Asymmetric α-Amino Acid Synthesis: Synthesis of (+)-Polyoxamic Acid using a [3,3]Allylic Trifluoroacetimidate Rearrangement

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The stereoselective [3,3] rearrangement of allylic trifluoroacetimidate (**15**) has been used in a synthesis of (+)-polyoxamic acid (**1**).

The [3,3] rearrangement of allylic *trichloro*-acetimidates has been widely used for the stereoselective synthesis of amines.[1] We report an extension of this work to include *trifluoro*-acetimidates and illustrate its potential for asymmetric L-α-amino acid synthesis.

Several syntheses of polyoxamic acid (**1**), a constituent amino acid of the polyoxins, *e.g.* polyoxin B (**2**), have been described.[2,3] Recently a convenient but non-stereoselective synthesis was reported which involved the thermal rearrangement of the allylic trichloroacetimidate (**3**).[4] This gave a 1 : 1 mixture of trichloroacetamides (**4**) and (**5**) which were separated and converted into polyoxamic acid (**1**) and its C(2)-epimer. It was decided to modify this approach in order to develop a stereoselective synthesis of polyoxamic acid.

Commercially available ethyl (*S*)-lactate (**6**) was converted into the stabilized ylide (**10**) by hydroxy protection, ester hydrolysis, and conversion of the free acid into the 2-mercaptopyridine thioester (**9**). Treatment of this thioester with an excess of methylenetriphenylphosphorane then gave the ylide as a crystalline solid, $[\alpha]_D^{20}$ −18.6° (*c* 1 in $CHCl_3$). The optical purity of the ylide was not formally established, but coupling with homochiral aldehydes appeared to give single diastereoisomers.

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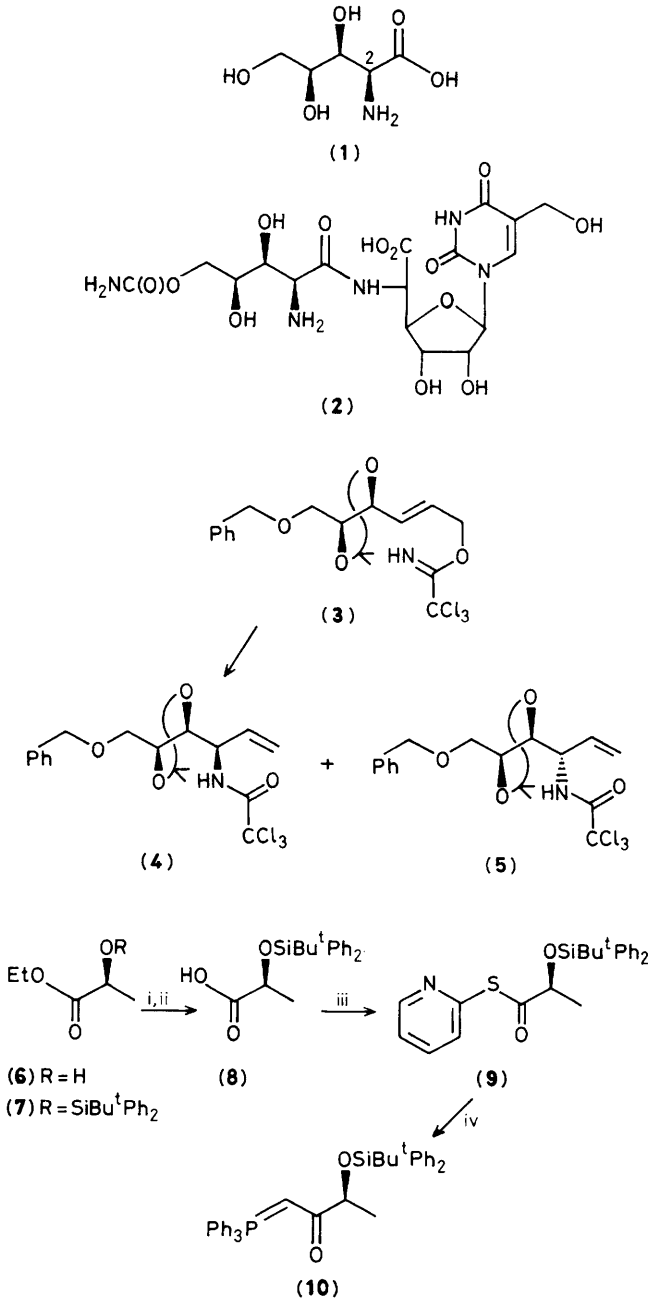
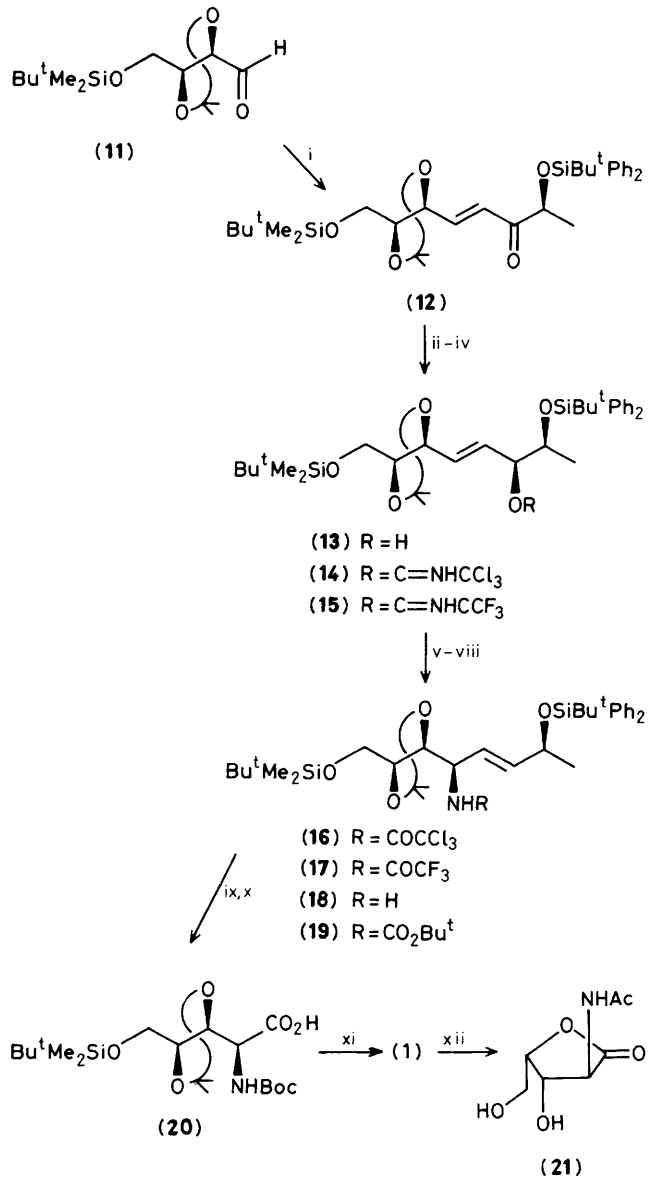


