



## Stereoselective synthesis of the lichen metabolite, (+) montagnetol and its congeners as antimicrobial agents

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### ABSTRACT

In view of structural diversity, (+) montagnetol, the major metabolite of the fruticose lichen, *Roccella montagnei* was synthesized along with three of its congeners by employing highly efficient protocols. (+) Montagnetol (2*R*, 3*S*; **11**) and (-) montagnetol (2*S*, 3*R*; **5**) were synthesized in 7 and 9 steps, respectively, from L-ascorbic acid. The two new congeners **3** (2*R*, 3*R*) and **6** (2*S*, 3*S*), which differ in configuration at C-2 and C-3 positions of the (+) montagnetol, were synthesized from (-) diethyl D-tartrate and (+) diethyl L-tartrate, respectively. The synthesized compounds were evaluated *in vitro* for antimicrobial activity against two Gram-positive (*S. aureus* and *E. coli*) and two Gram-negative (*S. typhi* and *P. aeruginosa*) bacteria and one fungal strain *Candida albicans*. Interestingly, the congener **3** showed promising anti-bacterial activity (MIC: 0.062 µg/ml) against *P. aeruginosa*, whereas the congener **6** displayed potent anti-fungal activity (MIC: 0.062 µg/ml) against *C. Albicans*.

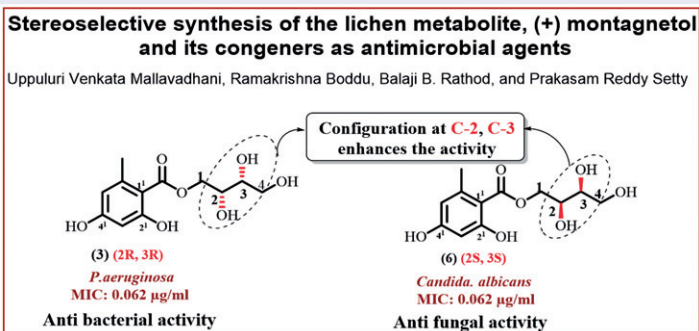
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Antimicrobial activity; diethyl tartrate; L-ascorbic acid; montagnetol; *Roccella montagnei*;

### GRAPHICAL ABSTRACT

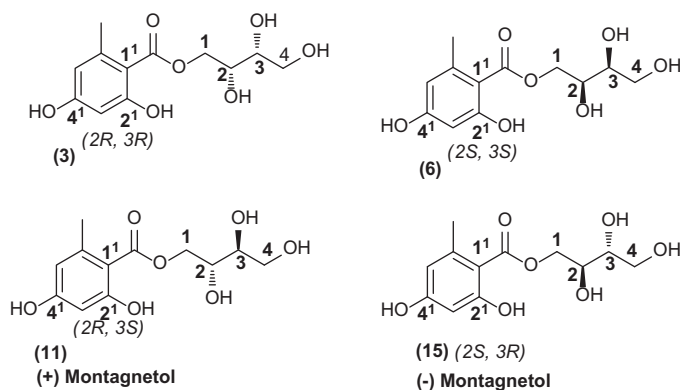


## Introduction

Lichens are one of the most important and rich natural sources for food, perfume, dyes, traditional and folk medicine for the past several centuries.<sup>[1–5]</sup> The lichenized fungi

