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Application of a New Tandem Isomerization−Aldolization Reaction of Allylic Alcohols to the Synthesis of Three Diastereoisomers of (2*R*)-1,2-*O*-Isopropylidene-4-methylpentane-1,2,3,5-tetraol

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The tandem isomerization−aldolization reaction of (2*R*)-1,2-*O*-isopropylidene-4-penten-1,2,3-triol **3** and formaldehyde gives a mixture of two aldol products **2a** and **2b**. The stereoselective reduction of each compound by L-Selectride affords two diastereoisomers of (2*R*)-1,2-*O*-Isopropylidene-4-methylpentane-1,2,3,5-tetraol while a third diastereoisomer is obtained by stereoselective reduction with $Me_4NHB(OAc)_3$.

Introduction

The total synthesis of natural products or analogues requires the development of new synthetic methodologies for the preparation of polyfunctional key intermediates with good control of the absolute configuration at the stereocenters. Polyols, such as selectively protected tetraol **1** (Figure 1), are particularly interesting since each diastereoisomer of such compounds should be a key intermediate for the synthesis of various natural products.

For example, the syn-anti isomer of **1** was used for the synthesis of the C14−C27 fragment of Tetronasin[1] and can also be considered as a C12−C16 fragment of Amphidinolide J[2] (Scheme 1) while the syn-syn isomer of **1** can be considered as a C39−C43 fragment of Altohyrtins.[3]

Two types of disconnections have already been reported for the synthesis of these compounds (Scheme 2): The first one involves either the addition of organometallic nucleophiles or an aldol condensation to (*R*)-2,3-Isopropylideneglyceraldehyde (Scheme 2, route A). This strategy can occur following either a stereoselective process or a nonstereoselective process. The stereoselective processes, in which for exemple allyl boronates or alkenyloxy dialkyloxyboranes derived from thioesters have been used,[4] give only one diastereoisomer (anti-syn or anti-anti), while the nonstereoselective processes afford a mixture of isomers with a low diastereoselectivity.[1,5] The second strategy uses Kishi's route for pentose synthesis, i.e., the addition of a nucleophile to an epoxyde, and gives either the syn-anti isomer in a nonregioselective manner or the anti-anti isomer depending on the epoxidation step.[2,6] So, these strategies employ different condensation reactions starting from (*R*)-2,3-Isopropylideneglyceraldehyde, but none of them offers a general method for the preparation of the four diastereoisomers. Finally, only two of these isomers are obtained following a complete stereo- and regioselective pathway and the synthesis and isolation of only three of the four diastereoisomers of **1** have been reported to date. The syn-syn isomer had only been isolated as a minor compound of a mixture.[5a]

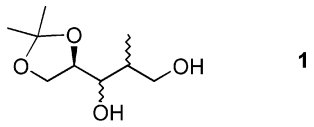

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FIGURE 1.

A third disconnection can be proposed in which the key step is a tandem isomerization−aldolization reaction (Scheme 2, route C). We have recently developed a new aldolization reaction in which an allylic alcohol is isomerized by a transition metal complex to an enol(ate) intermediate, which is trapped by an aldehyde to give the aldol products (Scheme 3).[7,8]

(1) Lee, H. W.; Lee, I.-Y. C. *Synlett* **1991**, 871.
(2) Kobayashi, J.; Sato, M.; Ishibashi, M. *J. Org. Chem.* **1993**, *58*, 2645.
(3) Anderson, J. C.; McDermott, B. P.; Griffin, E. J. *Tetrahedron* **2000**, *56*, 8747.
(4) (a) Roush, W. R.; Adam, M. A.; Walts, A. E.; Harris, D. J. *J. Am. Chem. Soc.* **1986**, *108*, 3422. (b) Gennari, C.; Bernardi, A.; Cardani, S.; Scolastico, C. *Tetrahedron* **1984**, *40*, 4059. (c) Mikami, K.; Terada, M.; Nakai, T. *Tetrahedron: Asymmetry* **1991**, *2*, 993. (d) Yang, H. W.; Romo, D. *J. Org. Chem.* **1998**, *68*, 1344.
(5) (a) Heathcock, C. H.; Young, S. D.; Hagen, J. P.; Pirrung, M. C.; White, C. T.; VanDerveer, D. *J. Org. Chem.* **1980**, *45*, 3846. (b) Mulzer, J.; de Lasalle, P.; Freissler, A. *Liebigs Ann. Chem.* **1986**, 1152.
(6) Scheuplein, S. W.; Kusche, A.; Brückner, R.; Harms, K. *Chem Ber.* **1990**, *123*, 917.
(7) (a) Crévisy, C.; Wietrich, M.; le Boulaire, V.; Uma, R.; Grée, R. *Tetrahedron Lett.* **2001**, *42*, 395. (b) Uma, R.; Davies, M.; Crévisy, C.; Grée, R. *Tetrahedron Lett.* **2001**, *42*, 3069.
(8) For a similar approach see: (a) Wang, M.; Li, C.-J. *Tetrahedron Lett.* **2002**, *43*, 3589. (b)Yang, X.-F.; Wang, M.; Varma, R. S.; Li, C.-J. *Org. Lett.* **2003**, *5*, 657.

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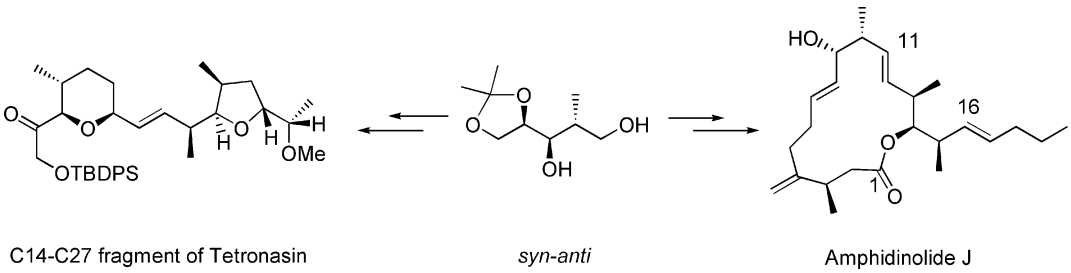
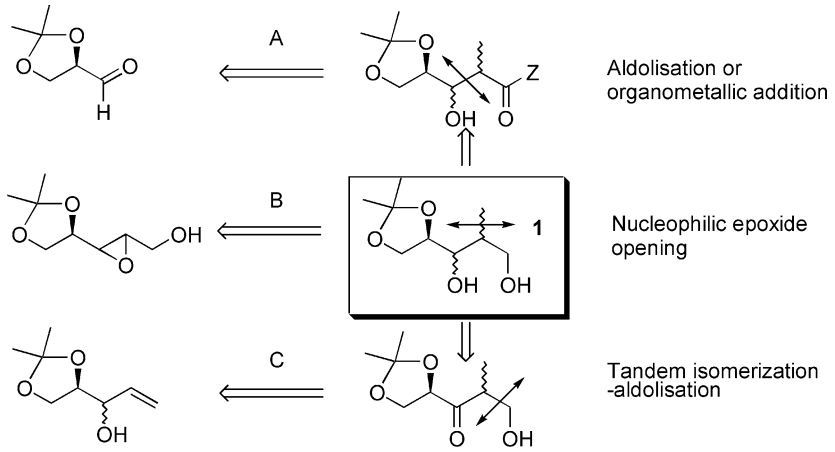
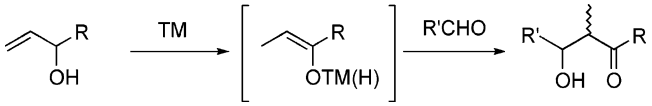
SCHEME 1



