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Synthesis of α,β-Unsaturated Spirolactams by Intramolecular Cyclization of Endocyclic N-Acyliminium Ions.

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Abstract: *The synthesis of (±)-6-benzyl-3-methyl-3-en-1,6-diazaspiro[4.5]decane-2,7-dione (**18**), the spiro moiety of (±)-pandamarine has been achieved by oxidative cyclization of the (Z) and (E) isomers of 5-(N-benzyl-4-carboxamido-butylidene)-3-methyl-3-en-pyrrolin-2-one (**15a**) and (**15b**). The stereoselectivity exhibited in the intramolecular cyclization by both butylidene precursors has also been discussed.*

The [4.5]spiro lactam moiety is present in some naturally occurring piperidine alkaloids like (±)-pandamarine (**1**) and (-)-pandamarilactone (**2**) (Fig.1) which have been isolated from the leaves of *Pandanus amaryllifolius* Roxb[1]. The leaves of this *Pandanus* species, also known as "pandan-mabango" or fragrant screwpine, are used popularly in the Philippines as flavouring for rice because it emits a peculiar odor similar to "amber-mohor" rice[2]. As (±)-pandamarine (**1**) occurs as a racemate, it has been proposed that it might be derived from cyclization of a symmetrical intermediate such as (**3a**), or the tautomeric imine, which could be formed from (2*S*)-4-hydroxy-4-methyl-glutamic acid, also isolated from some *Pandanus* species[3].

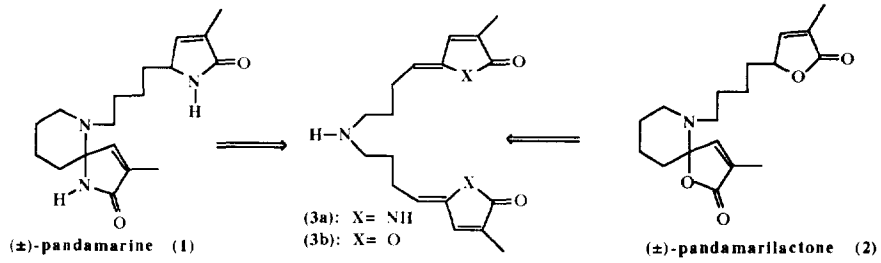


Fig. 1

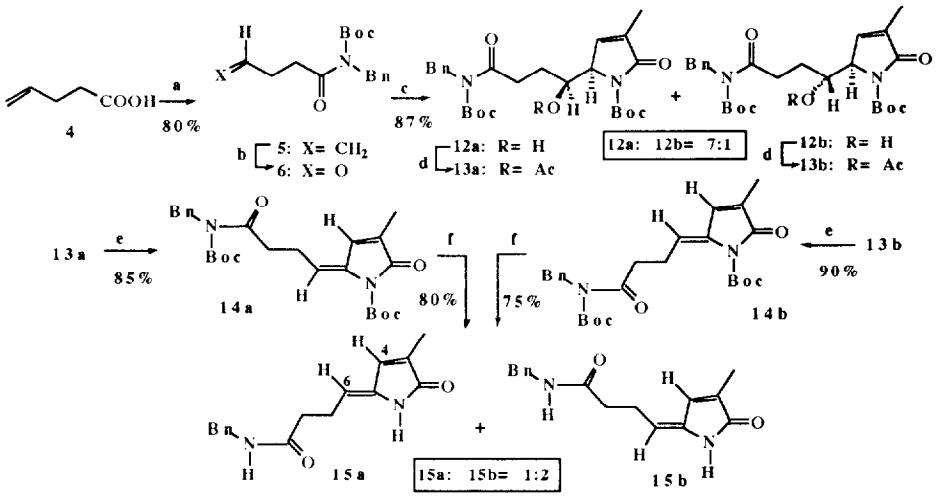
As part of a project aimed at the synthesis of 1,6-diazaspiro[4.5]decanes we recently reported a new synthetic method to prepare spirolactams and spirolactones based on a diphenyl phosphorazidate DPPA-promoted decarbonylation procedure[4]. We now wish to report our results on the synthesis of 6-benzyl-3-methyl-3-en-1,6-diazaspiro[4.5]decane-2,7-dione (**18**) by electrophilic cyclization of two olefinic precursors (**15a**) and (**15b**) in an attempt to test if the above mentioned biosynthetic proposal might have any synthetic value.

