HETEROCYCLES, Vol. 60, No. 2, 2003, pp. 309 - 319
Received, 17th September, 2002, Accepted, 21st November, 2002, Published online, 9th December, 2002

CHEMISTRY OF INDOLES CARRYING A BASIC FUNCTION. PART VII.[1] A NEW ASPECT OF STOBBE REACTION

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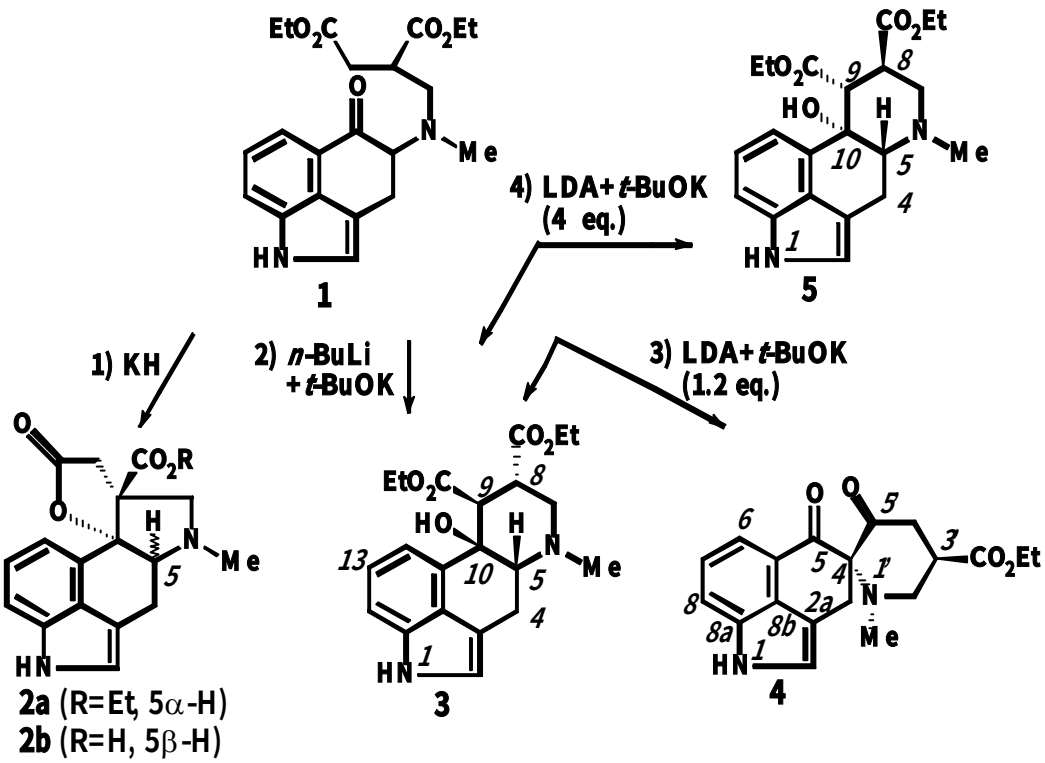
Abstract — While performing Stobbe reactions of a succinic diester derivative (**1**) different routes were found leading to different indole derivatives (**2**-**5**) depending on the reaction conditions applied, thus widening the scope and limitation of this useful procedure. Simpler pyrrolidine (**13**) and piperidine derivatives (**14**, **15**) were also achieved through application of the intramolecular Stobbe reaction.

The Stobbe condensation is well established and widely used reaction in synthetic organic chemistry,[2] leading to alkylidenesuccinic acids as a rule. Formation of an intermediary lactone ester is suggested, although very rarely isolated. While working on the synthesis of ergot alkaloids[3] we have found that, depending on the reaction conditions, particularly on the nature of the metal used, one can steer the Stobbe reaction in different directions.

Ketone (**1**) was allowed to react with potassium hydride in the presence of a crown ether, lactone isomers (**2**) were isolated as only products. Applying the so called "super base" (a mixture of *n*-BuLi solution and *t*-BuOK; Schlosser's procedure) the adduct (**3**) was obtained.[3] However, when using another superbase (LDA and *t*-BuOK) in slight excess (1.2 eq.) in THF at low temperature, in addition to adduct (**3**) the spiro diketone (**4**) representing a new heterocyclic ring system and formed through an internal Claisen condensation, was also isolated (yields, **3**: 18 %; **4**: 13 %). To our knowledge such keto ester formation has never been observed while performing a Stobbe condensation.



