Tetrahedron Letters, Vol. 34, No. 42, pp. 6769-6772, 1993
Printed in Great Britain

0040-4039/93 $6.00 + .00
Pergamon Press Ltd

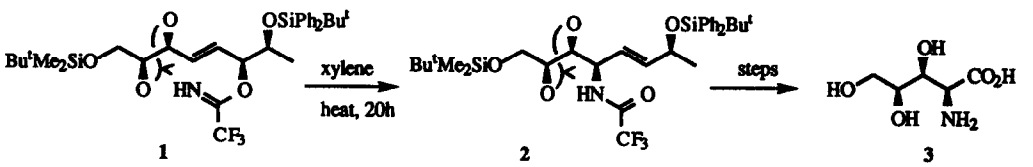
Asymmetric α-Aminoacid Synthesis using [3.3] Rearrangement of Allylic Trifluoroacetimidates: Synthesis of Thymine Polyoxin C

Anqi Chen, Ian Savage, Eric J. Thomas,* and Peter D. Wilson

Department of Chemistry, University of Manchester, Manchester, M13 9PL, U.K.

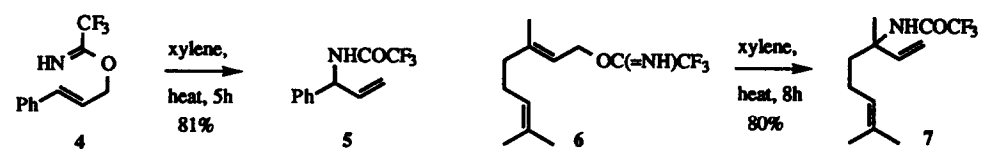
Abstract: Improved procedures are reported for the synthesis of chiral trifluoroacetimidates and are applied to complete a total synthesis of thymine polyoxin C.

The [3.3] rearrangement of allylic *trichloro*acetimidates has been widely used for the stereoselective synthesis of amines.[1] Recently we reported that allylic *trifluoro*acetimidates rearrange under significantly milder conditions than their trichloro analogues, and described a synthesis of (+)-polyoxamic acid **3** using the [3.3] rearrangement of the trifluoroacetimidate **1**.[2] We now describe improvements to these procedures together with an investigation into the scope of the trifluoroacetimidate rearrangement, and a total synthesis of thymine polyoxin C **34**.

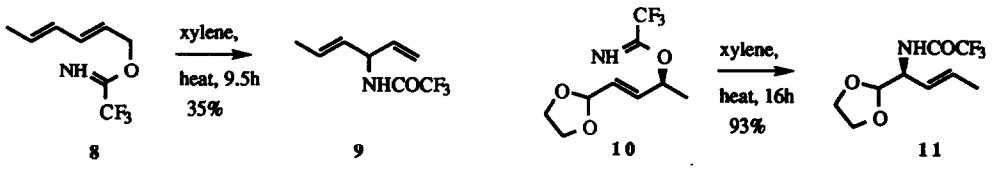


1 **2** **3**

The trifluoroacetimidates **4**, **6**, **8**, and **10** were prepared from the corresponding alcohols by treatment with *n*-butyllithium followed by addition of an excess of trifluoroacetonitrile[3] in solution at -78 °C in tetrahydrofuran. Best yields were obtained using less than one mole equivalent of the butyllithium, with 20 mole % usually being adequate.[5] The [3.3] rearrangements of the trifluoroacetimidates were then carried out by heating in xylene under reflux and gave the allylic trifluoroacetamides **5**, **7**, **9**, and **11**, respectively, with typical yields being 80-90%, even for the formation of the tertiary amine derivative **7**.

