WITTIG REACTIONS OF 1-ALKOXYCARBONYL-2-HYDROXYPYRROLIDINES AND -PIPERIDINES: SYNTHESES OF (±)-HYGRINE AND (±)-2-EPILASUBINE II

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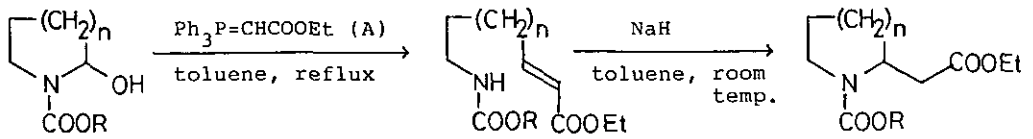
Abstract — One-pot reactions of 1-alkoxycarbonyl-2-hydroxypyrrolidines and -piperidines with Wittig reagents stabilized by carbonyl groups give α-alkylated pyrrolidines and piperidines in good yields. The syntheses of (±)-hygrine and (±)-2-epilasubine II using the Wittig products are described.

Reactions for introducing functional groups at the α-position of cyclic amines are currently of great interest,[1] in view of the many such derivatives as alkaloids, antibiotics and medicines consisting of the α-substituted cyclic amine structures that have been obtained in this way. In our previous paper,[2] we reported that reactions of 1-ethoxycarbonyl-2-hydoxypyrrolidine 2, readily obtainable from 2-pyrrolidinone in three steps,[3] with carbonyl compounds in the presence of a base give α-alkylated pyrrolidines in moderate to high yields. In the present study, reactions of 2-hydroxycarbamates (1-7) with Wittig reagents stabilized by carbonyl groups were carried out as an alternative means for introducing carbon-functional groups at the α-position of cyclic amines.[4] The results of applying this method to the alkaloid syntheses of (±)-hygrine and (±)-2-epilasubine II are presented.

A detailed study was first made of the reaction of hydroxycarbamate 2 with ethyl triphenylphosphonoacetate (A) to give mainly the unsaturated ester 8. The following solvents were used (reaction conditions and yield of 8 are indicated in parenthesis): 1) dichloromethane (reflux, 24 h; 0%), 2) dimethyl sulfoxide (room temperature, 4 h; 10.5%), 3) dimethoxyethane (reflux, 12 h; 65.4%), 4) toluene (reflux, 1.5 h; 80.3%). The products, obtained by refluxing in toluene, were separated by chromatography into E-isomer 8 and Z-isomer 10 in 80.3% and 4.7% yields, respectively. A similar reaction of six-membered hydroxycarbamate 5 was

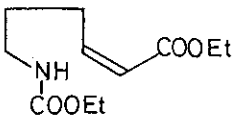
Scheme 1



1 n=1, R=Me
2 n=1, R=Et
3 n=1, R=$CH_2CH=CH_2$
4 n=1, R=l-menthyl
5 n=2, R=Me
6 n=2, R=$CH_2CH=CH_2$
7 n=2, R=l-menthyl

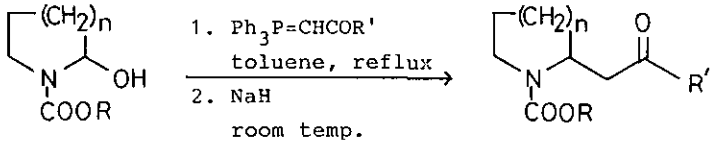
8 n=1, R=Et (80.3%)
9 n=2, R=Me (70.9%)

11 n=1, R=Et (78.3%)
12 n=2, R=Me (87.2%)



10 (4.7%)

Table I. One-Pot Reactions of 2-Hydroxycarbamates (1-7) with Stabilized Wittig Reagents (A-D)



1-7 → 11-22

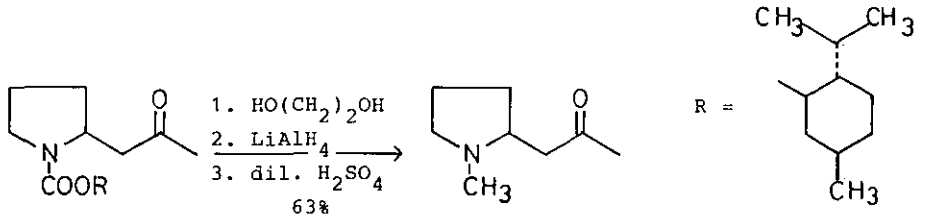
Run	2-Hydroxycarbamates	$Ph_3P=CHCOR'$*	Products (11-22)	Isolated Yield (%)
1	2	A	11: n=1, R=Et, R'=OEt	76.0
2	2	C	13: n=1, R=Et, R'=Me	74.5
3	1	D	14: n=1, R=Me, R'=CH=CHPh	69.0
4	3	A	15: n=1, R=$CH_2CH=CH_2$, R'=OEt	86.1
5	4	B	16: n=1, R=l-menthyl, R'=OMe	87.4
6	4	C	17: n=1, R=l-menthyl, R'=Me	90.9
7	5	A	12: n=2, R=Me, R'=OEt	51.5
8	5	C	18: n=2, R=R'=Me	43.3
9	6	C	19: n=2, R=$CH_2CH=CH_2$, R'=Me	27.4
10	6	B	20: n=2, R=$CH_2CH=CH_2$, R'=OMe	55.4
11	7	C	21: n=2, R=l-menthyl, R'=Me	67.0
12	5	D	22: n=2, R=Me, R'=t-CH=CHPh	6.6

