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Asymmetric synthesis and its applications: towards the synthesis of bryostatin 1

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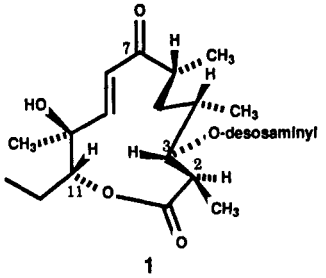
Abstract – After a brief introduction that outlines our general strategy for the stereoselective synthesis of complex natural products, based on the rule of multiple asymmetric synthesis, this article will present a critical evaluation of reagents recently developed to effect asymmetric aldol and allyl- and crotylboration, perhaps the two most important carbon, carbon bond forming reactions in the synthesis of polyketide-type natural products. Some emphasis will be placed on the mechanistic and synthetic aspects of newly discovered (*R*-) and (*S*)-2-trimethylsilylborolane mediated reactions.

The latter half of the article will deal with the application of these reactions as illustrated by our work directed towards the synthesis of bryostatin 1, $C_{47}H_{68}O_{17}$, a marine natural product isolated in minute quantities from *Bulgula neritina*. Bryostatins are potential anti-leukemic agents.

INTRODUCTION

In the twenty year development of our macrolide project, two events stand out, the synthesis of methylmycin (1) (1975) (ref. 1) and 6-deoxyerythronolide B (2) (1981) (ref. 2). The former synthesis established that the seco-acid corresponding to a macrolide could be macrolactonized and the latter led to the establishment of a general strategy for acylic stereoselection, based on the rules of double asymmetric synthesis (ref. 3). In the reaction of a chiral substrate with a chiral reagent, the use of an *S* or *R* reagent with



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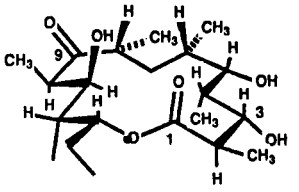
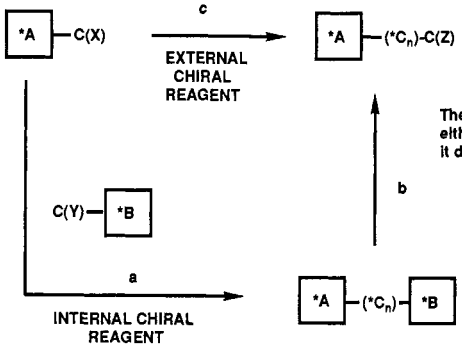


2

a large diastereofacial selectivity enhances the apparent facial selectivity of the substrate in the matched pair reaction and overrides it in the mismatched pair reaction. In this way the stereochemical course of the reaction is controlled by the reagent. This mutual stereochemical interaction between two reactants, represented in Process 1, creates a stereogenic center or centers on a chiral substrate and can be executed in two different ways. Reaction of the substrate A*-C(X) with a selected "internal" reagent *B-C(Y) (step a)

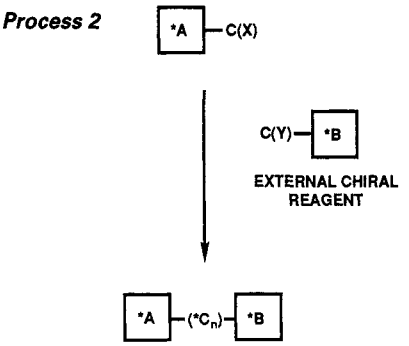
Process 1



The reaction involving a chiral reagent provides the product which either does or does not contain the chiral moiety of the reagent. If it does, the reagent is called 'INTERNAL', and if not, 'EXTERNAL'.

provides the product which contains, in addition to newly formed stereogenic centers, the chiral moiety of the reagent. The chiral moiety must be removed (step b) in order to obtain *A-*C_n-C(Z) which is ready for further transformation. This pathway (a + b) has been utilized widely, but is obviously circuitous, and one

can conceive of an "external" chiral reagent capable of directly converting *A-C(X) into *A-(*C_n)-C(Z) (step c) (ref. 4). While the advantage of the "external" chiral reagent over the "internal" one in Process 1 is clear, the crucial role of the former becomes even more evident in Process 2 which involves the assembly of the two prefixed chiral fragments with the concomitant creation of a stereogenic center or centers. Consider the case where two fragments *A-C(X) and *B-C(Y) are combined via an aldol reaction. One general way

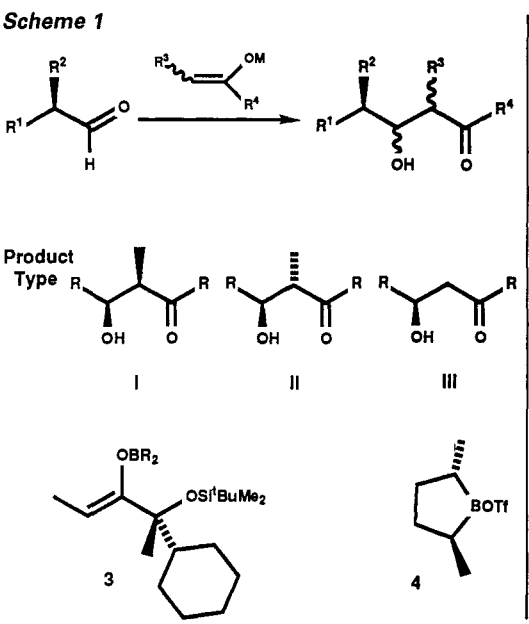


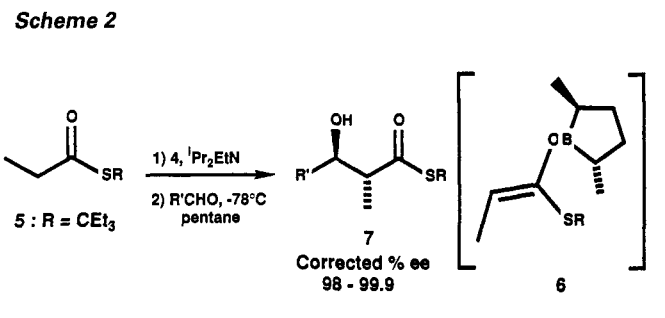
to gain stereochemical control is to incorporate in the reaction system a third chiral component, which can be selected. Thus, *B-C(Y) may be converted to the enolate containing a chiral moiety which exerts a dominant effect in determining the stereochemical course of the reaction.

