Pergamon

Tetrahedron: Asymmetry, Vol. 7, No. 10, pp. 2775-2778, 1996

0957-4166/96 $15.00 + 0.00

PII: S0957-4166(96)00359-X

An Enantioselective Synthesis of the *Strychnos* Alkaloid (-)-Tubifoline

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Abstract: An enantioselective synthesis of the *Strychnos* alkaloid (-)-tubifoline, involving the kinetic resolution of racemic 1-(3-pyridyl)ethanol, the orthoester Claisen rearrangement of the enantiopure allylic alcohol **5**, Smith indolization of the resulting 4-piperidineacetate **6**, photocyclization of chloroacetamide **9**, and final transannular cyclization, is reported.

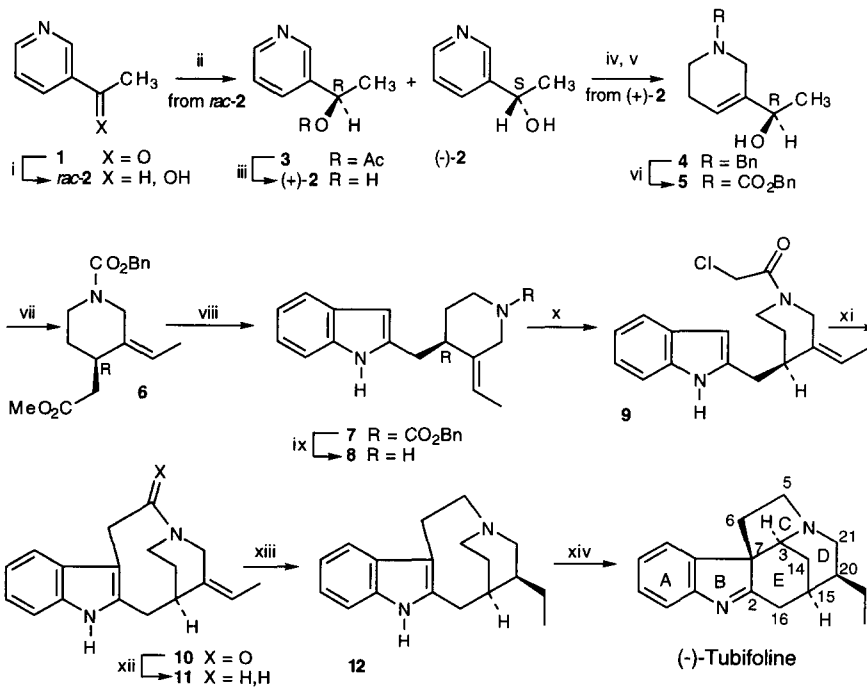
Although *Strychnos* indole alkaloids have received increasing attention from the synthetic standpoint during recent years and numerous alkaloids of this group have been synthesized in the racemic series,[1] the synthesis of these alkaloids in enantiopure form has been little explored. Until now, only two routes have culminated in the enantioselective synthesis of *Strychnos* alkaloids, providing access to Wieland-Gumlich aldehyde and (-)-strychnine,[2] *ent*-strychnine,[2] and *ent*-tubotaiwine.[1a,3] In addition, a few enantiopure intermediates[4] and models[5] have been prepared.

We report here the first enantioselective synthesis of the *Strychnos* alkaloid (-)-tubifoline.[6] Our approach is based on the consideration that in tubifoline all stereogenic carbons common to two or more rings are configurationally correlated because, starting from an enantiopure 3-substituted 4-(2-indolylmethyl)piperidine, the absolute configuration at the piperidine 4-position (C-15 in the biogenetic numbering[7]) determines the configuration of C-3 (a bridgehead position) and C-7, the latter as a consequence of the axial disposition of the piperidine nitrogen with respect to the carbocyclic E ring. On the other hand, the configuration of C-20 (15-H/20-H *cis*-relationship) would be easily attainable by hydrogenation of an exocyclic ethylidene double bond from the most accessible face of a tetracyclic 3,7-seco derivative.

Accordingly, we envisaged the enantiopure 4-(indolylmethyl)piperidine **8**, in which the configuration at C-4 is the same as at C-15 in *Strychnos* alkaloids, as a suitable starting material for the synthesis of (-)-tubifoline. This piperidine was prepared from 3-acetylpyridine **1**, as outlined in Scheme 1, the key steps being the kinetic resolution of the racemic alcohol *rac*-**2**, the orthoester Claisen rearrangement of the enantiopure allylic alcohol **5**, and the Smith indolization of the resulting 4-piperidineacetate.