* A: R'=OEt, B: R'=OMe, C: R'=Me, D: R'=trans-CH=CHPh

then carried out to afford the unsaturated ester 9 in good yield (70.9%).[5] The intramolecular Micheal addition of these unsaturated esters 8 and 9 was successfully carried out by stirring them with equivalent quantities of sodium hydride in toluene at room temperature to give cyclic amines 11 and 12 in 78.3% and 87.2% yields, respectively. In consideration of the above results, the conversion of hydroxyurethanes 2 and 5 to cyclic amines 11 and 12 was carried out in one-pot by refluxing 2 and 5 with a Wittig reagent in toluene followed by the addition of sodium hydride,[6] giving 11 and 12 in 76% and 51.5% overall yields, respectively. The results by one-pot Wittig reactions of 1-alkoxycarbonyl-2-hydroxypyrrolidines (1-4) and -piperidines (5-7) are summarized in Table I. Generally, the yields of the pyrrolidine derivatives (11, 13-17) were high, with those of piperidine derivatives (12, 18-22) being moderate to low. This appeared to depend on hydroxycarbamate stability, the hydroxycarbamates of pyrrolidine (1-4) being more stable than those of piperidine (5-7)[2,7]

Compound 17, having a chiral group at the N-position and whose separation into diastereomers was expected,[8,9] was converted to hygrine 23 following a method in the literature,[10] (Scheme 2). The ketalization of 17 and subsequent reduction with lithium aluminum hydride and hydrolysis with aqueous sulfuric acid afforded racemic hygrine 23 in 63% overall yield. No diastereomer at the 2-position of pyrrolidine ring of 17 or other intermediates could be separated.

