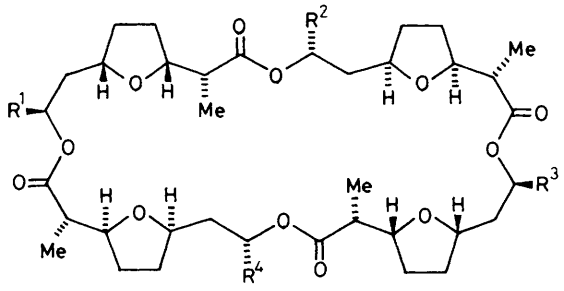
An Enantioselective Route to Nonactic Acid and its Homologues

Philip C. Bulman Page, John F. Carefull, Laurence H. Powell, and Ian O. Sutherland

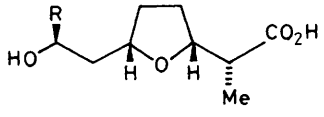
The Robert Robinson Laboratories, University of Liverpool, P.O. Box 147, Liverpool L69 3BX, U.K.

Enantioselective routes to the aldehyde (**10**) and the lactone (**9**) are described; these products may be converted into (−)-nonactic acid (**2**) and (+)-nonactic acid (**3**) by procedures used previously for the synthesis of (±)-nonactic acid.

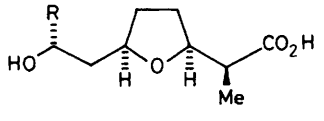
The macrotetrolide nactin antibiotics (**1**) are selective ionophores[1] and have attracted considerable attention from synthetic chemists.[2] A satisfactory synthesis of the antibiotics requires enantioselective synthesis of each of the enantiomers of the hydroxy acid units that are combined together in the macrotetrolides. A number of syntheses of (±)-nonactic acid (**2** + **3**) have been described[2] and satisfactory control of the relative configurations of the four chiral centres has been achieved;[3,4] however the control of absolute configuration has not yet been accomplished in a completely satisfactory manner. Thus syntheses of each of the enantiomers (**2**) and (**3**) have been described[5,6] but in each case the synthetic sequence was long and only in the most recent synthesis[6] was total control of relative configuration achieved. Analogy with an earlier synthesis[3] indicates that enantioselective synthesis of the diol (**4**) would be a simple solution to the stereochemical problems posed by the synthesis of (−)-nonactic acid (**2**). The allylic alcohol (**5**) (*E* : *Z* ratio, 96 : 4) was prepared (95% yield) by reaction of (*E*)-but-2-enal with but-3-enylmagnesium bromide. Catalytic enantioselective epoxidation of the (±)-alcohol (**5**), using the excellent procedure described by Sharpless[7] and L-(+)-di-isopropyl tartrate as the source of enantioselectivity, gave the expected kinetic resolution. After 45% epoxidation the mixture of epoxide (**6**) and unchanged allyl alcohols was isolated and reduced[7,8] with Red-Al to give a mixture of the diol (**4**) [40% yield based upon (±)-(**5**)] and allyl alcohols (**5**) which was readily separated by chromatography on alumina. The epoxide (**6**) could also be isolated by chromatography of the products from the epoxidation reaction (45% conversion) on silica gel although this procedure resulted in major losses of the unchanged allyl alcohols. The epoxy alcohol (**6**)† $[\alpha]_D^{23}$ −28.3° (*c* 1.04 in EtOH) was shown to be a single diastereoisomer (n.m.r. and capillary g.c.) with 96% enantiomeric excess (e.e.) on the basis of the ^{19}F n.m.r. spectrum of its ester with (+)-α-methoxy-α-trifluoromethylphenylacetic acid.[9] Analysis of the recovered allyl



