Pergamon

Tetrahedron: Asymmetry Vol. 6, No. 12, pp. 2971-2976, 1995
Elsevier Science Ltd
Printed in Great Britain
0957-4166/95 $9.50+0.00

0957-4166(95)00394-0

Baker's Yeast Reduction of Prochiral γ-Nitroketones. II.[1] Straightforward Enantioselective Synthesis of 2,7-Dimethyl-1,6-dioxaspiro[4.4]nonanes

Ernesto G. Occhiato, Antonio Guarna*, Francesco De Sarlo and Dina Scarpi

Dipartimento di Chimica Organica "Ugo Schiff", Centro di Studio sulla Chimica e la Struttura dei Composti Eterociclici e loro Applicazioni - CNR, Università di Firenze, via Gino Capponi 9, I-50121, Firenze (Italy)

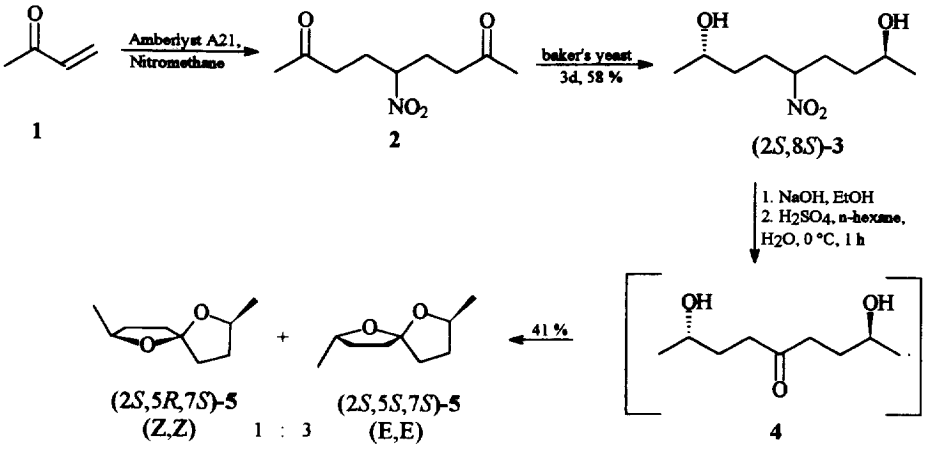
Abstract: The baker's yeast reduction of 5-nitro-2,8-nonanedione **2** afforded the corresponding (2*S*,8*S*)-5-nitro-2,8-nonanediol **3** with complete diastereoselectivity and high enantioselectivity. The conversion of **3** into the thermodynamic (E,E)/(Z,Z) (3:1) mixture of optically active (95% e.e.) 2,7-dimethyl-1,6-dioxaspiro[4.4]nonanes **5** was then achieved by spontaneous cyclization under the acidic conditions of the Nef reaction.

The spiroketal structure is widely found in many naturally occurring compounds which can have a number of interesting pharmacological properties.[2] Among them, 2,7-dialkyl-1,6-dioxaspiro[4.4]nonanes, due to their volatility, are important insect pheromone components,[2,3] and recently the simplest member of this class of compounds, the 2,7-dimethyl substituted, was found as a mixture of isomers in rum volatiles.[4]

Nitrodiols[5] have already been used as precursors in the synthesis of these compounds and therefore, continuing our study on biotransformations and their applications in organic synthesis,[1,6] we started to investigate the baker's yeast reduction of symmetrical nitrodiketones in order to obtain the enantiomerically pure precursors of spiroketals. In particular, we focused our efforts on the synthesis of optically active 2,7-dimethyl-1,6-dioxaspiro[4.4]nonanes **5** as depicted in Scheme 1. The symmetrical diketone **2** was prepared as reported[5] by addition of nitromethane to the vinylketone **1** in presence of Amberlyst A21. The baker's yeast reduction of **2** was carried out in aqueous solution at 30 °C with glucose as nutrient and in aerobic conditions, according to the procedure already reported by us.[1] It is known that the baker's yeast reduction of symmetrical diketones having the two carbonyl groups in 1,4 or more distant positions occurs indipendently on the two oxo groups. In such compounds the bioreduction affords (*S*,*S*) diols, according to the Prelog's rule,[7] in high diastereomeric and enantiomeric excesses, although the yields are lowered by increasing the chain length of the substrates.[8] The result of the bioreduction of **2** is consistent with these general observations, obtaining the diol **3** in 58 % yield and with (2*S*,8*S*) absolute configuration. The yield of this biotransformation appears to be only slightly lowered with respect to the bioreduction of 5-nitropentan-2-one **6** (74%) carried out in the same conditions[6].

