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Silicon-Directed Stereoselective Synthesis of 2-Vinyl-1,3-diols. Stereo-Divergence with and without the Silyl Group Related to the Synthesis of Avenaciolide and Isoavenaciolide

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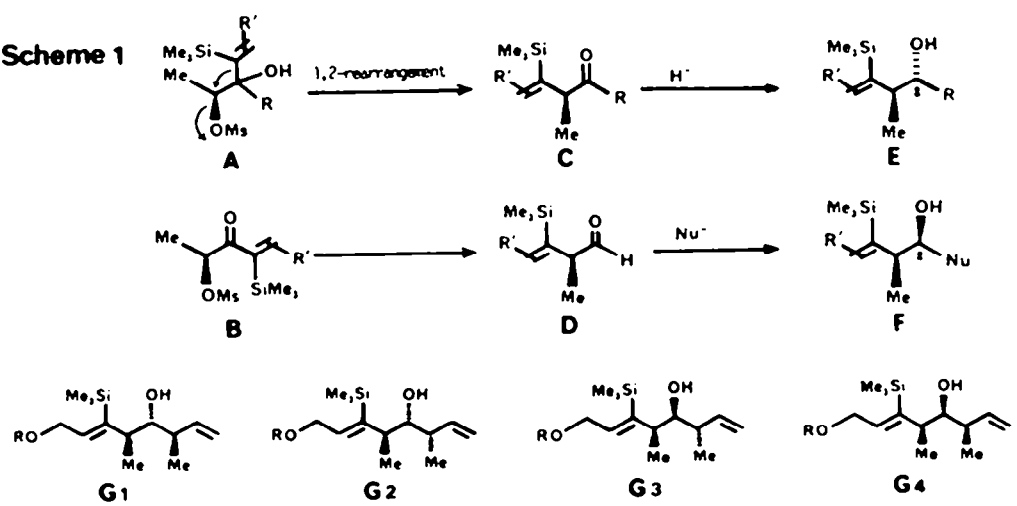
Abstract: *A flexible approach to the stereoisomers of 2-vinyl-1,3-diols via the reduction of 2-vinyl aldols is described. The presence of the TMS group at the α-position of the vinyl group firmly establishes the syn relationship between the newly-formed hydroxyl group and the vinyl group. To examine the effect of the TMS group, comparison experiments were performed for the compounds with and without the TMS group, where complete reversal of the diastereo-selection was observed in the reduction of the anti-aldols. This stereo-divergence was useful in the selective synthesis of a pair of isomeric lactones, avenaciolide and isoavenaciolide.*

Introduction

The importance of acyclic stereocontrol is now well recognized. The rapid progress of this field is best illustrated by the impressive advance of the aldol and related reactions in the last decade.[1)]

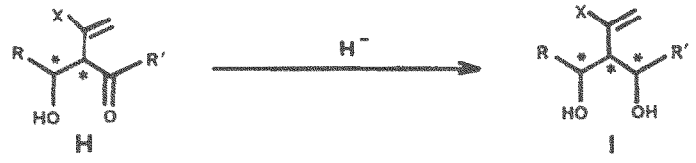
We have disclosed a new method for acyclic stereocontrol, whose utility has been demostrated in macrolide synthesis.[2)] The method relies on the stereospecificity of 1,2-rearrangements, but also includes some new aspects of organosilicon chemistry. Scheme 1 shows the versatile roles of silicon in our process. Specifically, two effects due to the TMS groups are notable: (1) The rate-enhancing effect[3)] in the 1,2-rearrangement which allows the reaction to proceed under mild conditions; (2) The stereo-directing effect in the second step which makes the α-chiral carbonyl compounds C and D highly "Cram-selective".[4)] These features are the basis of the enantio- and diastereo-controlled approach to E and F. Furthermore, the "Cram-selectivity" enables selective access to the useful synthons G with three consecutive chiral centers.[5)]

Scheme 1



*Deceased June 24, 1987.

This paper describes the reduction of 2-vinyl aldols H as a route to the isomeric 2-vinyl-1,3-diols I.[6] The work focuses on the effect of the TMS group on the diastereo-facial selection. Stereo-divergent syntheses of two isomeric lactones, avenaciolide and isoavenaciolide, are also reported in this paper.[7]



H I

Results and Discussion

Synthesis of 2-Vinyl Aldols. The aldols with the C(2)-vinyl group 3-8 (see Scheme 2) were synthesized by the Lewis acid-promoted 1,2-rearrangement of epoxy alcohols or their corresponding TMS ethers[8] as typified in the two examples shown below. Three procedures (methods A, B, C) were developed for this conversion.

(eq.1)

1 X : H
1′ X : SiMe$_3$

4

method A : 1, $BF_3 \cdot OEt_2$ / CH_2Cl_2, -78→ -40°C
method C : 1′, 2 mol % Me_3SiI / CH_2Cl_2, -78→ -10°C

(eq.2)

2 7

method B : 2, $(i\text{-PrO})_2TiCl_2$ / CH_2Cl_2, -78→ 0°C

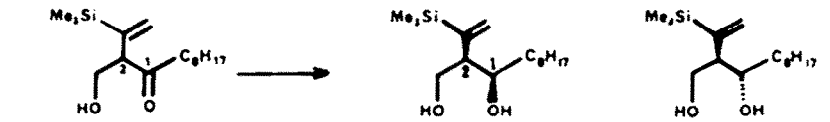
The suitable method may be chosen in the following manner. Method A is suitable in the case where the migrating group has a high migratory aptitude (MA) such as the TMS-vinyl group (eq 1). In contrast, if the MA is low as in the case of the simple vinyl group in (eq 2), the epoxy alcohol is better converted to its TMS ether such as 2 which has higher reactivity than the parent alcohol, and subsequent treatment with Lewis acid gives generally higher yields (method B). Method C is the catalytic procedure which often gives better yields than the stoichiometric ones and is especially useful for large scale reactions.[8b] The methods for the synthesis of 3-8 and the yields are listed in the experimental section.

Stereoselective Reduction. The 2-vinyl aldols 3-8 were reduced with $LiBEt_3H$ (Super Hydride®)[9] and DIBAL[10] as summarized in Scheme 2. The arbitrary numbering for these systems is shown in the scheme and used throughout this paper.

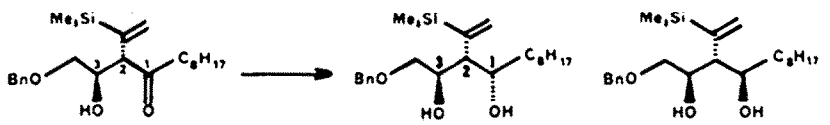
In the reductions of 3-5 with the TMS-vinyl group, the 1,2-syn isomers 9, 11, 13 were produced as the sole products by employing $LiBEt_3H$. This means the diastereo-selection leading to the 1,2-syn isomers is a uniform trend without regard to the stereochemistry or the substituent at C(3). In contrast, the influence of C(3) is significant on the stereochemical outcome in the DIBAL cases.

For the aldols 6-8 with the simple vinyl group, the selectivity changed dramatically depending on the substrates. Especially, in contrast to 4, the reduction of 7 showed a completely reversed selectivity to give the anti-anti isomer 18. This reversal is particularly marked with $LiBEt_3H$.

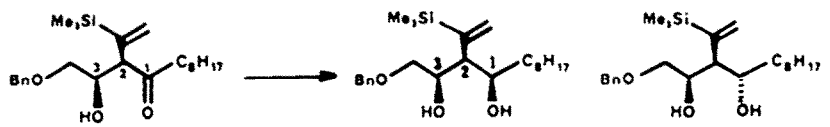
Scheme 2 [a)]



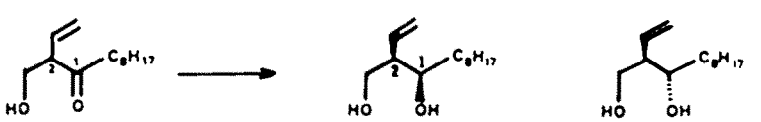
	3 → 9	3 → 10
$LiBEt_3H$	>99	<1
DIBAL	81	19



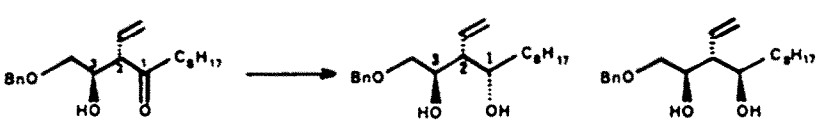
	4 → 11	4 → 12
$LiBEt_3H$	>99	<1
DIBAL	40	60



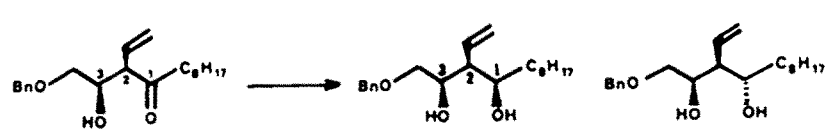
	5 → 13	5 → 14
$LiBEt_3H$	>99	<1
DIBAL	>99	<1



	6 → 15	6 → 16
$LiBEt_3H$	66	34
DIBAL	37	63



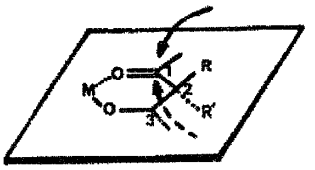
	7 → 17	7 → 18
$LiBEt_3H$	2	98
DIBAL	14	86



	8 → 19	8 → 20
$LiBEt_3H$	>99	<1
DIBAL	>99	<1

a) All reactions were carried out at -78°C in THF.

