(*R*)-2,3-*O*-Cyclohexylideneglyceraldehyde, a Versatile Intermediate for Asymmetric Synthesis of Homoallyl and Homopropargyl Alcohols in Aqueous Medium

Angshuman Chattopadhyay

Bio-organic Division, Bhabha Atomic Research Centre, Bombay-400085, India

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Zn-mediated allylation and propargylation of (*R*)-2,3-*O*-cyclohexylideneglyceraldehyde (**1**) in aqueous medium following Luche's procedure afforded the *anti* homoallylic **3** and homopropargylic **8** alcohols in good yield and with high stereoselectivity. Crotylation of **1** under similar conditions afforded appreciable amounts of ery*thro*-**5** and *threo*-**6** alcohols. In each case, the diastereo alcohols are separable by column chromatography. Compound **8** on appropriate chemical manipulation of its functionalities gave the (*S*)-enantiomer of (*R*)-**13**, a useful synthon of LTB_4. Compound **3** on chemical elaboration afforded a diversely functionalized triol derivative **15**, a potentially useful synthon for many bioactive compounds.

Stereocontrol in C−C bond-forming reactions has gained considerable attention[1] over the last two decades. In this endeavor, enantioselective addition of different organometallics to an array of prochiral carbonyls with or without the presence of any chiral auxiliary has been explored extensively from both mechanistic and synthetic viewpoints. Consequently, there has been an increasing demand for carrying out these additions in aqueous medium[2] with a view to establishing their practical viability. Usually, any organometalation of a carbonyl compound in aqueous medium is considered to be operationally useful, when the reaction proceeds at a reasonably faster rate without affecting the other functionalities of both the reactant as well as the product, and the isolation of the product is relatively simple and straightforward.

Recently, we reported[3] a practical method for preparation of (*R*)-2,3-cyclohexylideneglyceraldehyde (**1**) that has some operational advantages over many other chirally oxygenated aldehydes due to its being less prone to polymerization, less volatile, and less water soluble. Considering its easy availability and being a stable derivative of the simplest variety of chiral hydroxy aldehyde, there is a scope for investigation of the possibility of some organometallic additions to **1** in the presence of water and simultaneous study of the diastereoselectivities of the successful reactions. The three reactions chosen in this endeavor are allylation, crotylation, and propargylation since allyl[4] and crotylmetalations[5] of aldehydes have proven to be valuable alternatives to conventional aldol methodologies and all these reactions are expected to produce either the functionally rich homoallylic alcohols or homopropargylic alcohols that are required for our ongoing program on synthesis of bioactive compounds. It is noteworthy that allylmetalation has emerged as an important reaction type, and hence, there has been an extensive development of stereodifferentiating allylation of varied types both in aqueous[6,7] and anhydrous conditions.[4,5] Moreover, applications of some homoallylic alcohols in natural product synthesis are well documented.[8] Likewise, metal-mediated propargylation of carbonyls under anhydrous conditions for stereoselective synthesis of homopropargylic alcohols and utilization of some of them in synthesis of bioactive compounds continue to draw attention,[9] albeit in less number. Recent reports indicate that In,[10a] Sn,[10b] Zn-mediated[10c] Barbier-type additions of propargyl hal-