The bioreduction of **2** is highly diastereoselective because no *meso* forms of **3** were detected in the product: in fact, in the ^{13}C-NMR spectrum the signals of the C-5 carbons (CH-NO_2) at 89.3 ppm and 88.1 ppm are absent (Table 1) whereas only the signal at 88.8 ppm of the (2*S*,8*S*) enantiomer is observed.

Scheme 1



The e.e. (95%) and absolute configuration (2*S*,8*S*) of **3** were determined by comparison of the value and sign of its specific rotation ($[\alpha]_D$ +23.4, *c* 0.30, chloroform) with those of a 1:1 mixture of the enantiomerically pure (2*S*,8*S*) diol and the optically inactive (2*S*,5*RS*,8*R*) *meso* forms ($[\alpha]_D$ +12.3, *c* 0.77, chloroform) obtained as shown in scheme 2. Although affected by some uncertainty, this procedure proved to give a measure of the e.e. of **3**. On the other hand, more acceptable measurements (e.g. ^{1}H- and ^{13}C-NMR spectroscopy of Mosher's ester of **3** or gas-chromatographic analysis) failed to give satisfactory results.

The baker's yeast reduction of **6** afforded **7** with (S) absolute configuration and >99% e.e.[1,6] Protection with TBDMSCl/imidazole in DMF[9] and conjugate addition to methylvinylketone on basic alumina without solvent[10] yielded (8*S*)-**9**. With respect to the reported procedure,[10,11] the addition of the nitrocompound to methylvinylketone was much slower and required 48 h at room temperature and the addition of 0.1 equivalents of NEt_3. The reason of that could be the presence, in our case, of the sterically hindered TBDMS group which prevents compound **8** from being easily absorbed on the alumina surface. Finally, reduction of the carbonyl group in **9** with $NaBH_4$ in $MeOH/H_2O$[12] and acidic work-up (HCl 2N was added up to pH 3 with stirring at r.t. for 1 h) gave, with an overall yield of 17 %, a mixture of (2*S*,8*S*)-**3** and (2*S*,5*RS*,8*R*)-**3** in 1 : 1 ratio determined by measuring the areas of the C-5 signals in the decoupled ^{13}C-NMR spectrum.[13]

Treatment of (2*S*,8*S*)-**3** (scheme 1) with NaOH in ethanol and then with the two-layer system, dil. H_2SO_4/hexane[5] at 0 °C for 1 h, afforded **5** through spontaneous cyclization of the intermediate **4**, in 41 % yield after bulb to bulb distillation at 62 °C (20 mbar). Table 1 compares the proton and carbon NMR chemical shifts of the methyl groups in (E,E), (Z,Z) and (E,Z) isomers.

The analysis of the ^{1}H- and ^{13}C-NMR spectra of **5** shows the absence of the (E,Z) diastereoisomer deriving from spiroketalization of the two diol *meso* forms (2*S*,5*R*,8*R*)-**3** and (2*S*,5*S*,8*R*)-**3**, thus confirming the high diastereoselectivety of baker's yeast reduction of **2**. Indeed, in the ^{1}H-NMR spectrum only the doublets at 1.19 ppm and 1.28 ppm, corresponding to the E,E (2*S*,5*S*,7*S* absolute configuration) and Z,Z (2*S*,5*R*,7*S*

absolute configuration) diastereoisomers, are present in 3 : 1 ratio, and analogously, in the ^{13}C-NMR spectrum, only the signals at 21.1 ppm (E,E) and 22.8 ppm (Z,Z) are present.

