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Chemomicrobial synthesis of (*R*)- and (*S*)-lavandulol

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ABSTRACT

(*R*)- and (*S*)-Lavandulol are important compounds in the cosmetics industry and in pheromone research. We have developed syntheses of (*R*)- and (*S*)-lavandulol from (*S*)- and (*R*)-limonene, respectively, by microbial Baeyer–Villiger oxidation of the intermediate unsaturated hydroxy ketone. It has been found that the same strain of *Acremonium roseum* can be successfully used in the key step of the synthesis of both enantiomers of lavandulol.

(*R*)-Lavandulol (**6-R**) and its acetate (**5-R**) are valuable components of French lavender oil, but their content in it amounts to only about 1–3%.[1] According to recent findings, a richer source of these compounds is the essential oil obtained from *Tanacetum* sp. (23–35%, of unknown configuration).[2] (*R*)-Lavandulol and its esters have been identified in the pheromones of some global insect pests.[3]

The (*S*)-enantiomer (**6-S**), like the senecioate and isovalerate esters, has been identified in the female sex pheromones of the vine mealybug.[4] For several years, it has been known that it is only the (*R*)-enantiomer which has the fresh odor reminiscent of herbs and lemon, while its antipode is almost odorless.[5] So, easy access to the two lavandulol enantiomers is of importance both in perfumery and in control of insect populations. Lavandulol is an acyclic monoterpene alcohol inconsistent with the isoprene rule, and thus its carbon skeleton may not be obtained by ordinary isomerization (rearrangement) of popular terpene hydrocarbons such as pinene, myrcene, or limonene, which are commonly used for the production of regular terpene alcohols (linalool, citronellol, menthol, α-terpineol). Even though a number of papers have been published concerning the synthesis of both lavandulol enantiomers **6** and enzymatic separation of their racemate,[5–7] the only commercially available substances are racemic lavandulol and its acetate. This work presents an efficient method for the synthesis of (*R*)- and (*S*)-lavandulol (**6-R** and **6-S**) from (*S*)- and (*R*)-limonene, respectively. In view of its low cost and ready availability of both enantiomers, limonene represents an ideal starting material for a practical synthesis of lavandulol (Scheme 1).

Both enantiomeric ketoaldehydes **1** are easily obtainable from limonenes.[8] In our study, **1-S** {97% pure, GC; ($[\alpha]_D^{22}$ −12.3 (*c* 2.3, $CHCl_3$)} was obtained by ozonolysis of (*S*)-limonene, and **1-R** {98% pure, GC; ($[\alpha]_D^{21}$ +15.2 (*c* 1.6, $CHCl_3$)} by ozonolysis of (*R*)-limonene.[8g] Our strategy of a two-step reconstruction of the carbon skeleton of lavandulol relies on the addition of two carbon atoms in a Grignard reaction and a subsequent loss of two carbon atoms in a Baeyer–Villiger reaction. Our initial attempts to shorten the chain in ketone **3** through a Baeyer–Villiger oxidation with *m*-chloroperbenzoic acid or with bis-trimethylsilyl peroxide, which is supposed to provide selective oxidation in the presence of C=C[9] bonds, were completely unsuccessful. On the other hand, the enzymatic Baeyer–Villiger oxidation is known to tolerate unsaturation in substrates[10] and the microbial B.V. oxidation is known on a kilogram scale.[11] Therefore, with a view to the synthesis of a sensory-active (*R*)-lavandulol (**6-R**), we attempted to conduct a biotransformation of hydroxy ketone **3-S** ($[\alpha]_D$ −4.83) using microorganisms.

