AN ASYMMETRIC TOTAL SYNTHESIS OF UNNATURAL (+)-ANISOMYCIN†

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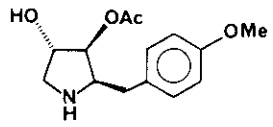
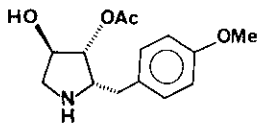
Abstract - Utilizing the valine-based chiral formamidine of 2,5-dihydropyrrole, enantioselective alkylation with p-methoxybenzyl chloride gave, after several subsequent synthetic manipulations, the unnatural enantiomer, (+)-anisomycin, in 22% overall yield and 88-90% ee.

Synthetic efforts leading to the racemic antibiotic anisomycin[1] have been reported[2] by a number of laboratories in recent years. There have also been three reports[3] of non-racemic synthesis based on carbohydrate starting materials, but to date its synthesis has not been described via asymmetric induction. It is noteworthy that modern asymmetric synthesis has as its prime value, not only to reach products in high ee's, but the ability to prepare either enantiomer in a predictable manner. Furthermore, those engaged in asymmetric synthesis should periodically prepare the unnatural enantiomer to demonstrate that the method truly fulfills the requirements set forth and provide those enantiomers which are either available in very short supply or are, in fact, nonexistent.



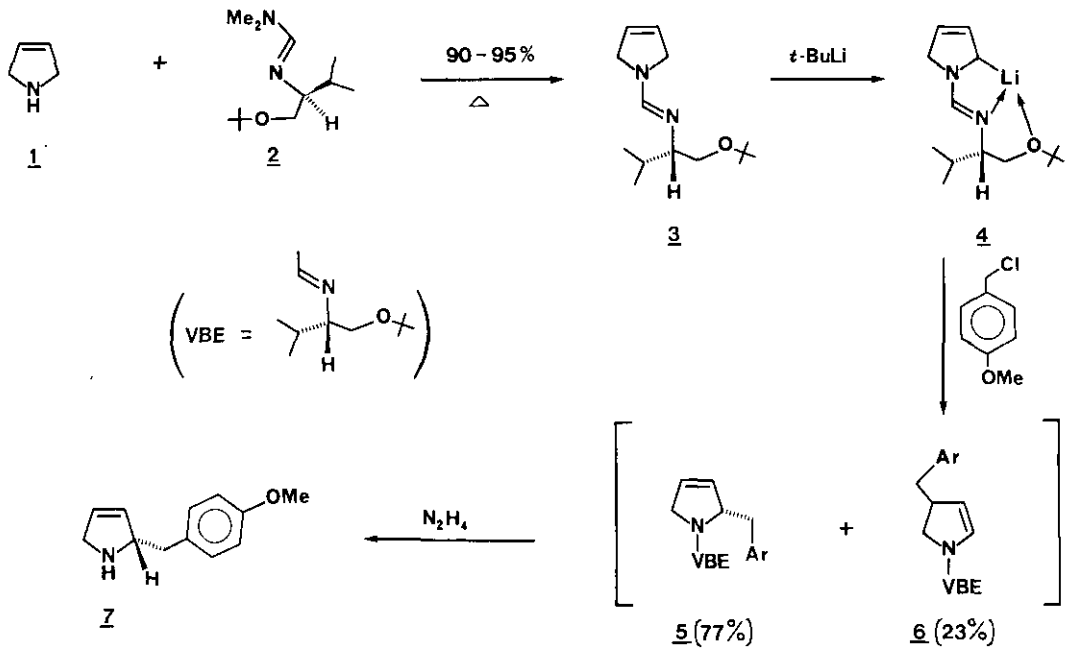
(−)-Anisomycin



(+)-Anisomycin

As part of a program involved in asymmetric alkylation of chiral α-amino carbanions,[4] which has thus far led to enantioselective syntheses of isoquinoline alkaloids,[5] morphine alkaloids,[6] and indole alkaloids[7] in greater than 90% ee, we have tested the methodology with a view to reach (+)-anisomycin. Our scheme was initiated by treating dihydropyrrole 1 with the dimethylaminoformamidine of (S)-valinol-t-butyl ether 2 in toluene and heating to reflux to afford the pyrroline formamidine 3 ($[\alpha]_D$ = -16.3°) as previously described.[6b] Metalation with s-butyllithium (THF-hexane, 1:1,

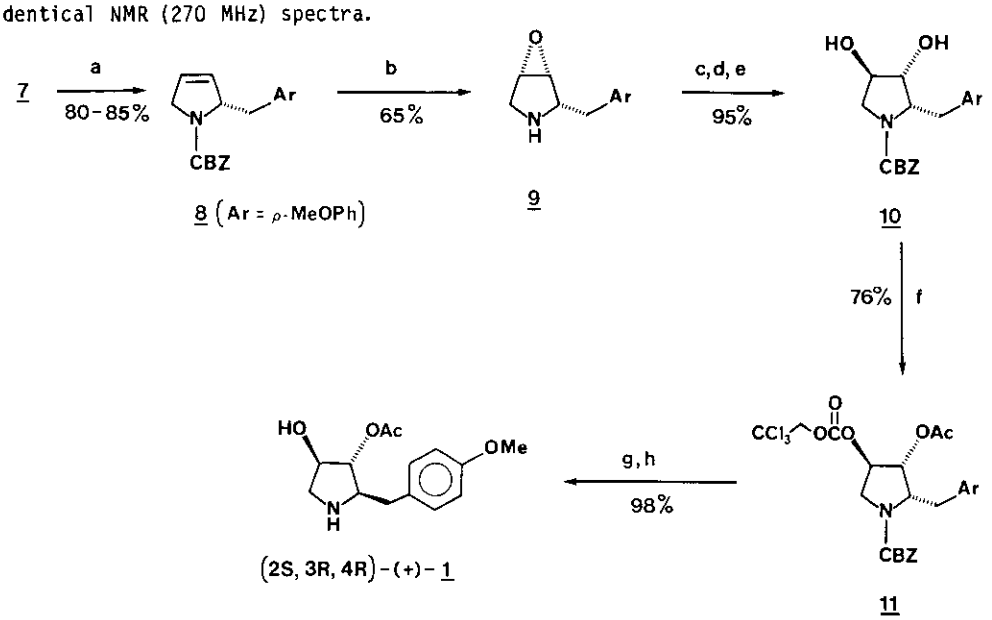
†Dedicated to Professor Gilbert Stork on the occasion of his 65th birthday.



