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Total synthesis of (−)-microcarpalide from D-mannitol☆

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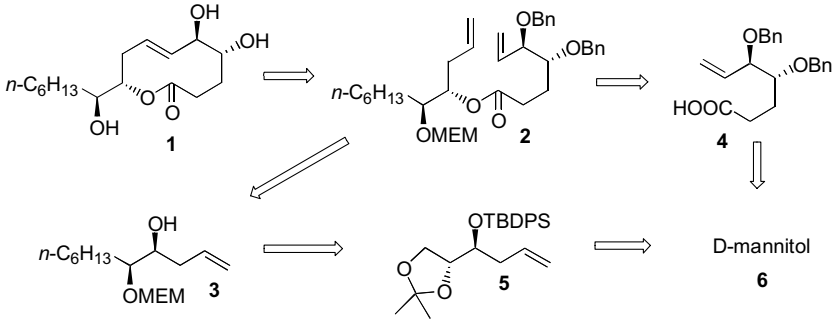
Abstract—The total synthesis of the actin-targeting metabolite (−)-microcarpalide is described. Ring-closing metathesis of a dienic ester was used as the key step. D-Mannitol was used as the chiral pool material for the construction of the olefinic acid moiety as well as the olefinic alcohol moiety of the molecule.

Microcarpalide **1** has been recently characterized as a new secondary metabolite produced by an endophytic fungus isolated from the bark of the tropical tree *Ficus microcarpa* L.[1] Bioassay-guided purification of the fermentation broth using immunofluorescence microscopy to test anticytoskeletol activity led to the isolation of a new substance displaying remarkable disrupting action on actin microfilaments, to which the structure **1** was assigned. Microcarpalide was found to disrupt actin microfilaments in approximately 50% of A-10 cells (from rat smooth muscle).[1] Moreover, it displayed weak cytotoxicity towards mammalian cells,[1] thus providing an attractive tool for studying cell motility and metastasis, and a potential lead structure to develop new anticancer drugs. By virtue of such potent biological activities, the apparently simple, yet stereochemically demanding macrocyclic ring structure of this new fungal metabolite has aroused the interest of synthetic organic chemists world-wide, and as a result several total syntheses have appeared.[2] Herein, we report a convergent approach for the total synthesis of (−)-microcarpalide starting from a cheap starting material, D-mannitol.

The retrosynthetic scheme for **1** was based on coupling two partners, **3** and **4**, via esterification (Scheme 1) and subsequent ring closing metathesis (RCM).[3] D-Mannitol was used as the chiral pool source for construction of both the coupling partners.

Synthesis of the olefinic alcohol **3** (Scheme 2) commenced from **7**, which was prepared as an inseparable 90:10 diastereomeric mixture in favour of the required isomer according to the reported procedure.[4] TBDPS protection of the resulting alcohol afforded **8**. Acetonide



Scheme 1. Retrosynthetic analysis.

Keywords: Microcarpalide; Ring-closing metathesis; Allylation; D-Mannitol.
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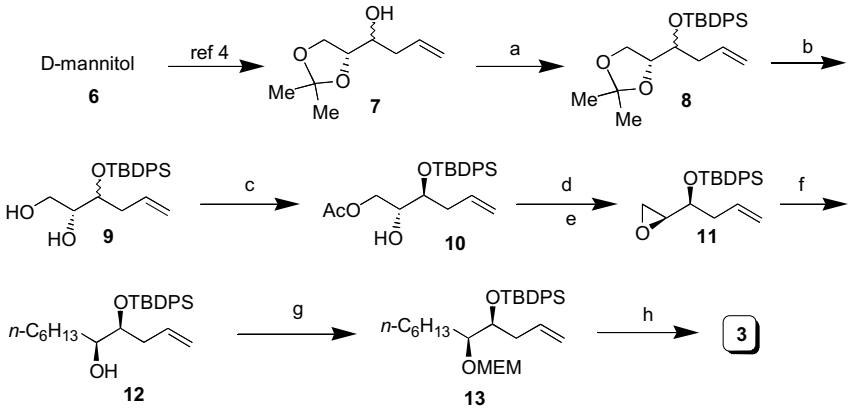
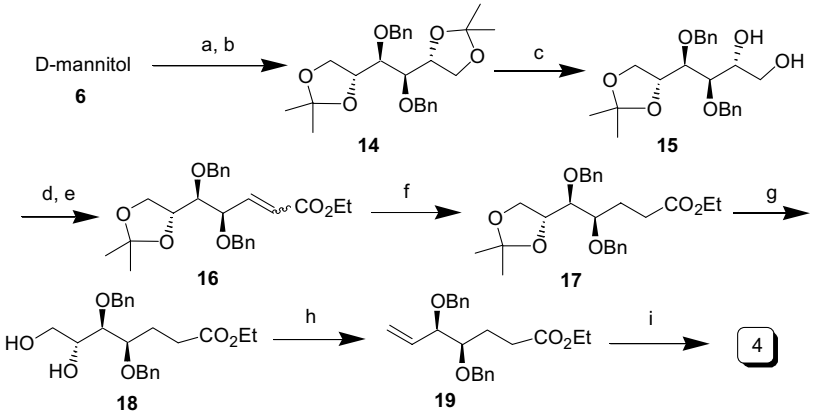


Scheme 2. Reagents and conditions: (a) TBDPSCl, imidazole, DMAP (cat), DMF, rt, 12 h, 95%; (b) 50% AcOH in water, rt, 12 h, 98%; (c) AcCl, 2,4,6-collidine, CH_2Cl_2, −78 °C, 85%; (d) MsCl, Et_3N, CH_2Cl_2, 0 °C; (e) K_2CO_3, MeOH, rt, 70% in two steps; (f) $CH_3(CH_2)_4MgBr$, CuI, THF, −23 °C, 70%; (g) MEMCl, DIPEA, CH_2Cl_2, 80%; (h) TBAF, THF, rt, 24 h 90%.



