Pergamon

Tetrahedron: *Asymmetry* 11 (2000) 1691–1695

TETRAHEDRON: *ASYMMETRY*

Enzyme-catalyzed synthesis and absolute configuration of (1*S*,2*R*,5*S*)- and (1*R*,2*S*,5*R*)-2-(1-hydroxyethyl)-1-(methoxymethyloxyethyl)cyclobutane-1-carbonitrile, key intermediates for the preparation of chiral cyclobutane-containing pheromones

I. Petschen, M. P. Bosch and A. Guerrero*

Department of Biological Organic Chemistry, Institute for Chemical and Environmental Research, CSIC, Jordi Girona 18-26, 08034 Barcelona, Spain

Received 24 February 2000; accepted 14 March 2000

Abstract

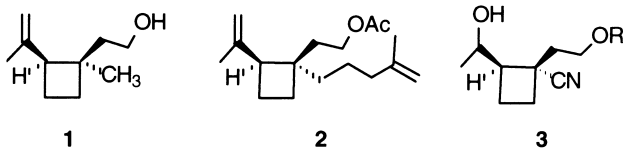
Formal synthesis of chiral grandisol and the oleander scale pheromone and their antipodes can be achieved through a convenient lipase-catalyzed enantiodifferentiation process of the common cyclobutane intermediate (±)-2-(1-hydroxyethyl)-1-(methoxymethyloxyethyl)cyclobutane-1-carbonitrile **3**. The resolution afforded both enantiomers in almost enantiomerically pure form and their absolute configurations were assigned on the basis of the $\Delta\delta$ values for their (*R*)- and (*S*)-MTPA esters.

Cyclobutane derivatives are remarkable compounds not only because they are present in the basic structure of natural products,[1] but also because they can be readily transformed into a variety of synthetically useful derivatives by further modifications, such as ring enlargement or ring opening reactions.[2] Some of them have important implications in the medical/pharmaceutical field, for instance as inhibitors of the replication of herpes symplex type-1 and type-2 viruses, varicella zoster virus, human cytomegalovirus and HIV[3] or as anti-leukemics.[4] Others are important as pest control agents, such as the cotton boll-weevil pheromone (grandisol, **1**)[5] and the oleander scale pheromone **2**[6] (Fig. 1).

Compound **3** is a common intermediate for the synthesis of grandisol (R = THP)[7] and the oleander scale pheromone (R = MOM),[6b] both in their racemic forms. Asymmetric synthesis of one or both enantiomers of grandisol have been based on crystallization of diastereomeric salts/esters,[8] transformation of homochiral starting materials of natural origin,[9] and asymmetric

* Corresponding author. E-mail: agpqob@iiqab.csic.es

0957-4166/00/$ - see front matter
PII: S0957-4166(00)00101-4

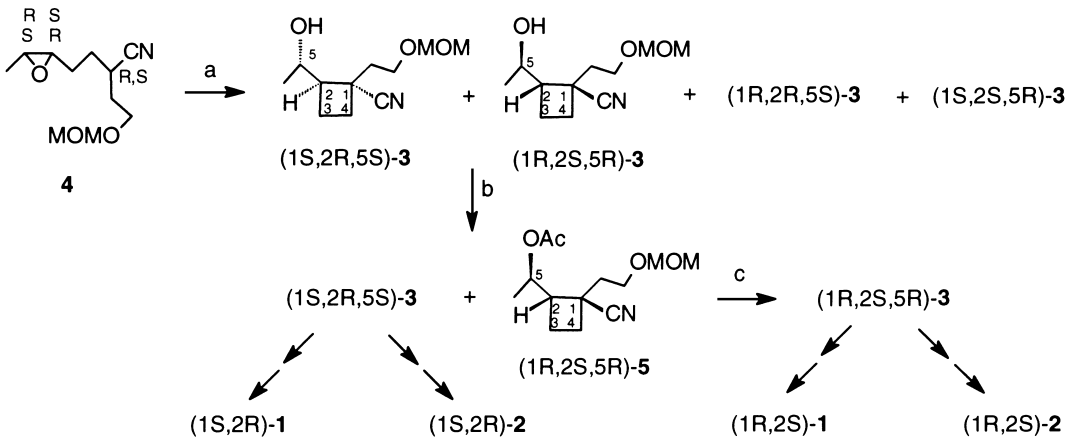


1 2 3

Figure 1.

