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Investigation of the Diastereofacial Selectivity of the Addition of 1-Metalated (*E*)- and (*Z*)-Hept-1-enes to the COREY Aldehyde - A Comparison between Vinyllithium and Vinyltitanium Compounds[1,2]

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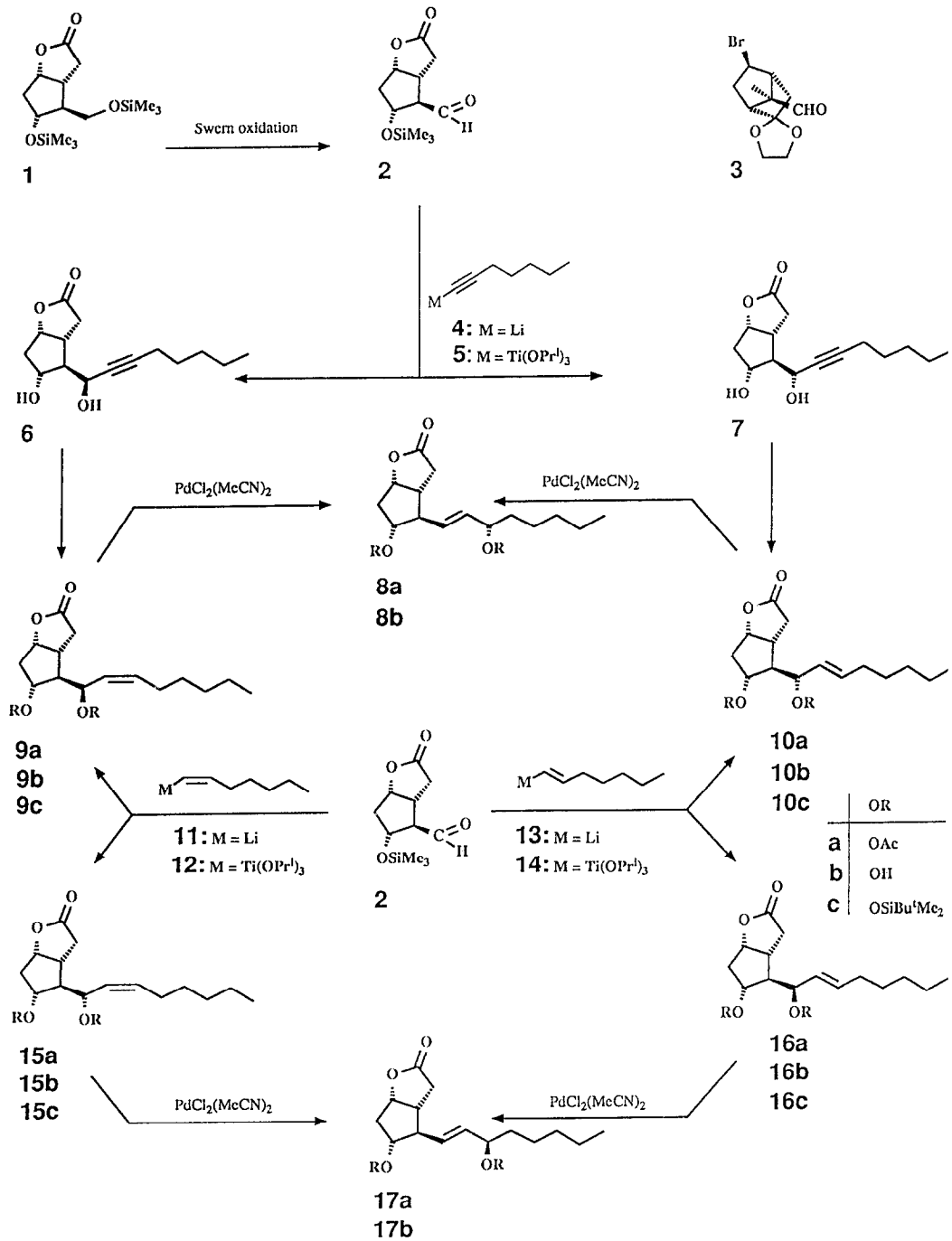
Abstract: In connection with the synthesis of prostaglandin intermediates a comparison of the addition of (*Z*)- and (*E*)-hept-1-enyllithium and (*Z*)- and (*E*)-hept-1-enyltitanium triisopropoxide to the COREY aldehyde revealed that the lithium compounds are preferentially added by a *si*-attack, the titanium compounds, however, by a preferred *re*-attack. The diastereoselectivity of the lithium compounds was generally better than that of the titanium analogues. This result is explained by assuming a different chelation tendency of the metals. Molecular mechanics calculations support this interpretation.

