Stereoselective Hydroformylation: Key Step for the Assembly of Polypropionate Subunits

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An anti-selective hydroformylation of 2-propylidene-substituted 1,3-dioxanes **16**, **17**, and **26** with excellent levels of acyclic stereocontrol has been achieved. The basis of this result was a careful substrate design making use of a *syn*-pentane interaction as the decisive stereochemical control element. Confirmation of this working hypothesis came from conformational analysis studies on alkenic substrate **16** employing 2D NOESY experiments in solution and MACROMODEL/MM3* calculations. This stereoselective, transition metal-catalyzed, C−C bond-forming reaction could serve as a key step for the construction of the all-anti and syn-anti stereotriad building blocks **20**, **21**, and **31**, which should be well-suited for target-oriented polypropionate synthesis. Application of this methodology for the construction of a C5−C11 building block for the synthesis of bafilomycin A_1 is described.

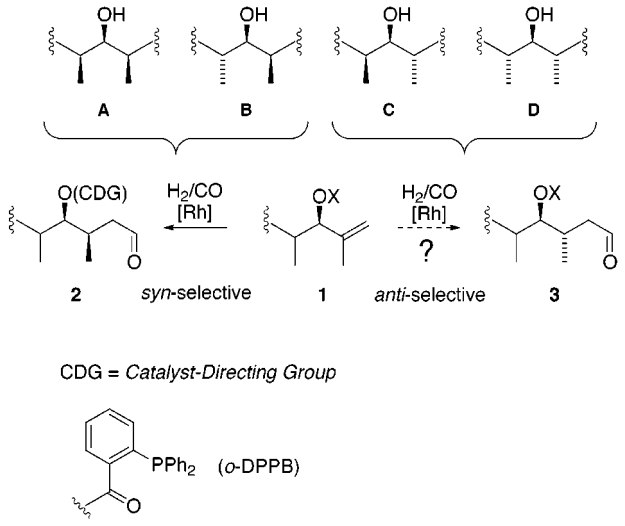
Introduction

An interesting class of natural products with an exceptional profile of biological activity are polypropionates.[1] Nature assembles these compounds along the polyketide pathway. However, the demand for a practical and flexible access to natural and artificial polypropionate structures has driven the development of important new synthetic methods.[2] Among these, a particularly useful strategy is to divide longer polypropionate chains into shorter subunits consisting of an alternating methyl-hydroxyl-methyl array.[3] The term stereotriad has been suggested for building blocks of this type. Subsequent combination of these units with the aid of fragment-coupling reactions allows the construction of more elaborate polyketide chains. Four different stereotriads may be differentiated (**A**−**D**, Scheme 1).

An attractive but hitherto unexplored alternative access to stereotriad structures could make use of a transition metal-catalyzed C−C bond-forming reaction. For instance, hydroformylation of a methallyl alcohol derivative **1** may furnish building blocks **2** or **3**, respectively, provided that stereochemistry of the hydroformylation could be controlled. In fact, we recently showed that a syn-selective hydroformylation (**1**→**2**) can be realized employing the concept of a substrate-bound catalyst-directing group (CDG).[4] As an ideal CDG, the *o*-diphenylphosphanyl benzoate system (*o*-DPPB) was identified.[5] Thus, hydroformylation of methallyl alcohol derivatives **4** and **6** gave the corresponding all-syn and anti-syn stereotriads **A** and **B** (Scheme 2) in excellent yield and diastereoselectivities on a multigram scale.[6]

Both structures are ideally equipped with functional groups that allow a facile chain extension into both directions of the main chain. However, since the CDG-controlled hydroformylation of methallyl alcohol deriva-

Scheme 1



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(1) See, for example: (a) Davies-Coleman, M. T.; Garson, M. J. *Nat. Prod. Rep.* **1998**, *15*, 477−493. (b) Rohr, J. *Angew. Chem., Int. Ed.* **2000**, *39*, 2847−2849. (c) Henkel, T.; Brunne, R. M.; Müller, H.; Reichel, F. *Angew. Chem., Int. Ed.* **1999**, *38*, 643−647. (d) Omura, S. *Macrolide Antibiotics*; Academic Press, Inc.: New York, 1984.

(2) See, for example: (a) Evans, D. A.; *Aldrichimica Acta* **1982**, *15*, 23−32. (b) Masamune, S.; Choy, W. *Aldrichimica Acta* **1982**, *15*, 47−64. (c) Mukayama, T. *Org. React.* **1982**, *28*, 203−331. (d) Heathcock, C. H. *Aldrichimica Acta* **1990**, *23*, 99−111. (e) Danishefsky, S. J. *Aldrichimica Acta* **1986**, *19*, 59−69. (f) Hanessian, S. *Aldrichimica Acta* **1989**, *22*, 3−14. (g) Marshall, J. A.; Perkins, J.; Wolf, M. A. *J. Org. Chem.* **1995**, *60*, 5556−5559. (h) Marshall, J. A.; Maxson, K. *J. Org. Chem.* **2000**, *65*, 630−633. (i) Vogel, P.; Sevin, A.-F.; Kernen, P.; Bialecki, M. *Pure Appl. Chem.* **1996**, 68, 719−722. (j) Jain, N. F.; Takenaka, N.; Panek, J. S. *J. Am. Chem. Soc.* **1996**, *118*, 12475−12476. (k) Hanessian, S.; Wang, W.; Gai, Y.; Olivier, E. *J. Am. Chem. Soc.* **1997**, *119*, 10034−10041. (l) Hanessian, S.; Ma, J.; Wang, W. *Tetrahedron Lett.* **1999**, *40*, 4627−4630. (m) Hanessian, S.; Wang, W.; Gai, Y.; Olivier, E. *J. Am. Chem. Soc.* **1997**, *119*, 10034−10041.

(3) Hoffmann, R. W. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 489.

(4) Breit, B. *Chem. Eur. J.* **2000**, *6*, 1519−1524.

(5) (a) Breit, B. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2835−2837. (b) Breit, B. *Liebigs Ann. Chem.* **1997**, 1841−1851.

(6) Breit, B.; Dauber, M.; Harms, K. *Chem. Eur. J.* **1999**, *5*, 2819−2827.

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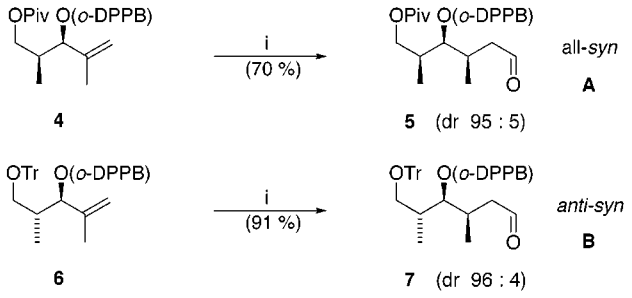
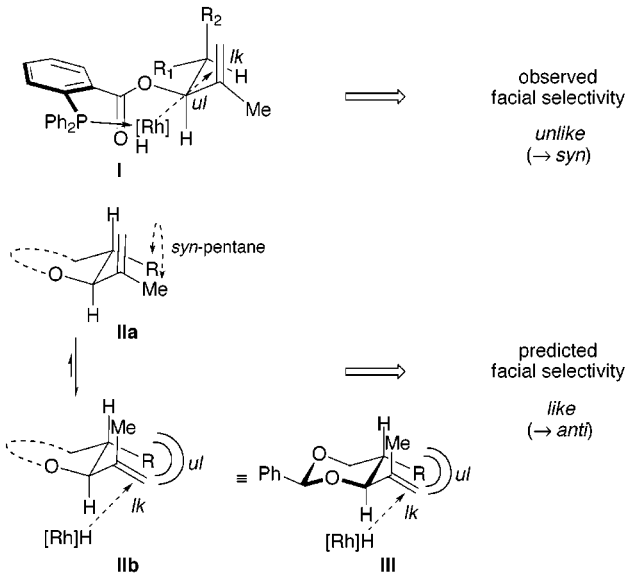
Scheme 2[a]



[a] Reaction conditions: (i) 0.7 mol % $[Rh(CO)_2acac]$, 2.8 mol % $P(OPh)_3$, toluene, 90 °C, 20 bar (H_2/CO, 1:1), 24 h.

Scheme 3



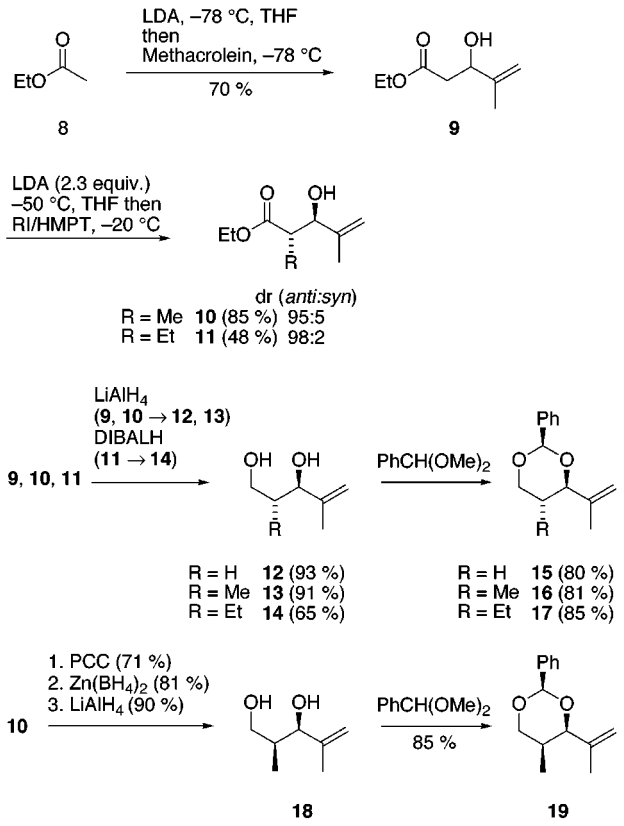
tives is strictly syn-selective, this approach is restricted so far to the construction of stereotriads **A** and **B**. To provide a similar entry to stereotriads **C** and **D**, an anti-selective hydroformylation reaction becomes mandatory.

