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A NEW SYNTHESIS OF (-)-ANISOMYCIN OR (+)-ANISOMYCIN STARTING FROM D-TYROSINE OR L-TYROSINE

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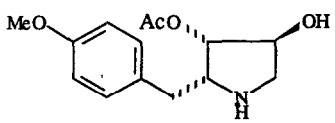
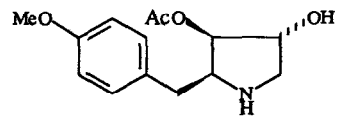
Abstract: (*R*)-2-(*p*-methoxyphenyl)methyl-2,5-dihydropyrrole (-)-2 and its (*S*)-isomer (+)-2, chiral intermediates for (-)-anisomycin (-)-1 and (+)-anisomycin (+)-1, have been efficiently synthesized via an exclusively *cis*-olefination step starting from D-tyrosine and L-tyrosine, respectively.

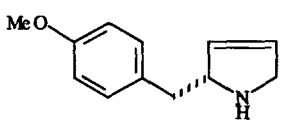
The diverse biological activities[1] of the antifungal antibiotic (-)-anisomycin (-)-1[2,3] have stimulated a great deal of interest in its chemical synthesis both in the racemic[4] and chiral modes.[5] These synthetic efforts include an efficient stereoselective synthesis of (±)-anisomycin (±)-1, elaborated from the crucial intermediate (±)-2-(*p*-methoxyphenyl)methyl-2,5-dihydropyrrole (±)-2.[4b]



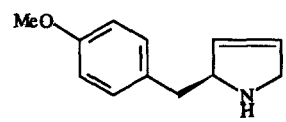
(-)-1



(+)-1



(-)-2

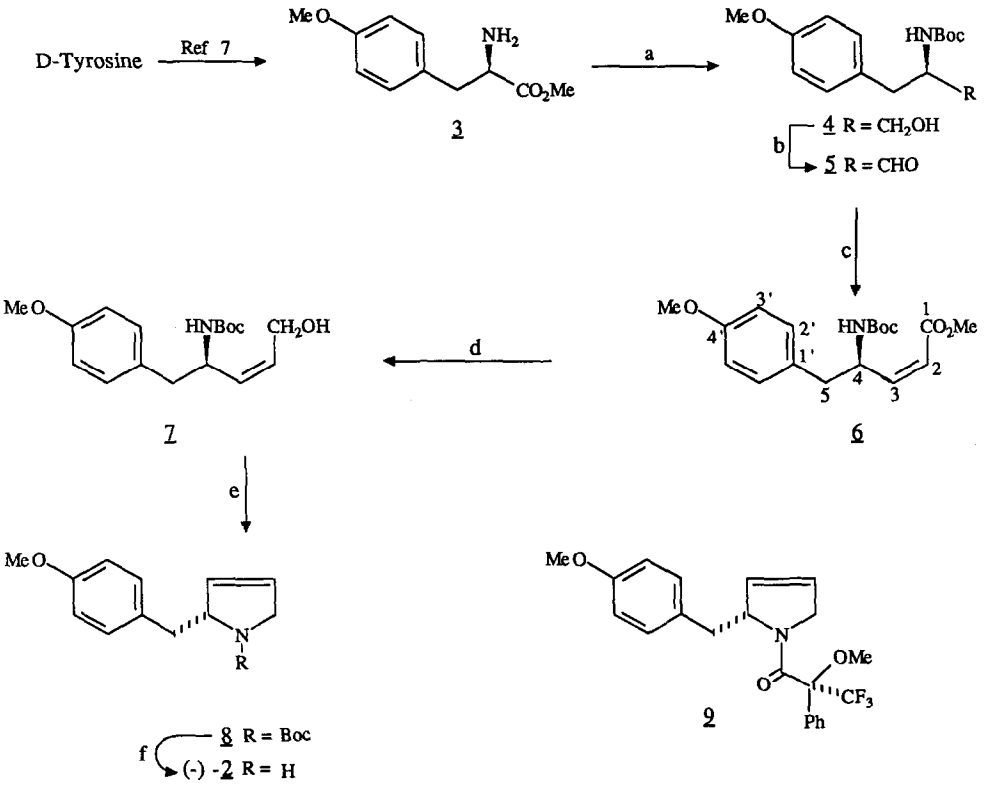


(+)-2

A recent communication[6] reported an asymmetric synthesis of the (*S*)-isomer (+)-2 and its transformation into unnatural (+)-anisomycin (+)-1 following the previously outlined route in the racemic series.[4b] We wish to report here a new synthesis of (*R*)-2-(*p*-methoxyphenyl)methyl-2,5-dihydropyrrole (-)-2 and its (*S*)-isomer (+)-2 from D-tyrosine and L-tyrosine,

respectively, which also constitutes a formal total synthesis of (-)-anisomycin (-)-1 and (+)-anisomycin (+)-1.

