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Synthetic studies on the A83586C and bryostatin antitumor macrolides and the monamycin antibiotics*

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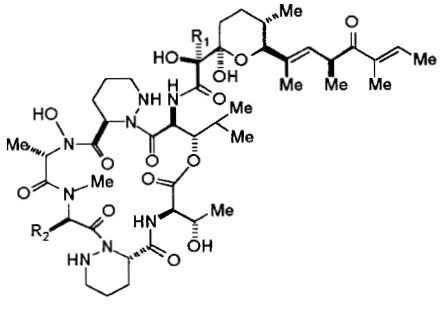
Abstract: After a brief summary of our asymmetric total syntheses of A83586C and 4-*epi*-A83586C, we will go on to describe some of our synthetic work on the monamycins, and our most recent total synthesis studies on the bryostatin antitumor macrolides.

INTRODUCTION

Pharmacologically active complex natural products and their synthetic analogues continue to provide fascinating insights into the mechanisms of many important biological processes, and for this reason, chemical interest in the synthesis of such structures remains high [1]. In this mini-review, we will highlight several total synthesis programs that are currently being carried out in our laboratories, two of which were initiated with important cancer biology goals in mind.

DELINEATING THE ROLE PLAYED BY E2F TRANSCRIPTION FACTOR COMPLEXES IN PROLIFERATIVE DISEASE THROUGH USE OF PROBES BASED ON THE A83586C/GE3 CLASS OF ANTITUMOR ANTIBIOTICS

E2F transcription factors are heterodimeric proteins found in all eukaryotes [2]. They bind to and stimulate the transcription of genes necessary for S-phase entry and cellular proliferation (e.g., DNA-polymerase-α, dihydrofolate reductase, thymidine kinase, cyclins A/E, E2F1, cdc-2). In normal cells, many E2F transcription factors have their biological behavior tightly regulated by reversible complexation with the retinoblastoma protein (pRb). However, in a large number of cancers, the pRbs are deleteri-