1 2 3 4 7

-110° C, 0.03-0.04 M in 3) gave the lithiated species 4 after 15 min which was treated with p-methoxybenzyl chloride producing 5 and 6 as a result of direct and allyl transposed alkylation. The undesired alkylated product 6 posed no serious problem since the mixture 5, 6, when treated with the hydrazine reagent,[8] resulted in destruction of 6 and furnishing only the 2-aryldihydropyrrole 7[9] (53% overall from 3). *The enantiomeric ratio of 7 was assessed by reduction of the olefinic bond* (Rh/C-H_2, MeOH, 50 psi, 5 h) and transforming the pyrrolidine to its α-naphthoyl amide.[6b] HPLC analysis using the Pirkle Column[6b] showed that the dihydropyrrole 7 contained a 95:5 ± 1 ratio of enantiomers. The sequence to anisomycin was continued following the route outlined by Hall[2e] in the racemic series. Thus, 7 was acylated to the N-CBZ derivative 8 ($[\alpha]_D$ +1.4°) which was converted to the syn-epoxide 9 ($[\alpha]_D$ +0.27°, mp 73-75° C). The CBZ group was removed by catalytic hydrogenation to allow epoxide ring opening which was performed by heating in trifluoroacetic acid. The carbobenzoxy group was reinstalled to give 10 ($[\alpha]_D$ +0.09°, mp 125-126° C) in 95% yield from 9. The unhindered 4-hydroxy group in 10 was selectively transformed into the trichloroethyl carbonate due to the steric crowding at the 3-hydroxyl and the latter esterified with

acetic anhydride affording 11 in 76% yield. Without purification, 11 was subjected to zinc reduction to remove the trichloroethyl carbonate and directly reduced with H_2-Pd to remove the CBZ group. This sequence gave (+)-anisomycin in 98% yield, mp 142-143° C, mixed mp with authentic (-)-1, mp[10] 120-123° C; $[\alpha]_D^{25}$+21.9° (c 0.28, EtOH). Natural (-)-anisomycin[11] showed $[\alpha]_D^{25}$ -25.8° (c 0.3, EtOH). Both samples (+)-1, (-)-1 had identical NMR (270 MHz) spectra.



a) $PhCH_2OCOCl$, CH_2Cl_2, Et_3N, 25° C; b) aq $HClO_4$, 0° C, N-iodosuccinimide, KOH; c) H_2-Pd/C MeOH, 2 h); d) NaO_2CCF_3-TFA, 120° C; e) $PhCH_2OCOCl$, THF, Na_2CO_3; f) CCl_3CH_2OCOCl, DMAP, CH_2Cl_2; f) Ac_2O, DMAP, CH_2Cl_2; g) Zn-HOAc-THF, 25° C, 1 h; h) H_2, Pd/C, MeOH).

Based on the chiral HPLC analyses of 7 (95:5 ± 1) and the specific rotations, this synthesis was accomplished in 22% overall yield from 3 and with an enantiomeric purity of 85-90%, as its nonexistent unnatural enantiomer. The use of (R)-valinol would, undoubtedly furnish the natural enantiomer of 1.

ACKNOWLEDGEMENT

The authors are grateful to the National Science Foundation for financial support of this work. We thank Professor Stan Hall of Rutgers-Newark for spectra and helpful discussions related to Anisomycin.

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8. The formamidines were readily cleaved (5 → 7) by dissolving in ethanol-H_2O, 4:1, and adding glacial acetic acid-hydrazine (3.5:2, v/v), stirring at 50° C for 6 h, cooling and neutralizing with 10% KOH.
9. Bp (bulb-to-bulb) 170° C (0.3 mm Hg), $[\alpha]_D$ +9.26° (c 0.55, THF); ^{1}H-NMR (270 MHz, $CDCl_3$) 7.13 (d, J = 8.5 Hz, 2 H), 6.83 (d, J = 8.5 Hz, 2 H), 5.81 (br. d., J = 16.5 Hz, 2 H), 4.21 (br. s., 1 H), 3.78 (s, 3 H), 3.73 (m, 2 H), 2.71 (d, J = 6.8 Hz, 2 H), 2.15 (br. s, 1 H, exchanges with D_2O). This product matched all spectral data reported for racemic 7 (ref. 2e).
10. Racemic anisomycin was reported to have mp 126-127° C (ref. 2e).

11. We thank Dr. N. Belcher of Chas. Pfizer for an authentic sample of (-)-anisomycin.

Received, 26th May, 1986