Synthesis of Stereopentad Analogues of the C14−C22 Segment of Callystatin A through Additions of Chiral Allenylzinc Reagents to Stereotriads

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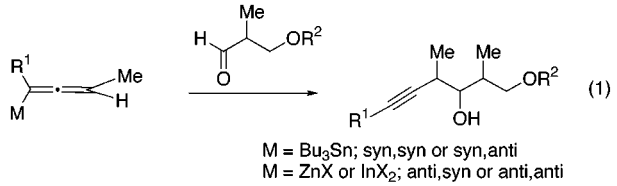
The addition of (*P*)- and (*M*)-allenylzinc reagents, prepared in situ through Pd-catalyzed metalation of (*R*)- and (*S*)-3-butyn-2-ol mesylates, to diastereomeric stereotriad aldehydes **8**, **13**, **18**, and **23** of syn,syn, syn,anti, anti,anti, and anti,syn stereochemistry was examined. Additions to the former two aldehydes afforded the four anti adducts with high diastereoselectivity and negligible mismatching. Significant mismatching was observed with the latter two aldehydes and the (*M*)-allenylzinc reagent. An evaluation of possible transition states is presented in consideration of steric and dipolar control elements.

Introduction

Polyketide natural products[1] have played a major role in the development of synthesis methodology for acyclic stereocontrol. This remarkably diverse family possess a wide range of important biological activity with proven or potential use in medicine. The most common synthetic approach for constructing the various stereotriad[1] and higher subunits of these compounds involves diastereo- and enantioselective carbon−carbon bond forming reactions related to variants of the aldol reaction. Allylborane and boronate, allylsilane, and allyltitanate additions have also been applied with great success.[2] Other less used, but no less important, methods have also been developed over the years, and new methodology continues to appear.[3] Many of these approaches utilize a chiral auxiliary or substrate to effect stereochemical control.

Additions of chiral nonracemic allenylmetal reagents to chiral α-methyl propanal derivatives have also proven useful for the assembly of stereotriad segments of polyketide natural products (eq 1).[4] These reagents rely upon allene chirality to favor one of the two possible diastereomeric transition states in the addition and thus differ in a fundamental way from the aforementioned methods in which a chiral auxiliary or catalyst provides the control element. The chiral allenylmetal methodology provides access to all isomers of the homopropargylic alcohol stereotriad adducts with excellent diastereo- and enantioselectivity. In addition, the acetylenic grouping of the adducts can be further elaborated, both functionally and for chain extension by a variety of protocols.[5]The overall utility of the methodology is reflected in applications to a number of important natural products.[6]



Chiral allenylzinc and indium reagents are readily available through oxidative transmetalation of transient allenylpalladium intermediates derived from sulfonic esters of (*R*)- or (*S*)-3-butyn-2-ol derivatives (eq 2).[7] When these transmetalations are conducted in the presence of substrate aldehydes, anti homopropargylic alcohol adducts are formed with high diastereoselectivity. The

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(1) For an insightful review on polyketide natural product stereochemistry and conformation, see Hoffmann, R. W. *Angew. Chem., Int. Ed.* **2000**, *39*, 2054.

(2) Representative leading references. Aldol: Evans, D. A.; Carter, P. H.; Carreira, E. M.; Prunet, J. A.; Charette, A. B.; Lautens, M. *Angew. Chem., Int. Ed.* **1998**, *37*, 2354. Paterson, I.; Scott, J. P. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1003. Allylmetalations: Boronate; Scheidt, K. A.; Tasaks, A.; Bannister, T. D.; Wendt, W. R.; Roush, W. R. *Angew. Chem., Int. Ed.* **1999**, *38*, 1652. Borane; Guo, J.; Duffy, K. J.; Stevens, K. L.; Dalko, P. I.; Roth, R. M.; Hayward, M. M.; Kishi, Y. *Angew. Chem., Int. Ed.* **1998**, *37*, 187. *Silane*; Panek, J. S.; Jain, N. F. *J. Org. Chem.* **1998**, *63*, 4572. *Titanate*: Bouzbouz, S.; Popkin, M. E.; Cossy, J. *Org. Lett.* **2000**, *2*, 3449.

(3) Other imaginative, but to date less widely used, approaches to the stereocontrolled synthesis of polypropionate segments include the following. Oxabicyclo[3.2.1] cleavage: Hunt, K. W.; Grieco, P. A. *Org. Lett.* **2001**, *3*, 481. Kim, H.; Hoffmann, H. M. R. *Eur. J. Org. Chem.* **2000**, 2195. Epoxide rearrangement: Jung, M. E.; Marquez, R. *Org. Lett.* **2000**, *2*, 1717. Ketene aldol: Calter, M. A.; Bi, F. C. *Org. Lett.* **2000**, *2*, 1529. Hydroformylation: Breit, B.; Zahn, S. K. *Tetrahedron Lett.* **1998**, *39*, 1901. 1,4-Additions: Hanessian, J.; Ma, J.; Wang, W. *Tetrahedron Lett.* **1999**, *40*, 4627. Nitrile oxide cycloadditions: Bode, J. W.; Fraefal, N.; Muri, D.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2001**, *40*, 2082. Hetero Diels−Alder: Myles, D. C.; Danishefsky, S. J. *Pure Appl. Chem.* **1989**, *61*, 1235.

(4) Reviews: (a) Marshall, J. A. *Chem. Rev.* **1996**, *96*, 31. (b) Marshall, J. A. *Chem. Rev.* **2000**, *100*, 3163.

(5) (a) Marshall, J. A.; Yanik, M. M. *J. Org. Chem.* **1999**, *64*, 3798. (b) Marshall, J. A.; Yanik, M. M. *Tetrahedron Lett.* **2000**, *41*, 4717. (c) Marshall, J. A.; Yanik, M. M. *Org. Lett.* **2000**, *2*, 2173.

(6) Natural products: (a) Zincophorin. Marshall, J. A.; Palovich, M. R. *J. Org. Chem.* **1998**, *63*, 3701. (b) Discodermolide. Marshall, J. A.; Johns. B. A. *J. Org. Chem.* **1998**, *63*, 7885. (c) Callystatin A. Marshall, J. A.; Fitzgerald, R. A. *J. Org. Chem.* **1999**, *64*, 4477. (d) Aplyronine A. Marshall, J. A.; Johns, B. A. *J. Org. Chem.* **2000**, *65*, 1501. (e) Balifomycin. Marshall, J. A.; Adams, N. D. *Organic Lett.* **2000**, *2*, 2897. Marshall, J. A.; Adams, N. D. *J. Org. Chem.*, in press. (f) Tautomycin. Marshall, J. A.; Yanik, M. M. *J. Org. Chem.* **2001**, *66*, 1373.

