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Studies in Polypropionate Synthesis: Stereoselective Synthesis of (–)-Denticulatins A and B.

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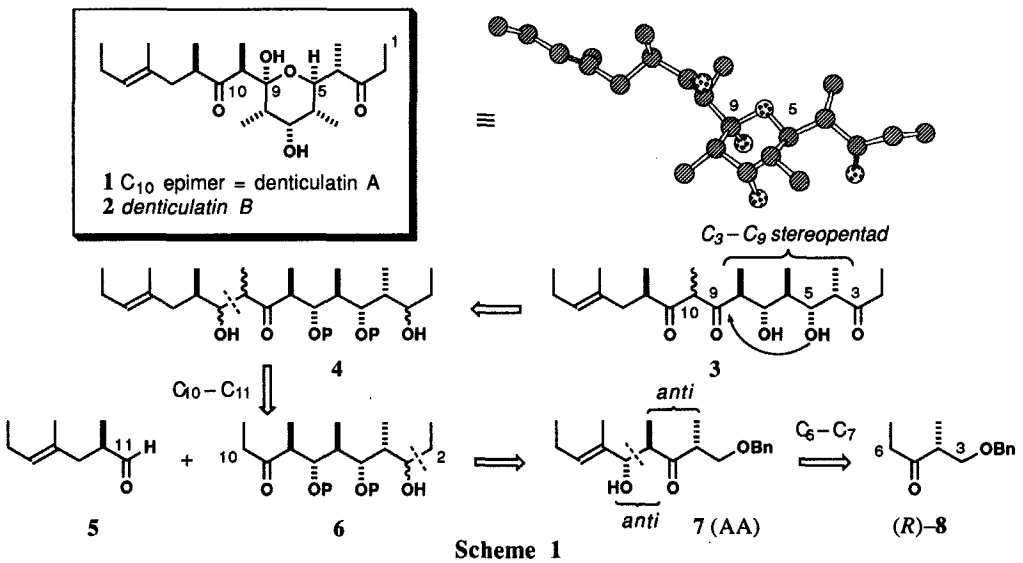
Abstract: (–)-Denticulatin B (**2**) was prepared in 9 steps (20% yield) with 70% overall ds starting from the ethyl ketone (*R*)-**8**. Key steps are the novel boron-mediated aldol/reduction, **8** → **12**, the titanium aldol coupling, **6** + **5** → **18**, and the HF-pyridine cyclisation, **20** → **2**. Epimerisation at C_{10} in **20** led to (–)-denticulatin A (**1**).

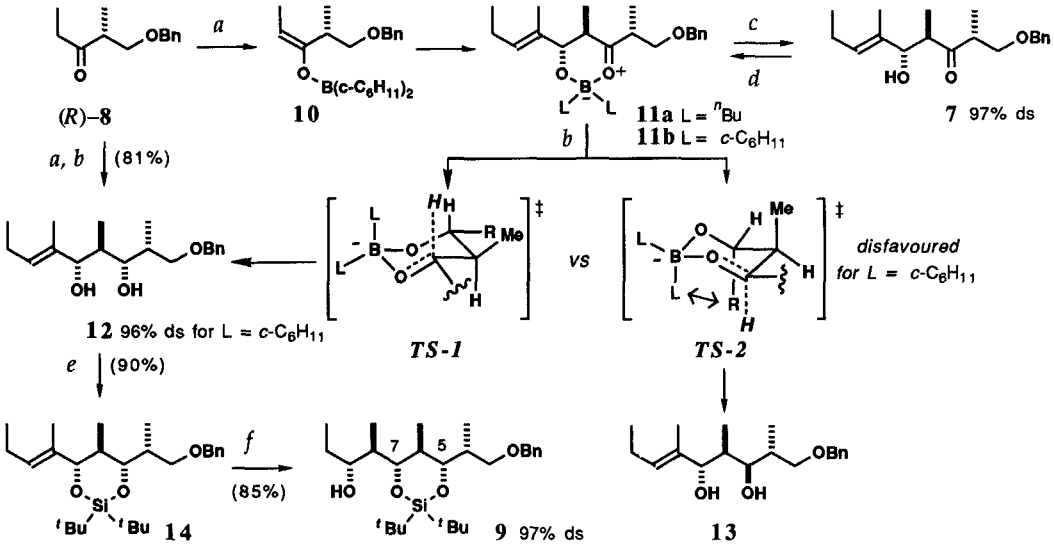
Denticulatins A and B,[1] **1** and **2** in **Scheme 1**, were first isolated in 1983 by Faulkner's group from the pulmonate mollusc *Siphonaria denticulata*. As polypropionate metabolites,[2] the denticulatins[2a] and other compounds[2b,3] from siphonariid molluscs (false limpets) are biosynthetically related to the macrolide and polyether actinomycete antibiotics. Unlike the latter, however, they usually show low antimicrobial activity and their biological role is uncertain. Structurally, the denticulatins are epimers at C_{10} and have an acid-labile, thermodynamically-favoured, hemiacetal between the C_5 hydroxyl and the C_9 ketone groups. For synthetic purposes,[4,5] Ziegler and Becker[4] have shown that they can be obtained as a mixture from a protected version of the open-chain triones **3** under careful acid treatment. As part of our studies in polypropionate synthesis, we now report a short, enantiocontrolled synthesis of the denticulatins, exploiting some novel aldol methodology. Notably, this allows the first stereoselective synthesis of (–)-denticulatin B.



