Stereoselective Synthesis of Alcohols, L[◇]

Stereoselective Synthesis of a C-15/C-27 Segment of the Venturicidines

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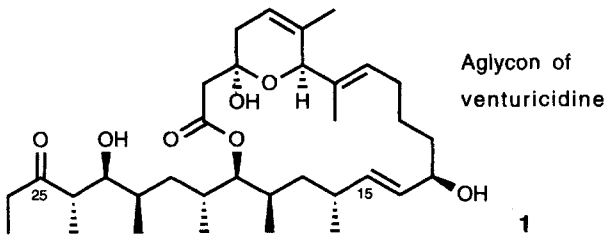
Chain extension of an aldehyde by two "propionate" units has been attained by stereoselective allylboration with the chiral 1-methylbutenyl boronate **3** to give, e.g., the homoallylic alcohol **6**, followed by a regioselective hydroboration/carbonylation procedure to give, e.g., the epimeric aldehydes **8**. The latter were converted into the lactols **10**, which equilibrated to the desired epimer. The lactols could again be subjected to an allylboration reaction, initiating a second round of the chain extension protocol. This technique has been used to synthesize in 15 steps the venturicidene C-15/C-27 segment **23**, containing 8 stereogenic centers with the proper absolute configuration.

The venturicidines **1** are antifungal antibiotics[2] whose structure and absolute configuration were established by X-ray crystallography already in the 1960's[3]. It was only recently that syntheses of the venturicidine aglycon were completed[4,5]. The polypropionate-derived structural segment C-15/C-27 is remarkable, because the sequence of the stereogenic centers resembles that in syndiotactic polypropylene and might have particular conformational properties[6]. In fact, this segment of the molecule is fully extended in the crystalline state[3]. Moreover, this particular sequence of stereogenic centers is an attractive target to develop new and more efficient strategies for stereoselective synthesis. Thus, one strategy based on ring opening of an octalin nucleus has recently been reported[7].



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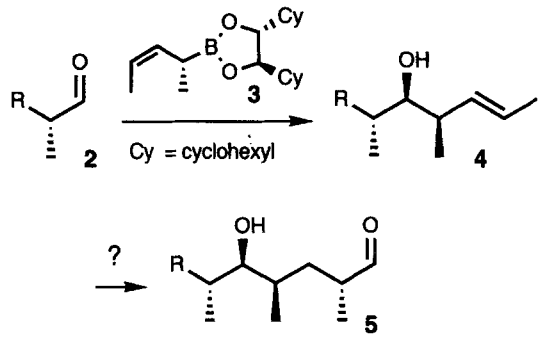
We were interested to develop an iterative procedure for acyclic structures such as that found in the venturicidine C-15/C-27 segment, and we envisaged a sequence of two operations, by which an aldehyde could be extended by two propionate subunits. In the first operation an aldehyde **2** is converted to a homoallylic alcohol **4**[8] under reagent control of diastereoselectivity. Use of the chiral 1-methylbutenyl boronate **3** should guarantee high levels of asymmetric induction[9,10,11].



The second step consists of a stereoselective hydroformylation to convert the alkene **4** into the aldehyde **5**. The latter should be the starting point for the next round of this chain extension protocol. The realization of this plan has been communicated before[12]. We report here on the details of its execution.

Exploratory Studies

The chain elongation of the alkene **4** to the aldehyde **5** is formally a hydroformylation reaction. Hydroformylations of homoallylic alcohols with a terminal alkene have been realized before[13], but little is known about the regio- and stereoselective hydroformylation of internal alkenes[14]. For this reason the indirect hydroformylation sequence developed by Brown[15] seemed attractive to us. We therefore tested the regio- and stereoselectivity of this reaction on the model system **6**[16].

Hydroboration of **6a** with 9-BBN proceeded with full regioselectivity with formation of the alcohol **7a**, while the diastereoselectivity remained modest. We therefore examined briefly the effect of other alcohol-protecting groups on the diastereoselectivity of the reaction. The data recorded

[◇] Part IL: Ref.[1].

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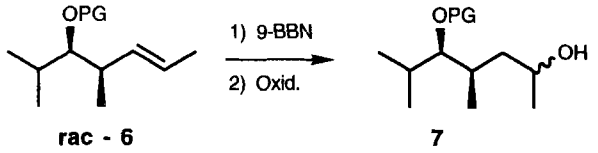
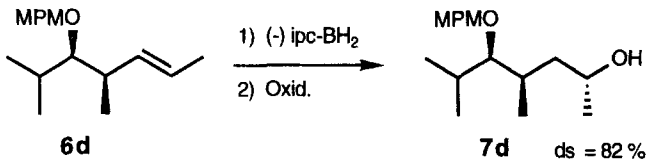


		Yield	Diastereomer Ratio
7a	H	68 %	62 : 38
b	$SiMe_3$	59 %	55 : 45
c	$SiMe_2tBu$	50 %	52 : 48
d	$CH_2C_6H_4OMe$	83 %	61 : 39

for **6b–d** showed no improvement. Next, attempts were made to increase the diastereoselectivity by use of a chiral reagent. This required the use of enantiomerically enriched alcohol **6** or its derivatives. Reaction of the compounds **6b** or **6c** (95% e.e.) with (−)-isopinocampheylborane[17] resulted in low regioselectivity[18]. However, the reaction of **6d** with isopinocampheylborane proceeded with good regioselectivity. The diastereoselectivity was increased by double steroedifferentiation to 82:18. In view of the known sense of asymmetric induction of (−)ipcBH_2[17], this suggests that the major diastereomer of the product has the relative configuration shown for **7d**.

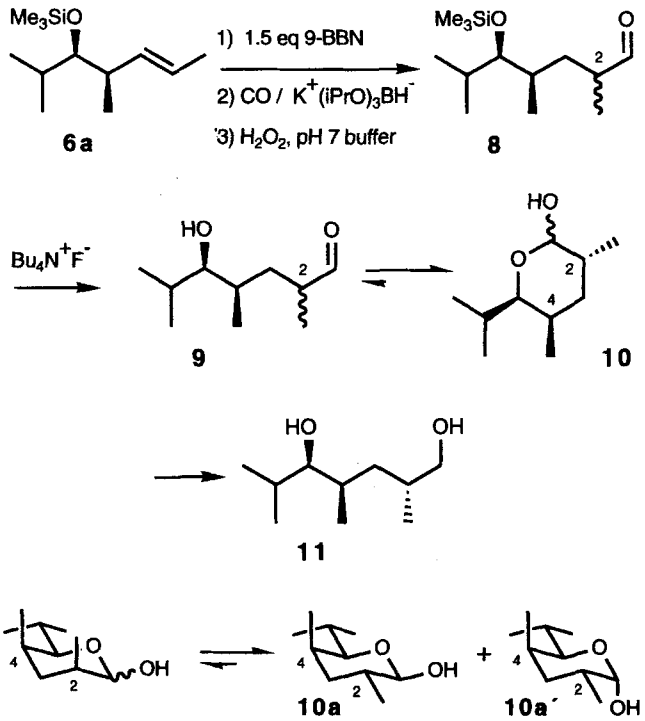


While excellent regioselectivity in the hydroboration reaction could be attained, we postponed further attempts to improve the diastereoselectivity and turned our attention to the hydroformylation step.

Reaction of the alkene **6b** with 9-BBN, followed by treatment with CO and potassium hydrotriisopropoxyborate and an oxidative workup according to Brown[15] furnished the aldehyde **8** in >90% yield as a 55:45 mixture of diastereomers. When applied to the alkenes **6a**, **6c**, or **6d** no hydroformylation could be achieved.

The CH acidity of the aldehyde **8** offers the possibility of epimerisation at the stereocenter C-2. While in the aldehyde **8** there is no driving force to favor a single diastereomer, such a driving force can be installed by desilylation to the hydroxy aldehyde **9**, which cyclizes to the lactols **10**. Epimerisation of the lactols **10** is possible via the substoichiometric equilibrium amounts of the hydroxy aldehyde **9**. Acid-[19] as well as base-catalysed[20] epimerization of such lactols has been reported. The equatorial arrangement of the C-2 methyl group is clearly favored on account of the axial methyl group at C-4.