(7) (a) Allenylzinc reagents: Marshall, J. A.; Adams, N. D. *J. Org. Chem.* **1999**, *64*, 5201. (b) Allenylindium reagents: Marshall, J. A.; Grant, C. M. *J. Org. Chem.* **1999**, *64*, 8214. (c) Allenylsilicon reagents: Marshall, J. A.; Maxson, K. *J. Org. Chem.* **2000**, *65*, 630.

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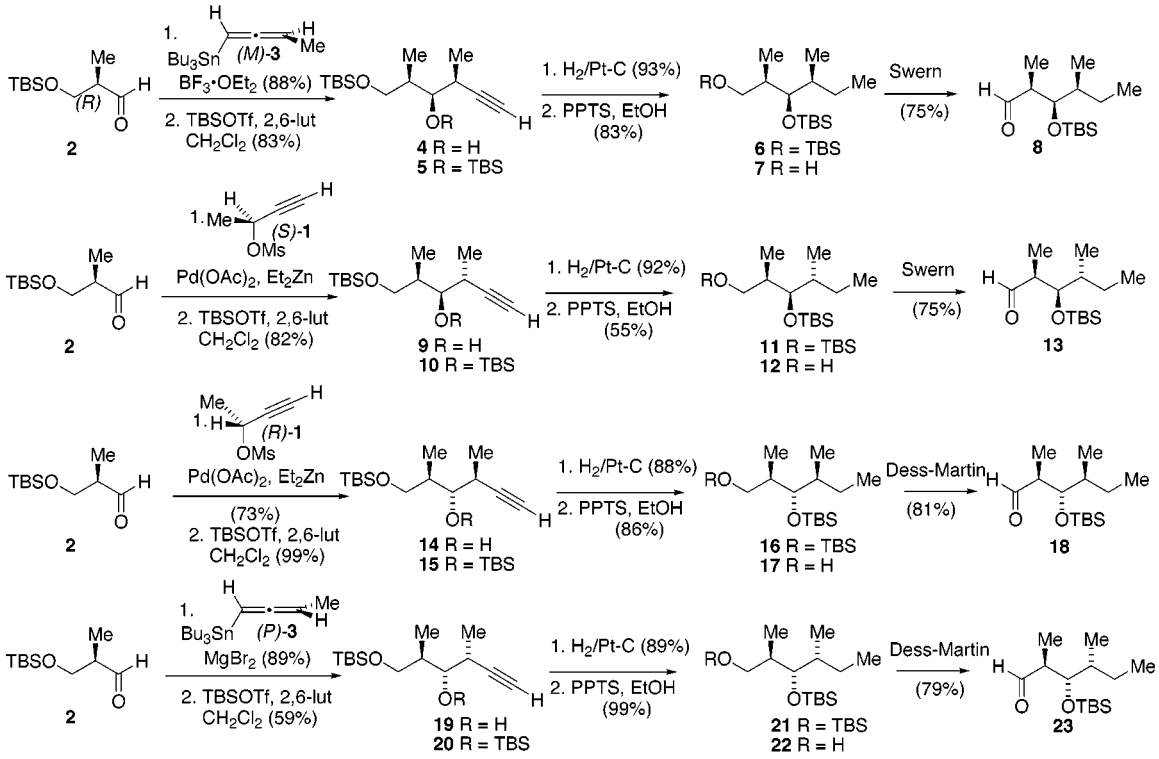
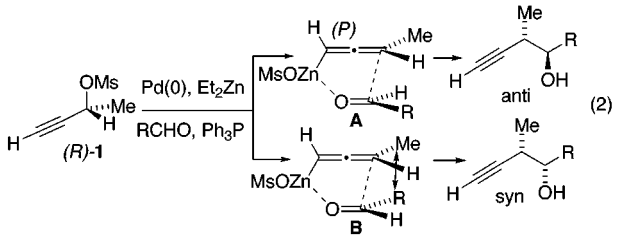
Scheme 1

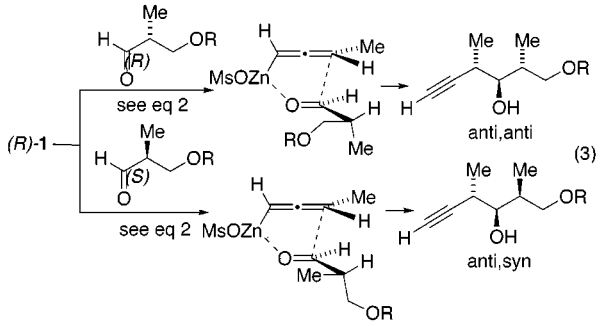


preference for anti over syn adducts can be attributed to an unfavorable eclipsing interaction between the allenyl Me and the aldehyde R substituent in the transition state leading to the syn adduct (see **B** in eq 2).



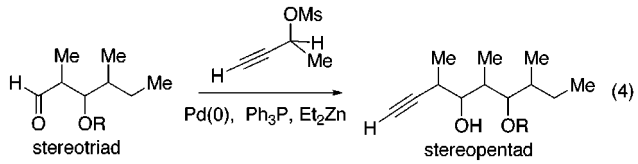
(2)

Interestingly, high diastereoselectivity is observed in additions to *both* enantiomers of the aforementioned α-methyl propanal derivatives to afford the anti,anti and anti,syn adducts (eq 3). Thus, the preference for the anti transition state overrides Felkin−Anh considerations in these additions with a resulting absence of mismatching.[8]



(3)

The thrust of the present study was to examine reactions of chiral allenylzinc reagents with isomeric stereotriads to afford various stereopentad adducts (eq 4). These arrays are present in a number of stereochemically complex polyketide natural products with potential as medicinal agents.[2] In the present study it was of interest to determine both the effect of the longer chain α−substituent on Felkin−Anh control of the addition and the role of the *β*-oxygen substituent as a dipolar control element. A previous investigation of such α,*β*-substituent effects has been reported for Mukaiyama aldol and allylmetal additions that proceed through acyclic transition states.[9] The present investigation differs in two important respects: (1) The additions proceed through cyclic, as opposed to acyclic transition states; (2) The reagents are allenic rather than allylic or enolic.



