Stereospecific Synthesis of Chiral Acetic Acid from Glycine

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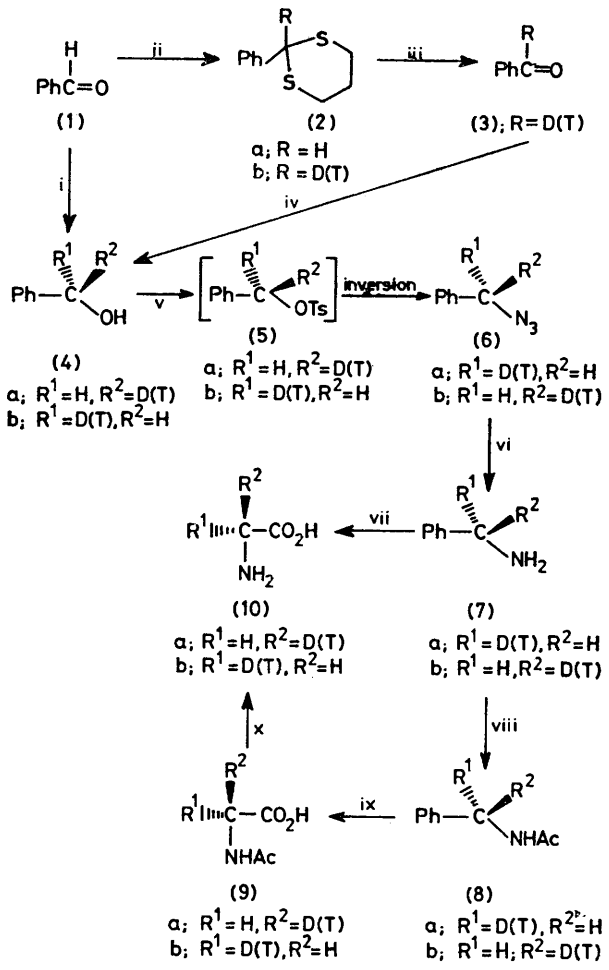
Summary A convenient chemical synthesis of (2*R*)-[^{1}H,^{2}H,^{3}H]acetic acid from (2*R*)-[^{2}H]glycine in high (92%) optical yield is described.

THE use of chiral acetic acid, first introduced for the solution of biosynthetic problems by Cornforth[1] and Arigoni[2] in 1969, continues apace[3] and a new synthesis has been reported.[4] Our requirement for substantial (1—5 g) quantities of

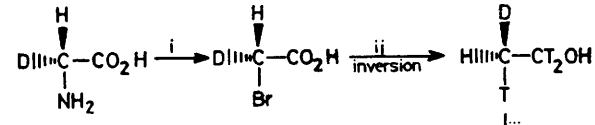


SCHEME 1. i, HLAD, NAD+, 1-[^{2}H or ^{3}H]cyclohexan-1-ol, (78%); ii, propane-1,3-dithiol, Bu^{n}Li, D_2O(TH_2O), (90%); iii, $CuCl_2$, CuO, (86%); iv, HLAD, NAD+, EtOH, (80%) or $Na_2S_2O_4$, H_2O, (70%); v, TsCl, NaN_3, (86%); vi, $LiAlH_4$, (92%); vii, RuO_4,[7] (39%); viii, Ac_2O, pyridine, (94%); ix, O_3, HCO_2H, $CHCl_3$, H_2O_2, (60%);[8] x, hog kidney acylase I, (93%).[8] HLAD = Horse liver alcohol dehydrogenase. Ts = $MeC_6H_4SO_2$-*p*.

chiral glycine has led to an improved sequence for the preparation of this species (*R* or *S*; ^{2}H or ^{3}H) as summarized in Scheme 1, which includes several modifications of literature procedure,[5] and which provides a viable synthetic method to chiral acetate.

Starting from [^{1}H]benzaldehyde (**1**), (**4a**; R^2 = ^{2}H or ^{3}H) is prepared in 78% overall yield whilst (**4b**; R^1 = ^{2}H or ^{3}H) is synthesized from (**3**; R = ^{2}H or ^{3}H) in 80% yield. Compounds (**4a,b**) are then converted as shown, with one inversion of configuration (**5**→**6**) into the (*R*)-(**10b**) and (*S*)-(**10a**) [$^2H_1$ (or $^3H_1$)]glycines [*ca.* 92—96% ^{2}H (*m/e* 76) by mass spectrometry], respectively. The absolute configuration of each ^{2}H species was established by comparison of the o.r.d. curves with the published data.[6]

A sample of (*R*)-[$^2H_1$]glycine (optical purity, 96%) was converted (0·5—1·0 g scale) into (*R*)-[^{2}H]bromoacetic acid (*m/e* 139·141; M^+) (retention) and the latter reduced to (2*S*)-[$^1H_1$,$^2H_1$,$^3H_1$]ethanol with lithium aluminium tritide (inversion) as shown in Scheme 2. Without isolation,



SCHEME 2. i, $NaNO_2$, KBr, H^+, 0 °C, 1 h, 5%; ii, $LiAlT_4$ (50 mCi mmol^{-1}); iii, $Cr_2O_7^{2-}$.

chromic acid oxidation of the evaporated, ethereal extract from this reduction furnished a specimen of chiral acetic acid whose configuration was determined by the coupled enzyme assay[1,2] to be (*R*)-[$^2H_1$,$^3H_1$] (92% optical purity measured on a 1 mCi mmol^{-1} sample). The use of these samples now easily available in 100—500 mg quantities in porphyrin and corrin biosynthesis is under investigation.

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