Tetrahedron Letters 51 (2010) 6174–6176

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Stereoselective total synthesis of achaetolide and reconfirmation of its absolute configuration

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ARTICLE INFO

Article history:
Received 28 July 2010
Revised 16 September 2010
Accepted 19 September 2010
Available online 9 October 2010

ABSTRACT

The **s**tereoselective total synthesis of achaetolide **1** has been achieved and its absolute stereochemistry has been reconfirmed to be 3*S*,6*R*,7*S*,9*R* configuration. Keck allylation, Sharpless asymmetric dihydroxylation, and ring closing metathesis are the key steps involved in the target synthesis.

Lactone containing molecules have attracted significant attention due to their potent biological activities.[1] Fungi have been a great source for several lactone containing macrolides which are being continuously isolated. A few recently isolated 10-membered macrolides include achaetolide **1**,[2] decarestrictines A, D and J **3**–**6**,[3] herbarumins I–III **7**–**9**,[4] microcarpalide **2**[5] (Fig. 1), modiolides A and B[6] and stagonolides A-I.[7] Many of these molecules exhibit potent biological activities, such as antibacterial, antifungal, cytotoxic, and phytotoxic properties. The potent biological properties coupled with the scarce availability of these natural materials have made them good target molecules for total synthesis. Achaetolide, isolated from the culture broth of *Achaetomium cristalliferum* in 1983, was found to increase transpiration of cut barley leaves. Very recently, Takada and co-workers have established the structure of achaetolide[8] by relative stereochemical assignment involving ^{1}H NMR analysis and Mosher's method. In continuation of our interest in targeting lactone containing molecules[9] for total synthesis, herein we describe the stereoselective total synthesis of achaetolide and re-confirm its absolute configuration.

Retrosynthetically, the target molecule was envisioned to be obtained from the intermediate **10** by deprotection of isopropylidene moiety. The compound **10** could be obtained by coupling two key fragments, acid **11** and alcohol **12,** involving esterification followed by a ring closing metathesis to realize the 10-membered macrolide skeleton (Scheme 1). While the acid **11** could be obtained from commercially available D-aspartic acid or 3-butene-1-ol, the alcohol **8** was obtained from commercially available *n*-octanal.

Accordingly, our synthesis started with the Keck allylation of *n*-octanal employing *S*-BINOL, Ti(O^{i}Pr)$_4$, and allyltributyltin to provide the homoallyl alcohol **13** in 91% yield with 93% ee.[10] The chiral secondary alcohol was protected as the corresponding *tert*-butyldimethylsilyl ether **14**. Ozonolysis followed by Horner–Emmons olefination of **14** using Ando's protocol gave α,β-unsaturated ester

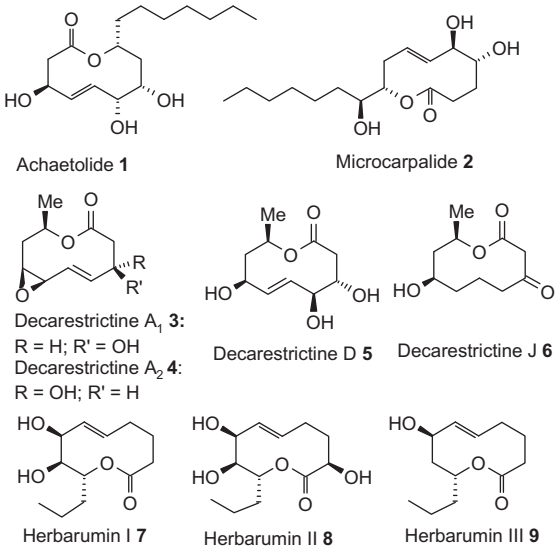

Figure 1. Few 10-membered macrolides.