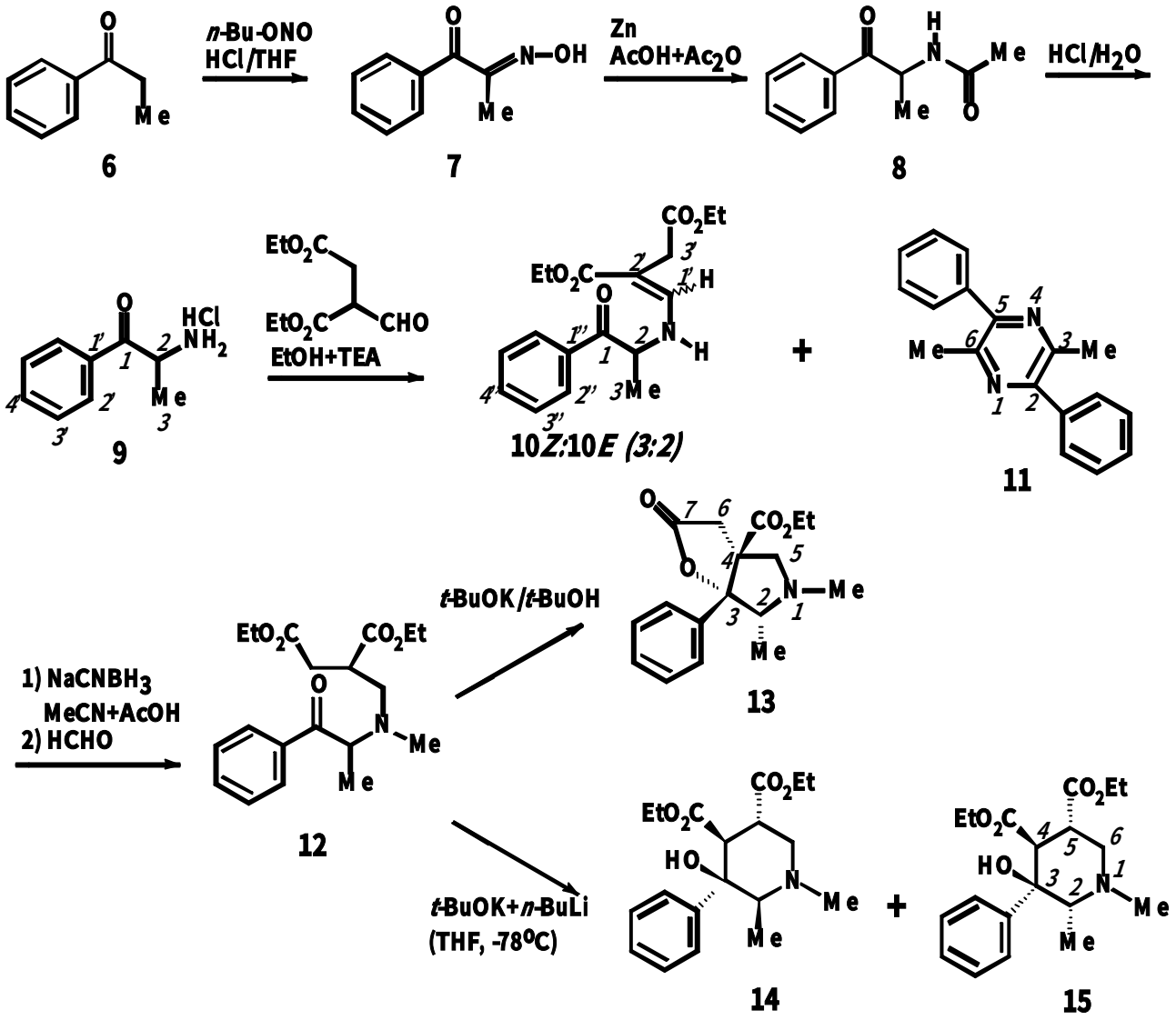
The fourth modification (LDA and *t*-BuOK, 4 eq.) afforded again **3** as a major product. *Trans*-isomer with ergoline ring (**5**) was also isolated as a minor component (yields, **3**: 21 %; **5**: 4.2 %).

The above investigations suggest that it may be possible to steer the Stobbe reaction; experiments aimed at finding the optimal conditions for making the reaction even more selective with a view to preparing lactones, spiro keto esters, hydroxy esters or unsaturated half-ester at will, are in progress in the field of the synthesis of ergoline derivatives.

Since the described reactions resulted in different products but the classical condensation product, we suggest using the phrase "*Stobbe reaction*" instead of "*Stobbe condensation*".

Looking through the literature of the last decade we were not able to find any examples a similar aldol-type cyclization by the intramolecular Stobbe reaction. (Nevertheless, a few examples for a further cyclization could be found where the carboxyl group of the half-ester participates in an intramolecular Friedel-Crafts acylation).[4] In connection with our attempt to extend our way to more simple products, we chose propiophenone as starting material (**6**) where the phenyl group is suitable for ring A of Uhle-ketone′s derivatives and the methyl group substitutes for ring C. Oxime (**7**)[5] was reduced and acylated in one step[6] yielding acetamide (**8**, yield: 86 %)[7] and **8** was transformed to hydrochloride salt of amino ketone derivative (**9,** yield: 54 %)[8] by hydrolysis.[9] Compound (**9**) was allowed to react with diethyl formylsuccinate in a condensation step (1 h, room temperature). After working up the reaction mixture, enamine (**10**, yield: 85%) was obtained as an isomeric mixture beside a minor product (**11**[10], 11**%**) forming in a self-condensation. (The ratio of **10Z** : **10E** proved to be about 3 : 2 determined by NMR