(4)

For our aldehyde substrates, we selected the four stereotriad isomers represented by **8**, **13**, **18**, and **23** (Scheme 1). The choice of a *β*-OTBS ether was based on the findings by Evans that such ethers exhibit a significant dipole effect.[9] The stereopentads resulting from the planned additions to these aldehydes are related to the C14−C22 segment of the marine-sponge derived antitumor compound, callystatin A, and analogues thereof (Figure 1).[10] Accordingly, these studies address practical as well as fundamental stereochemical issues.

Results

The synthesis of the stereotriad aldehyde substrates, outlined in Scheme 1, utilizes methodology developed

(8) Chérest, M.; Felkin, H.; Prudent, N. *Tetrahedron Lett.* **1968**, 2119. Anh, N. T.; Eisenstein, O. *Nouv. J. Chem.* **1977**, *1*, 61.

(9) Evans, D. A.; Duffy, J. D.; Dart, M. J. *Tetrahedron Lett.* **1994**, *35*, 8537. Evans, D. A.; Dart, M. J.; Duffy, J. L.; Yang, M. G. *J. Am. Chem. Soc.* **1996**, *118*, 4322.

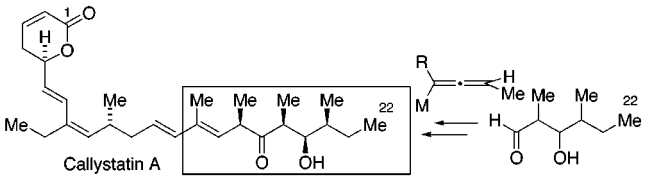
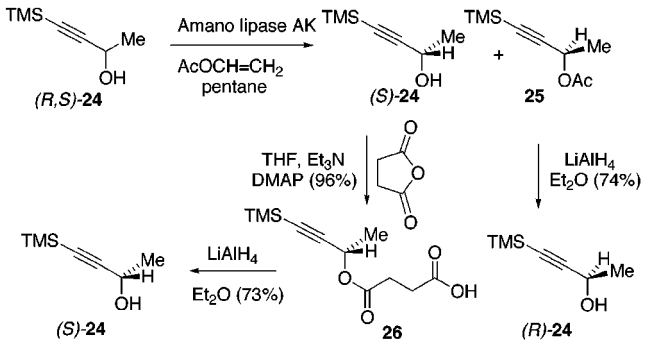


Figure 1. Relationship of the present studies to the C14−C22 segment of Callystatin A.

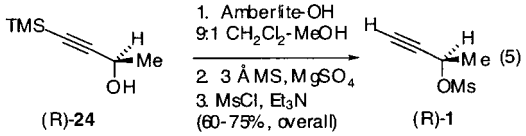
Scheme 2



over the past several years in our laboratory.[1,3] This chemistry has been discussed in a number of reviews,[4] and detailed pathways for the additions to aldehyde **2** need not be reiterated here. It suffices to say that the syn,syn adduct **4** arises via an acyclic Felkin−Anh transition state and the syn,anti adduct (right-to-left) **19** also results from an acyclic transition state but with "chelation" control. The two anti adducts **9**[6d] and **14**[6e] are reagent-controlled products resulting from cyclic transition states (see eq 3).

In our initial investigations of the allenylpalladium transmetalation methodology we utilized (*R*)- and (*S*)-3-butyn-2-ol from commercial sources. However, the increasing cost of these alcohols prompted our search for a more economical supply. To date, we have developed two synthetic routes that fulfill our needs. The first employs commercially available, and relatively inexpensive, (*R*)- and (*S*)-lactic esters as the starting materials.[6f] The second, which we selected for the present studies, utilizes Amano AK lipase to effect a multigram scale kinetic resolution of racemic, moderately priced 4-TMS-3-butyn-2-ol (*R*,*S*)-**24** through enantioselective acetylation with vinyl acetate to afford unchanged (*S*)-4-TMS-3-butyn-2-ol ((*S*)-**24**) and the acetate of (*R*)-4-TMS-3-butyn-2-ol (**25**), both of >95% ee (Scheme 2).[11] The two are readily separated through treatment of the mixture with succinic anhydride and extraction of the (*S*)-succinate **26** with aqueous $NaHCO_3$. Reduction of each ester with $LiAlH_4$ or DIBAL-H affords the enantiomeric butynols (*S*)- and (*R*)-**24** of high ee.

Because of their volatility and water solubility the parent butynols are best converted to the mesylate derivatives (*R*)- or (*S*)-**1** without isolation. This can be accomplished through TMS cleavage with Amberlite-OH resin in CH_2Cl_2−MeOH solvent. The methanol cosolvent is removed by stirring the mixture with 3 Å molecular seives and $MgSO_4$. After filtration, the CH_2Cl_2 solution of 3-butyn-2-ol is treated with MsCl and Et_3N to form the stable mesylate which can be isolated by extraction in the usual way (eq 5).



Exposure of the syn,syn aldehyde **8** to the (*P*)-allenylzinc reagent, generated in situ from the propargylic mesylate (*R*)-**1** and diethylzinc in the presence of 10 mol % $Pd(OAc)_2 \cdot PPh_3$, afforded the anti adduct **27** with no trace of the syn isomer **28**, according to analysis of the ^1H NMR spectrum. However, a small amount of the diastereomeric anti product **29** (ratio = 91:9) was also produced. This latter product most likely results from partial racemization of the intermediate allenyl Pd precursor of the allenylzinc reagent.[12,13] When this experiment was repeated with mesylate (*S*)-**1**, a 92:8 mixture of the anti adducts **29** and **27** was formed free of any syn adduct **30** (Scheme 3).

Additions to the syn,anti aldehyde **13** proceeded analogously. Both the (*P*)- and (*M*)-allenylzinc reagents derived from mesylates (*R*)- and (*S*)-**1** afforded the anti adducts **31** and **33** as near-exclusive products. In the former case the alternative anti adduct **33** derived from the (*M*)-allenylzinc reagent (ratio = 94:5) was also produced. Barely detectable signals for what may be the syn adduct **32** were also observed in the ^1H NMR spectrum of this mixture. The reaction proceeding from mesylate (*S*)-**1** and aldehyde **13** afforded a 92:6:2 mixture of the anti products **33**, **31**, and the (presumed) syn isomer **34**. Thus, to the extent that negligible amounts of the syn isomers can be detected, the foregoing additions resemble those leading to the anti adducts **13** and **18** (Scheme 1) in which reagent control overrides Felkin−Anh preferences.