Scheme 1

Scheme 1 outlines our strategy for the synthesis of the denticulatins *via* **3** and **4** — based on aldol-type disconnections of the C_{10}–C_{11} and C_6–C_7 bonds. A stereoselective synthesis of denticulatin B (or A) relies on control at C_{10} by a suitable aldol coupling between **5** and **6**. The sequence of five contiguous chiral centres linking C_3 and C_9 should be amenable to our general protocol[6] for the synthesis of such stereopentads. In this case, the appropriate precursor is the *anti-anti* aldol adduct **7** derived from the ethyl ketone (*R*)-**8**.[7,8]

The synthesis of the C_3–C_{10} segment **9**, with the two hydroxyl groups at C_5 and C_7 protected as the cyclic di-*tert*-butylsilylene derivative, is shown in **Scheme 2**. We anticipated that this silyl protecting group might be removed under mild conditions using buffered HF-pyridine[9] as the final, hemiacetal-forming, step of our denticulatin synthesis, thus avoiding any competing[4] dehydration. Addition of the *E* enol dicyclohexyl borinate **10**, obtained by enolisation of (*R*)-**8** with $(c\text{-}C_6H_{11})_2BCl/Et_3N$, to (*E*)-2-methyl-2-pentenal gave on oxidative work-up the expected[7] *anti-anti* aldol isomer **7** with 97% ds.[10] Reduction to the corresponding *syn* 1,3-diol **11** was initially attempted using[7] $LiBH_4$ on the di-*n*-butylboron aldolate **11a** derived from **7** ($^nBu_2BOMe$, THF-MeOH). This led to an inseparable *ca* 1:1 mixture of **12** and **13**, indicating poor reduction stereoselectivity.[11] Fortunately, this problem was easily overcome by employing a *one-pot* aldol/reduction.

