Tetrahedron Letters, Vol.32, No.8, pp 1031-1034, 1991
Printed in Great Britain

0040-4039/91 $3.00 + .00
Pergamon Press plc

DIASTEREOSPECIFIC SYNTHESIS OF D- AND L-*allo*-THREONINES AND TRICHLORINATED DERIVATIVES SUITABLE FOR THE PREPARATION OF TRITIUM LABELLED MATERIAL.

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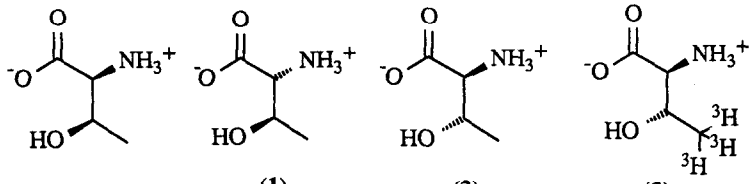
Summary: D- or L- serine can be converted to L- or D-γ,γ,γ-trichloro-*allo*-threonine, which on catalytic hydrogenolysis give diastereomerically pure L-*allo*- or D-*allo*-threonine respectively. This procedure can be adapted to the preparation of tritium labelled material.

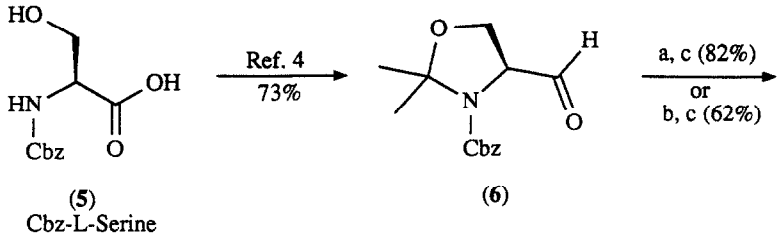
L-Threonine is an essential amino acid and a primary component of most proteins and many naturally occurring compounds. The corresponding D- and L-*allo*-threonines (**1,2**) though more rarely encountered in nature, are found as constituents of biologically active peptides[1], and derivatives of these amino acids have been used as starting materials for the preparation of carbapenem antibiotics and other molecules of therapeutic interest[2]. Routine use of these amino acids as building blocks has however been limited by their high cost. In addition for the need to develop efficient procedures for preparing these compounds, we were interested in derivatives of these amino acids that would allow facile incorporation of tritium, and thus provide a radio labelled version suitable for biochemical studies (**3**).



L-Threonine (1) D-*allo*-Threonine (2) L-*allo*-Threonine (3) $^3H_3$-D-*allo*-Threonine

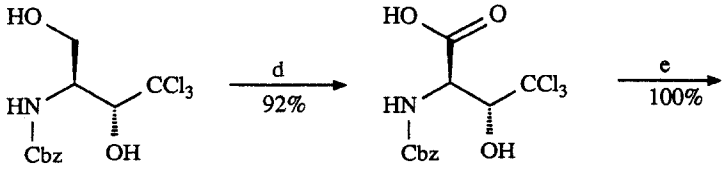
For practical purposes, any synthesis of radio labelled *allo*-threonine should be designed so that the radio isotope is introduced in the last step or after incorporation of the amino acid into the biological molecule of interest. One such way would be catalytic hydrogenolysis of a halo derivative using tritium gas.

SCHEME



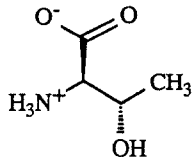
(5)
Cbz-L-Serine

(6)



(7)
Mp 91-93.5 °C

(4)
Mp 165-168 °C



(1)
D-*allo*-Threonine

Cbz = $C_6H_5CH_2OOC$-

Reagents and conditions: a) $Cl_3CCOOTMS$ (1.3 eq.), anh. K_2CO_3 (0.02 eq.), 18-crown-6 (0.02 eq.), neat, 90°C, 1/2 h. b) Aluminum foil (1.2 eq.), $PbCl_2$ (0.12 eq.), CCl_4 (2.5 eq.), DMF, room temperature, 3h. c) MeOH, Dowex-50W-H^+, room temperature, 12h. d) Jones, acetone, room temperature, 2h. e) H_2, 1 atm, 20% $Pd(OH)_2/C$ (cat.), MeOH, 3h.

