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Stereoselective Preparation of (5E)- and (5Z)-5-Benzylidene-3-methyl-3-pyrrolin-2-ones. Application to the Synthesis of Ampullicine and Isoampullicine.

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Abstract: The application of N-Boc-5-phosphoranylidene- and N-Boc-5-diethylphosphonate-3-methyl-3-pyrrolin-2-ones to the stereoselective synthesis of (5E)- and (5Z)-3-methyl-5-benzylidene-3-pyrrolin-2-ones is examined. The stereoselective synthesis of the growth regulators Ampullicin and Isoampullicin by using both Wittig intermediates has also been achieved.

The 5-ylidene-3-methyl-3-pyrrolin-2-one system is present in a group of natural products, various members of which have been discovered since the begining of the present decade. For example, the growth regulators Ampullicin (**1**) and Isoampullicin (**2**) (Fig. 1) are two sesquiterpene metabolites isolated by Tsuneda and col.[1] from a culture filtrate of *Ampulliferina*-like fungus sp. No. 27 obtained from a dead pine tree (*Pinus thunbergii*). On the other hand, the 1,6-diazaspiro[4.5]decane structure (**3**) of (±)-pandamarine, the major alkaloid isolated from the leaves of *Pandanus amarillifolius* Roxb. has been determined by X-ray difraction.[2] As (±)-pandamarine occurs as a racemate, the secundary amine (**4**) has been proposed by Byrne and col. as the biosynthetic symmetrical precursor of the natural alkaloid.

As a part of a program aimed to the synthesis of (**1**), (**2**), (**3**) and (**4**), we were interested in the development of a stereoselective method to prepare (Z)- and (E)-5-ylidene-3-methyl-3-pyrrolin-2-ones in order to facilitate the access to the above mentioned natural products by stereoselective convergent strategies.

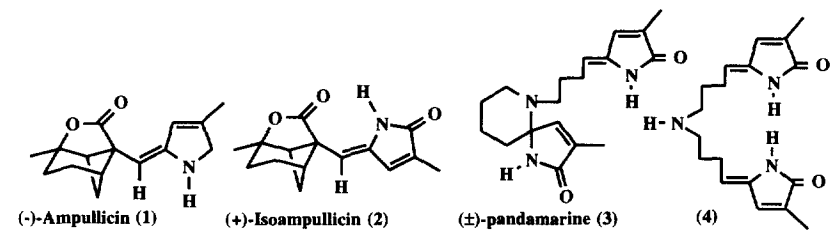
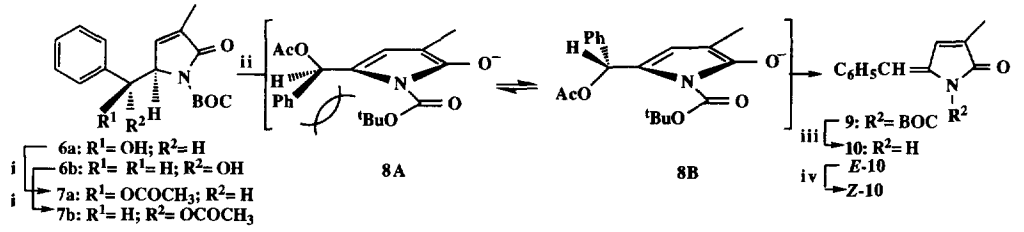


Fig.1

Condensation of N-Boc-3-methyl-3-pyrrolin-2-one **5**,[3-4] with benzaldehyde (LDA, THF, -78°C) exhibited moderate stereoselectivity (**6a**: **6b**= 3:1); both diastereomers , **6a** (mp 116-118 °C) and **6b** (mp 134-136 °C) were separated by HPLC [μ-porasil, 7.8 x 300mm; CH_2Cl_2: IPA (5%)] and their relative configurations assigned based on reported data.[5] Best results were obtained as follows: fluoride ion-promoted condensation of

N-(*tert*-butoxycarbonyl)-2-(*tert*-butyldimethylsiloxy)pyrrole (TBSOP)[5] with benzaldehyde in THF at -78 °C led to the *erythro* isomer **6a** in high yield (>98%). The *threo* isomer **6b**, was obtained in almost pure form (>99%) by condensation of TBSOP with benzaldehyde in the presence of $TiCl_4$ in THF at -78 °C.

