A Total Synthesis of Plumericin, Allamcin, and Allamandin. 2. A Biomimetic Strategy

Barry M. Trost,* James M. Balkovec, and Michael K.-T. Mao

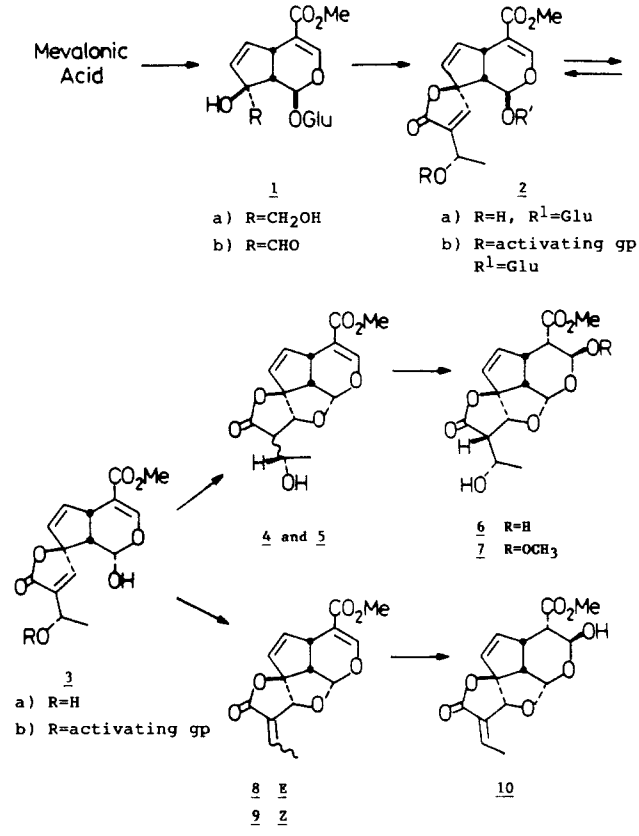
Contribution from the McElvain Laboratories of Organic Chemistry, Department of Chemistry, University of Wisconsin—Madison, Madison, Wisconsin 53706. *Received December 2, 1985*

Abstract: An efficient synthesis of plumeria and allamanda sesquiterpenoids, compounds that possess cytotoxic, antileukemic, antimicrobial, and antifungal activities, is reported. Analysis of the biosynthesis of plumericin and allamandin suggested formation of the tetracyclic framework from a tricyclic plumieride-type precursor. Exploration of this concept in two series demonstrated its validity. The requisite key intermediates were synthesized by using the concepts of substitutive spiroannulation to effect a stereocontrolled geminal alkylation of a carbonyl group with simultaneous substitution at the α position and sulfenylation–aldol condensation to elaborate an α-(hydroxyalkyl)-α,β-unsaturated carbonyl unit. In this way, an isoallamandin analogue has been synthesized. An alternative strategy introduced the carbomethoxy group at the final stage of synthesis. A general method to carbomethoxylate an enol ether as required to convert descarbomethoxyplumericin to plumericin was developed. By using these three key methods, (±)-plumericin was synthesized in 16 steps from cycloocta-1,3-diene and (±)-allamandin in one more step by hydration of plumericin. Descarbomethoxyallamandin, which was synthesized as an intermediate, was subsequently discovered as a natural product and named allamcin. The biosynthetic implications are discussed. A chromatographic resolution of *cis*-bicyclo[3.3.0]oct-7-en-*endo*-2-ol, an early intermediate, via the *O*-methylmandelate, which simultaneously establishes optical purity and absolute stereochemistry, offers the opportunity to convert this synthesis into one of the optically active series.

The broad diversity of biological activity exhibited by the iridoids has generated much interest in methods for their synthesis. We were especially attracted to the plumeria and allamanda type since (1) members of this class exhibit cytotoxic, antileukemic, antimicrobial, and antifungal activities,[1] (2) their densely functionalized skeletons offered a major synthetic challenge, and (3) no total syntheses of this family save for the simplest member fulvoplumierin has previously been recorded.[3]

Although very few biosynthetic investigations have been reported for the plumeria and allamanda type iridoids, a reasonable biosynthetic scheme may be proposed.[4] In 1964, Yeowel and Schmid reported that plumieride **4** is biosynthesized in *P. acutifolia* from mevalonic acid and acetate via L-citronellal and iridodial.[4b] The recent isolation of 10-dehydrogardenoside **1b**, which logically may derived by oxidation of gardenoside, from a plant containing allamanda iridoids[4c] suggests that this may be an intermediate along the biosynthetic pathway. A biomimetic transformation of **1b** into plumieride has been performed.[5] It can be imagined that removal of the glucose from **2a** permits the anomeric center to equilibrate. When the α-anomer **3** is formed, the proximity of the hydroxyl group of the enoate unit facilitates the intramolecular Michael reaction to form allamandicin (**5**)[3] and isoallamandicin (**6**).[3,6] Hydration of allamandicin would produce allamancin **6**; whereas, methanolysis would produce the corresponding methyl ether **7**. Alternatively, if the R group of **3** is functionalized in such a way as to increase the propensity of oxygen to be a leaving group **3b**, such a Michael addition may occur with expulsion of the side chain hydroxyl group to form plumericin (**8**) and isoplumericin (**9**).[7] Hydration of plumericin would complete the biosynthesis of allamandin (**10**).[7c,8]

Scheme I. Hypothetical Biosynthesis of Allamanda Type Iridoids



(1) For recent reviews, see: Buzogany, K.; Cucu, V. *Farmacia* **1983**, *31*, 129. Tietze, L.-F. *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 828. Sainty, D.; Bailleul, F.; Delaveau, P.; Jacquemin, H. *J. Nat. Prod.* **1981**, *44*, 576. El-Naggar, L. J.; Beal, J. L. *J. Nat. Prod.* **1980**, *43*, 649. Van der Sluis, W. G.; Labadie, R. P. *Pharm. Wiekbl.* **1978**, *113*, 21. Sticher, O. In "*New Natural Products and Plant Drugs with Pharmacological, Biological or Therapeutical Activity*; Wagner, H., Wolff, P., Eds., Springer-Verlag: Berlin, 1977; p 137. Inouye, H.; Ueda, S.; Takeda, Y. *Heterocycles* **1976**, *4*, 527. Jensen, S. R.; Nielsen, B. J.; Dahlagren, R. *Bot. Not.* **1975**, *128*, 148. Sticher, O.; Junod-Busch, U. *Pharm. Acta Helv.* **1975**, *50*, 127.

(2) Buchi, G.; Carlson, J. A. *J. Am. Chem. Soc.* **1968**, *90*, 5336.

(3) For a compilation of plumeria and allamanda type iridoids see Table I in supplementary material.

(4) (a) For some biosynthetic studies related to other iridoids, see: Inouye, H. *Planta Med.* **1978**, *33*, 193. Damtoft, S. *Phytochemistry* **1983**, *22*, 1929. Uesato, S.; Ueda, S.; Kobayashi, K.; Miyauchi, M.; Inouye, H. *Chem. Pharm. Bull.* **1983**, *31*, 4185. Damtoft, S.; Jensen, S. R.; Nielsen, B. J. *J. Chem. Soc. Perkin Trans. 1* **1983**, 1943. Uesato, S.; Matsuda, S.; Iida, A.; Inouye, H.; Zenk, M. H. *Chem. Pharm. Bull.* **1984**, *32*, 3764. Bellesia, F.; Pagnoni, U. M.; Pinetti, A.; Trave, R. *J. Chem. Res., Synop.* **1984**, 192 and earlier references contained therein. (b) Yeowel, P. A.; Schmid, H. *Experentia* **1964**, *20*, 250. (c) Abe, F.; Mori, T.; Yamauchi, T. *Chem. Pharm. Bull.* **1984**, *32*, 2947.

(5) Inouye, K.; Takeda, Y.; Nishimura, H.; Inouye, H. *Chem. Pharm. Bull.* **1979**, *27*, 3115.

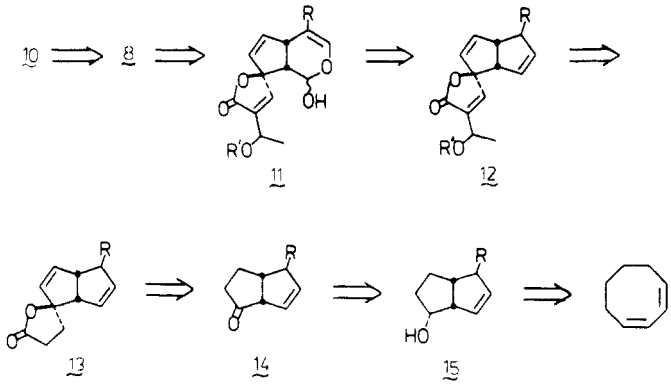
(6) For independent thoughts on this process see Yamauchi T.; Abe, F.; Tali, M. *Chem. Pharm. Bull.* **1981**, *29*, 3051.

(7) (a) Little, J. E.; Johnstone, D. B. *Arch. Biochem.* **1951**, 445. (b) Albers-Schonberg, G.; Schmid, H. *Helv. Chim. Acta* **1961**, *44*, 1447. (c) Kupchan, S. M.; Dessertine, A. L.; Blaycock, B. T.; Bryan, R. F. *J. Org. Chem.* **1974**, *39*, 2477.

(8) Abe, F.; Mori, T.; Yamauchi, T. *Chem. Pharm. Bull.* **1984**, *32*, 2947. (b) Pai, B. R.; Subramaniam, P. S.; Rao, U. R. *Indian J. Chem.* **1970**, *8*, 851.

0002-7863/86/1508-4974$01.50/0

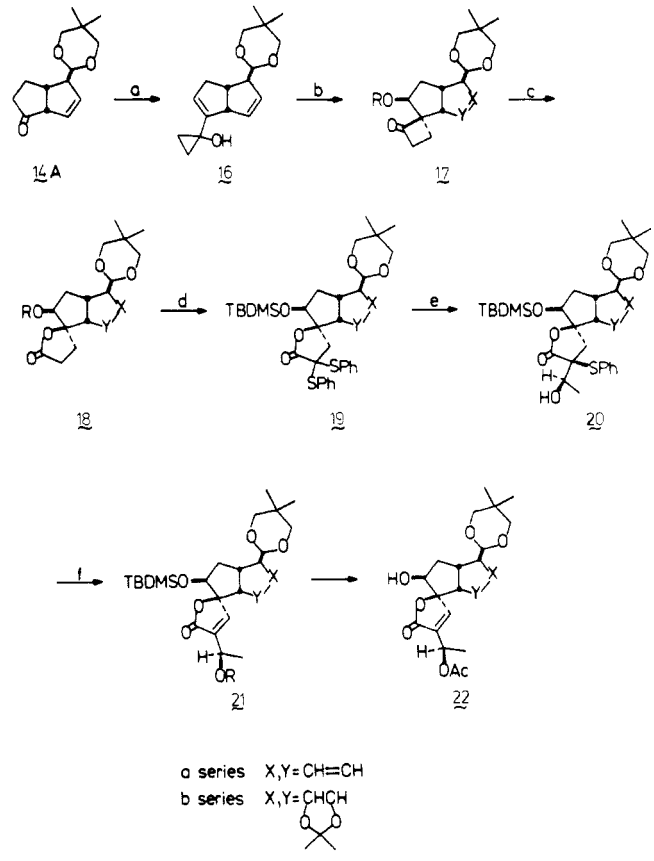
Scheme II. Retrosynthetic Analysis of Allamandin–Plumericin



The possibility that the tetrahydrofuran ring arises by an intramolecular Michael addition as depicted in Scheme I suggested the use of such an approach in a synthesis of plumericin and subsequently allamandin. Such a strategy has the additional virtue that entries into both groups of plumeria and allamanda iridoids would be possible. With this key concept in mind, a retrosynthetic analysis evolved as outlined in Scheme II with the tricyclic **11**, which corresponds to plumieride, as the key intermediate. The stereochemistry at the anomeric center is irrelevant since this center should easily epimerize and only the α-anomer can cyclize. As previously noted, a cyclopentene represents a synthon for the pyran ring which simplifies the structure to **12**.[9] This intermediate raises the problem of chemoselective oxidative olefin cleavage. The sulfur-based strategy reported in the accompanying manuscript[10] provides the basis to elaborate a saturated lactone such as **13** into the substituted butenolide **12**. The substitutive spiroannulation sequence makes the largest jump to a simple saturated (with respect to the ketone-bearing ring) ketone **14**. Such a spiroannulation must control stereochemistry at the spiro center relative to the ring juncture. Elaboration of ketone **14** from **15**, which ultimately derived from cylcoocta-1,3-diene, is outlined in the accompanying manuscript. In this paper, we report the successful execution of this scheme.[11]

