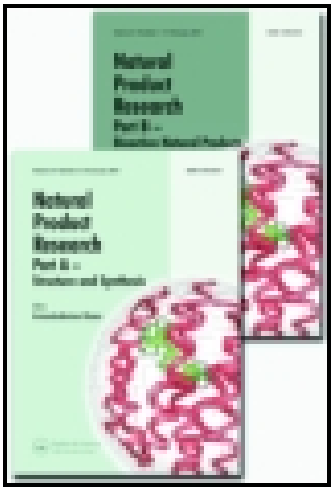

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Formal synthesis of (−)-pereniporin B and (−)-cinnamosmolide

Alexandru Ciocarlan[ab]*, Aculina Aricu[a], Nicon Ungur[a], Andrei Biriiac[a], Mihai Coltsa[a], Alina Nicolescu[bc], Calin Deleanu[bc] and Nicoleta Vornicu[d]

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The paper describes a new pathway for an efficient synthesis of natural and bioactive drimanic compounds (−)-pereniporin B (**1**) and (−)-cinnamosmolide (**2**) from ketodiol **7**, an intermediate obtained before from accessible labdane diterpenoid (+)-larixol (**3**). The key step involves allylic bromination of acetate **8** with *N*-bromosuccinimide. The *in vitro* antimicrobial and antifungal activities of all compounds are also reported. Their structures were confirmed by both spectroscopic data and chemical transformations.

Keywords: (−)-pereniporin B; (−)-cinnamosmolide; (+)-larixol; formal synthesis

1. Introduction

Drimane sesquiterpenoids have a wide range of biological activities (Jansen & de Groot 2004; Fraga 2013). Drimanic lactone pereniporin B (**1**) and its acetate cinnamosmolide (**2**) were isolated from several species of *Canellaceae* family: *Cinnamosma fragrans* (Canonica et al. 1967), *Capsicodendron dinisii* (Mahmoud et al. 1980) and *Cinnamosma madagascariensis* (Harinantenaina et al. 2008), from the culture filtrate of *Perenniporia medullaepanis* (*Basidiomycete*) (Kida et al. 1986), and from the stem bark of *Warburgia ugandensis* (*Warburgia*) (Rajab & Ndegva 2000), Figure 1.

It has been reported that pereniporin B (**1**) is a plant growth inhibitor (Kida et al. 1986), while cinnamosmolide (**2**) showed *in vitro* antifungal activity against dermatophites *Tricophyton rubrum*, *Tricophyton mentagraphytes* and *Microsporum gypseum* (Canonica et al. 1969).

Both metabolites were found to exhibit cytotoxic activity: pereniporin B (**1**) against friend leukaemia cells (F5-5) (Morioka et al. 1985) and cinnamosmolide (**2**) against the 9KB5 carcinoma in cell culture (Mahmoud et al. 1980).

First total syntheses of racemic pereniporin B (**1**) and cinnamosmolide (**2**) were performed in nine steps starting from a drimanic allylic alcohol, with ∼5% overall yield (Naito et al. 1980). Since then several syntheses of **1** in an optically active form have been described, involving 28 steps (1.8% yield) and (*S*)-3-hydroxy-2,2-dimethyl-1-cyclohexanone as starting material (Mori & Takaishi 1989). The enantioselective synthesis of pereniporin B (**1**) was performed (Burke et al. 1991) in 19 steps (∼3% yield) from an aliphatic vinylsulphoxide. Another accessible natural diterpenoid zamoranic acid was used for six-step synthesis of pereniporin B (**1**) in 11% yield by Urones et al. (1994). The only nine-step synthesis of

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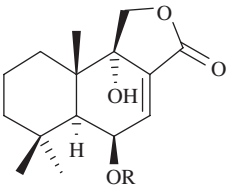


1 R = H
2 R = Ac

Figure 1. (−)-Pereniporin B **1** and (−)-cinnamosmolide **2**.

cinnamosmolide (**2**) was reported in 14% overall yield by transformation of uvidin A (Garlaschelli et al. 1991).

