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Synthesis of Enantiomerically Pure (R)- and (S)-3-Methyl-2-cyclopenten-1-ol

Xiaoming Zhou and Pierre J. De Clercq*

University of Gent, Department of Organic Chemistry, Laboratory for Organic Synthesis, Krijgslaan, 281 (S.4), B-9000 GENT (Belgium)

and

Jacek Gawronski

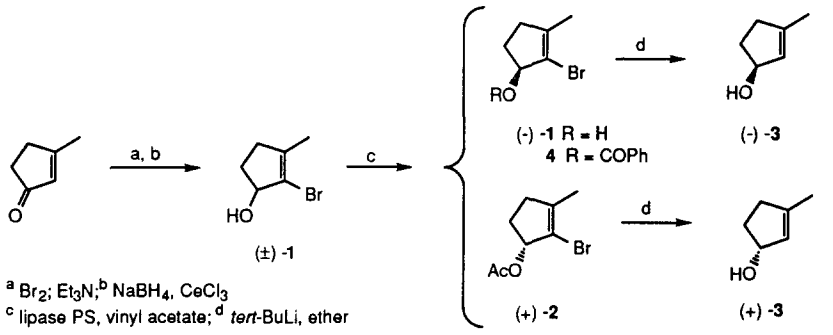
Adam Mickiewicz University, Department of Chemistry, Laboratory for Natural Products, Grunwaldzka, 6, P-60-780 POZNAN (Poland)

Abstract *: (R)- and (S)-3-methyl-2-cyclopenten-1-ol are prepared from 3-methyl-2-cyclopentenone with high enantiomeric purity (>95 %) through a 4-step sequence involving the enantioselective enzymatic esterification of 2-bromo-3-methyl-2-cyclopenten-1-ol with lipase PS and vinyl acetate.*

2-Cyclopentenols in enantiomeric pure form are substrates with a high synthetic potential. Recently, we needed (R)- and (S)-3-methyl-2-cyclopenten-1-ol for synthetic purposes. Quite to our surprise we found out that the synthesis of the enantiomerically pure derivatives had not been reported yet.[1] In principle the asymmetric reduction of 3-methyl-2-cyclopentenone should provide for the most direct access to the title compounds.[2,3] An alternative approach would consist in the kinetic enzymatic resolution of the racemic alcohol (via esterification) or of a corresponding ester (via hydrolysis). However, the resolution of 2-cyclopentenol by enzymatic hydrolysis of the acetate has been reported to proceed with low enantioselectivity.[4] This is not really surprising in view of the small steric difference between a $-CH_2-$ and a -CH= moiety. In contrast 2-iodo-2-cyclopentenol has been successfully resolved with the immobilized lipase Novo SP-435 (isopropenyl acetate:hexane (1:4), 1.5 h at 50°C)[5,6]. Also 2-trimethylsilylethynyl-2-cyclopentenol has been resolved via esterification with vinyl acetate in the presence of lipase PS (Amano).[7,8] Very recently, multi-step sequences have been developed for the synthesis of the enantiomers of 2-cyclopentenol in which the enzymatic kinetic resolution step is effected on an intermediate in which a large and, via elimination removable substituent has been introduced : esterification of *trans*-2-thiophenylcyclopentanol (isopropenyl acetate, lipase PCL, Amano),[9] and hydrolysis of the butyrate derived from *trans*-2-bromocyclopentanol (lipase P, Amano).[10,11] In a similar vein we wish to report herein the synthesis of both enantiomers of 3-methyl-2-cyclopentenol in high optical purity, via a 4-step sequence starting from 3-methyl-2-cyclopentenone in which the kinetic resolution is realized via enzymatic esterification of 2-bromo-3-methyl-2-cyclopentenol.[12]

The known (±)-**1** is readily obtained from 3-methyl-2-cyclopentenone via 2 steps involving bromination-elimination to 2-bromo-3-methyl-2-cyclopentenone followed by $NaBH_4$-$CeCl_3$ reduction.[13] Treatment of (±)-**1** with lipase PS (Amano) in the presence of vinyl acetate (2 equiv) in toluene led after 7 hours to acetate (R)-(+)-**2** (colourless oil,[14] 44 % yield; 96 % ee) and to (S)-(-)-**1** (mp : 47.5-49°C,[14] 43 % yield; 96 % ee) after chromatographic separation on silica gel.[15] This result is very similar to that obtained for 2-iodo-2-cyclopentenol.[5] The absolute configuration of (-)-**1** was unequivocally established via CD of the corresponding benzoate **4** (obtained with benzoic acid, DCC and DMAP in CH_2Cl_2; 74 % yield).[16] Treatment of the vinylic

bromides (-)-**1** and (+)-**2** with *tert*-butyllithium in ether led to the desired 3-methyl-2-cyclopentenols (-)-**3** (75 % yield; 96 % ee) and (+)-**3** (85 % yield, 96 % ee), respectively.[13,15,17]



