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Synthesis of Nonactin and the Proposed Structure of Trilactone

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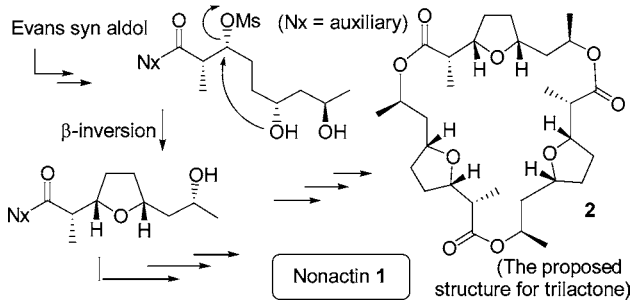
ABSTRACT



An efficient enantioselective route to nonactin using a novel *β*-inversion of an Evans syn aldol to construct the THF ring is presented. Through total synthesis, the structure for trilactone proposed in the literature is shown likely to be incorrect.

Nonactin (**1**) is the simplest member of a large family of ionophore antibiotics known as macrotetrolides or polynactins generated by *Streptomyces griseus* subspecies *griseus* ETH A7796 (DSM40695).[1] These compounds display pronounced antibacterial,[2] insecticidal,[3] antitumoral,[4] and immunosuppressive[5] activities and therefore have received considerable attention from synthetic chemists. Up to now, most synthetic studies on the polynactins (Figure 1) have been directed toward nonactin, presumably because it has the highest symmetry and thus requires the minimum workload in synthesis. In this communication, we wish to report a new approach to nonactin[6,7] and the recently proposed[8] structure for trilactone **2**, a natural product related to nonactin.

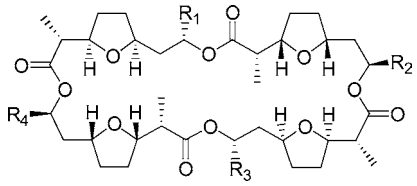


Figure 1. General structure of polynactins. For nonactin (**1**), R_1-R_4 = Me.

(1) For reviews, see: (a) Keller-Schierlein, W.; Gerlach, H. *Fortschr. Chem. Org. Naturst*. **1968**, *26*, 161−189. (b) Nawata, Y.; Ando, K.; Iitaka, Y. *Met. Ions Biol. Syst.* **1985**, *19*, 207−227. (c) Zizka, Z. *Folia Microbiol.* **1998**, *43*, 7−14.

(2) Nefelova, M. V.; Sverdlova, A. N. *Antibiot. Med. Biotekhnol.* **1985**, *30*, 261−264; *Chem. Abstr*. **1985**, *102*, 201065.

(3) (a) Oishi, H.; Sugawa, T.; Okutomi, T.; Suzuki, K.; Hayashi, T.; Sawada, M.; Ando, K. *J. Antibiot.* **1970**, *23*, 105−106. (b) Shopotova, L. P.; Shenin, Y. D. *Zh. Prikl. Khim.* **1993**, *66*, 1334−1338; *Chem. Abstr*. **1994**, *120*, 158329.

(4) Borrel, M. N.; Pereira, E.; Fiallo, M.; Garnier-Suillerot, A. *Eur. J. Biochem*. **1994**, *223*, 125−133.

(5) (a) Callewaert, D. M.; Radcliff, G.; Tanouchi, Y.; Shichi, H. *Immunopharmacology* **1988**, *16*, 25−32. (b) Tanouchi, Y.; Shichi, H. *Immunology* **1988**, *63*, 471−475.

(6) There are five total syntheses of nonactin in the literature: (a) Gerlach, H.; Oertle, K.; Thalmann, A.; Servi, S. *Helv. Chim. Acta* **1975**, *58*, 2036−2043. (b) Schmidt, U.; Gombos, J.; Haslinger, E.; Zak, H. *Chem. Ber.* **1976**, *109*, 2628−2644. (c) Bartlett, P. A.; Meadows, J. D.; Ottow, E. *J. Am. Chem. Soc.* **1984**, *106*, 5304−5311. (d) Kim, B. H.; Lee, J. Y. *Tetrahedron* **1996**, *52*, 571−588. (e) Fleming, I.; Ghosh, S. K. *J. Chem. Soc., Perkin Trans. 1* **1998**, 2733−2747. For a comprehensive review, see: (f) Fleming, I.; Ghosh, S. K. *Stud. Nat. Prod. Chem.* **1996**, *18*, 229−268.

