Synthesis of the Tricyclic Core of the Marine Alkaloid Lepadiformine

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Abstract: A stereoselective synthesis of the tricyclic core in racemic form of the marine alkaloid Lepadiformine is described from 4-methoxy-3-pyrrolin-2-one (methyl tetramate). Key steps involve 5,5-dialkylation of the tetramate, metathesis closure to an A/C 1-azaspiracycle and stereoselective hydrogenation for the *trans* A/B 1-azadecalin system.

Key words: marine alkaloid, metathesis, silyloxypyrrole alkylation, tetramate reduction, 1-azaspiro[4.5]decane

Considerable interest has been shown recently in the synthesis of the marine alkaloid Lepadiformine **1**, a tricyclic perhydropyrrolo[2,1-*j*]quinoline isolated[1] from the tunicate *Clavelina lepadiformis* and reported to have moderate in vitro cytotoxic activity against certain tumour cell lines,[1] as well as various cardiovascular effects in vivo and in vitro.[2] The early syntheses[3] utilised cycloaddition methodology for construction of the pivotal tertiaryaza stereogenic centre of the *trans*-1-azadecalin A/B ring junction. More recently, Weinreb has demonstrated the application of an intramolecular spirocyclisation of an *N*-acyliminium ion with an allylsilane to accomplish the first enantioselective synthesis[4] of the alkaloid, thus establishing its absolute configuration. A key intermediate in Weinreb's synthesis was a 1-azaspiro[4.5]decyl unit used as an A/C ring-system template. Recent publications on the construction of the natural products FR901483[5] and (–)-TAN1251A[6] have highlighted the use of substituted 1-azaspiro[4.5]decanes, and in this communication we disclose a novel strategy for accessing this ring system as a 6-ketone[7] with subsequent conversion of it in moderate stereoselectivity to the tricyclic core of Lepadiformine in racemic form (Figure 1).

Our strategy centred around a sequence involving 5,5-dialkylation of a tetramate derivative, followed by chain extension and metathesis to the substituted azaspirocycle. 5-Alkylation of the lithium dienolate of N-protected tetramates with primary alkylating agents is well established in the literature,[8] however in our hands allylation of 1-benzyl-4-methoxy-3-pyrrolin-2-one produced significant quantities of the α-alkylation product. Thus we resorted to using a procedure reported by Jones[8a] involving allylation of the dianion of 4-methoxy-3-pyrrolin-2-one **2** with one equivalent of allyl bromide. 5-Allyltetramate **3a** was obtained in 79% isolated yield after column chromatography. Phase transfer[9] protection of the lactam nitrogen of **3a** produced the N-protected derivative **3b** in excellent yield setting the stage for construction of the pivotal tertiaryaza centre (Scheme 1).

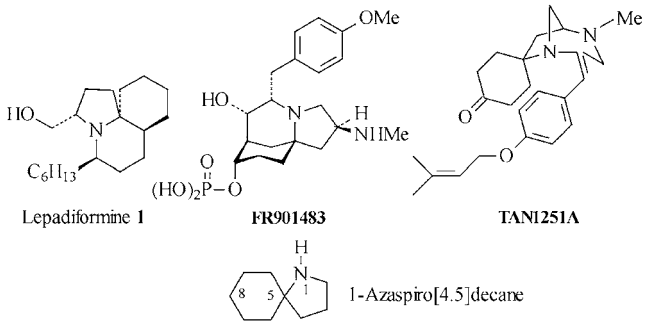
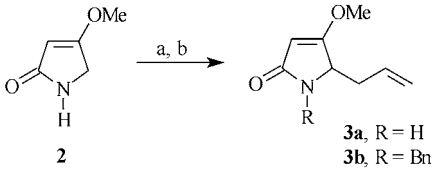


Figure 1 Lepadiformine and other azaspirocyclic natural products



Scheme 1 *Reagents and conditions*: (a) *n*-BuLi (2 equiv), THF, –78 °C, allyl bromide (1 equiv), 79%; (b) KOH, Bu_4NHSO_4, THF, 88%.

