Additions of Enantioenriched Allenylzinc and Indium Reagents to Lactic Aldehyde Ethers

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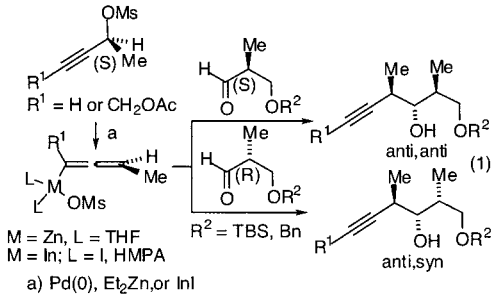
Allenylzinc and indium reagents were generated in situ through Pd(0)-catalyzed metalation of (*R*)- and (*S*)-3-butyn-2-ol methanesulfonate with Et_2Zn and InI. These reagents add to the benzyl and TBS ethers of (*S*)-lactic aldehyde to afford diastereomeric stereotriads in moderate to high yield. The (*S*)/(*S*) combination afforded the anti,anti adducts with 94:6−100:0 diastereoselectivity. The (*R*)/(*S*) combination was mismatched, affording a mixture of anti,syn and syn,anti adducts in diastereomeric ratios of ca. 80:20−85:15. Addition of the racemic allenylmetal reagents to the (*S*)-lactic aldehyde ethers afforded the products of matched and mismatched pairings in equal amount.

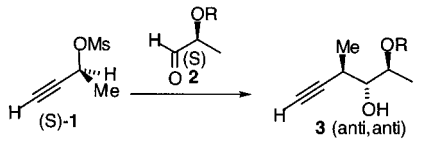
In two previous reports we described additions of enantioenriched allenylzinc and indium reagents, prepared in situ through oxidative transmetalation of transient allenylpalladium mesylates with Et_2Zn and InI, to α-methyl-*β*-OR aldehydes (eq 1).[1,2] It was found that these additions proceed with greater than 95% diastereoselectivity to afford anti adducts irrespective of the configuration of either reacting partner. The reagents depicted in eq 1 afforded anti,anti adducts with the (*S*)-aldehydes and anti,syn adducts with the (*R*)-aldehydes with minimal mismatching.



Considering the potential applications of these reagents to the synthesis of polyketide and related natural products,[3] we initiated further investigations with other relevant classes of nonracemic aldehydes. We were particularly interested in probing the degree of reagent vs substrate stereocontrol in such reactions. In this report we describe our findings on additions of nonracemic allenylzinc and indium reagents to the benzyl[4] and TBS[5] ethers **2a** and **2b** of (*S*)-lactic aldehyde.

The allenylmetal species were generated in situ from the mesylates (*S*)- and (*R*)-**1** of 3-butyn-2-ol as previously described.[1,2] The allenylzinc reactions were conducted at −78 °C initially with warming to −20 °C overnight in the presence of 5 mol % of a 1:1 mixture of $Pd(OAc)_2$ and Ph_3P as the catalyst precursor. The allenylindium additions were carried out at room temperature in 3:1 THF−HMPA containing a small amount of water. Commercial grade InI was used for conversion of the transient allenypalladium intermediate to the allenylindium reagent in situ. Diastereomeric ratios were determined by integration of the ^1H NMR spectra of the crude product mixtures. Results from the (*S*)-mesylate reactions are summarized in Table 1. The benzyloxy aldehyde **2a** afforded a 94:6 mixture of products favoring the anti,-anti adduct **3a** with the allenylzinc reagent. The minor product was not characterized but is assumed to be the syn,syn adduct. This assumption was reinforced by comparison of the ^1H NMR spectrum of the 94:6 mixture with that of an authentic sample of the syn,syn isomer prepared by $BF_3{\cdot}OEt_2$-promoted addition of the *(P)*-allenyl tributylstannane from *(R)*-**1a** to aldehyde **2a**, as previously described.[6] The allenylindium reagent yielded the anti,anti adduct **3a** as the sole product. Additions to the silyloxy aldehyde **2b** also proceeded with no detectable formation of diastereomers to produce the anti,anti adduct **3b** from both reagents.

