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Stereoselective Synthesis of 3-Aryloctahydroindoles and Application in a Formal Synthesis of (−)-Pancracine

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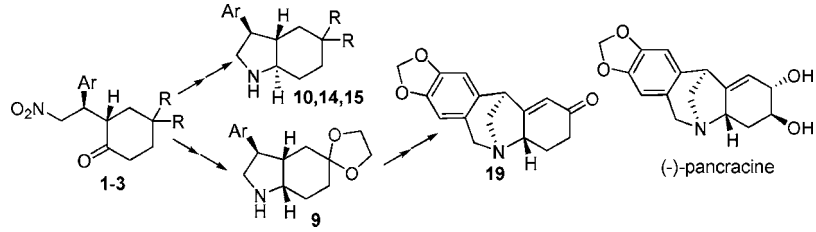
ABSTRACT



A stereoselective synthesis of 3-aryloctahydroindoles from enantiomerically enriched γ-nitroketones has been developed. Reduction of imines derived form the nitroketones provides the *trans*-fused octhaydroindole motif selectively. The *cis*-octahydroindole skeleton is accessible by an invertive cyclization strategy involving a diastereomerically pure nitromesylate intermediate. This approach was employed in the synthesis of an advanced intermediate to (−)-pancracine. The γ-nitroketone starting materials are readily available via an organocatalytic Michael reaction.

The octahydroindole ring system has attracted considerable attention due to its importance in natural product chemistry and medicine. For example, the octahydroindole motif is found in several bioactive natural products such as the Amaryllidaceae[1] and sceletium[1,2] alkaloids and also the aeruginosins.[3] Recently, applications of octahydroindole scaffolds in the diversity-oriented synthesis of Amaryllidaceae alkaloid type structures,[4] glycomimetics,[5] and glycosidase inhibitors[6] have been reported. The stereochemistry of the ring junction in the octahydroindole influences its biological profile. Thus, *cis*-octahydroindoles have been utilized in peptide β-turn mimics[7] and also have noradrenaline uptake inhibitor activity,[8] whereas the *trans*-octahydroindole motif has been employed in ACE inhibitors.[9] The synthesis of octahydroindoles therefore continues to be actively investigated,[10] and selective access to either the *cis*- or the *trans*-octahydroindole motif is of particular interest. Herein, we describe preliminary results on a simple, stereoselective approach to *cis*- or *trans*-3-aryloctahydroindoles from readily available γ-nitroketone precursors.

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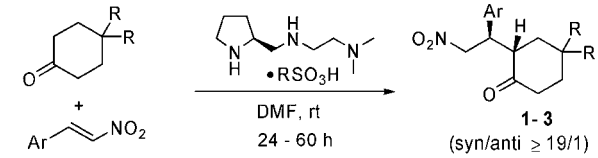
Our interest in octahydroindoles stems from our studies on the enantioselective organocatalytic synthesis of γ-nitroketones from cyclic ketones and 2-nitrovinyl arenes via an enamine-based, organocatalytic Michael addition reaction.[11] A large number of studies[12] have demonstrated the utility of this reaction, and the development of new catalysts for this reaction continues at a remarkable pace. Clearly, the full potential of the organocatalytic ketone−nitroalkene Michael reaction will be realized when the enantiomerically enriched γ-nitroketone products find applications in other synthetic endeavors.[13]

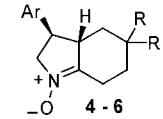
Generally, γ-nitrocarbonyl compounds can be converted to the corresponding nitrones[14] or pyrrolines[15] selectively, and these can serve as precursors to pyrrolidines.[16] Hence, at the outset, a stereoselective synthesis of octahydroindoles from cyclohexanone-derived γ-nitroketones, by reduction of the derived nitrones or imines,[17] appeared attractive. Stereocontrol in the reduction step may be anticipated to be a function of the stereocenters α and/or β′ to the ketone. These stereocenters, in turn, are readily set by the organocatalytic Michael addition reaction. While a few reports describe the reduction of tetrahydrobenzo[*e*]indole and tetrahydropyrrolo[*f*]quinoline ring systems (embedded imine functionality) to the corresponding *cis*-fused hexahydro products,[15] reduction of a hexahydro[2*H*]indole to a mixture of *cis* and *trans* octahydroindoles is also reported.[18] The challenges associated with the conversion of tetralin-based γ-nitroketones into *cis*- or *trans*-hexahydrobenz[*e*]indoles have been detailed in a recent study.[19] Evidently, methodology that provides stereocontrolled access to octahydroindoles would be useful.

