Total Synthesis of (+)-Calyculin A and (−)-Calyculin B: Asymmetric Synthesis of the C(9−25) Spiroketal Dipropionate Subunit

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Abstract: An asymmetric synthesis of the stereochemically fully endowed C(9−25) spiroketal fragment (+)-**BC** of the calyculins (**1**−**8**) is described. Highlights of the synthesis include: a highly diastereoselective IBr-induced iodocarbonate cyclization to introduce the C(21) stereocenter in epoxide (+)-**18**, fragment unions exploiting the reaction of acyl anion equivalents with epoxides to construct masked advanced aldols (−)-**35** and (+)-**71** as single diastereomers, chelation-controlled addition of the C(14−15) vinyl group to aldehyde (+)-**38** to set the stereogenicity at C(16), selective reduction of the C(13) ketone via 1,3-induction, and development of an orthogonal protection scheme permitting both convenient installation of the C(17) phosphate group and flexibility in subsequent fragment couplings.

In 1986 Fusetani and co-workers reported the isolation and X-ray structural analysis of (−)-calyculin A (**1**, Figure 1), an architecturally novel marine metabolite derived from the Pacific sponge *Discodermia calyx*.[1] Seven additional congeners, B−H (**2**−**8**) isolated from the same source were disclosed in 1988[2] and 1990.[3] More recently, calyculin J (**9**), the calyculinamides (**10**−**12**), and dephosphonocalyculin A (**13**) were reported.[4] The absolute stereochemistry of calyculin A, assigned initially via the circular dichroism of the C(33−37) amino acid fragment obtained by degradation,[5] was subsequently confirmed via asymmetric synthesis of the antipode.[6] Structural assignments of (−)-calyculins B−H were based on spectral comparison with those of (−)-calyculin A;[1] calyculin J, the calyculinamides, and dephosphonocalyculin A were characterized by chemical correlation.[4]

The calyculins display a wide variety of biological activities. Most, including dephosphonocalyculin A, are potent inhibitors of protein phosphatases 1 and 2A.[3,7,8] Calyculins A−D also exhibit potent cytotoxicity against L1210 leukemia cells,[2] and significant inhibition of cell division in the fertilized egg assay of both the starfish *Asterina pectinifera* and *Hemicentrotus pulcherrimus*.[2] (−)-Calyculin A also stimulates contraction of smooth muscles,[9] promotes tumor growth in mice,[10] and displays in vivo antitumor activity against Ehrlich and P388 leukemia in mice.[1] Given the potent phosphatase inhibitory activity in conjunction with the remarkable cell membrane permeability, (−)-calyculin A has recently found application in the study of intracellular signal transduction.[8,11]

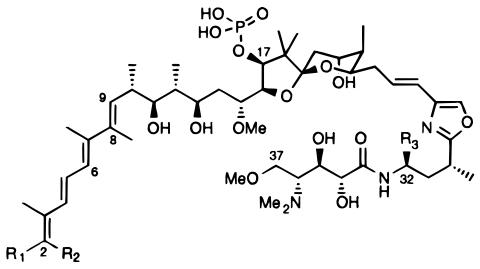

Figure 1. The absolute stereochemistry depicted represents the antipodes of the natural products.

(1) Kato, Y.; Fusetani, N.; Matsunaga, S.; Hashimoto, K.; Fujita, S.; Furuya, T. *J. Am. Chem. Soc.* **1986**, *108*, 2780.

(2) Kato, Y.; Fusetani, N.; Matsunaga, S.; Hashimoto, K.; Koseki, K. *J. Org. Chem.* **1988**, *53*, 3930.

(3) Matsunaga, S.; Fujiki, H.; Sakata, D.; Fusetani, N. *Tetrahedron* **1991**, *47*, 2999.

(4) (a) Matsunaga, S.; Wakimoto, T.; Fusetani, N.; Suganuma, M. *Tetrahedron Lett.* **1997**, *38*, 3763. (b) Dumdei, E. J.; Blunt, J. W.; Munro, M. H. G.; Pannell, L. K. *J. Org. Chem.* **1997**, *62*, 2636.

(5) Matsunaga, S.; Fusetani, N. *Tetrahedron Lett.* **1991**, *32*, 5605.

(6) Hamada, Y.; Tanada, Y.; Yokokawa, F.; Shioiri, T. *Tetrahedron Lett.* **1991**, *32*, 5983.

(7) Ishihara, H.; Martin, B. L.; Brautigan, D. L.; Karaki, H.; Ozaki, H.; Kato, Y.; Fusetani, N.; Watabe, S.; Hashimoto, K.; Uemura, D.; Hartshorne, D. J. *Biochem. Biophys. Res. Commun.* **1989**, *159*, 871.

(8) Sheppeck, J. E., II; Gauss, C.-M.; Chamberlin, A. R. *Bioorg. Med. Chem.* **1997**, *5*, 1739 and references therein.

(9) (a) Ishihara, H.; Ozaki, H.; Koichi, S.; Masatoshi, H.; Karaki, H.; Watabe, S.; Kato, Y.; Fusetani, N.; Hashimoto, K.; Uemera, D.; Hartshorne, D. J. *J. Pharmacol. Exp. Ther.* **1989**, *250*, 388. (b) Hartshorne, D. J.; Ishihara, H.; Karaki, H.; Ozaki, H.; Sato, K.; Hori, M.; Watabe, S. *Adv. Prot. Phosphatases*; Merlevede, W., Di Salvo, J., Eds.; Leuven University Press: Louvain, Belgium, 1988; Vol. 5, pp 219−231.

(10) Fujiki, H.; Suganuma, M.; Yoshizawa, H.; Sugimura, T.; Manam, S.; Kahn, S. M.; Jiand, W.; Hoshina, S.; Weinstein, I. B. *Mol. Carcinog.* **1989**, *2*, 184.

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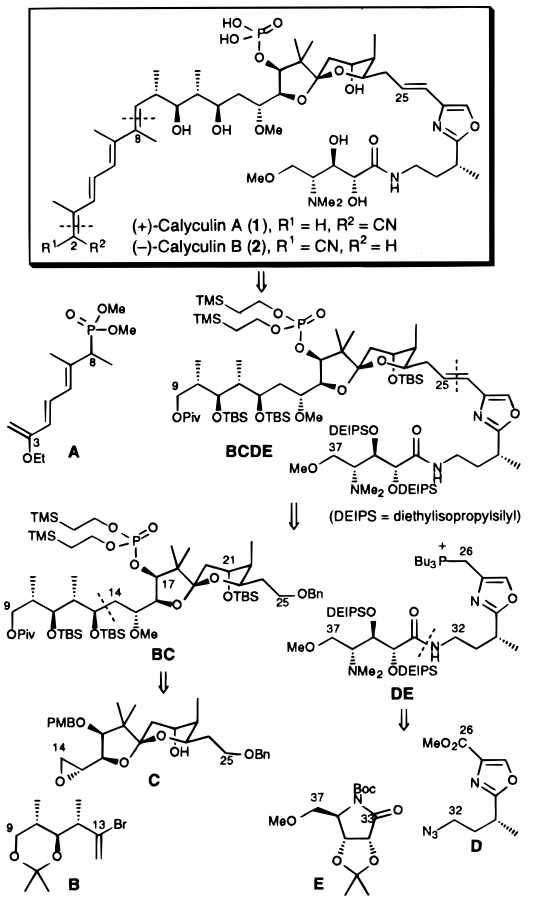
Not surprisingly, the calyculins have also attracted the attention of the synthetic community, culminating in recent notable total syntheses of the unnatural and natural antipodes of calyculin A [i.e., (+)-**1** and (−)-**1**, respectively] by Evans[12] and Masamune,[13] a formal total synthesis of (−)-calyculin A by Shioiri exploiting an advanced Masamune intermediate,[14] and a synthesis of calyculin C by Armstrong.[15] A number of synthetic approaches have also been reported.[6,16]

Intrigued by the diverse biological activities, as well as the interesting architectural features, in particular those of the [5.6] spiroketal, a central theme in our phyllanthostatin and breynolide synthetic ventures, we initiated work on the total synthesis of both calyculin A and B.[17] Elucidation of the absolute stereochemistry of (−)-calyculin A after the start of this synthetic program revealed that the natural products were enantiomeric to our targets. Our strategy is, of course, viable for the natural calyculins with minor modification.

Synthetic Analysis. From the outset, we envisioned an approach (Scheme 1) which would provide both calyculins A and B (**1** and **2**) from a common advanced intermediate, avoid extensive manipulations of the light-sensitive[3] C(1−9) cyanotetraene, and permit flexibility in fragment coupling. Accordingly, disconnections at the C(2) and C(8) olefins led to phosphonate **A**, possessing a latent C(3) carbonyl for penultimate Peterson olefination to access both **1** and **2**, after construction of a C(8,9) trisubstituted olefin. Disconnection of **BCDE** at the C(25) olefin revealed subtargets **BC**, envisioned to arise via coupling of an acyl anion equivalent (e.g., **B**) with epoxide **C**, and **DE**, available from oxazole **D** and lactam **E**. In this the first of two full accounts, we present the asymmetric synthesis of the stereochemically fully endowed C(9−25) **BC** fragment corresponding to the enantiomer of the calyculins.[17a,18] In the accompanying paper we present the synthesis of fragments **A**, **D**, and **E**, their union, and completion of the total syntheses of (+)-calyculin A and (−)-calyculin B.

