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# Diastereoselective Intramolecular Ritter Reaction: Generation of a *Cis*-Fused Hexahydro-4a*H*-indeno[1,2-*b*]pyridine Ring System with 4a,9b-Diangular Substituents

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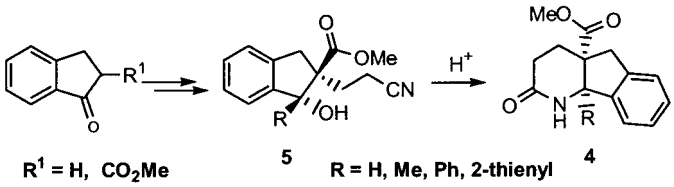
## ABSTRACT




**Indanol intermediates 5, prepared via Michael addition of 1-indanone β-ketoester and acrylonitrile followed by reduction or Grignard reaction of the ketone group, were submitted to intramolecular Ritter reaction using various acid reaction conditions to produce tricyclic lactams 4. This *cis*-fused hexahydro-4a*H*-indeno[1,2-*b*]pyridine ring system, substituted at both angular positions 4a and 9b, provides access to constrained analogues of non-peptide $NK_1$-antagonists with monocyclic piperidine structure.**

In our search for improved non-peptide $NK_1$-antagonists, we focus on conformationally constrained modifications of the 2,3-substituted piperidines **1** (CP-96345)[1] and **2** (CP-99994).[2] Considering the structural features of these first-generation non-peptide $NK_1$-antagonists, we envisaged specifically substituted tricyclic piperidines **3** as target molecules (Figure 1). The partial incorporation of the pharmacophoric group, i.e., the *N*-benzyl-1-phenyl-1,2-diaminoethane moiety,[3] in a tricyclic ring system instead of a monocyclic piperidine structure should allow us to further define the spacial requirements for the "bioactive conformation".

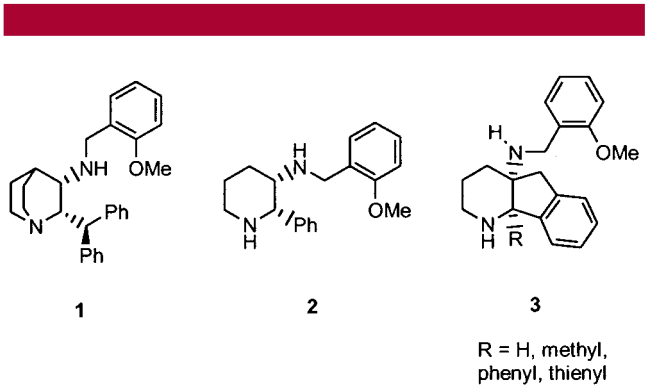



**Figure 1.** Piperidine non-peptide NK1-antagonists **1** and **2** and conformationally constrained target structure **3**.

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(1) (a) Snider R. M.; Constantine, J. W.; Lowe, III; J. A.; Longo, K. P.; Lebel, W. S.; Woody, H. A.; Drozda, S. E.; Desai, M. C.; Vinick, F. J.; Spencer, R. W.; Hess, H.-J. *Science* **1991**, *251*, 435. (b) Lowe, J. A., III; Drozda, S. E.; Snider, R. M.; Longo, K. P.; Bordner, J. *Bioorg. Med. Chem. Lett.* **1991**, *1*, 129.

(2) Desai, M. C.; Lefkowitz, S. L.; Thadeio, P. F.; Longo, K. P.; Snider, R. M. *J. Med. Chem.* **1992**, *35*, 4911.

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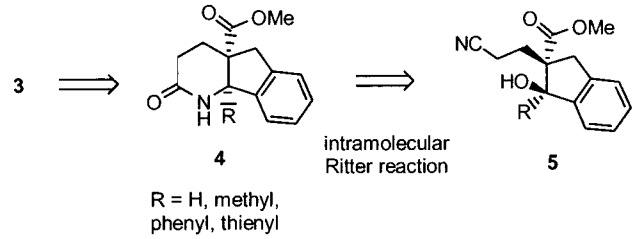
In this paper we describe the application of an intramolecular Ritter reaction to 2-(cyanoethyl)-1-hydroxy-2-indanecarboxylates **5** in order to prepare 9b-substituted 2-oxo-1,2,3,4,5,9b-hexahydro-4a*H*-indeno[1,2-*b*]pyridine-4a-carboxylates **4** (Scheme 1). Compounds **4** can serve as key