A83586C, R_1 = Et, R_2 = Me
GE3, R_1 = Me, R_2 = $CH_2CH(Me)_2$

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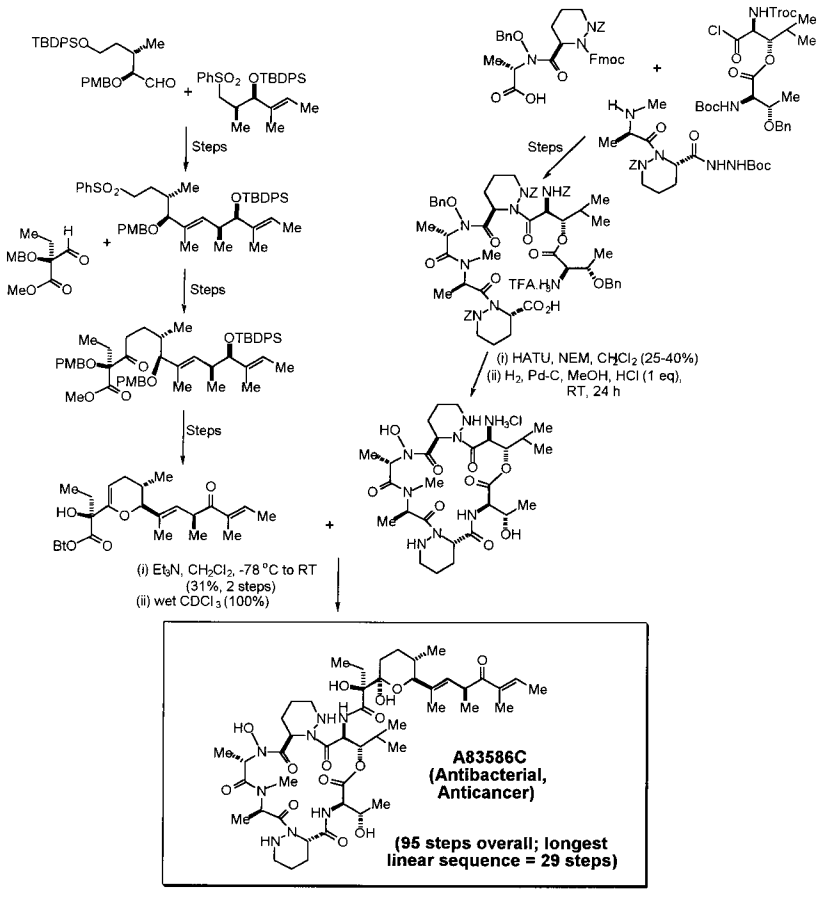
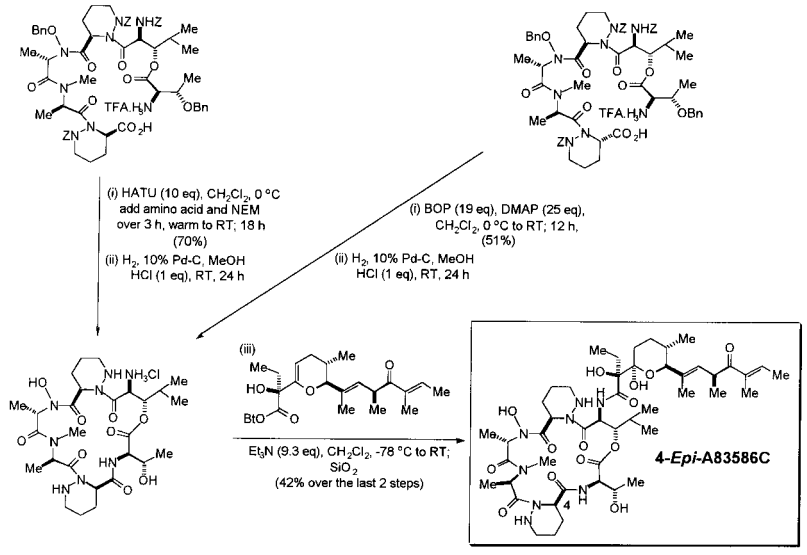
ously mutated or functionally inactivated, with the consequence that they can no longer bind E2Fs. This means that the latter can continuously drive transcription and uncontrolled cell division. Small molecule inhibitors of E2F activity might serve as powerful new antiproliferative drugs, and for this reason, there is substantial pharmaceutical interest in the development of such therapeutics. Controlled inhibition of E2F might not only provide an effective drug treatment for many cancers, it could also provide a reliable method for controlling vascular diseases such as artherosclerosis, vein graft disease, postangioplasty restenosis, and transplant vasculopathy [3]. The proliferation of vascular smooth muscle cells is now widely regarded as a key event in plaque formation in primary artherosclerosis, and it is intimately associated with entry into cell cycle. It also occurs rapidly following vascular injury, being strongly stimulated by growth factors produced by damaged vascular cells; these include platelet-derived growth factor, angiotensin II, and basic fibroblast growth factor. Such proliferation can often result in the formation of a major vascular occlusion. The latter is one of the most frequently cited causes of failure in human bypass surgery and balloon angioplasty [3,4]. Inhibiting E2F could thus lead to significant new breakthroughs in cardiovascular medicine.

One noteworthy family of natural products that can inhibit E2F are molecules of the A83586C/GE3 class [5,6]. At present, little is known about how these compounds function in this capacity. Structurally related probe molecules might significantly improve our understanding of the molecular events surrounding inhibition of E2F by these drugs, and it was with their creation in mind that we completed the first asymmetric total synthesis of A83586C in July 1997. The pathway that was developed is summarized below (Scheme 1) [7].



Scheme 1 Summary of the first asymmetric total synthesis of antitumor antibiotic A83586C [7].

The hallmark of our synthesis was the highly chemoselective endgame that was implemented. It featured a remarkable "biogenetically modelled" union between two fully elaborated fragments devoid of all protecting group functionality, and afforded a glycal that could readily be coaxed into undergoing a highly chemo- and regioselective hydration reaction at C(30) to install the hemiketal unit found in the natural product. Significantly, this transformation was accomplished without perturbation of other delicate functionality within the target structure. We had long considered that a strategy that completely dispensed with protecting groups at the final stages would be a prerequisite for success in the A83586C venture, given the significant amount of acid-, base-, and nucleophile-sensitive functionality embedded within its skeletal array, and its known susceptibility to oxidation and reduction.

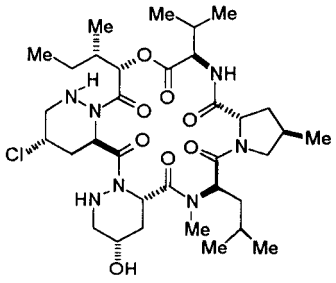


Scheme 2 Synthetic routes to 4-epi-A83586C; the first synthetic analog of the GE3/A83586C class [8].

