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Stereoselective synthesis of (−)-microcarpalide

Subhash P. Chavan* and Cherukupally Praveen

Division of Organic Chemistry: Technology, National Chemical Laboratory, Pune 411 008, India

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Abstract—A highly convergent and efficient synthesis of (−)-microcarpalide, a 10-membered lactone displaying remarkable microfilament disrupting activity is described. Ring-closing metathesis and Sharpless asymmetric dihydroxylations are the key steps. Our strategy highlights the application of novel hydroxy lactone precursors for the stereoselective synthesis of (−)-microcarpalide.

Microcarpalide (**1**) has recently been isolated from the fermentation broths of an unidentified endophytic fungus growing on the bark of the tropical tree *Ficus microcarpa* Hemscheidt and co-workers named this 10-membered cytotoxic lactone, which shows remarkable antimicrofilament activity, microcarpalide.[1]

We have recently demonstrated the usefulness of the hydroxy lactones **5** and **6** for the synthesis of several biologically active natural products.[2] As part of our ongoing program aimed at exploring the use of hydroxy lactones **5** and **6**, we undertook the stereoselective synthesis of microcarpalide. The biological activity and structural features of microcarpalide have fostered significant interest in its synthesis[3] and encouraged us to attempt its total synthesis.

As shown in the retrosynthetic analysis, (Scheme 1), our strategy is a convergent approach, that combines fragments **3** and **4** via esterification followed by ring-closing metathesis.[4] The key fragments **3** and **4** can be obtained from enantiomeric lactones **5** and **6**, respectively. The olefinic acid fragment **3** was obtained from the hydroxy lactone **5**, while the olefinic alcohol fragment **4** was readily obtained from the enantiomeric hydroxylactone **6**. Both enantiomeric lactones **5** and **6** were readily obtained from *cis*-2-butene-1,4-diol[2] using a Claisen *ortho* ester rearrangement[5] and Sharpless asymmetric dihydroxylation[6] as key steps.

The synthesis of the alcohol fragment **4** commenced with a TBDMS protection of hydroxylactone **6** to furnish **8**. DIBAL-H reduction of **8** and subsequent three-carbon Wittig homologation of the resulting lactol gave a mixture of compounds **9a** and **b** in an almost 1:1 ratio, due to silyl group migration, as an inseparable mixture. Removal of the benzyl protection and reduction of the double bond was performed by using 10% Pd–C in methanol under an H_2 atmosphere. Selective tosylation of primary hydroxyl group using tosyl chloride and pyridine for 24 h then delivered a mixture of **10a** and **b**. This mixture on treatment with 1 M TBAF solution in dry THF gave the epoxy alcohol **11**. The epoxy alcohol was protected as its methoxymethyl (MOM) ether and the resultant epoxide **12** on treatment with an excess lithium acetylide[7] gave the terminal alkyne **13**, which on partial hydrogenation using Lindlar's catalyst gave the olefinic fragment **4** (Scheme 2).

Construction of the acid fragment **3** began with the dimethoxypropane mediated ring-opening of hydroxylactone **5**, which in turn was obtained from the γ,δ-unsaturated ester **14** using Sharpless asymmetric dihydroxylation in which AD-mix-β was used to install the required chirality. Thus hydroxy lactone **5** on reaction with 2,2-dimethoxypropane in methanol in the presence of a catalytic amount of *p*-TSA delivered the acetonide ester **15**. Removal of the benzyl protection with 10% Pd–C under H_2 atmosphere furnished alcohol **16**. Swern oxidation[8] and subsequent one-carbon homologation with methylene triphenylphosphorane in dry THF at

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* Corresponding author. Tel./fax: +91 20 5893614; e-mail: spchavan@dalton.ncl.res.in