Scheme 2



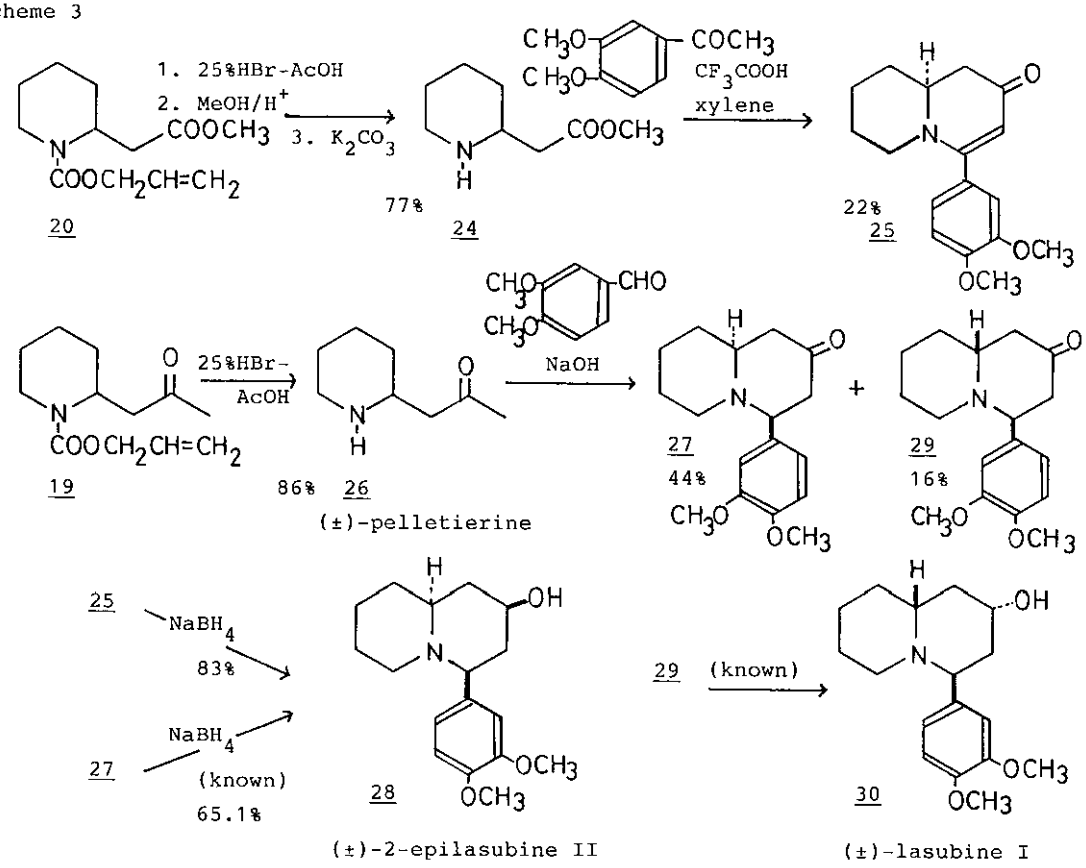
17 23 1-menthyl

(±)-hygrine

(±)-Epilasubine II 28 was synthesized using Wittig products 19 and 20. Carbamate 20 was hydrolyzed by 25% hydrobromic acid in acetic acid[11] to amine 24 in 77% yield, which, without purification, was refluxed with 3,4-dimethoxyacetophenone in xylene in the presence of trifluoroacetic acid to give quinolizidinone 25 in 22% yield. The reduction of 25 with sodium borohydride in ethanol gave (±)-2-epilasubine II 28 as a single product in 83% yield (Scheme 3). The reaction of carbamate 19 with 25% hydrobromic acid in acetic acid produced (±)-pelletierine 26 in 86%

yield. This compound has been used for the syntheses of (±)-lasubine I 30 and (±)-2-epilasubine II 28.[12] Following the method,[12] pelletierine 26 was condensed with veratraldehyde in the presence of a base to give trans-quinolizidinone 27 and cis-quinolizidinone 29 in 44% and 16% yields, respectively.[13] The reduction of 27 with sodium borohydride gave (±)-2-epilasubine II 28 in 65% yield; it was identical with the sample obtained from 20 as described before. Synthesis of (±)-lasubine I 30 from cis-quinolizidinone 29 has been reported.[12]

Scheme 3



Based on the data presented above, the reactions of 2-hydroxycarbamates with the Wittig reagent stabilized by carbonyl groups may be concluded to serve as a means for obtaining α-alkylated pyrrolidine and piperidine derivatives by which alkaloid syntheses can be effectively carried out . This method is applicable to the transformation of commercially available lactams into α-alkylated cyclic amines.

EXPERIMENTAL

All melting points were determined by micro-melting point apparatus (Yanagimoto) without correction. Ir and mass spectra were measured on Hitachi 200-10 and Hitachi M-80 spectrometers, respectively. ^{1}H-Nmr spectra were recorded on a Varian EM-390 instrument. Chemical shifts were recorded in ppm downfield from an internal standard (tetramethylsilane). The following abbreviations were used: s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet, br=broad. Chromatographic separations were made using a silica gel (Wako-gel C-200) column. Thin-layer chromatography (tlc) was carried out with pre-coated silica gel plates (Kiesel 60 F-254, Merck). The physical properties and elemental analyses of Wittig products (8-22 except 13) are listed in Tables II and III, respectively. The physical data of compound 13 are presented in our previous paper.[2]

2-Hydroxycarbamate (1-7) -- Hydroxycarbamates (1-7) were prepared by the acidic hydrolysis[2] of the corresponding 2-ethoxycarbamates.[3] Their elemental anlyses, except that of compound 4, failed to provide satisfactory data owing to instability during distillation. But their mass spectra showed the same fragment pattern (M^+-OH). The physical properties of compounds 2 and 3 are given in the privious paper[2]. 1: oil (quant. yield), ir (neat) 3410, 1700 cm^{-1}, ^{1}H-nmr ($CDCl_3$) δ 1.81 (m, 4H, CH_2 x 2), 3.04-3.61 (m, 3H, NCH_2, CHOH), 3.74 (s, 3H, OCH_3), 5.41-5.61 (m, 1H, NCHOH). 4: oil (78%), ir ($CHCl_3$) 3450, 1700 cm^{-1}, ^{1}H-nmr ($CDCl_3$) δ 0.78 (d, J=7.5Hz, 3H, $CHCH_3$), 0.89 (d, J=7.5Hz, 6H, $CH(CH_3)_2$), 1.07-2.07 (m, 13H, CH_2 x 5, CH x 3), 3.10-3.67 (m, 2H, NCH_2), 4.00 (br, 1H, OH), 4.40-4.78 (m, 1H, CHOCO), 5.33-5.56 (m, 1H, NCHOH). Anal. Calcd for $C_{15}H_{27}NO_3$: C, 66.88; H, 10.10; N, 5.17. Found: C, 67.10; H, 10.24; N, 5.17. 5: oil (93%), ir (neat) 3440, 1680 cm^{-1}, ^{1}H-nmr ($CDCl_3$) δ 1.37-2.17 (m, 6H, CH_2 x 3), 2.92-3.47 (m, 1H, HCHN), 3.68 (s, 3H, OCH_3), 3.70-4.03 (m, 2H, HCHN, OH), 5.60 -5.83 (m, 1H, OCHN). 6: oil (quant. yield), ir (neat) 3440, 1680 cm^{-1}, ^{1}H-nmr ($CDCl_3$) δ 1.38-2.22 (m, 6H, CH_2 x 2), 2.92-3.52 (m, 1H, HCHN), 3.68-4.05 (m, 2H, HCHN, OH), 4.47-4.75 (m, 2H, OCH_2CH), 5.08-5.55 (m, 2H, $CH=CH_2$), 5.65-6.22 (m, 2H, $CH_2CH=CH_2$, NCHO). 7: oil (64.6%), ir (neat) 3400, 1670 cm^{-1}. ^{1}H-nmr ($CDCl_3$) δ 0.78 (d, J=7Hz, 3H, $CHCH_3$), 0.88 (d, J=7Hz, 6H, $CH(CH_3)_2$), 1.35-2.45 (m, 15H, CH_2 x 6, CH x 3), 2.78-3.33 (m, 1H, HCHN), 3.67-4.02 (m, 1H, HCHN), 4.35-4.78 (m, 1H, CHOCO), 5.62-5.85 (m, 1H, NCHOH).