As a direct consequence of our synthesis, the first totally synthetic analogs of the A83586C/GE3 class of antitumor antibiotics were recently made available to biologists, who are now evaluating their effects on E2F transcriptional behavior. It is hoped that probe molecules such as 4-*epi*-A83586C [8] (Scheme 2) might provide powerful new insights into the detailed mechanistic workings of the various E2F/DP proteins, and allow the identification of important new therapeutic targets for the future treatment of proliferative disease.

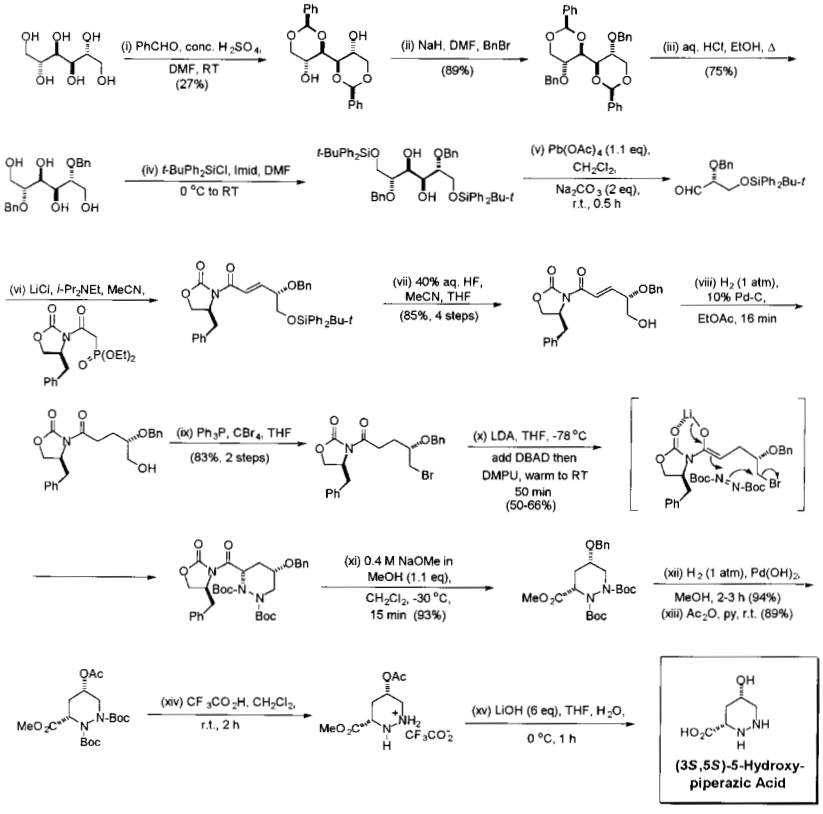
DEVELOPMENT OF THE TANDEM ELECTROPHILIC HYDRAZINATION-NUCLEOPHILIC CYCLIZATION REACTION FOR BUILDING FUNCTIONALIZED PIPERAZIC ACID DERIVATIVES; APPLICATIONS TO A FUTURE MONAMYCIN H_1 SYNTHESIS

One of the main synthetic dividends that arose from our work on A83586C was our development of the tandem electrophilic hydrazination/nucleophilic cyclization protocol for building functionalized piperazic acid derivatives in homochiral form [9,10]. Not only did this advance underpin our success in the A83586C undertaking, it also provided us with the vehicle needed for performing subsequent synthetic work on other antibiotic classes, most notably the monamycin cyclodepsipeptides [11]. In this regard, we recently completed the first enantiospecific total synthesis of (3*S*,5*S*)-5-hydroxypiperazic acid and (3*R*,5*S*)-5-chloropiperazic acid, through use of this tandem process in the key ring-assembly steps. Both of these molecules are constituents of the most potent and complex member of this family, monamycin H_1. Our methodological work in this area has thus provided the technology needed for a future total

