# Total Synthesis of Bryostatin 2

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**Abstract:** The total synthesis of the marine macrolide bryostatin 2 is described. The synthesis plan relies on aldol and directed reduction steps in order to construct the *anti*-1,3-diol array present in each of the principal subunits (A, B, and C). These fragments were coupled using a Julia olefination and subsequent sulfone alkylation. A series of functionalization reactions provided a bryopyran seco acid, which was macrolactonized under Yamaguchi conditions. Installation of the two enoate moieties took advantage of asymmetric phosphonate and aldol condensation strategies. Reduction of the $C_{20}$ ketone and simple protecting group operations then completed the synthesis of bryostatin 2. This flexible approach should provide access to a series of new analogues of this clinically important marine natural product.

## Introduction

Bryostatin 1 (**1a**) has captured the attention of the chemical, biological, and medical communities since Pettit first reported its structure determination in 1982.[3] Following the discovery of bryostatin 1, 17 other bryostatins have been isolated and fully characterized (Figure 1). While some congeners (**1b**−**d**) differ from bryostatin 1 (**1a**) only in the acyl residues appended to the $C_7$ and $C_{20}$ hydroxyls, others (e.g., **1e** and **2**) embody significant changes in the $C_{19}$−$C_{27}$ region of the bryostatin nucleus. Our interest in the synthesis of bryostatin was motivated by three circumstances: (i) the strict polyacetate origin of the bryostatin macrolides offered an ideal forum for the extension of our aldol-based approach to polypropionate natural products;[4] (ii) the clinically relevant bryostatin 1 remains a scarce and expensive commodity;[5] and (iii) simpler analogues might prove to be viable medicinal agents and useful biological probes. In this study, we describe the details[6] of our synthesis of bryostatin 2 (**1b**), a natural congener[7] and synthetic precursor[8] of **1a**.

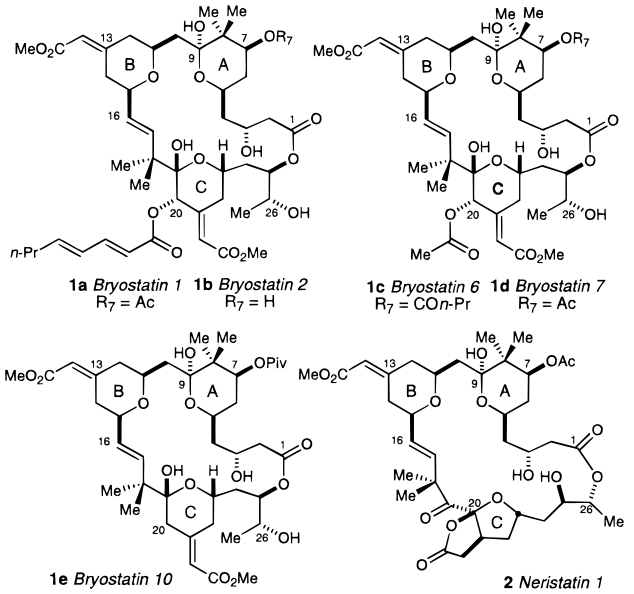


**Figure 1.** Representative members of the bryostatin macrolides.

**Structure.** Bryostatin 1 was first isolated in 1968 from the bryozoan *Bugula neritina* (Linnaeus), an innocuous filter feeder with a propensity for attaching to ship hulls and boat docks.[9] The structure of bryostatin 1 was determined through single-crystal X-ray diffraction analysis (Figure 2) and confirmed using a combination of $^1$H NMR, $^{13}$C NMR, IR, and high-resolution

(1) This work is taken in part from the Ph.D. Thesis of P. H. Carter, Harvard University, 1998.

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(5) (a) Extractive isolation proceeds in ca. $1.3 \times 10^{-6}$% yield (18 g of bryostatin from 14 000 kg of animal) on industrial scale. Schaufelberger, D. E.; Koleck, M. P.; Beutler, J. A.; Vatakis, A. M.; Alvarado, A. B.; Andrews, P.; Marzo, L. V.; Muschik, G. M.; Roach, J.; Ross, J. T.; Lebherz, W. B.; Reeves, M. P.; Eberwein, R. M.; Rodgers, L. I.; Testerman, R. P.; Snader, K. M.; Forenza, S. *J. Nat. Prod.* **1991**, *54*, 1265−1270. (b) The current market price for bryostatin 1 is $1156 (U.S.)/500 $\mu$g: LC Laboratories, Woburn, MA. (c) Marine aquaculture methods are currently being implemented in an attempt to solve the supply problem; cf. *New Scientist* **1996**, 14 Sept, 38−42.

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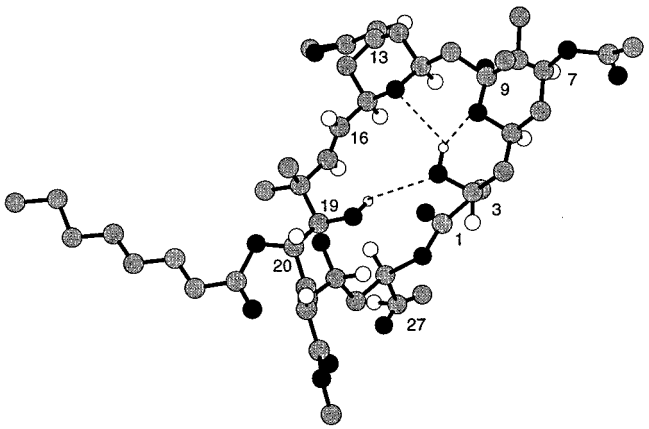


**Figure 2.** X-ray crystal structure of bryostatin1.[9b]

mass spectrometry.[9b,10] The absolute configuration of bryostatin 1 was tentatively assigned on the basis of the small anomalous dispersion effects of oxygen and carbon in the crystal structure[9b,11] and later confirmed via analysis of the heavy-atom dispersion effects in the X-ray structure of a *p*-bromobenzoate derivative.[12]

As can be seen in Figure 2, bryostatin 1 displays several distinctive architectural features. The macrolide houses three pyran rings (two of which are hemiketals), a 20-membered lactone, two exocyclic $\alpha,\beta$-unsaturated esters ($C_{13}$, $C_{21}$), one *trans* olefin ($C_{16}-C_{17}$), and an unusual octadienyl ester side chain ($C_{20}$). The three-dimensional structure is organized about the $C_3$ hydroxyl group, which serves as a hydrogen bond acceptor for the $C_{19}$ lactol ($O_3-H-O_{19}$ distance of 2.71 Å) and a bifurcated hydrogen bond donor for the $O_5$ and $O_{11}$ ether oxygens ($O_3-H-O$ distances of 3.00 and 2.84 Å, respectively).[9b] The solution structure of the $C_{20}$-desoxymacrolide bryostatin 10 (**1e**) has been determined recently using 2D-NMR ROESY technique and shows close homology with the solid-state structure depicted in Figure 2.[13] This well-defined tertiary structure has important ramifications for the solution reactivity of the bryostatins (vide infra).

**Biological Activity.** The bryostatins are a family of potent antitumor agents,[14] and bryostatin 1 exhibits significant in vivo antineoplastic activity against murine leukemia, B-cell lymphoma, reticulum cell sarcoma, ovarian carcinoma, and melanoma.[3,14,15] The bryostatins also display a diverse range of other biological effects in vitro and in vivo, including stimulation of T-cells and the immune system,[16] stimulation of the hematopoietic system,[17] activation of protein kinase C (PKC) through ultrapotent (picomolar) binding to the phorbol ester binding site,[18] and disruption of phorbol ester-induced tumor promotion.[19] These effects are noteworthy for two reasons: (i) antineoplastic agents typically *antagonize* the immune and hematopoietogenic systems,[17] but bryostatin *potentiates* them; and (ii) exogenous agonists of PKC, such as the phorbol esters, are usually tumor promoters, but bryostatin acts as an antitumor agent.[20]

The combined antitumor, immunopotentiating, and hematopotentiating properties of bryostatin 1 made it a promising candidate for clinical trials, and the results from the Phase I study (which began in early 1991) have demonstrated that bryostatin 1 may be administered safely (muscle soreness was the dose-limiting toxicity) and can induce a tumor response with a wide range of tumors.[21] More recent tests have shown that bryostatin may synergize with both tamoxifen (in vitro) and paclitaxel (in vivo),[22] and future clinical trials will probably assess the use of these combination therapies. The U.S. National Cancer Institute has moved bryostatin into Phase II trials against non-Hodgkin's lymphoma, melanoma, and renal cancer.[14]

**Synthesis Plan.** The unusual structure, potent biological activity, and relative scarcity of the bryostatins make them attractive targets for total synthesis.[23] Accordingly, several groups,[23,24] including our own,[25] have initiated programs directed toward the total synthesis of the bryostatins. Most notable among these efforts is the total synthesis of bryostatin 7 reported by the Masamune group.[26]

Our plan for the synthesis of bryostatin 1 is outlined in Scheme 1. Initial scission (transform **T1**) of the $O_{25}-C_1$ lactone bond (macrocyclization transform[27]), followed by further disconnection at the $C_9-C_{10}$ C-glycoside bond (sulfone alkylation and hydrolysis[28]) and the $C_{16}-C_{17}$ trans olefin (Julia−Lythgoe

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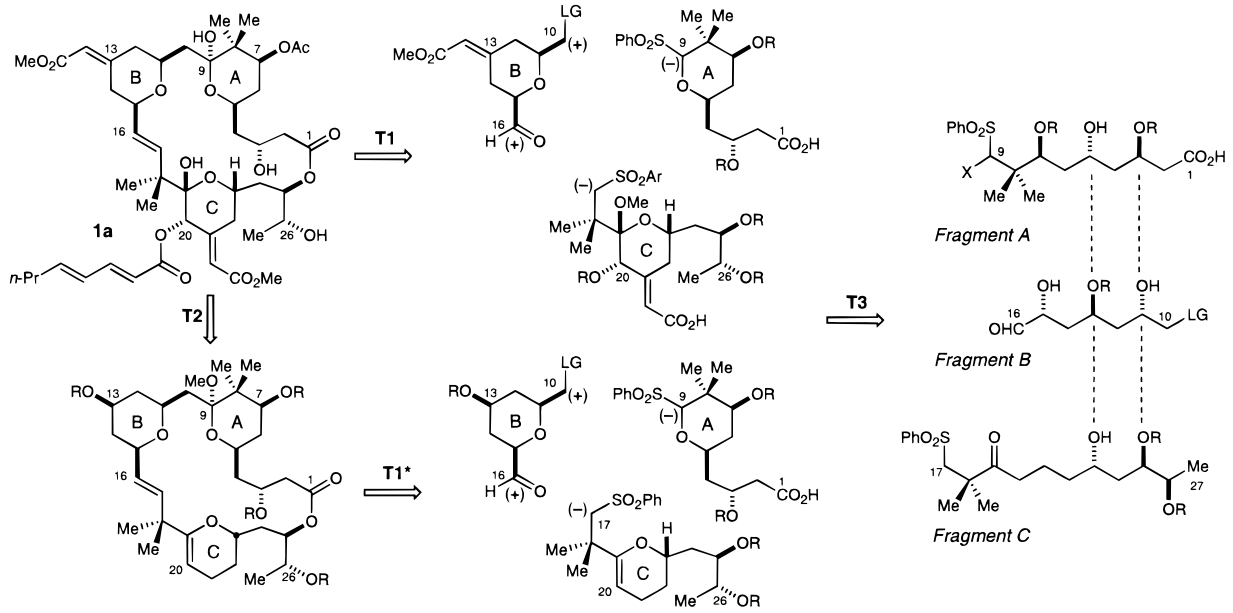
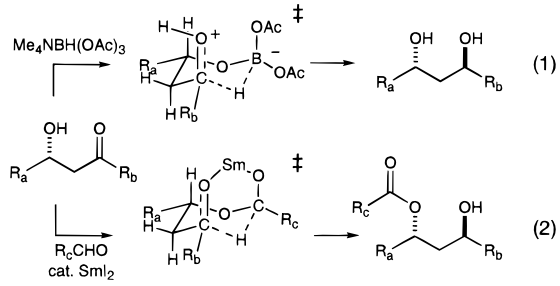
**Scheme 1**




olefination[29]), provided three subunits of comparable complexity. Although each of these fragments could be readily synthesized, the presence of the exocyclic enoate moieties complicated the indicated fragment assemblage operations (vide infra). Accordingly, we revised our plan in order to accommodate a late-stage introduction of these groups (transform **T2**) while maintaining the same fragment coupling strategy (transform **T1***). Each of these strategies will be discussed in some detail in the text.

