Tetrahedron Letters,Vol.30,No.38,pp 5065-5068,1989 0040-4039/89 $3.00 + .00
Printed in Great Britain Pergamon Press plc

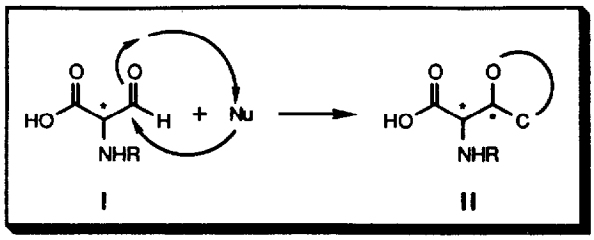
GLYCOSYL α-AMINOACIDS VIA STEREOCONTROLLED BUILDUP OF A PENALDIC ACID EQUIVALENT. AN ASYMMETRIC SYNTHESIS OF THYMINE POLYOXIN C.

Philip Garner* and Jung Min Park

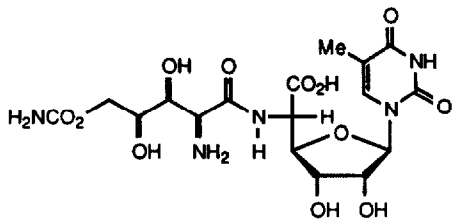
Department of Chemistry
Case Western Reserve University
Cleveland, Ohio 44106-2699

Summary: A new strategy for assembly of glycosyl α-aminoacids via the stereocontrolled buildup of a serine-derived penaldic acid equivalent (i.e. **I** → **II**) is illustrated by the asymmetric synthesis of thymine polyoxin C.

The development of a general and stereocontrolled route to glycosyl α-aminoacids would provide a novel synthetic entry to the polyoxins (Cf. **1**)[1] and structurally related antibiotics.[2] Although a variety of synthetic approaches to such systems have been reported over the years,[3] none of them satisfactorily addressed the dual criteria mentioned above. With this in mind, we began to explore a conceptually different strategy for the asymmetric synthesis of glycosyl (and other atypical) α-aminoacids which involves the stereocontrolled buildup of a serine-derived penaldic acid equivalent (i.e. **I** → **II**).[4] We now report the first successful application of this strategy to glycosyl α-aminoacids in



I **II**



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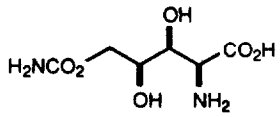

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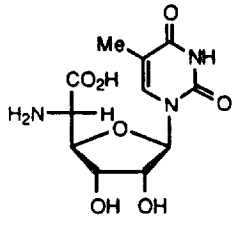
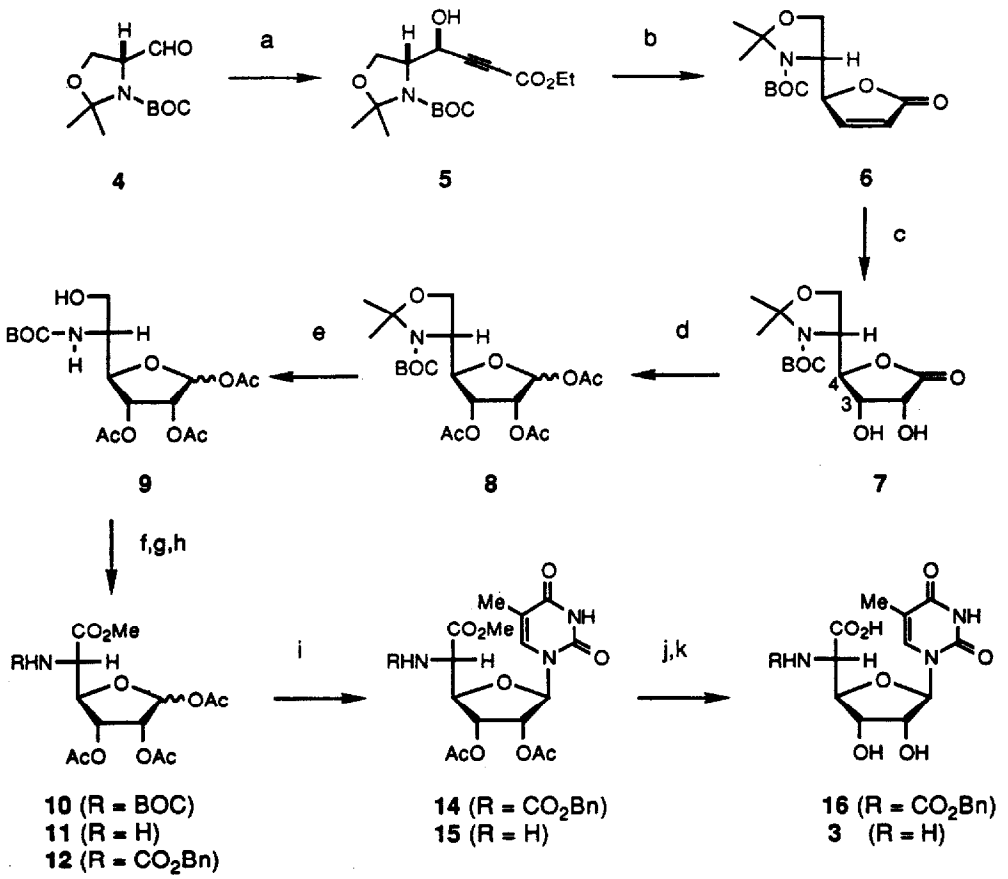