(**1**) R^1, R^2, R^3, R^4 = Me or Et

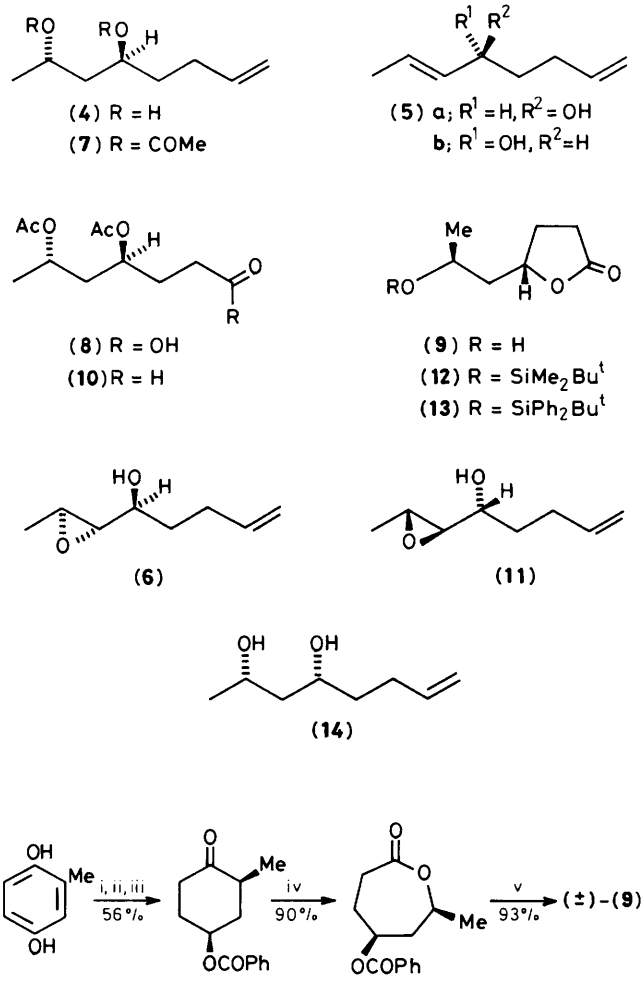


(**2**) R = Me, (−)-nonactic acid



(**3**) R = Me, (+)-nonactic acid

† The absolute configurations of products (**6**)—(**10**) are based upon the established enantioselectivity of the Sharpless epoxidation procedure.[7]



Scheme 1. *Reagents:* i, H_2, Rh/Al_2O_3, EtOH; ii, PhCOCl, C_5H_5N, CH_2Cl_2; iii, CrO_3, H^+; iv, *m*-$ClC_6H_4CO_3H$, $NaHCO_3$, CH_2Cl_2, 0 °C; v, NaOMe, MeOH.

alcohol (**5**) showed that it was enriched in the (*Z*)-diastereoisomer which is consumed more slowly in the epoxidation reaction than the (*E*)-allyl alcohol (**5a**).

The diacetate (**7**) of the (*S,S*)-diol (**4**) reacted with ruthenium trichloride–sodium periodate[10] to give the acid (**8**) (86%) which, on methanolysis using potassium carbonate–methanol, gave the lactone (**9**) (>80%). The racemate of lactone (**9**) has been converted[4] into (±)-nonactic acid and the synthesis of the enantiomer (**9**) therefore provides a synthetic route to (−)-nonactic acid (**2**). Alternatively the aldehyde (**10**), obtained from the diacetate (**7**) by ozonolysis followed by reduction of the ozonide with dimethyl sulphide (97%), also provides a route to (−)-nonactic acid (**2**) by a literature procedure.[3,6]

The relative configuration of the two chiral centres in the lactone (**9**) follows from the established diasteroselectivity of the Sharpless epoxidation.[7] This configuration also follows from direct comparison (n.m.r. spectrum) of the optically active lactone (**9**) with the corresponding racemate prepared by the route outlined in Scheme 1. The ^1H n.m.r. spectra of the optically active lactone and racemic lactone‡ were identical as were the spectra of their t-butyldimethylsilyl (**12**) and t-butyldiphenylsilyl (**13**) derivatives. The configuration at C-4 of the epoxy alcohol (**6**) was inverted by the procedure of Mitsonobu and co-workers[11] and the product reduced with Red-Al to give the (*S,R*)-diol (**14**), $[\alpha]_D^{23}$ + 18.1° (*c* 2.49 in CCl_4) [lit.[12] $[\alpha]_D^{25}$ + 18.4° (*c* 1.0 in CCl_4)]. This result confirms the absolute configuration and optical purity assigned to the epoxy alcohol (**6**).