The two α,β-anti aldehyde diastereomers **18** and **23** exhibited typical matched behavior with the (*P*)-allenylzinc reagents derived from mesylate (*R*)-**1** affording negligible amounts of syn **36**/**40** or diastereomeric anti byproducts (Scheme 4). Additions of the (*M*)-allenylzinc reagent from mesylate (*S*)-**1**, on the other hand, were significantly mismatched. In each case the combined syn and ent-anti diastereomers **38**/**42** and **35**/**39** accounted for approximately one-third of the total stereopentad products.

Structure Correlations

The configurational relationships between propargylic mesylates and the derived allenylzinc reagents have been well established as has the stereochemistry of the ensuing homopropargylic alcohol products (see eqs 2 and 3).[4,6,7]

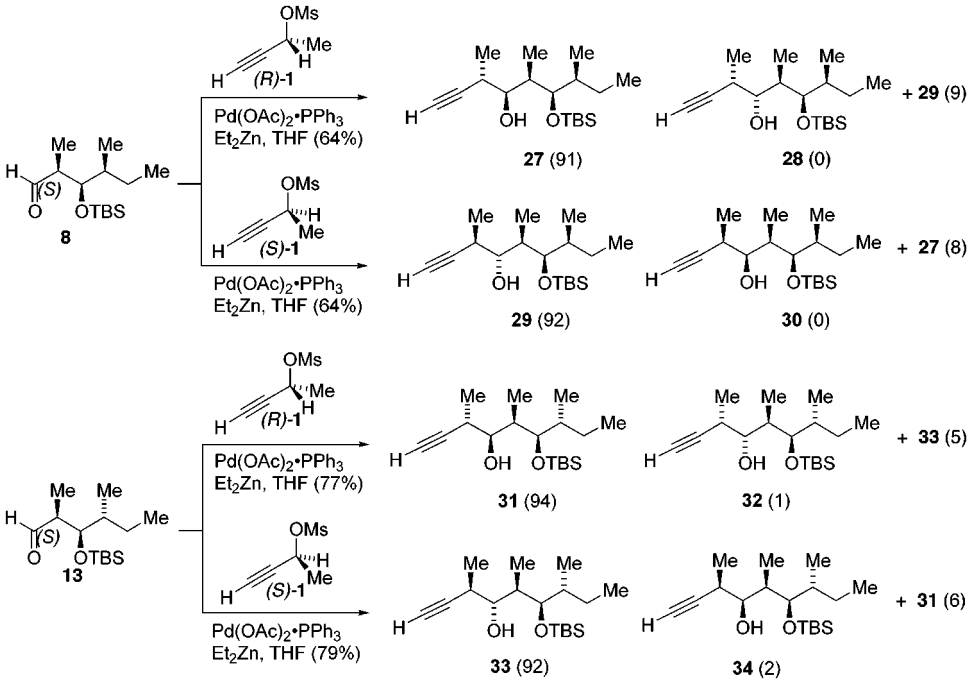
(10) Previous syntheses. (a) Kobayashi, M.; Higuchi, K.; Murakami, N.; Tajima, H.; Aoki, S. *Tetrahedron Lett.* **1997**, *38*, 2859. (b) Murakami, N.; Wang, W.; Aoki, M.; Tsutsui, Y.; Sugimoto, M.; Kobayashi, M. *Tetrahedron Lett.* **1998**, *39*, 2349. (c) Crimmins, M. T.; King, B. W. *J. Am. Chem. Soc.* **1998**, *120*, 9084. (d) Smith, A. B., III; Brandt, B. M. *Org. Lett.* **2001**, *3*, 1685.

(11) Cf. Burgess, K.; Jennings, L. D. *J. Am. Chem. Soc.* **1991**, *113*, 6129. Beresis, R. T.; Solomon, J. S.; Yang, M. G.; Jain, N. F.; Panek, J. S. *Org. Synth.* **1997**, *75*, 78. The kinetic resolution sequence leading to the enantiomeric TMS butynols was developed by Matt Yanik in our laboratory. Details will be disclosed in due course pending further investigations on applications of the derived allenylsilane reagents.

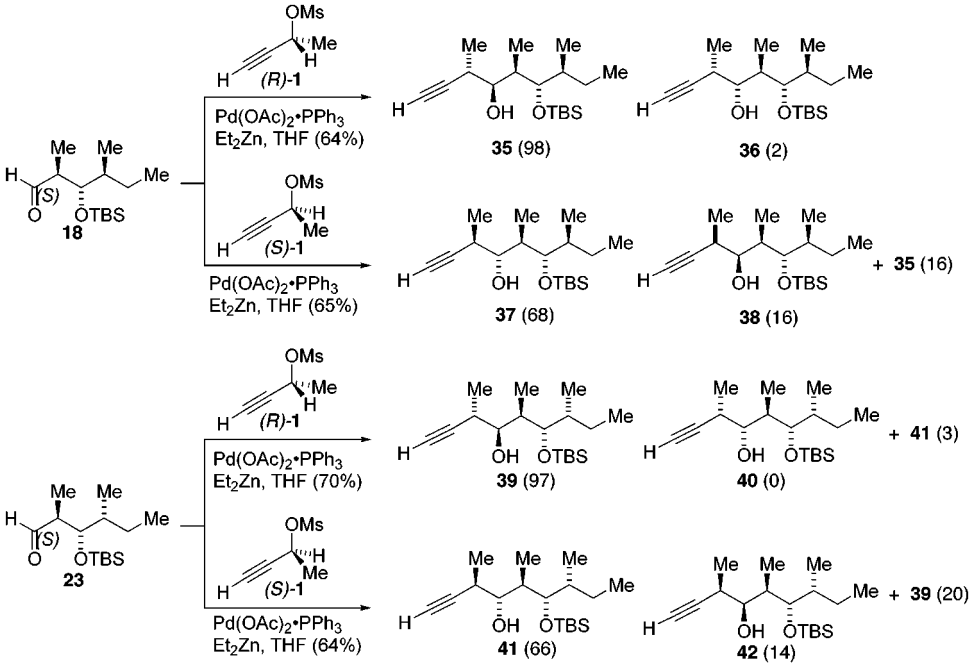
(12) Chiral allenylpalladium compounds are racemized by Pd(0) catalysts. Elsevier: C. J.; Vermeer, P. *J. Org. Chem.* **1985**, *50*, 3042. See also Marshall, J. A.; Wolf, M. A.; Wallace, E. M. *J. Org. Chem.* **1997**, *62*, 367.

