A Concise Synthesis of (±)-t-Butyl 8-*O*-t-Butyldimethylsilylnonactate

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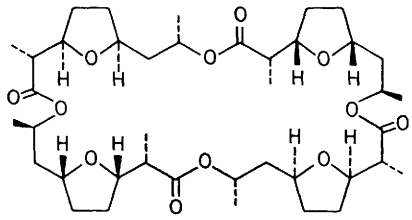
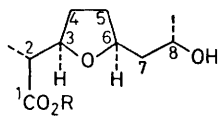
The racemic title compound was prepared in seven steps from 2,3,4-tri-*O*-acetyl-D-ribonolactone (**3**) *via* the highly stereoselective hydrogenations of 3-acetoxy-5-methylenefuran-2(5*H*)-one (**4**) and, subsequently, 2*S*(*R*)-[2*S*(*R*)-(t-butyldimethylsilyloxy)propyl]-5-[1-(t-butyloxycarbonyl)ethylidene]tetrahydrofuran (**9**).

Nonactin (**1**) is an antibiotic ionophore produced by *Streptomyces*. It is notable for the ability to mediate cation transport. In particular potassium ions are readily complexed. Nonactin (**1**) is a tetrameric mesomolecule composed of alternating dextro- and laevo-rotatory nonactic acid (**2a**)† units. Although methyl nonactate (**2b**) has been synthesised by several groups in racemic form[1,2] or as dextro- or laevo-rotatory enantiomers,[3] all these syntheses involve numerous stages. In addition, with one excellent exception,[1] these syntheses involve at least one step of low stereoselectivity.

Herein, we report a seven-stage, highly stereoselective synthesis of (±)-t-butyl 8-*O*-t-butyldimethylsilylnonactate (**10**) which is clearly amenable to multigram synthesis (Scheme 1).

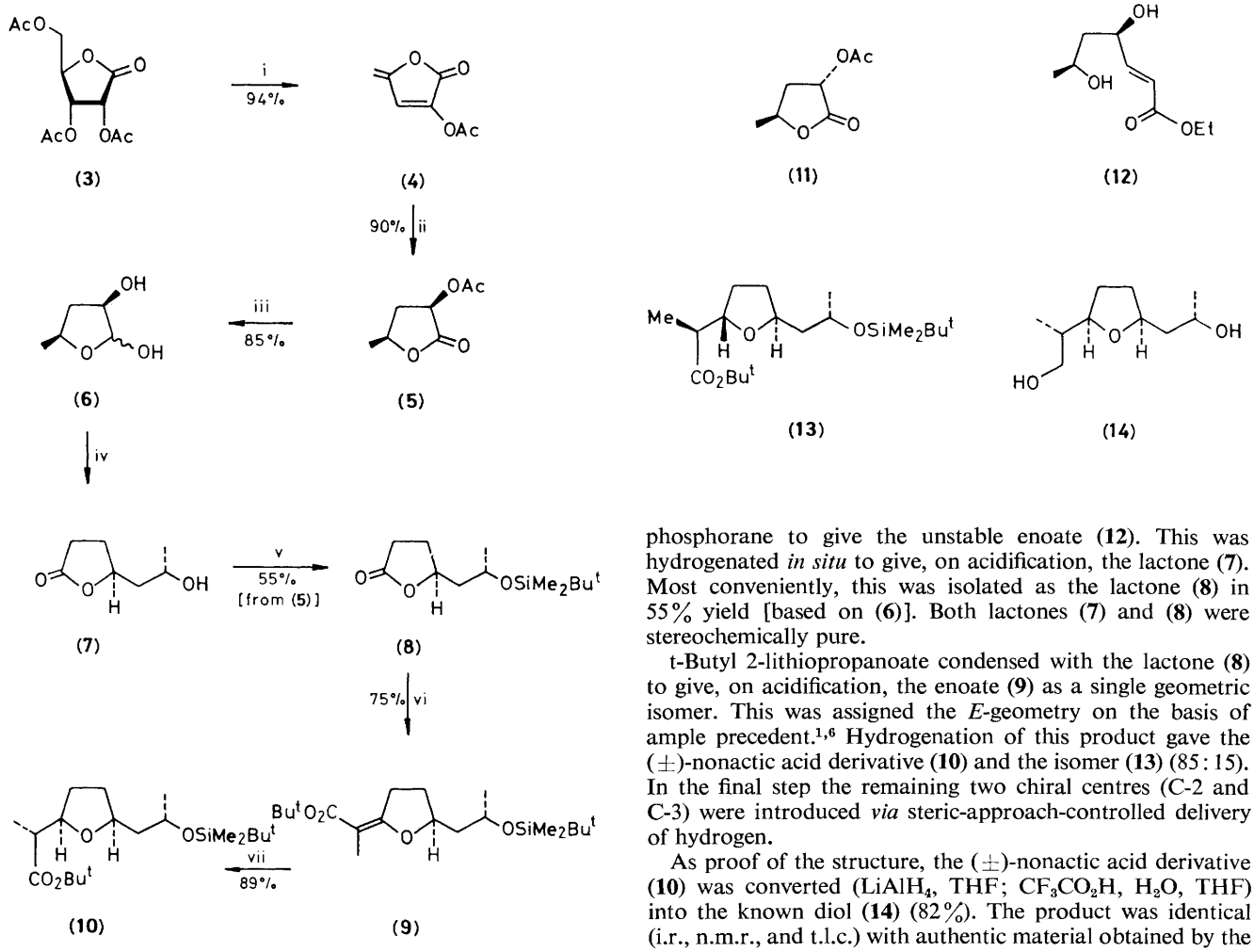


(**1**)



(**2**)
a; R = H
b; R = Me

† Structures (**2**) and (**5**)—(**14**) refer to racemic modifications.



