °C. A 7.0 M solution of HCl in THF (4.0 mL, 0.028 mol) was added to the slurry dropwise over 15 min at 0 °C while maintaining the rate of gas evolution by the rate of HCl/THF addition. The HCl solution was prepared by bubbling HCl gas through THF while maintaining the temperature at <25 °C using a cooling bath. The concentration of HCl was determined by NaOH titration using a phenolphthalein indicator. **CAUTION**: During the addition of the HCl solution to the borane, H_2 gas evolves. The rate of gas evolution was controlled by the rate of HCl addition. The mixture becomes a clear solution within 15 min after the addition of HCl. After 30 min, the resulting chloroborane solution was used for a chiral reduction by addition of the ketone in THF.

NMR studies indicate that the chloroborane slowly decomposes in THF (~5% per day). The pinene used in this preparation must *not* be dried over molecular sieves, since this will decompose the pinene.

Preparation of Lactone 1. (–)-Chlorodiisopinocampheylborane (6.0 g, 0.0187 mol) was dissolved in 6 mL of dry THF (KF ≤ 70 μg/mL) and cooled to 0 °C under N_2. Keto ester **7** (5.0 g, 0.0111 mol) dissolved in 5 mL of THF was added dropwise. The mixture was stirred at 0 °C for 4 h and then allowed to stand at 0–5 °C for 24–48 h until HPLC assay showed no ketone remaining: HPLC conditions [Zorbax C-8 CH_3CN/H_2O/phosphoric acid, 70:30:0.1, isocratic; flow = 1.5 mL/min; UV detection at 254 nm] ketone **7** t_R = 8.1 min, hydroxy ester **8a** t_R = 5.3 min. Water (5 mL) was added dropwise over 15 min while maintaining the reaction temperature at <10 °C. Methanol (13 mL) was added dropwise over 10 min followed by 15 mL of 5 M NaOH (15 min), again keeping the temperature at <10 °C.

The bright yellow mixture was allowed to warm to 23 °C and stirred for 1.5 h until HPLC showed no starting material. The orange solution was poured into 100 mL of *tert*-butyl methyl ether (MTBE) and 37 mL of saturated aqueous $NaHCO_3$. The aqueous phase was washed with 80 mL of MTBE, acidifed to pH 2 using 6 M HCl, and extracted with toluene (2 × 90 mL). Pyridinium *p*-toluenesulfonate (30 mg) was added, and the toluene solution was heated to 70 °C under vacuum to azeotropically remove water. The reaction was followed by HPLC assay. After ~45 min, the mixture was cooled to rt and washed with 100 mL of saturated $NaHCO_3$, and the toluene was removed in vacuo to a volume of 5.5 mL. Hexanes (23 mL) was added dropwise over 3 h. The mixture was stirred for 2 h at rt, and then the white solid was filtered. The cake was washed with 10% toluene in hexanes (10 mL) and dried in vacuo to provide 2.85 g of lactone **1** (68% from keto ester **7**, >99.5% ee).

Lactone Purification. If the direct crystallization from toluene/hexanes does not provide a lactone with ≥99.5% ee a purification method has been developed. The method, as described below, has been used to upgrade lactone of 98% ee to ≥99.5% ee in 93% yield. Lactone **1** (6.0 g) suspended in 2.5 mL of ethyl acetate and 2.5 mL hexane was stirred for 16 h. Hexane (20 mL) was added dropwise (30 min), and the mixture was stirred