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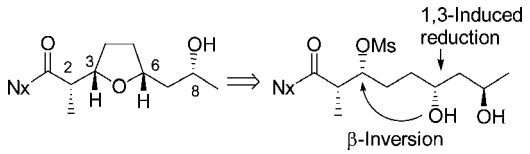
Because nonactin consists of residues of (+)- and (−)-nonactic acids, its synthesis usually starts from the construction of these two building blocks. In the present work, the stereogenic center at C-8 of the nonactic acids was derived through a Jacobsen hydrolytic kinetic resolution (HKR)[9] of racemic 2-methyl-oxirane. The epoxide and the diol obtained in the HKR were used in the synthesis of (+)- and (−)-nonactic acid, respectively, and thus made full use of the racemic starting material. The C-6 stereogenic center was established by a $Me_4NBH(OAc)_3$[10] reduction. The C-2 and C-3 were first generated by a Crimmins[11] modification of the Evans aldolization as a syn aldol. Then, in a later step when closing the THF ring, the configuration at C-3 was inverted.

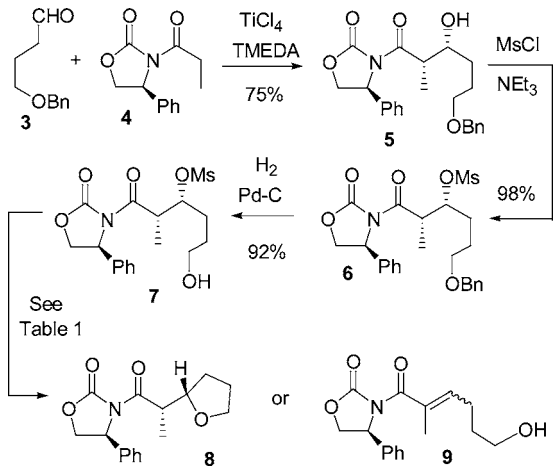
Because the β-inversion in the presence of the carbonyl group has never been reported before and potential risks such as α-racemization and β-elimination do exist, to be on the safe side, we did a model study to check the feasibility of the β-inversion strategy (Scheme 1) before starting the real synthesis.

Scheme 1



Condensation of aldehyde **3**[12] with imide **4**[13] under the Crimmins conditions led to syn aldol **5** in 75% isolated yield (Scheme 2). The β-OH was then converted to the corresponding mesylate with careful control of the quantity of the base. The benzyl protecting group was removed by hydrogenolysis to give the ring-closure precursor **7**.

Scheme 2



The ring closure was then examined under a variety of conditions (Table 1). Despite the precaution to avoid using excess base, β-elimination occurred readily in most cases (Table 1, entries 2−5, 7, and 8), giving conjugated alkene **9** as the only product. Finally, we gratifyingly found that the expected **8** was formed cleanly (Table 1, entry 11) when using pyridine as solvent and running the reaction temperature at 140 °C (bath). With 2,6-lutidine, the temperature could be lowered to 120 °C (Table 1, entry 12). At even lower temperature, essentially no reaction took place (Table 1, entry 13).

