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Total synthesis of microcarpalide

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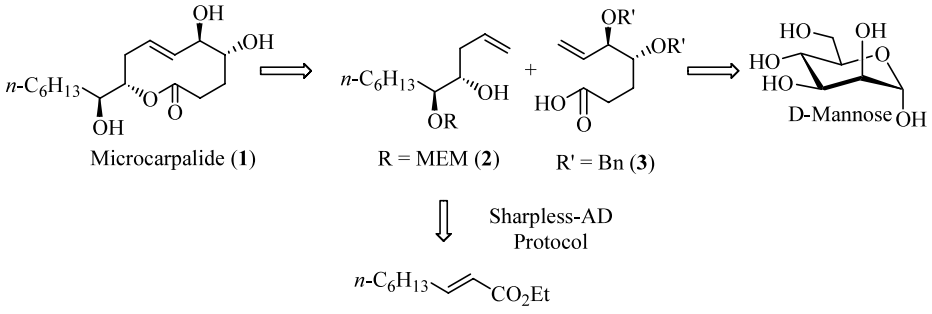
Abstract—A total synthesis of the natural product microcarpalide is described. Ring-closing metathesis of a dienic ester was used as the key step. Mannose was used as the chiral pool material for the construction of the olefinic-acid and a Sharpless asymmetric dihydroxylation reaction provided the chiral precursor for the synthesis of the olefinic-alcohol.

Microcarpalide, a ten-membered cyclic lactone (a C_{16}-nonenolide) recently isolated and characterized by Hemscheidt and co-workers[1] from the fermentation broths of an unidentified endophytic fungus growing on the bark of *Ficus microcarpa*, has been shown to be a promising microfilament disrupting agent. Herein, we report a convergent approach for a total synthesis of microcarpalide.

The retro-synthetic scheme for **1** was based on the coupling reaction between two partners **2** and **3** via esterification (Scheme 1) and subsequent ring closing metathesis (RCM).[2,3] Our general synthetic strategy towards the total synthesis of microcarpalide envisaged the enantioselective preparation of the key fragment **2** via a Sharpless asymmetric dihydroxylation, and D-mannose as a chiral pool source with a zinc-mediated elimination of an α-iodo acetonide derivative for the preparation of the other coupling partner.

Synthesis of the olefinic alcohol **2** (Scheme 2) was initiated by the Sharpless asymmetric dihydroxylation[4] of the unsaturated ester **4** with commercially available AD-mix-α. Isopropylidenation of the resulting diol **5** and subsequent reduction using DIBAL-H provided the alcohol **6**. The tosylate **7** obtained upon treating **6** with *p*-TsCl in pyridine, following acid catalyzed deisopropylidenation, was reacted with 1.5 equiv. of K_2CO_3 in methanol and the free hydroxyl group of resulting epoxide **8** was protected as its methoxyethoxymethyl (MEM) ether to furnish **9**. Opening the epoxide **9** with an excess of lithium acetylide[5] and partial hydrogenation of the resulting acetylene **10** with Lindlar catalyst achieved the olefinic alcohol **2**.[6]

The synthesis of acid component **3** commenced with **11** which was synthesized according to the literature procedure[7] from D-mannose (Scheme 3). Protection of the hydroxyl group of **11** as its MEM-ether, hydrogena-



Scheme 1. Retrosynthetic analysis for microcarpalide **1**.

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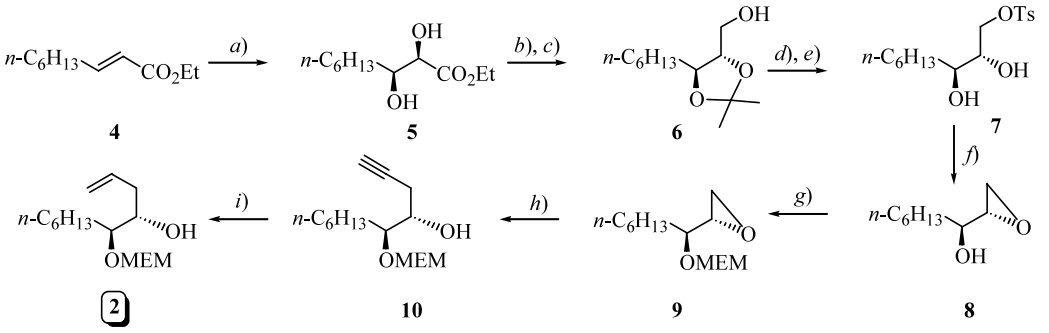
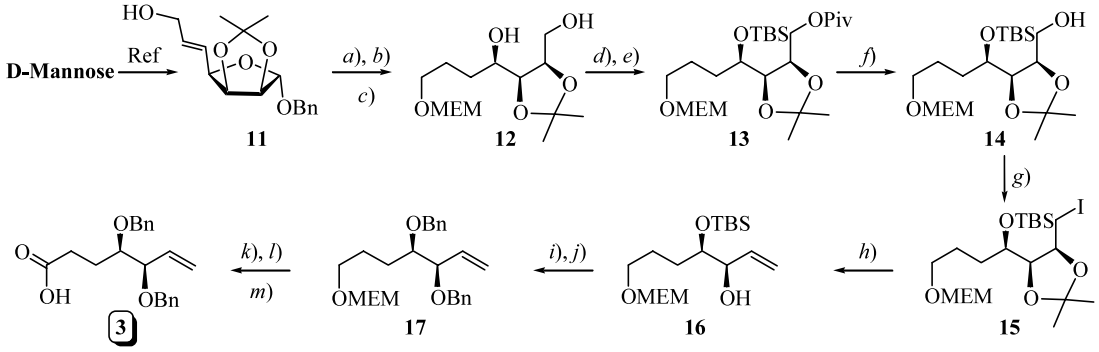