Prologue. Because of the stereochemical requirements imposed upon the substitutive spiroannulation, our first strategy employed the use of OH^+ to initiate ring expansion of the vinyl cyclopropanol **16** which is available from ketone **14A** by our standard sequence[9,12] as outlined in Scheme III. Hydroxylation proceeds as before to generate a single diastereomer. On the basis of epoxidation from the convex face of the bicyclo[3.3.0]octyl system and migration of the cyclopropyl bond trans to the epoxide, the stereochemistry depicted in **17** is assigned. Comparison of the ^{13}C data with related compounds reinforces this assignment. Most distinguishable is the β-carbon of the cyclobutanone ring which appears at fields higher than 20 ppm when it is cis to a neighboring alkyl group

Scheme III.[a] Hydroxylative Substitutive Sprioannulation Approach



[a] (a) i. *c*-$C_3H_5S^+Ph_2BF_4^-$, KOH, Me_2SO, 25 °C; ii. $LiN(C_2H_5)_2$, pentane, 25°C, 70–88%; (b) *t*-C_4H_9OOH, $VO(acac)_2$, $PhCH_3$, −10 °C, 61%; (c) for "a" series: H_2O_2, NaOH, CH_3OH, −25 °C, 92%; for b series: MCPBA, $NaHCO_3$, CH_2Cl_2, 0 °C, 78%; (d) LDA, THF, HMPA, $PhSSO_2Ph$, −78 °C to −20 °C, 63–58%; (e) C_2H_5MgBr, THF, −10 °C then gaseous CH_3CHO, 65–58%; (f) i. MCPBA, CH_2Cl_2, −78 °C; ii. $CaCO_3$, CCl_4, reflux 76–51%.

but at lower field when it is trans.[13] The heteroatom substitution does not alter this trend. In **17a**, this carbon appears at δ 18.49, even upfield of the two methyl groups which appear at δ 21.75 and 23.19, in excellent agreement with the simpler models. Since yields of subsequent reactions frequently were lower when the free alcohol was used, the alcohol is converted to the *tert*-butyldimethylsilyl ether at this stage. Basic hydrogen peroxide effects the Baeyer–Villiger oxidation of the cyclobutanone to the lactone **18a**[14] and avoids any chance of olefin epoxidation. Bissulfenylation[15] to **19a** and aldol condensation[10,16] proceed just as in the model series. The adduct **20**, which is a crystalline solid, appears to be a single diastereomer using spectroscopic and chromatographic criteria. Based upon the chelation model, the stereochemistry depicted in **20a** is assigned.[17] Sulfoxide elimination[15] produces the butenolide **21a** which also appears to be diastereomerically pure as determined by its chromatographic and spectroscopic properties.

With the entire carbon framework of allamandin assembled, the stage is set for oxidative cleavage. Unfortunately, ozonolysis of **21a** (R = Ac or Ms) leads only to unidentifiable complex

(9) For iridoid syntheses based upon a bicyclo[3.3.0]octene, see: Matthews, R. S.; Whitesell, J. K. *J. Org. Chem.* **1975**, *40*, 3312. Aw-Yung, B. W.; Fleming, I. *J. Chem. Soc., Chem. Commun.* **1977**, 81. Whitesell, J. K.; Matthews, R. S.; Helbing, A. M. *J. Org. Chem.* **1978**, *43*, 784. Obara, H.; Kimura, H.; Suzuki, M.; Onodera, J. *Bull. Chem. Soc. Jpn.* **1978**, *51*, 3610. Hiroi, K.; Muira, H.; Kotsuji, K.; Sato, S. *Chem. Lett.* **1981**, 559. Trost, B. M.; Chan, D. M. T. *J. Am. Chem. Soc.* **1981**, *101*, 5972. Callant, P.; Ongena, R.; Vandewalle, M. *Tetrahedron* **1981**, *37*, 2085. Whitesell, J. K.; Matthews, R. S.; Minton, M. A.; Helbing, A. M. *J. Am. Chem. Soc.* **1981**, *103*, 3468. Kon, K.; Isoe, S. *Helv. Chim. Acta* **1983**, *66*, 755. Wender, P. A.; Dreyer, G. B. *Tetrahedron Lett.* **1983**, *24*, 4543. Hewson, A. T.; MacPherson, D. T. *Tetrahedron Lett.* **1983**, *24*, 5807. Caille, J. C.; Bellamy, F.; Guilard, R. *Tetrahedron Lett.* **1984**, *25*, 2345. Ritterskamp, P.; Demuth, M.; Schaffner, K. *J. Org. Chem.* **1984**, *49*, 1155. Demuth, M.; Chandrasekhari, S.; Schaffner, K. *J. Am. Chem. Soc.* **1984**, *106*, 1092. Trost, B. M.; Nanninga, T. N. *J. Am. Chem. Soc.* **1985**, *107*, 1293.

(10) Trost, B. M.; Mao, M. K.-T.; Balkovec, J. M.; Buhlmayer, P., preceding paper in this issue. Preliminary reports of portions of this work appeared, see: Trost, B. M.; Mao, M. K.-T. *J. Am. Chem. Soc.* **1983**, *105*, 6753. Trost, B. M., Mao, M. K.-T. *Tetrahedron Lett.* **1980**, *21*, 3523.

(11) For a preliminary report of a portion of this work, see: Trost, B. M.; Balkovec, J. M.; Mao, M. K.-T. *J. Am. Chem. Soc.* **1983**, *105*, 6755. Trost, B. M.; Balkovec, J. M. *Tetrahedron Lett.* **1985**, *26*, 1807.

(12) Trost, B. M.; Bogdanowicz, M. J. *J. Am. Chem. Soc.* **1973**, *95*, 5311.

(13) Trost, B. M.; Scudder, P. H. *J. Am. Chem. Soc.* **1977**, *99*, 7601.

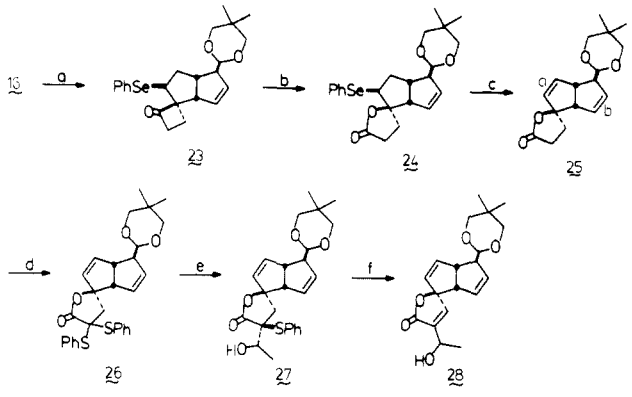
(14) Trost, B. M.; Bogdanowicz, M. J. *J. Am. Chem. Soc.* **1973**, *95*, 5321.

(15) Trost, B. M.; Salzmann, T. N.; Hiroi, K. *J. Am. Chem. Soc.* **1976**, *98*, 4887. Trost, B. M.; Rigby, J. *J. Org. Chem.* **1978**, *43*, 2938. For facile bissulfenylation of lactams, see: Zoretic, P. A.; Soja, P. *J. Org. Chem.* **1976**, *41*, 3587. Guzman, A.; Muchowski, J. M.; Saldana, J. *Chem. Ind. (London)* **1977**, 357.

(16) For an alternative using amide bases, see: Hoye, T.; Kurth, M. J. *J. Org. Chem.* **1980**, *45*, 3549. Hirayarna, M.; Gamoh, K.; Ikekawa, N. *J. Am. Chem. Soc.* **1982**, *104*, 3735.

(17) For a review, see: Reetz, M. T. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 556.

Scheme IV.[a] Selenium-Initiated Substitutive Spiroannulation Approach



[a] (a) phSeBr, $(C_2H_5)_3N$, CH_2Cl_2, −78 °C, 91%; (b) NaOH, H_2O_2, CH_3OH, H_2O, 0 °C then $NaHSO_3$, 77%; (c) MCPBA, CH_2Cl_2 then $CH_2{=}CHOCH_2iCH_3$, room temperature 90%; (d) $LiN(C_2H_5)_2$, $PhSSO_2Ph$, THF, −78 °C, 91%; (e) C_2H_5MgBr, THF, 0 °C then CH_3CHO, 97%; (f) MCPBA, CH_2Cl_2, −78 °C then CCl_4, $CaCO_3$, reflux 85%.

mixtures. Attempted hydroxylation with osmium tetroxide (stoichiometrically or catalytically) returns starting material. Priming the double bond for the ultimate cleavage must occur earlier in the sequence.

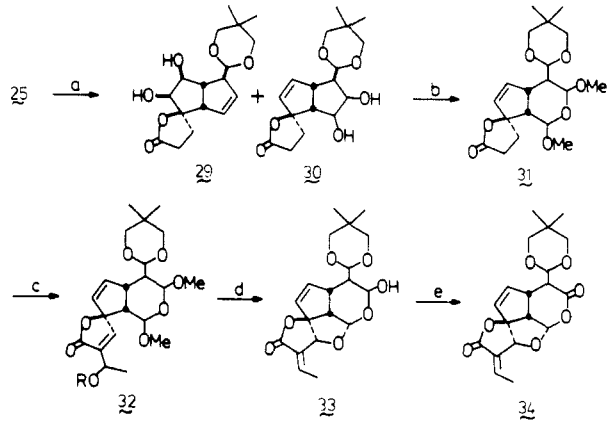
While **14A** is readily hydroxylated, the resultant ketone fails to undergo the sulfur ylide reaction. The initial product of substitutive spiroannulation **17** (R = TBDMS) also smoothly hydroxylates utilizing catalytic osmylation.[18] Working up the diol by dissolving in acetone in the presence of a few drops of sulfuric acid and anhydrous magnesium sulfate gives the crystalline acetonide **17b**, mp 135–8 °C, (88% overall yield from **17a** to **17b**). Baeyer–Villiger oxidation proceeds conveniently with buffered MCPBA to give the lactone **18b** which also is elaborated in the same fashion via the bissulfenylated lactone **19b** to the homogeneous aldol adduct **20b** and butenolide **21b** (R = H). Acetylation followed by desilylation produces **22**. Because of the anticipated sensitivity of the pyran ring system, introduction of the 6,7-double bond should occur at this stage. Acylation of the hydroxyl group of **22** proves to be a major obstacle since neither a xanthate nor a thionocarbonate can be made. The mesylate forms nicely, but all attempts to effect an elimination to an olefin fail. With the inability to effect this dehydration, an alternative electrophile for the substitutive spiroannulation that will more easily introduce a double bond must be found.

An electrophilic selenium reagent seemed ideal to resolve the problem of olefin introduction.[19] Early results in our model series with phenylselenenyl chloride and triethylamine however discouraged this approach because of incomplete and consequently unsatisfactory conversions. Switching to phenylselenenyl bromide and triethylamine and adding the vinylcyclopropanol **16** slowly to this reagent reveals the substitutive spiroannulation proceeds rapidly at −78 °C but becomes sluggish at approximately half conversion. However, by first reacting the substrate with 1.1 equiv of the reagent for 30 min at −78 °C followed by the addition of another 1.1 equiv of the selenium reagent, stirring for 1 h, and then allowing the temperature to rise slowly to 0 °C, essentially complete conversion results. Analysis of the product, a crystalline solid, mp 80.5–81.0 °C, by ^{13}C NMR shows a single methylene resonance at 18.1 ppm indicative of the desired stereochemistry of the cyclobutanone as in **23** (see Scheme IV). The stereoselectivity exhibited in this reaction can be rationalized as follows. The electrophilic selenium species approaches as expected from the convex face of **16** to generate an episelenonium ion rather than a carbonium ion (eq 1). This allows only one rotomer to rearrange,

(18) Van Rheenan, V.; Kelly, R. C.; Cha, D. Y. *Tetrahedron Lett.* **1976**, 1973. For a review, see: Schroder, M. *Chem. Rev.* **1980**, *80*, 187.

(19) For reviews, see: Clive, D. *Tetrahedron* **1978**, *34*, 1049. Reich, H. J. *Acc. Chem. Res.* **1979**, *12*, 22.

Scheme V.[a] Synthesis of an Allamandin Analogue



[a] (a) cat. OsO_4, NMO, CH_3CN, H_2O, −40 °C, major 52%, minor 19%; (b) KIO_4, ether, H_2O then TsOH, $HC(OCH_3)_3$, CH_3OH, 49%; (c) steps d, e, f from Scheme IV; (d) 88% HCO_2H, 16%; (e) CrO_3, H_2iSO_4, H_2O, CH_2Cl_2.

that one with a trans periplanar arrangement of C–C (cyclopropane) and C–Se bonds.