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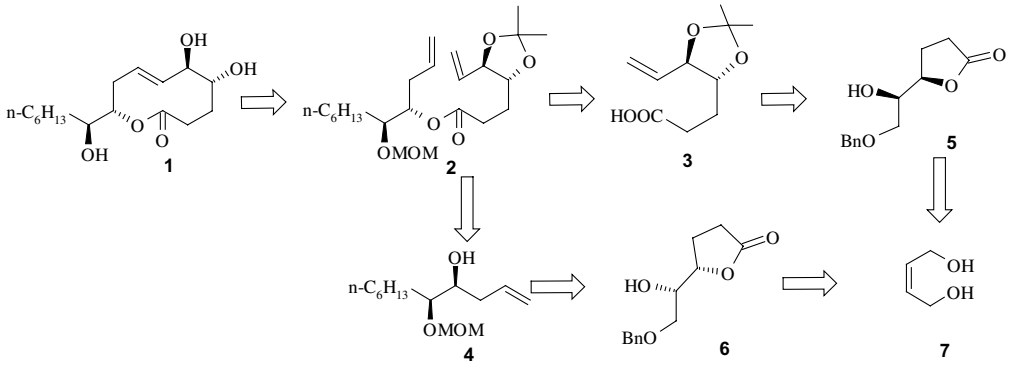
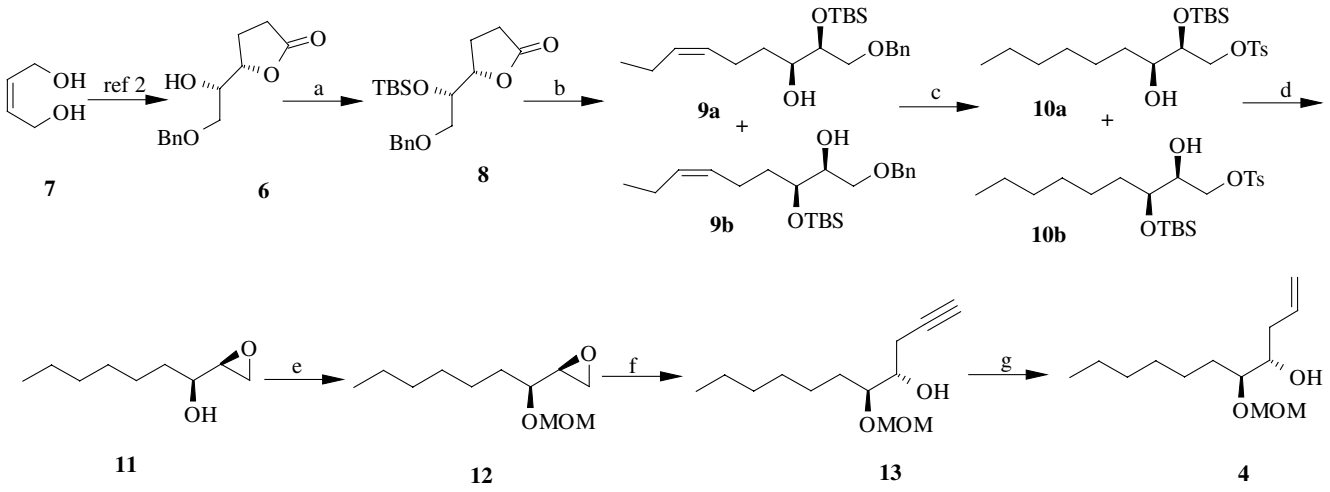


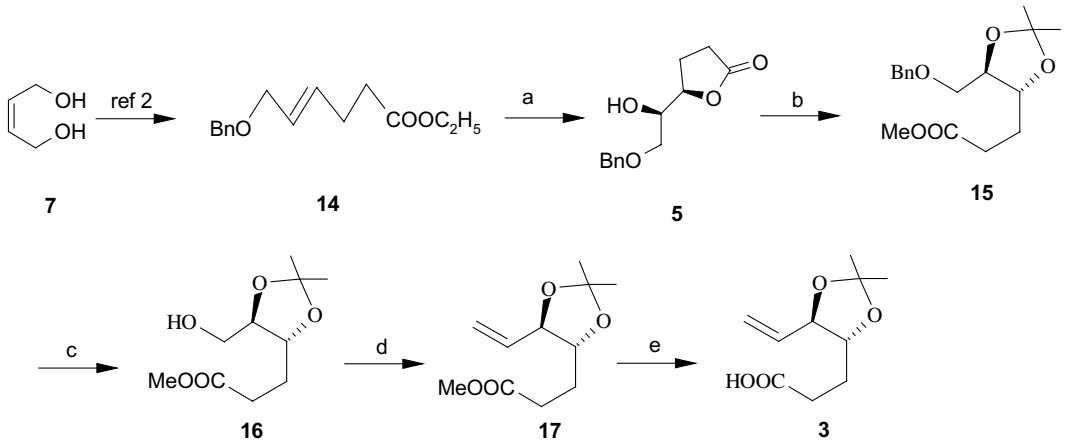
Scheme 1. Retrosynthetic analysis.