On the basis of published results concerning the catalytic activity of the strains *Rhodotorula rubra* AM4, *Rhodotorula* marina AM77 and *Acremonium roseum* AM346 in Baeyer–Villiger oxidation reactions, we chose these microorganisms for the screening procedure.[12] In the biotransformation of hydroxy ketone **3-S** whole enzymatic systems that have wild strains of *R. rubra* AM4, *R. marina* AM77 and *A. roseum* AM346 were used. The screening procedure led to the selection of *A. roseum* AM346 for the preparative transformation. This strain converted hydroxy ketone **3-S** in high yield into diol **4-R** through Baeyer–Villiger oxidation followed

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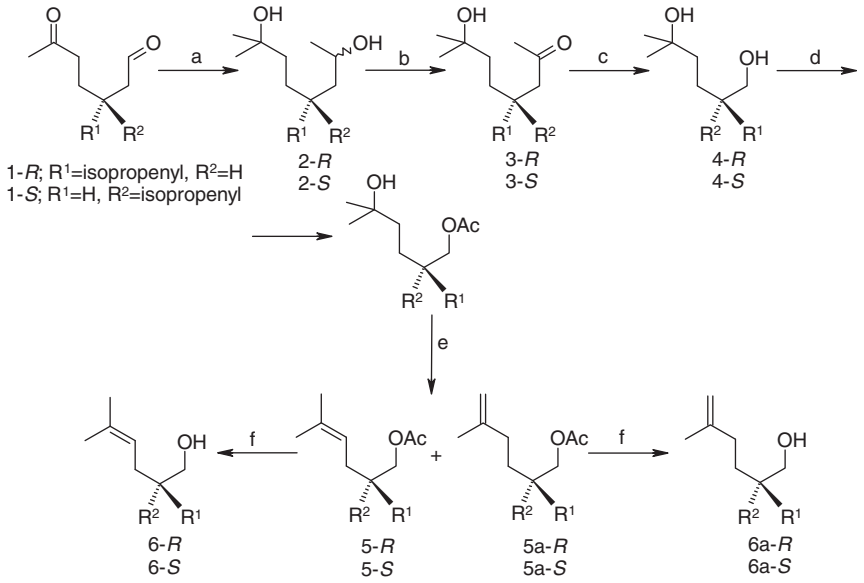

Scheme 1. Reagents and conditions: (a) MeMgCl, THF, 30 °C, 87%; (b) PCC, CH_2Cl_2, 72%; (c) *Acremonium roseum*, 11–18 days, 81–92%; (d) Ac_2O, py, 8 °C, 16 h, 94% (crude material); (e) $SOCl_2$, Et_3N, rt, 60% (crude material); (f) NaOH, MeOH, H_2O, 89% (crude material).

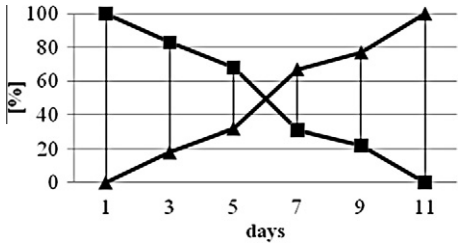

Figure 1. Time course (according to GC) in the biotransformation of **3-S** by *A. roseum* AM346.

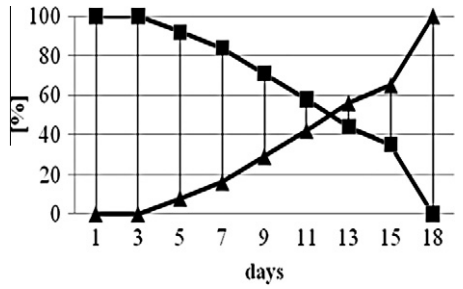

Figure 2. Time course (according to GC) in the biotransformation of **3-R** by *A. roseum* AM346.

by hydrolysis. The transformation process was monitored by means of TLC and GC analysis. After 3 days of incubation in a culture of *A. roseum* AM346, the amount of **3-S** gradually started to decrease whereas the amount of diol **4-R** increased in proportion (Fig. 1).

