A practical route to methyl nonactate

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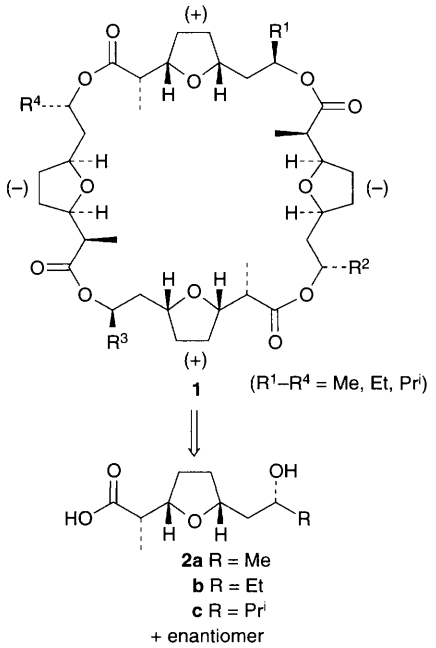
Methyl nonactate is available with excellent stereoselectivity in only six steps from furan by application of sequential transformations.

Actic acids **2** are the monomeric subunits of the macrotetrolides **1**, also known as actins or nactins, which have been isolated from various *Streptomyces* cultures (Scheme 1).[1] The neutral ionophores[2] **1** display pronounced antibacterial,[3] insecticidal[4] and in part immunosuppressive[5] activities. An unusual feature of the structurally elucidated macrotetrolides **1** is the alternating sequence[6] of (+)- and (−)-enantiomers of the building blocks **2**. With respect to an efficient synthesis of actins **1**, including the achiral S_4-symmetrical members such as nonactin (R^1–R^4 = Me)[7] and tetranactin (R^1–R^4 = Et),[8] an enantioselective preparation of both enantiomers of **2**[9] is thus required. Though several syntheses of nonactic acid **2a**[10,11] and some reports on the synthesis of its homologues[8,12] have been published, a short and general access to compounds **2a–c** is still highly desirable in view of the biological activities associated with the actins. Here we report a practical route to methyl nonactate which emerged from our studies on intramolecular Diels–Alder reactions of vinylsulfonates and the synthetic elaboration of the resultant sultones.[13]

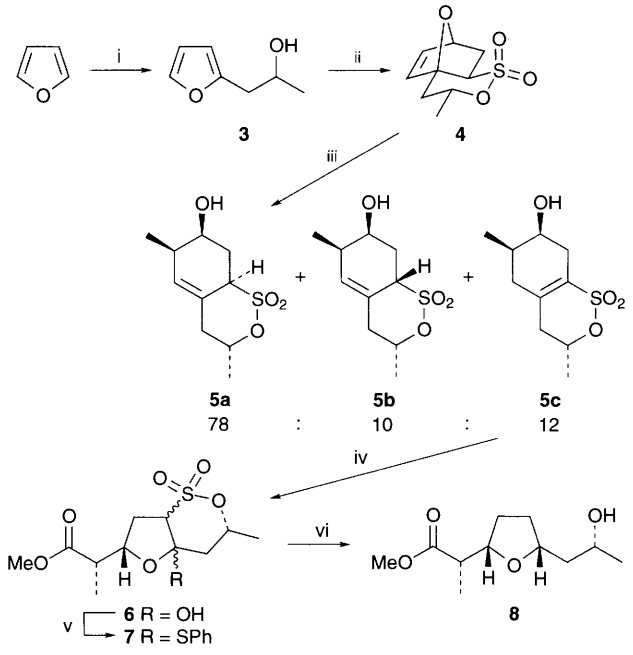
Alcohol **3**, prepared from furan and epoxypropane, reacted with vinylsulfonyl chloride to give sultone **4** by a tandem esterification/cycloaddition (Scheme 2).[13a] Subsequent treatment of **4** with 2 equiv. of methyllithium induced a tandem elimination/1,6-addition to yield the bicyclic compounds **5a–c**.[13c] Both the intramolecular Diels–Alder reaction to **4** and the alkoxide-directed C–C coupling involved in the formation of **5** occur with complete diastereoselectivity, whereas a less regio- and stereo-selective protonation of the intermediate allyllithium species produced upon 1,6-addition leads to a mixture of **5a–c**.

Ozonolysis of **5a**, obtained isomerically pure by base-catalysed equilibration of **5a–c** (Bu^tOK, 77%),[13c] followed by eliminative work-up[14] yielded a single hemi-acetal **6** (69%).† However, more straightforward and efficient is the corresponding transformation of the mixture **5a–c** under identical conditions. Only the allylic sultones **5a** and **5b** are attacked, while **5c** can be easily separated. The production of two diastereoisomeric methyl esters **6**‡ implies a regioselective cycloreversion of the primary ozonides from **5a** and **5b** with formation of the intermediate carbonyl oxide distal to the electron-withdrawing sulfonate function and cyclization of the resultant γ-hydroxy ketone moiety to a hemi-acetal. A Lewis acid-catalysed exchange of the hydroxy group in **6** against a phenylsulfanyl group[15] in **7**† sets the stage for a chemoselective reductive cleavage of both C–S bonds in one operation. Gratifyingly, upon treatment of **7** with Raney nickel, methyl nonactate **8** was directly obtained. Presumably, a reductive elimination first occurs to give a single 2,3-dihydrofuran[16] which in turn is immediately hydrogenated by the hydrogen adsorbed within the Raney nickel highly diastereoselectively (**8**:6-*epi*-**8**[7c,11] = 96:4)§ from the sterically less hindered π-face.

