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Asymmetric Allylation of Aldehydes Using Tiglyltitanocenes Attached to a Carbohydrate

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Key Words *: Carbohydrate-titanocenes; Homoallylic alcohols; Regiocontrol; Asymmetric induction.*

Abstract : η^3-Tiglyltitanium complexes bearing α- or β-glucopyranosyl auxiliaries were synthesized starting from the corresponding C1-dienopyranosides. These complexes were reacted with propanal and (-)-myrtenal to afford 4-hydroxy-3-methylvinylglycoside derivatives. In several cases, high diastereofacial selectivities were obtained. Thus, the reaction employing (-)-myrtenal and β-glucopyranosyl tiglyltitanium complex led to the unique (d.s.≥98%) 3R,4R-configurated compound bearing the sugar and pinenyl fragments, which can be considered as a promising new chiron. © 1997 Elsevier Science Ltd.

The control of the stereochemistry of C-C bond formation in the reactions of allylmetals with the carbonyl compounds is of significant synthetic interest.[1] The development of the enantioselective allylmetallation reactions especially receives great attention within the framework of methods for the synthesis of useful chirons.[2] In keeping with this aim, the allyltitanation reaction offers interesting opportunities. Since η^3-allyltitanocene complexes are available from the hydrotitanation of simple[3] or functionalized[4] dienes, the optically active diene precursors can be used to induce diastereofacial selectivity. In this matter, we recently reported on some asymmetric allyltitanation reactions, employing nopadiene-derived chiral allyltitanium complex and achiral or chiral aldehydes as electrophiles.[5] The diastereofacial selectivities have been shown to depend on the aldehyde alkyl group. Other chiral dienes should be employed to test the influence of the allyltitanium complex on the asymmetric induction.

Although carbohydrates can serve as chiral auxiliaries by conveying stereochemical information,[6] their use in the organometallic reactions are limited to a few cases.[7] Our interests in the asymmetric allyltitanation reaction prompted us to investigate the possibilities of employing carbohydrates in this field. Besides the synthetic goal which is the construction of stereogenic centers in a defined manner, carbohydrate-bearing allyltitanium complexes are promising models, that could explain factors governing asymmetric induction in

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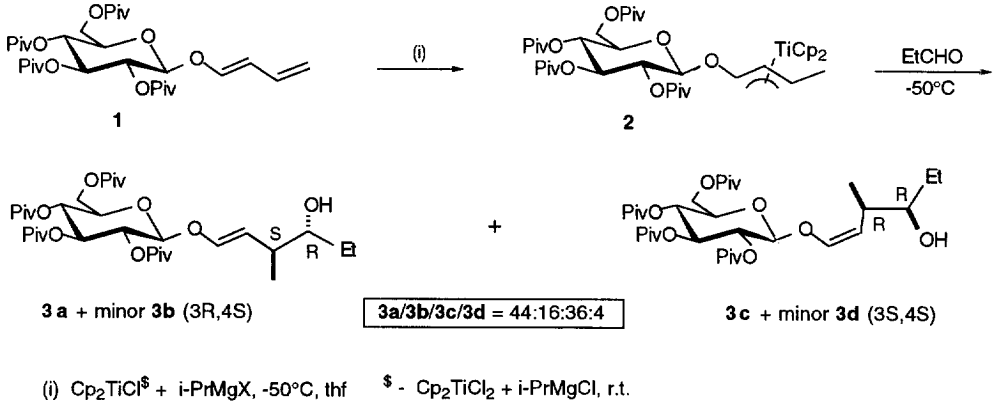
the allyltitanation reaction. We report herein on the preparation of such complexes, starting from the corresponding carbohydrate dienes, and on their use to perform the asymmetric allyltitanation reaction.

Results and Discussion

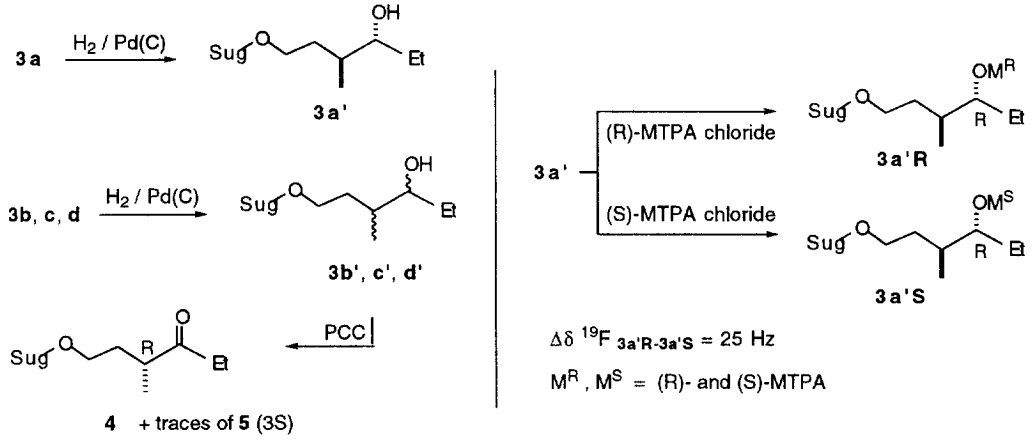
The carbohydrate anomeric dienes (dienyl glycosides) give a notable asymmetric induction in Diels-Alder reactions. Particularly, β-D-glucopyranosyl auxiliary provides a useful degree of diastereofacial selectivity on the corresponding dieno-pyranosides.[8] We investigated the stereochemical outcome of the addition of allyltitanium complexes derived from such compounds. Diene **1** bearing the 2,3,4,6-tetra-O-pivaloyl-β-glucopyranosyl auxiliary on C-1 (Scheme 1) was prepared by a route similar to that described for the synthesis of the acetyl-protected analogue.[8a,b] Thus, η^3-allyltitanocene complex **2** was obtained from **1** by reaction with the preformed Cp_2TiCl and one equivalent of Grignard reagent at -50°C in THF. Thereafter, propanal was added and the stirring continued at -50°C to -20°C for 1 h. After the conventional basic workup ($NaHCO_3$, then extraction with ether), a crude homoallylic alcohol **3** was isolated. Compound **3** was shown by ^1H and ^{13}C (invgate) NMR spectroscopy to be a 44:36:16:4 mixture of four diastereomers (**3a**:**3c**:**3b**:**3d** respectively). The crude product was flash-chromatographed to give **3a** in a diastereopure state and a mixture of three other stereomers (**3b-d**).



