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Synthesis of ajmalicine derivatives using Wittig–Horner and Knoevenagel reactions

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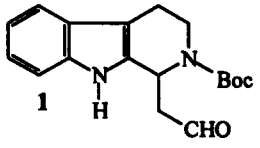
Abstract

2-(2,3,4,9-Tetrahydro-1*H*-β-carbolin-1-yl)acetaldehyde, synthesized from tryptamine in five steps, is easily homologated by Wittig–Horner or Knoevenagel reactions to substituted acrylates. These highly reactive compounds are key intermediates in the synthesis of analogs of the natural indol alkaloid ajmalicine.

Keywords: indolomonoterpenic alkaloids; ajmalicine; Knoevenagel reaction; Wittig–Horner reaction.

Heteroyohimbine indole alkaloids are synthetic targets for which various strategies were explored in order to build their five rings system. In the first stereoselective synthesis of ajmalicine,[1] an acrylate was used as a key intermediate and was prepared by means of reductive desulfenylation of a functionalized dithioacetal ester. However, substituted acrylates cannot be prepared by the same route.[2]

The search for a more flexible approach was undertaken in the framework of a project related to the synthesis of ajmalicine analogs. The aldehyde **1** has proved to be a useful starting material in the synthesis of various acrylates that were used in the synthesis of ajmalicine analogs. The aldehyde **1** is easily obtained in 41% yield from tryptamine. The Boc protecting group is stable under the basic reaction medium required for homologation reactions and can be cleanly removed.



The imine formed by tryptamine and benzaldehyde is reduced by $NaBH_4$ in MeOH to produce N_b-benzyl tryptamine **2**. Its condensation with methyl propiolate followed by acid catalyzed Pictet–Spengler cyclization yields the tetrahydro-β-carboline ester **3** in 90% yield.[3] Catalytic debenzylation of **3**, protec-

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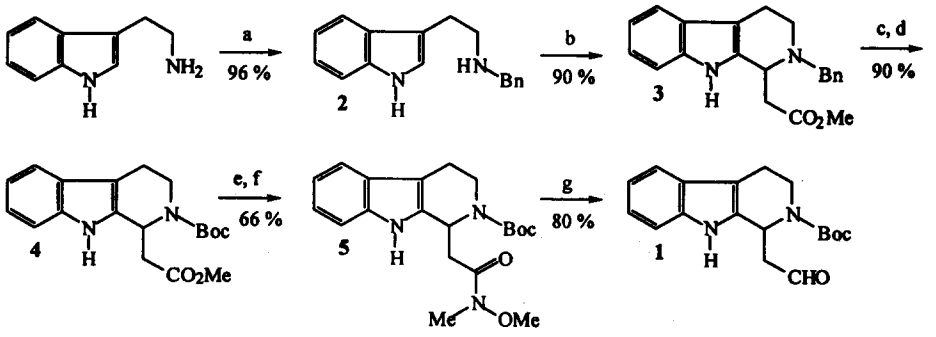
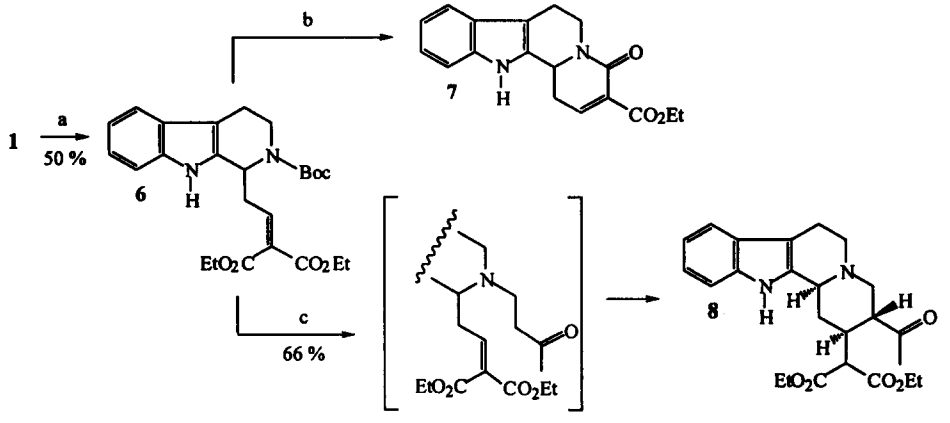
tion of the amine by a Boc group, conversion of the ester into *N*-methoxy-*N*-methylamide **5** and reduction of the latter yields aldehyde **1** as a stable solid (Scheme 1).[4]