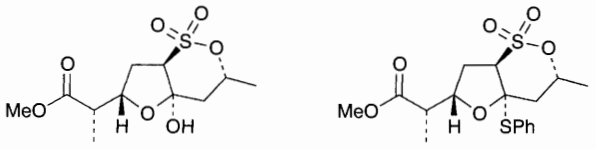
Saponification of **8** to nonactic acid **2a** is known[7b] and thus, our sultone route from furan to **8** consisting of only six steps due to the application of sequential transformations[17] also con-



Scheme 1



Scheme 2 *Reagents and conditions*: i, BuLi, THF, −78 °C then epoxypropane, −78 °C to room temp., 65%; ii, CH_2=$CHSO_2Cl$, Et_3N, THF, 0 °C to room temp., 90%; iii, MeLi, THF, −78 to 0 °C then sat. aqueous NH_4Cl, −78 °C to room temp., 54%; iv, O_3, $NaHCO_3$, CH_2Cl_2, MeOH, −78 °C then Ac_2O, pyridine, CH_2Cl_2, room temp., 66%; v, PhSH, BF_3·Et_2O, CH_2Cl_2, room temp., 93%; vi, Raney Ni, EtOH, room temp., 51%



6 (from **5a**) **7** (from **5a**)

Fig. 1

stitutes the shortest synthesis of acid **2a** with excellent stereocontrol. Since the tricyclic compounds corresponding to sultone **4** with an ethyl or isopropyl substituent instead of the methyl group are readily prepared in an analogous fashion,[13a] this reaction sequence should offer a general access to all actic acid homologues **2a–c**. Moreover, the transition to enantioselective synthesis is at hand, since the requisite enantiomerically pure epoxides which react with lithiated furan to the starting materials[7b,13a] for the tandem esterification/Diels–Alder reaction are easily available in both enantiomeric forms.[18]

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Footnotes

† The relative configuration of **6** and **7** obtained from pure **5a** (Fig. 1) was unambiguously established by X-ray diffraction analysis. *Crystal data* for **6** (from **5a**): $C_{11}H_{18}O_7S$, M = 294.3, triclinic, space group $P\bar{1}$ (No. 2), a = 8.370(1), b = 8.839(2), c = 10.027(2) Å, α = 77.56(2), β = 81.74(1), γ = 67.15(1)°, V = 666.1(2) Å^3, Z = 2, D_c = 1.467 g cm^{-3}, μ = 24.3 cm^{-1}, $F(000)$ = 312, colourless crystal with dimensions 0.5 × 0.3 × 0.2 mm, λ = 1.54178 Å, T = 223(2) K, Θ = 4.53–74.06°, $-10 \leqslant h \leqslant 9$, $-11 \leqslant k \leqslant 0$, $-12 \leqslant l \leqslant 12$, 2894 reflections collected, 2709 independent [R_{int} = 0.022], full-matrix least-squares refinement on F^2, 176 parameters, GOF on F^2 1.051, final R indices [$I > 2\sigma(I)$] R = 0.043 and wR^2 = 0.119, largest difference peak and hole 0.33 and −0.58 eÅ^3. For **7** (from **5a**): $C_{17}H_{22}O_6S_2$, M = 386.5, monoclinic, space group $P2_1/n$ (No. 14), a = 13.393(2), b = 9.320(2), c = 15.195(2) Å, β = 100.75(1)°, V = 1863.4(5) Å^3, Z = 4, D_c = 1.378 g cm^{-3}, μ = 28.6 cm^{-1}, $F(000)$ = 816, colourless crystal 0.3 × 0.2 × 0.2 mm, λ = 1.54178 Å, T = 223(2) K, Θ = 4.04–74.16°, $0 \leqslant h \leqslant 16$, $-11 \leqslant k \leqslant 0$, $-18 \leqslant l \leqslant 18$, 3959 reflections collected, 3795 independent [R_{int} = 0.016], full-matrix least-squares refinement on F^2, 230 parameters, GOF on F^2 1.237, final R indices [$I > 2\sigma(I)$] R = 0.037 and wR^2 = 0.104, largest difference peak and hole 0.36 and −0.35 eÅ^3. Atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre. See Information for Authors, Issue No. 1.

‡ Capillary GC/MS analysis of **6** [after silylation with *N,O*-bis-(trimethylsilyl)acetamide] obtained from the mixture of **5a** and **5b** showed two products (93 : 7) with nearly identical mass spectra.

§ According to capillary GC analysis of the crude product.

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