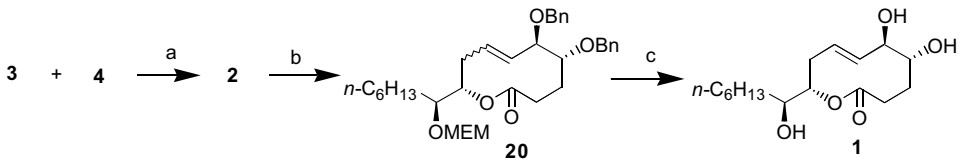
Scheme 3. Reagents and conditions: (a) 2,2-dimethoxypropane, DMF, PTSA (cat); 80%; (b) NaH, BnBr, TBAI, THF, 0 °C to rt, 95%; (c) MeOH, concd HCl, 0 °C to rt, 60%; (d) $NaIO_4$, THF–H_2O (2:1); (e) $Ph_3P{=}CHCO_2Et$, CH_2Cl_2, rt, 80% in two steps; (f) H_2, Pd/C, EtOAc, *n*-$BuNH_2$ (cat) 90%; (g) MeOH, HCl (cat), 0 °C to rt, 90%; (h) TPP, imidazole, I_2, toluene, 80 °C, 70%; (i) LiOH, THF–H_2O–MeOH (3:1:1), rt, 90%.

deprotection followed by selective acylation of the primary hydroxyl group gave **10**, as a pure diastereomer after the minor isomer had been easily separated by standard silica gel column chromatography. Conversion of **10** into the terminal epoxide **11** was achieved in two steps in good yield. Epoxide opening with *n*-pentyl cuprate reagent afforded alcohol **12**, which was then protected as its MEM-derivative **13**. Finally, desilylation of **13** afforded fragment **3**.[5]

The synthesis of fragment **4** also commenced with D-mannitol. Acetonide protection followed by benzylation according to the reported procedure gave **14**.[6] Selective monoacetonide deprotection afforded **15**.[6] Periodate cleavage of the resulting diol followed by two-carbon Wittig olefination gave **16** (*E*:*Z* = 7:3) (Scheme 3).

Olefin reduction with H_2 over Pd–C followed by acetonide deprotection with HCl (cat) in MeOH furnished diol **18**, which on treatment with TPP, imidazole and iodine in toluene afforded olefin ester **19**.[7] Saponification of ester **19** in THF–methanol–water (3:1:1) provided the desired acid fragment **4**.

The union of the two fragments **3** and **4** was achieved by using DCC to furnish the diene ester **2**. Treatment of **2** with the Grubbs first generation catalyst under high dilution (0.001 M in degassed CH_2Cl_2) furnished a



Scheme 4. Reagents and conditions: (a) DCC, DMAP, CH_2Cl_2, rt, 12 h, 80%; (b) 20 mol % of $(PCy_3)_2Ru(Cl)_2CH{=}Ph$, CH_2Cl_2, reflux, 28 h, 70%; (c) $TiCl_4$, CH_2Cl_2, 0 °C, 0.5 h, 75%.

10:1 *E*:*Z* mixture of macrocyclic lactones, from which the (*E*)-isomer **20** was isolated by silica gel column chromatography. Global deprotection of *E*-**20** gave microcarpalide **1** (Scheme 4).[2b] The spectroscopic and analytical data of compound **1** and other compounds were in good agreement with literature data.[2a,b,8]

In conclusion, we have achieved a convergent total synthesis of (−)-microcarpalide from the commercially available, cheap starting material D-mannitol. The preparation analogues and a study of their biological activities are currently under progress.

Acknowledgements

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8. Selected physical data of *E*-**20**. R_f = 0.5 (silica, 20% EtOAc in petroleum ether); $[\alpha]_D^{27}$ −35.5 (*c* 1.2, $CHCl_3$); ^{1}H NMR data ($CDCl_3$, 500 MHz): δ 7.28–7.35 (m, 10H), 5.64–5.73 (m, 1H), 5.63 (dd, *J* = 15.7, 2.0 Hz, 1H), 5.15 (dt, *J* = 9.5, 4.6 Hz, 1H), 4.77–4.81 (m, 2H), 4.65 (d, *J* = 12.1 Hz, 1H), 4.54 (d, *J* = 11.9 Hz, 1H), 4.47 (d, 1H, *J* = 12.8 Hz, 1H), 4.46 (d, *J* = 11.5 Hz, 1H), 4.07 (d, *J* = 4.1 Hz, 1H), 3.66–3.78 (m, 4H), 3.53–3.56 (m, 2H), 3.38 (s, 3H), 2.61 (dd, *J* = 14.3, 9.4 Hz, 1H), 2.22–2.32 (m, 2H), 2.11–2.20 (m, 1H), 1.96–2.04 (m, 1H), 1.54–1.59 (m, 3H), 1.26–1.32 (m, 8H), 0.88 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 175.2, 138.7, 138.4, 131.6, 128.3, 128.2, 127.6, 127.5, 127.2, 126.4, 95.3, 78.1, 71.7, 71.5, 71.3, 67.4, 59.0, 36.0, 31.7, 31.1, 29.4, 25.0, 22.5, 14.0; HRMS (ESI) calcd for $C_{34}H_{48}O_7Na$ $[M+Na]^+$ 591.3297. Found 591.3307.