Scheme 1

The stereostructures of **3a-d** have been established on the basis of NMR characteristics and chemical correlation in the following manner: (i) the *anti-trans* stereochemistry was assigned to **3a** from ^1H NMR vicinal coupling constants ($J_{1,2}$= 12.2 Hz and $J_{3,4}$=7.6 Hz); (ii) the 2D (COSY) analysis and the Heteronuclear Multiple Bond Correlation (HMBC) carried out on a mixture of stereomers **3b**,**c** and **d**, showed them to possess respectively *anti-trans* (**3b**), *syn-cis* (**3c**) and *syn-cis* (**3d**) configurations; (iii) hydrogenation of **3b**,**c**,**d** afforded a mixture of three stereomers (**3b'**,**c'** and **d'**), each of them different from that obtained by hydrogenating **3a** (compound **3a'**) (Scheme 2); (iv) PCC oxidation of a mixture of saturated alcohols **3b'-d'** (**3b'**/**3c'**/**3d'** = 29:64:7) afforded mainly one ketone (**4**);[9] (v) the absolute R configuration of the carbinol C atom in **3a'** (and thus in **3a**) has been established by Mosher's method using ^{19}F-NMR spectroscopy.[10] The

reactions of alcohol **3a'** with the Mosher (R)- and (S)-acid chlorides gave diastereomeric MTPA **3a'R** and **3a'S**. In these pairs of esters, the trifluoromethyl groups of **3a'R** exhibited higher chemical shift than that of **3a'S** ($\Delta\delta$ = 25 Hz), thus suggesting the R configuration of the carbinol C-4 atom in **3a'**. Consequently, the major *anti* diastereomer **3a** has been shown to possess the 3S, 4R configuration, and the second *anti-trans* diastereomer **3b** the opposite 3R,4S configuration. Furthermore, as deduced from (iv), **3b** and **3c** had the same absolute configuration on C-3 (3R) and **3d** had the opposite configuration (3S). Since **3c** and **3d** are both *syn* stereomers, the 3R, 4R and 3S, 4S configurations respectively have been attributed for them. The above assignments have also been compatible with the results of hydrogenation (iii).



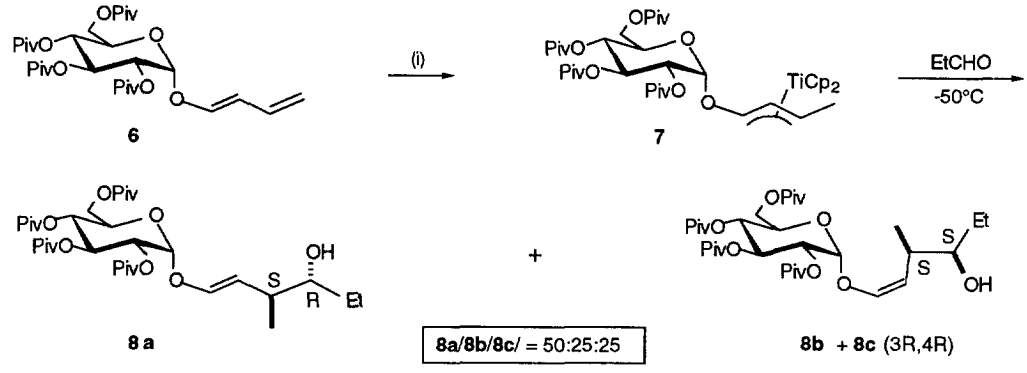
Scheme 2

The addition of propanal to complex **2** appeared to occur regiospecifically at the γ-C carbon atom, to produce the glycosyl enol ether **3** as a sole product. Such a regiochemistry is similar to that observed for the addition of electrophiles to a simpler 1-methoxy-crotyltitanocene.[11] Moreover, only four among eight possible stereomers have been formed. In fact, the outstanding stereochemical feature of this reaction is the exclusive coexistence of the *trans* and *anti* geometries on the one hand, and of the *cis* and *syn* geometries on the other. The diastereofacial selectivity is distinctly higher for the *syn* (d.s.= 80%) than for the *anti* (d.s. = 47%) diastereomers.

Owing to these results, it was of interest to study the effect of modifying the stereostructure of the allyltitanium complex on the stereochemistry. Especially, the inversion of configuration on the anomeric carbon atom, i.e. in the proximity of the reaction site, could provide useful information. Thus, the precursor diene **6** bearing α-glucopyranosyl auxiliary was prepared by a procedure similar to that employed for the synthesis of **1**.[8a,b] After that, complex **7** (Scheme 3) was formed and reacted as above with propanal to give homoallylic alcohol **8**. Analysis of the crude compound **8** by ^{1}H and ^{13}C NMR spectroscopy indicated the presence of only three stereomers in this case, in about 0.5 : 0.25 : 0.25 ratio.[12] The major isomer (**8a**) isolable by silica gel chromatography, was shown to possess *anti-trans* configuration, whereas the *syn-cis* configuration was attributed to both remaining isomers. The absolute configuration of the C-4 atom in **8a** was established using the Mosher method. Compound **8a** was hydrogenated and the saturated derivative **8a'** converted into the diastereomeric MTPA esters **8a'R** and **8a'S**, using (R)- and (S)-MTPA chlorides

respectively. The downfield ^{19}F chemical shift for the first compared with the second ($\Delta\delta$ = 5 Hz) was indicative of the C-4 R configuration in this compound, and then of the 3S, 4R stereochemistry in **8a**.

The afore-cited results are of interest in several aspects. The reactions occurring through the epimeric complexes **2** and **7** revealed similarities and also some differences. The *anti-trans* and *cis-syn* combined configurations are observed exclusively, independently of the α- or β-configuration of the anomeric center.