We herein describe in full detail on the development of such an anti-selective hydroformylation reaction, which enables the construction of stereotriad building blocks **C** and **D**. Additionally, we report on a first application of this methodology for the rapid assembly of a C5−C11 building block for the synthesis of bafilomycin A_1.[7]

Concept

The design of an anti-selective hydroformylation of methallyl alcohol derivatives started out from our hypothesized working model **I**, which describes the mode of action of the catalyst-directing *o*-DPPB group (Scheme 3). According to this model, the substrate passes reactive conformation **I**, preferentially, within the stereochemistry-determining hydrometalation step of the hydroformylation reaction. Thus, the ester unit within **I** adopts the typical preferred conformation of an ester derived from a secondary alcohol.[8] The catalytically active rhodium hydride species is coordinated to the phosphine function of the *o*-DPPB group and thus gets delivered to the ul face of the alkene because of minimziation of $A^{1,2}$ strain.

Scheme 4



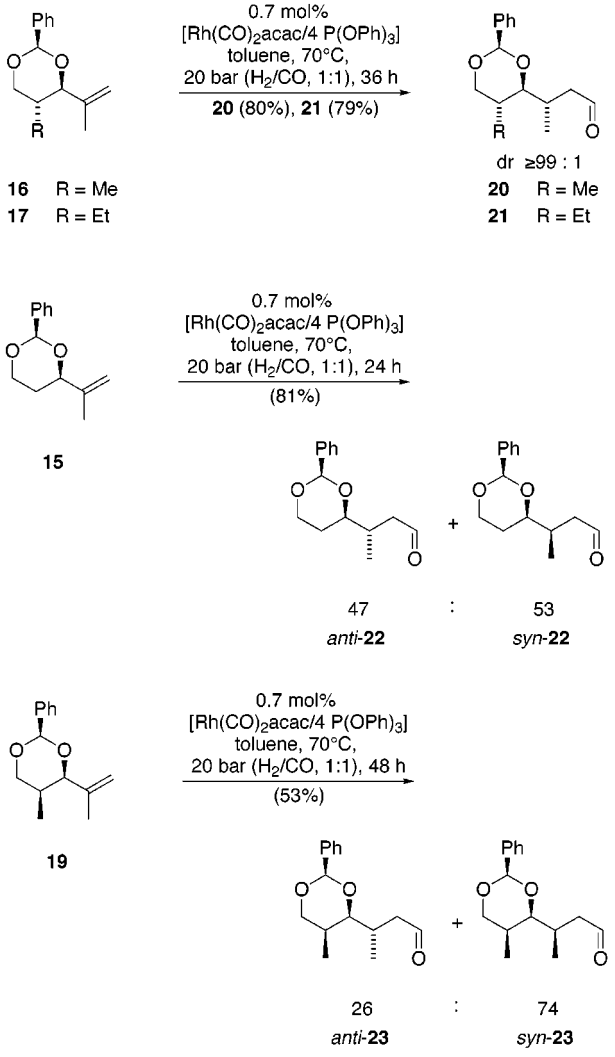
Hence, to achieve an anti-selective hydroformylation, the catalyst has to be forced to approach the lk face of the alkene function. For instance, if one would place a substituent R in a pseudoequatorial position, as indicated in **IIa**, a repulsive *syn*-pentane interaction would arise. The system will be forced to avoid this repulsive interaction and thus may adopt conformation **IIb**. Interestingly, in this case, the ul face of the alkene would be shielded by the substituent R, which may force the catalyst to approach from the lk face. The desired anti-selective hydroformylation would be the result. As a way to fix the crucial substituent R in the required equatorial-like position, we considered the incorporation of the system into a conformationally well-defined six-membered ring. For synthetic reasons, benzylidene acetals **III** were chosen.

Results and Discussion

Preparation of Alkenic Substrates. The starting point for the synthesis of the desired alkenic substrates was the addition of the enolate of ethyl acetate **8** to methacrolein to give the unsaturated *β*-hydroxy ester **9** (Scheme 4). This was transformed into the enolate with LDA (2.3 equiv) followed by treatment with excess alkyliodide in HMPT, according to the conditions of Fràter,[9] to give the methallyl alcohol derivatives **10** and **11**. Subsequent hydride reduction of esters **9**−**11** gave the diols **12**−**14** that were readily transformed into the benzylidene acetals **15**−**17**. In a similar manner, syn-derivative **19** was obtained from the known diol **18**.[10]

(7) Breit, B.; Zahn, S. K. *Tetrahedron Lett.* **1998**, *39*, 1901−1904.
(8) Schweizer, W. B.; Dunitz, J. D. *Helv. Chim. Acta* **1982**, *63*, 1547−1554.
(9) Fráter, G.; Müller, U.; Günther, W. *Tetrahedron* **1984**, *40*, 1269−1270.
(10) Nakata, T.; Fukui, M.; Ohtsuha, H.; Oishi, T. *Tetrahedron* **1984**, *40*, 2225−2231.

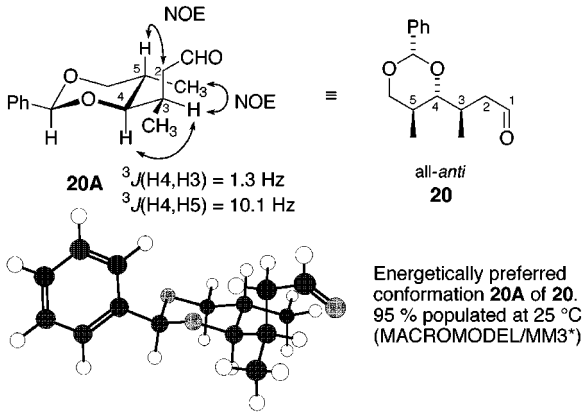
Scheme 5



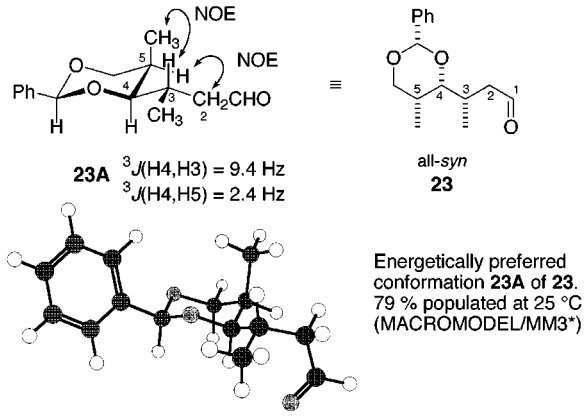
Hydroformylation of 2-Propylidene-Substituted 1,3-Dioxanes and Determination of Configuration: Construction of Stereotriads D. When the benzylidene acetals **16** and **17** were subjected to hydroformylation conditions (Scheme 5), aldehydes **20** and **21** were obtained in good yield and excellent diastereoselectivity (anti:syn ≥ 99:1). Conversely, for derivative **15**, which lacks the anti-configured methyl substituent, a stereorandom hydroformylation was observed. The hydroformylation of *syn*-acetal **19** proceeded rather sluggishly to give in low yield a mixture of *anti*-**23** and *syn*-**23** with reversed diastereoselectivity (26:74).

The configuration of the product aldehydes was determined by the combined use of experimental and theoretical methods. Thus, 2D NOESY spectroscopy and a conformational search performed with MACROMODEL/MM3* allowed determination of the preferred conformation of **20** in solution.[11,12] Accordingly, aldehyde **20** adopts conformation **20A** shown in Scheme 6 to the extent of 95% at 25 °C. Thus, the equatorial position of both alkyl substituents at C5 and C4 is reflected in the large vicinal coupling constant *J* (H4, H5) of 10.1 Hz. Decisive structural proof however was provided by 2D NOESY spectra. Thus, strong NOE contacts were observed between the proton at C3 and the methyl group at C5 as well as between the proton at C5 and the C2 methylene group. The small vicinal coupling *J* (H4, H3) of 1.3 Hz is

Scheme 6



Scheme 7



in agreement with the Carplus−Conrey equation and thus further supports the orientation of H3. Hence, aldehyde **20** occupies the indicated conformation **20A** in solution and thus posseses the all-anti configuration.

