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ALLYLBORATION-REACTIONS, THE KEY TO A SHORT SYNTHESIS OF BENZOYL-PEDAMIDE [1]

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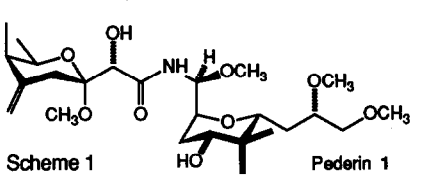
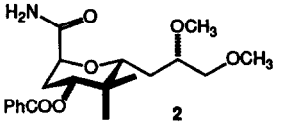
Abstract: *Benzoyl-pedamide (2) a key building block for the synthesis of pederin, has been synthesized in 13 steps from malic acid. The new stereogenic centers have been generated under reagent control of diastereoselectivity with selectivities of 87 and 80% using the newly developed chiral α-substituted allylboronate 16 as well as 21 as reagents.*

Pederin (**1**)[2], because of its unusual physiological activities[3], has become an important target for synthetic efforts. Based on the seminal work of Matsumoto[4] benzoyl-pedamide **2**[5] has been adopted as the key building block[6,7] for the B-ring-fragment in all subsequent synthesis of pederin[7,8]. For some syntheses of the related dibenzoylpederol **3** see ref.[7,9]. The original access to benzoyl-pedamide required 23 steps[5,6]. The sequence was shortened to 15 steps in an ingenious approach by Kocienski[7]. This sequence was, however, only partially stereoselective, requiring the separation of diastereomers by crystallisation.



Scheme 1 Pederin 1



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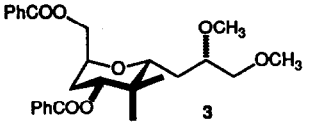
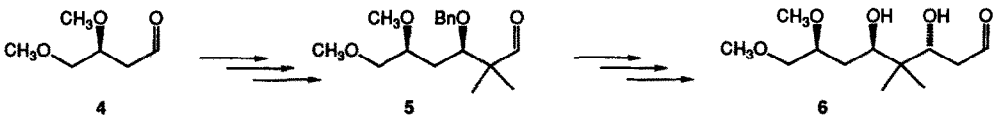


3

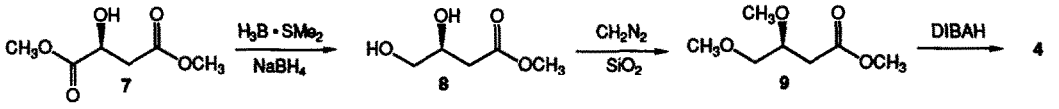
We would like to present here a shorter synthesis of benzoyl-pedamide which employs two stereoselective chain extension steps generating the 1,3,5..-polyol structural framework. The problem of stereoselectivity in the carbon-carbon bond forming steps was adressed by utilizing our recently developed stereoselective allylboration reactions[10,11]. In particular, for the first chain extension a new chiral reagent **16** was developed, which allows the generation of an alcohol stereogenic center next to a quaternary carbon.



Scheme 2

Stereoselective Synthesis of the Molecular Skeleton of Pedamide

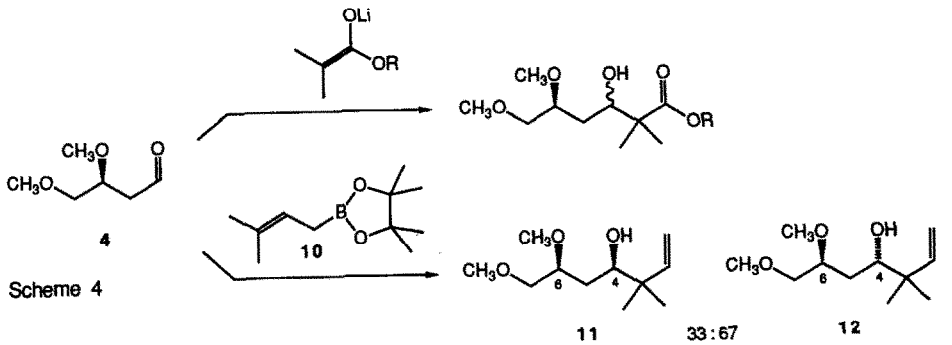
Like the synthesis of **2** by Kocienski[7] we departed from the aldehyde **4** which was prepared from malic acid. Instead of the seven step procedure described by Kocienski[7] we used a shorter sequence outlined in scheme 3.



Scheme 3

The problem in the earlier approaches was the methylation of the diol **8**[12] to the methoxy-compound **9**, which tends to undergo elimination under the basic conditions required. We avoided this difficulty by applying the mild methylation sequence of Ohno[13] which gave 80% of **9**. Recently another methylation procedure suitable for the **8**–**9** conversion has been described[14]. Subsequent reduction of the ester **9** to the aldehyde **4** was accomplished in 83% yield with DIBAH.

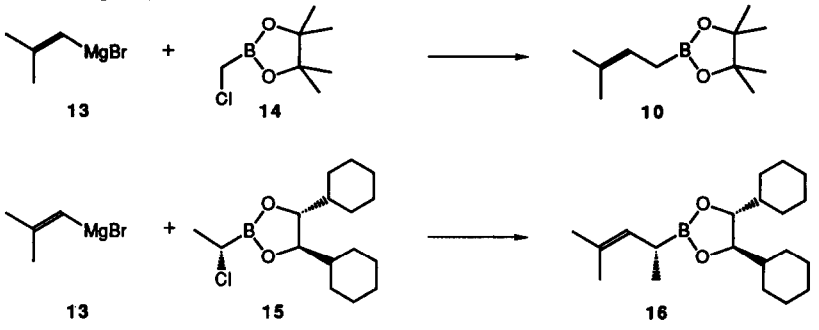
The chain extension of **4** to a compound of type **5** could in principle be effected by an aldol addition of an ester enolate. However, in the case of an aldehyde related to **4**, this proceeded[6] without any stereoselectivity. A recently described[15] chiral variant of the Mukaiyama aldol addition could probably remedy this deficiency. We, in turn, wanted to explore the level of stereoselectivity in chain extensions using γ,γ-disubstituted allylboronates.