Given the poor regioselectivity of alkylation of the tetramate lithium dienolate, we opted to investigate the use of the much softer silyl dienol ether (2-silyloxypyrrole). Although *N*-Boc-2-*tert*-butyldimethylsilyloxypyrrole from *N*-Boc-3-pyrrolin-2-one has been demonstrated by Casiraghi[10] to be a versatile building block in natural product synthesis for 5-regioselective alkylation reactions, no equivalent studies have been carried out on the silyl dienol ether from an appropriately N-protected 4-methoxy-3-pyrrolin-2-one. Jones reported[11] preparing the trimethylsilyl dienol ether of 4-methoxy-1-methyl-3-pyrrolin-2-one, but carried out no dissociative reactions on it. We rationalised that the 4-methoxy group enhancing the 5-coefficient in the HOMO would offset the increased steric factor caused by the 5-allyl substituent. Furthermore, we were interested in developing one-pot methodology using the cheaper chlorotrimethylsilane rather than trapping and isolating the more expensive *tert*-butyldimethylsilyl dienol ether used in Casiraghi's system. Thus we were gratified to find that sequential treatment of **3b** with

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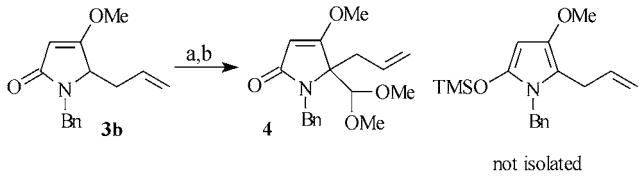
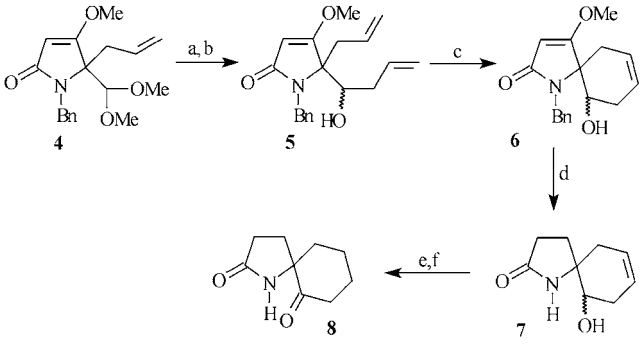
n-BuLi, TMSCl, $CH(OMe)_3$ and $BF_3{\cdot}OEt_2$ furnished exclusively the crystalline 5,5-disubstituted product **4** in 88% isolated yield after chromatography (Scheme 2).[12]



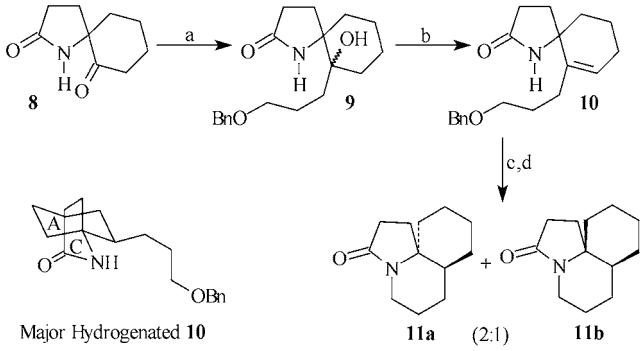
Scheme 2 *Reagents and conditions*: (a) *n*-BuLi (1.2 equiv), THF, –78 °C, TMSCl (1.5 equiv); (b) $HC(OMe)_3$, $BF_3{\cdot}OEt_2$, 88%.