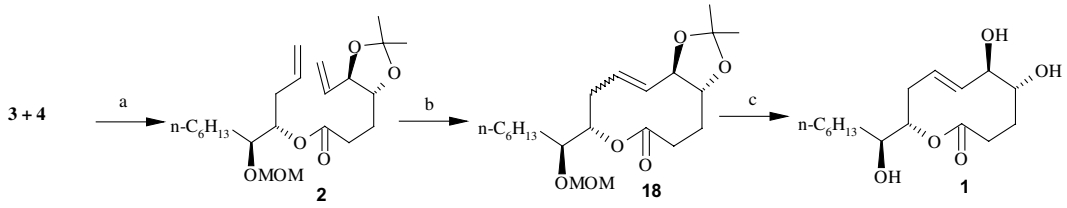
Scheme 2. Reagents and conditions: (a) TBDMSCl, imidazole, DMF, 90 °C, 18 h, 98%; (b) DIBAL-H, CH_2Cl_2, −78 °C, 1 h, $CH_3CH_2CH_2PPh_3^+Br^-$, LiHMDS, −78 °C to 0 °C, 3 h, 72%; (c) (i) 10% Pd–C, H_2, rt, 4 h, 96%; (ii) tosyl chloride, pyridine, CH_2Cl_2, 0 °C, 24 h, 92%; (d) 1 M TBAF, THF, 0 °C–rt, 6 h, 86%; (e) MOMCl, DIPEA, DCM, 0 °C–rt, 92%; (f) LiCCH:ethylenediamine, DMSO, rt, 12 h, 87%; (g) H_2, $Pd/BaSO_4$, quinoline, benzene, 1 bar, rt, 0.5 h, 92%.

−20 °C gave the olefinic ester **17**. Saponification of ester **17** with KOH in THF/methanol/water (2:2:1) afforded the desired acid fragment **3** (Scheme 3).

The union of the two fragments **3** and **4** was achieved by using DCC to furnish the diene ester **2**. Treatment of this diene ester **2** with the Grubb's first generation cata-



Scheme 3. Reagents and conditions: (a) AD-mix-β, $CH_3SO_2NH_2$, *t*-BuOH/H_2O (1:1), 24 h, 0 °C, 94%, 93% ee; (b) 2,2-DMP, catalytic *p*-TSA, methanol, rt, 3 h, 93%; (c) 10% Pd–C, H_2, ethyl acetate, rt, 8 h, 94%; (d) (i) oxalyl chloride, DMSO, Et_3N, DCM, −78 °C, 1 h; (ii) $CH_3PPh_3^+I^-$, *n*-BuLi, THF, −20 °C, 3 h, 52%; (for 2 steps) (e) KOH, THF/methanol/water, (2:2:1), rt, 8 h, 87%.



Scheme 4. Reagents and conditions: (a) DCC, DMAP, CH_2Cl_2, rt, 18 h, 76%; (b) $(PCy_3)_2Ru(Cl)_2CH{=}Ph$ (20 mol%), CH_2Cl_2, reflux, 28 h, 67%; (c) $BF_3{:}Et_2O$, $(CH_2SH)_2$, CH_2Cl_2, 0 °C, 1 h, 76%.

lyst under highly diluted, degassed conditions gave the 10-membered lactone as *E* and *Z* isomers in 67:33 ratio. The desired *E* isomer could be separated by column chromatography from the *Z* isomer. Global deprotection of *E* **18** gave microcarpalide **1** (Scheme 4). The spectroscopic and analytical data of compound **1** and other compounds were in good agreement with the literature data.[1,3,9]

In conclusion we have described a highly convergent and efficient synthesis of (−)-microcarpalide. Further work in this direction is underway in our laboratory.