Scheme 1. (a) C_6H_5CHO, toluene, then $NaBH_4$, MeOH; (b) $HC{\equiv}CCO_2Me$, MeOH, then CF_3CO_2H, CH_2Cl_2; (c) H_2 (1.1 bar), Pd/C, AcOH; (d) $(Boc)_2O$, CH_2Cl_2; (e) NaOH, water/acetone, then HCl; (f) HN(OMe)Me, HCl, DCC, NEt_3; (g) $LiAlH_4$, THF, 0°C

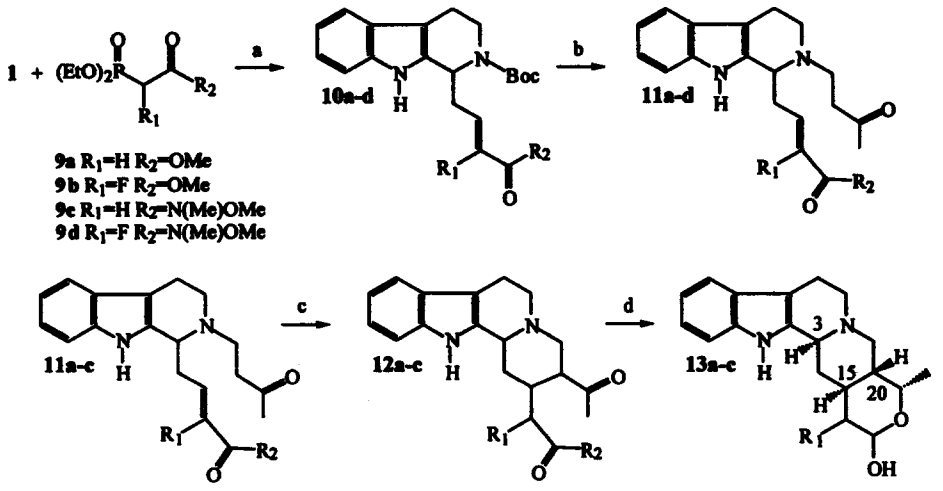
The importance of **1** in the synthesis of ajmalicine analogs was demonstrated by the preparation of several key compounds by means of Knoevenagel or Wittig–Horner reactions. Thus, treatment of aldehyde **1** with ethyl malonate in the presence of piperidine afforded the diester acrylate **6** as the major product. Removal of the Boc group by acid trifluoroacetic acid (TFA) affords the ester lactam **7** (Scheme 2). It is worth noting that analogs of lactam **7** were used by D'Angelo as key intermediates in the synthesis of *corynanthe* and *yohimbe* alkaloids.[5] Deprotection followed by in situ addition of methylvinyl ketone (MVK) exclusively gives the tetracyclic compound **8** with no trace of the uncyclized intermediate detected.



Scheme 2. (a) $H_2C(CO_2Et)_2$, piperidine, EtOH, reflux; (b) TFA, CH_2Cl_2; (c) TFA, CH_2Cl_2, then MVK