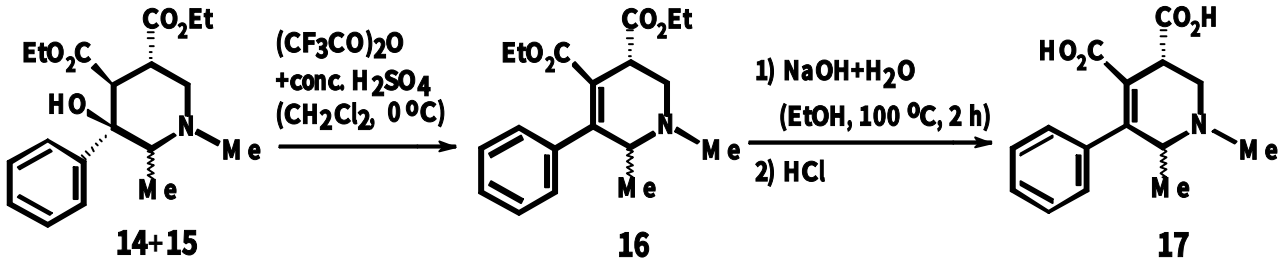
spectrum). In the next step enamine (**10**) was treated with $NaCNBH_3$ (acetonitrile + acetic acid, 5-10 ^oC, 0.5 h) and subsequently with aqueous formaldehyde (5-10 ^oC, 0.5 h). After a simple work up diethyl succinate derivative (**12**, yield: 75%) was isolated as diastereomeric mixture.



The intramolecular Stobbe reaction of keto diester (**12**) showed a similar tendency to tricyclic indole derivative (**1**). When the OK bond (*t*-BuOK/*t*-BuOH) forms in the initial step, pyrrolidine derivative with lactone ring (**13**, 20%) was isolated as the product. However, the formation of the OLi bond directs the ring closure towards six-membered piperidine derivatives. When **12** was allowed to react with superbase (*t*-BuOK+*n*-BuLi) hydroxy diesters (**14** and **15**; yield: 57 %) were obtained which could be separated by crystallization.

Hydroxy diester mixture (**14**, **15**) was appropriate for a model constructing the double bond of the ring D of ergolene derivatives. Although a successful dehydration in a similar case is reported using P_2O_5 +

$MeSO_3H$,[11] we were not able to obtain a conjugated diester starting from piperidine analogs (**14** + **15**) or our tetracyclic ergoline derivative (**1**) with this procedure. For this transformation trifluoroacetic anhydride + conc. sulfuric acid proved to be the only efficacious reagent in the case of the piperidine mixture (**14** + **15** → **16**, 50 %). In the next step diester (**16**) was hydrolysed into diacid (**17**, 85 %).



14+15 **16** **17**

The latter reactions serve as models for our efforts aiming at the synthesis of ergot alkaloids.

EXPERIMENTAL

Mps are uncorrected. MS spectra were run on an AEI-MS-902 (70 eV, direct insertion) and on a Kratos-MS-902 mass spectrometers. FAB-MS spectra were measured on a ZAB 2SEQ spectrometer. IR spectra were taken on a Nicolet 7795 FT-IR and on a Nicolet Magna 750 spectrophotometers. NMR measurements were carried out on a Varian Unity Inova (400 MHz for ^{1}H and 100 MHz for ^{13}C) and a Varian VXR-200 (200 MHz for ^{1}H and 50 MHz for ^{13}C) instruments. Chemical shifts are given relative to TMS=0.00 ppm.

(±)-5-Oxo-1,3,4,5-tetrahydrobenz[c,d]indole-4,6'-spiro[(1'-methyl-3'β-ethoxycarbonyl-5'-oxo)] piperidine (**4**)

To a solution of LDA (3.6 mmol) in THF (15 mL) *t*-BuOK (402 mg, 3.6 mmol) was added at -78 °C and the mixture was stirred for 15 min while the suspension turned into a yellow solution. To this solution compound (**1**) (1.15 g, 3.0 mmol) was added in THF (30 mL). The mixture was stirred for 30 min at the above temperature, then was allowed to warm up to -30 °C for 30 min. The mixture was treated with a mixture of acetic acid (1 mL) and THF (1 mL), then was evaporated under reduced pressure. The residue was dissolved in a mixture of chloroform (150 mL), water (25 mL) and 25% NH_4OH solution (2 mL). The phases were separated and the organic layer was washed with water (2x50 mL), dried (Na_2SO_4), filtered and evaporated *in vacuo*. The residue (1.05 g) was purified by column chromatography (eluent: CH_2Cl_2 - MeOH, 15/1, then hexane - ethyl acetate, 1/1) to afford **3** (212 mg, 18 %) and **4** (125 mg, 13 %, oil).

For the spectroscopic data of **3**, see: ref. 3.