Both of the aforementioned approaches to the bryostatins utilize the same set of acyclic precursors (transform **T3**). Inspection of these fragments (Scheme 1) reveals that they each contain a 1,3-*anti* diol unit, a fact which is consistent with the polyacetate-based biosynthesis of the bryostatins.[30] The presence of this stereoregular array served as the impetus for the development of two different stereoselective $\beta$-hydroxyketone reductions in our laboratory (eqs 1 and 2),[31] both of which have been employed in the synthesis of a number of polyacetate and polypropionate natural products. In parallel with these studies,




we have developed two general strategies for the enantioselective synthesis of $\beta$-hydroxyketones, and representative examples of each are shown below (eqs 3 and 4).[25a,32] The first approach (eq 3) relies on Sharpless asymmetric epoxidation[33] (or epoxidation with kinetic resolution) in order to establish the absolute asymmetry of an epoxystyrene precursor such as **3**. Subsequent protection, Birch reduction, and ozonolysis affords the $\beta$-hydroxyketoester. The second approach (eq 4) depends on aldol methodology to incorporate the absolute stereochemistry in $\beta$-hydroxyketoester **7**. Although the illustrated reaction derives its asymmetry from the chiral copper(II) complex **6**,[31] variants of this procedure that utilize chiral methyl ketones[34] and/or chiral aldehydes[35] to establish the stereochemistry of the $\beta$-hydroxyketone have been documented.

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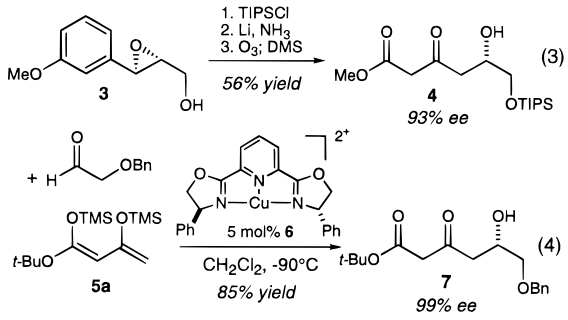
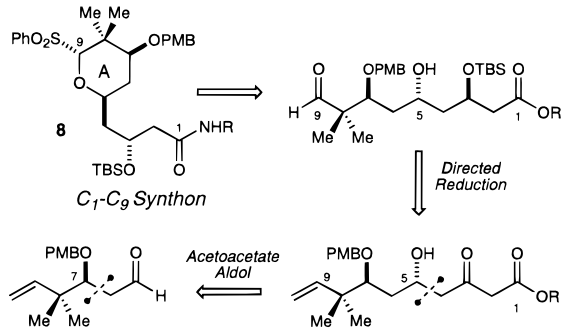



Both the epoxystyrene- and aldol-based strategies (eqs 3 and 4) have been combined with the reduction chemistry (eqs 1 and 2) in the syntheses of all three bryostatin acyclic building blocks illustrated in Scheme 1. Since the aldol/reduction approach is fundamentally more convergent and flexible, it is this method that has been utilized in the fragment syntheses described in the following three sections.[36]

### Synthesis of the $C_1-C_9$ Subunit

In consideration of the basic conditions of the $C_9-C_{10}$ sulfone alkylation reaction (vide infra), we elected to mask the $C_1$ carboxyl terminus as a secondary amide,[37] and thus formulated **8** as the $C_1-C_9$ synthon. Retrosynthetic removal of the $C_9$ sulfone group and the $C_1$ amide group from **8** provides a protected 1,3,5-*anti*,*anti* triol, the synthesis of which has served as a focal point for highlighting polyacetate synthesis methodology.[23] As shown in Scheme 2, we elected to address the synthesis of this stereoarray using the aforementioned aldol/reduction strategy. The successful execution of this plan is illustrated in Scheme 3.

**Scheme 2**




The stereoselective synthesis of synthon **8a** began with the dibutylboron triflate-mediated aldol reaction between excess (4*S*)-3-chloroacetyl-4-phenylmethyl-2-oxazolidinone[38] (**10**) and the known[39] 2,2-dimethyl-4,4-diphenyl-3-butenal (**9**), providing aldol **11** as a 9:1 mixture of diastereomers. Removal of the halide auxiliary was effected with zinc dust in glacial acetic acid[37] and afforded diastereomerically pure $\beta$-hydroxyimide **12** after silica gel chromatography. Subsequent reduction of the imide with lithium borohydride[40] gave the enantiopure diol **13** in 67% overall yield for the three steps and provided a 71% yield of recovered (4*S*)-4-phenylmethyl-2-oxazolidinone. The synthesis of aldehyde **15** was then completed in 90% yield with a simple three-step sequence of acetalization, regioselective reductive acetal cleavage (DIBAl-H, 0 °C),[41] and hydroxyl oxidation.

The aldol coupling of bis(trimethylsilyl)dienol ether **5b** with aldehyde **15** was only modestly stereoselective under standard conditions ($MgBr_2 \cdot OEt_2$, $BF_3 \cdot OEt_2$). While strong Lewis acids ($TiCl_4$, $TiCl_3(O\textit{i}\text{-Pr})$, $SnCl_4$) did not effect a clean reaction with **15**, the use of the mixed titanium species $TiCl_2(O\textit{i}\text{-Pr})_2$ ($CH_2Cl_2$, −78 °C) delivered a high-yielding, stereoselective reaction (93% yield, 6:1 diastereoselection).[42] The selectivity for this reaction could be improved with a modest reduction in chemical yield by using toluene as the reaction solvent (83% yield, 15:1 diastereoselection), a result which is consistent with the operation of electrostatic effects as the stereochemical control element.[35] The subsequent hydroxyl-directed anti reduction of aldol **16** ($Me_4NHB(OAc)_3$, MeCN/AcOH, −35 °C)[31a] proceeded smoothly, affording the diol **17** in good yield and stereoselectivity (ca. 10:1).[43] Lactonization under acidic conditions differentiated the diol functionality, and the remaining hydroxyl group was then silylated to provide lactone **18** in diastereomerically pure form after silica gel chromatography.

To advance lactone **18** to the complete A-ring fragment **8a**, we needed only to perform operations on the two termini of the fragment. Thus, lactone **18** was converted to anilide **19** in acceptable yield using the aluminate derived from trimethylaluminum and aniline hydrochloride. Treatment of **19** with ozone (10:1 $CH_2Cl_2$:MeOH, −78 °C) provided the cyclized lactols **20** as a 1.5:1 ($\beta$:$\alpha$) mixture of anomers in 72% yield. This transformation was plagued by two side reactions—epoxidation of the $C_9$ olefin (ca. 20% yield)[44] and oxidation of the *p*-methoxybenzyl group to a benzoate (ca. 5% yield)—which necessitated the use of minimal methanol in the solvent mixture and a rapid quench to provide for optimal material throughput. Preliminary experimental and computational results indicate that a subtle conformational effect is probably responsible for the spurious reactivity of **19** with ozone and its complete unreactivity toward dihydroxylation agents.[45] The product lactols **20**

(34) (a) Evans, D. A.; Coleman, P. J.; Côté, B. *J. Org. Chem.* **1997**, *62*, 788−789. (b) Lagu, B. R.; Liotta, D. C. *Tetrahedron Lett.* **1994**, *35*, 4485−4488. (c) Trost, B. M.; Urabe, H. *J. Org. Chem.* **1990**, *55*, 3982−3983. (d) Paterson, I.; Goodman, J. M.; Isaka, M. *Tetrahedron Lett.* **1989**, *30*, 7121−7124.

(35) Evans, D. A.; Dart, M. J.; Duffy, J. L.; Yang, M. G. *J. Am. Chem. Soc.* **1996**, *118*, 4322−4343 and references therein.

(36) For a discussion of the earlier approaches based on the epoxystyrene synthon strategy, cf.: (a) Carreira, E. M. Ph.D. Thesis, Harvard University, 1990. (b) Gauchet-Prunet, J. A. Ph.D. Thesis, Harvard University, 1993.

(37) Evans, D. A.; Carter, P. H.; Dinsmore, C. J.; Barrow, J. C.; Katz, J. L.; Kung, D. W. *Tetrahedron Lett.* **1997**, *38*, 4535−4538.

(38) Evans, D. A.; Sjogren, E. B.; Weber, A. E.; Conn, R. E. *Tetrahedron Lett.* **1987**, *28*, 39−42.

(39) (a) Julia, M.; Baillarge, M. *Bull. Soc. Chim. Fr.* **1966**, 734−742. (b) Zimmerman, H. E.; Pratt, A. C. *J. Am. Chem. Soc.* **1970**, *92*, 6259−6267.

(40) Penning, T. D.; Djuric, S. W.; Haack, R. A.; Kalish, V. J.; Miyashiro, J. M.; Rowell, B. W.; Yu, S. S. *Synth. Commun.* **1990**, *20*, 307−312.

(41) (a) Johansson, R.; Samuelsson, B. *J. Chem. Soc., Chem. Commun.* **1984**, 201. (b) Johansson, R.; Samuelsson, B. *J. Chem. Soc., Perkin Trans. 1* **1984**, 2371−2374.

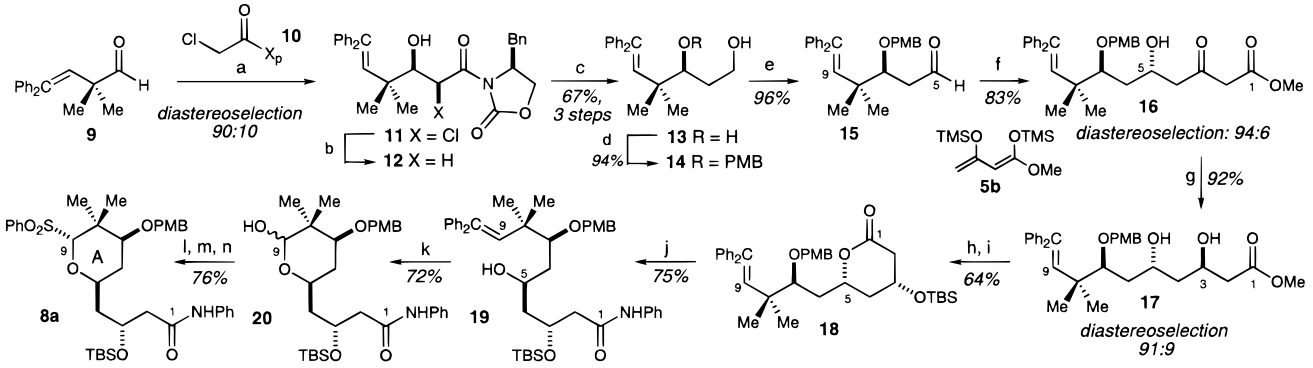
(42) (a) A similar result was obtained in the Felkin-selective addition to an α-substituted aldehyde during our synthesis of Lepicidin, cf.: Evans, D. A.; Black, W. C. *J. Am. Chem. Soc.* **1993**, *115*, 4497−4513. (b) The anti stereoselectivity for the aldol step was established by $^1$H NMR NOE analysis of sulfone **8**.

(43) The anti stereoselectivity for the reduction step was established by $^1$H NMR NOE analysis of lactone **18**.

(44) (a) Epoxidation of hindered olefins via the sterically less encumbered "end-on" approach of ozone to the olefin has been well documented, cf.: Bailey, P. S. *Ozonation in Organic Chemistry*; Academic: New York, 1978; Vol. 1, Chapter 11. (b) While the oxirane byproduct could not be converged to **20**, it could be recycled back to the starting olefin **19** via reductive removal of the oxygen ($SmI_2$, 50% yield, unoptimized).