For development of the metathesis chemistry required to generate the azaspirocycle, **4** was chemoselectively hydrolysed in quantitative yield to the aldehyde using overnight treatment with trifluoroacetic acid (1% H_2O). Subsequent addition of allyl Grignard gave homoallylic alcohol **5** in 76% yield (3:1), which was cleanly and rapidly metathesised with Grubb's catalyst[13] (2–5 mol%) to the 5,5-spirotetramate **6** in 92% yield. Given the scope of substitution in the metathesis reaction, a range of substitution patterns for the cyclohexane ring of the azaspirocycle may be envisaged. Derivatives of the 5,5-spirotetramate template of **6** have found use as potent herbicides,[14] but in the context of Lepadiformine it was desirable to reduce[15] the vinyl ether of the tetramate ring to afford the saturated C-ring. This was efficiently accomplished by sodium in refluxing liquid ammonia to afford **7** in which both the enol ether and benzyl groups had been completely reduced. Compound **7** was hydrogenated and oxidised to the saturated keto-γ-lactam **8**[7] (Scheme 3).



Scheme 3 *Reagents and conditions*: (a) CF_3CO_2H (1% H_2O), 35 °C, 95%; (b) allylMgCl, THF, –78 °C to 0 °C, 76% (3:1); (c) $RhCl_2(PCy_3)_2$=CHPh, CH_2Cl_2, 40 °C, 2 h; (d) Na, NH_3 (l), –33 °C, 85%; (e) H_2, Pd-C; (f) TPAP (5 mol%), NMO, CH_3CN, powdered mol. sieves, 78% over 2 steps.

Annulation of **8** to construct the B ring of the Lepadiformine tricyclic core was explored in a number of ways. Horner–Wittig olefination[16] with the carbanion of $Ph_2P(O)(CH_2)_3OBn$ successfully furnished the desired exocyclic olefinic lactam in high yield but in an unacceptably low conversion (ca. 10%) presumably due to the carbanion acting competitively as a base to regenerate starting material on work-up. Protection of the lactam NH before olefination resulted in no improvement. By comparison, Grignard addition with $BrMg(CH_2)_3OBn$[17] (3 equiv) gratifyingly resulted in an efficient addition to form the tertiary alcohol **9** as a mixture of diastereomers (4:3). Dehydration of **9** could be accomplished using a variety of conventional reagents (e.g. $POCl_3$ or $SOCl_2$, pyridine), but the best method[18] proved to be using anhydrous $CuSO_4$ in refluxing *p*-xylene, which returned a 91% yield of a mixture of endocyclic and exocyclic alkenes **10** (4:1) without formation of any rearrangement products. Hydrogenation of the double bonds of **10** with concomitant hydrogenolysis of the benzyl protecting group, mesylation and ring closure using sodium hydride to generate the lactam anion[19] resulted in a 2:1 mixture of diastereomeric tricycles **11a**,**b**, separable by chromatography. The major product **11a** was assigned as the desired *trans*-1-azadecalin ring system on the basis that the minor product **11b** had identical spectroscopic data to the known *cis*-1-azadecalin synthesised by Aube's group[20] via an intramolecular Schmidt reaction. The observed diastereoselectivity may be rationalised via hydrogenation of the least hindered face of the alkene(s) **10** (Scheme 4).



Scheme 4 *Reagents and conditions*: (a) $BrMg(CH_2)_3OBn$ (3 equiv), THF, 0 °C, 85%, (4:3); (b) $CuSO_4$, *p*-xylene, Δ, 91%; (c) H_2, Pd-C, 85% (2:1); (d) (i) MsCl, Et_3N, THF; (ii) NaH, DMF, 80% (2:1).

In conclusion, we have developed some new methodology for synthesising 5,5-spirotetramates and demonstrated a sequence for elaboration to the tricyclic core of Lepadiformine in moderate stereoselectivity. The strategy described herein augurs well[21] for the possibility of refinement into an enantioselective synthesis of the alkaloid as well as being able to furnish derivatives for structure-activity anti-cancer studies.

