The pyridinium reduction route to alkaloids: a synthesis of (±)-tashiromine

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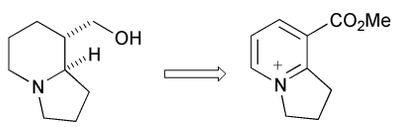
An indolizidine natural product, (±)-tashiromine, has been synthesized as a single diastereoisomer by a simple protocol. The key steps of the synthesis include a heterogeneous Sonogashira reaction and a stereoelectronically controlled reduction of a bicyclic pyridinium ion.

Introduction

Tashiromine **1**, an indolizidine alkaloid, was isolated from *Maakia Tashiroi*[1] and has been the subject of several total syntheses.[2] Tashiromine is an unusual indolizidine in that it has a hydroxymethyl substituent, rather than the more usual hydroxy groups.[3] Hydroxymethyl substituents are more common amongst the pyrrolizidines.



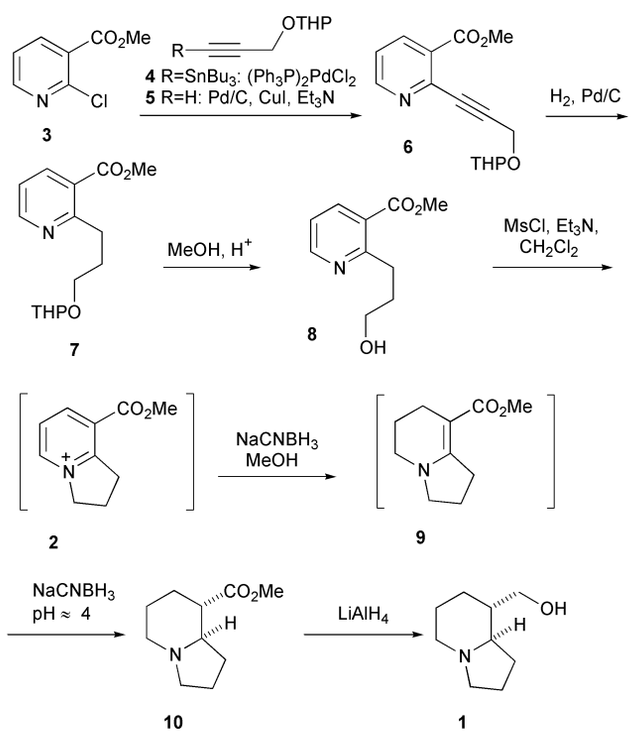
1 **2**

We envisioned that tashiromine **1** might be prepared from a bicyclic pyridinium salt **2** by a series of reductions.[4] This could then form the basis of a general approach to indolizidines. A similar strategy has been elegantly used by Ciufolini and Roschangar to prepare phenanthroizidine alkaloids.[5]

Results and discussion

Methyl 2-chloronicotinate **3** was coupled with the tri-*n*-butyltin derivative of the THP ether of propargyl (prop-2-ynyl) alcohol **4** under typical Stille conditions (Scheme 1).[6] Although aryl chlorides are generally unreactive in palladium catalysed reactions, in this case the chlorine is apparently activated by its position relative to the ring nitrogen and the ester group.[7] Sonogashira coupling of the corresponding terminal alkyne **5** under the usual homogeneous conditions was unsatisfactory. On the other hand, Sonogashira coupling using palladium on carbon as the source of palladium proceeded very well and had the advantage over the Stille reaction of avoiding the use of tin.[8] The yields of the two reactions were comparable (86 and 83%).

Reduction of the alkyne **6** to the corresponding protected propanol **7** and deprotection of the alcohol group proceeded routinely in 76% yield over the two steps.[9] Treatment of the alcohol **8** with mesyl chloride and a base directly yielded the pyridinium salt **2**. This was not isolated, but taken up in methanol and reduced with sodium cyanoborohydride, first under near-neutral conditions and then with occasional addition of methanolic HCl (Bromocresol Green indicator) in titration style to maintain a pH of about 4.[10] The intermediate before acidic reduction is the vinylogous carbamate **9**, which could be isolated but, in general, was not. The product of the



Scheme 1

acidic reduction is the saturated indolizidine ester **10**, as a single diastereoisomer in 66% yield from alcohol **8**. The ^{1}H and ^{13}C NMR spectra were in good agreement with those reported by Beckwith.[2a]