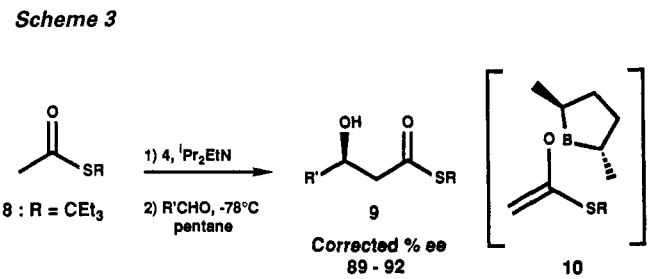
Processes 1 and 2 formulate two fundamental general transformations for which stereochemical control is urgently demanded. In viewing the progress of macrolide synthesis, it is seen that macrolide stereochemistry has developed into a more general problem of acylic stereocontrol which is in principle reduced to the preparation of chiral reagents and catalysts. This article first summarizes synthetic methodologies for aldol reactions and allylboration that have been recently developed for asymmetric C-C bond formation and then describes the application of the methodologies to our synthetic studies towards bryostatin 1.

THE ALDOL REACTION

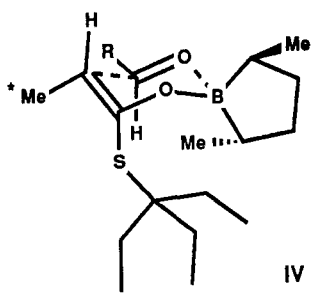
The aldol reaction shown in Scheme 1 provides three important types of β-hydroxycarbonyl compounds I-III. The "internal" reagent 3 has been extensively utilized (ref. 5), but our attention has been directed to preparing "external" enolate reagents using *trans*-2,5-dimethylborolanyl triflate 4 (ref. 4). Treatment of (*S*)-3-(3-ethyl)pentyl propanethioate 5 with the borolanyl triflate 4 in the usual manner (Scheme 2) provides the corresponding (*E*)-enolate 6 with a 30:1 anti-syn ratio and the aldol reaction of several achiral aldehydes (e.g., R=Propyl, isopropyl, *tert*-butyl, cyclohexyl) with 6 leads to the formation of the corresponding anti-β-hydroxy-α-methyl thioesters (7) of 98-99% ee. Replacing the propanethioate 5 by the ethanethioate 8 in the same reaction (Scheme 3) yields the β-hydroxycarbonyl product 9 through the enolate 10. In these aldol reactions with 10 the % ee's of the products decrease to roughly 90 (from 99 observed for those with 6).



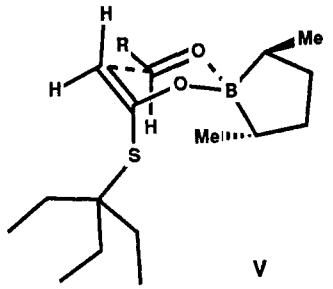




This decrease in facial selectivity is readily rationalized. In the presumed Zimmerman-Traxler transition state IV with the (*E*)-enolate, the asterisked methyl group "steers" the bulky thio group towards the borolane moiety, the chirality of which is thus transferred effectively. In the absence of this "steering effect", as may be the case for transition state V for reactions with **10**, the enantioselection decreases.



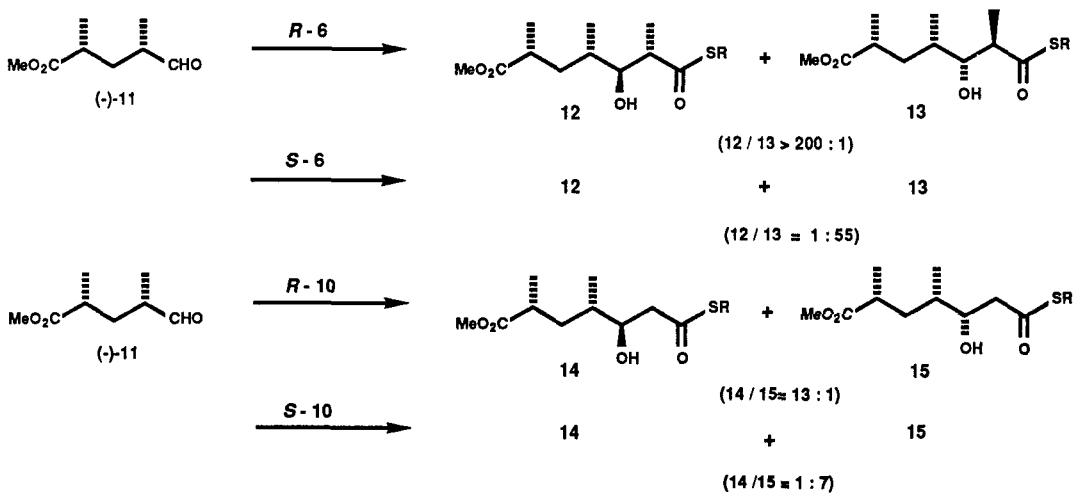
IV



V

A set of double asymmetric reactions have been carried out (Scheme 4) (ref. 6). Reactions of the aldehyde **11** with the *R* and *S* enolates [(*R*)-**6**, (*S*)-**6**] lead to the 2,3-anti aldols **12** and **13** with a **12**/**13** ratio of >200:1 for the matched pair and a 1:50 ratio for the mismatched pair. With the *R*- and *S*- enolates [(*R*)-**10**, (*S*)-**10**], these ratios decrease, as expected, to 13:1 and 1:7 for matched and mismatched pairs, respectively. While the reagent **6** is clearly capable of controlling the aldol stereochemistry, reagent **10** is placed in the borderline category as a reagent for effective double asymmetric synthesis.

