Stereoselective Synthesis of Alcohols, XXXVIII[1]

Stereoselective Total Synthesis of the Denticulatins

Marc W. Andersen, Bernhard Hildebrandt, Georg Dahmann, and Reinhard W. Hoffmann*

Fachbereich Chemie der Philipps-Universität, Marburg
Hans-Meerwein-Str., W-3550 Marburg, F.R.G.

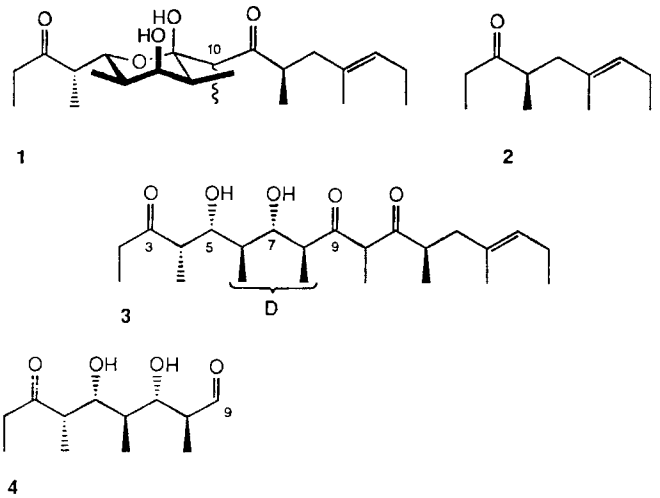
Received May 8, 1991

Key Words: Marine natural products / Hemiketal formation, selective / Denticulatins

The total synthesis of the denticulatins **1** is described. Key feature is the efficient generation of the C-1-to-C-9 building block **37** by three consecutive stereoselective carbon – carbon bond-forming steps using chiral allylboronates. The C-10-to-C-17 building block was obtained by kinetic Sharpless resolution of an allylic alcohol followed by an Ireland-Claisen rearrangement.

Marine organisms have provided chemists with a large number of new natural products, many of which are derived from a polypropionate biogenetic pathway[2]. Among these products are the denticulatins A and B, which were isolated by Faulkner from *Siphonaria denticulata*[3]. The structures have been elucidated by a single-crystal X-ray analysis to be **1**, differing in configuration at the epimerizable stereocenter at C-10. The absolute configuration was tentatively assigned from the sign of rotation of the degradation product **2** and was confirmed recently by the first total synthesis of the denticulatins by the group of Ziegler[4].

Scheme 1



While the biological significance of the denticulatins is not fully known – these compounds are ichtyotoxic and may be involved as antifeedants – the chemistry of these compounds provides several challenges and questions: First of all, the denticulatins contain a hemiketal ring. They are therefore formally derived from the dihydroxy triketone **3**, which could form two further hemiketals by addition of 7-OH to either the C-11 or the C-3 carbonyl group. It was not known, how readily these hemiketals equilibrated and what the factors are that determine their relative stability. From the point of synthesis, the long sequence of contiguous stereocenters is a challenge, since an efficient synthesis would require the controlled generation of the stereogenic centers in the same steps that are used to build the molecular skeleton. For this purpose several strategies for the synthesis of such structures have been developed[5] during the last decade, among which the aldol addition and the crotylmetal addition are most prominent. Nevertheless, the stereotriad D[5], occurring in many such polyketide natural products, is one which is still difficult to attain by these methods. We therefore felt that a synthesis of the denticulatins would provide a severe and realistic test for our ability to efficiently synthesize such molecules by using the crotylboration technique. Our synthesis of denticulatin[6] aimed at the construction of a protected equivalent of the aldehyde **4**, containing all the relevant stereocenters, which was to be combined with the ketone **2**. The same retrosynthetic scheme was the basis of Ziegler's synthesis of the denticulatins[4]. However, as will be shown below, stereoselective crotylboration afforded a much shorter access to the key aldehyde **4**.

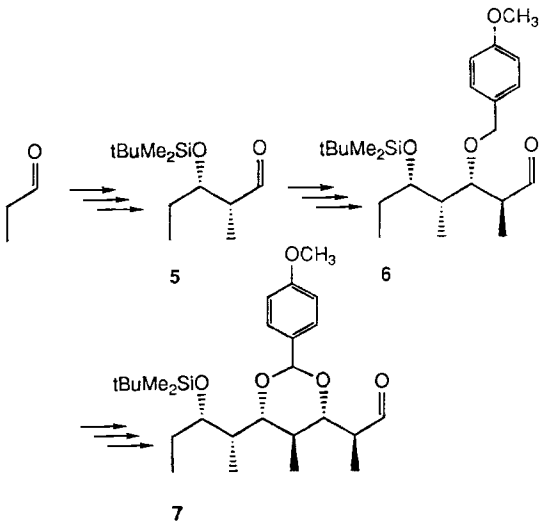
The Synthesis of the Aldehyde 7, the C-1-to-C-9 Building Block

The aldehyde **7** was considered to be a proper C-1-to-C-9 building block for the synthesis of the denticulatins. It was envisioned to be assembled by three consecutive stereoselective crotylboration sequences (Scheme 2).

The first sequence required a *syn*-selective chain elongation of propionaldehyde with control of absolute stereochemistry to give **5**. The second one required an *anti*-selective chain extension, in which substrate control of stereoselectivity was assumed to assist in obtaining the desired Cram product **6**. The third (again) *anti*-selective chain extension required reagent control of diastereoselectivity in

  0009–2940/91/0909–2127 $ 3.50+.25/0

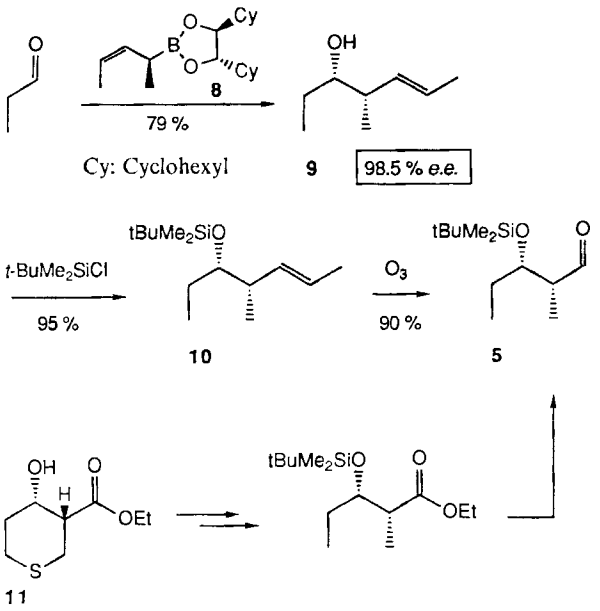
Scheme 2



order to attain the *anti*-Cram product **7**, i.e. to construct the stereotriad D[5].

The first chain extension was realized in 85% yield by using our recently developed chiral (*Z*)-pentenylboronate **8**[7]. The enantiomeric purity of the resulting alcohol **9** was determined by capillary gas chromatography of the carbamate obtained by reaction with (*S*)-(−)-1-phenylethyl isocyanate to be 98.5%.

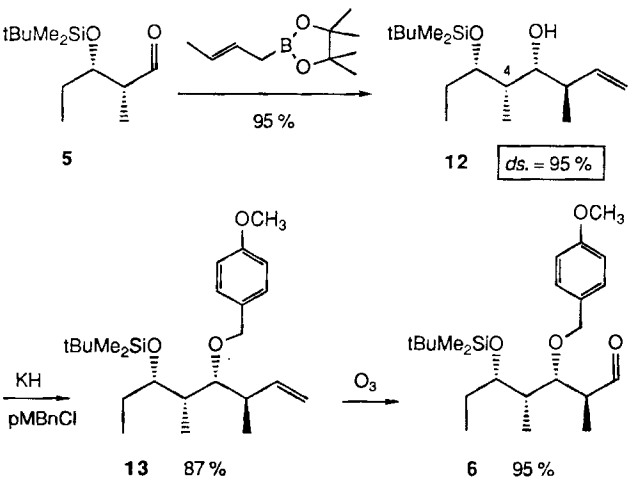
Scheme 3



Silylation, followed by ozonolysis, provided the required aldehyde **5**. The aldehyde was identical in its absolute configuration to material obtained earlier[8] from the hydroxy ester **11**, which had been used in our previous synthesis of anhydroserricornine[9]. The route via **11** lent itself more readily to scale-up and was at times used to procure larger supplies of the aldehyde **5**.

The next chain extension relied on the Cram selectivity found in the addition of (*E*)-crotylboronates [or (*E*)-enolates] to β-alkoxy-α-methyl aldehydes[10]. Our previously described[8] conversion of the aldehyde **5** into the homoallylic alcohol **12** and eventually into the aldehyde **6** was improved by workup of the ozonolysis mixture with triphenylphosphine.

Scheme 4

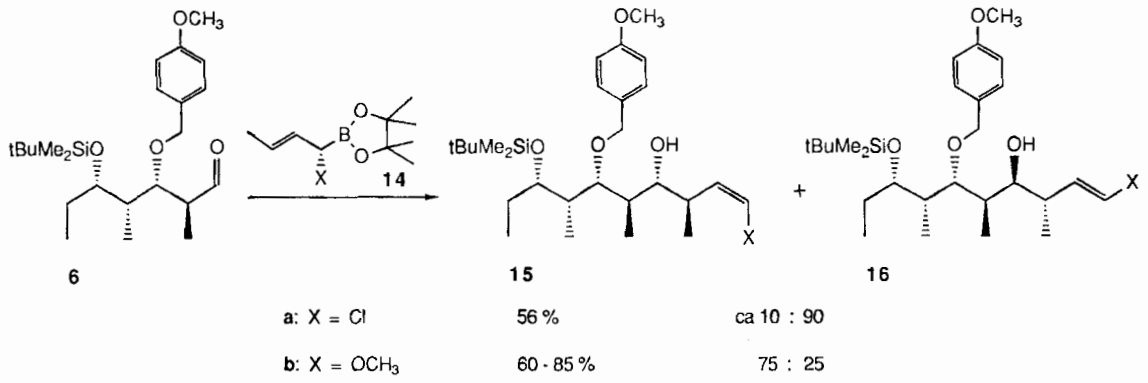


The relative configuration of the adduct **12**, as shown, was not explicitly proven at this stage. We noted, however, the characteristic ^{13}C-NMR chemical shift of $\delta = 6.8$ of the 4-CH_3 group. While it was obvious that the chain extension **5** → **12** profited from the high Cram selectivity of the aldehyde **5**, the same effect is now a severe obstacle in the conversion of the aldehyde **6** into the required *anti*-Cram product **15**. Model studies for this transformation had indicated[8] that the α-chiral (*E*)-crotylboronate **14a** possessed insufficient asymmetric induction to override the Cram selectivity of the aldehyde **6**. This proved true, as the undesired product **16a** of substrate control of stereoselectivity was formed in excess.

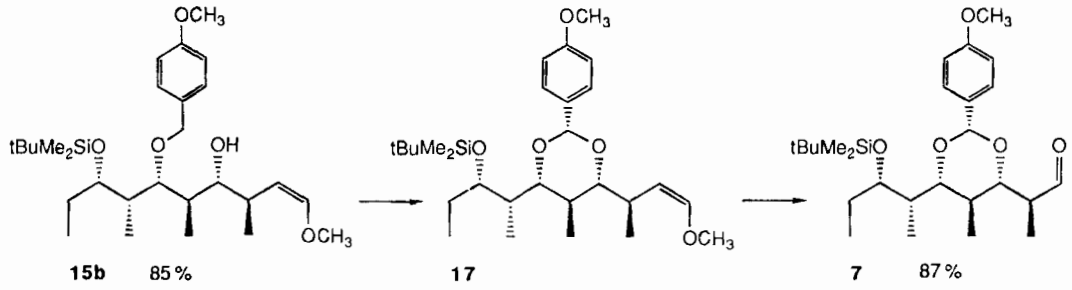
At this stage, assignment of the relative configuration of the newly formed stereocenters is no longer an easy task. In this respect the use of α-substituted crotylboronates for the chain extension is highly advantageous, since the configuration of the newly formed stereocenters is mechanistically connected with the configuration of the double bond that is generated[8]. Thus, in the case at hand, the product with the (*E*) double bond is the undesired Cram product, and the minor product with the (*Z*) double bond is the desired *anti*-Cram diastereomer. This shortcoming of the reagent **14a** led to the development of the chiral (*E*)-α-methoxycrotylboronate **14b**, as a reagent with a still higher asymmetric induction[11]. This crotylboronate **14b** eventually allowed us to perform the chain extension **6** → **15b** under the reagent-controlled selectivity of 3:1[12], as evidenced by the major diastereomer having a (*Z*)-enol ether function.

Chromatographic separation of the diastereomers proved to be easy. DDQ oxidation gave the acetal **17** as a single

Scheme 5



Scheme 6



isomer at the acetal carbon atom – the aryl group residing probably in an equatorial position[13]. At this stage the relative configuration of the stereocenters C-5 to C-7 could be unambiguously established from the coupling constants 5-H/6-H and 6-H/7-H being >10 Hz. The configuration at C-8 was assigned on the established *anti* selectivity on addition of the (*E*)-crotylboronates **14b** to aldehydes[11]. In the subsequent ozonolysis of the adduct **17** the *p*-methoxybenzylidene acetal turned out to be quite sensitive towards an oxidation to a benzoate. This necessitated careful ozonolysis at −90°C to provide the aldehyde **7**. The synthesis of the C-1-to-C-9 unit of the denticulatins bearing six contiguous stereocenters was thus accomplished in nine steps starting from propionaldehyde.