The stereoselective preparation of the *erythro* and *threo* hydroxy derivatives **6a** and **6b** allowed us to prepare the acetates **7a** and **7b** in quantitative yields (Scheme 1). Both acetates **7a** and **7b** gave separately the same geometrical isomer *E*-**9** (m.p. 80 °C) in quantitative yield when treated with DBU at room temperature. The stereochemistry of the exocyclic double bond of *E*-**9** follow unambiguosly fron ^{1}HNMR data[5] and has also been related by characteristic chemical shift data to known 3-pyrrolin-2-ones.[1] We assume that deprotonation of either **7a** or **7b** led to *E*-**9** through an E1cb mechanism[7] via allylic deprotonation and further stabilization of the resulting anion through the formation of the 2-alkoxypyrrole salt **8**. Steric factors force **8A** to collapse to *E*-**9** stereoespecifically, via the more stable intermediate **8B**. Treatment of *E*-**9** with trifluoroacetic acid (TFAA) in dichloromethane at 0 °C led to (5E)-5-benzylidene-3-methyl-3-pyrrolin-2-one *E*-**10** (m.p. 147-149 °C) in 88% yield. In the present work pure *Z*-**10** (m.p. 185-187 °C) has been prepared by isomerizing the *E*-**10** isomer with iodine in refluxing benzene in quantitative yields.



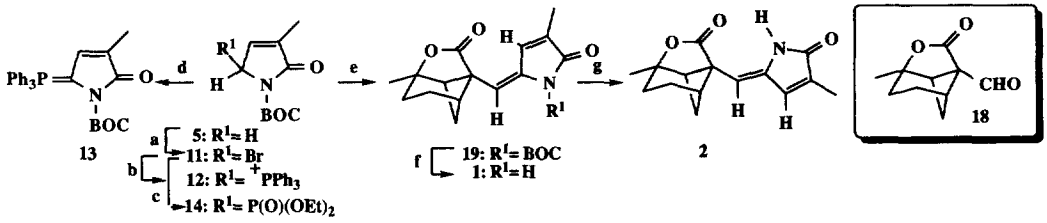
6a: R^1= OH; R^2= H
6b: R^1= R^1= H; R^2= OH
7a: R^1= $OCOCH_3$; R^2= H
7b: R^1= H; R^2= $OCOCH_3$

i: Ac_2O, Pyr, DMAP, CH_2Cl_2, rt, 98%; ii: DBU, toluene, rt, 15h, 100%; iii: TFAA, CH_2Cl_2, 0 °C, 1h, 88%; iv: I_2, benzene, reflux, 15h, 100%.

Scheme 1

The development of a stereoselective method to prepare the 5-alkylidene derivatives *E*-**10** and *Z*-**10** by using 5-phosphoranylidene- and 5-phosphonate- derivatives of **5**, has been achieved following previous work on 4-ylidenebutenolides.[6] We first examined the synthesis of *E*-**10** and *Z*-**10** from the N-tertbutoxycarbonyl-5-triphenylphosphoranylidene-3-methyl-3-pyrrolin-2-one **13** (Scheme 2). The phosphonium salt **12** was prepared from **5** by bromination with N-bromosuccinimide and AIBN in refluxing toluene[8] followed by reaction with triphenyl phosphine. Treatment of **12** with the anion from dimethyl sulfoxide gave a deep brown solution of the ylide **13** whose color was discharged on addition of benzaldehyde. Work up yielded a mixture of the geometrical isomers *E*-**10**: *Z*-**10**= 1:1 (^{1}HNMR analysis) in 38% yield. Identical result was obtained by treatment of **12** with aqueous NaOH in $CHCl_3$ followed by addition of benzaldehyde. It was found that the best yields were obtained when the phosphorane **13** was generated *in situ* from the salt **12** with sodium hydride in DMF. The product pyrrolinones could be prepared in 47% yield and the ^{1}HNMR spectrum indicated that the product was a 1: 1 mixture of the *E*-**10** and *Z*-**10** isomers.[9] It has been reported that the phosphonium ylide obtained from 4-bromo-2-butenolide exhibit a strong kinetic preference for the irreversible formation of the *erythro*-betaine intermediate which once formed collapses rapidily to the *E*-olefin product. The presence of the N-Boc moiety may help to understand the poor kinetic selectivity obtained in our case in terms of the steric hindrance which may have been developed in the TS leading to the less stable olefin *E*-**10**. However, the reaction of **11** with neat triethyl phosphite led to the phosphonate **14** which, after deprotonation with NaH in