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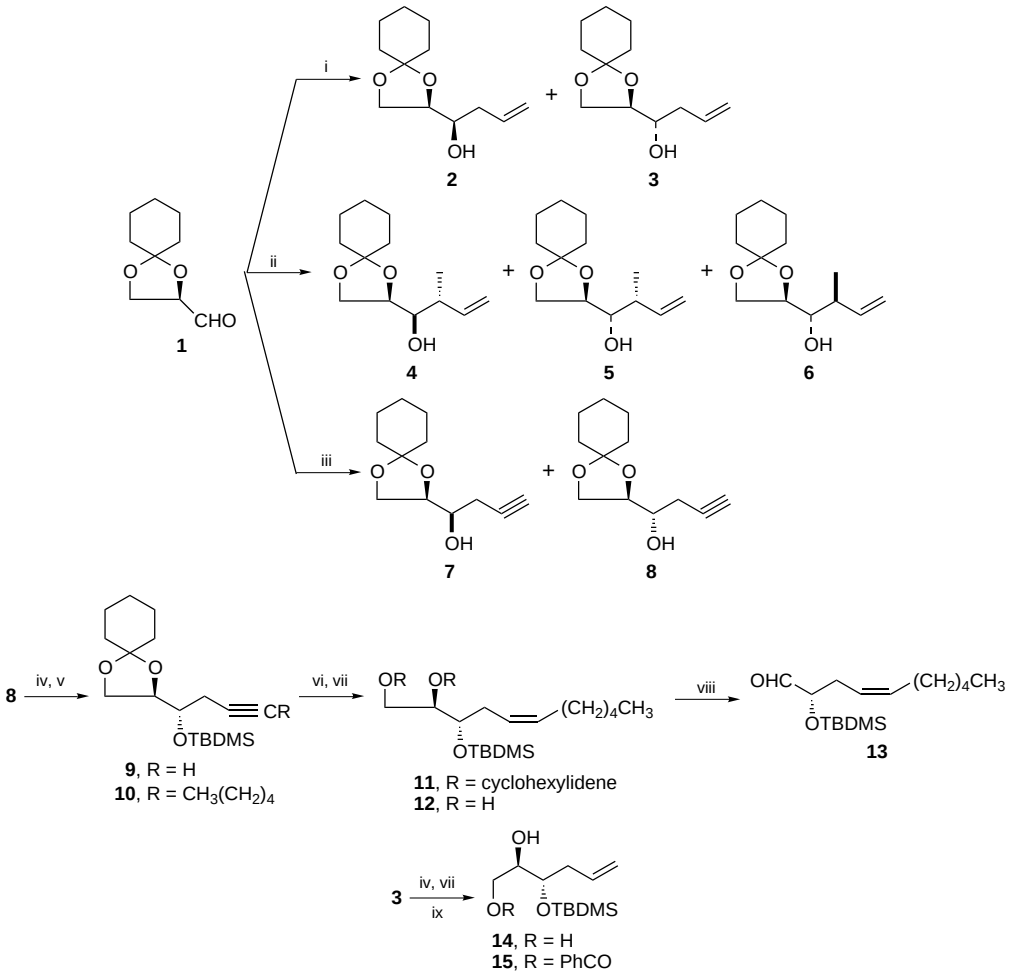
Scheme 1[a]



[a] Key: (i) allyl bromide/Zn/aqueous NH_4Cl; (ii) crotyl bromide/Zn/aqueous NH_4Cl; (iii) propargyl bromide/Zn/aqueous NH_4Cl; (iv) TBDMSCl/DMF; (v) *n*-BuLi/*n*-bromopentane; (vi) H_2/P(2)-Ni; (vii) CF_3CO_2H/H_2O; (viii) $NaIO_4$; (ix) PhCOCN/TEA.

ides to some achiral nonsugar carbonyls in aqueous medium gave rise to homopropargyl alcohols in association with some amount (2−16%) of allenic alcohols, whereas the study on enantioselectivity of these additions has not been considered.