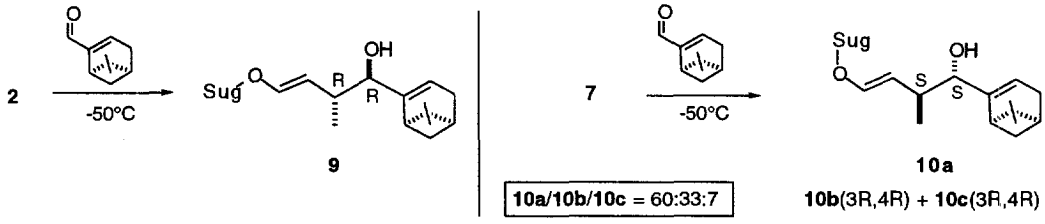


(i) $Cp_2TiCl^{\$}$ + i-PrMgX, -50°C, thf $^{\$}$ - Cp_2TiCl_2 + i-PrMgCl, r.t.

Scheme 3

On the contrary, the diastereofacial selectivities depended strikingly upon it. The facial selectivity appeared to be higher for the *syn* (d.s. = 80%) than for the *anti* (d.s. = 47%) isomer in the β series. Inversely, it was nil for the *syn* and excellent (d.s ≥ 95%) for the *anti* isomer in the α series. Noteworthy was the dramatic difference in the facial selectivities between the *anti* and *syn* pairs in the α series, markedly greater than that encountered in the β series.

The varying control of the diastereofacial selectivity in the reactions involving complexes **2** or **7** and propanal prompted us to extend our study to the reactions employing a chiral aldehyde. Thus, the reaction of complexes **2** and **7** with (-)-myrtenal was carried out as above to afford homoallylic alcohols **9** and **10** respectively. As outlined in Scheme 4, the stereochemical outcome of the two reactions was, however, markedly different.



Scheme 4

Starting from the α-glucopyranosyl complex **7** three diastereomers (**10a/10b/10c** = 60:33:7) were formed, whereas the reaction involving the β-glucopyranosyl complex **2** occurred with a remarkably high diastereoselection. Indeed, compound **9** was obtained in a practically diastereopure state (d.s.≥98%). The *anti-*

trans configuration was ascertained to **9** from ^{1}H NMR vicinal coupling constants (J_{12}= 12.2 Hz and J_{34}=8.5 Hz). Similarly, the separated diastereomers **10a**, **10b** and **10c** possessed *anti-trans*, *anti-cis* and *anti-trans* configurations respectively. As above, further stereochemical assignments rested upon the hydrogenation reaction and the Mosher analysis. Thus, selective hydrogenation of the enol double bond in **10b** and **10c** produced the unique saturated alcohol **11**, diastereomeric with that obtained by hydrogenation of **10a** (compound **12**). Therefore, **10b** and **10c** have been assumed to possess the same C-3,C-4 configuration, and **10a** to possess the opposite C-3,C-4 configuration. Compound **12** underwent reactions with (R)- and (S)-MTPA chlorides to give the corresponding esters. The upfield ^{19}F chemical shift for the first compared with the second ($\Delta\delta$ = 6 Hz) suggested the S configuration of the C-4 atom in **12**. Thus, the major isomer **10a** was assigned the 3S, 4S configuration and the isomers **10b** and **c** the 3R,4R configuration. In the same manner, compound **13** obtained by selective hydrogenation of **9** was assigned the 4R configuration. Consequently, the 3R,4R configuration has been attributed to **9**.

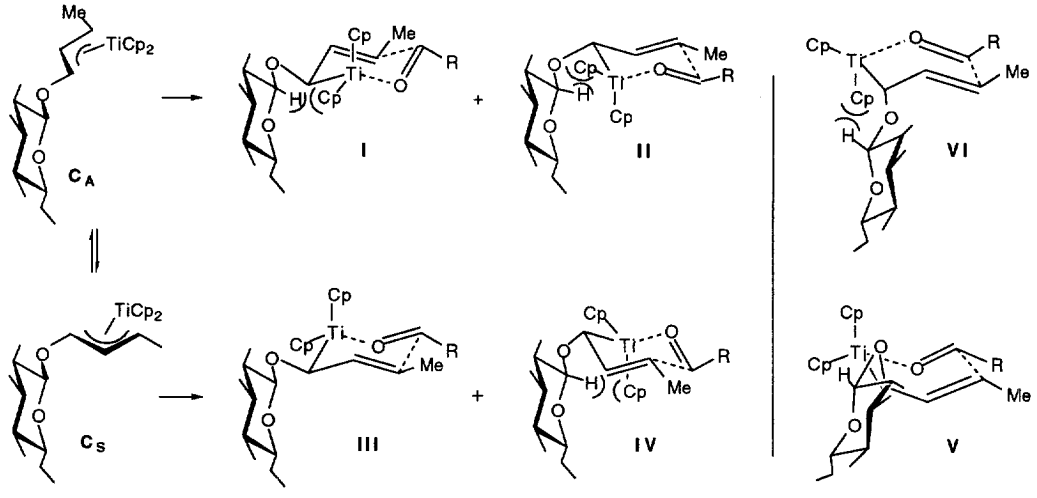


Figure 1

β-Glucopyranosyl dienes similar to **1** adopt the geometry, in which the diene moiety is planar and perpendicular with respect to the sugar,[8d,13] due to the exo anomeric effect.[14] These compounds are present in solution as a mixture of two conformers. In the major one, the s-trans-diene entity and the anomeric C-O bond possess an *anti*-disposition (**A**), whereas in the minor one they bear a *syn*-relationship (**S**). We assumed the allyltitanium complex **2** to be an equilibrated mixture of the corresponding conformers $\mathbf{C_A}$ and $\mathbf{C_S}$ (Figure 1). Starting from them, the conventional chair-like transition states **I-IV** with the bulky carbohydrate moiety in the equatorial position operate. These transition structures are proposed to rationalize the *anti-trans* stereoselectivity observed in the reaction involving propanal (Scheme 1). Among them, stereostructures **I** and **II** are prohibited, owing to the strongly repulsive interactions between the anomeric hydrogen and the Cp ring. Furthermore, **III** appeared as sterically less demanding than **IV**, in accordance with the preferred formation of the 3S,4R- (**3a**) over the 3R,4S-configurated **3b** isomer.