Scheme 1



The C(9−25) **BC** subtarget, the core of the calyculins, encompasses three stereochemical triads [i.e., C(10−13), C(15−17), and C(21−23)] comprising 11 of the 15 stereogenic centers and a heptasubstituted [5,6] spiroketal. From the retrosynthetic perspective, any successful synthesis of this fragment would require a highly stereoselective strategy, in concert with a carefully designed orthogonal functional group protection scheme.

Our strategy for **BC** relied on the successful attachment of the C(9−13) dipropionate side chain to the C(14−25) spiroketal (Scheme 1). Consistent with concurrent investigations on the utility of dithiane−epoxide coupling reactions for the union of complex fragments, as achieved in our syntheses of FK-506, rapamycin and discodermolide,[19] disconnection of the **BC** carbon framework at C(13−14) led to spiroketal epoxide **C** and an acyl anion equivalent. Although we focused first on exploiting a C(13) dithiane (vide infra), the eventual successful strategy employed a cuprate derived from vinyl bromide **B**.

(11) Cohen, P.; Holmes, C. F. B.; Tsukitani, Y. *Trends Biochem. Sci*. **1990**, *15*, 98.

(12) Evans, D. A.; Gage, J. R.; Leighton, J. L. *J. Am. Chem. Soc.* **1992**, *114*, 9434.

(13) Tanimoto, N.; Gerritz, S. W.; Sawabe, A.; Noda, T.; Filla, S. A.; Masamune, S. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 673.

(14) For a formal synthesis of (−)-**1**, see: Yokokawa, F.; Hamada, Y.; Shioiri, T. *J. Chem. Soc., Chem. Commun.* **1996**, 871.

(15) Ogawa, A. K.; Armstrong, R. W. *J. Am. Chem. Soc.* **1998**, *120*, 12435.

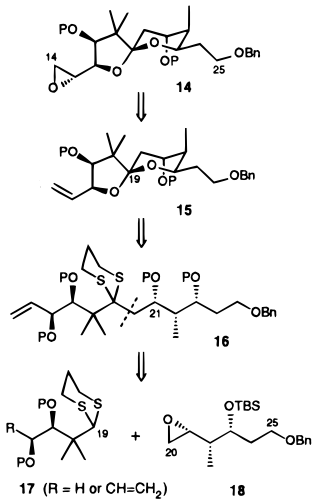
(16) (a) Evans, D. A.; Gage J. R. *Tetrahedron Lett*. **1990**, *31*, 6129. (b) Zhao, Z.; Scarlato, G. R.; Armstrong, R. W. *Tetrahedron Lett.* **1991**, *32*, 1609. (c) Hara, O.; Hamada, Y.; Shioiri, T. *Synlett* **1991**, 283. (d) Hara, O.; Hamada, Y.; Shioiri, T. *Synlett* **1991**, 285. (e) Koskinen, A. M. P.; Chen, J. *Tetrahedron Lett*. **1991**, *32*, 6977. (f) Yokokawa, F.; Hamada, Y.; Shioiri, T. *Synlett* **1992**, 149. (g) Yokokawa, F.; Hamada, Y.; Shioiri, T. *Synlett* **1992**, 151. (h) Evans, D. A.; Gage J. R. *J. Org. Chem*. **1992**, *57*, 1958. (i) Evans, D. A.; Gage J. R.; Leighton, J. L.; Kim, A. S. *J. Org. Chem*. **1992**, *57*, 1961. (j) Evans, D. A.; Gage J. R.; Leighton, J. L. *J. Org. Chem*. **1992**, *57*, 1964. (k) Vaccaro, H. A.; Levy, D. E.; Sawabe, A.; Jaetsch, T.; Masamune, S. *Tetrahedron Lett.* **1992**, *33*, 1937. (l) Matsubara, J.; Nakao, K.; Hamada, Y.; Shioiri, T. *Tetrahedron Lett*. **1992**, *33*, 4187. (m) Barrett, A. G. M.; Edmunds, J. J.; Horita, K.; Parkinson, C. J. *J. Chem. Soc., Chem. Commun.* **1992**, 1236. (n) Barrett, A. G. M.; Edmunds, J. J.; Hendrix, J. A.; Horita, K.; Parkinson, C. J. *J. Chem. Soc., Chem. Commun.* **1992**, 1238. (o) Barrett, A. G. M.; Edmunds, J. J.; Hendrix, J. A.; Malecha, J. W.; Parkinson, C. J. *J. Chem. Soc., Chem. Commun.* **1992**, 1240. (p) Barrett, A. G. M.; Malecha, J. W. *J. Chem Soc., Perkin Trans. 1* **1994**, 1901. (q) Ogawa, A. K.; DeMattei, J. A.; Scarlato, G. R.; Tellew, J. E.; Chong, L. S.; Armstrong, R. W. *J. Org. Chem.* **1996**, *61*, 6153. (r) Pihko, P. M.; Koskinen, A. M. P. *J. Org. Chem.* **1998**, *63*, 92.

(17) (a) Smith, A. B., III; Duan, J. J.-W.; Hull, K. G.; Salvatore, B. A. *Tetrahedron Lett.* **1991**, *32*, 4855. (b) Smith, A. B., III; Salvatore, B. A.; Hull, K. G.; Duan, J. J.-W. *Tetrahedron Lett.* **1991**, *32*, 4859. (c) Smith, A. B., III; Duan, J. J.-W.; Hull, K. G.; Salvatore, B. A.; Bertounesque, E. *Abstracts of Papers*, 203rd National Meeting of the American Chemical Society, San Francisco, CA.; American Chemical Society: Washington, DC, 1992, ORGN 216. (d) Salvatore, B. A.; Smith, A. B., III. *Tetrahedron Lett.* **1994**, *35*, 1329. (e) Smith, A. B., III; Iwashima, M. *Tetrahedron Lett.* **1994**, *35*, 6051. (f) Iwashima, M.; Kinsho, T.; Smith, A. B., III. *Tetrahedron Lett.* **1995**, *36*, 2199. (g) Smith, A. B., III; Friestad, G. K.; Duan, J. J.-W.; Barbosa, J.; Hull, K. G.; Iwashima, M.; Qiu, Y.; Spoors, P. G.; Bertounesque, E.; Salvatore, B. A. *J. Org. Chem.* **1998**, *63*, 7596. (h) Smith, A. B., III; Friestad, G. K.; Duan, J. J.-W.; Barbosa, J.; Hull, K. G.; Iwashima, M.; Qiu, Y.; Spoors, P. G.; Salvatore, B. A. *Abstracts of Papers*, 216th National Meeting of the American Chemical Society, Boston, MA.; American Chemical Society: Washington, DC, 1998, ORGN 456. (i) For complete details and additional examples, see: Smith, A. B., III; Cho, Y. S.; Friestad, G. K. *Tetrahedron Lett.* **1998**, *39*, 8765.

(18) Taken in part from the Ph.D dissertation of J. J.-W. Duan, University of Pennsylvania, 1992.

(19) For related examples, see: Smith, A. B., III; Condon, S. M.; McCauley, J. A. *Acc. Chem. Res.* **1998**, *31*, 35.

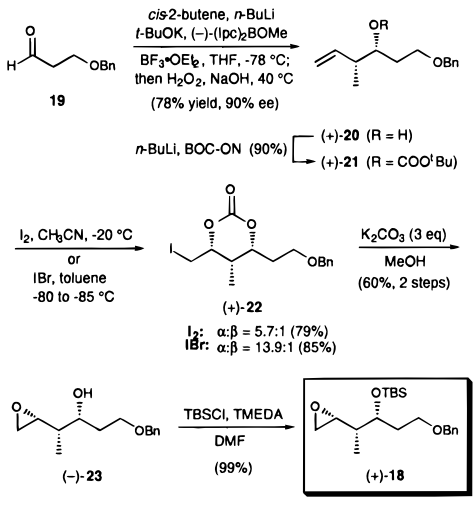
Scheme 2



Spiroketal epoxides of general structure **14** (Scheme 2) were envisioned to derive from substrate-directed diastereoselective epoxidation of vinyl spiroketal **15**, the latter arising from acyclic precursor **16** via an acid-catalyzed spiroketalization under thermodynamic control. That the desired C(19) *S* configuration would result was based on steric, anomeric, and hydrogen-bonding considerations, in conjunction with molecular mechanics calculations for a closely related model.[20] Precursor **16** in turn would be obtained by coupling epoxide **18** with dithiane **17**; this strategy held the promise of considerable flexibility in the introduction of the C(14−15) vinyl group (i.e., either before or after dithiane coupling).