INTRODUCTION

The palladium(II)-catalyzed [3,3]-sigmatropic rearrangement of allylic acetates, such as **9a** or **10a**, represents an interesting alternative for the construction of the (3S)-3-hydroxyoct-2(E)-enyl side chain of prostaglandins.[3-8] According to the regularities[3] governing the chirality transfer of this rearrangement both acetates **9a** and **10a** were expected to be convertible into the isomeric acetate **8a**, a valuable intermediate for the synthesis of prostaglandin $F_{2\alpha}$, whereas the acetates **15a** and **16a** should give rise to the (15*R*)-isomer **17a**. In recent times we have dealt with the preparation of the allylic alcohols **9b** and **10b** by a stereoselective addition of the 1-metalated hept-1-ynes **4** and **5** to the COREY aldehyde **2** followed by a specific *cis*- or *trans*-hydrogenation of the propargylic alcohols **6** or **7**. This strategy comprises the principal possibility to correct an unsufficient diastereoselectivity by a separation of the isomeric alcohols **6** and **7** prior to the appropriate hydrogenation to the allylic alcohols **9b** and **10b**. The results obtained applying this strategy have been published recently.[8] Continuing our studies, we have now been concerned with the diastereoselectivity of the addition of 1-metalated (*Z*)- and (*E*)-hept-1-enes, such as **11**-**14**, to the aldehyde **2**. Our main interest was directed to the question, whether the vinyl carbinols **9b** and **10b**, respectively, could be obtained with high diastereoselectivity. This was a prerequisite, because a simple procedure to convert the unwanted stereoisomers **15b** and **16b** into the $PGF_{2\alpha}$ intermediate **8a** does not exist.

A direct introduction of the (*R*)-1-hydroxyoct-1(*Z*)-enyl side chain was first achieved by Grieco et al. by the addition of (*Z*)-hept-1-enyllithium (**11**) to the bicyclic aldehyde **3**.[3] In this case the observed high diastereoselectivity seems to be caused by the unique steric situation of the carbonyl group. The behaviour of the sterically less demanding aldehyde **2** was therefore of general interest.



Scheme 1. Synthesis of Prostaglandin Intermediates by Addition of Vinyllithium and Vinyltitanium Compounds to the COREY Aldehyde 2