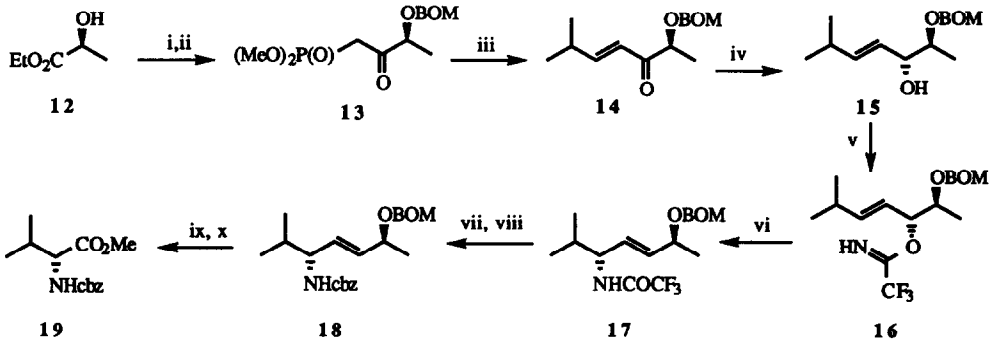


4 **5** **6** **7**



8 9 10 11

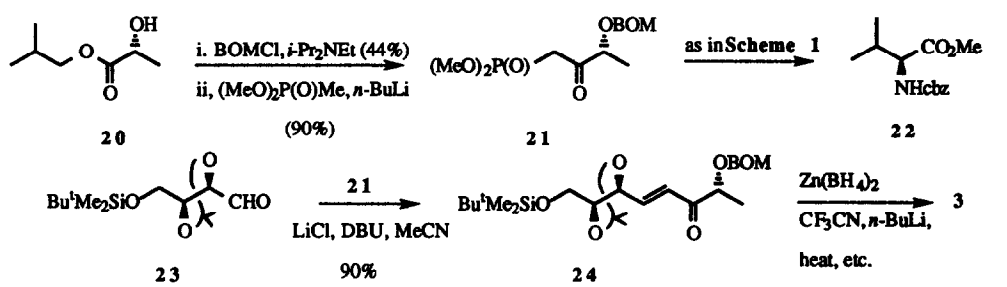
The application of the rearrangement for the synthesis of α-amino-acids was briefly investigated, see **Scheme 1**. The phosphonate **13**, which is more accessible than the ylid used in our earlier work,[2] was condensed with 2-methylpropanal to give the enone **14**. Reduction using zinc borohydride at -35 °C gave the *anti*-alcohol **15** containing less than 1% of its *syn*-diastereoisomer, and treatment with trifluoroacetonitrile gave the trifluoroacetimidate **16** which rearranged on heating under reflux in xylene to the trifluoroacetamide **17**. This was converted into the carbamate **18** and ozonolysis followed by oxidation of the crude ozonolysis product with bromine in methanol under buffered conditions gave the protected D-valine methyl ester **19**.[6] The e.e. of the protected D-valine methyl ester **19** was estimated to be *ca.* 85% by reduction to cbz-protected valinol ($LiBH_4$, 95%) followed by Mosher's derivatization.



12 13 14 15 16 17 18 19

Scheme 1: *Reagents;* i, BOMCl, *i*-Pr_2NEt (81%); ii, $(MeO)_2P(O)Me$, *n*-BuLi (85%); iii, LiCl, DBU, *i*-PrCHO, MeCN (80%); iv, $Zn(BH_4)_2$, Et_2O, -35 °C (95%; 98% d.e.); v, *n*-BuLi (0.2 mol equiv.), CF_3CN (90%); vi, xylene, reflux, 4h (89%); vii, $Ba(OH)_2$, MeOH; viii, BnOCOCl, $KHCO_3$ (86% from **17**); ix, O_3, DMS; x, $NaHCO_3$, Br_2, MeOH, H_2O (84% from **18**).