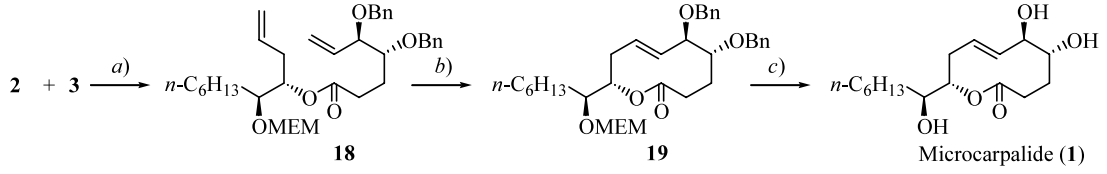
Scheme 2. *Reagents and conditions*: (a) AD-mix-α, *t*-BuOH, H_2O, 0°C, 10 h, 94%; (b) 2,2-dimethoxypropane, *p*-TsOH, CH_2Cl_2, 1.5 h, 96%; (c) DIBAL-H, CH_2Cl_2, −78°C, 1 h, 97%; (d) *p*-TsCl, pyridine, 0°C–rt, 96%; (e) conc. HCl (cat.), MeOH, 3 h, 87%; (f) K_2CO_3 (1.5 equiv.), MeOH, rt, 1.5 h, 85%; (g) MEM-Cl, $^iPr_2NEt$, CH_2Cl_2, rt, 4 h, 91%; (h) LiC≡CH:ethylenediamine, DMSO, rt, 12 h, 86%; (i) H_2, $Pd/BaSO_4$, quinoline, benzene, 1 bar, rt, 0.5 h, 91%.



Scheme 3. *Reagents and conditions*: (a) MEM-Cl, $^iPr_2NEt$, CH_2Cl_2, rt, 10 h; (b) H_2, 10% Pd–C, MeOH, 6 bar, 60°C, 4 h; (c) $LiAlH_4$, THF, rt, 1 h, 71% for three steps; (d) $(CH_3)_3CCOCl$, pyridine, 0°C–rt, 91%; (e) TBSCl, DMF, imidazole, rt, 4 h, 90%; (f) DIBAL-H, CH_2Cl_2, −78°C, 1 h, 89%; (g) I_2, PPh_3, imidazole, ether–benzene (2:1), rt, 1.5 h, 86%; (h) Zn, ethanol, reflux, 1.5 h, 96%; (i) n-$Bu_4N^+F^-$, THF, rt, 1 h, 85%; (j) NaH, BnBr, DMF, 0°C–rt, 88%; (k) PPTS, *t*-BuOH, 80°C, 1.5 h, 85%; (l) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78°C, 1 h; (m) $NaClO_2$, DMSO, NaH_2PO_4, rt, 1.5 h, 83% for two steps.

tion using 10% Pd–carbon, and subsequent reduction with lithium aluminum hydride gave the diol **12**. The TBS-ether **14** was obtained in 73% overall yield following selective pivaloylation of the C_1-OH, protection of the C_4-OH as its TBS ether, and reductive depivaloylation using DIBAL-H. Adopting the modified Corey protocol[8] for the conversion of a primary alcohol to the corresponding iodide using I_2, PPh_3, imidazole, in an ether–benzene (2:1) mixture, **14** was converted to the iodoacetonide **15** in good yield. A facile elimination of **15** resulting in the corresponding allylic alcohol **16** was then accomplished using freshly activated Zn in refluxing ethanol.[9] Removal of the TBS-protection and benzylation using NaH and BnBr gave **17** in 73% overall yield. The synthesis of the second key fragment, the olefinic acid **3** was completed by deprotection of the MEM-ether,[10] oxidation of the resulting primary alcohol to the corresponding aldehyde using Swern conditions and further oxidation using sodium chlorite in DMSO under buffered conditions.[11] The spectroscopic data of **3**[12] were in agreement with the assigned structure.

