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Chemoenzymatic enantioselective synthesis of the polypropionate acid moiety of dolabriferol

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Abstract—Dolabriferol is a marine polypropionate characterized by an unusual non-contiguous carbon skeleton. The two polypropionate subunits are linked by an ester function. The acid moiety of dolabriferol (ee = 97%) was synthesized in five steps and 58% overall yield via the enzymatic desymmetrization of *meso*-(*anti–anti*)-2,4-dimethyl-1,3,5-pentanetriol.

1. Introduction

Dolabriferol **1**, a secondary metabolite isolated from the skin of the anaspidean mollusk *Dolabrifera dolabrifera*, was first reported by Gavagnin et al. in 1996.[1] The structure was elucidated by spectral methods and single crystal X-ray analysis unambiguously established the relative configuration of dolabriferol to be (4*R**,6*S**,7*S**,12*S**,13*R**,15*R**,16*R**,18*R**). The absolute configuration of dolabriferol remains unassigned and because of its limited availability, its biological activity has not been explored.

Dolabriferol is a member of a large class of natural products sharing a polyketide/polypropionate biosynthesis.[2,3] These compounds possess remarkable biological and pharmacological activities (antibiotic, antifungal, anti-cancer, anti-inflammatory, immunosuppressant). Polypropionate subunits are aliphatic chains bearing alternating hydroxyl and methyl groups with a distinct stereochemistry.

A retrosynthetic analysis of dolabriferol **1** is shown in Scheme 1. Retrosynthetic simplification includes the bond disconnection of the ester and the ring opening of the cyclic hemiacetal **4** to generate two closely related fragments **2** and **3** that in turn, can be converted retrosynthetically to the common precursors **5** and **6**. This approach exploits the structural symmetry[4] of the polypropionate *anti–anti* stereotriad D. We have already described the enzymatic desymmetrization of **6** in a preliminary communication.[5] Hitherto diverse desymmetrizations leading to polypropionate fragments have been reported.[6] Herein we report the chemoenzymatic enantioselective synthesis of the acid moiety of dolabriferol.

2. Result and discussion

The stereoselective acylation of *meso*-3-(*tert*-butyldimethylsiloxy)-2,4-dimethyl-1,5-pentanediol **6**[7] by vinyl acetate in the presence of *Candida rugosa* lipase in hexane gave the corresponding (2*R*,3*R*,4*S*)-monoester **5** (Scheme 2) in high yield (94%) and high enantiomeric excess (97%).[5] The addition of intact molecular sieves to the medium in order to trap the by-product acetaldehyde is essential to achieve high enantioselectivity. Acetaldehyde may cause enzyme deactivation by formation of a Schiff's base with the terminal amino group of lysine residues.[8] However, finely powdered molecular sieves decrease the enzymatic activity by removing the structural water essential to the enzyme activity.[8] This reaction has been performed on several gram scale.

Oxidation of alcohol **5** with the Dess–Martin periodinane reagent provided the aldehyde **7** in a near-quantitative yield (Scheme 2). As aldehyde **7** is unstable, it is best prepared immediately prior to use in the next step. The addition of excess ethylmagnesium bromide to **7** produced a diastereomeric mixture of diol **8a**, **8b** with a preponderance of the *syn*-diastereoisomer **8a** (**8a**/**8b**: 6/1). This reaction also provoked the removal of the