Several diastereospecific routes to *allo*-threonines are reported in the literature[3], however none can be adapted easily to the preparation of tritiated material. We report herein a new procedure which provides the trichloro derivative (**4**), a precursor to the desired amino acid, in five steps from readily available carbobenzyloxy-L-serine (**5**) (Scheme).

The protected aldehyde derivative (**6**) readily available from L-serine[4] was reacted with trichloromethane anion generated from either trimethylsilyl trichloroacetate[5] or aluminum metal / carbon tetrachloride / lead(II) chloride[6] to give after hydrolysis of the acetonide, the diol (**7**) as a single crystalline diastereomer[7] (Scheme). The relative stereochemistry found in (**7**) was verified by comparison of the final product with authentic

D-*allo*-threonine. This stereochemistry can be rationalized by the model proposed by Cornforth[8]. In contrast, addition of methylmagnesium bromide or methyllithium to aldehyde (**6**) in THF at -78°C led to 1:1 mixtures of *threo* and *erythro* products. The increased steric bulk of the trichloromethane anion over the methyl anion is presumed to account for the difference in diastereoselectivity. Selective oxidation of the primary alcohol in diol (**7**) using Jones' reagent gave the trichlorinated *allo*-threonine derivative (**4**). This material was converted to D-*allo*-threonine (**1**) in quantitative yield by catalytic hydrogenolysis in methanol over 20% palladium hydroxide on charcoal. Derivatization followed by GC analysis on a chiral capillary column[9] and comparison with all four possible isomers of threonine confirmed the absolute and relative stereochemical assignments and showed diastereomeric purities to be in excess of 99% ($[\alpha]^{27}_D$ -9.7 ° (c = 1.0, H_2O); Lit.[10] : $[\alpha]^{26}_D$ -9.6 ° (c = 3.8, H_2O)). In a similar fashion, D-serine could be converted to isomerically pure L-*allo*-threonine.

Trichloro derivative (**4**) can be incorporated into peptides using standard coupling procedures and subsequently converted to the corresponding *allo*-threonine derivative by hydrogenolysis ($^1H_2$ or $^3H_2$). As an example, (**4**) was coupled to TFA.H-Asp(OBn)-Leu-OBn using BOP/NMM[11] to give the protected tripeptide which after hydrogenolysis ($Pd(OH)_2$/C in MeOH, 1 atm H_2) gave D-*allo*-Thr-Asp-Leu-OH. Protection of the hydroxyl function in the threonine derivative side chain (**4**) is not necessary as a consequence of the bulk and electronic nature of the adjacent trichloromethyl substituent.

References:

1. a) T.R. Burke, Jr., M. Knight, B. Chandrasekhar and J.A. Ferretti; *Tetrahedron Lett.* **1989**, *30*, 519. b) L.A. Flippin, K. Jalali-Araghi and P.A. Brown; *J. Org. Chem.* **1989**, *54* ,3006.

2. a) T. Nagahara and T. Kametani; *Heterocycles* **1987**, *25*, 729. b) M.J. Miller; *Acc. Chem. Res.* **1986**, *19*, 49. c) "*Asymmetric Synthesis - Construction of Chiral Molecules Using Amino Acids*" G.M. Coppola and H.F. Schuster; Wiley-Interscience **1987**, p 163.

3. a) P.J. Maurer, H. Takahata and H. Rapoport; *J. Am. Chem. Soc.* **1984**, *106*, 1095. b) D.A. Evans, E.B. Sjogren, A.E. Weber and R.E. Conn; *Tetrahedron Lett.* **1987**, *28*, 39. c) J.-P. Genet, S. Juge and S. Mallart; *Tetrahedron Lett.* **1988**, *29*, 6765. d) M.E. Jung and Y.H. Jung; *Tetrahedron Lett.* **1989**, *30*, 6637. e) D. Pons, M. Savignac and J.-P. Genet; *Tetrahedron Lett.* **1990**, *31*, 5023.

