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High-speed microwave-promoted Mitsunobu inversions. Application toward the deracemization of sulcatol

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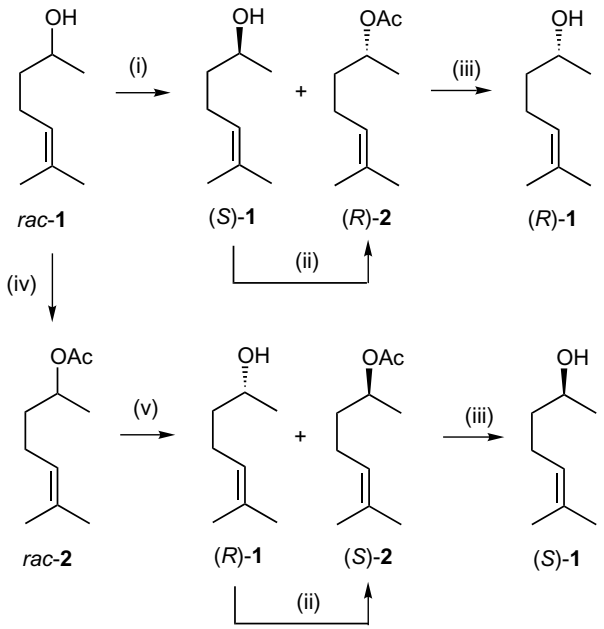
Abstract—An enantioconvergent synthesis of the aggregation pheromones (*R*)- and (*S*)-sulcatol (6-methyl-5-hepten-2-ol) is described. Key steps in the deracemization strategy are sequential combinations of enzymatic resolutions and Mitsunobu inversions. Racemization-free Mitsunobu transformations have been carried out within 5 min by microwave irradiation, providing the desired sulcatyl acetates with clean inversion of chirality. © 2001 Elsevier Science Ltd. All rights reserved.

High-speed microwave-assisted chemistry has attracted a considerable amount of attention in recent years and has been applied successfully in various fields of synthetic organic chemistry,[1–9] including cycloaddition reactions,[2] heterocycle synthesis,[3] solid- and fluorous-phase protocols,[4,5] drug discovery,[6] and the rapid preparation of radiolabeled materials.[7] Since the rate-acceleration effect in microwave-assisted reactions is essentially based on a rapid heating of the reaction mixture leading to unconventionally high reaction temperatures,[8] it is not surprising that the application of this methodology toward more delicate transformations, such as e.g. stereoselective synthesis has so far been limited. This is particularly true for enantioselective reactions, which normally require low temperatures in order to achieve high selectivities.[9]

One of the most powerful stereochemical transformations is the Mitsunobu reaction.[10] This transformation was found to be very efficient to invert the configuration of chiral secondary alcohols since a clean S_N2 process is generally observed ('Mitsunobu inversion').[10] A particularly valuable application of the Mitsunobu chemistry is its sequential combination with an enzymatic kinetic resolution step. In order to avoid the occurrence of an undesired enantiomer during an enantioselective enzymatic acylation, the remaining unreacted alcohol can be esterified with inversion via the Mitsunobu protocol to provide a single stereoisomer in 100% theoretical yield. Due to the apparent symmetry of enzymatic acylation and ester hydrolysis, either enantiomer can generally be accessed in high yield.[11]

Here we describe an application of the above strategy toward the deracemization of sulcatol (**1**), the male-produced aggregation pheromone of the ambrosia beetles



Scheme 1. *Reagents and conditions*: (i) *C. antarctica B* lipase (35 mg/mmol **1**), vinyl acetate (2.7 equiv.), hexane, 30°C, 30 h; (ii) see Table 1; (iii) $LiAlH_4$, THF, rt, 30 min; (iv), Ac_2O, DMAP (cat.), CH_2Cl_2, 42°C, 12 h; (v) *C. antarctica B* lipase (40 mg/mmol **2**), phosphate buffer, pH 7.5, 30°C, 30 h.

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Gnathotrichus sulcatus and *Gnathotrichus retusus*.[12] Several synthetic protocols for the preparation of either (*R*)- or (*S*)-sulcatol have been reported, including synthesis from chiral starting materials,[13] kinetic resolution by lipases,[14] asymmetric reduction with baker's yeast[15] or alcohol dehydrogenases,[15,16] or the reverse reaction.[17] The majority of these protocols involve cumbersome multistep transformations and provide only one of the desired enantiomers. On the contrary, the enantioconvergent approach described herein starts from commercially available *rac*-sulcatol and delivers both enantiomers in excellent enantiomeric purity and high chemical yield. The key step in our protocol relies on microwave-assisted high-speed Mitsunobu inversions providing rapid and racemization-free access to both (*R*)- and (*S*)-sulcatol. To our knowledge, this represents the first application of Mitsunobu chemistry carried out under microwave conditions.