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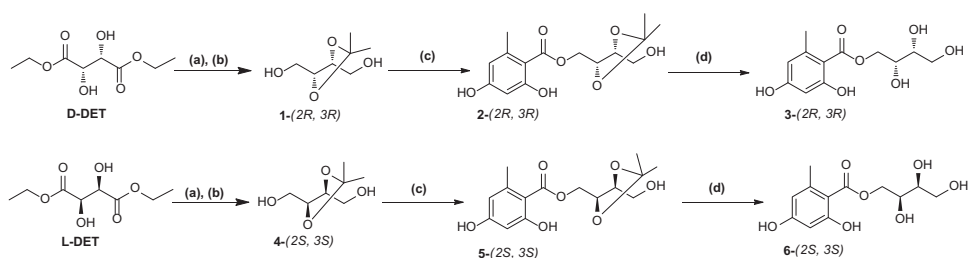
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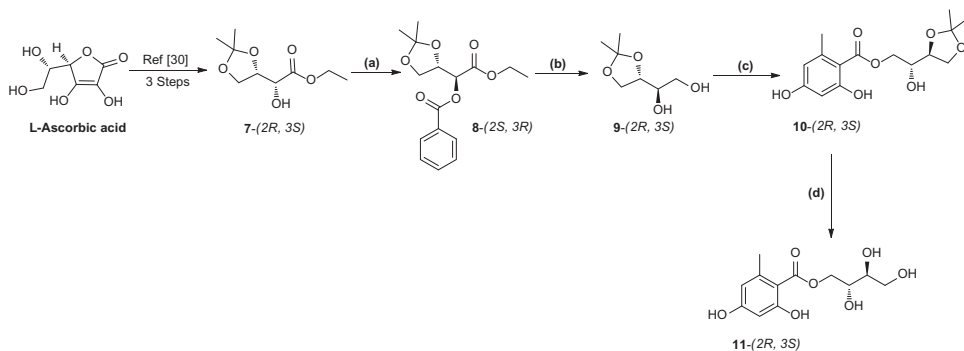
**Figure 1.** Montagnetol and its isomers.

produce a variety of secondary metabolites, which are unique and mostly phenolic in nature.<sup>[6–9]</sup> The lichen secondary metabolites exhibit promising and diverse biological activities, including anti-bacterial, anti-fungal, anti-inflammatory, anti-oxidant, anti-viral and anti-cancer.<sup>[10–16]</sup> The lichen genus *Roccella* of Roccellaceae family comprises of 40 species, which are distributed throughout the world.<sup>[17]</sup> *Roccella* species were used widely as sources for dyes and also in traditional medicine for diarrhea, cough, fever and inflammatory diseases.<sup>[18–20]</sup> Among the *Roccella* sp., *Roccella montagnei*, a fruticose lichen, produces biologically active secondary metabolites such as erythrin, roccellic acid, montagnetol, usnic acid, methyl orsellinate, and ergosterol.<sup>[21–22]</sup> Literature survey reveals that the thallus extracts of *R. montagnei* and some of its chemical constituents found with significant biological activities such as anti-viral, anti-microbial, anti-oxidant, anti-inflammatory, and anti-cancer.<sup>[23–25]</sup> However, systematic studies on the biological activities of montagnetol, the major metabolite of *R. montagnei* have not yet been done.