The required enantiopure (1*R*)-(3-pyridyl)ethanol (+)-**2**[8] was prepared in 45% yield by transesterification of the racemic alcohol *rac*-**2** with vinyl acetate promoted by lipase PS (Amano, *Pseudomonas sp.*) followed by methanolysis of the resulting acetate **3**.[9,10] In order to transfer the chirality from the side chain to the pyridine 4-position, pyridine alcohol (+)-**2** was converted to the allylic

tetrahydropyridine alcohol **5** as shown in Scheme 1 and then treated with methyl orthoacetate to stereoselectively afford the 3(*Z*)-ethylidene-4(*R*)-piperidineacetate **6** in 93% yield.[11,12] Smith indolization[13] of **6** (60%) followed by deprotection of the piperidine nitrogen (77%) led to the enantiopure 4-(2-indolylmethyl)piperidine **8**, which was then treated with chloroacetyl chloride to give chloroacetamide **9** in 85% yield. Photocyclization of **9**[14] upon irradiation with a medium-pressure mercury lamp took place in 45% yield to give the tetracyclic lactam **10** along with variable amounts (approximate ratio 3:1) of the *E* isomer coming from the photoisomerization of the ethylidene double bond. Interestingly, the NMR spectra of both **10** and its *E* isomer showed the existence of two rotamers due to the restricted rotation of the amide group (no coalescence was observed at 100°C).[15] $LiAlH_4$ reduction of the major *Z* isomer[16] led to the unsaturated tetracyclic amine **11**[17] which was then hydrogenated using either 10% Pd-C or PtO_2 as the catalyst. However, rather surprisingly, mixtures of the expected tetracyclic amine **12**[18,19] and the alkaloid (-)-tubifoline[20] were obtained.[21,22] Finally, amine **12** was converted to (-)-tubifoline (55% yield) by treatment with PtO_2 in the presence of oxygen, following the procedure previously reported.[6c,23] Minor amounts (<5%) of condyfoline[6c] were also isolated. The ^1H- and ^{13}C-NMR spectra of (-)-tubifoline were identical with those of the racemic product.[23b]



Scheme 1. *Reagents and Conditions:* (i) $NaBH_4$, MeOH, rt, 2h; (ii) $AcOCH{=}CH_2$, *Pseudomonas, sp,* TBME, rt, 40 h; (iii) K_2CO_3, MeOH, rt, 1 h; (iv) $C_6H_5CH_2Cl$, MeOH, 80°C, 3 h; (v) $NaBH_4$, MeOH, rt, 12 h; (vi) $ClCO_2Bn$, CH_2Cl_2, reflux, overnight; (vii) $CH_3C(OMe)_3$, DME, pivalic acid, reflux, 48 h; (viii) *o*-$MeC_6H_4NHSiMe_3$, *n*-BuLi, hexane, reflux, then **6**, THF, -78°C to rt; (ix) Me_3SiI, MeCN, 0°C, 30 min; (x) $ClCH_2COCl$, 2N NaOH-CH_2Cl_2, 0°C to rt; (xi) hv, Na_2CO_3, H_2O, MeOH, 15 min; (xii) $LiAlH_4$, THF, reflux; (xiii) H_2, PtO_2, EtOH; (xiv) O_2, PtO_2, AcOEt.

Acknowledgment: Financial support from the DGICYT, Spain (projects PB94-0214 and HI94-019) is gratefully acknowledged. Thanks are also due to the "Comissionat per a Universitats i Recerca" (Generalitat de Catalunya) for Grant SGR95-00428 and for a fellowship to M.-D. C.