SCHEME 2



SCHEME 3



This reaction follows the concept of atom economy,[9] occurs under mild conditions, and has been applied to various aldehydes, allylic alcohols, and transition metal catalysts. We are currently applying it to the synthesis of useful key intermediates, precursors of natural products, and we report here the synthesis of three diastereoisomers of compound **1** using this novel reaction.

Results and Discussion

Following our retrosynthetic analysis, the diastereoisomers of **1** can be obtained by stereoselective reductions of each diastereoisomer of ketone **2**. One, or both, of these two isomers can be obtained by a tandem isomerization−aldol condensation of the easily available allylic alcohol **3** and formaldehyde (Scheme 4).

(*R*)-2,3-Isopropylideneglyceraldehyde, which is obtained from D-mannitol following a known procedure,[10] is treated by vinylmagnesium bromide to give **3** as a mixture of two diastereoisomers in a 50/50 ratio (Scheme 5).

When this mixture of the two stereoisomers is reacted with formaldehyde in the presence of $Fe(CO)_5$ at 3 mol % and under irradiation the two diastereoisomeric aldol products **2** are obtained along with small quantities of the regioisomeric aldol **4**, the known ketone **5**,[11] and unexpected compound **6** (Scheme 6). Ketone **5** results from the competitive isomerization reaction of the allylic alcohol.[12] The mixture of diastereoisomeric hemiacetals **6,** which have been isolated and characterized as the silyl ethers **6a**, comes from the reaction of aldols **2** with formaldehyde and can be transformed back into **2** by treatment of the crude mixture with 5 mol % of PTSA in MeOH. Finally, the mixture of aldols **2** is isolated in good yield (80%)[13] and a moderate stereoselectivity (60/40) while the byproducts **4** and **5** are isolated in very low yield (2% each).[13] The latter result is particularly interesting since, under these conditions, the tandem isomerization−aldolization reaction usually gives more regioisomeric aldols and more ketone.[7a] The increase in the regioselectivity could be due to the presence of the oxygen atom on the carbon vicinal to the secondary carbinol. Moreover, it must be noticed that the formaldehyde added in the reaction is not strictly anhydrous. Contrary to most aldol additions, this reaction is compatible with the presence of moisture and an aqueous formaldehyde solution is used after dilution in THF and simple drying over magnesium sulfate. Therefore, it offers a very convenient method to perform the aldolization reaction with formaldehyde.[14] Besides, it is worth noting that a 95/5 syn/anti mixture of **3** has also been prepared following Sato's conditions[15] and used in the aldol reaction to check the effect of the stereochemistry of the starting allylic alcohol on the reactivity and the selectiv-

(9) (a) Trost, B. M. *Science* **1991**, *254*, 1471. (b) Trost, B. M. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 259.

(10) Dumont, R.; Pfander, H. *Helv. Chim. Acta* **1983**, *66*, 814.

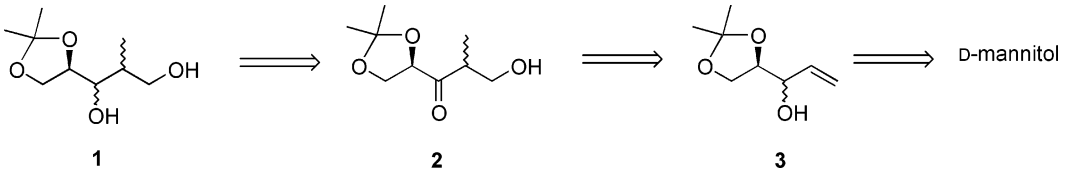
(11) (a) Hagen, S.; Lwande, W.; Kilaas, L.; Anthonsen, T. *Tetrahedron* **1980**, *36*, 3101. (b) Mulzer, J.; Pietschmann, C.; Buschmann, J.; Luger, P. *J. Org. Chem.* **1997**, *62*, 3938.

(12) Uma, R.; Crévisy, C.; Grée, R. *Chem. Rev.* **2003**, *103*, 27.

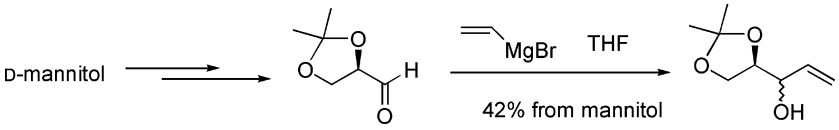
(13) When the reaction is performed on a larger scale (20 mmol) the isolated yield of diastereoisomeric aldol products decreases slightly (66%) while the yields of regioisomeric aldol and ketone increase (6%).

(14) Stork, G.; d'Angelo, J. *J. Am. Chem. Soc.* **1974**, *96*, 7114.