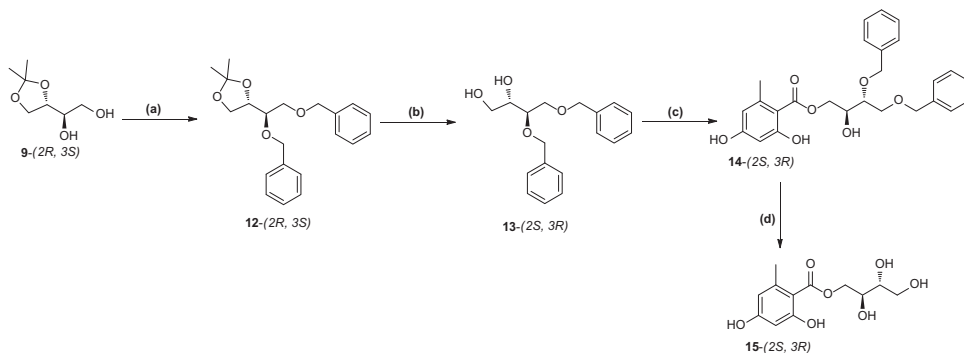
(+) Montagnetol, an erythrityl ester of orsellinic acid is found abundantly in the lichen *R. montagnei*.<sup>[26]</sup> Rao and Seshadri were the first to isolate montagnetol from *R. montagnei* and its structure was established on the basis of degradative studies without confirming their configuration.<sup>[27]</sup> In an attempt to confirm its structure, the same group synthesized racemic montagnetol from cis-2-butene-1,4-diol.<sup>[28]</sup> Barrett and coworkers reported an efficient biomimetic synthesis of (+) and (–) montagnetol from 1,3-dioxin-4-one.<sup>[29]</sup> Kumbaraci et al., synthesized (–)-montagnetol from commercially available orsellinic acid and erythritol.<sup>[30]</sup> Recently, we have reported the isolation of (+) montagnetol from *Roccella montagnei* in 4.66% yield and its structure was established by physical, chemical, and spectral data.<sup>[31]</sup> In fact, montagnetol can exist in any of the four possible isomeric forms (Figure 1). In order to compare the isolated montagnetol with the four possible structures and also for detailed biological studies to evaluate their anti-microbial potential, we have now taken up the synthesis of montagnetol along with three of its congeners. In this study, a new and short synthetic protocol has been employed to obtain (+) and (–) montagnetols from L-ascorbic acid. The various steps of the synthesis are summarized as follows: synthesis of  $\alpha$ -hydroxyl ester from L-ascorbic acid followed by Mitsunobu reaction, reduction, esterification and deprotection. The congeners **3** and **6** were synthesized from D and L diethyl tartrate, respectively, in good yields. The synthesized compounds were evaluated *in vitro* for their anti-microbial potential against two Gram-positive (*S. aureus*, *E. coli*) and two Gram-negative (*S. typhi*, *P. aeruginosa*) bacteria and anti-fungal activity against *C. albicans*.



**Scheme 1.** Synthesis of compounds **3** and **6**. Reaction Condition: (a) 2,2-DMP, *p*-TsOH, dry acetone, rt, 12 h; (b) LAH, dry THF, 70 °C, 1 h; (c) DCC, DMAP, THF, rt, 3 h; (d) *p*-TsOH, MeOH, rt, 1 h.



**Scheme 2.** Synthesis of (+) Montagnitol **11**. Reaction Condition: (a)  $\text{Ph}_3\text{P}$ , DEAD,  $\text{PhCOOH}$ , dry THF, rt, 12 h; (b) LAH, dry THF, 12 h; (c) Orsellinic acid, DCC, DMAP, THF, rt 3 h; (d) *p*-TsOH, MeOH, rt, 1 h.



**Scheme 3.** Synthesis of (-) Montagnitol **15**. Reaction Condition: (a) NaH, BnBr, DMF, rt, 12 h; (b) PTSA, MeOH, rt, 1 h; (c) orsellinic acid, DCC, DMAP, THF, rt 3 h, (d) Pd/C,  $\text{H}_2$ , EtOAc, 3 h.

## Results and discussion

### Chemistry

The (+) montagnitol (**11**) and three of its congeners (**3**, **6**, and **15**) were synthesized from commercially available starting material presented in Schemes 1, 2, and 3. As shown in Scheme 1, compound **3** (2*R*, 3*R*) and **6** (2*S*, 3*S*) were synthesized from (-) diethyl D-tartrate and (+) diethyl L-tartrate, respectively. Diols **1** (2*R*, 3*R*) and **4** (2*S*, 3*S*) were prepared from diethyl tartrate in two steps,<sup>[32,33]</sup> which were subjected to