The formation of *syn-cis* products **3c** and **3d** presumably arises *via* the competing boat-like transition states **V** and **VI**,[15] rather than the chair-like ones, which would involve the pseudo-axial carbohydrate and Me or R groups. The stereofacial differentiation in this case could be then associated with the destabilizing interactions in **VI**, which corresponds to the minor isomer **3d** (3S,4S). The absence of the *syn-cis* isomers starting from (-)-myrtenal can also be explained by assuming the competition between the chair- and boat-like arrangements, and is significant in this respect. Thus, the boat-like transition state should be disfavored for myrtenal, because of the marked interactions between the methyl and the bulky aldehyde group in this case.

Competing chair- and boat-like transition state models can also be assumed to rationalize the stereochemical outcome of the reactions involving α-glucopyranosyl complex **7**. The absence of the *syn*-configurated isomers starting from (-)-myrtenal can be due, as previously, to the disfavoring of the boat geometry in this case. Finally, the markedly higher diastereofacial selectivity observed in the reaction of (-)-myrtenal with **2** than with **7** might be attributed to the presence of a matched pair for the former.

In conclusion, diastereodifferentiation in the title reactions is subtly controlled by the structural changes in both partners. In several cases the excellent diastereofacial selectivities were observed. In this respect, the β- and the α-glucopyranosyl series appeared as complementary. The high d.s. values for syn- and anti-configurated isomers, respectively, were obtained in these cases. Moreover, the reaction employing (-)-myrtenal and β-glucopyranosyl complex **2** led stereoselectively (d.s.≥98%) to compound **9**, possessing both the sugar and the pinenyl fragment. Compound **9** may serve as a new chiron or ligand for asymmetric synthesis. Since the carbohydrate vinyl-glycoside auxiliary can be easily detached,[16] the reaction may be considered as a possible entry to the optically actif γ-hydroxyalkanals (hemiacetals).

Experimental Section

Methods and Materials. All manipulations were carried out under argon using vaccum line techniques. The solvents used were distilled under argon from sodium benzophenone ketyl. Carbohydrate dienes **1** and **6** were prepared by a reported procedure.[8a,b] Titanocene dichloride was prepared by a literature method.[17] Other substrates and reagents were purchased from Aldrich. Aldehydes were distilled under Ar prior to use. ^{1}H, ^{13}C and ^{19}F NMR spectra were recorded at 200 or 500, 50 and 188,3 MHz, respectively. Mass spectra were obtained by EI (70eV) technique. Column flash chromatography was performed on silica gel 60 (Merk).

Representative Procedure for the Preparation of Homoallylic Alcohols 3, 8, 9 and 10. Isopropylmagnesium chloride (0.5 mL, 2M solution in THF) was added via syringe at r.t. to a stirred suspension of titanocene dichloride (0.25 g, 1 mmol) in 6 mL of THF. After 0.5 h the resulting green solution of Cp_2TiCl was cooled to -50°C. A solution of i-PrMgCl in THF (0.5 mL, 1 mmol) and a carbohydrate diene **1** or **6** (1 mmol) in 5 mL of THF were added slowly and simultaneously by syringes. After stirring for 1 h the aldehyde was added neat, dropwise via syringe. The mixture was allowed to warm gradually to -20°C over a period of 1 h. The reaction mixture was poured into a separatory funnel containing 30 mL of ether, and treated with saturated aqueous $NaHCO_3$. The ether layer was separated and the aqueous layer was extracted with a second portion of ether. The combined organics were washed with water, dried over $MgSO_4$ and concentrated in vacuo. The residue was treated with ether/hexane = 1/1 (20 mL) and the titanium derivatives eliminated by filtration through a frit. After concentration of the organic filtrate in vacuo, the crude reaction mixture was