Ethyl (E and Z)-6-Ethoxycarbonylamino-2-hexenoate (8 and 10) -- A mixture of hydroxycarbamate 2 (954 mg, 6 mmol) and phosphonoacetate (A) (2.09 g, 6 mmol) in toluene (50 ml) was refluxed for 2.5 h under an Ar atmosphere followed by evaporation to give a semisolid, which, on chromatographic separation by elution with benzene-acetone (20:1), afforded 65 mg (4.7%) of 10 from the first crop and 1.103 g (80.3%) of 8 from the second.

Ethyl (E)-7-Methoxycarbonylamino-2-heptenoate (9)[5] -- In accordance with the method presented above, 324 mg (70.7%) of 9 were obtained by refluxing hydroxycarbamate 5 (318 mg, 2 mmol) and phosphonoacetate (A) (700 mg, 2 mmol) together in toluene (10 ml) for 2 h.

2-Acetonyl- and 2-Alkoxycarbonylmethylcarbamates (11-22) -- A) General method for preparing carbamates (11-22) by a one-pot reaction-- A typical procedure for

obtaining 2-ethoxycarbonylmethylcarbamate 11 is as follows: A mixture of 2 (120 mg, 0.75 mmol) and phosphonoacetate (A) (261 mg, 0.75 mmol) in toluene (15 ml) was refluxed for 2.5 h under an Ar atmosphere and cooled to room temperature. 18 mg (0.75 mmol) of NaH were added to the reaction mixture, followed by stirring at room temperature for 2 h, washing with brine and drying over $MgSO_4$. The solvent was evaporated and the residue purified on chromatography by elution with benzene-acetone (30:1) to give 130 mg (76%) of 11 as a colorless oil. B) The synthesis of carbamates (11 and 12) by the Michael addition of carbonyl compounds (8 and 9) -- A solution of 8 (112 mg, 0.49 mmol) in benzene (15 ml) in the presence of NaH (12 mg, 0.5 mmol) was stirred at room temperature for 2 h, washed with brine, dried over $MgSO_4$ and evaporated. Chromatographic separation of the residue by elution with benzene-acetone (30:1) gave 90 mg (78.3%) of 11 as a colorless oil. By the same method as that above, 12 was obtained in 87.2% yield from 9.

Synthesis of (±)-Hygrine (23) -- A mixture of acetonylcarbamate 17 (333 mg, 1.08 mmol), ethylene glycol (0.8 ml), p-toluenesulfonic acid (5 mg) and ethyl orthoformate (1.6 ml) was refluxed for 2.5 h and evaporated under reduced pressure to give an oil, which was dissolved in ether, washed with aq. $NaHCO_3$ and brine and dried over $MgSO_4$. Removal of ethylene glycol under reduced pressure gave crude ketal (324 mg), ^{1}H-nmr ($CDCl_3$) δ 0.78 (d, J=7Hz, 3H, $CHCH_3$), 0.90 (d, J=7Hz, 6H, $CH(CH_3)_2$), 1.37 (s, 3H, CH_3), 1.00-2.30 (m, 15H, CH_2 x 6, CH x 3), 3.34 (t, J=6.7 Hz, 2H, NCH_2), 3.80-4.00 (m, 1H, $NCHCH_2$), 3.90 (s, 4H, OCH_2CH_2O), 4.40-4.70 (m, 1H, CHOCO). This ketal, which could not be separated into diastereomers, was refluxed for 5 h with $LiAlH_4$ (61 mg) in abs. THF (2.5 ml). Excess $LiAlH_4$ was decomposed carefully with H_2O. The reaction mixture was basified with K_2CO_3 and extracted six times with ether. The extract was washed with brine, dried over $MgSO_4$ and evaporated to give crude aminoketal (287 mg) along with l-menthol, ^{1}H-nmr ($CDCl_3$) δ 1.32 (s, 3H, CCH_3), 2.30 (s, 3H, NCH_3), 3.92 (s, 4H, OCH_2CH_2O). This aminoketal was hydrolyzed with aq. H_2SO_4 (c.H_2SO_4 90 mg in H_2O 0.4 ml) at room temperature. The reaction mixture was washed with ether to remove l-menthol, basified with K_2CO_3 and extracted with ether. The extract was washed with brine, dried over $MgSO_4$ and evaporated carefully to give a crude oil (100 mg) of hygrine 23, which was purified by distillation to give 96 mg (63% overall yield from 17) of 23 as a colorless oil, bp 75°C (18 mmHg), $[\alpha]_D$=0, ms m/z 141 (M^+), ir (neat) 1710 cm^{-1}, ^{1}H-nmr ($CDCl_3$) δ 1.23-2.80 (m, 8H, CH_2 x 4), 2.17 (s, 3H, $COCH_3$), 2.30 (s, 3H, NCH_3), 3.03 (m, 1H, NCH). Picrate, mp 152-153°C. Anal. Calcd for $C_8H_{15}NO \cdot C_6H_3N_3$: C, 45.40; H, 4.90; N, 15.13. Found: C, 45.52; H, 4.90; N, 15.18.