(32) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

for 30 min. The white crystals were collected, washed with hexane 2 × 15 mL, and dried in vacuo (5.6 g). HPLC assay showed 99.8% ee: HPLC conditions [Zorbax C-8, CH_3CN/H_2O/phosphoric acid, 50:50:0.1 gradient over 10 min to 80:20:0.1; flow = 1.5 mL/min; UV detection at 254 nm] hydroxy acid **8b** t_R = 4.1 min, lactone **1** t_R = 8.9 min, toluene t_R = 8.0 min; chiral HPLC conditions [chirasphere column, 254 nm, hexane/THF/2-propanol, 83:12:5] major isomer t_R = 10.7 min, minor isomer t_R = 8.0 min. In addition, an NMR method using (*S*)-(+)-2,2,2-trifluoro-1-(9-anthryl)ethanol in CD_2Cl_2 was used to analyze the optical purity of the lactone: $[\alpha]_D$ = −24.1 (*c* = 1.06, $CHCl_3$); mp 82.5–83 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 7.27 (d, *J* = 1.9 Hz, 1 H), 6.84 (d, *J* = 1.9 Hz, 1 H), 5.38 (dd, *J* = 6.1, 8.1 Hz, 1 H), 3.92 (t, *J* = 6.8 Hz, 2 H), 3.84 (s, 3 H), 2.69–2.57 (m, 3 H), 2.20–2.13 (m, 1 H), 1.84 (sextet, *J* = 7.1 Hz, 2 H), 1.06 (t, *J* = 7.3 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.6, 152.9, 148.4, 136.9, 127.3, 109.9, 93.0, 80.1, 75.0, 56.1, 31.0, 29.0, 23.6, 10.7; IR ($CHCl_3$) 3000, 2960, 2870, 1770, 1455 cm^{-1}. Anal. Calcd for $C_{14}H_{17}O_4I$: C, 44.70; H, 4.55. Found: C, 44.90; H, 4.55.

Preparation of Sulfone 17. Iodo lactone **1** (2.0 g, 5.33 mmol) was dissolved in DMF (15 mL, KF < 200 μg/mL) at ambient temperature under N_2. Copper bronze (Aldrich) (0.51 g, 7.995 mmol) and then 2-hydroxyethyl disulfide (0.66 g, 4.264 mmol) was added to the solution. The mixture was heated to 108 °C for 22 h. The mixture was cooled to ambient temperature, and 40 mL of ethyl acetate was added (prior to filtration). The solution was stirred for 15 min and filtered through a Celite pad. The cake was washed with 25 mL of ethyl acetate. The combined organic extracts were washed with 3 × 40 mL of an NH_4Cl/NH_4OH solution (10:1 v:v, pH = 9.0) followed by 40 mL of H_2O. The organic extract was concentrated in vacuo to a volume of 4 mL. The solution was diluted and concentrated with 2 × 20 mL of acetonitrile and concentrated to ~4 mL. The acetonitrile solution was used directly in the next step. HPLC assay typically showed an 85–90% yield of the sulfide: HPLC conditions [Zorbax C-8, CH_3CN/H_2O/phosphoric acid, 60:40:0.1; flow = 1.5 mL/min; UV detection at 254 nm] iodolactone **1** t_R = 8.0 min, sulfide **16** t_R = 3.2 min; ^1H NMR (300 MHz, $CDCl_3$) δ 6.89 (d, *J* = 1.8 Hz, 1 H), 6.76 (d, *J* = 1.8 Hz, 1 H), 5.40 (dd, *J* = 6.0, 8.2 Hz, 1 H), 3.95 (t, *J* = 6.8 Hz, 2 H), 3.83 (s, 3 H), 3.66 (q, *J* = 6.0 Hz, 2 H), 3.04 (t, *J* = 5.9 Hz, 2 H), 2.69–2.59 (m, 4 H), 2.20–2.13 (m, 1 H), 1.81 (sextet, *J* = 7.1 Hz, 2 H), 1.03 (t, *J* = 7.4 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.8, 153.3, 147.5, 135.5, 129.8, 119.6, 108.4, 80.9, 75.2, 60.3, 56.1, 36.5, 31.0, 29.1, 23.5, 10.5; MS [EI] *m/e* 326.1211 (326.1188 calcd for $C_{16}H_{22}O_5S$).

