Allyltitanation−Mukaiyama Aldol Sequence: A Short Way To Control Five Stereogenic Carbon Centers

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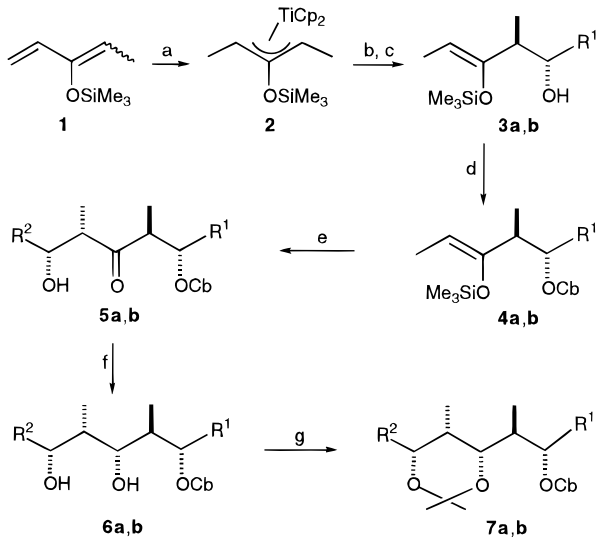
The stereoselective generation of contiguous methyl- and hydroxy-bearing stereocenters continues to receive great attention within the framework of methods for the synthesis of polypropionate-derived natural products.[1] Generally, the iterative strategies employed involve aldol reaction or allylation of an aldehyde by a suitable propionate equivalent. In this matter, we have recently described a simple procedure for preparing *anti* α-methyl-*β*-hydroxy silyl enol ethers.[2] It was our belief that these compounds could be used as versatile building blocks for stereocontrolled polypropionate synthesis.

On the basis of our previous work, we report herein that a combination of allyltitanation[3] and Mukaiyama aldol reactions can provide a short entry to stereopentad systems (i.e. possessing five contiguous stereocenters). Thus, η^3-allyltitanium complex **2** (Scheme 1) functionalized on the C-2 atom with a silyloxy group has been prepared in two separated reduction steps: Cp_2TiCl formed at first at rt was allowed to react at −20 °C with isopropylmagnesium chloride in the presence of 3-(trimethylsilyloxy)-1,3-pentadiene (**1**). Complex **2** formed *in situ* was used directly in the reaction with aldehydes RCHO (R = Et, CH=CH_2).

In the first sequence (compounds **3a** to **7a**, Scheme 1) **2** reacted with propionaldehyde to afford silyl enol ether **3a** in good yield and excellent *Z-anti* stereoselectivity (*anti*/*syn* >98/2, *Z*/*E* ≅ 100/0).[4] Protection of the hydroxyl group in **3a** as its carbamate proceeded without incident to give **4a** in 92% yield. The further titanium chloride-promoted Mukaiyama aldol reaction occurred with a high *syn* diastereoselectivity.[5] Since the Mukaiyama reaction involving simple aldehydes generally exhibits little simple diastereoselection,[6] the almost exclusive (with ds ≥ 95%) formation of **5a** is remarkable. The choice of a carbamate protective group is suggested to be decisive in influencing the stereochemical outcome of this reaction. The carbamate would play the role of

Scheme 1



a : R^1 = Et, R^2 = Et ; **b** : R^1 = CH=CH_2, R^2 = CH_2OBn

(a) Cp_2TiCl (preformed), i-PrMgCl, -20°C; (b) R^1CHO;
(c) $NaHCO_3$aq; (d) PhNCO, r.t.; (e) R^2CHO, $TiCl_4$, CH_2Cl_2;
(f) DIBALH, Et_2O, -78°C; (g) acetone, (TsOH).

the "protective group tuning"[7] as depicted in Figure 1. The mechanistic proposal involves an open transition state generally postulated for the Lewis acid-mediated Mukaiyama aldol reaction.[8] The highly predominant *syn* diastereoselection can be rationalized by assuming that the reaction proceeds preferentially through the bis-ligated staggered transition structure **S**.

