COMMUNICATION

Novel synthesis of the indolizidine alkaloid skeleton with appropriate functionality and stereochemistry for use as a 'chiral scaffold'

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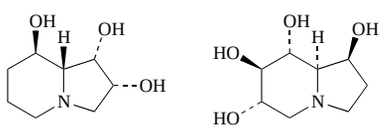
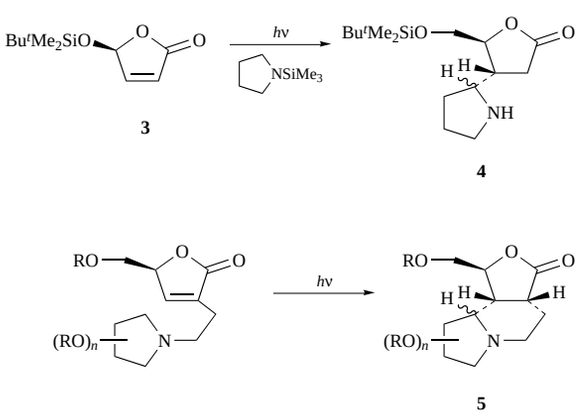
A stereocontrolled synthesis of the indolizidine alkaloid skeleton has been achieved *via* an intramolecular, photoinduced reaction of (5*S*)-5-triisopropylsilyloxymethyl-3-{2′-[(3″*S*)-3″-methoxypyrrolidinyl]ethyl}furan-2-(5*H*)-one, which can be obtained in a highly convergent fashion from (5*S*)-5-triisopropylsilyloxymethyltetrahydrofuran-2-one and (3*S*)-3-methoxypyrrolidine.

The interesting pharmacology exhibited by the indolizidine alkaloids ensures their popularity as targets for chemical synthesis. The glycosidase inhibitors swainsonine **1**[1] and castanospermine **2**[2] are but two members of a family that comprises several hundred known structures.[3] In addition to their inherent biological interest, structures of this type which possess much functionality and defined stereochemistry have great potential as 'chiral scaffolds' in combinatorial chemistry.[4]



1 **2**

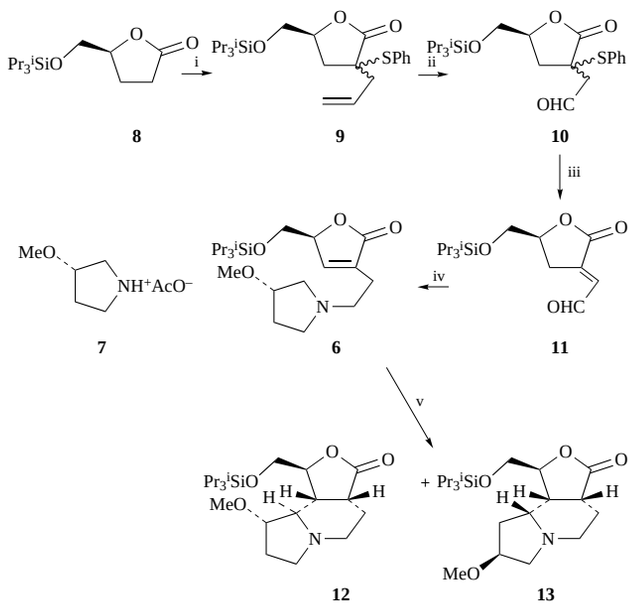
Our previous work on the photoinduced addition of 1-trimethylsilylpyrrolidine to the butenolide **3** to provide the adducts **4**[5] suggested that the intramolecular version of this process (shown in Scheme 1) should provide access to the basic skeleton **5** of the indolizidine alkaloids. This key intermediate is also appropriately functionalised for further elaboration into a wide variety of novel structures. The synthesis of compounds of general structure **5** *via* a highly convergent and stereocontrolled route is reported herein.



3 **4** **5**

Scheme 1

The substrate **6** for this intramolecular 6-*endo*-*trig* reaction was prepared by the route shown in Scheme 2. The requisite (3*S*)-3-methoxypyrrolidine **7** was synthesised from (2*S*)-malic acid using the route of Naylor *et al.*[6] but with minor modifications. The (5*S*)-5-triisopropylsilyloxymethyltetrahydrofuran-2-one **8** was readily accessible from (*S*)-glutamic acid,[7] and both compounds could be prepared on a multigram scale.