Construction of Epoxide 18: Development of an Improved Iodocarbonate Cyclization. The synthesis of epoxide (+)-**18** began with 3-benzyloxypropanal (**19**, Scheme 3), prepared either via the Kozikowski three-step synthesis[21] or more directly by monobenzylation of 1,3-propanediol (89% yield) and Swern oxidation. Reaction with the Brown allylboration agent, *Z*-crotyldiisopinocampheylborane,[22] furnished alcohol (+)-**20** both in good yield (78%) and enantiopurity (90% ee).[23]

Scheme 3

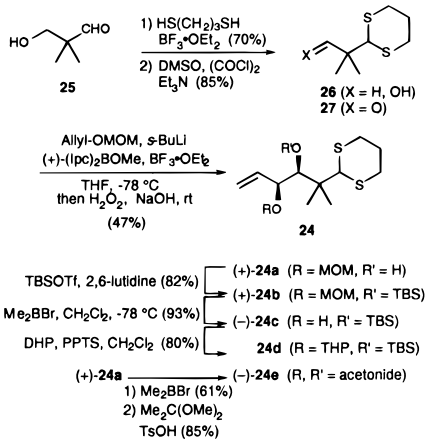


At this point, stereoselective conversion of alcohol (+)-**20** to α-epoxide (−)-**23** was required. As anticipated,[24] epoxidation with *t*-BuOOH/VO(acac)$_2$[25] provided a mixture of epoxides (α/β = 3:2). We therefore turned to the Bartlett iodine-induced carbonate cyclization[26] as a means of 1,3-stereoinduction. Treatment of the derived *tert*-butyl carbonate (+)-**21** (Scheme 3) with iodine in acetonitrile (−20 °C) furnished the desired isomer (+)-**22** (79%), albeit with only modest selectivity (5.7:1). We therefore embarked on a program to improve the Bartlett protocol. Best conditions were IBr in acetonitrile.[27] For example, treatment of (+)-**21** with IBr (toluene, −80 to −85 °C) significantly increased the selectivity (α/β =13.9:1) while maintaining the yield at 85%. Similar improvements in diastereoselectivity employing IBr proved general.[27]

Conversion of the major carbonate (+)-**22** to epoxide (−)-**23** was then achieved by treatment with potassium carbonate (3 equiv) in dry methanol. Although standard conditions for *tert*-butyldimethylsilyl (TBS) protection of alcohol (−)-**23** (TBSCl, imidazole, or TBSOTf, 2,6-lutidine) were unsatisfactory, the combination of TBSCl and TMEDA cleanly afforded (+)-**18**.

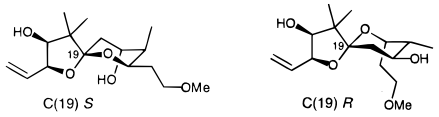
Dithiane Metalation: Allylic Ether Interference. To construct the C(19−20) bond via union of epoxide (+)-**18**, we first examined dithianes of general structure **24**. Conversion of commercially available 2,2-dimethyl-3-hydroxypropanal (**25**, Scheme 4) to the corresponding dithiane **26** and subsequent

Scheme 4



Swern oxidation provided aldehyde **27**. Asymmetric allylboration with *Z*-(γ-methoxymethoxyallyl)diisopinocampheylborane,[28]

(20) MM2 calculations of the spiroketal shown below revealed that the desired C(19) *S* isomer was 6.00 kcal/mol lower in strain energy than the corresponding C(19) *R* isomer.



(21) Kozikowski, A. P.; Stein, P. D. *J. Org. Chem.* **1984**, *49*, 2301.

(22) (a) Brown, H. C.; Bhat, K. S. *J. Am. Chem. Soc.* **1986**, *108*, 293. (b) Brown, H. C.; Bhat, K. S. *J. Am. Chem. Soc.* **1986**, *108*, 5919.

(23) The optical purity of alcohol (+)-**20** was determined by comparison of the optical rotation ($[\alpha]^{25}_D$ +12.1°, *c* 1.096, $CHCl_3$) with the literature value of its antipode ($[\alpha]^{25}_D$ −13.2°, *c* 0.972, $CHCl_3$) of known optical purity (98.5% e.e.). Kobayashi, Y.; Uchiyama, H.; Kanbara, H.; Kusakabe, M.; Sato, F. *Heterocycles* **1987**, *25*, 549.

(24) For a review on epoxidation of olefins, see: Rao, A. S.; Paknikar, S. K.; Kirtane, J.G. *Tetrahedron* **1983**, *39*, 2323.

(25) (a) Fukuyama, T.; Vranesic, B.; Negri, D. P.; Kishi, Y. *Tetrahedron Lett.* **1978**, 2741. (b) Mihelich, E. D.; Daniels, K.; Eickhoff, D. J. *J. Am. Chem. Soc.* **1981**, *103*, 7690.

(26) (a) Bartlett, P. A.; Meadows, J. D.; Brown, E. G.; Morimoto, A.; Jernstedt, K. K. *J. Org. Chem.* **1982**, *47*, 4013. (b) For cyclizations of lithium carbonates, see: Cardillo, G.; Orena, M.; Porzi, G.; Sandri, S. *J. Chem. Soc., Chem. Commun.* **1981**, 465. Bongini, A.; Cardillo, G.; Orena, M.; Porzi, G.; Sandri, S. *J. Org. Chem.* **1982**, *47*, 4626.

(27) (a) Duan, J. J.-W.; Sprengeler, P. A.; Smith, A. B., III. *Tetrahedron Lett.* **1992**, *33*, 6439. (b) Duan, J. J.-W.; Smith, A. B., III. *J. Org. Chem.* **1993**, *58*, 3703.

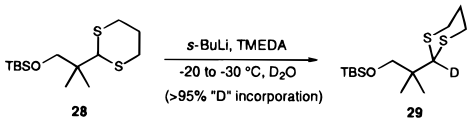
generated in situ from methoxymethyl allyl ether by successive treatment with *s*-butyllithium, (+)-*B*-methoxydiisopinocampheylborane, and boron trifluoride etherate then provided alcohol (+)-**24a** in 47% yield.[29] Simple protection of alcohol (+)-**24a** as a TBS ether furnished (+)-**24b**.

Cognizant that protecting groups can often prove critical in the metalation of dithianes,[30,31] we prepared three additional dithianes (**24c**−**e**). Selective removal of the methoxymethyl-protecting group in (+)-**24b** with bromodimethylborane (Me_2-BBr)[32] at −78 °C afforded dithiane (−)-**24c** (Scheme 4); hydroxyl protection as a tetrahydropyranyl ether gave dithiane **24d** as a diastereomeric mixture (∼1:1). A fourth dithiane, (−)-**24e**, was obtained by removal of the methoxymethyl moiety from (+)-**24a** and conversion to the acetonide.

Dithianes **24b**−**e** were then examined for their susceptibility to metalation. These studies were performed by treatment of the dithiane with one of a variety of bases, followed by addition of methyl alcohol-*d* or deuterium oxide; the extent of deuterium incorporation was determined by ^{1}H NMR. Various solvents, temperatures,[33] and additives [hexamethylphosphoramide (HMPA), tetramethylethylenediamine (TMEDA), 1,4-diazabicyclo[2.2.2]octane (DABCO),[34] or 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (DMPU)[35]] were explored. In general, the dithianes either decomposed or were recovered with little or no deuterium incorporation. The only successful case entailed treatment of (−)-**24e** with *n*-butyllithium and potassium *t*-butoxide in THF/pentane at −78 °C. Addition of D_2O afforded ∼60% deuterium incorporation; however recovery of (−)-**24e** was poor.

Although dithianes have been widely used as acyl anion equivalents, few reported examples include allylic ether functionality.[30,36,37d] In the successful cases, the allylic ether π-systems were not terminal. Our results suggest that the terminal allylic ether and not the protecting groups nor steric hindrance is the source of the difficulty[30,31,37] since the simpler dithiane **28** with both similar protection and steric hindrance was readily metalated (Scheme 5).[38]

Scheme 5



A possible explanation can be found in the interaction between the alkene π-system and the unfilled C−S σ* orbital (Figure 2). That the C−S σ* orbital plays a key stereoelectronic role in promoting dithiane acidity is now well established.[39] In particular, the unfilled σ* orbital has been invoked to explain both the enhanced acidity of the equatorial proton and the preferential equatorial conformation of the lithium in metalated dithianes.[39] For **24a**−**e**, the Thorpe−Ingold effect would promote conformations **i** and **ii** with the alkene in close proximity to the dithiane.[40]

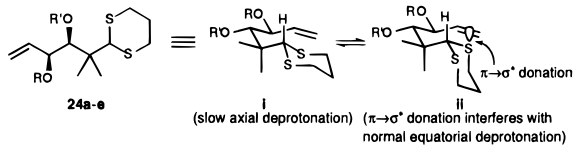
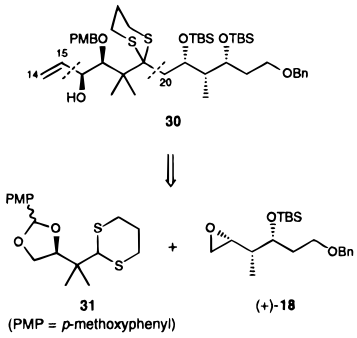


Figure 2.

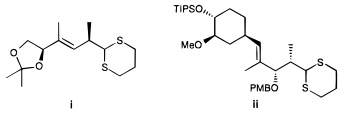
In conformation **i**, metalation would be expected to be slow due to inefficient overlap of the axial C−H bond with C−S σ*. In conformation **ii** the filled alkene π orbital could interact with C−S σ*, and thereby interfere with the role of the C−S σ* orbital in promoting dithiane C−H acidity. Thus, neither conformation favors deprotonation. Danishefsky recently invoked a similar conformation and π-donor effect to explain the anomalous stereoselectivity in an enolate aldol.[41]

Dithiane (−)-31: Precursor to Spiroketal 15. To avoid the above problem, while maintaining the same overall strategy for C(19−20) bond construction, we selected the simpler dithiane **31** (Scheme 6); introduction of the C(14−15) vinyl group would take place at a latter stage.

Scheme 6



The synthesis of dithiane **31** began with known alcohol (+)-**32** (Scheme 7), which was prepared from the dimethyl ester of



(28) Brown, H. C.; Jadhav, P. K.; Bhat, K. S. *J. Am. Chem. Soc*. **1988**, *110*, 1535.

(29) The modest yield of (+)-**24a** is partially due to dithiane oxidation during oxidative workup. The alternative oxidant trimethylamine *N*-oxide might potentially avoid this problem; see: Kabalka, G. W.; Hedgecock, H. C., Jr. *J. Org. Chem*. **1975**, *40*, 1776.