Scheme 4

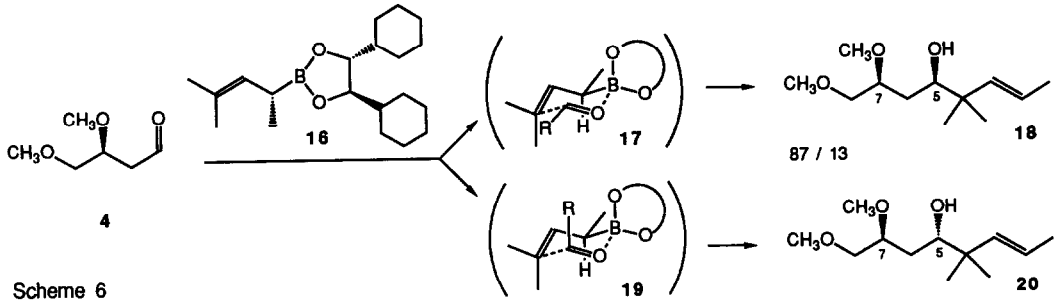
The reagent **10** was prepared from the Grignard reagent **13** and the α-chloromethylboronate **14**[16]. Reaction with the aldehyde **4** resulted in two products **11** and **12** in a 33:67 ratio. Based on the chemical shifts of the C-2 and C-4 carbon atoms in the ^{13}C-NMR-spectrum[17] we concluded that the undesired 4,6-*anti*-diastereomer predominated. Thus, in order to attain the desired 4,6-*syn*-product **11**

efficient reagent control of diastereoselectivity was required. For this reason, our attention was focussed on the chiral α-methyl substituted[18] allylboronates such as **16**, cf. also the chiral allylboranes described by H.C. Brown's group[19].



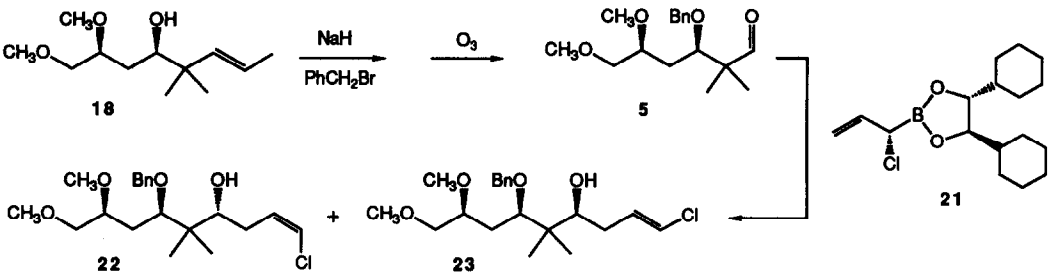
Scheme 5

The reagent **16** was prepared in 80% yield by reaction of the chiral α-chloro-ethylboronate **15**[18] with the Grignard reagent **13**. The resulting α-methyl-allylboronate **16** has the proper absolute configuration to create the desired 5-R-configuration in **18** upon reaction with the aldehyde **4**.



Scheme 6

Due to the steric hindrance involved, the aldehyde **4** was treated with the allylboronate **16** for 3 days at 4 kbar (or 1 d at 9 kbar). This led in high yield to a 87:13 mixture of diastereomers **18** and **20**, from which the major isomer could be isolated in 73% yield. The ^{13}C-NMR-data suggested[17] it to be the desired 5,7-*syn*-isomer **18**. The second isomer, probably **20**, had according to the ^{13}C-NMR-spectrum the 5,7-*anti*-configuration, yet it had an E-double bond as well. A more detailed study of an analogous reaction showed[11], that two routes contribute to the formation of the diastereomer **20**: First, the diastereomeric purity of the reagent **16** is not 100% but around 85% to 90% d.e. Any epi-**16** leads rapidly to **20**. Second, reactions of α,γ,γ-trisubstituted allylboronates show a slightly diminished (by 1-3%) simple diastereoselection [11]. Thus reaction via a chair transition state **19** with axial arrangement of the aldehyde residue or via the equivalent boat transition state (not shown) may account for ca. 1/3 of the amount of **20** formed. The major diastereomer **18** was then converted to the required aldehyde **5** by protection of the hydroxyl group (76%), followed by ozonolytic cleavage to give the aldehyde **5** in 90% yield.