(45) Molecular mechanics calculations (MM2 force field) indicate that the $C_3$ TBS ether forces the $C_7$ *p*-methoxybenzyl ether to rotate over the $C_9$ olefin. With the lactone **18**, where the TBS ether is conformationally constrained and the PMB ether can rotate away from the olefin (MM2), no epoxidation was observed. This product aldehyde could not be advanced to **20**.

**Scheme 3**[a]



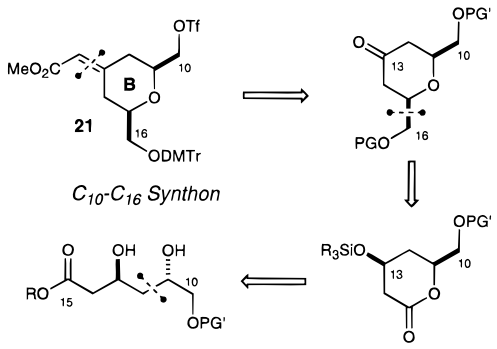

[a] Key: (a) 1.9 equiv of **10**, $Bu_2BOTf$, i-$Pr_2NEt$, then **9**, $CH_2Cl_2$, −78 → 0 °C, 20 h; (b) Zn, 2:1 THF/AcOH; (c) $LiBH_4$, MeOH, THF, 0 °C; (d) (i) $PMPCH(OME)_2$, 10 mol % PPTS, $CH_2Cl_2$, (ii) DIBAl-H, $CH_2Cl_2$, 0 °C; (e) $(COCl)_2$, DMSO, $NEt_3$, $CH_2Cl_2$, −78 °C; (f) $TiCl_2(Oi\text{-}Pr)_2$, $PhCH_3$, −78 °C, then **5b**, −78 °C; (g) $Me_4NHB(OAc)_3$, AcOH/MeCN, −35 °C; (h) PPTS, PhH, 80 °C; (i) TBSOTf, 2,6-lutidine, $CH_2Cl_2$, −10 °C; (j) $Me_3Al$, $HCl{\cdot}H_2NPh$, $CH_2Cl_2$, 30 °C, then **18**, 0 °C; (k) $O_3$, 10:1 $CH_2Cl_2$/MeOH, −78 °C, then $Me_2S$; (l) $Ac_2O$, pyr; (m) PhSTMS, $ZnI_2$, n-$Bu_4NI$, $CH_2Cl_2$; (n) m-CPBA, $NaHCO_3$, EtOAc.

were selectively acetylated in the presence of the anilide using acetic anhydride/pyridine (2 days, 23 °C) and then converted into the α-sulfide (TMSSPh, $ZnI_2$, *n*-$Bu_4NI$)[46] in good yield and diastereoselectivity (86% yield, 93:7 α:*β*).[47] Oxidation with *m*-CPBA under buffered conditions (solid $NaHCO_3$, EtOAc) provided the analytically pure sulfone **8a** in good yield.

### Synthesis of the $C_{10}$−$C_{16}$ Subunit

Retrosynthetic excision of the exocyclic enoate from the B-ring fragment **21** may be executed in either a diastereoselective (PG ≠ PG′) or enantioselective (PG = PG′) sense to afford a *β-C*-glycoside (Scheme 4). Subsequent removal of the $C_{16}$ hydroxymethyl group affords a *δ*-lactone, which may be obtained from the known[25a] 3,5,6-trishydroxy ester. The reduction of this plan to practice is shown in Schemes 5 and 6.

**Scheme 4**




At the time our work began, an enantioselective aldol-based approach to *δ*-hydroxy-*β*-ketoesters (eq 4) was not available. Thus, our initial synthesis of the fragment began with the hydroxyl-directed anti reduction of **4**,[25a,31a] which afforded diol **22** in good yield and stereoselectivity (Scheme 5). Cyclization of the diol ester occurred readily under acidic conditions (PPTS, PhH, 80 °C) and was followed by quantitative silylation of the $C_{13}$ alcohol to give lactone **23**. One-carbon homologation of **23** using benzyloxymethyllithium[48] proceeded smoothly to afford an α-lactol as a single diastereomer.[49] The subsequent reduction of the lactol using the conditions of Kishi ($BF_3{\cdot}OEt_2$, $Et_3SiH$)[50] was highly stereoselective (20:1 cis:trans)[51] and was accompanied by Lewis acid-catalyzed desilylation at $C_{13}$ to deliver the alcohol **24** in 89% yield. Removal of the bulky triisopropylsilyl ether (TBAF, THF, 0 °C), global silylation (TBSOTf, 2,6-lutidine, −78 °C), and hydrogenolysis of the benzyl ether provided the *cis,cis*-2,4,6-tetrahydropyran **25** in good yield. Oxidation to the labile $C_{16}$ aldehyde **26** was best accomplished using the method of Swern.

The illustrated route to **26** provided multigram quantities of **26** and allowed for the synthesis of the complete B-ring synthon via alcohol **24** (cf. Scheme 6). Once our exploratory experiments indicated that aldehyde **26** would be our target fragment (vide infra), we opted to incorporate our newly discovered catalytic aldol chemistry (eq 4)[32] into the synthesis of this fragment (Scheme 5, *ent*-**7** → **26**). Both of these approaches follow parallel chemical strategies (Scheme 5), but the second route is four steps shorter overall.[52]

Our initial efforts toward the bryostatin synthesis (Scheme 1, transform **T1**) required that we synthesize the complete $C_{10}$−$C_{16}$ synthon **21**, and our studies in this area are illustrated in Scheme 6. Oxidation[41] of alcohol **24** was followed by reductive removal of the benzyl protecting group ($H_2$, 10% Pd/C) to afford hydroxyketone **31** in 77% overall yield. Preliminary attempts to effect the intermolecular phosphonate condensation between **31** and trimethylphosphonoacetate under a variety of standard conditions provided the exocyclic enoate *E*-**34** in moderate yield (70%) and poor stereoselection (ca. 70:30 *E*:*Z*),[53] so we turned

(46) (a) Hanessian, S.; Guindon, Y. *Carbohydr. Res.* **1980**, *86*, C3. (b) Nicolaou, K. C.; Daines, R. A.; Ogawa, Y.; Chakraborty, T. K. *J. Am. Chem. Soc.* **1988**, *110*, 4696−4705. (c) Evans, D. A.; Truesdale, L. K.; Grimm, K. G.; Nesbitt, S. L. *J. Am. Chem. Soc.* **1977**, *99*, 5099−5116.

(47) Both the minor *β*-anomer and the $C_7$ *p*-methoxybenzoate impurity were removed at this stage by flash chromatography.

(48) Still, W. C. *J. Am. Chem. Soc.* **1978**, *100*, 1481−1486.

(49) The stereochemical assignment was based on the presence of a 2-Hz W-coupling between the lactol hydrogen and $C_{14}H_{ax}$. Given the propensity for lactols to equilibrate in aqueous media, this stereochemistry may arise from a postaddition isomerization, cf.: Dondoni, A.; Schurmann, M.-C. *J. Org. Chem.* **1994**, *59*, 6404−6412.

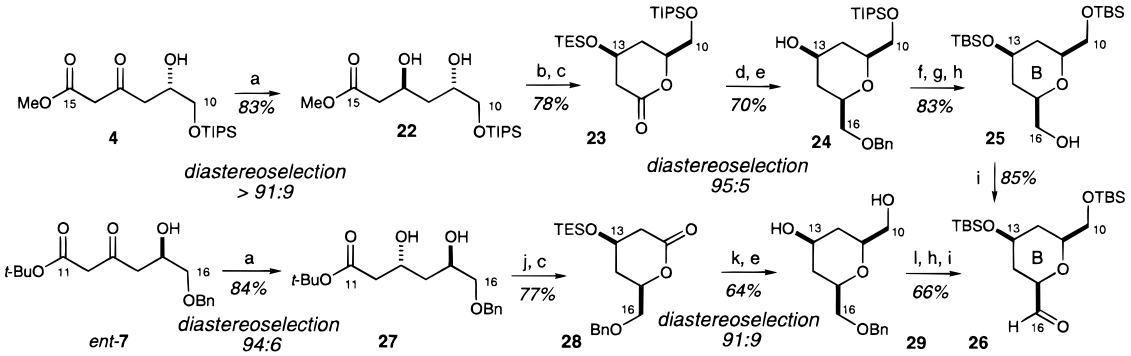
(50) Lewis, M. D.; Cha, J. K.; Kishi, Y. *J. Am. Chem. Soc.* **1982**, *104*, 4976−4978.

(51) The stereochemical outcome of the silane reduction was apparent from the high-field $^1H$ NMR spectrum of tetrahydropyran **24** (400 MHz, $C_6D_6$), which displayed identical axial (11 Hz) and equatorial (4.6 Hz) couplings for both ring methylenes ($C_{12}$ and $C_{14}$).

(52) Three steps are saved by the incorporation of the aldol chemistry, and one step is saved by the use of an in situ deprotection of the $C_{10}$ PMB ether.

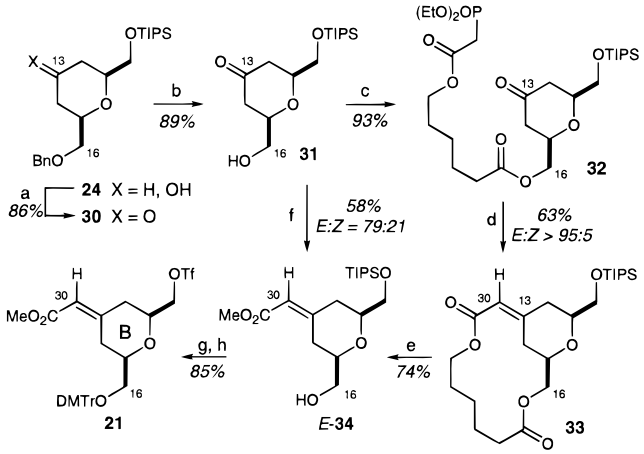
(53) (a) The reaction of trimethylphosphonoacetate with ketone **31** was screened under three conditions: LiCl, $NEt_3$, MeCN, 23 °C, 2 days (66:33 *E*:*Z*, 50% conversion); NaH, $PhCH_3$, 23 °C, 90 min. (70:30 *E*:*Z*); KHMDS, THF, 0 °C, 30 min. (50:50 *E*:*Z*). (b) Recent results from the laboratory of H. M. R. Hoffmann indicate that the exocyclic *ethyl* ester may be installed in good stereoselectivity (9:1 *E*:*Z*, 72% yield); cf. ref 24e.

**Scheme 5**[a]




[a] Key: (a) $Me_4NHB(OAc)_3$, AcOH/MeCN, −35 °C; (b) PPTS, 0.01 M PhH, 80 °C, −MeOH; (c) TESCl, imidazole, $CH_2Cl_2$, 0 °C; (d) $BnOCH_2Li$, THF, −78 → −50 °C; (e) $BF_3{\cdot}OEt_2$, $Et_3SiH$, $CH_2Cl_2$, −20 °C; (f) TBAF, THF, 0 °C; (g) TBSOTf, 2,6-lutidine, $CH_2Cl_2$, −78 °C; (h) 1 atm $H_2$, catalytic 10% Pd/C, AcOH, EtOAc; (i) $(COCl)_2$, DMSO, $NEt_3$, $CH_2Cl_2$, −78 → −50 °C; (j) $F_3CCO_2H$, $CH_2Cl_2$; (k) $PMBOCH_2Li$, THF, −78 → −50 °C; (l) TBSCl, imidazole, DMAP, $CH_2Cl_2$.