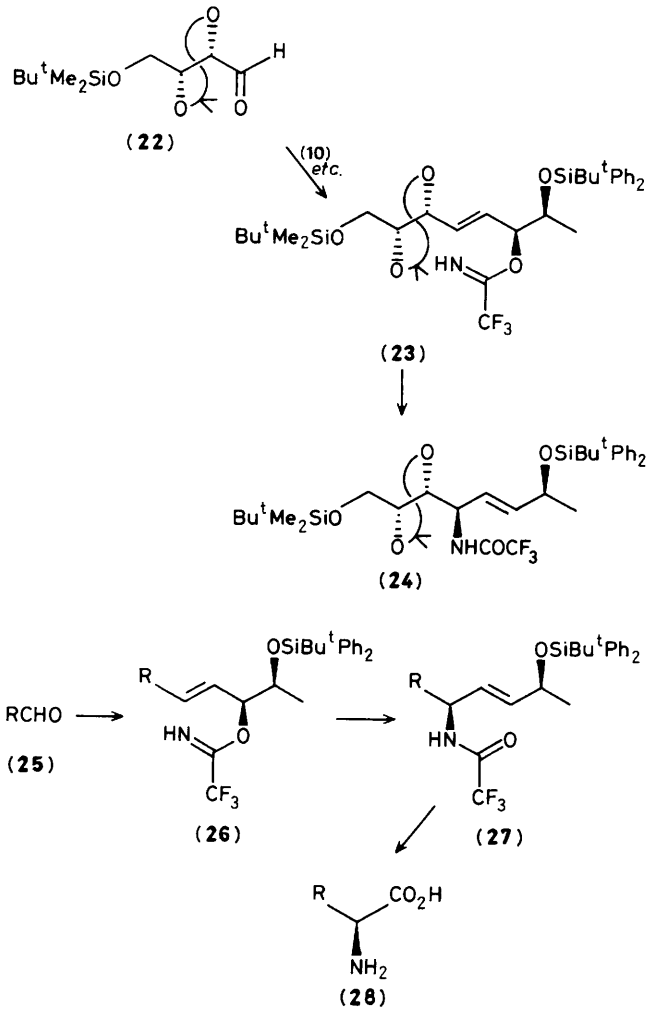
Scheme 1. *Reagents*: i, imidazole, Ph_2Bu^tSiCl, dimethylformamide (DMF), 92%; ii, KOH, MeOH; iii, dicyclohexylcarbodiimide, 2-mercaptopyridine, 70%; iv, 2.2 mol. equiv. Ph_3PCH_2, tetrahydrofuran (THF), 75%.