Scheme 7 80 : 20

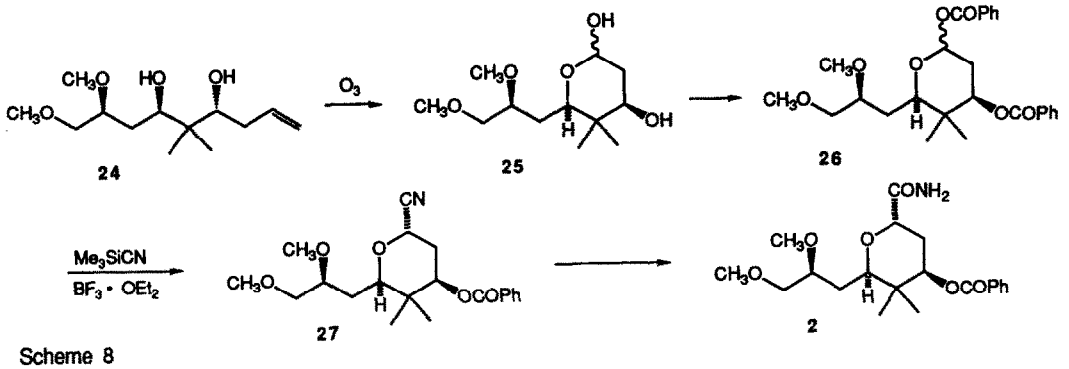
In the next chain extension step again the stereochemistry had to be controlled by a chiral reagent. We utilized the chiral α-chloroallylboronate **21**[10] as an equivalent for a chiral acetaldehyde enolate. This reagent adds with high asymmetric induction (>99%) to simple unfunctionalized aldehydes. The level of asymmetric induction is, however, somewhat compromised on addition to highly oxygenated aldehydes[10]. This turned out to hold also for the addition of **21** to the aldehyde **5**. The selectivity attained (80:20) in this mismatched case[20] was nevertheless better than the one (60:40) realized by using Roush's tartrate modified allylboronate[21].

The structural assignment of the diastereomers **22** and **23** obtained in 95% yield, rests on the fact that the major diastereomer has a Z-double bond, whereas the minor one has an E-double bond. In the addition reactions of α-substituted allylboronates to aldehydes the configuration of the newly formed stereocenter and that of the double bond are mechanistically linked[22]. Hence, the configuration of the double bond can generally be used as an indicator for the configuration of the newly formed stereocenter. MPLC separation of the diastereomers provided the desired alcohol **22** in 75% yield.

Thus, while the stereoselectivity in neither of the chain extension steps was complete, the level of stereoselectivity was nevertheless high enough to allow a rapid evolution of the synthesis of benzoyl-pedamide (**2**).

***Final Steps towards Benzoyl-pedamide* (2)**

First, the benzyl protecting group and the vinylic chlorine atom were reductively cleaved by lithium in liquid ammonia in one step. The resulting (86%) dihydroxy-olefin **24** was then directly ozonized to the lactol **25** (92%) which was obtained as an anomeric mixture. Benzoylation at both hydroxyl groups of **25** by standard procedure gave 77% of the dibenzoate **26**. The additional carbon was introduced as in the previous syntheses of benzoylpedamide[6,7] by treatment with trimethylsilyl cyanide and BF_3-etherate. In our hands this resulted in 98% of **27** with an axial/equatorial ratio of 97:3. This nitrile has been an intermediate in the pederin syntheses of both Oishi's[6] and Kocienski's[7] groups. For characterization it was hydrolyzed to benzoyl-pedamide **2** as described[7]. The material obtained showed the same spectral data as those reported in ref.[6,7].



Scheme 8

Our synthesis of benzoyl-pedamide (**2**) proceeded in 13 steps from malic acid and compares favorably with the previously published syntheses of these compounds. While our synthesis is as yet not fully stereoselective, it nevertheless brings with selectivities of 87:13 and 80:20 an improvement over extant syntheses. All in all, the present approach is a compromise between the aims of a short reaction sequence on the one hand, and high stereoselectivity on the other. Moreover the methods developed here and in particular the new reagent **16** are relevant for the synthesis of the related partial structures of the bryostatins[23], acutiphycin[24], oscillariolide[25], calyculin[26], or onnamide[27] as well as mycalamide[28].

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EXPERIMENTAL

All temperatures quoted are not corrected. - ^{1}H NMR and ^{13}C NMR: Bruker AM 300; WH 400. - Column chromatography: Kieselgel 60 (0.063 - 0.200 mm, Merck, Darmstadt). - Flash chromatography: Kieselgel 60 (0.040 - 0.063 mm, Merck, Darmstadt). - MPLC: Lichroprep Si 60 (Merck, Darmstadt). - Rotations: Perkin-Elmer Polarimeter 241.

1. *Methyl (3S)-3,4-dihydroxy-butanoate* (**8**): To a solution of 8.11 g (50 mmol) of dimethyl malate in 100 ml of anhydrous THF was added dropwise over 15 min 5.0 ml (50 mmol) of a 10 M solution of BH_3 in dimethyl sulfide. After stirring for 30 min 0.095 g (2.5 mmol) of $NaBH_4$ were added and the mixture was stirred for 1 h. 50 ml of methanol were added and after stirring for 30 min the solvents were removed i.vac. The residue was purified by flash chromatography using petroleum ether (b.p. 40-60°C)/ethyl acetate = 1:4 to give 5.30 g (80%) of the diol **8**. - $[\alpha]_D^{23}$ = -51.2 (c = 5.00, $CHCl_3$). - ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.46 (dd, J = 16.2 and 4.6 Hz, 1H), 2.54 (dd, J = 16.2 and 8.0 Hz, 1H), 2.90 (t, J = 6.0 Hz, 1H), 3.43 - 3.53 (m, 1H), 3.61 - 3.64 (m, 2H), 3.69 (s, 3H), 4.06 - 4.15 (m, 1H). - ^{13}C NMR (75 MHz, $CDCl_3$): δ = 37.4, 51.9, 65.7, 68.4, 173.0. $C_5H_{10}O_4$ (134.1) Calcd. C 44.77 H 7.51; Found C 44.75 H 7.22.

2. *Methyl (3S)-3,4-dimethoxy-butanoate* (**9**): 1.34 g (10 mmol) of methyl (3S)-3,4-dihydroxy-butanoate (**8**) was applied to 30 g of silica gel (Kieselgel 60, 0.063-0.200 nm, Merck, Darmstadt) and suspended in 100 ml of dry ether. After cooling to 0°C 200 ml of a 1 m solution of diazomethane in ether were added dropwise over 2 h. After stirring for 5 h at 0°C and reaching room temperature overnight the mixture was filtered, and the filtrate was concentrated. The residue was purified by flash chromatography using petroleum ether (b.p. 40-60°C)/ethyl acetate = 2:1 to give 1.30 g (80%) of **9** next to 0.19 g of a mixture of monomethylated derivatives.