SCHEME 4



SCHEME 5



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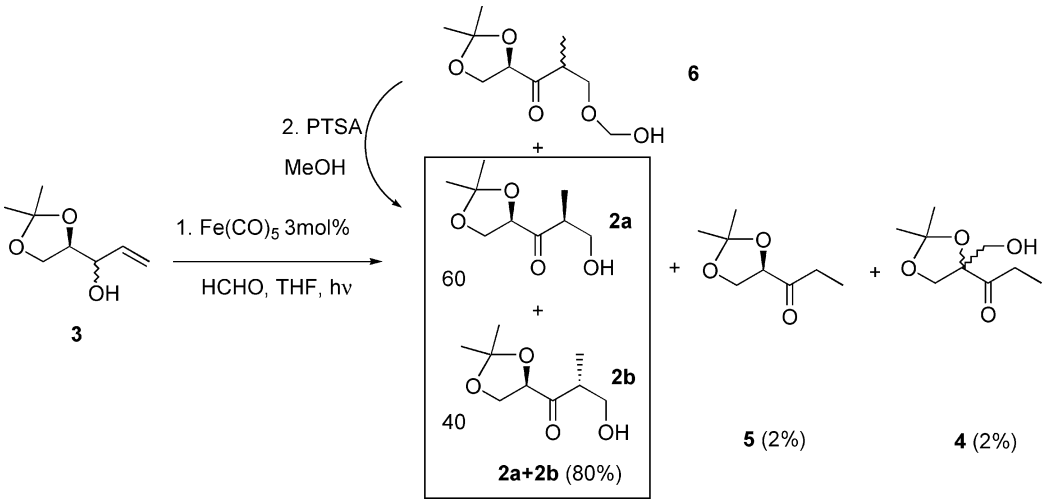
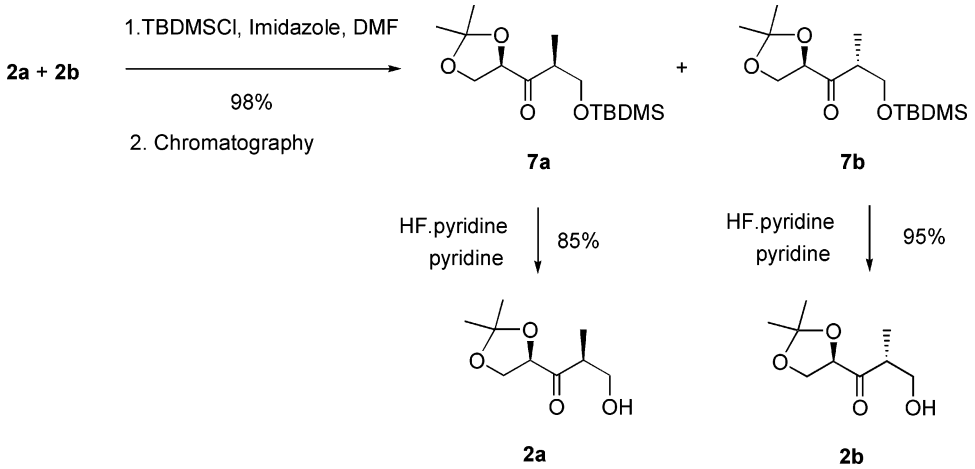


SCHEME 7



ity. Starting from this enriched mixture, the reaction affords exactly the same mixture of products and no significant difference in reactivity could be noticed. Therefore we have demonstrated for the first time that the configuration at the chiral carbon bearing the OH group does not influence the reactivity of this tandem isomerization−aldolization reaction.

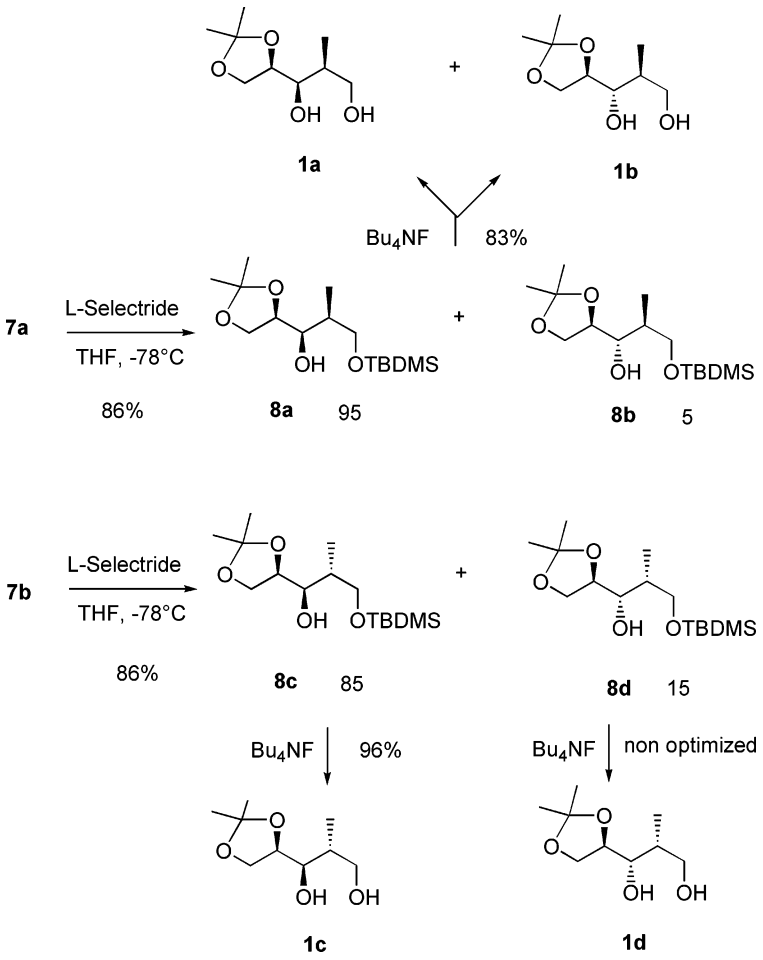
Although the mixture of the two diastereoisomers of **2** could not be separated by flash chromatography, the corresponding silyl ethers **7a** and **7b** could be separated. Therefore, after deprotection, both diastereoisomers **2a** and **2b** were isolated in a pure form (Scheme 7).

The reduction of ketones **7a**, **7b**, **2a**, and **2b** by various hydride donors was then studied. Each isomer can form two diastereoisomers respectively, **8a** (syn-syn*)* and **8b** (anti-anti*)* from **7a**, **8c** (syn-anti*)* and **8d** (anti-syn*)* from **7b**, **1a** (syn-syn*)* and **1b** (anti-anti*)* from **2a**, and **1c** (syn-anti*)* and **1d** (anti-syn*)* from **2b**.

As expected, sodium borohydride gives a mixture of two diastereoisomers in moderate selectivities (6/4 to 7/3

(15) (a) Sato, F.; Kusakabe, M. *Chem lett*. **1986**, 1473. (b) Sato, F.; Tanaka, Y.; Sato, M. *J. Chem. Soc., Chem. Commun*. **1983**, 165.