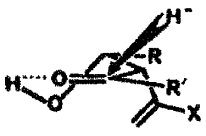
Mechanistic Rationalization. These data add a new insight into the reduction of the aldols and their derivatives. Relevant to this problem, the B-, Zn-, or Al-chelates are known to direct the 1,3-syn-selective reduction.[11,12] Although these are effective for the Type I substrates, the Type II cases are affected by the second factor, i.e. the Cram-type steric bias from the C(2)-substituent. Hence, the selectivity of the Type II cases is dependent on these two factors.



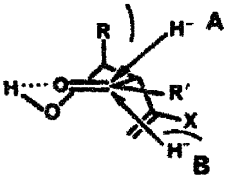
Type I : R = R' = H
Type II : R or R' ≠ H

Prior to the mechanistic discussion, the markedly different behaviors of $LiBEt_3H$ and DIBAL toward alcoholysis should be noted. Upon treatment of the reagents with sec-BuOH (1 equiv. / THF, -78 °C, 5 min), the H_2 evolution was ∿100 % (DIBAL) and less than 5 % ($LiBEt_3H$). These data suggest that the aldolate formation may precede or compete with the attack of H^- in the reductions with DIBAL, while the aldol itself is reduced with $LiBEt_3H$.

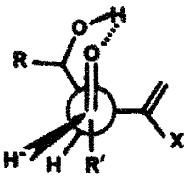
Since several factors seem to be operative in the DIBAL cases,[13] we limit the following discussion to the cases with $LiBEt_3H$. Described here is a model, slightly modified from the one in our previous report.[7a] That is the hydrogen-bonded models T_1, T_2, where the balance of the 1,2-effect (by $H_2C{=}C(X)$-) and the 1,3-effect (by R-) are considered. The outcome of the reactions with and without



T_1

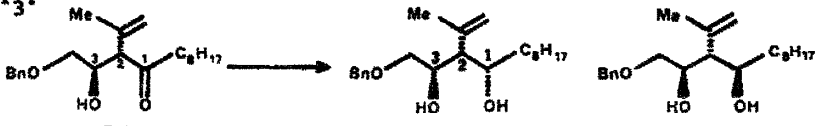


T_2



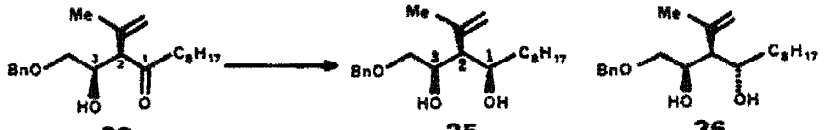
T_3

the TMS group provides support for this postulate. The reduction of syn aldols 5 and 8 leads uniformly and exclusively to syn-syn isomers 13 and 19, since two effects are synergistic as shown in T_1. On the other hand, these effects contradict each other for anti aldols 4 and 7 as shown in T_2. Depending on the relative importance of these effects, the favored trajectory of the H^- attack becomes A for 4 ($X=SiMe_3$) or B for 7 (X=H), respectively. Supportive evidence was obtained by reductions of 21 and 22 having $H_2C{=}C(Me)$-group which lies between $H_2C{=}C(SiMe_3)$- and $H_2C{=}CH$- with respect to the steric demand.[14] Diol 25 was obtained as the single product from 22 as expected, while a mixture of 23 and 24 was obtained in the reduction of 21, which indicates the 1,2- and 1,3-effects are comparable in this case. These data illustrate the extremely large directing effect of the TMS-vinyl group, which is more clearly visualized by the Felkin-Anh-type picture T_3.[15]



21 23 24

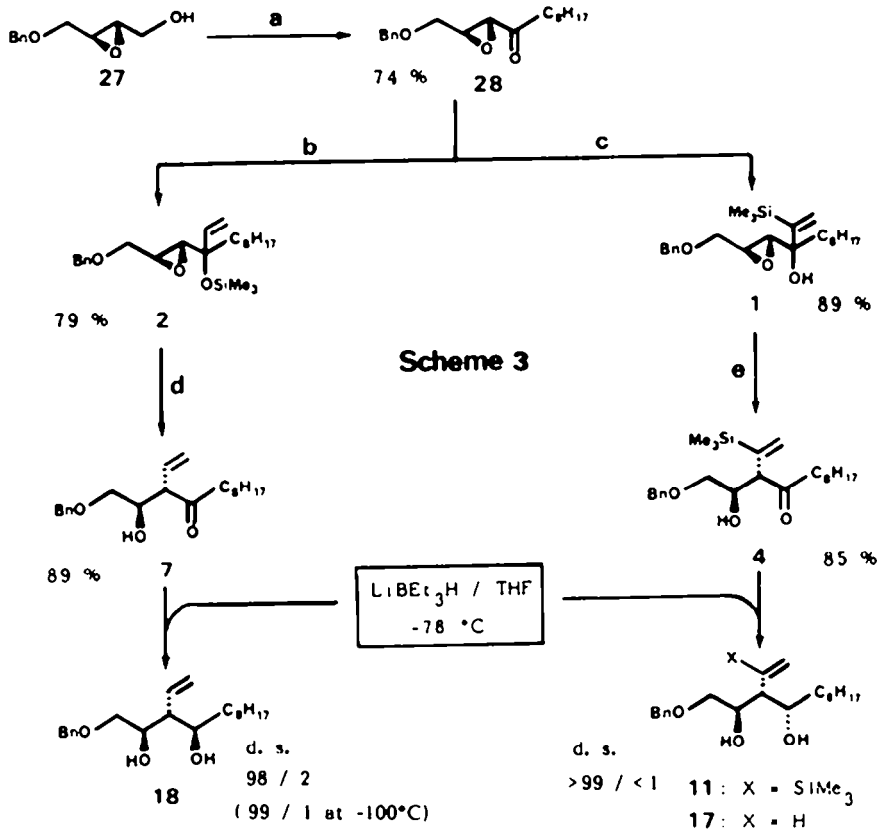
$LiBEt_3H$ / THF, -78°C 77 23



22 25 26

$LiBEt_3H$ / THF, -78°C >99 <1

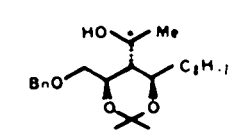
Syntheses of Avenaciolide and Isoavenaciolide. As an application, the synthesis of two isomeric lactones, avenaciolide (35a) and isoavenaciolide (35b) wes planned.[16] These compounds are the antifungal metabolites which were isolated from Aspergillus avenaceus, the fascinating structures of which have stimulated a number of studies on their total synthesis.[17,18] Scheme 3 is a summary of the initial reactions, which shows the divergence to these isomeric structures.[19] The common starting material is the known chiral epoxy alcohol 27, obtainable by the Sharpless reaction ($Ti(O\text{-}iPr)_4$, L-(+)-DET, TBHP).[20] The alcohol 27 was converted to the ketone 28 by the Swern oxidation[21] and alkylation in one pot, followed by the re-oxidation.



Scheme 3

Keys: a) Swern oxidn., $C_8H_{17}MgBr$ (in situ); Swern oxidn., b) $H_2C{=}CHMgBr$ / THF; TMSCl, Imidazole / DMF, c) $H_2C{=}C(SiMe_3)Li$ / THF, d) $(i\text{-}PrO)_2TiCl_2$ / CH_2Cl_2, -78 °C → 0°C, e) $BF_3{\cdot}OEt_2$ / CH_2Cl_2, -78 °C → -40 °C.

Elaboration of these 1,3-diols 18 and 11 led to the target lactones. Scheme 4 illustrates the synthesis of avenaciolide starting from 18. Diol 18 was first protected as acetonide 30a. Treatment of 30a with $BH_3{\cdot}THF$ led to poor yield (39 %) of 31a accompanied by substantial amounts of regioisomers 29 (31 %). The asterisked stereocenter (ratio: 1.7/1) was not specified. This unexpected regiochemistry of the hydroboration presumably comes from the chelation of the reagent to the benzyloxy side chain as depicted in Fig 1. This problem was overcome by the use of a bulkier reagent, dicyclohexylborane.