**Scheme 1.** Access to Tricyclic Target Structures via Intramolecular Ritter Reaction

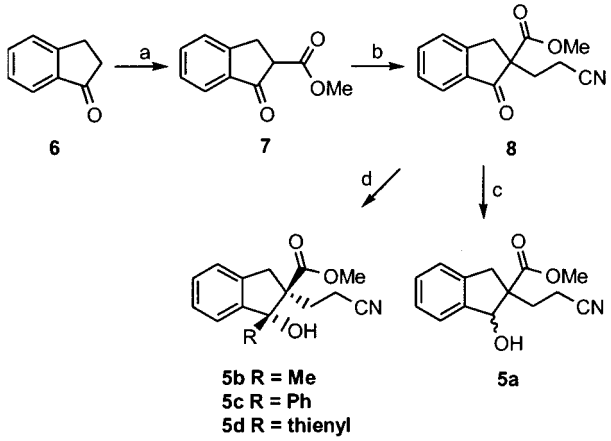



intermediates in the synthesis of target molecules **3**, which will be described in due course.

Little is known about the intramolecular applications of the Ritter reaction to alcohol derivatives.[4] However, the intermolecular Ritter reaction of both racemic and enantiomeric forms of 1,2-indanediols with acetonitrile has been exploited for their regio- and stereocontrolled conversion to *cis*-amino alcohols.[5] The relative configuration of the newly formed 1-amino function was controlled through intermediate formation of a *cis*-methyloxazoline ring involving the configurationally unmodified C-2 alcohol group. In the intramolecular Ritter reaction of compounds **5**, a similar control on the ring closing process apparently is exerted by the stereogenic center at C-2 when forming the carbon−nitrogen bond in the *cis*-fused lactam products. Although the basic indeno[1,2-*b*]piperidine ring system has been described,[6] to our knowledge compounds of type **4** with double angular substitution have not yet been reported.

*β*-Keto ester **7** was prepared by treatment of 1-indanone **6** with sodium hydride and dimethyl carbonate (Scheme 2).[7]

**Scheme 2.** Conversion of 1-Indanone to Intermediates **5**




a) NaH, $(CH_3O)_2CO$, reflux, 83% b) $CH_2$=CH-CN, *t*-BuOK, *t*-BuOH, 93% c) $NaBH_4$, MeOH, 0°C, 98% d) RMgBr, THF, -78 °C, 95 % (**5b**) 79% (**5c**) 84% (**5d**)

Subsequent Michael addition of **7** to acrylonitrile, using *t*-BuOH as a solvent and *t*-BuOK as a base catalyst, afforded the keto nitrile **8**.[8] When methanol was used instead of *t*-BuOH, nucleophilic addition of methoxide to the ketone function led to opening of the five-membered ring to form the corresponding diester product. Reduction with $NaBH_4$ afforded an almost 1:1 mixture of diastereomeric secondary alcohols **5a**. In contrast, upon Grignard reaction of **8** with freshly prepared alkyl- or arylmagnesium bromide at −78 °C, the tertiary alcohols **5b**−**d** were produced with diastereomeric excesses ranging from 50% (**5c**) to 98% (**5b** and **5d**).[9] The yields of these nucleophilic addition reactions were universally high despite steric hindrance.

In each case the structure of the major diastereomer was assigned on the basis of NOE correlations in the $^1$H NMR spectra, observed between a downfield 3-methylene proton and protons located on the variable 1-R substituent, i.e., $CH_3$ (**5b**), H-3 of the 2-thienyl group (**5d**), and the *ortho*-protons of the phenyl group (**5c**). The downfield 3-methylene proton was assigned to be *cis*-disposed with respect to the ester group by comparison with the spectrum of compound **7**.[10]

The high degree of diastereoselectivity may be explained by the formation of a cyclic $Mg^{2+}$ chelate involving both the ester and ketone carbonyl group. Inspection of a conformationally optimized model[11] reveals a nearly flat tricyclic structure with perpendicular orientation for the cyanoethyl side chain (Figure 2). Accordingly, nucleophilic attack will occur from the sterically less hindered side, resulting in a *cis*-relationship between the ester and the alkyl or aryl group.

Cyclization of compounds **5** to form the corresponding lactam compounds **4** was achieved through intramolecular Ritter reaction, i.e., internal addition of the nitrile group to

(4) For a review of the Ritter reaction, see: Krimen, L. I.; Cota, D. J. *Org. React.* **1969**, *17*, 213.