analyzed by ^{1}H and ^{13}C NMR (Invgate) spectroscopy to determine the isomer ratio. Flash chromatography separation on silica gel (230-400 mesh, hexane/ether/CH_2Cl_2 = 5:2:2 to 5:1:1 v/v) gave stereopure products and/or mixtures of stereomers as colorless syrups or solids (total yields are given). The spectral data of **3, 8, 9** and **10** are as follows: **3** (75%): **3a** $[\alpha]_D^{20}$ = +10°(c 1.6, $CHCl_3$); IR (neat) 3549, 3466, 1747, 1678 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 6.16 (dd, J=12.2, 1.0 Hz, 1H), 5.27 (dd, J=9.6, 9.6 Hz, 1H), 5.13-4.97 (m, 3H), 4.64 (d, J=8.1 Hz, 1H), 4.15 (dd, J=12.5, 1.8 Hz, 1H), 4.02 (dd, J=12.5, 5.3 Hz, 1H), 3.73 (ddd, J=9.6, 5.3, 1.8 Hz, 1H), 3.44 (ddd, J=12.1, 7.6, 5.0 Hz, 1H), 1.95 (dq, J=7.6, 7.6 Hz, 1H), 1.48-1.28 (m, 3H), 1.15 (s, 9H), 1.08 (s, 18H), 1.06 (d, J=7.6 Hz, 3H), 1.04 (s, 9H), 0.86 (t, J=7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 178.0, 177.1, 176.4, 176.3, 142.9, 110.3, 100.0, 72.5, 72.4, 71.9, 70.6, 67.6, 61.9, 38.8, 38.7, 36.9, 30.2, 27.0, 26.9, 23.6, 9.8; MS 629 (M^+, 1), 499 (96), 397 (54), 313 (34), 295 (55), 211 (77), 194 (45), 85 (100); Anal. calcd for $C_{33}H_{56}O_{11}$: C, 63.03; H, 8.98. Found: C, 63.06; H, 8.66%. **3(b+c+d)**:^{1}H NMR ($CDCl_3$) **3(b)** δ 6.15 (d, J=12.5 Hz, 1H), 5.27 (dd, J=9.3, 9.3 Hz, 1H), 5.13-4.97 (m, 2H), 4.66 (d, J=7.8 Hz, 1H), 4.43 (dd, J=9.8, 6.4 Hz, 1H), 4.20-3.95 (m, 2H), 3.77-3.50 (m, 1H), 3.29-3.17 (m, 1H), 2.14 (pseudosext., J=7.0, Hz, 1H), 1.80-1.70 (m, 1H, D_2O exchangeable), 1.50-1.18 (m, 2H), 1.14 (s, 9H), 1.07 (s, 18H), 1.04 (s, 9H), 0.94-0.79 (m, 6H); ^{1}H NMR ($CDCl_3$) **3(c)** δ 6.10 (d, J=6.4 Hz, 1H), 5.27 (dd, J=9.3, 9.3 Hz, 1H), 5.13-4.97 (m, 2H), 4.64 (d, J=7.8 Hz, 1H), 4.43 (dd, J=9.8, 6.4 Hz, 1H), 4.20-3.95 (m, 2H), 3.77-3.50 (m, 1H), 3.29-3.17 (m, 1H), 2.69-2.50 (m, 1H), 1.80-1.70 (m, 1H, D_2O exchangeable), 1.50-1.18 (m, 2H), 1.14 (s, 9H), 1.07 (s, 18H), 1.04 (s, 9H), 0.94-0.79 (m, 6H); ^{1}H NMR ($CDCl_3$) **3(d)** δ 6.09 (dd, J=6.3, 0.7 Hz, 1H) 5.27 (dd, J=9.3, 9.3 Hz, 1H), 5.13-4.97 (m, 2H), 4.66 (d, J=7.8 Hz, 1H), 4.44 (dd, J=9.8, 6.3 Hz, 1H), 4.20-3.95 (m, 2H), 3.77-3.50 (m, 1H), 3.29-3.17 (m, 1H), 2.69-2.50 (m, 1H), 1.80-1.70 (m, 1H, D_2O exchangeable), 1.50-1.18 (m, 2H), 1.14 (s, 9H), 1.07 (s, 18H), 1.04 (s, 9H), 0.94-0.79 (m, 6H); ^{13}C NMR ($CDCl_3$) δ 177.9, 177.02, 176.98, 176.31, 176.30, 176.22, 176.19, 142.8, 141.8, 141.6, 113.3, 112.01, 111.97, 100.3, 100.2, 99.9, 76.7, 76.6, 76.3, 72.5, 72.34, 72.31, 72.0, 71.82, 71.76, 70.7, 70.4, 67.6, 67.51, 67.46, 61.6, 61.5, 61.4, 38.7, 38.61, 38.56, 38.0, 34.7, 34.2, 27.4, 27.3, 27.0, 26.93, 26.88, 26.84, 26.7, 17.3, 17.2, 15.2, 10.2, 10.0; MS 629 (M^+, 3), 499 (71), 295 (31), 211 (62), 194 (68), 85 (79), 57 (100); Anal. calcd for $C_{33}H_{56}O_{11}$: C, 63.03; H, 8.98. Found: C, 63.15; H, 8.98%. **8** (80%): **8a** $[\alpha]_D^{20}$ = 107°(c 1.8, $CHCl_3$); IR (neat) 3558, 3456, 1734, 1675 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 6.13 (d, J=12.5 Hz, 1H), 5.56 (dd, J=9.8, 9.8 Hz, 1H), 5.23 (d, J=3.7 Hz, 1H), 5.09 (dd, J=9.8, 9.8 Hz, 1H), 4.79 (dd, J=9.8, 3.7 Hz, 1H), 4.13-3.90 (m, 3H), 3.53-3.40 (m, 1H), 1.97 (dq, J=7.6, 7.6 Hz, 1H), 1.59-1.55 (m, 1H, D_2O exchangeable), 1.48-1.35 (m, 3H), 1.17 (s, 9H), 1.11 (s, 18H), 1.09 (d, J=7.6 Hz, 3H), 1.08 (s, 9H), 0.89 (t, J=7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 177.9, 177.6, 176.9, 176.4, 142.3, 110.3, 94.8, 72.5, 72.4, 70.6, 69.3, 68.1, 67.4, 61.5, 38.8, 38.7, 38.7, 37.1, 30.2, 27.1, 27.03, 26.95, 26.87, 23.7, 9.8; MS 499 (31), 211 (74), 85 (34), 57 (100); Anal. calcd for $C_{33}H_{56}O_{11}$: C, 63.03; H, 8.98. Found: C, 63.04; H, 9.14%. **8(b+c)** ^{1}H NMR ($CDCl_3$) δ 6.10 (d, J=6.4 Hz, 1H), 6.04 (d, J=6.4 Hz, 1H), 5.51 (dd, J=9.8, 9.8 Hz, 1H), 5.50 (dd, J=9.8, 9.8 Hz, 1H), 5.20 (d, J=3.7 Hz, 1H), 5.19 (d, J=3.7 Hz, 1H), 5.11-4.95 (m, 2H), 4.80 (dd, J=8.5, 3.7 Hz, 1H), 4.76 (dd, J=8.5, 3.7 Hz, 1H), 4.51-4.39 (m, 2H), 4.11-3.89 (m, 6H), 3.40-3.26 (m, 2H), 2.77 (dq, J=4.2, 7.1 Hz, 1H), 2.75 (dq, J=4.2, 7.1 Hz, 1H), 1.83-1.75 (m, 2H, D_2O exchangeable), 1.60-1.25 (m, 4H), 1.12 (s, 18H), 1.07 (s, 36H), 1.06 (d, J=8.0 Hz, 6H), 1.04 (s, 18H), 0.87 (t, J=7.1 Hz, 6H); ^{13}C NMR ($CDCl_3$) δ 179.2, 179.1, 178.8, 178.8, 178.2, 178.1, 177.7, 177.6, 142.3, 142.1, 112.2, 112.1, 96.2, 96.1, 76.7, 76.5, 70.5, 70.4, 69.3, 68.3, 68.3, 67.5, 67.3, 61.5, 61.4, 38.7, 38.7, 38.58, 38.56, 34.4, 34.0, 27.69, 27.67, 27.64, 27.00, 26.9, 26.87, 26.84, 17.8, 17.7, 10.1, 10.0; MS 499 (76), 211 (51), 194 (69), 113 (21), 85 (100), 57 (100). **9** (78%) mp: 120-121°C; $[\alpha]_D^{20}$ = –9°(c 1.8, $CHCl_3$); IR (CsI) 3514, 1743, 1673 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 6.28 (d, J=12.2 Hz,