8 **9** **10** **11** **12** **13**

Scheme 2 *Reagents and conditions:* i, LDA, THF, −78 °C, then allyl bromide, then LDA, THF, PhSSPh, 52%; ii, O_3, CH_2Cl_2, −78 °C, then Me_2S, room temp., 2 days, 67%; iii, Oxone®, aq. MeOH, 88%; iv, NaC-**NBH$_3$**, MeOH, (3*S*)-3-methoxypyrrolidinium acetate, 56%; v, *hν*, MeCN, Ph_2CO, −50 °C, 21%

Allylation of the tetrahydrofuranone **8** (LDA–THF at −78 °C, then allyl bromide, 87%) followed by thiophenylation (LDA–THF at −78 °C, then PhSSPh, 60%) provided the 3,3-disubstituted derivative **9**, and this was subjected to ozonolysis (CH_2Cl_2 at −78 °C) and reductive processing (Me_2S at room temp. for 2 days) to yield the aldehyde **10** (60% overall). It was noted that this procedure also gave rise to 38% of the exocyclic alkene **11** and this became the major product (88% overall from **9**) if the product **10** was treated with Oxone® in aqueous methanol. We were delighted to discover that when compound **11** was reacted with the (3*S*)-3-methoxypyrrolidine under conditions of reductive amination ($NaCNBH_3$–MeOH)[8] the desired adduct **6** was obtained in a yield of 56%. All of these reactions have been carried out routinely on at least a half-gram scale.

Finally, irradiation of this compound in acetonitrile in the presence of 1 equiv. of benzophenone as photosensitiser (high pressure lamp at −50 °C) resulted in a rapid (30 min) consumption of starting materials and the formation of the two adducts **12** and **13** in a combined yield of 21% (and a ratio of *ca.* 1.6:1). When 1,4-dicyanonaphthalene was used in place of benzophenone, the yield rose to 40%. The structure of compound **12** has been confirmed by an X-ray structure determination† and that of compound **13** through extensive NMR experiments.

† We thank Dr M. G. B. Drew for the X-ray studies, which will be reported in detail elsewhere.

Although the yields of this photochemical step remain to be optimised, there is no reason why it should not also be viable with other substituted pyrrolidines. This possibility, combined with the presence within the adducts of latent functionality and many stereogenic centres (five centres from the two centres present in the starting materials), make them key intermediates for the construction of a wide variety of indolizidine-type compounds.

Experimental

Synthesis of (5*S*)-5-triisopropylsilyloxymethy-3-{2′-[(3″*S*)-3″-methoxypyrrolidinyl]ethyl}furan-2-(5*H*)-one 6 by reductive amination