2-Oxo-4-(3',4'-dimethoxyphenyl)-1,2,5,6,7,8,9,10-octahydro-trans-quinolizine (25) -- A solution of carbamate 20 (650 mg, 2.7 mmol) in 25% HBr-AcOH (2 ml) was stirred at room temperature overnight and evaporated to give an oil, which was refluxed with saturated HCl-MeOH (1 ml) for 3 h. After evaporation of the solvent, the residue was dissolved in H_2O, basified with K_2CO_3 and extracted five times with EtOAc. The extract was washed with brine, dried over $MgSO_4$ and evaporated to give crude oil (360 mg) of amine 24, ^{1}H-nmr ($CDCl_3$) δ 0.89 (m, 6H, CH_2 x 3), 2.36 (d, J=6Hz, 2H, CH_2CO), 2.49-3.19 (m, 4H, NCH_2, NHCH), 3.68 (s, 3H, OCH_3). A

mixture of amine 24 (360 mg), 3,4-dimethoxyacetophenone (531 mg, 2.1 mmol) and CF_3COOH (240 mg, 2.1 mmol) in xylene (50 ml) was refluxed for 48 h and , after dilution with benzene (50 ml), was washed with brine and aq. $NaHCO_3$, dried over $MgSO_4$ and evaporated to give an oil. Chromatographic separation of the latter by elution with $CHCl_3$ gave 360 mg (22%) of 25 as a yellow oil, exact ms calcd for $C_{17}H_{21}NO_3$ m/z 287.1520 (M^+), obsd m/z 287.1547, ir ($CHCl_3$) 1720, 1630 cm^{-1}, ^{1}H-nmr ($CDCl_3$) δ 0.92-2.82 (m, 8H, CH_2 x 4), 3.25-3.78 (m, 2H, NCH_2), 3.88 (s, 6H, OCH_3 x 2), 5.06 (s, 1H, C=CHCO), 6.81 (s, 1H, aromatic H), 6.88 (s, 2H, aromatic H).

2-Acetonylpiperidine (Pelletierine) (26) -- By the same method for obtaning 2-methoxycarbonylmethylpiperidine 24, pelletierine 26 was produced in 86% yield from carbamate 19 as an oil, ms m/z: 141 (M^+), ir ($CHCl_3$) 3320, 1710 cm^{-1}, ^{1}H-nmr ($CDCl_3$) δ 1.10-1.87 (m, 6H, CH_2 x 3), 2.12 (s, 3H, $COCH_3$), 2.49 (d, J=5Hz, 2H, $CHCH_2$), 2.40-3.23 (m, 3H, NCH_2, NCH). Picrate, mp 149-150°C. Anal. Calcd for $C_8H_{15}NO \cdot C_6H_3N_3O_7$: C, 45.40; H, 4.90; N, 15.13. Found: C, 45.33; H, 4.99; N, 14.86.