**Table 1.** Physical properties of synthesized compounds.

| Compound number        | Optical rotation [ $\alpha$ ]D20 | Ret. time |
|------------------------|----------------------------------|-----------|
| 3                      | -24.93 ( $c = 0.4$ , MeOH)       | 1.621     |
| 6                      | +21.02 ( $c = 0.43$ , MeOH)      | 1.708     |
| 11                     | +17.12 ( $c = 0.38$ , MeOH)      | 1.687     |
| 15                     | -10.36 ( $c = 0.6$ , MeOH)       | 1.679     |
| Montagnetol (Isolated) | +16.8 ( $c = 0.4$ , EtOH)        | 1.689     |

further mono esterification with orsellinic acid in presence of DCC and DMAP in THF at room temperature for 3 h to afford compounds **2** (2*R*, 3*R*) and **5** (2*S*, 3*S*) in 76 and 73% yields, respectively. Subsequent deprotection of the compounds **2** and **5** with TsOH in MeOH at room temperature for 1 h afforded compounds **3** (2*R*, 3*R*) and **6** (2*S*, 3*S*) in 90 and 95% yields, respectively. The structures of compounds **3** and **6** were established by physical and spectral data (IR,  $^1\text{H}$ ,  $^{13}\text{C}$  NMR, and HRMS). Compounds **3** and **6** showed the characteristic peaks in  $^1\text{H}$  NMR spectra at  $\delta$  2.50–2.52 and  $\delta$  6.22–6.27, respectively, indicating the aromatic methyl and two aromatic protons. The  $^{13}\text{C}$  NMR spectra of compounds **3** and **6** showed signals at  $\delta$  172.25 and  $\delta$  172.03 corresponding to carbonyl carbon in ester functionalities.

The (+) montagnetol (2*R*, 3*S*; **11**) was synthesized from L-ascorbic acid, which was converted into the  $\alpha$ -hydroxy ester (2*R*, 3*S*; **7**) in 76% yield.<sup>[34]</sup> Inversion of configuration at C-2 of  $\alpha$ -hydroxy ester **7** under the Mitsunobu conditions by using benzoic acid, triphenylphosphine, diisopropylazodicarboxylate (DIAD) in dry tetrahydrofuran at room temperature afforded the desired compound (2*S*, 3*R*; **8**) in 82% yield. Configuration at C-2 position of compound **8** was confirmed by its optical rotation and spectral data. The  $^1\text{H}$  NMR spectra of compound **8** showed doublet at  $\delta$  5.35 and the coupling constant of the C-2 and C-3 hydrogen atoms showed  $J = 4.27$  Hz, which indicates the two hydrogens are in anti-relation. The two ester groups of compound **8** (2*S*, 3*R*) were reduced by the  $\text{LiAlH}_4$  in dry THF to afford diol **9** (2*R*, 3*S*) in 82% yield. The selective esterification of diol **9** (2*R*, 3*S*) with orsellinic acid was achieved in THF under the DCC and DMAP conditions to furnish compound **10** (2*R*, 3*S*). This on further deprotection with TsOH in MeOH afforded (+) montagnetol **11** (2*R*, 3*S*) in 98% yield (Scheme 2).

Similarly, synthesis of (-) montagnetol **15** (2*S*, 3*R*) was synthesized from diol **9** (2*R*, 3*S*). The free hydroxy groups in diol **9** were protected with 2 equivalence of benzyl bromide in presence of sodium hydride in dry DMF solvent provided compound **12** (2*R*, 3*S*) in 92% yield, this was further deprotected with TsOH in MeOH solvent afforded compound **13** (2*S*, 3*R*). The esterification of primary hydroxy group in diol **13** with orsellinic acid under DCC, DMAP in THF at room temperature provided compound **14** (2*S*, 3*R*) in 60% yield. Finally, hydrogenolysis removed benzyl protecting group from **14** to give (-) montagnetol **15** (2*S*, 3*R*) (Scheme 3). The structures of the synthesized (+) and (-) montagnetols were confirmed by physical (Table 1) and spectral data and by comparison with literature data.<sup>[29,30]</sup>

## Biology

Anti bacterial and anti fungal activity for (+) montagnetol, along with congeners (**3**, **6**, and **11**) were evaluated using four bacterial (*P. aeruginosa*, *S. typhi*, *S. aureus*, and *E.*