The enantioconvergent approach to (*R*)- and (*S*)-sulcatol (**1**) is outlined in Scheme 1. *rac*-Sulcatol (**1**) was treated with vinyl acetate in the presence of *Candida antarctica B* lipase (Novo, DK). The kinetic resolution was conveniently carried out at 30°C and furnished after 30 h a 1:1 mixture of unreacted (*S*)-**1** and acetate (*R*)-**2** according to the Kazlauskas rule.[18] Excellent enantioselectivities (E >200) were achieved in a highly reproducible manner as confirmed by GC measurements [(ee >98% for (*S*)-**1** and (*R*)-**2**].[19]

The selectivity of this transformation was considerably higher than those previously reported using other lipase/solvent systems.[14] Next, we turned our attention to the Mitsunobu inversion of (*S*)-**1** to (*R*)-**2**. After removal of insoluble material by filtration and evaporation of solvent, the crude reaction mixture was subjected to typical Mitsunobu reaction conditions in anhydrous THF, using 3.5 equiv. of acetic acid in the presence of diisopropyl azodicarboxylate (DIAD) and triphenylphosphine.[10] To our surprise and disappointment, we discovered that in this case the classical Mitsunobu conditions failed. Even after considerable experimentation with respect to the nature of the solvent and the molar ratio, concentration, and addition sequence of reagents, only minor improvements were achieved. Typically, the conversion after 24 h at room temperature was around 13–17% and could not be further improved without adding fresh reagents.

We therefore considered using microwave irradiation as a tool to enhance the speed of the Mitsunobu inversion step. Since microwave chemistry invariably involves high reaction temperatures[1–9] this approach appears rather unconventional, considering the fact that Mitsunobu chemistry is typically carried out at or below room temperature.[10] As a 'proof of concept', our initial studies therefore involved racemic sulcatol as substrate. Using essentially the same conditions as for the attempted (conventional) Mitsunobu transformations described above, we soon discovered that rapid reaction rates could be achieved by irradiation of the reaction mixture in sealed glass vials employing a single-mode microwave cavity.[20] After a few optimization runs at different temperatures and reaction times it was found that complete conversion of alcohol *rac*-**1** to the acetate *rac*-**2** could be achieved after 7 min at 180°C (Table 1, entry 2). Note that despite the high reaction temperatures no byproducts could be identified in these Mitsunobu experiments. In order to ensure that any acetate **2** (being present in the reaction medium from the beginning) would not interfere with the Mitsunobu chemistry, a control experiment employing a 1:1 mixture of *rac*-**1**/*rac*-**2** was carried out (Table 1, entry 3). Having established the feasibility of the microwave-assisted Mitsunobu chemistry in the racemic series, we next moved to non-racemic substrates. Thus, mixtures of (*S*)-**1** and (*R*)-**2** obtained directly by purification through a short silica gel column (pentane/ether 5:1) from the enzymatic resolution experiments described above were subjected to the microwave Mitsunobu conditions. We were delighted to find that not only the reaction rates were as fast as in the racemic series, but also that the obtained enantiomeric purities of acetate (*R*)-**2** were ee >98% in all experiments despite the drastic reaction conditions.[19] After a second set of optimization runs (data not shown), the molar equivalents of reagents could be further reduced which also resulted in a reduction of the required irradiation time to 5 min (Table 1, entry 4).