15 (in 9:1 ratio *Z*:*E*).[11] Sharpless asymmetric dihydroxylation of the olefin **15** with AD$_{mix}$-β in *tert*-butanol and water yielded diol **16**. Protection of diol with 2,2-dimethoxy propane in the presence of PPTS yielded the ester **17** which was reduced with DIBAL-H to yield alcohol **18**. Swern oxidation followed by one carbon Wittig homologation with methyltriphenylphosphonium iodide in the presence of KO^{t}Bu, yielded the olefin **19** (Scheme 2). Exposure of **19** to TBAF yielded a key intermediate alcohol **12**. The other key fragment **11** was synthesized starting from D-aspartic acid following the known procedures.[12] Thus, the amino acid was subjected to diazotization followed by bromination to yield α-bromo succinic acid **20**. Reduction of the two carboxylic groups was achieved with BH$_3$–THF to provide 2-bromo-1,4-diol **21** which was converted to benzyl protected oxirane **22** in a one-pot reaction utilizing NaH and benzyl

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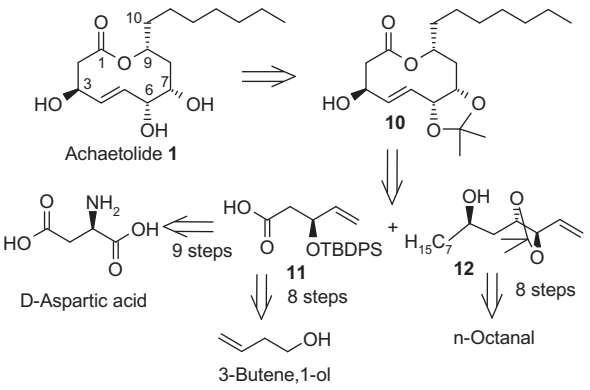
doi:10.1016/j.tetlet.2010.09.070



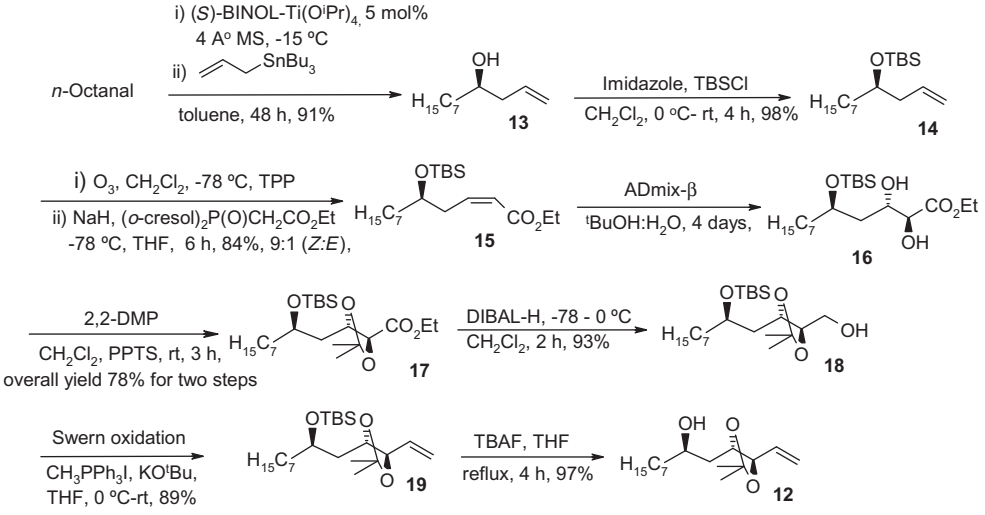
Scheme 1. Retrosynthesis.

bromide and TBAI. The compound **22** can also be obtained from homoallylic alcohol **13** in three steps involving, benzylation, epoxidation, and Jacobsen's kinetic resolution as reported earlier by our group.[13]