RESULTS

Solutions of (*Z*)- and (*E*)-hept-1-enyllithium[3] (**11** and **13**, respectively), prepared by reaction of (*Z*)- and (*E*)-1-iodohept-1-ene[9,10] with butyllithium in tetrahydrofuran or diethyl ether, were added at -78°C to the aldehyde **2** obtained by Swern oxidation from the bis(trimethylsilyl) ether **1**.[11,12] The reaction mixture was kept at this temperature for 15 min and then quenched with an ammonium chloride solution. Usual work-up afforded mixtures of the diastereomeric alcohols **9b/15b** and **10b/16b**, respectively. The structure assignment was made on the basis of the ^{13}C NMR spectra of these mixtures. According to regularities recognized by Hoffmann and Weidmann,[13] the signal at 71.28 ppm in the spectrum of the mixture of the (*Z*)-compounds was assigned to C-1' of the *anti*-diol **9b** and the signal at 73.46 ppm to C-1' of the *syn*-diol **15b**. In the spectrum of the (*E*)-compounds the signal at 72.59 ppm was attributed to C-1' of the *anti*-diol **16b** and the signal at 75.72 ppm to C-1' of the *syn*-diol **10b**. The ratio of these alcohols was determined by capillary GLC after conversion into the bis(tert-butyldimethylsilyl) ethers **9c**, **10c**, **15c**, and **16c**. The results are given in the Tables 1 and 2 (entries 1, 2, 6, and 7). In order to determine the influence of the solvent polarity on the diastereofacial selectivity, the addition of the vinyllithium compounds **11** and **13** to the aldehyde **2** was repeated in the presence of 30 equivalents of lithium chloride[14] (Tables 1 and 2, entries 3 and 8).

Table 1. Diastereoselectivity of the Addition of the 1-Metalated (*Z*)-Hept-1-enes **11** and **12** to the Aldehyde **2**

Entry	1-Metalated (*Z*)-Hept-1-ene	Solvent	Ratio of the Diastereomers **9b** : **15b** (*anti*/*syn*)
1	**11** (M = Li)	THF	83 : 17
2	**11** "	Et_2O	75 : 25
3	**11** "	Et_2O + 30 equiv. LiCl	79 : 21
4	**12** (M = $Ti(O^iPr)_3$)	THF	30 : 70
5	**12** "	Et_2O	36 : 64

In a second series of experiments the aldehyde **2** was treated at -78°C with the (*Z*)- and (*E*)-vinyltitanium compounds **12** and **14**, respectively. Solutions of these compounds in tetrahydrofuran or diethyl ether were prepared at -78°C by addition of an equivalent amount of chlorotitanium triisopropoxide[15] to solutions of the lithium compounds **11** and **13** in the corresponding solvent.[16] The ratio of the diastereomeric alcohols **9b/15b** and **10b/16b** obtained by the reaction of these solutions with the aldehyde **2** are given in Tables 1 and 2 (entries 4, 5, 9, and 10).

Table 2. Diastereoselectivity of the Addition of the 1-Metalated (*E*)-Hept-1-enes **13** and **14** to the Aldehyde **2**

Entry	1-Metalated (*E*)-Hept-1-ene	Solvent	Ratio of the Diastereomers **16b** : **10b** (*anti*/*syn*)
6	**13** (M = Li)	THF	89 : 11
7	**13** "	Et_2O	91 : 9
8	**13** "	Et_2O + 30 equiv. LiCl	95 : 5
9	**14** (M = $Ti(O^iPr)_3$	THF	41 : 59
10	**14** "	Et_2O	26 : 74

The conversion of the (*Z*)-allylic alcohols **9b/15b** (entry 1) via palladium(II)-catalyzed [3,3]-sigmatropic rearrangement of the diacetates **9a/15a** into a separable mixture of **8a** and **17a** with **8a** as the main component

was performed according to the already published procedure.[8] Analogously, a mixture of **8a** and **17a** with **17a** as the main component was obtained starting from the (*E*)-allylic alcohols **10b/16b** (entry 6).

DISCUSSION

The overall yield of the transfomation of the bis(trimethylsilyl) ether **1** into mixtures of the diastereomeric alcohols **9b/15b** and **10b/16b** was in the order of 30-40 %. This corresponds to results obtained in other transformations via the unstable and unpurified aldehyde **2**.[12]

With the vinyllithium compounds **11** and **13**, in all cases the *anti*-diols **9b** and **16b** were obtained as the major isomers (entries 1-3 and 6-8). The selectivity of (*E*)-hept-1-enyllithium (**13**) is significantly better than that of the (*Z*)-isomer **11**. The differences between tetrahydrofuran and diethyl ether are small. Even the addition of lithium chloride has only a slight effect on the selectivity (entries 3 and 8).

