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Enantioselective Syntheses of (+)-Methyl Nonactate and (-)-Methyl 8-*epi*-Nonactate via Asymmetric Cycloadditive Route

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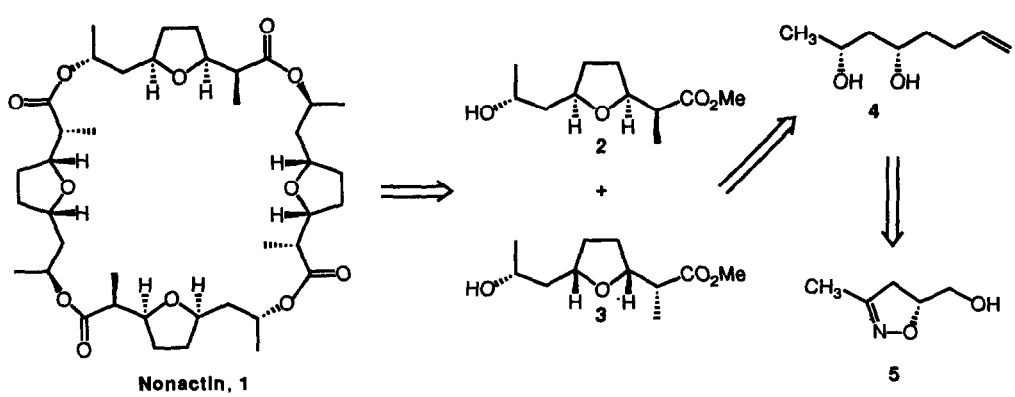
Abstract: Enantioselective routes to (+)-methyl nonactate (2) and (-)-methyl 8-epi-nonactate (3) are described. The cornerstone of this synthetic strategy is a combination of asymmetric silyl nitronate cycloaddition and asymmetric reduction, which provides the key syn-1,3-diol intermediate 4.

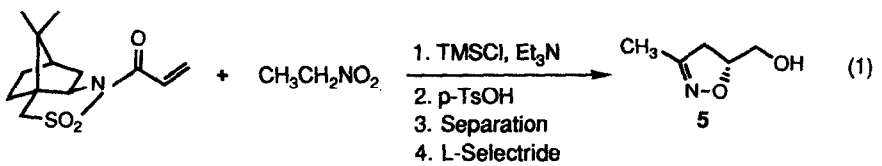
Nonactin (**1**) is an ionophoric macrotetrolide antibiotic isolated from a variety of *Streptomyces* cultures.[1] It is composed of two subunits of (+)-nonactic acid and two subunits of (-)-nonactic acid, arranged in an alternating order (S_4 symmetry).[2] There have been many reported syntheses of nonactic acid derivatives in both optically active and racemic form with varying success with respect to the degree of stereoselectivity.[3] We now report the enantioselective syntheses of both (+)-methyl nonactate (**2**) and (-)-methyl 8-*epi*-noanctate (**3**) via asymmetric cycloadditive route.

The key elements of our approach to both (+)-methyl nonactate (**2**) and (-)-methyl 8-*epi*-nonactate (**3**) are outlined in Scheme 1. The common precursor to **2** and **3** is envisioned to be the *syn*-1,3-diol **4**, which shoud be available from the 2-isoxazoline **5** in several steps including an asymmetric reduction. In turn, the optically active 2-isoxazoline **5** is prepared by the asymmetic silyl nitronate cycloaddition methodology.[4]



Scheme 1

The optically active starting material, 5-hydroxymethyl-3-methyl-2-isoxazoline (**5**),[5] was prepared by the standard procedures in 63% overall yield (Eq. 1).[4] The comparison of the optical rotation of **5** with the literature value[6] and NMR (^{1}H and ^{19}F) study of the corresponding Mosher's ester[7] indicated that **5** was more than 98% enantiomerically pure.



(1)