29

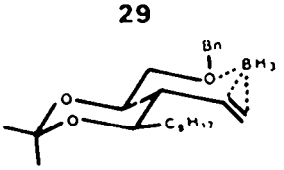


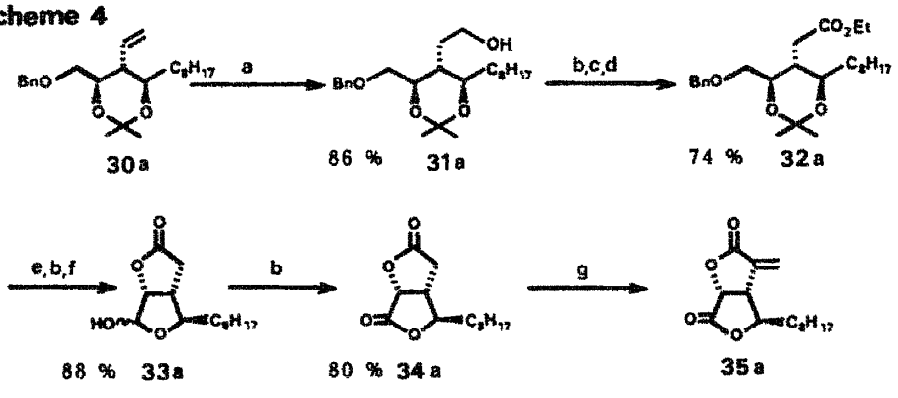
Fig.1

Our initial plan was to deprotect the benzyl group of

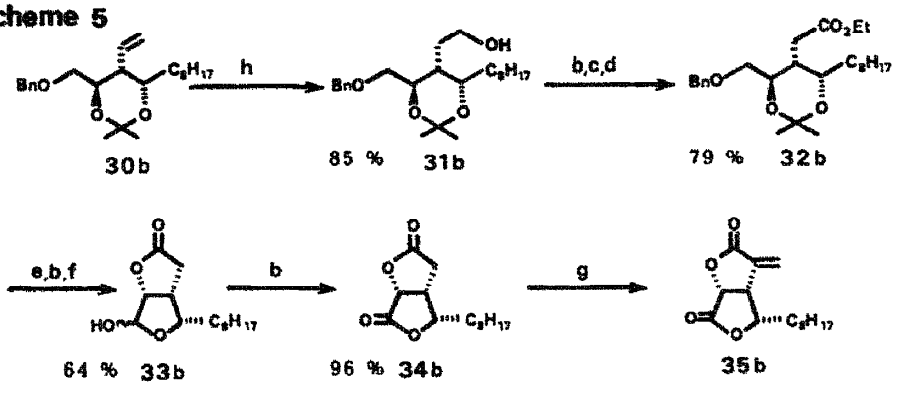
31a followed the oxidation of the resulting diol to the dicarboxylic acid corresponding to the bis-lactone 34a. However, all attempts to effect the simultaneous oxidation of the diol failed. Thus, the stepwise oxidation of 31a to obtain the bis-lactone 34a was adopted instead. This route requires several steps, all of which proceeded cleanly in high yields, and purification of the intermediates was unnecessary at most stages. Finally, the methylenation of 34a by Johnson's procedure[17c] afforded avenaciolide (35a), which was identical to the authentic sample kindly provided by Dr. Aldridge.

The synthesis of isoavenaciolide (35b) is depicted in Scheme 5. Desilylation of 11 (CsF / DMF) gave 17, which was then protected as acetonide to give 30b. The same sequence of the reactions as before was applied to 30b to give isoavenaciolide (35b). There were two major differences in this scheme from the avenaciolide synthesis. The regiochemical problem of the hydroboration of 30b was not serious in this case. The second point to be noted is the poor yield of the last step. The conversion of 34b to 35b has the precedents,[18a,b] however, the yield in our hands did not exceed 10 % despite several attempts with slight modifications of the original procedure or other methylenation reactions. We surmise that the highly base-sensitive nature of the bislactone 34b is the major reason for these results. There is still a need for new methylenation reactions which are applicable to sensitive lactones like 34b. Isoavenaciolide (35b), thus obtained, was again indistinguishable from an authentic specimen.

Scheme 4



Scheme 5



Keys: a) $(cyclo\text{-}C_6H_{11})_2BH$ / THF; H_2O_2, b) Swern oxidn., c) $NaClO_2$, pH 4, $Me_2C{=}CHMe$, / $tBuOH\text{-}H_2O$, d) $ClCO_2Et$, Et_3N; 4-DMAP, e) H_2, Pd-C, f) H^+ / dioxane-H_2O, g) Johnson's method (ref. 17c), h) $(Me_2CHCHMe)_2BH$ / THF; H_2O_2.

Conclusion

A flexible route to the stereoisomers of 2-vinyl-1,3-diols was developed. The starting 2-vinyl aldols are available in optically active forms by the combination of the Sharpless reaction and the stereospecific 1,2-rearrangement, which reinforces the value of the present method in the synthesis of the natural products. The utility of the process was demonstrated by an application to the stereo-divergent synthesis of avenaciolide and isoavenaciolide.

Experimental

General. Infrared (IR) spectra were recorded on a JASCO A-202 spectrometer. ^1H and ^{13}C NMR spectra were measured on a JEOL GX-400 spectrometer. The chemical shifts are expressed in parts per million downfield from internal tetramethylsilane (δ=0). Mass spectra (MS) were obtained with a Hitachi M-80 spectrometer. Melting points are uncorrected. All the experiments dealing with the air- and moisture-sensitive compounds were carried out under the atmosphere of dry argon. For thin layer chromatography (TLC) analysis, Merck precoated plates (silica gel 60 GF 254, #5715) were used. Products were purified by flash column chromatography by using Merck silica gel 60 (#7734) or preparative TLC by using Wako gel B-5F.

Synthesis of 4 by method A: To a solution of 1 (5.23 g, 16.3 mmol) in CH_2Cl_2 (50 ml) was slowly added $BF_3{\cdot}OEt_2$ (6.94 g, 48.9 mmol) in CH_2Cl_2 (10 ml) at -78 °C and stirred for 0.5 h. The solution was warmed slowly to -40 °C during 40 min, then poured into ice water-ether. Extraction and purification by column chromatography (hexane/AcOEt=6/1) gave 4 (4.44 g, 85 %) as an oil. $[\alpha]_D^{27}$ -93° (c 0.99, $CHCl_3$); ^1H NMR (CCl_4) δ 0.12 (s, 9H), 0.87 (t, 3H, J=7Hz), 1.2-1.4 (m, 12H), 2.3-2.4 (m, 2H), 3.31 (d, 1H, J=6Hz), 3.41 (dd, 1H, J_1=6Hz, J_2=10Hz), 3.46 (dd, 1H, J_1=6Hz, J_2=10Hz), 3.55 (d, 1H, J=7.5Hz), 4.1-4.2 (m, 1H), 4.52 (d, 1H, J=12Hz), 4.54 (d, 1H, J=12Hz), 5.63 (d, 1H, J=2Hz), 5.78 (d, 1H, J=2Hz), 7.3 (s, 5H); ^{13}C NMR ($CDCl_3$) δ -1.1, 14.1, 22.6, 23.4, 29.05, 29.11, 29.3, 31.8, 42.9, 58.3, 72.1, 72.2, 73.4, 127.7, 127.8, 128.4, 130.4, 138.0, 145.7, 211.5; IR (neat) 3450, 2940, 2835, 1705, 1445, 1400, 1355, 1240, 1110, 1080, 1020, 935, 835, 750, 730, 690 cm^{-1}; HRMS m/z 404.2742 (404.2744 calcd for $C_{24}H_{40}O_3Si$, M^+). Aldol 4 is also obtainable in excellent yield by method C (see below).

Synthesis of 7 by method B: A freshly prepared mixture of $TiCl_4$ (1.0 M stock solution in CH_2Cl_2, 5.3 ml) and $Ti(O\text{-}iPr)_4$ (1.05 g, 5.3 mmol) in CH_2Cl_2 (30 ml) was added slowly to a solution of 2 (713 mg, 1.76 mmol) in CH_2Cl_2 (30 ml) at -78 °C. After 0.5 h, the temperature was slowly raised to 0 °C. The solution was poured into a mixture of cold dilute HCl and ether. Extraction followed by column chromatography (hexane/AcOEt=87/13) gave 7 (524 mg, 89 %) as an oil. $[\alpha]_D^{28}$ -143° (c 0.98, $CHCl_3$); ^1H NMR (CCl_4) δ 0.86 (t, 3H, J=6Hz), 1.2-1.8 (m, 12H), 2.39 (t, 2H, J=7Hz), 2.6-2.8 (m, 1H), 3.2-3.6 (m, 1H), 3.8-4.1 (m, 1H), 4.44 (s, 2H), 5.0-5.3 (m, 2H), 5.71 (ddd, 1H, J_1=J_2=9Hz, J_3=17Hz), 7.22 (s, 5H); ^{13}C NMR ($CDCl_3$) δ 14.1, 22.6, 23.2, 29.10, 29.13, 29.4, 31.8, 43.0, 59.9, 71.4, 71.9, 73.5, 120.0, 127.79, 127.82, 128.4, 132.8, 137.2, 211.3; IR (neat) 3450, 2920, 2850, 1705, 1625, 1445, 1355, 1100, 915, 730, 695 cm^{-1}; HRMS m/z 333.2427 (333.2427 calcd for $C_{21}H_{33}O_3$, M^++1).

Synthesis of 4 by method C: Under protection from light, Me_3SiI (12 ul, 0.084 mmol) was added to a solution of epoxy silyl ether 1' (2.0 g, 4.20 mmol) in CH_2Cl_2 (8 ml) at -78 °C. The temperature was gradually raised to -10 °C during 1 h, and the reaction was stopped by the addition of pH 7 buffer and products were extracted with ether. The combined organic layer was concentrated in vacuo and diluted with 1,4-dioxane (4 ml), to which was added 2 N HCl (two drops) and stirred for 10 min to ensure the hydrolysis of the TMS ether of 4. Extractive workup followed by column chromatography (hexane/AcOEt=6/1) afforded aldol 4 as a colorless oil (1.66 g, 98 %).