photocycloaddition of a chiral enone with olefins,[10] among others. To our knowledge, however, in only one case was the synthesis of the active enantiomer conducted by transformation of a homochiral intermediate, which had been obtained by an enzymatic process involving stereoselective oxidation of a cyclobutane *meso*-diol with horse liver alcohol dehydrogenase.[11] We report herein the preparation for the first time of both enantiomers of the versatile cyclobutane **3** in enantiomerically pure form, and hence a formal synthesis of the enantiomers of grandisol and the oleander scale pheromone, through an efficient enzyme-induced enantiodifferentiation process.[12]

Compound **3** (R = MOM) was prepared by lithium hexamethyldisilazide-induced cyclization of δ-epoxynitrile **4** in 60% yield as 79/21 *trans*/*cis* mixture of isomers, which were separated by careful column chromatography.[6b] The reaction was regio- and stereoselective with the major isomer *trans*-**3** (48% yield) having the same relative configuration as the natural pheromones, that is with the methoxymethyloxyethyl and hydroxyethyl groups on the same side of the ring. Enantiodifferentiation of alcohol *trans*-**3** was tested by a transesterification process in the presence of different enzymes (*Pseudomonas cepacia* lipase, *Candida antarctica* lipase, *Pseudomonas fluorescens* lipase and lipase MY) in hexane and vinyl acetate as the acylating agent (Scheme 1). Lipase PS and PFL successfully esterified the (1*R*,2*S*,5*R*)-enantiomer to afford acetate (1*R*,2*S*,5*R*)-**5** and leaving unreacted the (1*S*,2*R*,5*S*)-enantiomer.[13] Homochiral acetate (1*R*,2*S*,5*R*)-**5** was hydrolyzed under mild conditions[14] and both enantiomeric alcohols duly characterized by their spectroscopic and analytical features. The yields of pure products ranged between 43 and 48% and their e.e. values were equal to or higher than 98% (E > 900 in both cases).



Scheme 1. (a) LiHMDS/benzene/**4**/0°C/3.5 h, 20°C/6 h; (b) lipase, vinyl acetate/hexane; (c) KCN/EtOH, reflux, 24 h

Enantiomeric excess values were determined on a chiral cyclodextrin GC column (Cydex B 25 m×0.22 mm, isothermal 150°C column temperature) and by ^{19}F NMR spectra of the Mosher esters of the alcohols.[15] It should be noted that, to our knowledge, only one report has been

found in the literature about utilization of lipase PS or PFL to prepare chiral cyclobutane derivatives, i.e. in the synthesis of a carbocyclic analogue of oxetanocin A through lipase PS in low e.e.[12c] and hydrolysis of a *meso*-cyclobutene diacetate with PFL in good e.e.[16] CAL was also highly effective in acylating the more reactive enantiomer in a short period of time (ee >99% after 3 h reaction) but the e.e. of the unreactive enantiomer was clearly insufficient. Lipase MY's active site did not recognize compound **3** as a proper substrate for enantiodifferentiation (Table 1).

Table 1
Chiral resolution of (1*S*,2*R*,5*S*)-**3** and (1*R*,2*S*,5*R*)-**3** through lipases

LIPASE	TIME	CONV. (%)	YIELD (%)[a] (1R,2S,5R)-**5**	E.e. (%)	YIELD (%)[a] (1S,2R,5S)-**3**	E.e. (%)	E
PS	21 h	42	41	>99	56	73	438
PS	96 h	50	43	>99	48	99	>1000
CAL	3 h 10 m	38	35	>99	58	60	368
PFL	10 h 25 m	44	40	>99	52	79	483
PFL	26 h 45 m	50	44	>99	47	98	922
MY	244 h	12	--	--	--	--	--

[a]Yields refer to pure isolated products after column chromatography purification.

Absolute configuration of the alcohols was assigned on the basis of the $\Delta\delta = \delta_S - \delta_R$ values for their (*S*)- and (*R*)-MTPA esters, as described by Kakisawa et al.[17] In the most stable conformation the ^{1}H NMR signals of the protons on the right side of the (*S*)-MTPA plane resonate at lower fields than those of the (*R*)-MTPA ester due to the diamagnetic effect of the benzene ring ($\Delta\delta > 0$). For the same reason, protons on the left side of the plane should provide negative $\Delta\delta$ values ($\Delta\delta < 0$). In our case, we prepared the (*S*)- and (*R*)-MTPA esters of both enantiomerically pure alcohols and recorded their ^{1}H NMR (300 MHz) spectra. The (*S*)-MTPA esters are shown in Fig. 2. The complete assignment of the protons was achieved by DQCOSY and HETCOR experiments and the $\Delta\delta = \delta_S - \delta_R$ values were determined. Most of the chemical shift differences were negative for the reactive enantiomer (for example, –0.064 ppm for proton at C-5, –0.042 ppm for proton at C-2 and –0.001 and –0.018 ppm for protons at C-3, among others), and the same values but positive were found for the unreactive enantiomer. As expected, the absolute magnitudes of the differences were proportional to the distance of the protons from the MTPA group. These results indicated that the absolute configuration of the lipase-recognized enantiomer should be *R* while that of the unrecognized enantiomer should be *S*. With the absolute configuration of both enantiomers established, application of the previously described methodology on (1*R*,2*S*,5*R*)-**3** should provide an efficient synthesis of grandisol[7] and the oleander scale pheromone[6b]