9: $[\alpha]_D^{20}$ = -5.32 (c = 1.90, $CHCl_3$). - ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.53 (d, J = 6.5 Hz, 2H), 3.35 (s, 3H), 3.39 (s, 3H), 3.43 (d, J = 4.8 Hz, 2H), 3.67 (s, 3H), 3.78 (tt, J = 6.5 and 4.8 Hz, 1H). - ^{13}C NMR (75 MHz, $CDCl_3$): δ = 36.6, 51.6, 57.7, 59.2, 73.5, 76.5, 171.9.
$C_7H_{14}O_4$ (162.2) Calcd. C 51.84 H 8.70; Found C 51.78 H 8.70.

3. *(3S)-3,4-Dimethoxy-butanal* (**4**): To a solution of 0.24 g (1.5 mmol) of methyl (3S)-3,4-dimethoxybutanoate (**9**) in 5 ml of anhydrous toluene was added at -78°C 2.05 ml (1.6 mmol) of a 0.78 M solution of diisobutylaluminium hydride in toluene. After stirring for 30 min at -78°C, 1 ml of 1 M sulfuric acid was added followed by 10 ml of ether. After the mixture reached room temperature, the phases were separated and the organic phase was washed with 2 ml of 0.25 M sulfuric acid, 2 ml of brine, dried with $MgSO_4$ and concentrated. The residue was purified by flash chromatography using petroleum ether (b.p. 40-60°C)/ethyl acetate = 3:1 to give 0.164 g (83%) of **4** as a colorless liquid. - $[\alpha]_D^{20}$ = -5.9 (c = 8.6, $CHCl_3$), ref. [7]: -7.8 (c = 9.2, $CHCl_3$). - ^{1}H-NMR- and ^{13}C-NMR-data agreed with those reported in ref. [7].

4. *2-(3-Methyl-2-butenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane* (**10**): To a solution of 1.76 g (10 mmol) of 2-chloromethyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**14**) [16] in 50 ml of THF was added at -78°C 11.1 ml (10 mmol) of a 0.9 M solution of 2-methyl-propenyl-magnesium bromide in THF. The temperature was allowed to rise overnight. After addition of 30 ml aqueous saturated NH_4Cl-solution the phases were separated and the aqueous phase was extracted three times with 30 ml each of ether. The combined organic phases were washed with 20 ml of brine, dried with $MgSO_4$ and concentrated. The residue was chromatographed over 80 g of silica gel with petroleum ether (b.p. 40-60°C)/ether = 30:1 to give 1.67 g (85%) of the allylboronate **10**, which was contaminated by ca. 15% of 2-(2-methyl-1-propenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane. - ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.22 (s, 12H), 1.57 (s, 3H), 1.58 (d, J = 6.9 Hz, 2H), 1.67 (d, J = 1.5 Hz, 3H), 5.20 (tq, J = 6.9 and 1.5 Hz, 1H). - ^{13}C NMR (75 MHz, $CDCl_3$): δ = 17.6, 24.8, 25.7, 83.1, 118.6, 131.4.
$C_{11}H_{21}BO_2$ (196.1) Calcd. C 67.38 H 10.79; Found C 67.32 H 10.92; Calcd. C 67.17 H 10.75 containing 15% of the vinylboronate.

5. *(6S)-4-Hydroxy-6,7-dimethoxy-3,3-dimethyl-1-heptene* (**11**) and (**12**): 0.132 g (1.0 mmol) of (3S)-3,4-dimethoxy-butanal (**4**) [7] and 0.196 g (1.0 mmol) of 2-(3-methyl-2-butenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**10**) were pressurized in 5 ml of petroleum ether (b.p. 40-60 °C) for 3 d to 4 kbar. The mixture was diluted by 50 ml of petroleum ether, washed with 20 ml of saturated NH_4Cl-solution. The aqueous phase was extracted 4 times with 20 ml each of petroleum ether. The combined organic phases were washed with 10 ml of brine, dried with $MgSO_4$ and concentrated. The diastereomer ratio of the 4R,6S- and the 4S,6S-isomers was determined by ^{13}C-NMR to be 33:67. The products were purified by flash chromatography with petroleum ether (b.p. 40-60 °C)/ethyl acetate = 3:1 to give 0.147 g (82%) of the alcohols **11** and **12**.
$C_{11}H_{22}O_3$ (202.3) Calcd. C 65.31 H 10.96; Found C 65.24 H 10.98.
(4R,6S)-**11**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.01 (s, 6H), 1.49 (ddd, J = 14.6, 10.3, and 8.5 Hz, 1H), 1.71 (ddd, J = 14.6, 4.0, and 1.6 Hz, 1H), 3.36 (s, 3H), 3.41 - 3.43 (m, 3H), 3.43 (s, 3H), 3.46 - 3.56 (m, 2H), 5.00 (dd, J = 17.1 and 1.5 Hz, 1H), 5.02 (dd, J = 11.3 and 1.5 Hz, 1H), 5.85 (dd, J = 17.1 and 11.3 Hz, 1H). - ^{13}C NMR (75 MHz, $CDCl_3$): δ = 22.1, 23.1, 33.4, 41.0, 57.4, 59.2, 74.3, 77.4, 80.9, 112.4, 145.6.
(4S,6S)-**12**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.00 (s, 3H), 1.01 (s, 3H), 1.45 (ddd, J = 14.5, 10.7, and 4.0 Hz, 1H), 1.71 (ddd, J = 14.5, 7.4, and 1.8 Hz, 1H), 2.33 (d, J = 4.0 Hz, 1H), 3.36 (s, 3H), 3.41 (s, 3H), 3.45 (dd, J = 4.7 and 1.0 Hz, 2H), 3.52 (ddd, J = 11.0, 4.0, and 2.1 Hz, 1H), 3.56 - 3.61 (m, 1H), 5.03 (dd, J = 17.4 and 1.4 Hz, 1H), 5.06 (dd, J = 10.9 and 1.4 Hz, 1H), 5.83 (dd, J = 17.4 and 10.9 Hz, 1H). - ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 22.4, 22.8, 33.5, 41.4, 57.8, 59.2, 74.5, 74.7, 78.0, 113.0, 145.4.

