An Enantioselective Synthesis of (-)-Nonactic Acid and (+)-8-*epi*-Nonactic Acid Using Microbial Reduction

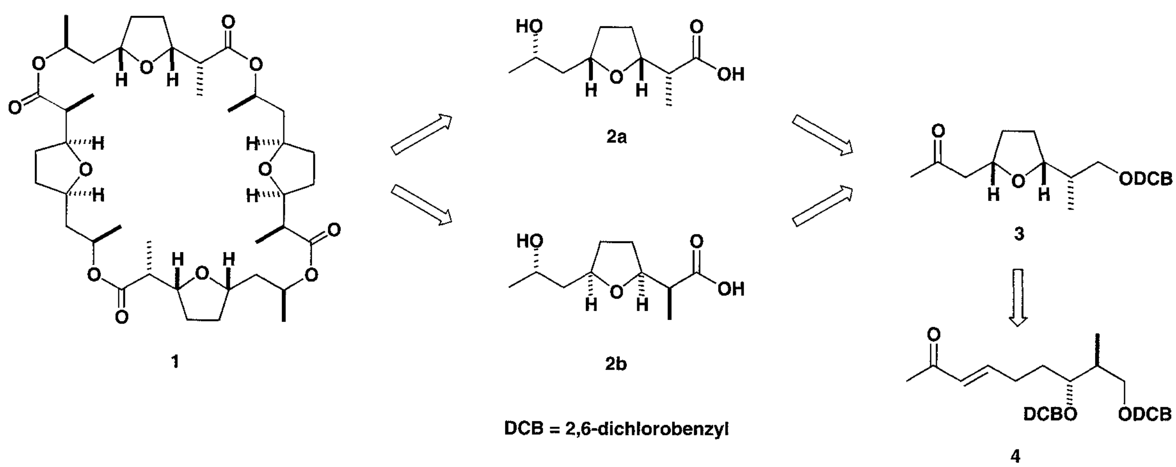
Kazuhiko Takatori, Kenji Tanaka, Katsunori Matsuoka, Kazuyoshi Morishita and Masahiro Kajiwara*

Department of Medicinal Chemistry, Meiji College of Pharmacy 1-22-1 Yato-cho, Tanashi-shi, Tokyo 188, JAPAN

Received 17 November 1996

Abstract: An enantioselective synthesis of (-)-nonactic acid (**2a**) and (+)-8-*epi*-nonactic acid (**2b**) is described. The microbial reduction of the *dl*-ketone **3** with baker's yeast gave two easily separable diastereomeric alcohols **11a** and **11b**, each in over 97% ee. These alcohols were converted to **2a** and **2b** in 4 steps.

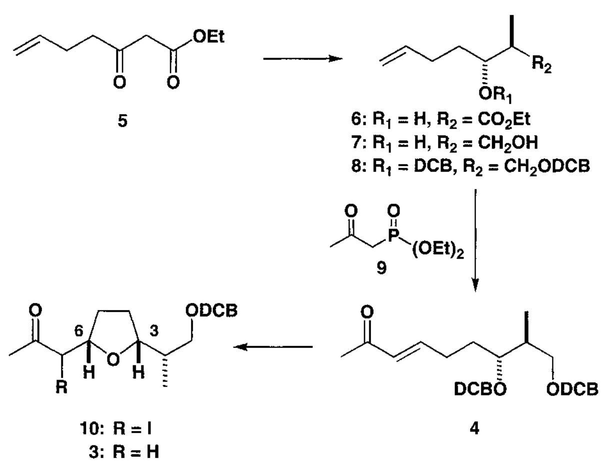
Nonactin (**1**), which has been isolated from a variety of *Streptomyces* species, is one of the macrotetrolide ionophore antibiotics.[1] It is a 32-membered macrocycle, having S4 symmetry, and consists of two molecules of (-)-nonactic acid and two molecules of (+)-nonactic acid arranged in alternating order through ester linkages. The synthesis of **1** has been accomplished by coupling of both enantiomers of nonactic acid or of optically active nonactic acid and its *ent*-8-*epi*-isomer.[2] Many syntheses of nonactic acid and its 8-*epi*-isomer have been reported,[3] but few have involved the syntheses of optically active nonactic acid and its *ent*-8-*epi*-isomer from a common intermediate.[2b,c,4] Here we describe a new enantioselective synthesis of both (-)-nonactic acid (**2a**) and (+)-8-*epi*-nonactic acid (**2b**) by using microbial reduction of the *dl*-ketone **3** as a common intermediate.