1H), 5.43-5.37 (m, 1H), 5.31 (dd, J=9.8, 9.8 Hz, 1H), 5.17-5.03 (m, 2H), 4.94 (dd, J=12.2, 9.1 Hz, 1H), 4.70 (d, J=8.1 Hz, 1H), 4.18 (dd, J=12.5, 2.0 Hz, 1H), 4.07 (dd, J=12.5, 4.9 Hz, 1H), 3.75 (ddd, J=9.8, 4.9, 2.0 Hz, 1H), 3.57 (d, J=8.5 Hz, 1H), 2.39 (ddd, J=8.6, 5.6, 5.6 Hz, 1H), 2.27-2.16 (m, 3H), 2.13-2.03 (m, 2H), 1.93-1.85 (m, 1H, D_2O exchangeable), 1.27 (s, 3H), 1.20 (s, 9H), 1.124 (s, 9H), 1.119 (s, 9H), 1.10 (d, J=8.5 Hz, 3H), 1.08 (s, 9H), 0.87 (d, J=8.3 Hz, 1H), 0.84 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 178.0, 177.1, 176.5, 176.3, 147.6, 143.3, 120.9, 113.3, 99.9, 78.7, 72.8, 71.8, 70.4, 67.4, 61.6, 41.3, 41.0, 38.8, 38.72, 38.68, 38.66, 37.8, 36.8, 31.8, 31.3, 27.1, 27.0, 26.1, 21.4, 17.8; MS 499 (25), 241 (16), 194 (21), 85 (41), 57 (100); Anal. calcd for $C_{40}H_{64}O_{11}$: C, 66.64; H, 8.95. Found: C, 66.74; H, 8.96%. **10** (75%): **10(a)** IR (neat) 3550, 1743, 1666 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.16 (dd, J=12.4, 1.0 Hz, 1H), 5.59 (dd, J=9.6, 9.6 Hz, 1H), 5.48-5.40 (m, 1H), 5.25 (d, J=3.7 Hz, 1H), 5.16 (dd, J=12.4, 8.5 Hz, 1H), 5.14 (dd, J=9.6, 9.6 Hz, 1H), 4.82 (dd, J=9.6, 3.7 Hz, 1H), 4.13-3.91 (m, 3H), 3.77 (d, J=8.3 Hz, 1H), 2.89-2.70 (m, 1H), 2.45-2.30 (m, 1H), 2.30-2.20 (m, 1H), 2.13-2.03 (m, 1H), 1.72-1.58 (m, 1H, D_2O exchangeable), 1.26 (s, 3H), 1.20 (s, 9H), 1.14 (s, 18H), 1.12 (d, J=7.3 Hz, 3H), 1.11 (s, 9H), 0.95 (d, J=6.8Hz, 1H), 0.82 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 178.0, 177.3, 176.9, 176.7, 149.1, 142.3, 118.2, 112.2, 94.8, 78.2, 70.6, 69.4, 68.1, 67.4, 61.5, 43.3, 40.8, 38.75, 38.66, 37.8, 36.5, 31.7, 31.1, 27.2, 27.1, 27.0, 26.3, 21.6, 15.7; MS 499 (23), 85 (19), 57 (100), 41 (19); Anal. calcd for $C_{40}H_{64}O_{11}$: C, 66.64; H, 8.95. Found: C, 66.84; H, 8.90%. **10(b+c)**: ^1H NMR ($CDCl_3$) **10 (b)** δ 6.15 (dd, J=6.4, 0.7 Hz, 1H), 5.57 (dd, J=9.6, 9.6 Hz, 1H), 5.50-5.43 (m, 1H), 5.25 (d, J=3.7 Hz, 1H), 5.12 (dd, J=9.6, 9.6 Hz, 1H), 4.90 (dd, J=9.6, 3.7 Hz, 1H), 4.54 (dd, J=9.5, 6.4 Hz, 1H), 4.13-3.91 (m, 3H), 3.74 (d, J=8.3 Hz, 1H), 2.89-2.70 (m, 1H), 2.45-2.30 (m, 1H), 2.30-2.20 (m, 2H), 2.13-2.03 (m, 2H), 1.72-1.58 (m, 1H, D_2O exchangeable), 1.29 (s, 3H), 1.19 (s, 9H), 1.15 (s, 18H), 1.13 (d, J=7.3 Hz, 3H), 1.11 (s, 9H), 1.10 (d, J=6.8 Hz, 1H), 0.86 (s, 3H); ^1H NMR ($CDCl_3$) **10(c)** 6.22 (d, J=12.4 Hz, 1H), 5.59 (dd, J=9.8, 9.8 Hz, 1H), 5.47-5.40 (m, 1H), 5.18-5.07 (m, 3H), 4.82 (dd, J=10.0, 3.9 Hz, 1H), 4.13-3.95 (m, 3H), 3.62 (d, J=8.3 Hz, 1H), 2.42-2.00 (m, 7H), 1.30 (s, 3H), 1.20 (s, 9H), 1.13 (s, 18H), 1.13 (d, J=7.3 Hz, 3H), 1.10 (s, 9H), 0.90 (d, J=6.8 Hz, 1H), 0.83 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 178;0, 177.9, 177.6, 176.9, 176.5, 176.4, 149.0, 147.7, 143.3, 141.2, 123.1, 119.2, 113.3, 112.7, 95.5, 95.0, 78.9, 78.4, 70.6, 70.5, 69.4, 69.3, 68.4, 68.1, 67.6, 67.4, 61.6, 61.5, 42.7, 41.6, 40.8, 40.6, 38.8, 38.7, 37.8, 37.7, 36.6, 33.6, 31.9,31.8, 31.3, 31.2, 27.2, 27.1, 27.0, 26.7, 26.2, 21.6, 21.4, 17.9, 17.6; MS 499 (30), 85 (25), 57 (100), 41 (30); Anal. calcd for $C_{40}H_{64}O_{11}$: C, 66.64; H, 8.95. Found: C, 66.89; H, 8.90%.