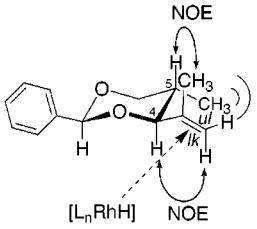
The configuration of the all-syn aldehyde **23** was determined in a similar manner. A conformational search performed with MACROMODEL/MM3* identified conformation **23A** shown in Scheme 7 to be populated to the extent of 79% at 25 °C.[12] In accord with this theoretical result are the vicinal coupling constants *J* (H4, H3) and *J* (H4, H5) with 9.4 and 2.4 Hz, respectively, as well as the observed NOE contacts (Scheme 7).

Model for Anti-Selective Hydroformylation. To rationalize the results of the hydroformylation, the stereochemistry determining step of the hydroformylation—the hydrometalation—had to be considered. This step has been shown to have a low activation barrier

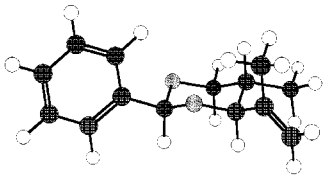
(11) For the combined use of vicinal coupling constants, 2D NOESY, and MM3 force-field calculations to determine preferred conformations of acyclic molecules in solution, see: (a) Breit, B. *Eur. J. Org. Chem.* **1998**, *1123*, 3−1134. (b) Göttlich, R.; Kahrs, C.; Krüger, J.; Hoffmann, R. W. *J. Chem. Soc., Chem. Commun.* **1997**, 247−251. (c) Göttlich, R.; Schopfer, U.; Stahl, M.; Hoffmann, R. W. *Liebigs Ann./Recl.* **1997**, 1757−1764. (d) Smith, R. J.; Williams, D. H.; Barna, J. C. J.; McDermott, I. R.; Haegele, K. D.; Piriou, F.; Wagner, J.; Higgins, W. *J. Am. Chem. Soc.* **1985**, *107*, 2849−2857. (e) Neuhaus, D.; Williamson, M. P. *The Nuclear Overhauser Effect in Structural and Conformational Analysis*; VCH: New York, 1989; p 412 and Chapter 11.

(12) Macromodel: Mohadi, F.; Richardson, N. G. J.; Guida, W. C.; Liskamp, R.; Lipto, M.; Caufield, C.; Chang, G.; Hendrickson, T.; Still, W. C. *J. Comput. Chem.* **1990**, *11*, 440−467. For compounds **16**, **20**, and **23**, molecular mechanics calculations (Monte Carlo conformational search) have been performed employing the MM3* force field implemented in Macromodel v6.0. A Boltzmann distribution over all low energy conformers (E_{rel} <25 kJ·mol^{-1} above the most stable conformer) resulted in the conformer population reported. For more details, see Supporting Information.

Scheme 8



Preferred conformation of **16** in solution according to 2D NOESY experiments.



16A

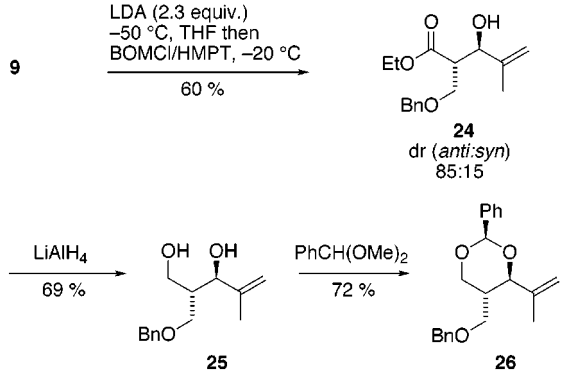
Energetically preferred conformation **16A** of **16**. 95 % populated at 25 °C (MACROMODEL/MM3*)

(≤10 kJ/mol) and to be exothermic and irreversible for most rhodium/triarylphosphine or phosphite catalysts.[13] Hence, according to the Hammond postulate, an early transition state is most likely. In this case, conformational effects stabilizing the ground state may well be effective in the structurally related transition state for hydrometalation. For these reasons, we investigated the preferred conformation of **16** (Scheme 8) in solution, employing 2D NOESY experiments. Accordingly, benzylidene acetal **16** adopts the preferred conformation **16A** in solution at 25 °C, as proposed by our model. This observation was confirmed by MACROMODEL/MM3* conformational search, indicating conformation **16A** to be populated to the extent of 95% at 25 °C.[12] This strong conformational preference originates from minimization of a repulsive *syn*-pentane interaction between the two methyl substituents as well as from minimization of the $A^{1,3}$ strain[14] within the alkene unit. Hence, the ul face of the alkene is shielded by the equatorially positioned methyl group at C5, which forces the catalyst to approach from the less hindered lk face. Thus, the methyl substituent at C5 is crucial and plays a 2-fold role. First, because of minimization of *syn*-pentane interaction, it induces a highly preferred conformation of the alkene moiety. Second, the same substituent shields the ul face and thus controls the catalyst approach to occur almost exclusively at the lk face.

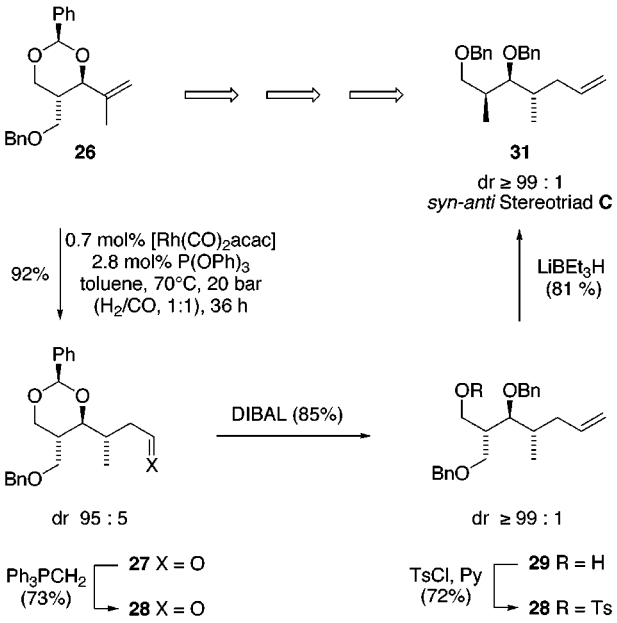
This interpretation was further supported by the results obtained for the benzylidene acetals **15** and **19** (Scheme 5). In these cases, the equatorial methyl substituent is either missing or oriented in an axial position. Accordingly, stereoinduction in the course of the hydroformylation of **15** and **19** was either absent (**15**) or rather low and reversed (**19**). Thus, the diastereoselective hydroformylation of benzylidene acetals **16** and **17** represents a special case, which allows the stereoselective construction of the all-anti stereotriad **D**.

Anti-Selective Hydroformylation for the Construction of Stereotriad C. The hydroformylation methodology developed so far provides access to stereotriad building blocks **A**, **B**, and **D**. Since the attempt of an anti-selective hydroformylation of *syn*-acetal **19** failed to give the desired stereotriad **C** building block *anti*-**23** as the major diastereomer (Scheme 5), an alternative access had to be found. Toward this end, we envisioned

Scheme 9



Scheme 10



benzyloxy-substituted benzylidene acetal **26** (Scheme 9) as the optimal precursor for an anti-selective hydroformylation. Functional group manipulations should allow transformation into a stereotriad **C** building block (Scheme 10).

Synthesis of the benzylidene acetal **26** commenced with an anti-selective Fràter alkylation of the dianion of *β*-hydroxyester **9** with BOMCl (Scheme 9). Standard $LiAlH_4$ reduction and benzylidene acetal protection provided alkene **26**.

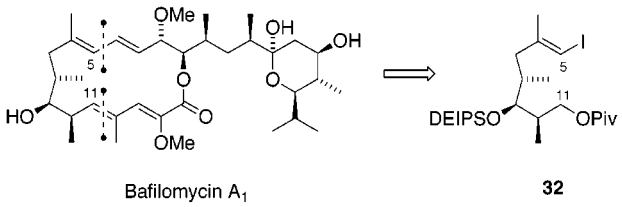
The sequence for the construction of the stereotriad **C** building block **31** started with the hydroformylation of acetal **26** (Scheme 10). Employing 0.7 mol % of a rhodium/triphenyl phosphite catalyst at 20 bar H_2/CO (1:1) and at 70 °C for 36 h gave aldehyde **27** in good yield (92%) and diastereoselectivity (anti:syn = 95:5). The reactive aldehyde function was transformed into a less reactive alkene by way of a Wittig olefination to give the terminal alkene **28**. Any other transformation of the aldehyde function may be envisioned at this stage. Regioselective benzylidene acetal ring opening with DIBAL yielded the primary alcohol **29**. Reductive removal of the alcohol function was achieved in two steps via the tosylate **30** followed by Super-Hydride reduction to give the desired syn-anti stereotriad building block **31** in diastereomerically pure form.