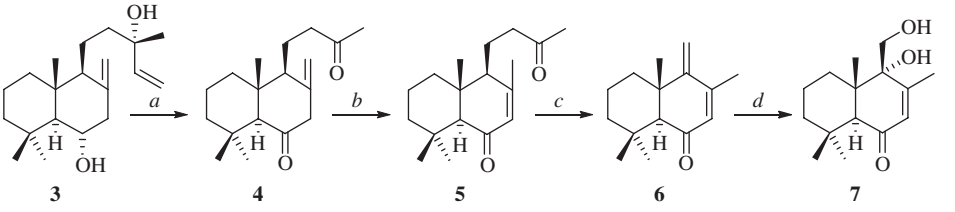
Herein we wish to report a new and efficient pathway for the synthesis of (−)-pereniporin B (**1**) and (−)-cinnamosmolide (**2**) from (+)-larixol (**3**) *via* key intermediate ketodiol **7**. It must be mentioned that previously compound **7** was isolated from natural sources in low amounts (Hayes et al. 1996; Zhou et al. 2011).

2. Results and discussion

A valuable intermediate ketodiol **7** was obtained earlier during the synthetic transformation of uvidin A into (−)-cinnamodial (Garlaschelli & Vidari 1989). The same diol **7** was prepared during conversion of (+)-larixol (**3**) into highly functionalised drimanes (Lagnel et al. 2000). (+)-Larixol (**3**) can be easily isolated from oleoresin of larch (*Larix* sp.) and due to hydroxyl group at C-6 is a suitable starting material for the synthesis of drimanes functionalised at the same position (Mills 1973). Recently we reported a new synthesis of natural drimanic compounds (−)-albrassitriol and (−)-6-*epi*-albrassitriol from (+)-larixol (**3**) where ketodiol **7** was obtained in 28.3% overall yield as indicated in Scheme 1 (Vlad et al. 2013).

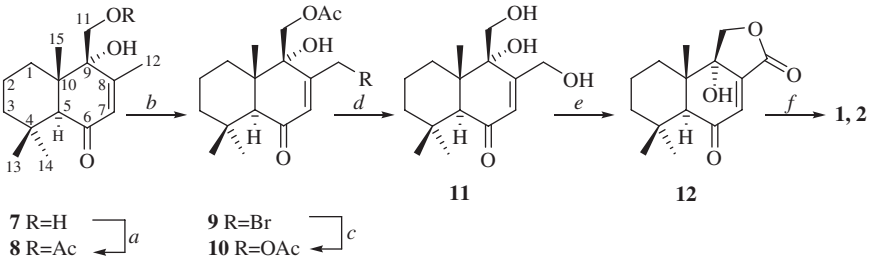
It is clear that more applications of dienone **7** for the synthesis of drimanes can be developed, especially when an easy fuctionalisation of the allylic methyl group C-12 can be accomplished. This has been achieved already by the allylic oxidation with selenium oxide (Garlaschelli & Vidari 1989). In our group the same transformation has been carried out using allylic bromination followed by the substitution of bromide by an acetate group as indicated in Scheme 2.

The acetylation of the primary hydroxyl group of **7**–**8** under standard conditions was made prior to the allylic bromination in order to prevent undesired oxidation at this position. The allylic bromination of **8** with *N*-bromosuccinimide (NBS) and subsequent replacement of bromine by treatment with KOAc gave **10** in high yield (Scheme 2).



3 **4** **5** **6** **7**

Scheme 1. Synthesis of 6-oxo-7-drimen-9α,11-diol **7** from (+)-larixol **3**. (a) CrO_3, AcOH, room temperature, 2 h, 48%; (b) NaOMe, MeOH, room temperature, 24 h, 97%; (c) $h\nu$, hexane, N_2, 5°C, 3 h, 67.5%; (d) OsO_4, Py, room temperature, 12 h, 90%.