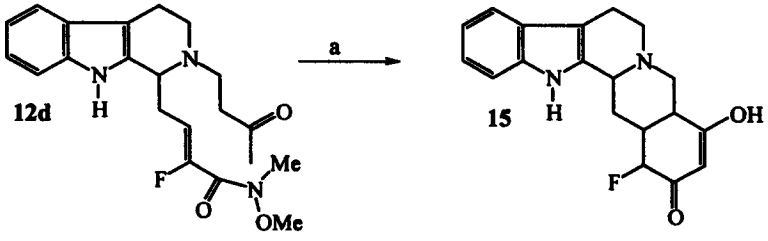
The tetracyclic diester **8** constitutes an important intermediate towards the synthesis of ajmalicine. The cyclization reaction is catalyzed by TFA and affords only one stereoisomer. A complete 1D and 2D homo- and heteronuclear NMR study of **8** shows that H-3, H-15 and H-20 are axial to the ring system. The homologation of **1** to other acrylates was also investigated by reacting it with different Wittig–Horner reagents **9a–d** in the presence of butyllithium as a base (Scheme 3).[6]

Acrylates **10a–c** can be further elaborated in three steps to the pentacyclic compounds **13a–c**. Removal of the Boc group and reaction with MVK affords the ketones **11a–c**. Their cyclization in the presence of pyrrolidine yields the tetracyclic compounds **12a–c** with a relative stereochemistry 3αH, 15αH, 20βH



Scheme 3. (a) BuLi, THF, –78°C; (b) TFA, CH_2Cl_2, then MVK, MeOH; (c) pyrrolidine, THF; (d) $NaBH_4$, MeOH, then diisoamylborane for **12a** and **12b** or $LiAlH_4$, THF, 0°C for **12c**

deduced from NMR spectral analysis. The conversion of **12a** into ajmalicine is already described.[2] The reduction of **12c** by $LiAlH_4$ in THF gives directly the naturally occurring ajmalicinial, **13c**.[7] The unnatural 16-fluoro ajmalicinial **13b** was obtained from **12b** in two steps: reduction of the ketone by $NaBH_4$ to the corresponding lactone and reduction of the latter by diisoamylborane in THF.[8] When **11d** was subjected to cyclization conditions, the ketoenol **14** was obtained as the single product (Scheme 4). The tetracyclic ketone obtained after cyclization is not observed. Its enol form undegoes a *C*-acylation reaction with elimination of the *N*-methoxy-*N*-methylamino group.[1,9]



Scheme 4. (a) Pyrrolidine, THF

In conclusion, the efficient synthesis of 2-(2,3,4,9-tetrahydro-1*H*-β-carbolin-1-yl)acetaldehyde **1** and its easy homologation to activated acrylates opens a new and useful route to ajmalicine analogs.

Synthesis of **4** from **3**:[3] To a solution of **3** (10 g, 29.9 mmol) in acetic acid (30 mL) 0.2 g of 10% palladium on charcoal was added in small portions. The solution was stirred under H_2 atmosphere (1.1 bar) for 15 h, filtered on Celite. Most of the acetic acid was removed under reduced pressure. The crude material was treated with $NaHCO_3$ and extracted with CH_2Cl_2 to give 6.8 g of pure free amine. To an amine solution in CH_2Cl_2 (100 mL) di-*t*-butyldicarbonate (6.5 g, 30 mmol) was slowly added. After stirring at room temperature for 30 min, 2N HCl (50 mL) was added. Extraction with CH_2Cl_2, drying and evaporation afforded pure **4**.

N-Methoxy-*N*-methylamide **5**: Ester **4** (15 g, 43.6 mmol) in acetone (50 mL) was treated with 35% sodium hydroxide (30 mL) for 3 h. The acetone was evaporated and the residue was dissolved in $CHCl_3$, treated with 2N HCl (until pH 4). The $CHCl_3$ layer was separated and evaporation of the solvent gave the acid, purified by crystallization in ether (mp 132°C). To the acid (10 g, 30.3 mmol) in CH_2Cl_2 (25

mL) *N*-methoxy-*N*-methylhyamine hydrochloride (4.3 g, 45.4 mmol) and DCC (6.2 g, 30.3 mmol) were added. After 5 min stirring, NEt_3 (4 mL, 30.3 mmol) was added and the solution was further stirred at room temperature for 30 min. The solvent was evaporated and acetone was added. The precipitate of dicyclohexylurea was filtered off and the acetone was evaporated. The crude residue was dissolved in CH_2Cl_2, washed with 2N HCl and concentrated to give the amide **5**, crystallized in ether (mp 129°C).