(13) Poisson and Normant have found that chiral allenylzinc bromide reagents are configurationally stable to ca. −10 °C. Poisson, J.-F.; Normant, J.-F. *Synlett* **2001**, 305.

Scheme 3



Scheme 4

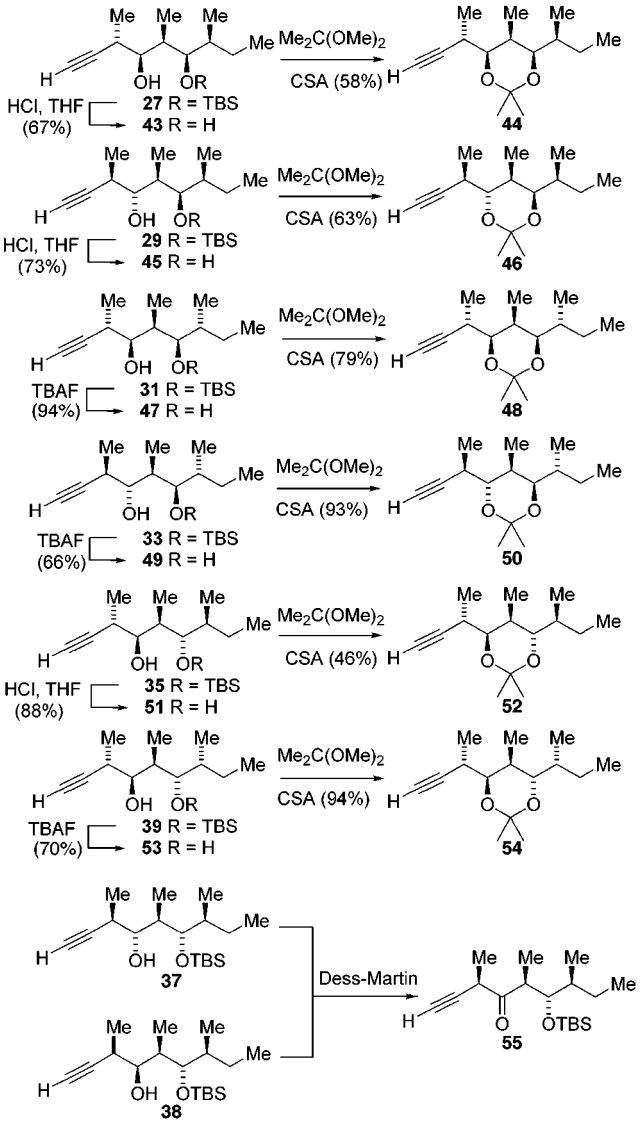


Nonetheless, we elected to confirm our assignments through correlation of the newly formed carbinol stereocenter and the resident OTBS center of the aldehyde stereotriad substrates. Such a correlation would confirm our assumption that the major product was formed via the anti pathway (eq 2). The fact that the major product of the (*P*)-allenylzinc addition was present as a minor product in the analogous addition of the (*M*)-allenylzinc reagent (by virtue of the racemization side reaction) provides additional support for this assumption.

Assignment of the 1,3-diol stereochemistry was achieved through conversion of the stereopentad adducts to the acetonides **44**, **46**, **48**, **50**, **52**, and **54** derived from the syn,syn and syn,anti aldehydes **8** and **13** and the two matched adducts **35** and **39** from additions to the anti,-anti and anti,syn aldehyde adducts **18** and **23** (Scheme 5). The syn acetonides **44** and **48** showed distinctly different chemical shifts for the acetonide methyl groups in the range of 20 and 30 ppm whereas the corresponding signals for the anti isomers **46**, **50**, **52**, and **54** were closely spaced near 25 ppm.[14] The inseparable diastereomeric mixture of acetonides obtained from the mismatched adducts **37** and **41** could not be analyzed because of overlapping signals. However, small samples of **37** and **38** could be isolated through careful chromatography. Upon oxidation[15] each gave rise to ketone **55** in accord with the assigned structures.

(14) Rychnovsky, S. D.; Skalitzky, D. J. *J. Org. Chem.* **1993**, *58*, 3511.

Scheme 5



Transition State Analysis

In our analysis of probable transition states we incorporate conclusions reached by Evans and co-workers in their proposed stereochemical model for merged 1,2- and 1,3-asymmetric induction in Mukaiyama aldol and related additions to aldehydes.[9] Thus, we assume that the orientation of the β-stereocenter will favor conformers in which (1) dipole repulsion between the carbonyl oxygen and the OR substituent is minimized and (2) the β-alkyl substituent (R in Figure 2) preferentially adopts an anti vs gauche conformation relative to the main carbon chain for steric reasons. We assume that dipole considerations will override conformational preferences when the two factors are in conflict. The other factors that play a role in the present addition reactions are (1) steric interactions between the allenic methyl group and the aldehyde α-substituent, as illustrated in eq 2 (**A** vs **B**), and (2) Felkin−Anh orientation of the aldehyde α-methyl substituent. Of these, the allenic methyl steric interactions are considered paramount in view of the absence of a mismatched syn adduct from additions leading to **9** and **14** (Scheme 1 and eq 2).

Transition state representations illustrating the relationship of these four factors are presented in Figure 2. In all cases the avoidance of an allenic methyl/aldehyde substituent eclipsing interaction, denoted as "steric," results in a preference for the anti adducts. Felkin−Anh orientation, while not crucial, likely plays a more important role than is seen in additions leading to the anti triads (eq 3) by virtue of the longer β-carbon chain in the triad aldehydes compared to propanal **2**. The most serious mismatching occurs when the transition state for the anti adduct lacks two of the four favorable orientational factors as in **AAA** while the corresponding syn arrangement, **SSA**, lacks only one (steric), albeit perhaps the most important of the four.