Table 1. Representative Results of the Attempted Cyclization of **7**

entry	conditions (concn of **7**, M)	outcome
1	Et_3N/CH_2Cl_2/rt/24 h (0.02)	no reaction
2	NaH/THF/rt/3 h (0.08)	**9** only
3	NaH/THF/−78 °C to rt/1 h (0.08)	**9** only
4	NaH/THF/−78 °C to rt/1 h (0.02)	**9** only
5	NaH/THF/−78 °C to rt/2 h (0.005)	**9** only
6	NaH/THF/−78 to −40 °C/4 h (0.001)	no reaction
7	NaHDMS/THF/HMPA/−78 to −40 °C/1 h (0.01)	**9** only
8	NaHDMS/Et_2O/−100 °C/1 h (0.07)	**9** only
9	*t*-BuOK/THF/rt/6 h (0.08)	no reaction
10	*t*-BuONa/THF/rt/12 h (0.08)	no reaction
11	pyridine (solvent)/140 °C/6 h (0.05)	**8** only
12	2,6-lutidine (solvent)/120 °C/1 h (0.06)	**8** only
13	2,6-lutidine (solvent)/75 °C/4.5 h (0.04)	no reaction

With a satisfactory means to close the THF ring in hand, we turned to the synthesis of (+)-nonactic acid (Scheme 3). Deprotonation of the dithiane **10**[14] with *n*-BuLi followed by reaction with epoxide **11**[9] gave alcohol **12** in 96% yield. The sulfur protecting group was removed with I_2,[15] and the carbonyl group was stereoselectively reduced with Me_4NBH-

(7) For syntheses of nonactic acid published after 1996, see: (a) Bratt, K.; Garavelas, A.; Perlmutter, P.; Westman, G. *J. Org. Chem.* **1996**, *61*, 2109−2117. (b) Kiyota, H.; Abe, M.; Ono, Y.; Oritani, T. *Synlett* **1997**, 1093−1095. (c) Takatori, K.; Tanaka, K.; Matsuoka, K.; Morishita, K.; Kajiwara, M. *Synlett* **1997**, 159−160. (d) Mandville, G.; Girard, C.; Bloch, R. *Tetrahedron* **1997**, *53*, 17079−17088. (e) Meiners, U.; Cramer, E.; Frohlich, R.; Wibbeling, B.; Metz, P. *Eur. J. Org. Chem.* **1998**, 2073−2078. (f) Ahmar, M.; Duyck, C.; Fleming, I. *J. Chem. Soc., Perkin Trans. 1* **1998**, 2721−2732. (g) Lee, E.; Choi, S. J. *Org. Lett.* **1999**, *1*, 1127−1128. (h) Wang, Y.; Metz, P. *Tetrahedron: Asymmetry* **2000**, *11*, 3995−3999. (i) Fraser, B.; Perlmutter, P. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2896−2899. (j) Jeong, J. W.; Woo, B. Y.; Ha, D. C.; No, Z. *Synlett* **2003**, 393−395. (k) Ireland, R. E.; Vevert, J. P. *Can. J. Chem.* **1981**, *59*, 572−583. (l) Kim, B. H.; Lee, J. Y. *Tetrahedron Lett.* **1992**, *33*, 2557−2560. For other routes published by 1996, see ref 6f above.

(8) Rezanka, R.; Spizek, J.; Prikrylova, V.; Prell, A.; Dembitskyb, V. M. *Tetrahedron* **2004**, *60*, 4781−4787.

(9) Schaus, S. E.; Brandes, B. D.; Larrow, J. F.; Tokunaga, M.; Hansen, K. B.; Gould, A. E.; Furrow, M. E.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2002**, *124*, 1307−1315 and references therein.

(10) Evans, D. A.; Chapman, K. T.; Carreira, E. M. *J. Am. Chem. Soc.* **1988**, *110*, 3560−3578.

(11) Crimmins, M. T.; King, B. W.; Tabet, E. A. *J. Am. Chem. Soc.* **1997**, *119*, 7883−7884.

