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cis-Fused hexahydro-4a*H*-indeno[1,2-*b*]pyridines: transformation of bridgehead ester group and conversion to tricyclic analogues of NK-1 and dopamine receptor ligands

Tom De Wit, Kristof Van Emelen,† Faye Maertens, Georges J. Hoornaert and Frans Compernolle*

Laboratorium voor Organische Synthese, Department of Chemistry, K. U. Leuven, Celestijnenlaan 200F, 3001 Leuven (Heverlee), Belgium

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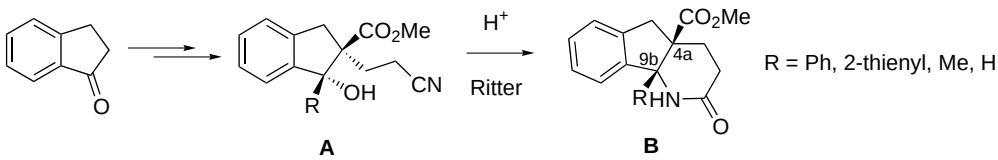
Abstract—The bridgehead ester group of *cis*-fused methyl 2-oxo-9b-phenyl-1,2,3,4,5,9b-hexahydro–4a*H*-indeno[1,2-*b*]pyridine-4a-carboxylates obtained via an intramolecular Ritter reaction, was transformed into acid, alcohol, aldehyde, and amine groups. Further elaboration afforded conformationally constrained tricyclic analogues of NK-1 antagonists and a bicyclic dopamine receptor ligand. © 2001 Elsevier Science Ltd. All rights reserved.

Recently, the intramolecular Ritter reaction of indanols of type **A** was shown to provide tricyclic piperidinones of type **B** substituted at both bridgehead positions 4a and 9b (Scheme 1). Various R-groups introduced via nucleophilic addition to the carbonyl group, e.g. Ph, thienyl, Me, and H, are tolerated in the crucial acid-catalyzed cyclization step, resulting in the desired structural variation at the 9b-position.[1]

We conceived compounds **B** as precursors for the construction of conformationally constrained analogues of bioactive molecules containing various arylalkyl-(di)amine pharmacophoric units. For instance, transforming the ester group into a complex benzylamino or benzyloxy substituent, e.g. a 2-methoxybenzylamino group, was envisioned as a key-step for the generation of constrained analogues of existing non-peptide NK-1 antagonists.[2,3] Thus, in target molecules of type **C** (Fig. 1, Y = NH), the diamine substructure $Ar_2C(NHR)$-C(NHR) is incorporated into the framework of the tricyclic ring system and the 4a, 9b bridgehead substituents. In this context it should be noticed that not only a C_2, but also a C_3 interconnection (Y = CONH, CH_2O) between the two heteroatoms is of



Scheme 1.

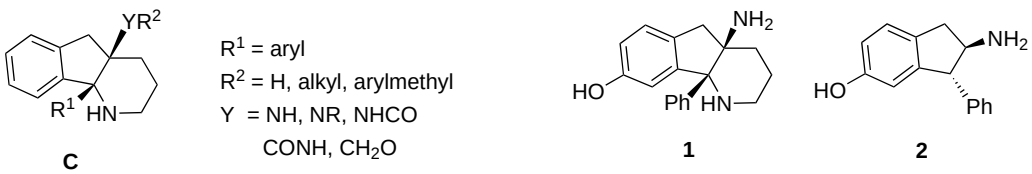


Figure 1.

Keywords: piperidinones; diamines; Curtius reaction; aldehydes.

* Corresponding author. Tel.: +32-16-327407; fax: +32-16-327990; e-mail: frans.compernolle@chem.kuleuven.ac.bem

† Current address: Janssen Research Foundation, Turnhoutseweg 30, 2340 Beerse, Belgium.

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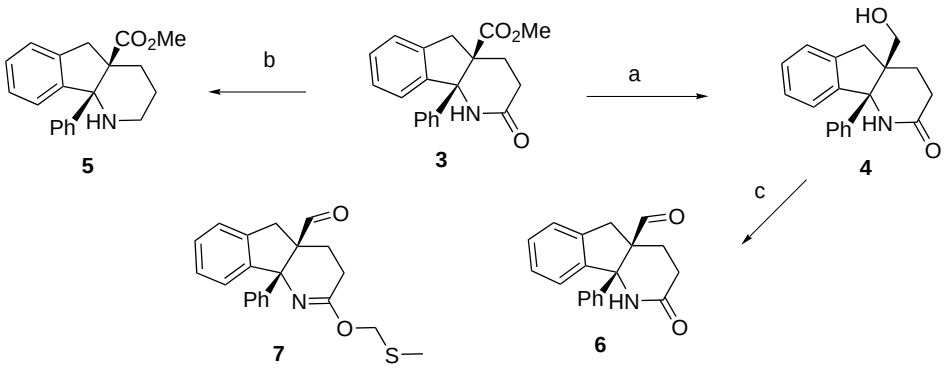
interest for both NK-1[4] and dopamine receptor activity.[5]