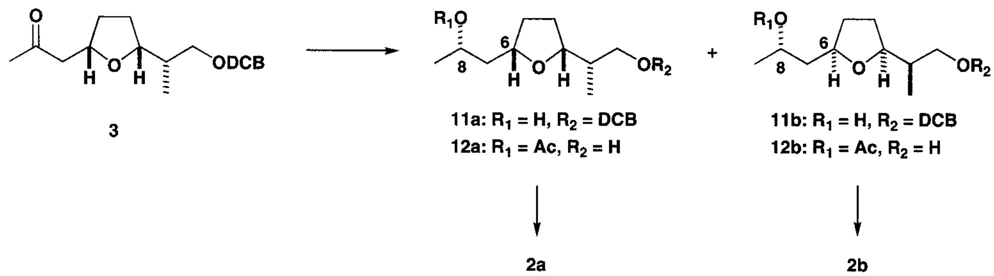
Scheme 1

In our synthetic approach (Scheme 1), the key step is the microbial reduction of the *dl*-ketone **3** with baker's yeast (*Saccharomyces cerevisiae*) to afford two optically active diastereomers having the required stereochemistry for the synthesis of **2a** and **2b**. Although this step requires highly enantioselective reduction, this can be expected, because baker's yeast reduction of methyl ketones such as ethyl acetoacetate[5] and of α- or β-heteroatom-substituted ketones[6] has been reported to give the corresponding highly optically pure alcohols. The *dl*-ketone **3** is prepared by diastereoselective iodo-etherification[7] of the (*E*)-α,β-unsaturated ketone **4**.

The synthetic pathway to **3** is shown in Scheme 2. Reduction of the β-ketoester **5**, prepared from the dianion of ethyl acetoacetate and allyl bromide, with $NaBH_4$ and then *anti*-selective methylation (LDA 2 eq. / THF, then MeI / HMPA at -40 °C)[8] of the α-position of the ester carbonyl group gave the β-hydroxyester **6** in 51% yield (*anti* : *syn* = 92 : 8).[9] Further reduction of the carbonyl group in **6** with $LiAlH_4$, followed by protection of the resulting two hydroxyl groups in **7** with 2,6-dichlorobenzyl (DCB) groups (2,6-dichlorobenzyl bromide, NaH / THF-DMF) gave **8** in 98% yield. Ozonolysis of **8** (O_3 / MeOH then Me_2S) and Honner-Emmons reaction of the resulting aldehyde and the β-ketophosphonate **9**[10] in 6 M K_2CO_3 aq. gave the (*E*)-α,β-unsaturated ketone **4** in 77% yield. Cyclization of **4** to the *cis*-tetrahydrofuran ring was carried out by Bartlett's iodo-etherification with good selectivity.[7] Treatment of **4** with iodine in the presence of $NaHCO_3$ in CH_3CN at room temperature for 24 h afforded the *cis*-cyclized product **10**, which showed positive NOE between protons attached to C-3 and C-6 in the ^1H-NMR spectrum, in 91% yield. However, the relative stereochemistry of C-7 was not determined. Radical cleavage of the C-I bond in **10** was achieved by treatment with *n*-Bu_3SnH and AIBN to give the *dl*-ketone **3**, with the required common relative stereochemistry for C-2, C-3 and C-6 in nonactic acid and its *ent*-8-*epi*-isomer, in 94% yield (*cis* : *trans* = 96 : 4).



Scheme 2



Scheme 3

The key step in this synthesis, the microbial reduction of **3**, proceeded smoothly as follows (Scheme 3). A suspension of baker's yeast (230 g, Oriental Yeast Co. Ltd.) and glucose (20 g) in tap water (1400 ml) was stirred at room temperature for 1 h. To the above suspension was added a solution of the *dl*-ketone **3** (2.20 g, 6.37 mmol) in ethanol (6 ml). The reaction mixture was stirred vigorously at room temperature for 72 h, then centrifuged, and the supernatant was extracted 5 times with AcOEt. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, and evaporated. The crude mixture was easily separated by flash column chromatography on silica gel (hexane : ether = 6 : 1) to afford **11a** (30%), **11b** (34%) and recovered starting material (7%).[11] Isomerization at C-6 in **11a** and **11b** *via* β-elimination-conjugate addition in **3** was not observed. This microbial reduction proceeded with high enantioselectivity, and the optical purity of **11a** and **11b** was over 97% ee in each case, as determined from the ^{19}F-NMR spectra of the corresponding MTPA esters. The absolute configuration of C-8 in both **11a** and **11b** was *S*.[12] This result is consistent with the exception to Prelog's rule for baker's yeast reduction.[13] The reaction rate was nearly equal for the two enantiomers of **3**. Although the enzyme(s) reducing **3** was not identified, it did not recognize the absolute configuration of the other asymmetric centers in **3**. This substrate-non-enantiospecific and product-enantioselective reduction[14] is convenient for our synthetic purpose.