Thus, on deprotection of the aldehyde **8** with either tetrabutylammonium fluoride or with potassium carbonate in methanol, a 4:1 anomer mixture of the lactols **10** was obtained. Analysis of the ^{1}H-NMR coupling constants suggested that both anomers have the same relative configuration at C-2 and C-4. That this is the case was shown by



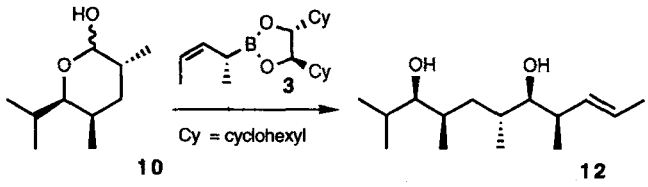
reduction of the anomer mixture of **10** to a configurationally homogeneous diol **11**. Moreover, we subsequently obtained the C-2 epimer of **10** by a different route[21]. Finally, but not of relevance here, the major anomer **10a** is the β-anomer with δ(1-H) = 4.18, whereas **10b** has δ(1-H) = 4.99[22].

Thus, the insufficient diastereoselectivity on hydroboration of the alkene **6** can be remedied by later equilibration at the stage of the lactol **10**, favoring the diastereomer with the desired relative configuration at C-2 and C-4.

The continuation of the iterative chain extension strategy requires that the aldehyde **9** serves as the substrate for the next allylboration reaction (cf. the conversion of **2** to **4**). However, the aldehyde **9** is present only in substoichiometric amounts in equilibrium with the lactol. The very low concentration of the aldehyde should decrease the rate of the bimolecular allylboration reaction. We were, however, encouraged by the report of a successful allylboration of a lactol[23].

In the event, reaction of the enantiomerically enriched lactol **10** with the appropriate enantiomerically enriched 1-methylbutenylboronate **3**[9] could not be achieved at room temperature, nor at temperatures up to 100 °C. However, it was known that the rate of allylboration reactions can be increased by the application of high pressure[11,24]. Reaction of **10** with the allylboronate **3** in petroleum ether for 10 days at 10 kbar and 20 °C proceeded with 65% conversion but rather low product selectivity to give the diol **12** in 34% yield.

We speculated that the ring opening of the lactol **10** to the aldehyde **9** might be rate limiting, and therefore that a catalyst for this step might be beneficial. For this reason we carried out the reaction in the presence of 2-pyridone, a compound known to catalyse the mutarotation of glu-

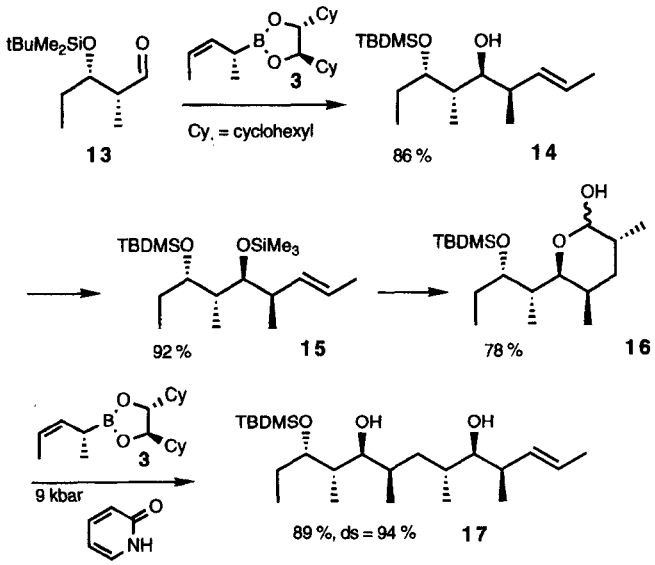


cose[25]. In the presence of pyridone, other parameters remaining the same, both the conversion and selectivity increased to 70% allowing **12** to be obtained in 50% yield, next to recovered starting material.

At this stage we felt confident that the iterative chain extension route would be viable to generate the sequences of stereogenic centers found in the venturicidine C-15/C-27 segment.

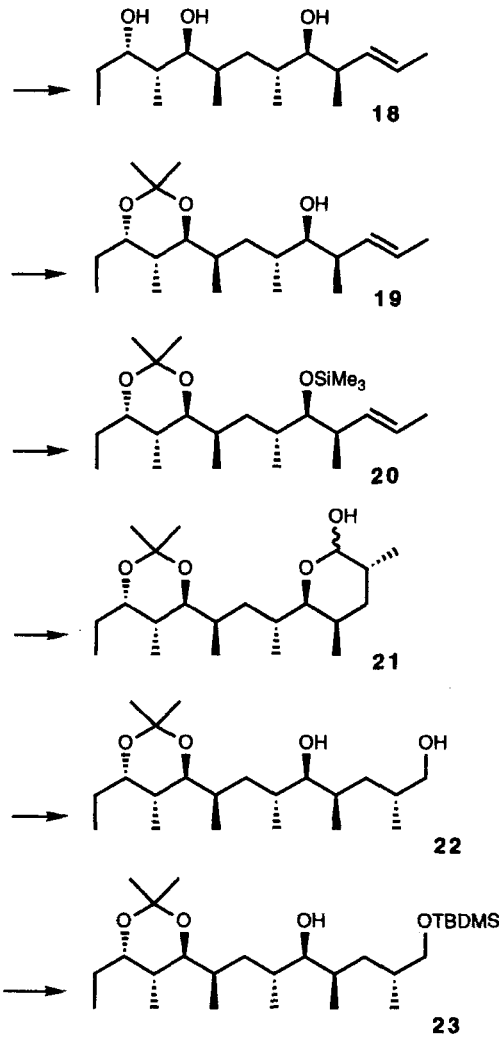
Synthesis of the C-15/C-27 Segment of Venturicidine

After the exploratory studies had been successful, we initiated a stereoselective synthesis of the C-15/C-27 segment of the venturicidines. The plan was to arrive at the compound **23**, a known intermediate in Oishi's synthesis[5] of the venturicidine aglycon. To apply our iterative sequence, the aldehyde **13** was the requisite starting point. Aldehyde **13** can be obtained either from propionaldehyde as described in ref.[26] or from thiodipropionic acid as described in ref.[27].



Reaction of the aldehyde **13** with the (*R*,*R*,*R*)-1-methylbutenylboronate **3** for seven days at room temperature furnished 86% of the homoallylic alcohol **14** as a pure diastereomer. Since the alkene double bond was found to be *E*-configurated, we assume[9,28] that the new stereogenic centers have the configuration as shown. The alcohol **14** was silylated to **15**, the starting material for the hydroformylation sequence. This sequence could be readily effected to give 78% of the lactol **16**. In the course of this reaction sequence, the trimethylsilyl group had to be deprotected selectively in the presence of the *tert*-butyldimethylsilyl group, a transformation which could be achieved with potassium carbonate in refluxing methanol. At this point, the next chain extension had to be performed under high pressure. Reaction of the lactol **16** with the 1-methylbutenylboronate **3** for four days at 9.8 kbar in the presence of 2-pyridone furnished 89% of the desired triol derivative **17**. The stereoselectivity in this step was not quantitative; **17** was obtained as a 94:6 diastereomer mixture. As the alkene double bond of the major diastereomer was again *E*-configurated, we assume[9,28] that the new stereogenic centers have the configuration as shown (the minor diastereomer had a *Z* double bond!).

To establish the protective group pattern present in the target molecule **23**, a number of refunctionalization steps had to be performed. First, **17** was desilylated to give the triol **18** (100%). The latter was converted into the acetonide **19** (87%). This allowed us to establish the relative configuration at C-23 and C-25 (venturicidine numbering), as **19** showed the diagnostic[29] ^{13}C-chemical shifts for a *trans*-disubstituted diol acetonide; i.e. signals of *gem*-dimethyl groups at $\delta = 23.6$ and the acetal carbon at $\delta = 100.0$.



Next, the remaining alcohol function was silylated to give the alkene **20** in quantitative yield. To continue in our chain extension sequence, the alkene **20** was subjected to the indirect hydroformylation reaction followed by formation of the lactol **21** under epimerizing conditions (78%). With all

stereogenic centers properly set up, the lactol was reduced to the diol **22** (91%). Finally, the primary alcohol function was protected as *tert*-butyldimethylsilyl ether to give **23** (95%), the intermediate in Oishi's synthesis[5]. The material obtained showed identical 300-MHz ^{1}H-NMR data to those published. Moreover, the mass spectrum was identical to one kindly provided to us by Dr. *H. Akita* (Toho-University, Tshiba, Japan). This identity established that all stereocenters in **23** had been synthesized in the correct manner, a distinct attribute to the high stereoselectivity exerted by the chiral 1-methylbutenylboronate **3**. Furthermore, the new iterative strategy allowed a direct and convenient route to this venturicidine building block with its eight stereogenic centers.