The amidobutylidene derivatives (**15a**) and (**15b**), substrates for the cyclization process were envisaged to be easily accessible from aldehyde (**6**) (Scheme 1).

Amidation of 4-pentenoic acid (**4**) with benzylamine by using N,N′-dicyclohexylcarbodiimide in the presence of N-hydroxysuccinimide provided the olefinic benzamide (**5**) in excellent yield. Ozonolysis of (**5**) followed by reductive work up afforded the aldehyde (**6**) quantitatively.

The preparation of (**11**)[5] was achieved from the commercially available 3-methyl-2-pyrrolidone (**7**) in a five-step sequence with 56% overall yield. In order to have access to the key precursors (**15a**) and (**15b**) it was necessary to append the pyrrolinone fragment (**11**) to the aldehyde (**6**), taking into consideration the stereochemistry of the two newly generated stereocenters[6]. The tetrabutylammonium fluoride-promoted addition of (**11**) to (**6**) (THF, -78°C, 1h) proceeded with excellent *erythro* selectivity, to give a mixture of stereoisomers (**12a**: **12b**= 7:1) in 87% yield after flash chromatography[7].

The transformation of (**12a**) and (**12b**) into the acetates (**13a**) and (**13b**) followed by treatment with DBU in benzene at room temperature led stereospecifically to the butylidene derivatives (**14a**) and (**14b**) respectively. Deprotection of the two N-Boc functionalities present in (**14a**) and (**14b**) took place quantitatively by treatment with trifluoroacetic acid (5 eq) in dichloromethane at room temperature; however, we were unable to avoid the exocyclic double bond isomerization under the reaction conditions and the mixture of isomers (**15a**: **15b**= 1:2) was obtained in both cases with excellent yields. Flash chromatography (Cl_3CH: MeOH= 9:1) of the crude mixture allowed us the isolation and characterization of both isomers[8].

