Tin Derivatives for Synthesis: Preparation of Chiral Macrocycles

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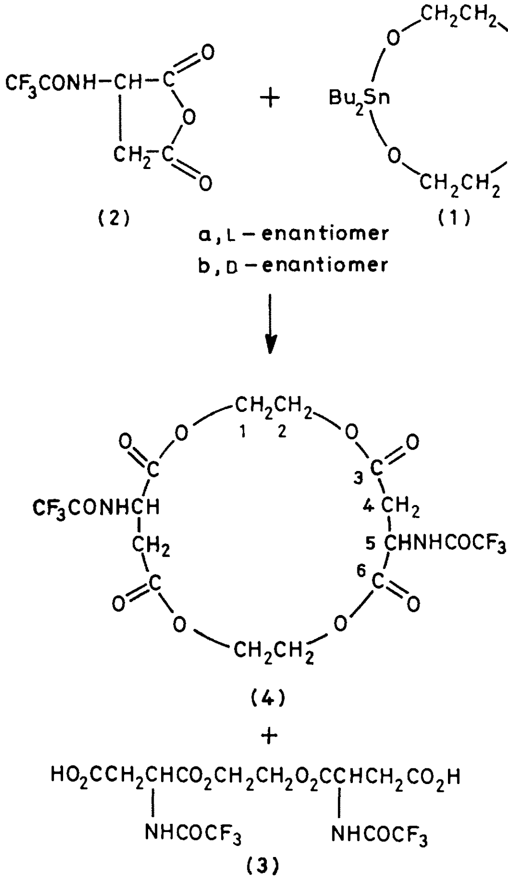
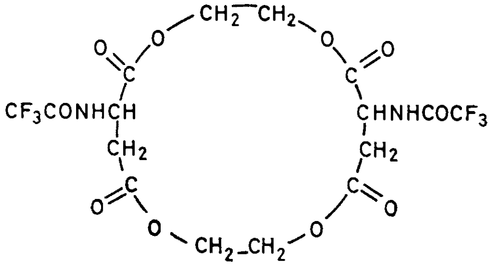
Summary The efficient preparation of macrocyclic amino acid derivatives *via* the use of tin as covalent template is described.

We have recently described the use of tin derivatives as covalent templates for the preparation of macrocyclic dicarbamates[1] and tetralactones[2] from di-isocyanates and diacyl chlorides, respectively. We now report the condensation of cyclic stannoxanes[3] with cyclic anhydrides. This reaction occurs under neutral conditions and thereby allows the preparation of sensitive chiral structures.