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8. (+)-**2**: $[\alpha]_D^{22}$ +52.8 (*c* 1.40, $CHCl_3$) [lit.[9a] $[\alpha]_D^{22}$ +52.4 (*c* 1.40, $CHCl_3$)]. The e.e. of (+)-**2** (96%) was determined by HPLC using a chiral column (Chiralcel OB, 9:1 hexane-*i*-PrOH). **3**: $[\alpha]_D^{22}$ +100.0 (*c* 0.96, $CHCl_3$) [lit.[9a] $[\alpha]_D^{22}$ +99.6 (*c* 0.96, $CHCl_3$)].
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12. **6**: $[\alpha]_D^{22}$ +7.5 (*c* 0.5, MeOH); ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 1.38 (m, 1H, H-5), 1.58-1.88 (m, 4H, H-5, CH_3), 2.35 (dd, *J*= 15.0, 7.7 Hz, 1H, CH_2CO_2), 2.60 (dd, *J*= 15.0, 7.0 Hz, 1H, CH_2CO_2), 2.71 (m, 1H, H-4), 3.34 (ddd, *J*= 13.0, 9.0, 3.5 Hz, 1H, H-6), 3.68 (s, 3H, CH_3O), 3.69 (d, *J*= 14.4 Hz, 1H, H-2), 3.82 (m, 1H, H-6), 4.44 (d, *J*= 14.4 Hz, 1H, H-2), 5.14 (s, 2H, CH_2O), 5.24 (m, 1H, =CH), 7.35 (m, 5H, C_6H_5); ^{13}C-NMR ($CDCl_3$, 50 MHz) δ 12.9 (CH_3), 32.1 (C-5), 37.0 (CH_2CO_2), 38.3 (C-4), 42.8 (C-6), 43.3 (C-2), 51.5 (CH_3O), 67.0 (CH_2O), 118.0 (=CH), 127.7 (C-*p*), 127.8 (C-*o*), 128.4 (C-*m*), 135.1 (C-3), 136.7 (C-*ipso*), 155.0 (NCO_2), 172.8 (CO_2).
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14. (a) For a related photocyclization, see: Wu, A.; Snieckus, V. *Tetrahedron Lett.* **1975**, 2057. (b) For a review, see: Sundberg, R. J. *Organic Photochemistry*, Padwa, A., Ed. Vol. 6, pp 121-176, Marcel Dekker: New York, 1983.