Scheme 2

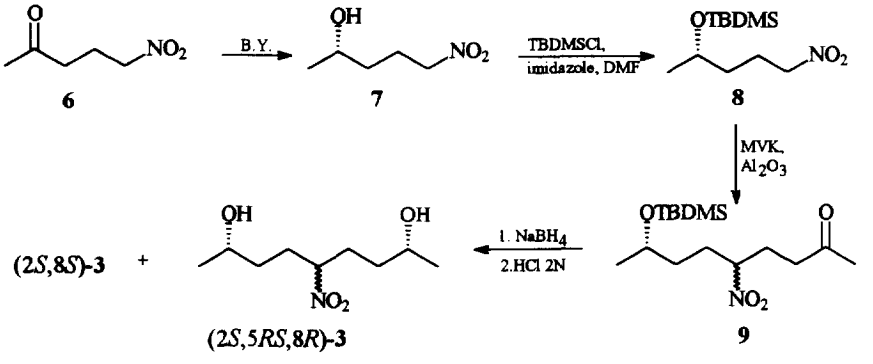


Table 1. Most significant ^{1}H-NMR and ^{13}C-NMR chemical shifts (in ppm) of 5-nitro-2,8-nonanediols and 2,7-dimethyl-1,6-dioxaspiro[4.4]nonanes.

		^{13}C-NMR				^{1}H-NMR
		C-5	C-2	C-7	CH_3	CH_3
3	(2*S*,8*S*)	88.8				
	meso forms	89.3, 88.1				
5	E,E		74.1	74.1	21.1	1.19
	Z,Z		75.8	75.8	22.8	1.28
	E,Z		75.8	73.9	22.8, 21.4	1.27, 1.17

The specific rotation of **5** was $[\alpha]_D$ -16.5 (*c* 0.57, chloroform). It has already been established[9, 2, 14] that the spirocyclization in acidic medium occurs with complete retention of configuration of the two carbinolic stereocenters, and therefore we can assign to both E,E-**5** and Z,Z-**5** the same e.e. (95 %) determined for their precursors (2*S*,8*S*)-**3**.

In conclusion, the baker's yeast reduction of prochiral nitrodiketones, compared to other routes, appears to be a very staightforward and short way to obtain optically active precursors of spiroketals. Furthermore, considering the large spectrum of compounds that are accepted as substrates by the yeast, this methodology could be extended to the synthesis of more complex spiroketals structures.

Experimental

Melting points were determined with a Büchi 510 apparatus. IR spectra were recorded with a Perkin Elmer 881 spectrophotometer. ^{1}H- and ^{13}C-NMR were recorded in $CDCl_3$ on a Varian Gemini at 200 MHz. MS spectra were obtained at 70 eV with a Carlo Erba QMD 1000 spectrometer and an Hewlett Packard A-5790-5970 GC-MS instrument. Elemental analysis were performed with a Perkin Elmer 240 C and gas-chromatographic analysis with a Hewlett Packard 5890 A instrument, equipped with a HP1 capillary column (100% methylsilicone, 0.53 mm i.d.). The R_f values refer to TLC on 0.25 mm silica gel plates (Merck F_{254}). Chromatografic purifications were performed by flash column chromatography on silica gel. Baker's yeast (Saccharomyces cerevisiae, Type II) was purchased from Sigma. Compound **2** was synthesised according to tthe reported procedure.[5]

(2*S*,8*S*)-(+)-5-Nitro-2,8-nonanediol (3). Nitrodiketone **2** (750 mg, 3.73 mmoles) was added to fermenting baker's yeast (80 g) in a solution of glucose (2 g) in 250 ml of water at 30 °C and under vigorous stirring. After 3 days the conversion of nitrodiketone (determined by GLC) was complete. The solution was therefore saturated with NaCl and continuosly extracted with ether (150 ml) with a liquid-liquid extractor for 18 h. After drying over sodium sulphate end evaporation of the solvent, chromatography (eluant ethyl acetate) afforded pure **3** (437 mg, 58 %). R_f 0.37. $[\alpha]^{20}_D$ +23.4 (*c* 0.30, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ 4.53 (m, 1 H), 3.78 (m, 2 H), 2.20-1.20 (m, 10 H), 1.18 (d, J = 6.3 Hz, 6 H). ^{13}C-NMR ($CDCl_3$) δ 88.8 (d, 1 C), 67.6 (d, 1 C), 66.8 (d, 1 C), 35.1 (t, 1 C), 34.6 (t, 1 C), 30.4 (t, 1 C), 29.9 (t, 1 C), 23.8 (q, 1 C), 23.7 (q, 1 C). Anal. calcd. for $C_9H_{19}NO_4$: C, 52.67; H, 9.33; N, 6.82. Found: C, 52.37; H, 9.32; N, 6.66.

