Pergamon

Tetrahedron: Asymmetry, Vol. 7, No. 1, pp. 9-12, 1996

0957-4166/96 $15.00 + 0.00

0957-4166(95)00408-4

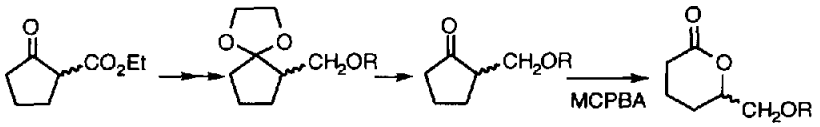
A Chemoenzymatic Preparation of Both Enantiomers of ω-Hydroxymethyl-Substituted Lactones

Didier Buisson and Robert Azerad

Laboratoire de Chimie et Biochimie Pharmacologiques et Toxicologiques associé au CNRS, Université René Descartes-Paris V, 45 rue des Saints-Pères, 75270-Paris Cedex 06, France

Abstract: (*R*)- and (*S*)-δ-hydroxymethyl valerolactone and ε-hydroxymethyl caprolactone were prepared as *tert*-butyldiphenylsilyl derivatives, in good yields and high enantiomeric purities, in a 5 step sequence, starting from the microbial stereospecific reduction of ethyl 2-oxocyclopentane or 2-oxocyclohexane carboxylates respectively.

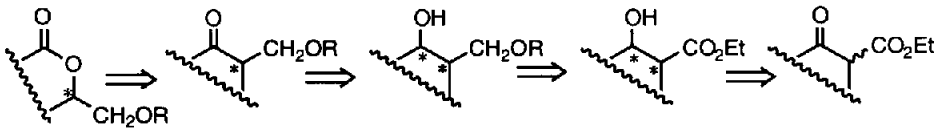
Enantiomerically pure substituted lactones are important building blocks for a variety of natural biologically active products and pharmaceuticals. Of particular interest are protected 5-hydroxymethyl lactones [1-3], which have been prepared in racemic or homochiral forms, used for the synthesis of LTB_5 [1], malyngolide [4], and are potentially useful for the synthesis of various insect pheromones. Recently, an efficient and inexpensive synthesis of a protected (±)-6-hydroxymethyl-tetrahydro(2*H*)-pyran-2-one **3** has been reported [5], *via* a regioselective Baeyer-Villiger reaction of the corresponding *tert*-butyldiphenylsilyl ether of (±)-2-hydroxymethylcyclopentanone **2**, itself obtained in three steps by acetal protection, reduction and deprotection, from ethyl 2-oxocyclopentane carboxylate **1**. Owing to the usually high stereoselectivity of the Baeyer-Villiger reaction [6,7], one may expect that the use of an enantiomerically pure suitably protected 2-hydroxymethylketone, in place of the racemic one, would result in an enantiomeric synthesis of the corresponding hydroxymethyl lactone.



1 R = *t*-BuPhe$_2$Si **2** **3**

Enantiomeric 2-hydroxymethyl cycloalkanones have been shown to be easily accessed by chemoenzymatic methods from (±)-cyclic β-oxoesters (Scheme 1). One method is based on a chemical reduction of the carbonyl group, followed by enzymatic resolution of one of the diastereomeric hydroxyesters [8,9]. After reduction of the carboxyester group, which does not modify the stereochemistry at the α-carbon [10], and protection of the resulting hydroxymethyl group, the secondary alcohol function may be oxidized back to the carbonyl group required for the Baeyer-Villiger oxidation [11]. An even more attractive solution for obtaining in high yield *a single hydroxyester stereoisomer* is to replace the initial hydroxyester resolution by a microbial reduction[12,13]of the corresponding (±)-cyclic β-oxoester, making use of the fast spontaneous epimerization of the substrate in the incubation medium, combined with the stereospecific reduction of a single enantiomer[10,14-17]. Such a diastereoselective and enantiospecific preparation of general-use cyclic synthons, having two