In contrast to the vinyllithium compounds **11** and **13**, the titanium analogues **12** and **14** afford the *syn*-alcohols **10b** and **15b** as the main isomers (entries 4, 5, 9, and 10) in all cases. The diastereoselectivity, however, is generally lower than with the corresponding lithium compounds. The difference between (*Z*)- and (*E*)-vinyltitanium compounds is only small. The solvent also has just a slight influence on the ratio of diastereomers.

In order to compare the experimental results with the Cram[17] and Felkin-Anh[18] model and to get a closer insight into the stereochemistry of the reactions, molecular mechanics calculations were carried out with the program PCMODEL.[19]

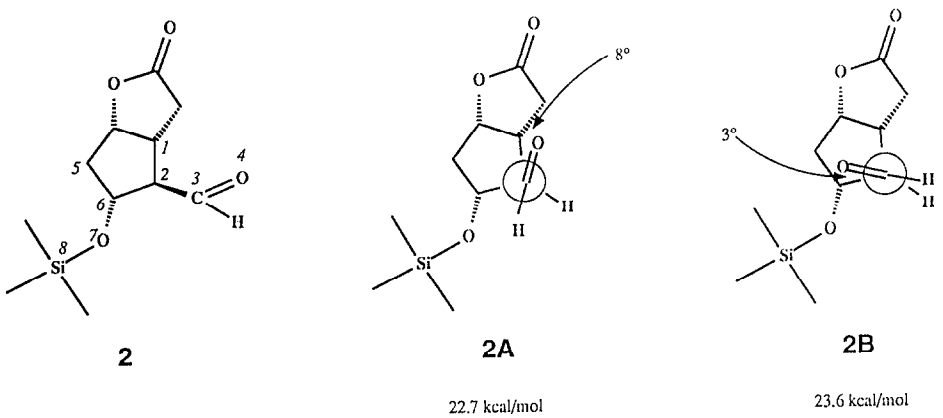


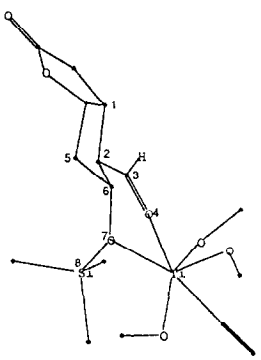
Figure 1. Numbering of the Dihedral Angles and Lowest Energy Conformations of the Aldehyde **2**

In the case of the aldehyde **2** the carbonyl as well as the trimethylsilyloxy group were rotated about 360° in steps of 30° and optimized by keeping the dihedral angles *∠1234* and *∠5678* fixed. From the resulting 144 conformations those with the lowest energies were again optimized with free dihedral angles. The results for the four conformations with the lowest energies are shown in Table 3. It can be seen that there exist two pairs of conformers with very similar dihedral angles. A simplified representation of one conformer of each pair is shown in Figure 1 with a view along the bond between the carbonyl group and the ring carbon atom. The fact that the energy calculated for the conformer **2A** is by 0.9 kcal/mol lower than that calculated for **2B** correlates well with the preferential formation of the anti-diols **9b** and **16b** via a *re*-attack of the lithium compounds **11** and **13**. The observed diastereoselectivity can be explained on the basis of the acyclic Cram model.[17]

Table 3. Energies and Dihedral Angles for Lowest Energy Conformations of Aldehyde **2**

∠1234 \ *∠5678*	286°	272°	265°	271°
352°	22.7 kcal/mol			
353°		22.9 kcal/mol		
117°			23.6 kcal/mol	
118°				23.6 kcal/mol