Scheme 2. Formal synthesis of pereniporin B **1** and cinnamosmolide **2**. (a) Ac_2O, Py, room temperature, 12 h, 86%; (b) NBS, CCl_4, reflux, 9 h, 91%; (c) KOAc, DMSO, room temperature, 1 h, 98%; (d) K_2CO_3, MeOH, room temperature, 0.5 h, 99%; (e) MnO_2, CH_2Cl_2, room temperature, 70 h, 93%; (f) performed by (Canonica et al. 1969; Burke et al. 1991).

The acetate groups in **10** were hydrolysed leading to the known triol **11** (Urones et al. 1997; Zhou et al. 2011), which after oxidation of the least hindered hydroxyl group with MnO_2 followed by spontaneous cyclisation and oxidation led to lactone **12** (Kubo et al. 1983). The transformation of precursor **12** into pereniporin B (**1**) was reported earlier (Burke et al. 1991). It includes treatment of lactone **12** with DIBAL-H, followed by Fetizon's oxidation of the resulted lactols. Cinnamosmolide (**2**) can be prepared from pereniporin B (**1**) by its acetylation under standard conditions (Canonica et al. 1969).

Compounds **7**–**12** were screened for their *in vitro* antifungal and antibacterial activity against pure cultures of three fungi species (*Aspergillus niger*, *Penicillium frequentans*, *Alternaria alternata*) and against both Gram-negative (*Pseudomonas aeruginosa*) and Gram-positive bacteria (*Bacillus polymyxa).* According to these assays, bromide **9** exhibited good antifungal activity with a minimum inhibitory concentration (MIC) value of 0.85 μg/mL in comparison with the reference compound caspafungin (0.42 μg/mL) and good antimicrobial activity 0.90 μg/mL in comparison with the reference compound kanamycin (0.50 μg/mL). Noteworthy, the antifungal activity of bromide **9** is higher than that reported for cinnamosmolide (**2**) (Canonica et al. 1969).

3. Experimental

3.1. *General experimental procedure*

Melting points (m.p.) were taken on a Boethius (VEB Analytik, DDR) hot stage apparatus. Optical rotations were determined on a Perkin-Elmer 241 polarimeter (Perkin-Elmer, Norwalk, CT, USA) with a 1 dm microcell, in $CHCl_3$. IR spectra were obtained on Bio-Rad-Win-IR (Bio-Rad, Cambridge, MA, USA) and Perkin-Elmer spectrometers (Perkin-Elmer, Norwalk, CT, USA). ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ on Bruker AC-E 200 (Bruker BioSpin, Rheinstetten, Germany) and Bruker Avance DRX 400 spectrometers (Bruker BioSpin, Rheinstetten, Germany). Chemical shifts are given in ppm in δ scale and referred to $CHCl_3$ (δ_H at 7.26 ppm) and to $CDCl_3$ (δ_C 77.00 ppm), respectively. Coupling constants (J) are reported in Hertz (Hz). The H, H-COSY, H, C-HSQC and H, C-HMBC experiments were recorded using standard pulse sequences, in the version with z-gradients, as delivered by Bruker Corporation (Bruker BioSpin, Rheinstetten, Germany). Carbon substitution degrees were established by the DEPT pulse sequence. For analytical TLC, Sorbfil silica-gel plates were used. The TLC plates were sprayed with conc. H_2SO_4 and heated at 80°C for 5 min. Column chromatography was carried out on Across silica gel (60–200 mesh) using petroleum ether (PE) (b.p. 40–60°C) and the gradient mixture of PE and

EtOAc. All solvents were purified and dried by standard techniques before use. Solutions in organic solvents were dried over anhydrous Na_2SO_4, filtered and evaporated under reduced pressure.