(5) (a) Senanayake, C. H.; Robert, F. E.; DiMichele, L. M.; Ryan, K. M.; Liu, J.; Fredenburgh, L. E.; Foster, B. S.; Douglas, A. W.; Larsen, R. D. *Tetrahedron Lett.* **1995**, *36*, 3993 (b) Senanayake, C. H.; DiMichele, L. M.; Liu, J.; Fredenburgh, L. E.; Ryan, K. M.; Roberts, F. E.; Larsen, R. D.; Verhoeven, T. R.; Reider, P. J. *Tetrahedron Lett.* **1995**, *36*, 7615.

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(7) Binder, B.; Noe, C. R. *Monatsh. Chem.* **1977**, *108*, 839.

(8) All new compounds were characterized by analytical data (NMR, MS, IR) including elemental analysis or exact mass measurement.

(9) The diastereomeric excess was determined from integration of the signals corresponding to the AB pattern of the 5-$CH_2$ protons. **5b**, de = 98%: 2.83 ppm (d, 0.01H, $^2J$ = 16 Hz, H-3); 2.86 ppm (d, 0.99H, $^2J$ = 16 Hz, H-3). **5c**, de = 50%: 2.96 ppm (d, 0.25H, $^2J$ = 16 Hz, H-3); 2.99 (d, 0.75H, $^2J$ = 16 Hz, H-3). **5d**, de = 98%: 2.96 ppm (d, 0.01H, $^2J$ = 16 Hz, H-3); 2.99 ppm (d, 0.99H, $^2J$ = 16 Hz, H-3).

(10) The $^1$H NMR spectrum of compound **7** displayed an ABX coupling pattern for H-2 and the two H-3 protons: H-2, 3.73 ppm ($^3J$ = 4 and 8 Hz); H-3 (*cis with the ester function*), 3.55 ppm ($^2J$ = 17 Hz, $^3J$ = 4 Hz); H-3 (*trans with the ester function*), 3.37 ppm ($^2J$ = 17 Hz, $^3J$ = 8 Hz).

(11) Model calculations were carried out using the molecular mechanics method of HyperChemTM: Release 4.5, Hypercube, Inc.

(12) (a) Schwenker, G.; Metz, G. *J. Chem. Res., Synop.* **1985**, 112. (b) Metz, G. *J. Chem. Res., Synop.* **1985**, 382. (c) Metz, G. *J. Chem. Res., Synop.* **1987**, 66.

(13) Chang, S.-J *Org. Process Res. Dev.* **1999**, *3*, 232.

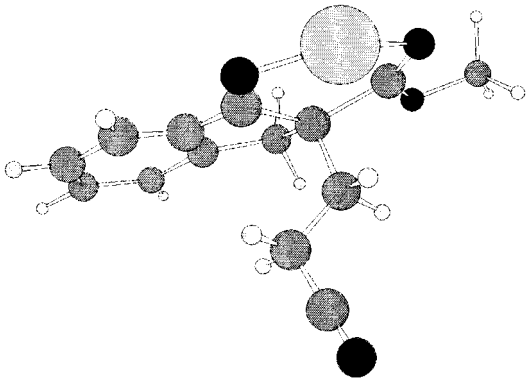
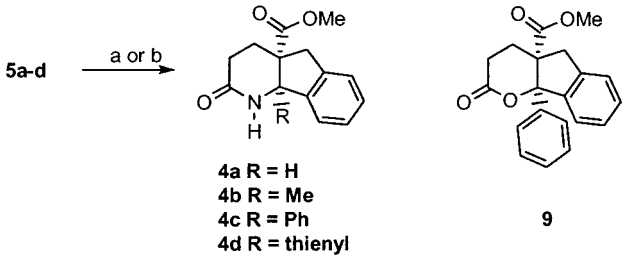


**Figure 2.** Cyclic $Mg^{2+}$ chelate postulated as intermediate in the Grignard reaction of $\beta$-ketoester **8**.

a stabilized carbocation intermediate generated from the benzylic alcohol group in an acidic medium (Scheme 3). In view of the higher stability expected for a dibenzylic carbocation, cyclization was first attempted using compound **5c**.