Bafilomycin A_1 C5−C11 Building Block Synthesis. The macrolide antibiotic bafilomycin A_1 constitutes

(13) (a) Jardine, F. H. *Polyhedron* **1982**, *1*, 569−605. (b) Ziegler, T.; Versluis, L. *Adv. Chem. Ser.* **1992**, *230*, 75−93. (c) van Leeuwen, P. W. N. M.; van Koten, G. *Stud. Surf. Sci. Catal.* **1993**, *79*, 199. (d) Horiuchi, T.; Shirakawa, E.; Nozaki, K.; Takaya, H. *Organometallics* **1997**, *16*, 2981−2986. (e) Casey, C. P.; Petrovich, L. M. *J. Am. Chem. Soc.* **1995**, *117*, 6007−6014.

(14) Hoffmann, R. W. *Chem. Rev.* **1989**, *89*, 1841−1860.

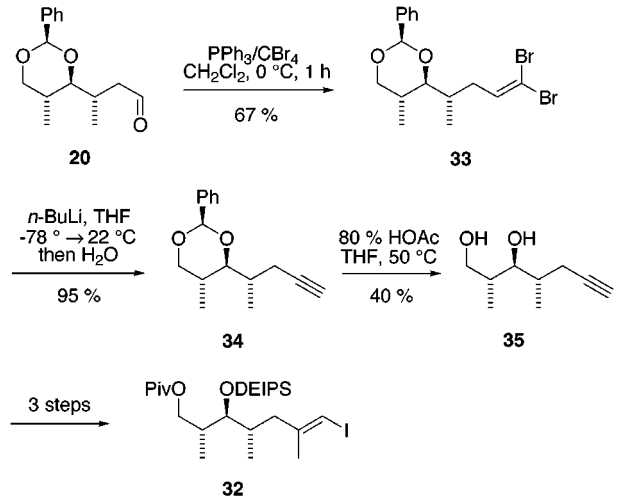
Scheme 11[a]



Bafilomycin A_1 **32**

[a] DEIPS = diethylisopropyl silyl.

Scheme 12



20 **33** **34** **35** **32**

an attractive target to explore the synthetic utility of the methodology described herein. Following the convergent retrosynthetic analysis, according to Toshima et al., the known C5−C11 building block **32** became of primary interest (Scheme 11).[15] This building block **32** has been synthesized employing a rather long sequence consisting of 13 steps.[15]

Our synthesis of **32** started from β-hydroxyester **9**. Its resolution employing the Sharpless epoxidation protocol has been described.[16] Fráter alkylation, reduction, and protection as the benzylidene acetal provided alkene **16**, which was hydroformylated to give aldehyde **20**. Subsequent Corey−Fuchs chain elongation furnished the terminal acetylene **34**,[17] which was deprotected to afford the 1,3-diol **35** (Scheme 12). Transformation of this diol into the key building block **32** within three steps has been reported previously.[15] Thus, hydroformylation methodology provides an efficient access to the central building block **32** for the total synthesis of the macrolide bafilomycin A_1.

Conclusion

Anti-diastereoselective hydroformylation of benzylidene acetals **16**, **17**, and **26** has been achieved with high levels of acyclic stereocontrol. This result could be achieved on the basis of a careful substrate design making use of *syn*-pentane interaction as a stereochemical control element. All-anti stereotriad building blocks **20** and **21** as well as the syn-anti stereotriad building block **31** could be obtained in good yield and excellent levels of diastereoselectivity. These stereotriad building blocks are ideally prepared to allow facile polyketide chain extension into both directions of the main chain. Hence, the complete set of all four possible stereotriads is now accessible via stereoselective hydroformylation chemistry. A first application of this methodology was demonstrated with the efficient synthesis of a C5−C11 building block for the synthesis of bafilomycin A_1.

Experimental Section

General. Reactions were performed in flame-dried glassware either under argon (purity >99.998%) or under nitrogen. The solvents were dried by standard procedures, distilled, and stored under argon. All temperatures quoted are not corrected. ^{1}H and ^{13}C NMR spectra were recorded on 200, 300, 400, and 500 spectrometers (p = pseudo, m_c = multiplet centered). Melting points: melting point apparatus by Dr. Tottoli (Büchi). Elemental analyses: CHN-rapid analyzer (Heraeus). Flash chromatography: silica gel 40−63 μm. Hydroformylation reactions were performed in 100 and 200 mL stainless steel autoclaves equipped with magnetical stirrers. Gases: carbon monoxide (2.0) and hydrogen (3.0). The following compounds have been prepared by known procedures: **9**,[16] **10**,[6] **13**,[6] and **18**.[6]

Ethyl-(2*R,3*S**)-(±)-3-hydroxy-2-ethyl-4-methylpent-4-enoate (11).** To a solution of diisopropylamine (2.32 g, 23.0 mmol) in THF (4 mL) was added dropwise a solution of 1.48 M *n*-butyllithium in hexanes (15.5 mL, 23.0 mmol) at −78 °C. The solution was allowed to warm to 0 °C and stirred for another 15 min at this temperature, followed by cooling to −50 °C. Subsequently, ester **9** (1.58 g, 10.0 mmol) was added such that the temperature of the reaction mixture rose to −25 °C, followed by addition of a solution of ethyliodide (15.6 g, 100 mmol) in HMPT (2 mL) such that the temperature of the reaction mixture rose to 0 °C, and it was stirred for another 2.5 h at this temperature. The reaction mixture was quenched at 0 °C by addition of saturated aqueous NH_4Cl solution (15 mL) and water (20 mL). The organic phase was separated, and the aqueous phase was washed with two portions of *tert*-butyl methyl ether (20 mL each). The combined organic phases were dried ($NaSO_4$), and the solvent was removed in vacuo. GC analysis of the residual oil showed a conversion of 82% and a dr (anti:syn) of >98:2. The crude product was purified by flash chromatography with petroleum ether/EtOAc (9:1) to give **11** (900 mg, 48%) as a colorless oil. ^{1}H NMR (300.133 MHz, $CDCl_3$): δ 0.87 (pt, J = 7.5 Hz, 3H), 1.22 (t, J = 7.1 Hz, 3H), 1.43−1.63 (m, 2H), 1.69 (s, 3H), 2.48 (ddd, J = 9.3, 7.2, 5.2 Hz, 1H), 2.63 (bs, 1H, OH), 4.05−4.18 (m, 3H), 4.86 (m_c, 1H), 4.92 (m_c, 1H). ^{13}C NMR (75.469 MHz, $CDCl_3$): δ 11.6, 14.2, 17.4, 22.7, 50.5, 60.4, 76.4, 113.0, 144.9, 175.2. Anal. Calcd for $C_{10}H_{18}O_3$: C, 64.49; H, 9.74. Found: C, 64.72; H, 9.81.

(2*R,3*R**)-(±)-2-Ethyl-4-methylpent-4-en-1,3-diol (14).** To a solution of DIBALH (8 mL, 1 M in hexane) in toluene (2.5 mL) was added at 0 °C a solution of ester **11** (466 mg, 2.5 mmol) in toluene (1.5 mL). After the mixture was stirred for 20 min at this temperature, TLC showed complete consumption of the starting material. The reaction was quenched by the subsequent addition of a solution of methanol in toluene (3.5 mL, 1:1) and water (5 mL). After the solution was stirred for 30 min at ambient temperature, a colorless precipitate formed that was removed by filtration over Celite followed by washing with additional *tert*-butyl methyl ether (200 mL). The combined organic phases were dried ($MgSO_4$) and concentrated, and the residual colorless oil was purified by flash chromatography with petroleum ether/EtOAc (7:3) to give diol **14** (234 mg, 65%) as colorless platelike crystals: mp 52−56 °C. ^{1}H NMR (300.133 MHz, $CDCl_3$): δ 0.91 (pt, J = 7.4 Hz, 3H), 1.21−1.44 (m, 2H), 1.57 (m_c, 1H), 1.70 (m, 3H), 2.94 (bs,

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1H), 3.06 (bs, 1H), 3.63 (dd, J = 10.8, 6.4 Hz, 1H), 3.82 (d, J = 10.6 Hz, 1H), 4.06 (d, J = 7.0 Hz, 1H), 4.86 (m_c, 1H), 4.94 (m_c, 1H). ^{13}C NMR (75.469 MHz, $CDCl_3$): δ 11.7, 17.7, 21.1, 43.5, 64.1, 80.3, 112.5, 146.4. Anal. Calcd for $C_8H_{16}O_2$: C, 66.63; H, 11.18. Found: C, 66.50; H, 11.39.