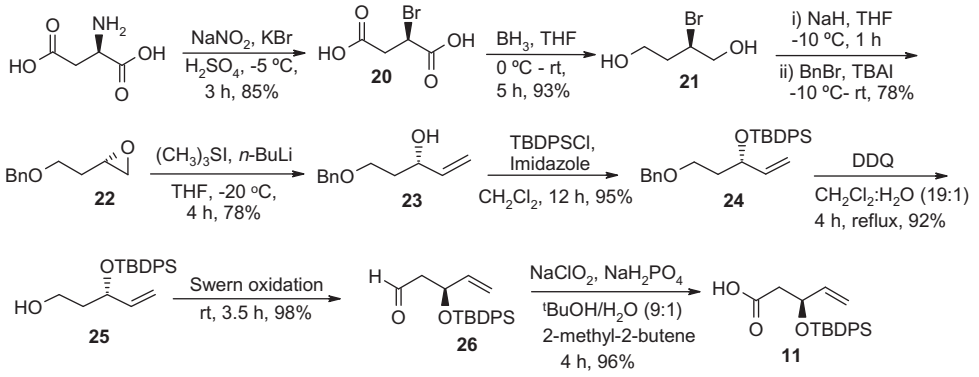
Treatment of the chiral epoxide **22** with trimethylsulfonium iodide and *n*-butyllithium provided the chiral secondary allyl alcohol **23**.[14] The secondary hydroxyl group was protected as the *tert*-butyldiphenylsilyl ether **24** and was further treated with DDQ to get the free primary alcohol **25**. The resulting alcohol was sequentially oxidized to aldehyde **26** under Swern conditions and then to acid **11** with sodium chlorite ($NaClO_2$), sodium dihydrogen phosphate (NaH_2PO_4) in *tert*-butanol-water in an overall 96% yield (Scheme 3).[15]

With the two key intermediates acid **11** and alcohol **12** in hand, the stage was set for their coupling to realize the macrolide skeleton. The coupling of acid **11** and alcohol **12** was achieved using DCC, DMAP to give an ester **27** in 61% yield (90% based on recovered starting material). When attempts were made for ring closing metathesis, both Grubbs' 1st and Grubbs' 2nd generation catalysts did not give the product as expected and ended up with recovery of the starting material. Incidentally, similar results were also observed during the total synthesis of stagonolide B,[9b] wherein identical substitution was present in the precursor for ring closing metathesis. Based on our earlier experience, we proceeded further for desilylation to get the free hydroxyl group. Thus, treatment of **27** with triethylamine tris(hydrogen fluoride) ($Et_3N{\cdot}3HF$) in tetrahydrofuran provided free allyl alcohol **28**. Ring closing metathesis was attempted directly by exposing the substrate **28** to Grubbs 2nd generation catalyst under reflux condition in 1,2-dichloroethane to yield the product 10[16] with isopropylidene protection along with a byproduct **29**. The product **10** was treated with TFA at 0 °C for 2 h to yield the target molecule, achaetolide **1** in 86% yield (Scheme 4). The spectroscopic data[17] of the synthetic compound were found to be similar to that of the natural product.[2,8]

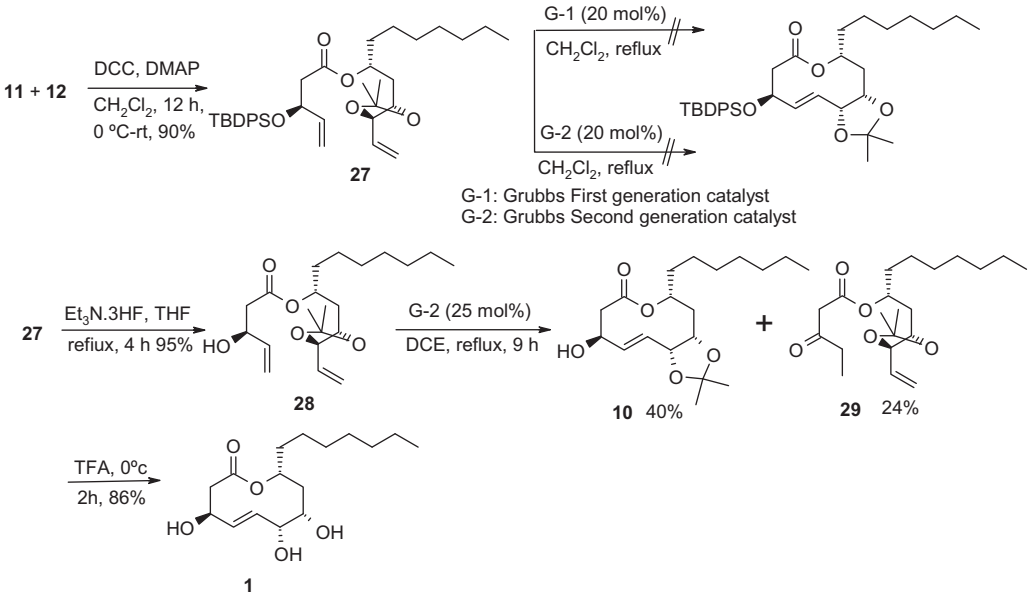
In conclusion, we have accomplished the total synthesis of achaetolide **1** following a convergent approach. The overall yield was found to be 12.4% and 11.6% starting from *n*-octanal and