The resulting alcohols **11a** and **11b** were converted to nonactic acid and its *ent*-8-*epi*-isomer, respectively. Acetylation of the hydroxyl group of **11a** and **11b** with Ac_2O in pyridine and then cleavage of the 2,6-dichlorobenzyl ether groups with hydrogen and 10% Pd-C in AcOEt gave **12a** and **12b** in 76% and 58% yields, respectively. Finally, Jones oxidation of the primary hydroxyl group in **12a** and **12b** to the corresponding carboxyl group, hydrolysis of the acetyl group with K_2CO_3 and acidic extraction gave optically pure (-)-nonactic acid (**2a**) and (+)-8-*epi*-nonactic acid (**2b**) in 95% and 80% yields, respectively. The physical data of the methyl esters of **2a** and **2b**, obtained by treatment with CH_2N_2, were identical with the literature values, though the optical rotations, observed as $[\alpha]_D^{25}$ -13.9° (*c* = 1.10, $CHCl_3$) and $[\alpha]_D^{25}$ +24.2° (*c* = 1.12, $CHCl_3$), were somewhat different from the reported ones, $[\alpha]_D^{25}$ +13.1° (*c* = 0.708, $CHCl_3$) and $[\alpha]_D^{25}$ -23.1° (*c* = 1.07, $CHCl_3$), respectively.[2c] Nonactin has been synthesized from the enantiomers of **2a** and **2b**, *i.e.*, (+)-nonactic acid and (-)-8-*epi*-nonactic acid, as reported by Bartlett *et. al.*[2c]

Thus, the synthesis of nonactic acids **2a** and **2b** was accomplished by using microbial reduction of the *dl*-ketone **3** with baker's yeast *via* the optically active alcohols **11a** and **11b**.

References and Notes

(1) (a) Corbaz, R.; Ettlinger, L.; Gaumann, E.; Keller-Schielein, W; Kradolfer, F.; Neipp, L.; Prelog, V.; Zahner, H. *Helv. Chim. Acta* **1955**, *38*, 1445. (b) Dominquez, J.; Dunitz, J. D.; Gerlach, H.; Prelog, V. *ibid.* **1962**, *45*, 129. (c) Gerlach, H.; Prelog, V. *Justus Liebigs Ann. Chem.* **1963**, *669*, 121. (d) Keller-Schielein, W. *Fortschr. Chem. Org. Naturst.* **1968**, *26*, 161. (e) *idem ibid.* **1973**, *30*, 313. (f) Prestegard, J. H.; Chan, S. I. *J. Am. Chem. Soc.* **1970**, *92*, 4440.

(2) (a) Gerlach, H.; Oertle, K.; Thalmann, A.; Servi, S. *Helv. Chim. Acta* **1975**, *58*, 2036. (b) Schmidt, U.; Gombos, J.; Haslinger, E.; Zak, H. *Chem. Ber.* **1976**, *109*, 2628. (c) Bartlett, P. A.; Meadows, J. D.; Ottow, E. *J. Am. Chem. Soc.* **1984**, *106*, 5304. (d) Fleming, I.; Ghosh, S. K. *J. Chem. Soc., Chem. Commun.* **1994**, 2287. (e) Lee, J. Y.; Kim, B. H. *Tetrahedron Lett.* **1995**, *36*, 3361.

(3) (a) Honda, T.; Ishige, H.; Araki, J.; Akimoto, S.; Hirayama, K.; Tsubuki, M. *Tetrahedron* **1992**, *48*, 79. (b) Takatori, K.; Tanaka, N.; Tanaka, K.; Kajiwara, M. *Heterocycles* **1993**, *36*, 1489. (c) Lee, J. Y.; Kim, B. H. *Tetrahedron* **1996**, *52*, 571, and references cited therein.

(4) (a) Batmangherlich, S.; Davidson, A. H. *J. Chem. Soc., Chem. Commun.* **1985**, 1399. (b) Kim, B. H.; Lee, J. Y. *Tetrahedron Lett.* **1992**, *33*, 2557. (c) Solladié, G.; Dominguez, C. *J. Org. Chem.* **1994**, *59*, 3898.