Monoperoxyphthalic acid magnesium salt (13.66 g, 27.6 mmol) was suspended in 40 mL of H_2O at ambient temperature. A solution of sulfide **16** (5.0 g, 15.3 mmol) in 27 mL of acetonitrile was added dropwise over 15 min while keeping the temperature at <30 °C. The mixture was then heated to 50 °C for 2 h. After determining by HPLC that no sulfide or sulfoxide remained, the reaction mixture was cooled to room temperature, 65 mL of saturated $NaHCO_3$ was added over 5 min (gas evolution), and the mixture was extracted with 55 mL of ethyl acetate. The aqueous layer was back extracted with 55 mL of ethyl acetate, and the combined organics were washed with saturated $NaHCO_3$ (2 × 65 mL) and 5% aqueous NaCl (50 mL). The organic extracts were concentrated in vacuo to a volume of 20 mL. DMF (20 mL) was added, and the mixture was then reconcentrated in vacuo to ca. 20 mL. The solution is used directly for the next step. HPLC assay shows a 5.2-g (95%) yield: HPLC conditions [Zorbax C-8, CH_3CN/H_2O/phosphoric acid, 30:70:0.1 gradient over 10 min to 80:20:0.1; flow = 1.5 mL/min; UV detection at 254 nm] sulfide t_R = 9.9 min, sulfoxide t_R = 5.5 min, sulfone t_R = 7.7 min; $[\alpha]_D$ = −17.6 (*c* = 1.1, $CHCl_3$); mp 75–77 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 7.43 (d, *J* = 1.8 Hz, 1 H), 7.20 (d, *J* = 1.9 Hz, 1 H), 5.50 (dd, *J* = 6.0, 8.7 Hz, 1 H), 4.12 (m, 2 H), 3.96 (t, *J* = 5.2 Hz, 2 H), 3.92 (s, 3 H), 3.67–3.63 (m, 2 H), 2.79–2.66 (m, 4 H), 2.23–2.10 (m, 1 H), 1.86 (sextet, *J* = 7.2 Hz, 2 H), 1.03 (t, *J* = 7.4 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.3, 154.1, 146.8, 135.6, 133.1, 117.4, 114.7, 80.2, 76.5, 57.5, 56.5, 30.9, 29.1, 23.2, 10.3; IR ($CHCl_3$) 3540, 3010, 2960, 1780, 1485, 1460, 1305 cm^{-1}. Anal. Calcd for $C_{16}H_{22}O_7S$: C, 53.66; H, 6.19; S, 8.95. Found: C, 53.73; H, 6.25; S, 9.06.

Preparation of Silyl Ether 18. Imidazole (0.85 g, 12.57 mmol) was added to a solution of sulfone **17** (3.0 g, 8.38 mol) in 6 mL of DMF (KF = 278 μg/mL) at room temperature. A solution of *tert*-butyldimethylsilyl chloride (1.39 g, 9.2 mmol) in 3 mL of DMF was added over 10 min while keeping the temperature at ≤30 °C. The mixture was stirred at 25 °C for 2 h and the reaction followed by HPLC. Once complete, ethyl acetate (38 mL) was added and the mixture was washed with H_2O (25 mL) and then with 5% aqueous NaCl (2 × 25 mL). The organic extracts were concentrated in vacuo to a volume of 10 mL. Toluene (50 mL) was added and the solution concentrated to a volume of 10 mL and checked by NMR for ethyl acetate (typically <5% EtOAc). HPLC assay shows a 3.6-g. (95%) yield: HPLC conditions [Zorbax C-8, CH_3CN/H_2O/phosphoric acid, 50:50:0.1 gradient to 80:20:0.1 over 8 min; flow = 1.5 mL/min; UV detection at 294 nm] alcohol t_R = 3.0 min, silyl ether **18** t_R = 14.1 min; $[\alpha]_D$ = −11.8 (*c* = 1.1, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.38 (d, *J* = 1.9 Hz, 1 H), 7.15 (d, *J* = 1.9 Hz, 1 H), 5.46 (dd, *J* = 5.8, 8.6 Hz, 1 H), 4.10 (m, 2 H), 3.95 (t, *J* = 6.1 Hz, 2 H), 3.89 (s, 3 H), 3.72–3.57 (m, 2 H), 2.67–2.61 (m, 3 H), 2.20–2.10 (m, 1 H), 1.86 (sextet, *J* = 7.2 Hz, 2 H), 1.03 (t, *J* = 7.4 Hz, 3 H), 0.73 (s, 9 H), −0.092 (s, 3 H), −0.097 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.4, 154.0, 146.9, 135.1, 134.5, 117.2, 114.3, 80.4, 76.1, 57.6, 57.1, 56.4, 30.9, 29.1, 25.6, 23.2, 18.0, 10.3, −5.7; IR (thin film) 3060, 2940, 1775, 1600, 1480, 1460, 1315, 1280, 1250 cm^{-1}. Anal. Calcd for $C_{22}H_{36}O_7SSi$: C, 55.90; H, 7.68; S, 6.78. Found: C, 55.97; H, 7.83; S, 7.06.

