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STEREOSELECTIVE SYNTHESIS OF TILIVALLINE

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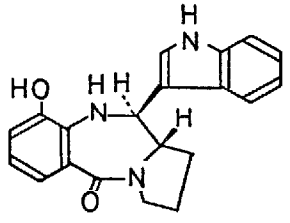
Abstract: Tilivalline (1b) was easily synthesized by converting lactam 3b to the acyliminium precursor 5b followed by stereoselectively introducing indole from the less hindered side of 5b.

Tilivalline (1b) is a metabolite that was isolated by Mohr and Budzikiewicz[1] from Klebsiella pneumoniae var. oxytoca. It has an interesting structure similar to those of anthramycin antibiotics.[2] The synthesis of 1b has been successfully carried out by nonstereoselective[1] and stereoselective[3] methods. The latter means in particular appear to include many fascinating but complex reactions. The present communication reports a convenient and stereoselective synthesis of 1b in short steps.

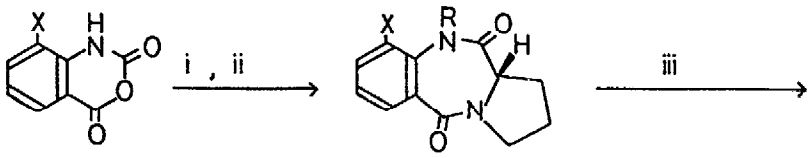
The approach to this synthesis is based on the use of readily available optical lactam 3 the prospects of the conversion of which into benzodiazepines possessing appropriate substituents appear promising.[4] As a model experiment, the synthesis of deoxytilivalline (1a) was carried out as follows: Treatment of pyrrolobenzodiazepine 3a, obtained in high yield from isatoic anhydride 2a and L-proline by the known method,[5] with benzyl chloroformate gave the N-benzyloxycarbonyl compound 4a (61.9%)[6], mp 119-120°, $[\alpha]_D^{21}$+84.8° (c=1.05, MeOH). Controlled reduction[7] of 4a with $NaBH_4$ afforded alcohol 5a[8] (69.0%), whose condensation with indole produced 6a (50.2%), mp 223-225°, $[\alpha]_D^{21}$+107.3° (c= 0.40, $CHCl_3$) as the sole product. Stereoselectivity in this reaction was reasonable if the nucleophile (indole) may be considered to attack from the less hindered side[3] on the acyliminium intermediate[9] formed from alcohol 5a. Finally catalytic hydrogenation of 6a gave 1a (51.8%)[10], mp 220-224°, $[\alpha]_D^{21}$ +58.7° (c=1.01, $CHCl_3$).

Tilivalline (1b) was synthesized by the above route, but under refined conditions. The condensation of 3-benzyloxyisatoic anhydride 2b[11] with L-proline gave diazepine 3b (84%), mp 178-182°, $[\alpha]_D^{23}$+391.1° (c=1.00, $CHCl_3$) which was subsequently converted to carbamate 4b (88%), $[\alpha]_D^{25}$+62.4° (c=0.97, MeOH). The controlled reduction[7] of compound 4b with $NaBH_4$ provided alcohol 5b (76%), mp 193-196°, $[\alpha]_D^{23}$+128.5° (c= 0.99, $CHCl_3$) which was, via acyliminium ion, condensed with indole to afford 6b exclusively (93%), mp 260-265°, $[\alpha]_D^{21}$+267.3° (c=1.38, $CHCl_3$). The catalytic hydrogenation of 6b gave tilivalline (1b) (82%), mp 190-200°, $[\alpha]_D^{23}$+210° (c=



Tilivalline (1b)

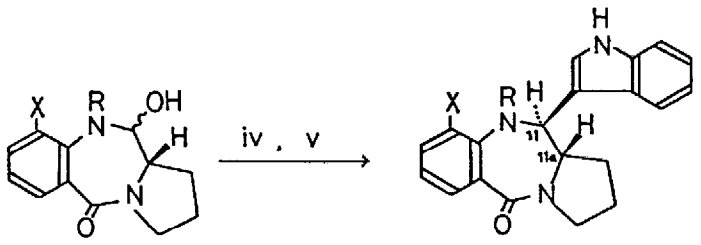
1.01, MeOH). The spectral data (IR, ^{1}H- and ^{13}C-NMR, mass, and UV) of the synthetic tilivalline showed complete agreement with those of an authentic sample provided through the courtesy of Prof. Shioiri.



2a: X=H
2b: X=OBn

3a: X=R=H,
3b: X=OBn, R=H,

4a: X=H, R=Cbz
4b: X=OBn, R=Cbz



5a: X=H, R=Cbz
5b: X=OBn, R=Cbz

6a: X=H, R=Cbz,
6b: X=OBn, R=Cbz,

1a: X=R=H
1b: X=OH, R=H

OBn = OCH_2Ph, Cbz = $COOCH_2Ph$

i) L-proline, DMSO, 110°, 6h; ii) n-BuLi or $(TMS)_2NLi$, THF, rt, 30 min; CbzCl, rt, 2 h; iii) $NaBH_4$/EtOH-THF/H^+, 0°; iv) indole, AcOH, sealed tube, 150°, 5 h; v) 5% Pd-C, MeOH-THF (1:1), H_2, 2 atm.

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References and Notes

1. N. Mohr and H. Budzikiewicz, Tetrahedron, 38, 147 (1982).
2. For anthramycin antibiotics, see L. H. Hurley, J. Antibiot., 30, 349 (1977); L. H. Hurley and D. E. Thurston, Pharm. Res., 52 (1984).
3. S. Mori, T. Aoyama, and T. Shioiri, Tetrahedron Lett., 27, 6111 (1986).
4. For conversion of lactams to α-substituted cyclic amines, see T. Nagasaka, M. Abe, N. Ozawa, Y. Kosugi, and F. Hamaguchi, Heterocycles, 20, 985 (1983); T. Nagasaka, H. Tamano, T. Maekawa, and F. Hamaguchi, Heterocycles, 26, 617 (1987).
5. W. B. Wright, Jr., H. J. Brabander, E. N. Greenblatt, I. P. Day, and R. A. Hardy, Jr., J. Med. Chem., 21, 1087 (1978).
6. Isolated yield; all new compounds were fully characterized by ^{1}H- and ^{13}C-NMR, IR, mass spectrometry and found to give satisfactory analyses (C, H, N) or exact masses.
7. T. Nagasaka, H. Tamano, and F. Hamaguchi, Heterocycles, 24, 1231 (1986).
8. The stereochemistry of α-hydroxyamines (5a and 5b) was not examined.
9. T. Shono, H. Hamaguchi, and Y. Matsumura, J. Am. Chem. Soc., 97, 4264 (1975).
10. Optimum conditions were not determined in the model experiments for 1a. Based on the ^{1}H-NMR signals of 1a (4.73 ppm, d, J=9 Hz, and 4.27, m), the protons at C-11 and C-11a were concluded to have a trans configuration.
11. Compound 2b (68%), mp 204-206° was obtained by reaction of 3-benzyoxyphthalic anhydride with TMS-N_3 along with 6-benzyloxyisatoic anhydride (8.6%), mp 229°. Cf., G. Caronna, Gazz. chim. ital., 71, 470 (1941). The details of this reaction are to be published in the near future.

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