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Experimental

Reactions were performed in flame-dried glassware under nitrogen. All temperatures quoted are not corrected. – ^{1}H, ^{13}C NMR: Bruker AC 300. – Boiling range of petroleum ether: 40–60°C. – Flash chromatography: Silica gel Si 60 E. Merck AG, Darmstadt, 40–63 μm.

1. *(3E,4R*,5R*)-4,6-Dimethyl-5-(trimethylsilyloxy)-2-heptene* (**6b**): 20.0 ml (137 mmol) of 1-(trimethylsilyl)imidazole was added to a solution of 6.85 g (48.1 mmol) of (3*R**,4*R**,5*E*)-2,4-dimethyl-5-hepten-3-ol (**6a**) in 30 ml of anhydrous dimethylformamide. After 15 h thin layer chromatography indicated complete reaction. Water (120 ml) was then added, the phases were separated, and the aqueous phase was extracted six times with 50-ml portions of petroleum ether. The combined organic phases were dried with $MgSO_4$ and concentrated. The residue, 10.25 g (99%) of **6b**, was used without further purification. – ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.10 (s, 9H), 0.82 (d, *J* = 6.7 Hz, 3H), 0.84 (d, *J* = 6.7 Hz, 3H), 0.91 (d, *J* = 6.7 Hz, 3H), 1.64 (d, *J* = 6.1 Hz, 3H), 1.72 (m, 1H), 2.22 (sext, *J* = 6.8 Hz, 1H), 3.17 (dd, *J* = 6.2 and 5.0 Hz, 1H), 5.29 (ddq, *J* = 15.3, 7.7, and 1.3 Hz, 1H), 5.40 (dq, *J* = 15.4 and 6.0 Hz, 1H). – ^{13}C NMR (75 MHz, $CDCl_3$): δ = 0.9 (3 C), 16.2, 17.2, 18.0, 20.0, 31.1, 40.5, 82.4, 123.8, 135.7.

2. *(3E,4R*,5R*)-5-(tert-Butyldimethylsilyloxy)-4,6-dimethyl-2-heptene* (**6c**): 791.3 mg (5.3 mmol) of *tert*-butylchlorodimethylsilane and 357.4 mg (5.3 mmol) of imidazole were added to a solution of 500.0 mg (3.5 mmol) of **6a** in 5 ml of anhydrous dimethylformamide. Once thin layer chromatography had indicated complete reaction, 5 ml of water was added, and the phases were separated. The aqueous phase was extracted twice with 2 ml of ether. The combined organic phases were washed with 2 ml of brine, dried with $MgSO_4$ and concentrated. Flash chromatography of the residue with petroleum ether/ether (20:1, containing 0.1% of triethylamine) afforded 852.8 mg (95%) of **6c** as a colorless oil. – ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.03 (s, 6H), 0.85 (d, *J* = 6.8 Hz, 3H), 0.88 (d, *J* = 6.3 Hz, 3H), 0.91 (s, 9H), 0.95 (d, *J* = 6.8 Hz, 3H), 1.64 (d, *J* = 4.4 Hz, 3H), 1.68–1.81 (m, 1H), 2.23–2.30 (m, 1H), 3.23 (dd, *J* = 5.3 and 4.7 Hz, 1H), 5.30–5.47 (m, 1H). – ^{13}C NMR (75 MHz, $CDCl_3$): δ = –3.7, –3.5, 16.3, 17.6, 18.0, 18.5, 20.5, 26.2, 31.7, 40.8, 81.3, 123.4, 135.9. – The (4*R*,5*R*) enantiomer showed $[\alpha]_D^{20}$ = +21.7 (*c* = 0.95, $CHCl_3$).

3. *(3E,4R*,5R*)-5-(4-Methoxybenzyloxy)-4,6-dimethyl-2-heptene* (**6d**): A solution of 270.0 mg (1.9 mmol) of **6a** in 1 ml of anhydrous dimethylformamide was added dropwise at 0°C to a suspension of 269 mg (9.0 mmol) of sodium hydride (80% in white oil) in 5 ml of anhydrous dimethylformamide. The suspension was stirred for 1 h at room temp., cooled to 0°C, and 0.30 ml (2.5 mmol) of 4-methoxybenzyl chloride was added. The mixture was stirred for 2 h, at which point thin layer chromatography indicated complete reaction. The reaction was quenched by careful addition of 5 ml of ice/water. The phases were separated, and the aqueous phase was extracted twice with 10 ml of ether. The combined organic phases were washed with 20 ml of brine, dried with $MgSO_4$ and concentrated. Flash chromatography of the residue with petroleum ether/ether (10:1) furnished 480.0 mg (96%) of **6d** as a colorless liquid. – ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.94 (d, *J* = 6.6 Hz, 3H), 0.97 (d, *J* = 6.7 Hz, 3H), 1.06 (d, *J* = 6.8 Hz, 3H), 1.67 (d, *J* = 4.9 Hz, 3H), 1.80–1.92 (m, 1H), 2.40 (m, 1H), 2.96 (dd, *J* = 6.4 and 5.1 Hz, 1H), 3.80 (s, 3H), 4.45 and 4.47 (AB system, *J* = 10.6 Hz, 2H), 5.36–5.58 (m, 2H), 6.87 (broad d, *J* = 8.7 Hz, 2H), 7.29 (broad d, *J* = 8.7 Hz, 2H). – ^{13}C NMR (75 MHz, $CDCl_3$): δ = 16.2, 17.4, 18.0, 20.0, 30.9, 40.0, 55.2, 74.8, 88.8, 113.7, 123.8, 129.2, 131.5, 135.4, 159.0. – $C_{17}H_{26}O_2$ (262.4): calcd. C 77.82, H 9.99; found C 77.67, H 9.77. – The (4*R*,5*R*) enantiomer showed $[\alpha]_D^{20}$ = +42.9 (*c* = 1.13, $CHCl_3$).

4. *(2RS,4R*,5R*)-4,6-Dimethyl-2,5-heptanediol* (**7a**): 4.1 ml (2.02 mmol) of a 0.5 M solution of 9-borabicyclononane in THF was added to a solution of 143.2 mg (1.0 mmol) of **6a** in 3 ml of THF. After 1 h at 0°C, the mixture was heated at reflux for 12 h. After cooling to 0°C, 2 ml of 3 M NaOH and 2 ml of 30% aqueous H_2O_2 were added. After the vigorous reaction had ceased, the mixture was stirred for 1 h at room temp. The phases were separated, and the aqueous phase was extracted three times with 10 ml of ether. The combined organic phases were washed with 10 ml of brine, dried with $MgSO_4$ and concentrated. Flash chromatography of the residue with petroleum ether/ether (1:1) furnished 112 mg (68%) of a 62:38 diastereomer mixture of **7a** as a colorless oil. – $C_9H_{20}O_2$ (160.3): calcd. C 67.45, H 12.58; found C 67.66, H 12.35. – Major diastereomer: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.83–0.88 (m, 6H), 0.96 (d, *J* = 6.6 Hz, 3H), 1.17 (d, *J* = 4.5 Hz, 3H), 1.31–1.53 (m, 2H), 1.56–1.73 (m, 1H), 1.80–1.92 (m, 1H), 2.70 (broad s, 2H), 3.15 (dd, *J* = 8.2 and 4.5 Hz, 1H), 3.84–4.00 (m, 1H). – ^{13}C NMR (75 MHz, $CDCl_3$): δ = 12.8, 19.3, 19.4, 24.7, 30.9, 32.4, 44.2, 66.1, 80.0. – Minor diastereomer: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.97 (d, *J* = 6.5 Hz, 3H), 1.19 (d, *J* = 4.7 Hz, 3H), 3.14 (dd, *J* = 8.4 and 5.2 Hz, 1H). – ^{13}C NMR (75 MHz, $CDCl_3$): δ = 12.0, 19.2, 19.5, 24.0, 31.2, 32.0, 43.8, 64.9, 80.2.