(30) Corey, E. J.; Hua, D. H.; Pan, B.-C.; Seitz, S. P. *J. Am. Chem. Soc*. **1982**, *104*, 6818.

(31) Park, P.; Broka, C. A.; Johnson, B. F.; Kishi, Y. *J. Am. Chem. Soc*. **1987**, *109*, 6205.

(32) Guindon, Y.; Morton, H. E.; Yoakim, C. *Tetrahedron Lett*. **1983**, *24*, 3969.

(33) The temperature of the deprotonation study was limited to 0 °C or below due to the observation that S_N2' displacement by the *n*-butyl group begins to occur at 0 °C or above. For example, when **24d** was treated with *n*-BuLi/TMEDA/THF for 10 min at −20 °C and then at 1 h at 0 °C, the S_N2' product was isolated in 24% yield as well as recovered starting material with no deuterium incorporation.

(34) Screttas, C. G.; Eastham, J. F. *J. Am. Chem. Soc*. **1965**, *87*, 3276.

(35) Mukhopadhyay, T.; Seebach, D. *Helv. Chim. Acta* **1982**, *65*, 385.

(36) During our successful rapamycin and FK506 syntheses, the dithianes **i** and **ii**, each containing nonterminal allylic ethers, were successfully metalated (*t*-BuLi, HMPA/THF, −78 °C). (a) Smith, A. B., III; Condon, S. M.; McCauley, J. A.; Leazer, J. L., Jr.; Leahy, J. W.; Maleczka, R. E., Jr. *J. Am. Chem. Soc.* **1997**, *119*, 947. (b) Smith, A. B., III; Chen, K.; Robinson, D. J.; Laakso, L. M.; Hale, K. J. *Tetrahedron Lett.* **1994**, *35*, 4271.

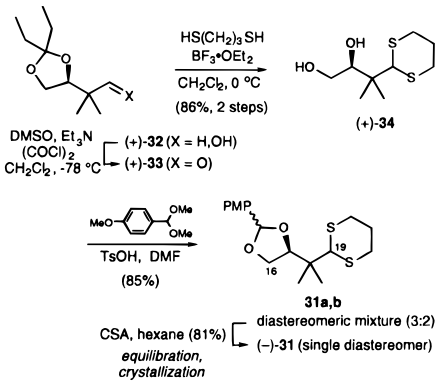
(37) Dithianes bearing acetonides, *tert*-butyldimethylsilyl ethers, tetrahydropyranyl ethers, and methoxymethyl ethers have been successfully metalated. (a) Toshima, H.; Suzuki, T.; Nishiyama, S.; Yamamura, S. *Tetrahedron Lett.* **1989**, *30*, 6725. (b) Khandekar, G.; Robinson, G. C.; Stacey, N. A.; Steel, P. G.; Thomas, E. J.; Vather, S. *J. Chem. Soc., Chem. Commun*. **1987**, 877. (c) Mori, Y.; Suzuki, M. *Tetrahedron Lett*. **1989**, *30*, 4383. (d) Jones, A. B.; Villalobos, A.; Linde, R. G., II; Danishefsky, S. J. *J. Org. Chem*. **1990**, *55*, 2786.

(38) We and others have shown that hindered dithianes can be successfully deprotonated.[31,36,37a]

(39) Seebach, D.; Gabriel, J.; Hässig, R. *Helv. Chim. Acta* **1984**, *67*, 1083 and references therein.

(40) (a) Beesley, R. M.; Ingold, C. K.; Thorpe, J. F. *J. Chem. Soc*. **1915**, *107*, 1080. (b) Eliel, E. L.; Wilen, S. H.; Mander, L. N. *Stereochemistry of Organic Compounds*; Wiley: New York, 1994; pp 682−683.

Scheme 7

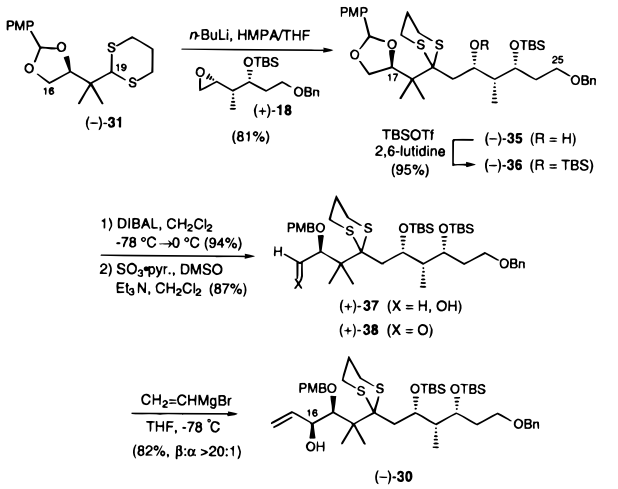


(S)-malic acid.[42] Swern oxidation[43] and treatment with 1,3-propanedithiol and boron trifluoride etherate provided the dithiane along with concomitant removal of the pentylidene moiety; the yield of diol (+)-**34** was 86% (two steps). Diol protection proceeded smoothly to furnish **31** as a 3:2 mixture of diastereomeric *p*-methoxybenzyl acetals (85% yield). Acid-catalyzed equilibration with camphorsulfonic acid (CSA) in hexanes led to crystallization of one diastereomer; reequilibration of the mother liquors effected complete conversion to a single diastereomer in 81% yield (acetal configuration not determined).

In contrast with dithianes **24b**−**e**, metalation of (−)-**31** (*t*-BuLi, HMPA/THF, −78 °C, 15 min or *n*-BuLi, TMEDA, −20 °C, 1.5 h) proceeded without complication, as judged by deuterium incorporation (^{1}H NMR; >90%) This result is again in accord with our speculation that the allylic ether moiety in dithianes **24b**−**e** prevents successful metalation.

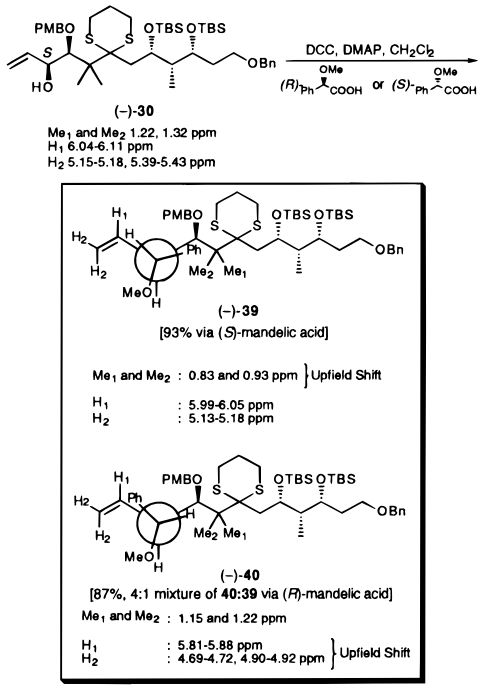
Metalation of **31a,b** (3:2 mixture of diastereomers, 1.5 equiv) with *n*-butyllithium (1.5 equiv) in THF and TMEDA (6 equiv) followed by addition of DMPU (6 equiv) and epoxide (+)-**18** (1 equiv) at −20 °C led to alcohol **35** in 90% yield. In the absence of DMPU, the yield of **35** decreased to 75%.[44] Upon scale-up, best results entailed deprotonation of (−)-**31** (single diastereomer) with *n*-BuLi in 10% HMPA/THF (Scheme 8), followed by introduction of a slight excess (1.1 equiv) of epoxide (+)-**18**; these conditions afforded 120 g of alcohol (−)-**35** in a single experiment (81% yield). Importantly, the dithiane−epoxide coupling tactic generates a single masked aldol.

Scheme 8



With the C(19−20) linkage established, we turned to introduction of the C(14−15) vinyl substituent. Protection of alcohol (−)-**35** as the TBS ether [(−)-**36**; Scheme 8] followed by DIBAL reductive cleavage of the *p*-methoxybenzylidene acetal[45] furnished alcohol (+)-**37** in 94% yield, nicely exposing the primary alcohol with concomitant orthogonal protection of the C(17) secondary alcohol as the *p*-methoxybenzyl (PMB) ether. Parikh−Doering oxidation (DMSO, SO_3•pyr, Et_3N)[46] followed by addition of vinylmagnesium bromide furnished alcohol (−)-**30** in 81% yield (two steps) with excellent diastereoselectivity (>20:1, ^{1}H NMR). The C(16) *S* configuration of (−)-**30**, initially assigned on the basis of a chelation-control model,[47] was confirmed by ^{1}H NMR analysis of the corresponding mandelate esters[48] as illustrated in Scheme 9.

Scheme 9



Spiroketalization. To our delight treatment of (−)-**30** with a mixture of 48% aqueous hydrogen fluoride, acetonitrile, and dichloromethane (1:9:50) for 12 h at room temperature provided spiroketal (+)-**44a** as the only diastereomer in 88% yield (Scheme 10). Interestingly, Evans and co-workers obtained a 5:1 diastereomeric mixture with a closely related substrate.[12]

(41) Harris, C. R.; Kuduk, S. D.; Balog, A.; Savin, K. A.; Danishefsky, S. J. *Tetrahedron Lett.* **1999**, *40*, 2267.

(42) (a) Seebach, D.; Aebi, J.; Wasmuth, D. *Organic Syntheses;* Wiley & Sons: New York, 1990; Collect. Vol. VII, p 153. (b) Lavallée, P.; Ruel, R.; Grenier, L.; Bissonnette, M. *Tetrahedron Lett.* **1986**, *27*, 679.