Scheme 4



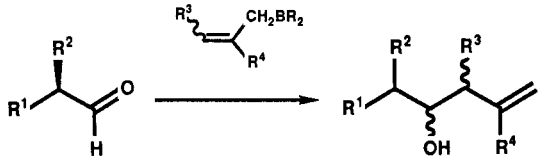
It should be added here to what extent one can attain face-selection in the aldol reaction using the enolates derived from methyl ketones. This problem has a direct bearing on Process 2 that connects two chiral fragments with the concomitant formation of a stereogenic center or centers. When the chiral enolates generated from three representative methyl ketones (RCOMe, R=cyclohexyl, *tert*-butyl, phenyl) and **4** are allowed to react with isobutyraldehyde, the enantio purity of the resulting 3-hydroxyketones ranges between 30-60%. We must conclude at this stage that the aldol methodology in Process 2 is useful only for matched pair reactions and a few examples will appear shortly in the bryostatin synthesis. Further design of new reagents is being intensely pursued.

ALLYL- AND CROTYLBORATION

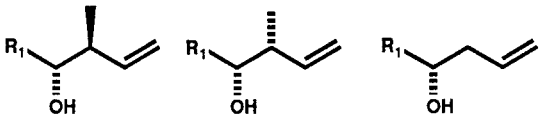
Allyl- and crotylboration, reactions pioneered by R.M. Hoffmann (ref. 7), effect a nucleophilic addition to provide the corresponding homoallylic alcohols (Scheme 5). These reactions are synthetically equivalent to the aldol reaction and there are three important types of homoallylic products VI-VIII, for which the three borane reagents **16**-**18** are readily conceivable.

(*E*)-(*S*,*S*)-Reagent **16** readily adds to achiral aldehydes to provide, with a 20/1 anti-syn selectivity, the anti-homoallylic products **19** of 95-97% ee. Crotylboration with the corresponding (Z)-reagent **17** proceeds similarly to yield predominantly the syn products **20** of slightly decreased % ee, 86-97 (Scheme 6). Double

Scheme 5

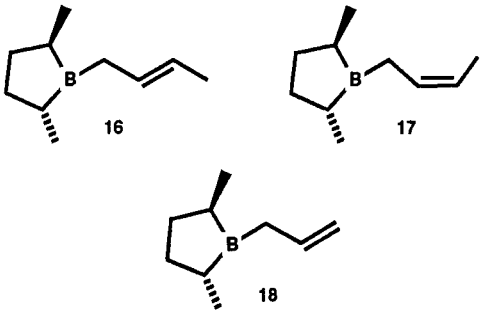


Product Type



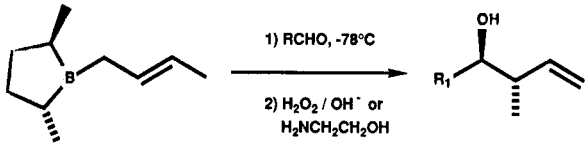
VI VII VIII

Reagents



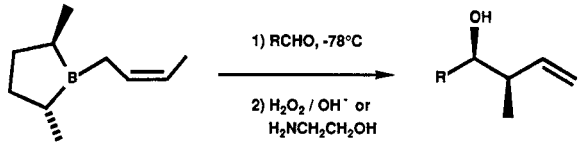
16 17 18

Scheme 6



(*E*) - (*S*, *S*) - 16

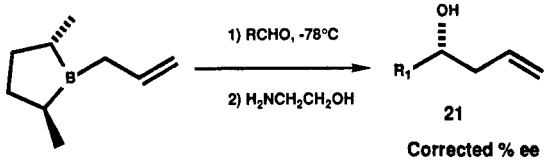
19
Corrected % ee
95 - 97



(*Z*) - (*S*, *S*) - 17

20
Corrected % ee
86 - 97

Scheme 7

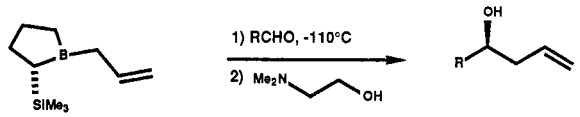


(*R*, *R*) - 18

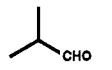
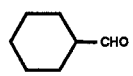
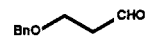
21
Corrected % ee
85 - 93

asymmetric reactions with (*R*)-glyceraldehyde acetonide show that matched reactions with (*E*)-(*R*,*R*)-**16** and (*Z*)-(*R*,*R*)-**17** provide the expected diastereomeric homoallylic alcohols with high ratios (48:1, 99:1) and mismatched ones with (*E*)-(*S*,*S*)-**17** low ratios (1:7.6, 1:5.7), in conformity with the rule of double asymmetric synthesis. Allylboration with achiral aldehydes proceeds with somewhat decreased stereoselectivity, the % ee of the homoallylic products **21** being 85-93 (Scheme 7). In this connection the reagent (*S*)-**22**, *B*-allyl-2-(mono)-trimethylsilylborolane should be mentioned (ref. 8). Reagent **22** does achieve better enantioselectivity (89-95% ee, Table 1) than *B*-allyl-2,5-dimethylborolane **18**, and can be prepared much more readily than the latter. After the reaction trimethylsilylborolane can be recovered without loss of optical purity. The mechanistic aspect of this allylboration is interesting. In brief, from the inspection of the absolute configuration of the product, one arrives at the conclusion that the aldehyde is approaching