Acknowledgement

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(12) The following **experimental procedure** for conversion of **3b** to **4** applies: The substrate **3b** (0.73g, 3mmol) was dissolved in anhyd THF (30 mL) under N_2 and cooled to –78 °C. A solution of *n*-BuLi in hexane (2.25 mL of a 1.6 M solution, 3.6 mmol, 1.2 equiv) was added dropwise. After stirring for 30 min at –78 °C TMSCl (0.57 mL, 4.5 mmol, 1.5 equiv) was added dropwise and the solution was stirred for a further 30 min at –78 °C. Trimethyl orthoformate (1.00 mL, 9.0 mmol, 3 equiv) was then added, followed by $BF_3{\cdot}OEt_2$ (0.57 mL, 4.5 mmol, 1.5 equiv). The reaction was allowed to slowly warm to –20 °C over 2 h. Sat. $NaHCO_3$ solution was then added and the THF was removed by evaporation. The remaining aqueous layer was extracted with 3 portions of EtOAc. The organic layers were combined, dried and concentrated to give an oily residue. The product was isolated by column chromatography to give the acetal as an oil that slowly crystallised as a colourless, waxy solid **4** (0.699 g, 2.20 mmol) in 88% yield based on recovered starting material (0.125 g, 0.51 mmol). Data for **4**: IR: ν_{max} (CH_2Cl_2) = 3019, 1669, 1640, 1346 cm^{-1}. Found: M^+ (+ H), 318.17144. $C_{18}H_{24}NO_4$ requires M^+: 318.17053. ^1H NMR (400 MHz, $CDCl_3$): δ = 2.37 (1 H, ddt, *J* = 1.1, 7.7, 14.7 Hz, CH_2), 2.54 (1 H, dd, *J* = 6.6, 14.7 Hz, CH_2), 3.27 (3 H, s, OCH_3), 3.32 (3 H, s, OCH_3), 3.75 (3 H, s, OCH_3), 4.21 (1 H, s, OC*H*O), 4.61 (2 H, s, PhCH_2), 4.84 (2 H, m, CH=CH_2), 5.12 (1 H, s, H-3), 5.18 (1 H, m, C*H*=CH_2), 7.15–7.38 (5 H, m, aromatic). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 33.8 (*C*H_2), 43.6 (Ph*C*H_2), 57.8, 57.9 and 58.0 (3 × O*C*H_3), 71.8 (C-5), 95.2 (C-3), 107.6 (O*C*HO), 118.6 (CH=*C*H_2), 126.6, 128.0 and 128.5 (aromatic), 130.9 (*C*H=CH_2), 139.6 (aromatic), 172.2 (C-4), 174.5 (*C*=O).
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(20) (a) Aubé, J.; Milligan, G. L. *J. Am. Chem. Soc.* **1991**, *113*, 8965. (b) Data for the *trans* diastereomer **11a,** (7a*S**,11a*S**)-Decahydro-3*H*-pyrrolo[2,1-*j*]quinolin-3-one: IR: ν_{max} (CH_2Cl_2) = 2935, 2864,1674, 1418 cm^{-1}. Found: M^+, 193.14725. $C_{12}H_{19}NO$ requires M^+: 193.14666. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.11–1.39 (4 H, m, CH_2), 1.41–1.87 (10 H, m, CH_2), 1.93 (1 H, dd, *J* = 7.7, 12.3 Hz, CH_2), 2.20 (1 H, dd, *J* = 8.8, 16.5 Hz, H-2), 2.49 (1 H, dddd, *J* = 0.9, 7.9, 12.6, 16.5 Hz, H-2), 2.77 (1 H, dddd, *J* = 1.1, 7.0, 11.2, 13.7 Hz, H-5), 3.88 (1 H, dd, *J* = 8.4, 13.7 Hz, H-5). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.4 (*C*H_2), 22.5 (*C*H_2), 23.5 (*C*H_2), 24.9 (*C*H_2), 26.0 (*C*H_2), 27.4 (*C*H_2), 30.6 (*C*H_2), 33.3 (C-5), 33.8 (C-2), 42.1 (C-7a), 64.1 (C-11a), 175.9 (*C*=O).
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