5. *(2RS,4R*,5R*)-4,6-Dimethyl-5-(trimethylsilyloxy)-2-heptanol* (**7b**): 261.3 mg (1.2 mmol) of **6b** and 3.7 ml (1.8 mmol) of a 0.5 M solution of 9-BBN in THF were allowed to react as described under 4. Flash chromatography of the product with petroleum ether/ethyl acetate (3:2) containing 0.1% triethylamine, furnished 153.8 mg (59%) of a 55:45 diastereomer mixture of **7b**, followed by 70.0 mg (36%) of a 55:45 diastereomer mixture of **7a**. – **7b**: $C_{12}H_{28}O_2Si$ (232.4): calcd. C 62.01, H 12.14; found C 62.28, H 12.30. – Major diastereomer: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.10 (s, 9H), 0.83–0.89 (m, 9H), 1.17 (d, *J* = 6.1 Hz, 3H), 1.33–1.45 (m, 2H), 1.72–1.89 (m, 3H), 3.15 (dd, *J* = 7.2 and 3.5 Hz, 1H), 3.82–3.92 (m, 1H). – ^{13}C NMR (75 MHz, $CDCl_3$): δ = 0.89, 14.9, 19.2, 20.1, 23.5, 31.1, 33.7, 44.2, 66.3, 81.7. – Minor diastereomer: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.10 (s, 9H), 1.19 (d, *J* = 6.1 Hz, 3H), 3.18 (dd, *J* = 7.0 and 3.6 Hz, 1H). – ^{13}C NMR (75 MHz, $CDCl_3$): δ = 0.83, 14.4, 19.5, 20.2, 24.5, 31.1, 33.1, 44.6, 60.1, 82.9.

6. *(2RS,4R*,5R*)-5-(tert-Butyldimethylsilyloxy)-4,6-dimethyl-2-heptanol* (**7c**): 286 mg (1.1 mmol) of **6c** and 2.9 ml (1.5 mmol) of

a 0.5 M solution of 9-BBN in THF were allowed to react as described under 4. Flash chromatography with petroleum ether/ether (5:1), containing 0.1% triethylamine, furnished 140.8 mg (50%) of a 52:48 diastereomer mixture of **7c** as an oil. – $C_{15}H_{34}SiO_2$ (274.5): calcd. C 65.63, H 12.48; found C 65.81, H 12.62. – Major diastereomer: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.02 (s, 3H), 0.04 (s, 3H), 1.19 (s, 9H), 1.14–1.17 (m, 9H), 1.55 (d, J = 6.2 Hz, 3H), 1.72–1.82 (m, 1H), 1.95–2.06 (m, 1H), 2.28–2.48 (m, 3H), 4.35 (dd, J = 5.3 and 3.0 Hz, 1H), 5.10–5.19 (m, 1H). – ^{13}C NMR (75 MHz, $CDCl_3$): δ = −3.8, −3.7, 15.8, 18.4, 19.2, 20.4, 23.2, 26.1, 31.8, 33.9, 44.1, 66.6, 80.4. – Minor diastereomer: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.04 (s, 3H), 0.05 (s, 3H), 0.83–0.93 (m, 9H), 0.90 (s, 9H), 1.18 (d, J = 6.2 Hz, 3H), 1.29 (ddd, J = 14.0, 8.2, and 3.0 Hz, 1H), 1.50 (ddd, J = 14.0, 9.3, and 5.5 Hz, 1H), 1.79–1.83 (m, 3H), 3.23 (dd, J = 6.3 and 2.9 Hz, 1H), 3.80 (m, 1H). – ^{13}C NMR (75 MHz, $CDCl_3$): δ = −3.9, −3.7, 15.9, 18.4, 19.6, 20.4, 24.4, 26.1, 31.6, 34.9, 44.3, 66.4, 81.8.

7. *(2RS,4R*,5R*)-5-(4-Methoxybenzyloxy)-4,6-dimethyl-2-heptanol* (**7d**): 377 mg (1.4 mmol) of **6d** and 4.0 ml (2.0 mmol) of a 0.5 M solution of 9-BBN in THF were allowed to react as described under 4. Flash chromatography of the residue with petroleum ether/ether (5:1) furnished 328 mg (83%) of a 61:39 diastereomer mixture of **7d**. – $C_{17}H_{28}O_3$ (280.4): calcd. C 72.82, H 10.06; found C 72.86, H 10.03. – Major diastereomer: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.89 (d, J = 6.7 Hz, 3H), 0.91 (d, J = 6.9 Hz, 3H), 0.96 (d, J = 6.7 Hz, 3H), 1.11 (d, J = 6.2 Hz, 3H), 1.37–1.54 (m, 2H), 1.79–2.00 (m, 3H), 2.94 (dd, J = 7.1 and 3.6 Hz, 1H), 3.75 (s, 3H), 3.79–3.89 (m, 1H), 4.42 and 4.49 (AB system, J = 10.9 Hz, 2H), 6.83 (broad d, J = 8.7 Hz, 2H), 7.24 (broad d, J = 8.7 Hz, 2H). – ^{13}C NMR (75 MHz, $CDCl_3$): δ = 15.1, 19.1, 20.1, 23.5, 30.8, 32.5, 44.1, 55.2, 66.1, 74.5, 88.1, 113.7, 129.1, 131.2, 158.0. – Minor diastereomer: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.88 (d, J = 6.8 Hz, 3H), 1.15 (d, J = 6.2 Hz, 3H), 2.89 (dd, J = 7.3 and 3.5 Hz, 1H). – ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.5, 19.3, 20.2, 24.5, 30.9, 32.6, 44.2, 55.2, 66.0, 74.4, 89.2, 113.7, 129.1, 131.2, 158.0.

649 mg (1.6 mmol) of bis(isopinocampheyl)borane–tetramethylethylenediamine adduct was dissolved in 3 ml of THF, and 0.37 ml (3.0 mmol) of BF_3–ether was added dropwise. The mixture was stirred for 1 h and the BF_3–TMEDA adduct was filtered under nitrogen over a glass frit covered with Kieselguhr. The precipitate was washed twice with a minimum amount of anhydrous THF, and the combined filtrates were cooled to −30°C. To this solution 298 mg of (3*R*,4*R*)-**6d** was added, and the mixture was stirred for 2 d at −18°C. 0.4 ml of methanol was then added followed by 2 ml of 3 N NaOH and 2 ml of 30% aqueous hydrogen peroxide. The phases were separated, and the aqueous phase was extracted three times with ether. The combined organic phases were washed with brine and dried with $MgSO_4$. Concentration of the solution followed by flash chromatography with petroleum ether/ether (5:1) furnished 224 mg (70%) of a 82:18 diastereomer mixture of **7d**.

8. *(3R,4R,5E)-2,4-Dimethyl-5-hepten-3-ol* (**6a**): 5.2 ml (57 mmol) of isobutyraldehyde was added to a solution of 5.83 g (19 mmol) of (*R*,*R*,*R*)-**3**[9] in 70 ml of anhydrous petroleum ether. After stirring for 2 d, 2.5 ml (19 mmol) of triethanolamine was added. After stirring for a further hour, the mixture was filtered and the filtrate carefully concentrated. The residue was purified by flash chromatography with petroleum ether/ether (15:1) to give 1.83 g (68%) of **6a** as a colorless liquid, which showed the same spectral data as racemic **6a**[16]. Mosher analysis with (*S*)-(+)-methoxy(trifluoromethyl)phenylacetyl chloride attested 95% e.e.

9. *(2RS,3R,5R,6R)-Tetrahydro-6-isopropyl-3,5-dimethyl-2H-pyran-2-ol* (**10**): 474 mg (2.2 mmol) of (3*R*,4*R*)-**6b** and 5.8 ml (2.9 mmol) of a 0.5 M solution of 9-BBN in THF were allowed to react as described under 4. Instead of the oxidative workup, the solution was cooled to 0°C, and 2.5 ml (2.2 mmol) of a 0.87 M solution of potassium hydrotriisopropoxyborate in THF was added. Dry carbon monoxide was slowly introduced into the reaction mixture. With continuous passage of carbon monoxide, the mixture was stirred for 1 h until thin layer chromatography indicated complete reaction. The mixture was cooled to 0°C and was then purged with nitrogen. An oxidative workup as described under 4. was then carried out. Flash chromatography of the residue with petroleum ether/ether (20:1) containing 0.1% of triethylamine furnished 508 mg (95%) of a 55:45 mixture of the aldheyde **8** as a colorless oil. – Major diastereomer: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.10 (s, 9H), 0.82 (d, J = 6.5 Hz, 3H), 0.83 (d, J = 6.8 Hz, 3H), 0.87 (d, J = 6.7 Hz, 3H), 1.08 (d, J = 6.9 Hz, 3H), 1.53–1.76 (m, 4H), 2.30–2.39 (m, 1H), 3.12–3.17 (m, 1H), 9.52 (d, J = 2.6 Hz, 1H). – ^{13}C NMR (75 MHz, $CDCl_3$): δ = 0.9, (13.1, 14.4, assignment to the anomers uncertain), 18.9, 20.0, 31.3, 33.4, 36.1, 44.1, 81.8, 205.0. – Minor diastereomer: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.81 (d, J = 6.8 Hz, 3H), 0.86 (d, J = 6.7 Hz, 3H), 9.60 (d, J = 6.7 Hz, 1H). – ^{13}C NMR (75 MHz, $CDCl_3$): δ = 0.93, (13.6, 14.0, assignment to the anomers uncertain), 19.2, 20.1, 31.2, 33.3, 35.2, 44.3, 82.1, 205.0.