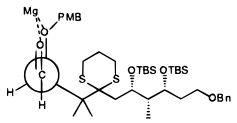
(43) (a) Mancuso, A. J.; Swern, D. *Synthesis* **1981**, 165. (b) Tidwell, T. T. *Synthesis* **1990**, 857. (c) Tidwell, T. T. *Org. React.* **1991**, *39*, 297.

(44) DMPU is known to facilitate opening of epoxides with dithiane anions. Lipshutz, B. H.; Moretti, R.; Crow, R. *Tetrahedron Lett.* **1989**, *30*, 15.

(45) Takano, S.; Akiyama, M.; Sato, S.; Ogasawara, K. *Chem. Lett.* **1983**, 1593.

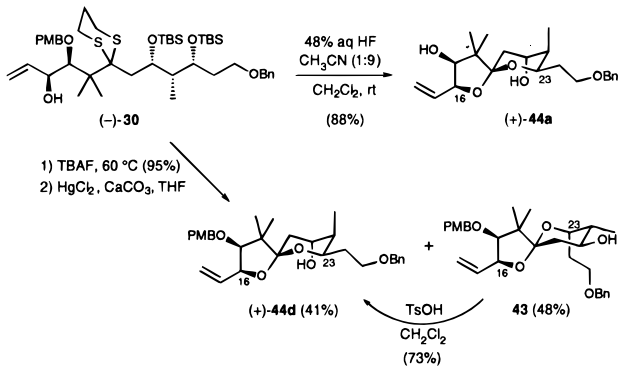
(46) Parikh, J. R.; Doering, W. E. *J. Am. Chem. Soc.* **1967**, *89*, 5505.

(47) The selectivity can be rationalized via the chelation-controlled model illustrated below.



(48) 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**, *51*, 2370.

Scheme 10

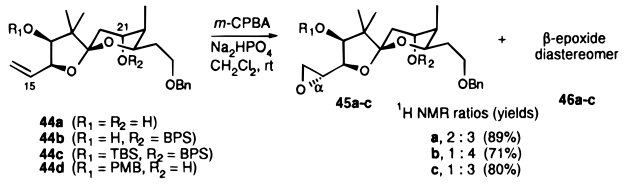


The stereochemistry of spiroketal (+)-**44a** was assigned on the basis of both proton coupling constants and nOe measurements.[49]

To retain the useful PMB ether at C(17) an alternate protocol was developed (Scheme 10). Treatment of (−)-**30** with tetrabutylammonium fluoride furnished the corresponding triol in 95% yield; removal of the dithiane with concomitant spiroketalization ($HgCl_2$, $CaCO_3$) then afforded a mixture of spiroketal epimers (**44d** and **43**) in a combined yield of 89%. Although the undesired spiroketal epimer predominated (48% yield), presumably as a result of kinetic control, it could be readily separated and converted entirely to (+)-**44d** upon exposure to TsOH in CH_2Cl_2 (73% yield). Thus, the total yield of (+)-**44d** for the two steps was 76%. The structure of (+)-**44d** was subsequently confirmed by crystallographic analysis of the corresponding β-epoxide (vide infra).

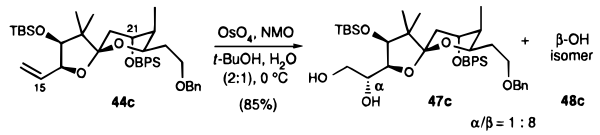
Epoxidation of the C(15−16) Olefin: A Difficult Maneuver. Although our analysis of vinyl spiroketals such as **44a** did not yield a clear-cut stereochemical prediction for epoxidation, Ōmura and co-workers[50] observed a modest preference in the *m*-CPBA epoxidation of two related 2-alkenyltetrahydrofurans. In our case however, treatment of vinylspiroketals **44a**−**c**[18] (Scheme 11) with *m*-CPBA furnished predominantly the undesired β-epoxides **46a**−**c**,[51] whereas **44d** gave a complex mixture. Metal-catalyzed epoxidation with *t*-butyl hydroperoxide and $VO(acac)_2$ or $Mo(CO)_6$ resulted only in decomposition.

Scheme 11



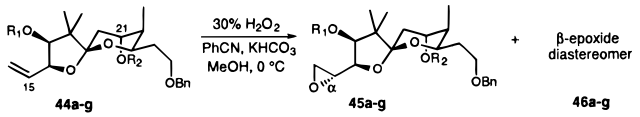
We next explored catalytic osmium tetroxide dihydroxylation of **44c**. Although osmylation and peracid epoxidation often afford complementary stereoselectivities,[52] dihydroxylation of **44c** provided the α and β diols **47c** and **48c** in a 1:8 ratio[53] (85% yield, Scheme 12). To surmount the apparent intrinsic substrate diastereofacial bias via reagent control, we turned to the Sharpless asymmetric dihydroxylation (AD) process.[54] In no case however were we able to override the intrinsic substrate bias. For a detailed discussion of these studies see our earlier publication.[17f]

Scheme 12



Fortunately, after considerable experimentation we discovered that Payne epoxidation (peroxybenzimidic acid)[55] of **44d** occurred with complete reversal of the intrinsic diastereofacial bias (9.5:1; 89% yield; Table 1).[17e] Despite the structural similarities between peracids and peroxybenzimidic acid, peracid and Payne epoxidations have previously expressed opposite diastereofacial preferences.[56] Interestingly, differential protection of the two secondary hydroxyl groups (e.g., **44b**) led to a dramatic reversal of diastereoselectivity. Taken together these results suggest an unusually complex interplay of conformational effects and steric and hydrogen bonding interactions in the Payne epoxidation process.

Table 1. Payne Epoxidation of Vinyl Spiroketals

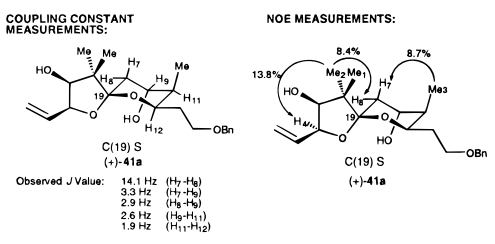


alkene	α/β (**45**:**46**)[a]	yield (%)[b]
44a ($R_1 = R_2 = H$)	3:1	82
44b ($R_1 = H$, $R_2 = BPS$)	1:18	86
44c ($R_1 = TBS$, $R_2 = BPS$)		no reaction[c]
44d ($R_1 = PMB$, $R_2 = H$)	9.5:1[d]	89
44e ($R_1 = Ac$, $R_2 = H$)	4:1	85
44f ($R_1 = TBS$, $R_2 = H$)	8.6:1	80
44g ($R_1 = Ac$, $R_2 = BPS$)		no reaction[c]

[a] Determined by ^1H NMR spectroscopy. [b] Combined isolated yield. [c] No reaction occurred at 0 °C or at room temperature. [d] Ratio of (+)-**C**:**46d**.

Importantly, epoxides (+)-**C** and (+)-**46a** formed good quality single crystals for X-ray crystallography, thus permitting

(49) Except for the large geminal coupling between H_7 and H_8 (14.1 Hz), all other coupling constants were small, falling in the range of 1.9 Hz to 3.3 Hz, suggesting no diaxial coupling in the pyran ring; large coupling constants (5−10 Hz) would be expected for diaxial hydrogens in the C(19) *R* chair isomer. A twist boat conformation would also result in coupling constants larger than the observed 3.3 Hz. NOE enhancements of the H_4 (13.8%) and H_8 (8.4%) hydrogens when the Me_2 was irradiated support assignment of the C(19) *S* isomer.



(50) Kawahata, Y.; Takatsuto, S.; Ikekawa, N.; Murata, M.; Ōmura, S. *Chem. Pharm. Bull.* **1986**, *34*, 3102.

(51) The fact that the major products in all three cases [(+)-**46a**, (+)-**46b** and (+)-**46c**] possess the same epoxide configuration was confirmed by chemical conversion of (+)-**46c** to (+)-**46b** and (+)-**46b** to (+)-**46a** with tetrabutylammonium fluoride.

(52) For discussion, see: Chao, T.-M.; Baker, J.; Hehre, W. J.; Kahn, S. D. *Pure Appl. Chem.* **1991**, *63*, 283.

(53) The major isomer was readily converted to β-epoxide **46c** (TsCl, pyridine; K_2CO_3, MeOH; 86%). The configurations of the oxidation products were correlated with the known epoxide **46b** or the tetraol. The latter structures were determined via X−ray crystallographic analyses.

(54) Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483.

(55) Payne, G. B. *Tetrahedron* **1962**, *18*, 763.

(56) (a) Carlson, R. G.; Behn, N. S. *J. Org. Chem.* **1967**, *32*, 1363. (b) Woodward, R. B.; Gosteli, J.; Ernest, I.; Friary, R. J.; Nestler, G.; Raman, H.; Sitrin, R.; Suter, C.; Whitesell, J. K. *J. Am. Chem. Soc.* **1973**, *95*, 6853.

stereochemical assignment not only of the epoxide but also the spiroketal.[57] Having established a viable sequence to epoxide **C**,[58] we turned to the attachment of a C(9−13) subunit.