THF at room temperature followed by addition of benzaldehyde afforded the diastereomer *E*-**9** exclusively, which has been isolated by flash chromatography in 75% yield. Deprotection of *E*-**9** by treatment with trifluoroacetic acid in dichloromethane at 0 °C led quantitatively to *E*-**10**.[11]



a: NBS, AIBN,tol, reflux, 85%; **b**: Ph_3P, benzene, reflux, 4h, 88%; **c**: $P(OEt)_3$, neat, 100%; **d**: DMSO, NaH, rt,15h, 38%; **e**: 14, NaH, THF, **18**, 76%; **f**: TFAA, CH_2Cl_2, 0 °C, 1h, 85%; **g**: I_2, benzene, reflux, 100%.

Scheme 2.

Analogously, the treatment of the phosphonate **14** with NaH in THF followed by the addition of the optically active carbaldehyde **18**[12] led to the exclusive formation of the N-Boc-ampullicin, **19** (m.p. 127-129 °C). Flash chromatography of the crude product allowed us to isolate **19** in 76% yield.[13] Deprotection of **18** by treatment with trifluoroacetic acid in dichloromethane at 0 °C led exclusively to **1**, which was isolated by flash chromatography in 85% yield. The thermodynamically more stable geometrical isomer isoampullicin **2** has been quantitatively prepared by isomerizing the 5E isomer (**1**) with iodine in refluxing benzene for 15h. The spectroscopic properties obtained for both geometrical isomers were identical to those described in the literature for ampullicin **1** and isoampullicin **2**.[1, 12]

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3. The N-Boc-3-methyl-3-en-pyrrolin-2-one **5**[4] (LDA, THF, -78 °C) reacted with a range of aldehydes, giving mixtures of *erythro* and *threo* isomers. Yields ranged from 65% to 85%, with a marked preference for the *erythro* diastereomer (from 3:1 to >98: 2, increasing with the steric bulk of the aldehyde). Martin, M. J. unpublished results.
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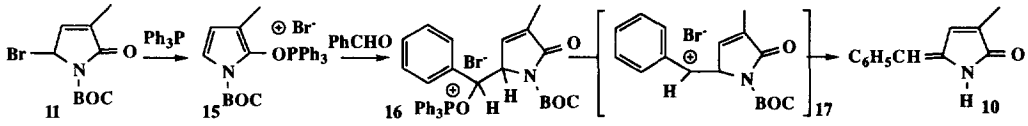
9. It has also been found that the treatment of the bromide **11** with triphenylphosphine followed by addition of benzaldehyde in $CHCl_3$ at room temperature (without addition of base) led overnight to a mixture of the geometrical isomers *E*-**10**: *Z*-**10**= 1: 4 (^{1}HNMR analysis). The rationale under this result may reside in the formation of an alkoxyphosphonium intermediate **15** formed through bromide displacement in **11** by the triphenyl phosphine. This species may promote the condensation with benzaldehyde leading to a benzylic alkoxonium derivative **16**, which would undergo elimination (triphenyl phosphine oxide) giving rise to a benzylic carbonium ion **17** which will collapse with concomitant N-BOC deprotection to the thermodynamically more stable isomer *Z*-**10**, as the major component of the reaction mixture. (See Ref. 10).



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11. No trace of the geometrical isomer *Z*-**10** was detected by ^{1}HNMR analysis of the crude reaction mixture.
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13. All new compounds were characterized by spectroscopic methods. Correct microanalytical data have been obtained. For example:

6a: IR (film) ν : 3424; 1776; 1728; 1365 cm^{-1}. ^{1}HNMR: δ($CDCl_3$): 1.58 (s, 9H, $C(CH_3)_3$); 1.82 (t, J= 2 Hz, 3H, CH_3); 4.72 (sextet, J= 2 Hz,1H, NCH); 5.39 (d, J= 2 Hz, 1H, CHOH); 6.52 (quintet, J= 2 Hz, =CH); 7.32 (m, 5H, Ar) ppm. ^{13}CNMR: δ($CDCl_3$): 10.88 (q); 28.13 (q); 66.47 (d); 71.85 (d); 83.45 (s); 125.56 (d); 127.71 (d); 128.30 (d); 135.99 (s); 139. 08 (d); 139. 72 (s); 150. 59 (s); 170.02(s) ppm. MS (e/z, %): 304 (M+1, 15); 248 (98); 230 (45); 204 (40); 186 (35); 141 (100); 123 (25); 107 (95).