The unusual reaction conditions employing 'microwave flash heating' deserve further comment. As seen in Fig. 1, a rapid heating of the reaction mixture can be observed. Within only 70 seconds the maximum preselected temperature of 180°C was reached, leading to an internal pressure of ca. 10–13 bar. This temperature was then kept for the remaining irradiation period

Table 1. Microwave-promoted Mitsunobu inversions under different reaction conditions in THF (2 mL)

Entry	Substrate	AcOH (equiv.)[a]	PPh_3 (equiv.)[a]	DIAD (equiv.)[a]	Temp. (°C)	Time (min)	Conv.[b]	ee (%)[b]
1	*rac*-**1** (1.3 mmol)	3.8	2.9	2.6	160	5	72	–
2	*rac*-**1** (1.3 mmol)	2.4	2.9	2.6	180	7	>99	–
3	*rac*-**1**/*rac*-**2** (0.6 mmol each)	4.2	3.0	2.5	180	7	>99	–
4	(*S*)-**1**/(*R*)-**2** (0.5 mmol each)	2.5	2.3	1.9	180	5	>99	>98
5	(*R*)-**1**/(*S*)-**2** (0.5 mmol each)	2.5	2.3	1.9	180	5	>99	>98

[a] Equivalents are based on the amount of alcohol component.
[b] Conversions (conv.) and enantiomeric purities (ee) as determined by GC (see Ref. 19).

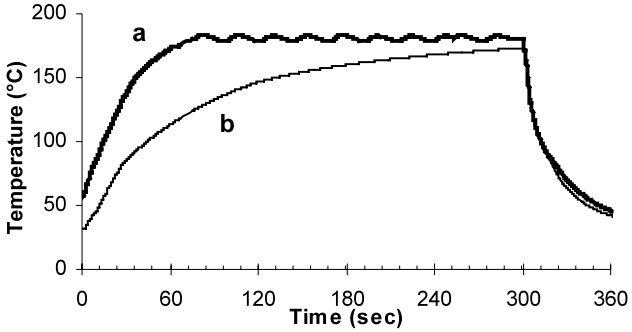

Figure 1. Heating profiles for microwave-assisted Mitsunobu inversions (**a**, for conditions see Table 1, entry 4) and pure THF (3 mL) (**b**). The initial microwave output during the heating period was 300 W in both cases. Temperatures were recorded on the outer surface of the glass vials by an IR sensor.

through regulation of the microwave output power. Importantly, the heating profile of the pure solvent differed significantly. Since THF does not effectively couple with microwave irradiation,[8] it is evident that the bulk of the microwave energy was absorbed by the substrate and reagent molecules (and possibly the ionic intermediates during the Mitsunobu reaction) which act as 'molecular radiators'.[9] Whether this effect indeed contributes to the observed rate enhancements remains unclear at this point.

The synthesis of the desired target molecule (*R*)-sulcatol was completed by reductive deacylation with $LiAlH_4$ in THF under standard reaction conditions. Based on the commercially available racemic starting material, an overall isolated yield of 80% (>98% ee) over 3 steps was achieved. In order to obtain the opposite enantiomer, (*S*)-**1**, the racemic alcohol was first (chemically) acetylated with acetic anhydride, and the resulting acetate *rac*-(**2**) was then hydrolyzed employing *C. antarctica B* lipase (Scheme 1). Again, excellent selectivities were obtained (E >200) leading to a 1:1 mixture of (*R*)-**1** and (*S*)-**2**. As expected, the microwave-promoted Mitsunobu inversion proceeded as well as for the opposite enantiomeric pairs (Table 1, entry 5) and provided acetate (*S*)-**2**, which was subsequently transformed to (*S*)-sulcatol by $LiAlH_4$ reduction. Here an overall yield of 74% (>98% ee) over four steps was achieved.

In conclusion, we have demonstrated that microwave irradiation can be successfully employed to perform rapid and racemization-free Mitsunobu inversions in cases where the conventional protocol failed. The concept of high-speed Mitsunobu chemistry was applied to an enantioconvergent synthesis of (*R*)- and (*S*)-sulcatol, which delivers both enantiomers of this pheromone and chiral building block[21] in high overall yields and excellent enantiomeric purities.