The indicated inverted diastereoselectivity of the vinyltitanium compounds is parallel to earlier observations concerning a comparison of alkynyllithium and alkynyltitanium compounds[8]. In order to explain this inverted diastereoselectivity, a chelation between the vinyltitanium compound and the aldehyde **2** was considered. By molecular mechanics calculation the lowest energy conformation of **2C**, a chelate formed from aldehyde **2** and ethynyltitanium trimethoxide as a model compound, was determined. The starting geometry of the aldehyde **2** was that of the conformer **2B**. Within the energy minimization the dihedral angle *∠1234* changed from 117° to 141°, whereas the final value for the dihedral angle *∠5678* changed from 265° to 346°. The thus obtained data for the lowest energy conformation of **2C** are represented in Figure 2. The calculation suggests that chelation forces the carbonyl group into a position being nearly eclipsed to the C-C bond adjacent to the silyloxy group. This, finally, results in a slightly better accessibility of the carbonyl group from the *si*-side and a slightly preferred formation of a *syn*-diol, such as **10b**.



Ti-OSi 2.02 Å
Ti-O=C 2.62 Å
∠1234 141°
∠5678 346°
∠SiO-Ti-OMe^1 136°
∠SiO-Ti-OMe^2 106°
∠SiO-Ti-OMe^3 86°
∠SiO-Ti-O=C 75°
∠SiO-Ti-C≡C 136°

2C

Figure 2. Lowest Energy Conformation of the Chelate **2C** Formed from Aldehyde **2** and Ethynyltitanium Trimethoxide Calculated by Using the Program PCMODEL^R

CONCLUSION

This investigation has shown that the vinyltitanium compounds **12** and **14** react at -78°C with the aldehyde **2** forming mixtures of diastereomeric allylic alcohols. The yield is comparable with that obtained using the corresponding vinyllithium compounds **11** and **13** under the same conditions. The diastereoselectivity of the vinyltitanium compounds, however, is significantly lower than with the lithium analogues. Since the titanium compounds are preferentially added by a *si*-attack, the main isomers are the *syn*-diols **10b** and **15b**. The lithium compounds, in contrast, afford preferentially the *anti*-alcohols **9b** and **16b** by a *re*-attack. For the synthesis of the prostaglandin intermediate **8b** only the use of (*Z*)-hept-1-enyllithium (**11**) can be considered, because only this vinyl compound affords **9b** with an almost satisfying diastereoselectivity. **10b**, the other

potential precursor of **8b**, is not accessible with the required selectivity, neither by using vinyltitanium nor vinyllithium compounds. **16b**, the precursor of the unnatural (15*R*)-prostaglandins, however, can be obtained with high diastereoselectivity by using the vinyl compound **13**. In conclusion, this investigation provides further evidence that the originally observed high diastereoselectivity of alkyltitanium triisopropoxide additions to aldehydes[20] does not hold for the vinyl analogues.[16]

EXPERIMENTAL

General. The ^{1}H NMR spectra were recorded at 300 MHz and the ^{13}C NMR spectra at 75 MHz on a Varian Gemini 300 instrument. Chemical shifts are related to tetramethylsilane. Flash chromatography[21] was carried out using silica gel 60 (0.040-0.063 mm). GLC was performed on a Varian Aerograph 2400 equipped with a glass capillary (42 m x 0.28 mm, 0.3 % OV-1). Elemental analyses were determined on a Carlo Erba Autoanalyzer 1106.

(1*S**,5*R**,6*R**,7*R**)-7-Trimethylsilyloxy-3-oxo-2-oxabicyclo[3.3.0]octane-6-carbaldehyde (2)

A solution of dimethyl sulfoxide (11.5 mL, 162.3 mmol) in dichloromethane (9 mL) was added at -78°C to a solution of oxalylchloride (7 mL, 80.2 mmol) in dichloromethane (9 mL). The mixture was stirred under argon for 5 min. Then a solution of **1**[12] (10.0 g, 31.6 mmol) in dichloromethane (13 mL) was added followed by triethylamine (45 mL, 323.5 mmol) after another hour. Then the reaction mixture was warmed up to 20°C, diluted with water (300 mL) and extracted with EtOAc (3 x 150 mL). The crude aldehyde **2** obtained by evaporation of the solvent at reduced pressure was used without further purification.