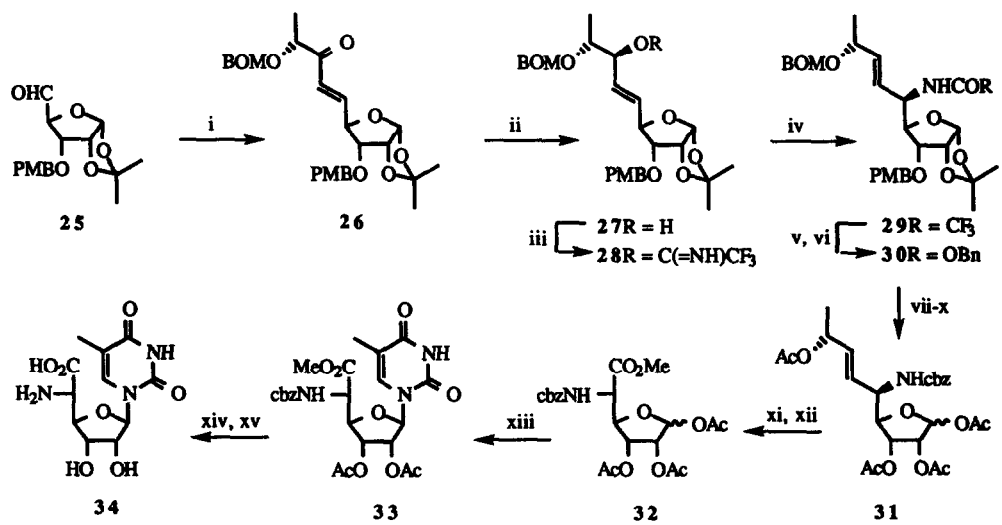
The (*R*)-phosphonate **21** was prepared from isobutyl (*R*)-lactate **20**, and incorporated into syntheses of the cbz-protected L-valine methyl ester **22** and polyoxamic acid **3** so showing that both D- and L-α-amino-acids are available from the appropriate ketophosphonate **13** or **21** using the trifluoroacetimidate rearrangement.



20 21 22 23 24

It was decided to test the usefulness of the [3.3] rearrangement of trifluoroacetimidates for complex synthesis, and thymine polyoxin C **34** was chosen as a suitable target. The polyoxins are a group of nucleoside antibiotics which have been widely studied[7] including several syntheses of thymine polyoxin C and syntheses of the structurally related nikkomycins.[8,9]

Diacetone D-glucose was converted into its C(3) epimer which was protected as its *p*-methoxybenzyl ether and hydrolysed followed by oxidative cleavage to give the aldehyde **25**. Condensation of this aldehyde with the ketophosphonate **21** gave the enone **26** which was reduced with zinc borohydride followed by treatment with trifluoroacetonitrile to give the trifluoroacetimidate **28**. This rearranged cleanly on heating in solution in xylene (8h) to give the trifluoroacetamide **29**. After conversion of the trifluoroacetamide into the carbamate **30** it remained to cleave the alkene to form the carboxylic acid and to convert the ribose ring into the required mononucleoside to complete a synthesis of the polyoxin. The sequence of reactions followed to effect these transformations involved oxidative removal of the PMB group, acetylation at C(3'), hydrolysis of the acetonide, which was accompanied by loss of the BOM group, and acetylation to give the tetra-acetate **31**. Ozonolysis with a dimethyl sulphide work-up followed by oxidation of the crude aldehyde so obtained using bromine in methanol gave the methyl ester **32** which was taken through to the nucleoside **33** using standard conditions. Deprotection gave thymine polyoxin C **34**. The structures of the ribose derivative **32** and the protected polyoxin **33** were established by comparison of their spectroscopic data with those of the authentic materials.[8] The structure of the thymine polyoxin C **34** was confirmed by direct comparison (NMR, MS, IR, TLC) with an authentic sample.



Scheme 2: ***Reagents;*** i, **21**, LiCl, DBU, MeCN, r.t. 15h (96%); ii, $Zn(BH_4)_2$, Et_2O, -40 °C (98%, >96% d.e.); iii, *n*-BuLi (0.2mole equiv.), CF_3CN (93%); iv, xylene, heat under reflux (99%); v, $Ba(OH)_2$, MeOH; vi, cbzCl, $KHCO_3$ (96% from **29**); vii, DDQ, CH_2Cl_2, pH 7 buffer, *t*-BuOH; viii, Ac_2O, Et_3N, DMAP; ix, 70% AcOH in H_2O, 70 °C, 40h; x, Ac_2O, Et_3N, DMAP (73% from **30**); xi, O_3, MeOH, -78 °C, then Me_2S; xii, Br_2, MeOH, H_2O, $NaHCO_3$ (74% from **31**); xiii, 2,4-bis(trimethylsilyloxy)-5-methylpyrimidine, TMSOTf, CH_2Cl_2, heat under reflux (82%); xiv, LiOH, THF, H_2O; xv, H_2, 10% Pd/C, MeOH, r.t. followed by purification on a Dowex ion exchange column, eluted using a pH 3.1 buffer of pyridine and acetic acid (3 : 17) (47% from **33**)