Preparation of Butyrolactol 19. To a solution of the lactone **18** (1.607 kg, 3.405 mol) in dry toluene (13 L, KF = 13 μgm/mL) at −72 °C was added a 1.5 M toluene solution of DIBALH (3.50 L, 5.25 mol) dropwise at a rate of 2 L/h. The internal temperature was maintained below −60 °C during this addition. The mixture was stirred at −70 °C for 1 h, while the reaction progress was monitored by HPLC. Upon completion, the reaction was quenched through the addition of methanol (1.5 L) while maintaining a temperature of <−60 °C. The mixture was warmed to −20 °C followed by the addition of saturated aqueous potassium sodium tartrate solution (12 L) while maintaining the reaction temperature between −10 and 0 °C. The mixture was stirred at 0 °C for 3 h, and then the two phases were separated. The aqueous layer was extracted with ethyl acetate (12 L). The combined organic layers were washed with deionized water (2 × 8 L) followed by saturated NaCl solution (10 L). The organic layer was concentrated to afford 1.799 kg of a pale yellow oil. HPLC assay shows 1.565 kg (97%) of lactol **19**: HPLC [Zorbax Rx C-8, CH_3CN/H_2O/phosphoric acid, 50:50:0.1 gradient elution to 80:20:0.1 over 8 min; flow = 1.5 mL/min; UV detection at 292 nm] lactone **18** t_R = 11.4 min, lactol **19** t_R = 10.4 min.

The product is an inseparable 1:1 mixture of anomers. The proton intensities listed below are given relative to the number of protons from the molecular formula of **19**: $[\alpha]_D$ = −19.5 (*c* = 1.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.45 (d, *J* = 1.9 Hz, 0.5 H), 7.42 (d, *J* = 1.9 Hz, 0.5 H), 7.35 (d, *J* = 1.9 Hz, 0.5 H), 7.13 (d, *J* = 1.9 Hz, 0.5 H), 5.78 (dd, *J* = 5.1, 1.9 Hz, 0.5 H), 5.65 (br s, 0.5 H), 5.22 (apparent t, *J* = 7.0 Hz, 0.5 H), 5.00 (dd, *J* = 9.2, 6.3 Hz, 0.5 H), 4.10 (t, *J* = 6.8 Hz, 2 H, $OCH_2CH_2CH_3$), 3.96 (t, *J* = 6.2 Hz, 2 H, CH_2OSi), 3.90 (s, 3 H, OCH_3), 3.66 (t, *J* = 6.3 Hz, 2 H, $SO_2CH_2CH_2$), 3.10 (br s, 0.5 H, OH), 2.84 (br s, 0.5 H, OH), 2.57–1.70 (m, 4 H), 1.87 (sextet, *J* = 7.1 Hz, 2 H, $OCH_2CH_2CH_3$), 1.04 (t, *J* = 7.4 Hz, 3 H, $OCH_2CH_2CH_3$), 0.77 (s, 9 H, Si-t-Bu), 0.05 (s, 6 H, $Si(CH_3)_2$); IR (thin film) 3450, 2950, 1600, 1480, 1460, 1315 cm^{-1}. Anal. Calcd for $C_{22}H_{38}O_7SSi$: C, 55.66; H, 8.07; S, 6.75. Found: C, 55.91; H, 8.27; S, 6.88.

Preparation of Silyl Acetal 2. To a solution of the lactol **19** (1.522 kg, 3.211 mol) in DMF (KF = 55 μg/mL) at 25 °C under N_2 was added imidazole (0.48 kg, 7.059 mol), followed by *tert*-butyldimethylsilyl chloride (0.53 kg, 3.533 mol). The mixture was stirred at 25 °C, under N_2, for 3 h. The progress of the reaction was monitored by HPLC. Once complete, the reaction was diluted with EtOAc (20 L) and deionized H_2O (10 L). The organic layer was separated then washed with deionized H_2O (3 × 10 L) followed by saturated NaCl solution (10 L). The organic phase was concentrated in vacuo, diluted with toluene (2 L), and then reconcentrated to afford 2.170 kg of a yellow oil. HPLC assay shows 1.898 kg (100%) of silyl acetal **2**. HPLC conditions [Zorbax Rx C-8, CH_3CN/H_2O/phosphoric acid, 70:30:0.1 gradient elution to 95:5:0.1 over 15 min; flow = 1.5 mL/min; UV detection at 292 nm] lactol **19** t_R = 5.2 min, silyl lactols **2** t_R = 19.4, 19.6 min. Analysis by ^1H NMR shows <2 mol % of DMF remaining.

Analysis by capillary gas chromatography shows <0.1% ethyl acetate. GC conditions [DB-1 column, 30 m, temperature gradient 40–100 °C at a rate of 10 °C/min] ethyl acetate t_R = 2.2 min, toluene t_R = 3.5 min.