3.1.1. *(1S,2R)-2-Hydroxy-1,3,7,7-tetramethyl-5-oxobicyclo[4.4.0]dec-3-en-2-ylmethyl acetate (**8**)*

To a solution of **7** (100 mg, 0.40 mmol), prepared by the procedure of Vlad et al. (2013), in dry Py (5 mL), Ac_2O (0.5 mL) was added and the resulted mixture was stirred overnight at room temperature. Then the reaction mixture was diluted with water (30 mL) and extracted with diethyl ether (3 × 20 mL). After solvent removal the crude product (119 mg) was subjected to column chromatography on SiO_2 (12 g, eluent: PE–EtOAc 4:1) to afford **8** (112 mg, 96%) as white solid (MeOH), m.p. 87–88°C, $[\alpha]_D^{20}$ − 9.5 (c = 1.0, $CHCl_3$); IR ($CHCl_3$) ν 3620, 3505, 2923, 2950, 1755, 1674, 1230, 901 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz, ppm): δ 5.76 (1H, d, 1.2 Hz, H-7), 4.38 (1H, d, 12.4 Hz) and 4.26 (1H, d, 12.4 Hz, H-11), 2.81 (1H, s, H-5), 2.14 (3H, s, OAc), 1.94 (3H, d, 1.6 Hz, H-12), 1.20 (3H, H-15), 1.20 − 1.90 (7H, m), 1.16 (3H, s, H-13), 1.03 (3H, s, H-14); ^{13}C NMR ($CDCl_3$, 100 MHz, ppm): δ 199.7 (C-6), 170.9 (C═O), 152.9 (C-8), 129.9 (C-7), 75.1 (C-9), 64.7 (C-11), 55.3 (C-5), 45.6 (C-10), 42.4 (C-3), 33.8 (C-14), 32.2 (C-4), 31.9 (C-1), 21.8 (C-13), 21.1 (OAc), 19.80 (C-12), 18.1 (C-2), 17.9 (C-15); $C_{17}H_{26}O_4$ found (%) C, 69.58; H, 9.05; required (%) C, 69.36; H, 8.90.

3.1.2. *(1S,2S)-3-Bromomethyl-2-hydroxy-1,7,7-trimethyl-5-oxobicyclo[4.4.0]dec-3-en-2-ylmethyl acetate (**9**)*

To a solution of **8** (200 mg, 0.68 mmol) in dry CCl_4 (10 mL), NBS (363 mg, 2.04 mmol) was added and the resulted mixture was refluxed for 9 h. After cooling, the reaction mixture was filtered and the solvent removed to yield the crude product (260 mg), which was purified by column chromatography on SiO_2 (23 g, eluent: PE–EtOAc 4:1) to afford **9** (230 mg, 91%) as white solid (MeOH), m.p. 80–81°C; $[\alpha]_D^{20}$ −16.7 (c = 0.6, $CHCl_3$); IR ($CHCl_3$) ν 3578, 2954, 2930, 1730, 1675, 1350, 1210, 1015, 945, 780 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz, ppm): δ 6.03 (1H, s, H-7), 4.54 (1H, d, 12.4 Hz) and 4.38 (1H, d, 12.4 Hz, H-11), 4.19 (1H, d, 11.2 Hz) and 4.13 (1H, d, 11.2 Hz, H-12), 2.96 (1H, s, H-5), 2.18 (3H, s, OAc), 2.04–1.17 (7H, m), 1.18 (3H, s, H-15), 1.16 (3H, s, H-13), 1.02 (3H, s, H-14); ^{13}C NMR ($CDCl_3$, 100 MHz, ppm): δ 199.7 (C-6), 170.7 (C═O), 149.9 (C-8), 132.9 (C-7), 75.3 (C-9), 64.1 (C-11), 55.6 (C-5), 46.2 (C-10), 42.2 (C-3), 33.5 (C-14), 32.2 (C-4), 31.8 (C-1), 31.4 (C-12), 21.7 (C-13), 21.1 (OAc), 18.0 (C-2), 17.8 (C-15); $C_{17}H_{25}O_4Br$ found (%) C, 54.51; H, 6.60; Br, 21.13; required (%) C, 54.70; H, 6.75; Br, 21.41.