Table 1. Matched Additions of AllenylIM Reagents to Aldehyde 2



R	method[a]	yield, %	dr
Bn **2a**	A	70	94:6
Bn **2a**	B	89	100:0
TBS **2b**	A	70	100:0
TBS **2b**	B	63	100:0

[a] Method A: $Pd(OAc)_2{\cdot}PPh_3$ (5 mol %), Et_2Zn (3.0 equiv), THF, −78 to −20 °C. Method B; $Pd(dppf)Cl_2$, InI, THF−HMPA (3:1), room temp. [b] Major isomer.

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(2) Marshall, J. A.; Grant, C. M. *J. Org. Chem.* **1999**, *64*, 8214.
(3) Cf. Marshall, J. A.; Johns, B. A.; *J. Org. Chem.* **2000**, *65*, 1501. Marshall, J. A.; Adams, N. D. *Org. Lett.* **2000**, *2*, 2897.
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(5) Massad, S.; Hawkins, L. D.; Baker, D. C. *J. Org. Chem.* **1983**, *48*, 5188.
(6) Marshall, J. A.; Wang. X.-j. *J. Org. Chem.* **1991**, *56*, 3211.

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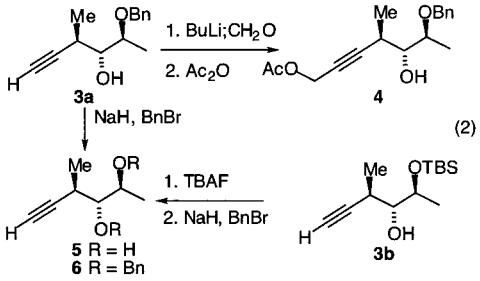
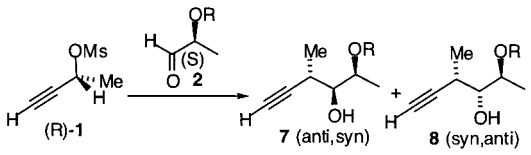
The stereochemistry of adduct **3a** was determined through conversion to the known anti,anti propargylic acetate **4**[6] by formylation and acetylation according to eq 1. The ^{1}H NMR spectrum of this derivative was identical to that of an authentic sample. However the rotation, $[\alpha]_D = +70.9$, was significantly lower than the reported value of +97.0.[6] The discrepancy was suspected to be the result of a sample mix-up in the reported work, as loss of ee in the present case could only come about if both the allenylzinc and the aldehyde epimerized to exactly the same degree under the reaction conditions. Since neither showed any tendency to epimerize in the course of these studies, we consider this possibility unlikely. The stereochemistry of the TBS derivative **3b** was determined through conversion to the bis-benzyl ether **6**. The identical ether was obtained upon benzylation of adduct **3a**.



Additions of the allenylzinc and indium reagents from the mesylate (*R*)-**1** to aldehydes **2a** and **2b** are summarized in Table 2. In each case a mixture of anti,syn

Table 2. Mismatched Additions of AllenylIM Reagents to Aldehyde 2

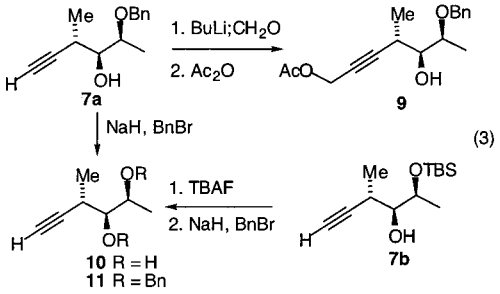


R	method[a]	yield, %	dr
Bn **2a**	A	70	86:14
Bn **2a**	B	77	76:18[c]
TBS **2b**	A	75	85:15
TBS **2b**	B	66	80:20