The product is a 2:1 mixture of anomers which are not separated. The proton intensities listed below are given relative to the number of protons from the molecular formula of 2: $[\alpha]_D$ = −11.2 (c = 1.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.40 (m, 1 H), 7.37 (d, J = 1.9 Hz, 0.3 H), 7.11 (d, J = 1.9 Hz, 0.6 H), 5.71 (dd, J = 4.6, 1.3 Hz, 0.6 H), 5.60 (d, J = 3.9 Hz, 0.3 H) 5.14 (t, J = 6.8 Hz, 0.6 H), 4.91 (m, 0.3 H), 4.10 (m, 2 H, $OCH_2CH_2CH_3$), 3.95 (m, 2 H, CH_2OSi), 3.89 (s, 3 H, OCH_3), 3.65 (t, J = 6.4 Hz, 2 H, $SO_2CH_2CH_2$), 2.49 (m, 0.6 H), 2.23 (m, 0.3 H), 2.15–1.65 (m, 3 H), 1.87 (sextet, J = 7.3 Hz, 2 H, $OCH_2CH_2CH_3$), 1.04 (t, J = 7.4 Hz, 3 H, $OCH_2CH_2CH_3$), 0.91 (s, 9 H, Si-t-Bu), 0.77 (s, 9 H, Si-t-Bu), 0.13 (m, 6 H, $Si(CH_3)_2$), −0.05 (s, 6 H, $Si(CH_3)_2$); IR (thin film) 2950, 2850, 1600, 1480, 1460, 1310 cm^{-1}. Anal. Calcd for $C_{28}H_{52}O_7Si_2S$: C, 57.10; H, 8.89; S, 5.44. Found: C, 57.00; H, 9.15; S, 5.35.

Preparation of Dilithium Tetrachlorocuprate in Tetrahydrofuran (0.5 M). To a dry 500-mL volumetric flask under N_2 was added anhydrous LiCl (21.6 g, 0.502 mol) followed by anhydrous $CuCl_2$ (33.7 g, 0.250 mol). To the flask was added sieve-dried, nitrogen degassed tetrahydrofuran (300 mL, KF = 7 μgm/mL). The resulting slurry exotherms to 30 °C and was swirled to dissolve the salts. After 2–3 h, the solution was diluted to the 500 mL mark with dry THF. The suspension was aged for 24 h before use.

Preparation of (3,4,5-Trimethoxyphenyl)magnesium Bromide (20). In a 22-L, three-neck flask fitted with an overhead stirrer, a 2-L addition funnel, and an N_2 inlet was charged magnesium turnings (0.228 kg, 9.91 mol). The flask was then charged with nitrogen degassed, tetrahydrofuran (4.5 L, KF = 14 μgm/mL). In a separate vessel, the bromide (NIPA Chemical Co.) was dissolved in degassed tetrahydrofuran (4.5 L) resulting in a total volume of ca. 6 L. To the flask containing the Mg turnings, with stirring at 25 °C under N_2, was then added a 300-mL portion of the bromide/THF solution. To this mixture was added solid I_2 (4.5 g, 0.018 mol), and the mixture was stirred for 0.5 h. The reaction initiates as indicated by a temperature rise to 34 °C. The remainder of the bromide/THF solution was added over 6 h while maintaining the reaction temperature between 25 and 30 °C, by immersing the reaction vessel in a cold water bath (10 °C), as needed. After addition was complete, the reaction was stirred at 25 °C under N_2 for 18 h. The stirrer was turned off, and once the magnesium has settled, the supernatant was assayed by titration and by capillary gas chromatography (after protonation with H_2O). A total of 9 L of a dark green solution was obtained for which the concentration of active Grignard was 0.95 M. The yield of active Grignard reagent was 96%. This solution should be used within 1–2 days of preparation. The Grignard reagent was titrated by adding 1.0 mL to a dry flask under N_2, containing ca. 3 mg of 1,10-phenanthroline in 1 mL of dry tetrahydrofuran. The resulting wine red solution is back titrated with a solution of menthol in xylene of known concentration (typically 1 M) until the red color discharges. The number of millimoles of menthol required is the concentration of the Grignard reagent.