(±)-4-Methyl-pent-4-en-1,3-diol (12). To a suspension of $LiAlH_4$ (248 mg, 6.5 mmol) in ether (30 mL) was added at 0 °C dropwise a solution of ester **9** (791 mg, 5.0 mmo) in ether (5 mL). After the mixture was stirred for 1 h at this temperature, TLC showed complete consumption of the starting material. The reaction mixture was quenched by the subsequent addition of water (0.25 mL), 15% aqueous NaOH (0.25 mL), and water (0.75 mL) and stirred for another 30 min at ambient temperature. Subsequently, $MgSO_4$ (4 g) was added, followed by filtration of the reaction mixture through a pad of Celite. The Celite pad was washed with *tert*-butyl methyl ether (100 mL), and the combined organic phases were concentrated in vacuo. Purification of the crude product via flash chromatography with petroleum ether/EtOAc gave diol **12** (540 mg, 93%) as a colorless oil. ^{1}H NMR (300.133 MHz, $CDCl_3$): δ 1.64 (s, 3H), 1.66−1.75 (m, 2H), 3.68 (m_c, 2H), 4.16 (dd, 1H, J = 7.4 Hz, J = 4.9 Hz, 1H), 4.76 (m_c, 1H), 4.91 (m_c, 1H). ^{13}C NMR (75.469 MHz, $CDCl_3$): δ 17.9, 36.5, 60.5, 74.4, 110.4, 147.1. Analytical data correspond to those reported previously.[18]

General Procedure for Benzylidene Acetal Formation. To a solution of 1,3-diol (1 equiv) and (2-dimethoxymethyl)-benzene (1−1.1 equiv) in CH_2Cl_2 (0.2 M) was added *p*-toluenesulfonic acid monohydrate (5 mol %). After the mixture was stirred for 17 h at ambient temperature, TLC showed complete consumption of the starting material. Saturated aqueous $NaHCO_3$ solution was added, and the organic layer was separated. The aqueous layer was washed with two portions of CH_2Cl_2. The combined organic layers were dried ($MgSO_4$) and concentrated. Flash chromatography petrol ether/*tert*-butyl methyl ether (19:1) gave the corresponding benzylidene acetals as colorless oils.

(2*R,4*R**,5*R**)-(±)-5-Methyl-2-phenyl-4-(prop-2-enyl)-[1,3]dioxane (16).** From diol **13** (1.69 g, 13.0 mmol) and (2-dimethoxymethyl)benzene (2.08 g, 13.7 mmol) was obtained acetal **16** (2.29 g, 81%). ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.71 (d, J = 6.7 Hz, 3H), 1.81 (s, 3H), 2.05 (m_c, 1H), 3.55 (pt, J = 11.1 Hz, 1H), 3.87 (d, J = 10.0 Hz, 1H), 4.18 (dd, J = 11.2, 4.7 Hz, 1H), 4.96−4.99 (m, 2H), 5.54 (s, 1H), 7.31−7.35 (m, 3H), 7.47−7.52 (m, 2H). ^{13}C NMR (50.329 MHz, $CDCl_3$): δ 12.3, 17.5, 31.2, 73.1, 88.2, 101.1, 114.9, 126.2 (2C), 128.2 (2C), 128.7, 138.6, 142.6. Anal. Calcd for $C_{14}H_{18}O_2$: C, 77.03; H, 8.31. Found: C, 76.91; H, 8.40.

(2*R,4*R**,5*R**)-(±)-5-Ethyl-2-phenyl-4-(prop-2-enyl)[1,3]-dioxane (17).** From diol **14** (87 mg, 0.6 mmol) and (2-dimethoxymethyl)benzene (91 mg, 0.6 mmol) was obtained acetal **17** (118 mg, 85%). ^{1}H NMR (300.133 MHz, $CDCl_3$): δ 0.90 (pt, J = 6.7 Hz, 3H), 1.33−1.41 (m, 2H), 1.83 (s, 3H), 1.91 (m_c, 1H), 3.59 (t, J = 11.2 Hz, 1H), 3.96 (d, J = 10.1 Hz, 1H), 4.34 (dd, J = 11.3, 4.7 Hz, 1H), 4.97−5.00 (m, 2H), 5.53 (s, 1H), 7.28−7.38 (m, 3H), 7.47−7.52 (m, 2H). ^{13}C NMR (75.469 MHz, $CDCl_3$): δ 10.9, 17.5, 20.6, 37.4, 71.4, 87.1, 101.1, 115.2, 126.2 (2C), 128.1 (2C), 128.7, 138.7, 142.8. Anal. Calcd for $C_{15}H_{20}O_2$: C, 77.55; H, 8.68. Found: C, 77.35; H, 8.63.

(2*R,4*R**)-(±)-2-Phenyl-4-(prop-2-enyl)[1,3]dioxane (15).** From diol **12** (480 mg, 4.1 mmol) and (2-dimethoxymethyl)-benzene (624 mg, 4.1 mmol) was obtained acetal **15** (670 mg, 80%). ^{1}H NMR (500.130 MHz, $CDCl_3$): δ 1.60 (m_c, 1H), 1.81 (s, 3H), 1.97 (m_c, 1H), 4.01 (m_c, 1H), 4.25−4.32 (m, 2H), 4.90 (s, 1H), 5.07 (s, 1H), 5.58 (s, 1H), 7.30−7.37 (m, 3H), 7.50 (m_c, 2H). ^{13}C NMR (125.758 MHz, $CDCl_3$): δ 18.6, 30.1, 67.1, 80.0, 101.2, 111.1, 126.1 (2C), 128.1 (2C), 129.9, 138.8, 144.7. Anal. Calcd for $C_{13}H_{16}O_2$: C, 76.43; H, 7.90. Found: C, 76.19; H, 7.92.

(2*R,4*R**,5*S**)-(±)-2-Phenyl-4-(prop-2-enyl)-5-methyl-[1,3]dioxane (19).** From diol **18** (273 mg, 2.1 mmol) and (2-dimethoxymethyl)benzene (352 mg, 2.3 mmol) was obtained acetal **19** (391 mg, 85%). ^{1}H NMR (500.130 MHz, $CDCl_3$): δ 1.06 (d, J = 7.4 Hz, 3H), 1.71 (s, 3H), 1.76−1.80 (m, 1H), 4.06 (dd, J = 10.7, 1.3 Hz, 1H), 4.14 (dd, J = 10.7, 2.7 Hz, 1H), 4.34 (s, 1H), 4.93 (m_c, 1H), 5.12 (s, 1H), 5.57 (s, 1H), 7.31−7.39 (m, 3H), 7.53−7.55 (m, 2H). ^{13}C NMR (125.758 MHz, $CDCl_3$): δ 11.0, 19.1, 30.5, 73.3, 81.3, 101.5, 110.5, 126.2, 128.2 (2C), 128.7 (2C), 138.9, 142.2. Anal. Calcd for $C_{14}H_{18}O_2$: C, 77.03; H, 8.31. Found: C, 76.82; H, 8.26.

General Procedure for the Hydroformylation of 2-Propenylidene Acetals. To a solution of $[Rh(CO)_2(acac)]$ (0.9 mg, $3.5\cdot10^{-3}$ mmol) in toluene (3 mL) at 20 °C (exclusion of air and moisture), $P(OPh)_3$ (4.5 mg, $1.4\cdot10^{-2}$ mmol) was added, and the resulting mixture was stirred at this temperature for 15 min. Subsequently, the corresponding alkene (0.5 mmol) was added, and the resulting solution was cannulated into a stainless steel autoclave, which had been evacuated and refilled with argon several times. The flask and cannula were rinsed with an additional 2 mL of toluene. The autoclave was heated to 70 °C and then pressurized successively with carbon monoxide (10 bar) and hydrogen (10 bar), and the reaction mixture was stirred under these conditions for 24−36 h. The autoclave was then cooled rapidly to 20 °C, and the contents were filtered through a small plug of silica with 30 mL of *tert*-butyl methyl ether. After evaporation of the solvent in vacuo, the crude product was analyzed by GC and NMR to determine the diastereomer ratio. Subsequent flash chromatography with petroleum ether/*tert*-butyl methyl ether (4:1) provided the corresponding aldehydes.

(3*R)-(±)-3-[(2*S**,4*R**,5*S**)-5-Methyl-2-phenyl[1,3]-dioxane-4-yl]butanal (20).** Colorless oil (99 mg, 80%); diastereomer ratio ≥99:≤1 (anti:syn). ^{1}H NMR (300.133 MHz, $CDCl_3$): δ 0.79 (d, J = 6.6 Hz, 3H), 1.14 (d, J = 6.7 Hz, 3H), 1.89 (m_c, 1H), 2.41−2.55 (m, 2H), 2.60−2.70 (m, 1H), 3.38 (dd, J = 10.1, 1.3 Hz, 1H), 3.49 (pt, J = 11.1 Hz, 1H), 4.10 (dd, J = 11.2, 4.8 Hz, 1H), 5.46 (s, 1H), 7.31−7.39 (m, 3H), 7.43−7.47 (m, 2H), 9.82 (m_c, 1H). ^{13}C NMR (75.469 MHz, $CDCl_3$): δ 12.1, 18.3, 28.9, 31.2, 44.9, 72.9, 86.7, 101.2, 126.0 (2C), 128.1 (2C), 128.6, 138.7, 202.3. Anal. Calcd for $C_{15}H_{20}O_3$: C, 72.55; H, 8.12. Found: C, 72.56; H, 8.15.

(3*R)-(±)-3-[(2*S**,4*R**,5*S**)-5-Ethyl-2-phenyl[1,3]dioxane-4-yl]butanal (21).** Colorless oil (104 mg, 79%); diastereomer ≥99:≤1 (anti:syn). ^{1}H NMR (400.130 MHz, $CDCl_3$): δ 0.94 (pt, J = 7.3 Hz, 3H), 1.08 (m_c, 1H), 1.18 (d, J = 6.8 Hz, 3H), 1.51 (m_c, 1H), 1.78 (m_c, 1H), 2.48−2.57 (m, 2H), 2.65−2.70 (m, 1H), 3.51 (d, J = 10.2 Hz, 1H), 3.58 (pt, J = 11.2 Hz, 1H), 4.32 (dd, J = 11.2, 4.5 Hz, 1H), 5.48 (s, 1H), 7.36−7.42 (m, 3H), 7.49−7.51 (m, 2H), 9.86 (m_c, 1H). ^{13}C NMR (100.613 MHz, $CDCl_3$): δ 10.7, 18.3, 20.3, 28.5, 37.2, 44.8, 71.1, 85.1, 101.0, 125.9 (2C), 128.1 (2C), 128.6, 138.7, 202.4.