The synthetic pathways toward (+)-methyl nonactate (**2**) and (-)-methyl 8-*epi*-nonactate (**3**) from **5** are shown in Scheme 2. The hydroxy group of 2-isoxazoline **5** was protected with *tert*-butylchlorodimethylsilane (93%) and then the reductive cleavage of **6** by Curran's method[8] gave the β-hydroxy ketone **7** in 86% yield. Asymmetric reduction of the β-hydroxy ketone **7** using diethylmethoxyborane-sodium borohydride in tetrahydrofuran provided the *syn*-1,3-diol derivetive **8** with an excellent *syn* selectivity (*syn:anti*=96:4).[9] The *syn*-diol derivative **8** was easily separated in 86% yield by flash column chromatography. Other known reduction methods[10] were not practical due to the low *syn*-selectivity (34-70%). Both hydroxy groups of the resulting *syn*-diol derivative **8** were protected with 2,2-dimethoxypropane (93%) and subsequent desilylation with tetrabutylammonium fluoride (TBAF) afforded the acetonide **10** in 93% yield. After tosylation (87%), many experiments were carried out to optimize the allylation of the resulting tosylate **11**. Finally, the allylation of **11** with allylmagnesium chloride was completed within 4hr in the presence of copper iodide(I) under refluxing condition. Allylation followed by deprotection with *p*-toluenesulfonic acid produced the key *syn*-1,3-diol intermediate **4**[5] in 86% overall yield. The conversion of **4** to (+)-methyl nonactate (**2**) and (-)-methyl 8-*epi*-nonactate (**3**) was achieved by the elegant method of Bartlett[3j,n] under slightly modified conditions. The diol **4** was protected with 1,1'-carbonyldiimidazole (73%). Sequential ozonolysis (85%), aldol condensation of the resulting aldehyde with the trimethylsilyl enol ether of methyl propionate according to the Mukaiyama method (91%),[11] and pyridinium chlorochromate (PCC) oxidation (81%)[12] gave the β-keto ester **12**. From the β-keto ester **12**, (+)-methyl nonactate (**2**) was obtained by *O*-cyclization (77%) of the potassium enolate of **12** and Rh-catalyzed hydrogenation (91%). On the other hand, (-)-methyl 8-*epi*-nonactate (**3**) was prepared by methanolysis and acid-catalyzed dehydration (80% overall), and Rh-catalyzed hydrogenation (83%). ^{1}H NMR spectra of (+)-methyl nonactate (**2**)[5] and (-)-methyl 8-*epi*-nonactate (**3**)[5] are in accord with the corresponding spectra provided by Professor P.A. Bartlett.

Since a variety of enantiomerically pure 2-isoxazoline derivatives[13] are available using the asymmetric silyl nitronate cycloaddition methodology,[4] our approach is generally applicable to the syntheses of natural[14] and unnatural[3w] homologs of (+)- and (-)-methyl nonactate.

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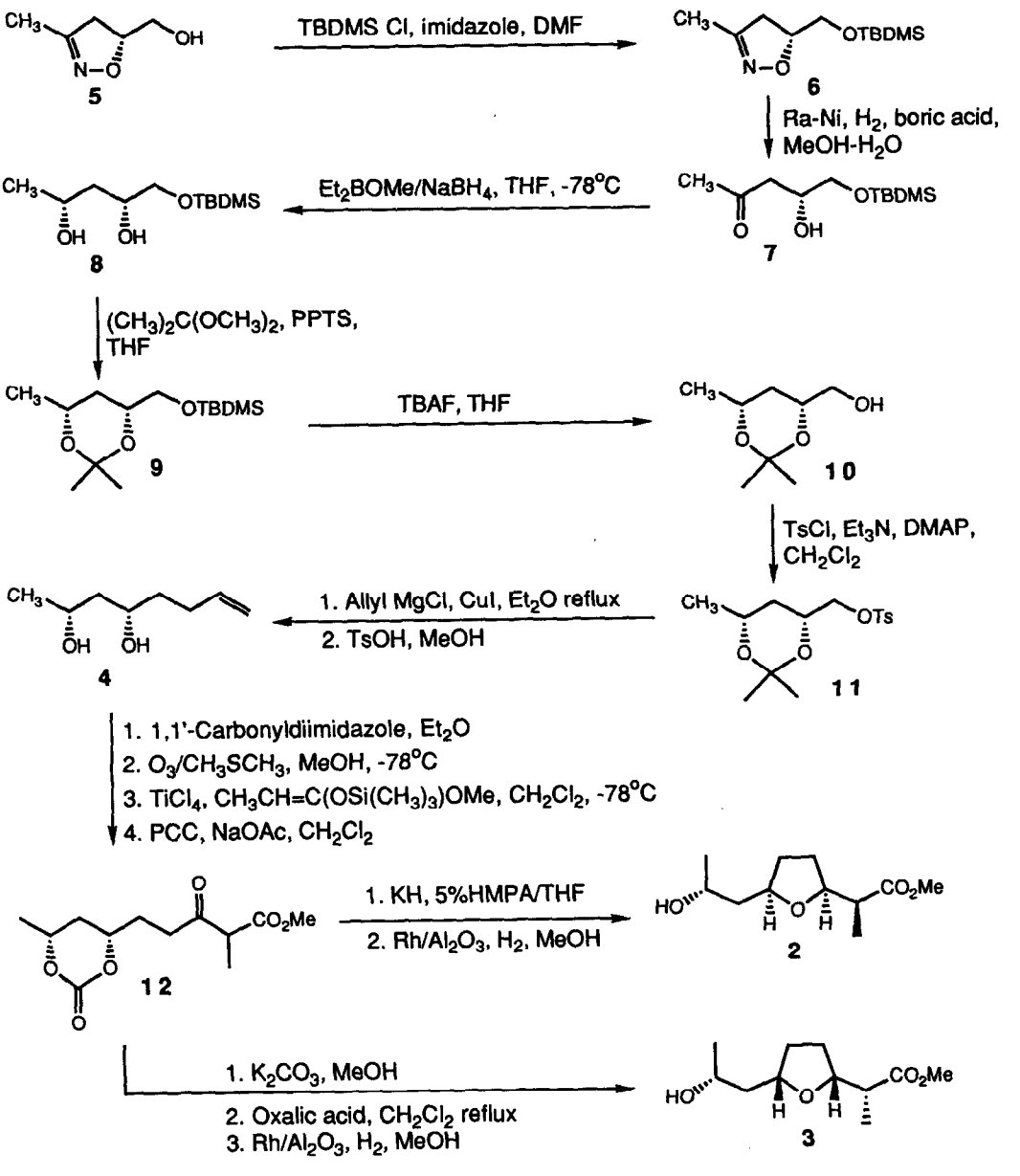
TBDMS Cl, imidazole, DMF
Ra-Ni, H_2, boric acid, MeOH-H_2O
$Et_2BOMe/NaBH_4$, THF, -78°C
$(CH_3)_2C(OCH_3)_2$, PPTS, THF
TBAF, THF
TsCl, Et_3N, DMAP, CH_2Cl_2
1. Allyl MgCl, CuI, Et_2O reflux
2. TsOH, MeOH
1. 1,1'-Carbonyldiimidazole, Et_2O
2. O_3/CH_3SCH_3, MeOH, -78°C
3. $TiCl_4$, $CH_3CH=C(OSi(CH_3)_3)OMe$, CH_2Cl_2, -78°C
4. PCC, NaOAc, CH_2Cl_2
1. KH, 5%HMPA/THF
2. Rh/Al_2O_3, H_2, MeOH
1. K_2CO_3, MeOH
2. Oxalic acid, CH_2Cl_2 reflux
3. Rh/Al_2O_3, H_2, MeOH
5
6
7
8
9
10
11
4
12
2
3