Compound (**4**): IR (KBr): 3400, 1760, 1730, 1640, 1610 cm^{-1}. MS (*m/z*, %): 340.1431 (calcd: 340.1423, $C_{19}H_{20}N_2O_4$, 100, M^+), 295 (23.3), 253 (15.8), 225 (42.5), 169 (45.0), 130 (76.6). ^1H NMR (400 MHz, $CDCl_3$), δ : 1.25 (3H, t, *J*=7.1 Hz, CH_2CH_3), 2.28 (3H, s, NCH_3), 2.65 (1H, dd, *J*=16.9, 9.8 Hz, H-4'$_\beta$), 2.92 (1H, t, *J*=9.3 Hz, H-2'$_\beta$), 2.93 (1H, dd, *J*=16.9, 3.9 Hz, H-4'$_\alpha$), 3.02 (1H, m, *J*=9.8, 9.3, 8.0, 3.9 Hz, H-3'), 3.22 (1H, dd, *J*=16.7, 0.9 Hz, H-3$_\alpha$), 3.68 (1H, dd, *J*=16.7, 1.4 Hz, H-3$_\beta$), 3.50 (1H, dd, *J*=9.3, 8.0 Hz, H-2'$_\alpha$), 4.16 (2H, q, *J*=7.1 Hz, OCH_2), 7.12 (1H, m, *J*=1.6, 1.4, 0.9 Hz, H-2), 7.29 (1H, dd, *J*=7.7, 7.2 Hz, H-7), 7.55 (1H, dd, *J*=7.7, 0.5 Hz, H-8), 7.57 (1H, dd, *J*=7.2, 0.5 Hz, H-6), 8.31 (1H, d, *J*=1.6 Hz, N*H*); ^{13}C NMR (100 MHz, $CDCl_3$), δ : 14.18 (CH_2CH_3), 30.45 (C-3), 33.38 (C-4'), 36.17 (NCH_3), 43.90 (C-3'), 56.34 (C-2'), 60.70 (OCH_2), 74.77 (C-4), 108.62 (C-8b), 115.84 (C-6), 116.70 (C-8), 121.48 (C-2), 123.20 (C-7), 125.34 (C-5a), 131.64 (C-2a), 134.77 (C-8a), 172.23 (CO_2Et), 195.70 (C-5), 214.96 (C-5').

The spiro structure of **4** follows from the long-range heterocorrelations of the quaternary carbons C-4 and C-5'. In addition to the inter-ring connections with H-3 protons, C-4 showed long-range correlations with the NCH_3 and H4'$_\alpha$ protons. Similarly, C-5' gave heterocorrelations both with H3$_\alpha$ and H3$_\beta$ protons. The stereochemical assignment of the piperidyl ring is based on the characteristic NOE effects of the H-3 protons. Selective irradiation of the H-3$_\beta$ proton resulted in signal enhancement of the H-2'$_\beta$ resonance, while NOE effects was observed between H-3$_\alpha$ and NMe protons. The configuration of the C-3' chiral center as depicted in Scheme 1, is deduced from the characteristic coupling constants of the H-3' proton (9.8 and 9.3 Hz), which indicate the axial orientation of this proton.

(±)-8β,9α-Dicarboethoxy-10α-hydroxyergoline (5β-H) (**5**)

The "super base" was prepared from LDA (26 mmol/40 mL THF) and *t*-BuOK (26 mmol) as described above. To this reagent compound (**1**) (3.4 g, 6.0 mmol) was added in THF (100 mL) and was allowed to react according to the above procedure. The reaction mixture was decomposed with aqueous HCl (1N, 120 mL) and extracted with ethyl acetate (500 mL). The organic phase was extracted with water (2x200 mL). The pH of the combined aqueous phase was adjusted about 8-9 with concentrated aqueous ammonium hydroxide solution (3 mL) and extracted with chloroform (400 mL, 2x200 mL), dried (Na_2SO_4). The filtrate was evaporated under reduced pressure. The residue (2.0 g) was crystallized from ethyl acetate to yield **3** (495 mg, 15%).

The mother liquor was purified with column chromatography (Merck 9385, eluent: chloroform - hexane - ethyl acetate, 2/1.5/1.5). After the chromatography a further portion of **3** (194 mg, 5.8%) and the *trans*-isomer (**5**) (140 mg, 4.2%) was obtained.

Compound (**5**): mp 158-161 ^oC, IR (KBr): 3400, 3280, 1733, 1372, 1340, 1205, 1190, 1159 cm^{-1}. MS (*m/z*, %): 386.1829 (calcd: 386.1842, $C_{21}H_{26}N_2O_5$, 100, M^+), 368 (14.9), 341 (41), 313 (15), 295 (16.4),

267 (7.8), 240 (33.5), 221 (14.2). ^{1}H NMR (400 MHz, $CDCl_3$), δ: 1.28, 1.41 (2x3H, 2xt, *J*=7.1 Hz, CH_2CH_3), 2.41 (1H, dd, *J*=11.4, 4.5 Hz, H-5), 2.51 (3H, s, NCH_3), 2.57 (1H, dd, *J*=11.7, 11.6 Hz, H-7$_\beta$), 3.16 (1H, m, *J*=14.5, 11.4, 1.7 Hz, H-4$_\alpha$), 3.18 (1H, dd, *J*=11.7, 3.9 Hz, H-7$_\alpha$), 3.18 (1H, d, *J*=12.1 Hz, H-9), 3.23 (1H, dd, *J*=14.5, 4.5 Hz, H-4$_\beta$), 3.44 (1H, m, *J*=12.1, 11.6, 3.9 Hz, H-8), 4.12-4.48 (2x2H, m, 2xCH_2CH_3), 4.96 (1H, br s, O*H*), 6.84 (1H, dd, *J*=7.4, 0.7 Hz, H-12), 6.94 (1H, dd, *J*=1.7, 1.6 Hz, H-2), 7.07 (1H, dd, *J*=7.7, 7.4 Hz, H-13), 7.26 (1H, dd, *J*=7.7, 0.7 Hz, H-14), 8.12 (1H, br d, *J*=1.6 Hz, N*H*); ^{13}C NMR (100 MHz, $CDCl_3$), δ : 13.85, 14.07 (2xCH_2CH_3), 22.48 (C-4), 42.90 (NCH_3), 43.18 (C-8), 49.43 (C-9), 58.00 (C-7), 60.94, 61.63 (2CH_2CH_3), 68.51 (C-5), 70.54 (C-10), 110.48 (C-3), 110.97 (C-14), 112.83 (C-12), 118.44 (C-2), 122.20 (C-13), 125.59 (C-16), 133.20 (C-11), 134.25 (C-15), 172.25, 175.80 (2xCO_2Et).