The other 2-vinyl aldols were prepared via either of the three methods. The yields and the physical data of the products are listed below.

3: Yield 83 % (method A). ^1H NMR (CCl_4) δ 0.17 (s, 9H), 0.8-1.05 (m, 3H), 1.1-1.7 (m, 12H), 2.2-2.6 (m, 3H), 3.0-3.4 (m, 2H), 3.4-3.8 (m, 1H), 5.33 (s, 2H); IR (neat) 3400, 2905, 2845, 1700, 1450, 1400, 1360, 1240, 1120, 1080, 1035, 940, 830, 755, 710, 685 cm^{-1}; HRMS m/z 269.1925 (269.1935 calcd for $C_{15}H_{29}O_2Si$, M^+-CH_3).

5: Yield 89 % (method B); ^1H NMR (CCl_4) δ 0.10 (s, 9H), 0.7-1.7 (m, 15H), 2.3-2.7 (m, 3H), 3.4-3.6 (m, 3H), 3.9-4.1 (m, 1H), 4.40 (s, 2H), 5.60 (d, 1H, J=2Hz), 5.73 (d, 1H, J=2Hz), 7.20 (s, 5H); IR (neat) 3475, 2910, 2850, 1700, 1445, 1400, 1355, 1245, 1090, 1020, 930, 835, 730 cm^{-1}; HRMS m/z 405.2842 (405.2823 calcd for $C_{15}H_{29}O_2Si$, M^+-CH_3).

6: Yield 56 % (method B); ^1H NMR ($CDCl_3$) δ 0.88 (t, 3H, J=7Hz), 1.1-1.7 (m, 12H), 2.22 (t, 1H, J=6.5Hz), 2.4-2.6 (m, 2H), 3.3-3.4 (m, 1H), 3.6-3.7 (m, 1H), 3.8-3.9 (m, 1H), 5.25-5.3 (m, 2H), 5.7-5.8 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 14.1, 22.6, 23.4, 29.11, 29.13, 29.3, 31.8, 42.1, 59.0, 62.8, 120.2, 132.6, 211.8; IR (neat) 3450, 2910, 2850, 1710, 1630, 1455, 1400, 1365, 1255, 1125, 1040, 920, 720 cm^{-1}; HRMS m/z 194.1668 (194.1669 calcd for $C_{13}H_{22}O$, M^+-H_2O).

8: Yield 33 % (method B); ^1H NMR ($CDCl_3$) δ 0.88 (t, 3H, J=7Hz), 1.0-1.4 (m, 10H), 1.4-1.7 (m, 2H), 2.3-2.6 (m, 2H), 2.88 (d, 1H, J=3.5Hz), 3.36 (dd, 1H, J_1=5Hz, J_2=10Hz), 3.4-3.5 (m, 2H), 4.1-4.25 (m, 1H), 4.51 (s, 2H), 5.26 (d, 1H, J=17 Hz), 5.32 (d, 1H, J=10.5Hz), 5.86 (ddd, 1H, J_1=10Hz, J_2=10.5Hz, J_3=17Hz), 7.3 (s, 5H); ^{13}C NMR ($CDCl_3$) δ 14.1, 22.6, 23.3, 29.08, 29.11, 29.3, 31.8,

42.3, 59.4, 69.9, 71.4, 73.3, 121.0, 127.78, 127.81, 128.4, 132.1, 137.8, 211.8; *IR* (neat) 3450, 2910, 2850, 1705, 1625, 1445, 1350, 1150, 995, 910, 730, 695 cm^{-1}; *HRMS* m/z 333.2437 (333.2728 calcd for $C_{21}H_{33}O_3$, M^++1).

21: Yield 88 % (method B); ^1H NMR ($CDCl_3$) δ 0.87 (t, 3H, J=7Hz), 1.3 (br, 10H), 1.5-1.6 (m, 2H), 1.70 (s, 3H), 2.35-2.45 (m, 1H), 2.48-2.56 (m, 1H), 3.4-3.45 (m, 2H), 4.25 (ddd, 1H, J_1=10Hz, J_2=J_3=3.5Hz), 4.51 (d, 1H, J=12Hz), 4.56 (d, 1H, J=12Hz), 4.91 (s, 1H), 4.97 (m, 1H), 7.3-7.4 (m, 5H); *IR* (neat) 3450, 2920, 2850, 1710, 1640, 1450, 1360, 1115, 1090, 895, 735, 700 cm^{-1}; *HRMS* m/z 347.2560 (347.2584 calcd for $C_{22}H_{35}O_3$, M^++1).

22: Yield 32 % (method B); ^1H NMR ($CDCl_3$) δ 0.88 (t, 3H, J=7Hz), 1.3 (br, 10H), 1.45-1.55 (m, 2H), 1.76 (s, 3H), 2.33 (ddd, 1H, J_1=10Hz, J_2=J_3=7Hz), 2.51 (ddd, 1H, J_1=10Hz, J_2=J_3=7Hz), 3.4-3.5 (m, 2H), 3.51 (dd, 1H, J_1=10Hz, J_2=4Hz), 4.25-4.3 (m, 1H), 4.48 (d, 1H, J=12Hz), 4.54 (d, 1H, J=12Hz), 5.01 (s, 1H), 5.08 (m, 1H), 7.3-7.4 (m, 5H); *IR* (neat) 3480, 2930, 2860, 1710, 1640, 1450, 1360, 1105, 890, 735, 700 cm^{-1}; *HRMS* m/z 328.2374 (328.2400 calcd for $C_{22}H_{32}O_2$, M^+-H_2O).

A typical procedure for the reduction is described for compound **4**: $LiBEt_3H$ (1.0 M / THF, 35 ml) was added slowly to **4** (5.77 g, 14.0 mmol) in THF (30 ml) at -78 °C and stirred for 1 h. The reaction was stopped by slow addition of 3 N NaOH (0.5 ml). The mixture was warmed to 0 °C, to which was added slowly 3 N NaOH (10 ml) and 30 % H_2O_2 (30 ml) and stirred for 1 h. Extraction followed by column chromatography (hexane/AcOEt=4/1) gave **11** (5.42 g, 95 %) as a single isomer. $[\alpha]_D^{28}$ -8.4° (c 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.08(s, 9H), 0.87 (t, 3H, J=7Hz), 1.2-1.3 (m, 14H), 2.50 (dd, 1H, J_1=3Hz, J_2=10Hz), 2.7 (br, 1H), 2.9 (br, 1H), 3.29 (dd, 1H, J_1=9Hz, J_2=3Hz), 3.55 (dd, 1H, J_1=9Hz, J_2=8Hz), 3.8 (br, 1H), 4.19 (d, 1H, J=8Hz), 4.21 (d, 1H, J=8Hz), 4.50 (s, 2H), 5.57 (d, 1H, J=2Hz), 5.76 (d, 1H, J=2Hz), 7.2-7.4 (m, 5H); ^{13}C NMR ($CDCl_3$) δ -1.1, 14.1, 22.7, 26.6, 29.3, 29.6, 29.7, 31.9, 33.0, 50.6, 71.5, 72.4, 73.27, 73.34, 127.8, 127.9, 128.1, 128.5, 137.8, 149.8; *IR* (neat) 3450, 2900, 2850, 1445, 1400, 1360, 1240, 1080, 1025, 930, 835, 750, 730, 695 cm^{-1}; *HRMS* m/z 406.2888 (406.2900 calcd for $C_{24}H_{42}O_3Si$, M^+).

The C(2) proton of the corresponding isopropylidene derivatives showed the following coupling constants: $J_{1\text{-}2}$=6.8Hz, $J_{2\text{-}3}$=9.8Hz.

Physical data for the other diols are listed below. The stereostructures of the diols are deduced from the coupling constants of the C(2) proton of the corresponding isopropylidene (Ip) or carbonate (Cb) derivatives, which are also added at the end of the data of the each diols

9: ^1H NMR ($CDCl_3$) δ 0.15 (s, 9H), 0.90 (t, 3H, J=7Hz), 1.2-1.4 (m, 14H), 1.8 (br, 1H), 2.0 (br, 1H), 2.61 (ddd, 1H, J_1=J_2=J_3=6Hz), 3.7-3.8 (m, 1H), 3.8-3.9 (m, 1H), 5.70 (d, 1H, J=2Hz), 5.68 (d, 1H, J=2Hz); ^{13}C NMR ($CDCl_3$) δ -1.2, 14.1, 22.7, 26.1, 29.3, 29.6, 29.7, 31.9, 34.1, 51.5, 63.4, 72.4, 128.1, 150.9; *IR* (neat) 3350, 2910, 2850, 1635, 1455, 1415, 1370, 1120, 1040, 910, 795 cm^{-1}; *HRMS* m/z 268.2201 (268.2220 calcd for $C_{16}H_{32}OSi$, M^+-H_2O); [Cb: $J_{1\text{-}2}$=4.0Hz, $J_{2\text{-}3}$=4.0Hz, 7.9Hz].