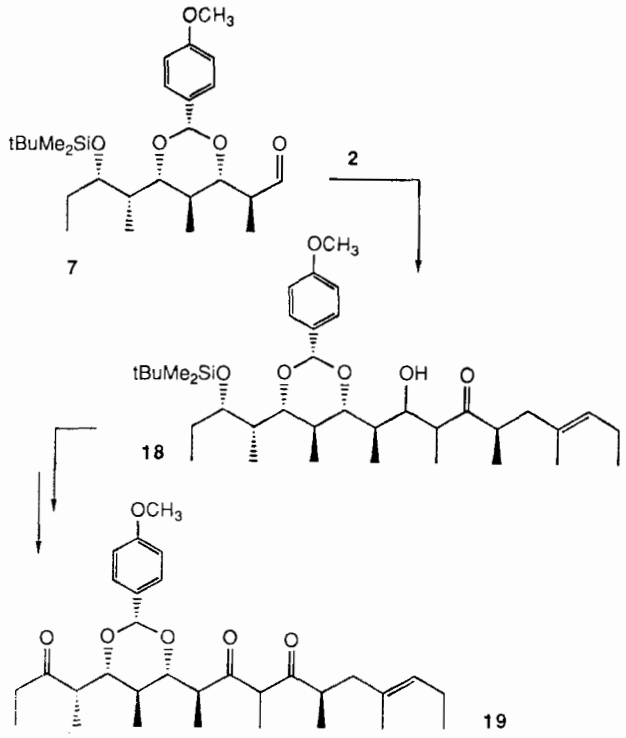
The Synthesis of the Protected Denticulation Precursor 19

The projected synthesis of the denticulatins now required an aldol addition of the ketone **2** to the aldehyde **7**, followed by functional group manipulations, to give the protected derivative **19** of the dihydroxy triketone **3**.

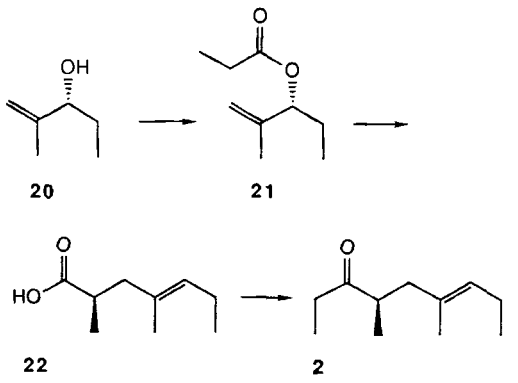
This required the optically active ketone **2**, which was prepared from the allylic alcohol **20** by using chirality transfer in a Claisen rearrangement (Scheme 8).

The allylic alcohol **20** had already been subjected to resolution by Sharpless epoxidation by Overman[14]. The allylic alcohol **20** obtained this way had 99.6% e.e. as evidenced by GC analysis using a chiral stationary phase. Conversion into the propionate **21** was followed by Ireland-Claisen rearrangement via the (*E*)-enolate (THF/HMPA) to give the acid **22**. The extent of chirality transfer was not established at this stage, rather the acid was directly converted into the desired ketone **2**. The latter has a noteable tendency to racemize upon storage or distillation. To establish the absolute configuration of the ketone **2**, it has been synthesized[4,15] via the RAMP hydrazone of 3-pentanone[16]. The recent careful evaluation of the maximal optical rotation of this ketone **2**[4] indicated that our material had an optical purity of only 70–85% depending both on the level of chirality transfer

Scheme 7



Scheme 8



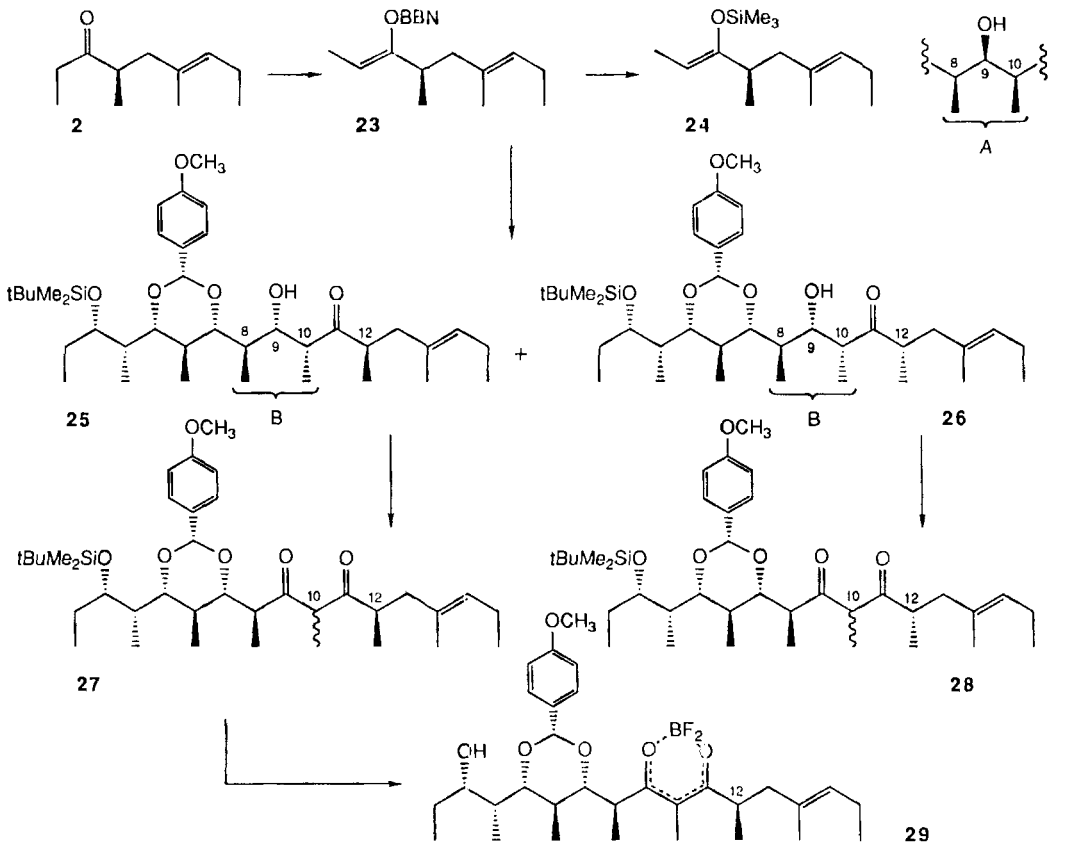
in the Claisen rearrangement[17] and partial racemization during distillation.

The aldol addition of the ketone **2** to the aldehyde **7** was first tried using lithium enolates. Yields ranged from 60 to 70% providing two to four diastereomeric adducts. Reaction of the enol borinate **23**[18,19] derived from **2** with the aldehyde **7** gave 88% of only two diastereomers in a 3:1 ratio. The diastereomers could be readily separated by chromatography and were eventually assigned the structures **25** and **26**.

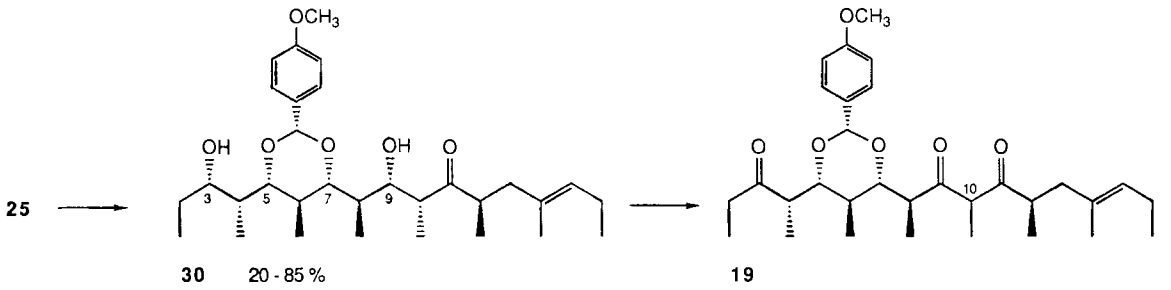
First of all, both adducts appeared to be *syn* at C-9/C-10 according to the 9-H/10-H coupling constants of 1.1 and 1.6 Hz, respectively (ref.[20] and references therein). This should result if the double bond in the enol borinate **23** is (*Z*). This in turn was substantiated by conversion[19] of the enol borinate to the enol silyl ether **24**, which was obtained as a 92:8 (*Z*)/(*E*) mixture. If **25** and **26** are both *syn*, one could have the stereotriad B and the other the stereotriad A[5]. If this is the only structural difference between the compounds **25** and **26**, each of them should be oxidized to the same mixture of C-10-epimeric diketones. However, Swern oxidation of the separated diastereomers led to *different* pairs of β-diketones each. The structural difference between **25** and **26** resides therefore *outside* the C-9/C-10 region. It is highly probable that the compounds **25** and **26** are epimers at C-12, due to the reduced enantiomeric purity of the ketone **2**, cf. p. 2132 . There is the faint possibility that compounds **25** and **26** are epimers at C-8, as a consequence of an unintended epimerization of the aldehyde **7**. Stereoisomers at C-8 should have a different folding of the molecular backbone; however, the ^{13}C-NMR spectra of **25** and **26** were so similar as to render this unlikely. Still, it was not settled whether the diastereomers **25** and **26** contain both the same stereotriad A or B at C-8 to C-10. There is substantial precedent[10,21] that the addition of (*Z*)-enolates to aldehydes of the type **7** provides the *anti*-Cram products, i.e. stereotriad B, in good selectivities, cf. p. 2132.

Oxidation of **25** to the diketone **27** seemed to be a logical first step en route to the desired triketone **19**. However, subsequent liberation of the 3-OH function in **27** by cleavage of the *tert*-butyldimethylsilyl ether group could not be effected without witnessing decomposition[22]. A high lability

Scheme 9



Scheme 10



of the *p*-methoxybenzylidene acetal in this molecular environment was noted. Deprotection with $LiBF_4$ led to the boron heterocycle **29**, which turned out to be an inert substance with respect to completing the synthesis of the denticulatins. Anyhow, our plan called for deprotection at 3-OH of **25** before simultaneous oxidation of 3- and 9-OH. The recurring difficulties in our attempts to cleave the silyl group of compound **25** under standard conditions[22] were therefore troublesome. Eventually, a combination of $LiBF_4$, K_2CO_3, and molecular sieves (3 Å) in acetonitrile gave the desired diol **30**, albeit in widely varying yields (20–85%). Again, the lability of the *p*-methoxybenzylidene acetal proved to be responsible. The diol **30** exists in the 3-OH/5-O hydrogen-bonded form, as evidenced from the ^{13}C-NMR chemical shift of 4-CH_3 at $\delta = 4.8$[23]. Hence, coordination of a Lewis acid to the 3-O would reinforce proton transfer to the 5-O and initiate facile cleavage of the *p*-methoxybenzylidene acetal.

The data at hand for the product **30** do not allow to differentiate from a product in which the benzylidene acetal has migrated from 5-OH/7-OH either to 3-OH/5-OH or to 7-OH/9-OH. The former, but not the latter would become apparent after oxidation of **30** to a triketone. Such migration of a *p*-methoxybenzylidene group has been observed in related cases under the influence of $LiBF_4$[22]!

Provided that the benzylidene group still bridges 5- and 7-OH, the next step toward our goal was the simultaneous oxidation of both secondary alcohol functions at C-3 and C-9. This was effected by Collins oxidation, which gave the triketone **19** as a 1:1 mixture of C-10 epimers. This compound marked the stage "target minus one" in our synthesis of the denticulatins. It was therefore even more disappointing that we were unable to cleave the *p*-methoxybenzylidene acetal without obtaining mainly elimination products. One should recall that the acetal in **30** was so labile towards traces of acids, that **30** could hardly be obtained; however, once the acetal was flanked by two carbonyl groups it could not longer be cleaved by acid, DDQ, Ce^{IV}, NBS, or selective hydrogenation[22]. Ziegler[4] was successful in his synthesis of the denticulatins utilizing an intermediate essentially identical to **19**. However, perhaps in a better anticipation of the difficulties, he had protected the C-5/C-7 diol system as the *p*-methoxyacetophenone acetal, which was sufficiently more labile to be successfully cleaved in the ultimate step of his synthesis. Faced with these difficulties, we could have gone back to change the C-5/C-7 diol protecting group to bring our synthesis to a successful end. This actually would have been superfluous after Ziegler had published[4] his synthesis. Rather, we changed the strategies and aims of our synthesis more profoundly.

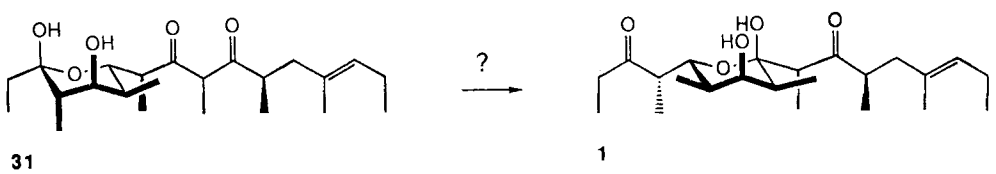
The C-3/C-7 Hemiketal Route to the Denticulatins

We gained new motivation by adressing the question, whether the "wrong" hemiketal **31** would spontaneously isomerize to the "correct" hemiketal **1** of denticulatin.

The synthesis of a protected form of **31** would imply only minor changes in the route previously explored. All it required is to raise the oxidation state at C-3 early in the synthesis. Thus, the intermediate **13** was deprotected at 3-OH, oxidized to the ketone **33**, and subjected to ozonolysis.