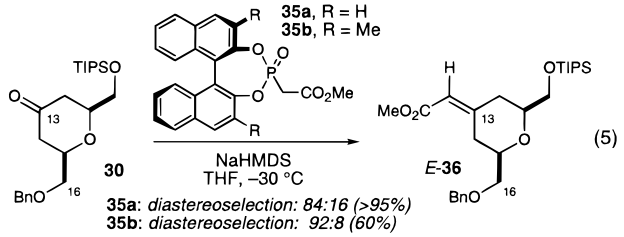
**Scheme 6**[a]




[a] Key: (a) $(COCl)_2$, DMSO, $NEt_3$, −78 °C; (b) $H_2$, 10% Pd/C, catalytic AcOH, EtOAc; (c) $(EtO)_2P(O)CH_2CO_2(CH_2)_5CO_2H$, BOPCl, DMAP, $CH_2Cl_2$; (d) 50 equiv of LiCl, 2 equiv of DBU, 1 mM MeCN; (e) $K_2CO_3$, MeOH; (f) NaHMDS, 2 equiv of **35a**, THF, −78 °C, then **31**, −78 → 0 °C; (g) DMTrCl, i-$Pr_2NEt$, DMAP, $CH_2Cl_2$; (h) (i) TBAF, THF, 0 °C; (ii) $Tf_2O$, 2,6-lutidine, $CH_2Cl_2$, −10 °C.

to the use of the tethered phosphonate strategy[25b] (Scheme 6). Acylation of the $C_{16}$ hydroxyl of **31** with 6-[(diethoxyphosphonyl)acetyl]oxyhexanoic acid[25b] (BOPCl, DMAP) provided phosphonate **32**, which was readily cyclized under soft enolization conditions (LiCl, syringe pump addition of 2 equiv of DBU)[54] to afford enoate **33** in 63% yield and excellent stereoselectivity (>95:5 *E*:*Z*, $^1$H NMR). The subsequent cleavage of the tether ($K_2CO_3$, MeOH, 23 °C)[25b] proceeded without incident to afford enoate *E*-**34** in 74% yield (43% yield overall).[55] We speculated that the use of a chiral phosphonate reagent[56] might improve the process and thus examined the use of methyl (*R*)-[(2,2′-bishydroxy-1,1′-binaphthyl)phosphonyl]acetate (**35a**), a reagent introduced by Fuji.[57] We found that the condensation of the sodium anion of **35a** with hydroxyketone **31** (THF, −78 → 0 °C) afforded a 58% yield (unoptimized) of a 79:21 mixture of *E*- and *Z*-**34**, which could be separated by silica gel chromatography (Scheme 6).

The olefination of **30** with chiral phosphonate **35a** was also evaluated (eq 5). A careful study of reaction parameters[58] led to acceptable (*E*) selectivity (84:16 *E*:*Z*,), and this diastereoselection could be further improved (92:8 *E*:*Z*) by utilizing the more hindered phosphonate[57b] **35b**. Taken together with the fact that phosphonate **35a** is a (*Z*)-selective olefinating reagent with aldehydes,[59] these data point to a mechanism of stereoinduction in which the kinetic facial bias exerted by **35a** in the initial aldol step is transferred to enoate geometry through kinetic trapping of the intervening aldolate.[60]




(5)

## Synthesis of the $C_{17}$−$C_{27}$ Subunit

In analogy with our previous work on cytovaricin,[61] we planned to carry the C-ring exocyclic enoate through the Julia coupling as its exocyclic acid in order to avoid any problems with proton transfer, and we thus formulated the C-ring synthon as **38**. Retrosynthetic removal of the exocyclic acid and $C_{19}$−$C_{20}$ diol afforded glycal **39**, which could be derived from the acyclic precursor via cyclization/dehydration (Scheme 7). This protected ketotriol was then dissected into ketone **40** and ketoaldehyde **41** using our aldol/reduction strategy. The imple-

(54) Blanchette, M. A.; Choy, W.; Davis, J. T.; Essenfeld, A. P.; Masamune, S.; Roush, W. R.; Sakai, T. *Tetrahedron Lett.* **1984**, *25*, 2183−2186.

(55) The geometry of the olefin in *E*-**34** was evident from the NOE enhancement between the exocyclic vinyl-H and the equatorial $C_{12}$H and the pronounced deshielding of the $C_{14}$ equatorial proton relative to the $C_{12}$ equatorial proton. The opposite deshielding pattern was seen for the *Z* isomer.

(56) For leading references to the recent literature, cf.: (a) Abiko, A.; Masamune, S. *Tetrahedron Lett.* **1996**, *37*, 1077−1080. (b) Denmark, S. E.; Rivera, I. *J. Org. Chem.* **1994**, *59*, 6887−6889.

(57) (a) Tanaka, K.; Ohta, Y.; Fuji, K.; Taga, T. *Tetrahedron Lett.* **1993**, *34*, 4071−4074. (b) Tanaka, K.; Otsubo, K.; Fuji, K. *Tetrahedron Lett.* **1996**, *37*, 3735−3738.

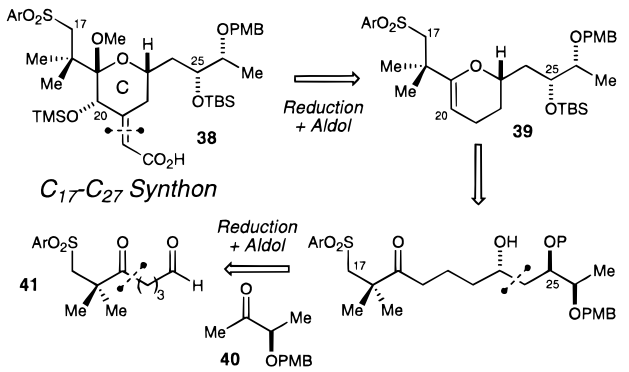
(58) The following parameters were examined: counterion (Li, Na, K, and Zn), solvent (THF, $Et_2O$, $PhCH_3$, and THF/HMPA), and temperature (0, −35, −65, and −78 °C).

(59) (a) The reaction of either **35a** or **35b** with dihydrocinnamaldehyde (NaHMDS, THF, −78 °C) afforded an 82:18 *Z*:*E* mixture of olefins. (b) The *Z* stereoselectivity of achiral phenolic phosphonates with simple aldehydes has recently been documented, cf.: Ando, K. *J. Org. Chem.* **1997**, *62*, 1934−1939.

(60) For discussions regarding the mechanism of the Horner−Wadsworth−Emmons olefination, cf.: (a) Maryanoff, B. E.; Reitz, A. B. *Chem. Rev.* **1989**, *89*, 863. (b) Vedejs, E.; Peterson, M. J. *Top. Stereochem.* **1994**, *21*, 1−157.

(61) Evans, D. A.; Kaldor, S. W.; Jones, T. K.; Clardy, J.; Stout, T. J. *J. Am. Chem. Soc.* **1990**, *112*, 7001−7031.

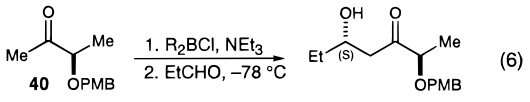
**Scheme 7**




mentation of this plan for the synthesis of **38** and **39** is shown in Schemes 8 and 9.

Conversion of 2,2-dimethyl-1,3-propanediol (**42)** into the sulfonylaldehyde **43** proceeded over four standard steps (Scheme 8: monotosylation, sulfide displacement, sulfide oxidation, and alcohol oxidation) in 76% overall yield and was routinely performed on large (>500 mmol) scale. Reaction of aldehyde **43** with the Grignard reagent derived from 5-bromo-1-pentene ($CH_2Cl_2/Et_2O$, 0 °C) was followed by Swern oxidation ($CH_2Cl_2$, −78 → 0 °C) to provide a $C_{19}$ ketone in 82% yield for the two steps.[62] Oxidation of the terminal alkene was best accomplished using an osmium-mediated dihydroxylation (catalytic in $K_2OsO_4{\cdot}(OH_2)_2$)[63] and was followed by diol cleavage with sodium periodate to afford the desired keto aldehyde **41a** as a white solid in 95% yield overall. The requisite ketone partner **40** for the ensuing aldol reaction was prepared using a kinetic resolution strategy,[33] as shown in Scheme 8. The indicated route (resolution, protection, ozonolysis) is operationally convenient (three steps, one purification) and proceeds well on large scale (>250 mmol).

Reaction of **41a** with the lithium enolate of **40** was both low yielding (<40% yield) and poorly diastereoselective (<3:1). After some optimization,[64] it was found that the aldol reaction of **40** and **41a** could be efficiently mediated using the chiral IPC enolates[65] of Paterson and Brown (Scheme 8); reaction of a slight excess of the chiral boron enolate of **40** with **41a** delivered aldol **46** in 86% yield and 93:7 diastereoselectivity. As shown in eq 6, the success of the (−)-DIPCl[66] reaction is a result of double stereodifferentiation: reaction of **40** and propionaldehyde with (−)-DIPCl afforded the desired 5*S* diastereomer with enhanced diastereoselection, and (+)-DIPCl afforded the undesired 5*R* diastereomer in lower diastereoselectivity and chemical yield.[67]




(6)

| B ligand | (*S*):(*R*) | yield |
|---|---|---|
| R = *c*-Hex: | 66:34 | (25%) |
| R = (–)-IPC: | 95:05 | (66%) |
| R = (+)-IPC: | 18:82 | (44%) |

With aldol adduct **46** in hand, we focused on completing the synthesis of the 1,2,4-*syn*,*anti* stereochemical array (Scheme 8). Directed reduction[31a] of **46** with $Me_4NHB(OAc)_3$ was both regio- and diastereoselective, but the resulting 1,3-diol was difficult to differentiate in a high-yielding manner. Accordingly, we turned to the samarium-catalyzed Tishchenko reduction[31b] of aldol **46** (catalytic $SmI_2$, excess *p*-$NO_2$PhCHO), which provided diastereomerically pure nitrobenzoate **47** in excellent yield, regioselectivity, and diastereoselectivity (>95:5 ds).[68] The product diol monoester **47** was next silylated (TBSOTf, 2,6-lutidine) and deprotected (LiOH, aqueous THF/MeOH) to afford the target hydroxyketone **48** in 90% overall yield.[69] The synthesis of glycal **39a** was completed by the dehydration of **48** under acidic conditions (catalytic CSA, PhH, azeotropic removal of water at 80 °C, 92−96% yields).

The synthesis of the $C_{17}-C_{27}$ glycal **39** (Scheme 8) was very reliable on large scale and was independently carried out with a variety of functional groups at $C_{17}$ ($SO_2$Ph, $SO_2$(*N*-Me)Im,[70] 3,4-$(MeO)_2PhCH_2O$) in order to assay different coupling strategies (vide infra). For the sake of illustration, the elaboration of the imidazolyl sulfone glycal **39b** to the complete $C_{17}-C_{27}$ synthon is detailed below (Scheme 9). Epoxidation of glycal **39b** with *m*-CPBA proceeded with in situ methanolysis to afford the hydroxyketal as a mixture of four diastereomers ($^1$H NMR analysis), which was immediately oxidized with the Dess−Martin periodinane[71] to give the ketone **49** as an inseparable 4.5:1 mixture of diastereomers in 61% overall yield.[72] Ketone **49** was readily condensed with glyoxylic acid monohydrate under basic conditions (aqueous NaOH, THF, 23 °C)[73] to give the exocyclic carboxylic acid (single olefin isomer), which was directly esterified by *brief*[74] treatment with dimethylformamide dimethylacetal in refluxing benzene to provide the (*E*) olefin **50** in 77% yield for the two-step procedure. Since this compound was prone to olefin isomerization, it was immediately reduced under Luche conditions ($NaBH_4$, $CeCl_3$)[75] to afford the axial alcohol **51** as a single diastereomer—an outcome which is consistent with steric control of the approach of the borohydride

(62) (a) The use of methylene chloride as a cosolvent was essential. (b) Addition of this Grignard reagent to the $C_{19}$ carboxylic acid or Weinreb amide was low-yielding.

(63) (a) Minato, M.; Yamamoto, K.; Tsuji, J. *J. Org. Chem.* **1990**, *55*, 766−768. (b) Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483−2547.

(64) (a) A study of the aldol reaction of **40** (and other protected variants: TBDPS, MEM, BOM, Bn) with propionaldehyde demonstrated that only moderate yields (25−50%) and low selectivities (<3:1 diastereoselection in the desired sense) could be obtained using a wide array of metal centers (Li, B, Sn, Zn, Mg, Ti) and enolization conditions. (b) For the obtainment of the undesired 1,4-*syn* diastereomer in high stereoselectivity, cf. ref 34c.

