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Efficient enantioselective synthesis of (+)-sclareolide and (+)-tetrahydroactinidiolide: chiral LBA-induced biomimetic cyclization

Kiran B. Upar, Sanjay J. Mishra, Shrikant P. Nalawade, Soni A. Singh, Reena P. Khandare, Sujata V. Bhat *

Laboratory for Advanced Research in Natural and Synthetic Chemistry, V. G. Vaze College, Mumbai University, Mithagar Road, Mulund (East), Mumbai 400 081, India

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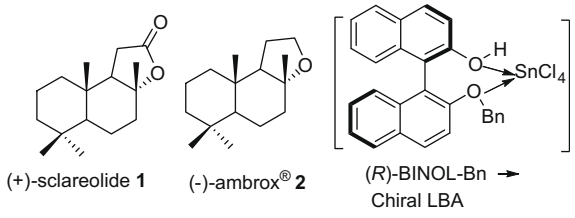
ABSTRACT

An efficient enantioselective synthesis of the lactones (+)-sclareolide and (+)-tetrahydroactinidiolide has been achieved through Lewis acid-assisted chiral Brønsted acid-induced enantioselective cyclization of terpenic carboxylic acids. The reaction sequence involved the [2,3] sigmatropic rearrangement of an allylic alcohol and biomimetic cyclization of terpenic acid in the presence of (*R*)-2-benzyloxy-2′-hydroxy-1,1′-binaphthyl and tin tetrachloride as key steps. The cyclization gave lactones in good yield and with high enantiomeric excess.

1. Introduction

(+)-Sclareolide **1**, a constituent of *Arnica angustifolia*, *Sideritis nutans, and Kyllinga erecta* displays phytotoxic, antifungal, and cytotoxic activities against human cancer cell lines.[1] (+)-Sclareolide **1** is obtained from oxidative degradation of more abundant labdane terpenes, such as (−)-sclareol, (+)-*cis*-abienol, (−)-labdanoic acid, and manoyl oxide.[2] It is mainly used in the perfume industry for the synthesis of the natural ambergris substitute product (−)-ambrox® **2**.[3] (+)-Sclareolide **1** has also been employed in the synthesis of various natural products such as wiedendiol,[4] (+)-hedychilactone,[5] hispanane-like terpene derivatives,[6] β-methylfurolabdanes,[7] acuminolide and 17-*O*-acetylacuminolide,[8] (+)-zerumin B,[9] onceradiene analogue,[10] austrodoral,[11] pelorol,[12] austrodoric acid,[13] (+)-coronarin-A,[14] (+)-puupehenone,[15] coscinosulfate A,[16] (−)-yatellaquinone,[17] and sulfircin.[18] Actinidiolide derivatives have been found to have insect pheromone activity and are useful as tobacco flavor enhancers.[19]



(+)-sclareolide **1** (-)-ambrox® **2** (*R*)-BINOL-Bn → Chiral LBA

The construction of polycyclic molecules from acyclic precursors is a general theme in biosynthesis. Over the last two decades the biomimetic cyclization of polyene molecules have been developed to a high degree of sophistication and practical utility.[20] Lewis acid-assisted chiral Brønsted acid (chiral LBA)-induced enantioselective cyclization of homofarnesol with a hydroxy group as a nucleophilic terminator gave (−)-ambrox® in 54% yield with 42% ee.[21] Alternatively the synthesis of (−)-ambrox® (76% ee) was achieved via the enantioselective cyclization of an (*E*,*E*)-homofarnesyl-triethylsilyl ether induced by chiral LBA and subsequent diastereoselective cyclization of the resulting chiral bicyclic and monocyclic products induced by achiral LBAs.[21] Similar enantioselective cyclization of 2-(polyprenyl)-phenol derivatives gave polycyclic terpenoids bearing the chroman skeleton in excellent yield and good ee %.[22] Herein, we report the enantioselective synthesis of (+)-sclareolide **1** and (+)-tetrahydroactinidiolide **9** through biomimetic cyclization of homofarnesic acid **5** and homogeranic acid **8,** respectively, in the presence of chiral LBA.