(1)

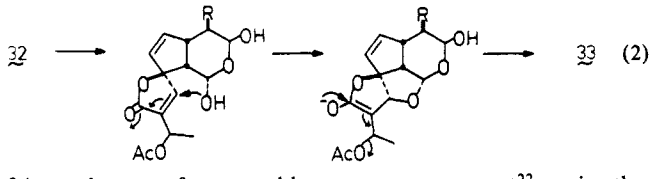
With the desired isomer in hand, Baeyer–Villiger oxidation with basic hydrogen peroxide gives a very polar substance, presumably the hydroxyacid–selenoxide of **24**. Normal reductive workup of the reaction with aqueous sodium hydrogen sulfite also effected selenoxide reduction to give the lactone as a foam. Differentiation between the cyclobutanone and the γ-butyrolactone is not trivial. The most diagnostic indication that the oxidation proceeds arises in the ^{13}C NMR spectrum where the carbonyl carbon shifts from δ 212.0 in **23** to 173.8 in **24**. The problem previously encountered of the "wrong" group migrating[20] during ring expansion was thwarted by this method. This can be explained by proposing that the cyclobutanone rearrangement is much faster than selenide oxidation. TLC analysis of the oxidation of the selenide with MCPBA at −78 °C reveals the formation of a polar product, presumably the selenoxide. At this point, addition of ethyl vinyl ether as a trap for both excess MCPBA and selenenic acid and then allowing the temperature to rise to ambient afforded the desired diene **25**. The selenoxide elimination was monitored by TLC and was not sufficiently complete until 27 h later; normally such eliminations proceed in a matter of minutes. Perhaps steric crowding inhibits attainment of the necessary conformation for the cis syn elimination. The steric congestion in this region was previously noted by the failure of alcohol **22** to acylate. Bissulfenylation to **26** and subsequent aldol condensation to **27** proceed in outstanding yields by the same conditions previously developed. Oxidation of **27** to its sulfoxide which is directly eliminated gives **28** which again possesses the carbon skeleton of allamandin and, this time, all the requisite double bonds. Once again, the approach stumbled because of the inability to effect chemoselective oxidative olefin cleavage. However, it should be noted that this sequence is extraordinarily efficient—the tricyclic system **28** is obtained in 42% overall yield from **14A**.

By using a simpler substrate such as lactone **25**, hopefully some of the difficulties being encountered may be minimized. The steric hindrance of the spiro center and the inductive effect of the lactone compared to an acetal argues for chemoselective hydroxylation of olefin b over olefin a in **25**. Hydroxylation with catalytic osmium tetroxide in wet acetonitrile at −40 °C forms two products (see Scheme V). The major product (52% yield) proves to be the desired diol **30**; whereas, the minor product **29** (19% yield) arises from hydroxylation of the wrong double bond. Thus, the

(20) Trost, B. M.; Buhlmayer, P.; Mao, M. K.-T. *Tetrahedron Lett.* **1982**, *23*, 1443.

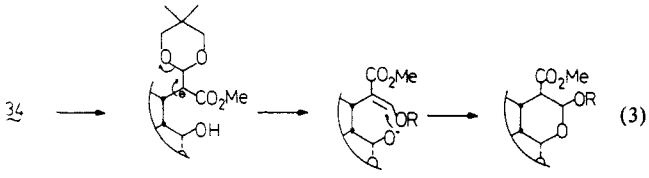
chemoselectivity is in the desired direction but not as high as we ultimately want.

With **30** in hand, we chose to effect oxidative cleavage first and then elaborate the lactone. Gratifyingly, both proceed well to give the butenolide **32**. Hydrolysis of the acetal proves especially difficult. Of the multitude of acid conditions examined, only 88% formic acid succeeds and gives directly the cyclized product **33**. The cyclization is evident by the changes in the ^{1}H NMR spectrum: the appearance of a quartet of doublets (J = 7, 0.5 Hz) at 7.15 and a doublet (J = 7 Hz) at δ 2.05 is consistent with the formation of the expected E isomer[21] of the α-ethylidene lactone by the mechanism outlined in eq 2. Oxidation of this lactol to



(2)

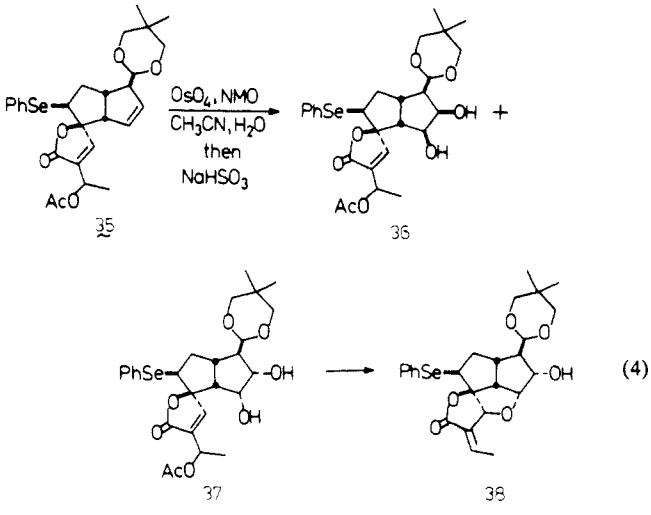
34 sets the stage for an acyl lactone rearrangement[22] to give the O-methyl acetal of allamandin (eq 3). The ^{1}H NMR spectral



(3)

assignments for **34** are shown in Table II which appears as supplementary material. Unfortunately, due to the limited amount of material in hand, only a single reaction which failed was carried out.

While this route only provides the acetal of an isoallamandin, several aspects are very encouraging. The methodology for elaborating the carbon skeleton works very well in highly functionalized systems. Furthermore, the critical biomimetic cyclization proceeds as envisioned. The facility of this cyclization is also encountered in our studies of the hydroxylation of **35** where a 2:1 mixture of **36** and **38** are formed. The latter presumably arises

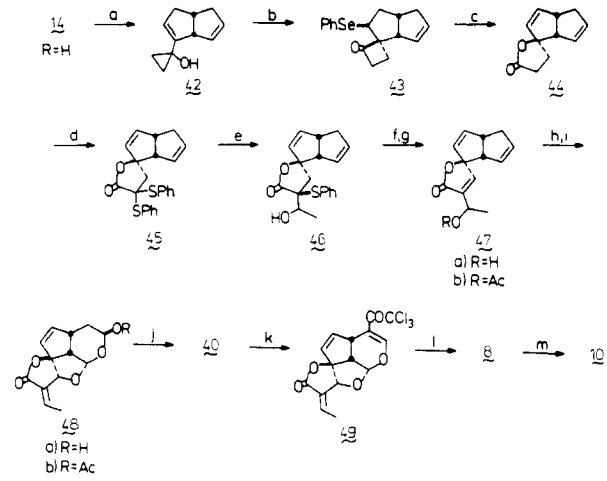


(4)

from the lack of stereocontrol during the hydroxylation leading by partial α-attack to some α-diol **37**. The proximity of the hydroxyl group in **37** corresponds to the situation in the pyran series. Thus, Michael addition concommittant with β-elimination results in only **38** being isolated. With the critical problems of this class of compounds identified, the stage is set for the final assault.

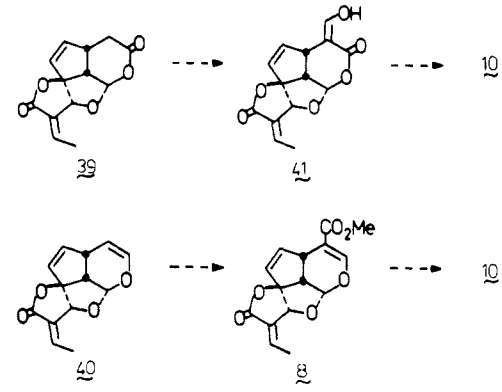
An Efficient Total Synthesis. It is clear that the difficulty in the selective oxidation of the desired olefin of **25** or **28** arises from

Scheme VI.[a] Biomimetic Synthesis of Allamcin, Plumericin, and Allamandin



[a] (a) i. c-$C_3H_5S^+Ph_2BF_4^-$, KOH, Me_2SO, 25 °C; ii. $LiN(C_2H_5)_2$, pentane 82%; (b) PhSeBr, CH_2Cl_2, $(C_2H_5)_3N$, −45 °C, 88%; (c) MCPBA, CH_2Cl_2, −78 °C then warm to 0 °C, $C_2H_5OCH{=}CH_2$, room tempeature, 65–70%; (d) LDA, THF, $PhSSO_2Ph$, −78 °C, 95%; (e) C_2H_5MgBr, THF, 0 °C then CH_3CHO, 100%; (f) MCPBA, CH_2Cl_2, −78 °C then CCl_4, $CaCO_3$, reflux, 82%; (g) Ac_2O, C_5H_5N, DMAP, CH_2Cl_2, 0 °C, 92%; (h) i. OsO_4, NMO, THF, H_2O, 0 °C, 90%; ii. $NaIO_4$, ether, H_2O then NaOAc, 89%; (i) Ac_2O, i-$(C_2H_5)_2NC_3H_7$ DMAP, CH_2Cl_2; (j) FVT, 500 °C at 0.005 mmHg, 81–90% from **47a**; (k) CCl_3COCl, 2,6-di-*tert*-butylpyridine, CH_2Cl_2, room temperature, 85%; (l) $Mg(OCH_3)_2$, CH_3OH, −45 °C, 90%; (m) 0.01 N $HClO_4$, 95–100 °C, 55%.

the presence of the exo protected carboxaldehyde. This group undoubtedly blocks the exo face of the molecule leading to competition among the desired oxidation, that of the endo face of the olefin, and that of the olefin adjacent to the spirolactone. Several options are conceivable to rectify this problem. One option is to invert the stereochemistry so that the acetal group is on the α face of the bicyclooctane so that it would no longer block the convex face. Since the stereochemistry at this center is ultimately equilibrated, the stereochemistry at this stage is irrelevant. A second option is to reduce the steric size of the group. For example, an aldehyde has a smaller A-value than the corresponding acetal.[23] An even smaller group is hydrogen which then requires introduction of a carboxylic carbon at a late stage, i.e., after the hydroxylation. Two options exist for incorporation of such a carbon—via a lactone such as **39** or an enol ether such as **40**. The



former requires well-known chemistry—a formylation α to a carbonyl group.[24] The resultant isoallamandin **41** simply must be isomerized to complete the synthesis. Our difficulty in isomerizing lactone acetal **34** makes this approach less appealing. An

(21) Ohaga, K.; Matsu, T. *Bull. Chem. Soc. Jpn.* **1973**, *46*, 2181. Tanaka, K.; Aneme, H.; Yamagishi, N.; Ono, N.; Kaji, A. *Chem. Lett.* **1978**, *197*; **1978**, 653.

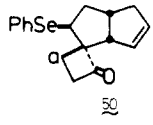
(22) Korte, F. *Angew. Chem.* **1959**, *71*, 709.

(23) Cf. Hirsch, J. A. *Top. Stereochem.* **1967**, *1*, 199.

(24) In addition to formylations with ethyl formate, use of amide acetals and orthoformates have been successful. See: Bredereck, H.; Simchen, G.; Rebsdat, S.; Kantlehner, W.; Horn, P.; Wahl, R.; Hoffmann, H.; Grieshaber, P. *Chem. Ber.* **1968**, *101*, 41. Suzuki, M.; Yanagisawa, A.; Noyori, R. *Tetrahedron Lett.* **1982**, *23*, 3595.

alternative via **40** is more attractive since it directly produces plumericin which must only be hydrated to complete the synthesis of allamandin. The lack of precedent for this latter path makes it a more tenuous proposal but an attracitve area for new methodology. Following this option, the retrosynthetic analysis of Scheme II resolves the problem to a synthesis of **11** R = H which, in turn, derives from the ketone **14**, R = H, a substrate we employed in our model studies and which is available in >80% overall yield in 3 steps from cyclooctadiene.[25] With a belief that we should be able to devise a method for carbomethoxylation of an enol ether, we began our synthesis as outlined in Scheme VI.