6. *(4R,5R)-2-((1R)-1,3-Dimethyl-2-butenyl)-4,5-dicyclohexyl-1,3,2-dioxaborolane* (**16**): To a solution of 4.82 g (15 mmol) of (4R,5R)-2-dichloromethyl-4,5-dicyclohexyl-1,3,2-dioxaborolane[18] in 150 ml of anhydrous THF was added at -78°C 8.45 ml (15 mmol) of a 1.78 M solution of methyllithium in ether. After stirring for 1 h at -78°C 13.0 ml (13 mmol) of a 1 M solution of $ZnCl_2$ in THF was added. After stirring for 30 min the mixture was allowed to reach room temperature. After stirring for another 3 h the mixture was cooled to -78°C and a solution of 24.2 ml (15 mmol) of a 0.62 M solution of 2-methyl-propenyl-magnesium bromide in THF was added dropwise. After reaching room temperature 50 ml of saturated aqueous NH_4Cl-solution was added. The phases were separated and the aqueous phase was extracted three times with 50 ml each of ether. The combined organic extracts were washed with 30 ml of brine, dried with $MgSO_4$ and concentrated. The crude product was purified by column chromatography over 200 g of silica gel with petroleum ether (b.p. 40-60 °C)/ether = 15:1 to give 3.82 g (80%) of **16** as a colorless oil. $[\alpha]_D^{20}$ = 29.9 (c = 2.00, $CHCl_3$). - ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.90 - 1.34 (m, 15H), 1.54 - 1.74 (m, 16H), 1.99 - 2.09 (m, 1H), 3.82 (d, J = 5.0 Hz, 2H), 5.08 (d sept, J = 9.5 and 1.4 Hz, 1H). - ^{13}C NMR (75 MHz, $CDCl_3$): δ = 16.4, 17.9, 25.8, 25.9, 26.0, 26.5, 27.3, 28.2, 43.0, 83.1, 127.2, 129.9.
$C_{20}H_{35}BO_2$ (318.3) Calcd. C 75.47 H 11.08; Found C 75.17 H 10.99.

7. *(7S,2E)-5-Hydroxy-7,8-dimethoxy-4,4-dimethyl-2-octene* (**18**): 0.955 g (3.0 mmol) of (4R,5R)-2-((1R)-1,3-dimethyl-2-butenyl)-4,5-dicyclohexyl-1,3,2-dioxaborolane (**16**) and 0.396 g (3.0 mmol) of (3S)-3,4-dimethoxybutanal (**4**) were pressurized in 5 ml of petroleum ether (40-60°C) for 3 d to 4 kbar. Workup as described under 2. resulted in 0.475 g (73%) of the alcohol **18**. $[\alpha]_D^{20}$ = +0.7 (c= 2.70, $CHCl_3$) - ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.97 (s, 6H), 1.47 (ddd, J = 14.6, 10.4, and 8.2 Hz, 1H), 1.66 - 1.68 (m, 4H), 1.72 (dd, J = 4.3 and 1.7 Hz, 1H), 3.31 (d, J = 2.1 Hz, 1H), 3.36 (s, 3H), 3.42 (s, 3H), 3.40 - 3.44 (m, 2H), 3.46 - 3.56 (m, 1H), 5.34 - 5.49 (m, 2H). - ^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.3, 22.8, 23.6, 33.2, 40.4, 57.3, 59.2, 74.3, 77.7, 80.8, 122.8, 138.2.
$C_{12}H_{24}O_3$ (216.3) Calcd. C 66.63 H 11.82; Found C 66.69 H 12.02.

8. *(2E,5R,7S)-5-Benzyloxy-7,8-dimethoxy-4,4-dimethyl-2-octene*: 1.774 g (8.2 mmol) of (2E,5R,7S)-5-hydroxy-7,8-dimethoxy-4,4-dimethyl-2-octene (**18**) was added dropwise to a suspension of 0.36 g (15 mmol) of sodium hydride in 40 ml of DMF at room temperature. After stirring for 1 h a solution of 3.42 g (20 mmol) of benzyl bromide in 10 ml of DMF was added dropwise over 15 min. After stirring for 1 d 20 ml of water and 20 ml of ether were added. The aqueous phase was extracted 4 times with 30 ml each of ether. The organic phase was washed with 10 ml of brine, dried with $MgSO_4$ and concentrated. Flash chromatography with petroleum ether (b.p. 40-60 °C)/ethyl acetate = 10 : 1 resulted in 1.91 g (76 %) of the benzyl derivative as a colorless oil. - ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.04 (s, 3H), 1.05 (s, 3H), 1.68 (d, J = 5.8 Hz, 3H), 1.69 - 1.79 (m, 2H), 3.13 (dd, J = 7.3 and 3.9 Hz, 1H), 3.36 (s, 3H), 3.38 (s, 3H), 3.37 - 3.48 (m, 3H), 4.60 (s, 2H), 5.41 (dq, J = 15.7 and 5.8 Hz, 1H), 5.52 (dq, J = 15.7 and 1.0 Hz, 1H), 7.25 - 7.39 (m, 5H). - ^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.2, 23.2, 24.6, 33.4, 41.6, 57.2, 59.1, 73.7, 74.8, 78.7, 84.1, 122.2, 127.3, 127.5, 128.2, 138.5, 139.2.
$C_{19}H_{30}O_3$ (306.5) Calcd. C 74.47 H 9.87; Found C 74.43 H 9.86.