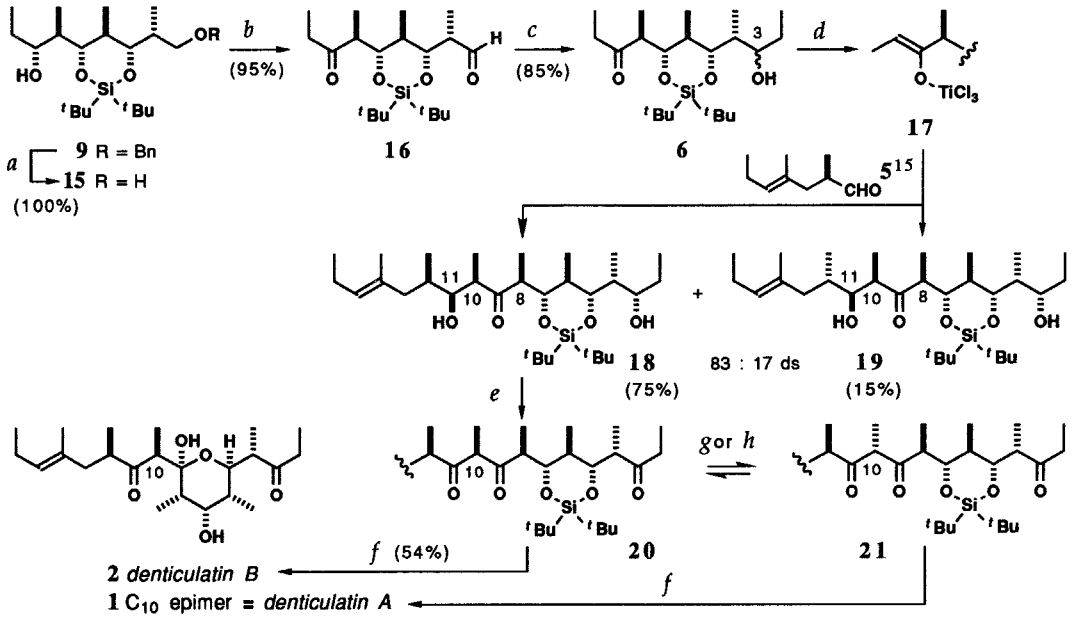


Scheme 2 (*a*) $(c\text{-}C_6H_{11})_2BCl$, Et_3N, Et_2O, -15 °C, 2 h; (*E*)-EtCH=C(Me)CHO, 2 h; (*b*) $LiBH_4$, 1 h, -78 °C; H_2O_2, 10% NaOH, MeOH, 2 h; (*c*) H_2O_2, MeOH-pH7 buffer; (*d*) $^nBu_2BOMe$, THF-MeOH, -78 °C; (*e*) $^tBu_2Si(OTf)_2$, 2,6-lutidine, CH_2Cl_2, 20 °C, 4 h; (*f*) $BH_3{\bullet}SMe_2$, THF, 20 °C, 18 h; H_2O_2, 10% NaOH, THF, 21 h.

When the intermediate dicyclohexylboron aldolate[7] **11b**, formed from (*R*)-**8** and the aldehyde, was now reduced *in situ* by $LiBH_4$, this provided the required stereotetrad **12**[10] (m.p. 64-65 °C, pentane; $[\alpha]_D^{20}$ = +15.6° (*c* 1.4, $CHCl_3$)) with much improved diastereoselectivity (96% ds) in 81% yield. Assuming both reductions occur through the chelated structures **11a–b**, this ligand effect may be rationalised as follows. With *n*-butyl ligands on boron in **11a**, reduction can take place through the competing chair-like transition states ***TS-1*** (R and Me equatorial with gauche interaction) → **12** and ***TS-2*** (R and Me now axial with L ↔ R diaxial interaction) → **13**. For the more sterically demanding cyclohexyl ligands, however, the L ↔ R interaction in ***TS-2*** becomes more severe and high reduction stereoselectivity ensues by preferred axial attack of hydride *via* ***TS-1***. This novel one-pot procedure should be useful for the preparation of related stereotetrads to **12**.[6] Hydroxyl protection to give **14** was next accomplished in 90% yield by reaction of **11** with $^tBu_2Si(OTf)_2$/lutidine. Hydroboration of **14** using $BH_3{\bullet}SMe_2$ in THF and oxidative workup then gave **9**[10], $[\alpha]_D^{20}$ = –10.4° (*c* 0.9, $CHCl_3$), with 97% ds in 85% yield. Thus the C_3–C_{10} segment **9** is obtained in 61% yield in effectively only three steps from (*R*)-**8** with 93% ds for setting up the six contiguous stereocentres.

The remainder of the synthesis is shown in **Scheme 3**. Debenzylation of **9** by catalytic hydrogenolysis led quantitatively to diol **15** (m.p. 95-96 °C, pentane; $[\alpha]_D^{20}$ = –2.7° (*c* 1.0, $CHCl_3$)), which was then oxidised using PCC to give the ketoaldehyde **16** (95%). Completion of the synthesis of the ethyl ketone **6** now required chemoselective addition of an ethyl organometallic reagent to the aldehydic carbonyl group. This was best

achieved by adding EtMgBr to **16** in Et_2O solution at -100 °C, warming briefly to -50 °C, and quenching with MeOH. This provided **6** in 85% yield as a 6:1 mixture of isomers at the temporary C_3 stereocentre.[12] The major isomer of **6**[10] (m.p. 58-59 °C, pentane; $[\alpha]_D^{20} = -8.2°$ (*c* 1.9, $CHCl_3$)), assumed to be 3*S* corresponding to the Cram-Felkin adduct, was initially used to complete the synthesis.