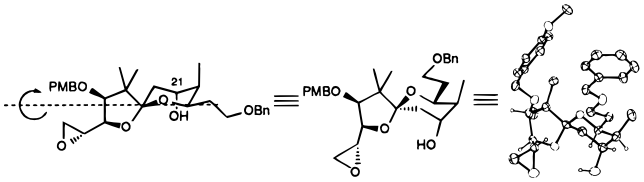
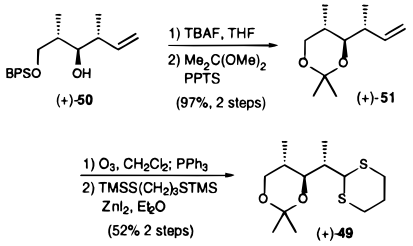


Figure 3. ORTEP Drawing of Epoxide (+)-**C**

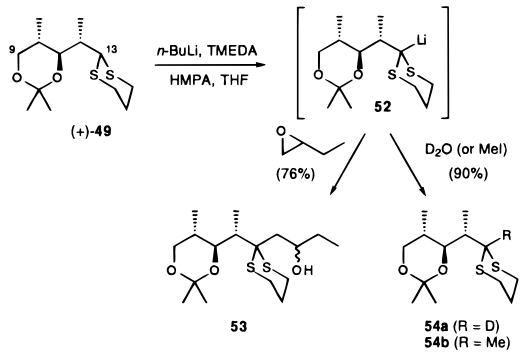
Fragment Coupling via a Dithiane. Dithiane (+)-**49** was prepared beginning with the Roush crotylboration product (+)-**50**[59] (Scheme 13). Protecting-group interchange to acetonide (+)-**51**, ozonolysis, and conversion of the resultant aldehyde to the corresponding dithiane (1,3-propanedithio-bis-trimethylsilane, ZnI_2)[60] afforded (+)-**49** in 50% yield.

Scheme 13



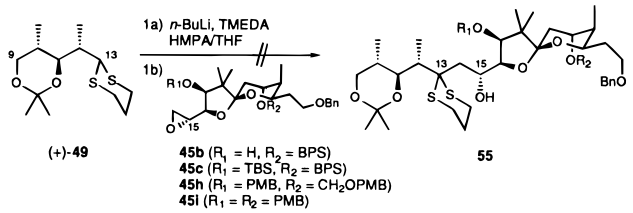
Metalation of (+)-**49** (Scheme 14) was successfully effected with *n*-butyllithium (TMEDA, HMPA/THF, 1.5 h, 0 °C) as determined via D_2O treatment and NMR analysis (∼90% *d*). Moreover, the metalated dithiane reacted smoothly with both 1,2-epoxybutane (76% yield) and methyl iodide (90% yield).

Scheme 14



Unfortunately, lithiated **49** (*n*-butyllithium, TMEDA, HMPA/THF) failed to react with epoxides **45b,c** and **45h,i**[61] required for the calyculin synthesis (Scheme 15). The use of other bases (*t*-BuLi or *n*-BuLi/*t*-BuOK) and/or additives (DMPU or HMPA) provided no improvement. In most cases, both starting materials were recovered.

Scheme 15



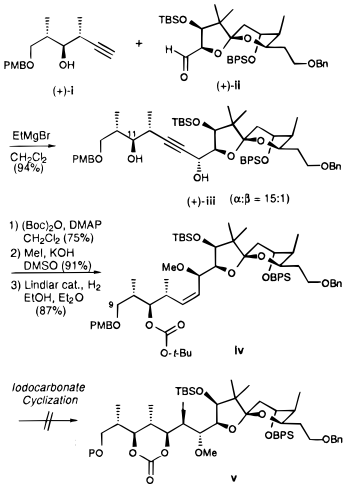
In an attempt to circumvent the lack of reactivity we reversed the functionality, attaching the dithiane moiety to the spiroketal with the expectation that metalation of **56a** would lead to successful coupling with epoxide **57**. This alternative benefited from the Nakata precedent[62] that reaction of lithiated 1,3-dithiane with a similar epoxide proceeded in 99% yield. In the event, the reactivity of the epoxide (**45**) proved to be sensitive to the nature of protecting groups; with a TBS group at C(21) no reaction occurred. However, the PMB-protected epoxide **45i** afforded an encouraging 65% yield of **56a** after in situ *O*-methylation at C(15).

Also encouraging, metalation of dithiane **56a** with *n*-BuLi in 10% HMPA/THF, followed by treatment with D_2O afforded the deuterated dithiane (**56b**) in 90% yield with 95% incorporation of one deuterium (Scheme 16). However, exposure of the metalated dithiane to epoxide **57** led to no coupling; only modest recovery of the dithiane was possible (48−59%).[63,64]

Fragment Coupling via a Vinyl Cuprate. Thwarted by the unusually recalcitrant dithiane−epoxide coupling, we shifted

(57) The epoxides described in Table 1 were chemically correlated with (+)-**C** or (+)-**46a**, thereby confirming the structural assignments.

(58) We also explored an alternative which would (a) address the C(15) stereochemistry by chelation-controlled addition of acetylene **i** to aldehyde **ii** and (b) further elucidate the scope of the IBr-induced iodocarbonate cyclization, in this context to be used to install and define the C(13) oxygen stereogenicity after reductive removal of the iodide. We successfully achieved the former objective via reaction of aldehyde **ii** with the acetylenic Grignard reagent derived from **i** to afford adduct **iii** (α/β = 15:1), presumably through magnesium chelation. Unfortunately, the iodocarbonate cyclization could not be realized; under a variety of conditions, no reaction or decomposition occurred. We speculate that steric hindrance at the olefin of carbonates **iv** and a related C(9) acetate precludes the reaction under mild conditions; the lability of the spiroketal functionality and protecting groups towards iodine monobromide prevented more forcing conditions. For complete details and for preparation of **i** and **ii**, see: Duan, J. J.-W. Ph.D. Thesis, University of Pennsylvania, 1992.



(59) Roush, W. R.; Palkowitz, A. D.; Ando, K. *J. Am. Chem. Soc.* **1990**, *112*, 6348.

(60) Evans, D. A.; Truesdale, L. K.; Grimm, K. G.; Nesbitt, S. L. *J. Am. Chem. Soc.* **1977**, *99*, 5009.

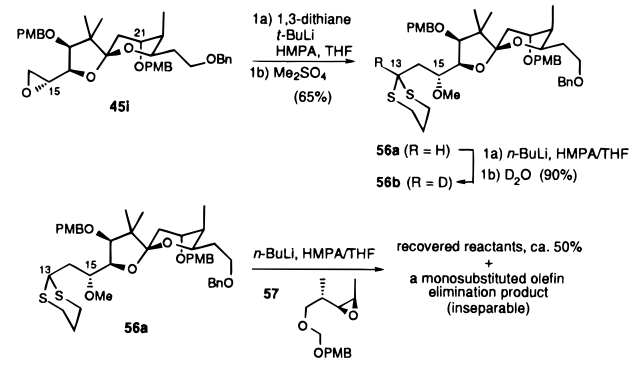
(61) Protected spiroketals **45h** and **45i** were prepared from (+)-**C** by reaction with $PMBOCH_2Cl$ ($^iPr_2NEt$, CH_2Cl_2) and *p*-methoxybenzyl chloride (KHMDS, THF), respectively. The former reagent was obtained by known methods. (a) Corey, E. J.; Bock, M. G. *Tetrahedron Lett.* **1975**, 3269. (b) Benneche, T.; Strande, P.; Undheim, K. *Synthesis* **1983**, 762.

(62) Nakata, T.; Fukui, M.; Ohtsuka, H.; Oishi, T. *Tetrahedron* **1984**, *40*, 2225.

(63) Coupling experiments with the TBS-protected analogue of **57** were likewise unsuccessful.

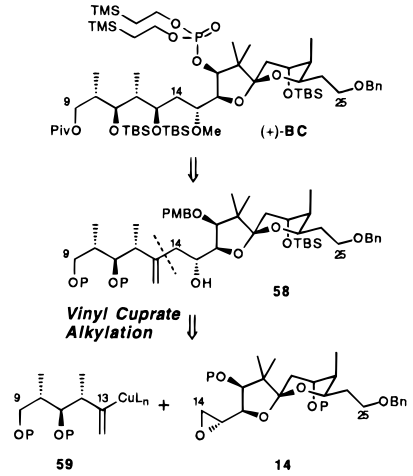
(64) A side product derived from dithiane **56a** exhibiting ^1H NMR signals associated with a monosubstituted alkene was isolated in low yield (<10%); this material evidently formed by elimination of the benzyloxy group from C(25). For a similar side reaction in our penitrem synthetic studies, see: Smith, A. B., III; Haseltine, J. N.; Visnick, M. *Tetrahedron* **1989**, *45*, 2431.

Scheme 16



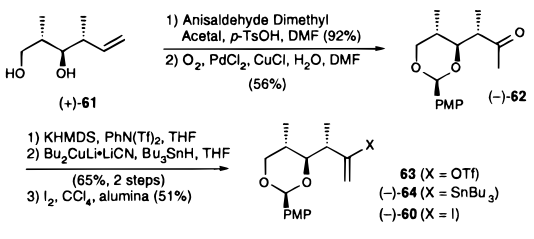
our focus to an alternate acyl anion equivalent. The reaction of a mixed vinyl cuprate with an epoxide[65] appeared to be an attractive option; oxidative cleavage of the resulting exomethylene unit would be equivalent to removal of a dithiane to unmask the aldol linkage. For this strategy, we required a vinyl halide for in situ generation of **59** (Scheme 17).

