Crown Ether Derivatives of L-(3,4-dihydroxyphenyl)alanine: Crowned DOPA

Michele Berthet and Etienne Sonveaux*

Laboratoire de Chimie Organique de Synthèse, Université Catholique de Louvain, 1, Place L. Pasteur, B-1348 Louvain-La-Neuve, Belgium

L-[3,4-(1,4,7,10,13-pentaoxatridecamethylene)phenyl]alanine and L-[3,4-(1,4,7,10,13,16-hexaoxahexadecamethylene)phenyl]alanine have been synthesised without racemization and characterised spectroscopically.

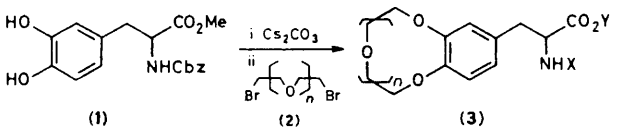
The synthesis and cation binding properties of polymers bearing crown ether side chains have been the subject of several recent publications.[1] Sandwich type 1:2 complexes between the metal cation and two adjacent crown moieties have been observed[2] and low molecular weight compounds tailored for such sandwich complexation have been found.[3]

Polypeptides with crown ether side chains are potentially useful for the resolution of racemic ammonium salts or amino-acids. In sandwich type complexes the ligand cavity might be inherently chiral because its shape is partially determined by the peptide backbone conformation. The functionalization of α-helical poly(glutamate) by crown ethers was described recently.[4]

We report the synthesis of the new optically pure amino-acids (**3h, i**). In these amino-acids the crown-ether function is linked to the α-carbon by a rather rigid chain in order to favour the interaction between the polypeptide backbone and the binding site in the polymer. Compounds (**3h, i**) might be suitable monomers for the synthesis of polypeptides bearing crown ethers as O,O′-diprotected (3,4-dihydroxyphenyl)alanine (DOPA) derivatives are known to polymerize easily.[5]

The key point in the synthesis of L-(**3h, i**) was to construct a macrocycle on a suitably protected L-DOPA derivative without extensive racemization. This was achieved by using the dicaesium salt of *N*-benzyloxycarbonyl-L-DOPA methyl ester (**1**)[6] as the nucleophile in the reaction with the oligo-(ethylene glycol) dibromides (**2a, b**).[7] The crown ethers L-(**3a**) {yield 18%, m.p. 105.5 °C, $[\alpha]_D^{20}$ −3.26° (*c* 1.01, MeOH)} and L-(**3b**) {yield 37%, m.p. 126.5 °C, $[\alpha]_D^{20}$ −5.98° (*c* 1.07, MeOH)} were obtained and fully characterised.

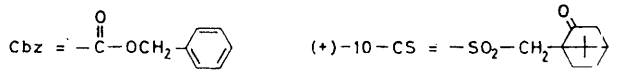
The optical purity of L-(**3a**) was checked by deprotection to L-(**3c**) (H_2, Pd, methanolic hydrochloric acid, yield 95%) and coupling[8] with (+)-camphorsulphonyl chloride to give



(1) (2) (3)

a; $n = 3$ b; $n = 4$

a; $n = 3$, X = Cbz, Y = Me
b; $n = 4$, X = Cbz, Y = Me
c; $n = 3$, X = H, Y = Me
d; $n = 4$, X = H, Y = Me
e; $n = 3$, X = (+)-10-CS, Y = Me
f; $n = 3$, X = Cbz, Y = H
g; $n = 4$, X = Cbz, Y = H
h; $n = 3$, X = Y = H
i; $n = 4$, X = Y = H



(3e) (yield 81%). When D,L-DOPA was used as the starting material, an equimolar mixture of the two diastereoisomers of (**3e**) was obtained. The 200 MHz ^{1}H n.m.r. spectrum of this mixture featured several well-resolved signals assignable to both diastereoisomers [δ (Me_4Si, $CDCl_3$), diastereoisomer derived from L-(**3c**), 6.16 (1H, d, N*H*), 3.41 (1H, d, SO_2HCH), 2.87 (1H, d, SO_2HCH), 0.98 (3H, s, CH_3CCH_3), and 0.86 (3H, s, CH_3CCH_3); diastereoisomer derived from D-(**3c**), 5.64, 3.25, 2.70, 0.98, and 0.78 (same assignments)]. A careful inspection of the spectrum of (**3e**) obtained from optically pure L-DOPA showed the presence of only 2% of the unwanted diastereoisomer. It was thus concluded that practically no racemization occurs under the reaction conditions used to prepare L-(**3a**).

The amino-acid esters L-(**3a**, **b**) were saponified by the usual procedure[9] (yield 70—80%) to the corresponding acids L-(**3f**, **g**) which gave crystalline salts with dicyclohexylamine (DCHA) [L-(**3f**)–DCHA salt, m.p. 140 °C; L-(**3g**)–DCHA salt, m.p. 127 °C].

Further deprotection of L-(**3f**, **g**) (H_2, Pd, propan-2-ol–aqueous hydrochloric acid) led to the spectroscopically pure amino-acids L-(**3h**, **i**) [yield 80—90%; ^{13}C n.m.r., δ (Me_4Si, D_2O), L-(**3h**)–HCl salt, 171.9 (CO_2H), 148.2, 147.5, 127.3, 122.5, 114.1, 113.7 (carbons of the aromatic ring, Ar),[10] 69.7, 69.3, 68.7, 67.9—68.0 (macrocycle), 54.5 ($NH_3^+CHCO_2H$), and 35.3 p.p.m. ($ArCH_2CH$); L-(**3i**)–HCl salt, 171.4 (CO_2H), 147.5, 146.9, 126.8, 122.3, 113.3, 112.9 (carbons of the Ar),[10] 69.8, 69.6, 69.5, 68.7, 67.4 (macrocycle), 54.2 (NH_3^+-$CHCO_2H$), and 35.3 p.p.m. ($ArCH_2CH$)].

Prof. L. Ghosez and I.R.S.I.A. (fellowship to M.B.) are acknowledged for financial support.

Received, 9th August 1982; Com. 945

References

1 For a recent review, see: L. J. Mathias and K. B. Al-Jumah, *Polym. News*, 1979, **6**, 9.
2 J. Smid, S. C. Shah, R. Sinta, A. J. Varma, and L. Wong, *Pure Appl. Chem.*, 1979, **51**, 111.
3 M. R. Johnson, I. O. Sutherland, and R. F. Newton, *J. Chem. Soc., Chem. Commun.*, 1979, 306.
4 J. Anzai, A. Ueno, Y. Suzuki, and T. Osa, *Makromol. Chem., Rapid Commun.*, 1982, **3**, 55.
5 W. D. Fuller, M. S. Verlander, and M. Goodman, *Biopolymers*, 1978, **17**, 2939.
6 The protected DOPA derivative was described by F. Siuda and A. Habal, *J. Med. Chem.*, 1974, **17**, 1173.
7 According to a general method described by B. J. van Keulen, R. M. Kellogg, and O. Piepers, *J. Chem. Soc., Chem. Commun.*, 1979, 285.
8 H. Furukawa, Y. Mori, Y. Takeuchi, and K. Ito, *J. Chromatogr.*, 1977, **136**, 428.
9 M. Bodanszky, Y. S. Klausner, and M. A. Ondetti, 'Peptide Synthesis,' Wiley, New York, 1976, p. 51.
10 The detailed assignment follows the same lines as for DOPA-hydrochloride, see: R. Haran, F. Nepveu-Juras, and J. P. Laurent, *Org. Magn. Reson.*, 1979, **12**, 153.