**Table 2.** Zone of inhibition of synthetic compounds (mm).

| Compound number | Microorganisms       |                 |                  |                |                    |
|-----------------|----------------------|-----------------|------------------|----------------|--------------------|
|                 | Bacterial strains    |                 |                  |                | Fungal strains     |
|                 | <i>P. aeruginosa</i> | <i>S. typhi</i> | <i>S. aureus</i> | <i>E. coli</i> | <i>C. albicans</i> |
| 3               | 15                   | 13              | 10               | 9              | 10                 |
| 6               | 10                   | 10              | 11               | 11             | 15                 |
| 11              | 10                   | 9               | 10               | 8              | 10                 |
| 15              | 10                   | 11              | 10               | 10             | 10                 |
| Streptomycin    | 25                   | 24              | 25               | 22             | 20                 |

**Table 3.** *In vitro* antibacterial and antifungal activity of montagnetol and its isomers ( $\mu\text{g/mL}$ ).

| Compound number | Microorganism        |                 |                  |                |                    |
|-----------------|----------------------|-----------------|------------------|----------------|--------------------|
|                 | Bacterial strains    |                 |                  |                | Fungal strains     |
|                 | <i>P. aeruginosa</i> | <i>S. typhi</i> | <i>S. aureus</i> | <i>E. coli</i> | <i>C. albicans</i> |
| 3               | 0.062                | 0.125           | 0.125            | 0.5            | 0.125              |
| 6               | 0.25                 | 0.25            | 0.5              | 0.25           | 0.062              |
| 11              | 0.25                 | 0.25            | 0.5              | 0.5            | 0.125              |
| 15              | 0.5                  | 0.25            | 0.5              | 0.25           | 0.125              |
| Streptomycin    | 0.015                | 0.015           | 0.007            | 0.125          | 0.031              |

*coli*) and one yeast strain (*C. albicans*). Well plate method is followed for both antibacterial and antifungal activities evaluation by measuring the zone of inhibitions. For antibacterial activity, test strains used include *Escherichia coli*, *Salmonella typhi*, *Staphylococcus aureus*, and *Pseudomonas aeruginosa*, which were grown in nutrient agar. For antifungal studies test strains used are *Candida albicans* and the medium used is yeast extract peptone dextrose. The compounds (3, 6, 11, and 15), along with standard (Streptomycin) were used for activity studies were dissolved DMSO to get a final concentration of 1.0 mg/ml. DMSO as such used as control. The media, petri dishes were autoclaved at 121 °C for 15 min. After sterilization the plates were poured with appropriate medium, kept for 30 min at room temperature for solidification.<sup>[35]</sup> Later the plates were inoculated with 60  $\mu\text{l}$  of test inoculums using sterile cotton swabs. An 8 mm width size wells were made with sterile cork borer and in each well exactly 100  $\mu\text{l}$  of sample were loaded. Control and standard also placed in separate wells. The plates were initially incubated for 20–30 min at 4 °C to allow the compounds to diffuse into the agar, and then subsequently incubated for 24 h at 37 °C for bacteria and 48 h at 28 °C for fungi. Zone diameters were expressed in mm using calibrated scale. Experiment was triplicate to minimize the deviations. The bio activity profile of synthesized compounds is presented in Tables 2 and 3.

It is evident from the data that limited inhibition of growth of all selected microbial strains was observed with starting compound i.e., (+) montagnetol. The derivatives of montagnetol however, slightly differed with anti microbial properties. This can be evidenced from the fact that compound 3 revealed antibacterial activity against *P. aeruginosa* where the zone of inhibition was noticed to be 15 mm while this compound against *S. typhi* showed lesser antibacterial activity (13 mm) compared to *P. aeruginosa*. There was no variation was noticed in terms of bioactivity profile with other tested bacterial strains (*S. aureus* and *E. coli*). However, the compound 6 did not show any inhibitory activity against all tested bacterial and revealed its effectiveness against *C.*