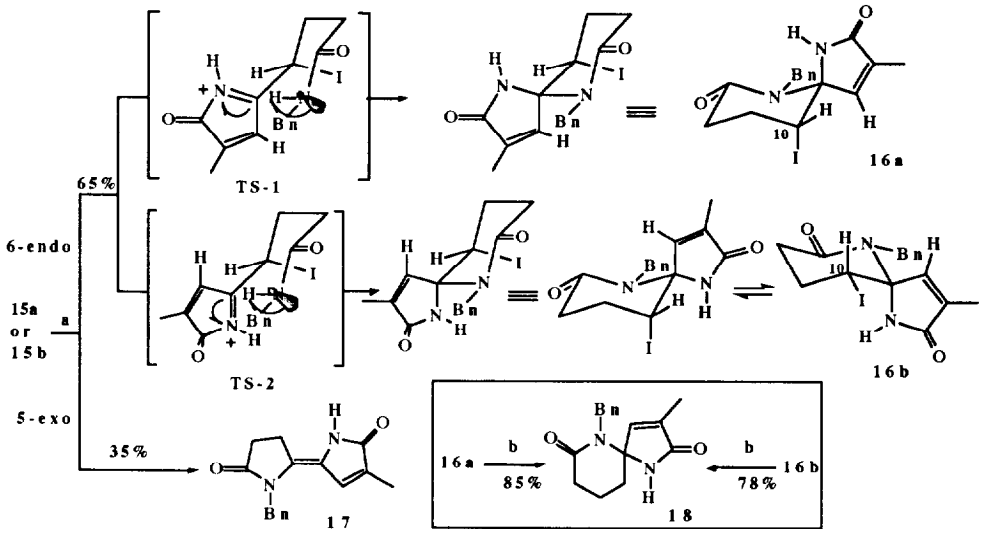


a: i) $C_6H_5CH_2NH_2$, N-hydroxysuccinimide, DCC, rt, 3h.; ii) $(^tBuOCO)_2O$, THF, reflux; **b**: O_3, CH_2Cl_2,-78°C, $S(CH_3)_2$; **c**: **11**, Bu_4NF (1.1 eq.), THF, -78°C; **d**: Ac_2O, pyr, DMAP, CH_2Cl_2; e: benzene, DBU (1.1 eq.)rt,5h.; f: CF_3COOH (5 eq.), CH_2Cl_2, rt.

Scheme 1

Acidic catalysis has been intensively used to generate endocyclic iminium ions and promote intramolecular cyclizations[9]. However, our substrates (**15a**) and (**15b**) have been shown to be extremely reluctant to undergo intramolecular cyclization under drastic acidic conditions. Treatment of (**15a**) and (**15b**) with refluxing trifluoroacetic acid for three days, polyphosphoric acid at 160°C for 72h. and a 1: 10 solution of P_4O_{10} in methanesulfonic acid[10] at room temperature for three days led to the recovery of the starting material. We assume that the tendency to aromatization of the pyrrolinone moiety to the 5-substituted-2-hydroxy-pyrrole under the reaction conditions might account for the exhibited reluctance to cyclization.

Oxidative cyclization of either (**15a**) or (**15b**) by treatment with N-iodosuccinimide NIS and sodium bicarbonate in dichloromethane at 0 °C led to the same mixture of iodolactams (65%) (**16a**: **16b**=3:1) and the pyrrolinone (**17**) (35%)[11]. Presumably, a thermodynamic mixture of cis- and trans-substituted iodonium ions was formed which partially cyclized via 5-exo-cyclization to (**17**), but also led to the mixture of iodolactams via 6-endo cyclization. We assume that the iodoiminium species indicated in Scheme 2 are most probably the cationic intermediates leading to **16a** and **16b**. Our results indicate that the cyclization via the chair-like transition state having the iminium cation in a pseudo-equatorial orientation (TS-1) is more facile than that with an axial orientation (TS-2). Note the relative orientation of the iminium cation and the electron pair of the nitrogen which is antiperiplanar in TS-1 and synclinal in TS-2 [12].



a: NIS (2 eq.), $NaHCO_3$ (2 eq.) CH_2Cl_2, 0°C, 1h.; **b**: n-Bu_3SnH, AIBN, THF, 45°C, 1h.

Scheme 2

Treatment of both iodolactams (**16a**) and (**16b**) with tri-n-butyltin hydride and AIBN in THF at 45°C led to (±)-6-benzyl-3-methyl-3-en-1,6-diazaspiro[4.5]decane-2,7-dione (**18**) with excellent yields.

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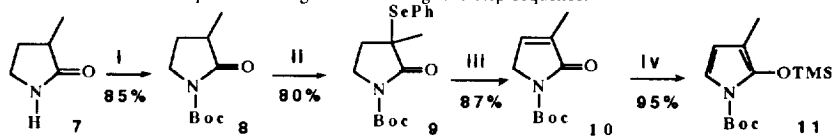
2. Buttery R. G.; Juliano, B. O.; Ling, L. C. *Chem. & Ind*, **1983**, 478.
3. Byrne, L. T.; Guevara, B. Q.; Patalinghug, W. C.; Recio, B. V.; Ualat, C. R.; White, A. H. *Aust. J. Chem.*, **1992**, *45*, 1903-1908.
4. Martín, M. J.; Bermejo, F.; *Tetrahedron Lett.*, **1994**, *35*, 4235-4238.
5. The synthesis of **11** was accomplished through the following five-step sequence:



I: $(t\text{-BuOCO})_2O$, THF, reflux; **II**: LDA, -78°C, PhSeCl; **III**: AcOH, H_2O_2; **IV**: TMSOTf, Et_3N, ether, 0°C.