Scheme 2

References and Notes

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5. **Compound 5**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.97 (3H, s), 2.08 (1H, br. s) 2.80 (1H, dd, J=16.8, 7.3Hz), 2.95 (1H, dd, J=16.8, 10.6Hz), 3.54 (1H, dd, J=12.2, 4.5Hz), 3.74 (1H, dd, J=12.2, 3.2Hz), 4.65 (1H, m) ; ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.0, 40.0, 63.7, 80.1, 155.9; $[\alpha]_D^{23}$ -170.3° (c 1.1, $CHCl_3$), lit.[6] $[\alpha]_D^{25}$ -172° (c 1.0, $CHCl_3$); **Compound 4**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.19 (3H, d, J=6.4Hz), 1.44-1.62 (4H, m), 2.10-2.20 (2H, m), 2.59 (2H, br. s), 3.84-3.92 (1H, m), 4.01-4.08 (1H, m), 4.95-5.08 (2H, m), 5.76-6.00 (1H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.3, 28.7, 37.2, 44.7, 69.1, 72.5, 114.9, 138.4; $[\alpha]_D^{23}$ -18.2° (c 1.0, CCl_4), lit.[3n] $[\alpha]_D^{25}$ -18.3° (c 0.75, CCl_4); **Compound 2**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.12 (3H, d, J=7.0Hz), 1.19 (3H, d, J=6.3Hz), 1.59-1.78 (4H, m), 1.96-2.05 (2H, m), 2.53 (1H, m), 2.86 (1H, br. s), 3.68 (3H, s), 3.92-4.16 (3H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.5, 23.1, 28.8, 30.5, 42.6, 45.3, 51.7, 65.1, 77.2, 81.0, 175.2; $[\alpha]_D^{27}$ +19.6° (c 1.44, $CHCl_3$), lit.[3n] $[\alpha]_D^{25}$ +13.1° (c 0.708, $CHCl_3$), lit.[3i] $[\alpha]_D^{25}$ +22.1° (c 0.7, $CHCl_3$), lit.[3f] for (-) isomer $[\alpha]_D^{20}$ -17.8° (c 3.6, $CHCl_3$); **Compound 3**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.11 (3H, d, J=7.0Hz), 1.15 (3H, d, J=6.1Hz), 1.49-1.67 (4H, m), 1.96-2.04 (2H, m), 2.54 (1H, m), 3.56 (1H, br. s), 3.68 (3H, s), 3.95-4.08 (3H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.4, 23.4, 28.5, 31.7, 44.6, 45.3, 51.7, 67.8, 80.2, 81.6, 175.2; $[\alpha]_D^{22}$ -31.5° (c 1.43, $CHCl_3$), lit.[3n] $[\alpha]_D^{25}$ -23.1° (c 1.07, $CHCl_3$), lit.[3i] for (+) isomer $[\alpha]_D^{25}$ +32.9° (c 1.07, $CHCl_3$).
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