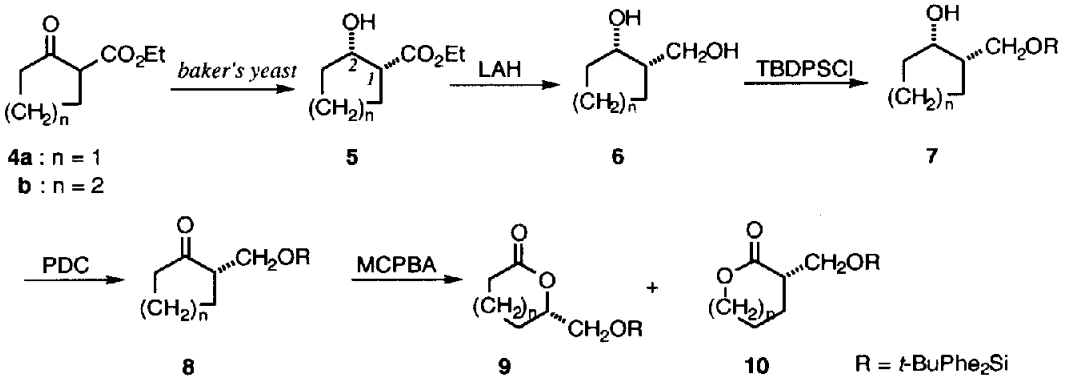
asymmetric centers, has been up to now moderately explored [4,11,15,18-23]. The chemical counterpart of this method (so-called "dynamic kinetic resolution"), using catalytic hydrogenation in the presence of an asymmetric BINAP-Ru(II) complex, has been recently and concurrently developed [24-27].



Scheme 1

We briefly describe herein the use of our microbial reduction method for obtaining, in good yields and high enantiomeric purities, both enantiomers of δ-hydroxymethyl valerolactone and ε-hydroxymethyl caprolactone.

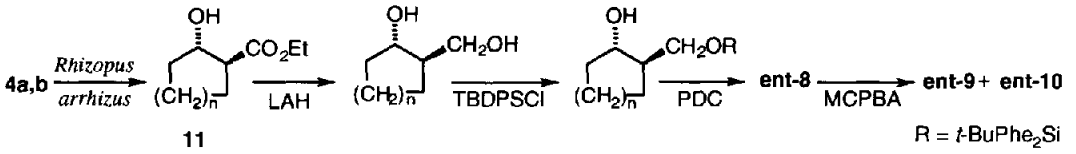
The reduction of ethyl 2-oxocyclopentanecarboxylate **4a** by baker's yeast [14] (Scheme 2) afforded a major *cis* diastereomer (*cis/trans* ratio≥9:1) with a 1*R*,2*S* configuration. After separation by flash chromatography, the *cis* hydroxyester **5a** (52% yield, 95% e.e.) was reduced with lithium aluminium hydride to give the (1*S*,2*S*)-diol **6a** (91% yield) which was protected with *tert*-butyldiphenylsilylchloride [11] to give the corresponding silyl derivative **7a** (87% yield). Oxidation with pyridinium dichromate in the presence of pyridinium trifluoroacetate [28] afforded the protected (*S*)-2-hydroxymethyl cyclopentanone **8a** (71% yield). In our hands, contrarily to the previously described reaction [5], the oxidation of **8a** by *m*-chloroperbenzoic acid afforded a mixture of hydroxymethyl lactones **9a** + **10a** (16:1, 80% yield) which were separated by flash chromatography and characterized by ^{1}H- and ^{13}C-NMR [29]. The major, enantiomerically pure, oily (*S*)-5-*tert*-butyldiphenylsilyloxymethyl lactone **9a**, $[\alpha]_D^{20}$ +10, $[\alpha]_{365}^{20}$ +34 (c 0.7, $CHCl_3$), was thus obtained in 5 steps and a final 22% yield from the oxocarboxylate **4a**. A purified sample of the isomeric lactone **10a** showed $[\alpha]_D^{20}$ −18, $[\alpha]_{365}^{20}$ −63 (c 0.5, $CHCl_3$).



Scheme 2

The enantiomeric protected (*R*)-lactone **ent-9a**, $[\alpha]_D^{20}$ −11, $[\alpha]_{365}^{20}$ −37 (c 0.86, $CHCl_3$), was similarly obtained in a final 23 % yield, starting from the reduction of ethyl 2-oxocyclopentanecarboxylate **4a** by

Rhizopus arrhizus [10] (Scheme 3), which afforded the *trans* enantiomerically pure (1*S*,2*S*)-hydroxyester **11a** (57% yield, after chromatographic separation from the *cis* isomer; initial *cis/trans* ratio, 2:8). The isomeric (*R*)-lactone **ent-10a** showed $[\alpha]_D^{20}$ +17, $[\alpha]_{365}^{20}$ +59 (c 0.63, $CHCl_3$).



Scheme 3

It was attractive to apply such reactions to the synthesis of both enantiomers of the homologous 7-membered lactone, which might also constitute useful lactonic synthons. Baker's yeast [10,14,15,19] (Scheme 2) allowed again the preparation of the nearly enantiomerically pure *cis* (1*R*,2*S*)-hydroxyester **5b** (80% yield, after chromatographic separation from a small amount of the *trans* isomer). Reduction to **6b** (92% yield), protection to **7b** (97% yield), PDC oxidation to **8b** (78% yield) and MCPBA oxidation, led to the exclusive formation of the protected (*S*)-hydroxymethyl lactone **9b** [29], m.p. 68-69° C, $[\alpha]_D^{20}$ – 4, $[\alpha]_{365}^{20}$ –17 (c 1.3, $CHCl_3$), in a final 46% yield from the oxocarboxylate **4b**.