3

the form of a stereocontrolled and asymmetric synthesis of thymine polyoxin C (**3**). This substance, which is obtained along with 5-O-carbamoylpolyoxamic acid (**2**)[4b] after acid hydrolysis of polyoxin J (**1**), is representative of the α-aminouronic acid nucleoside residues found in the polyoxin, neopolyoxin, and nikkomycin families of antibiotics.[1] Furthermore, since both **3** and its corresponding uracil derivative have been the target of previous syntheses,[3b-d,i] the comparative utility of our approach can be readily evaluated.

Scheme I[a]



[a]Reagents: (a) LiC≡CCO$_2$Et, THF-HMPA, -78°C, 78% (b) i) KOH, EtOH, 0°C ii) H_2, Pd/BaSO$_4$, quinoline iii) 1N HCl, 69% (c) cat. OsO$_4$, Me$_3$NO, ^{n}BuOH-CCl$_4$-H$_2$O, 58% (d) I) DIBAL, toluene, -78°C ii) Ac$_2$O-pyridine, 80% (e) AcOH, 40°C, 77% (f) i) cat. RuO$_4$-H$_2$O, NaIO$_4$, aq Me$_2$CO ii) CH$_2$N$_2$, Et$_2$O, 0°C, 68% (g) TFA, CH$_2$Cl$_2$, 100% (h) ClCO$_2$Bn, aq NaHCO$_3$, 0°C, 82% (i) 2,4-bis(trimethylsiloxy)-5-methylpyrimidine (**13**), TMSOTf, ClCH$_2$CH$_2$Cl, reflux, 75% (j) LiOH, THF, 0°C (k) H_2, Pd/C, MeOH, 54%.

The synthesis begins with D-serinal derivative **4**,[5] a compound which we and others have already shown to be a very useful homochiral building block.[4,6] Addition of lithio ethyl propiolate to this aldehyde proceeded with good (13:1) erythro-selectivity to give the propargylic alcohol **5** in 78% isolated yield after flash chromatography.[7] This stereochemical outcome (which was later proven by correlation with **3**) is consistent with a Felkin-Anh transition state[8] and was expected on the basis of prior experience with additions to **4** under nonchelating conditions. A sequence involving (i) saponification,[9] (ii) semi-hydrogenation (H_2 atm, Pd/BaSO$_4$, quinoline) of the resulting propiolate salt, and (iii) acid-catalyzed lactonization led to isolation of the butenolide **6** in 69% overall yield after chromatography. This substance underwent a very selective (ds $\geq$ 18:1) cis-hydroxylation (cat. OsO$_4$,