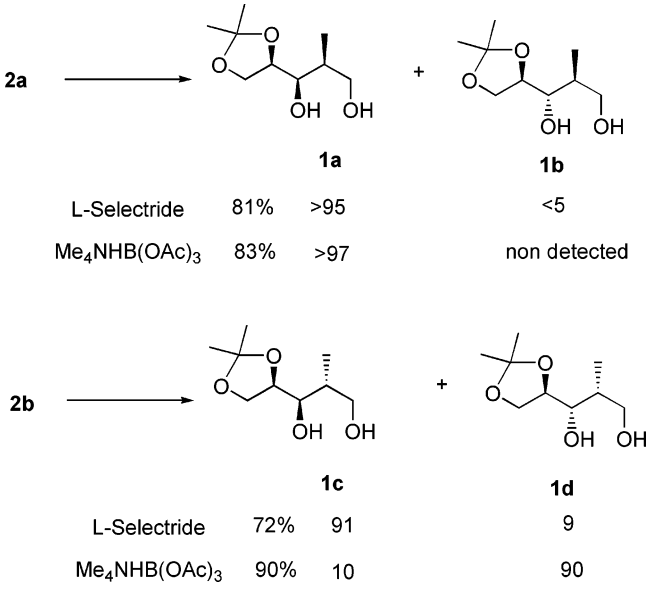
SCHEME 8



depending on the substrate). Better selectivities were obtained with Evans' reagent[16] or L-Selectride (Scheme 8). Treatment of compound **7a** by L-Selectride gives isomers **8a** and **8b**[6] in a very good ratio (95/5) and a high yield (86%). After deprotection of the silyl group with fluoride ions (83%), the two diastereoisomers **1a** and **1b** can be separated by chromatography. It is worth noting that the isolation of isomer **1a** (syn-syn)[5a] in a pure form is reported here for the first time. Reduction of compound **7b** with L-Selectride gives a mixture of isomers **8c**[6] and **8d** in a fairly good ratio (85/15) and a high yield (86%). The two isomers can be separated at this step. Compounds **1c**[5a,b,6] and **1d**[4b,5a,b] can be obtained after desilylation by fluoride ions (96% for **1c**[17]). The spectral data obtained for **1a**, **1b**, **1c**, and **1d** are in complete agreement with those reported in the literature.[4b,5a,b,6]

Reduction of the carbonyl group of **2a** by L-Selectride gives mainly the isomer **1a** as the isomer **1b** is only detected on the crude NMR spectra but with a ratio higher than 95/5 in favor of **1a** (Scheme 9). Reduction of compound **2b** by L-Selectride gives **1c** as the major stereoisomer (ratio 91/9). The isolated yields are high for both reactions (81 and 72%, respectively).

SCHEME 9



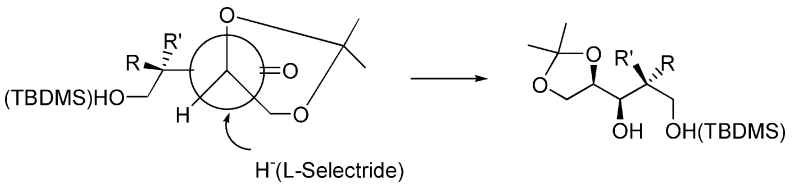
For both reactions, the stereochemistry of the major product can be explained by application of Felkin-Anh's model assuming that the alkoxy group mainly controls the direction of approach of the reagent (Scheme 10).

The diastereoselectivity of the reduction of **2a** under Evans' conditions is better since the isomer **1b** was not

(16) Evans, D. A.; Chapman, K. T.; Carreira, E. M. *J. Am. Chem. Soc*, **1998**, *110*, 3560.

(17) The deprotection reaction of compound **8d** has been performed on a very small scale and has not been optimized. Furthermore, compound **1d** is more easily obtained by the stereoselective reduction of **2b** under Evans' conditions.

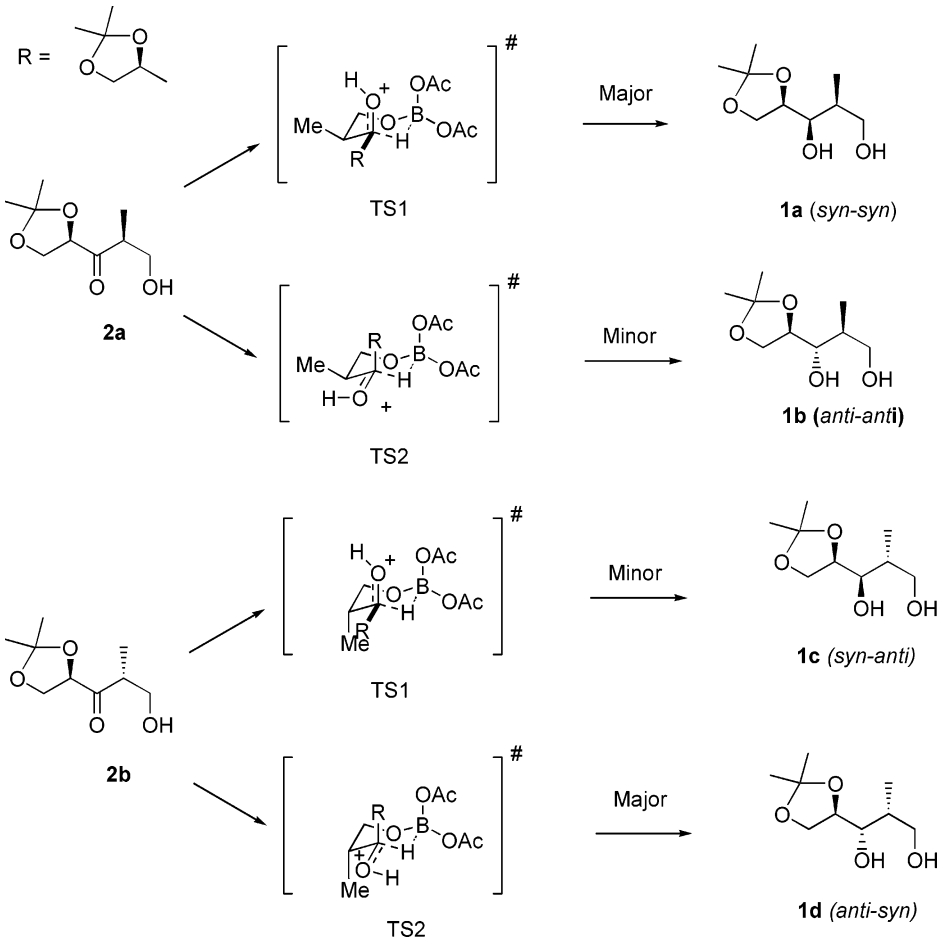
SCHEME 10



R = H ; R' = Me **2a** (**7a**) **1a** (**8a**)

R = Me ; R' = H **2b** (**7b**) **1c** (**8c**)

SCHEME 11



detected on the NMR spectra of the crude mixture (Scheme 9). It is interesting to note that, under Evans' conditions, an inversion of the stereochemistry of the reduction of **2b** is observed as the major isomer is now compound **1d** (ratio 90/10). The isolated yields are high for both reactions (83% and 90%, respectively).

The stereochemical course of reduction under Evans' conditions can be rationalized via two diastereoisomeric TS, each of which involves intramolecular hydride delivery (Scheme 11). In the case of **2a** the major product is formed via the TS1 because the 1,3-diaxial interaction between the di-*O*-isopropylidene group and the OAc destabilizes TS2 to a greater extent than the 1,3-diaxal interaction between the OH^+ and OAc destabilizes the TS1. In the case of **2b** the stereochemical course is different because the interaction between the Me and the di-*O*-isopropylidene group contributes to an extra destabilization of TS1. So, the major product is now the anti-syn diastereoisomer **1d**.