The stereochemistry of the piperidyl ring followed from the NOE experiments. Irradiation of the OH resonance gave NOE enhancements on H-8 and H-4$_\alpha$ (axial) protons, while no NOE was observed on H-5. Moreover, NOE connection was found between H-5 and H-9$_\beta$ (axial) protons. These findings are in agreement with the *trans* junction of ring C and D. The value of the H-8 and H-9 coupling (12.1 Hz) reveals the *trans*-diaxial position of the protons, consequently the diequatorial relation of the carbethoxy groups.

N-(1-Methyl-2-oxo-2-phenylethyl)acetamide (**8**)

To a solution of **7** (20.7 g, 127 mmmol) in a mixture of acetic acid (96.2 mL, 1.68 mol) and acetic anhydride (36.6 mL, 388 mmol) at 0-5 °C, zinc dust (33.6 g, 0.52 mol) was added portionwise during about 1.5 h while the temperature was kept about 40 °C and the mixture was stirred intensively. The reaction mixture was stirred further for 0.5 h and the precipitated was filtered off. The filtrate was evaporated under reduced pressure. The residue was dissolved in a mixture of chloroform (300 mL) and water (200 mL). After separation of the phases, the organic layer was dried (Na_2SO_4) and evaporated. The residue was purified by chromatography (eluent: hexane - ethyl acetate, 1/1) to yield **8** (20.8 g, 86%) as a colourless oil. An analytical sample was crystallized from hexane, mp 89-90 °C [lit.,[7a] mp 90 °C].

2-Amino-1-phenylpropane-1-one hydrochloride (**9**)

Acetamide (**8**, 71 g, 0.37 mol) was dissolved in hydrochloric acid (1050 mL, 20%) and was refluxed for 4 h, then stirred at rt overnight. The reaction mixture was evaporated under reduced pressure and the residue was triturated with ether to result crystalline material. The precipitated crystals were filtered off, washed with ether and benzene to yield **9** (37.3 g, 54%), mp 120-122 °C [lit.,[8] mp 121-123 °C].

(±)-E/Z-N-(Propiophenone-2-yl)-2′,3′-diethoxycarbonyl-1′-propenylamine (**10**) and ***2,5-dimethyl-3,6-diphenyl-1,4-pyrazine*** (**11**)

To a solution of amino ketone hydrochloride salt (**9**, 5.5 g, 29.6 mmol) in EtOH (40 mL) diethyl formylsuccinate (6.5 mL, 32.0 mmol) and TEA (4.2 mL, 30.1 mmol) were added at rt. The reaction mixture was stirred for 1 h, then the solvents were evaporated under reduced pressure. The residue was dissolved in a mixture of chloroform (100 mL) and water (20 mL) and the pH was adjusted to 8-9 with saturated Na_2CO_3 solution. The phases were separated and the organic phase was washed with brine (20 mL), dried (Na_2SO_4) and evaporated. The residue was chromatographed (eluent: toluene - methanol, 10/1) to yield **11** as a minor product (0.85 g, 11%), mp 122-123 ^oC [lit.,[10b] mp 121-122 ^oC].

The substance eluted afterwards was the main product (**10**) (8.5 g, 85%) as an oil.

IR (KBr): 2980, 1735, 1686, 1636, 1373, 1218, 1188 cm^{-1}. MS (*m/z*, %): 333.1570 (calcd: 333.1576, $C_{18}H_{23}NO_5$, 8.3, M^+), 288 (5.8), 260 (16.6), 182 (70.8), 154 (58.3). ^1H NMR (400 MHz, $CDCl_3$), δ: 1.22, 1.28 (2x3H, t, *J*=7.0 Hz, 2xCH_2CH_3), 1.48 (3H, d, *J*=6.9 Hz, H-3), 3.02 (2H, br s, H-3′), 4.1-4.25 (2x2H, m, 2xCH_2CH_3), 4.88, 4.97 (1H, m, H-2), 5.93, 8.37 (1H, dd, *J*=13.1, 7.7 Hz, N*H*), 6.67, 7.50 (1H, d, *J*=13.1 Hz, H-1′), 7.35-7.90 (5H, m, H-aromatics); ^{13}C NMR (100 MHz, $CDCl_3$), δ: 14.12, 14.19, 14.37, 14.49 (2xCH_2CH_3), 20.70, 21.64 (C-3), 30.95, 35.83 (C-3′), 57.23, 57.31 (C-2), 59.22, 59.63, 60.38, 60.77 (2xCH_2CH_3), 90.13, 93.46 (C-2′), 128.44, 128.84, 133.17, 133.94 (C-2″, C-3″, C-4″, C-5″, C-6″), 133.75, 134.20 (C-1″), 146.03, 149.30 (C-1′), 168.37, 169.13, 171.86, 173.18 (2xCO_2Et), 198.05, 198.32 (C-1).