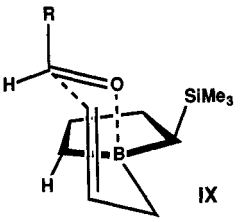
Table 1



S - 22

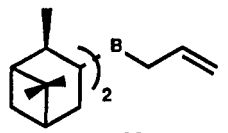
Entry	Aldehyde	Isolated Yield %	Corrected %ee (Conf.)
1		82	96 (*S*)
2		86	96 (*S*)
3		82	96 (*S*)
4		82	96 (*S*)

the borolane from the trimethylsilyl side of the ring as depicted in IX. The question of whether the TMS group is acting as a steric bulk or is attracting the carbonyl group through chelation is currently under investigation.



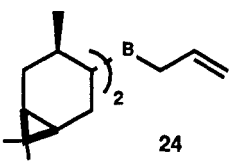
IX

Before concluding this discussion of the C,C bond forming reactions, some other reagents should be listed. Excellent allyborating reagents (**23-25**) have recently been developed by H.C. Brown (ref. 9) and W. R. Roush (ref. 10), the ranges of % ee achieved are shown below. Mention also should be made of a



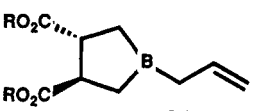
23

83 - 96%ee



24

86 - 99%ee

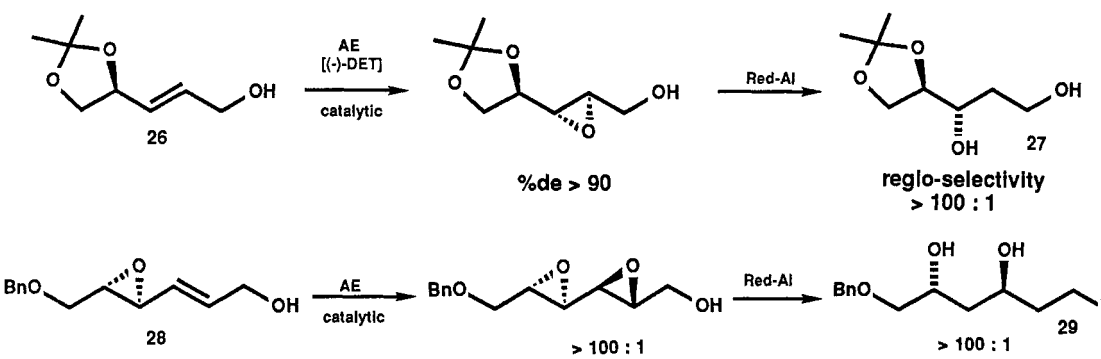


25

71 - 87%ee

Brown, H. C. **Roush, W. R.**

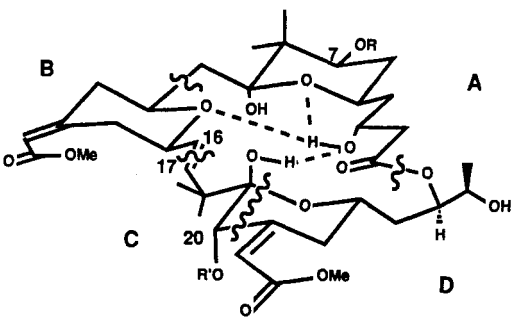
Scheme 8



somewhat older but reliable route for the construction of the 1,3-diol system that involves a combination of Sharpless epoxidation and Redal reduction, as shown in Scheme 8 (**26**→**27**; **28**→**29**) (ref. 11). In summarizing the current status of stereochemical control with respect to the above carbon, carbon bond forming reactions, nearly perfect chiral reagents are now at hand for either acetate or propionate addition to chiral substrates, whereas stereoselective aldol reactions with methyl- and ethylketones demand the development of improved external reagents. How this status is reflected on the total synthesis of bryostatin will be shown in the following section.

TOWARDS THE SYNTHESIS OF BRYOSTATINS

Massive efforts of Pettit, Kamano and their groups at Arizona in isolating antileukemic agents have yielded 13 bryostatins in recent years (ref. 12). All of them are structurally similar, but bryostatins 1, 2, 4-10 differ in the substituents at the C(7) and C(20) positions and bryostatins 11-13 lack a substituent at C(20). For bryostatin 1 (**30**), R and R' are acetyl and octa-2,4-dienoyl, respectively. The source of these bryostatins is *Bugula neritina*, fouling organisms that are attached to and grow on ship hulls. The extracts of the



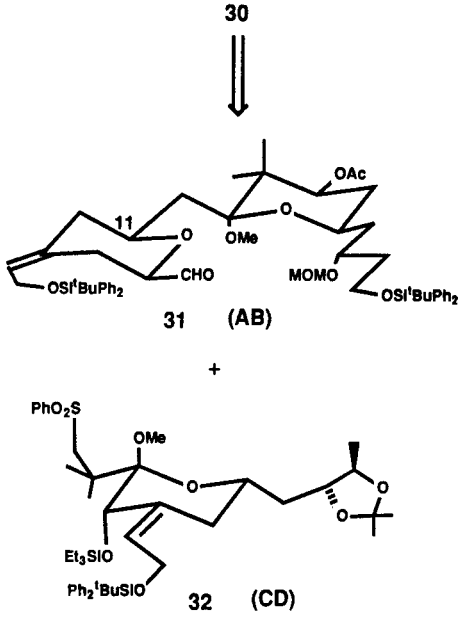
Bryostatin 1 (30)