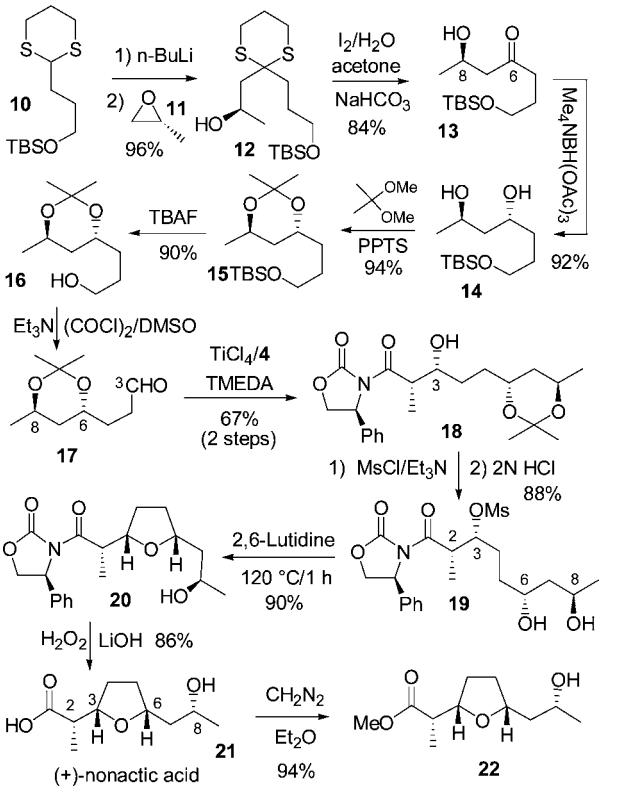
(12) Matsuda, F.; Kito, M.; Sakai, T.; Okada, N.; Miyashita, M.; Shirahama, H. *Tetrahedron* **1999**, *55*, 14369−14380.

(13) Ager, D. J.; Allen, D. R.; Schaad, D. R. *Synthesis* **1996**, 1283−1285.

(14) Wu, Y.-K.; Huang, J.-H.; Shen, X.; Hu, Q.; Tang, C.-J.; Li, L. *Org. Lett.* **2002**, *4*, 2141−2144.

(15) Nicolaou, K. C.; Bunnage, M. E.; McGarry, D. G.; Shi, S.; Somers, P. K.; Wallace, P. A.; Chu, X.-J.; Agrios, K. A.; Gunzner, J. L.; Yang, Z. *Chem. Eur. J.* **1999**, *5*, 599−617.

Scheme 3



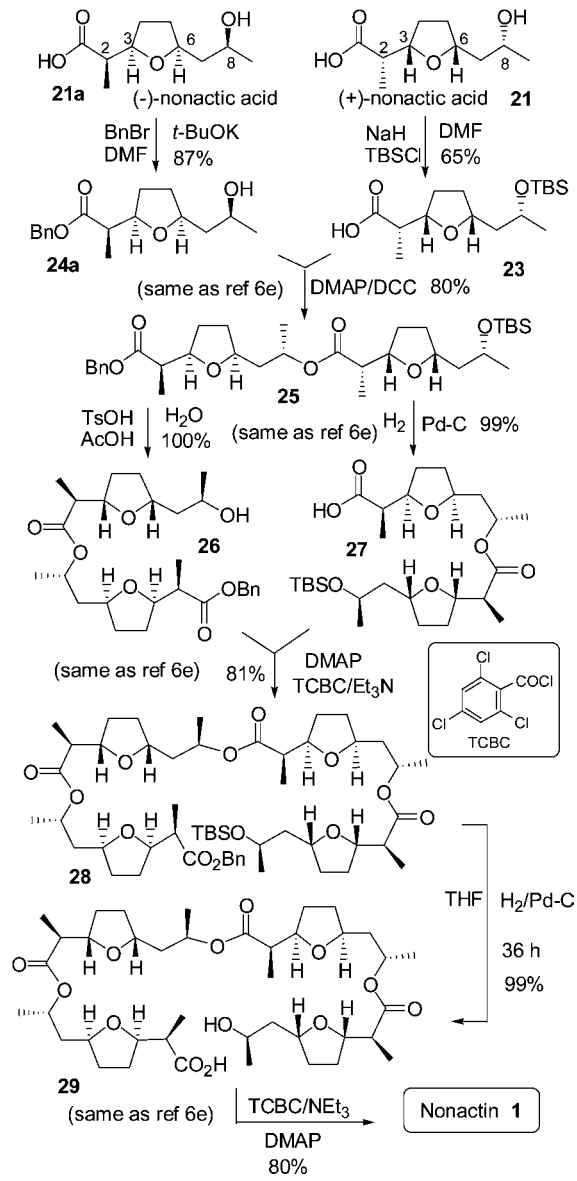
(OAc)$_3$ to create the stereogenic center at C-6. The two diastereomers (ca. 17:1) could be cleanly separated on silica gel. The diol **14** was then masked as an acetonide, and the terminal hydroxyl group was freed and oxidized to give the intermediate aldehyde **17**, which was immediately treated with imide **4** under the Crimmins conditions to give the syn aldol **18**.