Scheme 3 (*a*) H_2, 10% Pd/C, EtOH, 20 °C, 6 h; (*b*) PCC, CH_2Cl_2, 20 °C, 3 h; (*c*) EtMgBr, Et_2O, -100 °C, 15 min → -50 °C, 15 min; MeOH; (*d*) $TiCl_4$, 3 equiv, CH_2Cl_2, -78 °C, 30 min; $^iPr_2NEt$, 3.5 equiv, 1 h; **5**, 15 min; (*e*) $(COCl)_2$, DMSO, CH_2Cl_2, -78 °C, 45 min, Et_3N, → 0 °C, 5 min; (*f*) HF-pyridine, pyridine, THF, 20 °C, 4 h; (*g*) SiO_2, Et_2O/CH_2Cl_2; (*h*) Et_3N, CH_2Cl_2, 20 °C, 45 min.

A suitable stereoselective aldol coupling between **5** and **6** should allow the first selective synthesis of denticulatin A or B, provided subsequent epimerisation at C_{10} can be avoided.[4] This was found to be possible using the *Z* trichlorotitanium enolate[14] **17** generated from the ethyl ketone **6**. Enolisation of **6** under modified Evans conditions[14] ($TiCl_4$, 3 equiv, 30 min, -78 °C; $^iPr_2NEt$, 3.5 equiv, 1 h), followed by addition of **5**[15] (80% ee, 3 equiv), gave a separable 5:1 mixture of the two[17] 8,10-*syn*-10,11-*syn* aldol adducts **18**[10], $[\alpha]_D^{20}$ = +21.7° (*c* 1.8, $CHCl_3$), and **19**. The major isomer, obtained in 75% yield, was shown to be **18** by it's conversion into denticulatin B.[18] This indicates a very high level of diastereoface selectivity[14,19] for enolate **17**. Careful Swern oxidation of **18** then gave the trione **20**. By avoiding chromatography, this could be handled without significant epimerisation (<10%) at the C_{10} stereocentre. Treatment of **20** with HF-pyridine buffered by excess pyridine,[9] followed by crystallisation from pentane, gave pure (–)-denticulatin B (m.p. 135-137 °C, $[\alpha]_D^{20} = -29.3°$ (*c* 0.4, $CHCl_3$)) in 54% yield from **18**. Deliberate equilibration of the β-diketones **20** and **21** by silica gel chromatography (or Et_3N) gave a 70% yield of an *ca* 1:1 mixture of (–)-denticulatins A ($[\alpha]_D^{20}$ = -35.1° (*c* 0.4, $CHCl_3$)) and B on cyclisation. The ^1H and ^{13}C NMR spectra, m.p. and $[\alpha]_D^{20}$ for each isomer were in full accord with the reported data[1] for the individual denticulatins. Pure samples of the synthetic denticulatins A and B were found to interconvert on silica gel, indicating that the natural product from *Siphonaria denticulata* may actually be only a single compound which isomerises at C_{10} on chromatographic isolation.

In summary, this represents a short and highly efficient synthesis of the denticulatins (9 steps in 26% yield from (*R*)-**8**). Moreover, by exploiting substrate-based[5] control of acyclic stereochemistry, (–)-denticulatin B can be obtained stereoselectively for the first time (>70% overall ds and 20% yield).

Acknowledgement: We thank the SERC for support (Postdoctoral Award to MVP; grant GR/F 73458). IP thanks the Royal Society of Chemistry for a Hickinbottom Research Fellowship.