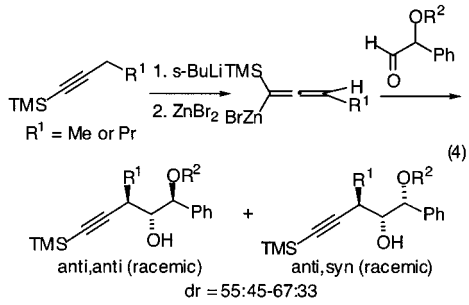
[a] Method A: $Pd(OAc)_2 \cdot PPh_3$ (5 mol %), Et_2Zn (3.0 equiv), THF, −78 to −20 °C. Method B: $Pd(dppf)Cl_2$, InI, THF−HMPA (3:1), room temp. [b] Major isomer. [c] The remaining 6% is the anti,anti isomer

and syn,anti adducts **7** and **8** was produced, favoring the former. A small amount of anti,anti adduct **3a** was detected in the ^{1}H NMR spectrum of the product obtained from aldehyde **2a** and the allenylindium reagent. We have previously found that allenylindium reagents derived from chiral stannanes are somewhat labile toward racemization[7] and suspect that adduct **3** is produced by this pathway.

The stereochemistry of the anti,syn adduct **7a** was confirmed in the same manner as **3a** through correlation with the known propargylic acetate **9** (eq 3).[6] In this case the rotation of the present sample ($[\alpha]_D = +49.4$) was in close agreement to the reported value of +48.1. Assignment of the syn,anti stereochemistry to the minor isomer was initially based on mechanistic considerations and later confirmed through comparison with an authentic sample prepared through $BF_3 \cdot OEt_2$-promoted addition of the *(M)*-allenyl tributylstannane derived from mesylate *(S)*-**1** to aldehyde **2a**.[6] The TBS ether **7b** was converted to the bis-benzyl ether **11** which was identical to the sample obtained through benzylation of adduct **7a**.

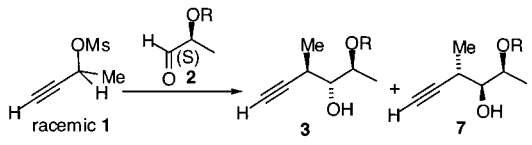


Poisson and Normant recently described additions of racemic allenylzinc bromide reagents, prepared through lithiation of TMS alkynes and subsequent treatment with $ZnBr_2$, to silyl ethers of racemic mandelic aldehyde (eq 4).[8] These reactions afforded mixtures of the anti,anti and anti,syn adducts in ratios ranging from 55:45 to 67:33, suggestive of a minimal to slight kinetic preference in the additions.



To probe this possibility in the present system, we examined additions of the racemic allenylzinc and indium reagents, derived from racemic mesylate **1**, to aldehydes **2a** and **2b** (Table 3). In each case, essentially 50:50

Table 3. Additions of Racemic AllenylIM Reagents to Aldehyde 2



R	method[a]	yield, %	dr
Bn **2**a	A	92	50:45[b]
Bn**2a**	B	72	50:38[c]
TBS **2b**	A	89	51:42[d]
TBS **2b**	B	73	53:43[e]

[a] Method A: $Pd(OAc)_2 \cdot PPh_3$ (5 mol %), Et_2Zn (3.0 equiv), THF, −78 to −20 °C. Method B: $Pd(dppf)Cl_2$, InI, THF−HMPA (3:1), room temp. [b] 5% syn,anti. [c] 12% syn,anti. [d] 7% syn,anti. [e] 4% syn,anti.

mixtures of the matched and mismatched adducts **3** and **7/8** were formed indicative of equal rates of addition for the two enantiomeric allenylmetal reagents with this aldehyde.

(7) Marshall, J. A.; Palovich, M. R. *J. Org. Chem.* **1997**, *62*, 6001.

(8) Poisson, J.-F.; Normant, J. F. *J. Org. Chem.* **2000**, *65*, 6553.