Allylation and crotylation of **1** have been separately attempted following the operationally simple Luche's procedure[6] using commercially available Zn dust and allyl and crotyl bromide, respectively. Here, both Zn dust and the bromide were added in excess in order to increase the reaction rate. In both the cases the aldehyde reacts completely with the formation of the corresponding homoallylic alcohols in good yield. Allylmetalation has been found to take place with high diastereoselective formation of the anti isomer **3** (*syn* **2**:*anti* **3** = 3.6:96.4) which is a good improvement of our earlier observation where allylation of **1** had been performed under anhydrous conditions using the allyl-Grignard. Each diastereo alcohol was isolated in pure form after separation by column chromatography. The crotylmetalation of **1**, using crotyl bromide (Fluka, containing 15% 1-bromo-3-butene) has been effected with regiospecificity where C−C bond formation has taken place exclusively at the γ-position. After column chromatography of the crude product, three (**4, 5**, and **6)** of the four possible diastereoalcohols were isolated separately in pure form in the proportion of 2.3:34.2:63.5, respectively, whereas the fourth one *i.e.*, the (2*R*,3*R*,4*S*)-isomer, has not been found to be isolated. The stereochemistry of each of the diastereomers has been identified by comparing the pattern of the signals in the region of δ 3.3−4.2 of their ^{1}H NMR spectra with those reported[5b,c] for the corresponding isopropylidene derivatives, which have been prepared under anhydrous conditions and were separated from each other on very small scales by HPLC[5b] and radial chromatography.[5c]

Luche's procedure has been extended for propargylmetalation of **1** by treating it with excess of propargyl bromide and Zn dust (Scheme 1). Here, **1** was found to be reacted completely after stirring for a longer duration (8 h). The reaction proceeded with the formation of homopropargylic alcohol in good yield (75%) and a very negligible amount (1.2%) of allenic compound, which was detected by the presence of the signals at δ 4.7 and δ 5.1 due to allenic protons compared to strong signals at δ 2.05 due to acetylene proton in the ^{1}H NMR spectrum of the residue after usual extraction and solvent removal under reduced pressure. This indicates that the propargylation has taken place with high regioselectivity. Furthermore, propargylation has been found to be associated with a very high diastereoselective formation of

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the *anti* isomer (*syn* **7**:*anti* **8** = 3:97), which is higher than our earlier observation[3] that involves propargylation with the Grignard under anhydrous conditions. The diastereo alcohols were isolated in pure form after being separated by column chromatography. This appears to be the first report on metal-mediated Barbier-type stereoselective propargylation of a chirally oxygenated carbonyl in the presence of water.

Here we have accomplished an inexpensive and operationally simple approach to the preparation of an appreciable amount of four functionally rich alcohols **3, 5, 6, 8** in optically pure form. The efficacy of this method is due to good reactivity of **1** in an aqueous environment followed by easy isolation and separability of the resulting diastereo alcohols, in each case, by simple column chromatography. The stable cyclohexylidene ketal functionality remains unaffected even on mild acid treatment during isolation of the product to dissolve the turbid metal complex in order to facilitate the extraction. Hence, the present approach is amenable to large scale synthesis of these four alcohols, which hold good promise in versatile synthetic manipulations.

The high *anti* selectivity during the formation of alcohol for all the three reactions suggests that these reactions proceed *via* a Felkin−Anh model[11] rather than by a chelation−Cram model[12] as the water solvates the metal ions and thereby competes with chelate complex. The crotylation using crotyl bromide, whose (*E*)-stereochemical purity is not available in detail, proceeds with the formation of predominantly *threo*-**6** (63.5%) and an appreciable amount of *erythro*-**5** (34.2%). Hence, it is not clearly understood about the nature of the intermediate during the reaction in aqueous medium, as the six-membered cyclic transition state[13] is expected to produce *threo*-isomer from (*E*)-bromide and *erythro*-isomer from (*Z*)-bromide stereoselectively, whereas the acyclic linear transition state[14] suggests *erythro* selectivity with (*E*)-bromide and poor selectivity with (*Z*)-bromide.

Silylation of the hydroxy group of **8** followed by C-alkylation of the terminal alkyne **9** gave **10**. Semihydrogenation of **10** with P(2)−Ni catalyst[15] produced **11**. Deketalization of **11** with aqueous trifluoroacetic acid followed by $NaIO_4$ cleavage of the resulting diol **12**, without purification, afforded the aldehyde (*S*)-**13**. (*R*)-**13** has been utilized[16] for the synthesis of the leukotriene (LTB_4),[17] the synthesis of which is of current interest. The physical and spectral properties of (*S*)-**13** ($[\alpha]^{24}$ −7.82°, (*c* 0.98, $CHCl_3$)) were found to be in accordance with those[16] of the (*R*)-enantiomer ($[\alpha]_D$ +7.9°, (*c* 1.0, $CHCl_3$)).