Hydrogenation of Homoallylic Alcohols 3, 8, 9, 10. The hydrogenation reactions were carried out under the atmospheric pressure of H_2 in methanol, using Pd/C as catalyst. Filtration through Celite and evaporation followed by silica gel chromatography (hexane/ether/CH_2Cl_2 = 3:2:2 v/v) afforded saturated derivatives in almost quantitative yields (≥95%). Spectral data and elemental analyses of **3a'**, **3(b'+c'+d')**, **8a'**, **11** and **12** are as follows: **3a'** $[\alpha]_D^{20} = -11°$(c 1.7, $CHCl_3$); IR (neat) 3548, 3456, 1740 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.29 (dd, J=9.4, 9.4 Hz, 1H), 5.12-4.92 (m, 2H), 4.46 (d, J=8.1 Hz, 1H), 4.20 (ddd, J=12.2, 1.9, 1.9 Hz, 1H), 4.02 (dd, J=12.2, 5.6 Hz, 1H), 3.87-3.73 (m, 1H), 3.68 (ddd, J=10.0, 5.6, 1.9 Hz, 1H), 3.53-3.37 (m, 2H), 1.60-1.30 (m, 6H), 1.19 (s, 9H), 1.12 (s, 18H), 1.10 (d, J=7.5 Hz, 3H), 1.08 (s, 9H), 0.90 (t, J=7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 178.1, 177.2, 176.4, 101.0, 73.0, 72.2, 71.1, 69.8, 68.1, 62.0, 38.8, 38.7, 38.6, 36.5, 30.1, 29.5, 27.1, 27.05, 27.03, 26.99, 22.1, 9.8; MS 631 (M^+, 9), 499 (61), 415 (50), 369 (59), 283 (56), 211 (61), 194 (60), 187 (59), 85 (86), 57 (100); Anal. calcd for $C_{33}H_{58}O_{11}$: C, 62.83; H, 9.27. Found: C, 63.17; H, 9.17%. **3(b'+c'+d')**: ^1H NMR ($CDCl_3$) **3(b')** δ 5.27 (dd, J=9.5, 9.5 Hz, 1H), 5.07 (dd, J=9.5, 9.5 Hz, 1H), 4.97 (dd, J=9.5, 8.1 Hz, 1H), 4.47 (d, J=8.1 Hz, 1H), 4.20 (dd, J=12.2, 2.0 Hz, 1H), 4.08-3.86 (m, 2H), 3.68 (ddd,

J=10.0, 5.6, 1.9 Hz, 1H), 3.52-3.38 (m, 1H), 3.35-3.33 (m, 1H), 1.82-1.27 (m, 6H), 1.19 (s, 9H), 1.12 (s, 18H), 1.07 (s, 9H), 0.92 (t, J=7.5 Hz, 3H), 0.81 (d, J=6.8 Hz, 3H); ^{1}H NMR ($CDCl_3$) **3(c')** δ 5.28 (dd, J=9.5, 9.5 Hz, 1H), 5.07 (dd, J=9.5, 9.5 Hz, 1H), 4.97 (dd, J=9.5, 8.1 Hz, 1H), 4.46 (d, J=8.1 Hz, 1H), 4.20 (dd, J=12.2, 2.0 Hz, 1H), 4.08-3.86 (m, 2H), 3.68 (ddd, J=10.0, 5.6, 1.9 Hz, 1H), 3.52-3.38 (m, 1H), 3.35-3.33 (m, 1H), 1.82-1.27 (m, 6H), 1.19 (s, 9H), 1.12 (s, 18H), 1.07 (s, 9H), 0.92 (t, J=7.5 Hz, 3H), 0.85 (d, J=6.8 Hz, 3H); ^{1}H NMR ($CDCl_3$) **3(d')** δ 5.31 (dd, J=9.5, 9.5 Hz, 1H), 5.07 (dd, J=9.5, 9.5 Hz, 1H), 4.97 (dd, J=9.5, 8.1 Hz, 1H), 4.48 (d, J=8.1 Hz, 1H), 4.20 (dd, J=12.2, 2.0 Hz, 1H), 4.08-3.86 (m, 2H), 3.68 (ddd, J=10.0, 5.6, 1.9 Hz, 1H), 3.52-3.38 (m, 1H), 3.35-3.33 (m, 1H), 1.82-1.27 (m, 6H), 1.19 (s, 9H), 1.12 (s, 18H), 1.07 (s, 9H), 0.92 (t, J=7.5 Hz, 3H), 0.86 (d, J=6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 178.0, 177.2, 176.5, 176.5, 101.1, 100.8, 77.2, 77.0, 76.0, 72.2, 72.1, 71.1, 68.1, 68.0, 67.9, 61.92, 61.86, 38.8, 38.7, 38.6, 35.2, 34.5, 33.2, 31.5, 31.4, 27.1, 27.05, 27.02, 27.0, 26.6, 15.8, 15.7, 13.1, 10.6, 10.2; MS 631 (M^+, 9), 499 (58), 211 (58), 194 (62), 143 (62), 85 (88), 57 (100); Anal. calcd for $C_{33}H_{58}O_{11}$: C, 62.83; H, 9.27. Found: C, 63.19; H, 9.20%. **8a'** $[\alpha]_D^{20}$ = +87°(c 1.7, $CHCl_3$); IR (neat) 3553, 3455, 1744 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 5.53 (dd, J=9.8, 9.8 Hz, 1H), 5.06 (dd, J=9.8, 9.8 Hz, 1H), 5.03 (d, J=3.8 Hz, 1H), 4.76 (dd, J=9.8, 3.8 Hz, 1H), 4.16-3.93 (m, 3H), 3.66 (ddd, J=9.8, 6.4, 6.4 Hz, 1H), 3.55-3.42 (m, 1H), 3.34 (ddd, J=9.8, 6.4, 6.4 Hz, 1H), 1.67-1.30 (m, 6H), 1.19 (s, 9H), 1.13 (s, 18H), 1.11 (d, J=7.3 Hz, 3H), 1.09 (s, 9H), 0.91 (t, J=7.3 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 178.0, 177.7, 177.0, 176.5, 95.4, 73.0, 71.2, 69.6, 68.3, 67.9, 67.5, 61.9, 38.8, 38.7, 36.6, 30.1, 29.4, 27.12, 27.07, 27.0, 26.98, 22.3, 9.9; MS 499 (26), 211 (16), 85 (30), 57 (100); Anal. calcd for $C_{33}H_{58}O_{11}$: C, 62.83; H, 9.27. Found: C, 62.43; H, 9.35%. **11** IR (neat) 3539, 1736 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 5.57 (dd, J=9.6, 9.6 Hz, 1H), 5.47-5.41 (m, 1H), 5.08 (dd, J=9.6, 9.6 Hz, 1H), 5.03 (d, J=3.7 Hz, 1H), 4.79 (dd, J=9.6, 3.7 Hz, 1H), 4.13-3.93 (m, 3H), 3.85-3.62 (m, 2H), 3.51-3.36 (m, 1H), 2.48-2.32 (m, 1H), 2.31-2.24 (m, 2H), 2.15-2.05 (m, 2H), 1.95-1.57 (m, 3H), 1.27 (s, 3H), 1.20 (s, 9H), 1.15 (s, 9H), 1.14 (s, 9H), 1.12 (d, J=7.3 Hz, 3H), 1.10 (s, 9H), 0.90 (d, J=6.8 Hz, 2H), 0.85 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 178.0, 177.8, 176.9, 176.6, 149.6, 117.1, 95.5, 77.7, 71.2, 69.71, 68.0, 67.47, 66.3, 61.9, 43.2, 41.0, 38.9, 38.73, 38.7, 37.8, 32.1, 31.8, 31.1, 30.8, 27.2, 27.1, 27.03, 26.3, 21.4, 13.1; MS 499 (6), 194 (6), 85 (13), 57 (100); Anal. calcd for $C_{40}H_{66}O_{11}$: C, 66.27; H, 9.45. Found: C, 66.60; H, 9.48%. **12** IR (neat) 3540, 1735 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 5.55 (dd, J=9.6, 9.6 Hz, 1H), 5.47-5.41 (m, 1H), 5.08 (dd, J=9.6, 9.6 Hz, 2H), 5.04 (d, J=3.7 Hz, 1H), 4.79 (dd, J=9.6, 3.7 Hz, 1H), 4.13-3.93 (m, 3H), 3.85-3.62 (m, 2H), 3.51-3.36 (m, 1H), 2.48-2.32 (m, 1H), 2.31-2.24 (m, 2H), 2.15-2.05 (m, 2H), 1.95-1.57 (m, 3H), 1.27 (s, 3H), 1.20 (s, 9H), 1.15 (s, 9H), 1.14 (s, 9H), 1.12 (d, J=7.3 Hz, 3H), 1.10 (s, 9H), 0.90 (d, J=6.8 Hz, 2H), 0.83 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 178.0, 177.8, 176.9, 176.6, 149.6, 118.2, 95.2, 79.2, 71.2, 69.67, 67.9, 67.55, 67.0, 61.9, 43.0, 40.9, 38.9, 38.73, 38.67, 37.9, 33.3, 31.9, 31.2, 30.8, 27.2, 27.1, 27.03, 26.3, 21.5, 16.6; MS 499 (8), 85 (13), 57 (100); Anal. calcd for $C_{40}H_{66}O_{11}$: C, 66.27; H, 9.45. Found: C, 65.52; H, 9.49.