Scheme 2.



Scheme 3.



Scheme 4.

D-aspartic acid, respectively. Also the absolute configuration of achaetolide has been reconfirmed to be 3*S*,6*R*,7*S*,9*R*.

Acknowledgment

B. Kumaraswamy and P. Shankar thank CSIR, New Delhi for financial assistance in the form of fellowships.

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16. The ^{1}H NMR of this compound revealed the presence of a single conformer as reported earlier by Tayone, W. C.; et al. See Ref. 8.
17. Spectroscopic data for representative examples: Compound **11**: Yellow liquid; $[\alpha]_D^{32}$ +9 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz; $CDCl_3$): δ 7.67–7.60 (m, 4H); 7.39–7.29 (m, 6H), 5.82 (ddd, *J* = 6.8, 10.6, 16.6 Hz, 1H), 5.03–4.94 (m, 2H), 4.53 (q, *J* = 6.8 Hz, 1H), 2.54 (dd, *J* = 6.8, 15.1 Hz, 1H), 2.41 (dd, *J* = 6.0, 15.1 Hz, 1H), 1.04 (s, 9H); ^{13}C NMR (75 MHz; $CDCl_3$): δ 175.8, 138.7, 135.9, 135.8, 133.4, 129.8, 129.8, 127.6, 127.4, 115.8, 115.8, 71.3, 43.0, 26.9, 19.2; IR (neat) υ_{max} = 3449, 2926, 2885, 1713, 1464, 1110, 772 cm^{-1}; HRMS *m*/*z* calculated for $C_{21}H_{26}O_3SiNa$ 377.1543 for (M+Na)$^+$, found 377.1534. Compound **16**: Colorless liquid; $[\alpha]_D^{30}$ −5.8 (*c* 1.3, $CHCl_3$); ^{1}H NMR (300 MHz; $CDCl_3$): δ 4.26 (qd, *J* = 7.0, 1.9 Hz, 2H), 4.21–4.12 (m, 2H), 4.02 = 3.91 (m, 1H), 1.4–1.72 (m, 1H), 1.59–1.46 (m, 1H), 1.40 (ddd, *J* = 1.51, 6.2, 14.73 Hz, 1H); 1.31 (s, 3H); 1.30–1.19 (m, 11H); 0.89 (s, 12H), 0.08 (d, 6H); ^{13}C NMR (75 MHz; $CDCl_3$): δ 172.5, 74.3, 70.6, 70.1, 61.7, 36.6, 36.1, 29.7, 29.3, 25.9, 25.5, 22.7, 18.0, 14.3, 14.2, −4.4, −4.8; IR (neat): υ_{max} = 3461, 2925, 2856, 1738, 1634, 1218, 772 cm^{-1}; HRMS *m*/*z* calculated for $C_{20}H_{42}O_5SiNa$ 413.2694 (M+Na)$^+$ found 413.2692. Compound **10**: light brown color; $[\alpha]_D^{27}$ −30 (*c* 0.4, $CHCl_3$); lit $[\alpha]_D^{24}$ −33 (*c* 0.34, $CHCl_3$);[8] ^{1}H NMR (300 MHz; $CDCl_3$): δ 5.56 (dd, *J* = 8.9, 16.0 Hz, 1H), 5.42 (dd, *J* = 7.7, 16.0 Hz, 1H), 4.63 (ddd, *J* = 5.6, 8.9, 