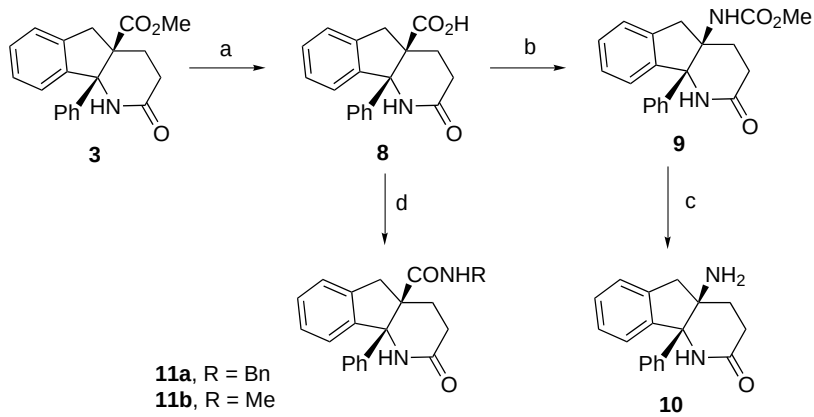
To accomplish our synthetic targets, extensive functional group manipulation is required at the bridgehead ester position 4a of compounds **B**, besides the structural variation at the 9b-position already described.[1] In this report we firstly deal with the general problem of converting the ester function into a number of other functional groups, i.e. the corresponding acid, alcohol, aldehyde, and amine functions. All of these might serve as precursor groups for further elaboration into angular 4a-substituents that are of pharmacological interest. Subsequently our general strategy is illustrated by (i) the generation of some advanced intermediates that may lead to target structures **C** (Y = NH, CONH), and (ii) the synthesis of compound **1**, a tricyclic analogue of the bicyclic dopamine receptor ligand **2**, *trans*-2-amino-3-phenyl-2,3-dihydro-1*H*-inden-5-ol.[6]

In a first approach to functionalise the angular 4a-position, tricyclic ester **3** was converted to the corresponding primary alcohol and aldehyde. Using $LiAlH_4$, selective reduction of the ester group was effected to form alcohol **4** while the lactam function was retained. In contrast, when using BH_3·DMS a reversal of chemoselectivity was observed, resulting in formation of amino ester **5** (Scheme 2). To prepare aldehyde **6**, alcohol **4** was submitted to Swern oxidation. However, due to further reaction of the lactam carbonyl group, methylthiomethyl enol ether **7** was obtained as a major side product. The latter was reconverted into aldehyde **6** via acid hydrolysis. Finally, formation of the side product could be suppressed by conducting the oxidation at low temperature (–65°C) for a short period of time (15 min).

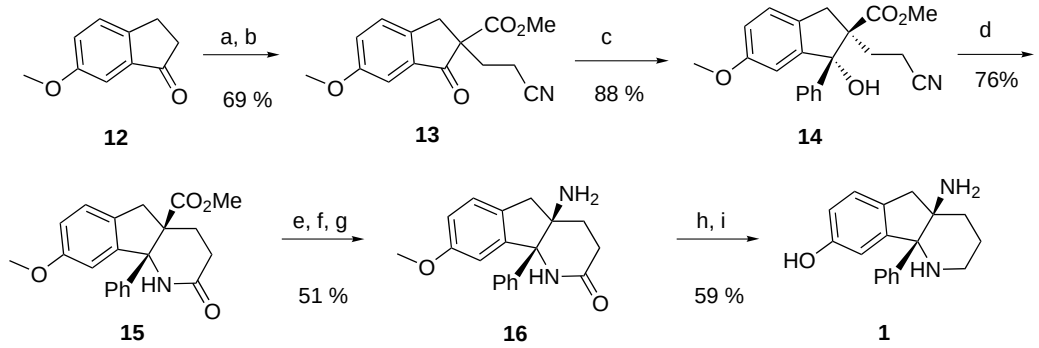
In a second approach (Scheme 3) we envisaged saponification of the ester function followed by appropriate activation of the corresponding acid, e.g. as the acyl azide. This could react further via either nucleophilic substitution or Curtius reaction. Drastic reaction conditions were required to hydrolyse the sterically hindered ester function. When using LiOH, MeOH–H_2O (3:1) or Me_3SiOK no conversion of starting material was observed.[7] Finally, hydrolysis was achieved using a 20% aq. NaOH–THF (1:1) solution in MeOH under reflux conditions.[8] Acid **8** was isolated in 70% yield. Subsequent Curtius reaction, when carried out under the usual conditions ($SOCl_2$, toluene; NaN_3), only resulted in recovery of starting acid. However, under modified conditions[9] using diphenylphosphoryl azide and Et_3N in toluene at reflux temperature followed by reaction



Scheme 2. *Reagents and conditions*: (a) $LiAlH_4$, Et_2O, 88%; (b) BH_3·DMS, THF, reflux, 81%; (c) $(COCl)_2$, DMSO, Et_3N, –65°C, 15 min, 54%.