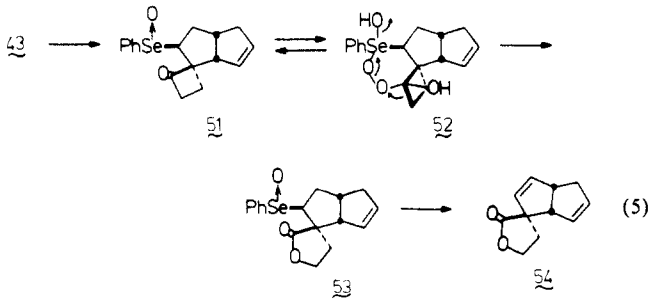
The vinylcyclopropanol **42** is available in 82% yield in a single operation. The pentane extracts of the Me_2SO reaction mixture from the sulfonium cyclopropylide addition to **14** which produces oxaspiropentane are concentrated and directly exposed to lithium diethylamide. Although vinylcyclopropanols are rather sensitive, **42** is easily purified by flash chromatography with no sign of acid induced isomerization to a spirocyclobutanone. Electrophilically initiated ring expansion of this vinylcyclopropanol at 0 °C gives complete conversion of starting material. ^{13}C NMR spectroscopic analysis reveals the desired product **43** ($\delta_{C(a)}$ 18.2) is contaminated by an appreciable amount (>10%) of the undesired cyclobutanone **50** ($\delta_{C(a)}$ 21.8). Lowering the temperature to −78 °C and then



allowing it to rise to −45 °C effects complete reaction after 4 h at the latter temperature. ^{13}C NMR spectroscopic analysis reveals only a single peak at δ 18.2 attributable to the desired cyclobutanone **43** with >100:1 diastereoselectivity.

The Baeyer–Villiger ring expansion to the γ-lactone proceeds as in the previously discussed cases to give, after reductive workup, a selenide–hydroxyacid. Dissolution of this material in benzene containing a few crystals of *p*-toluenesulfonic acid, and removal of the solvent in vacuo gives the selenide lactone. ^{13}C analysis easily verifies the desired Baeyer–Villiger reaction proceeded as evidenced by the replacement of the carbonyl carbon absorption at δ 212.7 for **43** by an absorption at δ 175 for the selenolactone. Oxidation to the selenoxide with MCPBA at −78 °C followed by the addition of a selenenic acid trap (ethyl vinyl ether) effects complete selenoxide elimination after 40 h at ambient temperature to give **44** as a crystalline product, mp 69–70 °C.

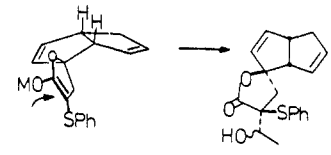
With the success of the Baeyer–Villiger elimination sequence, the possibility of a one-step transformation becomes attractive. We previously noted that an attempt to effect such a reaction with **43** using hydrogen peroxide in ethanol led to an abnormal lactone **54** (eq 5).[20] We interpreted the reaction as proceeding by initial



(5)

selenide oxidation to **51** which enabled formation of a cyclic peroxide **52**. The geometric constraints imposed by **52** forces migration of the normally less-preferred less-substituted carbon as depicted in **52** to give selenoxide **53** which subsequently eliminates. That selenoxide formation is faster than Baeyer–Villiger rearrangement as presumed is suggested by the above experiments with MCPBA. If the cyclic derivative accounts for this abnormal regioselectivity, then use of MCPBA, which cannot form such a cyclic peroxide, as a reagent should not be plagued by such a result. Experimentally, adding 2 equiv of MCPBA to **43** at −78 °C to effect selenide oxidation, raising the temperature to 0 °C to effect cyclobutanone oxidation, and then adding ethyl vinyl ether and stirring at ambient temperature led directly to diene–lactone **44** in 65% yield. None of the alternative lactone **54** could be detected. Clearly the intrinsic bias of this system is for the normally anticipated preferential migration of the more-substituted carbon. The observation that hydrogen peroxide induces different behavior than MCPBA speaks to the likelihood of the cyclic peroxide in the former case.

Desulfenylation–aldol condensation provides elaboration of the butenolide **44** to the key triene **47** via the bissulfenylated lactone **45**. Four possible isomers of **46** can form and all are seen (ratio approximately 5:5:1:1 by NMR spectroscopy). That the major isomers correspond to the two epimers at the hydroxyl-bearing carbon of **46** is suggested by oxidative–elimination which also gives rise to an ca. 1:1 mixture of allyl alcohols **47a**.[26] In this case, the facial selectivity of the aldol reaction with respect to the enolate is high but not with respect to the aldehyde. As drawn in eq 6,

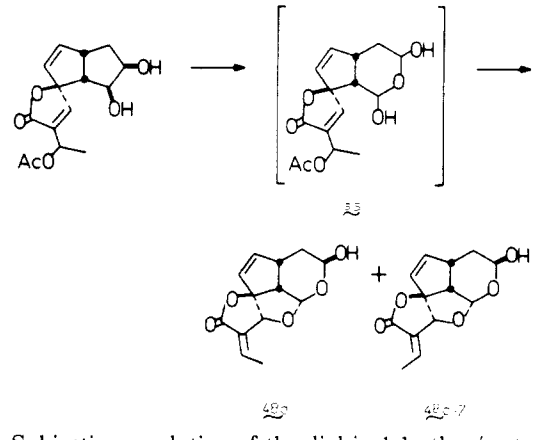


(6)

approach from the left side is sterically more accessible since the second cyclopentenyl ring blocks approach from the right. The low diastereoselectivity with respect to the aldehyde presumably arises because of the absence of any substitution on the cyclopentyl ring adjacent to the spiro lactone ring such as the oxygen function in **19** (Scheme III) which may be affecting the conformation of the bicyclo[3.3.0]octyl ring as well as directly influencing the approach of the aldehyde. For the purposes herein however this stereochemistry is irrelevant.

The stage is now set for the chemoselective oxidative cleavage of the acetate **47b**. Of the three olefins present, the C(2)–C(3) olefin is both the sterically most accessible and most electron rich. The acetal group found in **25** and **28**, to which we attribute our previous difficulties, is now absent. Hydroxylation via catalytic osmylation gives a single compound in 90% yield. The infrared spectrum shows incorporation of hydroxyl groups (3580 cm^{-1}, br), and the ^1H NMR spectrum shows retention of the butenolide olefin (δ 7.24) and the C(6)–C(7) olefin (δ 6.15 and 5.30). Indeed, cis hydroxylation appears to be completely chemoselective.

The presumed biomimetic step involves oxidative cleavage of the diol to the hydrated dialdehyde **55** which should cyclize to the extent that the hydroxyl group at C(1) is α (see eq 7).



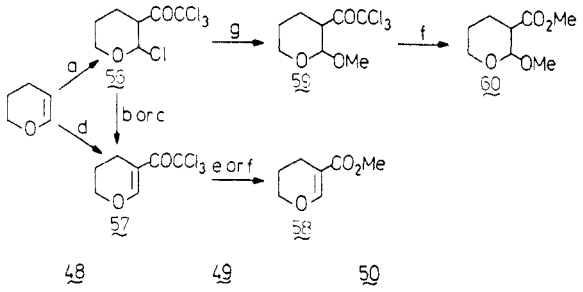
(7)

Subjecting a solution of the diol in 1:1 ether/water to sodium

(25) Apparu, M.; Barrelle, M. *Tetrahedron* **1978**, *34*, 1541. Whitesell, J. K.; Matthews, R. S.; Wang, P. K. S. *Synth. Commun.* **1977**, *7*, 355. Crandall, J. K.; Banks, D. B.; Colyer, R. A.; Watkins, R. J.; Arrington, J. P. *J. Org. Chem.* **1968**, *33*, 423. LeBel, N. A.; Spurlock, L. A. *Tetrahedron* **1964**, *20*, 215. Also, see: Bates, R. B.; McCombs, D. A. *Tetrahedron Lett.* **1969**, 977.

(26) See Table II in supplementary material for NMR assignments.

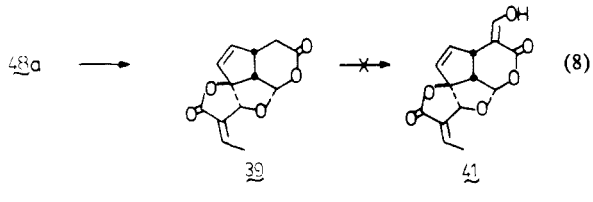
Scheme VII.[a] Carbomethoxylation of Dihydropyran



[a] (a) Cl_3CCOCl; (b) 60 °C, 15 mmHg; (c) $EtN(i\text{-}Pr)_2$; (d) Cl_3CCOCl, 2,6-di-*tert*-butylpyridine; (e) $Mg(OMe)_2$, MeOH; (f) Et_3N, MeOH; (g) MeOH, Na_2CO_3, ether.

metaperiodate[27] reveals rapid cleavage of the diol. TLC shows the presence of a major and minor product. The minor product ultimately proves to be allamcin **48a**. The direct formation of allamcin must reflect the amount of the α-C(1) anomer formed during cleavage since allowing the mixture to stand for long times does not change this ratio. The major product can be isolated as an unstable yellow oil. This material does not cyclize spontaneously as did the 4-substituted analogue in Scheme V. Exposure of this material to tertiary amines or aqueous K_2CO_3 leads only to low yields of allamcin **48a**. However, a solution of this compound in wet THF containing a suspension of acidic alumina does undergo cyclization after 24 h to give a 76% yield of **48a** and its geometric isomer **48a-Z** (3:1) as determined by integration of the ^1H NMR resonances at δ 2.08 and 2.21, respectively. More conveniently, addition of aqueous sodium acetate directly to the periodate cleavage reaction effects cyclization in 89% overall yield to give an 8:1 mixture of *E*/*Z* enones **48a** and **48a-Z**, mp 200–205 °C dec. The ^1H NMR and IR spectral characteristics as well as TLC behavior are identical with an authentic sample of (+)-allamcin.[8]

Allamcin **48a** could be oxidized to the corresponding lactone **39** (eq 8) by either Collins' reagent or Jones reagent. Unfortunately, all attempts to prepare the C-4 enolate of **39** followed by acylation failed. It appears that the compound is extremely sensitive to basic conditions.



(8)

An alternative approach to acylation of C(4) is possible through the enol ether **40**, which should be available by dehydration of allamcin, via reaction with a carbon dioxide equivalent of sufficient electrophilicity.[28] Examination of the carbomethoxylation of 3,4-dihydropyran tests the feasibility of this approach. The sensitivity of dihydropyran to Lewis acids led to examination of trichloroacetylation as a synthon for a carbomethoxy group since Effenberger showed that trichloroacetyl chloride forms an adduct with dihydropyran in the absence of any catalyst.[29] The 1:1 adduct **56** forms as described in excellent yield (see Scheme VII). This adduct can be dehydrohalogenated under vacuum or by the addition of Hunig's base to give the vinylogous trichloroacetate **57**. The haloform cleavage to **58** occurs either by exposure of **57** to a methanolic solution of magnesium methoxide (97% yield) or by allowing trichloro ketone **57** to stand in methanol containing 10% V/V triethylamine for 12 h (96% yield).

Applying this method toward a substitution pattern similar to allamandin involves quenching intermediate **56** into a mixture of methanol and anhydrous Na_2CO_3 which leads to a 3:6:1 mixture of *cis*-**59**/*trans*-**59**/**57** as evidenced by the ^1H NMR signals at δ 5.00 (d, J = 3 Hz), 4.44 (d, J = 8 Hz), and 8.28 (s), respectively. Similarly, this mixture underwent the haloform cleavage in methanol/triethylamine (10:1) to give a corresponding mixture of *cis*- and *trans*-**60** with a small amount of vinylogous carbonate **58**.

In regard to the problem of acylation of the more complex enol ether **40**, it was reasoned that the trichloroacetyl chloride would need to be freed completely of HCl. This could be accomplished by the addition of a proton scavenger, 2,6-di-*tert*-butylpyridine. The addition of 2 equiv of trichloroacetyl chloride and 2 equiv of the acid scavenger to dihydropyran leads to the direct isolation of enone **57** in 95% yield. While the highly successful model studies are promising, the application of this method to the functionally complex **40** remained to be established. Allamcin is dehydrated in low yield utilizing *p*-toluenesulfonic acid in benzene in the presence of molecular sieves. On the other hand, flash vacuum thermolysis of the corresponding crude acetate[30] at 500 °C and 0.005 mmHg affords an 89% yield of descarbomethoxyplumericin **40**[26] as a crystalline solid, mp 105–107 °C (Scheme VI).

To descarbomethoxyplumericin **40**, dissolved in a minimal amount of dichloromethane, is added 2,6-di-*tert*-butylpyridine (5 equiv) followed by carefully distilled trichloroacetyl chloride (50 equiv). The product is purified by preparative TLC to give an 85% yield of acylated enol ether. Methanolysis of **49** at −45 °C gives, after recrystallization from methanol, a 90% yield of plumericin (**8**), mp 176–8 °C, whose spectral characteristics are identical with those published for the natural product.[7c,8] Chromatography of the mother liquor gives a small amount of isoplumericin **9** which had been carried through from the cyclization step (**47** → **48**, Scheme VI). The spectral characteristics are identical with those reported for natural isoplumericin.[7,8,26] The final task that remains is the conversion of plumericin into the ultimate target allamandin.