(65) (a) Ramachandran, P. V.; Xu, W.-C.; Brown, H. C. *Tetrahedron Lett.* **1996**, *37*, 4911−4914. (b) Paterson, I.; Goodman, J. M.; Lister, M. A.; Schumann, R. C.; McClure, C. K.; Norcross, R. D. *Tetrahedron* **1990**, *46*, 4663−4684.

(66) DIPCl is a trademark of the Aldrich Chemical Co. (DIP = diisopinocampheyl).

(67) Assuming a base level selectivity of 89:11 for the reaction of *n*-alkylaldehydes with these IPC enolates (ref 65b), our stereoselectivities are roughly in accord with the precepts for double diastereodifferentiation: calculated value = 8/1 × 2.2/1 = 17.8/1 ratio of *S*/*R*; actual value = 19/1; cf.: Masamune, S.; Choy, W.; Peterson, J. S.; Sita, L. R. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 1−30.

(68) Analysis of the NOE spectrum of an ortho ester derivative of **47** (synthesized in two steps: (i) LiOH, (ii) DDQ, $K_2CO_3$) secured the stereochemical assignment for both the aldol and reduction steps.

(69) Note that the use of *p*-nitrobenzoate as the $C_{23}$ hydroxyl protecting group was critical to the success of this sequence (**46** → **48**): the $C_{23}$ acetate was too labile and underwent migration during the silylation reaction, and the $C_{23}$ benzoate was too difficult to remove.

(70) The use of *N*-methyl imidazolyl sulfones has been reported to improve the Julia olefination, cf.: Kende, A. S.; Mendoza, J. S. *Tetrahedron Lett.* **1990**, *31*, 7105−7108.

(71) (a) Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277−7287. (b) For an improved preparation of the reagent, cf.: Ireland, R. E.; Liu, L. *J. Org. Chem.* **1993**, *58*, 2899.

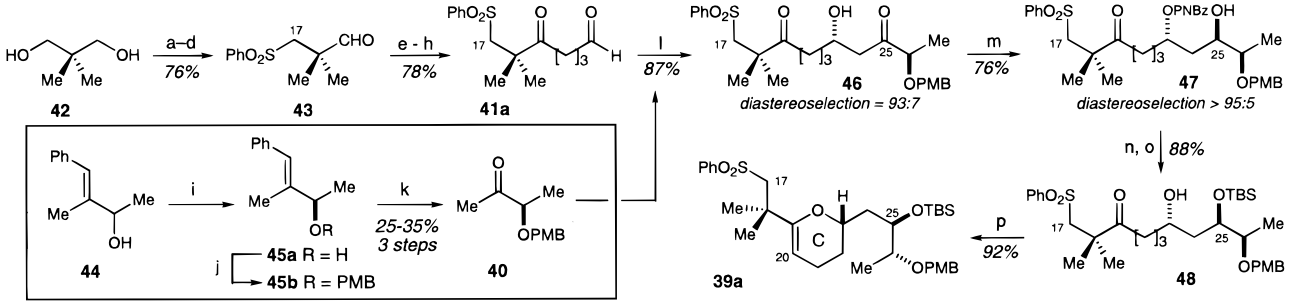
(72) Inexplicably, the yields for this two-step transformation were much higher in the phenyl sulfone (81%) and dimethoxybenzyl (100%) series. The diastereoselectivity was unaffected by the $C_{17}$ substituent.

(73) Pettit, G.; Green, B.; Dunn, G. L. *J. Org. Chem.* **1970**, *35*, 1367−1376.

(74) Reaction times longer than 20−30 min provided for considerably reduced yields because of olefin isomerization (*E* → Z).

(75) Luche, J. L. *J. Am. Chem. Soc.* **1978**, *100*, 2226.

**Scheme 8**[a]

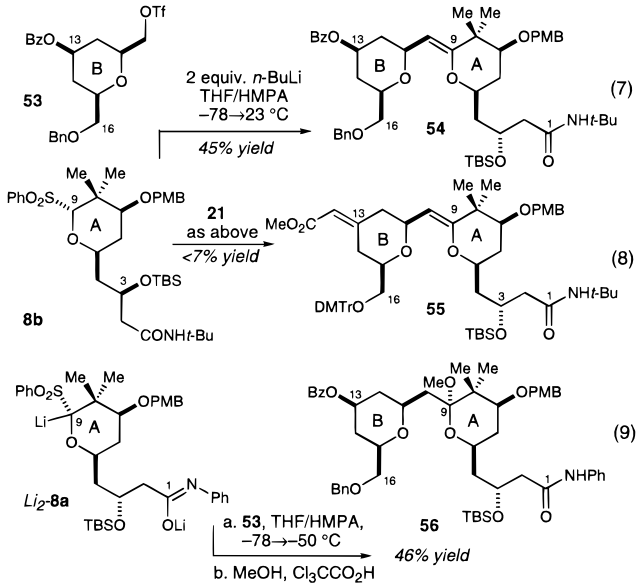


[a] Key: (a) 0.2 equiv of TosCl, pyr, $CH_2Cl_2$, 0 → 23 °C; (b) PhSH, NaH, DMF, 80 °C; (c) m-CPBA, $CH_2Cl_2$, 0 → 23 °C; (d) $(COCl)_2$, DMSO, $NEt_3$, $CH_2Cl_2$, −78 → 0 °C; (e) $BrMg(CH_2)_3CH{=}CH_2$, 1:1 $Et_2O/CH_2Cl_2$, 0 → 23 °C; (f) $(COCl)_2$, DMSO, $NEt_3$, $CH_2Cl_2$, −78 → −50 °C; (g) 2 mol % $K_2OsO_4(OH)_2$, 2 mol % quinuclidine, $K_3Fe(CN)_6$, $K_2CO_3$, 1:1 t-BuOH/$H_2O$; (h) $NaIO_4$, $NaHCO_3$, 2:2:1 t-BuOH/$H_2O$/THF; (i) 15 mol % L-(+)-DIPT, 10 mol % Ti(Oi-Pr)$_4$, 0.7 equiv of t-$BuO_2H$, $CH_2Cl_2$, −20 °C; (j) NaH, PMBBr, catalytic n-$Bu_4NI$, THF, 0 → 23 °C; (k) $O_3$, $CH_2Cl_2$/MeOH, −78 °C, then $Me_2S$, −78 → 23 °C; (l) **40**, (−)-DIPCl, $NEt_3$, $CH_2Cl_2$, −78 °C; then **41a**, −70 °C; (m) 20 mol % $SmI_2$, *p*-$NO_2$PhCHO, THF, 0 °C; (n) TBSOTf, 2,6-lutidine, $CH_2Cl_2$, −15 °C; (o) LiOH, 2:2:1 THF/MeOH/$H_2O$; (p) 5 mol % CSA, PhH, 80 °C.

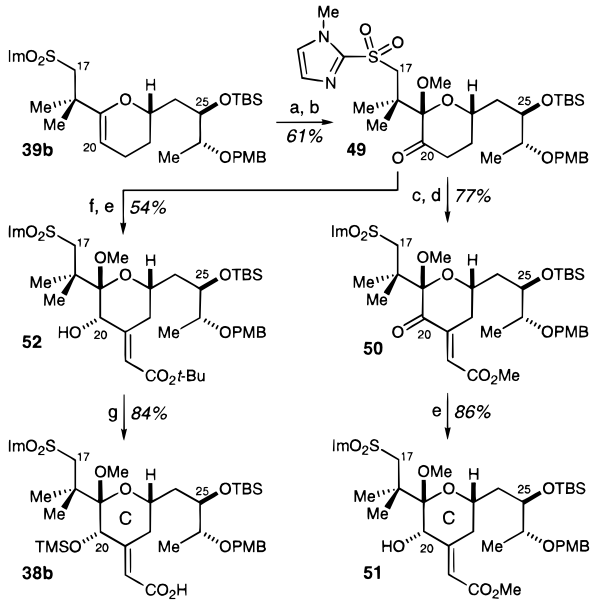
reagent. The desired exocyclic carboxylic acid **38b** could be synthesized along similar lines: introduction of the exocyclic *tert*-butyl ester was accomplished using the aldol condensation of *tert*-butylglyoxylate[76] and the potassium enolate of **49** and was followed immediately by Luche reduction to give the diastereomerically pure alcohol **52** (54% yield, two steps). Deprotection of the *tert*-butyl ester using trimethylsilyl triflate[77] proceeded with concomitant protection of the axial alcohol to provide the target acid **38b** in 84% yield.[78]

## Fragment Coupling

Our initial studies on the A−B fragment coupling utilized *tert*-butyl amide[79] **8b** and triflate[80] **53** and revealed that the lithiated dianion of sulfone **8b** could be condensed with **53** in the presence of HMPA at −78 °C (eq 7). Upon warming of the reaction mixture to room temperature,[81] elimination of phenyl sulfinate[82] afforded enol ether **54** (45% yield), which could be converted to the $C_9$ mixed methyl ketal using trichloroacetic acid in methanol (66% yield, 30% overall). However, when the dianion of sulfone **8b** was added to the fully functionalized triflate **21**, the enol ether **55** was only isolated in ca. 7% yield (eq 8). The majority of the sulfone **8b** was recovered unchanged from this reaction, and the bulk of triflate **21** had been converted into a $C_{10}$−$C_{12}$ cyclopropane,[83] presumably via a proton-transfer/intramolecular alkylation sequence.



**Scheme 9**[a]



[a] Key: (a) m-CPBA, MeOH, −20 °C; (b) Dess−Martin periodinane, pyr, $CH_2Cl_2$; (c) $OHCCO_2H$, aqueous NaOH, THF; (d) $(MeO)_2CHNMe_2$, PhH, 80 °C; (e) $NaBH_4$, $CeCl_3{\cdot}(OH_2)_7$, MeOH, −78 °C; (f) KOt-Bu, $OHCCO_2$t-Bu, THF, −15 °C; (g) TMSOTf, 2,6-lutidine, $CH_2Cl_2$, 0 °C.

It was eventually discovered that the use of the *tert*-butyl amide **8b** was not synthetically viable,[84] and so we turned to the use of other amide residues. Interestingly, the use of a $C_1$

(76) Subasinghe, N.; Schulte, M.; Chan, M. Y.-M.; Roon, R. J.; Koerner, J. F.; Johnson, R. L. *J. Med. Chem.* **1990**, *33*, 2734−2744.

(77) (a) Jones, A. B.; Villalobos, A.; Linde, R. G.; Danishefsky, S. J. *J. Org. Chem.* **1990**, *55*, 2786. (b) Evans, D. A.; Ng, H. P.; Rieger, D. L. *J. Am. Chem. Soc.* **1993**, *115*, 11446−11459.

(78) Irradiation of either the exocyclic olefin resonance or the equatorial proton at $C_{20}$ produced a large NOE enhancement of the other resonance. Likewise, the chemical shifts and coupling constants of $C_{20}H_{eq}$ and $C_{22}H_{eq}$ were in accord with the assigned stereochemistry.

(79) The preparation of *tert*-butyl amide **8b** was identical to that for anilide **8a**, with the exception of the transamidation of lactone **18** (*t*-$BuNH_2$, $Me_2AlCl$, THF, room temperature, 16 h, 96% yield).

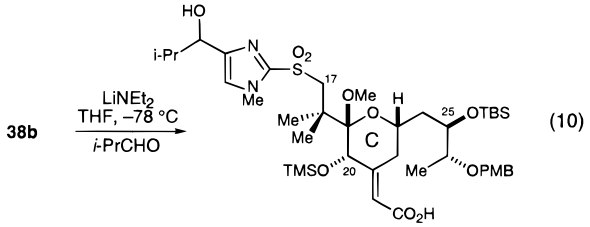
(80) (a) Triflate **53** was prepared from alcohol **24** in three steps and 89% overall yield: (i) $Bz_2O$, DMAP; (ii) TBAF, THF, 0 °C; (iii) $Tf_2O$, 2,6-lutidine, −10 °C. See the Supporting Information for details. (b) Note that the analogous $C_{10}$ iodide was not reactive toward $C_9$ sulfonyl anions.