A solution of the aldehyde **11** (1.50 g, 4.81 mmol) in dry methanol (25 ml) was added to a solution of amine salt **7** (0.77 g, 4.81 mmol) in dry methanol (20 ml) under argon. $NaCNBH_3$ (0.22 g, 3.37 mmol) was then added and the reaction was stirred at room temperature for 1 h at which point no starting material remained. The reaction was then diluted with CH_2Cl_2 (50 ml) and washed with aqueous $NaHCO_3$ (10 ml saturated, diluted with 10 ml water). The aqueous phase was extracted with more CH_2Cl_2 (3 × 10 ml) and the combined organic phases were dried over anhydrous $MgSO_4$, filtered and evaporated *in vacuo* to give an oil. Purification by flash column chromatography, eluting with diethyl ether–methanol (19:1 with 1% ammonia) gave the required amine as an oil (1.06 g, 2.68 mmol, 56%); R_f 0.38 (diethyl ether–methanol, 19:1 with 1% ammonia); $[\alpha]_D^{25}$ −11.9 (*c* 1.31 in $CHCl_3$); ν_{max}(film)/cm^{-1} 2941, 2864, 2804s (C–H alkyl), 1758s (C=O lactone 5-ring); δ_H(250 MHz, $CDCl_3$) 1.05 (3 H, m, Me_2CHSi), 1.06 (18 H, s, Me_2CHSi), 1.81 (1 H, m, 4″-H_a), 2.47 (1 H, m, 4″-H_b), 2.51 (3 H, m, 1′-H_a, 2′-H_a, 5″-H_a), 2.79 (5 H, m, 2″-H_{ab}, 5″-H_b, 2′-H_b, 1′-H_b), 3.29 (3 H, s, OMe), 3.83 (1 H, dd, J_{gem} 10.6, *J* 5.5, 6-H_a), 3.92 (1 H, m, 3″-H), 3.99 (1 H, dd, J_{gem} 10.6, *J* 4.4, 6-H_b), 4.95 (1 H, m, 5-H), 7.18 (1 H, d, *J* 1.5, 4-H); δ_C(250 MHz, $CDCl_3$), 11.8 (Me_2CHSi), 17.9 (Me_2CHSi), 24.5 (1′-C), 28.0 (4″-C), 52.5 and 53.8 (2′-C and 5″-C), 46.5 (OMe), 59.6 (2″-C), 63.6 (6-C), 80.1 (3″-C), 81.5 (5-C), 133.3 (3-C) 146.9 (4-C), 173.6 (2-C) [HRMS: found, 398.2724 (MH^+). $C_{21}H_{40}NO_4Si$ requires 398.2727].

Benzophenone sensitised irradiation of alkene 6

The alkene **6** (883 mg, 2.22 mmol) and benzophenone (405 mg, 2.22 mmol) in a Pyrex vessel were dissolved in acetonitrile and degassed by bubbling argon through a needle for 1 h. The solution was then cooled to −52 °C (dry ice–acetonitrile) and irradiated for 30 min (keeping the temperature below 7 °C). The solvent was then removed and the resulting yellow oil was purified by flash column chromatography in diethyl ether followed by diethyl ether–methanol (19:1 with 1% methanol) to give the cyclised product as a mixture of two isomers (189 mg, 0.47 mmol, 21%) and recovered starting material (163 mg, 0.41 mmol, 18.5%). The two isomers were inseparable by standard column chromatography but could be separated by flash chromatography on silica impregnated with $AgNO_3$. Elution with diethyl ether–methanol (9:1) afforded two tricyclic products; compound **12**: R_f 0.15 (diethyl ether–methanol, 9.5:0.5); $[\alpha]_D^{25}$ +28.8 (*c* 1.2 in chloroform); ν_{max}(film)/cm^{-1} 2944s, 2865s, 2783 (C–H alkyl), 1769s (C=O lactone 5-ring); δ_H($CDCl_3$, 400 MHz) 1.05 (3 H, m, Me_2CHSi), 1.06 (18 H, s, Me_2CHSi), 1.59 (1 H, m, 3-H_a), 1.73 (1 H, dd, *J* 17.6 and 7.0, 8-H), 1.89 (1 H, m, 11-H_a), 1.95 (1 H, dd, J_{gem} 11.4, *J* 1.8, 12-H_a), 2.06 (1 H, m, 3-H_b), 2.17 (1 H, d, J_{gem} 12.5, 11-H_b), 2.29 (1 H, q, *J* 9.2, 2-H_a), 2.59 (1 H, dd, *J* 10.8 and 7.5, 4-H), 2.92 (1 H, m, 12-H_b), 3.01 (1 H, t, *J* 8.6, 2-H_b), 3.09 (1 H, t, *J* 6.8, 9-H), 3.29 (3 H, s, OMe), 3.65 (1 H, m, 10-H), 3.84 (1 H, dd, J_{gem} 10.8, *J* 3.1, SiOC*H*H), 3.92 (1 H, dd, J_{gem} 10.8, *J* 4.9, SiOCH*H*), 4.60 (1 H, t, *J* 4.2, 7-H); δ_C($CDCl_3$, 400 MHz) 12.1 (Me_2CHSi), 18.2 (Me_2CHSi), 22.9 (11-C), 28.4 (3-C), 37.4 (9-C), 42.0 (4-C), 50.5 (12-C), 53.1 (2-C), 57.4 (OMe), 64.5 ($SiOCH_2$), 68.8 (8-C), 80.0 (7-C), 86.7 (10-C), 178.5 (5-C) [HRMS: found, 398.2734 (MH^+). $C_{21}H_{40}NO_4Si$ requires 398.2726]. Compound **13**: R_f 0.07 (diethyl ether–methanol, 9.5:0.5); $[\alpha]_D^{25}$ −11.2 (*c* 0.54 in chloroform); ν_{max}(film)/cm^{-1} 2929s, 2868s (C–H alkyl), 1781s (C=O lactone 5-ring); δ_H($CDCl_3$, 400 MHz) 1.04 (3 H, m, Me_2CHSi), 1.05 (18 H, s, Me_2CHSi), 1.49 (1 H, m, 10-H_a), 1.66 (1 H, dd, *J* 17.6 and 7.0, 8-H), 1.83 (1 H, m, 2-H_a), 2.13 (3 H, m, 3-H_{ab}, 12-H_a), 2.46 (1 H, dt, J_{gem} 14.5, *J* 7.3, 10-H_b), 2.53 (1 H, m, 4-H), 2.97 (1 H, m, *J* 9.2, 2-H_b), 3.07 (1 H, t, *J* 7.3, 9-H), 3.16 (1 H, d, J_{gem} 10.6, 12-H_b), 3.28 (3 H, s, OCH_3), 3.84 (2 H, m, 11-H and SiOC*H*H), 3.90 (1 H, dd, J_{gem} 9.7, *J* 4.8, SiOCH*H*), 4.08 (1 H, t, *J* 4.2, 7-H); δ_C($CDCl_3$, 400 MHz) 11.8 (Me_2CHSi), 17.9 (Me_2CHSi), 22.3 (3-C), 37.1 (9-C), 38.0 (10-C), 43.0 (4-C), 49.7 (2-C), 56.5 (OCH_3), 60.5 (12-C), 64.2 ($SiOCH_2$), 64.3 (8-C), 77.8 (11-C), 80.8 (7-C), 178.0 (5-C) [HRMS: found, 398.2749 (MH^+). $C_{21}H_{40}NO_4Si$ requires 398.2726].