Scheme 17



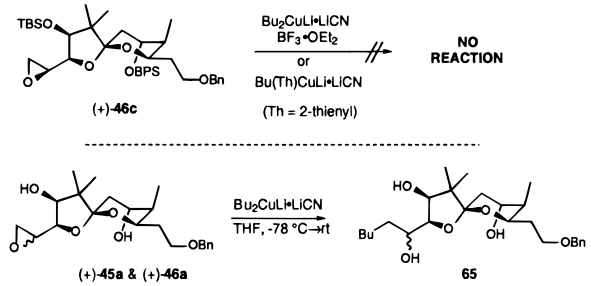
We first employed vinyl iodide (−)-**60** (Scheme 18), prepared from Roush crotylboration product (+)-**50** (Scheme 13). Protection as a *p*-methoxybenzylidene acetal (Scheme 18), followed by Wacker oxidation[66] led to methyl ketone (−)-**62** in modest yield. Conversion to the kinetic enol triflate[67] and treatment with in situ-generated $Bu_2CuLi{\cdot}LiCN$,[68] furnished vinyl stannane (−)-**64** which was then transformed to vinyl iodide (−)-**60** (I_2, CCl_4).[69,70] Although the overall yield for this five-step process was not suitable for large-scale material advancement, we proceeded with initial attempts to effect the coupling reaction.

Scheme 18



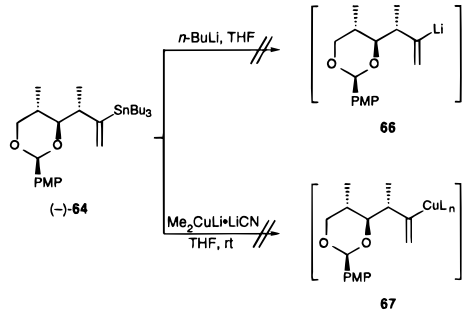
Model studies with *n*-butyl cuprates revealed that protecting groups again play an important role in the reactivity of spiroketal epoxides. For example, fully protected epoxide (+)-**46c** failed to react with lithium di-*n*-butylcyanocuprate in the presence of boron trifluoride etherate or lithium *n*-butyl-2-thienylcyanocuprate (Scheme 19). In contrast, a diastereomeric mixture of dihydroxyl epoxides (+)-**45a** and (+)-**46a** reacted smoothly with lithium di-*n*-butylcyanocuprate at −78 °C to yield **65**. With this encouraging result, we proceeded with the coupling employing cuprate **59**.

Scheme 19



Initially, we planned to generate vinyl lithium **66** from vinyl stannane (−)-**64** via transmetalation.[70] However, when a mixture of (−)-**64** and *n*-butyllithium was stirred at −78 °C, no reaction occurred (Scheme 20). At −40 °C or above, transmetalation was accompanied by decomposition. The reasons responsible for the sluggish tin−lithium exchange remain unknown, although Collins reported that exchange reactions can be affected by olefin stereochemistry.[71] Attempts to convert (−)-**64** directly to cuprate **67** with lithium dimethylcyanocuprate[72] resulted in decomposition.

Scheme 20



We next explored the formation of vinyl lithium **66** via lithium−iodine exchange[73] (Scheme 21). Treatment of (−)-**60** in tetrahydrofuran with *tert*-butyllithium at −78 °C for 30 min generated the desired vinyl lithium (**66**) without incident. The mixed cuprate (6 equiv) derived from **66** and lithium 2-thienylcyanocuprate reacted with epoxide (+)-**45a** (1 equiv) smoothly to furnish triol (+)-**68** in 95% yield. This gratifying result, although requiring a large excess of vinyl cuprate due to the free hydroxyls in epoxide (+)-**45a**, validated our approach. We

(65) (a) Bartlett, P. A.; Meadows, J. D.; Ottow, E. *J. Am. Chem. Soc.* **1984**, *106*, 5304. (b) Lipshutz, B. H.; Kozlowski, J. A.; Parker, D. A.; Nguyen, S. L.; McCarthy, K. E. *J. Organomet. Chem.* **1985**, *285*, 437.

(66) (a) Tsuji, J.; Nagashima, H.; Nemoto, H. *Organic Syntheses;* Wiley & Sons: New York, 1990; Collect. Vol. VII, p 137. (b) Tsuji, J. *Synthesis* **1984**, 369.

(67) McMurry, J. E.; Scott, W. J. *Tetrahedron Lett.* **1983**, *24*, 979.

(68) Gilbertson, S. R.; Challener, C. A.; Bos, M. E.; Wulff, W. D. *Tetrahedron Lett*. **1988**, *29*, 4795.

(69) Davies, J.; Roberts, S. M.; Reynolds, D. P.; Newton, R. F. *J. Chem. Soc., Perkin Trans. 1* **1981**, 1317.

(70) Hanson, R. N.; El-Wakil, H. *J. Org. Chem.* **1987**, *52*, 3687.

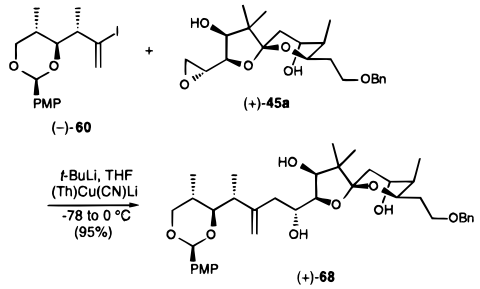
(71) Collins, P. W.; Jung, C. J.; Gasiecki, A.; Pappo, R. *Tetrahedron Lett*. **1978**, 3187.

(72) Behling, J. R.; Babiak, K. A.; Ng, J. S.; Campbell, A. L.; Moretti, R.; Koerner, M.; Lipshutz, B. H. *J. Am. Chem. Soc*. **1988**, *110*, 2641.

(73) Corey, E. J.; Beames, D. J. *J. Am. Chem. Soc.* **1972**, *94*, 7210.

next sought both to improve the preparation of the vinyl halide, in particular the Wacker oxidation, and to minimize the amount of the cuprate. During this refinement, vinyl bromide (+)-**B** emerged as a more viable cuprate precursor (vide infra).

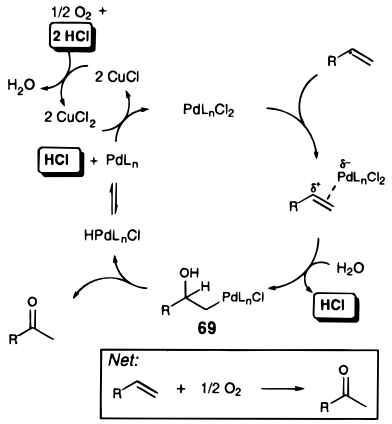
Scheme 21



Wacker Oxidation: Improved Conditions for Acid-Sensitive Substrates.[17i] Although the palladium-catalyzed Wacker oxidation of terminal olefins to methyl ketones occupies a prominent position among methods for synthesis of natural products,[74] oxidation of (+)-**51** employing the standard Tsuji conditions (10 mol % $PdCl_2$, 2 equiv CuCl, O_2, DMF, H_2O)[66] proved both sluggish, and on larger scales led both to partial acetonide hydrolysis and problematic emulsions.[75]

Examination of the accepted Wacker catalytic cycle[66] (Scheme 22) reveals that 1 equiv of HCl is extruded during the formation of the organopalladium intermediate (**69**) and a second is formally lost from palladium hydride prior to regeneration of $PdCl_2$ for a new catalytic cycle. Although 2 equiv of HCl are taken up in the copper redox shuttle, and thus net production of HCl is not expected, transient accumulation of HCl must occur. Not unexpectedly, addition of base (Na_2CO_3) shuts down the catalytic cycle. We reasoned that replacing CuCl with $Cu(OAc)_2$ (i.e., replacing HCl in the catalytic cycle with HOAc) might suppress the hydrolysis of the acetonide while maintaining a weakly acidic medium to permit catalytic turnover.[76]

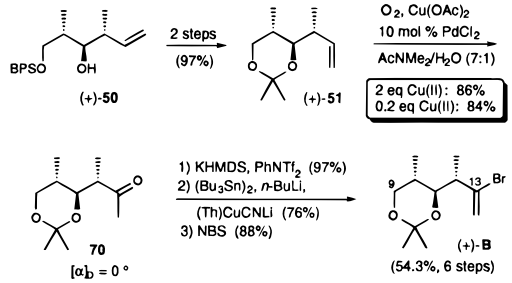
Scheme 22



To this end, alkene (+)-**51** (29 mmol) was added to $PdCl_2$ (10 mol %) and $Cu(OAc)_2 \cdot H_2O$ (58 mmol) in $AcNMe_2/H_2O$ (7:1, 57 mL) and the ambient atmosphere replaced with oxygen (Scheme 23). After complete consumption of (+)-**51** (30 h, TLC), pure **70** [(86% yield, $[\alpha]^{23}_D$ 0° (*c* 2.93, $CHCl_3$)] was obtained following aqueous workup and chromatography. Gratifyingly, no evidence of acetonide hydrolysis was detected either by TLC or ^{1}H NMR.

Subsequent experimentation provided further insight and improvement. The utilization of copper(II) acetate could be reduced to substoichiometric levels (20 mol % $Cu(OAc)_2$, 2 d, 84% yield of **70**; Scheme 23). In addition, since the $Cu(OAc)_2$

Scheme 23

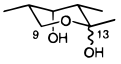


redox shuttle begins with Cu(II), preoxidation of the catalyst system by O_2 is not required.[77] The amount of insoluble material is also reduced; thus, the reactions are more easily stirred, perhaps facilitating oxygen uptake. Removal of soluble $Cu(OAc)_2$, even in stoichiometric amounts, is also greatly facilitated without formation of emulsions upon workup. Finally scale-up (63 mmol) afforded a similar yield of ketone **70** (82%). Methyl ketone **70** (Scheme 23) was next transformed to the kinetic enol triflate, followed by reaction with the mixed stannyl thienyl cuprate derived from lithium 2-thienylcyanocuprate.[78] Titration of the resultant vinyl stannane with *N*-bromosuccinimide completed the preparation of vinyl bromide (+)-**B**. The optimized route provided (+)-**B** in 54% yield (six steps) from the Roush crotylboration product (+)-**61**.

