Tetrahedron Letters 50 (2009) 6402–6403

Contents lists available at ScienceDirect

Tetrahedron Letters

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

Facile asymmetric synthesis of spongianone analogue through biomimetic cyclization

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ARTICLE INFO

Article history:
Received 23 July 2009
Revised 18 August 2009
Accepted 21 August 2009
Available online 24 August 2009

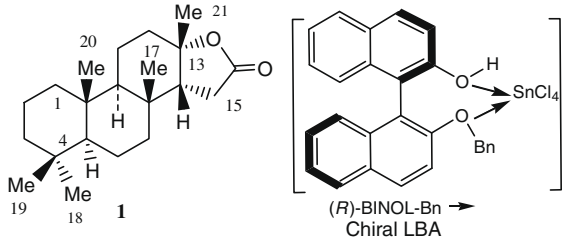
Keywords:
Chiral LBA
BINOL
Biomimetic cyclization
Tetracyclic (+)-γ-lactone
Spongianone

ABSTRACT

Facile synthesis of (+)-tetracyclic-homoditerpene lactone has been achieved from sclareol through [2,3] sigmatropic rearrangement followed by biomimetic cyclization.

Cascade reactions are some of the most powerful tools for the total synthesis of complex natural products, since complicated structures can be constructed directly in one-pot sequences. The benefits of cascade reactions include atom economy, as well as savings in labor, resource management, and waste generation.[1] The construction of polycyclic molecules from acyclic precursors is a general theme in biosynthesis. During the last two decades, the biomimetic cyclization of polyene molecules has been developed to a high degree of sophistication and practical utility.[2] The Lewis acid-assisted chiral Brønsted acids (chiral LBAs) prepared in situ from chiral alcohols and tin(IV) chloride were found to be highly effective as artificial cyclases for the enantioselective biomimetic cyclization of polyprenoids.[3]

Continuing our efforts in this field, we report herein facile asymmetric synthesis of tetracyclic homoditerpene (+)-γ-lactone **1,** an analogue of spongianone (**2**), which is a metabolite of marine sponge *Dictyodendrilla cavernosa.*[4] The synthesis of tetracyclic lactone **3** has been reported through chlorosulfonic acid cyclization of homoterpenic acid **4**.[5] Similarly murrayanolide (**5**), a metabolite of marine sponge *Dendrobeania murrayana*,[6] is a diacetoxy-tetracyclic-γ-lactone.



The present synthetic approach to the tetracyclic (+)-γ-lactone **1** from (−)-sclareol (**6**) involves the [2,3] sigmatropic rearrangement of an allylic alcohol to the homologous amide followed by the hydrolysis of the amide to acid and biomimetic enatioselective cyclization of the resulting acid promoted by (*R*)-2-benzyloxy-2′-hydroxy-1,1′-binaphthyl [(*R*)-benzyl-BINOL] and $SnCl_4$ (chiral LBA).

The commercial sample of (+)-sclareol (**6**) [7] was heated with *N,N*-dimethylformamide dimethyl acetal (DMFDMA) to obtain one carbon homologation to the corresponding starting materials with incorporation of terminal amide functionality. Thus, the refluxing of a mixture of (−)-sclareol and DMFDMA in xylene for 14 h yielded an *E*/*Z*-mixture of the β,γ-unsaturated amides **7a** and **7b** (2.2:1) in 80% yield (Scheme 1), which were easily separated by silica gel column chromatography.[8] The alkaline hydrolysis of amide 7**a** afforded the acid **8**, which was subjected to cyclization in the presence of (*R*)-benzyl-BINOL and $SnCl_4$ at −78 °C for 3 h and subsequently at −20 °C for 3 days to give tetracyclic (+)-lactone (**1**),[9] yield 58.6%, ee = 96%.

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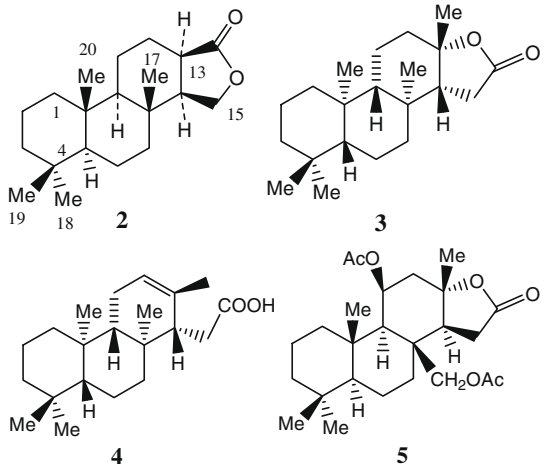
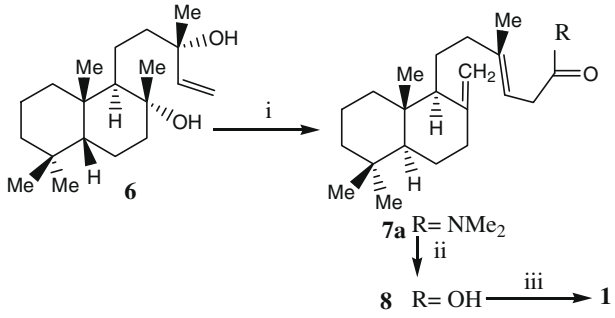
doi:10.1016/j.tetlet.2009.08.066