The stereopentad **6a** was finally obtained with 92% ds by DIBALH reduction.[9] The major isomer was isolable by silica gel chromatography (20% Et_2O/CH_2Cl_2). Compound **6a** was transformed in acetonide **7a** in order to confirm the relative stereochemistry of 1,3-diol fragment. This stereochemistry has been demonstrated to be *syn* on the basis of the ^{13}C NMR resonances of the three acetonide carbons.[10]

The presented strategy can be applied to synthons with functionalized end groups, thus ensuring the further extension of the molecular skeleton in two directions. An example is given in Scheme 1 (sequence **3b** to **7b**). The 1,2-addition of acrolein to the complex **2** occurred cleanly to produce in good yield the corresponding silyl enol ether **3b**.[11] The reaction of the carbamate protected **4b** with benzyloxy acetaldehyde afforded the aldol product **5b** as the sole stereoisomer (*1,2-syn-4,5-anti*). Further DIBALH reduction produced stereoselectively (ds = 98%) pentad **6b** analogous to **6a**.

We next examined whether it was possible to bypass the isolation (and successive protection) of enol silanes

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(3) (a) Sato, F.; Iijima, S.; Sato, M. *Tetrahedron Lett.* **1981**, *22*, 243. (b) Kobayashi, Y.; Umeyama, K.; Sato, F. *J. Chem. Soc., Chem. Commun.* **1984**, 621. (c) Collins, S.; Dean, W. P.; Ward, D. G. *Organometallics* **1988**, *7*, 2289. (d) Szymoniak, J.; Felix, D.; Besançon, J.; Moïse, C. *Can. J. Chem.* **1995**, *73*, 1368.

(4) No trace of *E* isomer was detected by ^1H and ^{13}C NMR. The *Z*/*E* ratio decreased slightly for branched saturated aldehydes (up to *Z*/*E* = 85/15 for pivalic aldehyde); unpublished data.

(5) (a) The relative *syn* relationship at the two new centers was assigned on the basis of the ^{13}C NMR shifts using Heathcock rule, ref 5b. (b) Heathcock, C. H.; Pirrung, M. C.; Sohn, J. E. *J. Org. Chem.* **1979**, *44*, 4294.

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(9) Kiyooka, S.; Kuroda, H.; Shimasaki, Y. *Tetrahedron Lett.* **1986**, *27*, 3009.

(10) (a) Rychnovsky, S. D.; Skalitzky, D. J. *Tetrahedron Lett.* **1990**, *31*, 945. (b) Evans, D. A.; Rieger, D. L.; Gage, J. R. *Tetrahedron Lett.* **1990**, *31*, 7099.

(11) Adduct **3b** obtained with ds ≥ 90%, was easily isolated by silica gel chromatography (9% Et_2O/hexane).

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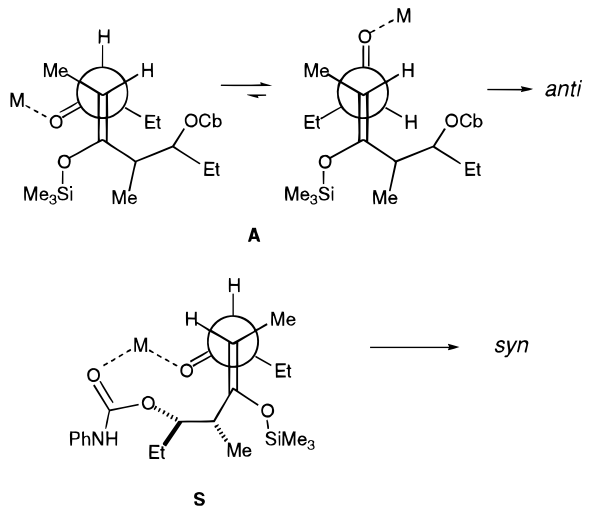
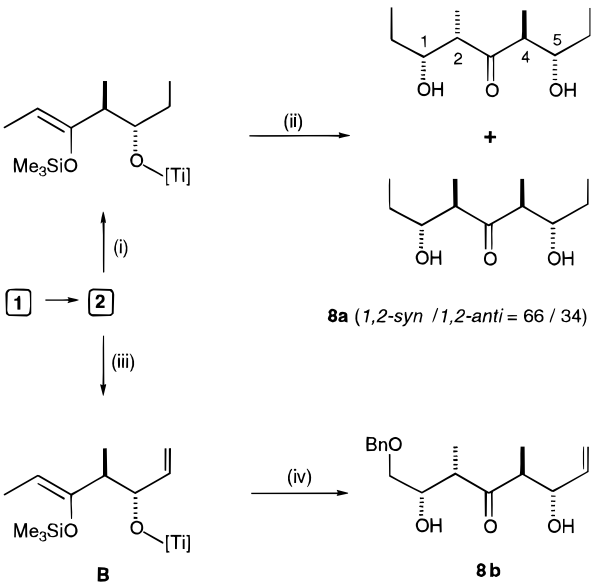