R = Ac ;
R' = octa - 2,4 - dienoyl

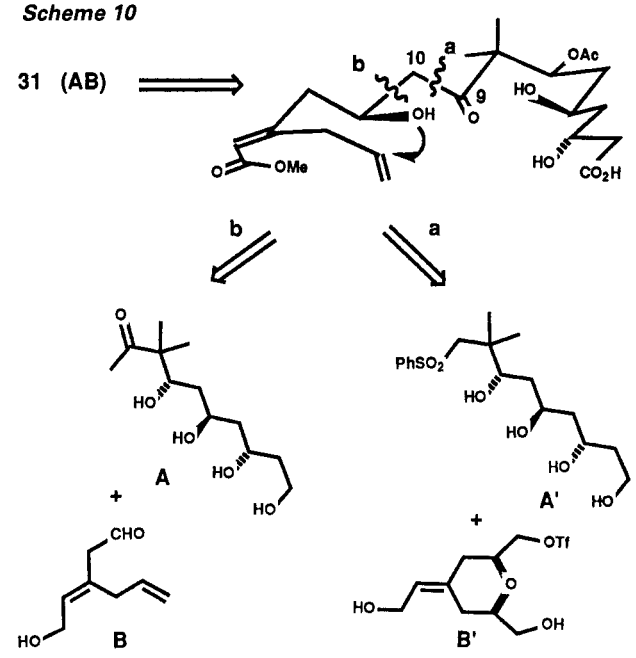
marine natural products have been screened against the marine P388 *lymphocytic leukemia*. One ton of wet organism yields only 630 mg of bryostatin 1, the most abundant member, and much lesser amounts of other members which are apparently more physiologically active. Since bryostatins are now in Phase 2 of clinical tests and the entire process of the isolation apparently requires one good year of "hard labor", the synthetic approach to bryostatins appears well justified in terms of their supply even for screening.

The logical retrosynthetic dissection of bryostatin 1 is rather straightforward: Cleavage of the lactonic linkage and the C(16) - C(17) double bond leads to the two major fragments AB (31) and CD (32) (Scheme 9).

Scheme 9



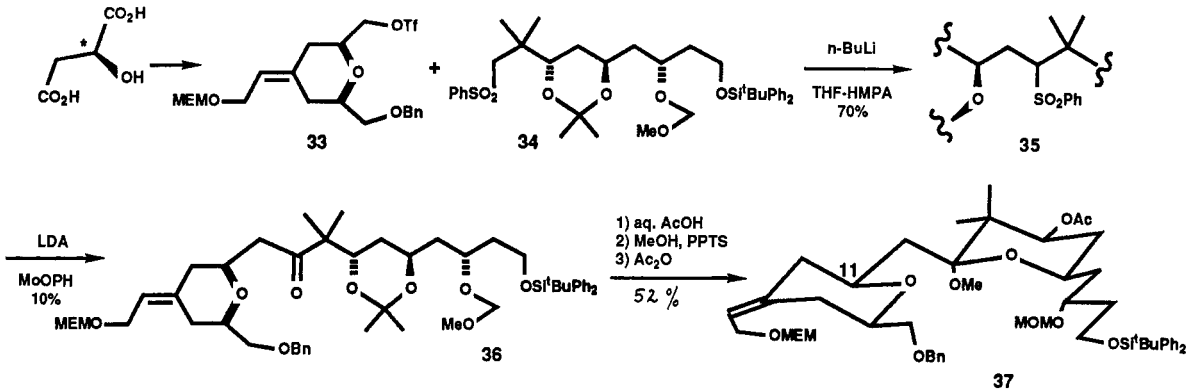
Scheme 10



Fragment AB (31) can be further dissected either through the C(9) - C(10) bond (a) or the C(10) - C(11) bond (b), generating fragments A' + B' and A + B (Scheme 10). Since the A',B' assembly does not involve the creation of a new stereogenic center, whereas the A,B assembly does, the former approach was first examined.

The construction of the AB fragment is outlined in Scheme 11, omitting the processes leading to 33 and 34. Despite the neopentyl type substitution the monoanion generated from 34 undergoes a smooth S_N2 type substitution reaction with the triflate 33 even in the presence of the β-alkoxy substituent. This is expected from our earlier experiments encountered in the amphotericin B synthesis (ref. 13). However, generation of a ketone functionality from the resulting β-alkoxysulfone 35 through the Little procedure (ref. 14) provided a maximum yield of only 10%, so despite the successful construction of 37 from 36, the first