(3*R)-[(2*S**,4*R**)-(±)-2-Phenyl[1,3]dioxane-4-yl]butanal (*syn*-22) and (3*S**)-[(2*S**,4*R**)-(±)-2-Phenyl[1,3]dioxane-4-yl]butanal (*anti*-22).** Colorless oil (95 mg, 81%); diastereomer ratio 47:53 (anti:syn). ^{1}H NMR (300.133 MHz, $CDCl_3$): δ 0.99 (d, J = 6.6 Hz, 3H) [1.03 (d, J = 6.8 Hz, 3H)], 1.60 (m_c, 1H) [1.41 (m_c, 1H)], 1.70−1.93 (m, 1H), 2.21−2.44 (m, 2H), 2.63−2.74 (m, 1H), 3.58 (ddd, J = 10.7, 7.5, 2.5 Hz, 1H) [3.79 (ddd, J = 11.5, 4.2, 2.4 Hz, 1H)], 3.09 (m_c, 1H), 4.27 (m_c, 1H), 5.46 (s, 1H) [5.48 (s, 1H)], 7.31−7.36 (m, 3H), 7.43−7.47 (m, 2H), 9.73 (pt, J = 2.1 Hz, 1H) [9.76 (pt, J = 1.9 Hz, 1H)]. ^{13}C NMR (75.469 MHz, $CDCl_3$): δ 16.0 [15.0], 29.0 [27.1], 33.8 [32.5], 47.4 [46.7], 66.9, 80.6 [79.5], 101.1 [101.2], 126.0 [125.9] (2C), 128.1 (2C), 128.6 [128.7], 138.5 [138.7], 202.2 [202.0]. HRMS (EI) calculated for $C_{14}H_{18}O_3$, 234.1256; found, 234.1228.

(3*R)-(±)-3-[(2*R**,4*R**,5*S**)-5-Methyl-2-phenyl[1,3]-dioxane-4-yl]butanal (*syn*-23) and (3*S**)-(±)-3-[(2*R**,4*R**,5*S**)-5-Methyl-2-phenyl[1,3]dioxane-4-yl]butanal (*anti*-23).** Colorless oils, could be separated by flash chromatography. *syn*-**23** (46 mg, 37%), *anti*-**23** (19 mg, 15%). Diastereomer ratio of the crude product was 26:74 (anti:syn). *syn*-**23**: ^{1}H NMR (300.133 MHz, $CDCl_3$): δ 1.11 (d, J = 6.3 Hz, 3H), 1.18 (d, J = 6.9 Hz, 3H), 1.65 (m_c, 1H), 2.18 (ddd, J = 15.8, 9.3, 3.1 Hz, 1H), 2.28 (m_c, 1H), 2.46 (m_c, 1H), 3.61 (dd, J = 9.4, 2.4 Hz, 1H), 4.02 (dd, J = 11.4, 1.8 Hz, 1H), 4.06 (dd, J = 11.4, 1.9 Hz, 1H), 5.49 (s, 1H), 7.32−7.40 (m, 3H), 7.47−7.51 (m, 2H), 9.78 (dd, J = 12.9, 1.4 Hz, 1H). ^{13}C NMR (75.469 MHz,

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$CDCl_3$): δ 11.2, 16.7, 30.0, 30.3, 45.8, 73.8, 83.1, 101.8, 126.0 (2C), 128.2 (2C), 128.7, 138.8, 201.6. *anti*-**23**: ^{1}H NMR (300.133 MHz, $CDCl_3$): δ 0.92 (d, J = 6.7 Hz, 3H), 1.17 (d, J = 6.9 Hz, 3H), 1.71 (m_c, 1H), 2.19−2.37 (m, 2H), 2.70 (ddd, J = 15.9, 7.9, 2.4 Hz, 1H), 3.54 (dd, J = 9.8, 2.2 Hz, 1H), 4.03 (m_c, 2H), 5.44 (s, 1H), 7.30−7.39 (m, 3H), 7.43−7.48 (m, 2H), 9.68 (t, J = 2.1 Hz, 1H). ^{13}C NMR (75.469 MHz, $CDCl_3$): δ 10.7, 15.1, 29.7, 30.4, 48.3, 73.7, 83.6, 101.7, 125.9 (2C), 128.1 (2C), 128.6, 138.6, 202.4.

Ethyl-(2*R,3*S**)-(±)-2-(benzyloxymethyl)-3-hydroxy-4-methylpent-4-enoate (24).** To a solution of diisopropylamine (4.93 g, 48.7 mmol) in THF (20 mL) was added at −70 °C a solution of 1.55 M *n*-butyllithium in hexanes (31.5 mL, 48.7 mmol).The reaction mixture was allowed to warm to −20 °C, was kept for 30 min at this temperature, and was subsequently cooled to −70 °C. A solution of ester **9** (3.08 g, 19.5 mmol) in THF (3 mL) was added. The reaction mixture was allowed to warm to −20 °C and stirred for 1 h at −20 °C. A solution of HMPT (1 mL) in THF (3 mL) was added. The reaction mixture was cooled to −70 °C, and a solution of benzyloxymethyl chloride (4.90 g, 23.4 mmol) in HMPT (1 mL) and THF (10 mL) was added at such a rate as to keep the reaction temperature at −60 °C. The reaction mixture was allowed to warm to −20 °C, was stirred for 1.5 h at this temperature, and was then warmed to 0 °C. Subsequently, saturated aqueous NH_4Cl solution (50 mL) was added. The mixture was washed with water (200 mL), the organic phase was separated, and the aqueous phase was extracted 3× with *tert*-butyl methyl ether (100 mL each). The combined organic phases were dried (Na_2SO_4), and the solvent was removed in vacuo. Flash chromatography with petroleum ether/EtOAc (8:2) furnished the alkylation product **24** (3.28 g, 60%) as a pale yellow oil. The diastereomer ratio anti:syn was determined as 85:15 (^{1}H NMR). ^{1}H NMR (500.130 MHz, $CDCl_3$): δ 1.25 (pt, J = 7.4 Hz, 3H), 1.73 (s, 3H) [1.75], 2.98 (m_c, 1H), 3.65 (dd, J = 9.4, 5.4 Hz, 1H), 3.70 (dd, J = 9.4, 5.4 Hz, 1H), 4.18 (pq, J = 7.4 Hz, 2H), 4.34 (m_c, 1H), 4.48 (d, J = 12.1 Hz, 1H), 4.51 (d, J = 12.1 Hz, 1H), 4.90 (s, 1H), 4.97 (s, 1H), 7.26−7.36 (m, 5H). ^{13}C NMR (125.758 MHz, $CDCl_3$): δ 14.1 [14.0], 17.8, 49.3, 60.8 [60.7], 68.9 [68.7], 73.2 [73.4], 73.9, 112.8, 127.5 (2C), 127.6, 128.3 (2C), 137.8, 144.5, 173.3. Signals of the minor syn diatereomer are listed in brackets. Anal. Calcd for $C_{16}H_{22}O_4$: C, 69.04; H, 7.97. Found: C, 68.72; H, 8.05.

(2*R,3*S**)-(±)-2-(Benzyloxymethyl)-4-methylpent-4-en-1,3-diol (25).** To a suspension of $LiAlH_4$ (0.71 g, 18.7 mmol) in ether (60 mL) was added dropwise at 0 °C a solution of ester **24** (3.02 g, 10.8 mmol) in ether (30 mL). The reaction mixture was stirred for another 2 h at 0 °C until TLC showed complete consumption of the starting material. The reaction was quenched by successive addition of water (0.71 mL), 15% aqueous NaOH (0.71 mL), and water (2.13 mL) and stirred until a white precipitate formed. The mixture was extracted 3× with *tert*-butyl methyl ether (100 mL each), the combined organic phases were dried ($MgSO_4$), and the solvent was removed in vacuo. Flash chromatography with petroleum ether/*tert*-butyl methyl ether (1:1) furnished diol **25** (1.75 g, 69%) as a colorless viscous oil. Diastereomer ratio anti:syn (85:15). ^{1}H NMR (500.130 MHz, $CDCl_3$): δ 1.72 (s, 3H), 1.98 (m_c, 1H), 2.85 (bs, 1H), 3.00 (bs, 1H), 3.57 (dd, J = 9.3, 6.3 Hz, 1H), 3.63 (dd, J = 9.3, 6.3 Hz, 1H), 3.87 (m_c, 2H), 4.29 (d, J = 6.0 Hz, 1H), 4.47 (d, J = 12.0 Hz), 4.47 (d, J = 12.0 Hz, 1H), 4.92 (s, 1H), 5.02 (s, 1H), 7.26−7.36 (m, 5H). ^{13}C NMR (125.758 MHz, $CDCl_3$): δ 18.0 [18.4], 42.6 [42.8], 62.3 [63.0], 70.4 [69.3], 73.4 [73.6], 76.2 [75.7], 112.1 [111.7], 127.6 (2C), 127.7, 128.4 (2C), 138.0, 145.7. Signals of the minor syn diatereomer are listed in brackets. HRMS (EI) calculated for $C_{14}H_{20}O_3$, 236.1412; found, 236.1397.