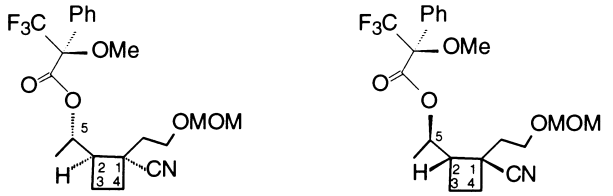


Figure 2. (*S*)-MTPA esters of (1*S*,2*R*,5*S*)-**3** (left) and (1*R*,2*S*,5*R*)-**3** (right)

in enantiomerically pure forms. Similarly, the antipodes of these pheromones could be prepared from the (1*S*,2*R*,5*S*)-enantiomer.

Acknowledgements

Financial support was provided by CICYT (projects AGF95-0185, AGF97-1217-C02-01) and Comissionat per a Universitats i Recerca (1997SGR-00021). We gratefully acknowledge Kenogard for a fellowship to I.P.

References

1. Thomas, A. F.; Bessière, Y. In *The Total Synthesis of Natural Products*; Apsimon, J., Ed. The synthesis of monoterpenes, 1980–1986. John Wiley and Sons: New York, 1988; Vol. 7, p. 275.
2. Carruthers, W. *Cycloaddition Reactions in Organic Synthesis*; Pergamon Press: New York, 1990.
3. Bisacchi, G. S.; Braitman, A.; Cianti, C. W.; Clark, J. M.; Field, A. K.; Hagan, M. E.; Hockstein, D. R.; Malley, M. F.; Mitt, T.; Slusarchyk, W. A.; Sundeen, J. E.; Terry, B. J.; Toumari, A. V.; Weaver, E. R.; Young, M. G.; Zahler, R. *J. Med. Chem.* **1991**, *34*, 1415.
4. Bloor, S. J. *Tetrahedron Lett.* **1993**, *34*, 5617.
5. Tumlinson, J. H.; Hardee, D. D.; Gueldner, R. C.; Thompson, A. C.; Hedin, P. A.; Minyard, J. P. *Science* **1969**, *166*, 1010.
6. (a) Einhorn, J.; Guerrero, A.; Ducrot, P. H.; Boyer, F. D.; Gieselmann, M.; Roelofs, W. *Proc. Natl. Acad. Sci. USA* **1998**, *95*, 9867. (b) Petschen, I.; Parrilla, A.; Bosch, M. P.; Amela, C.; Botar, A. A.; Camps, F.; Guerrero, A. *Chem. Eur. J.* **1999**, *5*, 3299. (c) Boyer, F.-D.; Ducrot, P.-H. *Eur. J. Org. Chem.* **1999**, 1201.
7. Stork, G.; Cohen, J. F. *J. Am. Chem. Soc.* **1974**, *96*, 5270.
8. Rossini, G.; Marotta, E.; Raimondi, A.; Righi, P. *Tetrahedron: Asymmetry* **1991**, *2*, 123 and references cited therein.
9. Hobbs, P. D.; Magnus, P. D. *J. Am. Chem. Soc.* **1976**, *98*, 4594.
10. Demuth, M.; Palomer, A.; Sluma, H. D.; Dey, A. K.; Krüger, C.; Tsay, Y.-H. *Angew. Chem., Int. Ed.* **1986**, *25*, 1117.
11. Jakovak, I. J.; Goodbrand, H. B.; Lok, K. P.; Jones, J. B. *J. Am. Chem. Soc.* **1982**, *104*, 4659.
12. For reviews, see: (a) Chen, C. S.; Sih, C. J. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 695. (b) Klibanov, A. M. *Acc. Chem. Res.* **1990**, *23*, 114. (c) Theil, F. *Chem. Rev.* **1995**, *95*, 2203.
13. Enzymatic resolution of (1*S*,2*R*,5*S*)-**3** and (1*R*,2*S*,5*R*)-**3**. In a 10 ml Erlenmeyer flask were placed 50 mg (0.235 mmol) of racemic *trans*-**3** in 3 mL of hexane, 100 mg of *Pseudomonas cepacia* lipase and 0.217 mL (2.35 mmol) of vinyl acetate. The flask was capped, placed in a thermostatted bath at 37°C and shaken at 80 units/min. The reaction was monitored by TLC, and when the transformation was ca. 50% (96 h) the mixture was filtered off and the enzyme washed with ether. The solvent was stripped off and the resulting crude purified by column chromatography on silica flash to furnish 25.7 mg (43%) of the corresponding acetate (1*R*,2*S*,5*R*)-(+)-**5** and 24.0 mg (48%) of unreacted (1*S*,2*R*,5*S*)-(–)-**3**. (1*R*,2*S*,5*R*)-(+)-**5**: IR (film), ν 2979, 2952, 2885, 2825, 2229, 1733, 1110, 1056, 1041, 927 cm^{-1}. ^{1}H NMR (300 MHz), δ 4.90 (dq, J = 10.5 Hz, J′ = 6.0 Hz, 1H), 4.60 (s, 2H), 3.71 (m, 2H), 3.36 (s, 3H), 2.95 (q, J = 9.0 Hz, 1H), 2.41 (m, 1H), 2.16 (m, 1H), 2.07 (m, 1H), 2.06 (s, 3H), 2.05 (m, 1H), 1.86 (m, 1H), 1.78 (m, 1H), 1.13 (d, J = 6.3 Hz, 3H) ppm. ^{13}C NMR (75 MHz), δ 170.45, 123.32, 96.58, 69.33, 64.36, 55.38, 47.28, 34.61, 30.12, 28.23, 21.25, 20.41, 16.88 ppm. MS (EI) m/z (%): 180 (7), 138 (5), 122 (5), 110 (7), 107 (11), 94 (8), 81 (7), 55 (9), 45 (100), 43 (79). $[\alpha]_D^{20}$ = +63 (*c* 1.7, $CHCl_3$) for an e.e. ≥99%. (1*S*,2*R*,5*S*)-(–)-**3**: IR (film), ν 3475, 2931, 2885, 2225, 1442, 1375, 1213, 1153, 1110, 1039, 921 cm^{-1}. ^{1}H NMR (300 MHz), δ 4.62 (s, 2H), 3.82 (m, 1H), 3.80 (m, 1H), 3.72 (dt, J = 9.9 Hz, J′ = 6.0 Hz, 1H), 3.36 (s, 3H), 2.66 (q, J = 9.9 Hz, 1H), 2.43 (m, 1H), 2.35 (dt, J = 14.4 Hz, J′ = 6.9 Hz, 1H), 2.03 (m, 1H), 2.02 (m, 1H), 1.93 (dt, J = 14.4 Hz, J′ = 6.0 Hz, 1H), 1.70 (m, 1H), 1.08 (d, J = 6.0 Hz, 3H). ^{13}C NMR (75 MHz), δ: 123.70, 96.54, 66.80, 64.75, 55.55, 50.74, 34.95, 30.55, 29.36, 20.65, 20.17. MS (EI) m/z (%): 152 (9, M^+–OCH_2OCH_3), 125 (12), 94 (18), 81 (21), 45 (100). $[\alpha]_D^{20}$ = –2.3 (*c* 2.0, $CHCl_3$) for an e.e. ≥99%.