With this objective in mind, γ-nitroketones **1**[12h]−**3** were prepared by employing our secondary−secondary diamine salt catalyzed Michael addition protocol.[11] The nitroketones were obtained in good yield and high diastereomeric and enantiomeric excess. Partial reduction of the nitro group[17c] in **1**, **2**, and **3** with Zn/aq NH_4Cl provided the cyclic nitrones **4**−**6**, respectively, in good yields (Scheme 1).

Scheme 1. Synthesis of 3-Arylhexahydroindole 1-Oxides



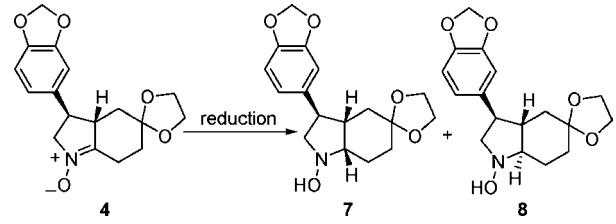
	Ar	R	yield(%)	ee[a]
1	3,4-(OCH_2O)-Ph	$O(CH_2)_2O$	90	89
2	4-OMe-Ph	H	83	99
3	2-naphthyl	H	90	99
4	3,4-(OCH_2O)-Ph	$O(CH_2)_2O$	70	b
5	4-OMe-Ph	H	74	b
6	2-naphthyl	H	63	b



[a]Chiral HPLC [b]same as precursor

The nitrone **4** was chosen as a candidate for reduction studies toward the octahydroindole system. Treatment of **4** with $NaBH_4$ in methanol provided a 2/1 mixture of the *cis*- and *trans*-hydroxylamines **7** and **8**, respectively.[20] A brief survey of reducing conditions was conducted (Table 1) with

Table 1. Reduction of Nitrone **4**



entry	reducing agent/conditions	**7**/**8**	yield **7** + **8** (%)
1	$NaBH_4$/MeOH, rt	1.5/1	50
2	$NaBH(OAc)_3$, rt	1/1	76
3	$NaBH_3CN$/AcOH, −10 °C	2/1	44
4	$NaBH_3CN$/pivalic acid, 0 °C	2.5/1	67
5	L-Selectride	1/1	89
6	$LiAlH_4$	1/1	90
7	H_2, Pd/C, 1 atm		
8	Pd/C, HCO_2NH_4	*a*	50

[a] *trans*-Octahydroindole **10** was obtained.

the objective of improving the *cis*/*trans* ratio. However, selective reduction of **4** to **7** or **8** was not observed in any of

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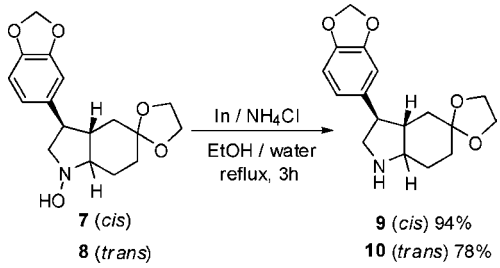
(19) Degnan, A. P.; Meyers, A. I. *J. Org. Chem.* **2000**, *65*, 3503.

(20) Hydroxylamines **7** and **8** are only moderately stable at ambient temperature and gradually decompose to the nitrone **4** in solution.

these experiments, and the best result was obtained with sodium cyanoborohydride/pivalic acid (**7**/**8** = 2.5/1). Surprisingly, the catalytic hydrogenation of **4** (H_2, Pd/C, 1 or 3 atm; H_2, PtO_2, 1 atm) in ethanol generated a mixture of products which did not contain any of the anticipated hydroxylamines.[21] Transfer hydrogenation of **4** provided the *trans*-octahydroindole product. This stereochemical result is comparable to previous observations by Sanchez on the catalytic hydrogenation (RaNi, *i*-PrOH, 50 psi, 55 °C) of an analogue of **1**, lacking the dioxolane functionality, which provided only the corresponding *trans*-octahydroindole (presumably by reduction of the nitrone formed in situ).[17b] Hydrogenation of **1** under less forcing conditions (RaNi, 45 psi, EtOH, ambient temperature) provided the pyrroline analogue (imine) of nitrone **4**.