(+)-Nonactic acid (**3**) is formally derivable by synthesis from enriched allyl alcohol (**5b**)§ or from racemic alcohol (**5**) by carrying out the epoxidation in the presence of D-(−)-tartrate, thus allowing preparation of both enantiomers of nonactic acid by complementary strategies from a single racemic starting material. Homologues of nonactic acid, such as dinactic acid, should also be obtainable by a similar route starting with a homologue of (*E*)-but-2-enal.

We thank Dr. John Ruddock for helpful discussions and Pfizer Central Research and the S.E.R.C. for financial support.

Received, 12th December 1984; Com. 1750

References

1 R. Corbaz, L. Ettlinger, E. Gäuman, W. Keller-Schierlein, F. Kradolfer, L. Niepp, V. Prelog, and H. Zähner, *Helv. Chim. Acta*, 1955, **38**, 1445; H. Gerlach, R. Hüttor, W. Keller-Schierlein, J. Seibl, and H. Zähner, *ibid.*, 1967, **50**, 1782; M. Dobler, 'Ionophores and their Structure,' Wiley, New York, 1981.
2 G. Beck and E. Henseleit, *Chem. Ber.*, 1971, **104**, 21; M. J. Arco, M. H. Trammel, and J. D. White, *J. Org. Chem.*, 1976, **41**, 2075; H. Gerlach and H. Wetter, *Helv. Chim. Acta*, 1974, **57**, 2306.
3 P. A. Bartlett and K. K. Jernstedt, *Tetrahedron Lett.*, 1980, **21**, 1607.
4 A. G. M. Barrett and H. G. Sheth, *J. Chem. Soc., Chem. Commun.*, 1982, 170.
5 R. E. Ireland and J.-P. Vevert, *J. Org. Chem.*, 1980, **45**, 4259.
6 P. A. Bartlett, J. D. Meadows, and E. Ottow, *J. Am. Chem. Soc.*, 1984, **106**, 5304.
7 K. B. Sharpless and T. R. Verhoeven, *Adrichimica Acta*, 1979, **12**, 63; T. Katsuki and K. B. Sharpless, *J. Am. Chem. Soc.*, 1980, **102**, 5974; V. S. Martin, S. S. Woodard, T. Katsuki, Y. Yamada, M. Ikeda, and K. B. Sharpless, *ibid.*, 1981, **103**, 6237; B. E. Rossiter, T. Katsuki, and K. B. Sharpless, *ibid.*, 1981, **103**, 464; K. B. Sharpless, S. S. Woodard, and M. G. Finn, *Pure Appl. Chem.*, 1984, **55**, 1823.
8 J. M. Finan and Y. Kishi, *Tetrahedron Lett.*, 1982, **23**, 2719.
9 J. A. Dale, D. L. Dull, and H. S. Mosher, *J. Org. Chem.*, 1969, **34**, 2543.
10 H. J. Carlsen, T. Katsuki, V. S. Martin, and K. B. Sharpless, *J. Org. Chem.*, 1981, **46**, 3936.
11 T. Kurihara, Y. Nakajima, and O. Mitsunobu, *Tetrahedron Lett.*, 1976, 2455; W. R. Roush, R. J. Brown, and M. DiMare, *J. Org. Chem.*, 1983, **48**, 5083.
12 W. S. Johnson, C. Edington, J. D. Elliott, and I. R. Silverman, *J. Am. Chem. Soc.*, 1984, **106**, 7588.

‡ The spectrum was also identical with that of the racemic lactone (**9**) prepared by an alternative procedure. We thank Dr. A. G. M. Barrett for providing this sample.

§ For example, 80% epoxidation of a recovered sample of alcohol (**5b**) gave the epoxide (**11**), $[\alpha]_D^{23}$ + 28.1° (*c* 1.59 in EtOH), with >92% e.e.