(±)-N-(Propiophenone-2-yl)-2′,3′-diethoxycarbonyl-1′-propylamine (**12**)

To a cold (5-10 ^oC) solution of enamine (**10**, 7.5g, 22.46 mmol) in acetonitrile (580 mL) acetic acid (90 mL) was added. The whole was stirred for 10 min then $NaCNBH_3$ (5.63 g, 89.5 mmol) was added in portionwise (10-15 min). The reaction mixture was stirred for 20 min at the above temperature The mixture was treated with formaldehyde (136 mL, 37% solution in water) and stirred further for 30 min. The mixture was diluted with water (390 mL) and chloroform (1.5 L). The pH was adjusted to 8-9 with with saturated $NaHCO_3$ solution (1.24 L). The phases were separated and the aqueous phase was extracted with chloroform (200 mL). The combined organic phase was washed with water (200 mL) and brine (200 mL), dried (Na_2SO_4) and evaporated. The residue was chromatographed (eluent: hexane - ethyl acetate 8/2) to give **12** (5.6 g, 75%) as a colourless oil.

IR (KBr): 2982, 1734, 1687, 1449, 1372, 1229, 1178, 1103, 1031 cm^{-1}. MS (*m/z*, %): 260 (4.1), 228 (17.4), 170 (18.3), 154 (13.3), 128 (48.3), 105 (100). ^1H NMR (diastereomers, 400 MHz, $CDCl_3$), δ: 1.14, 1.26 (2x3H, 2xt, *J*=7.0 Hz, CH_2CH_3), 1.25 (3H, d, *J*=6.9 Hz, H-3), 2.28, 2.30 (3H, s, NCH_3), 2.38, 2.46

(2H, dd, *J*=16.6, 5.0 Hz, H-3′), 2.48-2.90 (2H, m, H-1′), 2.86-2.98 (1H, m, H-2′), 3.91-4.07 (1H, m, H-2), 4.05-4.29 (2x2H, m, 2xCH_2CH_3), 7.40-8.0 (5H, m, H-aromatics); ^{13}C NMR (100 MHz, $CDCl_3$), δ: 9.12, 9.94 (C-3), 14.02, 14.09 (2xCH_2CH_3), 34.16 (C-3′), 37.43, 37.77 (NCH_3), 40.54, 40.60 (C-2′), 55.11, 55.50 (C-1′), 60.49, 60.54 (2xCH_2CH_3), 63.28, 63.40 (C-2), 128.30, 128.72 (C-2″, C-3″, C-5″, C-6″), 132.74, 132.77 (C-4″), 136.40, 136.45 (C-1″), 171.89, 171.90, 173.71, 174.03 (2xCO_2Et), 200.29, 200.35 (C-1). Anal. Calcd for $C_{19}H_{27}NO_5$: C, 65.30, H, 7.78, N, 4.00. Found: C, 65.36, H, 7.72, N, 4.06.

(±)-1,2α-Dimethyl-3β-phenyl-4β-ethoxycarbonylpyrrolidine-3α,4α-butyrolactone (**13**)

To a solution of **12** (700 mg, 2.0 mmol) in *t*-BuOH (4 mL) at rt, *t*-BuOK (340 mg, 3.0 mmol) was added, and the mixture was stirred for 1 h. The reaction mixture was poured to a mixture of chloroform (75 mL), water (25 mL) and aqueous HCl solution (1N, 3 mL). After extraction the phases were separated and the organic phase was washed with water (2x20 mL), dried (Na_2SO_4). The residue (0.5 g) was chromatographed (eluent: toluene - MeOH, 10/1) to give **13** (120 mg, 20%) as an oil. An analytical samples was crystallized from ether, mp 90-91 ^{o}C.

IR (KBr): 1780, 0760, 1700 cm^{-1}. ^{1}H NMR (400 MHz, C_6D_6), δ: 0.88 (3H, d, *J*=6.4 Hz, CH_3), 1.41 (3H, t, *J*=7.1 Hz, CH_2CH_3), 2.00 (3H, s, NCH_3), 2.42 (1H, q, *J*=6.4 Hz, H-2), 2.49 (1H, d, *J*=17.9 Hz, H-6$_\alpha$), 3.04 (1H, d, *J*=10.0 Hz, H-5$_\beta$), 3.24 (1H, d, *J*=17.9 Hz, H-6$_\beta$), 3.37 (2H, q, *J*=7.1 Hz, CH_2CH_3), 6.95-7.35 (5H, m, H-aromatics); ^{13}C NMR (100 MHz, $CDCl_3$), δ: 11.90 (CH_3), 13.29 (CH_2CH_3), 39.30 (NCH_3), 40.71 (C-6), 59.00 (C-4), 61.44 (CH_2CH_3), 65.61 (C-5), 71.60 (C-2), 97.48 (C-3), 125.50, 127.15 (C-2′, C-3′, C-5′, C-6′), 128.15 (C-4′), 137.73 (C-1′), 170.71 (C-7), 174.65 (CO_2Et). Anal. Calcd for $C_{17}H_{21}NO_4$: C, 67.30, H, 6.97, N, 4.61. Found: C, 67.41, H, 6.91, N, 4.66.