*albicans*. This data further suggested that configuration change of hydroxyl group at C-2 and C-3 positions observed to be critical for certain microbial growth inhibition as noticed that compound **6** inhibited growth of fungal strain (*C. albicans*) while compound **3** did not show any effect on *C. albicans*. To evaluate the MIC (minimum inhibitory concentration), the compounds were serially diluted from 500 to 1.9 µg/ml and one tube without drug serves as control. All the tubes were inoculated with 1 ml of respective cultures (*P. aeruginosa*, *S. typhi*, *S. aureus*, *E. coli* and *C. albicans*) having an OD of 0.2 (~McFarland standard) and the tubes were incubated at 37 °C for 12–16 h. The turbidity of each tube was measured with respect to control tube. MIC values are defined as the lowest concentration of compound at which growth is completely inhibited.<sup>[36]</sup> After incubation the culture from each tube was plated in nutrient agar to evaluate the MBC concentration. The concentration at which the cells are completely dead was defined as minimum bactericidal concentration. The MIC and MBC, results showed that compound **3** had very lower MIC (0.062 µg/ml) and MBC (0.125 µg/ml) values against *P. aeruginosa* and *C. albicans*, indicating the potential nature these compounds (Table 3).

## Conclusions

In conclusion, we have synthesized (+) montagnetol **11** (2R, 3S) along three of its congeners **3** (2R, 3R), **6** (2S, 3S) and **15** (2S, 3R) from commercially available starting materials. The synthesized compounds were evaluated for their antimicrobial potential. Interestingly, compound **3** was found to exhibit promising anti-bacterial against *P. aeruginosa*, and compound **6** displayed potent anti-fungal activity against *C. albicans*. The MIC values of compounds **3** and **6** found many folds more than montagnetol. The configuration of compound **3** and **6** at C-2 and C-3 position seems to be responsible for the enhanced anti-bacterial and anti-fungal activities.

## Experimental

This includes general procedure for the synthesis of compounds. Experimental procedures for the intermediate and spectral data of all compounds are presented in [supporting information](#).

### (2S,3R)-2,3,4-trihydroxybutyl 2,4-dihydroxy-6-methylbenzoate (**15**)

A suspension of compound **14** (200 mg, 0.44 mmol) and 10% palladium/carbon (50 mg) in dry ethyl acetate (5 mL) was stirred in H<sub>2</sub> for 2 h (TLC control). The suspension was then filtered through celite, and the filtrate was evaporated. The residue was purified by column chromatography using chloroform and methanol get the desired compound solid **15** (98 mg, 82%) as white colored solid; mp: 138–139 °C; IR (KBr, cm<sup>-1</sup>): 3372, 2926, 1642, 1581, 1458, 1322, 1271, 1168, 1038; <sup>1</sup>H NMR (300 MHz, acetone-*d*<sub>6</sub>): δ 11.56 (s, 1H), 9.43 (s, 1H), 6.27 (d, *J* = 2.44 Hz, 1H), 6.22 (d, *J* = 2.44 Hz, 1H), 4.59 (dd, *J* = 11.49, 2.8 Hz, 1H), 4.41 (dd, *J* = 11.49, 6.49 Hz, 2H), 4.20 (s, 1H), 3.95–3.97 (m, 2H), 3.82–3.77 (m, 1H), 3.70–3.66 (m, 2H), 2.51 (s, 3H); <sup>13</sup>C NMR

(125 MHz, acetone- $d_6$ +CDCl<sub>3</sub>):  $\delta$  173.22, 166.82, 163.97, 145.31, 113.03, 106.22, 102.36, 73.67, 71.93, 68.65, 65.26, 25.39; HRMS (ESI):  $m/z$  calcd for C<sub>12</sub>H<sub>16</sub>NaO<sub>7</sub> [M + Na]<sup>+</sup> 295.0788, found 295.0778.

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