Having completed the synthesis of both fragments **2** and **3**, it remained to couple the two fragments and achieve subsequent RCM. The coupling reaction of **2** and **3** was carried out using DCC to furnish the diene ester **18**[14a] in good yield. Following contemporary results[2,3] and the information provided by the Fürstner[2] and Marco[3] groups, RCM of **18** with the first generation Grubbs' catalyst (Scheme 4) under high dilution conditions gave the *E*- and *Z*-isomers of **19**[14b] in a 10:1



Scheme 4. *Reagents and conditions*: (a) DCC, DMAP, CH_2Cl_2, rt, 18 h, 76%; (b) $(PCy_3)_2Ru(Cl)_2$=CH-Ph (20 mol%), CH_2Cl_2, reflux, 28 h, 67%; (c) $TiCl_4$, CH_2Cl_2, 0°C, 0.5 h, 76%.

ratio. Surprisingly and gratifyingly, attempted MEM-deprotection using $TiCl_4$ also resulted in debenzylation,[13] thus furnishing microcarpalide **1** in 76% yield. The spectroscopic and analytical data $\{[\alpha]_D^{25} = -23.2$ (c 0.7, MeOH)$\}$ of compound **1** were in agreement with the reported data.[1,3]

In conclusion, we have developed a total synthesis of microcarpalide using both the chiral pool approach and an asymmetric dihydroxylation which is characterized by considerable flexibility for the construction of related unnatural analogues for structure activity studies. Work in this direction is progressing in our laboratory.