The β-hydroxyl group was then converted to a mesylate. Using the conditions developed in the model reaction, we obtained the desired ring-closure product **20** in 90% yield as expected. On hydrolytic removal of the chiral auxiliary with LiOH/H_2O_2, (+)-nonactic acid **21** was obtained. Because the ^{1}H NMR data for **21** in the literature were not as well resolved as those for its methyl ester, we also transformed **21** to ester **22** (94% yield) by treatment with CH_2N_2. We were pleased to find that all spectroscopic data including optical rotation of ester **22** were in full consistence with those reported in the literature, further confirming that neither racemization nor elimination−addition occurred during the construction of the THF ring under the unconventional lutidine conditions. It is interesting to note that later we found that the ring closure of mesylate **19** (neat) could also occur spontaneously at ambient temperature after 10 days.

The (−)-nonactic acid **21a** was synthesized in a similar fashion and comparable yield, but with (*S*)-2-methyl-oxirane **11a** (prepared from the diol generated in the HKR) and the antipode of imide **4** in place of epoxide **11** and **4**, respectively.

The remaining steps were done essentially following the route described by Fleming and Ghosh.[6e] Thus, acids **21** and **21a** were then converted to acid **23** and ester **24a**, respectively, and coupled to each other by treatment with DCC/DMAP to yield dimer **25** (Scheme 4). Part of **25** was

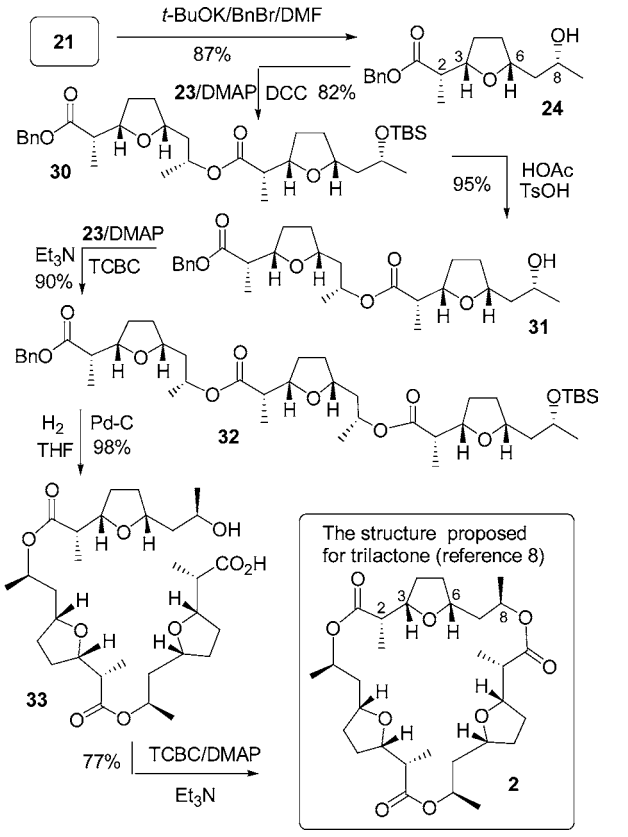
Scheme 4



deprotected on the hydroxyl group end to afford alcohol **26**. The remainder was subjected to hydrogenolysis to release a free carboxylic group. Alcohol **26** and acid **27** were coupled to give tetramer **28**. Removal of the benzyl group and the TBS group, however, was done in one operation by extending the hydrogenolysis time to 36 h instead of in two steps as described[6e] by Fleming and Ghosh. A final Yamaguchi lactonization gave the end product nonactin **1** in 80% yield, with all spectroscopic data in full consistence with those reported[6e] in the literature.