rel-(4S,10S)-2-Oxo-4-(3',4'-dimethoxyphenyl)-trans-quinolizidine (27) and rel-(4S,10R)-2-Oxo-4-(3',4'-dimethoxyphenyl)-cis-quinolizidine (29) -- A mixture of pelletierine 26 (154 mg, 1.1 mmol), veratraldehyde (274 mg, 1.65 mmol) and 1% aq. NaOH (2.2 g, 1.6 mmol) was stirred at 70°C for 12 h under an Ar atmosphere, acidified with K_2CO_3 and extracted with $CHCl_3$. The extract was washed with brine, dried over $MgSO_4$ and evaporated to give an oil, which, on chromatographic separation by elution with $CHCl_3$-MeOH (40:1), gave 116 mg (44%) of 27 as colorless crystals from the first crop and 50 mg (16%) of 29 as a yellow oil from the second one. 27: mp 78-80°C (lit.[12], mp 83-84°C), ms m/z 289 (M^+), ir ($CHCl_3$) 2830, 2780, 1710 cm^{-1}, ^{1}H-nmr ($CDCl_3$) δ 1.07-2.93 (m, 13H, CH_2 x 6, CH), 3.21 (dd, J=11Hz, 4Hz, 1H, CHAr), 3.87 (s, 3H, OCH_3), 3.89 (s, 3H, OCH_3), 6.84 (s, 2H, aromatic H), 6.93 (s, 1H, aromatic H). 29: ms m/z, 289 (M^+), ir($CDCl_3$) 1710 cm^{-1}, ^{1}H-nmr ($CDCl_3$) δ 1.03-3.08 (m, 1H, CH_2 x 6, CH), 3.88 (s, 6H, OCH_3), 4.21 (dd, J=6Hz, 4Hz, 1H, CHAr), 6.72 (s, 2H, aromatic H), 6.78 (s, 1H, aromatic H).

(±)-2-Epilasubine II (28) -- To a solution of 25 (110 mg, 0.38 mmol) in EtOH (2 ml) was added $NaBH_4$ (40 mg, 1.05 mmol). The reaction mixture was stirred at room temperature for 43 h and evaporated to a semisolid, which was extracted with $CHCl_3$. The extract was dried over $MgSO_4$ and evaporated to give an oily residue, which, on chromatographic separation by elution with $CHCl_3$-MeOH (40:1), gave an oil. This oil afforded a colorless powder from hexane. 92 mg (82.5%), mp 137-139°C (lit.[12], mp 141-142°C), exact ms calcd for $C_{17}H_{25}NO_3$ m/z 291.1833 (M^+), obsd m/z 291.1833, ir ($CHCl_3$) 3600, 3400, 2910, 2840, 2790 cm^{-1}, ^{1}H-Nmr ($CDCl_3$) δ 1.07-2.79 (m, 14H, CH_2 x 6, CH X 2), 2.89 (dd, J=11Hz, 3Hz, 1H, CHAr), 3,64 (br, 1H, OH), 3.84 (s, 3H, OCH_3), 3.86 (s, 3H, OCH_3), 6.79 (s, 2H, aromatic H), 6.91 (s, 1H, aromatic H). Anal. Calcd for $C_{17}H_{25}NO_3$: C, 70.07; H, 8.65; N, 4.81. Found: C, 69.81; H, 8.64; N, 4.46. By the above method, 28 was also obtained from 27 in 65.1% yield and found to be identical in all respect with the 28 above and an authentic sample.

Table II. Physical Properties of the Wittig Reaction Products

8 bp 135°C (2 mmHg), ms m/z 229 (M^+), ir (neat) 3350, 1720, 1660 cm^{-1}, ^{1}H-nmr ($CDCl_3$) δ 1.20 (t, J=7Hz, 3H, OCH_2CH_3), 1.28 (t, J=7Hz, 3H, OCH_2CH_3), 1.52-1.82 (m, 2H, $NHCH_2CH_2$), 2.05-2.38 (m, 2H, $CH_2CH=CH$), 3.15 (q, J=7Hz, 2H, $NHCH_2CH_2$), 4.15 (q, J=7Hz, 2H, OCH_2CH_3), 4.05 (q, J=7Hz, 2H, OCH_2CH_3), 4.77 (br, 1H, NH), 5.79 (dt, J=16.5Hz, 1.5Hz, 1H, $CH=CHCO$), 6.90 (dt, J=16.5Hz, 6Hz, 1H, $CH=CHCO$).

9 bp 120°C (2 mmHg), CI ms m/z 230 (M^++1), ir (neat) 3340, 1710, 1650 cm^{-1}, ^{1}H-nmr ($CDCl_3$) δ 1.30 (t, J=7.5Hz, 3H, OCH_2CH_3), 1.43-1.80 (m, 4H, CH_2 x 2), 2.03-2.47 (m, 2H, $CH_2CH=CH$), 2.97-3.37 (m, 2H, $NHCH_2$), 3.37 (s, 3H, OCH_3), 4.17 (q, J=7.5Hz, 2H, OCH_2CH_3), 4.76 (br, 1H, NH), 5.80 (dt, J=16.5Hz, 1Hz, $CH=CHCO$), 6.97 (dt, J=16.5Hz, 6Hz, 1H, $CH=CHCO$).

10 bp 137°C (2 mmHg), ms m/z 229 (M^+), ir (neat) 3340, 1720 cm^{-1}. ^{1}H-nmr ($CDCl_3$) δ 1.20 (t, J=7Hz, 3H, OCH_2CH_3), 1.25 (t, J=7Hz, 3H, OCH_2CH_3), 1.52-1.93 (m, 2H, $NHCH_2CH_2$), 2.65 (q, J=6Hz, 2H, $CH_2CH=CH$), 3.00-3.43 (m, 2H, $NHCH_2CH_2$), 4.05 (q, J=7Hz, 2H, OCH_2CH_3), 4.13 (q, J=7Hz, 2H, OCH_2CH_3), 5.17 (br, 1H, NH), 5.77 (d, J=12Hz, 1H, $CH=CHCO$), 6.17 (dt, J=12Hz, 6.5Hz, 1H, $CH=CHCO$).