Reaction of the aldehyde **34** with the simple (*E*)-crotylboronate led to two adducts which cyclized spontaneously to the pyranose forms **35a** and **36a**. The configurational assignment was readily attained based on the coupling constants $J_{4,5}$, $J_{5,6}$, and $J_{6,7}$ in the ^1H-NMR spectra. Moreover, **35a** showed the 3-OH signal shifted downfield to $\delta = 6.1$ due to intramolecular hydrogen bonding. The structural assignments revealed that substrate control of diastereoselectivity favored the undesired isomer **36a** by 4:1. Thus, in the chain extension of the aldehyde **34** again reagent control of diastereoselectivity was required to override the asymmetric induction of the substrate aldehyde. At this stage a number of chiral (*E*)-crotylborating agents[24,25] were tested, all of which provided the desired product **35** as the predominant isomer. The highest selectivity was attained by the chiral α-methoxycrotylboronate **14b**[11]. With the latter reagent the adduct **35b** [having a (*Z*)-enol ether function] dominated by 4:1 over **36b** [with an (*E*)-enol ether group].

Scheme 11

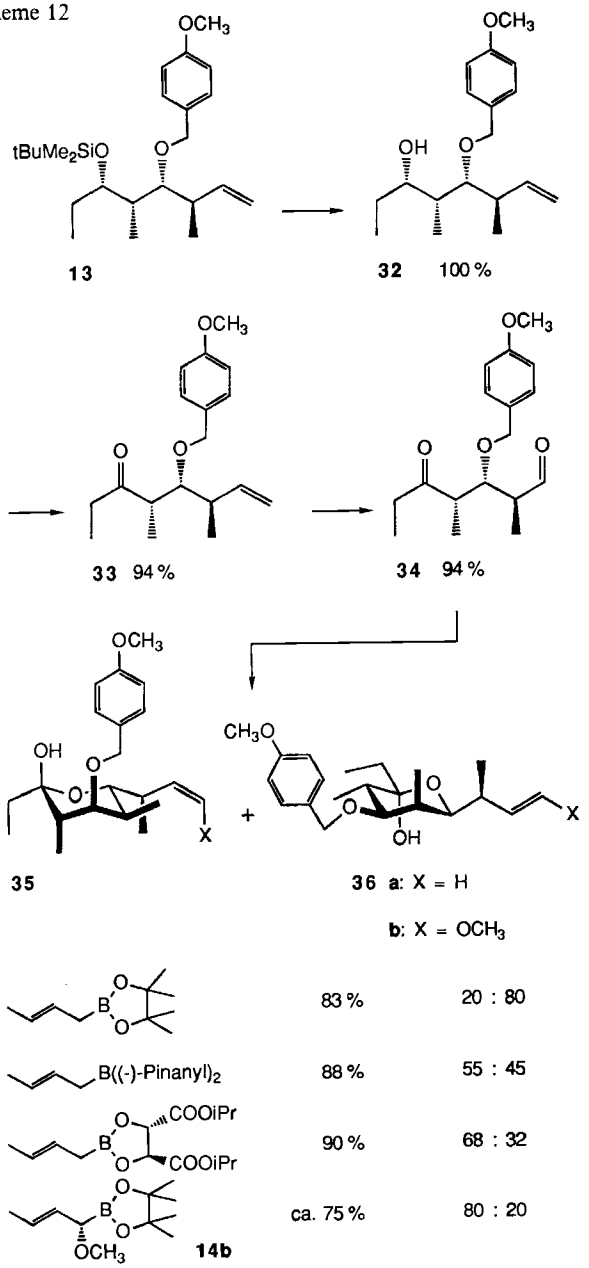


The (*Z*)-enol ether **35b** was subjected to ozonolysis requiring special care to avoid over-oxidation. The resulting aldehyde **37** (85%) represented another C-1-to-C-9 unit of the denticulatins available in ten steps from propionaldehyde. The completion of the molecular skeleton of the denticulatins utilized the steps developed earlier: Reaction of the aldehyde **37** with the enol borinate from the ketone **2** gave again two aldol adducts in a 78:22 ratio.

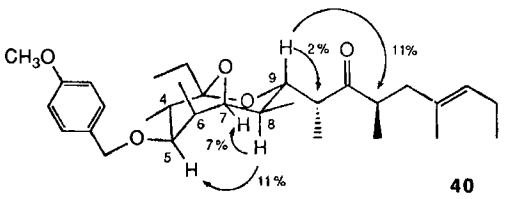
In order to prove that the minor epimer resulted from *ent*-**2**, the reaction was repeated using the racemic enol borinate. This led to the same two products **38** and **39**, now with the undesired 12-epi compound **39** predominating by 4:1. This demonstrated that the two diastereomers differ at C-12. Moreover there is a small kinetic resolution of the racemic enol borinate by the aldehydes **37**, the undesired combination **37** + *ent*-**2** reacting faster than the desired one **37** + **2**!

An opportunity to establish the configuration at C-9 came inadvertently: Traces of acid converted either adduct **38** or **39** into a corresponding bicyclic acetal e.g. **40**. ^{1}H-NMR coupling constants and NOE experiments showed the acetal to exist in the chair/boat conformation and established a *trans* relationship of the hydrogen atoms at C-8 and C-9. This proved that the addition of the enol borinate **23** to the aldehyde **37** afforded solely the *anti*-Cram adduct, i.e. the formation of the stereotriad B, in line with other findings on related systems[10,21].

Scheme 12



Scheme 14



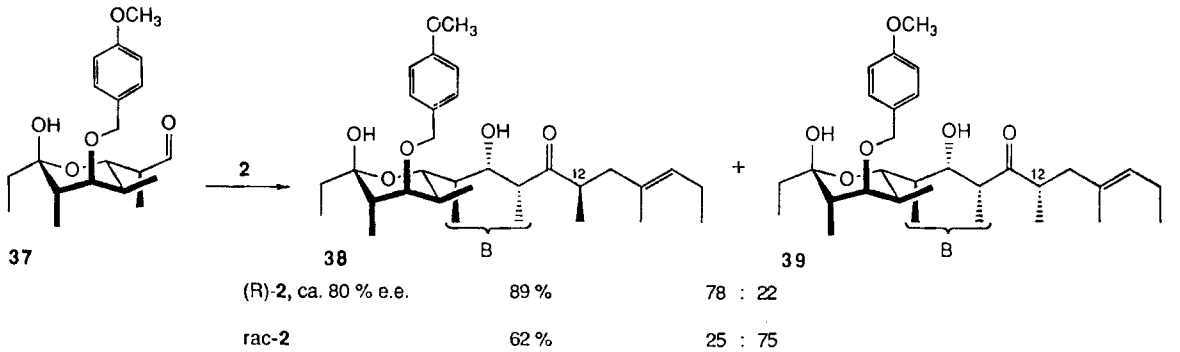
$J_{4,5}$ = 10.5 Hz, $J_{5,6}$ = 5.1 Hz, $J_{6,7}$ = 1.9 Hz,

$J_{7,8}$ = 2.5 Hz, $J_{8,9}$ = 10.4 Hz.

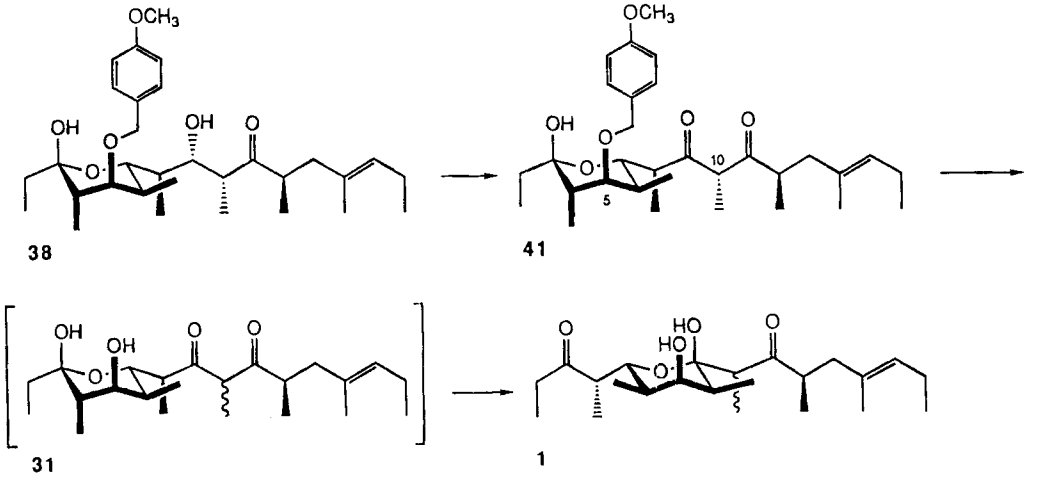
The sensitivity of **38** towards acid augured badly for the required oxidation at 9-OH. While blocking of 3-OH to a full acetal earlier in the synthesis remained a possibility, we eventually found in the Dess-Martin reagent[26] a method to cleanly afford the desired C-5-protected pre-denticulatin **41**; note that the C-10 stereocenter remained unepimerized.

We had hoped that the *p*-methoxybenzyl group could now be readily removed. However, again this "last" step

Scheme 13



Scheme 15



turned out to be refractory. Of course, acidic conditions were counter-indicated, but also oxidative or hydrogenolytic or reductive (Li/NH_3) methods either failed or led to destructive transformations[22]. In the lithium/ammonia reduction, the β-diketone unit could be the culprit. An in-situ protection of this unit appeared possible by deprotonation. As it turned out, two equivalents of lithium diisopropylamide (probably deprotonation of 3-OH and 10-H) set the stage for a successful reductive cleavage of the *p*-methoxybenzyl group by lithium in ammonia. The product isolated was not the hemiketal **31**, but rather a mixture of the C-10-epimeric denticulatins **1** in 58% yield. They were indentified by comparison with a sample of the natural denticulatins generously supplied by Dr. *M. Garson*, Wollongong, Australia, and by reference to spectra kindly provided by Dr. *J. Faulkner*, La Jolla, U.S.A. This transformation not only concluded our synthesis, but also established that the pre-denticulatin **31** isomerizes spontaneously to denticulatin. The driving force could possibly be sought in the fact that the number of axial substituents on the hemiketal ring decreases in this rearrangement.

This work was supported by the *Deutsche Forschungsgemeinschaft* and the *Fonds der Chemischen Industrie*. We thank Prof. *Hensel* (Marburg) for permission to use his high-pressure equipment. We would also like to thank Miss *Sonja Wißner* and Miss *Sabine Gärtner* for skillful assistance. We are grateful to the *BASF Aktiengesellschaft* for supply of chemicals.

Experimental

All temperatures quoted are not corrected. – ^1H NMR, ^{13}C NMR: Bruker WH-400, AC-300, Varian CFT-20, XL-100. – MS: Varian MAT 711. – Optical rotations: Perkin-Elmer Polarimeter 141. – Flash chromatography: Silica gel 60 (0.040–0.063 mm); Merck. – Column chromatography: Silica gel 60 (0.063–0.200 mm); Merck. – Preparative gas chromatography: Wilkens Aerograph A-90-P3. – Analytical gas chromatography: Siemens Sichromat 3, 1 bar He. – Elemental analyses: Heraeus CHN-Rapid.

1. *(3S,4S,5E)-4-Methyl-5-hepten-3-ol* (**9**): 3.02 g (ca. 9 mmol) of crude (4*S*,5*S*)-4,5-dicyclohexyl-2-[(1*S*,2*Z*)-1-methyl-2-butenyl]-1,3,2-dioxaborolane (**8**)[7] and 635 mg (10.9 mmol) of propionaldehyde were dissolved in 40 ml of dry petroleum ether (b.p. 40–60°C) and left for 3 d at −15°C. A solution of 1.36 g (9.10 mmol) of triethanolamine in 5 ml of anhydrous CH_2Cl_2 was added. After stirring for 3 h at room temperature, 100 ml of saturated aqueous NH_4Cl solution was added. The mixture was extracted four times with 50 ml each of ether, and the combined organic phases were washed twice with 50 ml of brine. The organic phase was dried with $MgSO_4$ and concentrated. The residue was chromatographed on 50 g of silica gel with petroleum ether (b.p. 40–60°C)/ether (10:1) to give 823 mg (70%) of **9** as a colorless liquid. The ^1H-NMR and ^{13}C-NMR spectra agreed with those reported in ref.[27] and showed the diastereomeric purity to be 97%. A small sample was purified by bulb-to-bulb distillation at 50°C (bath)/0.5 Torr. – $[\alpha]_D^{20} = -39.5$ ($c = 2.2$ in CH_2Cl_2).

$C_8H_{16}O$ (128.2) Calcd. C 74.94 H 12.58
Found C 74.80 H 12.73

20 µl of the product was derivatized as described in ref.[28] with (*S*)-(−)-1-phenylethyl isocyanate. Analytical GC (0.3 mm × 30 m, glass capillary column with SE 52, 185°C) showed an enantiomeric purity of 92–98.5% e.e.