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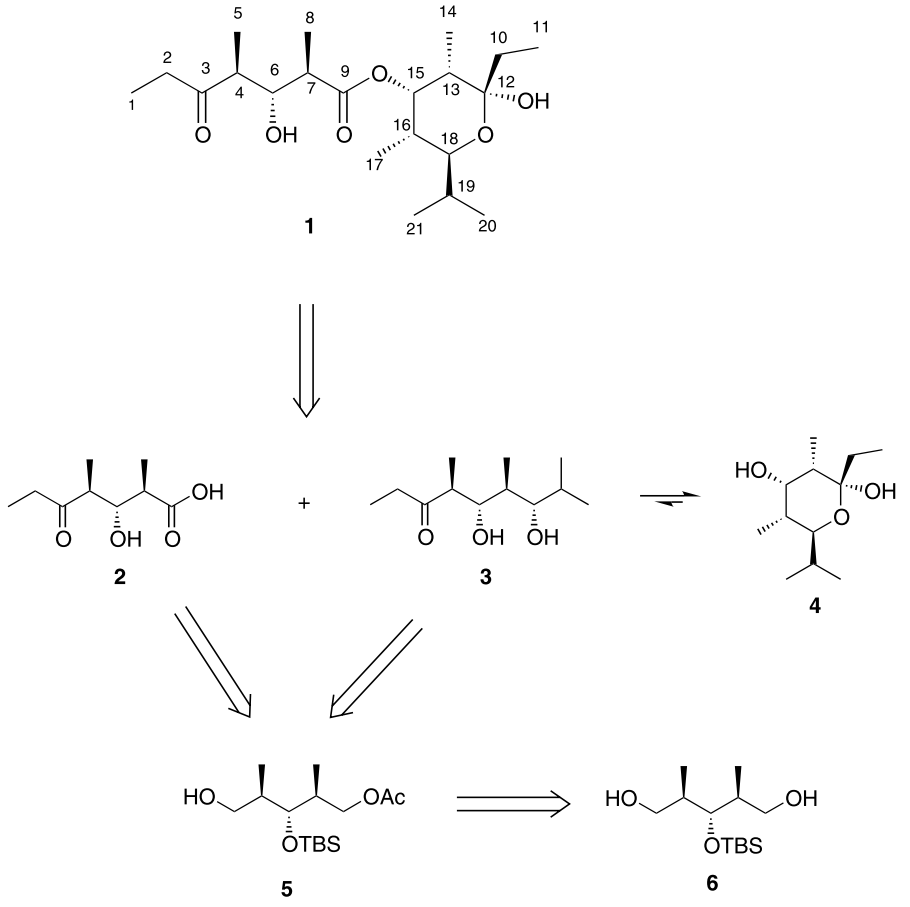
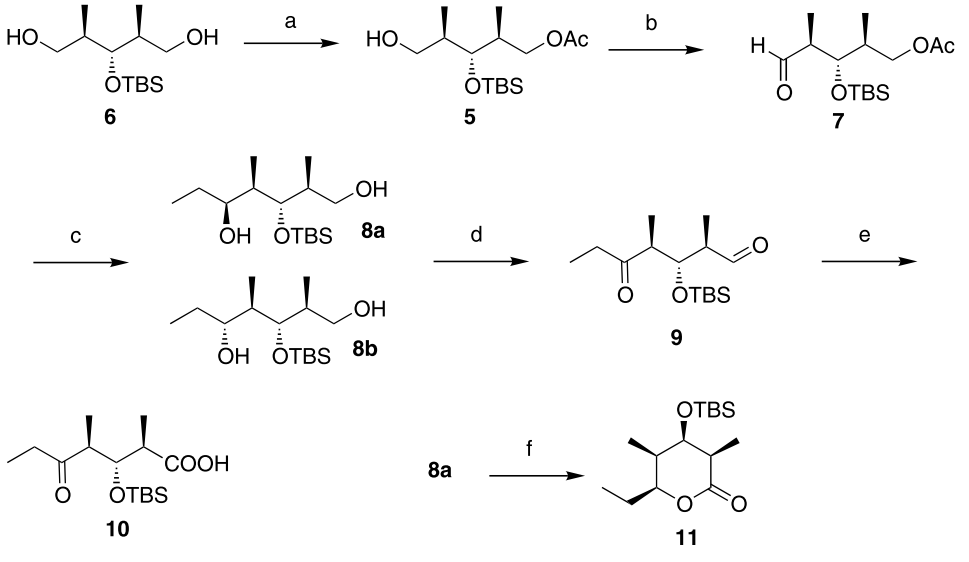
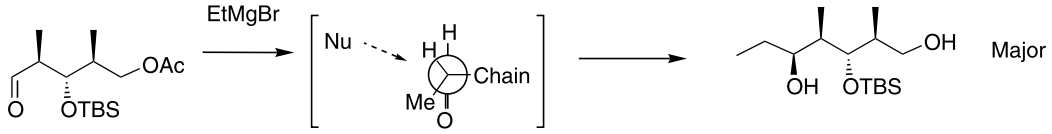


Scheme 1.



Scheme 2. *Reagents and conditions*: (a) *Candida rugosa* lipase, vinyl acetate, hexane, 94% ee = 97%; (b) Dess–Martin periodinane, CH_2Cl_2; (c) EtMgBr, THF, 87% (two steps) **8a**/**8b** = 6/1; (d) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, 84%; (e) $RuCl_3$, $NaIO_4$, CCl_4, H_2O, CH_3CN, 85%; (f) PDC, DMF, 56%.

acetate group. Attempts to oxidize both alcohol functions of **8a**,**b** in a one-pot procedure using pyridinium dichromate provided a diastereomeric mixture of lactones. This result can be explained by the fast oxidation of the primary alcohol to an acid followed by lactonisation, thus preventing any oxidation of the secondary alcohol. However, this reaction was used to confirm the stereochemistry of the Grignard reaction. The relative configuration of the major product **8a** was predicted by the Felkin–Anh model (Scheme 3). To confirm the



Scheme 3.

stereochemistry between the newly installed hydroxyl group and the adjacent methyl group, the diastereoisomers were easily separated by flash chromatography and the major isomer was converted to the lactone **11** of known relative configuration[9] by oxidation with pyridinium dichromate.