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References

1. Ratnayake, A. S.; Yoshida, W. Y.; Mooberry, S. L.; Hemscheidt, T. *Org. Lett.* **2001**, *3*, 3479–3481.
2. (a) Fürstner, A.; Radkowski, K. *Chem. Commun.* **2001**, 671–672; (b) Fürstner, A.; Radkowski, K.; Wirtz, C.; Goddard, R.; Lehmann, C. W.; Mynott, R. *J. Am. Chem. Soc.* **2002**, *124*, 7061–7069.
3. During our work in progress, Marco and co-workers reported the first total synthesis of microcarpalide using RCM as the key transformation. See: Murga, J.; Falmoir, E.; Garcia-Fortanet, J.; Carda, M.; Marco, J. A. *Org. Lett.* **2002**, *4*, 3447–3449.
4. (a) Sharpless, K. B.; Amberg, W.; Bennani, Y. L.; Crispino, G. A.; Hartung, J.; Jeong, K.-S.; Kwong, H.-L.; Morikawa, K.; Wang, Z.-M.; Xu, D.; Zhang, X.-L. *J. Org. Chem.* **1992**, *57*, 2768–2771; (b) Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483–2547.
5. Hanack, M.; Kunzmann, E.; Schumacher, W. *Synthesis* **1978**, 26.
6. *Spectral data of* ***2***: ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.90 (t, 3H, $J=6.6$ Hz), 1.21–1.38 (m, 8H), 1.44–1.61 (m, 2H), 2.10–2.39 (m, 2H), 2.81 (s, 1H, -OH), 3.37–3.49 (m, 1H), 3.39 (s, 3H, -OMe), 3.52–3.84 (m, 5H), 4.70–4.87 (m, 2H, -OCH_2O-), 5.06–5.17 (m, 2H), 5.88 (br. ddt, 1H, $J=17.4$, 10.6, 7.0 Hz). ^{13}C NMR (50 MHz, $CDCl_3$) δ 14.1, 22.6, 25.1, 29.4, 30.8, 31.7, 37.8, 58.9, 67.6, 71.7, 72.0, 82.4, 95.9, 117.1, 134.9. Anal. calcd for $C_{15}H_{30}O_4$: C, 65.66; H, 11.02. Found: C, 65.07; H, 10.83.
7. (a) Moore, B. S.; Cho, H.; Casati, R.; Kennedy, E.; Reynolds, K. A.; Mocek, U.; Beale, J. M.; Floss, H. G. *J. Am. Chem. Soc.* **1993**, *115*, 5254–5266; (b) Coutrot, P.; Grison, C.; Lecouvey, M. *Bull. Soc. Chim. Fr.* **1997**, *134*, 27–46.
8. Smith, A. B., III; Qiu, Y.; Jones, D. R.; Kobayashi, K. *J. Am. Chem. Soc.* **1995**, *117*, 12011–12012.
9. Rama Rao, A. V.; Reddy, E. R.; Joshi, B. V.; Yadav, J. S. *Tetrahedron Lett.* **1987**, *28*, 6497–6500.
10. Monti, H.; Leandri, G.; Klos-Ringuet, M.; Corriol, C. *Synth. Commun.* **1983**, *13*, 1021–1026.
11. Dalcanale, E.; Montanari, F. *J. Org. Chem.* **1986**, *51*, 567–569.
12. *Spectral data of* ***3***: ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.61–1.80 (m, 1H), 1.83–1.99 (m, 1H), 2.33–2.44 (m, 2H), 3.52 (ddd, 1H, $J=9.3$, 6.0, 3.7 Hz), 3.90 (t, 1H, $J=6.5$ Hz), 4.38 (d, 1H, $J=12.2$ Hz), 4.52 (d, 1H, $J=11.3$ Hz), 4.64 (d, 1H, $J=12.1$ Hz), 4.76 (d, 1H, $J=11.3$ Hz), 5.32 (br. dd, 1H, $J=18.4$, 1.7 Hz), 5.36 (br. dd, 1H, $J=9.1$, 1.8 Hz), 5.81 (br. ddd, 1H, $J=18.3$, 10.9, 7.5 Hz), 7.25–7.33 (m, 10H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 26.3, 30.9, 70.5, 73.3, 80.2, 82.7, 96.1, 118.8, 127.4, 127.6, 127.9, 128.2, 135.1, 138.5, 138.6, 178.7. Anal. calcd for $C_{21}H_{24}O_4$: C, 74.09; H, 7.11. Found: C, 74.16; H, 7.49.
13. (a) Corey, E. J.; Gras, J. L.; Ulrich, P. *Tetrahedron Lett.* **1976**, *11*, 809–812; (b) Bhatt, M. V.; Kulkarni, S. V. *Synthesis* **1983**, 249–334.
14. (a) *Spectral data of* ***18***: ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.87 (t, 3H, $J=6.9$ Hz), 1.21–1.34 (m, 8H), 1.46–1.54 (m, 2H), 1.67–1.74 (m, 1H), 1.88–1.95 (m, 1H), 2.25–2.46 (m, 4H), 3.37 (s, 3H), 3.49–3.54 (m, 3H), 3.58 (br. ddd, 1H, $J=6.2$, 5.6, 4.3 Hz), 3.66–3.73 (m, 2H), 3.87 (t, 1H, $J=6.7$ Hz), 4.38 (d, 1H, $J=11.9$ Hz), 4.52 (d, 1H, $J=11.4$ Hz), 4.62 (d, 1H, $J=11.9$ Hz), 4.71–4.77 (m, 3H), 4.99–5.07 (m, 3H), 5.27–5.33 (m, 2H), 5.71 (dddd, 1H, $J=17.1$, 10.1, 7.6, 6.6 Hz), 5.80 (ddd, 1H, $J=17.3$, 10.6, 7.6 Hz), 7.25–7.30 (m, 10H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.12, 22.65, 25.41, 26.33, 29.47, 30.52, 31.81, 34.71, 59.00, 67.49, 70.65, 71.83, 73.41, 78.13, 80.17, 82.60, 96.23, 117.62, 118.85, 127.49, 127.55, 127.73, 127.93, 128.33, 134.08, 135.23, 138.56, 138.75, 172.84. Anal. calcd for $C_{36}H_{52}O_7$: C, 72.45; H, 8.78. Found: C, 72.08; H, 9.13. (b) *Spectral data of* ***19***: ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.87 (t, 3H, $J=6.9$ Hz), 1.26–1.32 (m, 8H), 1.54–1.59 (m, 3H), 2.02 (ddd, 1H, $J=15.2$, 10.6, 6.2 Hz), 2.17 (ddd, 1H, $J=14.7$, 10.6, 1.4), 2.24–2.30 (m, 2H), 2.61 (dd, 1H, $J=14.7$, 9.2 Hz), 3.38 (s, 3H), 3.54–3.56 (m, 2H), 3.67–3.78 (m, 4H), 4.07 (br. d, 1H, $J=4.5$ Hz), 4.47 (d, 1H, $J=11.9$ Hz), 4.48 (d, 1H, $J=12.5$ Hz), 4.54 (d, 1H, $J=11.9$ Hz), 4.65 (d, 1H, $J=12.5$ Hz), 4.78–4.81 (m, 2H), 5.15 (dt, 1H, $J=9.2$, 4.6 Hz), 5.64 (dd, 1H, $J=15.8$, 2.1 Hz), 5.64–5.73 (m, 1H), 7.28–7.35 (m, 10H). ^{13}C NMR (125 MHz, $CDCl_3$) 14.01, 22.56, 25.03, 29.39, 31.15, 31.71, 36.06, 59.00, 67.40, 71.34, 71.54, 71.78, 78.19, 95.36, 126.47, 127.22, 127.52, 127.61, 128.30, 128.36, 131.69, 138.45, 138.79, 175.17. Anal. calcd for $C_{34}H_{48}O_7$: C, 71.80; H, 8.51. Found: C, 71.97; H, 8.98.