The Synthesis of (+)- and (−)-t-Butyl Nonactate from L-Glutamic Acid

Shari Batmangherlich and Alan H. Davidson*

Department of Applied Chemistry, UWIST, P.O. Box 13, Cardiff CF1 3XF, U.K.

A short enantiodivergent route to (+)- and (−)-t-butyl nonactate (**2b**) from lactone (**3**) is described; a method for determining the optical purity of these compounds which can be used to resolve (±)-methyl nonactate (**2c**) is reported.

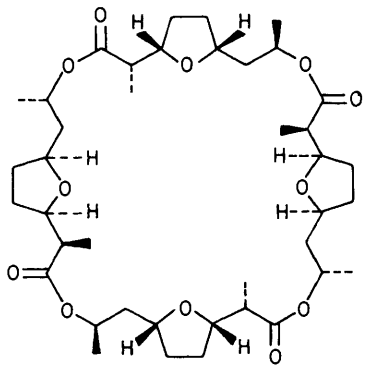
Nonactin[1] (**1**) is a tetrameric ionophore antibiotic composed of the two enantiomers of nonactic acid (**2a**) arranged in a (+)-(−)-(+)-(−) sequence. Any viable synthesis of nonactin therefore requires the production of reasonable quantities of both (+)- and (−)-nonactic acid (**2a**) in optically pure form.[2—4] In this communication we describe a short enantiospecific synthesis of (+)- and (−)-t-butyl nonactate (**2b**) from the readily available optically active lactone (**3**) by two almost identical routes. Either enantiomer is obtained simply by altering the substituent on the primary hydroxy group of lactone (**3**).

Lactone (**3**) is available in two steps and on a large scale from inexpensive L-glutamic acid.[5] For the synthesis of the (−)-enantiomer of (**2b**) it was converted into the silyl ether (**4**) which when reacted with the lithium anion of t-butyl propionate gave, after dehydration, the (*E*)-alcohol (**5**).[2,6] In this sequence the stereochemistry at C-6 is retained. Hydrogenation of (**5**) and removal of the protecting group produced the (−)-enantiomer of the key alcohol (**6**) together with a small amount (5%) of another isomer† [overall yield from (**3**), 60%].

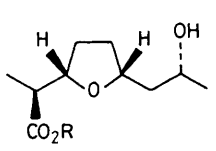
For the synthesis of the (+)-enantiomer, lactone (**3**) was first converted into the toluene-*p*-sulphonate (**7**) which when reacted with the lithium anion of t-butyl propionate in hexamethylphosphoric triamide/tetrahydrofuran (HMPA/THF) gave the (*E*)-alcohol (**8**).‡ This reaction proceeds *via* the epoxide (**9**) hence the stereochemistry at C-6 is inverted.[7]

† It might be expected that the other isomer is simply the one resulting from addition of hydrogen from the more hindered face but Bartlett (ref. 2) has reported that under the hydrogenation conditions isomers resulting from epimerisation at C-2 can also be produced.

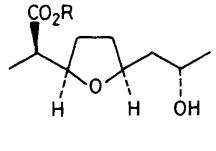
‡ Previously we reported (ref. 7) that this reaction gave mainly the (*Z*)-isomer which had to be isomerised to the (*E*)-isomer. If the lithium anion of t-butyl propionate is added to (**7**) dissolved in HMPA/THF (1 : 1) the (*E*)-isomer is obtained directly.



(1)

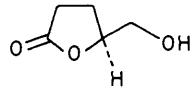


(+)-(2)

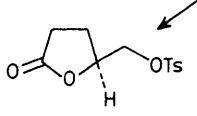


(-)-(2)

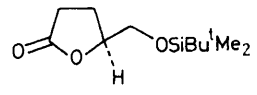
a; R = H
b; R = Bu^t
c; R = Me



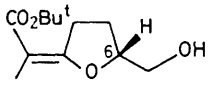
(3)



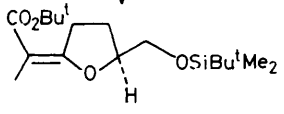
(7)



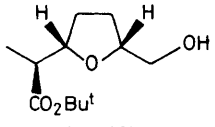
(4)



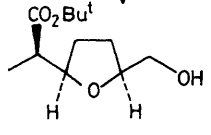
(8)



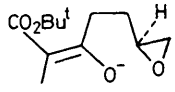
(5)



(+)-(6)



(-)-(6)

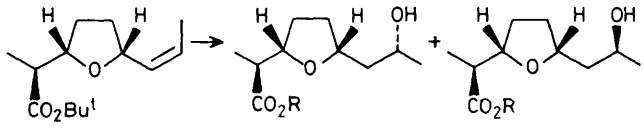


(9)

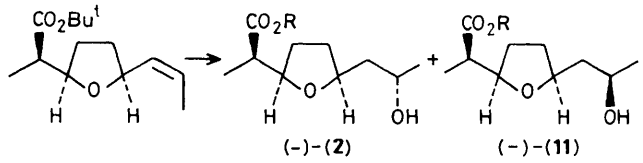
Ts = *p*-MeC$_6$H$_4$SO$_2$

Hydrogenation of (**8**) produced the (+)-enantiomer of the key alcohol (**6**) together with a small amount (10%) of another isomer† [overall yield of (**6**) from (**3**), 55%].