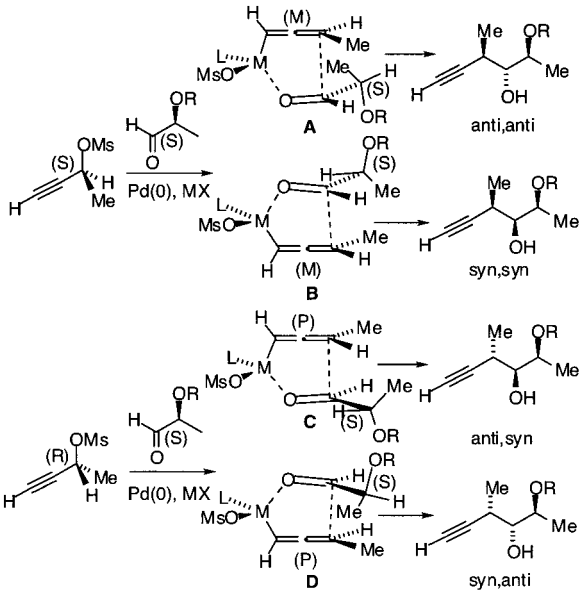


Figure 1. Transition states for additions of allenylIM reagents to α-oxygenated aldehydes.

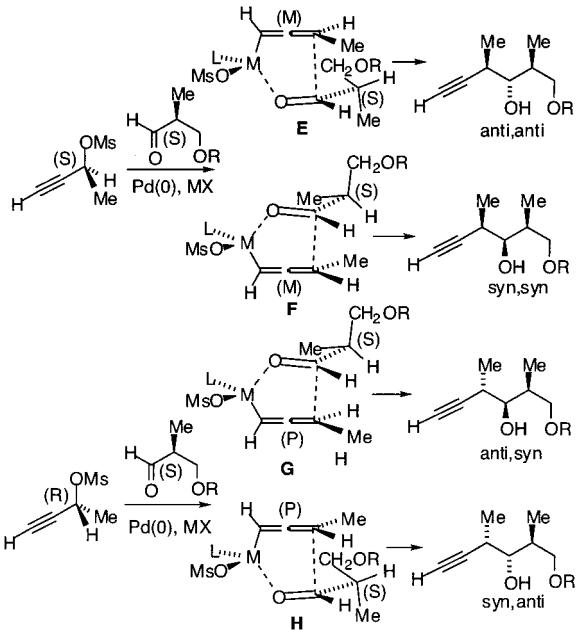


Figure 2. Transition states for additions of allenylIM reagents to α-methyl-*β*-oxygenated aldehydes.

The present findings are consistent with the transition state formulations depicted in Figure 1. Accordingly, the matched (*S*)/(*S*) pairing proceeds via the cyclic array **A** in which addition to the aldehyde carbonyl occurs in the Felkin−Anh mode[9] with an anti arrangement of the allenyl methyl and aldehyde substituents. The alternative arrangement **B** is disfavored both by the non Felkin−Anh mode of addition to the carbonyl and the requisite eclipsing of the allenyl methyl and aldehyde substituents. The apparent absence of the corresponding minor adduct arising from the TBS protected aldehyde **2b** could be the result of a minor chelation pathway in the allenylzinc addition to aldehyde **2a**, but not **2b**.

The mismatched (*R*)/(*S*) pairing could lead to the anti,-syn adduct through transition state **C** and the syn,anti adduct via **D**. The former pathway entails non Felkin−Anh addition but anti disposed methyl and aldehyde substituents. The latter array proceeds through the Felkin−Anh mode of carbonyl addition but requires eclipsing of the methyl and aldehyde substituents. This interaction is the more costly one and thus disfavors the **D** arrangement leading to the syn,anti adduct.

The present findings provide a facile method for the preparation of anti,anti and anti,syn stereotriads such as **3** and **7**, particularly the former. We have previously shown the syn,syn; syn,anti; and anti,syn isomers can be obtained with excellent diastereoselectivity from enantioenriched allenylstannanes.[6] Thus all isomers of this stereotriad are now readily accessible. The oxidative transmetalation methodology[10] is convenient and does not generate potentially hazardous byproducts. The allenylindium protocol is particularly convenient as the reactions take place at room temperature in only a few hours. However, partial racemization can take place in additions to less reactive aldehydes and HMPA is used as a cosolvent. The allenylzinc reagents, by contrast, appear to be configurationally stable. However, lower temperatures are required and reactions are best conducted at 0.1 M concentrations or less to minimize ethyl addition to the aldehyde.