This product was isolated after 11 days in a 92% yield (191 mg from 240 mg of substrate) with 82% ee by chiral-GC ($[\alpha]_D$ −4.92). In the light of the above result, it was important to find out whether this key step in lavandulol synthesis could also be conducted with the other enantiomeric hydroxy ketone **3-R** ($[\alpha]_D$ +6.00) using the same microorganism. The biotransformation of hydroxy ketone **3-R** in a culture of *A. roseum* AM346 gave diol **4-S** as the only product of the Baeyer–Villiger oxidation. The time course of diol formation was measured by TLC and GC (Fig. 2).

To isolate the product, a large-scale incubation of hydroxy ketone **3-R** by *A. roseum* AM346 was carried out for 18 days. After the biotransformation, the culture was extracted as described in the Experimental Section in the Supplementary data, and the metabolic product (**4-S**) was isolated in an 81% yield (266 mg from 380 mg of substrate) as the pure *S*-enantiomer (100% ee by chiral-GC, $[\alpha]_D$ +6.14). It seems that one of the reasons for such a high yield from the biotransformations and for the product purity is the relatively good solubility of the hydroxy ketone **3** in the aqueous microbiological medium. After selective acetylation, diol **4-R** was dehydrated by thionyl chloride in triethylamine, yielding a mixture of lavandulyl acetate (**5-R**) and isolavandulyl acetate (**5a-R**) in a ratio of 1:1. Alkaline hydrolysis of the acetates resulted in the formation of a mixture of alcohols **6-R** and **6a-R** which were then separated on a silica gel column impregnated by silver nitrate to deliver pure (*R*)-lavandulol (**6-R**; 80% ee, chiral-GC) and (*R*)-isolavandulol (**6a-R**; 95% pure, GC).

In summary, we have developed a novel chemomicrobial procedure to synthesize optically active lavandulol from natural limonene. The methodology developed is suitable for the preparation of both enantiomers of lavandulol, the optical purity of which is dependent on the ee of the limonene used. This sequence represents the first application of limonene and the first application of microbial Baeyer–Villiger oxidation for the synthesis of a natural monoterpene alcohol inconsistent with the isoprene rule.

Supplementary data

Supplementary data (experimental procedures and characterization data for all new compounds along with copies of ^1H, ^{13}C NMR spectra) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.06.072.

References and notes

1. (a) Schinz, H.; Seidel, C. F. *Helv. Chim. Acta* **1942**, *25*, 1572; (b) Schinz, H.; Bourquin, J. P. *Helv. Chim. Acta* **1942**, *25*, 1591; (c) Bohlmann, F.; Zdero, C.; Faass, U. *Chem. Ber.* **1973**, *106*, 2904.