Figure 1. Selected staggered transition states for the $TiCl_4$-mediated reaction of enol silane **4a** with propanal (Cb = carbamate).

Scheme 2



2a,**b**. As a result, we developed a one-pot procedure which enables the direct conversion of silyloxy diene **1** into dihydroxy ketones **8a**,**b** bearing four stereogenic carbon centers (Scheme 2). Allyltitanation reactions involving aldehydes R^1CHO (R^1 = Et or $CH{=}CH_2$) were started up as previously. However, instead of hydrolyzing the reaction mixture, the solvent was evaporated *in vacuo*. Thereafter, Mukaiyama aldol reactions involving aldehydes R^2CHO (R^2 = Et or $BnOCH_2$) were carrried out as above in CH_2Cl_2 at −78 °C. Hydrolytic workup followed by flash chromatography gave adducts **8a**,**b** in the yields 43% and 40%, respectively, i.e. similar to those obtained in a three-step synthesis of **5a**,**b** (Scheme 1).

The stereochemical outcome of the two one-pot procedures outlined in Scheme 2 (i, ii, and iii, iv) differs strikingly. Indeed, unlike **8b** possessing a practically unique *1,2-syn-4,5-anti* stereochemistry,[12] **8a** has been demonstrated to be a 66:34 mixture of two stereoisomers, *1,2-syn-4,5-anti* and *1,2-anti-4,5-anti*, respectively. In other words, the Mukaiyama aldolization step leading to **8b** shows a total *syn* diastereoselectivity, whereas that leading to **8a** reveals a considerable loss of stereoselectivity. The differences noted for the two reactions contrast significantly with the invariably high stereoselectivities for both analogous Mukaiyama aldol reactions, resulting in **5a** and **5b** (Scheme 1).

These observations support the influence of the carbamate group on the stereoselectivity. Thus, the protective group tuning is consistent with the markedly higher *syn* selectivity of the Mukaiyama aldol reaction affording **5a** rather than with the analogous one affording **8a** (Scheme 2). The poor stereoselectivity for the latter (*syn*/*anti*=66:34) is in accordance with a similar result reported for the reaction of a simple (Z)-enol silane and propanal/$TiCl_4$.[13] On the other hand, both enol silanes **4b** (Scheme 1) and **B** (Scheme 2) react stereoselectively with an α-alkoxy aldehyde, revealing the conventional chelation-controlled Mukaiyama aldol reaction[14] in this case.

In summary, the polypropionate buiding blocks can be prepared stereoselectively, in a short way based on the combination of allyltitanation and Mukaiyama aldol reaction. Particularly, the direct generation of four stereogenic carbon centers has been achieved by a one-pot procedure. In the stereopentads obtained, three hydroxy-substituted secondary carbons alternate with two tertiary carbons, unlike the constitution usually found in the literature. The described method might be extended to other stereosequences by varying the reducing agents in the last step,[15] as well as the conditions of the Mukaiyama aldol reaction. Moreover, the enantioselective variant could be envisaged.[16] Finally, the carbamate protection of the β-hydroxy group in the silyl enol ether has been suggested as the factor which controls the stereochemistry of the Mukaiyama aldol reaction (protective group tuning). The marked increase in a simple diastereoselection for the reactions involving nonchelating aldehydes can be achieved in this way.