2. Results and discussion

The present synthetic approach to (+)-sclareolide **1** and (+)-tetrahydroactinidiolide **9** from (*E*)-(+)-nerolidol **3** and (*R*)-(−)-linalool **6,** respectively, involves the [2,3] sigmatropic rearrangement of an allylic alcohol to the homologous amide followed by hydrolysis of the amide to the acid and biomimetic enantioselective cyclization of acid promoted by (*R*)-2-benzyloxy-2′-hydroxy-1,1′-binaphthyl [(*R*)-benzyl-BINOL] and $SnCl_4$ (chiral LBA).

(*E*)-(+)-Nerolidol **3** and (*R*)-(−)-linalool **6** were heated with *N*,*N*-dimethylformamide dimethyl acetal (DMFDMA) to achieve one carbon homologation to the corresponding starting materials with incorporation of a terminal amide functionality. Thus, refluxing a mixture of (+)-(*E*)-nerolidol and DMFDMA in xylene for 14 h yielded an *E*/*Z*-mixture of the β,γ-unsaturated amides **4a** and **4b** (2.2:1) in 79% yield (Scheme 1), which were easily separated by silica gel column chromatography.[23] The alkaline hydrolysis of

* Corresponding author. Tel.: +91 022 21631421x113; fax: +91 022 21634262.
E-mail address: sujata8b@gmail.com (S.V. Bhat).

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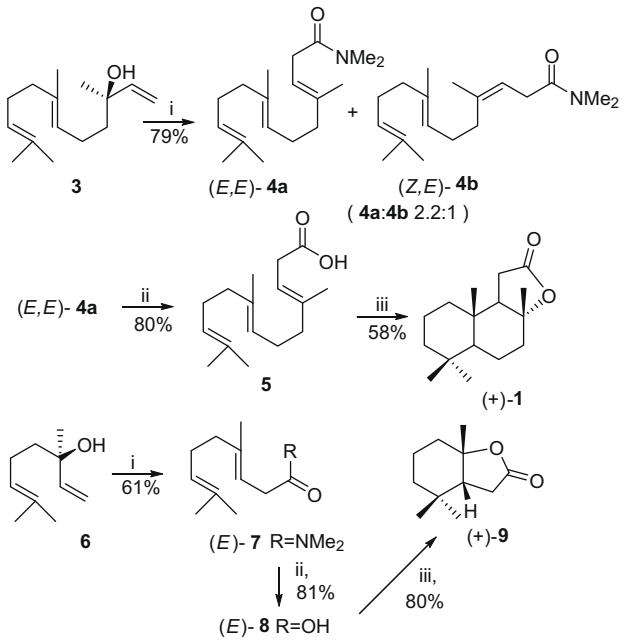

Scheme 1. Enantioselective synthesis of (+)-sclareolide and (+)-tetrahydroactinidiolide. Reaction conditions: (i) DMFDMA, xylene, reflux, 14 h; (ii) KOH, MeOH–water, reflux, 12 h; (iii) 2-benzyloxy-2′-hydroxy-1,1′-binaphthyl, $SnCl_4$, toluene, −78 °C, 3 h, and at −20 °C, 3 d.

amide **4a** afforded homofarnesic acid **5**,[21] 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 d to give (+)-sclareolide **1** in 58.6% yield and 88% ee (Fig. 1). A similar reaction sequence starting from (*R*)-(−)-linalool **6** gave amide **7,** which on hydrolysis gave homogeranic acid **8**,[24] while cyclization in the presence of (*R*)-benzyl-BINOL and $SnCl_4$ gave (+)-tetrahydroactinidiolide **9** in 80% yield and 90% ee.

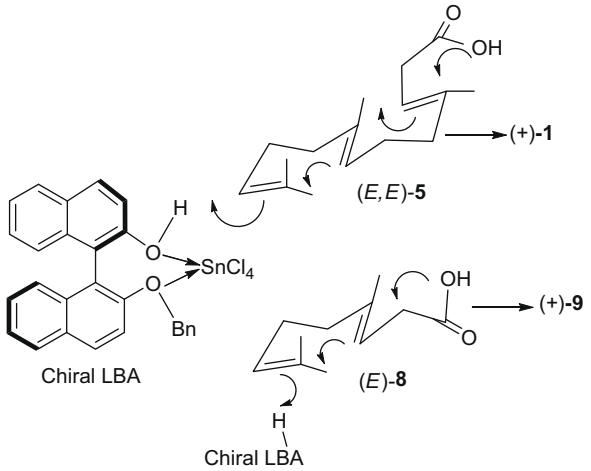

Figure 1. Enantioselective cyclization of (*E,E*)-**5** and (*E*)-**8** induced by (*R*)-benzyl-BINOL-$SnCl_4$.