2. *(2E,4S,5S)-5-(tert-Butyldimethylsilyloxy)-4-methyl-2-heptene* (**10**): A mixture of 0.50 g (3.9 mmol) of **9**, 0.88 g (5.9 mmol) of *tert*-butylchlorodimethylsilane, and 0.53 g (7.8 mmol) of imidazole in 3 ml of DMF was stirred for 1 d at room temperature; 50 ml of ether and 50 ml of saturated aqueous NH_4Cl solution were 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 twice with 50 ml of brine, dried with $MgSO_4$, and concentrated in vacuo. The residue was filtered through 20 g of silica gel with petroleum ether (b.p. 40–60°C)/ether (10:1) to give 0.90 g (95%) of **10**. – ^1H NMR (300 MHz, $CDCl_3$): δ = 0.02 (s, 6H), 0.83 (t, J = 7.4 Hz, 3H), 0.88 (s, 9H), 0.91 (d, J = 6.8 Hz, 3H), 1.41 (m, 2H), 1.62 (d, J = 4.5 Hz, 3H), 2.20 (m, 1H), 3.39 (dt, J = 5.5 and 5.5 Hz, 1H), 5.30–5.46 (m, 2H). – ^{13}C NMR (75 MHz, $CDCl_3$): δ = −4.5, −4.3, 9.4, 15.5, 18.1, 18.2, 25.9, 26.7, 41.1, 77.4, 123.9, 134.6. – A sample was purified by bulb-to-bulb distillation at 75°C/0.5 Torr. – $[\alpha]_D^{20} = -21.4$ ($c = 2.10$ in CH_2Cl_2).

$C_{14}H_{30}OSi$ (242.5) Calcd. C 69.35 H 12.47
Found C 68.97 H 12.70

3. *(2R,3S)-3-(tert-Butyldimethylsilyloxy)-2-methylpentanal* (**5**): Into a solution of 327 mg (1.35 mmol) of **10** in 15 ml of CH_2Cl_2 was introduced at −78°C ozone until the blue color of the solution persisted. The solution was purged with nitrogen for 15 min. After addition of 354 mg (1.35 mmol) of triphenylphosphine, the mixture

was allowed to reach room temperature. The solvents were removed in vacuo, and the residue was chromatographed on 20 g of silica gel with petroleum ether (b.p. 40–60°C)/ether (50:1) to give 280 mg (90%) of the aldehyde **5** as a colorless liquid. The NMR spectra agreed with those reported in ref.[8]. $-[\alpha]_D^{20} = -52.4$ (c = 11.0 in $CDCl_3$).

4. *(3R,4R,5S,6S)-6-(tert-Butyldimethylsilyloxy)-4-(p-methoxybenzyloxy)-3,5-dimethyl-1-octene* (**13**): To a suspension of 4.8 g (40 mmol) of potassium hydride in 50 ml of dry THF was added over 15 min 6.0 g (21 mmol) of (3*R*,4*R*,5*S*,6*S*)-6-(*tert*-butyldimethylsilyloxy)-3,5-dimethyl-1-octen-4-ol (**12**)[8] at 0°C. The mixture was stirred at room temperature until the evolution of hydrogen slowed down; 5 ml of DMF was added followed by 3.3 g (21 mmol) of freshly prepared *p*-methoxybenzyl chloride. The exothermic reaction was allowed to proceed until TLC indicated complete consumption of the starting material. The reaction mixture was cooled to 0°C, and excess of KH was destroyed by *dropwise* addition of saturated aqueous NH_4Cl solution. The mixture was partitioned between 100 ml of saturated aqueous NH_4Cl solution and 100 ml of ether. The aqueous phase was extracted three times with 100 ml each of ether, and the combined organic extracts were dried with Na_2SO_4. The solvents were removed in vacuo, and the residue was flash-chromatographed with petroleum ether (b.p. 40–60°C) and than petroleum ether (b.p. 40–60°C)/ether (20:1) affording 7.4 g (87%) of the benzyl ether **13**. The NMR spectra agreed with those reported in ref.[8].

5. *(1Z,3R,4R,5R,6R,7S,8S)-8-(tert-Butyldimethylsilyloxy)-1-methoxy-6-(p-methoxybenzyloxy)-3,5,7-trimethyl-1-decen-4-ol* (**15b**): 0.80 g (2.0 mmol) of (2*S*,3*S*,4*S*,5*S*)-5-(*tert*-butyldimethylsilyloxy)-3-(*p*-methoxybenzyloxy)-2,4-dimethylheptanal (**6**)[8] and 0.62 g (2.9 mmol) of 2-[(1*S*,2*E*)-1-methoxy-2-butenyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**14b**)[11] were dissolved in toluene to 5 ml. The mixture was pressurized for 12 h at 4 kbar and than poured into a solution of 0.50 g (3.3 mmol) of triethanolamine in 2 ml of CH_2Cl_2. After stirring for 12 h, the mixture was partitioned between 10 ml of saturated aqueous $NaHCO_3$ solution and 25 ml of ether. The aqueous phase was extracted three times with 25 ml each of ether, and the combined organic extracts were washed with 10 ml of brine and dried with Na_2SO_4. The organic extracts were filtered, and the solvents were removed in vacuo. The crude products were separated by flash chromatography using petroleum ether (b.p. 40–60°C)/ether (9:1) to give 0.57 g (63%) of **15b** and 0.14 g (16%) of the (1*E*,3*S*,4*S*,5*R*,6*R*,7*S*,8*S*) isomer **16b**.

15b: ^{1}H NMR (400 MHz, CD_2Cl_2): δ = 0.05 (s, 3H), 0.06 (s, 3H), 0.85 (d, J = 6.9 Hz, 3H), 0.85 (t, J = 7.5 Hz, 3H), 0.90 (s, 9H), 0.93 (d, J = 7.0 Hz, 3H), 1.03 (d, J = 6.9 Hz, 3H), 1.53 (ddq, J = 7.5, 5.0, and 5.0 Hz, 1H), 1.60 (ddq, J = 7.5, 5.0, and 5.0 Hz, 1H), 1.86 (ddq, J = 9.1, 6.9, and 5.3 Hz, 1H), 1.93 (ddq, J = 7.0, 5.0, and 3.7 Hz, 1H), 2.83 (dddq, J = 9.9, 6.9, 6.2, 2.6, 1.2, and 0.8 Hz, 1H), 3.27 (dd, J = 2.6 and 1.2 Hz, 1H), 3.42 (ddd, J = 9.1, 2.6, and 2.6 Hz, 1H), 3.53 (s, 3H), 3.55 (dd, J = 5.3 and 3.7 Hz, 1H), 3.59 (ddd, J = 5.0, 5.0, and 5.0 Hz, 1H), 3.77 (s, 3H), 4.44 (dd, J = 9.9 and 6.2 Hz, 1H), 4.45 and 4.50 (AB system, J_{AB} = 10.7 Hz, 2H), 5.90 (dd, J = 6.2 and 0.6 Hz, 1H), 6.84 (m, 2H), 7.24 (m, 2H). – ^{13}C NMR (100 MHz, C_6D_6): δ = −4.0, −3.9, 10.2, 11.3, 14.9, 18.5, 19.6, 26.3, 27.1, 32.3, 40.4, 41.2, 54.8, 58.9, 73.7, 76.5, 78.2, 83.7, 108.2, 114.1, 129.5, 131.3, 146.4, 159.8.

16b: ^{1}H NMR (300 MHz, $CDCl_3$ over K_2CO_3): δ = −0.07 (s, 6H), 0.78 (t, J = 7.2 Hz, 3H), 0.86 (s, 9H), 0.87 (d, J = 6.4 Hz, 3H), 0.95 (d, J = 6.8 Hz, 3H), 1.25 (d, J = 6.4 Hz, 3H), 1.50 (m, 2H), 1.90 (m, 2H), 2.10 (ddq, J = 8.7, 6.4, and 1.3 Hz, 1H), 3.52–3.45 (m, 6H), 3.52 (d, J = 0.9 Hz, 1H), 3.73 (s, 3H), 4.50 (s, 2H), 4.65 (dd, J = 12.7 and 8.7 Hz, 1H), 6.30 (d, J = 12.7 Hz, 1H), 6.80 (d, J = 8.7 Hz, 2H), 7.20 (d, J = 8.7 Hz, 2H). – ^{13}C NMR (75 MHz, $CDCl_3$ over K_2CO_3): δ = −4.5, 9.3, 9.7, 11.2, 18.4, 26.0, 26.1, 27.7, 35.3, 36.6, 39.0, 55.3, 55.9, 74.1, 74.7, 76.0, 86.9, 106.8, 113.9, 129.4, 130.6, 147.4, 159.3.

6. *(2R,4R,5R,6R)-4-[(1S,2S)-2-(tert-Butyldimethylsilyloxy)-1-methylbutyl]-6-[(1R,2Z)-3-methoxy-1-methyl-2-propenyl]-2-(p-methoxyphenyl)-5-methyl-1,3-dioxane* (**17**): A solution of 0.45 g (0.91 mmol) of the alcohol **15b** in 20 ml of CH_2Cl_2 was stirred for 1 h with 0.50 g of molecular sieves (4 Å) at room temperature. 0.24 g (1.10 mmol) of DDQ was added. The color changed from green to pale yellow over 15 min, after which TLC indicated complete reaction. The mixture was filtered, and the filtrate was partitioned between 25 ml of saturated aqueous $NaHCO_3$ solution and 50 ml of ether. The aqueous phase was extracted three times with 25 ml each of ether, and the combined organic phases were washed with 10 ml of water and 10 ml of brine. The organic phase was dried with $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash chromatography using petroleum ether (b.p. 40–60°C)/ether (9:1) to give 0.38 g (85%) of the acetal **17** as a colorless oil. – ^{1}H NMR (400 MHz, CD_2Cl_2): δ = 0.06 (s, 3H), 0.07 (s, 3H), 0.79 (d, J = 6.6 Hz, 3H), 0.91 (t, J = 7.6 Hz, 3H), 0.92 (s, 9H), 0.95 (d, J = 7.1 Hz, 3H), 1.11 (d, J = 7.0 Hz, 3H), 1.61 (m, 2H), 1.73 (ddq, J = 10.1, 9.7, and 6.6 Hz, 1H), 1.91 (ddq, J = 7.1, 7.1, and 6.6 Hz, 1H), 3.08 (m, 1H), 3.35 (dd, J = 9.7 and 2.1 Hz, 1H), 3.56 (s, 3H), 3.60 (dd, J = 10.1 and 1.6 Hz, 1H), 3.66 (m, 1H), 3.80 (s, 3H), 5.45 (dd, J = 10.0 and 6.3 Hz, 1H), 5.54 (s, 1H), 5.95 (dd, J = 6.3 and 0.8 Hz, 1H), 6.87 (m, 2H), 7.38 (m, 2H). – ^{13}C NMR (100 MHz, CD_2Cl_2): δ = −3.8, −3.6, 9.4, 10.8, 11.8, 18.8, 26.2, 30.6, 33.9, 38.9, 55.7, 59.7, 76.2, 81.3, 86.6, 100.2, 108.1, 113.7, 127.6, 133.0, 146.8, 159.7.

$C_{28}H_{48}O_5Si$ (492.8) Calcd. C 68.25 H 9.82
Found C 68.07 H 8.92

7. *(2S)-2-{(2S,4S,5S,6R)-6-[(1S,2S)-2-(tert-Butyldimethylsilyloxy)-1-methylbutyl]-2-(p-methoxyphenyl)-5-methyl-1,3-dioxan-4-yl}-propanal* (**7**): A solution of 1.00 g (2.02 mmol) of the enol ether **17** in 40 ml of CH_2Cl_2 was cooled to −85°C, and ozone was introduced until the blue color persisted. Excess of ozone was purged by nitrogen for 5 min. The temperature was raised to 0°C, and 0.80 g of zinc powder, 0.5 ml of acetic acid, and 2 drops of water were added. The mixture was allowed to warm to room temperature over 2 h. The precipitate was filtered, and the mixture was carefully washed twice with 5 ml each of aqueous saturated $NaHCO_3$ solution. The aqueous phase was extracted twice with 25 ml each of ether, and the combined organic extracts were dried with $MgSO_4$. The solution was concentrated, and the residue was purified by flash chromatography with petroleum ether (b.p. 40–60°C)/ether (9:1 and subsequently 3:1) to give 0.87 g (87%) of the aldehyde **7** as a colorless oil. – ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.75 (s, 6H), 0.76 (d, J = 6.61 Hz, 3H), 0.85 (m, 12H), 0.92 (d, J = 7.14 Hz, 3H), 1.25 (d, J = 7.04 Hz, 3H), 1.50 (m, 2H), 1.85 (m, 2H), 2.63 (m, 1H), 3.56 (m, 2H), 3.64 (dd, J = 10.2 and 1.95 Hz, 1H), 3.75 (s, 3H), 5.40 (s, 1H), 6.85 (d, J = 8.7 Hz, 2H), 7.29 (d, J = 8.7 Hz, 2H), 9.74 (d, J = 2.7 Hz, 1H). – ^{13}C NMR (75 MHz, $CDCl_3$): δ = −4.1, −4.3, 9.4, 10.5, 11.7, 11.8, 18.2, 26.0, 25.9, 33.4, 38.4, 47.9, 55.3, 75.6, 80.8, 84.1, 100.3, 113.4, 127.2, 131.5, 159.8, 204.4.