9. *(3R,5S)-3-Benzyloxy-5,6-dimethoxy-2,2-dimethyl-hexanal* (**5**): Into a solution of 1.500 g (4.9 mmol) of the compound obtained under 8. in 50 ml of CH_2Cl_2 was introduced at -78°C a stream of ozone in oxygen until the blue color persisted. An excess of ozone was purged by a stream of nitrogen. 1.97 g (7.5 mmol) of triphenylphosphine were added and the mixture was allowed to reach room temperature. After concentration the residue was taken up in 75 ml of petroleum ether (b.p. 40-60°C) and was filtered. The filtrate was concentrated and the residue was purified by flash chromatography with petroleum ether (b.p. 40-60°C)/ethyl acetate = 5:1 to give 1.30 g (90%) of the aldehyde **5** as a colorless oil. - ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.04 (s, 3H), 1.13 (s, 3H), 1.72 - 1.87 (m, 2H), 3.32 - 3.48 (m, 3H), 3.35 (s, 3H), 3.38 (s, 3H), 3.63 (dd, J = 5.9 and 5.0 Hz, 1H), 4.48 and 4.60 (AB-system, J = 11.5 Hz, 2H), 7.25 - 7.35 (m, 5H), 9.58 (s, 1H). - ^{13}C NMR (75 MHz, $CDCl_3$): δ = 17.5, 19.2, 33.2, 51.2, 57.3, 59.2, 72.8, 74.1, 78.0, 80.0, 127.5, 127.6, 128.3, 138.4, 205.9.
$C_{17}H_{26}O_4$ (294.4) Calcd. C 69.36 H 8.90; Found C 69.26 H 8.74.

10. *(6R,8S)-6-Benzyloxy-1-chloro-4-hydroxy-8,9-dimethoxy-5,5-dimethyl-1-nonene* (**22**) and (**23**): To a solution of 3.21 g (10 mmol) of (4R,5R)-2-dichloromethyl-4,5-dicyclohexyl-1,3,2-dioxaborolane [18] in 50 ml of THF was added at -78°C over 15 min. 6.7 ml (10 mmol) of a 1.5 M solution of vinylmagnesium chloride in ether. After stirring for 1 h a solution of 1.16 g (8.5

mmol) of $ZnCl_2$ in 10 ml of THF was added dropwise. The mixture was allowed to reach room temperature. After stirring for 3 h the solvents were removed i.vac. and the residue was taken up in 50 ml of petroleum ether (b.p. 40-60 °C). The suspension was stirred for 30 min and filtered. The filtrate was concentrated and once more triturated with 50 ml of petroleum ether as above. Concentration of the filtrate gave 2.50 g of crude (4R,5R)-2-((1S)-1-chloro-2-propenyl)-4,5-dicyclohexyl-1,3,2-dioxaborolane (**21**) which was dissolved in 5 ml of petroleum ether. 1.12 g (3.8 mmol) of the aldehyde **5** was added and the solution was kept for 3 d at room temperature. The mixture was partitioned between 10 ml of saturated aqueous NH_4Cl-solution and 20 ml of petroleum ether (b.p. 40-60°C). The aqueous phase was extracted three times with 30 ml each of petroleum ether. The combined organic phases were washed with 10 ml of brine, dried with $MgSO_4$ and concentrated. Flash chromatography with petroleum ether (b.p. 40-60°C)/ethyl acetate = 4:1 gave 1.34 g (95%) of a 80:20 mixture of the alcohols **22** and **23**. The diastereomeres were separated by MPLC with petroleum ether (40-60°C)/ethyl acetate = 4:1 to give 1.05 g (75%) of **22** and 0.22 g (16%) of **23**.

(1Z,4R,6R,8S)-**22**: $[\alpha]_D^{21}$ = 40.2 (c= 4.12 $CHCl_3$). - ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.89 (s, 3H), 1.05 (s, 3H), 1.82 (dd, J = 15.0 and 6.5 Hz, 1H), 1.93 (ddd, J = 15.0, 6.5, and 3.9 Hz, 1H), 2.20 (ddd, J = 14.7, 10.2, and 6.4 Hz, 1H), 2.41 (dd, J = 14.5 and 6.9 Hz, 1H), 3.32 - 3.47 (m, 4H), 3.36 (s, 3H), 3.41 (s, 3H), 3.72 (broad d, J = 10.2 Hz, 1H), 3.83 (broad s, 1H), 4.57 and 4.65 (AB-system, J = 11.2 Hz, 2H), 5.96 (dt, J = 7.1 and 6.9 Hz, 1H), 6.08 (d, J = 7.1 Hz, 1H), 7.26 - 7.35 (m, 5H). - ^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.3, 22.0, 29.9, 33.3, 41.8, 57.4, 59.2, 73.5, 74.4, 75.2, 78.8, 85.6, 118.7, 127.7, 128.4, 129.9, 138.0.