While it can be envisioned that simple acid-catalyzed hydration of the C(3)–C(4) olefin of plumericin **8** should lead to the thermodynamic array of the β-hydroxy ester of allamandin **10**, repeated attempts utilizing mild aqueous acidic conditions ($HClO_4$/aqueous CH_3CN/room temperature, 6 N or 12 N HCl/room temperature, acidic Al_2O_3/aqueous THF, wet silica gel,[31] $AgClO_4$/aqueous CH_3CN[32]) either give no reaction or else decomposition products. When **8** is refluxed with 0.24 N hydrochloric acid for 5.5 h, the single product, obtained in ca. 90% yield, proved to be allamcin **48a** by comparison with the ^1H NMR spectrum and TLC behavior of authentic synthetic material. Apparently, hydrolysis of the ester with concommitant olefin hydration followed by decarboxylation leads to this result.

The activation of olefins by cationic rhodium complexes[33] allows the addition of ethanol[33b] or amines[33c] to 1,3-dienes. The affinity exhibited above might activate the more electron-rich C(3)–C(4) olefin of **8** toward addition of water while leaving the ester intact. Therefore, a suspension of plumericin in 0.011 M aqueous $RhCl_3 \cdot 3H_2O$ containing a small amount of methanol is refluxed for 4 h. Preparative TLC gives three bands: (1) unreacted plumericin (25%), (2) allamandin contaminated with unidentified byproducts, and (3) a trace of allamcin **48a**. The middle band was triturated with ether to give pure allamandin **10** (16%), mp 207–208.5 °C. The spectral characteristics of this material were identical with

(27) Cf. Kon, K.; Isoe, S. *Tetrahedron Lett.* **1980**, *21*, 3399.
(28) For a review, see: Effenberger, F. *Angew. Chem., Int. Ed. Engl.* **1969**, *8*, 295. Cf. Muhmel, G.; Hanke, R.; Breitmaier, E. *Synthesis* **1982**, 673. Chan, J. H.; Hall, S. S. *J. Org. Chem.* **1984**, *49*, 195.
(29) (a) Effenberger, F.; Maier, R.; Schonwalder, K.-H.; Ziegler, T. *Chem. Ber.* **1982**, 2766. (b) Murai, S.; Kuroki, Y.; Hasegawa, K.; Tsutsumi, S. *J. Chem. Soc., Chem. Commun.* **1972**, 946. (c) Bailey, D. H.; Johnson, R. E.; Albertson, N. F. *Org. Synth.* **1971**, *51*, 100 and references therein.
(30) Cr. Depuy, C. H.; King, R. W. *Chem. Rev.* **1960**, *60*, 431. For our apparatus, see: Trost, B. M.; Godleski, S. A.; Ippen, J. *J. Org. Chem.* **1978**, *43*, 4559.
(31) Huet, F.; Lechevallier, A.; Pellet, M.; Conia, J. M. *Synthesis* **1978**, 63.
(32) Tietze, L.-F., private communication.
(33) (a) Cramer, R. *Acc. Chem. Res.* **1968**, *1*, 186. (b) Dewhirst, K. C. *J. Org. Chem.* **1967**, *32*, 1297. (c) Baker, R.; Halliday, D. E. *Tetrahedron Lett.* **1972**, 2773.

those of an authentic sample of (+)-**10** kindly provided by Professor John M. Cassady.

Since $RhCl_3 \cdot 3H_2O$ reacts with water to liberate HCl, plumericin was refluxed with 0.02 N HCl–CH_3CN (3:1) for 4 h to give a mixture of **8**, pure allamandin **10**, and a considerable amount of **48a**. Conditions that utilize a higher pH and a less nucleophilic counter ion, 0.010 N perchloric acid, affords recovered **8** (31%), allamandin[26] (39%, 55% based upon recovered **8**), and allamcin **48a** (6%).

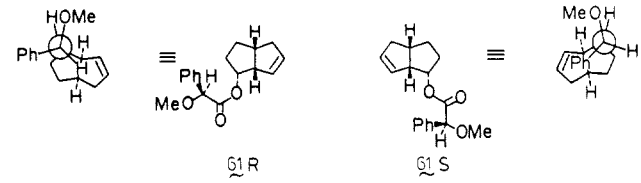
Discussion

The synthesis of allamcin, plumericin, and allamandin summarized in Scheme VI requires only 9, 13, and 14 steps, respectively, from the previously known bicyclic ketone **14** (R = H) which, in turn, is available in only three steps from cycloocta-1,3-diene. The conciseness of the route evolved from the absence of any protecting group chemistry which stems from the development of new methodology. The ring system arose from our α-substitution–spiroannulation for elaboration of carbonyl groups and the desulfenylative–aldol condensation facilitated creation of the remainder of the carbon skeleton; whereas, the sulfenylation–dehydrosulfenylation methodology adjusted the oxidation pattern. While these methods, which were previously developed in our laboratories, played a key role in establishing the basic plan, the carbomethoxylation approach was an outgrowth of this project. The structural simplification provided by the existence of this methodology provides a new flexibility in the synthesis of natural products containing a 3-carboxydihydropyran unit which is quite common.[34]

The facility of the ring closure **11** → **8** (Scheme II) embodied in the conversion of **47** → **48** (Scheme VI) depicted in eq 2 supports the proposal for the biosynthesis as outlined in Scheme I. It appears that epimerization at the anomeric center of **2** in going to **3**, Scheme I, is not likely to be spontaneous. As noted in eq 7, the observation of both **48a** and **55** in the initial cleavage and the requirement that a weak acid (e.g., alumina) or base (acetate ion) catalyzes the cyclization of **55** suggests that **55** is the β-anomer and isomerizes to the α-anomer only upon addition of a catalyst. The hydration of plumericin to allamandin and hydration–decarbomethoxylation of plumericin to allamcin establish chemical feasibility for these steps in the biosynthetic scheme and lend support to the proposal of Scheme I. Inspection of our synthesis and many plumera and allamanda type iridoids summarized in Table I[3] suggests that this approach may be applicable to every entry of the table except for fulvoplumierin. Indeed, four of these entries, plumericin, isoplumericin, allamcin, and allamandin, have resulted so far. Curiously, allamcin (referred to as descarbomethoxyallamandin) was synthesized as a racemate[11] prior to its isolation.[8a]

Because of the possible broad application of this strategy and the general usefulness of **15** (R = H) as a building block, we sought a method of resolution. The flexibility of having either enantiomeric series also led to this decision. At the beginning of our work, a resolution via crystallization of the (−)-camphanyl esters had been reported.[35] Subsequently, a resolution via the urethane has also been reported.[36]

Our approach focused on the use of (*S*)-O-methylmandelates which provides an opportunity for chromatographic resolution and simultaneously permits evaluation of the optical purity and absolute configuration by NMR spectroscopy.[37,38] The racemic alcohol **31** (R = H) is esterified by the method of Stadler[39] which employs the Vilsmeier type reagent made from oxalyl chloride–DMF in acetonitrile (88% yield). Flash chromatography using 1:19 v:v of ethyl acetate: hexane with one recycling of the middle fractions gives a 97% recovery of **61*R***, $[\alpha]^{26}_D$ +157° (*c* 4.44, CH_3OH), and 95% recovery of **61S**, $[\alpha]^{26}_D$ −19.2° (*c* 2.54, CH_3OH). The less polar ester shows absorptions for the vinyl



61R 61S

protons at δ 5.38 and 5.68; whereas, the more polar ester shows these absorptions at δ 4.86 and 5.40. By using Mosher's model[37] and viewing **61R** and **61S** in an extended Newman projection, the absolute stereochemistry can be assigned as shown. The assignment is confirmed by basic hydrolysis (THF, aqueous potassium hydroxide) of **61R** to (+)-**31** (R = H), $[\alpha]_D$ +121, *c* 1.135 ($CHCl_3$) [lit.[36] (enantiomer) $[\alpha]_D$ −124, *c* 6 ($CHCl_3$)].

Up to this point, we have drawn the stereochemistry of allamandin as originally assigned. Kupchan et al. assigned the C(3)–C(4) stereochemistry of allamandin based upon the observed coupling constants $J_{1,9}$, $J_{4,5}$, and $J_{3,4}$ and the inspection of Dreiding models.[7c] The C(3)–C(4) stereochemistry of the natural product is undoubtedly the thermodynamically most stable. This is evidenced by the obtention of **10** via synthesis which does not control these centers. However, depending on the conformation of the tetrahydropyran ring, one can argue that **62** or even **63** is a viable

62 R_1=CO_2Me, R_4=OH, R_2=R_3=H
63 R_1=CO_2Me, R_3=OH, R_2=R_4=H
64 R_2=CO_2Me, R_4=OH, R_1=R_3=H

65

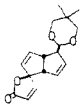
structure. Also, the stereochemistry of α-gardiol, β-gardiol, and allamcin are assigned by analogy to **10**. To help answer this question of relative stereochemistry, MM2 calculations[40] were performed on the possible stereoisomers and conformers of the allamandin system. The results are summarized in Table III which appears in the supplementary material. Although the calculations do not include hydrogen bonding, which is presumably important in this case, they do suggest that simple inspection of a model may not answer the question of the relative stereochemistry. Structure **10** should be regarded as tentative until the stereochemistry at C(3) and C(4) is proven.

As for MM2 calculations on the two possible anomeric isomers **48a** and **65** of the allamcin system, **48a**, the isomer possessing the 3-β-OH, has the lowest steric energy. The lowest energy conformer is the one with the axial hydroxyl group as summarized in Table IV which appears in the supplementary material. This supports the originally assigned stereochemistry. The failure of the programs used to take into account all effects (eg., H bonding is ignored) and the possibility that the global minimum conformation in each case has not been found make the absolute values calculated meaningless. While the relative magnitudes are more meaningful, the closeness of the numbers indicates that additional experimental work must be done to unambiguously establish stereochemistry.

The cytotoxicity of several synthetic intermediates were tested under the auspices of the National Institutes of Health. The

(34) For a recent example of the use of this method, see: Martin, S. F.; Benage, B. *Tetrahedron Lett.* **1984**, *25*, 4863.
(35) Kuritani, H.; Takaoka, Y.; Shingu, K. *J. Org. Chem.* **1979**, *44*, 452.
(36) Whitesell, J. K.; Minton, M. A.; Felman, S. W. *J. Org. Chem.* **1983**, *48*, 2193.
(37) Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512.
(38) Trost, B. M. *ACS Symposium Ser.* **1982**, *185*, 1. For illustrations of the tripartite use of O-methylmandelates for several cases, see: Trost, B. M.; Godleski, S. A.; Genet, J. P. *J. Am. Chem. Soc.* **1978**, *100*, 3930. Trost, B. M.; Curran, D. P. *Tetrahedron Lett.* **1981**, *22*, 4929. Trost, B. M.; McDougal, P. G. *Tetrahedron Lett.* **1982**, *23*, 5497. Trost, B. M.; Belletire, J. L.; Godleski, S.; McDougal, P. G.; Balkovec, J. M.; Baldwin, J. J.; Christy, M. E.; Ponticello, G. S.; Varga, S. L.; Springer, J. P. *J. Org. Chem.* **1986**, in press.
(39) Stadler, P. A. *Helv. Chim. Acta* **1978**, *61*, 1675.
(40) W. Clark Still's molecular modeling program Model version 1.3 was used. The following torsional parameters for atom types (3 2 1 6) were utilized: V_1 = 0, V_2 = 0, V_3 = 0. Note: *MM2* approximates conjugated π-systems; the C(11)–C(12) bond length is ca. 1.35 Å.

Table V. Cytotoxicity of Allamandin and Analogues

compd	ED_{50} (μg/mL)	compd	ED_{50} (μg/mL)
		28[b]	>10[c]
8	2.7[d]	**39**[b]	2
9[a]	2.6[d]	**40**[b]	0.2
10[a]	2.1[d]	**47a** or **47b**[b]	>10[c]
4[a]	>10[c,d]	**48a**[b]	3
21b[b]	1	**64b**[b]	0.3
	>10[c]		>10[c]

[a] Enantiomerically pure naural products. [b] Racemic. [c] An activity >10 μg/mL is considered inactive. [d] Data from ref 7c.

results, summarized in Table V, list activities as the ED_{50} (effective dose required to inhibit 50% of control growth). The tests were performed in vitro against cells derived from human carcinoma of the nasopharynx (KB).[41] It appears that the α-ethylidene lactone is the main source of the cytotoxicity.[42] The notable exception is **21** whose activity, by comparison with the other entries, cannot reside in the butenolide alone. The very high activity of **40** and **48**, which, being racemic, is more than an order of magnitude more active than the natural products, may suggest the pyranyl unit via a stabilized carbocationic center α to oxygen also is an active site. The tenfold enhancement in activity in going from **48a** to **48b** which simply involves conversion of the anomeric hydroxyl group to an acetoxy group supports such an interpretation.