2. (a) Verma, M.; Singh, S. K.; Bhushan, S.; Pal, H. C.; Kitchlu, S.; Koul, M. K.; Thappa, R. K.; Saxena, A. K. *Planta Medica* **2008**, *74*, 515–520; (b) Kitchlu, S. K.; Kaul, M. K.; Bhan, M. K.; Thapa, R. K.; Agarwal, S. G. *Flavour Fragr. J.* **2006**, *21*, 690; (c) Zohreb, H.; Tayebeh, B.; Tahereh, G.; Shiva, M.; Abdolhossein, R. *J. Essent. Oil Res.* **2007**, *19*, 11; (d) Lampasona, M. E. P.; Catalan, C. A. N.; Gedris, T. E.; Herz, W. *Phytochemistry* **1997**, *46*, 1077.
3. (a) Ho, H.-Y.; Su, Y.-T.; Ko, C.-H. *J. Chem. Ecol.* **2009**, *35*, 724; (b) Cross, J. V.; Hesketh, H.; Jay, C. N.; Hall, D. R.; Innocenzi, P. I.; Farman, D. I.; Burgess, C. M. *Crop Protection* **2006**, *25*, 144; (c) Hamilton, J. G. C.; Hall, D. R.; Kurk, W. D. J. *J. Chem. Ecol.* **2005**, *31*, 1369; (d) Zhang, A.; Amalin, D.; Shirali, S.; Serrano, M. S.; Franqui, R. A.; Oliver, J. E.; Klun, J. A.; Aldrich, J. R.; Meyerdirk, D. E.; Lapointe, S. L. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 9601; (e) Eisner, T.; Deyrup, M.; Jacobs, R.; Meinwald, J. *J. Chem. Ecol.* **1986**, *12*, 1407.
4. (a) Zada, A.; Dunkelblum, E.; Assael, F.; Harel, M.; Cojocaru, M.; Mendel, Z. *J. Chem. Ecol.* **2003**, *29*, 977; (b) Hinkens, D. M.; McElferesh, J. S.; Millar, J. G. *Tetrahedron Lett.* **2001**, *42*, 1619.
5. Sakauchi, H.; Kiyota, H.; Takigawa, S.; Oritani, T.; Kuwahara, S. *Chem. Biodiv.* **2005**, *2*, 1183.
6. (a) Zhang, A.; Nie, J. *J. Agric. Food Chem.* **2005**, *53*, 2451; (b) Metha, G.; Karmakar, S.; Chattopadhyay, S. K. *Tetrahedron* **2004**, *60*, 5013; (c) Faure, S.; Piva, O. *Synlett* **1998**, 1414; (d) Piva, O. *J. Org. Chem.* **1995**, *60*, 7879; (e) Cardillo, G.; D'Amico, A.; Orena, M.; Sandri, S. *J. Org. Chem.* **1988**, *53*, 2354.
7. (a) Zada, A.; Dunkelblum, E. *Tetrahedron: Asymmetry* **2006**, *17*, 230; (b) Cross, H.; Marriott, R.; Grogan, G. *Biotechnol. Lett.* **2004**, *26*, 457; (c) Olsen, T.; Kerton, F.; Marriott, R.; Grogan, G. *Enzym. Microb. Technol.* **2006**, *39*, 621; (d) Zada, A.; Harel, M. *Tetrahedron: Asymmetry* **2004**, *15*, 2339.
8. (a) Binder, C. M.; Bautista, A.; Zaidlewicz, M.; Krzeminski, M. P.; Oliver, A.; Singaram, B. *J. Org. Chem.* **2009**, *74*, 2337; (b) Srikrishna, A.; Babu, N. C. *Tetrahedron Lett.* **2001**, *42*, 4913; (c) Breitenbach, R.; Chiu, C. K.-F.; Massett, S. S.; Meltz, M.; Murtiashaw, C. W.; Pezzullo, S. L.; Staigers, T. *Tetrahedron: Asymmetry* **1996**, *7*, 435; (d) Auer, L.; Weymuth, C.; Scheffold, R. *Helv. Chim. Acta* **1993**, *76*, 810; (e) Wu, X. M.; Funakoshi, K.; Sakai, K. *Tetrahedron Lett.* **1992**, *33*, 6331; (f) Ronchetti, F.; Toma, L. *Tetrahedron* **1986**, *42*, 6535; (g) Kula, J.; Podlejski, J. *Liebigs Ann. Chem.* **1985**, 2098; (h) Wolinsky, J.; Slabaugh, M. R.; Gibson, T. *J. Org. Chem.* **1964**, *29*, 3740.
9. Gottlich, R.; Yamakoshi, K.; Sasai, H.; Shibasaki, M. *Synlett* **1997**, 971.
10. Taschner, M. J.; Peddada, L. *J. Chem. Soc., Chem. Commun.* **1992**, 1384.
11. Hilker, I.; Wohlgemuth, R.; Alphand, V.; Furstoss, R. *Biotechnol. Bioeng.* **2005**, *92*, 702.
12. Gliszczynska, A.; Wawrzenczyk, C. *J. Mol. Catal. B: Enzym.* **2008**, *52–53*, 40–48.