(1*S**,5*R**,6*R**,7*R**)-7-Hydroxy-6-[(1*R**)-1-hydroxyoct-2(*Z*)-enyl]-2-oxabicyclo[3.3.0]octan-3-one (9b) and (1*S**,5*R**,6*R**,7*R**)-7-Hydroxy-6-[(1*S**)-1-hydroxyoct-2(*Z*)-enyl]-2-oxabicyclo[3.3.0]octan-3-one(15b)

(a) From Aldehyde 2 and (Z)-Hept-1-enyllithium in Tetrahydrofuran (Entry 1):
A 1.35 M solution of n-butyllithium (0.65 mL, 0.88 mmol) was added at -78°C to (*Z*)-iodohept-1-ene[9] (200 mg, 0.89 mmol) in THF (10 mL). After stirring for 5 min a solution of the aldehyde **2** (205 mg) in THF (5 mL), obtained by Swern oxidation from **1** (290 mg, 0.92 mmol), was added to the mixture. Stirring was continued at -78°C for a further 10 min. Then the mixture was poured into a saturated aqueous NH_4Cl solution (20 mL) and extracted with EtOAc (4 x 30 mL). The combined extracts were dried with Na_2SO_4 and concentrated under reduced pressure. The residue was dissolved in methanol (20 mL) and stirred at 20°C with the acidic ion-exchange resin Wofatit KPS (1 mL) for 30 min. After removal of the ion-exchange resin by filtration, the solvent was evaporated under reduced pressure. Flash-chromatography of the residue with EtOAc/hexane (7:3) yielded a 83:17 mixture of **9b** and **15b** (85 mg, 35 % related to **1**) in form of a colourless oil: ^{1}H NMR: δ 0.83 (3H, t, J = 7 Hz, 8'-H_3), 4.09 (1H, dt, J = 6.5 and 6.5 Hz, 7-H), 4.33 (0.8H, m, 1'-H of **9b**), 4.43 (0.2 H, dd, J = 9 and 6 Hz, 1'-H of **15b**), 4.84 (1H, m, 1-H), 5.40 (1H, dd, J = 11 and 9 Hz, 2'-H), 5.55 (1H, dt, J = 11 and 8 Hz, 3'-H); ^{13}C NMR of **9b**: δ 13.96 (C-8'), 22.47 (C-5'), 31.43 (C-6'), 35.26 (C-4'), 35.49 (C-4), 38.71 (C-8), 39.69 (C-5), 57.89 (C-6), 71.28 (C-1'), 75.97 (C-7), 82.53 (C-1), 129.77 (C-3'), 134.44 (C-2'), 176.84 (C-3); ^{13}C NMR of **15b**: δ 13.96 (C-8') 22.47 (C-5'), 31.43 (C-6'), 35.26 (C-4'), 36.45 (C-4), 37.39 (C-8), 40.63 (C-5), 56.94 (C-6), 73.46 (C-1'), 77.23 (C-7), 83.52 (C-1), 129.95 (C-3'), 135.13 (C-2'), 175.75 (C-3). Anal. calcd. for ($C_{15}H_{24}O_4$): C, 67.14; H, 9.01. Found: C, 67.14; H, 8.86.

(b) From Aldehyde 2 and (Z)-Hept-1-enyllithium in Diethyl Ether (Entry 2):
(Z)-1-Iodohept-1-ene[9] (100 mg, 0.45 mmol) dissolved in Et_2O (3 mL) was treated according to procedure (a) with a 1.75 M solution of n-butyllithium (0.25 mL, 0.44 mmol) and then with a solution of the aldehyde **2** (250 mg) in Et_2O (3 mL), obtained from **1** (350 mg, 1.11 mmol) by Swern oxidation. The reaction mixture

was stirred at -78°C for a further 10 min. Work-up according to procedure (a) afforded a 75:25 mixture of **9b** and **15b**.