3. Conclusion

In conclusion, a new approach to the synthesis of (+)-sclareolide **1** and (+)-tetrahydroactinidiolide **9** has been developed starting from (*E*)-(+)-nerolidol **3** and *(R)*-(−)-linalool **6**, respectively.

Interestingly, the chiral LBA-induced polyene cyclization with a carboxylic group as a terminator resulted in lactones with good yield and high enantiomeric excess. The method is practical and in view of the commercial importance and wide synthetic applications of lactones **1** and **9** the present method assumes greater significance.

4. Experimental

4.1. General methods

GC analysis of the products was performed on instrument equipped with a flame ionization detector, using a capillary column (cross-linked methyl siloxane, 30 m × 0.25 μm × 0.32 mm). GC–MS analysis was carried out on an instrument, which was coupled with a mass spectrometer with a quadrapole mass detector, using 5% phenyl-methyl siloxane column (30 m × 250 μm × 0.25 μm). The enantiomeric excess of the final lactones was obtained in GC analysis using a chiral βeta Dex 120 column (30 m × 0.25 μm × 0.25 mm). ^{1}H NMR spectra were recorded on 400 MHz instrument and ^{13}C spectra were recorded on 75 and 100 MHz instruments. IR spectra were recorded on FTIR instrument.

4.2. Synthesis of (*E,E*)-4,8,12-trimethyl-3,7,11-tridecatrienoic acid *N,N*-dimethylamide 4a

A mixture of (+)-(*E*)-nerolidol **3** (22.2 g, 0.1 mol), *N,N*-dimethylformaldehyde dimethyl acetal (DMFDMA, 95.2 g, 0.8 mol), and xylene (200 mL) was refluxed for 14 h with continuous removal of methanol (Dean-Stark device). The mixture was concentrated in vacuo to yield a residue (26.2 g) which, after silica gel column chromatography, yielded Δ^{3E}-amide **4a** (14.4 g, 55%, hexane: ethyl acetate 92:8) and Δ^{3Z}-amide **4b** (6.55 g, 25%, hexane–ethyl acetate 92:8).

4.2.1. Compound 4a

IR (Liquid) 1648 ($CONMe_2$) cm^{-1}; ^{1}H NMR (400 MHz) δ 1.58 (br s, 6H), 1.65 (s, 3H), 1.67 (s, 3H), 2.93, 2.96 (2s, 6H), 3.04 (d, J = 6.7, 2H), 5.04–5.10 (m, 2H), 5.30 (td, J = 6.7, 1.1, 1H); ^{13}C NMR (100 MHz) δ 172.0, 138.0, 135.1, 131.2, 124.2, 123.8, 116.8, 39.6, 39.5, 37.3, 35.4, 33.7, 26.6, 26.4, 25.6, 17.6, 16.4, 15.9; MS *m*/*z* (rel. int.) 277 (M^+, 1), 208 (8), 194 (1), 154 (2), 141 (5), 140 (7), 121 (12), 87 (21), 72 ($CONMe_2^+$, 100), 69 (26), 41 (36).

4.2.2. Compound 4b

IR (Liquid)1648 ($CONMe_2$) cm^{-1}; ^{1}H NMR (400 MHz) δ 1.55 (br s, 6H), 1.63 (s, 3H), 1.70 (s, 3H), 2.88, 2.95 (2s, 6H), 3.03 (d, J = 6.7, 2H), 5.01–5.10 (m, 2H), 5.29 (td, J = 6.7, 1.3, 1H); ^{13}C NMR (100 MHz) δ 171.8, 138.0, 135.3, 131.2, 124.1, 123.6, 117.5, 39.6, 37.2, 35.3, 33.1, 32.1, 26.5, 26.0, 25.5, 23.3, 17.5, 15.8; MS *m*/*z* (rel. int.) 277 (M^+, 1), 208 (12), 195 (1), 154 (2), 141 (5), 140 (35), 121(15), 87 (19), 72 ($CONMe_2^+$, 100), 69 (29), 41 (47).