Vinyl Cuprate−Epoxide Coupling: Optimization. To minimize consumption of vinyl bromide (+)-**B**, as well as to facilitate subsequent manipulations, we explored the coupling reaction with the C(21) hydroxyl in spiroketal (+)-**C** protected. As observed previously with vinyl iodide (−)-**60**, the protection scheme proved to have a dramatic effect on the coupling reaction. Although initial experiments suggested the use of a 2-trimethylsilylethoxymethyl (SEM) ether for C(21) protection, removal of this group presented significant challenges later in the synthesis. We therefore chose a TBS group; accordingly, we proceeded with epoxide **45j** (Scheme 24), prepared in 98% yield by silylation of (+)-**C**. Optimal conditions[79] entailed generation of the vinyl lithium species (2 equiv *t*-BuLi, Et_2O, −78 → 0 °C, 30 min), introduction of freshly prepared lithium 2-thienylcyanocuprate (−78 → −45 °C, 30 min), and addition of the epoxide at −78 °C, followed by stirring for 2 d at −5 °C. Under these conditions, the desired coupling product (+)-**71** formed in 83% yield on ∼2 g scale. Importantly, this coupling tactic again generated a single diastereomeric masked aldol.

(74) (a) For an application to synthesis of pseudomonic acid C, see: Balog, A.; Yu, M. S.; Curran, D. P.; Yu, G.; Carcanague, D. R.; Shue, Y.-K. *Synth. Commun.* **1996**, *26*, 935. (b) For an application to synthesis of swinholides, see: Paterson, I.; Cumming, J. G.; Smith, J. D.; Ward, R. A.; Yeung, K.-S. *Tetrahedron Lett.* **1994**, *35*, 3405. (c) For other recent synthetic applications, see: Pellissier, H.; Michellys, P.-Y.; Santelli, M. *Tetrahedron Lett.* **1994**, 35, 6481; Money, T.; Wong, M. K. C. *Tetrahedron* **1996**, *52*, 6307.

(75) The major side product had ^{1}H NMR properties consistent with hemiketal **i**.

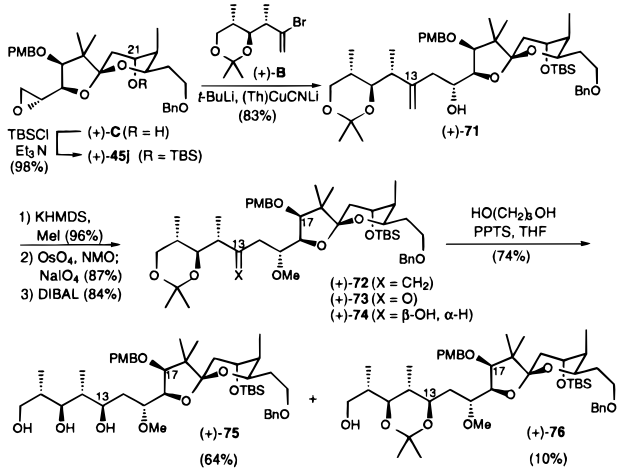


(76) Cupric acetate has been employed in industrial Wacker oxidations, see: Hrusovsky, M.; Vojtko, J.; Cihova, M. *Hung. J. Ind. Chem.* **1974**, *2*, 137; *Chemical Abstracts* **1975**, *82*, 139205.

(77) With CuCl as the redox shuttle reagent, a mixture of $PdCl_2$ and CuCl is typically stirred under O_2 for 1−2 h prior to introduction of the alkene substrate. It has been noted that the use of $CuCl_2$ leads to chlorinated byproducts, see ref 66.

(78) Piers, E.; Tillyer, R. D. *J. Org. Chem.* **1988**, *53*, 5366.

Scheme 24

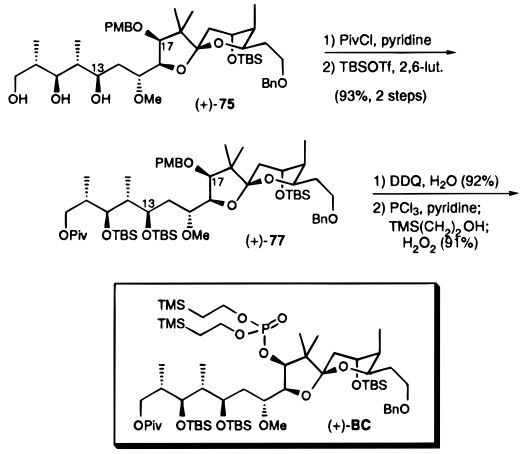


Elaboration of the C(9−25) BC Subtarget. We next addressed introduction of both the C(13) stereogenic center and the C(17) phosphate, along with functional group manipulations required to prepare **BC** for union with subtargets **A** and **DE** (see Scheme 1). *O*-Methylation installed the C(15) *O*-methyl group (Scheme 24); oxidative cleavage of the alkene using catalytic osmylation and sodium periodate exposed the C(13) carbonyl. Selective DIBAL reduction then afforded β alcohol (+)-**74** (β/α >12:1), presumably by internal delivery of hydride via prior coordination with the C(15) methoxyl group.[80]

To facilitate manipulations leading to the anticipated Horner-Emmons olefination at C(9), the acetonide was removed to afford triol (+)-**75**. On a small scale this transformation proceeded in 64% yield; on scale-up the yield decreased to 51%. A mitigating feature of this transformation was the isolation of acetonide migration product (+)-**76** (10% yield),[81] which upon ^{13}C NMR spectroscopic analysis of the acetonide signals permitted assignment of the stereochemical course of the DIBAL reduction.[82]

Completion of the C(9−25) subtarget entailed conversion of triol (+)-**75** to the corresponding primary monopivaloate ester (Scheme 25), silylation of the two secondary hydroxyl groups with TBSOTf to afford (+)-**77** in excellent yield, and orthogonal deprotection by oxidative hydrolysis of the PMB ether with DDQ to furnish the C(17) alcohol in 92% yield. Phosphorylation using the three-stage protocol introduced by Evans[12] completed construction of the fully elaborated C(9−25) subtarget (+)-**BC** in 91% yield.

Scheme 25



In summary, assembly of (+)-**BC**, the C(9−25) spiroketal dipropionate fragment for the unnatural antipodes of the calyculins, has been achieved in a convergent, completely stereocontrolled fashion. The longest linear sequence spans 26 steps from commercially available 1,3-propanediol, providing (+)-**BC** in 3.8% overall yield (87% yield per step). The accompanying paper describes the preparation of subtargets **A** and (+)-**DE**, their union with (+)-**BC**, and completion of the total synthesis of (+)-calyculin A and (−)-calyculin B.

Acknowledgment. Support was provided by the National Institutes of Health (National Cancer Institute) through Grant CA-19033 and postdoctoral fellowships to G.K.F. and K.G.H. We also thank DuPont Pharmaceuticals, Inc. and Zeneca Pharmaceuticals, Inc. for support of this work. In addition, we thank Drs. George T. Furst and Patrick J. Carroll and Mr. John Dykins of the University of Pennsylvania Spectroscopic Service Center for assistance in securing and interpreting high-field NMR spectra, X-ray crystal structures, and mass spectra, respectively.

Supporting Information Available: Spectroscopic and analytical data and experimental procedures for all synthetic intermediates (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

JA992134M

(79) Coupling in THF resulted in modest yields (6−37%), consistent with observations by others of decreased cuprate reactivity in THF; for example, see: Bertz, S. H.; Eriksson, M.; Miao, G.; Snyder, J. P. *J. Am. Chem. Soc.* **1996**, *118*, 10906. Analysis by TLC could distinguish between cuprate protonolysis product (+)-**51** and the corresponding oxidative homocoupling product (identified by ^{1}H NMR only); both were cleanly and selectively formed upon quenching of an aliquot of the vinyl cuprate with deoxygenated water and air, respectively. The vinyl lithium gave no homocoupling product. The occurrence of oxidative homocoupling provided a convenient TLC marker to indicate both formation and persistence of the vinyl cuprate during the coupling reaction. The vinyl cuprate proved quite stable in Et_2O, persisting for at least 2 days at −5 °C.

(80) Solladié reported the anti reduction of β-arylsulfinyl ketones with DIBAL, see: Solladié, G.; Demailly, G.; Greck, C. *Tetrahedron Lett.* **1985**, *26*, 435. Although Solladié proposed an alternative mechanism, internal delivery of hydride has been proposed to explain these results; see: Evans, D. A.; Chapman, K. T.; Carreira, E. M. *J. Am. Chem. Soc.* **1988**, *110*, 3560.

(81) Acetonide migration product (+)-**76** and the product of desilylation of triol (+)-**75** (isolated from larger scale deprotection experiments) could each be readily redirected to the synthetic sequence.

(82) (a) Rychnovsky, S. D.; Skalitzky, D. J. *Tetrahedron Lett.* **1990**, *31*, 945. (b) Evans, D. A.; Rieger, D. L.; Gage, J. R. *Tetrahedron Lett.* **1990**, *31*, 7099.