In 2004, Rezanka[8] and co-workers reported a novel nonactin natural analogue trilactone **2**. Because this compound has never been synthesized up to now, we performed the work outlined in Scheme 5. In the endeavor, the acid **21**

Scheme 5



was first converted to its benzyl ester **24** by treatment with *t*-BuOK/BnBr, which was coupled with acid **23** to yield the dimer **30**. The TBS protecting group was then removed with HOAc/TsOH, and another molecule of **23** was coupled onto the dimer, giving trimer **32**. Deprotection of both the carboxylic and the hydroxyl group ends was realized by hydrogenolysis over Pd−C. Finally, the trilactone ring was closed under the Yamaguchi conditions to afford the target molecule **2**. However, to our surprise, neither the optical rotation ($[\alpha]^{24}_D$ +1.5 (*c* 0.1, EtOH); cf lit.[8] $[\alpha]^{25}_D$ +14.5 (*c* 0.09, EtOH)) nor the NMR data (Table 2 and Supporting Information) of **2** were consistent with those reported[8] for trilactone. We then noticed that in that paper the data for "methyl nonactate" obtained by degradation of trilactone were also incompatible with those reported[7] by others,

Table 2. Comparison of the ^{1}H NMR Data

signals (δ) of **2**	signals (δ) of trilactone (ref 8)
1.09 (d, J = 7.0 Hz, 9H)	1.10 (dd, J = 2.7, 6.7 Hz, 9H)
1.26 (d, J = 6.3 Hz, 9H)	1.25 (d, J = 6.4 Hz, 9H)
1.68−1.42 (m, 6H)	1.40 (m, 3H)
	1.48 (ddd, J = 14.0, 11.3, 3.4 Hz, 3H)
	1.63 (m, 3H)
1.85−1.70 (m, 6H)	1.80 (ddd, J = 14.0, 12.1, 3.5 Hz, 3H)
2.00−1.90 (m, 6H)	1.82 (m, 3H)
	1.98 (m, 3H)
2.44 (quint, J = 7.3 Hz, 3H)	2.57 (dq, J = 9.8, 6.7 Hz, 3H)
3.88 (tt, J = 5.2, 8.2 Hz, 3H)	3.90 (m, 3H)
3.95 (quart, J = 6.9 Hz, 3H)	4.01 (dddq, J = 10.0, 9.8, 7.0, 2.7 Hz, 3H)
4.94 (sext, J = 6.3 Hz, 3H)	4.90 (ddq, J = 11.3, 6.4, 3.5 Hz, 3H)

confirming that the structure previously proposed for trilactone is likely incorrect.

In brief, a new total synthesis of nonactin has been developed. (*R*)- and (*S*)-2-methyl-oxirane obtained from Jacobsen HKR of the racemate were utilized to construct the C-8 stereogenic center of (+)- and (−)-nonactic acid, respectively. The C-6 configuration was established through a 1,3-asymmetric reduction. The C-2/C-3 stereogenic centers were introduced by a Crimmins modification of the Evans aldolization followed by a β-inversion when forming the THF ring. Such a transformation with the leaving group at the carbon β to a carbonyl group (which made the substrate labile to such side reactions as α-racemization and β-elimination), to the best of our knowledge, has never been reported before. Finally, through total synthesis, the structure previously proposed for trilactone is shown likely to be incorrect.

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Supporting Information Available: Experimental procedures, physical and spectroscopic data for all new compounds, ^{1}H NMR spectra of **5**−**9**, **12a**, **13a**, **14a**, **15a**, **16a**, **18**, **18a**, **19**, **19a**, **20a**, **24**, **30**−**33**, and **2**, and ^{13}C NMR spectra of **14a**, **18**, **32**, and **2** (41 pages). This material is available free of charge via the Internet at http://pubs.acs.org.

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