Experimental Section

General. All manipulations were carried out under argon using vacuum line techniques. The solvents used were distilled under Ar atmosphere from sodium benzophenone ketyl. Titanocene dichloride,[17] 3-(trimethylsilyloxy)-1,3-pentadiene,[18] and (benzyloxy)acetaldehyde[19] were prepared according to published procedures. Other reagents were purchased from Aldrich Chemical Co. Aldehydes and $TiCl_4$ were distilled under Ar prior to use. Melting points are uncorrected. ^1H and ^{13}C NMR spectra were recorded at 200 or 500 and 50 MHz, respectively. Mass spectra were obtained by EI (70 eV) technique. Gas chromatography (GC) was carried out on a 30 m × 0.25 mm copper

(12) Adduct **8b** was contaminated by about 5% of *1,2-syn-4,5-syn* isomer.

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column packed with methyl silicone with a flow rate of 1.6 mL/min. Column flash chromatography was performed on silica gel 60 (Merck).

***(Z)-anti* α-Methyl-*β*-Hydroxy Enol Silanes (3) and Related Carbamates (4).** Complex **2** was formed in the same way as that previously described,[2] at −15 °C, starting from 3-(trimethylsilyloxy)-1,3-pentadiene (6.6 mmol, ca. 1 mL), preformed Cp_2TiCl (6 mmol in 30 mL of THF), and i-PrMgCl (6 mmol in 3 mL of THF). The aldehyde (propanal or acrolein) (6 mmol) was added neat by syringe, and the stirring was continued for 20 min at −15 °C. The reaction mixture was diluted with Et_2O (150 mL) and treated with ice-cold saturated aqueous $NaHCO_3$ (40 mL). The combined organics were washed with H_2O and concentrated in vacuo. The residue was treated with Et_2O/hexane = 1:1, and the titanium derivatives were eliminated by filtration. The major portion of Cp_2TiCl_2 can be recovered by acidifying the aqueous layer. After concentration of the filtrate in vacuo, the crude product was purified by flash chromatography (9 to 10% Et_2O/hexane). **3a** (64%): colorless oil; ^{1}H NMR (C_6D_6) δ 0.1 (s, 9H), 1.07 (t, J = 7.0 Hz, 3H), 1.08 (d, J = 6.8 Hz, 3H), 1.44 (d, J = 6.8 Hz, 3H), 1.46−1.60 (m, 2H), 2.36 (d, J = 6.1 Hz, 1H, D_2O exchangeable), 2.51 (dq, J = 6.3, 6.8 Hz, 1H), 3.49 (pseudoquintet, J = 6.1 Hz, 1H), 4.64 (q, J = 6.8 Hz, 1H); ^{13}C NMR (C_6D_6) δ 0.2, 10.5, 11.7, 15.2, 28.5, 38.9, 75.5, 101.5, 153.9. Anal. Calcd for $C_{11}H_{24}O_2Si$: C, 61.05; H, 11.18. Found: C, 60.78; H, 10.94. **3b** (58%): ^{1}H NMR (CD_3COCD_3) δ 0.18 (s, 9H), 0.94 (d, J = 6.9 Hz, 3H), 1.55 (d, J = 6.9 Hz, 3H), 2.54 (dq, J = 6.5, 6.9 Hz, 1H), 3.25 (d, J = 5.1 Hz, 1H, D_2O exchangeable), 3.90−4.02 (m, 1H), 4.67 (q, J = 6.9 Hz, 1H), 5.02−5.26 (m, 2H), 5.79−5.97 (m, 1H); ^{13}C NMR (CD_3COCD_3) δ 0.6, 11.8, 14.7, 40.5, 75.5, 101.4, 115.0, 141.7, 154.1; MS m/z 214 (M^+, 15), 199 (18), 183 (50), 158 (60), 143 (33), 129 (84), 117 (74), 73 (100). Anal. Calcd for $C_{11}H_{22}O_2Si$: C, 61.63; H, 10.34. Found: C, 61.35; H, 10.20. Carbamate protection of the hydroxyl group was performed in toluene (15 mL) within a 24 h period at rt, using a twofold molar excess of phenyl isocyanate. Flash chromatograpy purification gave the following: **4a** (92%): mp 64−65°C; ^{1}H NMR (C_6D_6) δ 0.19 (s, 9H), 0.94 (t, J = 7.3 Hz, 3H), 1.03 (d, J = 6.9 Hz, 3H), 1.42−1.60 (m, 2H), 1.63 (d, J = 6.9 Hz, 3H), 2.92 (dq, J = 6.5, 6.9 Hz, 1H), 4.63 (q, J = 6.9 Hz, 1H), 5.16 (m, 1H), 6.25 (br s), 6.75−7.25 (m, 5H); ^{13}C NMR (C_6D_6) δ 0.3, 9.6, 11.7, 13.9, 24.7, 37.5, 77.3, 99.5, 118,5, 123.0, 129.1, 139.1, 153.2, 177.3; MS m/z 335 (M^+, 20), 282 (10), 210 (15), 198 (100), 169 (38). Anal. Calcd for $C_{18}H_{29}NO_3Si$: C, 64.44; H, 8.71. Found: C, 64.51; H, 8.64. **4b** (94%): colorless oil; ^{1}H NMR (CD_3COCD_3) δ 0.19 (s, 9H), 0.97 (d, J = 6.9 Hz, 3H), 1.58 (d, J = 6.9 Hz, 3H), 2.80−2.95 (m, 1H), 4.61 (q, J = 6.9 Hz, 1H), 5.15−5.30 (m, 2H), 5.38 (m, 1H), 5.78−5.95 (m, 1H), 6.95−7.60 (m, 5H), 8.55 (br s, 1H); ^{13}C NMR (CD_3COCD_3) δ 0.4, 7.8, 13.5, 37.7, 78.0, 101,4, 116.7, 119.2, 123.2, 130.2, 140.5, 140.7, 153.0, 213.6; MS m/z 333 (M^+, 15), 282 (20), 196 (83), 158 (25), 91 (30), 77 (100). Anal. Calcd for $C_{18}H_{27}NO_3Si$: C, 64.83; H, 8.16. Found: C, 64.41; H, 8.07.