With regard to the greater degree of mismatching observed with α-OR as opposed to α-methyl,*β*-OR aldehydes, it is possible that the benzyloxy and silyloxy substituents are more disposed than CH_2OR toward the anti orientation in the Felkin−Anh transition state conformation of the aldehydes. A strong preference of this nature would disfavor alternative conformers in which the α-OR group is syn to the aldehyde oxygen or hydrogen with a resulting decrease of torsional strain in the transition state.[11] Such conformers would be especially important in transition state **C** leading to the anti,syn adduct. The corresponding α-center in the α-methyl-*β*-OR aldehydes could adopt conformation **E** with the CH_3 anti to the forming bond and the CH_2OR syn to the carbonyl oxygen in a Felkin−Anh arrangement (Figure 2). In this way the anti,anti product would be formed with minimal steric or torsional strain. The anti,syn product would arise via transition state **G** in which the CH_2OR substituent assumes the anti orientation. The various possibilities are depicted in Figure 2. The anti,anti and anti,syn diastereomers are the nearly exclusive products obtained from the (*M*)- and (*P*)-reagents, presumably by way of transition states **E** and **G**. The syn,syn and syn,-anti adducts would be formed via **F** and **H** which are energetically unfavorable by virtue of the developing eclipsing interactions between the methyl group and aldehyde substituent.

The present findings provide insight regarding matching/mismatching characteristics of allenylzinc and indium additions to α-substituted aldehydes, a reaction that has proven useful for the synthesis of polyketide natural products.[3] The absence of appreciable mismatching in additions to α-methyl-*β*-oxygenated aldehydes,

(9) Chérest, M.; Felkin, H.; Prudent, N. *Tetrahedron Lett.* **1968**, 2199. Anh, N. T.; Eisenstein, O. *Nouv. J. Chim.* **1977**, *1*, 61.

(10) Marshall, J. A. *Chem. Rev.* **2000**, *100*, 3163.

(11) The same conclusion can be drawn for the Cornforth transition state conformation in which the OR substituent adopts an anti coplanar orientation with respect to the carbonyl group in order to minimize dipole repulsion. Cornforth, J. W.; Cornforth, R. H.; Mathew, K. K. *J. Chem. Soc.* **1959**, 112.

contrasted with the pronounced matching/mismatching observed in the present work with protected lactic aldehydes, appears to be related to the Felkin−Anh or Cornforth[11] preferences of the aldehydes rather than a departure from the attack angle of the allenylmetal reagent or other fundamental transition state parameters. Additional studies, currently in progress, on more extended-chain α-methyl aldehydes should shed further light on this question.

Experimental Section

(2*S*,3*R*,4*S*)-(+)-2-*tert*-Butyldimethylsilyloxy-4-methyl-5-hexyn-3-ol (3b). A. Standard Procedure For Method A. To a solution of $Pd(OAc)_2$ (15 mg, 0.070 mmol) in THF (20 mL) at −78 °C was added PPh_3 (18 mg, 0.070 mmol). Upon complete dissolution of the PPh_3, mesylate (*S*)-**1** (200 mg, 1.35 mmol) and aldehyde (*S*)-**2b** (170 mg, 9.0 mmol) were added followed by dropwise addition of diethylzinc (2.7 mL, 1 M in hexane, 2.7 mmol). The solution was then warmed to −20 °C. After 14 h, the reaction mixture was quenched with sat. aqueous NH_4Cl ***(Caution: evolution of gaseous ethane results)*** and diluted with diethyl ether. After the mixture was warmed to room temperature, the layers were separated, and the ether layer was washed with saturated brine. The aqueous layer was extracted with diethyl ether, and the combined extracts were dried over $MgSO_4$. The solvent was removed under reduced pressure, and the residue was chromatographed on silica gel (10:1 hexanes/EtOAc) to give 138 mg (70%) of alcohol **3b** as a single diastereomer: $[\alpha]^{20}_D = +36.0$ ($c = 2.57$, $CHCl_3$); IR (film) υ 3441, 2121 cm $^{-1}$; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.76 (m, 1H), 3.17 (m, 1H), 2.91 (m, 1H), 2.12 (d, J = 2.4 Hz, 1H), 1.86 (d, J = 8.1 Hz, 1H), 1.25 (d, J = 13.5 Hz, 3H), 1.23 (d, J = 12.0 Hz, 3H), 0.89 (s, 9H), 0.09 (d, J = 3.0 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 84.9, 78.6, 71.1, 69.9, 28.5, 25.8, 19.6, 18.0, −4.25, −4.92. Anal. Calcd for $C_{13}H_{26}O_2Si$: C, 64.41; H, 10.81. Found: C,64.11; H,10.73.