Scheme 2. *Reagents:* i, (**10**), benzene, heat, 5 h, 90%; ii, L-Selectride, −78 °C, then AcOH, −78 °C, 90%; iii, butyl-lithium then Cl_3CCN, −78 → 15 °C, 80%; iv, butyl-lithium then F_3CCN, mol. sieves, −78 °C, 30 min., 75%; v, (**14**) → (**16**), xylene, heat, 48 h, 30—40%; vi, (**15**) → (**17**), xylene, heat, 20 h, 90%. vii, (**17**) → (**18**), $NaBH_4$, EtOH, 70%; viii, $(Boc)_2O$, Et_3N, 100%; ix, O_3, MeOH, dimethyl sulphide, 90%; x, RuO_4, 80%; xi, CF_3CO_2H, 90%; xii, $(MeCO)_2O$, 60%.

Condensation of the L-tartrate derived aldehyde (**11**) with ylide (**10**) gave E-enone (**12**) which was reduced to alcohol (**13**) using L-Selectride.[5] The reduction of enone (**12**) by other reducing agents was also stereoselective giving alcohol (**13**) as the major or exclusive product, but in some cases the work-up was complicated by migration of the neighbouring t-butyldiphenylsilyl group. Treatment with base and trichloroacetonitrile converted alcohol (**13**) into its trichloroacetimidate (**14**), but in our hands thermal rearrangement of this was inefficient and gave only modest yields of the required trichloroacetamide (**16**)(30—40%) owing to competing decompostion under the prolonged conditions required (150 °C for *ca.* 48 h).

Since the [3,3] rearrangement of allylic imidates is accelerated by electron withdrawing substituents on the imidate carbon, the preparation and rearrangement of the trifluoroacetimidate (**15**) was investigated to see whether improved yields of product could be obtained. Sequential treatment of alcohol (**15**) with n-butyl-lithium and an excess of trifluoroacetonitrile in tetrahydrofuran at −78 °C gave the desired trifluoroacetimidate (**15**) which was stable at room temperature and could be purified by flash chromatography, but which rearranged smoothly in solution in xylene heated under reflux (20 h) to provide the trifluoroacetamide (**17**) (90%) as a single diastereoisomer as judged by ^1H n.m.r. spectroscopy (sensitivity 1—2%). Conversion of the trifluoroacetamide (**17**) into polyoxamic acid (**1**) was then effected by reductive removal of the trifluoroacetyl group using $NaBH_4$, N-protection using



Boc anhydride (Boc = Bu^{t}CO), ozonolysis–oxidation to provide the free carboxylic acid (**20**), and acid hydrolysis to remove all the protecting groups simultaneously. The L-polyoxamic acid so obtained had $[\alpha]_D$ +6° (*c* 1 in H_2O), and was converted into lactone (**21**) using acetic anhydride, the structure of this lactone being confirmed by direct comparison with a sample of the authentic material.‡

To demonstrate that the stereochemistry of the rearrangement was determined by the configuration of the trifluoroacetimidate substituent, rearrangement of the D-tartrate-derived trifluoroacetimidate (**23**) was investigated. This was prepared from aldehyde (**22**) using ylide (**10**), and was found to rearrange highly stereoselectively giving the trifluoroacetamide (**24**) as the exclusive product (^{1}H n.m.r.).

Overall, the conversion of aldehyde (**11**) into polyoxamic acid (**1**) corresponds to a stereoselective Strecker synthesis, and the chemistry involved should be useful for the asymmetric synthesis of other L-α-amino acids from aldehydes, *i.e.* (**25**) → (**28**).[6] The rearrangement of trifluoroacetimidates would appear to proceed under milder conditions than those required for the corresponding trichloroacetimidates, and the removal of the trifluoroacetyl group from the rearrangement product can be achieved under mild conditions.

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