485 mg (2.8 mmol) of the aldehyde **8**, generated as described above, was taken up in 5 ml of anhydrous THF, and 2.6 ml (2.6 mmol) of a 1.0 M solution of tetrabutylammonium fluoride in THF was added. The mixture was stirred until thin layer chromatography indicated complete conversion and then filtered through a 5-cm layer of silica gel. After concentration in vacuo, the residue was dissolved in 15 ml of anhydrous methanol. 150 mg of potassium carbonate was added, and the suspension was maintained at reflux for 5 h. The mixture was poured into 15 ml of brine and extracted three times with 20 ml of ether. The combined organic extracts were dried with Na_2SO_4 and concentrated. Flash chromatography of the residue with petroleum ether/ether (5:1) furnished 327 mg (95%) of the lactols **10** as a 4:1 anomeric mixture. The mixture solidified on storage at 4°C. – $C_{10}H_{20}O_2$ (172.3): calcd. C 69.72, H 11.70; found C 69.75, H 11.71. – Major anomer: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.77 (d, J = 6.7 Hz, 3H), 0.81 (d, J = 6.3 Hz, 3H), 0.84 (d, J = 7.0 Hz, 3H), 0.94 (d, J = 6.5 Hz, 3H), 1.30 (ddd, J = 13.7, 13.7, and 4.3 Hz, 1H), 1.52–1.85 (m, 4H), 2.93 (dd, J = 9.8 and 2.2 Hz, 1H), 3.42 (broad s, 1H), 4.18 (d, J = 8.0 Hz, 1H). – ^{13}C NMR (75 MHz, $CDCl_3$): δ = 12.0, 16.7, 18.2, 20.3, 29.0, 29.5, 32.3, 39.1, 84.6, 102.2. – Minor anomer: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.82 (d, J = 6.8 Hz, 3H), 0.89 (d, J = 7.0 Hz, 3H), 0.90 (d, J = 6.5 Hz, 3H), 3.46 (dd, J = 10.3 and 2.4 Hz, 1H), 4.99 (d, J = 3.4 Hz, 1H). – ^{13}C NMR (75 MHz, $CDCl_3$): δ = 11.4, 16.8, 18.2, 28.5, 28.7, 29.4, 33.7, 39.1, 75.4, 94.9.

10. *(2R*,4R*,5R*)-2,4,6-Trimethyl-1,5-heptanediol* (**11**): A solution of 703 mg (4.1 mmol) of a 5:1 anomer mixture of the lactols **10** in 10 ml of ether was added dropwise at 0°C to a suspension of 2.0 g of $LiAlH_4$ in 50 ml of ether. After stirring for 5 h at room temp., the mixture was carefully poured onto 150 g of ice. Semiconcentrated sulfuric acid was added until the pH was <1.0. The phases were separated, and the aqueous phase was extracted three times with 30-ml portions of ether. The combined organic phases were washed with 30 ml of brine and concentrated. Flash chromatography of the residue with petroleum ether/ether (5:1) changing to pure ether afforded 628 mg (88%) of the diol **11** as a colorless oil, which was diastereomerically pure according to the ^{13}C-NMR spectrum. – ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.84 (d, J = 7.2 Hz, 3H), 0.88 (d, J = 6.4 Hz, 3H), 0.90 (d, J = 6.7 Hz, 3H), 0.95 (d, J = 6.6 Hz, 3H), 1.09 (ddd, J = 13.3, 9.6, and 4.8 Hz, 1H),

1.32 (ddd, J = 13.3, 9.8, and 4.5 Hz, 1H), 1.39 (broad s, 1H), 1.68 (broad s, 1H), 1.72 (m, 3H), 3.05 (dd, J = 7.4 and 4.1 Hz, 1H), 3.45 (m, 2H). – ^{13}C NMR (75 MHz, $CDCl_3$): δ = 12.8, 16.3, 18.2, 19.5, 30.9, 32.2, 33.1, 37.6, 68.9, 81.1. – $C_{10}H_{22}O_2$ (174.3): calcd. C 68.92, H 12.72; found C 68.68, H 12.66.

11. *(3R,4R,6R,7R,8R,9E)-2,4,6,8-Tetramethyl-9-undecene-3,7-diol* (**12**): 689 mg (4.0 mmol) of (3*R*,5*R*,6*R*)-**10** was dissolved in 3 ml of anhydrous petroleum ether. 3.65 g (12 mmol) of (*R*,*R*,*R*)-**3** and 38 mg (0.4 mmol) of 2-hydroxypyridine were added. The mixture was placed in a Teflon tube and pressurized for 10 d at 10 kbar. 0.5 ml (3.5 mmol) of triethanolamine was added, the mixture was stirred for 1 h and then filtered. The filtrate was concentrated, and the residue was separated by flash chromatography with petroleum ether/ethyl acetate (4:1) to furnish 475 mg (50%) of **12** and 200 mg (30%) of recovered **10**. – **12**: M.p. 103 °C. – $C_{15}H_{30}O_2$ (242.4): calcd. C 74.33, H 12.47; found: C 74.20, H 12.76. – ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.84 (d, J = 6.6 Hz, 3H), 0.90 (d, J = 6.7 Hz, 3H), 0.91 (d, J = 6.7 Hz, 3H), 0.96 (d, J = 6.6 Hz, 3H), 1.01 (d, J = 6.8 Hz, 3H), 1.07 (ddd, J = 13.5, 10.6, and 2.7 Hz, 1H), 1.46 (ddd, J = 13.2, 10.8, and 2.6 Hz, 1H), 1.63 (d, J = 6.3 Hz, 3H), 1.60–1.80 (m, 5H), 2.29 (sext, J = 6.8 Hz, 1H), 3.01 (dd, J = 6.8 and 4.6 Hz, 1H), 3.13 (dd, J = 5.8 and 5.8 Hz, 1H), 5.29 (ddq, J = 15.4, 7.4, and 1.3 Hz, 1H), 5.43 (dqd, J = 15.4, 6.2, and 0.5 Hz, 1H). – ^{13}C NMR (75 MHz, $CDCl_3$): δ = 12.9, 15.0, 16.6, 17.9, 18.0, 19.7, 31.0, 32.7, 32.9, 35.0, 39.7, 80.1, 81.9, 125.3, 134.4.

λ [nm]	589	578	546	436	365	
$[\alpha]^{20}$	62.9	65.4	74.3	126.4	194.8	c = 1.43 ($CHCl_3$)
$[\alpha]^{20}$	67.6	70.4	80.0	136.6	211.7	c = 1.12 (Ethanol)

12. *(2E,4R,5S,6S,7S)-7-(tert-Butyldimethylsilyloxy)-4,6-dimethyl-2-nonen-5-ol* (**14**): 626 mg (2.7 mmol) of (2*R*,3*S*)-3-(tert-butyldimethylsilyloxy)-2-methylpentanal (**13**)[26] and 2.48 g (8.1 mmol) of (*R*,*R*,*R*)-**3** in 10 ml of anhydrous 1,2-dimethoxyethane were allowed to react for one week. Then, 0.36 ml (2.7 mmol) of triethanolamine was added, and the mixture was stirred for 1 h. The precipitate was filtered over a 1.5-cm layer of silica gel. The filtrate was concentrated, and the residue was purified by flash chromatography with petroleum ether/ether (100:1) to give 694 mg (86%) of **14** as a colorless oil. – ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.07 (s, 3H), 0.10 (s, 3H), 0.79 (d, J = 7.1 Hz, 3H), 0.87 (t, J = 7.3 Hz, 3H), 0.88 (s, 9H), 0.96 (d, J = 6.8 Hz, 3H), 1.51–1.57 (m, 2H), 1.66 (d, J = 5.5 Hz, 3H), 1.77–1.85 (m, 1H), 2.15–2.25 (m, 1H), 3.52 (ddd, J = 8.7, 3.2, and 3.2 Hz, 1H), 3.73–3.79 (m, 2H), 5.38–5.56 (m, 2H). – ^{13}C NMR (75 MHz, $CDCl_3$): δ = –4.43, –4.38, 11.1, 12.55, 12.63, 18.0, 18.1, 25.0, 25.8, 38.8, 39.3, 77.1, 78.4, 124.1, 135.4. – $[\alpha]_D^{20}$ = –20.2 (c = 2.72 ($CHCl_3$). – $C_{17}H_{36}SiO_2$ (300.6): calcd. C 67.94, H 12.07; found C 68.00, H 12.11.