15. **10** (*Z* amide bond; major rotamer: ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 1.37 (m, 1H, H-14), 1.46 (m, 1H, H-14), 1.59 (dt, *J*= 6.8, 1.5 Hz, 3H, H-18), 2.62-3.00 (m, 3H, H-15 and 2H-16), 3.10 (m, 1H, H-3), 3.40 (dm, *J*= 17.0 Hz, 1H, H-21), 3.60 (m, 1H, H-3), 3.70 (d, *J*= 16.3 Hz, 1H, H-6), 4.15 (d, *J*= 16.3 Hz, 1H, H-6), 5.29 (m, 1H, H-19), 5.40 (dm, *J*= 17.0 Hz, 1H, H-21), 7.05-7.50 (m, 4H, Ar), 8.00 (br s, 1H, NH); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 12.5 (C-18), 25.5 (C-14), 30.3 (C-16), 33.1 (C-6), 37.3 (C-15), 43.3 (C-3), 43.9 (C-21), 105.3 (C-7), 110.6 (C-12), 117.6 (C-9), 117.8 (C-19), 119.3 (C-10), 121.6 (C-11), 128.1 (C-8), 133.6 (C-13), 134.8 (C-2), 139.1 (C-20), 172.7 (C-5); **10** (*E* amide bond; minor rotamer): ^{1}H-NMR ($CDCl_3$, 300 MHz, significant signals) δ 1.08 (dt, *J*= 6.8, 1.5 Hz, 3H, H-18), 1.87 (m, 1H, H-14), 2.18 (m, 1H, H-14), 3.73 (d, *J*= 16.3 Hz, 1H, H-6), 4.10 (d, *J*= 16.3 Hz, 1H, H-6), 4.19 (dm, *J*= 17.3 Hz, 1H, H-21), 4.80 (m, 1H, H-3), 5.01 (m, 1H, H-19), 7.80 (br s, 1H, NH); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 12.4 (C-18), 29.7 (C-14), 31.3 (C-16), 33.3 (C-6), 38.2 (C-3), 38.4 (C-15), 49.1 (C-21), 104.8 (C-7), 110.3 (C-12), 117.4 (C-9), 119.0 (C-10), 118.5 (C-19), 121.3 (C-11), 127.8 (C-8), 133.9 (C-13), 134.7 (C-2), 136.4 (C-20), 173.3 (C-5).
16. From the synthetic standpoint it was more convenient to use the mixture of *Z/E* lactams and then to hydrogenate the resulting *Z/E* mixture of unsaturated tetracyclic amines.
17. **11**: $[\alpha]_D^{22}$ -6.64 (*c* 0.5, MeOH); ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 1.58 (d, *J*= 6.8 Hz, 3H, H-18), 1.67 (m, 1H, H-14), 1.89 (m, 1H, H-14), 2.52 (m, 1H, H-3), 2.82 (m, 1H, H-6), 2.95-3.24 (complex signal, 7H), 3.32 (d, *J*= 17.0 Hz, 1H, H-21), 3.60 (d, *J*= 17.0 Hz, 1H, H-21), 5.34 (m, 1H, H-19), 7.10 (m, 2H, H-10, H-11), 7.28 (m, 1H, H-12), 7.47 (m, 1H, H-9), 7.78 (br s, 1H, NH); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 12.5 (C-18), 24.6 (C-6), 26.7 (C-14), 36.7 (C-16), 36.8 (C-15), 44.8 (C-3), 47.7 (C-21), 57.6 (C-5), 110.4 (C-12), 110.8 (C-7), 117.6 (C-9), 118.6 (C-19), 118.7 (C-10), 120.6 (C-11), 128.2 (C-8), 135.0 (C-13), 135.2 (C-2), 142.7 (C-20).
18. **12**: $[\alpha]_D^{22}$ -46.3 (*c* 0.385, AcOEt) [lit.[6c] $[\alpha]_D^{23}$ -51.4±5 (*c* 0.389, AcOEt)]; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 0.94 (t, *J*= 7.5 Hz, 3H, H-18), 1.31 (m, 2H, H-19), 1.66-1.84 (m, 2H, H-14), 2.42 (m, 1H, H-15), 2.56 (t, *J*= 11.0 Hz, 1H, H-21), 2.74-3.20 (complex signal, 10H), 7.12 (m, 2H, H-10, H-11), 7.30 (m, 1H, H-12), 7.51 (m, 1H, H-9), 7.84 (br s, 1H, NH); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 12.0 (C-18), 24.1 (C-19), 24.8 (C-6), 28.0 (C-14), 30.3 (C-20), 30.4 (C-16), 38.5 (C-15), 45.2 (C-3), 48.5 (C-21), 55.9 (C-5), 110.3 (C-12), 110.7 (C-7), 117.4 (C-9), 118.7 (C-10), 120.5 (C-11), 128.5 (C-8), 134.8 (C-2), 136.1 (C-13).
19. (a) Amine **12** is a known product, first prepared by degradation of akuammicine: Smith, G. T.; Wróbel, J. T. *J. Chem. Soc.* **1960**, 792. For syntheses of *rac*-**12**, see: (b) Dadson, B. A.; Harley-Mason, J.; Foster, G. H. *Chem. Commun.* **1968**, 1233. (c) Ban, Y.; Yoshida, K.; Goto, J.; Oishi, T.; Takeda, E. *Tetrahedron* **1983**, *39*, 3657. (d) See also reference 14a.
20. (-)-Tubifoline: $[\alpha]_D^{22}$ -303 (*c* 0.61, AcOEt) [lit.[6c] $[\alpha]_D^{22}$ -356±15 (*c* 0.179, AcOEt)]. The e.e. (95%) was determined by HPLC using a chiral column (Chiralcel OD, 75:25:0.1 hexane-*i*-PrOH-DEA, 0.5 cm^3 min^{-1}, 254 nm) and racemic tubifoline as reference.
21. Typical experimental procedure: A solution of **11** (370 mg, 1.4 mmol) in absolute EtOH (100 mg) was stirred under H_2 atmosphere in the presence of 370 mg of PtO_2 for 12 h. The catalyst was removed by filtration through a Celite pad, and the solution was concentrated. The residue was chromatographed (silica gel, 97:3 Et_2O-DEA) to give **12** (200 mg, 54% yield) and (-)-tubifoline (74 mg, 20% yield). The ratio amine **12**/(-)-tubifoline was variable and, in some runs, operating on a lower scale, (-)-tubifoline was obtained as the major or even the exclusive product. Condyfoline[6c] (bond formed C_7-C_{21}) was also isolated as a minor product in some runs.
22. For a similar "spontaneous" transannular oxidative cyclization in a tetracyclic stemmadenine-type system, see reference 4a.
23. (a) For previous syntheses of racemic tubifoline by oxidative transannular cyclization of *rac*-**12**, see references 19b,c. (b) For a different total synthesis of racemic tubifoline, see: Amat, M.; Linares, A.; Bosch, J. *J. Org. Chem.* **1990**, *55*, 6299.

(*Received in UK* 15 *July* 1996; *accepted* 3 *September* 1996)