11 bp 98°C (2 mmHg), ms m/z 229 (M^+), ir (neat) 1730, 1700 cm^{-1}, ^{1}H-nmr ($CDCl_3$) δ 0.58 (t, J=7Hz, 6H, CH_3CH_2 x 2), 1.57-2.02 (m, 4H, CH_2 x 2), 2.10-2.50 (m, 2H, CH_2CO), 3.2 (t, J=6Hz, CH_2N), 3.97-4.33 (m, 1H, $NCHCH_2$), 4.13 (q, J=7Hz, 4H, CH_3CH_2 x 2).

12 bp 125°C (2 mmHg), ms m/z 229 (M^+), ir (neat) 1730, 1700 cm^{-1}, ^{1}H-nmr ($CDCl_3$) δ 1.23 (t, J=7.5Hz, 3H, OCH_2CH_3), 1.39-1.79 (m, 6H, $CH_2CH_2CH_2$), 2.57 (d, J=7.5Hz, 2H, CH_2CO), 2.66-3.06 (m, 1H, HCHN), 3.68 (s, 3H, OCH_3), 4.10 (q, J=7.5Hz, 2H, OCH_2CH_3), 3.79-4.29 (m, 1H, HCHN), 4.56-4.89 (m, 1H, $NCHCH_2$).

14 oil, ms m/z 273 (M^+), ir (neat) 1680, 1610, 1570 cm^{-1}. ^{1}H-nmr ($CDCl_3$) δ 1.43-1.97 (m, 4H, CH_2 x 2), 2.27-2.37 (m, 2H, CH_2CO), 3.20-3.50 (m, 2H, NCH_2), 3.60 (s, 3H, OCH_3), 4.00-4.33 (m, 1H, $NCHCH_2$), 6.57 (d, J=17Hz, 1H, $COCH=CHPh$), 7.23-7.60 (m, 5H, aromatic H), 7.53 (d, J=17Hz, 1H, $COCH=CHPh$).

15 bp 121°C (2 mmHg), ms m/z 241 (M^+), ir (neat) 1740, 1700 cm^{-1}, ^{1}H-nmr ($CDCl_3$) δ 1.23 (t, J=7.5Hz, 3H, OCH_2CH_3), 1.31-2.11 (m, 4H, CH_2 x 2), 2,11-2.50 (m, 2H, CH_2CO), 3.28-3.54 (m, 2H, NCH_2), 3.95-4.37 (m, 1H, $NCHCH_2$), 4.13 (q, J=7.5Hz, 2H, OCH_2CH_3), 4.48-4.72 (m, 2H, $CH_2CH=CH_2$), 5.05-5.46 (m, 2H, $CH=CH_2$), 5.72-6.21 (m, 1H, $CH=CH_2$).

16 bp 137°C (3 mmHg), ms m/z 325 (M^+), ir (neat) 1740, 1700 cm^{-1}, ^{1}H-nmr ($CDCl_3$) δ 0.78 (d, J=7Hz, 3H, $CHCH_3$), 0.90 (d, J=7Hz, 6H, $CH(CH_3)_2$), 1.07-2.27 (m, 13H, CH_2 x 5, CH x 3), 2.27-2.53 (m, 2H, CH_2CO), 3.23-3.54 (m, 2H, NCH_2), 3.67 (s, 3H, OCH_3), 4.01-4.38 (m, 1H, $NCHCH_2$), 4.38-4.73 (m, CHOCO).

17 oil, ms m/z 309 (M^+), ir (neat) 1680 cm^{-1}, ^{1}H-nmr ($CDCl_3$) δ 0.78 (d, J=7Hz, 3H, $CHCH_3$), 0.90 (d, J=7Hz, 6H, $CHMe_2$), 1.08-2.25 (m, 13H, CH_2 x 5, CH x 3), 2.18 (s, 3H, $COCH_3$), 2.25-2.58 (m, 2H, $CHCH_2CO$), 3.22-3.48 (m, 2H, NCH_2), 4.00-4.33 (m, 1H, $NCHCH_2$), 4.43-4.73 (m, 1H, CHOCO).

(continued)

(continued)

18 bp 123-126°C (2 mmHg), ms m/z 199 (M^+), ir (neat) 1690 cm^{-1}, ^{1}H-nmr ($CDCl_3$) δ 1.10-1.77 (m, 6H, CH_2 x 3), 2.17 (s, 3H, $COCH_3$), 2.68 (d, J=7Hz, 2H, $CHCH_2CO$), 2.77-3.03 (m, 1H, HCHN), 3.65 (s, 3H, OCH_3), 3.80-4.13 (m, 1H, HCHN), 4.57-4.87 (m, 1H, CH_2CHN).