trimethylamine N-oxide)[10] to give the diol **7** in 58% yield after chromatography. It was expected that osmylation would occur preferentially from the less hindered α-face,[11] a prediction initially supported by ^{1}H NMR data for **7** ($J_{3,4}$ = 0 Hz, ∠ 90°) and again confirmed by chemical correlation with **3**. Lactone to lactol reduction (DIBAL, toluene, -78°C) followed by acetylation of the resulting crude triols led to isolation of a (4:1) mixture of anomeric triacetates **8** in 80% combined yield with the β-anomer predominating. Release of the masked glycinyl appendage commenced with acetolysis of the 2,2-dimethyloxazolidine ring (AcOH, 40°C) to give the N-BOC aminoalcohol **9** in 77% yield (based on recovered **8** at 40% conversion; prolonged reaction led to amine deprotection). This compound was oxidized (cat. $RuO_4 \cdot H_2O$, $NaIO_4$) and the resulting carboxylic acid was esterified with diazomethane to produce the N-BOC aminoester **10** in 68% yield. At this point the BOC moiety was replaced by the more robust benzyloxycarbonyl group via a two-step sequence (TFA, CH_2Cl_2, then $ClCO_2Bn$, $NaHCO_3$) that led to the N-protected aminoester **12** (via aminoester **11**) in 82% overall yield. Coupling of **12** with 2,4-bis(trimethylsiloxy)-5-methylpyrimidine (**13**)[12] using glycosylation methodology developed by Vorbrüggen (TMSOTf, $ClCH_2CH_2Cl$, 30 min reflux)[13] afforded the N^1-nucleoside **14** in 75% yield after chromatography along with a small amount (<10%) of the N-deprotected nucleoside **15**.[14] Under these reaction conditions, none of the kinetically favored N^3-nucleoside was observed. Saponification of **14** (LiOH, THF, 0°C) followed by hydrogenolysis (H_2-Pd/C, MeOH) of **16** resulted in a 54% yield of synthetic thymine polyoxin C (**3**) that was shown to be identical to an authentic sample prepared from naturally-derived polyoxin C.[15] This 15-step synthesis of thymine polyoxin C (**3**) from the penaldic acid equivalent **4** illustrates the viability and efficacy of our approach to glycosyl α-aminoacids. Application of this general strategy to even more complex and less accessible glycosyl α-aminoacid targets (Cf. ref. 2) will be reported on in due course.[16]

REFERENCES AND NOTES

1. (a) Isono, K.; Asahi, K.; Suzuki, S. *J. Am. Chem. Soc.* **1969**, *91*, 7490. (b) For a comprehensive review of the polyoxins, see: Isono, K.; Suzuki, S. *Heterocycles* **1979**, *13*, 333.

2. (a) Amipurimycin: Goto, T.; Toya, Y.; Ohgi, T.; Kondo, T. *Tetrahedron Lett.* **1982**, 1271. (b) Miharamycin: Seto, H.; Koyama, M.; Ogino, H.; Tsuruoka, T.; Inouye, S.; Otake, N. *Ibid.* **1983**, 1805.

3. Carbohydrate templates: (a) Naka, T.; Hashizume, T.; Nishimura, M. *Tetrahedron Lett.* **1971**, 95; (b) Ohrui, H.; Kuzuhara, H.; Emoto, S. *Ibid.* **1971**, 4267; (c) Tabusa, F.; Yamada, T.; Suzuki, K.; Mukaiyama, T. *Chem. Lett.* **1984**, 405. Strecker methodology: (d) Damodaran, N. P.; Jones, G. H.; Moffatt, J. G. *J. Am. Chem. Soc.* **1971**, *93*, 3812; (e) Robins, M. J.; Parker, J. M. R. *Can. J. Chem.* **1983**, *61*, 312, 317; (f) Fiandor, J.; Garcia-López, M.-T.; De las Heras, F. G.; Méndez-Castrillón, P. P. *Synthesis* **1987**, 978. Ugi 4-component condensation: (g) Joullié, M. M.; Wang, P. C.; Semple, J. E. *J. Am. Chem. Soc.* **1980**, *102*, 887; (h) Semple, J. E.; Wang, P. C.; Lysenko, Z.; Joullié, M. M. *Ibid.* **1980**, *102*, 7505; (i) Tsuchida, K.; Mizuno, Y.; Ikeda, K. *Nucleic Acids Symp. Series* **1980**, *8*, s49. Reduction of α-oximinoesters: (j) Masamune, T.; Ono, M. *Chem. Lett.* **1975**, 625. Hydrogenation of α,β-unsaturated α-aminoacids: (k) Bischofberger, K.; Hall, R. H.; Jordaan, A. *J. C. S. Chem. Comm.* **1975**, 806. Nitrone cycloaddition: (l) Vasella, A.; Voeffray, R. *Helv. Chim. Acta* **1982**, *65*, 1134.

4. (a) Garner, P. *Tetrahedron Lett.* **1984**, 5855. (b) Garner, P.; Park, J. M. *J. Org. Chem.* **1988**, 53, 2979.