$C_{26}H_{44}O_5Si$ (464.7) Calcd. C 62.20 H 9.40
Found C 62.19 H 8.68

8. *(3R)-2-Methyl-1-pentene-3-ol* (**20**): A solution of anhydrous *tert*-butyl hydroperoxide in CH_2Cl_2 was prepared as follows: 50 ml of 70% *tert*-butyl hydroperoxide was carefully mixed with 84 ml of CH_2Cl_2. The phases were separated after 1 min, and the aqueous

phase was discarded. From the organic phase 61 ml of an azeotrope boiling at 38–40°C was distilled. The residual solution was added to a solution of 40.1 g (0.40 mol) of *rac*-2-methyl-1-penten-3-ol, 28.4 g (0.10 mol) of titanium tetraisopropoxide, and 28.1 g (0.12 mol) of (+)-diisopropyl tartrate in 4 l of anhydrous CH_2Cl_2 at −20°C. The mixture was kept for 20 d at −25°C. A solution of 100 g of tartaric acid in 250 ml of water was added with vigorous stirring. The mixture was concentrated to ca. 500 ml in vacuo, and a solution of 70 g of Na_2SO_3 in 400 ml of water was added. After stirring for 2.5 h, a peroxide test was negative. The mixture was concetrated to 50 ml, and the residue was fractionated to give at 31–53°C/12 Torr 15.6 g (78%) of the crude alcohol **20**. Redistillation over a 10-cm Vigreux column gave 10.6 g (53%) of **20**; b.p. 125–128°C. – $[\alpha]_D^{20} = +5.0$ (c = 0.65, $CHCl_3$). – ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.87 (t, J = 6.5 Hz, 3H), 1.54 (m, 2H), 1.69 (s, 3H), 1.72 (s, 1H), 3.96 (t, J = 6.5 Hz, 1H), 4.82 (m, 1H), 4.91 (m, 1H). – ^{13}C NMR (100 MHz, $CDCl_3$): δ = 9.6, 17.1, 27.4, 77.0, 110.8, 147.1.

$C_6H_{12}O$ (100.2) Calcd. C 71.95 H 12.08
Found C 71.75 H 12.20

0.15 ml of isopropyl isocyanate and 1 mg of the alcohol **20** were heated under reflux for 1 h under anhydrous conditions. The excess of the isopropyl isocyanate was removed in a stream of nitrogen, and the residue was taken up in CH_2Cl_2. Analysis of the product [0.3 mm × 40 m capillary GC column with XE 60/(*S*)-valine-(*S*)-α-phenylethylamide, 90°C[29]] showed an enantiomeric purity of 98% e.e. In order to verify the absolute configuration 200 mg (2.0 mmol) of **20** was treated with 375 mg (2.5 mmol) of *tert*-butylchlorodimethylsilane and 350 mg (5.0 mmol) of imidazole in 5 ml of DMF. After 3 d at room temperature, the mixture was extracted 5 times with 15 ml each of petroleum ether (b.p. 40–60°C). The extracts were washed twice with 20 ml each of 1 N hydrochloric acid and were dried with $MgSO_4$. Concentration gave 390 mg (91%) of (*R*)-3-(*tert*-butyldimethylsilyloxy)-2-methyl-1-pentene. – $[\alpha]_D^{20} = +6.9$ (c = 2.65, $CDCl_3$), cf. the rotation of the (*S*) isomer: $[\alpha]_D^{20} = -5.9$ (c = 2.38, $CDCl_3$)[9].

9. *[(3R)-2-Methyl-1-penten-3-yl] Propionate* (**21**): To a mixture of 4.0 g (40 mmol) of **20** and 3.8 g (48 mmol) of pyridine in 40 ml of CH_2Cl_2 was added at 0°C 3.7 g (40 mmol) of propionyl chloride. The mixture was kept under reflux for 30 min and was hydrolyzed by pouring it into ice-cold water. The aqueous phase was extracted three times with 60 ml each of CH_2Cl_2. The organic phase was dried with Na_2SO_4 and concentrated. Fractionation gave 4.8 g (76%) of **21**; b.p. 52–55°C/13 Torr. – $[\alpha]_D^{20} = +27.9$ (neat, d = 0.8798). – ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.86 (t, J = 7.5 Hz, 3H), 1.14 (t, J = 7.5 Hz, 3H), 1.63 (m, 2H), 1.70 (s, 3H), 2.33 (q, J = 7.5 Hz, 2H), 4.87 (m, 1H), 4.93 (m, 1H), 5.10 (t, J = 6.7 Hz, 1H). – ^{13}C NMR (100 MHz, $CDCl_3$): δ = 8.5, 9.0, 17.4, 25.1, 27.2, 77.6, 111.9, 142.6, 172.8.

$C_9H_{16}O_2$ (156.2) Calcd. C 69.19 H 10.32
Found C 68.99 H 10.47

10. *(2R,4E)-2,4-Dimethyl-4-heptenoic Acid* (**22**): To a solution of 1.55 g (11.0 mmol) of cyclohexylisopropylamine in 10 ml of anhydrous THF was added at −78°C 7.00 ml of a 1.55 M solution of *n*-butyllithium in *n*-hexane (11.0 mmol). After warming to 0°C over 15 min, the mixture was recooled to −78°C, and 7.00 ml of HMPT and after an interval of 5 min 1.56 g (10.0 mmol) of **21** in 2 ml of anhydrous THF were added. Subsequently, a solution of 1.59 g (10.5 mmol) of *tert*-butylchlorodimethylsilane in 4 ml of anhydrous THF was added, and the mixture was allowed to reach room temperature over 60 min. The mixture was heated at reflux for 4 h. 9 ml of 10% aqueous hydrochloric was added dropwise resulting in an exothermic reaction. After stirring for 2 h, 50 ml of a 5% aqueous NaOH solution was added. The mixture was stirred for 10 min and was extracted twice with 50 ml each of ether. The aqueous phase was acidified with ca. 7 ml of concentrated aqueous hydrochloric acid under cooling with ice. This mixture was extracted four times with 50 ml each of ether. The extracts were dried with $MgSO_4$ and concentrated to leave 1.33 g of a yellowish oil which was distilled at 60–70°C/0.1 Torr to give 0.85 g (54%) of **22** as a colorless liquid. – $\alpha_D^{20} = +1.86$ (neat, l = 1 dm). – ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.91 (t, J = 7.5 Hz, 3H), 1.10 (d, J = 7.0 Hz, 3H), 1.58 (s, 3H), 1.98 (m, 3H), 2.05 (m, 1H), 2.60 (m, 1H), 5.17 (t, J = 7.0 Hz, 1H), 11.5 (br., 1H). – ^{13}C NMR (25 MHz, $CDCl_3$): δ = 14.2, 15.4, 16.2, 21.2, 37.9, 43.6, 129.5, 131.0, 183.4.

$C_9H_{16}O_2$ (156.2) Calcd. C 69.19 H 10.32
Found C 68.99 H 10.61

11. *(4R,6E)-4,6-Dimethyl-6-nonen-3-one* (**2**): To a solution of 0.77 g (4.93 mmol) of **22** in 5 ml of ether was added at −78°C 38.0 ml (10.2 mmol) of a freshly prepared solution (0.27 M in ether) of ethyllithium. The mixture was allowed to reach room temperature over 1 h. It was recooled to −78°C after 14 h; 1.0 ml of acetone was added, the mixture was kept at −78°C for 0.5 h and was subsequently warmed to 0°C. After 1 h at this temperature, the mixture was poured into 50 ml of 2 N aqueous hydrochloric acid. The phases were separated, and the aqueous phase was extracted three times with 50 ml each of petroleum ether (b.p. 40–60°C). The combined organic phases were washed with 10 ml of brine and dried with Na_2SO_4. Concentration at 40°C 12 Torr gave 0.82 g (99%) of the crude ketone **2**. – $[\alpha]_D^{20} = -18.6$ (c = 8.01, $CDCl_3$). – ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.91 (t, J = 7.6 Hz, 3H), 1.05 (t, J = 7.2 Hz, 3H), 1.13 (d, J = 6.8 Hz, 3H), 1.57 (s, 3H), 1.92 (dd, J = 15.0 and 7.7 Hz, 1H), 1.97 (dq, J = 7.3 and 7.3 Hz, 2H), 2.30 (dd, J = 14.0 and 7.0 Hz, 1H), 2.42 (qd, J = 7.3 and 1.4 Hz, 2H), 2.68 (q, J = 7.0 Hz, 1H), 5.11 (t, J = 7.1 Hz, 1H). – ^{13}C NMR (25 MHz, $CDCl_3$): δ = 7.5, 14.0, 15.5, 16.0, 21.0, 34.3, 43.2, 44.1, 128.9, 131.3, 214.9. – A sample was purified by preparative gas chromatography on a 1.5 m × 0.63 cm column with 5% SE 30 on chromosorb G, AW-DMCS 60/80 mesh, 200 ml He/min, 70°C.

$C_{11}H_{20}O$ (168.3) Calcd. C 78.51 H 11.98
Found C 78.28 H 12.19

12. *(2Z,4R,6E)-4,6-Dimethyl-3-(trimethylsilyloxy)-2,6-nonadiene* (**24**): To a solution of 0.10 g (0.595 mmol) of **2** in 5 ml of ether was added at −78°C 0.11 ml (0.66 mmol) of ethyldiisopropylamine followed by addition of 1.20 ml (0.595 mmol) of a 0.5 M solution of 9-borabicyclononyl triflate in *n*-hexane. The temperature was raised to 0°C for 1 h and then lowered to −78°C. 1.42 ml (1.96 mmol) of a 1.50 M solution of *n*-butyllithium in *n*-hexane was added followed by 0.25 ml (2.0 mmol) of chlorotrimethylsilane. After reaching room temperature, the mixture was partitioned between 10 ml of saturated aqueous NH_4Cl solution and 20 ml of ether. The aqueous phase was extracted three times with 20 ml each of ether, and the combined organic phases were dried with $MgSO_4$ and filtered. Concentration in vacuo afforded 0.13 g (93%) of the crude enol silyl ether **24**. NMR analysis showed it to be a 92:8 (*Z*)/(*E*) mixture.

(*Z*)-**24**: ^{1}H NMR (300 MHz, $CDCl_3$ over K_2CO_3): δ = 0.14 (s, 9H), 0.64 (d, J = 6.81 Hz, 3H), 0.66 (t, J = 7.50 Hz, 3H), 1.45 (dd, J = 5.11 and 0.91 Hz, 3H), 1.52 (s, 3H), 1.90 (m, 2H), 2.10 (m, 1H), 2.25 (dd, J = 12.97 and 4.12 Hz, 1H), 2.65 (m, 1H), 4.47 (q, J = 6.20 Hz, 1H), 5.11 (t, J = 6.26 Hz, 1H). – ^{13}C NMR (75 MHz, $CDCl_3$ over K_2CO_3): δ = −3.0, 10.8, 14.2, 15.4, 17.2, 21.1, *37.6*, 45.1, 99.8, 128.3, 132.5, 155.8. – The following ^{13}C-NMR signals of (*E*)-**24** could be recorded: δ = −3.1, 11.3, 15.7, *31.7*, 44.1, 97.8,

127.8, 132.6, 155.4. – The (*E*)/(*Z*) assignment of **24** in based on the values reported in *italics*.

13. *(2R,3S,4R,6RS,8E)-2-{(2R,4R,5R,6R)-6-[(1S,2S)-2-(tert-Butyldimethylsilyloxy)-1-methylbutyl]-2-(p-methoxyphenyl)-5-methyl-1,3-dioxan-4-yl}-3-hydroxy-4,6,8-trimethyl-8-undecen-5-one* (**25**, **26**): 0.50 g (2.9 mmol) of **2** (ca. 85% ee) was converted into the enol BBN derivative as described under 12. To this was added at −78°C a solution of 0.84 g (1.8 mmol) of the aldehyde **7** in 5 ml of ether. After reaching room temperature, the mixture was poured into 15 ml of a phosphate buffer (pH = 7). The phases were separated, and the aqueous phase was extracted 5 times with 25 ml each of ether. The combined organic extracts were washed with 10 ml of brine. After removal of the solvents in vacuo, the residue was taken up in 5 ml of methanol, cooled to 0°C and treated dropwise with 2 ml of 30% aqueous H_2O_2. After the exothermic reaction ceased, the mixture was stirred for an additional hour at 0°C. 10 ml of water was added, and the reaction mixture was extracted three times with 50 ml each of ether. The combined organic extracts were washed with 10 ml of brine, dried with Na_2SO_4, and concentrated. The crude product was separated by flash chromatography with petroleum ether (b.p. 40−60°C)/ether (20:1 and subsequently 10:1) to give 0.75 g (65%) of **25** and 0.27 g (23%) of **26**.