The impurity profile was determined by capillary gas chromatography. A 1-mL sample was added to 4 mL of tetrahydrofuran containing 0.05 mL of H_2O under N_2, followed by addition of saturated NH_4Cl (5 mL). The organic phase (upper layer) was analyzed without further dilution: GC conditions [DB-5 column, 10 m, temperature gradient 100–250 °C at rate of 10 °C/min; maintain 250 °C for 5 min] trimethoxybenzene (protonated Grignard) t_R = 3.9 min, Grignard dimer t_R = 17.5 min. The area percent for the trimethoxybenzene peak must be ≥85% with no other peak >4% by area.

A 12-L flask is fitted with a stirring paddle, a 2-L addition funnel, and an N_2 inlet. To this flask was added the Grignard reagent via canula transfer (0.95 M, 7 L, 6.65 mol), and the vessel was cooled to 0 °C in a ice–H_2O bath. To the Grignard reagent was added a solution of dilithium tetrachlorocuprate (0.5 M, 0.25 L, 0.125 mol). The mixture was stirred at 0 °C for 15 min and then used immediately for the coupling reaction.

Preparation of MK-287 TBDMS Ether (4). In a 72-L flask the silyl acetal 2 (2.95 kg, 5.02 mol) was dissolved in degassed, methylene chloride (17 L, KF = 10 μg/mL). The mixture was cooled to −60 °C under N_2, and then TMSBr (0.73 L, 5.53 mol) was added over 5 min, maintaining the temperature at −60 °C. The mixture was stirred at −60 °C for 1.5 h. The Grignard/Li_2CuCl_4 mixture was transferred via canula to the reaction vessel containing the α-bromo ether 3. The transfer requires 2 h, and the reaction temperature was maintained at −60 °C during the addition. The mixture was stirred for 1 h at −60 °C and quenched with 10:1 saturated NH_4Cl/NH_4OH (20 L) and then deionized H_2O (10 L) to dissolve the salts. The mixture was stirred for 1.5 h without external cooling and then transferred to a 100-L reactor. The organic layer (lower layer) was removed, and the aqueous layer was extracted with EtOAc (20 L). The combined organics were washed with brine (20 L). HPLC assay shows 2.72 kg, 4.36 mol, of product (87% yield): HPLC conditions [Zorbax Rx C-8, CH_3CN/H_2O/phosphoric acid, 70:30:0.1 gradient elution to 95:5:0.1 over 15 min; flow = 1.5 mL/min; UV detection at 292 nm] MK-287 silyl ether 4 t_R = 11.4 min. The level of cis isomer present can be accurately determined using silica gel HPLC, HPLC conditions [Zorbax sil, hexanes/ethyl acetate, 70:30 isocratic; flow = 1.5 mL/min; UV detection at 294 nm] MK-287 silyl ether 4 t_R = 7.1 min, cis isomer t_R = 9.9 min. Ratios of 90:1 are typical. Samples enriched in the cis isomer can be analyzed by 300-MHz ^1H NMR. The aromatic proton adjacent to the sulfone is most diagnostic. In $CDCl_3$, this proton appears at δ = 7.47 ppm in the trans isomer and at δ = 7.57 ppm for the cis isomer. The HPLC area percent of MK-287 silyl ether is 85%.

Purification of MK-287 Silyl Ether by Silica Gel Chromatography. A column was slurry packed with silica gel (15 kg, 60–200 mesh) in hexanes. A toluene solution of MK-287 TBS ether (containing 2.7 kg of 4) was absorbed onto silica gel (2.5 kg) in hexanes (5 L), and the slurry was loaded onto the column. Once the level reaches the silica gel, the column was loaded with hexanes. The column was eluted with hexanes (100 L) followed by 97:3 (v:v) hexanes/ethyl acetate (100 L), then 5:1 hexanes/ethyl acetate (265 L), and finally with 2:1 hexanes/ethyl acetate. The column was eluted at a rate of 1 L/min. The eluent was collected in 20-L fractions.