Similarly, using *Rhizopus arrhizus* [10] (Scheme 3) for the reduction of **4b** to the enantiomerically pure *trans* (1*S*,2*S*)-hydroxyester **11b** (65% yield) and the same sequence of reactions, it was possible to obtain the enantiomeric (*R*)-lactone **ent-9b**, m.p. 69-70° C, $[\alpha]_D^{20}$ +4, $[\alpha]_{365}^{20}$ +18 (c 1.31, $CHCl_3$), in a final 32 % yield.

It is still possible to increase the convenience and the total yield of such conversions by effecting the separation of diastereomeric *cis* and *trans* derivatives, if necessary, at the protected diol stage, where a clear-cut separation is generally obtained, in place of the hydroxyester stage.

In conclusion, the easy availability of such versatile homochiral building blocks suggests that they will find a number of promising applications, as new members of the chiral pool, in the synthesis of a range of natural products. Work is in progress to extend this method to the stereospecific preparation of other lactonic synthons.

Acknowledgements. We want to thank E. Gaudemer and V. Cot for participating, in the course of their graduation scholarships, to the large scale synthesis and purification of intermediates.

References and Notes

1. Corey, E. J.; Pyne, S. G.; Su, W.-G. *Tetrahedron Lett.* **1983**, *24*, 4883-4886.
2. Gerth, D. B.; Giese, B. *J. Org. Chem.* **1986**, *51*, 3726-3729.
3. Pianetti, P.; Pougny, J.-R. *J. Carbohyd. Chem.* **1988**, *7*, 811-815.
4. Sato, T.; Maeno, H.; Noro, T.; Fujisawa, T. *Chem.Lett.* **1988**, 1739-1742.
5. Taylor, R. K.; Wiggins, K.; Robinson, D. H. *Synthesis* **1990**, 589-590.
6. Mislow, K.; Brenner, J. *J. Am. Chem Soc.* **1953**, *75*, 2318-2322.
7. Krow, G. R. In *Organic reactions*, Paquette, L. Ed; J.Wiley & Sons: New York, 1993, vol.43, pp.251-798.
8. Kanerva, L. T.; Sunholm, O. *Acta Chem. Scand.* **1991**, *47*, 823-825.
9. Kanerva, L. T.; Kosonen, M.; Vänttinen, E.; Huuhtanen, T. T.; Dahlqvist, M. *Acta Chem. Scand.* **1992**, *46*, 1101-1105.