Scheme

Condensation of the distannoxane (**1**) with trifluoroacetyl aspartic anhydride (**2**)[4] afforded the tetrafunctional macrocyclic product (**4**) as indicated in the Scheme. The detailed procedure involved treatment of the stannoxane (**1**) (2·88 mmol) and L-aspartic anhydride (**2a**) (6·89 mmol) in boiling chloroform (150 ml) for 1·5 h. The mixture was then concentrated *in vacuo* and chromatographed on silica gel. Elution with benzene–ethyl acetate afforded 3·73 × 10^{-1} mmol (13%) of (**3a**) and 2·03 mmol (70%) of (**4a**). Compound (**3a**) exhibited m.p. 138—140 °C; $[\alpha]_D$ −31·5 (*c* 0·475 in ethanol); i.r. (Nujol) ν 3300, 1755, 1550, 1170, 910, and 890 cm^{-1}; n.m.r. (Me_2SO) δ 2·730 (dd, J_{gem} 17 Hz, J_{vic} 6·2 Hz, 2H, CH_2CO_2H), 2·88 (dd, J_{gem} 17 Hz, J_{vic} 5·1 Hz, 2H, CH_2CO_2H), 3·62 (s, 4H, OCH_2CH_2O), 4·701 (d of d, J_{vic} 8·6 Hz, J_{vic} 5·0 Hz, 2H, $-CHCH_2CO_2H$), and 9·87 (d, J_{vic} 9 Hz, 2H, NH); mass spectrum, highest fragment *m/e* 466 ($C_{14}H_{14}F_6N_2O_{10}H_2O$). Compound (**4a**) exhibited $[\alpha]_D$ −26·3 (*c* 1·73 in ethanol); i.r. (nujol) ν 3300, 1720, 1550, 1280, 1220, 1180, 1075, and 900 cm^{-1}; ^1H n.m.r. (CD_3OD) δ 2·46 (dd, J_{gem} 17 Hz, J_{vic} 8·0 Hz, 1H, $-CH_2CO$), 2·58 (d of d, J_{gem} 17 Hz, J_{vic} 5·0 Hz, 1H, CH_2CO), 3·32 (dd, J_{vic} 4·5 and 5·4 Hz, 2H, $-CH_2O-$), 3·8 (dd, J_{vic} 4·5 and 5·4 Hz, 2H, $-CH_2O-$), and 4·48 (m, 1H, CHNH); ^{13}C n.m.r. (CD_3OD) δ 172·95 (s, CH_2CO), 170·2 (s, CHCO), 158·4 [q, $J(C-CF_3)$ 40 Hz, $COCF_3$], 116·75 (q, J_{CF} 286·5 Hz, CF_3), 67·75 (t, $-CH_2O-$), 60·25 (t, $-CH_2O-$), 50·25 (d, CHNH), and 35·5 p.p.m. (t, CH_2CO-); mass spectrum, M^+ *m/e* 510 ($C_{16}H_{16}F_6N_2O_{10}$). These i.r. and n.m.r. data, together with the mass spectrum of product (**4a**), are compatible with a cyclic 2 : 2 condensation product between the stannoxane (**1**) and the anhydride (**2**). Yet, two dimeric ring products could *a priori* have been formed with either antiparallel (**4**) or parallel (**5**) arrangements of the aspartic acid residues. Decoupling experiments established the presence of structure (**4**), as irradiation of the methylene protons at δ 3·23 caused collapse of the methylene multiplet at δ 3·812 p.p.m. to a singlet, and irradiation of the methylene protons at δ 3·812 p.p.m. collapse of those at δ 3·23 to a singlet.



(5)

As to the conformation of the macrocyclic tetralactone (**4**), careful inspection of the ^1H and ^{13}C n.m.r. data indicates the presence of a 1,6-hydrogen bond between the amide proton and the carbonyl oxygen at position 3. The ^1H as well as the ^{13}C signals for the C(2)-methylene group are at significantly lower fields than those of the C(1)-methylene group. These low-field signals of the C(2)-methylene group may be attributed to the adjacent electron sink caused by hydrogen bonding of the carbonyl group. Relaxation studies of the ^{13}C nuclei supported these assignments: the T_1 value for C(4) was found to be much larger than that for C(1) or C(2), indicating a smaller degree of rotational freedom for the former group.[5]

Application of the same procedure to D-trifluoroacetyl aspartic anhydride (**2b**) afforded the corresponding enantiomers (**3b**) {m.p. 140 °C, $[\alpha]_D$ + 30·7 (*c* 0·45 in ethanol)}, and (**4b**) {m p 76—78 °C, $[\alpha]_D$ + 26·1 (c 0·475 in ethanol)} Similarly, condensation of benzyloxycarbonyl aspartic anhydride, trifluoroacetyl glutamic anhydride, or diacetyl tartaric anhydride with the distannoxane (**1**) under analogous conditions provided the corresponding chiral macrocyclic tetralactones

The formation of the macrocyclic tetralactones (**4**) by condensation of anhydrides (**2**) with the distannoxane (**1**) may be visualized as occurring *via* an electrophilic attack of the anhydride carbonyl at the stannoxane oxygen and subsequent extrusion of dibutyltin oxide Although extrusion of tin oxide has so far not been reported in the literature, extrusion of tin sulphide is a quite common phenomenon[6] rendering the former pathway a plausible process The regiospecific formation of the antiparallel structure (**4**) in favour of the parallel structure (**5**) may be attributed to attack of the anhydride at the stannoxane at the most distant positions from each other

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[1] A Shanzer and M Mayer-Shochet, I U P A C International Symposium on Organic Synthesis, Jerusalem, 1978, Abstract p 80

[2] A Shanzer and N Mayer-Shochet, *J Chem Soc , Chem Commun* , 1980, 176

[3] W J Considine, *J Organomet Chem* , 1966, **5**, 263

[4] F Weygand, *Chem Ber* , 1957, **90**, 1896

[5] N K Wilson and J B Stothers, *Top stereochem* , 1974, **8**, 1

[6] A J Bloodworth and A G Davies, *Chem Ind* , 1972, 490