B. Standard Procedure For Method B: To a one-neck round-bottom flask with a magnetic stir bar were added THF (15 mL), HMPA (5 mL), mesylate (*S*)-**1** (205 mg, 1.38 mmol), and aldehyde (*S*)-**2b** (200 mg,1.06 mmol. The solution was stirred vigorously as $PdCl_2$(dppf) (56 mg, 0.07 mmol) and InI (384 mg, 1.60 mmol) were added sequentially. After 3 h, reaction was judged to be complete by TLC. The reaction mixture was diluted with 10% HCl and diethyl ether. The ether layer was separated, washed with brine, and dried over $MgSO_4$. The solvent was removed under reduced pressure, and the residue was chromatographed on silica gel (10:1 hexanes: EtOAc) to give 160 mg (63%) of alcohol **3b** as a single diastereomer: $[\alpha]^{20}_D = +34.2$ ($c = 0.90$, $CHCl_3$).

(2*S*,3*R*,4*S*)-(+)-2-Benzyloxy-4-methyl-5-hexyn-3-ol (3a). A. Method A. The standard procedure for method A was employed with $Pd(OAc)_2$ (30 mg, 0.14 mmol), PPh_3 (35 mg, 0.14 mmol), mesylate (*S*)-**1** (406 mg, 2.70 mmol), aldehyde (*S*)-**2a** (300 mg, 1.80 mmol), and diethylzinc (5.4 mL, 1 M in hexane, 5.40 mmol) in THF (20 mL) at −20 °C for 14 h to give 278 mg (70%) of alcohol **3a** and its syn diastereomer as a 94:6 inseparable mixture: $[\alpha]^{20}_D$ +76.2 ($c = 1.13$, $CHCl_3$); IR (film) υ 3464, 2119 cm $^{-1}$; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33 (m, 5H), 4.51 (dd, J = 11.4, 33.6 Hz, 2H), 3.59 (m, 1H), 3.34 (m, 1H), 3.07 (m, 1H), 2.14 (d, J = 2.4 Hz, 1H), 2.09 (d, J = 8.4 Hz, 1H), 1.31 (d, J = 13.2 Hz, 3H), 1.29 (d, J = 14.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.3, 128.4, 127.8, 127.6, 84.7, 77.4, 71.2, 71.1, 28.7, 17.9, 15.6.

B. Method B. The standard procedure for method B was employed with THF (10 mL), HMPA (3 mL), mesylate (*S*)-**1** (141 mg, 0.95 mmol), aldehyde (*S*)-**2a** (120 mg, 0.73 mmol), $PdCl_2$(dppf) (30 mg, 0.04 mmol), and InI (266 mg, 1.00 mmol). Purification by silica gel chromatography (4:1 hexanes/EtOAc) provided 142 mg (89%) of alcohol **3a** as a single diastereomer: $[\alpha]^{20}_D = +76.2$ ($c = 2.20$, $CHCl_3$).