25: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.03 (s, 6H), 0.80 (d, *J* = 6.5 Hz, 3H), 0.94 (m, 15H), 0.94 (t, *J* = 7.0 Hz, 3H), 0.99 (d, *J* = 6.9 Hz, 3H), 1.02 (d, *J* = 7.1 Hz, 3H), 1.06 (d, *J* = 7.1 Hz, 3H), 1.55 (m, 2H), 1.55 (s, 3H), 1.90 (m, 2H), 1.95 (dd, *J* = 14.6 and 7.4 Hz, 2H), 2.03 (m, 1H), 2.16 (m, 1H), 2.30 (dd, *J* = 13.6 and 7.3 Hz, 1H), 2.78 (dq, *J* = 7.8 and 1.1 Hz, 1H), 2.87 (q, *J* = 6.6 Hz, 1H), 3.14 (d, *J* = 2.7 Hz, 1H), 3.54 (d, *J* = 10.2 Hz, 2H), 3.60 (m, 1H), 3.80 (s, 3H), 4.07 (dt, *J* = 8.8 and 2.4 Hz, 1H), 5.11 (dt, *J* = 7.3 and 1.2 Hz, 1H), 5.43 (s, 1H), 6.86 (d, *J* = 6.7 Hz, 2H), 7.35 (d, *J* = 6.7 Hz, 2H). – ^{13}C NMR (75 MHz, $CDCl_3$): δ = −3.9, −4.4, 8.5, 9.2, 10.6, 12.1, 14.1 (2C), 15.7, 16.4, 18.1, 21.2, 25.9, 26.0, 33.9, 37.5, 38.5, 43.1, 43.2, 46.8, 55.2, 71.4, 75.6, 81.4, 86.5, 100.2, 113.3, 127.1, 129.3, 131.2, 132.0, 159.6, 219.0

$C_{37}H_{64}O_6Si$ (633.0) Calcd. C 70.21 H 10.19
Found C 70.71 H 10.49

26: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.03 (s, 6H), 0.80 (d, *J* = 6.5 Hz, 3H), 0.90 (m, 15H), 0.92 (t, *J* = 7.1 Hz, 3H), 0.97 (d, *J* = 6.8 Hz, 3H), 0.98 (d, *J* = 7.1 Hz, 3H), 1.09 (d, *J* = 7.1 Hz, 3H), 1.55 (m, 2H), 1.55 (s, 3H), 1.90 (m, 4H), 2.00 (m, 1H), 2.15 (m, 1H), 2.29 (dd, *J* = 13.2 and 7.1 Hz, 1H), 2.72 (dq, *J* = 7.1 and 1.6 Hz, 1H), 2.85 (q, *J* = 7.0 Hz, 1H), 3.03 (d, *J* = 2.5 Hz, 1H), 3.52 (dd, *J* = 9.9 and 1.7 Hz, 1H), 3.53 (dd, *J* = 9.9 and 1.6 Hz, 1H), 3.60 (m, 1H), 3.80 (s, 3H), 4.06 (dt, *J* = 8.96 and 2.1 Hz, 1H), 5.10 (t, *J* = 6.0 Hz, 1H), 5.40 (s, 1H), 6.86 (d, *J* = 6.7 Hz, 2H), 7.33 (d, *J* = 6.7 Hz, 2H). – ^{13}C NMR (75 MHz, $CDCl_3$): δ = −4.0, −4.2, 8.6, 9.3, 10.7, 12.1, 14.3, 15.5, 15.8, 16.5, 18.3, 21.3, 26.1 (2C), 33.8, 37.4, 38.4, 43.2, 43.7, 47.3, 55.3, 70.6, 75.7, 81.6, 86.5, 100.3, 113.4, 127.3, 129.6, 131.5, 132.3, 159.7, 219.7.

14. *(2S,4RS,6R,8E)-2-{(2S,4S,5S,6R)-6-[(1S,2S)-2-(tert-Butyldimethylsilyloxy)-1-methylbutyl]-2-(p-methoxyphenyl)-5-methyl-1,3-dioxan-4-yl}-4,6,8-trimethyl-8-undecene-3,5-dione* (**27**): To a solution of 0.180 ml (2.20 mmol) of pyridine in 10 ml of CH_2Cl_2 was added 0.112 g (1.12 mmol) of CrO_3. Stirring for 30 min resulted in a homogenous clear deep-red solution. A solution of 0.100 g (0.16 mmol) of the aldol **25** in 5 ml of CH_2Cl_2 was added. Under slight warming a brown precipitate formed. The mixture was stirred for 10 min and poured into 75 ml of ether. The mixture was filtered, the residue was washed with 100 ml of ether, and the combined organic solutions were washed with 25 ml of 1% aqueous hydrochloric acid. The aqueous phase was back-extracted twice with 25 ml of ether. The combined organic phases were dried with Na_2SO_4, filtered, and concentrated to give 0.100 g (100%) of the β-diketone **27** as a 10:1 epimer mixture (at C-10, denticulatin numbering).

(10*S*)-**27**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.03 (s, 6H), 0.76 (d, *J* = 7.0 Hz, 3H), 0.85 (m, 15H), 0.93 (d, *J* = 6.7 Hz, 3H), 0.92 (d, *J* = 7.0 Hz, 3H), 1.13 (d, *J* = 7.0 Hz, 3H), 1.25 (d, *J* = 6.2 Hz, 3H), 1.39 (s, 3H), 1.50 (m, 2H), 1.85 (m, 4H), 2.28 (dd, *J* = 13.6 and 6.6 Hz, 2H), 2.75 (q, *J* = 7.1 Hz, 1H), 2.90 (dd, *J* = 4.7 and 2.3 Hz, 1H), 3.55 (m, 3H), 3.74 (s, 3H), 3.95 (q, *J* = 7.0 Hz, 1H), 5.00 (t, *J* = 7.02 Hz, 1H), 5.35 (s, 1H), 6.80 (d, *J* = 8.8 Hz, 2H), 7.25 (d, *J* = 8.8 Hz, 2H). – ^{13}C NMR (75 MHz, $CDCl_3$): δ = −4.0, −4.3, 9.4, 10.6, 12.3, 13.2, 14.2, 14.7, 15.6, 16.5, 18.2, 21.2, 25.9, 26.0, 35.0, 38.2, 43.2, 43.6, 49.9, 55.2, 59.7, 75.6, 80.8, 85.2, 100.2, 113.5, 127.2, 129.6, 131.1, 131.4, 159.7, 208.5, 211.4. – The following signals of (10*R*)-**27** could be recorded in the ^{13}C-NMR spektrum: δ = −4.0, 10.4, 12.2, 13.8, 13.9, 15.5, 16.1, 34.0, 38.3, 42.5, 43.0, 49.6, 57.1, 80.7, 84.6, 100.1, 209.7.

A similar oxidation of the (12*S*) epimer **26** afforded a mixture of β-diketones **28** which showed the following different set of ^{13}C-NMR signals: δ = −4.3, 9.3, 10.6, 12.4, 13.1, 14.2, 14.5, 15.7, 16.3, 18.2, 21.3, 25.9, 26.0, 35.2, 38.2, 42.7, 43.0, 50.6, 55.3, 59.8, 75.5, 80.8, 85.2, 100.0, 113.4, 127.1, 129.6, 131.1, 131.4, 159.7, 208.6, 211.8.

15. *(2R,3S,4R,6R,8E)-2-{(2S,4R,5S,6S)-6-[(1R,2S)-2-Hydroxy-1-methylbutyl]-2-(p-methoxyphenyl)-5-methyl-1,3-dioxan-4-yl}-3-hydroxy-4,6,8-trimethyl-8-undecen-5-one* (**30**): A suspension of 0.15 g (1.6 mmol) of anhydrous $LiBF_4$, 0.17 g (1.6 mmol) of Na_2CO_3, and 0.20 g of molecular sieves (4 Å) in 5 ml of CH_3CN/CH_2Cl_2 (1:2) was stirred under nitrogen for 1 h. A solution of 0.10 g (0.16 mmol) of **25** in 2 ml of CH_2Cl_2 was added. Since after 2 h TLC indicated no reaction, further 0.17 g (1.6 mmol) of $LiBF_4$ was added, and the reaction was stirred for 5 d. The mixture was partitioned between 10 ml of saturated aqueous $NaHCO_3$ solution and 25 ml of ether. The aqueous phase was extracted four times with 10 ml each of ether. The combined organic extracts were dried with Na_2SO_4 and concentrated. Flash chromatography using petroleum ether (b.p. 40−60°C)/ether (9:1 and then 3:2) afforded 52 mg of the diol **30** and 24 mg of unreacted starting material.

30: ^{1}H NMR (400 MHz, $CDCl_3$ over K_2CO_3): δ = 0.87−0.80 (m, 18H), 1.07 (d, *J* = 6.97 Hz, 3H), 1.49 (s, 3H), 1.54 (m, 2H), 1.93 (m, 4H), 1.99 (m, 1H), 2.07 (m, 1H), 2.18 (dd, *J* = 12.2 and 6.4 Hz, 1H), 2.69 (dq, *J* = 6.95 and 2.8 Hz, 1H), 2.97 (q, *J* = 7.0 Hz, 1H), 3.35 (br. s, 1H), 3.46 (dd, *J* = 10.0 and 2.0 Hz, 1H), 3.66 (t, *J* = 6.5 Hz, 1H), 3.73 (s, 3H), 3.86 (m, 1H), 3.86 (dd, *J* = 9.9 and 2.9 Hz, 1H), 5.06 (t, *J* = 7.1 Hz, 1H), 5.39 (s, 1H), 6.80 (d, *J* = 6.3 Hz, 2H), 7.22 (d, *J* = 6.5 Hz, 2H). – ^{13}C NMR (75 MHz, $CDCl_3$): δ = 4.2, 8.8, 10.6, 12.0, 14.2, 15.7, 16.5, 17.2, 21.2, 28.0, 35.5, 37.2, 37.5, 41.1, 44.3, 48.3, 55.3, 78.9, 79.1, 82.3, 87.2, 100.4, 113.6, 127.1, 129.4, 130.8, 131.3, 159.9, 214.9.

16. *(2S,4RS,6R,8E)-2-{(2S,4S,5S,6R)-2-(p-Methoxyphenyl)-5-methyl-6-[(1S)-1-methyl-2-oxobutyl]-1,3-dioxan-4-yl}-4,6,8-trimethyl-8-undecen-3,5-dione* (**19**): To an oxidizing solution, prepared as described under **14**. from 0.37 g (4.6 mmol) of pyridine, 0.23 g (2.3 mmol) of CrO_3 in 15 ml of CH_2Cl_2, was added a solution of 60.0 mg (0.12 mmol) of the diol **30** in 3 ml of CH_2Cl_2. After 15 min at room temperature, the reaction mixture was worked up as described under **14**. Flash chromatography using petroleum ether (b.p. 40−60°C)/ether (10:1, 3:1, 1:1) afforded 30.7 mg (61%) of the trione **19** as a 1:1 epimer mixture (at C-10, denticulatin numbering). – ^{13}C NMR (75 MHz, $CDCl_3$; the values reported in *italics* refer to signals which are split to doublets due to epimers present; values in parentheses refer to signals of the epimeric compound:

δ = *7.5, 8.5, 11.9, 13.7, 14.1, 14.3,* 15.7, *16.5, 21.2, 34.5, 34.0,* 41.0, *44.3,* 48.1, *49.5,* 55.2, *58.5, 81.4,* 84.6 (84.2), 100.6 (100.2), *113.4, 127.1,* 129.4, *130.5,* 131.2, 159.5, *207.7, 208.9, 214.6.*

17. *(3S,4R,5R,6R)-5-(p-Methoxybenzyloxy)-4,6-dimethyl-7-oten-3-ol* (**32**): 2.50 g (6.16 mmol) of the diol derivative **13** was combined with 9.00 ml (9.00 mmol) of a 1 M solution of tetra-*n*-butylammonium fluoride in THF. After stirring for 3 d at room temperature, the starting material had been consumed. The mixture was partitioned between 100 ml of aqueous saturated NH_4Cl solution and 100 ml of ether. The aqueous phase was extracted three times with 50 ml each of ether, and the combined organic phases were washed with 50 ml of brine, dried with $MgSO_4$, and concentrated in vacuo. Flash chromatography with petroleum ether (b.p. 40–60°C)/ether (10:1 and then 3:1) afforded 1.80 g (100%) of the alcohol **32** as a colorless liquid. – ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.92 (t, *J* = 7.5 Hz, 3H), 0.96 (d, *J* = 7.2 Hz, 3H), 1.05 (d, *J* = 6.9 Hz, 3H), 1.45 (quint, *J* = 7.3 Hz, 1H), 1.60 (quint, *J* = 7.6 Hz, 1H), 1.75 (m, 1H), 2.60 (m, 1H), 2.90 (d, *J* = 2.2 Hz, 1H), 3.43 (dd, *J* = 6.9 and 4.0 Hz, 1H), 3.70 (m, 1H), 3.80 (s, 3H), 4.45 (d, *J* = 10.4 Hz, 1H), 4.70 (d, *J* = 10.3 Hz, 1H), 5.10 (m, 2H), 5.95 (ddd, *J* = 17.2, 10.2, and 8.0 Hz, 1H), 6.88 (d, *J* = 6.7 Hz, 2H), 7.30 (d, *J* = 6.70 Hz, 2H). – ^{13}C NMR (75 MHz, $CDCl_3$): δ = 6.7, 10.5, 16.9, 27.9, 38.6, 41.1, 55.2, 73.5, 76.4, 87.5, 113.8, 114.7, 129.4, 130.4, 141.5, 159.2.

$C_{18}H_{28}O_3$ (292.4) Calcd. C 73.93 H 9.65
Found C 74.10 H 9.97

18. *(4S,5R,6R)-5-(p-Methoxybenzyloxy)-4,6-dimethyl-7-octen-3-one* (**33**): To a solution of 1.80 g (6.16 mmol) of the alcohol **32** in 200 ml of CH_2Cl_2 was added 2.00 g (9.25 mmol) of pyridinium chlorochromate. The mixture was stirred for ca. 12 h and partitioned between 100 ml of 1% aqueous hydrochloric acid and 250 ml of ether. The aqueous phase was extracted three times with 100 ml each of ether, and the combined organic extracts were dried with Na_2SO_4. Removal of the solvents and flash chromatography of the residue with petroleum ether (b.p. 40–60°C)/ether (10:1 and then 3:1) afforded 1.70 g (95%) of the ketone **33** as a colorless oil. – ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.96 (t, *J* = 7.2 Hz, 3H), 1.04 (d, *J* = 6.9 Hz, 3H), 1.12 (d, *J* = 7.1 Hz, 3H), 2.24 (m, 1H), 2.40 (m, 2H), 2.74 (dq, *J* = 7.1 and 7.1 Hz), 3.56 (dd, *J* = 7.5 and 4.1 Hz, 1H), 3.72 (s, 3H), 4.40 (q, *J* = 10.7 Hz, 2H), 4.95 (m, 2H), 5.80 (ddd, *J* = 18.7, 10.5, and 8.4 Hz, 1H), 6.80 (d, *J* = 6.6 Hz, 2H), 7.20 (d, *J* = 6.7 Hz, 2H). – ^{13}C NMR (75 MHz, $CDCl_3$): δ = 7.7, 13.7, 17.7, 35.6, 42.2, 49.5, 55.3, 74.6, 83.6, 113.8, 115.1, 129.4, 130.9, 140.6, 159.3, 214.4.