To conclude, we have developed a new efficient route for the preparation of three diastereoisomers of (2*R*)-1,2-*O*-isopropylidene-4-methylpentane-1,2,3,5-tetraol. The strategy is based on a novel tandem isomerization−aldolization reaction of allylic alcohols and aldehydes that occurs under mild conditions in the absence of either a strong base or a Lewis acid. Both compounds of type **1** and type **2** are valuable key intermediates for the synthesis of natural products or analogues. The syn−syn isomer **1a** is especially interesting as its preparation and isolation is reported here for the first time.

Experimental Section

General Methods. All reactions were conducted under a nitrogen atmosphere. Tetrahydrofuran was distilled from sodium/benzophenone ketyl. Acetonitrile was distilled from

calcium hydride and stored over 3 Å molecular sieves. Acetic acid was dried by azeotropic distillation with benzene. Dimethylformamide was dried over 4 Å molecular sieves. All NMR data were obtained at 400 MHz for ^{1}H and 100 MHz for ^{13}C with TMS for ^{1}H or the signal of the solvant for ^{13}C (δ 77.0 ppm) as an internal standard. IR spectra were recorded on a FT-IR instrument with NaCl plates. Elemental analyses and mass spectra were performed at the CRMPO in Rennes (France). Optical rotation was recorded at 589 nm.

Aldolization of Allylic Alcohol 3 with Formaldehyde. To an 37% aqueous solution of formaldehyde (4.66 mL, 62.35 mmol of HCHO) in THF (10 mL) was added magnesium sulfate. The suspension was stirred 5 min then 3.81 mL (16.21 mmol of HCHO) of the supernatant was added to a solution of allylic alcohol **3** (1.97 g, 12.47 mmol) in anhydrous THF (35 mL) under a nitrogen atmosphere. The reaction mixture was stirred and $Fe(CO)_5$ (49 μL, 0.37 mmol) was added. The reaction mixture was irradiated with a Philips HPK 125-W lamp for 1.5 h until disappearance of allylic alcohol. The reaction mixture was filtered through silica gel (1.5 cm) with ether, and the solvents were evaporated under vacuum. To a solution of the crude product in MeOH (40 mL) at 0 °C was added PTSA (119 mg, 0.62 mmol). After 1.5 h, the mixture was quenched with a saturated solution of $NaHCO_3$ and the aqueous phase was extracted with CH_2Cl_2 (3 × 50 mL). The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (petroleum ether/Et_2O, 1/1 v/v) to give ketone **5** (45.8 mg, 2%), regioisomer **4** (43.7 mg, 2%), and an unseparable mixture of diastereoisomeric aldols **2a** and **2b** (60/40 by ^{1}H NMR, 1.87 g, 80%) as a colorless oil.

1,2-*O*-Isopropylidene-2-hydroxymethylpentan-3-one-1,2-diol (4). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 1.05 (t, J = 7.2 Hz, 3H), 1.47 (s, 3H), 1.48 (s, 3H), 2.26 (dd, J = 5.4, 7.7 Hz, 1H), 2.73 (q, J = 7.2 Hz, 2H), 3.67 (dd, J = 4.5, 11.3 Hz, 1H), 3.77 (dd, J = 7.8, 11.3 Hz, 1H), 4.00 (d, J = 9.3 Hz, 1H), 4.07 (d, J = 9.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 7.0, 25.9, 26.5, 32.6, 65.8, 68.7, 88.6, 111.6, 214.8; HRMS (EI) 70 eV calcd for $C_8H_{13}O_4$ [M − •Me]$^+$ 173.0814, found 173.0824 (6 ppm).

(2*R*)-1,2-*O*-Isopropylidenepentan-3-one-1,2-diol (5). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 1.04 (t, J = 7.2 Hz, 3H), 1.38 (s, 3H), 1.47 (s, 3H), 2.63 (q, J = 7.2 Hz, 2H), 3.96 (dd, J = 5.6, 8.7 Hz, 1H), 4.19 (dd, J = 7.8, 8.6 Hz, 1H), 4.43 (dd, J = 5.6, 7.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 6.9, 25.0, 26.0, 31.9, 66.6, 80.1, 110.8, 211.6.

Silylation of a Mixture of Diastereoisomeric Aldols 2a and 2b. To a solution of aldols **2a** and **2b** (60/40) (2.69 g, 14.30 mmol) in anhydrous DMF (10 mL) under a nitrogen atmosphere were added imidazole (1.26 g, 18.60 mmol) and TBDMSCl (2.80 g, 18.60 mmol). The reaction mixture was stirred at room temperature for 30 min and quenched with water (20 mL). The aqueous phase was extracted with Et_2O (3 × 40 mL). The organic layer was washed with water (2 × 15 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (petroleum ether/Et_2O, 5/1 v/v) to give a diastereoisomeric mixture of silylated aldols **7a** and **7b** (60/40 by ^{1}H NMR, 4.23 g, 98%) as a colorless oil. The two diastereoisomers **7a** and **7b** were separated by column chromatography (petroleum ether/Et_2O, 15/1 v/v).

(2*R*,4*S*)-1,2-*O*-Isopropylidene-5-*O*-*tert*-butyldimethylsilyl-4-methylpentan-3-one-1,2,5-triol (7a). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 0.02 (s, 3H), 0.04 (s, 3H), 0.86 (s, 9H), 1.03 (d, J = 6.9 Hz, 3H), 1.40 (s, 3H), 1.44 (s, 3H), 3.20 (ddq, J = 5.2, 7.0, 7.0 Hz, 1H), 3.70 (dd, J = 5.2, 9.6 Hz, 1H), 3.78 (dd, J = 7.4, 9.6 Hz, 1H), 4.13 (dd, J = 5.7, 8.6 Hz, 1H), 4.17 (dd, J = 7.5, 8.5 Hz, 1H), 4.53 (dd, J = 5.7, 7.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C −5.6, 12.7, 18.2, 25.2, 25.8, 26.0, 44.7, 65.3, 65.8, 80.2, 110.6, 211.9; HRMS (EI) 70 eV calcd for $C_{14}H_{27}O_4Si$ [M − •Me]$^+$ 287.16786, found 287.16729 (1 ppm); IR (neat) 1719 cm^{-1}. Anal. Calcd for $C_{15}H_{30}O_4Si$: C, 59.56; H, 10.00. Found: C, 59.72; H, 10.06. $[\alpha]^{22}_D$ +71.2 (*c* 1.05; $CHCl_3$).