(2*R,4*R**,5*R**)-(±)-5-(Benzyloxymethyl)-2-phenyl-4-(prop-2-enyl)[1,3]dioxane (26).** Following the general procedure for benzylidene acetal formation, from diol **25** (3.11 g, 13.0 mmol) and (2-dimethoxymethyl)benzene (1.98 g, 13.0 mmol) was obtained acetal **26** (3.04 g, 72%) in diastereomerically pure form as a colorless oil. ^{1}H NMR (500.130 MHz, $CDCl_3$): δ 1.82 (s, 3H), 2.28 (m_c, 1H), 3.30 (m_c, 1H), 3.36 (m_c, 1H), 3.92 (pt, J = 11.2 Hz, 1H), 4.25 (d, J = 10.4 Hz, 1H), 4.37−4.39 (m, 2H), 4.46 (d, J = 12.0 Hz, 1H), 4.97 (s, 1H), 5.03 (s, 1H), 5.55 (s, 1H), 7.29−7.53 (m, 10H). ^{13}C NMR (125.758 MHz, $CDCl_3$): δ 15.0, 36.9, 68.0, 70.0, 73.3, 83.4, 101.0, 115.0, 126.2 (2C), 127.5 (2C), 127.6, 128.2 (2C), 128.4 (2C), 129.0, 138.1, 138.5, 142.5. Anal. Calcd for $C_{21}H_{24}O_3$: C, 77.75; H, 7.46. Found: C, 77.48; H, 7.45.

(2*R,3*S**,4*S**,5*R**)-(±)-3-(5-Benzyloxymethyl-2-phenyl-[1,3]dioxan-4-yl)butanal (27).** Following the general procedure for hydroformylation of propylidene acetals, aldehyde **27** (163 mg, 92%) was obtained as a colorless oil; diastereromer ratio (between controlling and newly formed stereogenic center) 95:5 (anti:syn). ^{1}H NMR (500.130 MHz, $CDCl_3$): δ 1.13 (d, J = 6.7 Hz, 3H), 2.13 (m_c, 1H), 2.42−2.50 (m, 2H), 2.66 (m_c, 1H), 3.39 (m_c, 2H), 3.74 (d, J = 10.1 Hz, 1H), 3.81 (pt, J = 11.0 Hz, 1H), 4.27 (dd, J = 11.2, 4.1 Hz, 1H), 4.44 (d, J = 12.0 Hz, 1H), 4.49 (d, J = 12.0 Hz, 1H), 5.46 (s, 1H), 7.28−7.38 (m, 8H), 7.43−7.47 (m, 2H), 9.97 (m_c, 1H, CHO). ^{13}C NMR (125.758 MHz, $CDCl_3$): δ = 18.2, 29.3, 37.0, 45.0, 67.8, 69.5, 73.4, 82.8, 101.1, 126.0 (2C), 127.6 (2C), 127.8, 128.2 (2C), 128.4 (2C), 128.7, 137.9, 138.5, 202.4.

(1*R,2*S**,4*R**,5*S**)-(±)-5-Benzyloxymethyl-4-(1-methyl-but-3-enyl)-2-phenyl[1,3]dioxane (28).** To a suspension of methyltriphenylphosphonium bromide (171 mg, 0.48 mmol) in THF (10 mL) was added at 0 °C a solution of 1.22 M *n*-butyllithium in hexanes (0.36 mL, 0.44 mmol). The reaction mixture was stirred for 10 min at this temperature and for 30 min at rt. After the mixture was cooled to 0 °C, a solution of aldehyde **27** (142 mg, 0.4 mmol) in THF (4 mL) was added dropwise and stirred for another 10 min at this temperature. The reaction mixture was warmed to rt and stirred for 30 min until TLC showed complete consumption of the starting material. Saturated aqueous NH_4Cl solution (2 mL) and water (30 mL) were added. The mixture was extracted 3× with ether (20 mL each), the combined organic phases were dried (Na_2SO_4), and the solvent was removed in vacuo. Flash chromatography with petroleum ether/*tert*-butyl methyl ether (9:1) furnished alkene **28** (103 mg, 73%) as a colorless oil. ^{1}H NMR (500.130 MHz, $CDCl_3$): δ 1.04 (d, J = 6.9 Hz, 3H), 1.83 (m_c, 1H), 2.03 (m_c, 1H), 2.29−2.36 (m, 2H), 3.34 (dd, J = 9.8, 6.1 Hz, 1H), 3.40 (dd, J = 9.8, 4.1 Hz, 1H), 3.70 (d, J = 8.9 Hz, 1H), 3.80 (pt, J = 11.1 Hz, 1H), 4.29 (dd, J = 11.2, 4.7 Hz, 1H), 4.43 (d, J = 12.0 Hz, 1H), 4.49 (d, J = 12.0 Hz, 1H), 4.96−5.05 (m, 2H), 5.45 (s, 1H), 5.77 (m_c, 1H), 7.27−7.36 (m, 8H), 7.47−7.49 (m, 2H). ^{13}C NMR (125.758 MHz, $CDCl_3$): δ 16.9, 34.2, 34.4, 36.4, 67.7, 69.8, 73.2, 83.2, 101.0, 115.6, 126.0 (2C), 127.5 (2C), 127.7, 128.1 (2C), 128.4 (2C), 128.5, 138.0, 138.1, 138.9. Anal. Calcd for $C_{23}H_{28}O_3$: C, 78.38; H, 8.01. Found: C, 78.10; H, 8.03.

(2*R,3*R**,4*R**)-(±)-3-Benzyloxy-2-benzyloxymethyl-4-methylhept-6-en-1-ol (29).** To a solution of benzylidene acetal **28** (50 mg, 0.142 mmol) in CH_2Cl_2 (1.4 mL) at 0 °C was added dropwise a solution of 1.0 M DIBALH in hexanes (0.42 mL, 0.42 mmol). The reaction mixture was warmed during 3 h to rt. TLC showed complete consumption of the starting material. After the mixture was cooled to 0 °C, ethanol (2 mL) and a saturated aqueous solution of sodium potassium tartrate (5 mL) were added, and the resulting mixture was stirred for another 15 min. The mixture was extracted with three portions of CH_2Cl_2 (10 mL each). The combined organic phases were dried ($MgSO_4$), and the solvent was removed in vacuo. Flash chromatography with petroleum ether/*tert*-butyl methyl ether (7:3) furnished primary alcohol **29** (44 mg, 85%) as a colorless oil. ^{1}H NMR (500.130 MHz, $CDCl_3$): δ 0.94 (d, J = 6.5 Hz, 3H), 1.86−1.96 (m, 2H), 2.08 (m_c, 1H), 2.38 (m_c, 1H), 2.88 (m_c, 1H), 3.54 (m_c, 1H), 3.66 (m_c, 2H), 3.78 (m_c, 1H), 3.92 (m_c, 1H), 4.47−4.53 (m, 3H), 4.58 (m_c, 1H), 4.99−5.03 (m, 2H), 5.78 (m_c, 1H), 7.23−7.36 (m, 10H). ^{13}C NMR (125.758 MHz, $CDCl_3$): δ 16.2, 36.1, 36.9, 42.4, 62.4, 70.9, 73.4, 74.9, 83.8, 116.1, 127.6 (2C), 127.7 (2C), 127.8 (2C), 128.4 (2C), 128.5 (2C), 137.3, 138.1, 138.3. Anal. Calcd for $C_{23}H_{30}O_3$: C, 77.93; H, 8.53. Found: C, 77.79; H, 8.51.

(2*R,3*R**,4*R**)-(±)-3-Benzyloxy-2-benzyloxymethyl-4-methylhept-6-enyltoluene-4-sulfonate (30).** To a solution of alcohol **29** (40.1 mg, 113 μmol), pyridine (17.9 mg, 226 μmol), and DMAP (1 mg, 8 μmol) in CH_2Cl_2 at 0 °C was added a

solution of TsCl (23.6 mg, 124 μmol) in CH_2Cl_2 (0.3 mL). The reaction mixture was warmed to rt and stirred for another 12 h at this temperature. Saturated aqueous $NaHCO_3$ (2 mL) and water (10 mL) were added successively. The mixture was extracted with three portions of CH_2Cl_2 (10 mL each). The combined organic layers were dried ($MgSO_4$), and the solvent was removed in vacuo. Flash chromatography with petroleum ether/*tert*-butyl methyl ether (9:1) furnished tosylate **30** (27.1 mg, 72% of theory) as a colorless oil and starting material **29** (18.1 mg, 65% conversion). ^{1}H NMR (500.130 MHz, $CDCl_3$): δ 0.89 (d, J = 6.8 Hz, 3 H), 1.70 (m_c, 1 H), 1.86 (m_c, 1 H), 2.26 (m_c, 2 H), 2.40 (s, 3 H), 3.42−3.50 (m, 3H), 4.11 (dd, J = 9.8, 7.7 Hz, 1H), 4.30 (dd, J = 9.8, 3.8 Hz, 1H), 4.37−4.43 (m, 3H), 4.50 (d, J = 11.2 Hz, 1H), 4.95−5.00 (m, 2H), 5.69 (m_c, 1H), 7.17 (m, 2H), 7.25−7.33 (m, 10H), 7.34 (m, 2H). ^{13}C NMR (125.758 MHz, $CDCl_3$): δ 16.3, 21.6, 36.0, 36.3, 41.3, 67.9, 68.5, 73.2, 74.6, 81.3, 116.1, 127.5 (2C), 127.6 (2C), 127.9 (2C), 128.3 (2C), 128.4 (2C), 129.8 (2C), 133.0, 137.1, 138.0, 138.5, 144.6. An elemental analysis was not performed, since the tosylate was used immediately in the subsequent hydride reduction.