6b: IR (film) ν : 3424; 1778; 1726; 1370, 1325, 1168 cm^{-1}. ^{1}HNMR: δ($CDCl_3$): 1.61 (s, 9H, $C(CH_3)_3$); 1.70 (t, J= 2 Hz, 3H, CH_3); 4.79 (dq, J_1= 6Hz; J_2= 2Hz, 1H, NCH); 5.09 (d, J= 6 Hz, 1H, CHOH); 6.60 (quintet, J= 2Hz, 1H, =CH); 7.25 (m, 5H, Ar) ppm. ^{13}CNMR: δ($CDCl_3$): 10.70 (q); 28.14 (q); 64.94 (d); 75.56 (d); 83.76 (s); 126.67 (d); 128.18 (d); 128.29 (d); 135.28 (s); 139.21 (s); 140.59 (d); 151.73 (s); 169.35 (s) ppm. MS (e/z, %): 304 (M+1, 5); 248 (75); 230 (30); 204 (60);141 (100); 123 (30); 107 (60).

***E*-10**: IR (film) ν : 3400, 1693, 1219cm^{-1}. ^{1}HNMR: δ($CDCl_3$): 2.03 (d, J= 1.5 Hz, 3H, CH3); 6.43 (s, 1H, H-6); 7.13 (quintet, J= 1.5 Hz, 1H, H-4); 7.33 (m, 5H, C_6H_5); 8.90 (s broad, 1H, NH) ppm. ^{13}CNMR: δ($CDCl_3$): 16.35 (q); 112.93 (d); 113.34 (d); 127.80 (d); 128.72 (d); 129.12 (d); 135.40 (s); 136.68 (s); 137.50 (s); 171.92 (s) ppm. MS (e/z, %): 185 (47); 163 (12); 156 (20); 149 (30); 139 (11); 123 (11); 113 (2); 107 (39); 97 (46); 91 (11); 81 (28); 69 (70).

***Z*-10**: IR (film) ν : 3403, 1693, 1217cm^{-1}. ^{1}H NMR: δ($CDCl_3$): 2.0 (d, J= 1.5 Hz, 3H, CH_3); 6.00 (s, 1H, H-6); 6.74 (quintet, J= 1.5 Hz, 1H, H-4); 7.33 (m, 5H, C_6H_5); 7.93 (s broad, 1H, NH) ppm. ^{13}C NMR: δ($CDCl_3$): 16.85 (q); 111. 57 (d); 127.89 (d); 128.52 (d); 129.18 (d); 133.29(s); 134.15 (d); 135.23 (s); 136.46 (s); 173.06 (s) ppm. MS (e/z, %): 185 (37); 170 (5); 156 (15); 141 (8); 125 (8); 111 (15); 97 (24); 83 (30); 69 (51); 57 (65); 43 (100).

19: IR (film) ν : 2932, 1771, 1738, 1456, 1300, 1157, 1084 cm^{-1}. ^{1}HNMR: δ($CDCl_3$): 1.50 (s, 3H, H-10); 1.56 (s, 9H, ^{t}Bu); 1.72 (d, 1H, J= 11 Hz, H_{2exo}); 1.92-2.01 (m, 4H, H-4+H-5); 2.41 (quintet, 1H, J= 6 Hz, H_{2endo}) 2.7 (m, 2H, H-1+H-3); 6.71 (s, 1H, H-11); 6.79 (s, H-13); ^{13}C NMR: δ($CDCl_3$): 10.71 (q); 23.17 (t); 23.90 (t); 24.80 (q); 28.06 (q); 29.75 (t); 47.51 (d); 52.88 (d); 56.16 (s); 83.55 (s); 87.81 (s); 114.87 (d); 132.02 (d); 132.66 (s); 139.87 (s); 149.59 (s); 167.64 (s); 157.57 (s)ppm.

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