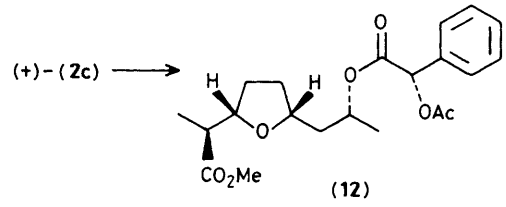
The two alcohols (+)- and (−)-(**6**) were converted into the corresponding benzoates and their optical rotations



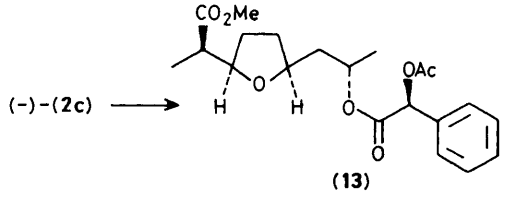
(10) (+)-(2) (+)-(11)



(-)-(2) (-)-(11)



(12)



(13)

a; R = H
b; R = Bu^t
c; R = Me

measured. These were equal in magnitude but opposite in sign indicating that the alcohols were indeed enantiomers of each other and that the reactions had proceeded with the expected stereochemistry. Alcohols (+)- and (−)-(**6**) have the correct absolute stereochemistry at four out of the five chiral centres for (+)- and (−)-nonactic acid. In order to introduce the fifth chiral centre at C-8, (**6**) was converted into the (*Z*)-olefin (**10**) [Swern oxidation, $Ph_3\overset{+}{P}$–$\bar{C}HCH_3$, 50% yield from (**6**)] as there have been several reports[8] that (*Z*)-olefins with adjacent chiral centres bearing oxygen atoms undergo highly stereoselective addition reactions. Bromohydrin formation using *N*-bromosuccinimide in Me_2SO/H_2O followed by reduction with Bu_3SnH and separation by flash column chromatography gave 8-*epi*-t-butyl nonactate (**11b**) and t-butyl nonactate (**2b**) in a ratio of 4 : 1 [combined yield 60% from (**10**)]. The stereochemistry at C-8 was determined by conversion of (**11b**) and (**2b**) into the methyl esters (**11c**) and (**2c**) which were compared to an authentic sample of methyl nonactate prepared by methanolysis of nonactin. The structure of (**11c**) was confirmed by comparison of its high field ^{1}H n.m.r. spectra with data reported in the literature.[2] White[9] has shown that the 8-*epi*-compound (**11c**) can be converted into methyl nonactate (**2c**) in two high-yielding steps. Furthermore the best method for coupling two nonactic acid sub-units is by displacement of an 8-*epi*-toluene-*p*-sulphonate with the carboxylate anion of nonactic acid.[3,4]

Both (+)- and (−)-enantiomers of (**6**) were taken through the above sequence and, therefore, both enantiomers of t-butyl nonactate and 8-*epi*-t-butyl nonactate were obtained. Since optically pure methyl nonactate can not be obtained

from natural sources it was decided to determine the optical purity of the synthetic materials by Whitesell's method[10] rather than rely upon a comparison of optical rotations with literature values. Reaction of (+)- and (−)-(**2c**) with (*S*)-*O*-acetylmandelic acid gave the two diastereoisomers (**12**) and (**13**). These were easily distinguishable in the high field ^{1}H n.m.r. spectrum and the optical purity of (+)-(**2c**) and (−)-(**2c**) could be determined (90% enantiomeric excess). This procedure also offered a method for the resolution[10] of methyl nonactate since reaction of (*S*)-*O*-acetylmandelic acid with racemic methyl nonactate (obtained by methanolysis of nonactin) gave a mixture of diastereoisomers which could be separated by either preparative thin layer chromatography or flash column chromatography.

In conclusion, we have developed a short enantiospecific synthesis of (+)- and (−)-t-butyl nonactate from L-glutamic acid based on our work on the addition of carbanions to lactones. A method for determining the optical purity and to resolve methyl nonactate has also been developed.

We thank the S.E.R.C. for financial support and Professor G. Procter for helpful discussions.

Received, 5th July 1985; Com. 957

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