3.1.3. *(1S,2S)-2-Hydroxy-1,7,7-trimethyl-2-methylcarbonyloxymethyl-5-oxobicyclo-[4.4.0]dec-3-en-3-ylmethyl acetate (**10**)*

The mixture of **9** (165 mg, 0.42 mmol) and KOAc (82 mg, 0.84 mmol) in dry dimethyl sulphoxide (DMSO) (5 mL) was stirred for 1 h at room temperature, then diluted with H_2O (10 mL) and extracted with Et_2O (3 × 15 mL). Next the organic layer was washed with H_2O (3 × 10 mL) and dried. After solvent removal the crude product was purified by column chromatography on SiO_2 (15 g, PE–EtOAc 4:1) to afford **10** (153 mg, 98%), as oil, $[\alpha]_D^{21}$ +23.1 (c = 0.8, $CHCl_3$); IR (film): ν 3595, 3475, 2943, 1725, 1664, 1342, 1197, 1098 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz, ppm): δ 5.98 (1H, s, H-7), 4.81 (1H, d, 15.2 Hz) and 4.67 (1H, d, 15.2 Hz, H-11), 4.39 (1H, d, 12.4 Hz) and 4.29 (1H, d, 12.0 Hz, H-12), 2.88 (1H, s, H-5), 2.13 (3H, s, OAc), 2.12 (3H, s, OAc), 1.20 (3H, s, H-15), 1.15 (3H, s, H-13), 1.03 (3H, s, H-14). ^{13}C NMR ($CDCl_3$,

100 MHz, ppm): δ 199.6 (C-6), 170.9 (C═O), 170.6 (C═O), 150.1 (C-8), 128.9 (C-7), 74.6 (C-9), 64.4 (C-11), 62.7 (C-12), 55.6 (C-5), 45.8 (C-10), 42.3 (C-3), 33.6 (C-14), 32.2 (C-4), 31.4 (C-1), 21.8 (C-13), 21.0 (OAc), 20.9 (OAc), 17.9 (C-15), 17.8 (C-2); $C_{19}H_{28}O_6$ found (%) C, 64.51; H, 7.73; required (%) C, 64.75; H, 8.00.

3.1.4. *(5S,6S)-5-Hydroxy-4,5-di(hydroxymethyl)-6,10,10-trimethylbicyclo[4.4.0]dec-3-en-2-one (**11**)*

To a solution of **10** (130 mg, 0.37 mmol) in MeOH (1.5 mL), a saturated solution of K_2CO_3 in MeOH (7 mL) was added. The reaction mixture was stirred for 0.5 h at room temperature, diluted with H_2O (15 mL) and extracted with Et_2O (3 × 10 mL), then the organic layer was washed with H_2O (3 × 10 mL) and dried. After solvent removal, the crude product (103 mg) was subjected to column chromatography on SiO_2 (10 g, PE–EtOAc 7:3) to give **11** (98 mg, 99%) as white solid (MeOH), m.p. 121–122°C; literature not reported (Urones et al. 1997; Zhou et al. 2011); $[\alpha]_D^{21}$ − 26.6 ($c = 0.4$, MeOH), literature $[\alpha]_D^{20}$ − 62.4° ($c = 0.94$, MeOH) (Urones et al. 1997); IR ($CHCl_3$): ν 3625, 3448, 2960, 1670, 1460, 1215, 1080 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz, ppm): δ 5.87 (1H, s, H-7), 4.49 (1H, d, 14.0 Hz) and 4.30 (1H, d, 14.0 Hz, H-12), 3.86 (2H, s, H-11), 2.87 (1H, s, H-5), 1.19 (3H, s, H-15), 1.15 (3H, s, H-13), 0.94 (3H, s, H-14). ^{13}C NMR ($CDCl_3$, 100 MHz, ppm): δ 200.7 (C-6), 153.4 (C-8), 128.8 (C-7), 75.1 (C-9), 64.8 (C-11), 62.2 (C-12), 56.1 (C-5), 45.3 (C-10), 42.3 (C-3), 33.6 (C-14), 32.2 (C-4), 31.2 (C-1), 21.8 (C-13), 17.9 (C-15), 17.7 (C-2); $C_{15}H_{24}O_4$ found (%) C, 67.31; H, 9.23; required (%) C, 67.14; H 9.01.