The cis-stereochemistry of C/D rings of (+)-homo-diterpene-γ-lactone **1** could be assigned by the comparison of ^{13}C NMR chemical shifts of lactone **1** with that of lactone **3**. The C-21 angular methyl group in lactone **1** appears at δ 29.7 as in lactone **3**, which appears at 29.8 ppm. The stereochemistry of the C-17 β-methyl group was obtained by the comparison of ^{13}C NMR chemical shifts of lactone **1** with that of lactone **2**. In lactone **1** C-17 β-methyl group appears at δ 15.7 ppm as in lactone **2**, which appears at 15.7 ppm.



Scheme 1. Synthesis of (+)-homo-diterpene-γ-lactone **1**. Reagents and conditions: (i) DMFDMA, xylene, reflux, 12 h; (ii) KOH, MeOH–water, reflux, 8h; (iii) 2-benzyloxy-2′-hydroxy-1,1′-binaphthyl, $SnCl_4$, toluene, −78 °C, 3 h and at −20 °C, 3 days.

In conclusion, we have achieved efficient enantioselective synthesis of spongianone analogue starting from sclareol through [2,3] sigmatropic rearrangement and chiral LBA-induced biomimetic cyclization as key steps.

Acknowledgments

We are grateful to Kelkar Education Trust, Mumbai, for encouragement and support. We are also thankful to the Department of Chemistry and Sophisticated Analytical Instrumentation Facility, Indian Institute of Technology, Mumbai, for NMR spectral data.

Supplementary data

Supplementary data (^1H NMR, ^{13}C NMR spectra and Chiral HPLC graph of tetracyclic-γ-lactone **1**) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.08.066.

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9. Synthesis of tetradecahydro-[3b,6,6,9a,11a-pentamethyl-(3a*R*,3b*R*,5a*S*,9a*S*,9b*R*,11a*S*)]phenanthro[2,1-*b*]furan-2(3*H*)-one (**1**): To a solution of (*R*)-2-benzyloxy-2′-hydroxy-1,1′-binaphthyl (260 mg, 0.69 mmol) in toluene (3 mL) was added tin(IV) chloride (0.4 mL, 3.37 mmol) at -20 °C and the solution was stirred for 30 min. This complex of 2-benzyloxy-2′-hydroxy-1,1′-binaphthyl–$SnCl_4$ prepared in situ was cooled to −78 °C and acid **8** (210 mg, 0.66 mmol) in toluene (6 mL) was added dropwise over a period of 5 min. The reaction mixture was stirred at −78 °C for 3 h and kept at −20 °C for 3 days, quenched with saturated aqueous $NaHCO_3$, and extracted with ethyl acetate. The combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated. The crude product was purified by column chromatography on silica gel to yield lactone (**1**) (150 mg, 71.4%, hexane–ethyl acetate 95:5); mp 166–168 °C (hexane); $[\alpha]_D^{25}$ +70.0 (*c* 0.64 $CHCl_3$), chiral HPLC (MeCN:H_2O—65:35, λ_{max} 216 nm, flow rate—0.5 mL/min) t_R = 5.1 (major isomer), 4.5 (minor isomer) min, ee = 96%, IR (KBr) 2936, 1772 (γ lactone), 1458, 1235, 946 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.81 (s, 3H), 0.86 (s, 3H), 0.87 (s, 3H), 0.92 (s, 3H), 1.31 (s, 3H), 1–1.66 (m, 14H), 1.68–1.80 (m, 2H), 2.24–2.33 (m, 1H), 2.39 (d, *J* = 18 Hz,1H), 2.72 (dd, *J* = 7.9, 18 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.7 (C-16), 85.8 (C-13), 56.8 (C-9), 56.5 (C-5), 55.4 (C-14), 42.5 (C-7), 42.0 (C-3), 40.1 (C-1), 37.4 (C-10), 36.5 (C-8), 35.1 (C-12), 33.4 (C-18), 33.3 (C-4), 32.9 (C-15), 29.7 (C-21), 21.5 (C-19), 18.5 (C-2), 18.1 (C-6), 17.9 (C-11), 16.3 (C-20), 15.7 (C-17), Anal. Calcd for $C_{21}H_{34}O_2$ (318.49): C, 79.19; H, 10.76. Found: C, 78.79; H, 10.77.