13. *(2E,4R,5S,6S,7S)-7-(tert-Butyldimethylsilyloxy)-4,6-dimethyl-5-(trimethylsilyloxy)-2-nonene* (**15**): 2.15 g (7.1 mmol) of **14** and 3.1 ml (21.4 mmol) of 1-(trimethylsilyl)imidazole were allowed to react in 10 ml of dimethylformamide as described under 1. Flash chromatography with petroleum ether/ether (100:1) containing 0.1% triethylamine furnished 2.43 g (92%) of **15** as a colorless liquid. – ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.05 (s, 6H), 0.09 (s, 9H), 0.77 (d, J = 7.0 Hz, 3H), 0.81 (t, J = 7.5 Hz, 3H), 0.88 (s, 9H), 0.90 (d, J = 6.8 Hz, 3H), 1.43–1.63 (m, 3H), 1.66 (d, J = 5.7 Hz, 3H), 2.23–2.33 (m, 1H), 3.54 (dd, J = 7.7 and 3.3 Hz, 1H), 3.80 (ddd, J = 7.1, 5.4, and 2.9 Hz, 1H), 5.32–5.46 (m, 2H). – ^{13}C NMR (75 MHz, $CDCl_3$): δ = –3.9, –3.4, 1.1, 9.7, 10.3, 13.2, 18.0, 18.3, 26.1, 28.6, 39.0, 41.2, 73.6, 78.5, 123.8, 136.7. – $[\alpha]_D^{20}$ = +22.0 (c = 1.71, $CHCl_3$). – $C_{20}H_{44}Si_2O_2$ (372.7): calcd. C 64.45, H 11.90; found C 64.77, H 11.52.

14. *(2RS,3R,5R,6S)-6-[(1S,2S)-2-(tert-Butyldimethylsilyloxy)-tetrahydro-1-methylbutyl]-3,5-dimethyl-2H-pyran-2-ol* (**16**): 2.11 g (5.7 mmol) of **15**, 18.2 ml (9.1 mmol) of a 0.5 M solution of 9-BBN in THF, and 8.1 ml (5.7 mmol) of a 0.7 M solution of potassium hydridotriisopropoxyborate in THF were allowed to react as described under 9. Flash chromatography of the crude product with petroleum ether/ether (50:1) containing 0.1% triethylamine furnished 2.11 g (92%) of a 55:45 mixture of epimeric aldehydes. – Major diastereomer: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.05 (s, 6H), 0.12 (s, 9H), 0.73 (d, J = 7.0 Hz, 3H), 0.81 (t, J = 7.4 Hz, 3H), 0.82 (d, J = 6.9 Hz, 3H), 0.86 (s, 9H), 1.08 (d, J = 6.9 Hz, 3H), 1.47–1.77 (m, 6H), 2.35–2.45 (m, 1H), 3.54–3.58 (m, 1H), 3.76–3.81 (m, 1H), 9.62 (d, J = 1.9 Hz, 1H). – ^{13}C NMR (75 MHz, $CDCl_3$): δ = –3.9, –3.1, 1.4, 10.0 (2 C), 13.0, 14.0, 18.4, 26.0, 28.7, 32.5, 36.4, 40.9, 44.0, 73.8, 78.0, 205.0. – Minor diastereomer: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.71 (d, J = 7.0 Hz, 3H), 1.07 (d, J = 6.9 Hz, 3H), 9.60 (d, J = 2.2 Hz, 1H). – ^{13}C NMR (75 MHz, $CDCl_3$): δ = –3.9, –3.1, 1.3, 9.9 (2 C), 12.4, 13.4, 18.4, 26.0, 28.7, 32.7, 36.2, 41.0, 44.3, 73.8, 77.1, 205.0.

2.0 g (5.0 mmol) of the above aldehyde was dissolved in 15 ml of anhydrous methanol and 5 ml of anhydrous ether. 50.0 mg (0.4 mmol) of potassium carbonate was added, and the mixture was refluxed for 6 h until thin layer chromatography indicated complete reaction. 50 ml of ether was added, and the mixture was washed with 50 ml of water. The phases were separated, and the aqueous phase was extracted with three 30-ml portions of ether. The combined organic phases were dried with $MgSO_4$ and concentrated. Flash chromatography of the residue with petroleum ether/ether (15:1) furnished 1.38 g (85%) of **16** as a 10:1 anomeric mixture. – Major anomer: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.02 (s, 3H), 0.04 (s, 3H), 0.71 (d, J = 6.9 Hz, 3H), 0.80 (t, J = 7.6 Hz, 3H), 0.87 (s, 9H), 0.92 (d, J = 6.3 Hz, 3H), 0.93 (d, J = 7.0 Hz, 3H), 1.44–1.66 (m, 6H), 1.73–1.76 (m, 1H), 2.48 (d, J = 6.1 Hz, OH), 3.36 (dd, J = 10.2 and 2.2 Hz, 1H), 4.02 (m, 1H), 4.22 (dd, J = 8.1 and 6.1 Hz, 1H). – ^{13}C NMR (75 MHz, $CDCl_3$): δ = –4.8, –3.6, 7.3, 10.3, 12.0, 16.7, 18.2, 26.0, 28.2, 28.8, 32.4, 37.4, 39.3, 71.3, 78.3, 102.0. – Minor anomer: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.72 (d, J = 6.8 Hz, 3H), 3.69 (dd, J = 10.2 and 2.2 Hz, 1H), 3.94 (m, 1H), 4.99 (m, 1H).

15. *(2E,4R,5R,6R,8R,9S,10S,11S)-11-(tert-Butyldimethylsilyloxy)-4,6,8,10-tetramethyl-2-tridecene-5,9-diol* (**17**): 288 mg (0.9 mmol) of the lactol **16**, 913 mg (3.0 mmol) of (*R*,*R*,*R*)-**3**, and 10 mg of 2-hydroxypyridine were allowed to react in dichloromethane for 4 d at 9.8 kbar as described under 11. Flash chromatography of the residue with petroleum ether/ether (4:1) furnished 302 mg (89%) of a 94:6 diastereomeric mixture of **17** as an oil. In addition, 27.6 mg (10%) of the starting lactol was recovered. – **17**: $C_{23}H_{48}SiO_3$ (400.7): calcd. C 68.94, H 12.07; found C 68.84, H 12.03. – ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.05 (s, 3H), 0.08 (s, 3H), 0.73 (d, J = 7.1 Hz, 3H), 0.77 (d, J = 6.4 Hz, 3H), 0.87 (d, J = 6.5 Hz, 3H), 0.87 (s, 9H), 0.89 (t, J = 7.3 Hz, 3H), 0.91 (d, J = 6.8 Hz, 3H), 0.99–1.10 (m, 1H), 1.48–1.69 (m, 6H), 1.58 (d, J = 6.3 Hz, 3H), 1.77–1.88 (m, 1H), 2.31 (sext, J = 6.7 Hz, 1H), 3.13 (dd, J = 5.8 and 5.5 Hz, 1H), 3.45 (dd, J = 9.0 Hz, 1H), 3.67 (ddd, J = 8.0, 4.8, and 3.0 Hz, 1H), 3.93 (s, OH), 5.31 (ddq, J = 15.4, 7.4, and 1.2 Hz, 1H), 5.45 (dq, J = 15.4 and 6.1 Hz, 1H). – ^{13}C NMR (75 MHz, $CDCl_3$): δ = –4.6, –4.5, 11.0, 11.4, 13.1, 14.9, 16.9, 17.9, 18.0, 24.4, 25.8, 32.4, 33.0, 35.4, 39.6, 39.7, 77.7,

79.3, 80.1, 124.2, 134.6. – $[\alpha]_D^{20}$ = +1.69 (*c* = 0.414, $CHCl_3$). – The following signals of the epimer were recorded: ^1H NMR (300 MHz, $CDCl_3$): δ = 3.23 (dd, *J* = 5.5 Hz, 1H), 3.53 (m, 1H), 5.25 (ddq, *J* = 10.5, 9.3, and 1.7 Hz, 1H), 5.58 (dq, *J* = 10.5 and 6.0 Hz, 1H). – ^{13}C NMR (75 MHz, $CDCl_3$): δ = 11.4, 13.0, 15.1, 16.9, 23.9, 40.0, 76.2, 78.5, 79.9, 125.7, 133.0.