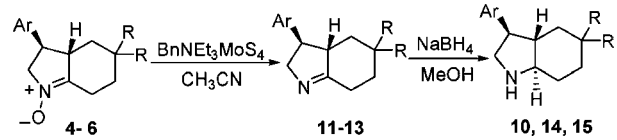
Hydroxylamines **7** and **8** were separated and reduced with indium metal[22] to the *cis*-octahydroindole **9** and its *trans* isomer **10**, respectively (Scheme 2). The stereochemical

Scheme 2. Reduction of Hydroxylamines **7** and **8**



assignments are based on ^{1}H NMR data for the *N*-Cbz derivative of **9** which is in agreement with that reported in the literature.[23] It is noteworthy that **9** is a known intermediate to the montanine-type Amaryllidaceae alkaloids, particularly (−)-pancracine.[23] Given the lack of stereoselectivity in the reduction of nitrone **4** and the known *cis* selectivity in the reduction of a tetrahydrobenzo[*e*]indole system,[15b,c] we turned our attention to the reduction of the imine analog of **4** as an alternative approach to the corresponding *cis*-octahydroindole. Although the required imine **11** can be obtained (along with nitrone **4**) by reduction of the nitroketone **1** with Zn/acetic acid, a more efficient route involves deoxygenation of the nitrone **4** with benzyltriethylammonium tetrathiomolybdate.[24] This method was also applicable to the nitrones **5** and **6** to provide the imines **12** and **13**, respectively, in reasonable yields (Table 2). Curiously, reduction

Table 2. Conversion of Nitrones **4**−**6** to *trans*-Octahydroindoles



compd	Ar	R	yield (%)	*trans*/*cis*
11	3,4-(OCH_2O)Ph	$O(CH_2)_2O$	70	
12	4-OMePh	H	62	
13	2-naphthyl	H	64	
10	3,4-(OCH_2O)Ph	$O(CH_2)_2O$	75	10/1
14	4-OMePh	H	75	>19/1[a]
15	2-naphthyl	H	72	6/1

[a] Single diastereomer by ^{1}H NMR

of the imines with $NaBH_4$ provided the *trans*-octahydroindoles[25] as the major products (Table 2) with some of the *cis* product being observed (^{1}H NMR) only in the reduction of **11** and **13** (*trans*/*cis* ratio of 10/1 and 6/1, respectively). The reasons for the marked difference in stereoselectivity of reduction of the nitrone **4** and the imine **11** as well as the imines **12** and **13** are not apparent. Also, the dependence of *trans*/*cis* ratios on the nature of the relatively similar 3-aryl substituents in **11**−**13** is intriguing.

Although the imine reduction method provides access to the *trans* 3-aryloctahydroindoles as major products, the *cis* isomers are not available in good yield from either the nitrones or the imines. Therefore, an alternative approach was examined for which **9** was chosen as the representative target. We reasoned that a strategy involving the direct assembly of the pyrrolidine ring by stereoselective C−N bond formation from an appropriate precursor derived from the nitroketone **1** would be more fruitful. Toward this end, the γ-nitroketone **1** was subjected to a stereoselective reduction with L-Selectride to provide the nitro alcohol **16** (axial alcohol) as a single diastereomer (Scheme 4). A Mitsunobu reaction of alcohol **16** (Ph_3P, di-2-methoxyethylazodicarboxylate (DMEAD),[26] 4-nitrobenzoic acid) followed by hydrolysis of the 4-nitrobenzoate provided the nitro alcohol **17** (equatorial alcohol) as a single diastereomer.[27] Mesylation of **17** provided the key substrate for the ring

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(22) Cicchi, S.; Bonanni, M.; Cardona, F.; Revuelta, J.; Goti, A. *Org. Lett.* **2003**, *5*, 1773.

(23) Ikeda, M.; Hamada, M.; Yamashita, T.; Matsui, K.; Sato, T.; Ishibashi, H. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1949. A one-step catalytic hydrogenation (H_2, Pd/C) of **4** to **9** is envisioned as an approach to the montanine alkaloids in a patent; see: Wang, W.; Wang, J.; Li, H. WO 2006007586. However, the actual implementation of this proposal is not described. Application of the organocatalytic Michael reaction to the synthesis of montanine alkaloids has also been indicated in a conference abstract; see: Wang, W.; Wang, J.; Li, H. Abstracts of Papers, 229th ACS National Meeting 2005, ORGN-356. However, to the best of our knowledge, a detailed report has not appeared in the journal literature. The earlier work by Sanchez[17b] and our results with **4** suggest that the stereoselective synthesis of *cis*-3-aryloctahydroindoles such as **9** by the catalytic hydrogenation of nitroketones such as **1** or nitrones such as **4** is challenging.