(81) If the reaction was quenched at lower temperatures (0 or −15 °C), significant amounts of the $C_9$ lactol were obtained, indicating that the sulfinate elimination was slower than the anion alkylation.

(82) This is consistent with the results of both Ley and Beau; cf. ref 28 and the following: Beau, J.-M.; Sinaÿ, P. *Tetrahedron Lett.* **1985**, *26*, 6189−6192.

benzyl (or PMB) amide resulted in the production of large amounts of the $N_1$,$C_9$-bisalkylation product, even at low reaction temperatures. This side reaction could be avoided by attenuating the nucleophilicity of the amide residue; the dianion of *N*-phenyl sulfone **8a** alkylated exclusively at the carbon center, giving the unstable[85] ketal **56** in 46% overall yield after methanolysis (eq 9).[86] With this result, we delayed further attempts at optimization until the real $C_9-C_{10}$ coupling was at hand (vide infra).

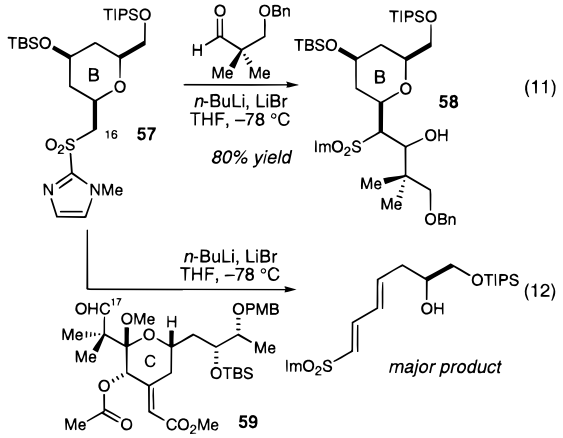
Our initial study of the $C_{16}-C_{17}$ Julia olefination utilized carboxylic acid **38b** in order to supress $C_{22}$ enolization of the enoate moiety.[87] Unfortunately, we found that reaction at $C_{17}$ could *not* be achieved, regardless of the experimental conditions[88] employed. Rather, the use of strong bases promoted deprotonation on the imidazole ring, as judged by quenching of the orange dianion of **38b** with deuterium chloride or simple aldehydes (eq 10).[89] In an attempt to override this preference



(10)

for spurious deprotonation, we examined a variety of structural modifications, including the use of the reduced oxidation state at the exocyclic ester, an unprotected hydroxyl at $C_{20}$,[90] and the phenyl sulfone at $C_{17}$.[91] Unfortunately, a high-yielding $C_{16}-C_{17}$ olefination was never obtained.

Since the problems associated with the Julia olefination stemmed from either the inability to enolize the sulfonylmethylene or the excessive basicity of the resultant anion, it was reasoned that the reverse coupling approach (unhindered $C_{16}$ sulfone and unenolizable $C_{17}$ aldehyde) might be successful.[92] Indeed, our first results with *N*-methyl imidazolyl sulfone[93] (**57**) were encouraging (eq 11): the lithium anion of **57** could be coupled with 3-benzyloxy-2,2-dimethylpropanal to give **58** in good yield (LiBr,[94] −78 °C[95]). Unfortunately, the fully elaborated C-ring aldehyde[96] **59** proved to be completely unreactive toward the B-ring sulfonylanion,[97] and only the undesired ring-opened product was obtained after prolonged reaction times (eq 12).




These exploratory results indicated that the steric congestion at $C_{17}$ was the dominant issue surrounding the $C_{16}-C_{17}$ olefination; accordingly, we explored the use of the less sterically crowded $C_{19}-C_{20}$ glycal **39a** (Scheme 10). Deprotonation of the sulfone **39a** with *n*-butyllithium was followed by addition of 1 equiv of aldehyde **26** to afford the hydroxysulfones as a mixture of four diastereomers.[98] Acetylation of the unpurified mixture ($Ac_2O$/DMAP) and purification by flash chromatography afforded the acetoxysulfones in 87% yield for the two steps. Acetoxysulfone elimination was most conveniently carried out according to the method of Pak,[99] which entailed forming a magnesium amalgam in situ with catalytic amounts of mercuric chloride. Under these conditions, the diastereomerically pure (*E*) olefin **60** ($^1$H NMR, $J$ = 16 Hz) was obtained in 74% yield (64% overall yield for the Julia olefination).

Based on these experiments, methods for forming both the $C_9-C_{10}$ and $C_{16}-C_{17}$ bond were in hand; however, the

(83) The cyclopropane was isolated in 77% yield when the coupling was carried out in the absence of HMPA.

(84) The *tert*-butyl amide could not be hydrolyzed in the presence of the $C_9$ ketal. For a discussion of amide hydrolysis, cf. ref 37.

(85) Ketal **56** was completely unstable when stored neat and reverted back to the enol ether and lactols after even 10−30 min at room temperature. In contrast, the benzyl, PMB, and *t*-Bu amide analogues were perfectly stable, even after prolonged storage.

(86) An equivalent amount of product could be isolated from the two-step, one-pot variant: $Li_2$-**8a** and **53**, THF, −78 → −15 °C, then MeOH, $Cl_3CCO_2H$ quench. The avoidance of HMPA required that a higher temperature be utilized in the alkylation step.

(87) Use of the methyl $C_{20}$-hydroxyester **51** was complicated by deprotonation at $C_{22}$ (data not shown).

(88) (a) The following variables were screened: base (*n*-BuLi, PhLi, LDA, $LiNEt_2$); solvent (THF, THF/HMPA); temperature (−78 °C, −40 °C); and aldehyde (*i*-PrCHO, *t*-BuCHO, PhCHO). (b) In addition, the following additives were evaluated: LiBr, $MgBr_2{\cdot}OEt_2$ (Danishefsky, S. J.; Selnick, H. G.; Zelle, R. E.; DeNinno, M. P. *J. Am. Chem. Soc.* **1988**, *110*, 4368), and $BF_3{\cdot}OEt_2$ (Achmatowicz, B.; Baranowska, E.; Daniewski, A. R.; Pankowski, J.; Wicha, J. *Tetrahedron* **1988**, *44*, 4989).

(89) The spurious deprotonation of *phenyl* sulfones is a common problem. Although our model studies clearly indicated that the *N*-methyl imidazolyl sulfone exerts a more powerful α-acidfying effect than the phenyl sulfone, this is apparently not enough to override the tremendous steric compression about $C_{17}$.

(90) Low yield (<20%) of the desired product could be obtained when the exocyclic ester was reduced *and* the $C_{20}$ hydroxyl group was left unprotected, provided $LiNEt_2$ was used as the base.

(91) While enolization of the *$C_{20}$-hydroxy* $C_{17}$-phenyl sulfone could be accomplished, the resultant anion (or modified variants thereof) proved to be more basic than nucleophilic.

(92) For the use of both ylide and nitronate anions generated $\beta$ to a THP oxygen, cf.: (a) McWhorter, W. W., Jr. Ph.D. Thesis, Harvard University, 1984. (b) Secrist, J. A., III; Wu, S.-R. *J. Org. Chem.* **1977**, *42*, 4084−4088. (c) Kobertz, W. R.; Bertozzi, C. R.; Bednarski, M. D. *J. Org. Chem.* **1996**, *61*, 1894−1897. (d) Martin, O. R.; Lai, W. *J. Org. Chem.* **1990**, *55*, 5188.

(93) Sulfone **57** was synthesized from alcohol **24** in five steps and 76% overall yield: (i) TBSOTf, 2,6-lutidine, −78 °C; (ii) $H_2$, 10% Pd/C; (iii) $Tf_2O$, 2,6-lutidine, −10 °C; (iv) LiSIm, THF, 0 °C; (v) *m*-CPBA. See the Supporting Information for details.

(94) For the use of LiBr with enolates, see: Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 1624.

(95) The sulfone anion decomposed slowly at −78 °C, producing about 10% of ring-opened elimination product in 1 h. For comparison, the lithium anion of a related phenyl sulfone anion *instantly* produced the undesired open-chain product, cf.: Barnes, N. J.; Davidson, A. H.; Hughes, L. R.; Procter, G. *J. Chem. Soc., Chem. Commun.* **1985**, 1292−1294.

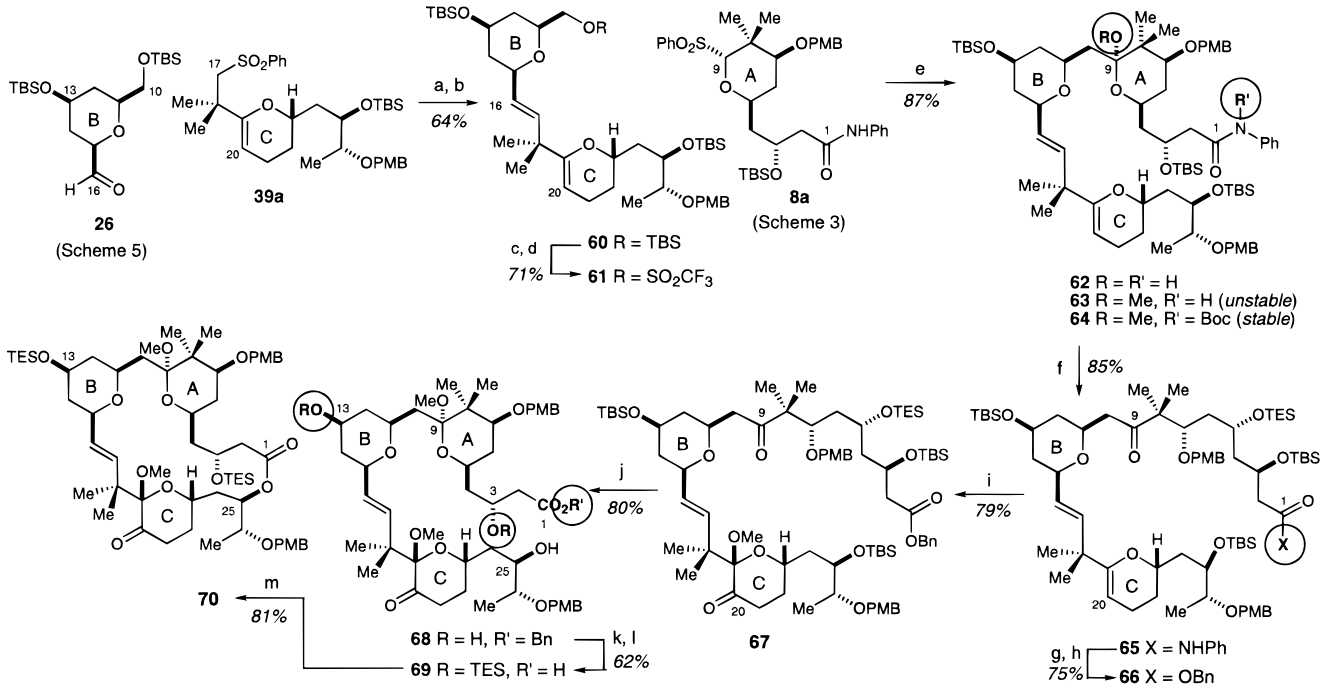
(96) Aldehyde **59** was made from the $C_{17}$-ODMB analogue of ester **51** in three steps: (i) $Ac_2O$, DMAP; (ii) DDQ, $H_2O/CH_2Cl_2$, 5 °C; (iii) Dess−Martin oxidation.

(97) The hindered aldehyde **59** was unreactive toward a number of standard enolate nucleophiles but could be engaged with unhindered silyl enol ethers under Lewis acid catalysis. For the reaction of a similar C-ring aldehyde with an allylboronate, cf.: Wender, P. A.; DeBrabander, J.; Harran, P.; Jimenez, J.-M.; Koehler, M.; Lippa, B.; Park, C.-M. *J. Am. Chem. Soc.* **1998**, *120*, 4534−4535.

(98) To obtain complete conversion, the addition step needed to be carried out at −50 °C.

(99) Lee, G. H.; Lee, H. K.; Choi, E. B.; Kim, B. T.; Pak, C. S. *Tetrahedron Lett.* **1995**, *36*, 5607−5610.