Silylation of the hydroxy group of **3** and subsequent deketalization afforded the diol **14** in good yield (84%). Selective monobenzoylation of the primary hydroxyl of **14** has been accomplished to give **15** in appreciable yield (83%). Compound **15** with its three hydroxyl groups, two of which are versatilely protected, in association with a terminal alkene is supposed to be of interest as a possible intermediate for the synthesis of sugar-modified nucleosides[18] as well as many carbohydrates and related polyols.[8e,f,19] Similarly, compounds **5**, **6**, and **8** with an identical reaction sequence should give rise to other functionalized triols of good synthetic potential.

Thus, a convenient procedure for stereoselective synthesis of a series of chiral functionalized homoallylic **3, 5, 6** and homopropargylic **8** alcohols starting from the aldehyde **1** has been presented. Hopefully, utilization of this protocol with its available enantiomer[20] will afford stereoselective synthesis of another series of diastereo alcohols with high optical purity.

Experimental Section

All bps are uncorrected. All the anhydrous reactions were carried out under argon atmosphere using freshly distilled anhydrous solvents. Unless otherwise mentioned, the organic extracts were dried over anhydrous Na_2SO_4.

General Procedure for Allylation, Crotylation, and Propargylation of 1. To a cold (10 °C) and well-stirred mixture of **1** (10.2 g, 0.06 mol), Zn dust (7.8 g, 0.12 mol for allylation and crotylation; 14 g, 0.21 mol for propargylation), and bromide (14.5 g for allylaion, 0.12 mol; 16.2 g for crotylation, 0.12 mol; 21.4 g, 0.18 mol for propargylation) in THF (50 mL) was added a saturated aqueous solution of NH_4Cl (30 mL) dropwise over a period of 30 min. The mixture was stirred for 4 h (allylation and crotylation) or for 8 h (propargylation) at ambient temperature until the aldehyde was totally consumed (by TLC). The mixture was filtered, and the precipitate was thoroughly washed with $CHCl_3$. The aqueous layer was separated and treated with 5% HCl to dissolve the suspended turbid material. The clear solution was extracted with $CHCl_3$. The combined organic layer was washed successively with 10% $NaHCO_3$, water, and brine. After solvent removal under reduced pressure, the residue was column chromatographed (silica gel), eluting with 0−25% EtOAc in hexane resulting in isolation of the diastereomers in pure form. Both for allylation and propargylation, the minor isomers (*2R,3R*)-**2** (0.33 g, 3%) and (*2R,3R*)-**7** (0.28 g, 2%), respectively, have been eluted first followed by the major isomers (*2R,3S*)-**3** (9.59 g, 75%) and (2*R*,3*S*)-**8** (9.17 g, 73%), respectively. The spectral and optical data of all these four compounds (**2, 3, 7**, and **8**) were found to be identical with those reported by us.[3] Column chromatography of the crotylated product sequentially isolated (*2R,3R,4R*)-**4**, (*2R,3S,4R*)-**5**, and (*2R,3S,4S*)-**6**.

(2*R*,3*R*,4*R*)-1,2-*O*-Cyclohexylidene-4-methyl-5-hexene-1,2,3-triol (4): yield 0.24 g (2%); R_f 0.83 (20% EtOAc/hexane); $[\alpha]^{23}$ +47.14° (*c* 1.4, $CHCl_3$); IR (film) 3400, 3005, 1650, 1475, 1390, 1130, 1060, 995, 920; ^{1}H NMR ($CDCl_3$) δ 1.09 (d, J = 6.6 Hz, 3H), 1.4−1.6 (m, 10H), 2.2−2.3 (m, 1H), 2.68 (br, s, D_2O exchangeable, 1H), 3.3−3.4 (m, 1H), 3.65−3.75 (m, 1H), 3.93−4.08 (m, 2H), 5.0−5.1 (m, 2H), 5.7−5.9 (m, 1H).

