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A stereocontrolled approach to (±)-nonactic acid

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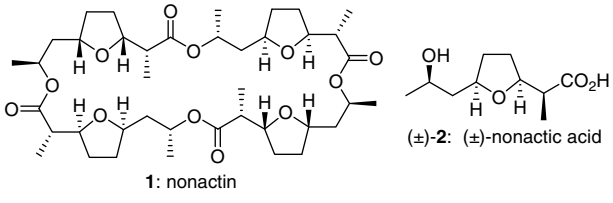
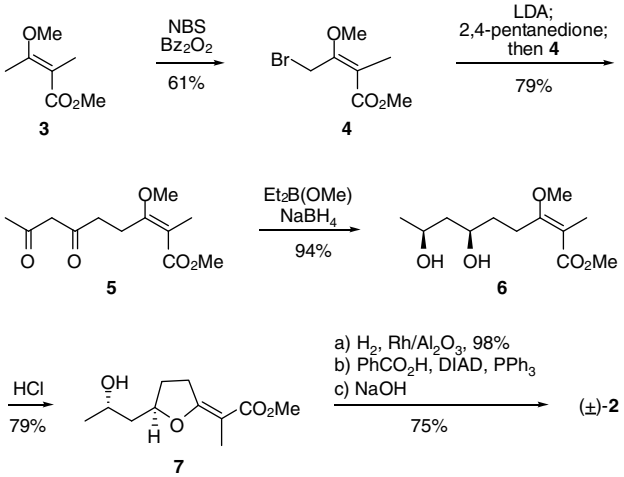
ABSTRACT

Racemic nonactic acid was efficiently constructed in a convergent, stereocontrolled fashion (7 steps, 27%). The present synthesis features a stereocontrolled 1,3-dione reduction with $NaBH_4/Et_2B(OMe)$ and an acid-promoted stereospecific cyclization in the formation of **7**.

Nonactin (**1**),[1] a 32-membered macrocycle, conceptually contains two molecules of (−)-nonactic acid and two molecules of (+)-nonactic acid arranged in an alternating order with four ester linkages, and represents the simplest member of a large group of ionophore antibiotics available from a variety of *Streptomyces* cultures.[2] These macrotetrolides (or polynactins) exhibit pronounced antibacterial,[3] insecticidal,[4] antitumoral,[5] and immunosuppressive[6] bioactivities. Due to its impressive pharmacological profile and novel and challenging structural characteristics, nonactin has been an alluring target molecule for the synthetic community.[7] Imaginably, extensive endeavors have been devoted to constructing monomeric nonactic acid (in all forms: (+)-,[7a,e,8] (−)-,[2a,7a,e,8d,e] and (±-)[9]) and its derivatives.[2a,7,8b,c,10] In asymmetric assembly of nonactic acid, either one[2a,7b,e,f,8c–e] or two[7a,c,8a,b] chiral segments could be accommodated into the final molecule. In contrast, the synthesis of the racemic form has to start with a single stereogenic center and must be fully stereocontrolled.[11] Herein, we wish to report a concise and convergent synthesis of (±)-nonactic acid ((±)-**2**) that contains four stereogenic centers.



As delineated in Scheme 1, the current synthesis commenced from (*E*)-methyl 3-methoxy-2-methyl-2-butenoate (**3**)[12] which is a known intermediate easily available from methyl acetylacetate through methylation at C-2 (MeI, K_2CO_3, MeCOMe, reflux) and from the subsequent enol ether formation ($HC(OMe)_3$, H_2SO_4, MeOH, reflux). Free radical reaction of **3** with NBS (100 mol %) in the presence of a catalytic amount of Bz_2O_2 in refluxing CCl_4



Scheme 1.

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afforded bromide **4** in 61% yield. Double deprotonation of 2,4-pentadione with LDA (200 mol %) at −78 °C followed by alkylation with **4** furnished the coupling product **5**, which was present in solution as a mixture of dione and ketoenol (in a ratio of ca. 1:4). Treatment of **5** with $NaBH_4$ and $Et_2B(OMe)$[13] stereoselectively formed *syn*-diol **6** in excellent yield (94%) via two successive reduction steps. The second reduction proceeded in a highly stereocontrolled manner because of the complexation effect of $Et_2B(OMe)$. Exposure of **6** to 5% HCl in methanol at room temperature effected the desired cyclization to stereospecifically produce the thermodynamically favored product **7**,[11,14] in which the (*E*) configuration of the carbon–carbon double bond allows maximum conjugation. The generation of **7** presumably involved hydrolysis, hemi-acetal formation, and dehydration. By three known transformations described previously (i.e., stereoselective hydrogenation,[7e] Mitsunobu benzoylation,[8a] and saponification of both ester groups[8a]), **7** was smoothly converted to (±)-**2** in 75% overall yield. The structure of (±)-**2** was confirmed by spectroscopic analysis.[8a,15]

In summary, racemic nonactic acid was efficiently constructed in a convergent, stereocontrolled fashion (7 steps, 27%). The present synthesis features a stereocontrolled 1,3-dione reduction with $NaBH_4/Et_2B(OMe)$ and an acid-promoted stereospecific cyclization in the formation of **7**.

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14. Compound **7**, a pale yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.23 (d, J = 6.3 Hz, 3H), 1.69–1.87 (m, 3H), 1.76 (s, 3H), 2.17–2.28 (m, 1H), 2.49 (s, 1H, OH), 2.81–2.94 (m, 1H), 3.18–3.27 (m, 1H), 3.67 (s, 3H), 3.97–4.08 (m, 1H), 4.45–4.54 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.2, 23.2, 30.3, 30.6, 43.7, 50.8, 66.1, 82.1, 97.2, 169.6, 169.8. ESI-MS 451 (2M+Na), 269 (M+Na+MeOH), 215 (M+H). ESI-HRMS calcd for $C_{11}H_{18}O_4$+Na 237.1103; found: 237.1097.
15. Compound (±)-**2**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.16 (d, J = 6.9 Hz, 3H), 1.22 (d, J = 6.6 Hz, 3H), 1.58–1.74 (m, 4H), 1.97–2.11 (m, 2H), 2.46–2.56 (m, 1H), 3.98–4.23 (m, 3H), 5.89 (br s, 2H, CO_2H & OH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.4, 22.9, 28.6, 30.5, 43.1, 45.2, 64.9, 76.8, 80.8, 178.0. ESI-MS 225 (M+Na), 203 (M+H). ESI-HRMS calcd for $C_{10}H_{18}O_4$+Na 225.1103; found: 225.1097.