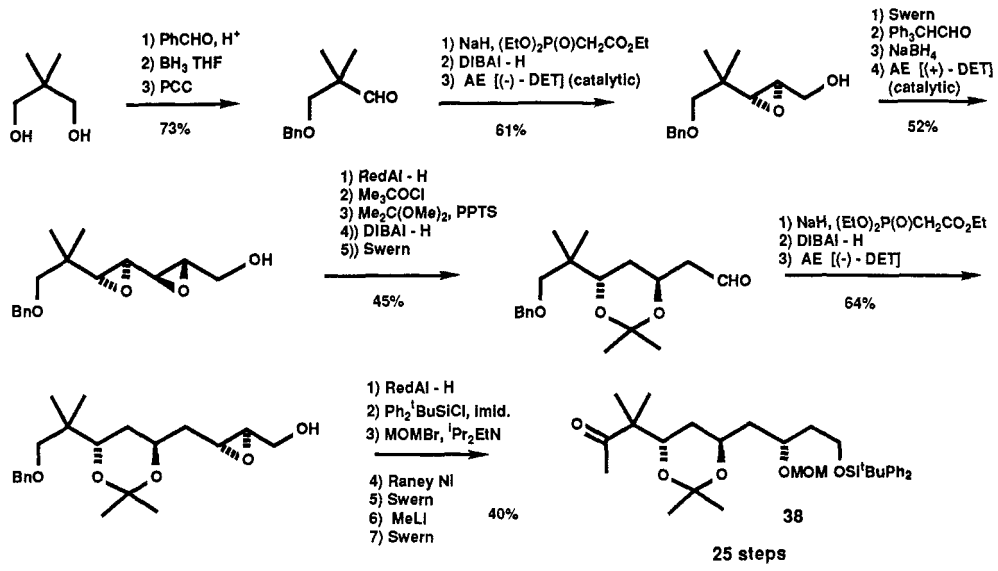
Scheme 11



approach (dissection a) was not viable. Compound 37 however, served to confirm the stereochemistry of the AB fragment prepared through the second approach (dissection b) (see below).

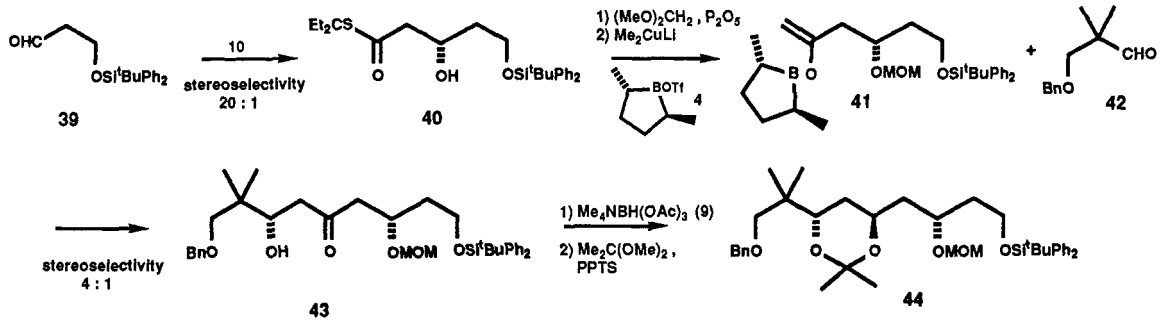
We now return to the synthesis of Fragment A (shown in Scheme 10) which is a nonan-1,3,5,7,9-pentanol. Our earlier approach examined in 1983 used a combination of asymmetric epoxidation and Redal reduction for the construction of 1,3-diols as summarized in Scheme 12. The stereochemistry of all newly created stereogenic centers in the intermediates and the final product **38** was secured and each step proceeded in good yield. However, due to the functional group transformations and protecting group manipulation necessary to execute the interactive sequence, the number of steps leading to **38** is 25, a number embarrassingly large for the creation of the three stereogenic centers. This drawback has now been remedied.

Scheme 12



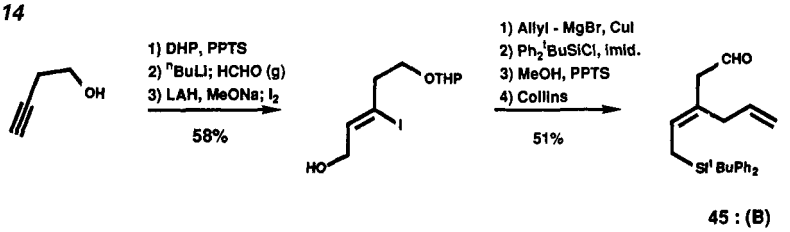
The borolane-mediated aldol reaction of **39** proceeded with respectable stereoselectivity to provide **40** which, after protection of the hydroxyl group and conversion into the corresponding methyl ketone, was subjected to a second aldol reaction again with the aid of the borolanyl triflate **4** (Scheme 13). The stereoselectivity of this aldol (**41** + **42**) is by no means high because it involves a methyl ketone, but the 4:1 ratio is appreciated in light of the fact that use of an achiral borinyl triflate such as 9-BBN leads to a 1:1 mixture of **43** and its diastereoisomer. Reduction of **43** with Saksena-Evans reagent is marvelous (ref. 15), effecting near-perfect stereoselection to provide **44**. The first aldol reaction (**39** + **10**) can be replaced by allyboration with (*S*)-**22** to bring about an equally satisfying result.

Scheme 13



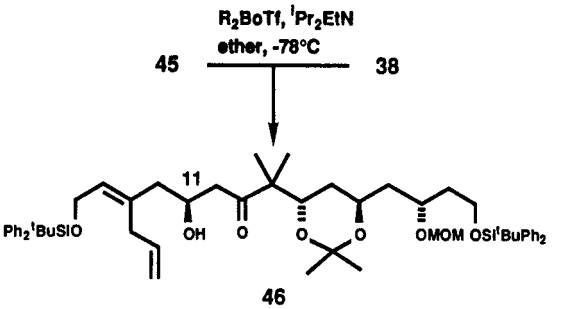
Synthesis of Fragment B which is achiral is straightforward: Application of Corey's trisubstituted olefin synthesis yielded the aldehyde **45** (Fragment B) without problem (Scheme 14).