10: ^1H NMR ($CDCl_3$) δ 0.15 (s, 9H), 0.90 (t, 3H, J=7Hz), 1.2-1.4 (m, 14H), 1.8 (br, 1H), 2.0 (br, 1H), 2.61 (ddd, 1H, J_1=J_2=J_3=6Hz), 3.7-3.75 (m, 1H), 3.75-3.8 (m, 1H), 3.8-3.9 (m, 1H), 5.53 (d, 1H, J=2Hz), 5.63 (d, 1H, J=2Hz); ^{13}C NMR ($CDCl_3$) δ -1.6, 14.1, 22.7, 25.6, 29.3, 29.5, 29.6, 31.9, 35.9, 51.1, 66.5, 76.7, 126.3, 150.8; *IR* (neat) 3350, 2910, 2850, 1635, 1455, 1415, 1370, 1120, 1040, 910, 795 cm^{-1}; *HRMS* m/z 285.2252 (285.2248 calcd for $C_{16}H_{33}O_2Si$, M^+-1); [Cb: $J_{1\text{-}2}$=10.8Hz, $J_{2\text{-}3}$=4.9Hz, 10.8Hz].

12: ^1H NMR ($CDCl_3$) δ 0.07 (s, 9H), 0.87 (t, 3H, J=7Hz), 1.2-1.4 (m, 14H), 1.4-1.7 (m, 2H), 2.31 (dd, 1H, J_1=J_2=9.5Hz), 3.27 (dd, 1H, J_1=8Hz, J_2=9Hz), 3.47 (dd, 1H, J_1=2.5Hz, J_2=9Hz), 3.87 (dd, 1H, J_1=J_2=9Hz), 4.0-4.2 (m, 1H), 4.48 (d, 1H, J=12Hz), 4.53 (d, 1H, J=12Hz), 5.49 (d, 1H, J=2Hz), 5.64 (d, 1H, J=2Hz), 7.2-7.4 (m, 5H); ^{13}C NMR ($CDCl_3$) δ -0.6, 14.1, 22.7, 25.6, 29.3, 29.6, 29.7, 31.9, 35.7, 54.0, 73.1, 73.3, 75.5, 75.8, 127.88, 127.93, 128.5, 137.7, 150.9; *IR* (neat) 3425, 2905, 2845, 1490, 1445, 1400, 1360, 1240, 1200, 1090, 930, 830, 750, 730, 695 cm^{-1}; *HRMS* m/z 407.2969 (407.2978 calcd for $C_{24}H_{43}O_3Si$, M^++1); [Ip: $J_{1\text{-}2}$=$J_{2\text{-}3}$=10.7Hz].

13: ^1H NMR ($CDCl_3$) δ 0.11 (s, 9H), 0.88 (t, 3H, J=7Hz), 1.2-1.4 (m, 14H), 2.3 (br, 1H), 2.38 (dd, 1H, J_1=J_2=5Hz), 2.5 (br, 1H), 3.4-3.5 (m, 2H), 3.9-4.0 (m, 1H), 4.1-4.2 (m, 1H), 4.54 (s, 2H), 5.74 (d, 1H, J=2.5Hz), 6.03 (d, 1H, J=2.5Hz), 7.35 (s, 5H); ^{13}C NMR ($CDCl_3$) δ -0.4, 14.2, 22.7, 26.1, 29.3, 29.6, 29.7, 31.9, 35.3, 53.0, 72.1, 72.9, 73.5, 127.88, 127.89, 128.5, 131.2, 137.8, 149.6; *IR* (neat) 3425, 2905, 2845, 1490, 1445, 1240, 1200, 1090, 1020, 930, 830, 750, 730, 695 cm^{-1}; *HRMS* m/z 407.2964 (407.2979 calcd for $C_{24}H_{43}O_3Si$, M^++1); [Ip: $J_{1\text{-}2}$=2.5Hz, $J_{2\text{-}3}$=2.0Hz].

14: This compound was isolated from a mixture of **13**/**14** (4/1) obtained by the reduction of **5** with $LiAlH_4$ in refluxing THF; ^1H NMR ($CDCl_3$) δ 0.09 (s, 9H), 0.88 (t, 3H, J=7Hz), 1.2-1.4 (m, 14H), 2.0 (br, 1H), 2.43 (dd, 1H, J_1=3Hz, J_2=9Hz), 3.0 (br, 1H), 3.5-3.6 (m, 2H), 3.8-3.9 (m, 1H), 4.1-4.2 (m, 1H), 4.52 (d, 1H, J=12Hz), 4.56 (d, 1H, J=12Hz), 5.58 (d, 1H, J=2.5Hz), 5.78 (d, 1H, J=2.5Hz), 7.3 (s, 5H); ^{13}C NMR ($CDCl_3$) δ -1.1, 14.1, 22.7, 25.9, 29.3, 29.6, 29.7, 31.9, 35.8, 71.4, 72.2, 72.8, 73.5, 127.9, 128.5, 128.6, 137.8, 150.2; *IR* (neat) 3425, 2900, 2840, 1705, 1445, 1400, 1360, 1240, 1080, 1020, 920, 900, 830, 800, 720, 690 cm^{-1}; *HRMS* m/z 407.2986 (407.2979 calcd for $C_{24}H_{43}O_3Si$, M^++1); [Ip: $J_{1\text{-}2}$=9.3Hz, $J_{2\text{-}3}$=6.4Hz].

15: ^1H NMR ($CDCl_3$) δ 0.88 (t, 3H, J=7Hz), 1.0-1.6 (m, 14H), 2.0 (br, 2H), 2.2-2.4 (m, 1H), 3.6-3.9 (m, 3H), 5.19 (d, 1H, J=18Hz), 5.27 (d, 1H, J=10Hz), 5.86 (ddd, 1H, J_1=9Hz, J_2=10Hz, J_3=18Hz); ^{13}C NMR ($CDCl_3$) δ 14.1, 22.7, 25.8, 29.2, 29.5, 29.6, 31.8, 35.0, 50.8, 64.8, 72.9, 119.1, 134.8; *IR* (neat) 3350, 2910, 2850, 1635, 1455, 1415, 1370, 1120, 1040, 995, 910 cm^{-1}; *HRMS* m/z 215.2029 (215.2009 calcd for $C_{13}H_{27}O_2$, M^++1); [Cb: $J_{1\text{-}2}$=3.0Hz, $J_{2\text{-}3}$=3.0Hz, 4.0Hz, J=9.0Hz (coupling with the vinyl proton)].

16: ^1H NMR ($CDCl_3$) δ 0.88 (t, 3H, J=7Hz), 1.1-1.7 (m, 14H), 2.2 (br, 1H), 2.3-2.4 (m, 1H), 2.45 (br, 1H), 3.6-3.9 (m, 3H), 5.1-5.2 (m, 2H), 5.6-5.7 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 14.1, 22.7, 25.3, 29.3, 29.5, 29.6, 31.9, 35.5, 51.6, 65.2, 74.7, 118.1, 136.2; *IR* (neat) 3310, 2910, 2850, 1630,

1455, 1125, 1050, 910 cm^{-1}; HRMS m/z 215.2028 (215.2009 calcd for $C_{13}H_{27}O_2$, M^++1); [Cb: J_{1-2}=8Hz, J_{2-3}=8Hz, 11Hz, J=8Hz (coupling with the vinyl proton)].

17: $[\alpha]_D^{25}$ -19° (c 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.87 (t, 3H, J=7Hz), 1.1-1.5 (m, 14H), 2.22 (t, 1H, J=8Hz), 2.6 (br, 1H), 2.9 (br, 1H), 3.42 (dd, 1H, J_1=7Hz, J_2=10Hz), 3.56 (dd, 1H, J_1=3Hz, J_2=9Hz), 3.9-4.0 (m, 2H), 4.52 (d, 1H, J=12Hz), 4.55 (d, 1H, J=12Hz), 5.08 (dd, 1H, J_1=1.5Hz, J_2=17Hz), 5.15 (dd, 1H, J_1=1.5Hz, J_2=10.5Hz), 5.76 (ddd, 1H, J_1=1.5Hz, J_2=10.5Hz, J_3=17Hz), 7.3 (s, 5H); ^{13}C NMR ($CDCl_3$) δ 14.1, 22.7, 26.0, 29.3, 29.6, 29.7, 31.9, 34.6, 51.5, 71.0, 71.3, 73.0, 73.4, 118.8, 127.8, 128.5, 134.5, 137.9; IR (neat) 3520, 2820, 2850, 1445, 1240, 1090, 930, 835, 750, 730, 695 cm^{-1}; HRMS m/z 334.2490 (304.2505 calcd for $C_{21}H_{34}O_3$, M^+); [Ip: J_{1-2}=5Hz, J_{2-3}=8Hz, J=10Hz (coupling with the vinyl proton)].