In view of the highly selective additions to the two α,β-syn aldehydes **8** and **13**, it can be surmised that the anti vs gauche orientation of the extended carbon chain, as in **ASS** vs. **AAS**, is a relatively unimportant conformational factor. It should be noted that rotation of the Cα−Cβ bond in **ASS** or **AAA** to place R in the anti position would lead to 1,3-dipole repulsion between the aldehyde C=O and the β-OR substituent. Dipole repulsion is assumed to be an important control element but its effect is not directly measurable in these studies. It seems unlikely that the stereochemistry of the γ-position exerts a significant influence, given the comparable steric and electronic attributes of the ethyl and methyl substituents. Although the foregoing conclusions regarding transition state preferences may prove useful in predicting the stereochemical outcomes of related additions, perhaps of greatest practical import is the finding that the allenylzinc methodology provides a workable route to six of the eight possible α,β anti stereopentad diastereomers.

Experimental Section

(*R*)-3-Butyn-2-yl Methanesulfonate (*R*)-1. To a stirring solution of (*R*)-TMS-butynol (4.00 g, 0.281 mmol) in 9:1 CH_2Cl_2:MeOH (14 mL) was added Amberlite IRA-400 (OH) (2.4 g, 60 wt %), and the mixture was stirred overnight. Molecular sieves (3 Å) and $MgSO_4$ were added, and stirring was continued for 30 min. The mixture was filtered through Celite, and the solids were rinsed with additional CH_2Cl_2 until a total volume of ~140 mL was obtained. After the solution was cooled to −78 °C, triethylamine (15.6 mL, 1.12 mmol, 4 equiv) and MsCl (6.6 mL, 0.844 mmol, 3 equiv) were added and the solution was stirred for 1.5 h. The reaction was quenched with $NaHCO_3$, extracted with CH_2Cl_2, and washed with brine. The organic extract was dried over $MgSO_4$, concentrated under reduced pressure, and chromatographed (elution with 3:1 pentane/ether) to give 3.14 g (75%) of a clear oil, $[\alpha]_D = +108.1$ (*c* 3.0, $CHCl_3$); lit.[16] $[\alpha]_D = +108.8$ (*c* 3.12 $CHCl_3$).

(2*R*,3*R*,4*S*)-(−)-1-(*tert*-Butyldimethylsilyloxy)-2,4-dimethyl-5-hexyn-3-ol (4). To a stirring solution of aldehyde **2** (4.00 g, 19.8 mmol) in CH_2Cl_2 (200 mL) at −78 °C was added allenylstannane (*M*)-**3**[17] (7.79 g, 22.7 mmol, 1.15 equiv). After 5 min, $BF_3{\cdot}OEt_2$ (7.32 mL, 3.00 equiv) was added over 10 min, and the mixture was stirred for 1 h and quenched with saturated $NaHCO_3$. The aqueous layer was extracted with Et_2O, washed with brine, and dried over $MgSO_4$. The solution was filtered, concentrated under reduced pressure, and chromatographed on silica gel (elution with 2.5% EtOAc/hexanes) to give 4.47 g (88%) of product as a separable 88:12 mixture of diastereomers. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.9 (d, $J = 3.0$ Hz, 1H), 3.72 (m, 2H), 3.52 (br, 1H), 2.52 (m, 1H), 2.16 (m, 1H), 2.06 (d, $J = 3$ Hz, 1H), 1.31 (d, $J = 9.0$ Hz, 3H), 1.01 (d, $J = 9.0$ Hz, 3H), 0.91 (m, 9H), 0.081 (s, 6H).

(15) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155; Meyer, S. D.; Schreiber, S. L. *J. Org. Chem.* **1994**, *59*, 7549.

(16) Marshall, J. A.; Adams, N. D. *J. Org. Chem.*, in press.

(17) Marshall, J. A.; Lu, Z.-H.; Johns, B. A. *J. Org. Chem.* **1998**, *63*, 817.