Scheme 14

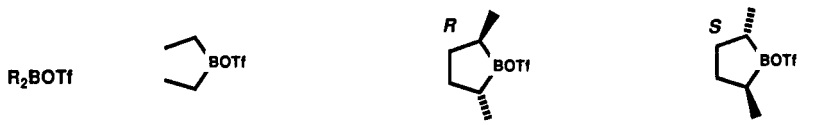


Coupling of **38** and **45** (Fragment A and B equivalents) represents another critical instance where the aldol reaction involves the enolate derived from a methyl ketone. As tabulated below (Scheme 15), (*R*)-dimethylborolanyl triflate is clearly a matched mediator for the ketone **38**, enhancing, although not to a large extent, the stereoselectivity of this coupling to 6:1, to provide **46** as the major product.

Scheme 15

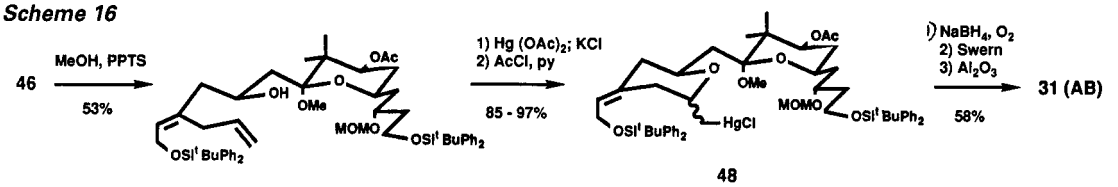


Stereoselectivity at C - 11



With all the carbons in place, **46** requires further modification in order to complete the construction of Fragment AB ready for coupling with the bottom half of bryostatin 1. While the first pyran formation (**46**→**47**) is triggered by deacetonization, the second one (**47**→**48**) is assisted by $Hg(OAc)_2$ (Scheme 16). The stereorandomness of this Hg-mediated cyclization shown in **48** is not critical as this pyran side chain is equilibrated to become equatorial at the aldehyde stage **31** (AB). It should be added here that final

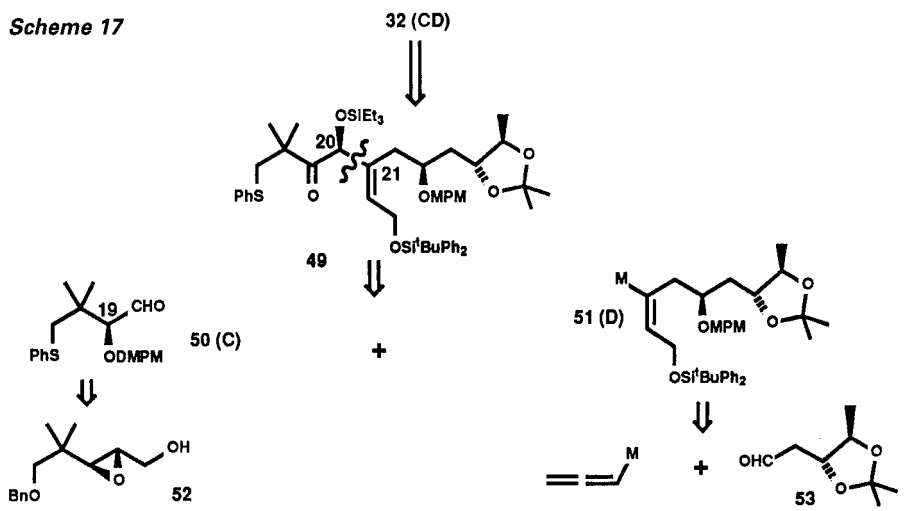
Scheme 16



confirmation of the C(11) stereochemistry of **31** (Schemes 9 and 15) has been made. Recall that compound **37** (Scheme 11) was prepared by a different route which secured the C(11) stereochemistry indicated in **37**. The assigned stereochemistry of **31** stands on a firm basis since both **31** and **37** have been converted into the same compound without affecting the stereogenic centers existing in both compounds.

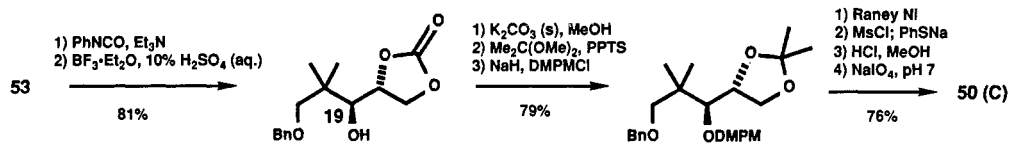
The bottom half of bryostatin, Fragment CD (**32**) is rewritten as shown in **49** and dissected in such a manner that reassembly provides opportunities to establish the proper C(21)-C(22) double bond geometry and the proper stereochemistry at C(20). The starting material for syntheses of Fragments C (**50**) and D (**51**) are **52** and **53**, as shown in Scheme 17.