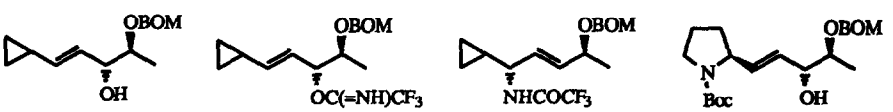
This synthesis of thymine polyoxin C **34** demonstrates the use of the [3.3] rearrangement of allylic trifluoroacetimidates for complex natural product synthesis. The rearrangement proceeds with excellent stereoselectivity, and requires less vigorous conditions than the rearrangement of the corresponding allylic trichloroacetimidates, although the latter compounds are more accessible. The ready availability of the enantiomeric phosphonates **13** and **21** from (*S*)- and (*R*)-lactates, coupled with the stereoselective reduction of the α-benzyloxymethoxy-ketones by zinc borohydride and the efficient rearrangement of the corresponding allyl trifluoroacetimidates, may be useful for the synthesis of both (*R*)- and (*S*)-α-amino-acids.

Acknowledgements

We thank the Wellcome Research Laboratories and the SERC for a CASE Award (to I.S.), the SERC for support (to P.D.W. and A.C.), and Merck, Sharp, and Dohme for generous support. We should also like to thank Professor P. Garner, of Case Western University, for spectra of the protected nucleoside **33**, Professor K. Isono, of Tokai University, for an authentic sample of thymine polyoxin C, and Dr. G. H. Whitham, the Dyson Perrins Laboratory, Oxford for helpful discussions.

References and Notes

1. Overman, L. E., *J.Am.Chem.Soc.*, **98**, 2901-2910 (1976).
2. Savage, I.; Thomas, E. J., *J.Chem.Soc.,Chem.Commun.*, 717-719 (1989).
3. The trifluoroacetonitrile (CAUTION: TOXIC) was conveniently generated by dehydration of trifluoroacetamide using P_2O_5, and was condensed at -78 °C.[4]
4. Gilman, H.; Jones, R. G., *J.Am.Chem.Soc.*, **65**, 1458-1460 (1943).
5. Although the conversion of an allylic alcohol into its trifluoroacetimidate using *n*-butyllithium and trifluoroacetonitrile was usually efficient, two cases were found which gave lower yields. The cyclopropylallyl alcohol **i** gave rise to a complex mixture of products which contained both the required trifluoroacetimidate **ii** and the rearranged trifluoroacetamide **iii** amongst other products, and the pyrrolidine containing allyl alcohol **iv** gave only a very low yield of the required trifluoroacetimidate together with a mixture of products that were not identified.



i ii iii iv

6. Williams, D. R.; Klingler, F. D.; Allen, E. E.; Lichtenthaler, F. W., *Tetrahedron Lett.*, **29**, 5087-5090 (1988).
7. Isono, K.; Suzuki, S., *Heterocycles*, **13**, 333-351 (1979); Isono, K.; Asahi, K.; Suzuki, S., *J.Am.Chem. Soc.*, **91**, 7490-7505 (1969).
8. Garner, P.; Park, J. M., *J.Org.Chem.*, **55**, 3772-3787 (1990); Ohrui, H.; Kuzuhara, H.; Emoto, S., *Tetrahedron Lett.*, 4267-4270 (1971); Damodaran, N. P.; Jones, G. H.; Moffatt, J. G., *J.Am.Chem.Soc.*, **93**, 3812-3813 (1971).
9. Barrett, A. G. M.; Lebold, S. A., *J.Org.Chem.*, **56**, 4875-4884 (1991).

(Received in UK 30 June 1993; accepted 20 August 1993)