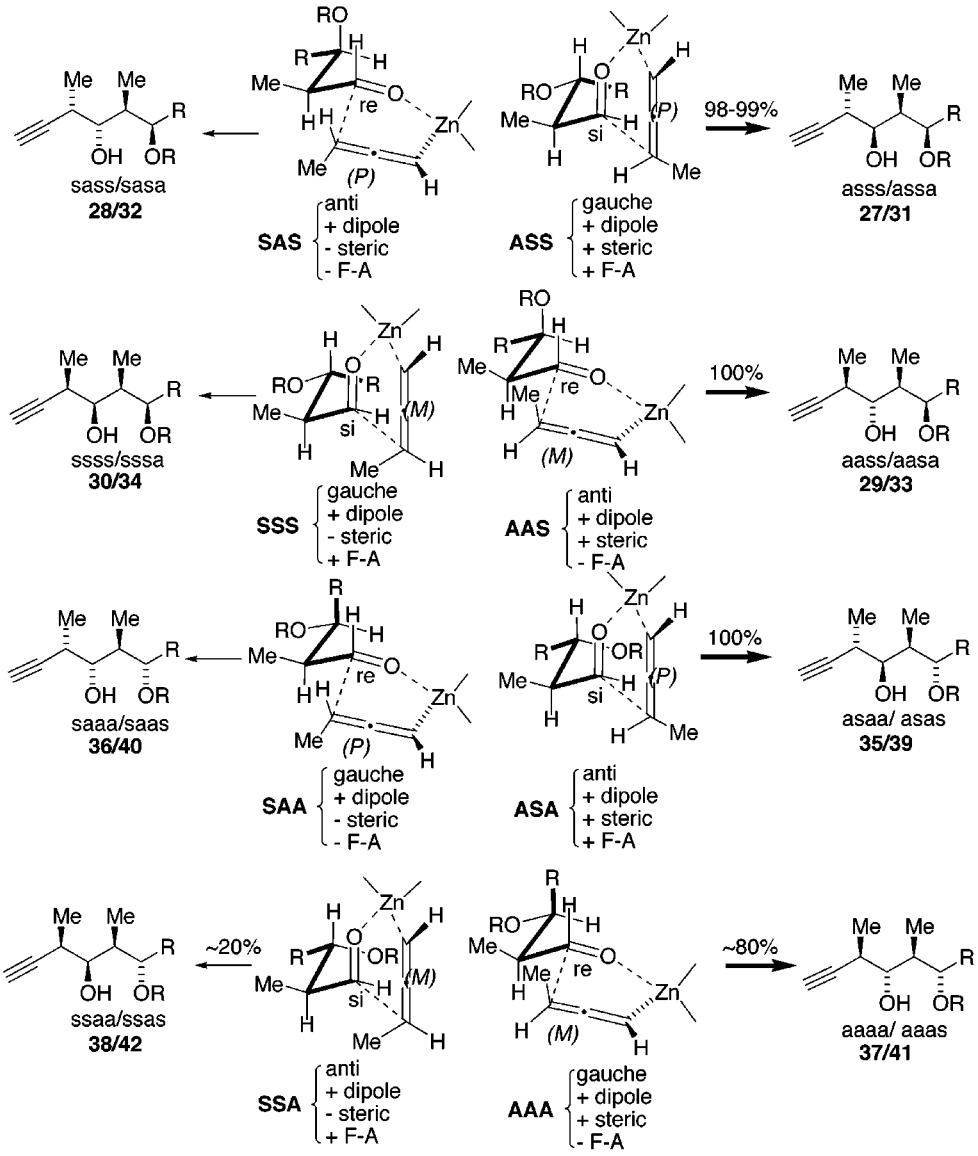


Figure 2. Possible transition state arrangements for additions of (*P*)- and (*M*)-allenylzinc reagents to the diastereomeric aldehyde stereotriads **8**, **13**, **18**, and **23.** The discriptors "anti" and "gauche" refer to the conformation of the aldehyde backbone (heavy lines), "+" and "−"designate favorable and unfavorable steric or dipolar relationships.

(2*R*,3*R*,4*S*)-(−)-1,3-Bis(*tert*-butyldimethylsilyloxy)-2,4-dimethyl-5-hexyne (5). General Procedure for Alcohol Silylations. To a solution of alcohol **4** (2.17 g, 8.45 mmol) in CH_2Cl_2 (84 mL) at 0 °C was added 2,6-lutidine (2.4 mL, 21.1 mmol, 2.5 equiv) and TBSOTf (5.02 g, 19.0 mmol, 2.25 equiv). The mixture was allowed to warm to room temperature and stirred for an additional 1 h. The reaction was quenched with saturated $NaHCO_3$, and the aqueous layer was extracted with CH_2Cl_2, washed with brine, and dried over $MgSO_4$. The solution was filtered, concentrated under reduced pressure, and chromatographed on silica gel (elution with 1% EtOAc/hexanes) to give 2.60 g (83%) of a clear oil. ^{1}H NMR ($CDCl_3$, 300 MHz); δ 3.76 (dd, J = 1.8, 7.5 Hz, 1H), 3.43 (m, 2H), 2.59 (m, 1H), 2.12 (m, 1H), 2.04 (d, J = 2.7 Hz, 1H), 1.19 (d, J = 6.9 Hz, 3H), 0.90 (m, 21H), 0.08 (m, 12H); ^{13}C NMR ($CDCl_3$, 75 MHz) ppm 86.3, 78.3, 69.9, 69.5, 69.4, 36.2, 30.2, 25.8, 17.7, 9.3, −5.6. −5.7.

(2*R*,3*R*,4*S*)-(−)-1,3-Bis(*tert*-butyldimethylsilyloxy)-2,4-dimethylhexane (6). General Procedure for the Hydrogenation of Alkynes. To a stirring solution of alkyne **5** (3.50 g, 9.44 mmol) in dry EtOH (50 mL) was added 5% Pt−C (1.84 g). The mixture was stirred under a hydrogen atmosphere for 4 h followed by addition of Norite decolorizing charcoal. Filtration through a column of Celite on silica gel and concentration under reduced pressure afforded 3.29 g (93%) of the reduced product as a clear oil that was used without further purification. ^{1}H NMR ($CDCl_3$, 300 MHz); δ 3.67 (dd, J = 1.2, 4.5 Hz, 1H), 3.47 (dd, J = 7.2, 9.6, 1H), 3.36 (dd, J = 6.3, 9.6 Hz, 1H), 1.76 (m, 1H), 1.49 (m, 2H), 1.04 (m, 1H), 0.84−0.96 (m, 27H), 0.032 (m, 12H).

(2*R*,3*R*,4*S*)-(−)-3-(*tert*-Butyldimethylsilyloxy)-2,4-dimethyl-1-hexanol (7). General Procedure for Selective Desilylation. To a solution of silyl ether **6** (3.24 g, 8.65 mmol) in 95% EtOH (87 mL) was added PPTS (217 mg, 0.865 mmol, 0.100 equiv). The mixture was stirred for 18 h, quenched with TEA (1 mL), and concentrated under reduced pressure. The residue was chromatographed on silica gel (gradient elution with 5% to 25% EtOAc/hexanes) to give 1.87 g (83%) of alcohol **7** as a clear oil. $[\alpha]^{20}_D$ −3.82 (*c* 1.96, $CHCl_3$); IR (neat) *v* 3353, 2960, 2951, 2855 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz); δ 3.63 (m, 2H), 3.45 (dd, J = 6.0, 10.5 Hz, 1H), 2.20 (s, 1H) 1.91 (m, 1H), 1.49 (m, 2H), 1.14 (m, 1H), 0.94 (m, 18H), 0.08 (m, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) ppm 77.2, 66.4, 39.5, 38.1, 27.3, 26.0, 25.6, 18.3, 15.3, 12.6, 12.2, −4.1, −4.2. Anal. Calcd for $C_{14}H_{32}O_2Si$: C, 64.55; H, 12.38. Found: 64.63, 12.57.

(2*S*,3*R*,4*S*)-3-(*tert*-Butyldimethylsilyloxy)-2,4-dimethylhexanal (8). General Procedure for Swern Oxidation of Alcohols (Oxidation Procedure A). To a stirring solution

of oxalyl chloride (0.080 mL, 0.92 mmol, 1.5 equiv) in CH_2Cl_2 (5 mL) at −78 °C was added DMSO (0.131 mL, 1.84 mmol, 3.00 equiv). The mixture was stirred for 15 min, and then alcohol **7** (160 mg, 0.614 mmol) in CH_2Cl_2 (1 mL) was added over 15 min, followed by triethylamine (0.385 mL, 2.70 mmol, 4.50 equiv) addition over 10 min. After 3 h, the temperature was raised to −40 °C, and the reaction was quenched with $NaHCO_3$. The layers were separated, and the CH_2Cl_2 layer was washed with water, dried over $MgSO_4$, and filtered. After concentration under reduced pressure, the oil was triturated with hexanes, filtered, and concentrated uder reduced pressure to give 119 mg (75%) of aldehyde **8** as a pale yellow oil which was used without further purification. ^{1}H NMR ($CDCl_3$, 300 MHz); δ 9.82 (s, 1H), 3.99 (m, 1H), 2.52 (m, 1H), 1.49 (m, 2 H), 1.15 (m, 1H), 1.07 (d, J = 6.6 Hz, 3H), 0.89 (m, 15H), 0.05 (m, 6H).