Scheme 1. Reagents and conditions (THF = tetrahydrofuran; DMF = dimethylformamide): i, DBU (1 equiv.), THF, —20 to 0 °C; dil. HCl; ii, H_2, Pd–$CaCO_3$, THF; iii, Bu^i_2AlH (3.1 equiv.), PhMe, —78 °C; HOAc; iv, $Ph_3P{=}CHCO_2Et$, THF; H_2, Rh–Al_2O_3, THF; CF_3CO_2H; v, Bu^tMe_2SiCl, imidazole, DMF; vi, MeCH=C(OBu^t)OLi (10 equiv.), THF; HOAc; Amberlite 120 H; vii, H_2, Rh–Al_2O_3, THF.

2,3,5-Tri-*O*-acetyl-D-ribonolactone (**3**) is an inexpensive, readily available starting material. On reaction with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), the double elimination of acetic acid occurred giving the diene (**4**), m.p. 75—76 °C.‡ Routinely, this was hydrogenated without purification to give the lactone (**5**).[4]§ Clearly this steric-approach-controlled hydrogenation[5] correctly established two of the four chiral centres of (±)-nonactic acid (C-6 and C-8). The isomeric lactone (**11**) was not detected [(**5**):(**11**) > 97:3]. The lactol (**6**), derived from (**5**) and di-isobutylaluminium hydride, condensed cleanly with ethoxycarbonylmethylenetriphenylphosphorane to give the unstable enoate (**12**). This was hydrogenated *in situ* to give, on acidification, the lactone (**7**). Most conveniently, this was isolated as the lactone (**8**) in 55% yield [based on (**6**)]. Both lactones (**7**) and (**8**) were stereochemically pure.

t-Butyl 2-lithiopropanoate condensed with the lactone (**8**) to give, on acidification, the enoate (**9**) as a single geometric isomer. This was assigned the *E*-geometry on the basis of ample precedent.[1,6] Hydrogenation of this product gave the (±)-nonactic acid derivative (**10**) and the isomer (**13**) (85:15). In the final step the remaining two chiral centres (C-2 and C-3) were introduced *via* steric-approach-controlled delivery of hydrogen.

As proof of the structure, the (±)-nonactic acid derivative (**10**) was converted ($LiAlH_4$, THF; CF_3CO_2H, H_2O, THF) into the known diol (**14**) (82%). The product was identical (i.r., n.m.r., and t.l.c.) with authentic material obtained by the reduction of nonactin (**1**).[7]

Clearly, the (±)-nonactic acid derivative (**10**) is now available in seven steps from readily available starting materials in an unoptimised overall yield of > 24%.

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‡ Compounds (**4**)—(**10**) were fully characterised by spectral data, including 250 MHz n.m.r. Compounds (**4**), (**6**), (**8**), (**9**), and (**10**) microanalysed correctly.

§ The known[4] mixture of lactones (**5**) and (**11**) was readily obtained *via* 2,4-dihydroxypentanenitrile, acid-catalysed hydrolysis, and acetylation. N.m.r. spectra are detailed elsewhere.[4] In addition sodium borohydride reduction of the lactone (**5**) gave *threo*-pentane-1,2,4-triol (100%) (microanalysed as the tri-benzoate). None of the *erythro*-isomer was detected by ^1H or ^{13}C n.m.r. spectroscopy.

References

1 P. A. Bartlett and K. K. Jernstedt, *Tetrahedron Lett.*, 1980, **21**, 1607.
2 H. Gerlach and H. Wetter, *Helv. Chim. Acta*, 1974, **57**, 2306; M. J. Arco, M. H. Trammell, and J. D. White, *J. Org. Chem.*, 1976, **41**, 2075; G. Beck and E. Henseleit, *Chem. Ber.*, 1971, **104**, 21.
3 R. E. Ireland and J.-P. Vevert, *Can. J. Chem.*, 1981, **59**, 572; U. Schmidt, J. Gombos, E. Haslinger, and H. Zak, *Chem. Ber.*, 1976, **109**, 2628; H. Zak and U. Schmidt, *Angew. Chem., Int. Ed. Engl.*, 1975, **14**, 432; K. M. Sun and B. Fraser-Reid, *Can. J. Chem.*, 1980, **58**, 2732.
4 C. Daremon, R. Rambaud, and M. Verniette, *C. R. Acad. Sci. Paris Sect. (C)*, 1971, **273**, 1273.
5 S. A. M. T. Hussain, W. D. Ollis, C. Smith, and J. F. Stoddart, *J. Chem. Soc., Perkin Trans.* 1, 1975, 1480.
6 T. A. Bryson, *J. Org. Chem.*, 1973, **38**, 3428; S. A. Krueger and T. A. Bryson, *ibid.*, 1974, **39**, 3167.
7 J. Dominguez, J. D. Dunitz, H. Gerlach, and V. Prelog, *Helv. Chim. Acta.*, 1962, **45**, 129.