(c) From Aldehyde 2 and (Z)-Hept-1-enyllithium in Diethyl Ether in the Presence of LiCl (Entry 3):
A 1.33 M solution of n-butyllithium (0.30 ml, 0.40 mmol) was added under stirring at -78°C to a mixture of (*Z*)-1-iodohept-1-ene[9] (100 mg, 0.45 mmol) and lithium chloride (600 mg, 14.15 mmol) in Et_2O (9 mL). After 5 min a solution of the aldehyde **2** (120 mg) in Et_2O (3 mL), obtained from **1** (165 mg, 0.52 mmol) by Swern oxidation, was added. After stirring at -78°C for a further 10 min, the mixture was worked up according to procedure (a) yielding a 79:21 mixture of **9b** and **15b**.

(d) From Aldehyde 2 and (Z)-Hept-1-enyltitanium Triisopropoxide in Tetrahydrofuran (Entry 4):
A 1.75 M solution of n-butyllithium (0.25 mL, 0.44 mmol) was added at -78°C to (*Z*)-1-iodohept-1-ene[9] (100 mg, 0.45 mmol) in THF (5 mL). After stirring for 5 min, a 1.73 M solution of chlorotitanium triisopropoxide[22] (0.40 mL, 0.69 mmol) in hexane was added at -78°C. After stirring for a further 15 min a solution of the aldehyde **2** in THF (3 mL), prepared by Swern oxidation of **1** (155 mg, 0.49 mmol), was added and stirring was continued at -78°C for a further 15 min. Then the mixture was quenched with a saturated aqueous $NaHCO_3$ solution (40 mL) and extracted with EtOAc (4 x 30 mL). Further work-up according to procedure (a) afforded a 30:70 mixture of **9b** and **15b**.

(e) From Aldehyde 2 and (Z)-Hept-1-enyltitanium Triisopropoxide in Diethyl Ether (Entry 5):
The aldehyde **2** in Et_2O (3 mL), obtained from **1** (155 mg, 0.49 mmol) by Swern oxidation, was treated as described in procedure (d) with the only difference that Et_2O was used instead of THF. Work-up afforded a 36:64 mixture of **9b** and **15b**.

(1*S,5*R**,6*R**,7*R**)-7-Hydroxy-6-[(1*S**)-1-hydroxyoct-2(*E*)-enyl]-2-oxabicyclo[3.3.0]octan-3-one (10b) and (1*S**,5*R**,6*R**,7*R**)-7-Hydroxy-6-[(1*R**)-1-hydroxyoct-2(*E*)-enyl]-2-oxabicyclo[3.3.0]octan-3-one (16b)**