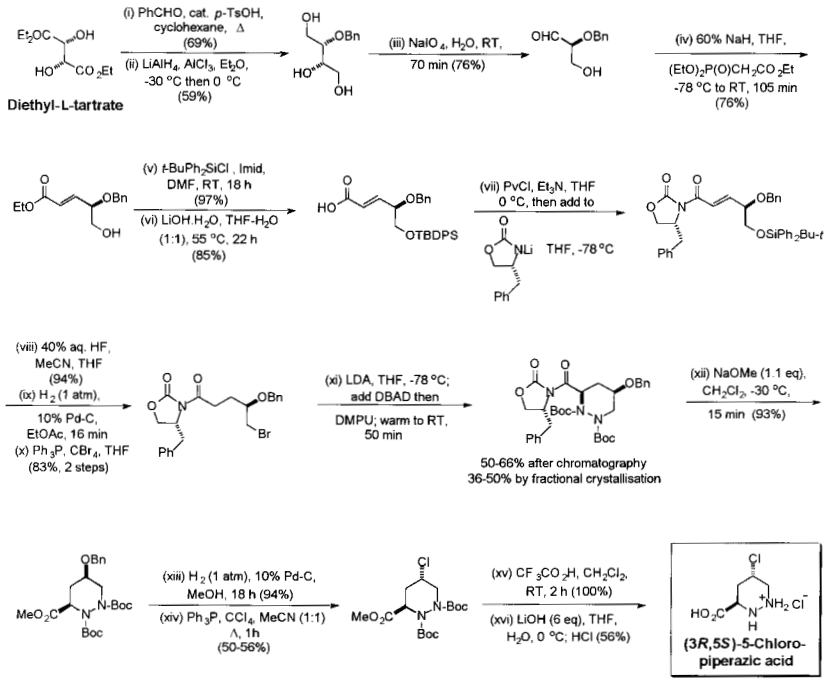


Monamycin H_1

synthesis of a monamycin antibiotic. Our original route to (3*S*,5*S*)-5-hydroxypiperazic acid began from D-mannitol and is shown in Scheme 3 [10]. While it was fully amenable to the production of multigram quantities of the target compound, it was not that readily adapted to the preparation of the (*3R*,5*R*)-enantiomer nor to (3*R*,5*S*)-5-chloropiperazic acid. In light of this, we decided to reexamine the problem, and recently formulated a new synthetic approach that allows all three piperazic acid derivatives to be obtained from diethyl tartrate. The new reaction sequence harnesses methodology originally developed by Jager for the production of homochiral ethyl-4-*O*-benzyl-4,5-dihydroxy-2-pentenoate [12]. Its basic concepts are illustrated in Scheme 4 for the synthesis of (3*R*,5*S*)-5-chloropiperazic acid.



Scheme 3 Our first-generation enantiospecific synthesis of (3*S*,5*S*)-5-hydroxypiperazic acid.

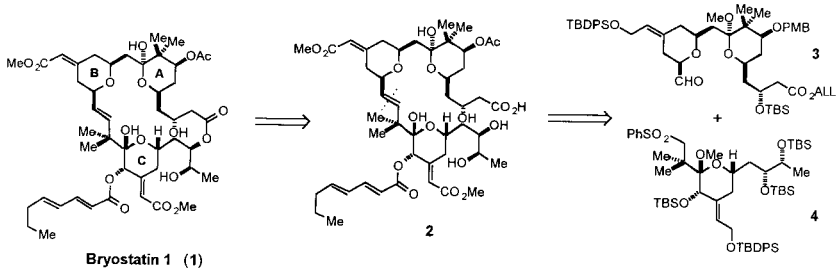


Scheme 4 First enantiospecific synthesis of (3*R*,5*S*)-5-chloropiperazic acid.

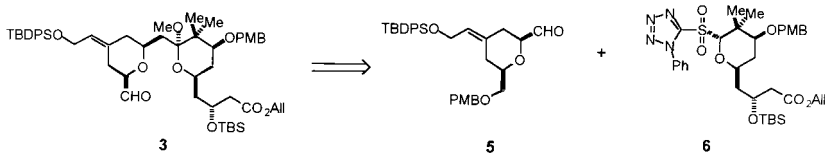
BRYOSTATINS, PROTEIN KINASE C MODULATION, AND THE BRYOSTATIN SYNTHETIC CHALLENGE

Bryostatin 1 is a novel protein kinase C (PKC)-modulating macrolactone showing exceptional antitumor properties against a range of murine tumors that include P388 lymphocytic leukemia, B16 melanoma, and M5076 reticulum cell sarcoma [13]. On account of these favorable pharmacological effects, bryostatin 1 was recently selected for phase II anticancer trials in humans [14], and in this capacity has already elicited a number of very favorable antitumor responses, one patient now having been completely cured. Given these encouraging findings, and the fact that bryostatin 1 remains exceedingly scarce in nature, synthetic interest in the bryostatins has continued to grow [15,16]. Currently, the most sought-after prize in the area is a synthetic route that will completely satisfy all future clinical demand. With this in mind, we took up the bryostatin synthetic challenge some years ago.