(5) (a) Mori, K. *Tetrahedron* **1981**, *37*, 1341. (b) Ohta, H.; Ozaki, K.; Tsuchihashi, G. *Agric. Biol. Chem.* **1986**, *50*, 2499.

(6) (a) Sih, C. J.; Chen, C-. S. *Angew. Chem. Int. Ed. Engl.* **1984**, *23*, 570. (b) Yamada, H.; Sugiyama, H.; Kajiwara, M. *Heterocycles* **1987**, *26*, 2841. (c) Fujisawa, T.; Kojima, E.; Sato, T. *Chem. Lett.* **1987**, 2227. (d) Kurumaya, K.; Takatori, K.; Isii, R.; Kajiwara, M. *Heterocycles* **1990**, *30*, 745.

(7) Rychnovsky, S. D.; Bartlett, P. A. *J. Am. Chem. Soc.* **1981**, *103*, 3963.

(8) (a) Frater, G. *Helv. Chim. Acta* **1979**, *62*, 2825. (b) Seebach, D.; Wasmuth, D. *ibid.* **1980**, *63*, 197.

(9) The relative stereochemistry of **6** was determined from the ^{1}H-NMR spectrum of the corresponding acetonide of **7**.

(10) Savignac, P.; Mathery, F. *Tetrahedron Lett.* **1976**, *33*, 2829.

(11) **11a**: ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 0.92 (3H, d, *J* = 6.7 Hz), 1.21 (3H, d, *J* = 6.2 Hz), 1.52-1.65 (2H, m), 1.66 (1H, ddd, *J* = 14.4, 7.2, 3.1 Hz), 1.74 (1H, ddd, *J* = 14.4, 7.7, 3.9 Hz), 1.85-1.97 (3H, m), 3.41 (1H, dd, *J* = 9.2, 6.9 Hz), 3.62 (1H, dd, *J* = 9.2, 4.8 Hz), 3.72 (1H, dt, *J* = 6.7, 7.4 Hz), 4.01-4.13 (2H, m), 4.72 (1H, d, *J* = 10.7 Hz), 4.76 (1H, d, *J* = 10.7 Hz), 7.17 (1H, m), 7.31 (2H, m). IR (neat) cm^{-1}: 3418, 2965, 2932, 2907, 2876, 1582, 1564, 1437, 1373, 1198, 1100, 1065, 997, 939, 768. EIMS *m/z* (%): 346 (3, M^+), 262 (15), 260 (23), 170 (43), 169 (16), 161 (68), 159 (100), 129 (84), 111 (31), 85 (56), 71 (62). HRMS Calcd for $C_{17}H_{24}Cl_2O_3$: 346.1102. Found: 346.1106 (M^+). $[\alpha]_D^{25}$ +2.40° (*c* = 1.04, $CHCl_3$). **11b**: ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 0.91 (3H, d, *J* = 6.7 Hz), 1.18 (3H, d, *J* = 6.4 Hz), 1.42-1.64 (3H, m), 1.68 (1H, dt, *J* = 14.1, 2.4 Hz), 1.81-2.03 (3H, m), 3.42 (1H, dd, *J* = 9.2, 6.9 Hz), 3.60 (1H, dd, *J* = 9.2, 4.9 Hz), 3.78 (1H, q, *J* = 7.4 Hz), 3.95-4.04 (2H, m), 4.71 (1H, d, *J* = 10.5 Hz), 4.75 (1H, d, *J* = 10.5 Hz), 7.17 (1H, m), 7.31 (2H, m). IR (neat) cm^{-1}: 3461, 2967, 2934, 2903, 2878, 1582, 1563, 1437, 1372, 1200, 1103, 1082, 997, 939, 768. EIMS *m/z* (%): 346 (2, M^+), 262 (15), 260 (23), 170 (37), 169 (11), 161 (66), 159 (100), 129 (67), 111 (25), 85 (49), 71 (84). HRMS Calcd for $C_{17}H_{24}Cl_2O_3$: 346.1102. Found: 346.1108 (M^+). $[a]_D^{25}$ +5.84° (*c* = 1.01, $CHCl_3$).

(12) The absolute configurations of **11a** and **11b** were determined by derivation to **2a** and **2b**, respectively.

(13) Prelog, V. *Pure Appl. Chem.* **1964**, *9*, 119.

(14) Newton, R. F.; Paton, J.; Reynolds, D. P.; Young, S.; Roberts, S. M. *J. Chem. Soc., Chem. Commun.* **1979**, 908.