A Versatile and Stereocontrolled Synthesis of Quinolizidines and Indolizidines using Trialkylsilyl Trifluoromethanesulphonate: Total Synthesis of (±)-Tylophorine

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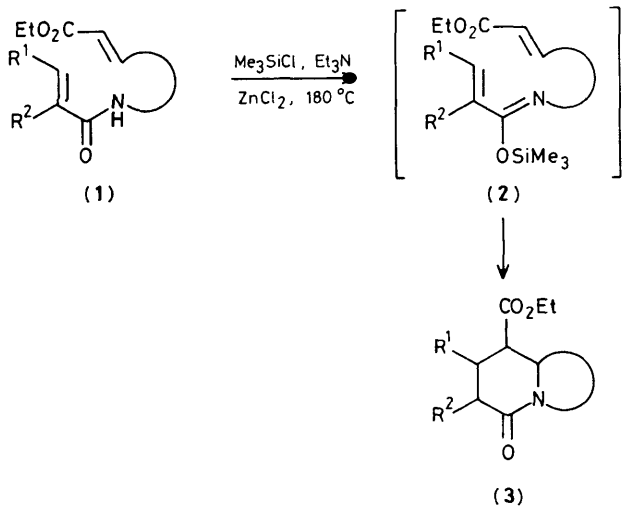
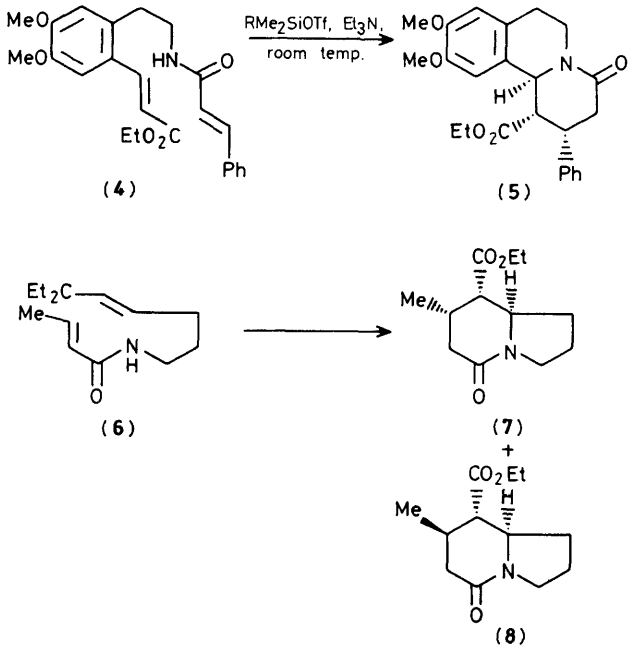
Quinolizidines and indolizidines were synthesised by reaction of α,β-unsaturated enamide esters with trialkylsilyl trifluoromethanesulphonate and triethylamine in dichloromethane; a short total synthesis of (±)-tylophorine (**16**) was achieved *via* annelation.

Recently we reported a new synthetic route to quinolizidine and indolizidine derivatives by the intramolecular Diels–Alder reaction of 1-aza-1,3-dienes (**2**).[1,2] The reaction was performed by heating the mixture of enamide ester (**1**), trimethylsilyl chloride, Et_3N, and $ZnCl_2$ in toluene or *o*-dichlorobenzene at 180 °C (Scheme 1). Altering the reaction conditions for the annelation led us to find a very effective and mild set of conditions. We now report a novel cyclisation reaction catalysed by trialkylsilyl trifluoromethanesulphonate and an application to the synthesis of tylophorine (**16**).†

† All new compounds gave analytical and spectral data in agreement with the proposed structures.