Scheme 3. *Reagents and conditions*: (a) 20% NaOH–THF; (1:1), MeOH, Δ*T*, 70%; (b) DPPA, Et_3N, toluene, Δ*T*; MeOH, Δ*T*, 90%; (c) *i*-PrOH–KOH, 83%; (d) DPPA, Et_3N, DMF, 0°C, 2 h; $BnNH_2$ or aq. $MeNH_2$, 81 and 67%.



Scheme 4. *Reagents and conditions*: (a) NaH, Me_2CO_3, 110°C, 91%; (b) CH_2CHCN, *t*-BuOK (cat.), *t*-BuOH, 76%; (c) PhMgBr, THF, −78°C, 88%; (d) $MeSO_3H$, rt, 76%; (e) 20% NaOH–THF (1:1), MeOH, ΔT, 70%; (f) DPPA, Et_3N, toluene, ΔT; MeOH, 90%; (g) *i*-PrOH–KOH, 83% h) $BH_3{\cdot}Me_2S$, THF, ΔT, 71%; (i) L-methionine, $MeSO_3H$, 83%.

with MeOH, the methyl carbamate **9** was obtained in 90% yield.[10] Final treatment with *i*-PrOH–KOH under reflux conditions afforded the amine **10** (83%).[11]

Obviously, bridgehead amine **10** can be used for further functionalization. Combined with the primary pharmacophore already present, i.e. the 1-phenyl-1,2-diaminoethane moiety, such derivatization allows to incorporate structural elements characteristic of already known non-peptide Substance P antagonists[2] and dopamine receptor ligands[5] (Fig. 1: target compounds of type **C**, Y = NH, NHCO). In a related application, the acyl azide intermediate formed in the preceding Curtius reaction could be intercepted via addition of an amine reagent at low temperature. Thus, treatment of acid **8** with DPPA in DMF at 0°C for 2 h, followed by addition of benzylamine or aqueous methylamine, furnished amides **11a** and **11b** in 81 and 67% yield, respectively. Further conversion of amides **11**, or the structurally related inverse amide intermediates that may be derived from *N*-acylation of **10**, to the corresponding target compounds **C** (Y = CONH, NHCO) still requires chemoselective reduction of the lactam carbonyl group as opposed to the amide group at the bridgehead position.

To prepare target compound **1**, a potential dopamine receptor ligand (Fig. 1), a sequence analogous to that described for amine **10** was applied. Starting from 6-methoxyindanone **12**, this proceeded via Michael addition of the corresponding β-ketoester to form the cyanoethyl compound **13** (yield over two steps 69%), Grignard reaction using phenylmagnesium bromide (88%), and cyclization through intramolecular Ritter reaction to produce lactam ester **14** (76%). The latter was transformed into amino lactam **15** (combined yield over three steps 51%). Subsequent reduction of the lactam group was effected with $BH_3{\cdot}DMS$ (71%). In the last step the methoxy group was demethylated using l-methionine in methanesulfonic acid,[12,13] to give the corresponding 3-hydroxy target compound **1** (83%) (Scheme 4).

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9. In a typical experiment 0.15 g acid **8** (0.50 mmol), 0.63 ml DPPA (6 equiv.), and 1 ml Et_3N (15 equiv.) was heated at reflux in 15 ml toluene for 1 h. Methanol (15 ml) was added and the mixture was heated further at reflux for 2 h, followed by evaporation, addition of a brine solution, extraction with ethyl acetate, and chromatographic purification (silica gel, CH_2Cl_2: MeOH 95/5); further crystallization from EtOH gave 0.16 g (90%) of the carbamate **9**

as a colorless crystalline solid; mp 260.5–260.9°C.

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11. All products were fully characterized by IR, ^{1}H and ^{13}C NMR, and elemental analysis or HRMS. Selected data for **10**: white solid, mp 258.6–260.2°C; IR (KBr): 3382, 3175, 3052, 2922, 1662, 1603 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6): 8.35 (s, 1H), 7.35 (d, 1H, $J=6$ Hz), 7.25 (m, 6H), 6.9 (d, 2H, $J=7$ Hz), 2.83 (d, 1H, $J=16$ Hz), 2.70 (d, 1H, $J=16$ Hz), 2.64 (ddd, 1H, $J=18$, 10, 6 Hz), 2.08 (ddd, 1H, $J=18$, 6, 5 Hz), 1.73 (m, 2H), 1.20 (s, 2H). ^{13}C NMR (100.6 MHz, DMSO-d_6): δ 27.4, 31.6, 44.8, 61.0, 73.3, 124.5, 124.7, 127.0, 127.5, 127.6, 127.7, 139.7, 141.5, 147.1, 170.3; MS [m/z (%)]: 278 ($M^{+\cdot}$, 1), 250 (50), 222 (93), 221 (100); HRMS calcd for $C_{18}H_{18}NO_2$ 278.1419, found 278.1415.
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