The stereochemistry of the ring junction follows from the NOE effect between H-5$_\beta$ and the aromatic protons. Further NOEs between C-2 methyl group and H-7$_\alpha$ and between H-2 and the aromatic protons also corroborate the stereochemical assignment of compound (**13**).

(±)-1,2β-Dimethyl-3β-hydroxy-3α-phenyl-4β,5α-diethoxycarbonylpiperidine (**14**)

and ***(±)-1,2α-dimethyl-3β-hydroxy-3α-phenyl-4β,5α-diethoxycarbonylpiperidine*** (**15**)

The "super base" was prepared from *t*-BuOK (1.44 g, 12.85 mmol) and *n*-BuLi solution (8.1 mL, 12.9 mmol) in THF (30 mL) at -78 ^{o}C. To this reagent compound (**12**) (3.0 g, 8.58 mmol) in THF (15 mL) was dropped (5 min) and the mixture was stirred for 20 min. The pH of the mixture was adjusted to about 6 with HCl/dioxane (6N) and evaporated. The residue was dissolved in a mixture of chloroform (250 mL) and water (50 mL). After extraction, the organic phase was washed with water (50 mL), dried (Na_2SO_4). The filtrate was evaporated under reduced pressure. The residue (2.9 g) was chromatographed (eluent:

chloroform - MeOH, 300/5) to give **14** and **15** as a diastereomeric mixture (oil, 1.71g, 57%). MS (*m/z*, %): 349.1886 (calcd: 349.1889, $C_{19}H_{27}NO_5$, 3.3, M^+), 304 (17.5), 157 (100). To separate of isomers for a correct structure elucidation, the mixture was crystallized (hexane - ethyl acetate, 8/2) to yield **15** (192 mg). The mother liquor was evaporated and triturated with hexane to yield **14** (233 mg).

Compound (**14**): mp 82-83 ^oC, IR (KBr): 3350, 1710, 1700 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$), δ: 0.70 (3H, t, *J*=7.1 Hz, CH_2CH_3), 0.79 (3H, d, *J*=6.8 Hz, CH_3), 1.23 (3H, t, *J*=7.1 Hz, CH_2CH_3), 2.38 (3H, s, NCH_3), 2.40 (1H, q, *J*=6.8 Hz, H-2), 2.42 (1H, overlapped, H-6$_\alpha$), 3.04 (1H, d, *J*=12.1 Hz, H-4), 3.29 (1H, dd, *J*=11.6, 4.5 Hz, H-6$_\beta$), 3.45 (1H, m, *J*=12.1, 12.0, 4.5 Hz, H-5), 3.65-3.81 (2H, m, CH_2CH_3), 3.74 (1H, br s, OH), 4.05-4.17 (2H, m, CH_2CH_3), 7.2-7.6 (5H, m, H-aromatics); ^{13}C NMR (100 MHz, $CDCl_3$), δ: 13.00 (CH_3), 13.38, 14.04 (2xCH_2CH_3), 41.19 (C-5), 42.60 (NCH_3), 53.97 (C-4), 57.46 (C-6), 60.20, 60.97 (2xCH_2CH_3), 66.71 (C-2), 75.32 (C-3), 124.95, 126.95, 126.92, 127.91 (C-aromatics), 142.54 (C-1′), 172.22, 172.31 (2xCO_2Et).

Compound (**15**): mp 110-112 ^oC, IR (KBr): 3380, 1700 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$), δ: 0.82 (3H, d, *J*=6.8 Hz, CH_3), 0.89 (3H, t, *J*=7.1 Hz, CH_2CH_3), 1.26 (3H, t, *J*=7.1 Hz, CH_2CH_3), 2.39 (3H, s, NCH_3), 2.61 (1H, m, H-6$_\alpha$), 2.69 (1H, q, *J*=6.9 Hz, H-2), 2.89 (1H, m, H-6$_\beta$), 3.49 (1H, overlapped, H-5), 3.51 (1H, overlapped, H-4), 3.80-4.21 (2x2H, m, CH_2CH_3), 4.62 (1H, br s, OH), 7.2-7.61 (5H, m, H-aromatics); ^{13}C NMR (100 MHz, $CDCl_3$), δ: 4.50 (CH_3), 13.57, 14.08 (2xCH_2CH_3), 41.58 (C-5), 42.55 (NCH_3), 44.08 (C-4), 47.05 (C-6), 60.41, 60.91 (2xCH_2CH_3), 65.42 (C-2), 75.81 (C-3), 127.02, 127.16, 127.31 (C-aromatics), 141.85 (C-1′), 172.36, 172.79 (2xCO_2Et).