Typical Procedure for Reactions of Enol Silanes 4 with Aldehydes. Monoprotected 1,5-Dihydroxy 3-Ketones (5). To a stirred solution of aldehyde (propanal or (benzyloxy)-acetaldehyde) (0.5 mmol) in 4 mL of CH_2Cl_2 at −78 °C were added ca. 0.5 g of molecular sieves (4 Å) and, slowly via syringe, a solution of $TiCl_4$ (0.5 mmol in 0.5 mL of CH_2Cl_2). After stirring for 5 min a solution of enol silane **4a** or **4b** (0.5 mmol in 2 mL of CH_2Cl_2) was added by syringe. The mixture was further stirred for 1.5 h at −78 °C. After quenching by rapid injection of 1.5 mL of saturated aqueous $NaHCO_3$, the resulting organic layer was extracted with ether, and the extract was washed with brine and dried over $MgSO_4$. After evaporation of the solvent in vacuo, the crude product was examined by ^{1}H NMR and gas chromatography to evaluate the isomers ratio. Flash chromatography purification gave the following: **5a** (69%): mp 118−119°C;^{1}H NMR (CD_3COCD_3) δ 0.92 (t, J = 7.5 Hz, 3H), 0.94 (t, J = 7.5 Hz, 3H), 1.03 (d, J = 6.9 Hz, 3H), 1.04 (d, J = 6.9 Hz, 3H), 1.32−1.45 (m, 2H), 1.50−1.75 (m, 2H), 2.80−2.95 (m, 1H), 3.21 (pseudoquintet, J = 7.0 Hz, 1H), 3.65 (d, J = 5.4 Hz, 1H, D_2O exchangeable), 3.73−3.85 (m, 1H), 4.95−5.05 (m, 1H), 6.95−7.60 (m, 5H), 8.64 (br s, 1H); ^{13}C NMR (CD_3COCD_3) δ 9.6, 11.1, 11.2, 12.2, 24.5, 28.7, 49.0, 52.4, 73.8, 77.0, 119.3, 123.5, 129.7, 140.4, 154.1, 215.1; MS m/z 321 (M^+, 34), 234 (10), 137 (49), 115 (50), 93 (100). Anal. Calcd for $C_{18}H_{27}NO_4$: C, 67.26; H, 8.47. Found: C, 67.36; H, 8.36. **5b** (72%): colorless oil; ^{1}H NMR (CD_3COCD_3) δ 0.99 (d, J = 7.0 Hz, 3H), 1.09 (d, J = 7.0 Hz, 3H), 3.00 (dq, J = 7.0, 5.5 Hz, 1H), 3.18 (dq, J = 7.0, 8.5 Hz, 1H), 3.35−3.60 (m, 2H), 3.97 (d, J = 5.1 Hz, 1H, D_2O exchangeable), 4.00−4.25 (m, 2H), 4.55−4.65 (m, 1H), 5.20−5.35 (m, 2H), 5.40 (m, 1H), 5.75−5.92 (m, 1H), 6.95−7.05 (m, 1H), 7.22−7.37 (m, 7H), 7.55 (m, 2H), 8.70 (br s, 1H); ^{13}C NMR (CD_3COCD_3) δ 11.6, 13.1, 49.3, 50.1, 71.3, 73.5, 73.8, 77.7, 118.9, 119.3, 123.6, 128.4, 128.6, 129.2, 129.7, 135.8, 139.6, 140.2, 153.3, 214.0; MS m/z 411 (M^+, 12), 290 (9), 168 (15), 119 (13), 91 (100). Anal. Calcd for $C_{24}H_{29}NO_5$: C, 70.05; H, 7.10. Found: C, 69.79; H, 7.31.