4. P.L. Beaulieu and P.W. Schiller; *Tetrahedron Lett.* **1988**, *29*, 2019.

5. J.M. Renga and P.-C. Wang; *Tetrahedron Lett.* **1985**, *26*, 1175.

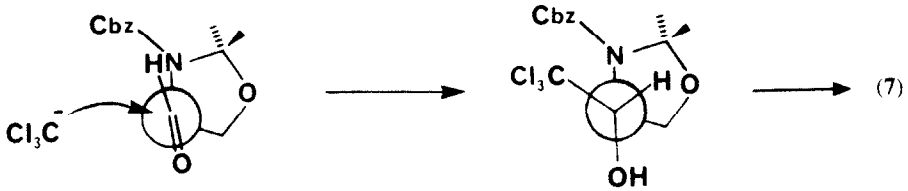
6. H. Tanaka, S. Yamashita, M. Yamanoue and S. Torii; *J. Org. Chem.* **1989**, *54*, 444.

7. Satisfactory spectroscopic (IR, ^1H NMR, ^{13}C NMR), FAB MS, and elemental C,H,N analysis data were obtained for all compounds:

(**7**). $[\alpha]^{30}_D$ -3.0 ° (c = 0.9, MeOH). Mp 91-93.5 °C. ^{13}C NMR ($CDCl_3$, 50 MHz) δ 155.92, 135.94, 128.59, 128.35, 128.16, 101.19, 84.50, 67.28, 62.70, 52.30. IR (CH_2Cl_2) 3500, 3260, 1680, 1550 cm^{-1}. MS (CI) m/z (rel intensity) 346 (13), 344 (65), 342 (70). Elemental analysis calculated for $C_{12}H_{14}Cl_3NO_4$: C, 42.07; H, 4.12; N, 4.09. Found: C, 42.28; H, 4.15; N, 4.06. ^1H NMR of diacetate prepared from (**7**) (acetic anhydride / pyridine, 18 h), ($CDCl_3$, 300 MHz) δ 7.40 (s, 5H), 5.59 (d, J = 4.8 Hz, 1H), 5.38 (broad d, J = 9.9 Hz, 1H), 5.17 (d, J = 4.7 Hz, 2H), 4.79 (dq, J = 9.7, 4.7 Hz, 1H), 4.32 (d, J = 4.6 Hz, 2H), 2.23 (s, 3H), 2.05 (s, 3H).

(4). $[\alpha]^{30}_D$ +8.9 ° (c = 1.7, MeOH). Mp 165-168 °C. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.3 (m, 5H), 6.10 (d, J = 7.6 Hz, 1H), 5.10 (d, J = 7.8 Hz, 2H), 4.91 (dd, J = 7.8, 3.3 Hz, 1H), 4.65 (d, J = 2.7 Hz, 1H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 172.04, 156.96, 135.31, 128.91, 128.54, 128.21, 99.95, 82.27, 68.07, 56.48. IR (neat) 3700-2400, 1710, 1520 cm^{-1}. MS (FAB) m/z (rel intensity) 359 (17), 357 (34), 355 (41). Elemental analysis calculated for $C_{12}H_{12}Cl_3NO_5$: C, 40.42; H, 3.39; N, 3.93. Found: C, 40.88; H, 3.52; N, 3.74.

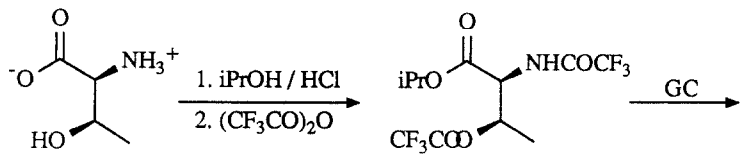
8. a) J.W. Cornforth, R.H. Cornforth and K.K. Mathew; *J. Chem. Soc.* **1956**, 112. b) P. Herold; *Helv. Chim. Acta* **1988**, *71*, 354.



erythro

The aldehyde carbonyl and nitrogen substituent are disposed in an antiperiplanar arrangement and attack by the bulky trichloromethane anion occurs from the least hindered side of the molecule to give the *erythro* product (**5**).

9. The stereochemical integrety of the amino acids prepared was verified by derivatization followed by capillary GC analysis on a CHIRASIL-VAL column (Alltech Ass.Inc.) according to published literature methods: a) H.Frank, A.Rettenmeier, H.Welcker, G.J.Nicholson and E.Bayer; *Anal. Chem.* **1982**, *54*, 715. b) R.H.Liu and W.W.Ku; *J. Chromatog.* **1983**, *271*, 309.



10. D.F. Elliott; *J. Chem. Soc.* **1950**, 62.

11. B. Castro, J.R. Dormoy, G. Evin and C. Selve; *Tetrahedron Lett.* **1975**, *16*, 1219.

(Received in USA 30 October 1990)