(a) From Aldehyde 2 and (E)-Hept-1-enyllithium in Tetrahydrofuran (Entry 6):
A 1.35 M solution of n-butyllithium (1.80 mL, 2.43 mmol) in hexane was dropped at -78°C to a stirred solution of (*E*)-1-iodohept-1-ene[10] (550 mg, 2.46 mmol) in THF (20 mL). After 5 min a solution of the aldehyde **2** (595 mg) in THF (5 mL) prepared by Swern oxidation of the bis-silyl ether **1** (850 mg, 2.69 mmol) was added. The solution was stirred for a further 10 min at -78°C, quenched with a saturated aqueous NH_4Cl solution (40 mL) and extracted with EtOAc (3 x 40 mL). The extract was dried with Na_2SO_4 and concentrated under reduced pressure. Flash chromatography of the residue with EtOAc/n-hexane (7:3) yielded a 11:89 mixture of **10b** and **16b** (256 mg, 36 % related to bis(trimethylsilyl) ether **1**) as a colourless oil: ^1H NMR: δ 0.83 (3H, t, J = 7.5 Hz, 8'-H_3), 4.08 (1H, m, 7-H), 4.14 (1H, m, 1'-H), 4.84 (1H, dt, J = 6.5 and 3 Hz, 1-H), 5.42 (1H, dd, J = 15.5 and 7 Hz, 2'-H), 5.64 (1H, dt, J = 15.5 and 7 Hz, 3'-H); ^{13}C NMR of **10b**: δ 13.99 (C-8'), 22.44 (C-7'), 28.77 (C-5'), 31.40 (C-6'), 32.11 (C-4'), 35.57 (C-4), 39.71 (C-8), 40.43 (C-5), 58.09 (C-6), 75.72 (C-1'), 76.86 (C-7), 82.97 (C-1), 130.61 (C-3') 134.66 (C-2'), 177.16 (C-3); ^{13}C NMR of **16b**: δ 13.99 (C-8'), 22.44 (C-7'), 28.83 (C-5'), 31.40 (C-6'), 32.16 (C-4'), 36.15 (C-4), 38.31 (C-8), 40.84 (C-5), 59.35 (C-6), 72.59 (C-1'), 74.33 (C-7), 84.12 (C-1), 130.45 (C-3'), 133.81 (C-2'), 177,69 (C-3); MS, m/e (%): 268 (M^+, 3), 250 (43), 233 (40), 232 (32), 224 (10), 197 (35), 179 (30), 169 (15), 149 (30), 124 (100); Anal. calcd. for ($C_{15}H_{24}O_4$): C, 67.14; H, 9.01. Found: C, 67.19; H, 8.94.

(b) *From Aldehyde 2 and (E)-Hept-1-enyllithium in Diethyl Ether (Entry 7):*
(*E*)-1-Iodohept-1-ene[10] (150 mg, 0.67 mmol) in dry Et_2O (5 mL) was treated according to procedure (a) with a 1.75 M solution of n-butyllithium (0.30 mL, 0.53 mmol) and then with a solution of the aldehyde **2** (150 mg) in Et_2O (3 mL) obtained from **1** (215 mg, 0.68 mmol) by Swern oxidation. The solution was stirred for a

further 10 min at -78°C and worked up as described for procedure (a) affording a 9:91 mixture of **10b** and **16b**.

(c) From Aldehyde 2 and (E)-Hept-1-enyllithium in Diethyl Ether in the Presence of LiCl (Entry 8):
A 1.33 M solution of n-butyllithium (0.30 mL, 0.40 mmol) in hexane was added under stirring at -78°C to a mixture of (*E*)-1-iodohept-1-ene[10] (100 mg, 0.45 mmol) and lithium chloride (600 mg, 14.15 mmol) in Et_2O (9 mL). After 5 min a solution of the aldehyde **2** (120 mg) in Et_2O (3 ml) prepared by Swern oxidation from **1** (165 mg, 0.52 mmol) was added. After stirring for a further 10 min the mixture was worked up according to procedure (a) affording a 5:95 mixture of **10b** and **16b**.

(d) From Aldehyde 2 and (E)-Hept-1-enyltitanium Triisopropoxide in Tetrahydrofuran (Entry 9):
A 59:41 mixture of **10b** and **16b** was obtained, when aldehyde **2** was treated with (*E*)-hept-1-enyltitanium triisopropoxide instead of (*Z*)-hept-1-enyltitanium triisopropoxide. The reaction was carried out in full analogy to the synthesis of **9b** and **15b** according to procedure (d).

(e) From Aldehyde 2 and (E)-Hept-1-enyltitanium Triisopropoxide in Diethyl Ether (Entry 10):
A 74:26 mixture of **10b** and **16b** was obtained, when aldehyde **2** was treated with (*E*)-hept-1-enyltitanium triisopropoxide. The reaction was carried out in full analogy to the synthesis of **9b** and **15b** according to procedure (e).

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