16. *(3S,4R,5S,6R,8R,9R,10R,11E)-4,6,8,10-Tetramethyl-11-tridecene-3,5,9-triol* (**18**): 0.64 ml (0.6 mmol) of a 1.0 M solution of tetrabutylammonium fluoride in THF was added to a solution of 250 mg (0.6 mmol) of **17** in 5 ml of anhydrous THF. The mixture was stirred until thin layer chromatography indicated complete reaction. The mixture was filtered over a bed of 5 cm of silica gel, and the filtrate was concentrated. Flash chromatography of the residue using ether as the eluent furnished 177.6 mg (100%) of the triol **17** as a viscous oil. – ^1H NMR (300 MHz, $CDCl_3$): δ = 0.82 (d, *J* = 6.4 Hz, 3H), 0.85 (t, *J* = 7.1 Hz, 3H), 0.86 (d, *J* = 7.1 Hz, 3H), 0.95 (d, *J* = 7.4 Hz, 3H), 0.97 (d, *J* = 6.7 Hz, 3H), 1.15–1.23 (m, 1H), 1.33–1.55 (m, 4H), 1.63 (d, *J* = 6.3 Hz, 3H), 1.62–1.81 (m, 2H), 1.78–1.81 (m, 1H), 1.83 (s, OH), 2.28 (sext, *J* = 6.8 Hz, 1H), 3.13 (dd, *J* = 5.8 and 5.8 Hz, 1H), 3.39 (dd, *J* = 7.0 and 4.8 Hz, 2H), 3.74 (m, 1H), 5.29 (ddq, *J* = 15.4, 7.5, and 1.3 Hz, 1H), 5.45 (dq, *J* = 15.4 and 6.2 Hz, 1H). – ^{13}C NMR (75 MHz, $CDCl_3$): δ = 10.9, 11.5, 12.5, 14.9, 16.7, 18.0, 26.3, 32.7 (2 C), 34.8, 38.2, 39.6, 74.9, 79.7, 80.0, 125.3, 134.2. – $[\alpha]_D^{20}$ = +25.4 (*c* = 17.4, CH_2Cl_2).

17. *(4S,5R,6S)-4-Ethyl-6-[(1R,3R,4R,5R,6E)-4-hydroxy-1,3,5-trimethyl-6-octenyl]-2,2,5-trimethyl-1,3-dioxane* (**19**): 1.0 ml (8.3 mmol) of 2,2-dimethoxypropane and ca. 5 mg of pyridinium *p*-toluenesulfonate were added to a solution of 396.0 mg (1.4 mmol) of the triol **18** in 5 ml of anhydrous CH_2Cl_2. After stirring for 12 h, thin layer chromatography indicated complete reaction. The solution was diluted with 20 ml of ether and was washed with 30 ml of a saturated aqueous $NaHCO_3$ solution. The phases were separated, and the aqueous phase was extracted three times with 20-ml portions of ether. The combined organic phases were dried with Na_2SO_4 and concentrated. Flash chromatography of the residue with petroleum ether/ether (10:1) containing 0.1% triethylamine furnished 392 mg (87%) of **19** as an oil. – ^1H NMR (300 MHz, $CDCl_3$): δ = 0.79 (d, *J* = 6.8 Hz, 3H), 0.83 (d, *J* = 6.6 Hz, 3H), 0.85 (d, *J* = 6.9 Hz, 3H), 0.88 (t, *J* = 7.4 Hz, 3H), 0.97 (d, *J* = 6.7 Hz, 3H), 1.06–1.17 (m, 1H), 1.27 (s, 3H), 1.28 (s, 3H), 1.32–1.48 (m, 3H), 1.63 (d, *J* = 6.7 Hz, 3H), 1.58–1.74 (m, 4H), 2.30 (sext, *J* = 6.6 Hz, 1H), 4.59 (dd, *J* = 7.3 and 7.3 Hz, 1H), 3.14 (dd, *J* = 5.7 and 5.6 Hz, 1H), 3.59 (ddd, *J* = 8.8, 4.6, and 4.6 Hz, 1H), 5.32 (ddq, *J* = 15.4, 7.2, and 1.2 Hz, 1H), 5.45 (dq, *J* = 15.4 and 6.0 Hz, 1H). – ^{13}C NMR (75 MHz, $CDCl_3$): δ = 10.5, 12.5, 14.1, 14.7, 16.3, 18.0, 23.6 (2 C), 25.3, 33.0, 33.8, 34.2, 36.4, 39.5, 71.1, 79.2, 79.8, 100.0, 125.0, 134.4. – $[\alpha]_D^{20}$ = +52.1 (*c* = 4.74, $CHCl_3$). – $C_{20}H_{38}O_3$ (326.5): calcd. C 73.57, H 11.73; found C 73.65, H 11.84.

18. *(4S,5R,6S)-4-Ethyl-6-[(1R,3R,4R,5R,6E)-1,3,5-trimethyl-4-(trimethylsilyloxy)-6-octenyl]-2,2,5-trimethyl-1,3-dioxane* (**20**): 313.0 mg (1.0 mmol) of **19** and 0.73 ml (5.0 mmol) of 1-(trimethylsilyl)imidazole were allowed to react in 5 ml of anhydrous dimethylformamide as described under 1. Flash chromatography of the crude product with petroleum ether/ether (100:1) containing 0.1% triethylamine furnished 377 mg (100%) of **20** as a colorless oil. – ^1H NMR (300 MHz, $CDCl_3$): δ = 0.09 (s, 9H), 0.82 (d, *J* = 6.5 Hz, 9H), 0.90 (t, *J* = 7.4 Hz, 3H), 0.93 (d, *J* = 6.7 Hz, 3H), 1.28 (s, 3H), 1.31 (s, 3H), 1.33–1.52 (m, 6H), 1.64 (d, *J* = 5.9 Hz, 3H), 1.69–1.75 (m, 1H), 2.29 (sext, *J* = 6.7 Hz, 1H), 3.06 (dd, *J* = 7.3 and 3.7 Hz, 1H), 3.21 (dd, *J* = 5.6 and 5.5 Hz, 1H), 3.62 (ddd, *J* = 8.7, 4.6, and 4.6 Hz, 1H), 5.28 (ddq, *J* = 15.8, 8.1, and 1.3 Hz, 1H), 5.39 (dq, *J* = 15.8 and 6.0 Hz, 1H). – ^{13}C NMR (75 MHz, $CDCl_3$): δ = 0.87, 10.5, 12.5, 13.6, 15.9, 16.6, 18.0, 23.7 (2 C), 25.4, 33.96, 34.03, 35.3, 36.6, 40.1, 71.2, 79.3, 82.4, 100.0, 123.9, 135.8. – $[\alpha]_D^{20}$ = +27.6 (*c* = 0.470, $CHCl_3$). – $C_{23}H_{46}SiO_3$ (398.7): calcd. C 69.29, H 11.63; found C 69.38, H 11.63.

19. *(2RS,3R,5R,6R)-6-[(1R,3R)-3-{(4S,5R,6S)-6-Ethyl-2,2,5-trimethyl-1,3-dioxan-4-yl}-1,3-dimethylpropyl]tetrahydro-3,5-dimethyl-2H-pyran-2-ol* (**21**): 131 mg (0.3 mmol) of **20**, 1.30 ml (0.7 mmol) of a 0.5 M solution of 9-BBN in THF, and 0.47 ml (0.3 mmol) of a 0.7 M solution of potassium hydridotriisopropoxyborate in THF were allowed to react as described under 9. Flash chromatography of the crude product with petroleum ether/ether (20:1) containing 0.1% triethylamine furnished 126.3 mg (90%) of a 52:48 mixture of epimeric aldehydes. – Major epimer: ^1H NMR (300 MHz, $CDCl_3$): δ = 0.11 (s, 9H), 0.78 (d, *J* = 6.7 Hz, 3H), 0.81 (d, *J* = 7.0 Hz, 3H), 0.83 (d, *J* = 6.3 Hz, 3H), 0.84 (d, *J* = 7.0 Hz, 3H), 0.90 (t, *J* = 7.3 Hz, 3H), 1.03 (d, *J* = 6.9 Hz, 3H), 1.17–1.48 (m, 4H), 1.28 (s, 3H), 1.30 (s, 3H), 1.59–1.78 (m, 6H), 2.38–2.43 (m, 1H), 3.08 (dd, *J* = 7.4 and 2.4 Hz, 1H), 3.17–3.22 (m, 1H), 3.61 (ddd, *J* = 8.8, 4.7, and 4.6 Hz, 1H), 9.58 (d, *J* = 2.5 Hz, 1H). – ^{13}C NMR (75 MHz, $CDCl_3$): δ = 0.98, 10.5, 12.4, 13.2, 13.3, 14.3, 15.8, 23.7, 25.3, 29.7, 32.9, 33.6, 34.0, 35.7, 36.5, 37.2, 44.1, 71.1, 79.2, 81.7, 100.1, 205.0. – Minor epimer: ^1H NMR (300 MHz, $CDCl_3$): δ = 0.76 (d, *J* = 6.6 Hz, 3H), 1.07 (d, *J* = 6.9 Hz, 3H), 9.60 (d, *J* = 1.9 Hz, 1H). – ^{13}C NMR (75 MHz, $CDCl_3$): δ = 0.98, 10.5, 12.4, 13.1, 13.4, 13.6, 16.0, 23.7, 25.3, 29.7, 32.9, 33.6, 34.0, 35.7, 36.5, 36.9, 44.2, 71.1, 79.2, 81.3, 100.1, 200.5.