References and Notes

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3. For example, see: *siphonarins*, (a) Hochlowski, J. E.; Coll, J. C.; Faulkner, D. J.; Biskupiak, J. E.; Ireland, C. M.; Qi-tai, Z.; Cun-heng, H.; Clardy, J. *J. Am. Chem. Soc.* **1984**, *106*, 6748; *maumvatin*, (b) Roll, D. M.; Biskupiak, J. E.; Mayne, C. L.; Ireland, C. M. *J. Am. Chem. Soc.* **1986**, *108*, 6680; *baconipyrones*, (c) Manker, D. C.; Faulkner, D. J.; Stout, T. J.; Clardy, J. *J. Org. Chem.* **1989**, *54*, 5371.
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10. All new compounds gave spectroscopic data in agreement with the assigned structures. **12** had ^{1}H NMR δ ($CDCl_3$, 400 MHz) 7.27-7.37 (5H, m), 5.33 (1H, t, *J*=6.9 Hz), 4.52 (2H, s), 4.16 (1H, s), 4.08 (1H, s), 3.90 (1H, d, *J*=9.2 Hz), 3.84 (1H, d, *J*=9.2 Hz), 3.55-3.60 (2H, m), 2.02 (2H, qd, *J*=7.5, 6.9 Hz), 1.92-1.97 (1H, m), 1.72-1.79 (1H, m), 1.60 (3H, s), 0.99 (3H, d, *J*=7.0 Hz), 0.95 (3H, t, *J*=7.5 Hz), 0.59 (3H, d, *J*=6.8 Hz); ^{13}C NMR δ ($CDCl_3$, 100 MHz) 137.9, 135.1, 130.8, 128.3, 127.6, 127.5, 85.2, 79.5, 75.4, 73.4, 37.7, 35.2, 20.6, 13.8, 13.2, 10.3, 9.2; HRMS (CI, NH_3) calc for $C_{19}H_{31}O_3$ (M^++H) 307.2273 found 307.2273. **9** had ^{1}H NMR δ ($CDCl_3$, 400 MHz) 7.26-7.34 (5H, m), 4.53 & 4.47 (2H, AB_q, J_{AB}=11.8 Hz), 3.97 (1H, dd, *J*=9.8, 1.8 Hz), 3.81 (1H, dd, *J*=9.8, 2.2 Hz), 3.68 (1H, m), 3.58 (1H, t, *J*=8.5 Hz), 3.34 (1H, dd, *J*=8.5, 5.9 Hz), 2.32 (1H, br s), 2.02-2.13 (2H, m), 1.92 (1H, qdd, *J*= 6.9, 6.2 2.3 Hz), 1.70 (1H, dqd, *J*=15.0, 7.5, 2.8 Hz), 1.37-1.47 (1H, m), 1.03 (3H, d, *J*=7 Hz), 1.02 (9H, s), 0.99 (9H, s), 0.97 (3H, t, *J*=7.3 Hz), 0.85 (3H, d, *J*=6.8 Hz), 0.79 (3H, d, *J*=6.8 Hz); ^{13}C NMR δ ($CDCl_3$, 100 MHz) 138.7, 128.3, 127.6, 127.4, 85.3, 79.3, 74.5, 73.4 73.3, 40.2, 39.7, 35.9, 28.0, 27.9, 27.3, 23.2, 20.1, 16.3, 12.4, 10.2, 9.3; HRMS (CI, NH_3) calc for $C_{27}H_{49}O_4Si$ (M^++H) 465.3400 found 465.3400. **6** (major isomer) had ^{1}H NMR δ ($CDCl_3$, 400 MHz) 4.01 (1H, dd, *J*=9.8, 2.1 Hz), 3.91 (1H, dd, *J*=9.7, 2.8 Hz), 3.84 (1H, s), 3.75 (1H, ddd, *J*=7.5, 5.7, 1.7 Hz), 2.75 (1H, qd, *J*=7.1, 2.8 Hz), 2.59 (1H, dq, *J*=18.7, 7.2 Hz) 2.49 (1H, dq, *J*=18.7, 7.2 Hz), 1.89 (1H, ddq, *J*=9.8, 9.7, 6.7 Hz), 1.71 (1H, qdd, *J*=7.0, 1.7, 1.7 Hz), 1.58 (1H, ddq, *J*=13.7, 7.5, 7.5 Hz), 1.37 (1H, dqd, *J*=13.7, 7.5, 5.7 Hz), 1.31 (3H, d, *J*=7.1 Hz), 1.04 (9H, s), 0.99 (3H, t, *J*=7.2 Hz), 0.94 (9H, s), 0.92 (3H, t, *J*=7.5 Hz), 0.90 (3H, d, *J*=7.0 Hz), 0.80 (3H, d, *J*=6.7 Hz); ^{13}C NMR δ ($CDCl_3$, 100 MHz) 213.2, 86.8, 82.7, 78.4, 49.7, 38.9, 37.7, 35.0, 27.8, 27.7, 26.9, 23.1, 20.1, 14.2, 12.5, 10.6, 7.3, 4.4; HRMS (CI, NH_3) calc