18: $[\alpha]_D^{29}$ +7.4° (c 0.99, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.87 (t, 3H, J=7Hz), 1.26-1.62 (m, 14H), 2.26 (ddd, 1H, J_1=J_2=J_3=9Hz), 3.1 (br, 1H), 3.38 (dd, 1H, J_1=7Hz, J_2=10Hz), 3.57 (dd, 1H, J_1=3Hz, J_2=10Hz), 3.8 (br, 1H), 3.8 (br, 1H), 3.9 (br, 1H), 4.51 (d, 1H, J=12Hz), 4.55 (d, 1H, J=12 Hz), 5.08 (dd, 1H, J_1=2Hz, J_2=10Hz), 5.10 (dd, 1H, J_1=2Hz, J_2=9Hz), 5.45 (ddd, 1H, J_1=J_2=10.5Hz, J_3=16.5Hz), 7.3 (s, 5H); ^{13}C NMR ($CDCl_3$) δ 14.1, 22.7, 25.1, 29.3, 29.6, 29.7, 31.9, 34.9, 53.3, 72.9, 73.3, 73.4, 73.7, 118.7, 127.8, 127.9, 128.9, 135.0, 137.8; IR (neat) 3400, 3075, 3025, 2920, 2850, 1635, 1490, 1450, 1360, 1200, 1100, 1025, 995, 915, 735, 695 cm^{-1}; HRMS m/z 316.2410 (316.2401 calcd for $C_{21}H_{32}O_2$, M^+-H_2O); [Ip: J_{1-2}=J_{2-3}=10Hz, J=10Hz(coupling with the vinyl proton)].

19: ^1H NMR ($CDCl_3$) δ 0.88 (t, 3H, J=7Hz), 1.0-1.6 (m, 14H), 2.10 (ddd, 1H, J_1=J_2=2.5Hz, J_3=10Hz), 2.9 (br, 2H), 3.44 (d, 2H, J=6.5Hz), 3.85 (br, 1H), 4.1 (br, 1H), 4.51 (d, 1H, J=12Hz), 4.56 (d, 1H, J=12Hz), 5.07 (dd, 1H, J_1=2Hz, J_2=18Hz), 5.26 (dd, 1H, J_1=2Hz, J_2=10.5Hz), 5.99 (ddd, 1H, J_1=10Hz, J_2=10.5Hz, J_3=18Hz), 7.2-7.4 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 14.1, 22.7, 25.7, 29.3, 29.5, 29.6, 31.9, 35.1, 50.7, 72.9, 73.4, 73.7, 74.6, 119.8, 127.80, 127.84, 128.5, 132.6, 137.8; IR (neat) 3400, 3060, 3025, 2910, 2850, 1630, 1495, 1445, 1090, 995, 910, 735, 695 cm^{-1}; HRMS m/z 334.2495 (334.2506 calcd for $C_{21}H_{34}O_3$, M^+); [Ip: J_{1-2}=J_{2-3}=2Hz, J=10.5Hz (coupling with the vinyl proton)].

20: ^1H NMR ($CDCl_3$) δ 0.88 (t, 1H, J=7Hz), 1.0-1.7 (m, 14H), 2.1-2.2 (m, 1H), 2.5 (br, 1H), 2.8 (br, 1H), 3.4-3.5 (m, 1H), 3.7-3.8 (m, 1H), 4.2-4.3 (m, 1H), 4.52 (d, 1H, J=12Hz), 4.57 (d, 1H, J=12Hz), 5.08 (dd, 1H, J_1=2Hz, J_2=17.5Hz), 5.16 (dd, 1H, J_1=2Hz, J_2=10.5Hz), 5.86 (ddd, J_1=10Hz, J_2=10.5Hz, J_3=17.5Hz), 7.15-7.40 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 14.1, 22.7, 25.7, 29.3, 29.57, 29.63, 31.9, 35.4, 51.7, 70.1, 73.0, 118.3, 127.7, 127.8, 128.5, 135.3, 137.9; IR (neat) 3400, 3060, 3010, 2910, 2850, 1705, 1630, 1490, 1445, 1085, 995, 910, 800, 730, 695 cm^{-1}; HRMS m/z 334.2484 (334.2505 calcd for $C_{21}H_{34}O_3$, M^+); [Ip: J_{1-2}=8.5Hz, J_{2-3}=5.5Hz, J=10.5Hz(coupling with the vinyl proton)].

23: ^1H NMR ($CDCl_3$) δ0.87(t, 3H, J=6.5Hz), 1.3 (br, 12H), 1.4-1.6 (m, 2H), 1.77 (s, 3H), 2.0 (br, 2H), 2.18 (dd, 1H, J_1=10Hz, J_2=3Hz), 3.39 (dd, 1H, J_1=9Hz, J_2=7Hz), 3.60 (dd, 1H, J_1=9Hz, J_2=3Hz), 3.95-4.0 (m, 1H), 4.13 (ddd, 1H, J_1=10Hz, J_2=J_3=3Hz), 4.53 (d, 1H, J=12Hz), 4.56(d, 1H, J=12Hz), 4.75 (s, 1H), 4.89 (m, 1H), 7.3-7.4 (m, 5H); IR (neat) 3450, 2920, 2850, 1640, 1450, 1360, 1070, 1020, 890, 735, 695 cm^{-1}; HRMS m/z 349.2731 (349.2739 calcd for $C_{22}H_{37}O_3$, M^++1); [Ip: J_{1-2}=5.4Hz, J_{2-3}=8.8Hz].

24: ^1H NMR ($CDCl_3$) δ0.87 (t, 3H, J=7Hz), 1.3 (br, 12H), 1.4-1.55 (m, 2H), 1.62(s, 3H), 2.1 (br, 2H), 2.12-2.18 (m, 1H), 3.35 (dd, 1H, J_1=10Hz, J_2=7Hz), 3.52 (dd, 1H, J_1=10Hz, J_2=3Hz), 3.88 (ddd, 1H, J_1=J_2=8Hz, J_3=2Hz), 4.07 (ddd, 1H, J_1=11Hz, J_2=7Hz, J_3=3Hz), 4.52 (d, 1H, J=12Hz), 4.54 (d, 1H, J=12Hz), 4.73 (s, 1H), 4.79 (s, 1H), 7.3-7.4 (m, 5H); IR (neat) 3360, 2925, 2850, 1725, 1640, 1450, 1270, 1200, 1100, 890, 735, 695 cm^{-1}; HRMS m/z 331.2631 (331.2635 calcd for $C_{22}H_{35}O_2$, M^+-OH); [Ip:J_{1-2}=J_{2-3}=10.7Hz].

25: ^1H NMR ($CDCl_3$) δ0.88 (t, 3H, J=7Hz), 1.3 (br, 12H), 1.4-1.6 (m, 2H), 1.89 (s, 3H), 2.15 (dd, 1H, J_1=J_2=5Hz), 2.3 (br, 2H), 3.46-3.54 (m, 2H), 3.88-3.92 (m, 1H), 4.14 (dd, 1H, J_1=J_2=5Hz), 4.55 (s, 2H), 4.82 (d, 1H, J=2Hz), 5.00 (s, 1H), 7.3-7.4 (m, 5H); IR (neat) 3400, 2920, 2850, 1635, 1450, 1360, 1090, 800, 730, 690 cm^{-1}; HRMS m/z 330.2552 (330.2556 calcd for $C_{22}H_{34}O_2$, M^+-H_2O); [Ip: J_{1-2}=J_{2-3}=3Hz].

Experimental procedures related to the synthesis of isoavenaciolide (35b).

The starting chiral epoxy alcohol 27 was obtained by the Sharpless oxidation. The enantiomeric purity (>95 %ee) was ascertained by the shift study according to ref. 20.

Synthesis of 28: DMSO (1.32 g, 16.8 mmol) in CH_2Cl_2 (5 ml) was added slowly to a solution of $(COCl)_2$ (1.09 g, 8.55 mmol) in CH_2Cl_2 (5 ml) and stirred for 5 min at -78 °C. To the mixture was added 27 (545 mg, 12.8 mmol) in CH_2Cl_2 (10 ml), stirred for 5 min, followed by the addition of Et_3N (2.29 g, 22.6 mmol) in CH_2Cl_2 (10 ml). After 10 min, the solution was gradually warmed to 0 °C. The reaction mixture was re-cooled to -78 °C and diluted with THF (20 ml), to which was added n-$C_8H_{17}MgBr$ (0.89 M / THF, 21 ml) and stirred for 1 h and quenched with pH 7 phosphate buffer. Extraction and column chromatography (hexane/AcOEt= 82/18) gave the alcohol, which was oxidized by the Swern procedure. Usual workup followed by column chromatography (hexane/AcOEt=8/1) afforded 28 (630mg, 73%) as an oil. $[\alpha]_D^{26}$ +13° (c 0.99, $CHCl_3$); ^1H NMR (CCl_4) δ 0.86 (t, 3H, J=7Hz), 1.0-1.7 (m, 12H), 2.2-2.3 (m, 2H), 3.15 (m, 2H), 3.2-3.5 (m, 1H), 3.6-3.8 (m, 1H), 4.50 (s, 2H), 7.25 (s, 5H); IR (neat) 2925, 2850, 1710, 1495, 1360, 1095, 1025, 880, 735, 695 cm^{-1}; HRMS m/z 305.2125 (305.2115 calcd for $C_{19}H_{29}O_3$, M^++1).