14.2 Hz, 1H), 4.38 (dd, *J* = 6.0, 8.9 Hz, 1H), 4.26 (q, *J* = 7.7 Hz, 1H), 3.91 (dd, *J* = 6.0, 10.2 Hz, 1H), 2.66 (dd, *J* = 7.8, 13.0 Hz, 1H), 2.16 (dd, *J* = 7.9, 13.0 Hz, 1H), 2.09 (dd, *J* = 5.5, 10.2 Hz, 1H), 1.52–1.46 m, 1H), (1.44 (d, *J* = 15.8 Hz, 1H), 1.33 (s, 4H), 1.19 (s, 3H), 1.16–1.08 (m, 10H), 0.79 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (75 MHz; $CDCl_3$): δ 170.0, 133.5, 129.6, 108.6, 80.8, 77.3, 74.9, 70.0, 43.8, 38.0, 35.7, 31.7, 29.3, 29.1, 28.0, 25.5, 25.3, 22.6, 14.0; IR (neat) υ_{max} = 3459, 2928, 1728, 1636, 1221, 771 cm^{-1}; HRMS *m*/*z* calculated for $C_{19}H_{32}O_5Na$ 363.2142 (M+Na)$^+$ found 363.2139. Achaetolide **1** $[\alpha]_D^{30}$ −25 (*c* 0.15, MeOH); lit $[\alpha]_D^{21}$ −27 (*c* 0.52, MeOH);[8] ^{1}H NMR (200 MHz; $CDCl_3$): δ 5.98 (dd, *J* = 3.2, 16.4 Hz, 1H), 5.66 (dd, *J* = 2.4, 16.4 Hz, 1H), 4.89–4.67 (m, 2H), 4.58–4.48 (m, 1H), 3.72 (d, *J* = 9.8 Hz, 1H), 2.56 (d, *J* = 3.3 Hz, 2H), 2.32–2.12 (m, 2H), 1.70–1.43 (m, 3H), 1.19–1.35 (m, 10H), 0.89 (t, *J* = 6.6 Hz, 3H); ^{1}H NMR (300 MHz; CD_3OD): major conformer δ 5.97 (dd, *J* = 3.2, 15.8 Hz, 1H), 5.70 (dd, *J* = 1.32, 15.8 Hz, 1H), 4.78–4.65 (m, 2H), 4.48–4.40 (m, 1H), 3.64 (d, *J* = 9.8 Hz, 1H), 2.51 (dd, *J* = 3.8, 11.8 Hz, 1H), 2.49 (dd, *J* = 3.4, 11.7 Hz, 1H), 2.40–2.32 (m, 1H), 1.88–147 (m, 2H), 1.42 (s, 1H), 1.34–1.25 (m, 10H), 0.89 (t, *J* = 6.4 Hz, 3H), minor conformer δ 5.58 (dd, *J* = 7.1, 16.4 Hz, 1H), 5.41 (dd, *J* = 8.8, 16.4 Hz, 1H), 4.48–4.40 (m, 1H), 4.28 (dd, *J* = 2.8, 6.6 Hz, 1H), 3.47–3.41 (m, 1H), 2.93 (dd, *J* = 7.55, 13.4 Hz, 1H), 2.42–2.31 (m, 1H), 2.26 (dd, *J* = 8.68, 13.4 Hz, 1H), 1.75–1.65 (m, 1H), 1.57–1.53 (m, 1H), 1.38 (s, 1H); ^{13}C NMR (75 MHz; CD_3OD): δ 172.2, 172.3, 136.6, 131.7, 131.1, 127.8, 78.3, 77.6, 76.7, 74.7, 74.6, 74.5, 71.6, 68.1, 38.3, 38.0, 37.6, 36.1, 33.0, 30.8, 30.6, 30.5, 30.4, 26.9, 26.3, 23.7, 14.4; IR(neat) υ_{max} = 3457, 2926, 2856, 1725, 1162 cm^{-1} HRMS *m*/*z* calculated for $C_{16}H_{28}O_5Na$ 323.1829 (M+Na)$^+$ found 323.1832.