(2*S*, 5*R*, 7*S*)- and (2*S*, 5*S*, 7*S*)-2,7-Dimethyl-1,6-dioxaspiro[4.4]nonanes (5). A solution of (2*S*,8*S*)-(+)-5-nitro-2,8-nonanediol (**3**) (400 mg, 1.95 mmoles) in 5 ml of anhydrous EtOH was added under nitrogen and stirring to a solution of NaOH (310 mg, 7.74 mmoles) in 5 ml of anhydrous EtOH. After 10 min at r.t. the solvent was evaporated and the residue dissolved in 10 ml of water and slowly added to the two-layer system 10 % H_2SO_4 (10 ml)/hexane (10 ml) at 0 °C. After 1 h the two phases were separated and the aqueous layer extracted with hexane. The organic layers were combined and dried over sodium sulphate. After careful distillation of the solvent, the residue was purified by Kugel-rohr distillation (62 °C/20 mbar) obtaining 124 mg of **5** (41 %) as a 3 : 1 mixture of diastereoisomers (E,E) and (Z,Z). $[\alpha]^{15}_D$ -16.5 (*c* 0.57, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ : 4.25-4.10 (m, 2 H, EE), 4.15-4.00 (m, 2 H, ZZ), 2.20-1.60 (m, 7 H), 1.50-1.35 (m, 1 H), 1.28 (d, J = 6.1 Hz, 6 H, ZZ), 1.19 (d, J = 6.1 Hz, 6 H, EE). ^{13}C-NMR ($CDCl_3$) δ : 114.9 (s, 1 C, EE, ZZ), 75.8 (d, 2 C, ZZ), 74.0 (d, 2 C, EE), 36.6 (t), 35.8 (t), 32.6 (t), 32.1 (t), 22.8 (q, 2 C, ZZ), 22.1 (q, 2 C, EE). Anal. calcd. for $C_9H_{16}O_2$: C, 69.19; H, 10.32. Found: C, 69.00; H, 10.12.

5-Nitro-2,8-nonanediols (2*S*,8*S*)- and (2*S*,5*RS*,8*R*)-(3). Compound **7**, prepared according to the reported procedure,[1,6] was protected as silyl ether **8** as reported.[9] 5-Nitro-2-*t*-butyldimethylsilyloxypentane (**8**) (800 mg, 3.23 mmoles) was treated at 0 °C with methylvinylketone (226.4 mg, 3.23 mmoles) under vigorous megnetic stirring in presence of basic Al_2O_3 (650 mg) (Fluka, activity 1) for 3 h. Then NEt_3 (30 µl, 0.1 eq.) was added and the reaction left aside overnight. After a further addition of 0.5 eq. of methylvinylketone and 24 h of reaction at r.t. no more starting material was detected by GLC. Diethyl ether was added and, after filtration of

the residue, the solvent removed obtaining crude **9** (1.0 g, GLC purity 73%) as a colourless oil which was used for the next step of reduction without purification.

9. ^{1}H-NMR ($CDCl_3$) δ: 4.45 (m, 1 H), 3.77 (m, 1 H), 2.47 (m, 2 H), 2.13 (s, 3 H), 2.09 (m, 2 H), 2.00-1.60 (m, 2 H), 1.40 (m, 2 H), 1.09 (d, J = 6.2 Hz, 3 H), 0.85 (s, 9 H), 0.02 (s, 6 H).