Fractions 14–23 contained 2.37 kg (87.8%) of the MK-287 TBS ether. The column recovery was 2.36 kg (87.4%). The HPLC area percent purity of this material was 90%. Silyl ether 4: $[\alpha]_D$ = −58.0 (c = 1.1, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.47 (d, J = 1.9 Hz, 1 H), 7.26 (d, J = 1.9 Hz, 1 H), 6.62 (s, 2 H), 5.24 (t, J = 7.3 Hz, 1 H), 5.19 (t, J = 7.3 Hz, 1 H), 4.11 (t, J = 6.8 Hz, 2 H, $OCH_2CH_2CH_3$), 3.97 (t, J = 6.4 Hz, 2 H, CH_2OSi), 3.91 (s, 3 H, OCH_3), 3.89 (s, 6 H, OCH_3), 3.84 (s, 3 H, OCH_3), 3.66 (dt, J = 6.3, 1.5 Hz, 2 H, $SO_2CH_2CH_2$), 2.47 (m, 2 H), 1.98 (m, 2 H), 1.87 (sextet, J = 7.3 Hz, 2 H, $OCH_2CH_2CH_3$), 1.05 (t, J = 7.4 Hz, 3 H, $OCH_2CH_2CH_3$), 0.78 (s, 9 H, Si-t-Bu), −0.04 (s, 6 H, $Si(CH_3)_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.5, 153.2, 145.6, 139.4, 138.8, 137.0, 133.8, 117.2, 114.6, 102.2, 81.5, 80.5, 75.9, 60.7, 57.4, 56.9, 56.1, 56.0, 35.4, 25.6, 23.1, 17.9, 10.2, −5.7; IR (thin film) 3000, 2950, 1590 cm^{-1}. Anal. Calcd for $C_{31}H_{48}O_9SiS$: C, 59.62; H, 7.69. Found: C, 59.50; H, 7.88.

Preparation of *trans*-(−)-2-((3-Methoxy-2-propoxy-5-(tetrahydro-5-(3,4,5-trimethoxyphenyl)-2-furanyl)phenyl)-sulfonyl)ethanol (MK-287) [Oxalic Acid Deprotection Method]. MK-287 TBS ether 4 (12 g, 0.0192 mole) was dissolved in methanol (160 mL). To this solution was added H_2O (40 mL), resulting in a cloudy mixture. To the resulting solution was added solid oxalic acid (3 g, 0.033 mole), and the reaction mixture was stirred at 23 °C. The progress of the reaction was monitored by HPLC until less than 0.5% starting material remains (typically 20 h). The volatiles were removed in vacuo (bath temperature at 35 °C) to afford a yellow solid suspended in water. The solid was dissolved in isopropyl acetate (200 mL) by warming to 40 °C. After cooling to 23 °C the organic phase was washed with 1 N NaOH (2 × 40 mL) followed by a saturated NaCl solution (40 mL). The organic phase was concentrated to a volume of 50 mL. To this mixture, with stirring, was added hexanes dropwise (150 mL). The resulting slurry was stirred at 23 °C for 2 h under N_2. The solid was filtered and washed with 3:1 hexane/isopropyl acetate (2 × 50 mL). The solid was dried in a vacuum oven at 23 °C with a N_2 purge, to yield 9.25 g of a white free-flowing

powder, 94% yield. HPLC assay shows this material is 98.8% pure by weight (96.7% pure by area). The product can be purified further by recrystallization from ethyl acetate/hexanes (1:2): HPLC conditions [Zorbax Rx C-8, CH_3CN/H_2O/phosphoric acid, 30:70:0.1 gradient elution to 95:5:0.1 in 15 min, maintain 95:5:0.1 for 5 min; flow in 1.5 mL/min; UV detection at 292 nm) MK-287 TBS ether t_R = 18.1 min, MK-287 t_R = 11.8 min. The optical purity of the product can be determined by chiral HPLC: HPLC conditions [Pirkle type IA D-phenylglycine, three analytical columns in series, hexane/chloroform/2-isopropanol, 55:45:5, isocractic; flow = 0.6 mL/min; UV detection at 292 nm] MK-287 t_R = 42 min, *RR* enantiomer t_R = 41 min; $[\alpha]_D$ = -72.8 (c = 1.0, MeOH); mp 110-112 °C; ^1H NMR (250 MHz, $CDCl_3$) δ 7.50 (d, J = 2.0 Hz, 1 H), 7.29 (d, J = 2.0 Hz, 1 H), 6.61 (s, 2 H), 5.24 (m, 1 H), 5.22 (m, 1 H), 4.11 (t, J = 7.1 Hz, 2 H, $CH_3CH_2CH_2O$), 3.92 (broad m, 2 H, CH_2OH), 3.92 (s, 3 H, OCH_3), 3.88 (s, 6 H, OCH_3), 3.83 (s, 3 H, OCH_3), 3.66 (m, 2 H, CH_2SO_2), 2.90 (broad t, 1 H, OH), 2.50 (m, 2 H), 1.99 (m, 2 H), 1.87 (sextet, J = 7.1 Hz, 2 H, $CH_3CH_2CH_2O$), 1.04 (t, J = 7.1 Hz, 3 H, $CH_3CH_2CH_2O$); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 152.2 (s), 151.8 (s), 144.3 (s), 138.8 (s), 137.5 (s), 135.9 (s), 131.4 (s), 116.7 (d), 114.4 (d), 101.9 (d), 81.6 (d), 80.5 (d), 76.3 (t), 61.1 (q), 57.8 (t), 56.8 (t), 56.6 (q), 56.5 (q), 36.38 (t), 36.35 (t), 24.1 (t), 11.5 (q); IR (KBr) 3524, 3050-2800, 1597, 1460, 1310, 1130, 1280, 1234, cm^{-1}. Anal. Calcd for $C_{25}H_{34}O_9S$: C, 58.85; H, 6.66; S, 6.28. Found: C, 58.79; H, 6.72; S, 6.20.