Synthesis of 1: n-BuLi (1.58 M / hexane, 2.62 ml, 4.14 mmol) was added dropwise to a solution of H_2C=C(Br)$SiMe_3$ (822 mg, 4.59 mmol) in THF (5 ml) at -78 °C, to which was added slowly 28 (630 mg, 2.07 mmol) in THF (5 ml). After 20 min, pH 7 phosphate buffer was added. Extraction and column chromatography afforded 1 (717 mg, 85.6 %) as an oil. ^1H NMR (CCl_4) δ 0.10 (s, 9H), 0.87 (t, 3H, J=7Hz), 1.0-1.7 (m, 14H), 1.78 (s, 1H), 2.90 (d, 1H, J=2Hz), 3.0-3.2 (m, 1H), 3.40 (dd, 1H, J_1=4.5Hz, J_2=10Hz), 3.59 (dd, 1H, J_1=4.5Hz, J_2=10Hz), 4.47 (s, 2H), 5.43 (d, 1H, J=1.5Hz), 5.63 (d,

1H, J=1.5Hz), 7.20 (s, 5H); IR (neat) 3430, 2990, 2840, 1445, 1355, 1240, 1100, 835, 730, 695 cm^{-1}; HRMS m/z 405.2781 (405.2822 calcd for $C_{24}H_{41}O_3Si$, M^++1).

Synthesis of 17: To CsF (4.25 g, 28 mmol), flame-dried in vacuo, was added a solution of 11 (2.34 g, 5.75 mmol) in DMF (50 ml), and the solution was stirred for 2.5 h at 100 °C. Extractive workup and evaporation gave 17 (2.09 g) which was identical with the sample of 17 obtained as one of the isomers formed by the reduction of 7. This was used without purification in the next step.

Synthesis of 30b: A solution of crude 17 (2.09 g, 5.75 mmol), 2,2-dimethoxypropane (7 ml, 58.8 mmol) and a catalytic amount of p-TsOH in CH_2Cl_2 (15 ml) was stirred overnight. The mixture was poured into cold 4 % $NaHCO_3$ solution, and extraction followed by column chromatography (hexane /AcOEt=12/1) afforded 30b (2.05 g, 95 % from 11) as a colorless oil. $[\alpha]_D^{26}$ -2.4° (c 1.1, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.87 (t, 3H, J=7Hz), 1.2-1.4 (m, 14H), 1.38 (s, 3H), 1.40 (s, 3H), 2.46 (ddd, 1H, J_1=10Hz, J_2=8Hz, J_3=5Hz), 3.52 (m, 2H), 3.83 (m, 1H), 4.57 (d, 1H, J=8Hz), 4.60 (d, 1H, J=8Hz); 4.89 (dd, 1H, J_1=17Hz, J_2=1.5Hz), 5.04 (dd, 1H, J_1=10Hz, J_2=1.5Hz), 5.82 (ddd, 1H, J_1=17Hz, J_2=J_3=10Hz), 7.32 (s, 5H); ^{13}C NMR ($CDCl_3$) δ 14.1, 19.5, 22.7, 24.8, 29.5, 30.0, 31.9, 45.0, 71.5, 71.6, 72.1, 73.4, 99.1, 118.6, 127.6, 127.8, 128.4, 132.6, 138.2; IR (neat) 3075, 2925, 2850, 1635, 1490, 1380, 1220, 1170, 1110, 1070, 1000, 810, 740, 700 cm^{-1}; HRMS m/z 359.2590 (359.2584 calcd for $C_{23}H_{35}O_3$, M^+-CH_3).

Synthesis of 31b: 2-Methyl-2-butene (6.17 g, 87.9 mmol) in THF (15 ml) was added to BH_3 (1.0 M / THF, 44 ml) at -20 °C. To the mixture was added 30b (2.05 g, 54.8 mmol) in THF (20 ml) and stirred for 1 h. The reaction was stopped by adding 3 N NaOH (16 ml) followed by 30 % H_2O_2 (15 ml). After stirring for 0.5 h, the mixture was extractively worked up. Purification by column chromatography (hexane/AcOEt=2.5/1) gave 31b (1.84 g, 86 %) as an oil. $[\alpha]_D^{25}$ -0.57° (c 1.1, $CHCl_3$); ^{1}H NMR (CCl_4) δ 0.81 (t, 3H, J=7Hz), 1.1-1.4 (m, 14H), 1.26 (s, 3H), 1.29 (s, 3H), 1.5-1.7 (m, 3H), 2.2 (br, 1H), 3.35-3.45 (m, 1H), 3.45-3.6 (m, 3H), 3.7-3.8 (m, 2H), 4.48 (d, 1H, J=12Hz), 4.54 (d, 1H, J=12Hz), 7.23 (s, 5H); IR (neat) 3400, 2925, 2850, 1450, 1365, 1250, 1220, 1200, 1165, 1050, 1010, 940, 830, 740, 700 cm^{-1}; HRMS m/z 377.2697 (377.2689 calcd for $C_{23}H_{37}O_4$, M^+-CH_3).

Synthesis of 32b: Application of the Swern procedure to 31b (150 mg, 0.38 mmol) gave the corresponding aldehyde, which was dissolved in a mixture of t-BuOH (1.5 ml), water (1 ml) and 2-methyl-2-butene (0.7 ml), to which was added NaH_2PO_4 (199 mg) and $NaClO_2$ (105 mg). After stirring for 10 min, cold 10 % tartaric acid solution was added. Extraction and evaporation gave the carboxylic acid, which was dissolved CH_2Cl_2 (3 ml), to which was added Et_3N (52 mg) in CH_2Cl_2 (0.75 ml) at 0 °C. $ClCO_2Et$ (70 mg) in CH_2Cl_2 (1 ml) was added and the mixture stirred for 10 min, to which was added 4-DMAP (64 mg) and stirred for 10 min. Extraction and purification on TLC (hexane/AcOEt= 6/1) gave 32b (131 mg, 79 %) as an oil. $[\alpha]_D^{25}$ 0.0° (c 1.1, $CHCl_3$); ^{1}H NMR (CCl_4) δ 0.7-1.7 (m, 26H), 1.8-2.6 (m, 3H), 3.3-3.9 (m, 4H), 3.93 (q, 2H, J=7.5Hz), 4.76 (s, 2H), 7.16 (s, 5H); IR (neat) 2900, 2830, 1725, 1445, 1370, 1220, 1145, 1100, 1020, 950, 900, 730, 695 cm^{-1}; HRMS m/z 419.2778 (419.2794 calcd for $C_{25}H_{39}O_5$, M^+-CH_3).

Synthesis of 33b: Benzyl ether 32b (141 mg, 0.33 mmol) in EtOH (3 ml) was stirred overnight under a hydrogen atmosphere in the presence of 5 % Pd/C. Filtration and evaporation gave the primary alcohol as an oil. Without purification, the alcohol was oxidized by the Swern procedure to give the corresponding aldehyde, which was treated with 1 N H_2SO_4 (1 ml) in 1,4-dioxane (3 ml) for 4 h. Extraction followed by column chromatography (hexane/AcOEt=2/1) gave 33b (57.2 mg, 69 %) as white crystals. $[\alpha]_D^{25}$ -40° (c 1.1, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.88 (t, 3H, J=7Hz), 1.2-1.4 (m, 12H), 1.6-1.7 (m, 2H), 2.4-2.7 (m, 2H), 2.62 (s, 1H), 3.13 (ddd, 1H, J_1=4Hz, J_2=5Hz, J_3=10Hz), 4.3-4.5 (m, 1H), 4.93 (d, 1H, J=7Hz), 5.45 (s, 1H); IR (neat) 3420, 2910, 2850, 1775, 1765, 1740, 1450, 1410, 1345, 1160, 1080, 1040, 960, 940, 890 cm^{-1}; HRMS m/z 257.1733 (257.1752 calcd for $C_{14}H_{25}O_4$, M^++1).

Synthesis of 34b: The Swern procedure was applied to 33b (9.6 mg, 0.037 mmol). Purification by column chromatography (hexane/AcOEt=3/2) gave 34b (9.1 mg, 96 %) as white crystals. Mp 109-111 °C; $[\alpha]_D^{25}$ -21° (c 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.89 (t, 3H, J=7Hz), 1.1-1.4 (m, 12H), 1.5-1.8 (m, 2H), 2.63 (d, 1H, J=10Hz), 3.47 (dddd, 1H, J_1=6Hz, J_2=J_3=J_4=9Hz), 4.5-4.7 (m, 1H), 5.15 (d, 1H, J=8Hz); ^{13}C NMR ($CDCl_3$) δ 14.1, 22.6, 25.5, 26.9, 29.1, 29.2, 29.3, 31.4, 31.8, 39.4, 78.0, 170.5, 173.7; IR (KBr) 2920, 2850, 1780, 1460, 1360, 1315, 1290, 1210, 1160, 1140, 1080, 1060, 995, 980, 940, 910, 870, 760, 725, 650, 570, 555, 530, 500 cm^{-1}; HRMS m/z 255.1621 (255.1595 calcd for $C_{14}H_{23}O_4$, M^++1).

Synthesis of Isoavenaciolide (35b): The procedure of F. Johnson was applied to 34b (58 mg, 0.23 mmol). Three recrystallizations from ether/hexane gave isoavenaciolide (35b) (16.2 mg, 10 %) as a white solid. This material was identical in all respects with the natural sample. Mp 129-130 °C; $[\alpha]_D^{32}$ -152° (c 0.38, EtOH); ^{1}H NMR ($CDCl_3$) δ 0.88 (t, 3H, J=8.5Hz), 1.2-1.8 (m, 14H), 3.95-4.05 (m, 1H), 4.7-4.8 (m, 1H), 5.11 (d, 1H, J=9Hz), 5.88 (d, 1H, J=2Hz), 6.61 (d, J=3Hz); IR (KBr) 2905, 2845, 1755, 1360, 1275, 1220, 1115, 1050, 985, 975, 925, 810, 655, 610 cm^{-1}; HRMS m/z 266.1519 (266.1517 calcd for $C_{15}H_{22}O_4$, M^+).