Swern oxidation of the diol mixture **8a**,**b** gave ketoaldehyde **9** which was further oxidized with $RuCl_3$ and $NaIO_4$ in CH_3CN–CCl_4–H_2O to give the carboxylic acid **10** {$[\alpha]_D^{22}=+20.4$ (*c* 2.45, $CHCl_3$)}. Compound **10** has already been reported by Hoffmann in the racemic form in a mixture containing 10% of a diastereoisomer.[9]

The enantioselective synthesis of (2*R*,3*R*,4*S*)-3-(*tert*-butyldimethylsiloxy)-2,4-dimethyl-5-oxoheptanoic acid **10** has been achieved in five steps with a 58% overall yield from the readily available *meso*-diol **6**. This compound corresponds to the polypropionate acid moiety of dolabriferol. Further studies devoted to the synthesis and the determination of the absolute configuration of dolabriferol are currently in progress.

3. Experimental

3.1. General

NMR spectra were recorded on Brucker AC 300 or Varian Inova AS 400 spectrometers (300 and 400 MHz respectively). Infrared spectra were recorded on a Bomem MB-100 spectrometer. Optical rotations were measured using a JASCO DIP-360 digital polarimeter. Flash column chromatography was carried out using 40–63 μm (230–400 mesh) silica gel. Lipase from *Candida rugosa* was purchased from Sigma Chemical Company.

3.2. (2*R*,3*R*,4*S*)-5-Acetoxy-3-(*tert*-butyldimethylsiloxy)-2,4-dimethyl-1-pentanol 5

Compound[7] **6** (172 mg, 0.665 mmol) was dissolved in hexane (23 mL) on molecular sieve (3Å, 100 mg). Lipase from *Candida rugosa* (100 mg) and vinyl acetate (0.3 mL, 3.15 mmol) were then added and the mixture stirred at room temperature. The reaction was monitored by thin layer chromatography (4 h). The reaction was quenched by filtration of the enzyme and the volatiles evaporated. The crude product was purified by flash chromatography on silica gel (eluant: ethyl acetate/hexane, 1:4) to give **5** (187.9 mg, 94%). $[\alpha]_D^{22}=-8.6$ (*c* 2.37, $CHCl_3$); IR (neat) 3450, 2950, 2920, 2850, 1745, 1250, 1030, 830, 765 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.07 (s, 3H), 0.10 (s, 3H), 0.90 (s, 9H), 0.97 (d, $J=6.9$ Hz, 3H), 0.99 (d, $J=6.8$ Hz, 3H), 1.55 (s, 1H), 1.88 (m, 1H), 2.04 (s, 3H), 2.07 (m, 1H), 3.65 (m, 3H), 3.90 (dd, $J=11.0$ and 7.2 Hz, 1H), 4.16 (dd, $J=11.0$ and 5.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ –4.50, –4.21, 13.89, 15.73, 18.09, 20.80, 25.88, 37.24, 37.55, 65.48, 66.23, 78.30, 170.92; HRMS (CI, NH_3) calcd for $C_{15}H_{33}O_4Si$ (MH^+) 305.2148, found 305.2159.

3.3. (2*S*,3*S*,4*S*)-5-Acetoxy-3-(*tert*-butyldimethylsiloxy)-2,4-dimethyl-1-pentanal 7

To a solution of Dess–Martin periodinane (705 mg, 1.66 mmol) in CH_2Cl_2 (7.5 mL) was added a solution of alcohol **5** (460 mg, 1.51 mmol) in CH_2Cl_2 (6 mL). After stirring for 1 h at room temperature, a solution of $NaHCO_3$ (satd) containing 25% sodium thiosulfate was slowly added (15 min). The mixture was extracted with Et_2O (2×10 mL) and the combined organic phases washed with water, brine, dried over $MgSO_4$ and then evaporated. The unstable aldehyde **7** was obtained in near-quantitative yield (455 mg) as a colorless oil and was used immediately in the next step. $[\alpha]_D^{22}=+17.5$ (*c* 1.85, $CHCl_3$); IR (NaCl) 2956, 2933, 2888, 2859, 1740, 1390, 1250, 1037, 838 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.03 (s, 6H), 0.90 (m, 12H), 1.12 (d, $J=7.2$ Hz, 3H), 2.05 (m, 4H), 2.56 (m, 1H), 3.94 (m, 2H), 4.15 (m, 1H), 9.76 (d, $J=2.0$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ –4.96, –4.81, 11.07, 13.83, 18.12, 20.91, 25.82, 37.26, 50.38, 66.09, 75.08, 171.72, 205.35.