(2*R*,4*R*)-1,2-*O*-Isopropylidene-5-*O*-*tert*-butyldimethylsilyl-4-methylpentan-3-one-1,2,5-triol (7b). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 0.02 (s, 3H), 0.04 (s, 3H), 0.86 (s, 9H), 1.05 (d, J = 7.1 Hz, 3H), 1.40 (s, 3H), 1.50 (s, 3H), 3.20 (dqd, J = 5.3, 7.1, 8.4 Hz, 1H), 3.56 (dd, J = 5.2, 9.6 Hz, 1H), 3.81 (dd, J = 8.5, 9.6 Hz, 1H), 4.01 (dd, J = 6.4, 8.5 Hz, 1H), 4.19 (dd, J = 7.8, 8.4 Hz, 1H), 4.55 (dd, J = 6.4, 7.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C −5.6, 13.2, 18.2, 25.1, 25.8, 25.9, 44.0, 64.8, 65.7, 80.2, 111.0, 212.1; HRMS (EI) 70 eV calcd for $C_{14}H_{27}O_4Si$ [M − •Me]$^+$ 287.16786, found 287.17010 (7 ppm); IR (neat) 1721 cm^{-1}. Anal. Calcd for $C_{15}H_{30}O_4Si$: C, 59.56; H, 10.00. Found: C, 59.81; H, 9.96. $[\alpha]^{22}_D$ +28.6 (*c* 0.99; $CHCl_3$).

***tert*-Butyldimethylsilyl Ethers of Hemiacetals 6 (6a).** The two diastereoisomers of compound **6a** were synthesized by silylation of the crude mixture of the aldolization reaction obtained before the treatment with APTS. ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 0.09 (s, 2 × 6H), 0.90 (s, 2 × 9H), 1.08 (d, J = 7.0, 3H, major isomer), 1.10 (d, J = 7.9, 3H, minor isomer), 1.40 (s, 2 × 3H), 1.45 (s, 3H), 1.49 (s, 3H), 3.26−3.34 (m, 2 × 1H), 3.56 (dd, J = 5.3, 9.3, 1H, minor isomer), 3.65−3.74 (m, 1H + 2H), 4.02 (dd, J = 6.2, 8.6, 1H, minor isomer), 4.11 (dd, J = 5.7, 8.6, 1H, major isomer), 4.18 (dd, J = 7.6, 8.6, 1H, major isomer), 4.19 (dd, J = 7.8, 8.6, 1H, minor isomer), 4.53−4.58 (m, 2 × 1H), 4.76−4.84 (m, 2 × 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C −5.1, 13.1, 13.6, 18.0, 25.0, 25.1, 25.6, 25.9 (2), 41.5, 42.2, 65.8, 65.9, 69.1, 69.6, 79.9, 80.0, 90.0, 110.6, 111.0, 211.7, 211.9. HRMS (EI) 70 eV calcd for $C_{15}H_{29}O_5Si$ [M − •Me]$^+$ 317.17843, found 317.1745 (12 ppm).

Desilylation of Silylated Aldol 7a. Pyridinium poly(hydrogen fluoride) (0.44 g, 70% hydrogen fluoride−30% pyridine, ∼15 mmol of fluoride) was added to a solution of pyridine (1.63 mL, 20 mmol) in anhydrous THF (10 mL) and a stock solution (∼1.2 N) of pyridinium fluoride was produced. The silylated aldol **7a** (1.017 g, 3.36 mmol) was dissolved in anhydrous THF (0.5 mL) and 0.631 mL (7.7 mmol) of pyridine. The stock solution (10 mL, ∼12 mmol of fluoride) was added and the reaction mixture was stirred at room temperature for 4 days. The reaction mixture was quenched with water (20 mL). The aqueous phase was extracted with AcOEt (3 × 30 mL). The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (petroleum ether/Et_2O, 1/1 v/v) to give the aldol **2a** (539.4 mg, 85%) as a colorless oil.

(2*R*,4*S*)-1,2-*O*-Isopropylidene-4-methylpentan-3-one-1,2,5-triol (2a). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 1.11 (d, J = 7.1 Hz, 3H), 1.40 (s, 3H), 1.50 (s, 3H), 2.27 (s, 1H), 3.25 (ddq, J = 4.7, 7.1, 7.1 Hz, 1H), 3.74 (dd, J = 4.7, 10.8 Hz, 1H), 3.78 (dd, J = 7.1, 10.8 Hz, 1H), 4.05 (dd, J = 5.7, 8.6 Hz, 1H), 4.22 (dd, J = 7.8, 8.6 Hz, 1H), 4.57 (dd, J = 5.7, 7.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 12.7, 24.9, 25.9, 44.2, 64.5, 66.3, 79.8, 110.9, 213.1; HRMS (EI) 70 eV calcd for $C_8H_{13}O_4$ [M − •Me]$^+$ 173.0814, found 173.0808 (3 ppm); IR (neat) 3479, 1715 cm^{-1}. Anal. Calcd for $C_9H_{16}O_4$: C, 57.43; H, 8.57. Found: C, 57.02; H, 8.82. $[\alpha]^{21}_D$ +83.6 (*c* 0.49; $CHCl_3$).

Desilylation of Silylated Aldol 7b. To a solution of silylated aldol **7b** (0.688 g, 2.27 mmol) in anhydrous THF (0.5 mL) was added 0.423 mL (5.2 mmol) of pyridine. The stock solution (10 mL, ∼12 mmol of fluoride) was added and the reaction mixture was stirred at room temperature for 4 days. The reaction mixture was then quenched with water (20 mL). The aqueous phase was extracted with AcOEt (3 × 30 mL). The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (petroleum ether/Et_2O, 1/1 v/v) to give the aldol **2b** (404.8 mg, 95%) as a colorless oil.

(2*R*,4*R*)-1,2-*O*-Isopropylidene-4-methylpentan-3-one-1,2,5-triol (2b). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 1.16 (d, J = 7.3 Hz, 3H), 1.40 (s, 3H), 1.48 (s, 3H), 2.22 (s, 1H), 3.24 (ddq, J = 4.2, 7.3, 7.8 Hz, 1H), 3.67 (dd, J = 4.2, 11.1 Hz, 1H), 3.78 (dd, J = 7.8, 11.1 Hz, 1H), 4.07 (dd, J = 5.7, 8.6 Hz, 1H), 4.20 (dd, J = 7.7, 8.6 Hz, 1H), 4.55 (dd, J = 5.7, 7.7 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 12.9, 25.0, 25.9, 44.1, 63.9, 66.0,

79.5, 111.0, 214.1; HRMS (EI) 70 eV calcd for $C_8H_{13}O_4$ [M − •Me]$^+$ 173.08138, found 173.0808 (3 ppm); IR (neat) 3485, 1716 cm^{-1}. Anal. Calcd for $C_9H_{16}O_4$: C, 57.43; H, 8.57. Found: C, 57.11; H, 8.85. $[\alpha]^{21}_D$ +80.9 (*c* 1.00; $CHCl_3$).