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Studies in the Benzannulation of a Cycloalkynone: An Approach to the Synthesis of Antibiotics Containing the Benz[*a*]anthracene Core Structure

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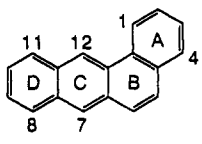
The chromium(0)-carbene complex benzannulation reaction was shown to be applicable to cyclodec-4-yn-1-one. Significant regioselectivity was realized in this reaction with ortho-substituted benzylchromium complexes. Reactions of a novel resultant fused cyclodecenone-naphthoquinone with several bases have been studied. Products apparently arising from either intramolecular Michael addition of a ketone enolate to the quinone or intramolecular aldol condensation of a quinone-stabilized anion with the ketone have been observed. The latter mode constitutes a route to the title substructure and, in principle, provides a route to reach certain angucycline antibiotics.

Background of the Problem

The angucyclines are antibiotics whose aglycon moieties are derivatives of benz[*a*]anthracene 1.[1] The antibiotics are divided into two major subclasses on the basis of structural features. The members of the first subclass,



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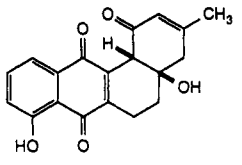

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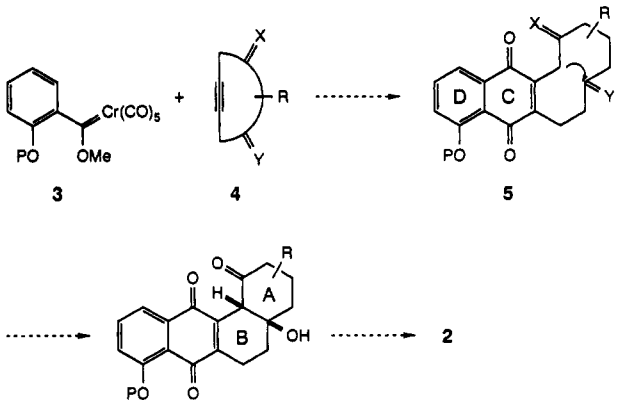
the angucyclinones, possess the benz[*a*]anthracene core structure but bear no *C*- or *O*-glycosyl domains. The members of the second subclass, the angucyclines, differ from the first in that they are glycosylated. Angucyclines are further divisible into systems bearing *C*- or *O*-glycosides as well as some which bear both *C*- and *O*-glycosidic linkages. Presently, more than 100 such antibiotics have been reported. All of the angucyclines isolated to date are secondary metabolites of the *Actinomycetes* group of microorganisms. In most cases, the organism which produces the antibiotic is a species of *Streptomycetes*. The angucyclines have been the subject of a recent comprehensive review.[2]

As a group the angucyclines display a wide range of biological activities. Individual members of this family of

Scheme I



antibiotics exhibit cytostatic, enzyme inhibitory, antibacterial, or antiviral activities. Additionally, a small number of angucyclinones inhibit platelet aggregation. OM-4842[3] and saquayamycins A-D[4] are perhaps the most compelling angucyclines, from a therapeutic standpoint, due to their activities against doxorubicin-resistant and adriamycin-resistant cell lines, respectively.

In proportion to the large number of structurally intriguing angucyclines, previous synthetic work in the area has been relatively sparse.[5] Our attention was drawn to

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