4.3. Synthesis of (*E,E*)-4,8,12-trimethyl-3,7,11-tridecatrienoic acid 5

A mixture of amide **4a** (12.5 g, 0.045 mol), KOH (3.135 g, 0.055 mol), H_2O (3 mL), and MeOH (30 mL) was refluxed for 12 h. After removing the solvent in vacuo the residue was fractionated into H_2O–ethyl acetate. To the H_2O layer, 2 M HCl was added until pH 3 and extracted with ethyl acetate (3 × 50 mL). The combined organic extracts were dried over anhydrous $MgSO_4$ and evaporated to yield a yellow viscous oil (10 g), which after silica gel column chromatography, yielded homofarnesic acid **5** (9.02 g, 80%, hexane–ethyl acetate 95:5). IR (Neat) 3420 (OH), 1710 (CO) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.50 (br s, 6H), 1.57 (s, 3H), 1.65 (s, 3H), 1.6–2.06 (m, 8H), 3.15 (d, J = 6.8 Hz, 2H), 5.04–5.15 (m, 2H),

5.25 (td, J = 6.4, 1.1 Hz, 1H), 10.0–10.5 (br s, 1H); MS m/z (rel. int.) 250 (M^+, 1), 205 (1), 195 (4), 136 (33), 121 (56), 105 (7), 95 (14), 81 (40), 69 (88), 53 (10), 41 (100). HRMS m/z calcd for $C_{16}H_{26}O_2$ 250.3812, found 250.3814.

4.4. (+)-Sclareolide 1 {(3a*R*,5a*S*,9a*S*,9b*R*)-(+)-1,2,3a,4,5,5a,6,7,8,9,9a,9b-dodecahydro-3a,6,6,9a-tetramethylnaptho[2,1-*b*]furan-2-one}

To a solution of (*R*)-2-benzyloxy-2′-hydroxy-1,1′-binaphthyl (260 mg, 0.69 mmol) in toluene (9 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′-binapthyl–$SnCl_4$ prepared in situ was cooled to −78 °C and homofarnesic acid **5** (600 mg, 2.4 mmol) in toluene (9 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 d, quenched with saturated aqueous $NaHCO_3$, and extracted with ethyl acetate. The combined organic extracts were dried over anhydrous $MgSO_4$ and concentrated. The crude product was purified by column chromatography on silica gel to yield (+)-sclareolide **1** (352 mg, 58.6 %, hexane–ethyl acetate 92:8); mp 120–122 °C (hexane); (Lit.[2] mp 121–124 °C); $[\alpha]_D^{25}$ = +42.6 (c 0.5 $CHCl_3$), Lit.[2] $[\alpha]_D^{25}$ = +47.3 (c 0.9 $CHCl_3$); GC (initial column temperature 171 °C for 5 min, heat 1 °C/min, final temperature 210 °C, injection temperature 230 °C), t_R = 37.2 (major isomer of **1**, 94 %), 37.8 (minor isomer of **1**, 6.0%) min, ee 88%. IR (KBr) 1770 (γ-lactone) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.83 (s, 3H), 0.88 (s, 3H), 0.90 (s, 3H), 1.04 (dd, J = 12.8, 3.7 Hz,1H), 1.21 (m, 2H), 1.32 (s, 3H), 1.35–1.5 (m, 6H), 1.88 (dq, J = 13.2, 3.7 Hz,1H), 1.95 (dd, J = 14.4, 6.7 Hz, 1H), 2.06 (dt, J = 12.0, 3.5 Hz,1H), 2.21 (dd, J = 16.8, 6.4 Hz,1H), 2.4 (dd, J = 16.8, 14.4 Hz,1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.7, 86.3, 59.1, 56.6, 42.2, 39.5, 38.7, 36.1, 33.2, 33.1, 28.7, 21.6, 20.9, 20.6, 18.1, 15.1, MS m/z (rel. int. %) 250 (M^+, 0.7), 235 (12), 206 (16), 191(13), 150 (15), 123 (49), 67 (77), 55 (66), 43 (100), HRMS m/z calcd for $C_{16}H_{26}O_2$ 250.3812, found 250.3807.