3.4. (2*S*,3*S*,4*R*,5*S*)- and (2*S*,3*S*,4*R*,5*R*)-3-(*tert*-Butyldimethylsiloxy)-2,4-dimethyl-1,5-heptanediol 8a and 8b

To a solution of aldehyde **7** (633 mg, 2.09 mmol) in dry THF (20 mL) were added 7 mL (7 mmol) of a 1.0 M solution of ethylmagnesium bromide in THF at 0°C under a dry atmosphere. After stirring for 30 min at 0°C, the solution was allowed to warm to room temperature and stirred for an additional 1.5 h. A satd aq. solution of NH_4Cl (10 mL) was slowly added and the mixture extracted with ethyl acetate. The organic phase was washed with 3 M HCl, satd aq. $NaHCO_3$, brine, dried over Na_2SO_4 and then concentrated. The crude product was purified by flash chromatography (hexane–ethyl acetate: 4/1) to give **8a** and **8b** (532 mg, 87% from **5**, diastereomer ratio, **8a**/**8b**=6/1) as two colorless oils.

Major diastereoisomer **8a**: $[\alpha]_D^{22}=-7.4$ (*c* 2.19, C_6H_6); IR (NaCl) 3380, 2950, 2920, 2850, 1460, 1250, 1030, 830 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.13 (s, 6H), 0.91 (s, 9H), 0.91 (t, $J=7.4$ Hz, 3H), 0.98 (d, $J=6.9$ Hz, 3H), 0.98 (d, $J=6.6$ Hz, 3H), 1.34 (m, 1H), 1.55 (m, 1H), 1.69 (m, 1H), 2.00 (m, 1H), 2.29 (br s, 2H), 3.63 (dd, $J=5.2$ and 10.6 Hz, 1H), 3.68 (dd, $J=5.1$ and 10.6

Hz, 1H), 3.73 (dd, $J=3.3$ and 7.0 Hz, 1H), 3.94 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −4.18, −3.84, 10.51, 11.37, 14.77, 18.29, 26.14, 27.79, 38.20, 39.23, 65.14, 72.36, 80.68, HRMS (CI, NH_3) calcd for $C_{15}H_{35}O_3Si$ (MH^+) 291.2355, found 291.2349.

Minor diastereoisomer **8b**: $[\alpha]_D^{22}=-2.5$ (*c* 1.90, C_6H_6); IR (NaCl) 3380, 2950, 2920, 2850, 1465, 1255, 1030, 835 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.11 (m, 6H), 0.88 (d, $J=7.1$ Hz, 3H), 0.91 (m, 12H), 0.97 (d, $J=7.1$ Hz, 3H), 1.34 (m, 1H), 1.63 (m, 1H), 1.82 (m, 1H), 1.95 (m, 1H), 2.56 (br s, 2H), 3.45 (dt, $J=2.8$ and 8.6 Hz, 1H), 3.56 (dd, $J=5.0$ and 11.1 Hz, 1H), 3.63 (dd, $J=6.7$ and 11.1 Hz, 1H), 3.84 (t, $J=4.4$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −4.49, −4.19, 9.29, 14.04, 15.65, 18.11, 25.96, 27.23, 39.05, 43.18, 65.63, 74.64, 79.80.

3.5. (2*R*,3*S*,4*S*)-3-(*tert*-Butyldimethylsiloxy)-2,4-dimethyl-5-oxoheptanal 9