6. For diastereocontrolled homologation of N-tert-butoxycarbonyl-2-(tert-butyldimethylsilyloxy)pyrrole and 2-(trimethyl silyloxy) furan, see: a) Rassu, G.; Casiraghi, G.; Spanu, P.; Pinna, L. *Tetrahedron: Asymmetry*, **1992**, *3*, 1035-1048; b) Casiraghi, G., Rassu, G.; Spanu P.; and Pinna, L. *J. Org. Chem.*, **1992**, *57*, 3760-3763; c) Harding, K. E.; Coleman, M. T. and Liu, L. T. *Tetrahedron Lett.*, **1991**, *32*, 3795-3798 and references therein.

7. For a review on the stereochemical outcome of similar systems see, Casiraghi, G.; Rassu, G. *Synthesis*, **1995**, 607-626.

8. The configuration of the double bond in **15a** and **15b** shown in Scheme 1 is based on comparison with the spectroscopic properties obtained for (-)-ampullicin and (+)-isoampullicin, two natural occurring γ-lactams with analogous structural arrangements. See, Kimura,Y.; Nakajima, H.; Hamasaki, T.; Matsumoto, T.; Matsuda, Y.; Tsuneda, A. *Agric. Biol. Chem.*, **1990**, *54* , 813-814. Furthermore, **15a** exhibited a NOE effect (9%) at the triplet which is shown at δ= 5.27 ppm (H-6) when the multiplet at δ= 6.50 ppm (H-4) was irradiated.

9. Hiemstra, H.; Speckamp, W. N.: Additions to N-acyliminium ions. In *Comprehensive Organic Synthesis* ; Trost, B. M.; Fleming, I. Eds.; Pergamon Press: New York & Oxford, 1991; vol. 2, pp. 1047-1082.