References and notes

1. The sole report that we could find about (R)- and (S)-3-methyl-2-cyclopenten-1-ol is related to the enantiomer separation of the racemic derivative ("seudenol") by high resolution gas chromatography on permethylated β-cyclodextrin in OV-1701; see : Schurig, V.; Nowotny, H.-P. *Journal of Chromatography* **1988**, *441*, 155-163.
2. The CBS process, (see : Corey, E.J.; Bakshi, R.K.; Shibata, S. *J. Am. Chem. Soc.* **1987**, *109*, 551-553), led in our hands to a low e.e (36 %).
3. The enantioselective reduction of 3-methyl-2-cyclohexenone to the corresponding cyclohexenol with lithium aluminum hydride/ephedrine has been reported : Kawasaki, M.; Suzuki, Y.; Terashima, S. *Chem. Pharm. Bull.* **1985**, *33*, 52-60; see also Wu, K.-M.; Okamura, W.H. J. Org. Chem. **1990**, *55*, 4025-4033. Ephedrine (both enantiomers) is now classified within the EEC as a precursor in drug manufacturing and is subject to special notifications.
4. Ito, S.; Kasai, M.; Ziffer, H.; Silverton, J.V. *Can. J. Chem.* **1987**, *65*, 574-582.
5. Johnson, C.R.; Sakaguchi, H. *Synlett* **1992**, 813-816.
6. For the CBS-reduction of 2-iodo-2-cyclopentenone (96 % ee), see : Kabat, M.; Kiegiel, J.; Cohen, N.; Toth, K.; Wovkulich, P.M.; Uskokovic, M.R. *Tetrahedron Lett.* **1991**, *32*, 2343-2346.
7. Takano, S.; Suzuki, M.; Ogasawara, K. *Tetrahedron : Asymmetry* **1993**, *4*, 1043-1046.
8. For the resolution of 2-methyl-2-cyclopentenol, see : Yoshida, N.; Miyazawa, K. Eur. Pat. Appl. EP 414,453. CA : **1991**, *115*, 48912u.
9. Gupta, A.K.; Kazlauskas, R.J. *Tetrahedron : Asymmetry* **1993**, *4*, 879-888.
10. Fukazawa, T.; Hashimoto, T. *Tetrahedron : Asymmetry* **1993**, *4*, 2323-2326.
11. For the lipase induced hydrolysis of the chloroacetate derived from 2,3-dimethylcyclopentanol, see : Lord, M.D.; Negri, J.T., Paquette, L.A. *J. Org. Chem.* **1995**, *60*, 191-195.
12. For the enzymatic hydrolysis of 2-bromo-2-cyclopentenyl acetate by *Rhizopus nigricans* (51 % ee of alcohol), see ref. 5.
13. Ziegler, F.; Nangia, A.; Schulte, G. *J. Am. Chem. Soc.* **1987**, *109*, 3987-3991.
14. All structures were confirmed via the usual physical and spectroscopic data. Relevant data (rotations, ^1H NMR in $CDCl_3$, 200 MHz) : for (S)-**1** : $[\alpha]_D$ = -46.6 (c 1.24, $CHCl_3$); ^1H NMR : 4.70 (1H, m), 2.58-2.20 (3H, m), 1.86 (1H, m), 1.80 (3H, s) ppm; for (R)-**2** : $[\alpha]_D$ = +21.7 (c 1.72, $CHCl_3$); ^1H NMR : 5.70 (1H, m), 2.62-2.25 (3H, m), 2.10 (3H, s), 1.87 (1H, m), 1.80 (3H, s) ppm; for (S)-**3** : $[\alpha]_D$ = -78.8 (c 0.98, $CHCl_3$); ^1H NMR : 5.45 (1H, m), 4.80 (1H, m), 2.52-2.16 (3H, m), 1.78 (3H, s), 1.71 (1H, m) ppm; for (R)-**3** : $[\alpha]_D$ = +79.3 (c 0.62, $CHCl_3$).
15. Yields are for isolated material and are calculated based on 50 % yield for perfect resolution. E.e. of (+)-**2** is taken as that of (+)-**1** obtained after LAH reduction (THF, rt, 81 %). E.e. determination of (-)-**1** and (+)-**1** via ^1H NMR in the presence of $Eu(hfc)_3$, and of (-)-**3** and (+)-**3** via gas chromatography using 50 % 2,3-di-O-methyl-6-O-*tert*-butyldimethylsilyl)b-cyclodextrin in 50 % OV-1701 as the chiral phase.
16. Following the Harada-Nakanishi model the observed negative exciton-coupled benzoate Cotton effect $\Delta\varepsilon$ = -13.1 (228 nm), ε = 14800 (228 nm) indicates the (S)-configuration. Harada, N.; Iwabuchi, J.; Yokota, Y.; Uda, H.; Nakanishi, K. *J. Am. Chem. Soc.* **1981**, *103*, 5590-5591.
17. Cyclopentenol **3** is rather acid sensitive (cf. dimerization via ether formation) : purification is advantageously performed via flash chromatography on aluminum oxide (EtOAc/hexane 1:5).

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