Stereopentads 6 and Related Acetonides 7. To a stirred solution of dihydroxy ketone (**5a** or **5b**) (0.2 mmol) in 5 mL of Et_2O was added DIBALH (1 mmol, 1 M solution in THF) dropwise at −78 °C. The stirring was continued at this temperature for 12 h (TLC monitoring), and then the solution was quenched with 10% HCl (5 mL). The mixture was extracted with ether and washed with brine. After elimination of the solvent, the product was examined by ^{1}H NMR to determine the stereoisomers ratio. The crude product was purified by flash chromatography on a short silica gel column eluting with CH_2Cl_2/Et_2O = 5:1. **6a** (88%): ^{1}H NMR (CD_3COCD_3) δ 0.85 (d, 3H, J = 7.0 Hz, 3H), 0.91 (d, J = 7.0 Hz, 3H), 0.93 (t, J = 7.8 Hz, 3H), 0.95 (t, J = 7.6 Hz, 3H), 1.45−1.60 (m, 2H), 1.66−1.78 (m, 2H), 1.79−1.83 (m, 1H), 2.10 (m, 1H), 3.63−3.80 (m, 2H), 4.10 (d, J = 4.0 Hz, 1H, D_2O exchangeable), 4.21 (d, J = 3.2 Hz, 1H, D_2O exchangeable), 5.22 (dt, J = 9.5, 3.4 Hz, 1H), 7.01 (br t, J = 7.8 Hz, 1H), 7.30 (t, J = 7.2 Hz, 2H), 7.61 (J = 7.8 Hz, 1H), 8.60 (br s, 1H); ^{13}C NMR (CD_3COCD_3) δ 5.1, 10.8, 10.9, 11.1, 38.4, 40.6, 77.6, 78.6, 79.2, 119.1, 123.2, 129.6, 140.7, 154.6; MS m/z 324 ($M^+ + 1$, 55), 248 (10), 237 (27), 157 (25), 137 (85), 84 (100). Anal. Calcd for $C_{18}H_{29}NO_4$: C, 66.84; H, 9.04. Found: C, 66.42; H, 8.85. **6b** (82%): ^{1}H NMR (CD_3COCD_3) δ 0.82 (d, J = 6.9 Hz, 3H), 0.92 (d, J = 7.3 Hz, 3H), 1.83−1.91 (m, 1H), 2.07−2.13 (m, 1H), 3.53 (br d, J = 5.8 Hz, 2H), 3.56−3.64 (m, 1H), 3.95−4.04 (m, 1H), 4.06 (d, J = 3.3 Hz, 1H, D_2O exchangeable), 4.34 (d, J = 4.0 Hz, 1H, D_2O exchangeable), 4.54 (s, 2H), 5.17−5.39 (m, 2H), 5.73−5.81 (m, 1H), 5.85−6.04 (m, 1H), 7.0 (ddd, J = 6.0, 10.7, 17.2 Hz, 1H), 7.25−7.40 (m, 7H), 7.52−7.61 (m, 2H), 8.70 (br s, 1H); ^{13}C NMR (CD_3COCD_3) δ 6.0, 10.8, 36.7, 40.9, 73.6, 73.7, 75.7, 75.8, 77.0, 117.3, 119.2, 123.4, 128.3, 128.5, 129.2, 129.7, 134.8, 139.8, 140.5, 153.8; MS m/z 413 (M^+, 5), 292 (10), 263 (10), 137 (50), 119 (5), 107 (23), 91 (100). Anal. Calcd for $C_{24}H_{31}NO_5$: C, 69.71; H, 7.56. Found: C, 69.93; H, 7.71. 1,3-Diol acetonides **7a** and **7b** were prepared in quantitative yield ($Me_2C(OMe)_2$, cat. PPTS, CH_2Cl_2). The ^{13}C NMR resonances of the acetonide carbons are as follows: for **7a** δ 19.9, 30.5; for **7b** δ 20.0, 31.3.