Reduction of Silylated Aldol 7a with L-Selectride. To a solution of **7a** (182.3 mg, 0.603 mmol) in anhydrous THF (5 mL) at −78 °C under a nitrogen atmosphere was added L-Selectride (904 μL, 0.904 mmol). The temperature was raised to −40 °C in 30 min and the reaction mixture was quenched with a saturated solution of NH_4Cl (5 mL). The aqueous phase was extracted with Et_2O (3 × 20 mL). The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (petroleum ether/Et_2O, 7/1 v/v) to give an unseparable mixture of diastereoisomeric products **8a** (major) and **8b** (minor) (95/5 by ^{1}H NMR, 158.4 mg, 86%) as a colorless oil. It was possible to separate the two diastereoisomers after desilylation.

(2*R*,3*R*,4*S*)-1,2-*O*-Isopropylidene-5-*O*-*tert*-butyldimethylsilyl-4-methylpentane-1,2,3,5-tetraol (8a) and (2*R*,3*S*,4*S*)-1,2-*O*-Isopropylidene-5-*O*-*tert*-butyldimethylsilyl-4-methylpentane-1,2,3,5-tetraol (8b). IR (neat) 3496 cm^{-1}; HRMS (EI) 70 eV calcd for $C_{14}H_{19}O_4Si$ [M − •Me]$^+$ 289.1826, found 289.1835 (3 ppm). Major product **8a**: ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 0.06 (s, 6H), 0.89 (s, 9H), 0.95 (d, *J* = 7.0 Hz, 3H), 1.39 (s, 3H), 1.44 (s, 3H), 1.58−1.68 (m, 1H), 2.80 (d, *J* = 4.4 Hz, 1H), 3.63−3.66 (m, 2H), 3.68 (dd, *J* = 7.6, 8.0 Hz, 1H), 3.72 (ddd, *J* = 3.0, 4.4, 6.5 Hz, 1H), 4.01 (dd, *J* = 6.3, 8.0 Hz, 1H), 4.17 (ddd, *J* = 6.3, 6.5, 7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C −5.6, −5.5, 10.8, 18.2, 25.6, 25.8, 26.7, 38.0, 66.3, 66.7, 73.3, 77.6, 109.4. Minor product **8b** (selected values): ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 0.08 (s, 6H), 1.08 (d, *J* = 7.2 Hz, 3H), 1.37 (s, 3H), 1.40 (s, 3H), 3.03 (d, *J* = 5.7 Hz, 1H), 3.52−3.57 (m, 2H), 4.08−4.13 (m, 2H).

Reduction of Silylated Aldol 7b with L-Selectride. To a solution of **7b** (258.6 mg, 0.855 mmol) in anhydrous THF (5 mL) at −78 °C under nitrogen atmosphere was added L-Selectride (1282 μL, 1.282 mmol). The temperature was raised to −40 °C in 30 min and the reaction mixture was quenched with a saturated solution of NH_4Cl (5 mL). The aqueous phase was extracted with Et_2O (3 × 20 mL). The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (petroleum ether/Et_2O, 7/1 v/v) to give a mixture of diastereoisomeric products **8c** (major) and **8d** (minor) (85/15 by ^{1}H NMR, 222.9 mg, 86%) as a colorless oil. The two diastereoisomers **8c** and **8d** were separated by column chromatography (petroleum ether/Et_2O, 10/1 v/v).

(2*R*,3*R*,4*R*)-1,2-*O*-Isopropylidene-5-*O*-*tert*-butyldimethylsilyl-4-methylpentane-1,2,3,5-tetraol (8c). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 0.07 (s, 6H), 0.90 (s, 9H), 0.98 (d, *J* = 6.9 Hz, 3H), 1.38 (s, 3H), 1.44 (s, 3H), 1.75−1.85 (m, 1H), 3.09 (d, *J* = 5.6 Hz, 1H), 3.45 (ddd, *J* = 4.5, 5.6, 5.9 Hz, 1H), 3.67 (dd, *J* = 6.2, 10.0 Hz, 1H), 3.74 (dd, *J* = 4.4, 10.0 Hz, 1H), 3.85 (dd, *J* = 6.9, 7.8 Hz, 1H), 4.02 (dd, *J* = 6.9, 7.8 Hz, 1H), 4.25 (ddd, *J* = 4.5, 6.9, 6.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C −5.6, −5.5, 14.2, 18.2, 25.5, 25.8, 26.5, 38.2, 66.0, 66.1, 74.8, 77.2, 109.1; IR (neat) 3493 cm^{-1}; $[\alpha]^{21}_D$ +1.3 (*c* 0.98; $CHCl_3$).

(2*R*,3*S*,4*R*)-1,2-*O*-Isopropylidene-5-*O*-*tert*-butyldimethylsilyl-4-methylpentane-1,2,3,5-tetraol (8d). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 0.08 (s, 6H), 0.90 (s, 9H), 1.02 (d, *J* = 7.1 Hz, 3H), 1.35 (s, 3H), 1.40 (s, 3H), 1.90−1.98 (m, 1H), 3.32 (d, *J* = 1.9 Hz, 1H), 3.70 (dd, *J* = 4.5, 9.8 Hz, 1H), 3.79 (ddd, *J* = 1.9, 2.5, 7.7 Hz, 1H), 3.84 (dd, *J* = 3.2, 9.8 Hz, 1H), 3.97 (dd, *J* = 5.4, 7.6 Hz, 1H), 4.03 (ddd, *J* = 5.4, 5.8, 7.7 Hz, 1H), 4.10 (dd, *J* = 5.8, 7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C −5.7, −5.6, 10.1, 18.1, 25.4, 25.8, 26.8, 35.6, 67.3, 69.0, 76.0 (2), 108.9; HRMS (EI) 70 eV calcd for $C_{14}H_{29}O_4Si$ [M − •Me]$^+$ 289.18351, found 289.18257 (3 ppm); $[\alpha]^{21}_D$ +18.2 (*c* 0.20; $CHCl_3$).

Desilylation of a Mixture of Diastereoisomeric Products 8a and 8b. To a solution of compounds **8a** and **8b** (198.6 mg, 0.652 mmol) in anhydrous THF (5 mL) was added tetrabutylammonium fluoride (848 μL of a 1 M solution in THF, 0.848 mmol). The reaction mixture was stirred at room temperature for 1 h and quenched with a saturated solution of NH_4Cl (5 mL). The aqueous phase was extracted with AcOEt (3 × 20 mL). The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (petroleum ether/Et_2O, 1/4 v/v) to give a diastereoisomeric mixture of diols **1a** (major) and **1b** (minor) (95/5 by ^{1}H NMR, 102.7 mg, 83%) as a colorless oil. The two diastereoisomers **1a** and **1b** were separated by column chromatography on silica gel (petroleum ether/Et_2O, 1/1 v/v).