In contrast, the reduction of the ethyl ester corresponding to **9** has been reported to give a mixture of diastereoisomers using sodium borohydride, and to give **10** (ethyl ester) using Raney nickel under forcing conditions (200 °C).[2b]

The stereochemistry is consistent with axial hydride delivery to the more stable conformation of the iminium ion formed by protonation of the vinylogous carbamate **9**, according to the principles of stereoelectronic control.[11] Reduction of the ester[2a,b] **10** yielded (±)-tashiromine **1** (96% yield). The spectroscopic data, especially the chemical shifts of the methylene protons α to the hydroxy group, were very close to those reported by Cha for the natural product, and quite unlike those reported by Cha for its epimer.[2h]

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Conclusion

A concise synthesis of (±)-tashiromine has been completed (5 laboratory operations). The relative simplicity of the procedures and the high diastereoselectivity recommend this strategy for the synthesis of more complex indolizidines, as well as other ring systems.

Experimental

Dioxane, THF and DME were purified by distillation from Na–benzophenone; dichloromethane was distilled from CaH_2; triethylamine was distilled from KOH; methanol was heated at reflux over, then distilled from Mg. NMR spectra were recorded on a Varian Gemini 2000 at 200 MHz (^{1}H) or 50 MHz (^{13}C) in $CDCl_3$ using Me_4Si or $CHCl_3$ as an internal reference. Coupling constants (J) are in Hz. IR spectra were recorded on a Perkin Elmer 1760X spectrometer. Mass spectra were recorded on a Finnigan Polaris and a Finnigan MAT in the EI mode.

Pyridyl alkyne 6

(a) A mixture of methyl 2-chloronicotinate **3** (2.66 g, 15.4 mmol), stannane **4** (3 g, 6.99 mmol) and bis(triphenylphosphine)palladium dichloride (123 mg, 0.18 mmol) in dioxane (8 cm^3) was heated at reflux under nitrogen for 1 hour. The mixture was cooled to room temperature and treated with an excess of saturated aqueous potassium fluoride. The precipitated tributyltin fluoride polymer was removed by filtration through Celite, washing with ethyl acetate. The solvents were evaporated and the residue was purified by flash chromatography on silica gel (24 g) eluting with 15 and 25% ethyl acetate–hexane to give the pyridyl alkyne **6** (3.66 g, 86%) as an oil. Found: C 65.4, H 6.2, N 5.0. $C_{15}H_{17}NO_4$ requires C 65.4, H 6.2, N 5.1%; ν/cm^{-1} 2943, 2865, 2236, 1729; δ_H 8.71 (1H, dd, J 5, 2, ArH), 8.23 (1H, dd, J 8, 2, ArH), 7.33 (1H, dd, J 5, 8, ArH), 5.05 (1H, m, OCHO), 4.62 (2H, s, CH_2O), 3.98 (3H, s, Me), 3.90 (1H, m, CH), 3.60 (1H, m, CH), 1.5–1.9 (6H, m, $(CH_2)_3$); δ_C 165.2, 152.3, 142.0, 138.0, 131.9, 128.4, 122.4, 96.6, 90.6, 84.0, 54.4, 52.4, 30.1, 25.3, 18.9; m/z (EI) 174 (100%), 160 (26), 85 (53).

(b) A mixture of methyl 2-chloronicotinate **3** (2 g, 11.67 mmol), potassium carbonate (4.04 g, 29.18 mmol), copper(I) iodide (88 mg, 0.47 mmol) and palladium on carbon (10%, 618 mg) in DME (40 cm^3) was stirred for thirty minutes under nitrogen. A solution of the alkyne **5** (4.08 g, 29.18 mmol) in DME (10 cm^3) was then added. The mixture was heated at reflux overnight, then cooled, filtered through Celite, washing with ethyl acetate, and concentrated. The residue was purified by flash chromatography on silica gel (90 g) eluting with 30% ethyl acetate–hexane to give the alkyne **6** (2.71 g, 83%).