for $C_{22}H_{44}O_4Si$ (M^++H) 401.3087 found 401.3087. **18** had ^{1}H NMR δ (C_6D_6, 400 MHz) 5.24 (1H, t, *J*=6.9 Hz), 3.96 (1H, dd, *J*=9.8, 3.8 Hz), 3.91 (1H, dd, *J*=9.7, 1.9 Hz), 3.79 (1H, br t, *J*=6.5 Hz), 3.75 (1H, dt, *J*=7.5, 3.5 Hz), 3.55 (1H, s), 2.89 (1H, qd, *J*=7.1, 3.8 Hz), 2.80 (1H, d, *J*=3.2 Hz), 2.76 (1H, qd, *J*=7.0, 3.8 Hz), 2.12 (1H, dd, *J*=12.8, 3.9 Hz), 1.93-2.03 (3H, m), 1.50-1.87 (4H, m), 1.55 (3H, s), 1.32-1.44 (1H, m), 1.14 (3H, d, *J*=7.0 Hz), 1.10 (6H, d, *J*=6.7 Hz), 1.09 (3H, t, *J*=7.0 Hz), 1.06 (9H, s), 1.05 (9H, s), 1.00 (3H, d, *J*=7.0 Hz), 0.94 (3H, t, *J*=7.5 Hz), 0.50 (3H, d, *J*=6.8 Hz); ^{13}C NMR δ (C_6D_6, 100 MHz) 216.0, 132.6, 128.9, 86.5, 81.7, 78.0, 74.6, 50.2, 47.4, 44.2, 39.5, 38.8, 33.6, 28.5, 27.7, 27.3, 23.2, 21.6, 20.3, 15.6, 15.4, 14.5, 14.0, 12.5, 11.0, 10.6, 5.2; HRMS (CI, NH_3) calc for $C_{31}H_{61}O_5Si$ (M^++H) 541.4288 found 541.4288.
11. Similar difficulties have previously been described for related reductions of *anti* α-methyl-β-hydroxyketones to *syn* 1,3-diols, see: Narasaka, K.; Pai F.-C. *Tetrahedron* **1984**, *40*, 2233.
12. Oxidation of each of these isomeric alcohols with PCC gave the same non-symmetrical dione, which helped confirm at this stage that the earlier hydroboration (**14** → **9**) had proceeded with the anticipated *anti* selectivity (*cf.* ref 13).
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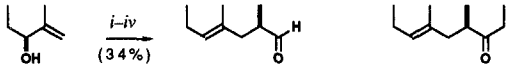
15. The aldehyde (*R*)-**5** was prepared from the kinetically-resolved allyl alcohol (*S*)-**22** as follows: (*i*) EtCOCl, pyridine, CH_2Cl_2, 20 °C, 2 h; (*ii*) Me_3SiCl, Et_3N, THF, LDA, -78 °C, 1 h → 70 °C, 4 h; 1 *M* HCl; (*iii*) $LiAlH_4$, Et_2O, 0 °C, 0.5 h; (*iv*) PCC, CH_2Cl_2, 20 °C, 3 h. ^{1}H NMR analysis of the MTPA ester after step (*iii*) indicated 80% ee, corresponding to *ca* 90% chirality transfer in the Ireland-Claisen step. A similar route to ethyl ketone **23** was used in the Hoffmann denticulatin synthesis (ref 5).



22 (≥98% ee)[16] **5** (80% ee) **23**

16. (*S*)-**22** was obtained by Sharpless kinetic resolution using (-)-*D*-diisopropyl tartrate. (a) Gao, Y.; Hanson, R. M.; Klunder, J. M.; Ko, S. Y.; Masamune, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765; (b) Overman, L. E.; Lin, N.-H. *J. Org. Chem.* **1985**, *50*, 3669.
17. In comparison, the same aldol reaction using LDA gave rise to a complex mixture of at least four isomers. This led to a mixture of the denticulatins.
18. The minor aldol isomer **19**, formed from the *ent*-**5** present, was taken on through Swern oxidation and cyclisation to give mainly 12-*epi*-denticulatin B.
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