**Scheme 10**[a]




[a] Key: (a) (i) n-BuLi, THF, −78 °C, then **26**, −78 → −50 °C; (ii) $Ac_2O$, DMAP, $CH_2Cl_2$; (b) Mg, 20 mol % $HgCl_2$, EtOH; (c) TBAF, THF, −15 °C; (d) $Tf_2O$, 2,6-lutidine, $CH_2Cl_2$, −10 °C; (e) **8a**, 2 equiv of n-BuLi, THF, −78 °C, then HMPA, then **61**, −78 °C; (f) TESCl, imidazole, MeCN; (g) $Boc_2O$, DMAP, MeCN; (h) BnOLi, 1:1 THF/DMF, −30 °C; (i) (i) m-CPBA, MeOH, −20 °C, (ii) $ClCH_2CO_2H$, MeOH, 0 °C, (iii) Dess−Martin periodinane, pyr, $CH_2Cl_2$; (j) HF·pyr, 4:4:1 THF/MeOH/pyr; (k) TESCl, DMAP, $CH_2Cl_2$, 10 °C (65% + 15% each of the mono- and tris-silylether); (l) 1,4-cyclohexadiene, 10% Pd/C (50 mol %), EtOAc; (m) 2,4,6-trichlorobenzoyl chloride, i-$PrNEt_2$, PhH, then DMAP, 1.0 mM PhH.

constraints of each coupling reaction (vide supra) required a slightly less convergent approach to the synthesis of the tricycle (Scheme 1, transform **T1***). Following this new plan, we investigated the two logical assemblage strategies (A + B → AB + C → ABC and B + C → BC + A → ABC) and discovered that the ABC tricycle could be accessed via either pathway. Since the yields for *both* fragment-coupling processes were higher with the second option (B + C → BC + A → ABC), we utilized this approach in our synthesis (Scheme 10). Due to the acid lability of the $C_{19}$−$C_{20}$ glycal, functionalization of the $C_{10}$ position could only be effected by selective desilylation of **60** under *basic* conditions (TBAF, THF, −15 °C, 75% yield).[100] Subsequent sulfonylation of the new hydroxyl group with trifluoromethanesulfonic anhydride (2,6-lutidine, −10 °C) delivered the unstable primary triflate **61** (95% yield), which was immediately[101] treated with 1.5 equiv of the dilithio anion of sulfonylamide **8a** (THF/HMPA, −78 °C) to deliver the ABC lactol **62** in 84−90% yield.[102] As expected on the basis of our earlier model studies, overalkylation of the sulfonylamide dianion $Li_2$-**8a** was not detected. Utilizing the illustrated sequence (Scheme 10), the ABC tricycle **62** was assembled in 19 linear steps (14% overall yield) from commercially available starting materials (toluenesulfonyl chloride and 2,2-dimethyl-1,3-propanediol) on a multigram scale.

## Macrocyclization

The $C_9$ lactol **62** (Scheme 10) was protected through a selective[103] methanolysis (PPTS, MeOH/$(MeO)_3CH$, **62** → **63**). In accord with earlier results on the AB bicyclic systems, we found that the *N*-aryl amide **63** was reverted to the starting lactol after purification ($t_{0.5} \approx 2$ h when neat). Although the exact origin of this lability is unclear at the present time, the *stability* of its *N*-benzyl analogue, the *N*-Boc-*N*-phenyl derivative **64**, and benzyl ester **68** all suggest that the $C_9$ ketal of **63** may be compromised by the acidity of the anilide N−H proton ($pK_a \approx$ 21.5, DMSO).[104] Attempts to circumvent this problem by making recourse to thioketalization or lactol acetylation were unsuccessful, and initial attempts to advance the *N*-Boc derivative **64** were compromised by the poor electrophilicity and base sensitivity of the Boc-anilide and the acid lability of the $C_{19}$−$C_{20}$ glycal. After some experimentation, it was discovered that the Boc-anilide was much more reactive when the A-ring was locked in its open-chain form and that the sensitivity of the C-ring glycal was eliminated upon oxidation. These observations led to the development of the successful route to the seco acid **69**. Functionalization of the A-ring began with silylation of the open-chain hydroxyketone as its $C_5$-OTES ether **65**. When trapped in this protected and extended tautomer, the $C_1$ anilide was now readily transesterified to the benzyl ester **66** ($Boc_2O$, then LiOBn).[105] It is noteworthy that the use of DMF[106] and low temperature (−30 °C) was critical to the success of the

(100) The temperature control of this reaction was critical to its success, as the lability of the secondary $C_{13}$-OTBS was quite similar to that of the primary $C_{10}$-OTBS. Less than 30% of the primary alcohol was isolated under a variety of acidic desilylation conditions.

(101) The triflate **61** decomposed rapidly (<10 min) when left in neat form. See the Supporting Information for the details of the purification of **61**.

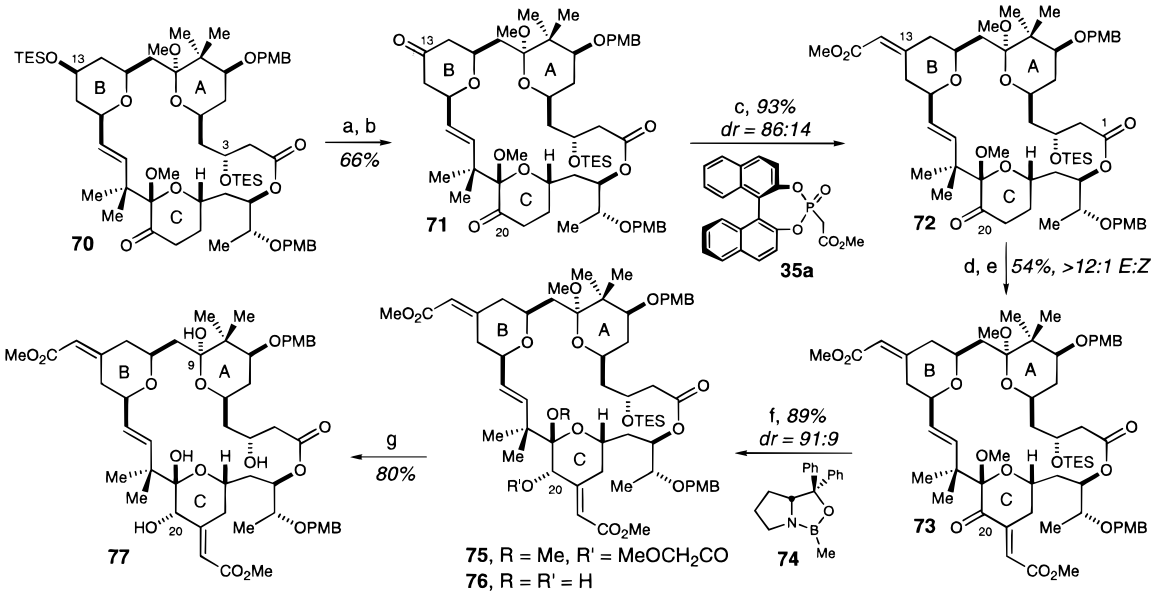
(102) In practice, the lactol **62** was obtained in 60−75% yield after chromatography. An additional 15−20% was isolated as the hydroxyketone tautomer, which was silylated (vide infra) to reconverge the material. See the Supporting Information for details.

(103) Our earlier results with acidic methanolysis of the A and C ring enol ethers showed that the equilibrium lay on the side of either the ketal (A ring) or the enol ether (C ring), depending on the position (exo or endo) and steric environment of the enol ether.

(104) For the $pK_a$ of *N*-phenyl acetamide, cf.: Bordwell, F. G. *Acc. Chem. Res.* **1988**, *21*, 456−463.

(105) Evans, D. A.; Ennis, M. D.; Mathre, D. J. *J. Am. Chem. Soc.* **1982**, *104*, 1737−1739.

**Scheme 11**[a]




[a] Key: (a) 20 mol % PPTS, 2:1 MeOH/$(MeO)_3CH$, $CH_2Cl_2$, −30 °C; (b) Dess−Martin periodinane, pyr, $CH_2Cl_2$; (c) **35a**, NaHMDS, THF, −78 °C, then **71**, −15 °C; (d) KHMDS, THF, −78 °C, then $OHCCO_2Me$, −78 °C; (e) $Et_3NSO_2NCO_2Me$, PhH; (f) **74**, $BH_3$·SMe, $CH_2Cl_2$, then MeOH, then $MAc_2O$, pyr, DMAP; (g) (i) PPTS, 3:1 THF/$H_2O$, (ii) $Na_2CO_3$, MeOH, (iii) pTsOH, 4:1 MeCN/$H_2O$.

latter reaction (**65** → **66**) and resulted in a dramatic suppression of the base-induced[107] elimination of the $C_3$-OTBS group. In contrast to the oxidation of glycal **39**, oxidation of the $C_{19}$−$C_{20}$ glycal (*m*-CPBA/MeOH, then Dess−Martin oxidation) delivered a 1:1 mixture of stereoisomers at $C_{19}$, along with unexpected substitution products ($C_{19}$OH and/or $C_{19}O_2CAr$). Incorporation of a thermodynamically controlled methanolysis step (MeOH, $ClCH_2CO_2H$, 0 °C) into the double oxidation sequence erased the effects of the unwanted substitution *and* corrected the stereochemical deficiencies of the process, delivering the oxoketal **67** as a single diastereomer in 79% overall yield.[108] Complete desilylation and concomitant cyclization of the A-ring was readily effected under buffered conditions (HF·Pyr, THF/MeOH/pyridine, 3 days) to afford the triol **68** in good yield.[109] Initial macrocyclization attempts focused on the carboxylic acid derivative of **68** (R, R′ = H); however, these studies were frustrated by the unexpected reactivity of the $C_3$ hydroxyl group, and only low-yielding cyclization reactions could be obtained.[110] These problems were circumvented via selective protection of the $C_3$ hydroxyl in the presence of the $C_{25}$ hydroxyl (TESCl, DMAP; 65% yield; 82% yield, based on recovered starting material). Subsequent selective debenzylation (cyclohexadiene, 10% Pd/C)[111] afforded the hydroxyacid **69**, which was smoothly cyclized under modified Yamaguchi conditions[112] to afford macrocycle **70** in 81% yield (Scheme 10).

## Synthesis of Bryostatin 2

With the macrocyclization accomplished, we addressed the late-stage installation of the enoate moieties. Selective removal of the $C_{13}$-OTES group of **70** afforded the $C_{13}$ alcohol, which was readily oxidized to the diketone **71** using the Dess−Martin procedure (Scheme 11).[71] Condensation of the $C_{13}$,$C_{20}$ diketone **71** with 4 equiv of the sodium anion of trimethyl phosphonoacetate (THF, 23 °C) selectively[113] derivatized the $C_{13}$ ketone to produce the $C_{13}$−$C_{30}$ enoate **72** in 100% yield and 64:36 *Z*:*E* diastereoselectivity. Following the precedent previously established in simple B-ring systems (eq 5), the use of the sodium anion of Fuji's chiral phosphonate **35a** provided an 85:15 mixture of diastereomers in 93% combined yield (75% isolated yield of **72**[114] after preparative TLC). Subsequent incorporation of the C-ring enoate was best accomplished using a two-step procedure (KHMDS, $OHCCO_2Me$; then Burgess reagent).[115] The ability of KHMDS to selectively enolize the $C_{20}$ ketone in the presence of the $C_1$ ester is precedented[116] and is apparently

(106) Jacobi has observed that DMF improves the ratio of exocyclic to endocyclic cleavage in the LiOOH-mediated hydrolysis of *N*-acyloxazolidinones, cf.: Jacobi, P. A.; Murphee, S.; Rupprecht, F.; Zheng, W. *J. Org. Chem.* **1996**, *61*, 2413−2427.

(107) Interestingly, the less basic magnesio species (MgOBn, BnOH) also inhibited the elimination reaction but resulted in the wrong cleavage regioselectivity (the anilide **65** was the major product).

(108) Only the final product **67** was purified via flash chromatography.