**Scheme 3.** Intramolecular Ritter Reaction of Nitrile Compounds **5**




Typical conditions for the Ritter reaction comprise the treatment of secondary and tertiary alcohols with concentrated sulfuric acid. In our hands, however, yields obtained under these conditions were low (20%). We investigated several alternative conditions to optimize the yield. Treatment of **5c** with 80% sulfuric acid at room temperature, as described by Metz[12] for the preparation of mixed dilactams, afforded the desired lactam **4c** in 60% yield besides the corresponding lactone **9** (20%). The latter may be formed by attack of the carbonyl oxygen of the primary amide, generated either directly from nitrile **5c** or indirectly from lactam **4c**, on the dibenzylic carbocation intermediate. Conducting the reaction in polyphosphoric acid at 135 °C provided **4c** in good yield (76%). However, extensive workup and column chromatography were required and scaling up this procedure was found to be extremely tedious. Finally, the cyclization reaction was shown to proceed readily by treatment of **5c** with methanesulfonic acid at room temperature affording **4c** in an excellent yield of 92%.

In a similar way, several side products were formed when applying the polyphosphoric acid procedure to the thienyl derivative **5d**, whereas the desired lactam **4d** was isolated in 85% yield when using methanesulfonic acid. However, even the latter conditions failed to effect the cyclization of alcohols **5a** and **5b**, most probably because of the less stabilized character of the intermediate carbocations. Consequently, we modified our procedure according to the conditions reported for the intermolecular Ritter reaction of secondary alcohols.[13] This modification involved the use of chlorobenzene as a solvent and heating with methanesulfonic acid at 70 °C, which effected conversion of alcohols **5a** and **5b** into tricyclic lactams **4a** and **4b** in 71% and 67% yields, respectively.

In all cases, the ring closure was shown to proceed diastereoselectively as only one stereoisomer was detected by TLC and $^1$H NMR analysis of crude compounds **4a**−**d**. However, the relative configuration, i.e., the *cis* or *trans* ring fusion, could not be determined from $^1$H NMR NOE difference experiments performed on either the ester compound **4c** or the corresponding alcohol, prepared by selective reduction of the ester group with $LiAlH_4$.

An X-ray analysis of **4c** unambiguously confirmed the *cis* annelation that was expected from the more probable *syn* attack of the nitrile on the planar dibenzylic cation (Figure 3). In addition, model calculations revealed the *cis* ring fusion

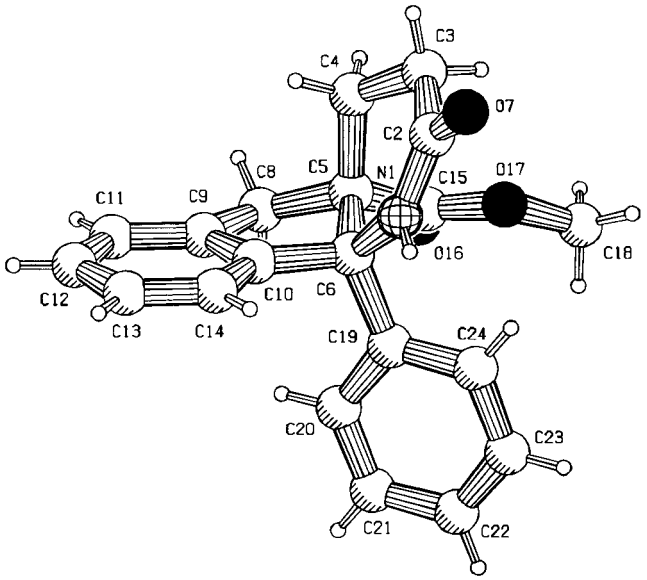



**Figure 3.** X-ray analysis of compound **4c**.

to be largely preferred over the *trans* one, due to the angular strain imposed on the *trans* product by the partially planar character of the cyclopentene and six-membered lactam ring moieties.[11]

The *cis* relation established between the transformable ester function in position 4a and the aryl substituents in position 9b of compounds **4c**,**d** is in accordance with target structures

**3** and with the 2,3-*cis* substitution pattern characteristic of model compounds **1** and **2**.

In conclusion, we have defined conditions that allow a diastereoselective synthesis of novel 9b-substituted 2-oxo-1,2,3,4,5,9b-hexahydro-4a*H*-indeno[1,2-*b*]pyridine-4a-carboxylates **4** via an intramolecular Ritter reaction. This reaction is applicable to 1-indanol derivatives **5** having either a secondary or a tertiary alcohol function substituted with a methyl, aryl, or heteroaryl group. Extension of this methodology to include other heteroaromatic ring systems and to form the corresponding five-membered ring lactams, and the eventual transformation of compounds **4a**,**b** into the target compounds **3**, will be reported in due course.

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**Supporting Information Available:** Experimental procedures and NMR and MS data for compounds **4a**−**d**, **5a**−**d**, **7**, and **8**. X-ray data for compound **4c**. This material is available free of charge via the Internet at http://pubs.acs.org.

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