10. Buisson, D.; Azerad, R. *Tetrahedron Lett.* **1986**, *27*, 2631-2634.
11. Barrett, A. G. M.; Capps, N. K. *Tetrahedron Lett.* **1986**, *27*, 5571-5574.
12. Servi, S. *Synthesis* **1990**, 1-25.
13. Csuk, R.; Glänzer, B. I. *Chem. Rev.* **1991**, *91*, 49-97.
14. Deol, B. S.; Ridley, D. D.; Simpson, G. W. *Aust. J. Chem.* **1976**, *29*, 2459-2467.
15. Fràter, G. *Helv. Chim. Acta* **1980**, *63*, 1383-1390.
16. Fràter, G.; Müller, U.; Günther, W. *Tetrahedron* **1984**, *40*, 1269-1277.
17. VanMiddleworth, F.; Sih, C. J. *Biocatalysis* **1987**, *1*, 117-127.
18. Hoffmann, R. W.; Helbig, W.; Ladner, W. *Tetrahedron Lett.* **1982**, *23*, 3479-3482.
19. Seebach, D.; Roggo, S.; Maetzke, T.; Braunschweiger, H.; Cercus, J.; Krieger, M. *Helv. Chim. Acta* **1987**, *70*, 1605-1615.
20. Azerad, R.; Buisson, D. In *NATO Advanced Research Workshop: Microbial Reagents in Organic Synthesis*; Servi, S. Ed; Kluwer Academic Publ.: Dordrecht, 1992; pp. 421-440.
21. Knight, D. W.; Lewis, N.; Share, A. C.; Haigh, D. *Tetrahedron: Asymmetry* **1993**, *4*, 625-628.
22. Buisson, D.; Cecchi, R.; Laffitte, J.-A.; Guzzi, U.; Azerad, R. *Tetrahedron Lett.* **1994**, *35*, 3091-3094.
23. Mehmandoust, M.; Buisson, D.; Azerad, R. *Tetrahedron Lett.* **1995**, *36*, 6461-6462.
24. Genêt, J. P.; Mallart, S.; Jugé, S., Fr. Patent, **1989**, n°89 11159.
25. Kitamura, M.; Ohkuma, T.; Tokunaga, M.; Noyori, R. *Tetrahedron: Asymmetry* **1990**, *1*, 1-4.
26. Kitamura, M.; Tokunaga, M.; Noyori, R. *J. Am. Chem. Soc.* **1993**, *115*, 144-152.
27. Genêt, J. P.; Pfister, X.; Ratovelomanana-Vidal, V.; Pinel, C.; Laffitte, J. A. *Tetrahedron Lett.* **1994**, *35*, 4559-4562.
28. Barco, A.; Benetti, S.; Pollini, G. P.; Baraldi, P. G.; Gandolfi, C. *J. Org. Chem.* **1980**, *45*, 4776-4778.
29. All new compounds were fully characterized by spectroscopic data (^{1}H- and ^{13}C-NMR, IR) and microanalysis and/or molecular ion mass measurements. Optical purities were determined by comparison with published optical rotations, when available, and/or by chiral GC or HPLC. Enantiomeric purities of lactones **9a-b** were determined by HPLC on a Chiralpak AD column (Daicel Chem. Ind., 250 x 4 mm, heptane-*i*PrOH 98:2, 1 mL.min^{-1}), and found to correlate, within the experimental error limits, with the enantiomeric excesses of hydroxyesters **5a-b** or **11a-b**.
9a, ^{1}H-NMR (250 MHz,$CDCl_3$) δ ppm, J Hz: 1.04 (9H, s, CH_3), 1.8 and 1.95 (4H, 2m, CH_2-4 and CH_2-5), 2.5 (2H, m, CH_2-3), 3.75 (2H, AB part of an ABX system, J_{AB}= 13, J_{AX}= 4.4, J_{BX}= 5.2, CH_2OSi), 4.37 (1H, m, H-6), 7.4 (6H, m, ArH), 7.65 (4H, m, ArH). ^{13}C-NMR (62.9 MHz,$CDCl_3$) δ ppm: 171.13 (CO), 135.63, 135.56, 129.85, and 127.79 (ArCH), 133.06 and 132.88 (ArC), 80.15 (CH-6), 65.58 (CH_2O), 29.82, 24.38, and 18.24 (CH_2), 26.74 (CH_3), 19.20 (quat.CMe_3).
10a, ^{1}H-NMR (250 MHz,$CDCl_3$) δ ppm, J Hz: 1.04 (9H, s, CH_3), 1.85-2.3 (4H, 2m, CH_2-4 and -6), 2.65 (2H, m, CH-3), 3.88 (1H, dd, $J_{3'a\text{-}3}$ = 3.6, $J_{3'a\text{-}3'b}$ = 10, H-3'a), 4.02 (1H, dd, $J_{3'b\text{-}3}$ = 6, $J_{3'b\text{-}3'a}$ = 10, H-3'b), 4.32 (2H, m, CH_2-6), 7.39 (6H, m, ArH), 7.64 (4H, m, ArH). ^{13}C-NMR (62.9 MHz,$CDCl_3$) δ ppm: 172.09 (CO), 135.70, 135.50, 129.85, 129.74 and 127.72 (ArCH), 133.42 and 133.00 (ArC), 71.54 and 64.26 (CH_2O), 42.75 (CH-6), 26.82 (CH_3), 22.84 and 22.26 (CH_2), 19.28 (quat.CMe_3).
9b, ^{1}H-NMR (250 MHz,$CDCl_3$) δ ppm, J Hz: 1.04 (9H, s, CH_3), 1.5, 1.95 and 2.18 (6H, 2m, CH_2-4, -5 and -6), 2.50 and 2.64 (2H, 2m, CH_2-3), 3.58 (1H, dd, $J_{3'a\text{-}3}$ = 7, $J_{3'a\text{-}3'b}$ = 10.3, H-3'a, CH_2OSi), 3.80 (1H, dd, $J_{3'b\text{-}3}$ = 5.6, $J_{3'b\text{-}3'a}$ = 10.3, H-3'b), 4.21 (1H, m, H-7), 7.4 (6H, m, ArH), 7.64 (4H, m, ArH). ^{13}C-NMR (62.9 MHz,$CDCl_3$) δ ppm: 175.04 (CO), 135.61, 129.86, and127.78 (ArCH), 133.19 (ArC), 80.20 (CH-6), 65.94 (CH_2O), 34.89, 31.06, 28.15 and 23.11 (CH_2), 26.86 (CH_3), 19.25 (quat.CMe_3).

(*Received in UK* 3 *October* 1995)