Protected pyridyl propanol 7

The pyridyl alkyne **6** (710 mg, 2.58 mmol) was taken up in methanol (15 cm^3) and stirred under hydrogen (balloon) in the presence of a 10% Pd/C catalyst (71 mg) for 3 h. The mixture was flushed with nitrogen and filtered through Celite. Evaporation of the solvent gave the crude pyridine **7** as an oil (722 mg, 99%) which was used without further purification. ν/cm^{-1} 2943, 2865, 1724; δ_H 8.61 (1H, dd, J 5, 2, ArH), 8.13 (1H, dd, J 7, 2, ArH), 7.19 (1H, dd, J 7, 5, ArH), 4.57 (1H, t, J 3, OCHO), 3.88 (3H, s, Me), 3.80 (2H, m, OCH_2), 3.45 (3H, m, OCH_2CH), 3.23 (2H, m, CH_2), 2.05 (2H, m, CH_2), 1.45–2.00 (6H, m, $(CH_2)_3$); δ_C 166.0, 162.0, 150.8, 138.0, 124.8, 120.3, 60.9, 51.6, 32.4, 31.8; m/z 194 (29%), 178 (100), 164 (9), 151 (29).

Pyridyl propanol 8

Toluene-p-sulfonic acid (500 mg, 2.9 mmol) was added to a solution of the pyridine **7** (544 mg, 1.95 mmol) in dry methanol (40 cm^3). After 40 minutes the mixture was neutralised with aqueous sodium carbonate and extracted with ethyl acetate. The extract was dried and evaporated. The residue was purified by flash chromatography on silica gel (16 g), eluting with 30 and 60% ethyl acetate–hexane to give the alcohol **8** (294 mg, 77%). ν/cm^{-1} 3377, 2943, 2865, 1724; δ_H 8.64 (1H, dd, J 5, 2, ArH), 8.20 (1H, dd, J 8, 2, ArH), 7.23 (1H, dd, J 5, 8, ArH), 3.95 (3H, s, Me), 3.66 (2H, t, J 5.5, OCH_2), 3.32 (2H, t, J 7, CH_2), 2.05 (2H, m, CH_2); δ_C 165.2, 152.3, 142.0, 138.0, 131.9, 128.4, 122.4, 96.6, 90.6, 84.0, 54.4, 52.4, 30.1, 25.3, 18.9; m/z (EI) 196 (26%), 178 (23), 164 (29), 151 (97), 136 (25), 93 (100); exact mass 195.089959, $C_{10}H_{13}NO_2$ requires 195.089543.

Indolizidine ester 10

Mesyl chloride (195 μL, 1.28 mmol) was added dropwise to a solution of the alcohol **8** (250 mg, 1.28 mmol) and triethylamine (473 μL, 3.42 mmol) in dichloromethane (20 cm^3) at 0 °C. The mixture was stirred for 30 minutes, then the volatiles were evaporated under reduced pressure and the residue was taken up in dry methanol (15 cm^3). Sodium cyanoborohydride (209 mg, 3.33 mmol) was added and the mixture was stirred for 3 h. Bromocresol Green was added and over the next 3 h the mixture was maintained at *ca.* pH 4 by gradual addition of a solution of hydrogen chloride in methanol (2 M, generated by cautious addition of acetyl chloride to methanol). After 3 h, the solution remained permanently acidic and the solvents were then removed under reduced pressure. The residue was neutralised with aqueous sodium bicarbonate and extracted with dichloromethane. The organic layer was dried (Na_2SO_4) and evaporated. The residue was purified by flash chromatography on silica gel (10 g) eluting with 2% methanol–chloroform to give the indolizidine ester **10** (155 mg, 66%). δ_H 3.62 (3H, s, OMe), 3.05 (2H, m, CH), 1.4–2.4 (12H, m, CH); δ_C 172.3, 65.3, 54.1, 52.3, 51.7, 47.8, 29.2, 28.2, 24.7, 20.5; m/z (EI) 183 (20%, M$^+$), 182 (20), 152 (11), 124 (29), 96 (100).