10. Eaton, P. E.; Carlson G. R. *J. Org. Chem.*, **1973**, *38*, 4071-4074.

11. All compounds were characterized by spectroscopic methods and satisfactorial elemental analysis. For example:

15a: IR(film) ν: 3441, 3335, 3081, 3019, 1692, 1665, 1547, 1441, 1215, 1165, 1078, 1030, 700 cm^{-1}.
^{1}HNMR: δ($CDCl_3$): 7.24 (m, 5H); 6.94 (m, 1H); 6.58 (quintet, J = 1 Hz, 1H); 5.27 (t, J = 8 Hz,1H); 4.40 (d, J = 6 Hz, 2H); 2.64 (q, J = 6 Hz, 2H); 2.45 (t, J = 6Hz, 2H); 1.62 (d, J =1 Hz, 3H) ppm.
^{13}CNMR:δ(CD_3OD): 10.30 (q); 24.67 (t); 36.36 (t); 44.09 (t); 114.44 (d); 127.80 (d); 128.06 (d); 129.26 (d); 134.01 (d); 136.39 (s); 139.28 (s); 139.86 (s); 145. 84 (s); 173. 50 (s) ppm.
15b: IR(film): 3439, 3318, 3069, 3017, 1688, 1680, 1454, 1433, 1358, 1217, 1150, 1080, 1030 cm^{-1}.
^{1}HNMR: δ($CDCl_3$): 7.85 (s, 1H); 7.23 (m, 5H); 6.96 (quintet, J = 1 Hz, 1H); 5.90 (m, 1H); 5.32 (t, J = 8 Hz, 1H); 4.40 (d, J = 6 Hz, 2H); 2.64 (q, J = 8 Hz, 2H); 2.36 (t, J = 9 Hz, 2H); 1.77 (d, J= 1 Hz, 3H) ppm.
^{13}CNMR: δ(CD_3OD): 10.73 (q); 24.87 (t); 37.20 (t); 44.09 (t); 114.44 (d); 128.07 (d); 128.40 (d); 129.18 (d); 129.44 (d); 135.67 (s); 139.60 (s); 139.86 (s); 146.50 (s) and 174.42 (s) ppm .
16a: ^{1}HNMR: δ($CDCl_3$): 8.66 (s, 1H); 7.21(m, 5H); 6.40 (s, 1H); 4.91(d, J = 16Hz,1H); 4.18 (m, $W_{1/2}$ = 8 Hz, 1H); 3.81(d, J = 16 Hz, 1H); 2.9 (m, 1H); 2.7 (m, 1H); 2.45 (m, 1H); 2.25 (m, 1H); 1.78 (d, J = 1.5 Hz, 3H) ppm.
^{13}CNMR: δ(CD_3OD): 10.05 (q); 29.18 (t); 31.02 (t); 31.20 (d); 45.23 (t); 78.89 (s); 126.91 (d); 127.35 (d); 128.26 (d); 136.96 (s); 139.40 (s); 145.74 (d); 169.66 (s); 172.13 (s) ppm.
16b: ^{1}HNMR: δ($CDCl_3$): 6.72 (s,1H); 6.27 (s,1H); 4.67 (d, J = 18 Hz, 1H); 4.42 (m, $W_{1/2}$ = 15 Hz, 1H); 4.10 (d, J= 16 Hz, 1H); 3.05 (m, 1H); 2.65 (m, 2H); 1.95 (m, 1H); 1.82 (d, J = 1.2 Hz, 3H) ppm.
^{13}CNMR: δ(CD_3OD): 10.12 (q); 31.26 (d); 32.36 (t); 34.67 (t); 44.59 (t); 78.96 (s); 127.49 (d); 127.58 (d); 128.35 (d); 135.45 (s); 137.01 (s); 144.23 (d); 170.85 (s); 172.30 (s) ppm.
17: IR(film) ν: 3287, 3021, 2926, 1712, 1634, 1553, 1441, 1215, 1155, 1030 cm^{-1}
^{1}HNMR: δ($CDCl_3$): 7.27 (m, 5H); 7.01 (m, 1H); 4.35 (m, 2H), 3.04 (t, J = 6 Hz, 2H); 2.45 (t, J = 6 Hz, 2H); 1.88 (d, J = 1.5 Hz, 3H) ppm.
^{13}CNMR: δ(C_5D_5N): 11.21 (q); 36.34 (t); 36.73 (t), 44.15 (t); 86.61 (s); 127,74 (d); 128.43 (s); 128.55 (d); 129.25 (d); 138.02 (s); 141.81 (s); 171.85 (s); 173.64 (s) ppm.
18: ^{1}HNMR: δ($CDCl_3$): 7.67 (s, 1H); 7.25 (m, 5H); 6.24 (m, 1H); 4.74 (d, J = 15 Hz, 1H); 4.01 (d, J = 15 Hz, 1H); 2.63 (m, 2H); 2.02 (m, 3H); 1.83 (d, J = 1.5 Hz, 3H); 1.65 (m, 1H) ppm.
^{13}CNMR: δ(CD_3OD): 10.14 (q); 18.30 (t); 32.37 (t); 34.75 (t); 44.55 (t); 76.38 (s); 44.55 (t); 34.75 (t); 32.37 (t); 18.30 (t); 10.14 (q) ppm.

12. The ^{1}HNMR analysis of the crude cyclization mixture exhibited the presence of two multiplets at δ: 4.42 ($W_{1/2}$= 15 Hz) and δ: 4.18 ($W_{1/2}$= 8 Hz) easily assignable to the H-10 protons of both isomers which, by integration, gave a ratio of **16a**:**16b**= 3: 1. For similar cyclizations, see a) Schoeemaker, H. E.; Speckamp, W. N. *Tetrahedron Lett.*, **1978**, 1515-1518; b) Schoeemaker, H. E.; Speckamp, W. N. *Tetrahedron Lett.*, **1978**, 4841-4844; c) Evans, D. A.; Thomas, E. W. *Tetrahedron Lett.*, **1979**, 411-414.

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