(2*R*,3*S*,4*R*)-1,2-*O*-Cyclohexylidene-4-methyl-5-hexene-1,2,3-triol (5): yield 3.6 g (27%); R_f 0.75 (20% EtOAc/hexane); $[\alpha]^{23}$ +29.65° (*c* 1.45, $CHCl_3$); IR (film) 3400, 3005, 1650, 1470, 1395, 1130, 1060, 995, 920; ^{1}H NMR ($CDCl_3$) δ 1.08 (d, J = 6.6 Hz, 3H), 1.4−1.6 (m, 10H), 2.11 (bs, D_2O exchangeable, 1H), 2.2−2.3 (m, 1H), 3.6−3.7 (m, 1H), 3.8−3.9 (m, 2H), 4.0−4.1 (m, 1H), 5.0−5.06 (m, 2H), 5.7−5.9 (m, 1H).

(2*R*,3*S*,4*S*)-1,2-*O*-Cyclohexylidene-4-methyl-5-hexene-1,2,3-triol (6): yield 6.65 g (49%); R_f 0.66 (20% EtOAc/hexane); $[\alpha]^{23}$ +2.60° (*c* 2.05, $CHCl_3$); IR (film) 3400, 3005, 1655, 1475, 1390, 1130, 1065, 995, 920; ^{1}H NMR ($CDCl_3$) δ 1.07 (d, J = 6.5 Hz, 3H), 1.4−1.6 (m, 10H), 2.15 (bs, 1H, D_2O exchangeable),

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2.3−2.4 (bm, 1H), 3.5−3.6 (m, 1H), 3.85−4.05 (m, 3H), 5.0−5.1 (m, 2H), 5.7−5.9 (m, 1H). Anal. Calcd for C_{13} H_{22} O_3: C, 68.99; H, 9.80. Found: C, 68.87; H, 9.92 for **4**; C, 68.89; H, 9.84 for **5**; C, 69.19; H, 9.77 for **6**.

(2*R*,3*S*)-3-[(*tert*-Butyldimethylsilyl)oxy]-1,2-cyclohexylidene-5-hexyne-1,2 diol (9). To a solution of **8** (4.2 g, 0.02 mol) and imidazole (2.04 g, 0.03 mol) in DMF (20 mL) was added *tert*-butyldimethysilyl chloride (3.5 g, 0.022 mol) at room temperature. The mixture was stirred overnight, treated with excess water, and extracted with ether. The organic layer was washed with water and brine, dried, and concentrated under reduced pressure. The residue was chromatographed (silica gel, 0−15% ether in hexane) to obtain pure **9** (5.9 g, 90%): $[\alpha]^{24}$ +13.62° (*c* 3.20, $CHCl_3$); IR (film) 3320, 1465, 1390, 1255, 1100, 930, 840, 770; ^{1}H NMR ($CDCl_3$) δ 0.09 (s, 6H), 0.89 (s, 9H), 1.4−1.6 (m, 10 H), 2.05 (t, J = 1.5 Hz, 1H), 2.4−2.6 (m, 2H), 3.5−3.7 (m, 1H), 3.8−4.1 (m, 3H). Anal. Calcd for $C_{18}H_{32}O_3$-Si: C, 66.62; H, 9.94. Found: C, 66.48; H, 9.84.