(1E,4S,6R,8S)-**23**: $[\alpha]_D^{21}$ = -20.6 (c= 5.08, $CHCl_3$): - ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.83 (s, 3H), 0.98 (s, 3H), 1.74 (dt, J = 15.0 and 6.4 Hz, 1H), 1.94 (ddd, J = 20.7, 6.8, and 3.6 Hz, 1H), 2.10 (dd, J = 10.0 and 5.9 Hz, 1H), 2.22 - 2.27 (m, 1H), 3.20 (dd, J = 3.1 and 0.7 Hz, 1H), 3.32 - 3.39 (m, 1H), 3.39 (s, 3H), 3.40 (s, 3H), 3.42 - 3.53 (m, 4H), 4.52 and 4.65 (AB-system, J = 11.5 Hz, 2H), 5.93 - 6.04 (m, 2H), 7.26 - 7.40 (m, 5H). - ^{13}C NMR (75 MHz, $CDCl_3$): δ = 17.0, 19.9, 33.4, 33.5, 42.8, 57.5, 59.3, 73.1, 74.1, 76.5, 78.7, 83.1, 118.3, 127.6, 128.4, 131.9, 138.6.
$C_{20}H_{31}ClO_4$ (370.9) Calcd. C 64.76 H 8.42; **22**: Found C 64.81 H 8.37; **23**: Found C 64.85 H 8.45.

11. *(4R,6R,8S)-4,6-Dihydroxy-8,9-dimethoxy-5,5-dimethyl-1-nonene* (**24**): Into a solution of 0.74 g (2 mmol) of the benzylether **22** in 20 ml of THF was condensed at -78°C 40 ml of NH_3 (dried over lithium). Ca. 0.07 g (10.0 mmol) of lithium were added in small portions until the blue color of the solution persisted. After stirring for 5 min solid NH_4Cl was added until the mixture was decolorized. The ammonia was allowed to evaporate and the residue was taken up in 10 ml of water and was acidified by addition of 2 N hydrochloric acid to pH = 5. The mixture was extracted 5 times with 20 ml each of ether. The combined organic phases were washed with 10 ml of brine, dried with $MgSO_4$ and concentrated. Flash chromatography with petroleum ether (b.p. 40-60°C)/ethyl acetate = 1:1 resulted in 0.425 g (86%) of the diol **24**. - $[\alpha]_D^{20}$ = + 16.2 (c = 1.00, $CHCl_3$). - ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.86 (s, 3H), 0.91 (s, 3H), 1.62 - 1.76 (m, 2H), 2.09 - 2.27 (m, 2H), 3.36 (s, 3H), 3.44 (s, 3H), 3.42 - 3.45 (m, 2H), 3.53 - 3.59 (m, 2H), 3.71 (ddd, J = 8.2, 3.0, and 1.7 Hz, 1H), 3.77 (d, J = 4.1 Hz, 1H), 4.26 (d, J = 1.6 Hz, 1H), 5.06 (dd, J = 9.9 and 1.8 Hz, 1H), 5.10 (dd, J = 17.1 and 1.8 Hz, 1H), 5.86 - 6.00 (m, 1H). - ^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.5, 21.1, 33.1, 36.6, 40.1, 57.4, 59.2, 74.0, 77.2, 78.6, 81.2, 116.4, 136.9.
$C_{13}H_{26}O_4$ (246.4) Calcd. C 63.38 H 10.64; Found C 63.22 H 10.62.

12. *(2R,4R)-4,6-Dihydroxy-2-[(2S)-2,3-dimethoxypropyl]-3,3-dimethyl-2H-tetrahydropyran* (**25**): Into a solution of 0.345 g (1.4 mmol) of the alkene **24** in 30 ml of CH_2Cl_2/methanol = 1:1 was introduced at -78°C a stream of ozone until a blue color persisted. Excess of ozone was removed by a stream of nitrogen, 0.55 g (2.1 mmol) of triphenylphosphine was added, and the mixture was allowed to reach room temperature. After concentration, the residue was flash chromatographed with ethyl acetate to give 0.32 g (92%) of the lactol **25** as a 60:40 (α:ß) anomeric mixture.
$C_{12}H_{24}O_5$ (248.3) Calcd. C 58.04 H 9.74; Found C 58.00 H 9.62.

25 (α-anomer, axial): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.83 (s, 3H), 0.91 (s, 3H), 1.46 - 1.57 (m, 1H), 1.64 - 1.75 (m, 1H), 1.86 (dd, J = 12.9 and 5.0 Hz, 2H), 3.35 (s, 3H), 3.36 (s, 3H), 3.38 - 3.52 (m, 6H), 3.70 (dd, J = 6.7 and 6.1 Hz, 1H), 5.30 (s, broad, 1H). - ^{13}C NMR (75 MHz, $CDCl_3$): δ = 11.3, 22.3, 29.8, 35.2, 38.5, 59.2, 65.8, 71.4, 74.3, 74.4, 78.1, 92.0.

25 (ß-anomer, equatorial): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.85 (s, 3H), 0.89 (s, 3H), 1.64 - 1.75 (m, 4H), 3.01 (dd, J = 7.5 and 5.2 Hz, 1H), 3.35 (s, 3H), 3.36 (s, 3H), 3.38 - 3.52 (m, 5H), 3.76 - 3.79 (m, 1H), 4.65 - 4.70 (m, 1H). - ^{13}C NMR (75 MHz, $CDCl_3$): δ = 12.4, 22.2, 29.8, 38.3, 39.1, 56.9, 60.3, 70.8, 74.1, 76.8, 78.0, 94.4.