(2*S*,3*R*,4*S*)-(+)-2-Benzyloxy-4-methyl-7-acetoxy-5-heptyn-3-ol (4). To a cold (−78 °C) solution of alcohol **3a** (150 mg, 0.71 mmol) in THF (10 mL) was added BuLi (0.80 mL, 2.5 M in hexanes, 2.00 mmol) dropwise. After 1 h the solution was allowed to warm to 0 °C, stir for 10 min, and then cooled back to −78 °C. Paraformaldehyde (64 mg, 0.20 mmol) was added, and the solution was allowed to warm to room temperature. After 3 h at room temperature, the reaction was judged to be complete by TLC. The reaction was quenched with saturated aqueous $NaHCO_3$ and extracted with diethyl ether. The ether extract was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was taken up in CH_2Cl_2 (10 mL) and cooled to −78 °C. Triethylamine (0.07 mL, 0.49 mmol), Ac_2O (0.04 mL, 0.46 mmol), and DMAP (2 mg) were added successively. After 10 min, the reaction was quenched at −78 °C with saturated aqueous $NaHCO_3$ and allowed to warm to room temperature. The organic layer was separated, dried over $MgSO_4$, and concentrated under reduced pressure. Purification of the residue by silica gel chromatography (4:1 hexanes/EtOAc) provided 88 mg (43% overall yield) of alcohol **4**. $[\alpha]^{20}_D = +70.9$ ($c = 0.42$, $CHCl_3$) lit. $[\alpha]^{20}_D = +97.0$ ($c = 2.58$, $CHCl_3$).[6] The disparity between these two values is attributed to a sample mixup in the referenced work.

(2*S*,3*R*,4*S*)-(+)-4-Methyl-5-hexyne-2,3-diol (5). To a stirred solution of silyl ether **3b** (60 mg, 0.25 mmol) in THF (5 mL) was added TBAF (0.30 mL, 1.0 M in THF, 0.30 mmol) at room temperature. The solution was stirred overnight and monitored by TLC. The reaction was quenched by addition of saturated brine solution and extracted with diethyl ether. The ether layer was dried over $MgSO_4$, and solvent was removed under reduced pressure. The residue was chromatographed on silica gel (1:1 hexanes:EtOAc) to yield 22 mg of diol **5** (70%). $[\alpha]^{20}_D = +18.2$ ($c = 1.85$, $CHCl_3$); IR (film) υ 3354, 2356 cm $^{-1}$; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.82 (m, 1H), 3.30 (m, 1H), 2.85 (m, 1H), 2.17 (d, J = 2.4 Hz, 1H), 1.27 (d, J = 6.3 Hz, 3H), 1.25 (d, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 84.9, 71.5, 69.2, 28.6, 18.8, 17.7.

(2*S*,3*R*,4*S*)-(+)-2,3-Bis-benzyloxy-4-methyl-5-hexyne (6). To a cold (0 °C) suspension of NaH (20 mg, 60% suspension in mineral oil, 0.50 mmol) in THF (10 mL) was added a solution of alcohol **5** (25 mg, 0.20 mmol) in THF (5 mL) dropwise. After 10 min, BnBr (0.05 mL, 0.43 mmol) was added, and the solution was warmed to room temperature and monitored by TLC. After 2 h, the solution was quenched carefully by dropwise addition of distilled H_2O. Once bubbling ceased, the solution was extracted with diethyl ether. The ether extract was dried over $MgSO_4$ and filtered, and the solvent was removed under reduced pressure. The residue was chromatographed on silica gel (10:1 hexanes/EtOAc) to yield benzyl ether **6** (52 mg, 87%). $[\alpha]^{20}_D = +10.2$ ($c = 2.54$, $CHCl_3$); IR (film) υ 2119, 1495, 1456 cm $^{-1}$; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34 (m, 10H), 4.73 (dd, J = 11.4, 9.0 Hz, 2H), 4.59 (dd, J = 23.4, 11.1 Hz, 2H), 3.80 (m, 1H), 3.30 (m, 1H), 3.03 (m, 1H), 2.09 (d, J = 2.4 Hz, 1H), 1.33 (d, J = 6.3 Hz, 3H), 1.26 (d, J = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.3, 128.3, 128,2, 127.9, 127,8, 127.5, 127.6, 84.5, 76.5, 74.9, 71.3, 69.8, 28.9, 18.0, 16.1.

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Supporting Information Available: Copies of ^{1}H NMR spectra for all intermediates and experimental procedures with spectral and rotation data for **4**, **6**, **7a**, **7b**, **9**, **10**, and **11**. This material is available free of charge via the Internet at http://pubs.acs.org.

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