5. (a) Garner, P.; Park, J. M. *J. Org. Chem.* **1987**, *52*, 2361. (b) Garner, P.; Park, J. M. Submitted to *Organic Syntheses.*

6. For recent applications of **ent-4** to sphingosine synthesis, see: (a) Dondoni, A.; Fantin, G.; Fogagnolo, M.; Medici, A. *J. Chem. Soc., Chem. Commun.* **1988**, 10; (b) Herold, P. *Helv. Chim. Acta* **1988**, *71*, 354; (c) Nimkar, S.; Menaldino, D.; Merrill, A. H.; Liotta, D. *Tetrahedron Lett.* **1988**, 3037; (d) Garner, P.; Park, J. M.; Malecki, E. *J. Org. Chem.* **1988**, *53*, 4395; (e) Radunz, H.-E.; Devant, R. M.; Eiermann, V. *Liebigs Ann. Chem.* **1988**, 1103.

7. Satisfactory IR, ^{1}H & ^{13}C NMR, and HRMS data have been obtained for all substances shown.

8. Anh, N. T. *Top. Curr. Chem.* **1980**, *88*, 145. See also: Wu, Y.-D.; Houk, K. N. *J. Am. Chem. Soc.* **1987**, *109*, 908.

9. When Lindlar semi-hydrogenation was attempted on either the ester **5** or its corresponding free acid, an unacceptable amount of overreduction was observed.

10. We thank Professor Frank Hauser (SUNY/Albany) for alerting us to the advantages of substituting trimethylamine oxide as the carrier oxidant in this reaction. Cf. Ray, R.; Matteson, D. S. *Tetrahedron Lett.* **1980**, 449; Hauser, F. M.; Rhee, R. P.; Ellenberger, S. R. *J. Org. Chem.* **1984**, *49*, 2236.

11. Stork, G.; Kahn, M. *Tetrahedron Lett.* **1983**, 3951; Lukes, R.; Moll, M.; Zobácová, A.; Jary, J. *Coll. Czech. Commun.* **1962**, *27*, 500.

12. Nishimura, T.; Iwai, I.; *Chem. Pharm. Bull.* **1964**, *12*, 352; Niedballa, U.; Vorbrüggen, H. *J. Org. Chem.* **1974**, *39*, 3654.

13. Vorbrüggen, H.; Krolikiewicz, K.; Bennua, B. *Chem. Ber.* **1981**, *114*, 1234.

14. We did have some preliminary indication that the benzyloxycarbonyl group would survive these acidic nucleosidation conditions (Cf. Paulsen, H.; Brieden, M.; Benz, G. *Liebigs Ann. Chem.* **1987**, 565). Longer reaction times, however, resulted in further deprotection and a proportional increase in the amount of **15** formed. Glycosylation could be achieved directly with the free amine **11** but this reaction was not clean and led to a rather low yield of nucleoside **15.**

15. Synthetic **3**: mp 182-185°C (shr at 160°C); [authentic **3**: mp 190-194°C (shr at 170°), lit.[1a] mp 240-244°C, lit.[3b] mp 242-244°C]; $[\alpha]_D$ +8.0° (*c* 0.37, H_2O) [lit.[1a] $[\alpha]_D$ +8.7° (*c* 0.208, H_2O), lit.[3b] $[\alpha]_D$ +8.2° (*c* 0.7, H_2O)]; ^{1}H NMR (400 MHz, D_2O + DCl, pD = 0.68, ambient T): δ 7.17 (s, H-6), 5.60 (d, *J* = 3.9 Hz, H-1'), 4.53 (t, *J* = 6.5 Hz, H-3'), 4.40 (d, *J* = 2.6 Hz, H-5'), 4.27 (dd, *J* = 6.1 & 4.0 Hz, H-2'), 4.20 (dd, *J* = 6.9 & 2.6 Hz, H-4'), 1.72 (s, 3H). An identical spectrum was obtained with an authentic sample of **3** prepared by hydrogenolysis of naturally-derived polyoxin C kindly provided by Dr. Kiyoshi Isono (Institute of Physical and Chemical Research/Saitama, Japan).[1a] The discrepancy in melting point between our samples of **3** (both synthetic & naturally-derived) and those reported in the literature are probably due to differences in the method of isolation/purification. Recrystallization of synthetic **3** from hot water raised its mp to 223-226°C (shr at 210°C).

16. This investigation was supported by Public Health Service Research Grant GM35557 from the National Institute of General Medical Sciences.

(Received in USA 15 June 1989)