(2*R*,3*S*)-3-[(*tert*-Butyldimethylsilyl)oxy]-1,2-cyclohexylidene-5-undecyne-1,2-diol (10). To a solution of **9** (4.86 g, 0.015 mol) in THF (30 mL) at −50 °C was added *n*-BuLi (10 mL of 1.6 M solution in hexane, 0.016 mol). After the mixture was stirred for 1 h, 1-bromopentane (3.0 g, 0.02 mol) in HMPA (15 mL) was added to it. The mixture was gradually brought to room temperature and stirred for 5 h, treated with water, and extracted with hexane. The organic layer was washed successively with water and brine and then dried. The residue after solvent removal under reduced pressure was column chromatographed (silica gel, 0−15% ether in hexane) to afford pure **10** (4.8 g, 81%): $[\alpha]^{24}$ +11.04° (*c* 3.66, $CHCl_3$); IR (film) 1455, 1370, 1250, 1130, 1120, 950, 835, 770; ^{1}H NMR ($CDCl_3$) δ 0.09 (s, 6H), 0.89−0.93 (t, J = 6.5 Hz, 3H overlapped with a s, 9H), 1.1−1.3 (m, 6H), 1.4−1.6 (m, 10 H), 2.3-2.6 (m, 4H), 3.5−3.7 (m, 1H), 3.8−4.1 (m, 3H). Anal. Calcd for $C_{23}H_{42}O_3Si$: C, 69.99; H, 10.73. Found: C, 70.14; H, 10.87.

(2*R*,3*S*)-3-[(*tert*-Butyldimethylsilyl)oxy]-1,2-cyclohexylidene-5(*Z*)-undecene-1,2-diol (11). Following an experimental procedure similar to that done by us,[15b] compound **10** (3.94 g, 0.01 mol) was semihydrogenated over P(2)−Ni catalyst, prepared from $Ni(OAc)_2$, $4H_2O$ (248 mg), and $NaBH_4$ (58 mg) in EtOH (15 mL) in the presence of 1,2-diaminoethane (0.2 mL). After the absorption of the required quantity of hydrogen, the mixture was filtered. The filtrate was concentrated under reduced pressure. The residue was mixed with excess water and extracted with hexane. The organic layer was washed successively with water and brine and then dried. The residue after solvent removal under reduced pressure was column chromatographed (silica gel, 0−15% ether in hexane) to afford pure **11** (3.2 g, 81%): $[\alpha]^{26}$ +18.95° (*c* 2.10, $CHCl_3$); IR (film) 3005, 1650, 1450, 1250, 1160, 1100, 1060, 950, 840, 770; ^{1}H NMR ($CDCl_3$) δ 0.09 (s, 6H), 0.89−0.93 (t, J = 6.5 Hz, 3H overlapped with a s, 9H), 1.1−1.3 (m, 6H), 1.4−1.6 (m, 10 H), 2.1−2.4 (m, 4H), 3.6−3.8 (m, 1H), 3.9−4.2 (m, 3H), 5.3−5.6 (m, 2H). Anal. Calcd for $C_{23}H_{44}O_3Si$: C, 69.64; H, 11.18. Found: C, 69.83; H, 11.08.

(2*S*,4*Z*)-2-[(*tert*-Butyldimethylsilyl)oxy]-4-decenal (13). Compound **11** (2.4 g, 0.006 mol) was mixed with 90% aqueous trifluoroacetic acid (15 mL), stirred for 3 h at 0 °C, and diluted with $CHCl_3$ and water. The aqueous layer was extracted with $CHCl_3$. The combined organic layers were washed successively with 2% $NaHCO_3$ and water until neutral. Solvent removal under reduced pressure gave the crude diol **12**. This crude product was dissolved in 60% aqueous acetonitrile (20 mL) and treated with $NaIO_4$ (1.9 g). The mixture was stirred for 1 h at room temperature and filtered. The filtrate was mixed with water and extracted thoroughly with $CHCl_3$. The organic layer was washed with water and concentrated under reduced pressure. The residue was chromatographed (Florisil, 0−25% ether in hexane) to furnish pure **13** (960 mg, 57%), which was found to be unstable on long standing: $[\alpha]^{24}$ −7.82° (*c* 0.98, $CHCl_3$) [lit.[16] $[\alpha]_D$ +7.9° (*c* 1, $CHCl_3$) of the (2*R*,4*Z*)-enantiomer]; IR (film) 3005, 2720 1710, 1650, 1120, 1060, 950; ^{1}H NMR ($CDCl_3$) δ 0.09 (s, 6H), 0.89−0.93 (t, J = 6.5 Hz, 3H overlapped with a s, 9H), 1.2−1.6 (m, 6H), 2.0−2.1 (m, 2H), 2.3−2.5 (m, 2H), 4.0−4.2 (m, 1H), 5.4−5.6 (m, 2H), 9.7 (d, J = 2 Hz, 1H).