Our latest retrosynthetic analysis of bryostatin 1 is summarized in Scheme 5. A "biomimetic" macrolactonization on *seco*-acid **2** is envisaged for forming the 20-membered macrocycle of the natural product. A Julia olefination is planned for installation of the C(16)-C(17)-(*E*)-disubstituted olefin, and a Kocienski olefination [17] is envisioned for connecting **5** with **6** (Scheme 6).

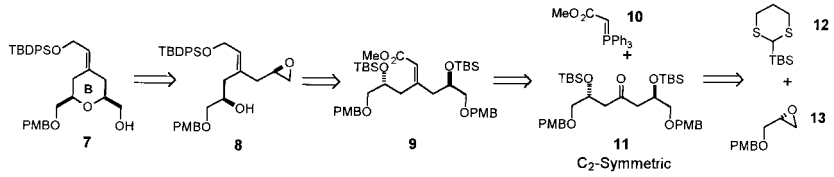


Scheme 5 Retrosynthetic analysis of bryostatin 1.



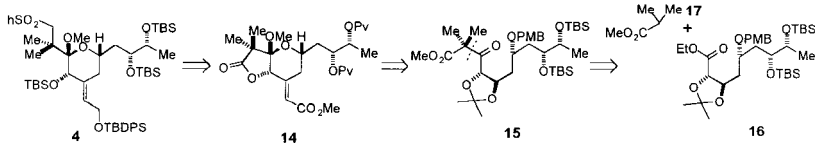
Scheme 6 Retrosynthetic analysis of the AB-ring system.

It was felt that if we could olefinate a C_2-symmetrical ketone such as **11**, then this could offer substantial synthetic advantages for controlling the remote exocyclic olefin geometry in the bryostatin B-ring, particularly if it were combined with an intramolecular Williamson etherification reaction to construct the pyran system, and a Smith–Tietze TBS-dithiane coupling tactic [18] to assemble the target ketone **11** (Scheme 7).



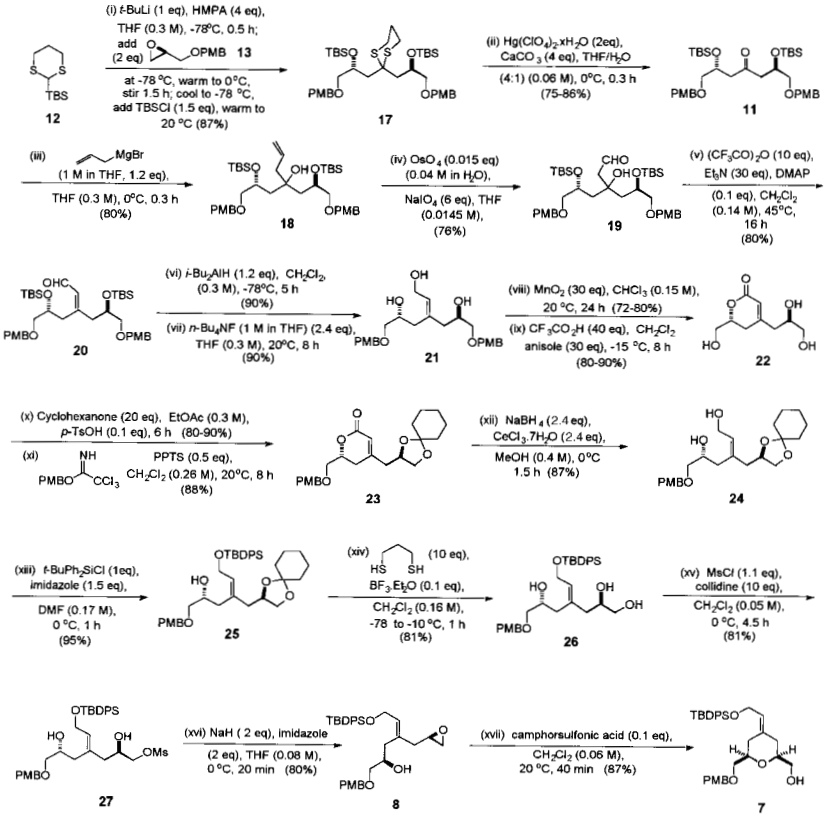
Scheme 7 Use of a C_2-symmetry-breaking tactic to control bryostatin B-ring olefin geometry.