Acknowledgements

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9. *Spectral data for compound* **3**: ^{1}H NMR (200 MHz, $CDCl_3$) δ, ppm: 1.38 (6H, s), 1.72–2.04 (2H, m), 2.38–2.57 (2H, m), 3.69 (1H, dt, J = 8.2, 3.9 Hz), 3.97 (1H, dd, J = 8.2, 7.2 Hz), 5.28 (1H, ddd, J = 10.2, 1.5, 0.8 Hz), 5.39 (1H, ddd, J = 17.2, 1.5, 0.8 Hz), 5.79 (1H, ddd, J = 17.2, 10.2, 7.3 Hz) ^{13}C NMR (50 MHz) δ: 26.5, 26.9, 27.1, 30.4, 79.5, 82.4, 108.8, 119.2, 135.1, 178.6 ppm. Anal. Calcd for $C_{10}H_{16}O_4$: C, 60.0; H, 8.0. Found: C, 59.8; H, 7.9. Compound **4**: ^{1}H NMR (200 MHz, $CDCl_3$) δ, ppm: 0.89 (3H, t, J = 6.8 Hz), 1.22–1.38 (8H, m), 1.46–1.62 (2H, m), 2.12–2.39 (2H, m), 2.71 (1H, d, J = 4.0 Hz, –OH), 3.32–3.39 (1H, m), 3.40 (3H, s), 3.56 (1H, m), 4.67 (2H, s), 5.06 (1H, m) 5.12 (1H, m), 5.86 (1H, m) ^{13}C NMR (50 MHz) δ: 14.0, 22.5, 25.1, 29.3, 30.8, 31.7, 37.8, 55.7, 72.0, 82.4, 97.0, 117.2, 134.9 ppm. Anal. Calcd for $C_{13}H_{26}O_3$: C, 67.77; H, 11.38. Found: C, 67.72; H, 11.14. Compound **2**: ^{1}H NMR (200 MHz, $CDCl_3$) δ, ppm: 0.89 (3H, t, J = 6.9 Hz), 1.28–1.34 (8H, m), 1.40 (6H, s), 1.50 (2H, m), 1.82 (1H, m), 1.95 (1H, m), 2.34–2.52 (4H, m), 3.39 (3H, s), 3.59 (1H, m), 3.70 (1H, td, J = 8.3, 3.4 Hz), 3.99 (1H, t, J = 7.9 Hz), 4.69 (2H, ABq, J = 3.4 Hz), 5.07 (2H, m), 5.09 (1H, dd, J = 17.6, 1.6 Hz), 5.26 (1H, d, J = 10.4 Hz), 5.37 (1H, d, J = 17.6 Hz), 5.77 (2H, m) ^{13}C NMR (75 MHz) δ: 14.0, 22.5, 25.3, 26.8, 26.9, 27.2, 29.3, 30.5, 30.7, 31.7, 34.6, 55.8, 73.7, 78.1, 79.5, 82.4, 96.7, 108.8, 117.6, 118.9, 133.9, 135.2, 172.5 ppm. Anal. Calcd for $C_{23}H_{40}O_6$: C, 66.95; H, 9.78. Found: C, 66.62; H, 10.04. Compound **18**: ^{1}H NMR (300 MHz, $CDCl_3$) δ, ppm: 0.89 (3H, t, J = 7.0 Hz), 1.24–1.36 (8H, m), 1.41 (6H, s), 1.60 (2H, m), 1.96–2.06 (2H, m), 2.28–2.64 (4H, m), 3.42 (3H, s), 3.62 (2H, m), 3.93 (1H, t, J = 8.8 Hz), 4.69 (2H, m), 4.95 (1H, ddd, J = 8.8, 3.8, 2.5 Hz), 5.35 (1H, dd, J = 15.8, 9.4 Hz), 5.78 (1H, ddd, J = 15.8, 11.4, 4.7 Hz), ^{13}C NMR (75 MHz) δ: 14.0, 22.6, 25.3, 25.4, 26.9, 27.1, 29.4, 30.5, 30.8, 31.7, 34.2, 56.0, 73.6, 79.3, 79.8, 84.4, 96.5, 108.8, 129.4, 130.1, 171.7 ppm. Anal. Calcd for $C_{21}H_{36}O_6$: C, 65.59; H, 9.43. Found: C, 65.3; H, 9.32. Compound **1**: colorless oil. $[\alpha]_D$ −22.3 (*c* 0.4; MeOH), lit.[1,3] $[\alpha]_D$ −22 (*c* 0.67; MeOH); Anal. Calcd for $C_{16}H_{28}O_5$ C, 63.97; H, 9.40. Found: C, 64.12; H, 9.28.