4.5. Synthesis of (*E*)-4,8-dimethyl-3,7-nonadienoic acid *N,N*-dimethylamide 7

A mixture of (*R*)-(−)-linalool **6** (12.0 g, 0.077 mol), DMFDMA (80.0 g, 0.77 mol), and xylene (180 mL) was refluxed for 14 h with continuous removal of methanol (Dean-Stark device). The mixture was concentrated in vacuo to yield a residue (14.0 g) which, after column chromatography over silica gel, yielded Δ^{3E}-amide **7** (10.0 g, 61%). IR (Neat) 2925, 1654 (CON–), 1448, 1395, 1262, 1132 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.59 (s, 3H), 1.65 (s, 3H), 1.60–1.68 (m. 4H), 1.75 (s, 3H), 2.94 (s, 2H), 2.97 (s, 3H), 3.0 (s, 3H), 5.10 (br s, 1H), 5.32 (t, J = 7 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.0, 137.9, 131.5, 124.0, 116.9, 39.6, 37.3, 35.5, 33.8, 26.5, 25.7, 17.6, 16.4, HRMS m/z calcd for $C_{13}H_{23}ON$ 209.3317, found 209.3298.

4.6. Synthesis of 4,8-dimethyl-3,7-nonadienoic acid 8

A mixture of amide **7** (3.0 g, 0.014 mol), KOH (1.3 g, 0.024 mol), H_2O (1 mL), and MeOH (9 mL) was refluxed for 12 h. After removal of the solvent the residue was fractionated into H_2O–ethyl acetate. To H_2O layer, 2 M HCl was added until pH 3 and extracted with ethyl acetate (3 × 15 mL). The combined organic extracts were dried over anhydrous $MgSO_4$ and evaporated to yield yellow viscous oil (2.5 g) which, after silica gel column chromatography, yielded homogeranic acid **8** (2.1 g, 81%, hexane–ethyl acetate 95:5). IR (Neat) 2922, 1710, 1416, 1378, 1302, 1260, 1223 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.60 (s, 3H), 1.64 (s, 3H), 1,68 (s, 3H), 2.05 (m, 4H), 3.10 (d, 2H, J = 7 Hz), 5.02–5.14 (m, 1H), 5.30 (t, J = 7 Hz, 1H), 10.2–10.4 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) 178.9, 139.7, 132.1, 123.9, 115.0, 39.5, 33.5, 26.5, 25.6, 17.6, 16.4. HRMS m/z calcd for $C_{11}H_{18}O_2$ 182.2627, found 182.2601.

4.7. (+)-Tetrahydroactinidiolide 9 [(3a*R*,7a*S*)-(+)-octahydro-4,4,7a-trimethyl-benzofuran-2-one]

To a solution of (*R*)-2-benzyloxy-2′-hydroxy-1,1′-binaphthyl (87 mg, 0.23 mmol) in toluene (3 mL) was added tin(IV) chloride (0.13 mL, 1.1 mmol) at −20 °C and the solution was stirred for 30 min. Subsequently this mixture was cooled to −78 °C and a solution of homogeranic acid **8** (150 mg, 0.82 mmol) in toluene (3 mL) was added dropwise over a period of 15 min. The reaction mixture was stirred at −78 °C for 3 h and kept at −20 °C for 3 d, quenched with cold water, and extracted with ethyl acetate. The combined organic extracts were dried over anhydrous $MgSO_4$ and concentrated. The crude product was purified by column chromatography on neutral alumina, to yield (+)-tetrahydroactinidiolide **9** (120 mg, 80%, hexane–ethyl acetate 95:5). $[\alpha]_D^{25}$ = +64 (c 1, hexane), Lit.[25] $[\alpha]_D^{25}$ = +71 (c 0.04 hexane); GC (initial column temperature 135 °C for 5 min, heat 1 °C/min, final temperature 210 °C, injection temperature 230 °C), t_R = 42.0 (major isomer of **9,** 95%), 42.5 (minor isomer of **9**, 5%) min, ee 90%. IR (KBr) 2940, 2871, 1765 (γ-lactone), 1458, 1382 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.91 (s, 3H), 1.05 (s, 3H), 1.32 (s, 3H), 1.6–1.4 (m, 4H), 1.84 (m, 2H), 2.07 (dd, J = 13.2, 8.8 Hz, 1H), 2.42 (dd, J = 8.4, 17.6 Hz, 1H), 2.53 (dd, J = 17.2, 12.8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.8, 86.1, 51.9, 34.7, 33.6, 33.3, 32.2, 30.1, 28.4, 26.9, 18.9. MS m/z (rel. int. %) 182 (M^+, 2), 167 (100), 139 (31), 126 (7), 111 (22), 96 (29), 81 (28), 69 (43), 55 (22), 43 (40); HRMS m/z calcd for $C_{11}H_{18}O_2$ 182.2627, found 182.2618.

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