The sterical arrangement of the substituents on the piperidine ring was determined on the basis of NOE experiments. Irradiation of the H-5 proton in **14** resulted in enhancement of H-6$_\beta$ and OH protons, while NOE connectivity was also found between H-4, H-2 and H-6$_\alpha$ protons. On the contrary, in compound (**15**) the irradiation of C-2 methyl group resonance gave NOE effects on H-4 and H-6$_\alpha$ protons. These observations suggest that the stereochemistry of the C-2 methyl group is α (axial) in **15**, while β (equatorial) in **14**. ^{13}C chemical shifts corroborate this assignment. A comparison of the spectra of the isomers reveals that the ^{13}C shifts of C-4, C-6 and C-2 methyl group are of 8.5-10.4 ppm smaller value in **15**, which is the consequence of the γ-gauche effects of the axial C-2 methyl group.

(±)-3,4-Dehydro-1,2-dimethyl-3-phenyl-4-ethoxycarbonyl-5-carboxypiperidine (**16**)

To a solution of hydroxy diester (**14** + **15**, 1.077g, 3.0 mmol) in CH_2Cl_2 (20 mL) at 0 ^oC trifluoroacetic anhydride (11 mL, 78.0 mmol), then conc. H_2SO_4 (96 %, 617 mg, 6.3 mmol) was added and the mixture was stirred for 15 min. While stirring and cooling aqueous NaOH solution (20 %, 36 mL) was added to the reaction mixture. The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (2x20

mL). The combined organic phase was washed with water (10 mL), brine (10 mL) and dried (Na_2SO_4). The filtrate was evaporated under reduced pressure and the residue was chromatographed (eluent: hexane - ethyl acetate, 1/1, then toluene - methanol, 10/1) to yield **16** (508 mg, 50 %) as an oil.

IR (KBr): 1720, 1700 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$), δ: 0.79, 0.85, 1.23, 1.28 (2x3H, t, *J*=7.1 Hz, 2xCH_2CH_3), 0.89, 1.11 (3H, d, *J*=6.7 Hz, CH_3), 2.43 (3H, s, NCH_3), 2.90-3.20 (2H, m, H-6), 3.15, 3.57 (1H, q, *J*=6.7 Hz, H-2), 3.68-3.74 (1H, m, H-5), 3.86-4.23 (2x2H, m, CH_2CH_3), 7.12-7.38 (5H, m, H-aromatics); ^{13}C NMR (100 MHz, $CDCl_3$), δ: 12.37, 16.52 (CH_3), 13.60, 13.71, 14.18, 14.40 (2xCH_2CH_3), 41.59, 42.60 (C-5), 42.72, 43.17 (NCH_3), 47.65, 50.98 (C-6), 60.27, 63.12 (C-2), 60.84, 61.53, 61.79, 62.14 (2xCH_2CH_3), 123.82, 124.80 (C-4), 126.22-128.71 (C-aromatics), 141.17, 141.24 (C-1′), 151.17, 153.48 (C-3), 167.44, 169.49, 173.26, 173.70 (2xCO_2Et). Anal. Calcd for $C_{19}H_{25}NO_4$: C, 68.86, H, 7.60, N, 4.22. Found: C, 68.95, H, 7.54, N, 4.17.

(±)-3,4-Dehydro-1,2-dimethyl-3-phenyl-4, 5-dicarboxypiperidine (**17**)

To a solution of **16** (425 mg, 1.28 mmol) in EtOH (10 mL) sodium hydroxide (1.4 g, 35.0 mmol) in water (5 mL) was added and the reaction mixture was stirred at 100 °C for 2 h. After cooling at rt, the pH of the mixture was adjusted to 2-3 with aqueous HCl solution (10 %). The mixture was evaporated under reduced pressure and the residue was chromatographed (eluent: EtOH - conc. NH_4OH, 5/1). The combined fractions were evaporated to dryness. The trace of water was removed with ethanol and diester (**17**, 300, 85 %) was isolated as crystals, mp 230-250 (decomp).

IR (KBr): 3400, 1580 cm^{-1}. FAB-MS (*m/z*, %): 276.1238 (calcd: 276.1236, $C_{15}H_{18}NO_4$, 100, M). ^1H NMR (400 MHz, DMSO-d_6), δ: 0.94 (3H, d, *J*=6.7 Hz, CH_3), 2.49 (3H, s, NCH_3), 3.07 (1H, dd, *J*=12.1, 4.5 Hz, H-6_A), 3.22 (1H, dd, *J*=12.1, 1.1 Hz, H-6_B), 3.28 (1H, dd, *J*=4.5, 1.1 Hz, H-5), 3.78 (1H, q, *J*=6.7 Hz, H-2), 7.1-7.3 (5H, m, H-aromatics).

ACKNOWLEDGEMENTS

The authors wish to thank *Dr. Á. Gömöry* for MS and *Dr. O. Egyed* for IR spectra. Support for this research under grant No. T 031753 from *National Scientific Research Foundation* (OTKA) is gratefully acknowledged.

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