(±)-Tashiromine 1

Lithium aluminium hydride (115 mg, 3.03 mmol) was added to a solution of the indolizidine ester **10** (109 mg, 0.60 mmol) in anhydrous THF (5 cm^3) at 0 °C. The reaction mixture was stirred at room temperature for 1 h. Excess hydride was then cautiously quenched with a little water. The precipitated white solids were removed by filtration, washing thoroughly with ethyl acetate. Evaporation of the volatiles gave tashiromine **1** (88 mg, 96%). ν/cm^{-1} 3403, 2924, 2859, 2789; δ_H 4.5 (1H, br s, OH), 3.59 (1H, dd, J 6, 11, CHHOH), 3.47 (1H, dd, J 6, 11, CHHOH), 3.25 (1H, m, CH), 1.5–2.6 (13H, m, CH); δ_C 66.4, 64.0, 52.8, 51.6, 42.5, 27.7, 26.5, 23.5, 19.9; m/z (EI) 155 (37%, M$^+$), 154 (47), 138 (54), 124 (45), 96 (100), 84 (60); exact mass 155.131025, $C_9H_{17}NO$ requires 155.131014.

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References

1 S. Ohmiya, H. Kubo, H. Otomasu and I. Murakoshi, *Heterocycles*, 1990, **30**, 537.

2 (*a*) A. L. J. Beckwith and S. W. Westwood, *Tetrahedron*, 1989, **45**, 5269; (*b*) M. Haddad, J. P. Célérier, G. Haviari, G. Lhommet, H. Dhimane, J. C. Pommelet and J. Chuche, *Heterocycles*, 1990, **31**, 1251; (*c*) Y. Nagao, W. M. Dai, M. Ochiai, S. Tsukagoshi and E. Fujita, *J. Org. Chem.*, 1990, **55**, 1148; (*d*) K. Paulvannan and J. R. Stille, *J. Org. Chem.*, 1994, **59**, 1613; (*e*) J. L. Gage and B. P. Branchaud, *Tetrahedron Lett.*, 1997, **38**, 7007; (*f*) D.-C. Ha, S.-H. Park, K.-S. Choi and C.-S. Yun, *Bull. Korean Chem. Soc.*,

1998, **19**, 728; (*g*) O. David, J. Blot, C. Bellec, M.-C. Fargeau-Bellassoued, G. Haviari, J.-P. Célérier, G. Lhommet, J.-C. Gramain and D. Gardette, *J. Org. Chem.*, 1999, **64**, 3122; (*h*) S.-H. Kim, S.-I. Kim, S. Lai and J. K. Cha, *J. Org. Chem.*, 1999, **64**, 6771.
3 For a recent review, see: J. P. Michael, *Nat. Prod. Rep.*, 2000, **17**, 579.
4 For examples of the use of pyridinium ions, see M. Shipman, *Contemp. Org. Synth.*, 1995, **2**, 1.
5 M. A. Ciufolini and F. Roschangar, *J. Am. Chem. Soc.*, 1996, **118**, 12082.
6 J. K. Stille, *Angew. Chem., Int. Ed. Engl.*, 1986, **25**, 508; T. N. Mitchell, *Synthesis*, 1992, 803; V. Farina, V. Krishnamurthy and W. J. Scott, *Org. React. (NY)*, 1997, **50**, 1.
7 R. W. Bates, *Organic Synthesis using Transition Metals*, Sheffield Academic Press, Sheffield, 2000, p. 11; R. Singh and G. Just, *J. Org. Chem.*, 1989, **54**, 4453; J. W. Tilley and S. Zawoiski, *J. Org. Chem.*, 1988, **53**, 386.
8 L. Bleicher and N. D. P. Cosford, *Synlett*, 1995, 1115; we omit water from the reported procedure to avoid ester hydrolysis.
9 For an alternative preparation of **8**, see J. Bédat, V. Levacher, G. Dupas, G. Quéguiner and J. Bourguignon, *Chem. Lett.*, 1996, 359.
10 A. Kümin, E. Maverick, P. Seiler, N. Vanier, L. Damm, R. Hobi, J. D. Dunitz and A. Eschenmoser, *Helv. Chim. Acta*, 1980, **63**, 1158; for recent examples of this reaction, see: J. P. Michael and D. Gravestock, *Pure Appl. Chem.*, 1997, **69**, 583; T. G. Back and K. Nakajima, *Org. Lett.*, 1999, **1**, 261.
11 P. Deslongchamps, *Stereoelectronic Effects in Organic Chemistry*, Pergamon Press, Oxford, 1983, pp. 211–221.