It appeared to us that an expedient approach to (-)-2 from D-tyrosine would involve a reaction sequence outlined in the following scheme.



Reactions conditions: a)i. $(Boc)_2O$, Na_2CO_3, H_2O-dioxane (1:1), RT, overnight, 95%; ii. $NaBH_4$-LiCl (1:1; 5 equiv.), EtOH-THF (4:3), RT, 95%. b) $(COCl)_2$, DMSO, CH_2Cl_2, Et_3N, -78°C. c) $(CF_3CH_2O)_2P(O)CH_2CO_2Me$, 18-crown-6, $(Me_3Si)_2NK$, THF, -78°C, 80% from 4. d) DIBAH, CH_2Cl_2, -78°C, 98%. e) i. MsCl, CH_2Cl_2, Et_3N, -10°C, 20 min., 93%; ii. NaH, CH_2Cl_2, RT, overnight, 94%. f) CF_3CO_2H, CH_2Cl_2, RT, 4h, 100%.

O-Methyl D-tyrosine methyl ester (3), readily obtained as its hydrochloride from D-tyrosine,[7] was treated with di-*tert*-butyl dicarbonate thereby protecting the amino group. Reduction of the ester function with sodium borohydride in the presence of lithium chloride[8] furni-

shed the alcohol (4) which was transformed into the aldehyde (5) by Swern oxidation.[9] Chain extension with the anion derived from bis(2,2,2-trifluoroethyl)(methoxycarbonylmethyl)-phosphonate at -78°C afforded exclusively[10] (Z)-α,β-unsaturated ester (6). In order to avoid or minimize any possible racemization of the chiral centre, the aldehyde (6) was used immediately, without purification, for the olefination step. Our strategy required that the olefination product (6) have the desired (Z) geometry of the double dond for the subsequent cyclization to the chiral 2,5-dihydropyrrole derivative (8). Reduction of the ester group of (6) with diisobutylaluminium hydride (DIBAH) provided the alcohol (7) which after mesylation followed by intramolecular cyclization led to the desired 2,5-dihydropyrrole derivative (8). Treatment with trifluoroacetic acid removed the *tert*-butyloxycarbonyl (Boc) group to give (*R*)-2-(*p*-methoxyphenyl)methyl-2,5-dihydropyrrole (-)-2. The overall yield of (-)-2 from (3) was *ca.* 62%.[11] The (*S*)-2,5-dihydropyrrole (+)-2 was also prepared in the same manner starting from L-tyrosine. Both samples (-)-2 and (+)-2 had identical spectral data which fully matched those previously reported[4b] for the racemic compound. The optical purity[12] of (-)-2 and (+)-2 was shown to be >95% by ^{1}H n.m.r. (400 MHz) analysis of their (*S*)-(-)-α-methoxy(trifluoromethyl)- phenylacetyl derivatives (Mosher amides, e.g., 9).[13]

Since (+)-2 had previously been transformed[6] into (+)-anisomycin (+)-1, the present work offers an alternative route to this antibiotic in its both enantiomeric forms. It is to be noted that a completely different approach to the synthesis of (-)-anisomycin starting from D-tyrosine has recently been reported.[14]

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References and Notes

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11. All reported yields (see scheme) are for materials isolated from column chromatography and all compounds gave spectroscopic data in agreement with the assigned structures. For example, 6 had $M^{+\cdot}$ at m/z 325; ^{1}H n.m.r. (400 MHz, $CDCl_3$) 1.38 (9H, s, Boc), 2.88 (2H, m, $-CH_2Ar$)), 3.70 (3H, s, Ar-OMe), 3.73 (3H, s, $-CO_2Me$), 4.76 (1H, br.s., NH), 5.21 (1H, m, H-4), 5.53 (1H, d, J = 11.5 Hz, H-2); 6.20 (1H, dd, J 11.5, 8 Hz, H-3), 6.84 and 7.17 (each 2H, d, J 8.5 Hz); ^{13}C n.m.r. (50.3 MHz, $CDCl_3$ δ 28.47 (3 x CH_3 of Boc), 39.66 (C-5), 50.95 (Ar-OCH_3), 51.42 (C-4), 55.39 (-$COOCH_3$), 79.66 (-$COOCMe_3$), 114.15 (2 x C-2'), 119.43 (C-2), 129.38 (C-1'), 130.38 (2 x C-3'), 150.51 (C-3), 155.43 (C-4'), 158.71 (-$COOCMe_3$), 166.25 (C-1); m.p. 112-114°C; $[\alpha]_D$ -65° (c 1.8, $CHCl_3$). The corresponding compound obtained from L-tyrosine showed $[\alpha]_D$ + 68.5° (c 2.46, $CHCl_3$).
12. (-)-2 and (+)-2 each obtained as oil, showed $[\alpha]_D$ -89.3° (c 1.26, THF) and + 87.7° (c 2.40, THF), respectively. Curiously, the literature[6] value + 9.26° for (+)-2 is different from that noted by us.
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