(2*R*,3*R*,4*S*)-1,2-*O*-Isopropylidene-4-methylpentane-1,2,3,5-tetraol (1a). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 0.98 (d, *J* = 7.1 Hz, 3H), 1.39 (s, 3H), 1.45 (s, 3H), 1.70−1.80 (m, 1H), 2.45 (br t, *J* ≈ 5.0 Hz, 1H), 2.63 (d, *J* = 5.2 Hz, 1H), 3.62−3.74 (m, 3H), 3.74 (dd, *J* = 7.2, 8.2 Hz, 1H), 4.04 (dd, *J* = 6.5, 8.2 Hz, 1H), 4.16−4.21 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 10.8, 25.5, 26.6, 38.0, 65.9, 66.3, 73.5, 76.8, 109.6; IR (neat) 3424 cm^{-1} ; $[\alpha]^{21}_D$ +8.0 (*c* 0.34; $CHCl_3$).

(2*R*,3*S*,4*S*)-1,2-*O*-Isopropylidene-4-methylpentane-1,2,3,5-tetraol (1b). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 0.96 (d, *J* = 7.1 Hz, 3H), 1.38 (s, 3H), 1.44 (s, 3H), 1.70−1.80 (m, 1H), 2.76 (br s, 1H), 2.84 (br s, 1H), 3.66−3.78 (m, 3H), 3.96 (dd, *J* = 7.2, 8.1 Hz, 1H), 4.04 (dd, *J* = 6.4, 8.1 Hz, 1H), 4.22 (ddd, *J* = 4.5, 6.4, 7.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 13.4, 25.3, 26.5, 36.9, 64.6, 67.4, 75.7, 77.2, 109.0.

Desilylation of Product 8c. To a solution of **8c** (64.6 mg, 0.212 mmol) in anhydrous THF (3 mL) was added tetrabutylammonium fluoride (276 μL of a 1 M solution in THF, 0.276 mmol). The reaction mixture was stirred at room temperature for 1 h and quenched with a saturated solution of NH_4Cl (5 mL). The aqueous phase was extracted with AcOEt (3 × 20 mL). The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (petroleum ether/Et_2O, 1/4 v/v) to give the diol **1c** (38.7 mg, 96%) as a colorless oil.

(2*R*,3*R*,4*R*)-1,2-*O*-Isopropylidene-4-methylpentane-1,2,3,5-tetraol (1c). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 0.98 (d, *J* = 7.1 Hz, 3H), 1.39 (s, 3H), 1.45 (s, 3H), 1.78−1.88 (m, 1H), 2.66 (s, 1H), 2.92 (s, 1H), 3.43−3.50 (br t, 1H), 3.67 (dd, *J* = 6.7, 11.2 Hz, 1H), 3.71 (dd, *J* = 4.0, 11.2 Hz, 1H), 3.84 (dd, *J* = 6.9, 8.1 Hz, 1H), 4.06 (dd, *J* = 6.6, 8.1 Hz, 1H), 4.25 (ddd, *J* = 4.1, 6.6, 6.9 Hz, 1H);^{13}C NMR (100 MHz, $CDCl_3$) δ_C 14.3, 25.2, 26.4, 38.4, 66.1, 66.3, 75.6, 76.8, 109.4; $[\alpha]^{21}_D$ −6.4 (*c* 0.75; $CHCl_3$); lit.[5b] $[\alpha]^{20}_D$ −5.1 (*c* 2.2; $CHCl_3$).

Desilylation of Product 8d. Compound **1d** was synthesized from **8d** with use of a similar procedure as for **8c**. The reaction was performed on a very small scale and was not optimized.

(2*R*,3*S*,4*R*)-1,2-*O*-Isopropylidene-4-methylpentane-1,2,3,5-tetraol (1d). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 1.02 (d, *J* = 7.1 Hz, 3H), 1.36 (s, 3H), 1.41 (s, 3H), 1.90−1.99 (m, 1H), 3.71 (dd, *J* = 5.7, 10.7 Hz, 1H), 3.79 (dd, *J* = 3.9, 10.7 Hz, 1H), 3.82 (dd, *J* = 3.6, 6.7 Hz, 1H), 3.94−4.01 (m, 1H), 4.06−4.12 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 10.6, 25.3, 26.7, 36.7, 66.7, 67.4, 74.9, 76.5, 108.9; $[\alpha]^{20}_D$ +18.2 (*c* 1.12; $CHCl_3$); lit.[5b] $[\alpha]^{20}_D$ +15.8 (*c* 2.3; $CHCl_3$)

Reduction of Aldol 2a with L-Selectride. Compounds **1a** and **1b** were obtained from **2a** following a similar procedure as for **7a** except that the aqueous phase was extraced with ethyl acetate and the organic layer was then washed with a saturated sodium and potassium tartrate solution.

Reduction of Aldol 2b with L-Selectride. Compounds **1c** and **1d** were obtained from **2b** following a similar procedure as for **7b** except that the aqueous phase was extraced with ethyl acetate and the organic layer was then washed with a saturated sodium and potassium tartrate solution.

Reduction of Aldol 2a with $Me_4NHB(OAc)_3$. To a solution of $Me_4NHB(OAc)_3$ (1.639 g, 6.23 mmol) in anhydrous acetonitrile (4.0 mL) and anhydrous acetic acid (2.5 mL) at −20 °C was added a solution of aldol **2a** (242.6 mg, 1.29 mmol)

in anhydrous acetonitrile (2.0 mL). The mixture was stirred for 1 h at −20 °C and quenched with saturated sodium and potassium tartrate solution (10 mL). A saturated solution of sodium bicarbonate was added until pH 8 was raised and the aqueous phase was extracted with AcOEt (3 × 20 mL). The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (hexane/AcOEt, 1/2 v/v + 0.2% Et_3N) to give the diols **1a** and **1b** (203.9 mg, 83%) as a colorless oil.

Reduction of Aldol 2b with $Me_4NHB(OAc)_3$. To a solution of $Me_4NHB(OAc)_3$ (1.066 g, 4.05 mmol) in 4.0 mL of anhydrous acetonitrile and 2.5 mL of anhydrous acetic acid at −20 °C was added a solution of aldol **2b** (157.7 mg, 0.84 mmol) in 2.0 mL of anhydrous acetonitrile. The mixture was stirred for 1 h at −20 °C and quenched with a sodium and potassium tartrate solution (10 mL). A saturated solution of sodium bicarbonate was added until pH 8 was raised and the aqueous phase was extracted with AcOEt (3 × 20 mL). The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (hexane/AcOEt, 1/2 v/v + 0.2% Et_3N) to give a mixture of diastereoisomeric diols **1d** (major) and **1c** (minor) (90/10 by ^1H NMR, 143.4 mg, 90%) as a colorless oil. The diol **1d** was purified by crystallization in CH_2Cl_2/hexane (mp 71 °C).

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