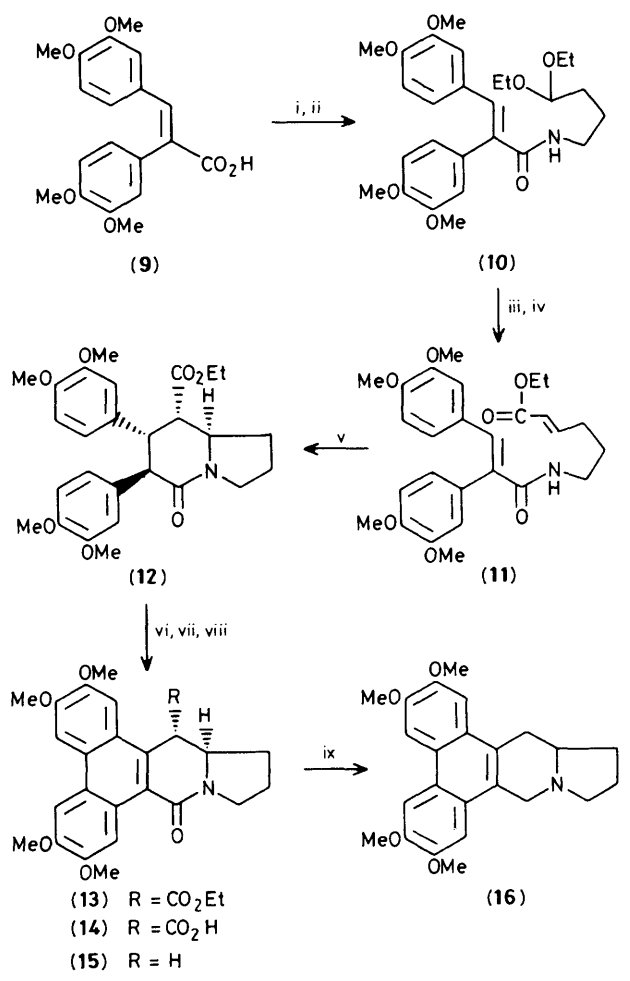
Scheme 1



Scheme 2

The annelation was accomplished by reaction of the enamide esters with an equimolar amount of trialkylsilyl trifluoromethanesulphonate and Et_3N in CH_2Cl_2 at ambient temperature (Scheme 2). Thus treatment of (**4**)[1] with t-butyldimethylsilyl trifluoromethanesulphonate (TBSOTf) or trimethylsilyl trifluoromethanesulphonate (TMSOTf) in the presence of Et_3N in CH_2Cl_2 for 1 h at 15 °C followed by the usual work-up, gave the benzo[*a*]quinolizidine (**5**)[1] in 83 or 75% yields. The reaction of (**6**)[2] with TBSOTf under the same conditions afforded two indolizidines (**7**)[2] and (**8**),[2] in 78 and 5% yields, respectively. The reaction did not proceed in the absence of Et_3N, and treatment of the enamide esters with other Lewis acids, such as $BF_3 \cdot Et_2O$, $TiCl_4$, and Et_2AlCl, yielded none of the desired products.

A short synthesis of (±)-tylophorine (**16**),[3] an antineoplastic alkaloid, was achieved according to the above methodology (Scheme 3). The acid (**9**)[4] was converted into the acid chloride and then condensed with 4-aminobutyraldehyde diethyl acetal to give the amide (**10**) in quantitative yield. Deprotection of



Scheme 3. *Reagents:* i, $(COCl)_2$; ii, $H_2N[CH_2]_3CH(OEt)_2$, $NaHCO_3$; iii, AcOH, H_2O; iv, $Ph_3P{=}CHCO_2Et$; v, TBSOTf, Et_3N, room temp.; vi, TTFA, $BF_3 \cdot Et_2O$, TFA; vii, KOH, MeOH; viii, HMPA, 230 °C; ix, $NaAl(OCH_2CH_2OMe)_2H_2$.

the acetal (**10**) using dilute AcOH, followed by Wittig reaction formed, in 93% yield, the enamide ester (**11**), which was subjected to the annelation using TBSOTf and Et_3N in CH_2Cl_2 for 5.5 h at 15 °C. The stereo-structure (**12**) of the product, m.p. 165—167 °C, isolated in 68% yield after purification by chromatography on silica gel, was deduced on the basis of the spectral analysis, [δ_H ($CDCl_3$) 0.95 (3H, t, *J* 8 Hz, OCH_2CH_3), 3.72, 3.75, and 3.80 (3H, 3H, and 6H, each s, 4 × OMe), 3.88 (2H, q, *J* 8 Hz, OCH_2CH_3)]. Oxidation of (**12**) with two moles of thallium(III) trifluoroacetate (TTFA) and $BF_3 \cdot Et_2O$ in a mixture of CH_2Cl_2 and CF_3CO_2H (TFA)[5] for 16 h at 4 °C produced in 83% yield the pentacyclic compound (**13**), m.p. 267—271 °C [δ_H ($CDCl_3$) 1.46 (3H, t, *J* 8 Hz, OCH_2CH_3), 3.93 and 4.10 (3H and 9H, each s, 4 × OMe), 7.20, 7.73, 7.75, and 8.79 (each 1H, each s, 4 × ArH)]. Hydrolysis of (**13**), followed by decarboxylation of the resulting acid (**14**) [δ_H ($CDCl_3$) 8.80 (1H, s, ArH)], conducted by heating a solution in hexamethylphosphoric triamide (HMPA) at 230 °C for 3 h, furnished (±)-9-oxotylophorine (**15**), m.p. 282—283 °C (lit.,[3b] m.p. 280—281 °C) in 65% overall yield. Reduction of (**15**) with sodium bis(2-methoxyethoxy)aluminium hydride in refluxing dioxane for 2 h gave (±)-tylophorine (**16**) in 87% yield.‡

‡ It was reported that reduction of (±)-9-oxotylophorine with $LiAlH_4$ or B_2H_6 gave poor results, ref. 3b.

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References

1 M. Ihara, T. Kirihara, A. Kawaguchi, K. Fukumoto, and T. Kametani, *Tetrahedron Lett.*, 1984, **25**, 4541.
2 M. Ihara, T. Kirihara, K. Fukumoto, and T. Kametani, *Heterocycles*, 1985, **23**, 1097.
3 Recent synthesis (a) J. E. Cragg, R. B. Herbert, F. B. Jackson, C. J. Moody, and I. T. Nicholson, *J. Chem. Soc., Perkin Trans. 1*, 1982, 2477; (b) H. Iida, Y. Watanabe, M. Tanaka, and C. Kibayashi, *J. Org. Chem.*, 1984, **49**, 2412 and references cited therein.
4 J. H. Russel and H. Hunziker, *Tetrahedron Lett.*, 1969, 4035.
5 E. C. Taylor, J. G. Andrade, G. J. H. Rall, and A. McKillop, *J. Am. Chem. Soc.*, 1980, **102**, 6513.