General Procedure for the One-Pot Allyltitanation−Mukaiyama Aldol Sequence: Dihydroxy Ketones 8. The first, allyltitanation step was carried out as described above. Complex **2** formed *in situ* in THF at −15 °C, starting from 4.4 mmol of silyloxy diene **1**, reacted with aldehyde (propanal or acrolein, 4 mmol) for 20 min. Thereafter, the solvent was removed thoroughly in vacuo at 0 °C. Anhydrous dichloromethane (20 mL) was then added, followed by ca. 2 g of molecular sieves (4 Å), and the mixture was cooled to −78 °C. In the second flask, to a stirred solution of aldehyde (propanal or (benzyloxy)acetaldehyde, 4 mmol in 25 mL of CH_2Cl_2) was added slowly by syringe at −78 °C a solution of 4 mmol of $TiCl_4$ in 4 mL of CH_2Cl_2. After 5 min the solution of the complex of aldehyde was transferred to the first flask via a needle file using an Ar vacuum line. The reaction mixture was stirred at −78 °C for 2 h. The cold mixture was quenched with 15 mL of saturated aqueous $NaHCO_3$. The solvent was evaporated in vacuo and the residue extracted with three portions of Et_2O. The extract was washed with brine and dried over $MgSO_4$. The solution was concentrated to about 10 mL and then filtered through Celite. The solvent was removed in vacuo to provide the crude hydroxy ketone (**8a** or **8b**). Further purification by flash chromatography (CH_2Cl_2/Et_2O = 85:15) provided pure products **8a** or **8b**, respectively, in 43% and 40% yield. The ratio of stereoisomers was determined by integrating the ^{1}H NMR signals assigned to the carbinol and carbonyl α-hydrogens for both crude and purified products and next confirmed by gas chromatography.

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