182 mg (0.4 mmol) of the epimeric aldehydes obtained as above were dissolved in 20 ml of anhydrous methanol. 250 mg (2 mmol) of potassium carbonate was added, and the mixture was refluxed for 5 h. 30 ml of ether was then added, and the mixture was washed with 30 ml of water. The phases were separated, and the aqueous phase was extracted with five 20-ml portions of ether. The combined organic extracts were dried with Na_2SO_4 and concentrated. Flash chromatography of the residue with petroleum ether/ether (5:1) furnished 123.5 mg (87%) of a 3:1 anomer mixture of **21** as a white solid. Melting range 75–78 °C. – $C_{21}H_{40}O_4$ (356.6): calcd. C 70.74, H 11.31; found C 70.91, H 11.53. – Major anomer: ^1H NMR (300 MHz, $CDCl_3$): δ = 0.75 (d, *J* = 6.7 Hz, 3H), 0.80 (d, *J* = 6.8 Hz, 3H), 0.84 (d, *J* = 6.6 Hz, 3H), 0.88 (d, *J* = 6.3 Hz, 3H), 0.88 (t, *J* = 7.1 Hz, 3H), 0.93 (d, *J* = 7.0 Hz, 3H), 1.28 (s, 3H), 1.29 (s, 3H), 1.31–1.40 (m, 4H), 1.56–1.63 (m, 4H), 1.64–1.84 (m, 3H), 3.00 (dd, *J* = 9.8 and 2.1 Hz, 1H), 3.05 (dd, *J* = 7.3 and 4.2 Hz, 1H), 3.20 (d, *J* = 5.5 Hz, OH), 3.60 (ddd, *J* = 8.8, 4.6, and 4.6 Hz, 1H), 4.22 (dd, *J* = 7.9 and 5.3 Hz, 1H). – ^{13}C NMR (75 MHz, $CDCl_3$): δ = 10.5, 12.1, 12.6, 14.2, 14.7, 16.7, 23.65, 23.67, 25.4, 29.2, 32.25, 32.37, 34.2, 36.7, 37.4, 39.3, 71.1, 79.2, 83.5, 100.1, 102.3. – Minor anomer: ^1H NMR (300 MHz, $CDCl_3$): δ = 0.76 (d, *J* = 6.7 Hz, 3H), 0.81 (d, *J* = 6.5 Hz, 3H), 0.92 (d, *J* = 6.7 Hz, 3H), 2.58 (d, *J* = 2.3 Hz, OH), 5.01 (dd, *J* = 5.6 and 5.1 Hz, 1H). – ^{13}C NMR (75 MHz, $CDCl_3$): δ = 11.4, 14.9, 16.7, 28.6, 28.9, 29.4, 32.1, 36.5, 37.1, 73.9, 79.3, 94.9.

20. *(4S,5R,6S)-4-[(1R,3R,4S,5R,7R)-4,8-Dihydroxy-1,3,5,7-tetramethyloctyl]-6-ethyl-2,2,5-trimethyl-1,3-dioxane* (**22**): To a solution of 80.5 mg (0.23 mmol) of the lactol **21** in 5 ml of anhydrous ether was added 7.8 mg (0.2 mmol) of $LiAlH_4$. The mixture was stirred for 30 min at 0 °C and was subsequently refluxed for 1 h. After this time, thin layer chromatography indicated complete reaction. 10 ml of ether and then 5 ml of a saturated aqueous $NaHCO_3$ solution were added carefully with ice cooling. The phases were separated, and the aqueous phase was extracted four times with 5 ml of ethyl acetate. The combined organic phases were

dried with Na_2SO_4 and concentrated. Flash chromatography of the residue furnished 75.0 mg (91%) of **22** as a colorless solid, m.p. 80.5°C. – ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.81 (d, *J* = 7.2 Hz, 3H), 0.83 (d, *J* = 6.8 Hz, 3H), 0.85 (d, *J* = 7.0 Hz, 3H), 0.87 (d, *J* = 6.7 Hz, 3H), 0.88 (d, *J* = 6.5 Hz, 3H), 0.89 (t, *J* = 7.2 Hz, 3H), 1.05–1.15 (m, 1H), 1.15–1.40 (m, 4H), 1.27 (s, 3H), 1.29 (s, 3H), 1.43–1.55 (m, 1H), 1.65–1.76 (m, 5H), 1.85 (s, 2 OH), 3.10 (dd, *J* = 7.2 and 3.9 Hz, 2H), 3.38 (dd, *J* = 8.9 and 6.5 Hz, 1H), 3.42 (dd, *J* = 8.9 and 6.9 Hz, 1H), 3.60 (ddd, *J* = 8.7, 4.6, and 4.5 Hz, 1H). – ^{13}C NMR (75 MHz, $CDCl_3$): δ = 10.5, 12.6, 12.8, 14.7, 16.0, 16.3, 23.57, 23.62, 25.3, 32.0, 33.0, 33.4, 33.6, 35.3, 36.1, 37.7, 68.8, 71.2, 79.2, 79.9, 100.1. – $[\alpha]_D^{20}$ = +19.8 (*c* = 2.58, $CHCl_3$). – $C_{21}H_{42}O_4$ (358.6): calcd. C 70.34, H 11.80; found C 70.26, H 11.99.

21. *(4S,5R,6S)-4-[(1R,3R,4S,5R,7R)-8-(tert-Butyldimethylsilyloxy)-4-hydroxy-1,3,5,7-tetramethyloctyl]-6-ethyl-2,2,5-trimethyl-1,3-dioxane* (**23**): 68.9 mg (0.19 mmol) of **22**, 31.7 mg (0.21 mmol) of *tert*-butylchlorodimethylsilane, and 14.3 mg (0.21 mmol) of imidazole were allowed to react in 1 ml of anhydrous DMF as described under 2. The crude product was purified by flash chromatography with petroleum ether/ethyl acetate (20:1) to give 85.4 mg (95%) of **23** as a viscous oil. – ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.03 (s, 6H), 0.81–0.95 (m, 18H), 0.89 (s, 9H), 1.08 (ddd, *J* = 13.3, 9.2, and 4.4 Hz, 1H), 1.21 (ddd, *J* = 13.7, 10.1, and 3.4 Hz, 1H), 1.29 (s, 3H), 1.31 (s, 3H), 1.33–1.46 (m, 3H), 1.48–1.59 (m, 2H), 1.67–1.78 (m, 5H), 3.12 (dd, *J* = 7.2 and 3.9 Hz, 2H), 3.36 (dd, *J* = 9.7 and 6.5 Hz, 1H), 3.44 (dd, *J* = 9.7 and 5.9 Hz, 1H), 3.62 (ddd, *J* = 8.8, 4.6, and 4.6 Hz, 1H). This corresponded to a ^{1}H-NMR spectrum kindly provided by *H. Akita*. – ^{13}C NMR (75 MHz, $CDCl_3$): δ = −5.3 (2 C), 10.5, 12.6, 13.0, 14.6, 16.0, 16.6, 18.4, 23.7 (2 C), 25.4, 26.0, 32.2, 33.1, 33.5, 33.6, 35.2, 36.2, 37.7, 69.0, 71.2, 79.3, 80.1, 100.1. – MS (EI), *m/z*: 457.0 [M − CH_3], 357.0, 327.0, 309, 275, 257, 195, 177, 157, 137, 123, 99, 83, 69, 58, 43. This corresponded to a mass spectrum kindly provided by *H. Akita*. – $[\alpha]_D^{20}$ = +32.8 (*c* = 2.10, $CHCl_3$).

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