Scheme 17



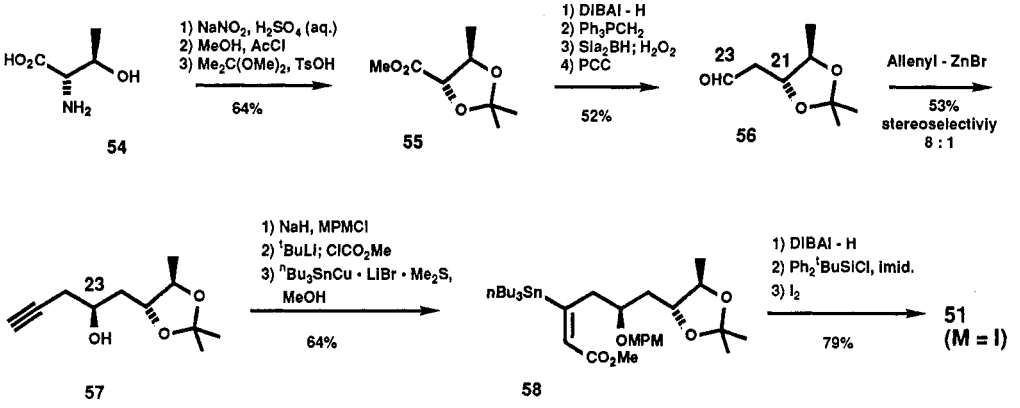
Conversion of compound **52** to **50** follows a sequence of reactions, epoxidation and epoxide ring opening, well established in our earlier saccharide synthesis (ref. 16). Note that Yonemitsu's DMPM (dimethoxyphenylmethyl) group (ref. 17) is used to protect the C(19)-OH functionality (Scheme 18). Using

Scheme 18



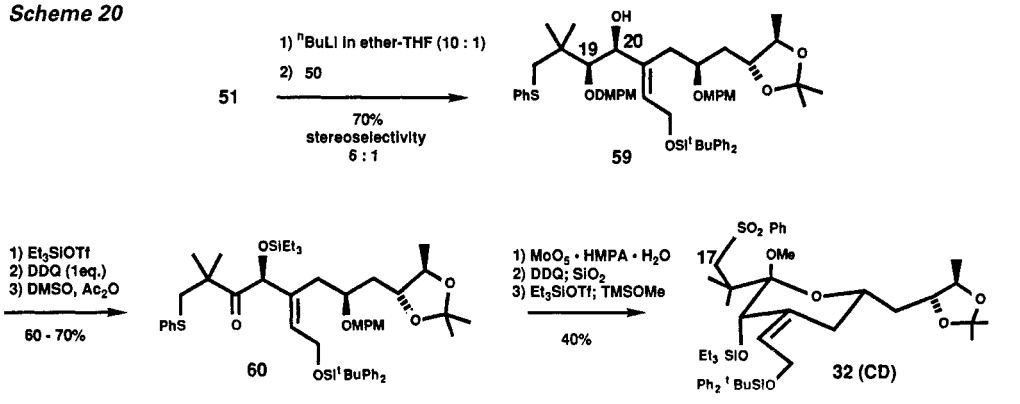
a known procedure threonin (**54**) was converted into the ester **55** (ref. 18) which was homologated to provide the aldehyde **56**. Coupling of **56** with allenyl-ZnBr proceeded through chelation with the C(21)-O functionality to create the C(23)-β-hydroxy group. Conversion of the resulting acetylenic compound **57** into

Scheme 19



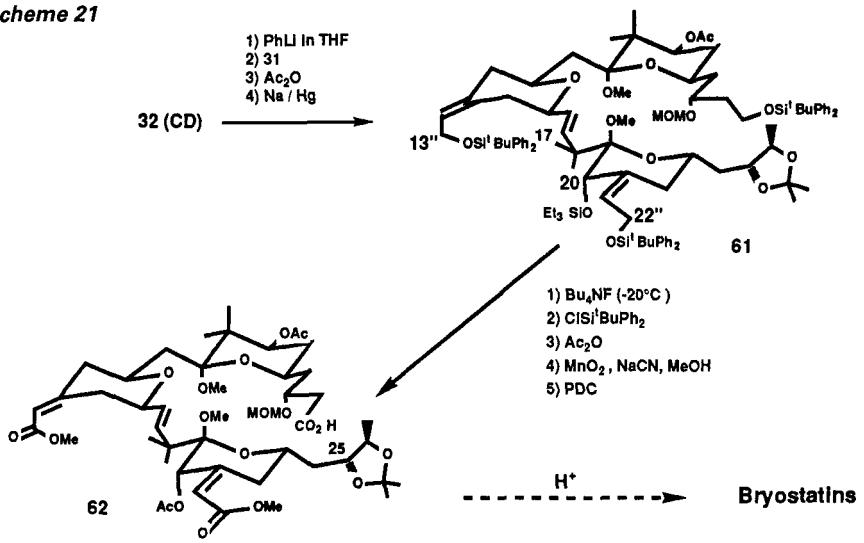
the tributyl-*E*-olefin **58** utilized Pier's method (ref. 19) to effect $(Bu)_3SnCu$ addition to the acetylenic linkage. The $(Bu)_3Sn$ group in **58** was subsequently replaced by I to provide **51** ready for the CD coupling. This coupling again takes advantage of metal chelation with the C(19)-O functionality in **50**. Thus, the lithium anion derived from **51** reacted with **50** with 6:1 stereoselection and the resulting product **59**, after functional

Scheme 20



transformations including the selective removal of DMPM and subsequent oxidation, was converted (through **60**) to **32** which was ready for coupling with the other half of bryostatin.

Scheme 21



Scheme 21 summarizes the AB-CD coupling. What appeared to be a straightforward application of the Julia-Lythogoe olefin synthesis from our model experiments has proved to be considerably more difficult. Because of steric congestion around the C(17) position (see Scheme 20) use of amine base such as LDA and Et_2NLi led to insufficient deprotonation, whereas stronger carbon bases such as *tert*- or n-butyl lithium effected removal of an aryl proton as well as a benzyl proton. A compromise was phenylithium, and with this base the final coupling has now been achieved to obtain **61**. The oxidation states both at the C(13") and C(22") positions have been adjusted and the C(20) hydroxyl group converted to the acetoxyl to provide compound **62**. The only task that remains to be achieved is macrolactonization.

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