Experimental Section

General Methods. See supplementary material.

Preparation of 2-(1′-Hydroxycyclopropyl)-*cis*-bicyclo[3.3.0]oct-2,7-diene (42). Powdered potassium hydroxide (85%, 3.05 g, 46.2 mmol) was added to 7.52 g (61.6 mmol) of bicyclic ketone **14** (R = H) and 20.3 g (64.6 mmol) of cyclopropyldiphenylsulfonium fluoroborate in 45 mL of Me_2SO at room temperature. After 45 min, 3.05 g (46.2 mmol) of potassium hydroxide was added, and stirring was continued for an additional 45 min. The reaction mixture was extracted with 3 × 300 mL of pentane, and the combined extracts were washed with saturated aqueous sodium bicarbonate, dried over sodium sulfate, and concentrated in vacuo at 0 °C to ca. 100 mL. The concentrated extract from above was added to 123 mmol of a suspension of lithium diethylamide in 75 mL of pentane at −78 °C. Upon complete addition, the flask was removed from the ice bath and stirred 2 h. The reaction was quenched by the addition of 100 mL of water and extracted with ether and dried (sodium sulfate), and the solvent was removed in vacuo to give an oil. Purification by flash chromatography (5 cm, 1.5 L hexanes, ether/hexanes, 1:5) gave 8.17 g (82%) of a clear oil, R_f 0.37 (ethyl acetate/hexanes, 1:4): 100-MHz ^{1}H NMR (CCl_4) δ 5.9–5.7 (m, 1 H), 5.7–5.5 (m, 1 H), 5.2 (dd, J = 4,2 Hz, 1 H), 3.7–3.5 (m, 1 H), 3.1–2.4 (m, 3 H), 2.4–1.9 (m, 3 H), 0.8 (t, J = 2 Hz, 2 H), 0.7 (t, J = 2 Hz, 2 H); 15-MHz ^{13}C NMR ($CDCl_3$) δ 147.2, 131.8, 129.3, 122.8, 58.1, 54.4, 40.4, 40.2, 14.8, 13.0; IR (CCl_4) 3590, 3400, 1580 cm^{-1}; calcd for $C_{11}H_{14}O$ 162.1045, found 162.1044.

Preparation of (1*S,2*R**)-*exo*-3-(Phenylselenenyl)-*cis*-bicyclo-[3.3.0]-oct-7-ene-2-spiro(2′-oxocyclobutane) (43).** A solution of 8.17 g (50.4 mmol) of vinyl cyclopropanol **42** in 35 mL of dichloromethane was added to 17.84 g (75.6 mmol) of phenylselenenyl bromide and 14.0 mL (101 mmol) of triethylamine in 35 mL of dichloromethane at −45 °C. After 4 h at −40 to −50 °C, the reaction was quenched by the addition of 50% saturated aqueous sodium hydrogen sulfate at −45 °C and allowing the mixture to warm to room temperature. The dark brown solution was extracted with ether and dried (magnesium sulfate), and the solvent was removed in vacuo to give a dark-brown oil. Purification by flash chromatography [5-cm column, elute with hexanes until diphenyl diselenide was eluted, then ether/hexanes, 1:5, to obtain a yellow oil then chromatograph oil on a new column] gave 14.03 g (88%) of a pale yellow oil that was essentially (>100:1) one cyclobutanone isomer by 15 MHz ^{13}C NMR, R_f 0.53 (ethyl acetate/hexanes, 1:4): 270-MHz ^{1}H NMR ($CDCl_3$) δ 7.56 (m, 2 H), 7.27 (m, 3 H), 5.82 (m, 1 H), 5.52 (m, 1 H), 3.39 (m, 1 H), 3.32 (dd, J = 12.0, 7.2 Hz, 1 H), 3.16–2.65 (m, 4 H), 2.30 (m, 1 H), 2.15–1.80 (m, 4 H); 15-MHz ^{13}C NMR ($CDCl_3$) δ 212.7, 133.6, 133.3, 132.4, 128.7, 128.1, 127.1, 76.8, 55.4, 46.2, 43.1, 42.0, 41.9, 37.9, 18.2; IR ($CHCl_3$) 1765, 1660, 1580, 1480 cm^{-1}; calcd for $C_{17}H_{18}OSe$ 318.0518, found 318.0518.

Preparation of (1*S,2*R**)-*cis*-Bicyclo[3.3.0]oct-3,7-diene-2-spiro-4′-γ-butyrolactone (44). Method A. Direct conversion of 43.** MCPBA (64%, 280 mg, 1.04 mmol) was added to a solution of 150 mg (0.472 mmol) of cyclobutanone **43** in 2 mL of dichloromethane at −78 °C. After 15 min, the mixture was warmed to 0 °C, and, after an additional 15 min, ethyl vinyl ether (0.285 mL, 2.83 mmol) was added. The reaction vessel was sealed and allowed to warm to room temperature. After 88 h, the mixture was diluted with ether, washed with saturated aqueous sodium bicarbonate, and dried (magnesium sulfate), and the solvent was removed in vacuo to give an oil. Purification by preparative TLC (20 cm × 40 cm × 2.5 mm, ether/hexanes, 1:1) gave 54 mg (65%) of white crystals, mp 69.5–70.0 °C, R_f 0.51 (ether).

Method B. Two-Step Conversion of 43. A cooled (0 °C) basic hydrogen peroxide solution (30% aqueous hydrogen peroxide, 10.6 mL, 100 mmol; 10% aqueous sodium hydroxide, 15.1 mL) was added to 3.17 g (10.0 mmol) of selenocyclobutanone **43** in 70 mL of THF and 35 mL of methanol at 0 °C. After 30 min, the reaction was quenched with reduction of the selenoxide by addition of an aqueous solution of sodium sulfite (35 g in 100 mL of water) and stirring 5 min. The mixture was poured into a rapidly stirring mixture of 50 mL of dichloromethane and 100 mL of saturated aqueous sodium hydrogen sulfate. After 30 min, the organic phase was separated, and the aqueous layer was extracted with 100 mL of dichloromethane followed by 2 × 100 mL of ethyl acetate. The combined organic phases were dried (magnesium sulfate), and the solvent was removed in vacuo to give an orange oil which was dissolved in ca. 20 mL of benzene containing a small amount of *p*-toluenesulfonic acid. The subsequent removal of the solvent in vacuo effected a dehydration to give the lactone. Purification by flash chromatography (5 cm; 500-mL hexanes; 1-L ether/hexanes, 1:3, 1-L ether/hexanes, 1:2; 100-mL fractions) gave 2.33 g (70%) of a white crystalline solid, mp 110–114 °C, R_f 0.58 (ether): IR ($CHCl_3$) 3080, 3060, 3010, 2960, 2920, 2860, 1770, 1580, 1475, 1450, 1435, 1280, 1230, 1200, 1160, 1060, 1040, 1020, 990, 960, 950, 925 cm^{-1}; 200-MHz ^{1}H NMR ($CDCl_3$) δ 7.50 (m, 2 H), 7.26 (m, 3 H), 5.84 (m, 1 H), 5.50 (m, 1 H), 3.30 (m, 1 H), 3.23 (dd, J = 12.5 Hz, 1 H), 3.0–1.85 (m, 8 H); 15-MHz ^{13}C NMR ($CDCl_3$) 175.4, 134.4, 132.9, 128.7, 128.5, 127.0, 126.8, 94.9, 60.0, 51.0, 41.7, 41.1, 36.9, 29.1, 26.5; IR ($CHCl_3$) 1770, 1580, 1475 cm^{-1}; calcd for $C_{17}H_{18}O_2Se$ 334.0467, found 334.0471.

MCPBA (85%, 2.19 g, 10.8 mmol) was added to 3.00 g (9.01 mmol) of selenolactone in 20 mL of dichloromethane at −78 °C. After 30 min, 4.54 mL (45.1 mmol) of ethyl vinyl ether was added, and the reaction was warmed to room temperature. The vessel was sealed, and the homogeneous mixture was stirred 40 h. Dilution with 100 mL of ether followed by 100 mL of a 5% aqueous disodium hydrogen phosphate wash, drying (magnesium sulfate), and removal of the solvent in vacuo gave an oil. Purification by flash chromatography (4 cm, ether/hexanes, 1:2) gave 1.59 g (quantitative) of a white powder, mp 69–70 °C, R_f 0.5 (ether); 200-MHz ^{1}H NMR ($CDCl_3$) δ 5.96 (dd, J = 5.5, 1.5 Hz, 1 H), 5.66 (m, 1 H), 5.59 (m, 2 H), 3.58 (m, 1 H), 3.46 (m, 1 H), 2.8–2.0 (m, 6 H); 15-MHz ^{13}C NMR ($CDCl_3$) δ 175.7, 141.4, 130.7, 129.0, 127.6, 98.5, 58.4, 46.7, 36.6, 30.0, 29.5; IR ($CHCl_3$) 1765, 1625 cm^{-1}. Anal. Calcd for $C_{11}H_{12}O_2$: C, 74.98; H, 6.86; M_r 176.0834. Found: C, 75.22; H, 7.00; M_r 176.0836.

Preparation of (1*S,2*R**)-*cis*-Bicyclo[3.3.0]oct-3,7-diene-2-spiro-4′-[(α,α-bis(phenylsulfenyl))-γ-butyrolactone] (45).** A solution of 280 mg (1.59 mmol) of butyrolactone **44** in 2.5 mL of THF was added to 3.34 mmol of LDA in 2.0 mL of THF at −78 °C. After 30 min, a solution of 835 mg (3.34 mmol) of phenyl (phenylthio)sulfonate[43] in 2.5 mL of THF was added. After 15 min, the mixture was warmed to room temperature and stirred for 1 h. An additional amount of phenyl (phenylthio)sulfonate (80 mg, 0.32 mmol) was added, and stirring was continued 15 min. The reaction was quenched by the addition of 15 mL of water. The mixture was extracted with 2 × 30 mL of ether, the combined organic phases were dried (magnesium sulfate), and the solvent was removed in vacuo to give an oil. Purification by flash chromatography (3 cm, ether/hexanes, 1:4) gave 594 mg (95%) of a white powder, mp 104–105 °C, R_f 0.3 (ether/hexanes, 1:4): 200-MHz ^{1}H NMR ($CDCl_3$) δ 7.65 (m, 4 H), 7.38 (m, 6 H), 5.92 (dd, J = 5.5, 1.5 Hz, 1 H), 5.58 (m, 1 H), 5.51 (dd, J = 5.5, 1.5 Hz, 1 H), 5.36 (m, 1 H), 3.48 (m, 1 H), 3.32 (m, 1 H), AB system 2.70 (d, J = 15 Hz, 1 H) and 2.46 (d, J = 15 Hz, 1 H), 2.52 (m, 1 H), 2.24–2.05 (m, 1 H); 15-MHz ^{13}C NMR ($CDCl_3$) δ 170.7, 142.2, 135.9, 135.8, 131.0, 130.3, 130.1, 129.6, 128.7, 127.7, 94.9, 62.9, 59.5, 46.5, 42.1, 36.7; IR ($CHCl_3$) 1755, 1615, 1580, 1470 cm^{-1}; calcd for $C_{23}H_{20}O_2S_2$ 392.0900, found 392.0906.

(41) Procedures used were those described in *Cancer Chemother. Rep.* **1962**, *25*, 1.

(42) Kupchan, S. M.; Eakin, M. A.; Thomas, A. M. *J. Med. Chem.* **1971**, *14*, 1147. Kupchan, S. M.; Fessler, D. C.; Eakin, M. A.; Giacobbe, T. J. *Science*, **1970**, *168*, 376.