19 bp 110°C (2 mmHg), CI ms m/z 226 (M^++1), ir (neat) 1750, 1690, 1650 cm^{-1}, ^{1}H-nmr ($CDCl_3$) δ 1.20-1.83 (m, 6H, CH_2 x 3), 2.17 (s, 3H, $COCH_3$), 2.67 (d, J=8Hz, CH_2CO), 2.80-3.03 (m, 1H, HCHN), 3.87-4.17 (m, 1H, HCHN), 4.47-4.63 (m, 2H, $CH_2CH=CH_2$), 4.63-4.93 (m, 1H, $NCHCH_2$), 5.07-5.43 (m, 2H, $CH_2CH=CH_2$) 5.70-6.17 (m, 1H, $CH_2CH=CH_2$).

20 bp 110°C (2 mmHg), ms m/z 241 (M^+), ir (neat) 1750, 1690, 1650 cm^{-1}, ^{1}H-nmr ($CDCl_3$) δ 1.20-1.87 (m, 6H, CH_2 x 3), 2.58 (d, J=7Hz, 2H, $CHCH_2CO$), 2.67-3.07 (m, 1H, HCHN), 3.63 (s, 3H, OCH_3), 3.90-4.20 (m, 1H, HCHN), 4.50-4.65 (m, 2H, $OCH_2CH=$), 4.65-4.90 (m, 1H, $NCHCH_2$), 5.08-5.45 (m, 2H, $CH_2CH=CH_2$), 5.72-6.18 (m, 1H, $CH_2CH=CH_2$).

21 bp 124°C (0.2 mmHg), ms m/z 323 (M_+), ir (neat) 1690 cm^{-1}, ^{1}H-nmr ($CDCl_3$) δ 0.77 (d, J=7Hz, 3H, $CHCH_3$), 0.88 (d, J=7Hz, 6H, $CH(CH_3)_2$), 1.35-2.45 (m, 15H, CH_2 X 6, CH x 3), 2.17 (s, 3H, $COCH_3$), 2.65 (d, J=7.5Hz, 2H, CH_2CO), 2.75-3.28 (m, 1H, HCHN), 3.85-4.25 (m, 1H, HCHN), 4.38-4.91 (m, 2H, $NCHCH_2$, CHOCO).

22 mp 85-86°C, ms m/z 287 (M^+), ir (neat) 1690 cm^{-1}, ^{1}H-nmr ($CDCl_3$) δ 1.33-1.90 (m, 6H, CH_2 x 3), 2.70-3.13 (m, 1H, HCHN), 2.92 (d, J=7Hz, 2H, CH_2CO), 3.68 (s, 3H, OCH_3), 3.83-4.25 (m, 1H, HCHN), 4.67-5.00 (m, 1H, $NCHCH_2$), 6.75 (d, J=16Hz, $COCH=CHPh$), 7.33-8.63 (m, 5H, aromatic H), 8.02 (d, J=16Hz, $COCH=CHPh$).

Table III. Results of Elemental Analyses of the Wittig Reaction Products*

Compound	Molecular Formula	Calculated			Found		
		C	H	N	C	H	N
8	$C_{11}H_{19}NO_4$	57.62	8.35	6.11	57.34	8.52	6.16
9	$C_{11H19}NO_4$	57.62	8.35	6.11	57.76	8.58	6.21
10	$C_{11}H_{19}NO_4$	57.62	8.35	6.11	57.88	8.45	6.08
11	$C_{11}H_{19}NO_4$	57.62	8.35	6.11	57.84	8.49	6.12
12	$C_{11}H_{19}NO_4$	57.62	8.35	6.11	57.48	8.46	6.29
13	$C_{10}H_{17}NO_3$	60.28	8.60	7.03	60.03	8.79	7.04
15	$C_{12}H_{19}NO_4$	59.73	7.94	5.81	59.20	7.97	5.70
16	$C_{18}H_{13}NO_4$	66.43	9.60	4.30	66.43	9.85	4.37
18	$C_{10}H_{17}NO_3$	60.28	8.60	7.30	60.24	8.76	7.02
19	$C_{11}H_{19}NO_3$	63.97	8.50	6.22	63.11	8.47	6.39
20	$C_{12}H_{19}NO_4$	59.73	7.94	5.81	59.45	7.77	5.84
21	$C_{19}H_{33}NO_3$	70.55	10.41	4.33	69.70	10.41	4.30

* 14: Exact mass calcd for $C_{16}H_{19}NO_3$ m/z 273.1363 (M^+), obsd m/z 273.1357.
22: Exact mass calcd for $C_{17}H_{21}NO_3$ m/z 287.1519 (M^+), obsd m/z 287.1501

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