3.1.5. *(9aS,9bS)-9b-hydroxy-6,6,9a-trimethyl-1,3,5,5a,6,7,8,9,9a,9b-decahydrobenzo[e]-isobenzofuran-3,5-dione (**12**)*

To a solution of **11** (30 mg, 0.112 mmol) in CH_2Cl_2 (3 mL), MnO_2 (195 mg, 2.24 mmol) was added. The reaction mixture was stirred for 70 h at room temperature, then filtered through SiO_2 (CH_2Cl_2). After solvent removal lactone **12** (26 mg, 93%) was obtained, as white solid (PE), m.p. 195–196°C, literature not reported (Kubo et al. 1983; Burke et al. 1991); $[\alpha]_D^{21}$ − 35.16 ($c = 0.3$, $CHCl_3$), literature not reported (Kubo et al. 1983; Burke et al. 1991); IR ($CHCl_3$): ν 3434, 2974, 1770, 1625, 1490, 1190, 1140, 1115 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz, ppm): δ 6.50 (1H, s, H-7), 4.53 (1H, d, 10.2 Hz) and 4.37 (1H, d, 10.2 Hz, H-11), 2.96 (1H, s, H-5), 2.40-1.35 (2H, m), 1.18 (3H, s, H-15) 1.17 (3H, s, H-14), 1.08 (3H, s, H-13); ^{13}C NMR ($CDCl_3$, 100 MHz, ppm): δ 199.3 (C-6), 168.4 (C-12), 141.8 (C-8), 131.0 (C-7), 74.9 (C-9), 55.7 (C-5), 45.5 (C-10), 42.6 (C-3), 33.5 (C-14), 32.3 (C-4), 31.5 (C-1), 30.9 (C-11), 21.3 (C-13), 19.6 (C-15), 17.2 (C-2); ($C_{15}H_{20}O_4$ found (%) C, 67.96; H 7.48; required (%) C, 68.16; H 7.63).

3.2. *Antimicrobial and antifungal activity*

Fungi: *A. niger* ATCC 53346, *P. frequentans* ATCC 10110 and *A. alternata* ATCC 8741, and Gram-negative bacteria *P. aeruginosa* ATCC 27813 and Gram-positive *B. polymyxa* were provided by the American Type Culture Collection (ATCC, USA).

Compounds caspafugin and kanamycin, both from Liofilchem (Roseto degli Abruzzi, Italy), were used as standards for antifungal and antibacterial activity testing. After 48 h of incubation, a symmetrical inhibition ellipse centred along the strip was formed. The MIC is read directly from the scale in terms μg/mL, at the point where the edge of the inhibition ellipse intersects with the MIC test strip.

Sample solutions of 0.5%, 1% and 2% concentrations were obtained by dissolution of appropriate amounts of tested compounds **7**–**12** in fixed volumes of DMSO.

It must be mentioned that for fungi, Sabouraud agar medium with dextrose was used (4%, SDA), and for bacteria a Standard I nutrient agar medium was used, both from Merck (Schwalbach Hesse, Germany).

Microorganism suspensions were prepared using the method of successive agar dilutions according to the standard MIC (Usta et al. 2007) and their cultivation was carried out according to standard procedures (SR-EN 1275:2006 and NCCLS guidelines) (NCCLS 2003). The final charge-stock inoculum was prepared as 1×10^{-4} μg/mL concentration and inoculated plates were incubated at 31°C for 7 days. First observations were made after 48 h and final observations after 7 days of incubation, establishing the MIC. Observations on the results were made by visual analysis, microscopy and photography, using a stereomicroscope Novex Ap-8 Euromex (Olimpus Europa Holding G.m.b.H., Hamburg, Germany) and Olympus SZY 160 microscope (Olympus Corporation, Shinjuku, Tokyo, Japan).

4. Conclusions

Thus, starting from (+)-larixol (**3**) *via* intermediate *6-oxo-7-drimen-9α,11-diol* (**7**), the formal synthesis of (−)-pereniporin B (**1**) and (−)-cinnamosmolide (**2**) has been achieved in nine steps leading to lactone **12** in ~20% overall yield.

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