Preparation of (1S*,2R*)-*cis*-Bicyclo[3.3.0]oct-3,7-diene-2-spiro-4′-[α-(1-hydroxyethyl)-α-(phenylsulfenyl)-γ-butyrolactone] (46). Ethylmagnesium bromide (2.05 M in ether, 2.66 mL, 5.45 mmol) was added to 0.710 g (1.81 mmol) of bissulfenylated lactone **45** in 10 mL of THF at 0 °C. After 90 min, 0.304 mL (5.43 mmol) of freshly distilled acetaldehyde followed by 10 mL of water were added. Ether extraction (2 × 70 mL), drying (magnesium sulfate) and removal of the solvent in vacuo gave an oil. Purification by flash chromatography (4 cm, ether/hexanes, 2:3) gave 0.590 g (quantitative) of a clear oil, R_f 0.57 (ether). This material was found to be a diastereomeric mixture by the doubling of the methyl doublet, δ 1.37 and 1.34, in the ^{1}H NMR: 200-MHz ^{1}H NMR ($CDCl_3$) δ 7.63 (m, 2 H), 7.40 (m, 3 H), 6.04 (m, 2 H), 5.70 (m, 2 H), 5.49 (dd, J = 5.5, 1.5 Hz, 1 H), 4.08 (q, J = 6.0 Hz, 1 H), 3.75–3.45 (m, 2 H), 3.2–2.0 (m, 4 H), 1.37 (d, J = 6 Hz, 1.5 H), 1.34 (d, J = 6 Hz, 1.5 H); IR ($CHCl_3$) 3520, 1750, 1620, 1460 cm^{-1}; calcd for $C_{19}H_{20}O_3S$ 328.1128, found 328.1134.

Preparation of (1S*,2R*)-*cis*-Bicyclo[3.3.0]oct-3,7-diene-2-spiro-4′-[α-(1-hydroxyethyl)-Δ^{α,β}-butenolide] (47a). MCPBA (85%, 1.29 g, 6.33 mmol) was added to 1.39 g (4.26 mmol) of aldol adduct **46** in 10 mL of dichloromethane at −78 °C. After 1.5 h at −78 °C, the mixture was warmed to room temperature and immediately quenched with 20 mL of saturated aqueous sodium hydrogen sulfite. After 10 min of vigorous stirring, the mixture was extracted with 3 × 75 mL of ether, washed with saturated aqueous sodium bicarbonate, and dried (magnesium sulfate), and the solvent was removed in vacuo to give a white solid.

A suspension of the above residue and 2.88 g (28.7 mmol) of calcium carbonate in 20 mL of carbon tetrachloride was rapidly heated to reflux for 20 min (bath temperature 90 °C). The mixture was cooled and filtered through a Celite pad, and the pad was subsequently washed with ether. Removal of the solvent in vacuo gave a yellowish solid. Purification by flash chromatography (5 cm, ether/hexanes, 2:3) gave 752 mg (82%) of a white solid which was a 1:1 mixture of epimeric alcohols by the doubling of the methyl signals δ 1.49 and 1.46 in the ^{1}H NMR spectrum; R_f 0.39 (ether): 200-MHz ^{1}H NMR ($CDCl_3$) δ 7.04 (d, J = 0.5 Hz, 1 H), 6.03 (dd, J = 6, 1.5 Hz, 1 H), 5.60 (m, 1 H), 5.42 (m, 1 H), 5.24 (m, 1 H), 4.64 (q, J = 5.5 Hz, 1 H), 4.10 (br s, 1 H), 3.63 (m, 1 H), 3.44 (m, 1 H), 2.55 (m, 1 H), 2.18 (m, 1 H), 1.49 (d, J = 6 Hz, 1.5 H), 1.46 (d, J = 6 Hz, 1.5 H); 15-MHz ^{13}C NMR ($CDCl_3$) δ 171.4, 148.3, 144.1, 137.2, 130.9, 128.6, 126.3, 98.9, 63.1, 59.3, 47.6, 36.4, 21.7; IR ($CHCl_3$) 3460, 1730, 1610 cm^{-1}; calcd for $C_{13}H_{14}O_3$ 218.0939, found 218.0944.

Preparation of (1S*,2R*)-*cis*-Bicyclo[3.3.0]oct-3,7-diene-2-spiro-4′-[α-(1-acetoxyethyl)-α,β-γ-butenolide] (47b). Pyridine (0.561 mL, 6.94 mmol) was added to 752 mg (3.47 mmol) of butenolide **47a** in 6 mL of dichloromethane, and the mixture was cooled to 0 °C. A catalytic amount (ca. 5 mg) of DMAP followed by 0.360 mL (3.82 mmol) of acetic anhydride was added, and the mixture stirred 1 h. The reaction was quenched by the addition of 4 mL of saturated aqueous sodium hydrogen sulfate and extracted with 100 mL of ether. The extracts were washed with 4 mL of saturated aqueous sodium bicarbonate and dried (magnesium sulfate), and the solvent was removed in vacuo to give 825 mg (92%) of a clear oil which was used without further purification, R_f 0.66 (ether). An analytically pure sample was obtained by preparative TLC (ether): 200-MHz ^{1}H NMR ($CDCl_3$) δ 7.00 (t, J = 0.5 Hz, 1 H), 6.10 (dd, J = 5, 1.5 Hz, 1 H), 5.65 (m, 2 H), 5.46 (m, 1 H), 5.28 (dd, J = 5, 1 Hz, 1 H), 3.68 (m, 1 H), 3.49 (m, 1 H), 2.60 (m, 1 H), 2.24 (m, 1 H), 2.08 (d, J = 1 Hz, 3 H), 1.51 (d, J = 6 Hz, 1.5 H), 1.48 (d, J = 6 Hz, 1.5 H); IR ($CHCl_3$) 1740, 1610 cm^{-1}. Anal. Calcd for $C_{15}H_{16}O_4$: C, 69.22; H, 6.20; M_r 260.1044. Found: C, 69.50; H, 6.45; M_r 260.1050.

Preparation of (1R*,2R*)-*exo*-7,8-Dihydroxy-*cis*-bicyclo[3.3.0]oct-3-ene-2-spiro-4′-[α-(1-acetoxyethyl)-Δα,β-γ-butenolide]. *N*-Methylmorpholine *N*-oxide monohydrate[18] (540 mg, 4.00 mmol) followed by 39 mg (0.15 mmol) of osmium tetroxide was added to 800 mg (3.08 mmol) of butenolide **47b** in 5 mL of THF and 5 mL of water at 0 °C. The reaction mixture was initially green in color, changed to green-black, and after 2.5 h back to green again. The reaction was quenched by adding florisil (ca. 1 g) and 6 mL of saturated aqueous sodium hydrogen sulfite, removing the ice bath, and stirring 20 min. The reaction mixture was filtered through a florisil pad which was subsequently washed with ca. 300 mL of ether acetate. The organic phase was dried (magnesium sulfate), and the solvent was removed in vacuo to give 880 mg of an oil. Purification by flash chromatography (3 cm, ethyl acetate/hexanes, 9:1) gave 810 mg (90%) of a colorless, viscous oil, R_f 0.26 (ethyl acetate): 200-MHz ^{1}H NMR ($CDCl_3$) δ 7.24 (d, J = 0.5 Hz, 1 H), 6.15 (dd, J = 5.5, 1.5 Hz, 1 H), 6–4.8 (br, 2 H), 5.56 (qd, J = 7, 1 Hz), 5.30 (dd, J = 5.5, 1 Hz, 1 H), 3.60 (m, 1 H), 2.79 (t, J = 7.5 Hz, 1 H), 2.08 (s, 3 H), 1.90 (dd, J = 7,1 Hz, 1 H), 1.60 (dt, J = 14, 5 Hz, 1 H), 1.49 (d, J = 7 Hz, 3 H); IR ($CHCl_3$) 3580, 1765, 1620, 1580 cm^{-1}; calcd for $C_{15}H_{18}O_6$ 294.1098, found 294.1096.

Preparation of Allamcin (48a). Method A. Alumina-Catalyzed Cyclization. Sodium metaperiodate (323 mg, 1.51 mmol) was added to a solution of 148 mg (0.503 mmol) of (1R*,2R*)-*exo*-7,8-dihydroxy-*cis*-bicyclo[3.3.0]oct-3-ene-2-spiro-4′-[α-(1-acetoxyethyl)-Δ^{α,β}-butenolide] in 6 mL of a 1:1 mixture of ether/water. After 30 min the reaction was extracted with 60 mL of ether and ethyl acetate and dried (magnesium sulfate), and the solvent was removed in vacuo to afford an unstable yellow oil presumably the cyclic hydrate of the dialdehyde.

The above oil was added to a suspension of acidic alumina (activity II–III) (1.5 g) in wet THF (1.5 mL water in 9 mL THF). After 24 h, no starting material could be detected by TLC. The addition of magnesium sulfate followed by filtration (washing the solid with ethyl acetate) and removal of the solvent in vacuo gave 96 mg (76%) of a very insoluble amorphous solid which was an ca. 3:1 mixture of E/Z enones as seen by the methyl doublets at δ 2.08 and 2.21 in the ^{1}H NMR spectrum, R_f 0.35 (ethyl acetate).

Method B. Sodium Acetate-Catalyzed Cyclization. Solid sodium periodate (574 mg, 2.64 mmol) was added to 263 mg (0.895 mmol) of the diol in 10 mL of a 1:1 mixture of ether and water. After 10 min, a solution of 1.5 g of sodium acetate in 10 mL of water was added to the discolored reaction mixture and stirred vigorously for 1 h. Extraction with 3 × 250 mL of ethyl acetate, drying (magnesium sulfate), and removal of the solvent in vacuo gave a very insoluble off-white powder. Washing the solid with 3 × 40 mL of ether gave a white powder (200 mg, 89%), mp 195–200 °C (dec), determined to be an ca. 8:1 mixture of E/Z enones by ^{1}H NMR as described above. The spectral characteristics and TLC behavior were identical with those of a sample of (+)-allamcin kindly provided by Professor T. Yamauchi,[8a] R_f 0.34 (ethyl acetate): 500-MHz ^{1}H NMR (Me_2SO-d_6) δ 6.90 (qd, J = 7.0, 2.0 Hz, 1 H), 6.01 (dd, J = 5.3, 2.0 Hz, 1 H), 5.79 (dd, J = 5.6, 2.8 Hz, 1 H), 5.50 (d, J = 4.8 Hz, 1 H), 4.99 (s, 1 H), 4.88 (dd, J = 8.8, 5.2 Hz, 1 H), 3.19 (m, 1 H), 2.84 (dd, J = 8.3, 4.8 Hz), 1.94 (dd, J = 9.0, 3.2 Hz, 0.5 H), 1.92 (d, J = 7.0 Hz, 3.5 H), 1.50 (ddd, J = 14.1, 9.0, 5.2 Hz, 1 H); 200-MHz ^{1}H NMR ($CDCl_3$) δ 7.10 (qd, J = 7, 1 Hz, 1 H), 5.99 (dd, J = 5.5, 2 Hz, 1 H), 5.75 (dd, J = 5.4, 2.5 Hz, 1 H), 5.67 (d, J = 5.2 Hz, 1 H), 5.22 (dd, J = 8.1, 5.4 Hz, 1 H), 5.08 (s, 1 H), 3.34 (m, 1 H), 3.00 (dd, J = 8.5, 4.5 Hz, 1 H), 2.35–1.40 (m, 3 H), 2.08 (dd, J = 7, 0.5 Hz, 3 H); IR ($CHCl_3$) 3340, 1760, 1730, 1680 cm^{-1}. Anal. Calcd for $C_{13}H_{14}O_5$: C, 62.39; H, 5.64; M_r 250.0837. Found: C, 62.56; H, 5.84; M_r 250.0842.

Preparation of 3-Dehydroallamcin (39). Method A. Collins Oxidation.[44] Collins reagent was prepared by the careful addition of 164 mg (1.64 mmol) of chromium(VI) oxide to a mixture of ca. 1.5 g of Celite, 0.265 mL (3.28 mmol) of pyridine, and 4 mL of dichloromethane at 0 °C and stirring 2 h at room temperature. After having been cooled to 0 °C, 44 mg (0.164 mmol) of solid allamcin **48a** was added. After 70 min, the reaction was diluted with 15 mL of ether, and the mixture was filtered through a Celite pad. The chromium residues were washed successively with 50 mL of dichloromethane and 50 mL of ether. The organic phase was washed with 10 mL of 50% saturated aqueous sodium hydrogen sulfate and dried (magnesium sulfate). Removal of the solvent in vacuo gave 46 mg (quantitative yield) of an oil, R_f 0.55 (ethyl acetate).