Experimental procedures related to the synthesis of avenaciolide (35a).

Following essentially the same procedures as above, synthesis of avenaciolide (35a) was performed from 28. Data of the intermediates and the differences of the procedures follow.

Synthesis of 2: To a solution of 28 (840 mg, 2.76 mmol) in THF (28 ml) was added slowly vinylmagnesium bromide (0.88 M / THF, 8.3 ml) at -78 °C and stirred for 0.5 h and quenched with pH 7 buffer. Extraction and evaporation gave the alcohol, which was dissolved in DMF (20ml), to which was added imidazole (931 mg, 13.6 mmol) and TMSCl (1.19 g, 10.9 mmol) in DMF (20 ml) and stirred overnight at 40 °C. Extraction and column chromatography (hexane/AcOEt=95/5) gave 2 (878 mg,

79.1 %) as an oil. ^{1}H NMR (CCl_4) δ 0.13 (s, 9H), 0.60-0.97 (m, 3H), 1.0-1.8 (m, 14H), 2.60 (d, 1H, J=2Hz), 2.8-3.0 (m, 1H), 3.2-3.6 (m, 1H), 4.36 (s, 2H), 4.98 (dd, 1H, J_1=2Hz, J_2=10Hz), 5.12 (dd, 1H, J_1=2Hz, J_2=18Hz), 5.64 (dd, 1H, J_1=10Hz, J_2=18Hz), 7.10 (s, 5H); IR (neat) 2920, 2850, 1445, 1400, 1395, 1245, 1100, 1040, 920, 895, 835, 750, 730, 695 cm^{-1}; HRMS m/z 405.2840 (405.2823 calcd for $C_{23}H_{41}O_3Si$, M^++1).

30a: Yield: quantitative; $[\alpha]_D^{28}$ +8.5° (c 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.87 (t, 3H, J=7Hz), 1.35 (br, 12H), 1.44 (s, 3H), 1.47 (s, 3H), 1.5-1.6 (m, 2H), 2.03 (ddd, 1H, J_1=J_2=J_3=10Hz), 3.47 (dd, 1H, J_1=6Hz, J_2=11Hz), 3.58 (dd, 1H, J_1=2Hz, J_2=11Hz), 3.62 (ddd, 1H, J_1=2Hz, J_2=10Hz, J_3=11Hz), 3.85 (ddd, 1H, J_1=2Hz, J_2=6Hz, J_3=10Hz), 4.5-4.6 (m, 2H), 5.08 (dd, 1H, J_1=1.5Hz, J_2=16Hz), 5.11 (dd, 1H, J_1=1.5Hz, J_2=10Hz), 5.82 (ddd, 1H, J_1=9.5Hz, J_2=10Hz, J_3=16Hz), 7.28 (s, 5H); ^{13}C NMR ($CDCl_3$) δ 14.1, 19.5, 22.7, 25.1, 29.3, 29.5, 29.6, 30.1, 31.9, 33.4, 46.8, 71.56, 71.63, 72.4, 73.3, 98.1, 119.4, 127.4, 127.7, 128.2, 135.1, 138.5; IR (neat) 2920, 2840, 1630, 1490, 1475, 1370, 1250, 1195, 1175, 1100, 990, 910, 730, 690 cm^{-1}; HRMS m/z 359.2577 (359.2584 calcd for $C_{23}H_{35}O_3$, M^+-CH_3).

Synthesis of 31a: Hydroboration of 30a (136 mg, 0.37 mmol) with dicyclohexylborane gave 31a (126 mg, 86 %). $[\alpha]_D^{30}$ +15° (c 0.90, $CHCl_3$); ^{1}H NMR (CCl_4) δ 0.7-1.3 (m, 3H), 1.0-1.8 (m, 14H), 2.0 (br, 1H), 3.2-3.9 (m, 6H), 4.50 (s, 2H), 7.30 (s, 5H); IR (neat) 3450, 2900, 2840, 1450, 1375, 1195, 1045, 940, 900, 730, 690 cm^{-1}; HRMS m/z 377.2711 (377.2689 calcd for $C_{23}H_{37}O_4$, M^+-CH_3).

32a: Yield: 74 %; $[\alpha]_D^{30}$ +17° (c 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.88 (t, 3H, J=7Hz), 1.20 (t, 3H, J=7Hz), 1.2-1.6 (m, 14H), 1.41 (s, 3H), 1.45 (s, 3H), 1.8-1.9 (m, 1H), 2.22 (dd, 1H, J_1=4Hz, J_2=17Hz), 2.33 (dd, 1H, J_1=5Hz, J_2=17Hz), 3.54 (dd, 1H, J_1=4Hz, J_2=11Hz), 3.59 (dd, 1H, J_1=5.5Hz, J_2=11Hz), 3.65-3.75 (m, 1H), 3.98 (ddd, 1H, J_1=J_2=4Hz, J_3=11Hz), 4.0-4.1 (m, 2H), 4.52 (d, 1H, J=12Hz), 4.53 (d, 1H, J=12Hz), 7.35 (s, 5H); IR (neat) 2920, 2850, 1730, 1450, 1375, 1255, 1170, 1100, 1020, 885, 730, 695 cm^{-1}; HRMS m/z 419.2771 (419.2794 calcd for $C_{25}H_{39}O_5$, M^+-CH_3).

Synthesis of 33a: This compound was prepared in a similar manner as 33b, except that the cyclization under acidic conditions required a longer reaction time (overnight at 30 °C). Mp 63.5-67 °C; $[\alpha]_D^{28}$ -33° (c 0.80, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.88(t, 3H, J=7Hz), 1.2-1.5 (m, 14H), 2.4-2.9 (m, 4H), 3.9-4.0 (m, 1H), 4.8-4.9 (m, 1H), 5.5-5.6 (m, 1H); IR (KBr) 3420, 2920, 2850, 1755, 1450, 1415, 1350, 1315, 1295, 1245, 1170, 1140, 995, 980, 950, 925, 910, 900 cm^{-1}; HRMS m/z 257.1768 (257.1752 calcd for $C_{14}H_{25}O_4$, M^++1).

34a: Yield: 80 %; $[\alpha]_D^{27}$ -3.5° (c 1.2, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.89 (t, 3H, J=7Hz), 1.3-1.5 (m, 12H), 1.7-1.8 (m, 2H), 2.55 (dd, 1H, J_1=4Hz, J_2=18Hz), 2.94 (dd, 1H, J_1=9.5Hz, J_2=18Hz), 3.0-3.1 (m, 1H), 4.55 (ddd, 1H, J_1=J_2=5Hz, J_3=7.5Hz), 5.01 (d, 1H, J=8Hz); ^{13}C NMR ($CDCl_3$) δ 14.1, 22.6, 24.9, 29.1, 29.2, 29.3, 31.8, 32.8, 35.5, 84.8, 169.8, 173.6; IR(neat) 2920, 2850, 1785, 1455, 1355, 1290, 1210, 1140, 1065, 970, 925, 850, 720 cm^{-1}; HRMS m/z 254.1511 (254.1516 calcd for $C_{14}H_{22}O_4$, M^+).

Synthesis of avenaciolide (35a): Johnson's procedure was applied to 34a (16.6 mg, 0.065 mmol) to afford avenaciolide 35a (5.9 mg, 34 %) as white crystals after recrystallization from ether/pentane. This compound was indistinguishable from the authentic sample. Mp 52.5-54 °C; $[\alpha]_D^{27}$ -41.8° (c 0.54, EtOH); ^{1}H NMR ($CDCl_3$) δ 0.89 (t, 3H, J=7Hz), 1.3-1.5 (m, 12H), 1.8-1.85 (m, 2H), 3.5-3.6 (m, 1H), 4.43 (m, 1H), 5.06 (d, 1H, J=9Hz), 5.88 (d, 1H, J=2Hz), 6.49 (d, 1H, J=2Hz); ^{13}C NMR ($CDCl_3$) δ 14.1, 22.6, 24.8, 29.1, 29.3, 31.8, 36.1, 44.2, 74.3, 85.1, 126.3, 134.6, 167.4, 169.7; IR (KBr) 2910, 2840, 1765, 1660, 1620, 1480, 1380, 1320, 1295, 1265, 1230, 1210, 1110, 1065, 1030, 1015, 1005, 960, 920, 810, 780, 710, 660, 620 cm^{-1}; HRMS m/z 267.1573 (267.1594 calcd for $C_{15}H_{23}O_4$, M^++1).

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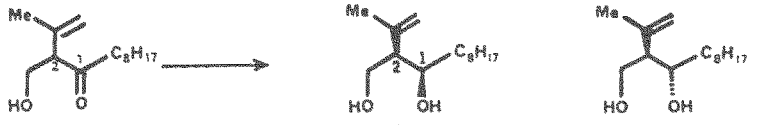

36 → 37 : 38

$LiBEt_3H$ / THF, -78°C >99 : <1

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