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NON-CARBOHYDRATE-BASED ENANTIOSELECTIVE SYNTHESIS OF D(-)-ALLOMUSCARINE

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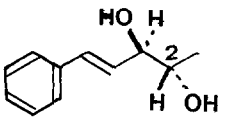
Among the easily accessible chiral products used as starting materials for enantioselective syntheses of natural products,[1] carbohydrates have received the widest attention. In the series of muscarine and its isomers, the C_6 chiral framework of L(+)-muscarine (12) has been built up[2] from L-arabinose through the intermediacy of L-glucosaminic acid, which ring closes to L-chitaric acid upon deamination, whereas D(-)-epiallomuscarine has been recently obtained[3] from D-glucose. However, in the abovementioned procedures, difficulties arise in the regioselective removal of oxygen functions, which cause low yield or the necessity of separation of isomers.

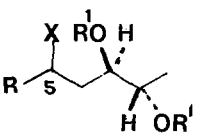
We report now the enantioselective non-carbohydrate-based formal synthesis of D(-)allo-muscarine (11), which occurs in Amanita muscaria,[4] using as chiral starting material the optically active, C_6-C_5 methyl diol (1), prepared from cinnamaldehyde and fermenting baker's yeast.[5] Indeed, the diol (1) shows the (2S,3R) absolute configuration present in positions 5 and 4 of L(+)-muscarine (12) and D(-)-allomuscarine (11), and seemed suitable for conversion through unexceptional steps into the C_6 α-amino acid (6), corresponding, apart from the chirality, to the compound used by Belleau et al. in the synthesis of L(+)-muscarine and L(+)-allomuscarine.[6]

Thus, compound (1) was converted into (2),[7] which is brominated (N-bromosuccinimide, CCl_4) to (3), yielding in turn upon azide displacement, the azide (4). The latter upon hydrogenation (PtO_2, ethyl acetate-acetic anhydride) gave the triacethyl derivative (5), oil, $[\alpha]_D^{20}$ -27.8 (c 1, $CHCl_3$), shown by ^{1}H-n.m.r. studies to be racemic at position 5, in ca. 70% yield from (1). The mixture (5) was ozonised in 90% formic acid, at 0°C. Typically, 7 g of (5) required 20 hr. After oxidative work up, the crude dried material was treated with 4N HCl for 4 hr at 100°C. The residue obtained upon evaporation of the acid separated from ethyl acetate-ethanol, in ca. 35% yield from(5), the amino γ-lactone hydrochloride (7),[8] ν_{CO} 1780, m.p. 218-220°C, n.m.r. see Table. A further crop of crystals was obtained on concentration, thus raising the yield to ca. 55%. The latter material was shown by ^{13}C n.m.r. spectroscopy to be compound (7) containing 10% of the isomer (8). The almost exclusive obtainment of the amino lactone (7) from (5) seems to be the expected consequence of the acid catalysed epimerization[2] of (8). The lactone (7) in 1N HCl was deaminated with 1.2 molar equiv. of $NaNO_2$ at 0°C, followed by 12 hr stirring at room temperature. The reaction mixture was evaporated and the residue treated with methanolic HCl to give the oily ester (9), $[\alpha]_D^{20}$ -23.6 (c 1, EtOH), in ca. 60% yield from (7). The ester (9), upon 24 hr treatment with 10% methanolic $NHMe_2$ gave in 80% yield an amide, m.p. 66°C, $[\alpha]_D^{25}$ -45.6 (c 1, EtOH), identified by comparison of these data with those reported in the literature[6] (m.p. 63-65°C, $[\alpha]_D$ +46.4) for

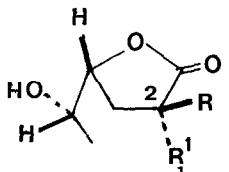
the (2S,4S,5R)-isomer, as compound (10). Since L(+)-allomuscarine has been obtained[6] from the (+)-amide, the synthesis of the negative isomer (10) from the diol (1) formally represents an enantioselective synthesis of D(-)-allomuscarine (11). Finally, the retention of configuration at C-2 in the ring closure in the deamination of the lactone (7) is in agreement with the results obtained with 2-amino-2-desoxy-D-mannonolactone.[8]



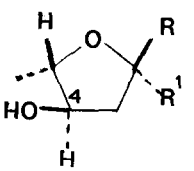
(1)



(2) R= C_6H_5; X= H; R^1= Ac
(3) R= C_6H_5; X= Br; R^1= Ac
(4) R= C_6H_5; X= N_3; R^1= Ac
(5) R= C_6H_5; X= NHAc; R^1= Ac
(6) R= CO_2H; X= NH_2; R^1= H



(7) R= H; R^1= NH_2.HCl
(8) R= NH_2.HCl; R^1= H



(9) R= CO_2Me ; R^1= H
(10) R= $CONMe_2$; R^1= H
(11) R= $CH_2NMe_3^+$; R^1=H
(12) R= H; R^1= $CH_2NMe_3^+$

TABLE: ^1H and ^{13}C-n.m.r. data for compounds (7)-(10)[a] (J in Hz)

	(7)(D_2O-TFA)		(9)($CDCl_3$)[b]		(10)($CDCl_3$)[b]			(7)	(8) (DMSO)
H-2	4.60 (J(2,3α)	10.5)	4.59 (J(2,3α)	3.7)	4.93(J(2,3α)	3.4)	C-1	172.3	172.7
H-3α	2.53 (J(3α,3β)	13.5)	2.10 (J(3α,3β)	13.5)	2.14(J(3α,3β)	13.5)	C-2	48.6	47.6
H-3β	2.98 (J(2,3β)	10.5)	2.49 (J(2,3β)	9.0)	2.36(J(2,3β)	8.0)	C-3	28.1	25.9
H-4	4.72 (J(4,3α)	9.0)	4.00 (J(4,3α)	2.8)	3.92(J(4,3α)	2.8)	C-4	81.2	81.5
	(J(4,3β)	2.5)	(J(4,3β)	5.8)	(J(4,3β)	6.0)			
H-5	4.24 (J(4,5)	3.0)	4.20 (J(4,5)	2.8)	4.11(J(4,5)	2.8)	C-5	65.9	66.3
CH_3	1.24 (J(5,Me)	6.5)	1.19 (J(5,Me)	6.5)	1.17(J(5,Me)	6.5)	CH_3	18.8	18.8

a) chemical shifts in ppm from TMS b) H-3α and H-3β may be interchanged

The cis configuration of the substituents derives from the difference in the chemical shifts of 3α and 3β (0.55 ppm) and from the value of the vicinal coupling constants 4,3β (2.5)Hz[9]

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