Acknowledgements

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References

1 S. M. Colegate, P. R. Dorling and C. R. Huxtable, *Aust. J. Chem.*, 1979, **32**, 2257; A. S. Howard and J. P. Michael, in *The Alkaloids*, ed. A. Brossi, Academic Press, London, 1986, vol. 28, p. 183.

2 L. D. Hohenschutz, E. A. Bell, P. J. Jewess, D. P. Leworthy, R. J. Pryce, E. Arnold and J. Clardy, *Phytochem.*, 1981, **20**, 811; A. S. Howard and J. P. Michael, (as in ref. 1); K. Burgesss and I. Henderson, *Tetrahedron*, 1992, **48**, 4045.

3 H. Takahata and T. Momose, in *The Alkaloids*, ed. G. A. Cordell, 1993, vol. 44, p. 189; J. P. Michael, *Nat. Prod. Rep.*, 1995, **12**, 465.

4 N. J. Terrett, M. Gardner, D. W. Gordon, R. J. Kobylecki and J. Stelle, *Tetrahedron*, 1995, **51**, 8135; F. Balkenhohl, C. von dem Bussche-Hunnefeld, A. Lansky and C. Zechel, *Angew. Chem.*, 1996, **35**, 2289.

5 E. S. de Alvarenga and J. Mann, *J. Chem. Soc., Perkin Trans. 1*, 1993, 2141.

6 A. Naylor, D. B. Judd, D. I. Scopes, A. G. Hayes and P. J. Birch, *J. Med. Chem.*, 1994, **37**, 2138.

7 S. Hannesian and P. J. Murray, *Tetrahedron*, 1987, **43**, 5055.

8 A. T. Austin and J. Howard, *J. Chem. Soc.*, 1961, 3593.

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