To a stirred solution of oxalyl chloride (120 μL, 1.83 mmol) in anhydrous CH_2Cl_2 (2 mL) at −78°C under dry nitrogen atmosphere was added anhydrous DMSO (150 μL, 2.11 mmol) in CH_2Cl_2 (1 mL) dropwise with the resulting mixture being allowed to react for 10 min at −78°C. Alcohol **8a**,**b** (102 mg, 0.35 mmol) in anhydrous CH_2Cl_2 (2 mL) was added, and the reaction mixture allowed to stir for 80 min at −78°C. On addition of anhydrous Et_3N (390 μL, 2.80 mmol), the dry ice/acetone bath was removed, and the reaction temperature allowed to return to room temperature. The reaction was diluted with ethyl acetate (100 mL) and the organic phase washed with 3 M HCl, aq. satd $NaHCO_3$, brine, dried over $MgSO_4$ and evaporated. The unstable aldehyde **9** was obtained in 84% yield (85 mg) as a colorless oil and was used immediately in the next step. $[\alpha]_D^{22}=-5.9$ (*c* 2.47, C_6H_6); IR (NaCl) 2936, 2859, 1720, 1392, 1255, 1065, 1039, 838 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ −0.04 (s, 3H), 0.07 (s, 3H), 0.82 (s, 9H), 0.90 (d, $J=7.1$ Hz, 3H), 1.01 (t, $J=7.3$ Hz, 3H), 1.12 (d, $J=6.8$ Hz, 3H), 2.50 (m, 3H), 2.83 (m, 1H), 4.34 (dd, $J=2.9$ and 8.4 Hz, 1H), 9.76 (d, $J=1.7$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −4.79, −4.66, 7.26, 9.93, 13.03, 18.05, 25.78, 36.87, 50.05, 50.85, 74.90, 203.36, 213.08;

3.6. (2*R*,3*R*,4*S*)-3-(*tert*-Butyldimethylsiloxy)-2,4-dimethyl-5-oxoheptanoic acid 10

Aldehyde **9** (54.0 mg, 0.188 mmol) was dissolved into a mixture of acetonitrile (0.4 mL), CCl_4 (0.1 mL), and water (0.6 mL). $RuCl_3{\cdot}nH_2O$ (1.1 mg, 5.3 μmol, 0.028 equiv.) and $NaIO_4$ (165 mg, 0.771 mmol) were successively added and the mixture stirred for 60 h at room temperature. Brine (50 mL) was then added to the mixture and the aqueous phase extracted with CH_2Cl_2 (4×100 mL). The combined organic phases were then dried over $MgSO_4$ and evaporated. The crude product was purified by flash chromatography (hexane:ethyl acetate, 4:1) to give acid **10** (48.4 mg, 85%) as a colorless oil. $[\alpha]_D^{22}=+20.4$ (*c* 2.45, $CHCl_3$); IR (NaCl) 3460–2400, 2930, 2850, 1710, 1460, 1380, 1255, 1070, 835, 775; ^1H NMR (400 MHz, $CDCl_3$) δ −0.05 (s, 3H), 0.06 (s, 3H), 0.81 (s, 9H), 0.93 (d, $J=7.1$ Hz, 3H), 0.99 (t, $J=7.2$ Hz, 3H), 1.13 (d, $J=7.2$ Hz, 3H), 2.48 (m, 2H), 2.66 (m, 1H), 2.84 (m, 1H), 4.32 (dd, $J=3.6$ and 8.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −5.03, −4.77, 7.29, 11.40, 12.61, 17.98, 25.75, 36.74, 43.86, 49.82, 75.26, 179.44, 213.31. HRMS (CI, NH_3) calcd for $C_{15}H_{31}O_4Si$ (MH^+) 303.1991, found 303.1996.

3.7. (3*R*,4*R*,5*R*,6*S*)-4-(*tert*-Butyldimethylsiloxy)-6-ethyl-3,5-dimethyltetrahydro-2*H*-pyran-2-one 11

To a solution of **8a** (70 mg, 0.241 mmol) in anhydrous DMF was added pyridinium dichromate (710 mg, 1.885 mmol). After stirring for 24 h at room temperature, ice (40 mL) was added and the mixture extracted with ether (3×50 mL). The combined organic phases were dried over $MgSO_4$ and evaporated. The crude product was purified by flash chromatography (hexane:ethyl acetate, 9:1) to give lactone **11**[8] (39 mg, 56%) as a colorless oil. IR (NaCl) 2940, 2880, 2850, 1740, 1460, 1355, 1255, 1200, 1090, 1030, 975, 835 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ −0.047 (s, 3H), −0.054 (s, 3H), 0.88 (s, 9H), 0.90 (d, $J=7.2$ Hz, 3H), 0.98 (t, $J=7.4$ Hz, 3H), 1.22 (d, $J=7.3$ Hz, 3H), 1.53 (m, 1H), 1.80 (m, 1H), 2.16 (m, 1H), 2.73 (q, $J=7.1$ Hz, 1H), 4.11 (m, 1H), 4.19 (t, $J=6.4$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −4.71, −4.40, 7.84, 10.39, 12.81, 18.19, 25.09, 25.81, 37.55, 40.29, 70.40, 80.91, 174.85.

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