This crude oil was then dissolved in a mixture of methanol (16 ml) and water (3.00 ml), this solution was cooled at 0-5 °C and then treated with $NaBH_4$ (239 mg, 6.28 mmoles) under magnetic stirring. After 7 h the reaction was complete and HCl 2N was added dropwise to the solution up to pH 3. The resulting suspension was left under stirring for 1 h at r.t. and then extracted with ether, washed with brine and dried overnight oversodium sulphate. After filtration and evaporation of the solvent the residue was chromatographed (eluant ethylacetate, R_f 0.37) obtaining (2*S*,8*S*)- and (2*S*,5*RS*,8*R*)-(**3**) (112 mg, 17%). $[\alpha]^{20}_D$ +12.3 (*c* 0.77, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ 4.53 (m, 1 H), 3.78 (m, 2 H), 2.20-1.20 (m, 10 H), 1.18 (d, J = 6.3 Hz, 6 H). ^{13}C-NMR ($CDCl_3$) δ 89.3 (d,1 C), 88.8 (d, 1 C), 88.1 (d, 1C), 67.4 (d), 66.7 (d), 35.0 (t), 34.6 (t), 30.4 (t), 30.3 (t), 29.9 (t), 29.7 (t), 23.8 (q), 23.7 (q).

Acknowledgments

We thank Ministry of University and Scientific and Technological Research (M.U.R.S.T. 60% and 40%) and CNR for financial support. We wish also to thank prof. Ballini of the University of Camerino, Italy, for his helpful suggestions, and Mrs. B. Innocenti (University of Firenze) for her technical support.

References and notes

1. Guarna, A.; Occhiato, E. G.; Spinetti, L. M.; Vallecchi, M. E.; Scarpi, D. *Tetrahedron*, **1995**, *51*, 1775.
2. Enders, D.; Dahmen, W.; Dederichs, E.; Gatzweiler, W.; Weuster, P. *Synthesis*, **1990**, 1013.
3. Francke, W.; Reith, W. *Liebigs Ann. Chem.*, I (**1979**). Francke, W.; Reith, W. Z. *Naturwiss*. **1980**, *67*, 149. Francke, W.; Reith, W. *Z. Naturforsch* **1981**, *26c*, 928. Bergstrom, G.; Tengo, W.; Reith, W.; Francke, W. *Z. Naturforsch*, **1982**, *37c*, 1124. Perkins, M. V.; Kitching, W.; Drew, R.A.I.; Moore, C. J.; König, W.A. *J.Chem. Soc. Perkin Trans I*, **1990**, 1111.
4. Heide, R.; Schaap, H.; Wobben, H. J.; De Valois, P. J.; Timmer, R. *Qual. Foods Beverages: Chem. Technol., (Proc. Symp. Int. Flavor Conf.)*, 2nd (**1981**), Volume 1, 183-200. Editors: Charalambous, George; Inglette, George. Publisher: Academic, New York, N. Y.
5. Ballini, R.; Bosica, G.; Uselli, A. *J. Heterocyclic Chemistry*, **1994**, *31*, 259.
6. Occhiato, E. G.; Guarna, A.; Spinetti, L. M. *Tetrahedron* **1993**, *49*, 10629.
7. Prelog, V. *Pure Appl. Chem.* **1964**, *9*, 119
8. Poppe, L.; Novak, L. *Selective Biocatalysis. A synthetic approach.* VCH publishers 1992.
9. Nakamura, K.; Kitayama, T.; Inoue, Y.; Ohno, A. *Tetrahedron*, **1990**, *46*, 7471.
10. Rosini, G.; Ballini, R.; Petrini, M.; Marotta, E. *Angew. Chem. Int. Ed. Engl.* **1986**, *25*, 941.
11. Ballini, R.; Petrini, M. *Synthesis*, **1986**, 1025.
12. Obol'nikova, E. A.; Samokhavlov, G. I. *Zh. Obs. Khim.* **1962**, *32*, 3556.

13. Albeit the ^{13}C-NMR spectrum was recorded in decoupled mode, we may assume that the structural differences among these diastereoisomers do not significantly affect the relaxation times of the C-5 carbon atoms; thus their signals have been used for the ratio determination.
14. Tu, Y. Q.; Moore, C. J.; Kitching, W. *Tetrahedron: Asymmetry*, **1995**, *6*, 397.

(*Received in UK* 30 *August* 1995; *accepted* 23 *October* 1995)