$C_{18}H_{26}O_3$ (290.4) Calcd. C 74.47 H 9.03
Found C 74.50 H 9.05

19. *(2S,3R,4S)-3-(p-Methoxybenzyloxy)-2,4-dimethyl-5-oxoheptanal* (**34**): Into a solution of 1.00 g (3.44 mmol) of the alkene **33** in 40 ml of CH_2Cl_2 was introduced at –78°C a stream of ozone until the blue color persisted. Excess of ozone was purged by a stream of nitrogen for 15 min; 1.00 g (3.82 mmol) of triphenylphosphine was added, and the reaction mixture was allowed to warm to room temperature. After stirring at 20°C for 5 h, the solvents were removed in vacuo, and the residue was separated by flash chromatography using petroleum ether (b.p. 40–60°C)/ether (10:1, 3:1, and then 1:1) to give 0.95 g (94%) of the aldehyde **34** as a colorless liquid. – ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.02 (t, *J* = 7.3 Hz, 3H), 1.10 (dd, *J* = 7.1 and 2.3 Hz, 3H), 1.20 (d, *J* = 7.2 Hz, 3H), 2.50 (m, 3H), 2.80 (dq, *J* = 6.8 and 6.8 Hz, 1H), 3.78 (s, 3H), 4.00 (t, *J* = 5.4 Hz, 1H), 4.45 (s, 2H), 6.84 (d, *J* = 8.7 Hz, 2H), 7.20 (d, *J* = 8.7 Hz, 2H), 9.64 (d, *J* = 2.4 Hz, 1H). – ^{13}C NMR (75 MHz, $CDCl_3$): δ = 7.7, 11.3, 12.9, 35.5, 48.8, 49.7, 55.4, 73.9, 80.9, 113.9, 129.6, 130.0, 159.5, 203.8, 213.8.

$C_{17}H_{24}O_4$ (292.9) Calcd. C 69.84 H 8.27
Found C 69.81 H 8.31

20. *(2S,3S,4R,5S,6R)-2-Ethyl-4-(p-methoxybenzyloxy)-3,5-dimethyl-6-[(1R)-1-methyl-2-propenyl]-tetrahydro-2H-pyran-2-ol* (**35a**): The reaction was carried out according to ref.[24]: 10.5 ml of a 0.65 M solution of diisopropyl (*S,S*)-tartrate derived (*E*)-crotylboronate in toluene was diluted with 20 ml of dry toluene and treated with 0.50 g of molecular sieves (4 Å) for 30 min. After cooling to –78°C, a solution of 0.80 g (2.7 mmol) of the aldehyde **34** in 15 ml of toluene was added dropwise over a period of 1 h. After stirring for 3 h at –78°C, the mixture was poured into 100 ml of saturated aqueous NH_4Cl solution, and the mixture was stirred for 12 h. After filtration, the mixture was extracted four times with 100 ml each of ether, and the combined organic extracts were dried with Na_2SO_4 and concentrated. ^{1}H NMR indicated the presence of two products in a 68:32 ratio. Flash chromatography with petroleum ether (b.p. 40–60°C)/ether (50:1, then 25:1, then 4:1) afforded 0.55 g (58%) of **35a** and then 0.25 g (26%) of **36a**.

35a: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.78 (d, *J* = 6.8 Hz, 3H), 0.84 (d, *J* = 7.0 Hz, 3H), 0.91 (t, *J* = 7.5 Hz, 3H), 1.04 (d, *J* = 6.8 Hz, 3H), 1.48 (m, 2H), 1.70 (dq, *J* = 12.2 and 6.4 Hz, 1H), 2.04 (dq, *J* = 7.1 and 2.6 Hz, 1H), 2.30 (ddq, *J* = 7.0, 6.0, and 2.0 Hz, 1H), 3.36 (t, *J* = 2.8 Hz, 1H), 3.56 (dd, *J* = 10.9 and 2.0 Hz, 1H), 3.74 (s, 3H), 4.32 (d, *J* = 10.9 Hz, 1H), 4.65 (d, *J* = 11.0 Hz, 1H), 4.95 (m, 2H), 5.80 (ddd, *J* = 18.4, 9.2 and 5.6 Hz, 1H), 5.95 (s, 1H), 6.81 (d, *J* = 8.3 Hz, 2H), 7.20 (d, *J* = 8.5 Hz, 2H). – ^{13}C NMR (75 MHz, $CDCl_3$): δ = 6.9, 13.2, 13.7, 18.2, 30.9, 31.4, 36.0, 39.6, 55.3, 72.2, 72.6, 84.9, 98.8, 113.9, 114.6, 128.6, 129.7, 140.1, 159.5. – The structure was confirmed by conversion into the aldehyde **37** described below.

36a: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.88 (d, *J* = 6.9 Hz, 3H), 0.90 (t, *J* = 7.4 Hz, 3H), 0.94 (d, *J* = 6.6 Hz, 3H), 1.02 (d, *J* = 6.6 Hz, 3H), 1.66 (m, 2H), 1.70 (s, 1H), 1.80 (dq, *J* = 11.9 and 6.6 Hz, 1H), 2.20 (ddq, *J* = 6.8, 4.7, and 2.1 Hz, 1H), 2.30 (m, 1H), 3.53 (dd, *J* = 11.2 and 4.7 Hz, 1H), 3.54 (dd, *J* = 7.8 and 2.1 Hz, 1H), 3.78 (s, 3H), 4.30 (d, *J* = 10.9 Hz, 1H), 4.55 (d, *J* = 10.9 Hz, 1H), 4.98 (m, 2H), 5.86 (ddd, *J* = 17.3, 10.4, and 6.9 Hz, 1H), 6.82 (d, *J* = 8.6 Hz, 2H), 7.26 (d, *J* = 8.7 Hz, 2H). – ^{13}C NMR (75 MHz, $CDCl_3$): δ = 4.8, 7.0, 12.1, 15.4, 32.1, 32.8, 36.7, 38.6, 55.3, 70.2, 74.0, 80.4, 99.6, 113.3, 113.8, 129.7, 131.0, 142.8, 159.2.

$C_{21}H_{32}O_4$ Calcd. 348.2302 Found 348.2296 (MS)

21. *(2S,3S,4R,5S,6R)-2-Ethyl-4-(p-methoxybenzyloxy)-6-[(1R,2Z)-3-methoxy-1-methyl-2-propenyl]-3,5-dimethyl-tetrahydro-2H-pyran-2-ol* (**35b**): 1.00 g (3.42 mmol) of the aldehyde **34** and 1.23 g (5.80 mmol) of the dioxaborolane **14b** were allowed to react in 5 ml of toluene as described under 5. Flash chromatography provided 0.77 g (60%) of the tetrahydropyran **35b** as a colorless oil. – ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.80 (d, *J* = 6.8 Hz, 3H), 0.82 (d, *J* = 7.1 Hz, 3H), 0.88 (t, *J* = 7.5 Hz, 3H), 1.00 (d, *J* = 7.0 Hz, 3H), 1.45 (m, 2H), 1.66 (ddq, *J* = 10.4, 6.9, and 2.5 Hz, 1H), 2.00 (dq, *J* = 7.1 and 2.7 Hz, 1H), 2.82 (ddq, *J* = 10.0, 7.1, and 2.2 Hz, 1H), 3.34 (t, *J* = 2.8 Hz, 1H), 3.48 (s, 3H), 3.52 (dd, *J* = 10.4 and 2.1 Hz, 1H), 3.74 (s, 3H), 4.30 (d, *J* = 11.0 Hz, 1H), 3.36 (dd, *J* = 10.1 and 6.3 Hz, 1H), 4.62 (d, *J* = 11.0 Hz, 1H), 5.84 (d, *J* = 6.63 Hz, 1H), 5.91 (s, 1H), 6.80 (d, *J* = 8.7 Hz, 2H), 7.18 (d, *J* = 8.7 Hz, 2H). – ^{13}C NMR (75 MHz, $CDCl_3$): δ = 6.8, 13.4, 13.7, 18.5, 29.9, 31.4 (2 C), 36.1, 55.2, 59.3, 72.1, 73.0, 85.0, 98.7, 108.1, 113.8, 128.5, 129.6, 145.9, 159.4.

$C_{22}H_{34}O_5$ (378.5) Calcd. C 69.81 H 9.05
Found C 69.66 H 9.03

As a second fraction, flash chromatography provided 0.21 g of a mixture of probably 4 compounds isomeric with **35b**, among which according to the ^{1}H-NMR spectrum are some containing (*E*)-enol ether functions.

22. *(2S)-2-[(2S,3S,4R,5S,6S)-6-Ethyl-6-hydroxy-4-(p-methoxybenzyloxy)-3,5-dimethyl-tetrahydro-2H-pyran-2-yl]propanal* (**37**): To a solution of 0.50 g (1.3 mmol) of the enol ether **35b** in 30 ml of CH_2Cl_2/CH_3OH (5:1) was added ca. 0.2 g of solid anhydrous Na_2CO_3 and a small amount of Sudan III indicator dye. The suspension was cooled to −85°C, and a stream of ozone was introduced until the indicator just decolorized. The excess of ozone was purged by bubbling a stream of nitrogen through the reaction mixture for 15 min; 0.50 g (1.9 mmol) of triphenylphosphine was added, and the reaction mixture was allowed to warm to 0°C. After stirring for 2 h, the mixture was partitioned between 50 ml of ether and 25 ml of brine. The aqueous phase was extracted four times with 25 ml each of ether, and the combined organic extracts were washed with 15 ml of brine, dried with $MgSO_4$, and concentrated in vacuo. Flash chromatography using petroleum ether (b.p. 40−60°C)/ether (10:1 and then 3:1) afforded 0.39 g (85%) of the desired aldehyde as a colorless oil. For spectral and analytical data see ref.[6]. − The same product was obtained in 90% yield by similar ozonolysis of the alkene **35a**.

23. *(2R,3S,4R,6R,8E)-2-{(2S,3S,4R,5S,6S)-6-Ethyl-6-hydroxy-4-(p-methoxybenzyloxy)-3,5-dimethyl-tetrahydro-2H-pyran-2-yl}-3-hydroxy-4,6,8-trimethyl-8-undecen-5-one* (**38**): 0.100 g (0.595 mmol) of **2** (ca. 85% e.e.) was allowed to react with 0.140 g (0.400 mmol) of the aldehyde **37** as described under 13. to give after flash chromatography 0.145 g (70%) of **38** and 0.039 g (19%) of the epimer **39** (at C-12, denticulatin numbering). For the spectroscopic and analytical data of **38** see ref.[6].

39: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.90 (m, 15H), 0.98 (d, *J* = 6.8 Hz, 3H), 1.04 (d, *J* = 7.1 Hz, 3H), 1.48 (m, 2H), 1.56 (s, 3H), 1.78 (m, 1H), 1.90 (m, 3H), 2.04 (dq, *J* = 7.1 and 2.6 Hz, 1H), 2.30 (dd, *J* = 13.8 and 7.5 Hz, 1H), 2.35 (m, 1H), 2.66 (dq, *J* = 7.1 and 2.1 Hz, 1H), 2.86 (dq, *J* = 14.0 and 7.0 Hz, 1H), 3.03 (d, *J* = 2.69 Hz, 1H), 3.55 (t, *J* = 2.8 Hz, 1H), 3.68 (dd, *J* = 11.1 and 2.0 Hz, 1H), 3.70 (s, 3H), 4.04 (dt, *J* = 8.8 and 2.3 Hz, 1H), 4.33 (d, *J* = 10.9 Hz, 1H), 4.62 (d, *J* = 10.5 Hz, 1H), 5.10 (t, *J* = 6.0 Hz, 1H), 5.99 (s, 1H), 6.82 (d, *J* = 8.7 Hz, 2H), 7.20 (d, *J* = 8.7 Hz, 2H). − ^{13}C NMR (75 MHz, $CDCl_3$): δ = 7.0, 8.6, 13.9, 14.1, 14.3, 15.8, 16.3, 16.6, 21.3, 31.5, 32.2, 36.1, 36.2, 43.1, 43.7, 47.7, 55.3, 71.0, 72.4, 74.0, 85.2, 99.3, 113.9, 129.6, 129.7, 129.8, 131.3, 159.5, 220.0.