Our retrosynthetic planning for the bryostatin 1 C-ring identified bicyclic lactone **14** as a key intermediate, and proposed the use of a stereospecific Wittig olefination to introduce the exocyclic double bond (Scheme 8). Further unravelling of the bicyclic array in **14** subsequently allowed β-keto ester **15** to be selected; its most logical site for disconnection was across its C(18)–C(19) bond through retro-Claisen condensation. The latter operation yielded ester **16**, all of whose stereocentres appeared installable through a series of Sharpless catalytic AD reactions on appropriate alkene precursors. With this as background, we will now describe recent progress.



Scheme 8 Our retrosynthetic strategy for the bryostatin 1 C-ring.

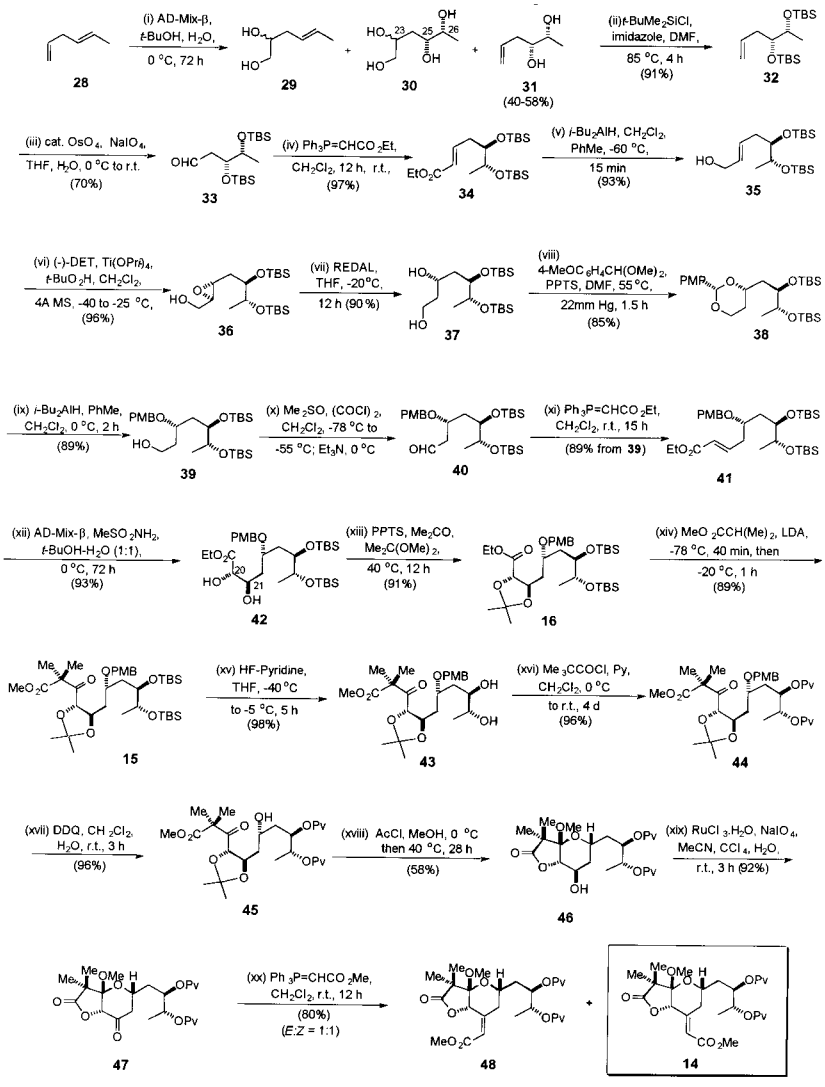
The route developed to the bryostatin B-ring is presented in Scheme 9 [16a]. It commenced with a Smith–Tietze bis-alkylation reaction [18] between 2-lithio-2-TBS-dithiane and the homochiral epoxide **13** [19], available in one step from commercially available (*S*)-glycidol. This afforded an intermediary alkoxide which was *O*-silylated *in situ* with TBSCl to give the product dithiane **17** in 87% yield. The thioketal unit of **17** was then detached with mercuric perchlorate in aq. THF. Unfortunately, the liberated ketone **11** was an unwilling participant in all relevant Wittig and Peterson olefination processes that we examined. Given these difficulties, an alternative method for the olefination of **11** was sought. After considerable effort, a solution to this problem was eventually found. Ketone **11** was reacted with allylmagnesium bromide to obtain **18**, and its double bond oxidatively cleaved. The resulting aldol adduct **19** was then subjected to a β-elimination to obtain **20**. 1,2-Reduction of **20** with DIBAL and *O*-desilylation finally delivered triol **21**. The latter was a key intermediate in the pathway we had originally formulated.