Method B. Jones Oxidation. A suspension of 12 mg (0.048 mmol) of allamcin **48a** was prepared in 2.0 mL of dichloromethane. Jones reagent[45] (1.17 M, 0.082 mL, 0.096 mmol) was added, and the reaction was vigorously stirred for 1 h at room temperature. The reaction was cooled to 0 °C and quenched with isopropanol. The mixture was diluted with ether and washed with 3 portions of water followed by saturated aqueous sodium bicarbonate. The organic phase was dried over magnesium sulfate and filtered through a small silica gel column (60–200 mesh, ether) to give a yellow oil. Purification by preparative TLC (20 cm × 20 cm × 0.25 mm, ethyl acetate) gave 10 mg (84%) of a clear oil: 200-MHz ^{1}H NMR ($CDCl_3$) δ 7.19 (qd, J = 8, 1 Hz, 1 H), 5.92 (m, 3 H), 5.19 (s, 1 H), 3.57 (m, 1 H), 3.32 (dd, J = 8.5, 5 Hz, 1 H), AB system: 2.72 (dd, J = 14, 3 Hz, 1 H) and 2.52 (dd, J = 14, 5 Hz, 1 H), 2.09 (d, J = 8 Hz, 3 H); IR ($CHCl_3$) 1755, 1682 cm^{-1}; calcd for $C_{13}H_{12}O_5$ 248.0681, found 248.0684.

Preparation of 4-Descarbomethoxyplumericin (40). Acetic anhydride (0.377 mL, 4.00 mmol) followed by 0.695 mL (4.00 mmol) of ethyldiisopropylamine was added to a suspension of 100 mg (0.400 mmol) of allamcin (**48a**) in 3.5 mL of dry dichloromethane. Upon addition of 1 mg of DMAP, the mixture rapidly darkened. After 5 min, the homogeneous reaction mixture was diluted with 10 mL of ether and washed with saturated aqueous sodium bicarbonate followed by 25% saturated

(43) Trost, B. M.; Massiot, G. S. *J. Am. Chem. Soc.* **1977**, *99*, 4405.
(44) Collins, J. C.; Hess, W. W. *Org. Synth.* **1972**, *52*, 5.
(45) Bowden, K.; Heilbroom, I. M.; Jones, E. R. H.; Weedon, B. C. L. *J. Chem. Soc.* **1946**, 39. Meinwald, J.; Crandall, J.; Hymans, W. E. *Org. Synth.* **1965**, *45*, 77.

aqueous sodium hydrogen sulfate. The solution was dried over magnesium sulfate, and removal of the solvent in vacuo gave a brown solid. This crude acetate was used directly in the flash vacuum thermolysis; however, an analytically pure sample of O-acetylallamcin (**48b**) for spectral characterization could be obtained by preparative TLC (ether), mp 147–149 °C, R_f 0.68 (ethyl acetate): 200-MHz ^{1}H NMR ($CDCl_3$) δ 7.12 (qd, J = 7.5, 1 Hz, 1 H), 6.08 (dd, J = 8, 6 Hz, 1 H), 6.02 (dd, J = 6, 1 Hz, 1 H), 5.78 (dd, J = 5, 3 Hz, 1 H), 5.60 (d, J = 5 Hz, 1 H), 5.07 (s, 1 H), 3.38 (m, 1 H), 3.20 (dd, J = 9, 5 Hz, 1 H), 2.3–2.1 (m, 1 H), 2.06 (s, 4.5 H), 2.03 (s, 1.5 H), 1.95–1.75 (m, 1 H); IR ($CHCl_3$) 1755, 1690, 1625 cm^{-1}; calcd for $C_{15}H_{16}O_6$ 292.0942, found 292.0942.

The brown solid from above was subjected to flash vacuum thermolysis (see general Experimental Section for details) (13-cm quartz tube), 500 °C, 0.005 mmHg). The resultant brown oil was purified by preparative TLC (20 cm × 20 cm × 2.5 mm, ethyl acetate) to give white crystals (75 mg, 81% based on **48a**), mp 105–107 °C, R_f 0.70 (ethyl acetate): 200-MHz ^{1}H NMR ($CDCl_3$) δ 7.12 (qd, J = 7, 1.0 Hz, 1 H), 6.29 (d, J = 6 Hz, 1 H), 5.88 (dd, J = 5.5, 2 Hz, 1 H), 5.64 (dd, J = 5, 2 Hz, 1 H), 5.50 (d, J = 6 Hz, 1 H), 5.08 (m, 2 H), 3.52 (m, 1 H), 3.27 (dd, J = 9, 5.5 Hz, 1 H), 2.06 (dd, J = 7, <0.5 Hz, 3 H); IR ($CHCl_3$) 1765, 1695, 1660, 1570 cm^{-1}; calcd for $C_{13}H_{12}O_4$ 292.0732, found 292.0736.

Preparation of 4-(Trichloroacetyl)-4-descarbomethoxyplumericin (49). 2,6-Di-*tert*-butylpyridine (0.097 mL, 0.43 mmol) followed by 0.480 mL (4.3 mmol) of carefully distilled trichloroacetyl chloride was added to a solution of 20 mg (0.086 mmol) of 4-descarbomethoxyplumericin (**40**) in 0.040 mL of dry dichloromethane. The reaction vessel was sealed, and the mixture was stirred 98 h. The resultant dark-brown reaction mixture was quenched by the addition of solid sodium carbonate (anhydrous), diluting with dichloromethane and stirring 10 min. Silica gel and magnesium sulfate were added followed by ca. 0.2 mL of methanol. Filtration and removal of the solvent in vacuo gave a brown oil. Preparative TLC (20 cm × 20 cm × 0.2 mm, ether) gave a white solid (28 mg, 85%), mp 180–181 °C, R_f 0.70 (ethyl acetate): 200-MHz ^{1}H NMR ($CDCl_3$) δ 8.16 (s, 1 H), 7.18 (qd, J = 7, 1 Hz, 1 H), 5.96 (dd, J = 6, 2 Hz, 1 H), 5.68 (m, 2 H), 5.12 (s, 1 H), 4.15 (dt, J = 10, 1 Hz, 1 H), 3.52 (dd, J = 10, 6 Hz, 1 H), 2.08 (d, J = 7 Hz, 3 H); IR ($CHCl_3$) 1765, 1685, 1615 cm^{-1}; calcd for $C_{15}H_{11}O_5{}^{35}Cl_2{}^{37}Cl$ 377.9640, found 377.9641.

Preparation of Plumericin (8). A solution of magnesium methoxide (0.5 M in methanol, 0.050 mL, 0.025 mmol) was added to 23 mg (0.061 mmol) of trichloro ketone **65** in 0.8 mL of a 5:3 mixture of methanol/THF at −45 °C. After 15 min, the clear solution was quenched at −45 °C by the addition of saturated aqueous ammonium chloride and then allowed to warm to room temperature. The mixture was diluted with water and exhaustively extracted with ethyl acetate. The combined extracts were dried (magnesium sulfate), and the removal of solvent in vacuo gave a solid. Recrystallization from methanol gave 16 mg (90%) of white crystals, mp 176–178 °C, R_f 0.68 (ethyl acetate). This material had identical IR,[7c] ^{1}H NMR,[7c] and mass spectral[8b] characteristics as that of natural plumericin: 200-MHz ^{1}H NMR ($CDCl_3$) δ 7.42 (s, 1 H), 7.15 (qd, J = 7, 1 Hz, 1 H), 6.02 (dd, J = 6, 1.5 Hz, 1 H), 5.62 (dd, J = 6, 2 Hz, 1 H), 5.56 (d, J = 6 Hz, 1 H), 5.12 (s, 1 H), 4.00 (dt, J = 9, 2 Hz, 1 H), 3.78 (s, 3 H), 3.42 (dd, J = 9, 6 Hz, 1 H), 2.06 (d, J = 7.5 Hz, 3 H); IR ($CHCl_3$) 1765, 1710, 1690, 1650, 1620 cm^{-1}; calcd for $C_{15}H_{14}O_6$ 290.0786, found 290.0787.

Preparative chromatography of the mother liquor (20 cm × 20 cm × 0.25 mm, ethyl acetate/hexanes, 1:1) gave a small amount of isoplumericin, R_f −0.70 (ethyl acetate). This isomer has been carried through the sequence from allamcin (**48a**). The spectral characteristics[7c,8b] were identical with those reported for the natural product: 200-MHz ^{1}H NMR ($CDCl_3$) δ 7.42 (s, 1 H), 6.81 (qd, J = 7, 0.5 Hz, 1 H), 6.02 (dd, J = 6, 2 Hz, 1 H), 5.61 (dd, J = 5, 2 Hz, 1 H), 5.56 (d, J = 6 Hz, 1 H), 4.82 (s, 1 H), 3.98 (dt, J = 9, 2 Hz, 1 H), 3.77 (s, 3 H), 3.42 (dd, J = 9, 6 Hz, 1 H), 2.31 (d, J = 7 Hz, 3 H); IR ($CHCl_3$) 1767, 1710, 1650 cm^{-1}; calcd for $C_{15}H_{14}O_6$ 290.0786, found 290.0791.

Degradation of Plumericin (8) to Allamcin (48a) by Acid-Catalyzed Hydrolysis/Decarboxylation. A suspension of plumericin (**8**) (1 mg, 0.003 mmol) in 1 mL of 0.24 N hydrochloric acid containing a drop of methanol was heated to reflux for 5.5 h. The reaction was cooled and extracted twice with ethyl acetate. The combined extracts were dried over magnesium sulfate, and the solvent was removed in vacuo to give 0.8 mg (90%) of a white solid identified as **48a** by 200-MHz ^{1}H NMR and behavior on TLC.

Preparation of Allamandin (10). Method A. Utilization of $RhCl_3 \cdot 3H_2O$. Rhodium trichyloride trihydrate (15 mg, 0.057 mmol) was dissolved in a suspension of 6.0 mg (0.021 mmol) of plumericin (**8**) in 5 mL of water containing 3 drops of methanol. After refluxing for 4 h, the black mixture was cooled and extracted twice with ethyl acetate. The extracts were dried (magnesium sulfate), and the solvent was removed in vacuo to give a brown oil. Purification by preparative TLC (20 cm × 20 cm × 0.2 mm, ethyl acetate/ether, 1:1) gave three UV active bands: (1) recovered starting material **8** (1.5 mg, 25%), (2) a mixture of allamandin (**10**) and unidentified products (1.8 mg), and (3) a trace of allamcin (**48a**). The mixture obtained from the middle chromatography band (2) from above was triturated with ether to give pure (±)-allamandin (1.0 mg, 16%, 21% based on recovered **8**), mp 207–208.5 °C.

Method B. Acid-Catalyzed Hydration of 8. Plumericin (**8**) (1.95 mg, 0.00672 mmol) was suspended in 2.0 mL of 0.010 N perchloric acid. After heating at 95–100 °C for 9 h, the brown reaction mixture was cooled and extracted with 3 × 5 mL of ethyl acetate. The combined extracts were dried over magnesium sulfate and concentrated in vacuo to afford a dark-brown solid. This material was purified by preparative TLC (20 cm × 20 cm × 0.2 mm, ethyl acetate) to give three products: unreacted plumericin **8** (0.6 mg, 31%), R_f 0.68, allamandin (**10**) (0.8 mg, 39%, 55% based on recovered **8**), R_f 0.57, and allamcin (**48a**) (0.1 mg, 6%), R_f 0.35. This material had identical TLC behavior and IR, 270-MHz ^{1}H NMR, and mass[7c] spectral characteristics as that of natural (+)-allamandin kindly provided by Professor J. M. Cassady: 270-MHz ^{1}H NMR ($CDCl_3$) δ 7.15 (qd, J = 7, 1.5 Hz, 1 H), 6.01 (dd, J = 6, 2 Hz, 1 H), 5.82 (dd, J = 6, 2 Hz, 1 H), 5.67 (d, J = 4.5 Hz, 1 H), 5.46 (dd, J = 8, 3 Hz, 1 H), 5.14 (br s, 1 H), 3.79 (s, 3 H), 3.61 (m, 1 H), 3.07 (dd, J = 8, 4.5 Hz, 1 H), 2.88 (d, J = 2.5 Hz, 1 H), 2.78 (dd, J = 8, 4.5 Hz, 1 H), 2.04 (d, J = 7 Hz, 3 H); IR ($CHCl_3$) 3360, 1735, 1680 cm^{-1}; calcd for $C_{15}H_{16}O_7$: 308.0891, found 308.0892.

Acknowledgment. We thank the National Institutes of Health for their generous support of our programs. We thank Professors John M. Cassady (Purdue) and T. Yamauchi (Fukuoka) for generous samples of allamandin and allamcin, respectively. We thank Professor W. C. Still for generously supplying a copy of his molecular mechanics program and help in using it.

Supplementary Material Available: Tables I, II, III, and IV; general experimental; preparation and characterization of **16**, **17a** (R = H), **17a** (R = TBDMS), **18a**, **19a**, **20a**, **21a**, **17b**, **18b**, **19b**, **20b**, **21b**, **23**, **24**, **25**, **26**, **27**, **28**, **29**, **30**, **31**, **32**, **33**, **57**, **58**, **59**, **60** (32 pages). Ordering information is available on any current masthead.