(2*R*,3*R*,4*R*)-1-*tert*-Butyldimethylsilyloxy-2,4-dimethyl-5-hexyn-3-ol (9). Standard Procedure for Allenylzinc Addition. To a stirring solution of $Pd(OAc)_2$ (5.5 mg, 0.025 mmol, 0.050 equiv) in THF (4.9 mL) at −78 °C was added PPh_3 (6.5 mg, 0.025 mmol, 0.050 equiv), aldehyde **8** (100 mg, 0.49 mmol), and mesylate (*R*)-**1** (109 mg, 0.74 mmol, 1.50 equiv). Diethylzinc (1.5 mL, 1 M in hexane, 3.00 equiv) was added over 10 min, and after stirring for 5 min the mixture was warmed to −20 °C and stirred overnight. The reaction was quenched with NH_4Cl:Et_2O (1:1), and the layers were separated. The Et_2O layer was washed with brine and stirred with $MgSO_4$ and Norite decolorizing charcoal. The solution was filtered and concentrated, followed by purification by column chromatography on silica gel (elution with 2.5% EtOAc/hexanes) to give 86.4 mg (68%) of product as a separable 95:5 mixture of alcohol **9** and its diastereomer **14** as a light yellow oil. The ^{1}H NMR spectrum was identical to that of a sample previously prepared through allenylindium addition to aldehyde **8**.[6d]

(3*R*,4*R*,5*R*,6*R*,7*S*)-(+)-6-(*tert*-Butyldimethylsilyloxy)-3,5,7-trimethyl-1-nonyn-4-ol (29). The general procedure for allenylzinc addition reactions was employed with $Pd(OAc)_2$ (35.0 mg, 0.155 mmol, 0.050 equiv), THF (31 mL), PPh_3 (41.0 mg, 0.155 mmol, 0.050 equiv), aldehyde **8** (800 mg, 3.10 mmol), mesylate (*S*)-**1** (690 mg, 4.65 mmol, 1.50 equiv), and diethylzinc (9.30 mL, 1 M in hexane) to give 619 mg (64%) of product as a separable 92:8 mixture of alcohol **29** and its diastereomer **27** as a light yellow oil. $[\alpha]^{20}_D$ +8.72 (*c* 2.12, $CHCl_3$); IR (neat) ν 3481, 3301, 2960, 2925, 2846 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz); δ 3.80 (m, 1H), 3.41 (m, 1H), 2.61 (m, 1H), 2.03 (m, 2H), 1.41 (m, 1H), 1.28 (d, J = 7.2 Hz, 3H), 0.96 (d, J = 6.9 Hz, 3H), 0.87 (m, 12H), 0.81 (d, J = 6.9 Hz, 3H), 0.11 (s, 3H), 0.07 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) ppm 84.7, 78.6, 75.8, 70.3, 41.5, 37.2, 30.2, 28.0, 30.0, 18.2, 17.8, 15.6, 12.9, 12.0, −4.2, −4.6.

syn-1,3-Diol Acetonide 44. General Procedure for Acetonide Formation (Procedure A). To a stirring solution of homopropargylic alcohol **27** (33.2 mg, 0.106 mmol) in THF (1.1 mL) was added 6 N HCl (1.1 mL). The reaction mixture was stirred for 4 h, quenched with $NaHCO_3$, and extracted with Et_2O. The extracts were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was chromatographed on silica gel (elution with 25% EtOAc/hexanes) and concentrated under reduced pressure to give 14.2 mg (67%) of crude diol **43**, which was used without further purification.

To a stirring solution of diol **43** (14.2 mg, 0.0720 mmol) in 2,2-dimethoxypropane (0.21 mL) at room temperature was added CSA (16.6 mg, 0.0720 mol, 1.00 equiv). The reaction mixture was stirred for 3 h, quenched with water, and extracted with ether. The extracts were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The product was chromatographed on silica gel (elution with 5% EtOAc/hexanes) to give 9.9 mg (58%) of acetonide **44** as a clear oil. ^{13}C NMR ($CDCl_3$, 75 MHz) ppm 99.1, 87.4, 77.7, 68.3, 35.3, 30.4, 29.9, 28.5, 23.5, 19.3, 15.9, 15.4, 10.8, 4.3.

syn-1,3-Diol Acetonide 48. General Procedure for Acetonide Formation (Procedure B). To a stirring solution of homopropargylic alcohol **31** (43.3 mg, 0.138 mmol) in THF (0.6 mL) was added TBAF (0.2 mL, 1 M in THF). The reaction mixture was stirred for 1 h, quenched with sat. NaCl (aq), and extracted with Et_2O. The extracts were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was chromatographed on silica gel (elution with 25% EtOAc/hexanes) and concentrated under reduced pressure to give 18.1 mg (94%) of diol **47**, which was used without further purification.

To a stirring solution of diol **47** (25.9 mg of combined samples from two experiments, 0.131 mmol) in 2,2-dimethoxypropane (5 mL) at room temperature was added CSA (30.3 mg, 0.131 mol, 1.00 equiv). The reaction mixture was stirred for 1 h, quenched with water, and extracted with ether. The extracts were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The product was chromatographed on silica gel (elution with 2.5% EtOAc/hexanes) to give 26.2 mg (79%) of acetonide **48** as a clear oil. ^{13}C NMR ($CDCl_3$, 75 MHz) ppm 99.1, 87.4, 77.2, 76.9, 68.3, 35.1, 30.5, 29.9, 28.5, 25.2, 19.3, 15.9, 13.4, 10.3, 4.1.

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Supporting Information Available: Experimental procedures for **10**−**13**, **16**−**23**, **27**, **31**, **33**, **35**, **37**, **39**, **41**, **46**, **50**, **52**, **54**, and **55**; ^{1}H NMR spectra for **4**−**8**, **10**−**13**, **16**−**18**, **20**−**23**, **27**, **29**, **31**, **33**, **35**, **37**, **39**, **41**, and **55**; ^{13}C NMR spectra for **44**, **46**, **48**, **50**, **52**, and **54**. This information is available free of charge via the Internet at http://pubs.acs.org.

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