(109) For another use of HF·Pyr/MeOH with a mixed methyl ketal, cf.: Nicolaou, K. C.; Daines, R. A.; Ogawa, Y.; Chakraborty, T. K. *J. Am. Chem. Soc.* **1988**, *110*, 4696−4705.

(110) The best result obtained with the carboxylic acid derivative of **68** (R = R′ = H) utilized the thiopyridyl ester (cf. Corey, E. J.; Nicolaou, K. C. *J. Am. Chem. Soc.* **1974**, *96*, 5614−5616) and provided the macrocycle in 14% yield for the two steps (thioester formation and cyclization).

(111) Felix, A. M.; Heimer, E. P.; Lambros, T. J.; Tzougraki, C.; Meienhofer, J. *J. Org. Chem.* **1978**, *43*, 4194−4196.

(112) (a) Evans, D. A.; Kim, A. S. *J. Am. Chem. Soc.* **1996**, *118*, 11323−11324. (b) Inanaga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M. *Bull. Chim. Soc. Jpn.* **1979**, *52*, 1989−1993.

(113) The $C_{20}$ ketone is both sterically crowded and electronically deactivated. Model studies with the C-ring intermediate **49** showed that this ketone failed to react with the sodium anion of trimethylphosphonoacetate, even over the course of several days.

(114) The olefin geometry of **73** was readily elucidated using $^1$H NMR (COSY-90, 500 MHz, $C_3D_6O$): $C_{14}H_{eq}$ ($\delta$ 3.81) was significantly downfield of $C_{12}H_{eq}$ ($\delta$ 2.37) in the $^1$H NMR spectrum of the *Z* diastereomer, and $C_{12}H_{eq}$ ($\delta$ 3.96) was significantly downfield of $C_{14}H_{eq}$ ($\delta$ 2.10) in the *E* diastereomer. In addition, the $C_{30}$H resonance exhibited a strong enhancement to the $C_{12}H_{eq}$ resonance in the NOESY spectrum of **73**.

(115) (a) Burgess, E. M.; Penton, H. R., Jr.; Taylor, E. A. *J. Org. Chem.* **1973**, *38*, 26−31. (b) The Burgess elimination needed to be carried out at low temperatures and worked up under basic conditions, in contrast to the literature reports. The acceleration in this reaction is probably attributable to the acidifying properties of the $C_{20}$ ketone.

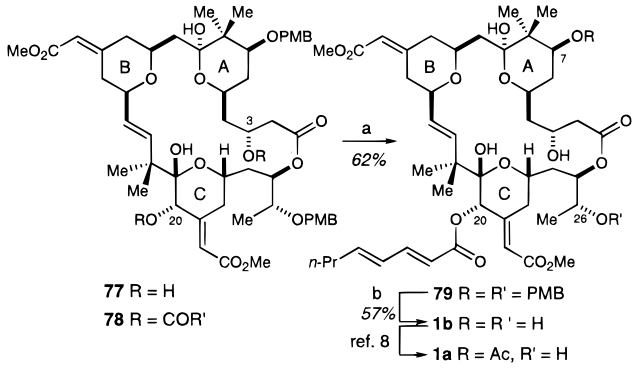
(116) (a) Ireland, R. E.; Gleason, J. L.; Gegnas, L. D.; Highsmith, T. K. *J. Org. Chem.* **1996**, *61*, 6856−6872. (b) Ireland, R. E.; Wipf, P.; Armstrong, J. D., III. *J. Org. Chem.* **1991**, *56*, 650−657.

favored in the present system by the conformation of macrolactone **73**.[117]

The reduction of ketone **73** proved quite troublesome, in contrast to the analogous reaction with simple C-ring systems (cf. **50** → **51**, Scheme 9). Reduction of **73** under standard Luche conditions ($NaBH_4$, $CeCl_3$) resulted in the formation of product **76** (30% yield, 65:35 diastereoselection), in which the $C_{19}$ ketal had been hydrolyzed. This reaction was not favorably influenced by changes in the reaction temperature, time, or workup, and all attempts to convert **76** into the deprotected **77** were ineffective due to the unexpected[118] stability of the $C_9$ ketal. It was reasoned that the $C_{19}$ lactol must be the source of this unusual stability at $C_9$; accordingly, the in situ acylation of the nascent hydroxyl $C_{20}$ was explored. In the event, reduction of **73** with $NaBH_4$ (10:1 THF/MeOH, −15 °C), followed by *anhydrous* quenching of the reaction mixture with isobutyraldehyde and addition of excess methoxyacetic anhydride (pyridine, DMAP), afforded compound **75** (ca. 50% yield, 60:40 diastereoselection, 25% isolated yield of **75**), in which the $C_{19}$ ketal had been maintained. Fortunately, the stereoselectivity of the reduction step could be improved by employing the CBS reagent[119] **74**, which delivered the desired **75** in excellent yield and selectivity[120] (>90% yield, 10:1 diastereoselection, 70% isolated **75**). Methoxyacetate **75** was then transformed to **77** via the three-step sequence: (i) desilylation and hydrolysis of $C_9$ (PPTS, aqueous THF); (ii) saponification of the methoxyacetate protecting group ($Na_2CO_3$, MeOH); and (iii) hydrolysis of $C_{19}$ and equilibration of $C_9$ (*p*-TsOH, aqueous MeCN). Not surprisingly, tetraol **77** existed in a solution conformation identical to that of bryostatin 10 (**1e**) according to high-resolution $^1H$ NMR analysis.[121]

With compound **77** in hand, we focused our attention on the synthesis of the $C_{20}$-oxygenated series of bryostatins. Use of anhydride chemistry (symmetric or Yamaguchi anhydride, DMAP) for the monoacylation of **77** resulted in bisacylation to form **78** (R′ = Me or $C_7H_{11}$) (Scheme 12). This problem was effectively circumvented by using carbodiimide activation: exposure of **77** to octadienoic acid, DIC, and DMAP ($CH_2Cl_2$, 23 °C) provided a 62% yield of the monoacylated **79**. Oxidative deprotection of the two *p*-methoxybenzyl ethers at $C_7$ and $C_{26}$ was best effected (57% yield) under buffered conditions (DDQ, pH 7 phosphate buffer, $CH_2Cl_2$) in order to avoid problems with the sensitive octadienoate side chain. The bryostatin 2 (**1b**) thus obtained was identical to a natural sample by several criteria: 500-MHz $^1H$ NMR ($CDCl_3$ or $C_6D_6$, including COSY-90), TLC $R_f$, HPLC retention time (including co-injection), and EI mass spectroscopy. The conversion of bryostatin 2 (**1b**) into bryostatin 1 (**1a**) via selective silylation of the $C_{26}$ hydroxyl group has been previously described by Pettit,[8] and we have exploited analogous chemistry to convert the $C_{20}$ acetate analogue of **79** into bryostatin 6 (**1c**).[122]

**Scheme 12**[a]




[a] Key: (a) (*E,E*)-2,4-octadienoic acid, DIC, DMAP, $CH_2Cl_2$; (b) DDQ, 10:1 $CH_2Cl_2$/pH 7 buffer.

## Conclusion

The total synthesis of bryostatin 2, a biologically potent marine macrolide, has been accomplished. The synthesis proceeds over 40 steps (longest linear sequence) and entails the convergent coupling of the three intact tetrahydropyran rings, followed by macrocyclization and late-stage installation of the two enoate functional groups. The absolute stereochemistry of each fragment was established using three distinct methods: an oxazolidinone-mediated aldol reaction, a copper-catalyzed enol-silane addition, and a catalytic epoxidation with kinetic resolution. The remaining hydroxyl stereocenters were established by internal relay, with the exception of the $C_{20}$ stereocenter, which was set via an oxazaborolidine-based reduction. The synthesis plan is flexible in the late stages and is thus well suited for analogue development, a task which has the potential to shed new light on the complex biological profile of the bryostatins.[123]

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(117) Subjection of open-chain precursors of **70** to KHMDS conditions resulted in instantaneous elimination of the $C_3$-OTES group.

(118) The acid lability of the $C_9$ ketal had been a liability throughout the course of the synthesis, and all compounds (except **76**) that contained this group had to be handled carefully in order to avoid spurious hydrolysis.

(119) (a) Corey, E. J.; Bakshi, R. K.; Shibata, S.; Chen, C.-P.; Singh, V. K. *J. Am. Chem. Soc.* **1987**, *109*, 7925−7926. (b) For a review, cf.: Corey, E. J.; Helal, C. J. *Angew. Chem., Int. Ed.* **1998**, *37*, 1986−2012. (c) Interestingly, the use of the B-Me catalyst was found to be superior to the B-Bu catalyst, presumably due to the large degree of steric crowding experienced in the transition state for the reduction. In addition, borane methyl sulfide was the only suitable hydride source for the reaction.

(120) (a) The CBS reagent **74** was uniquely capable of delivering a high-yielding, stereoselective reaction; all other chiral and achiral reducing agents either delivered the wrong diastereomer or delivered the desired product in low yields. (b) The stereochemical assignment was based on three factors: (i) analogy to the reactions of a system lacking the B-ring enoate (cf. ref 1), in which the stereochemistry of both product $C_{20}$ diastereomers was determined by NMR; (ii) NOESY analysis of **77**, which showed a cross-peak between $C_{20}$H and $C_{34}$H.; and (iii) the synthesis of **1b** and **1c** (vide infra).

(121) (a) With the hydroxyl groups at $C_3$, $C_9$, and $C_{19}$ deprotected, tetraol **77** is capable of forming the bryostatin hydrogen bonding network (cf. Figure 2). Indeed, analysis of the NOESY spectrum of **77** (500 MHz, benzene-$d_6$) reveals an identical set of enhancements to that seen in the ROESY spectrum of bryostatin 10 (cf. ref 13). Additional confirmation for the establishment of the hydrogen bonding network comes from the chemical shift data for the hydroxyl protons: the $C_{19}$ lactol ($\delta$ 5.48) and $C_3$ hydroxyl ($\delta$ 4.39) protons are significantly deshielded relative to their $C_9$ ($\delta$ 1.86) and $C_{20}$ ($\delta$ 1.32) counterparts. Finally, the IR spectrum of **77** shows two distinct, sharp bands for O−H stretching (3465 and 3363 $cm^{-1}$). (b) It should be noted that compound **77** is the first in the series of synthetic intermediates to adopt the "natural" conformation depicted in Figure 2. A first-order investigation of the solution structures of earlier intermediates has indicated that it is the nature of the $C_{19}$ ketal, and not the $C_3$ hydroxyl group, that dictates the preferred solution conformation of the molecule. For a more detailed discussion, see: Carter, P. H. Ph.D. Thesis, Harvard University, 1998.

(122) Intermediate **77** was converted into bryostatin 6 (**1c**) in 27% overall yield via the following five-step sequence: (i) $Ac_2O$, pyr; (ii) DDQ, 20:1 $CH_2Cl_2$:$H_2O$; (iii) TESCl, DMAP; (iv) ($n$-PrCO)$_2$O, pyr; (v) HF/MeCN/$H_2O$, 0 °C. The material exhibited spectral characteristics (exact mass FAB-MS, 500-MHz $^1H$ NMR) completely consistent with those reported by Pettit et al.: Pettit, G. R.; Kamano, Y.; Herald, C. L.; Tozawa, M. *Can. J. Chem.* **1985**, *63*, 1204−1208.

(123) For a completely different approach to analogue development, cf. the work of Wender et al.: (a) Wender, P. A.; DeBrabander, J.; Harran, P.; Jimenez, J.-M.; Koehler, M.; Lippa, B.; Park, C.-M. *J. Am. Chem. Soc.* **1998**, *120*, 4534−4535. (b) Wender, P. A.; DeBrabander, J.; Harran, P. G.; Jimenez, J.-M.; Koehler, M. F. T.; Lippa, B.; Park, C.-M.; Siedenbiedel, C.; Pettit, G. R. *Proc. Natl. Acad. Sci. U.S.A.* **1998**, *95*, 6624−6629.

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**Supporting Information Available:** Experimental details and analytical data regarding the preparation of all synthetic intermediates, and comparison spectra of natural and synthetic bryostatin 2 (**1b**) (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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