Acknowledgements

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References

1. For general reviews, see: (a) Caddick, S. *Tetrahedron* **1995**, *51*, 10403–10432; (b) Bose, A. K.; Banik, B. K.; Lavlinskaia, N.; Jayaraman, M.; Manhas, M. S. *Chemtech* **1997**, *27*, 18–24; (c) Loupy, A.; Petit, A.; Hamelin, J.; Texier-Boullet, F.; Jacquault, P.; Mathé, D. *Synthesis* **1998**, 1213–1234.
2. Review: de la Hoz, A.; Díaz-Ortis, A.; Moreno, A.; Langa, F. *Eur. J. Org. Chem.* **2000**, 3659–3673.
3. Review: Varma, R. S. *J. Heterocyclic Chem.* **1999**, *36*, 1565–1571.
4. Stadler, A.; Kappe, C. O. *Eur. J. Org. Chem.* **2001**, 919–925.
5. Olofsson, K.; Kim, S.-Y.; Larhed, M.; Curran, D. P.; Hallberg, A. *J. Org. Chem.* **1999**, *64*, 4539–4541.
6. Review: Larhed, M.; Hallberg, A. *Drug Discovery Today* **2001**, *6*, 406–416.
7. Review: Elander, N.; Jones, J. R.; Lu, S.-Y.; Stone-Elander, S. *Chem. Soc. Rev.* **2000**, 239–250.
8. (a) Langa, F.; de la Cruz, P.; de la Hoz, A.; Díaz-Ortiz, A.; Díez-Barra, E. *Contemp. Org. Synth.* **1997**, *4*, 373–386; (b) Gabriel, C.; Gabriel, S.; Grant, E. H.; Halstead, B. S. J.; Mingos, D. M. P. *Chem. Soc. Rev.* **1998**, *27*, 213–223.
9. For example, see: Kaiser, N.-F. K.; Bremberg, U.; Larhed, M.; Moberg, C.; Hallberg, A. *Angew. Chem.* **2000**, *112*, 3742–3744.
10. (a) Mitsunobu, O. *Synthesis* **1981**, 1–28; (b) Hughes, D. L. *Org. React. (N.Y.)* **1992**, *28*, 335–656; (c) Hughes, D. L. *Org. Prep. Proceed. Int.* **1996**, *28*, 127–164.
11. (a) Mitsuda, S.; Umemura, T.; Hirohara, H. *Appl. Microbiol. Biotechnol.* **1988**, *29*, 310–315; (b) For a recent application, see: Vänttinen, E.; Kanerva, L. T. *Tetrahedron: Asymmetry* **1995**, *6*, 1779–1786 and references cited therein.
12. Mori, K. *Tetrahedron* **1989**, *45*, 3233–3298.
13. Mori, K. *Tetrahedron* **1981**, *37*, 1341–1342 and references cited therein.
14. (a) Nakamura, K.; Kinoshita, M.; Ohno, A. *Tetrahedron* **1995**, *51*, 8799–8808; (b) Kinoshita, M.; Ohno, A. *Tetrahedron* **1996**, *52*, 5397–5406.
15. Belan, A.; Bolte, J.; Fauve, A.; Gourcy, J. G.; Veschambre, H. *J. Org. Chem.* **1987**, *52*, 256–260.
16. (a) Fantin, G.; Fogagnolo, M.; Giovannini, P. P.; Medici, A.; Pedrini, P. *Tetrahedron: Asymmetry* **1995**, *6*, 3047–3053; (b) Clair, N. S.; Wang, Y.-F.; Margolin, A. L. *Angew. Chem.* **2000**, *112*, 388–391.
17. Fantin, G.; Fogagnolo, M.; Medici, A.; Pedrini, P.; Fontana, S. *Tetrahedron: Asymmetry* **2000**, *11*, 2367–2373.
18. Kazlauskas, R. J.; Weissfloch, A. N. E.; Rappaport, A. T.; Cuccia, L. A. *J. Org. Chem.* **1991**, *56*, 2656.

19. All conversion rates and enantiomeric purities were analyzed by GC using a CP-Chirasil-DEX CB column (25 m, 0.32 mm, 0.25 μm film, H_2 14 psi, 100°C). Retention times [min] for **1**: 1.78 (*S*), 1.88 (*R*); for **2**: 1.95 (*S*), 2.28 (*R*). Absolute configurations were established by comparison of specific optical rotations with literature data.
20. Microwave experiments were preformed using Coherent Synthesis™ technology on a Smith Workstation employing sealed 5 mL process vials (Personal Chemistry AB, Sweden). The instrument features continuous microwave irradiation (0–300 W), online temperature (60–250°C) and pressure monitoring (1–20 bar) and built-in magnetic stirring.
21. (a) Mori, K.; Puapoomchareon, P. *Liebigs Ann. Chem.* **1989**, 1261–1262; (b) Liang, S.; Paquette, L. A. *Tetrahedron: Asymmetry* **1990**, *1*, 445–452; (c) Sugai, T.; Katoh, O.; Ohta, H. *Tetrahedron* **1995**, *51*, 11987–11998; (d) Geller, T.; Schmalz, H.-G.; Bats, J. W. *Tetrahedron Lett.* **1998**, *39*, 1537–1540.