13. *(2R,4R)-4,6-Dibenzoyloxy-2-[(2S)-2,3-dimethoxypropyl]-3,3-dimethyl-2H-tetrahydropyran* (**26**): To a solution of 0.25 g (1.0 mmol) of the lactol **25** and of 10 mg of 4-dimethylamino-pyridine in 10 ml of pyridine was added dropwise at 0°C 0.350 g (2.5 mmol) of benzoyl chloride. The mixture was allowed to reach room temperature and was stirred for 1 d. It was acidified by addition of 2 N hydrochloric acid and extracted 4 times with 30 ml each of ether. The combined organic phases were washed with 20 ml of saturated aqueous $NaHCO_3$-solution, 20 ml of brine, dried with $MgSO_4$ and concentrated. The crude product was purified by flash chromatography with petroleum ether (b.p. 40-60°C)/ethyl acetate = 5:1 to give 0.35 g (77%) of the dibenzoate **26** as a 44:56 α/ß-mixture.
$C_{26}H_{32}O_7$ (456.5) Calcd. C 68.40 H 7.07; Found C 68.18 H 7.14.

26 (α-anomer, axial): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.98 (s, 3H), 1.16 (s, 3H), 1.75 - 1.90 (m, 2H), 2.02 - 2.32 (m, 2H), 3.10 (s, 3H), 3.33 (s, 3H), 3.39 - 3.54 (m, 3H), 3.87 (dd, J = 9.5 and 2.8 Hz, 1H), 5.39 (dd, J = 11.8 and 5.1 Hz, 1H), 6.48 (d, J = 3.4 Hz, 1H), 7.41 - 7.50 (m, 2H), 7.55 - 7.62 (m, 1H), 8.04 - 8.13 (m, 2H). - ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.0, 22.4, 29.3, 31.1, 37.7, 56.9. 58.9, 73.0, 73.7, 75.9, 77.4, 92.3, 128.4, 128.5, 129.6, 129.8, 133.1, 164.9, 165.9.

26 (ß-anomer, equatorial): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.94 (s, 3H), 1.18 (s, 3H), 1.75 - 1.90 (m, 2H), 2.02 - 2.32 (m, 2H), 3.22 (dd, J = 10.6 and 5.1 Hz, 1H), 3.35 (s, 3H), 3.39 (s, 3H), 3.39 - 3.54 (m, 3H), 5.03 (dd, J = 11.9 and 4.8 Hz, 1H), 5.94 (dd, J = 10.1 and 2.4 Hz, 1H), 7.41 - 7.50 (m, 2H), 7.55 - 7.62 (m, 1H), 8.04 - 8.13 (m, 2H). - ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.8, 22.2, 29.3, 32.4, 38.2, 56.9, 59.2, 73.0, 74.5, 75.9, 77.6, 92.4, 128.3, 128.4, 129.6, 129.9, 133.4, 164.6, 164.7.

14. *(2R,4R,6S)-4-Benzoyloxy-6-cyano-2-[(2S)-2,3-dimethoxypropyl]-3,3-dimethyl-2H-tetrahydropyran* (**27**): To a solution of 0.170 g (0.37 mmol) of the dibenzoate **26** in 10 ml of acetonitrile was added dropwise at 0°C first 0.074 g (0.75 mmol) of cyano-trimethylsilane, than 0.053 g (0.37 mmol) of borontrifluoride-diethyletherate. After stirring for 4 h at 0°C 5 ml of saturated aqueous $NaHCO_3$-solution was added and the mixture was extracted 4 times with 20 ml each of ether. The combined organic phases were dried with $MgSO_4$ and concentrated to give 0.132 g (98%) of **27**. - $[\alpha]_D^{20}$ = 58.1 (c = 1.41, $CDCl_3$). - ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.97 (s, 3H), 1.10 (s, 3H), 1.74 (ddd, J = 14.1, 10.2, and 4.0 Hz, 1H), 1.87 (ddd, J = 14.1, 8.6, and 1.9 Hz, 1H), 2.13 (ddd, J = 13.3, 11.5, and 6.0 Hz, 1H), 2.20 (ddd, J = 13.3, 5.2, and 1.7 Hz, 1H), 3.39 (s, 3H), 3.40 (s, 3H), 3.44 - 3.56 (m, 2H), 3.68 (dd, J = 10.2 and 1.7 Hz, 1H), 4.94 (dd, J = 5.8 and 1.2 Hz, 1H), 5.17 (dd, J = 11.5 and 5.1 Hz, 1H), 7.45 (t, J = 7.5 Hz, 2H), 7.58 (tt, J = 7.5 and 1.25 Hz, 1H), 8.02 (dt, J = 7.1 and 1.35 Hz, 2H), cf. ref.[7] in the ^{1}H-NMR-spectra the presence of 3% of an isomer with an equatorial cyano group could be detected. - ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.4, 22.3, 29.6, 29.9, 38.5, 57.1, 59.2, 63.5, 72.6, 73.9, 77.5, 78.7, 117.0, 128.5, 129.6, 130.0, 133.3, 165.5.
$C_{20}H_{27}NO_5$ (361.4) Calcd. C 66.46 H 7.53 N 3.88; Found C 66.53 H 7.62 N 3.82.

15. *Benzoyl-pedamide* (**2**): 0.065 g (0.18 mmol) of the nitrile **27** were treated as described in ref.[7]. Flash chromatography with petroleum ether (40-60°C)/ethyl acetate = 1:1 resulted in 0.040 g (59%) of **2** as a colorless solid, m.p. 135-137°C (ref.[6]: m.p. 145-146°C; ref.[5]: m.p. 137-138°C). - $[\alpha]_D^{20}$ = 18.6 (c = 2.64, $CHCl_3$) (ref.[6]: 20.5 (c = 3.22, $CHCl_3$); ref.[5]: 15.9 (c = 3.24, $CHCl_3$)). - The ^{1}H-NMR-spectrum (300 MHz, $CDCl_3$), and the ^{13}C-NMR-spectrum (75 MHz, $CDCl_3$) agreed with those reported in ref.[7].

References and Notes

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