Scheme 9 A completely stereocontrolled route to the bryostatin B-ring.

We were now faced with the challenging prospect of having to differentiate between two partially masked terminal 1,2-diol units that were in a fairly similar environment. This was accomplished through chemoselective oxidation of the allylic alcohol in **21** with MnO_2. Initially, this afforded an enal which immediately underwent hemiacetalization and subsequent conversion to the α,β–unsaturated lactone in excellent yield. To complete the diol differentiation process, it was necessary to detach both PMB groups from this product with TFA/anisole [20], and block the hydroxyl groups of **22** with cyclohexylidene and PMB groups to obtain **23**. The lactone unit was then reductively ring-opened under Luche conditions [21] to procure diol **24**. The primary alcohol in **24** was now protected as a TBDPS ether, and the cyclohexylidene group chemoselectively removed with 1,3-propanedithiol and catalytic $BF_3.Et_2O$ at low temperature [22]. As long as the course of this reaction was carefully monitored by TLC, and due care was paid to keeping the temperature below –10 °C, high yields of the desired triol **26** could be isolated routinely. Regioselective *O*-mesylation was the next step in the synthesis. It was best accomplished using the mesyl chloride-collidine system of O'Donnell and Burke [23]. We had hoped that the dihydroxymesylate **27** would be directly convertible to **7** by treatment with 2 equiv. of NaH. However, these conditions only afforded the δ-hydroxy epoxide **8** in 80% yield. In order to bring about the desired pyran ring-closure process it proved necessary to treat **8** with cat. camphorsulfonic acid in CH_2Cl_2 [24]. This furnished pyran **7** in 87% yield as the sole reaction product, completing this completely stereocontrolled route to the bryostatin B-ring (6.34% overall yield from **12**).

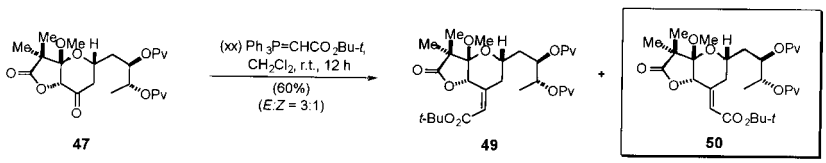
Turning attention now to the C-ring chemistry that has so far been developed [16b], at first we set about introducing the C(26), the C(25)- and the C(23)-hydroxy stereocenters of the C-ring sub-sector through a Sharpless AD reaction [25] on (*E*)-1,4-hexadiene with excess AD-mix-β (Scheme 10). While this reaction worked well at installing the C(25) and C(26)-hydroxyls with high stereocontrol, the sec-



Scheme 10 Route to the C-ring framework of bryostatin 1.

ond AD process on the terminal alkene proceeded without control, affording an inseparable 1:1 mixture of epimers at the C(23)-position. Given this limitation, we took a step back and focused on the selective dihydroxylation of **28** with a limited quantity of AD-mix-β (0.6 equiv), as described by Sharpless *et al.* [26]. Typically, this provided the volatile diol **31** in 45–59% yield and 94% ee. Our plan now was to introduce the C(23)-stereocenter through Sharpless asymmetric epoxidation [27]. After blocking the hydroxyls in **31** with TBSCl, the double bond of **32** was oxidatively degraded with cat. OsO_4 and $NaIO_4$, and the product aldehyde **33** taken forward to the allylic alcohol **35** by Wittig reaction and DIBAL reduction. The Sharpless AE on **35** proceeded efficiently and rapidly, enriching the optical purity of the product to 96% ee. Regioselective deoxygenation of **36** was next effected with REDAL; this produced the 1,3-diol **37** in good yield. Now we needed to selectively position a PMB group on the C(23)-OH, oxidize the C(21)-hydroxyl to the aldehyde, and implement a Wittig reaction on **40** with $Ph_3P{=}CHCO_2Et$. All these reactions proceeded satisfactorily and furnished the desired enoate **41** as a single geometrical isomer in 89% overall yield from **39**. A Sharpless AD reaction on **41** with AD-mix-