Oxidation of a Mixture of Alcohols 3(b'+c'+d') with Pyridinium Chlorochromate (PCC) : Ketone 4.[9] The described procedure[18] was employed with 140 mg (0.22 mmol) of **3(b'+c'+d')**, 5 mL of CH_2Cl_2 and 71 mg (0.33 mmol) of PCC. Flash chromatography purification on silica gel (hexane/ether/CH_2Cl_2 = 2:1:1 v/v) afforded **4** (97%) as a white solid: mp 78-79°C; $[\alpha]_D^{20}$ = −25°(c 1.9, $CHCl_3$); IR (CsI) 1742, 1718 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 5.26 (dd, J=9.5, 9.5 Hz, 1H), 5.05 (dd, J=9.5, 9.5 Hz, 12H), 4.95 (dd, J=9.5, 7.8 Hz, 1H), 4.42 (d, J=7.8 Hz, 1H), 4.13 (dd, J=12.2, 1.9 Hz, 1H), 4.00 (dd, J=12.2, 5.4 Hz, 1H), 3.73-3.60 (m, 2H), 3.41 (dt, J=9.5, 6.1 Hz, 1H), 2.68 (pseudosext., J=7.1 Hz, 1H), 2.41 (dq, J=2.2, 7.2 Hz, 2H), 2.0-1.8 (m, 1H), 1.55-1.40 (m, 1H), 1.16 (s, 9H), 1.10 (s, 9H), 1.09 (s, 9H); 1.06 (s, 9H), 1.00 (d, J=6.9 Hz, 3H), 0.97 (t, J=7.2 Hz,

3H); ^{13}C NMR ($CDCl_3$) 214.9, 177.9, 177.1, 176.36, 176.4, 100.9, 72.13, 72.1, 71.08, 67.8, 67.2, 61.8, 41.7, 38.8, 38.7, 38.6, 34.7, 32.4, 27.1, 27.0, 26.9, 16.7, 7.6; MS 629 (M^+, 5), 500 (100), 211 (50), 113 (66), 85 (57), 57 (75); Anal. calcd for $C_{33}H_{56}O_{11}$: C, 63.03; H, 8.98. Found: C, 63.33; H, 9.01.

Preparation of (+)- and (-)-MTPA Derivatives. (+)- and (-)-α-Methoxy-α-trifluoromethylphenylacetate (MTPA) esters were prepared routinely from (S)-(+) and (R)-(-)-MTPA chlorides and alcohols **3a'**, **8a'**, **9a'** and **12**, according to the described procedure.[10a,b] The ^{19}F NMR spectra were mesured on crude products: **3a'R**, δ -14001.8 Hz; **3a'S**, δ -14026.7 Hz; **8a'R**, δ -14004.4 Hz; **8a'S**, δ -14009.2 Hz; **9a'R**, δ -14011.8 Hz; **9a'S**, δ -14017.9 Hz; **12a'R**, δ -14017.9 Hz; **12a'S**, δ -14011.8 Hz.

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