14. Conventional basic hydrolysis of acetate **5** with K_2CO_3/MeOH produced a slight racemization (2%). Therefore, more neutral conditions (KCN/EtOH at reflux for 48 h) were applied. Purification of the crude by column chromatography afforded 15.4 mg (81%) of the corresponding alcohol (1*R*,2*S*,5*R*)-(+)-**3**, $[\alpha]_D^{20} = +2.3$ (*c* 1.5, $CHCl_3$) (e.e. $\geq$99%).
15. The calculated retention times for the *R* and *S* enantiomers of acetate **5** were 58.4 and 60.16 min, respectively, while the corresponding values for the *R* and *S* enantiomers of alcohol **3** were 67.21 and 69.24 min, respectively. The ^{19}F NMR signals of the Mosher esters were the following: (*R*)-MTPA of (1*S*,2*R*,5*S*)-**3**: δ –71.38; (*S*)-MTPA of (1*S*,2*R*,5*S*)-**3**: δ –71.63; (*R*)-MTPA of (1*R*,2*S*,5*R*)-**3**: δ –71.63; (*S*)-MTPA of (1*R*,2*S*,5*R*)-**3**: δ –71.38 ppm.
16. Harvey, I.; Crout, D. H. G. V. *Tetrahedron: Asymmetry* **1993**, *4*, 807.
17. Ohtani, I.; Kusumi, T.; Kashman, Y.; Kakisawa, H. *J. Am. Chem. Soc.* **1991**, *113*, 4092.