(2*R*,3*S*)-3-[(*tert*-Butyldimethylsilyl)oxy]-5-hexene-1,2 diol (14). To a solution of **3** (4.24 g, 0.02 mol) and imidazole (2.04 g, 0.03 mol) in DMF (20 mL) was added *tert*-butyldimethysilyl chloride (3.5 g, 0.022 mol) at room temperature. The mixture was stirred overnight, treated with excess water, and extracted with ether. The organic layer was washed with water and then concentrated under reduced pressure. The residue was mixed with 90% aqueous trifluoroacetic acid (20 mL), stirred for 3 h at 0 °C, and diluted with $CHCl_3$ and water. The aqueous layer was extracted with $CHCl_3$. The combined organic layers were washed successively with 2% $NaHCO_3$ and water until neutral. Solvent removal under reduced pressure followed by chromatography of the residue (silica gel, 0−7% MeOH in $CHCl_3$) gave pure diol **14** (4.15g, 84%): $[\alpha]^{24}$ +11.81° (*c* 1.20, $CHCl_3$); IR (film) 3450, 3005, 1650, 1465, 1390, 1255, 1120, 995, 920; ^{1}H NMR ($CDCl_3$) δ 0.09 (s, 6H), 0.89 (s, 9H), 2.1−2.3 (m, 2H), 2.5−2.7 (bm, D_2O exchangeable, 2H), 3.6−3.8 (m, 1H), 3.9−4.1 (m, 3H), 5.0−5.3 (m, 2H), 5.7−6.0 (m, 1H). Anal. Calcd for $C_{12}H_{26}O_3Si$: C, 58.53; H, 10.64. Found: C, 58.45; H, 10.84.

(2*R*,3*S*)-1-(Benzoyloxy)-3-[(*tert*-butyldimethylsilyl)oxy]-5-hexen-2 -ol (15). To a cooled (0 °C) solution of **14** (1.23 g, 0.005 mol) and trimethylamine (0.3 mL, 0.002 mol) in dichloromethane (40 mL) was added a solution of benzoyl cyanide (0.6 mL, 0.0051 mol) in dichloromethane (10 mL) dropwise over a period of 30 min. The mixture was stirred for an additional 30 min at 0 °C and treated with water. The organic layer was separated and washed with water and then brine. Solvent removal under reduced pressure followed by column chromatography (silica gel, 0−20% EtOAc in hexane) of the residue eluted first a little nonpolar impurity and then the monobenzoate **15** (1.45 g, 83%): $[\alpha]^{24}$ +33.03° (*c* 1.58, $CHCl_3$); IR (film) 3450, 3005, 1715, 1650, 1465, 1270, 1160, 1080, 995, 920 820, 770; ^{1}H NMR ($CDCl_3$) δ 0.09 (s, 6H), 0.89 (s, 9H), 2.1−2.3 (m, 2H), 2.8 (bm, D_2O exchangeable, 1H), 3.9−4.1 (m, 2H), 4.3−4.5 (m, 2H), 5.0−5.2 (m, 2H), 5.7−6.0 (m, 1H) 7.3−8.2 (m, 5H). Anal. Calcd for $C_{19}H_{30}O_4Si$: C, 65.10; H, 8.63. Found: C, 65.28; H, 8.74.

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