Aldehyde **1**: Amide **5** (2.5 g, 6.7 mmol) was cooled under nitrogen to 0°C. $LiAlH_4$ (1 M in THF, 4 mL) was added dropwise. After 30 min of stirring, the solution was hydrolyzed, extracted with ether, dried ($MgSO_4$) and evaporated to afford white crystals of **1**.

Compound **1**: mp 182°C (ether); MS (EI, 70 eV) m/e 314 ($M^{+\cdot}$, 15), 257 (25), 215 (25), 171 (100), 156 (80), 144 (85), 130 (30). IR ($CHCl_3$, cm^{-1}) 3400, 3300, 2900, 1720, 1400, 1160; ^1H NMR (300 MHz, $CDCl_3$) δ 9.8 (s, 1H), 8.5 (br s, 1H), 7.5 (d, *J*=7.2 Hz, 1H), 7.3 (d, *J*=7.2 Hz, 1H), 7.15 (t, *J*=7.2 Hz, 1H), 7.0 (t, *J*=7.2 Hz, 1H), 5.7 (br s, 1H), 4.4 (br s, 1H), 3.0 (d, *J*=6 Hz, 2H), 2.8 (dt, J_1=4 Hz, J_2=10 Hz, 2H), 2.5 (dd, J_1=4 Hz, J_2=10 Hz, H-5), 1.5 (br s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.3 (C-15), 160.2 (CO-C(CH_3)$_3$), 136 (C-13), 133 (C-2), 126.5 (C-8), 121.9 (C-11), 119.4 (C-10), 118 (C-9), 111 (C-12), 105 (C-7), 81 (C(CH_3)$_3$), 49 (C-3), 46.5 (C-5), 34 (C-14), 28.3 (C(CH_3)$_3$), 21.2 (C-6).

Compound **8**: MS (EI, 70 eV) m/e 427 (M+1, 8), 426 ($M^{+\cdot}$, 47), 383 (8), 267 (70), 184 (58), 170 (55), 115 (100); IR ($CHCl_3$, cm^{-1}) 3300, 3000, 2890, 1620, 1430, 1380, 1180; ^1H NMR (300 MHz, $CDCl_3$) δ 7.8 (br s, 1H), 7.4 (d, *J*=7.2 Hz, 1H), 7.3 (d, *J*=7.2 Hz, 1H), 7.15 (t, *J*=7.2 Hz, 1H), 7.10 (t, *J*=7.2 Hz, 1H), 4.3 (q, *J*=6 Hz, 2H), 4.20 (q, *J*=6 Hz, 2H), 4.15 (t, *J*=12.5 Hz, 1H), 3.95 (m, 1H), 3.5 (dd, J_1=2 Hz, J_2=14 Hz, 1H), 3.10 (td, J_1=5 Hz, J_2=12.5 Hz, 1H), 2.85 (m, 1H), 2.8 (m, 1H), 2.7 (dd, J_1=4 Hz, J_2=14 Hz, 1H), 2.65 (br d, *J*=13.6 Hz, 1H), 2.5 (m, 1H), 2.3 (s, 3H), 2.0 (q, *J*=12.5 Hz, 2H), 1.35 (t, *J*=6 Hz, 3H), 1.30 (t, *J*=6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 208.0 (C-19), 169 (CO_2Et), 168.7 (CO_2Et), 136.0 (C-13), 134.2 (C-2), 127 (C-8), 121.4 (C-11), 119.4 (C-10), 118 (C-9), 110.8 (C-12), 108.2 (C-7), 61.5 ($CO_2CH_2CH_3$), 61.3 ($CO_2CH_2CH_3$), 60.0 (C-3), 57.8 (C-21), 54.0 (C-5), 53.2 (C-16), 48.8 (C-20), 38.0 (C-14), 30.2 (C-15), 28.8 (C-18), 21.8 (C-6), 14.0 (2×$CO_2CH_2CH_3$).

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