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EXPEDITIOUS SYNTHESES OF METHYL 8-epi-NONACTATE AND METHYL NONACTATE

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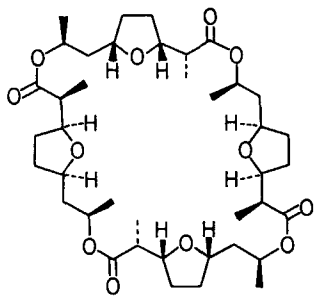
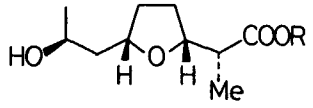
Summary. (±)-Methyl 8-epi-nonactate ((±)-4) and (±)-methyl nonactate ((±)-3) were derived from (±)-7-oxa-2-bicyclo[2.2.1]heptanone (6) in four and five synthetic steps, respectively.

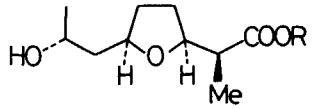
Nonactin 1 is a macrotetrolide antibiotic[1] composed of two subunits of (-)-nonactic acid ((-)-2) and two subunits of (+)-nonactic acid ((+)-2), arranged in an alternating order (S_4 symmetry).[2] The "Reverse Coupe du Roi"[2] approach to the synthesis of 1 requires either the production of both (-)-2 and tosylate of benzyl 8-epi-nonactate,[3] or the production of both (+)-2 and the mesylate of (-)-methyl-8-epi-nonactate ((-)-4).[4]



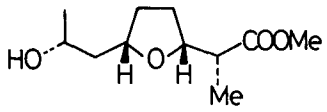
1



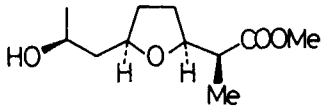
R = H (-)-2
R = Me (-)-3



(+)-2
(+)-3

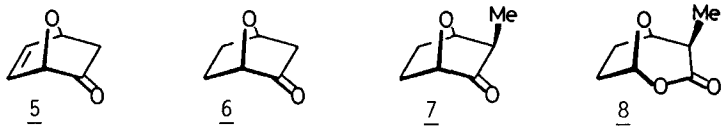


(-)-4

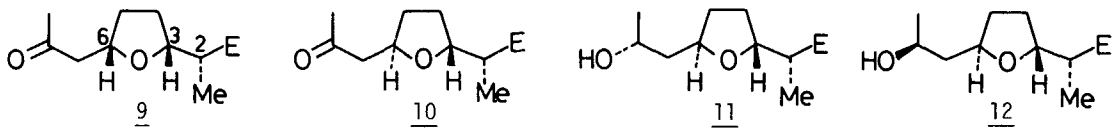


(+)-4

At least twelve syntheses of nonactic acids and derivatives have been described[5] with varying success with respect to the degree of stereoselectivity. We report here a new, short and stereoselective synthesis of methyl 8-epi-nonactate ((±)-4). It was transformed to methyl nonactate ((±)-3)[6] by the Mitsunobu displacement reaction.[7]



5 6 7 8



9 10 11 12

(±)-3 + (±)-4 1:10 9 + 10 4:3 E = COOMe

Catalytic hydrogenation (10 % Pd/C, THF, 20 °C, 24h) of 7-oxanorborn-5-en-2-one (5) gave 6 quantitatively.[9] KHMDS in THF (3 equiv., prepared from KH and $(TMS)_2NH$) was added to a 1:10 mixture of 6 and MeI in THF cooled to -50 °C. Work-up with 2N HCl and aq. $Na_2S_2O_3$ afforded 7 in 63 % yield (45 % based on 1-cyanovinyl acetate or furan[8]). Baeyer-Villiger oxidation of 7 with mCPBA and $NaHCO_3$ ($CHCl_3$, 12 °C, 12h) gave 8, an unstable lactone (94 %). Addition of 1 equiv. of 2-trimethylsilyloxypropene[10] to a 1:1 mixture of 8 and $TiCl_4$ (CH_2Cl_2, -78 °C, 3h)[11] furnished a 4:3 mixture of ketones 9 and 10 after work-up with aq KOH (pH 9, 20 °C, 12 h), then with 2N HCl (pH 2, 0 °C) and CH_2N_2 in Et_2O. Preparative HPLC (SiO_2, hexane/AcOEt 7:3) yielded 36 % of 9 and 27 % of 10. The latter could be recycled into a 4:3 mixture of 9/10 on treatment with 2N KOH (20 °C, 2h), then acidification and esterification (CH_2N_2). Reduction of 9 with L-selectride[6] (THF, -78 °C, 10 min) afforded a 10:1 mixture of (±)-4 and (±)-3. Column chromatography (SiO_2, AcOEt/hexane 1:1) afforded pure (±)-4 in 82 % yield. Under the same conditions, the reduction of 10 gave a 5:1 mixture of 11 and 12. The structures of 7 - 12 were given by their elemental analyses and spectral data.[12] Those of (±)-3, (±)-4, 11 and 12 were identical to data reported in the literature.[4]

Since 5 can be obtained optically pure in both enantiomeric forms,[8,13] our approach constitutes formally a synthesis of (+)- and (-)-nonactic acids and their 8-epi-derivatives.[14]

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References and footnotes.

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12. Characteristics of 7 : oil; ^{1}H-NMR ($CDCl_3$) : 4.43(m, H-C(1)); 4.28 (m, H-C(4)); 1.97 (q, J = 7.0 Hz, J(H-C(3), H-C(4)) = 0, proves the endo configuration of H-C(3)); 1.94 - 1.89 (m, H exo-C(5,6)); 1.71 - 1.61 (m, H endo-C(5,6)); 1.17 (d, J = 7.0, CH_3-C(3)). IR (CH_2Cl_2) : 1765 cm^{-1}. 8 : oil; ^{1}H-NMR ($CDCl_3$) : 5.90 (d, 4.0 Hz, H-C(1)); 4.47 (d, 7.0 Hz, H-C(5)); 2.5 (q, 7.3 Hz, H-C(4)); 2.37 - 2.06 (m, 3H); 1.84 (m, H endo-C(6)); 1.46 (d, CH_3). 9 : oil; ^{1}H-NMR ($CDCl_3$) : 4.24 (q, J = 6.5; H-C(6)); 4.04 (ddd, 6.5, 7.0, 8.0, H-C(3)); 3.7 (s, COOMe); 2.78 (dd, 16.0, 6.5, H-C(7)); 2.58 - 2.49 (m, H-C(2), H-C(7)); 2.17 (s, CH_3(9)), 2.17 - 1.96 & 1.69 - 1.47 (4m, H_2C(4), H_2C(5)); 1.13 (d, 7.0, CH_3-C(2)). IR (film) : 1740, 1710 cm^{-1}. (±)-4 : oil; ^{1}H-NMR ($CDCl_3$, 360 MHz) : 4.13 - 4.05 (m, H-C(8)); 4.04 - 3.96 (m, H-C(3), H-C(6)); 3.7 (s, COOMe); 3.2 (br s, OH); 2.56 (dq, 8.5, 7.0, H-C(2)); 2.09 - 1.97 (m, H_2C(4)); 1.71 - 1.49 (m, H_2C(5), H_2C(7)); 1.17 (d, 6.2, CH_3(9)); 1.13 (d, 7.0, CH_3-C(2)). IR (film) : 3500, 2980, 1740, 1460 cm^{-1}.
13. Details will be reported in a full-paper.
14. Saponifications of methyl esters 3 and 4 are known[4,5] to undergo without epimerization at C(2).

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