$C_{31}H_{48}O_5$ [$M^+ - H_2O$] Calcd. 500.3503
Found 500.3534 (MS)

24. *(2R,4R,6E)-2-[(1R,3S,4S,5R,6R,7R,8S)-1-Ethyl-7-(p-methoxybenzyloxy)-4,6,8-trimethyl-2,9-dioxabicyclo[3.3.1]non-3-yl]-2,4,6-trimethyl-6-nonen-3-one* (**40**): To a solution of 50 mg (0.10 mmol) of the aldol **38** in 5 ml of CH_2Cl_2 was added a small amount of *p*-toluenesulfonic acid which resulted in the immediate formation of a single new product. The solution was filtered through silica gel and was concentrated to give a quantitative yield of the bicyclic compound **40**. − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.77 (t, *J* = 7.5 Hz, 3H), 0.84 (d, *J* = 7.6 Hz, 3H), 0.85 (t, *J* = 6.6 Hz, 3H), 0.89 (d, *J* = 7.3 Hz, 3H), 0.90 (d, *J* = 6.9 Hz, 3H), 0.91 (d, *J* = 7.3 Hz, 3H), 1.01 (d, *J* = 7.02 Hz, 3H), 1.41 (m, 2H), 1.54 (s, 3H), 1.66 (ddq, *J* = 10.0, 7.2, and 3.1 Hz, 1H), 1.74 (dq, *J* = 10.5 and 6.6 Hz, 1H), 1.84 (dd, *J* = 13.4 and 7.5 Hz, 1H), 1.90 (m, 3H), 2.14 (dd, *J* = 13.1 and 6.6 Hz, 1H), 2.52 (dq, *J* = 6.9 and 2.5 Hz, 1H), 2.95 (dq, *J* = 14.3 and 6.8 Hz, 1H), 3.53 (dd, *J* = 2.5 and 1.9 Hz, 1H), 3.54 (dd, *J* = 10.5 and 5.1 Hz, 1H), 3.70 (s, 3H), 3.84 (dd, *J* = 10.4 and 2.5 Hz, 1H), 4.23 (d, *J* = 11.1 Hz, 1H), 4.46 (d, *J* = 11.1 Hz, 1H), 5.08 (t, *J* = 7.0 Hz, 1H), 6.82 (d, *J* = 8.7 Hz, 2H), 7.23 (d, *J* = 8.7 Hz, 2H). − ^{13}C NMR (75 MHz, $CDCl_3$): δ = 7.4, 8.7, 11.0, 12.0, 14.2, 15.7, 15.9, 18.1, 21.2, 30.3, 35.8, 36.6, 37.1, 40.8, 44.7, 47.4, 55.3, 70.2, 72.2, 75.8, 81.1, 102.5, 113.8, 129.5, 129.6, 130.5, 131.3, 159.2, 215.2.

$C_{31}H_{48}O_5$ Calcd. 500.3503
Found 500.3495 (MS)

Likewise the epimer **39** was converted into 12-*epi*-**40** (denticulatin numbering). − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.80 (t, *J* = 7.5 Hz, 3H), 0.87 (t, *J* = 7.0 Hz, 3H), 0.86 (d, *J* = 7.0 Hz, 3H), 0.88 (d, *J* = 6.7 Hz, 3 H), 0.92 (d, *J* = 7.1 Hz, 3H), 0.98 (d, *J* = 7.0 Hz, 3H), 1.03 (d, *J* = 7.0 Hz, 3H), 1.45 (m, 2H), 1.50 (s, 3H), 1.62 (ddq, *J* = 10.1, 6.5, and 3.6 Hz, 1H), 1.73 (dq, *J* = 10.5 and 6.5 Hz, 1H), 1.88 (dd, *J* = 14.2 and 9.4 Hz, 1H), 1.94 (m, 3H), 2.20 (dd, *J* = 14.5 and 5.7 Hz, 1H), 2.56 (dq, *J* = 7.0 and 2.6 Hz, 1H), 2.88 (ddq, *J* = 7.2, 4.5, and 2.1 Hz, 1H), 3.53 (dd, *J* = 3.6 and 1.1 Hz, 1H), 3.55 (dd, *J* = 10.5 and 5.1 Hz, 1H), 3.75 (s, 3H), 3.82 (dd, *J* = 10.3 and 2.6 Hz, 1H), 4.21 (d, *J* = 11.0 Hz, 1H), 4.47 (d, *J* = 11.0 Hz, 1H), 5.10 (t, *J* = 6.4 Hz, 1H) 6.83 (d, *J* = 8.7 Hz, 2H), 7.24 (d, *J* = 8.5 Hz, 2H). − ^{13}C NMR (75 MHz, $CDCl_3$): δ = 7.3, 9.3, 11.0, 12.0, 14.2, 15.8, 16.4, 18.1, 21.2, 30.3, 35.7, 36.6, 37.0, 40.6, 42.4, 46.4, 55.3, 70.0, 72.2, 75.7, 81.1, 102.3, 113.8, 129.2, 129.5, 130.5, 131.4, 159.2, 215.6.

25. *(2S,4S,6R,8E)-2-{(2S,3S,4R,5S,6S)-6-Ethyl-6-hydroxy-4-(p-methoxybenzyloxy)-3,5-dimethyl-tetrahydro-2H-pyran-2-yl}-4,6,8-trimethyl-8-undecene-3,5-dione* (**41**): A solution of 60 mg (0.12 mmol) of the aldol **38** and of 94 µl (1.20 mmol) of pyridine in 10 ml of anhydrous CH_2Cl_2 was stirred under nitrogen for 1 h with 100 mg of molecular sieves (3 Å). After cooling to −5°C, 49 mg (0.12 mmol) of the Dess-Martin reagent[26] was added at once. After stirring for 2 h at −5°C, a white precipitate had formed, and the suspension was added to a mixture (room temperature) containing 10 ml of ether, 10 ml of semisaturated aqueous $NaHCO_3$ solution and 110 mg of $Na_2S_2O_3$. Upon stirring vigorously for 2 h all the solids had dissolved. The phases were separated, and the aqueous phase was extracted four times with 25 ml each of ether. The combined organic extracts were washed successively with 5 ml of dilute aqueous hydrochloric acid, 5 ml of saturated aqueous $NaHCO_3$ solution, and 5 ml of brine. The organic phase was dried with Na_2SO_4 and concentrated to afford 58 mg (97%) of the crude diketone. Flash chromatography using petroleum ether (b.p. 40−60°C)/ether (3:1) afforded 51 mg (85%) of **41** which was essentially (>10:1) one stereoisomer. For spectroscopic and analytical data see ref.[6].

26. *(−)-Denticulatin A and B* (**1**): To a solution of 38.0 mg (74 µmol) of the diketone **41** in 3 ml of anhydrous THF was added at −78°C 0.26 ml (15 µmol) of a 0.566 M solution of lithium diisopropylamide in THF. An equal volume of anhydrous NH_3 was condensed into the reaction vessel at −78°C. Ca. 2 mg (ca. 0.3 mmol) of freshly cut lithium was added, which dissolved slowly upon stirring while the color changed from colorless to deep brown and colorless again over 0.5 h. Now ca. 0.1 g of solid NH_4Cl was added, and the excess of ammonia was allowed to evaporate under a stream of nitrogen. The residual solvents were removed at 0.2 Torr, and the residue was partitioned between 10 ml of saturated aqueous NH_4Cl solution and 10 ml of ether. The aqueous phase was extracted five times with 15 ml each of ether, and the combined organic phases were dried with Na_2SO_4 and concentrated. Flash chromatography of the residue using petroleum ether (b.p. 40−60°C)/ether (10:1, then 3:1, then 1:1) afforded 13.4 mg (58%, based on recovered starting material) of the denticulatins A and B as a 1.5:1 mixture {$[\alpha]_D^{21}$ = −33.3 (*c* = 0.42, $CHCl_3$)} as well as 7.80 mg of recovered starting material.

Denticulatin A: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.90–0.98 (m, 9H), 1.04 (t, *J* = 7.2 Hz, 3H), 1.05 (d, *J* = 7.2 Hz, 3H), 1.09 (d, *J* = 7.1 Hz, 3H), 1.19 (d, *J* = 7.35 Hz, 3H), 1.58 (s, 3H), 1.70–1.80 (m, 2H), 1.79 (m, 1H), 2.00 (m, 2H), 2.14 (dd, *J* = 13.9 and 4.6 Hz, 1H), 2.46–2.53 (m, 3H), 2.75 (q, *J* = 7.4 Hz, 1H), 2.96 (m, 1H), 3.37 (d, *J* = 8.8 Hz, 1H), 3.60 (dt, *J* = 8.9 and 2.6 Hz, 1H), 4.38 (dd, *J* = 10.8 and 2.9 Hz, 1H), 5.14 (br. t, *J* = 7.9 Hz, 1H), 6.09 (s, 1H). – ^{13}C NMR (75 MHz, C_6D_6): δ = 7.9, 8.1, 11.9, 13.5, 14.5, 15.5, 15.8, 21.6, 32.7, 37.7, 38.7, 42.6, 43.1, 47.2, 50.6, 69.7, 75.4, 103.0, 129.5, 131.7, 209.8, 218.9.

Denticulatin B: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.90–0.98 (m, 9H), 1.03 (d, *J* = 6.8 Hz, 3H), 1.05 (t, *J* = 7.0 Hz, 3H), 1.17 (d, *J* = 6.8 Hz, 3H), 1.20 (d, *J* = 7.0 Hz, 3H), 1.61 (s, 3H), 1.67–1.73 (m, 3H), 2.00 (m, 2H), 2.29 (br. d, *J* = 12.7 Hz, 1H), 2.46–2.53 (m, 3H), 2.67 (m, 1H), 2.96 (q, *J* = 7.0 Hz, 1H), 3.06 (d, *J* = 7.3 Hz, 1H), 3.55 (dt, *J* = 8.5 and 2.5 Hz, 1H), 4.40 (dd, *J* = 10.7 and 2.90 Hz, 1H), 5.18 (t, *J* = 7.2 Hz, 1H), 5.32 (s, 1H). – ^{13}C NMR (75 MHz, C_6D_6): δ = 7.7, 8.1, 12.2, 13.3, 14.5, 14.7, 15.2, 15.5, 21.7, 32.5, 37.7, 41.7, 42.9, 43.0, 47.0, 52.3, 69.3, 76.3, 101.9, 129.5, 132.0, 209.3, 218.4.

Cf. the data puplished by Faulkner[3] and Ziegler[4]. Comparison of the synthetic denticulatins with a sample of the natural product by ^{1}H-NMR spectroscopy and TLC in three solvent systems proved the two to be indistinguishable.

---

[1] For part XXXVII see: R. W. Hoffmann, J. J. Wolff, *Chem. Ber.* **124** (1991) 563.

[2] [2a] D. C. Manker, M. J. Garson, D. J. Faulkner, *J. Chem. Soc., Chem. Commun.* **1988**, 1061. – [2b] M. J. Garson, C. J. Small, B. W. Skelton, P. Thinapong, A. H. White, *J. Chem. Soc., Perkin Trans. 1*, **1990**, 805.

[3] J. E. Hochlowski, D. J. Faulkner, G. K. Matsumoto, J. Clardy, *J. Am. Chem. Soc.* **105** (1983) 7413.

[4] F. E. Ziegler, M. R. Becker, *J. Org. Chem.* **55** (1990) 2800.

[5] R. W. Hoffmann, *Angew. Chem.* **99** (1987) 503; *Angew. Chem. Int. Ed. Engl.* **26** (1987), 489.

[6] M. W. Andersen, B. Hildebrandt, R. W. Hoffmann, *Angew. Chem.* **103** (1991) 90; *Angew. Chem. Int. Ed. Engl.* **30** (1991), 97.

[7] R. W. Hoffmann, K. Ditrich, G. Köster, R. Stürmer, *Chem. Ber.* **122** (1989) 1783.

[8] R. W. Hoffmann, S. Dresely, B. Hildebrandt, *Chem. Ber.* **121** (1988) 2225.

[9] R. W. Hoffmann, W. Ladner, W. Helbig, *Liebigs Ann. Chem.* **1984**, 1170.

[10] [10a] R. W. Hoffmann, U. Weidmann, *Chem. Ber.* **118** (1985) 3966. – [10b] W. R. Roush, *J. Org. Chem.*, in press.

[11] R. W. Hoffmann, S. Dresely, *Chem. Ber.* **122** (1989) 903.

[12] R. W. Hoffmann, S. Dresely, *Tetrahedron Lett.* **28** (1987) 5303.

[13] Y. Oikawa, T. Nishi, O. Yonemitsu, *Tetrahedron Lett.* **24** (1983) 4037.

[14] L. E. Overman, N.-H. Lin, *J. Org. Chem.* **50** (1985) 3669.

[15] B. Hildebrandt, *Dissertation*, Univ. Marburg, 1986.

[16] D. Enders, U. Baus, *Liebigs Ann. Chem.* **1983**, 1439.

[17] [17a] M. Nagatsuma, F. Shirai, N. Sayo, T. Nakai, *Chem. Lett.* **1984**, 1393. – [17b] C. H. Heathcock, B. L. Finkelstein, E. T. Jarvi, P. A. Radel, C. R. Hadley, *J. Org. Chem.* **53** (1988) 1923.

[18] T. Mukaiyama, T. Inoue, *Chem. Lett.* **1976**, 559.

[19] D. A. Evans, J. V. Nelson, E. Vogel, T. R. Taber, *J. Am. Chem. Soc.* **103** (1981) 3099.

[20] H. O. House, D. S. Crumrine, A. Y. Teranishi, H. D. Olmstead, *J. Am. Chem. Soc.* **95** (1973) 3310.

[21] D. V. Patel, F. Van Middlesworth, J. Donaubauer, P. Gannett, C. J. Sih, *J. Am. Chem. Soc.* **108** (1986) 4603.

[22] M. W. Andersen, *Dissertation*, Univ. Marburg, 1990.

[23] R. W. Hoffmann, U. Weidmann, *Chem. Ber.* **118** (1985) 3980.

[24] W. R. Roush, A. D. Palkowitz, K. Ando, *J. Am. Chem. Soc.* **112** (1990) 6348.

[25] H. C. Brown, K. S. Bhat, R. S. Randad, *J. Org. Chem.* **54** (1989) 1570.

[26] D. B. Dess, J. C. Martin, *J. Org. Chem.* **48** (1983) 4155.

[27] [27a] M. W. Andersen, B. Hildebrandt, G. Köster, R. W. Hoffmann, *Chem. Ber.* **122** (1989) 1777. – [27b] D. S. Matteson, D. Majumdar, *J. Am. Chem. Soc.* **102** (1980) 7588.

[28] R. W. Hoffmann, S. Dresely, J. W. Lanz, *Chem. Ber.* **121** (1988) 1501.

[29] W. A. König, W. Francke, I. Benecke, *J. Chromatogr.* **239** (1982) 227.

[184/91]