(2*R,3*R**,4*R**)-(±)-1,3-Bis(benzyloxy)-2,4-dimethylhept-6-ene (31).** To a solution of tosylate **30** (27.1 mg, 53 μmol) in THF (0.6 mL) at 0 °C was added a solution of 1.0 M lithiumtriethylborohydride (Super-Hydride) in THF (424 μL, 424 μmol). The reaction mixture was stirred for another 30 min at this temperature and allowed to warm to rt overnight. TLC showed complete consumption of the starting material. Water (1 mL) was added, and the mixture was extracted with three portions of ether (20 mL each). The combined organic phases were dried, and the solvent was removed in vacuo. Flash chromatography with petroleum ether/*tert*-butyl methyl ether (9:1) furnished alkene **31** (14.5 mg, 81%) as a colorless oil. ^{1}H NMR (500.130 MHz, $CDCl_3$): δ 0.87 (d, J = 6.7 Hz, 3H), 0.92 (d, J = 6.8 Hz, 3H), 1.81 (m_c, 1H), 1.85−1.92 (m, 1H), 2.12 (m_c, 1H), 2.48 (m_c, 1H), 3.32−3.37 (m, 2H), 3.48 (pt, J = 8.7 Hz, 1H), 4.46 (d, J = 12.4 Hz, 1H), 4.49 (d, J = 12.4 Hz, 1H), 4.51 (d, J = 11.3 Hz, 1H), 4.58 (d, J = 11.3 Hz, 1H), 4.98−5.03 (m, 2H), 5.79 (m_c, 1H), 7.25−7.34 (m, 10H). ^{13}C NMR (125.758 MHz, $CDCl_3$): δ 10.9, 16.0, 35.6, 36.0, 37.6, 73.0, 73.5, 74.7, 83.3, 115.8, 127.3, 127.4 (2C), 127.5, 127.7 (2C), 128.2 (2C), 128.3 (2C), 137.8, 138.5, 139.3. Anal. Calcd for $C_{23}H_{30}O_2$: C, 81.61; H, 8.93. Found: C, 81.54; H, 8.98.

(2*R,4*S**,5*R**)-(±)-4-[(1*S**)-(4,4-Dibrom-1-methylbut-3-en-1-yl)-5-methyl-2-phenyl[1,3]dioxane (33).** To a solution of triphenylphosphane (5.43 g, 24.0 mmol) in CH_2Cl_2 (15 mL) was added dropwise at 0 °C a solution of tetrabromomethane (3.98 g, 12.0 mmol) in CH_2Cl_2 (10 mL). After the mixture was stirred for another 1 h at this temperature, a solution of aldehyde **16** (1.49 g, 6.0 mmol) in CH_2Cl_2 (5 mL) was added during 5 min and stirred for another 10 min at this temperature. Subsequently, silica gel (20 g) was added, and all volatile components were removed in vacuo. Flash chromatography with petroleum ether/*tert*-butyl methyl ether (19:1) gave dibromoalkene **33** (1.61 g, 67%) as a colorless viscous oil, which solidified slowly to give a colorless solid. mp 49−51 °C. ^{1}H NMR (300.133 MHz, $CDCl_3$): δ 0.79 (d, J = 6.7 Hz, 3H), 1.10 (d, J = 6.8 Hz, 3H), 1.97−2.19 (m, 3H), 2.34 (m_c, 1H), 3.36 (dd, J = 10.0, 2.1 Hz, 1H), 3.48 (t, J = 11.1 Hz, 1H), 4.11 (dd, J = 11.2, 4.7 Hz, 1H), 5.45 (s, 1H), 6.52 (t, J = 7.4 Hz, 1H), 7.29−7.38 (m, 3H), 7.45−7.49 (m, 2H). ^{13}C NMR (75.469 MHz, $CDCl_3$): δ 12.2, 17.3, 31.0, 33.2, 33.5, 73.1, 86.8, 89.0, 101.3, 126.0 (2C), 128.1 (2C), 128.6, 137.9, 138.8. Anal. Calcd for $C_{16}H_{20}Br_2O_2$: C, 47.55; H, 4.99. Found: C, 47.44; H, 5.00.

(2*R,4*S**,5*R**)-(±)-4-[4-(1*S**)-(1-Methylbut-3-en-1-yl)-5-methyl-2-phenyl[1,3]dioxane (34).** To a solution of dibromoalkene **33** (1.33 g, 3.3 mmol) in THF (18 mL) was added slowly at −78 °C a solution of 1.5 M *n*-butyllithium in hexanes (4.6 mL, 6.9 mmol). The reaction mixture was stirred for another 1.5 h at this temperature, allowed to warm to ambient temperature, and kept for 1 h at this temperature. Subsequently, water (5 mL) was added, and the organic phase was separated. The aqueous phase was washed with three portions of *tert*-butyl methyl ether (20 mL each). The combined organic phases were dried ($MgSO_4$), and the solvent was removed in vacuo. Flash chromatography with petroleum ether/*tert*-butyl methyl ether (19:1) gave alkyne **34** (766 mg, 95%) as a colorless oil. ^{1}H NMR (300.133 MHz, $CDCl_3$): δ 0.81 (d, J = 6.7 Hz, 3H), 1.21 (d, J = 6.7 Hz, 3H), 1.96 (t, J = 2.6 Hz, 1H), 2.02−2.27 (m, 3H), 2.46 (m_c, 1H), 3.40 (dd, J = 10.1, 2.0 Hz, 1H), 3.48 (t, J = 11.1 Hz, 1H), 4.11 (dd, J = 11.2, 4.8 Hz, 1H), 5.46 (s, 1H), 7.31−7.39 (m, 3H), 7.44−7.48 (m, 2H). ^{13}C NMR (75.469 MHz, $CDCl_3$): δ 12.3, 17.6, 19.4, 31.0, 33.9, 68.8, 73.1, 84.2, 86.2, 101.1, 126.0 (2C), 128.1 (2C), 128.6, 138.8. Anal. Calcd for $C_{16}H_{20}O_2$: C, 78.68; H, 8.25. Found: C, 78.62; H, 8.30.

(2*R,3*S**,4*S**)-(±)-2,4-Dimethylhept-6-en-1,3-diol (35).** A solution of acetal **34** (244 mg, 1.0 mmol) in acetic acid (3 mL, 80%) was stirred for 2 d at 40 °C. After being cooled to rt, the reaction mixture was poured into a saturated aqueous $NaHCO_3$ solution (50 mL). The organic phase was separated, and the aqueous phase was washed with four portions of *tert*-butyl methyl ether (30 mL each). The combined organic phases were dried (Na_2SO_4), and the solvent was evaporated in vacuo. Flash chromatography with pentane/*tert*-butyl methyl ether (1:1) gave diol **35** (61 mg, 40%) as a colorless oil. Additionally, a mixture consisting of both monoacetates and the diacetate of diol **34** was obtained (29 mg). Also, starting material (40 mg, 84% conversion) was recovered. Spectral and analytical data of diol **35**: ^{1}H NMR (400.130 MHz, $CDCl_3$): δ 0.96 (d, J = 7.0 Hz, 3H), 1.06 (d, J = 6.9 Hz, 3H), 1.86 (m_c, 1H), 1.93 (m_c, 1H), 1.97 (pt, J = 2.7 Hz, 1H), 2.23 (ddd, J = 16.9, 7.9, 2.7 Hz, 1H), 2.37 (ddd, J = 16.9, 4.2, 2.7 Hz, 1H), 2.97 (bs, 1H), 3.15 (bs, 1H), 3.41 (pt, J = 5.9 Hz, 1H), 3.61 (dd, J = 10.7, 6.2 Hz, 1H), 3.81 (dd, J = 10.7, 3.4 Hz, 1H). ^{13}C NMR (75.469 MHz, $CDCl_3$): δ 14.4, 16.7, 20.2, 35.5, 36.4, 66.9, 69.5, 80.5, 83.6. Anal. Calcd for $C_9H_{16}O_2$: C, 69.19; H, 10.32. Found: C, 68.99; H, 10.30.

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Supporting Information Available: Details of force-field calculations as well as NMR spectra of compounds. This material is available free of charge via Internet at http://pubs.acs.org.

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