β was used to set the C(20)-hydroxyl stereochemistry; it furnished diol **42** as essentially a single diastereoisomer. Protection of this functionality was deemed essential for successful implementation of the Claisen condensation process. Happily, the isopropylidenation and Claisen coupling steps both worked well; the desired β-keto ester **15** being isolated in 81% yield from **42**. The next phase of the synthesis was removal of the *O*-isopropylidene group with acidic methanol, and *in situ* butyrolactonization upon the C(20)-hydroxyl. We anticipated that the latter process would allow the C(20)- and C(21)-hydroxyl groups to be differentiated, and would set the stage for a tandem Fischer glycosidation [28] at C(19). Reasoning that installation of an electron-withdrawing ester group at C(20) would probably necessitate us using fairly forcing acidic conditions to bring about the desired glycosidation, we considered it best to replace the two TBS protecting groups of **15** with more acid-stable *O*-pivaloyl esters. The PMB ether was detached from **44** with DDQ to provide **45**. Treatment of compound **45** with methanolic HCl afforded the expected methyl glycoside **46** in 58% yield. A Sharpless oxidation [29] with $RuCl_3/NaIO_4$ subsequently provided ketone **47**, which reacted with $Ph_3P{=}CHCO_2Me$ to furnish a 1:1 mixture of exocyclic alkenes **14** and **48**, which were separated by preparative TLC. Wadsworth–Horner–Emmons conditions with $MeO_2CCH_2P(O)(OMe)_2$ gave similar results. Clearly, the butyrolactone unit was insufficiently bulky to direct the stereochemical course of olefination in favor of the desired product **14**. Given this impasse, we elected to investigate the effect of increasing the steric bulk of the ester component in our phosphorus ylide. To our delight, changing the ester alkoxy from OMe to OBu-*t* improved the stereoselectivity of olefination to 3:1 in favor of the desired isomer **50** (Scheme 11). Given this encouraging result, we are now modifying our synthetic pathway to provide an α-alkoxy ketone with a substantially more bulky protecting group on the C(20)-oxygen (e.g., a TES or TBS or PMB ether). Hopefully, these combined tactics will ultimately allow for the completely stereocontrolled introduction of the C-ring exocyclic olefin. Isomerization tactics might also prove useful here in the event of a mixture still being obtained. All of these studies will be the subject of future reports.



Scheme 11 Improving the stereoselectivity of the Wittig olefination of ketone 47 through use of a more sterically demanding ylide.

CONCLUSIONS

To summarize, we have accomplished the first total synthesis of the antitumor antibiotic A83586C through use of a novel, highly chemoselective, coupling strategy. Our work on this project has paved the way for the synthesis of novel probe molecules based on the A83586C/GE3 structure. Such molecules might prove useful for delineating the biological functioning of many individual E2F transcription factors, and provide powerful new insights into the events controlling the early stages of mammalian cell cycle. Ultimately, such work could lead to the development of a completely new class of antiproliferative drugs which could have a substantial impact on future cancer treatment and cardiovascular medicine.

Our efforts in the A83586C area have also resulted in the introduction of the tandem electrophilic hydrazination/nucleophilic cyclization protocol for building functionalized piperazic acids, and as a consequence, the prospects for achieving a future synthesis of the monamycins now look substantially enhanced.

Research by our group in the bryostatin field is also now starting to bear fruit. We have devised a fully stereocontrolled asymmetric synthesis of an appropriately protected bryostatin B-ring intermediate through exploitation of a subtle C_2-symmetry-breaking tactic for the control of exocyclic olefin geometry. We have also shown that it is possible to direct the stereochemical outcome of Wittig olefinations on C(20)-substituted C-ring ketone intermediates through use of sterically bulky ylides such as *t*-$BuO_2CCH{=}PPh_3$. Further synthetic work on the bryostatin class will be reported in due course.

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