(24) Ilankumaran, P.; Chandrasekaran, S. *Tetrahedron Lett.* **1995**, *36*, 4881.

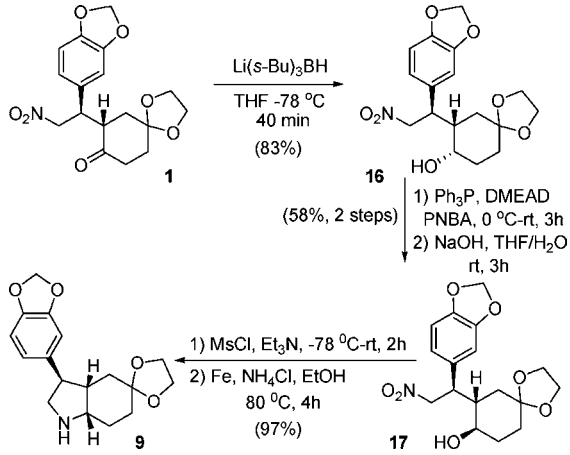
(25) The stereochemical assignments are based on the similarities in the ^{1}H NMR spectra of **10**, **14**, and **15**.

(26) The use of DMEAD, which is reduced to a water-soluble hydrazine dicarboxylate, simplifies the purification of the Mitsunobu product. (a) Sugimura, T.; Hagiya, K. *Chem. Lett.* **2007**, *36*, 566. (b) Haigya, K.; Marumoto, N.; Misaki, T.; Sugimura, T. *Tetrahedron* **2009**, *65*, 6109. DMEAD is commercially available.

(27) The ketone **1** was unreactive toward *i*-Bu_2AlO*i*-Pr, a reducing agent that is known to selectively generate equatorial alcohols from cyclic ketones; see: (a) Cha, J. S.; Kwon, O. O. *J. Org. Chem.* **1997**, *62*, 3019. (b) Bahia, P. S.; Jones, M. A.; Snaith, J. S. *J. Org. Chem.* **2004**, *69*, 9289.

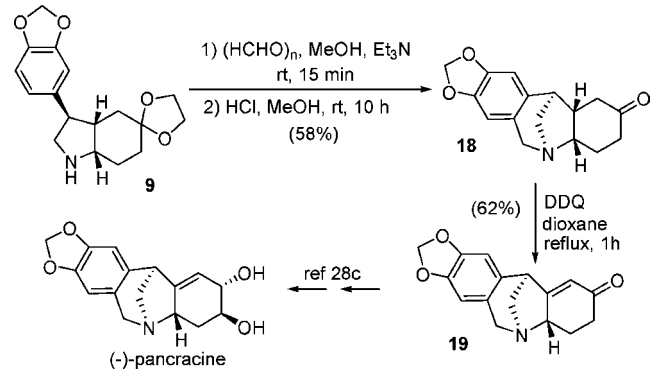
closure reaction. Gratifyingly, reduction of the nitro group in the mesylate with Fe/NH_4Cl directly provided the *cis*-octahydroindole **9** as a single diastereomer in excellent yield (97%, Scheme 3). This result is indicative of an S_N2-type

Scheme 3. Synthesis of *cis*-Octahydroindole **9**



reaction of the intermediate amino mesylate which proceeds with complete inversion at the ring junction. It is reasonable to assume that the overall conversion of **1** to **9** is representative of a general approach to *cis*-octahydroindoles from cyclohexanone-derived γ-nitroketones. The efficiency of the intramolecular nucleophilic displacement should render this strategy relatively insensitive to substitution in the γ-nitroketone starting material. Having established a stereoselective synthesis of the *cis*-octahydroindole **9**, we proceeded to utilize **9** in a formal synthesis of (−)-pancracine.[28] Treatment of **9** with aqueous formaldehyde followed by removal of the acetal protecting group, by adaptation of the literature method,[23] provided the methanomorphanthridine **18**. Oxidation of **18** with DDQ, as described by Hoshino,[28g] provided **19** which is an advanced intermediate in the Overman synthesis of (−)-pancracine.[28c] (Scheme 4). In conclusion, a stereoselective synthesis of *cis*- as well as *trans*-3-aryloctahydroindoles was developed from enantiomerically enriched γ-nitroketones. The methodology was applied in a short formal synthesis of (−)-pancracine. These studies

Scheme 4. Conversion of **9** to (−)-Pancracine Intermediate **19**



highlight the utility of the organocatalytic synthesis of γ-nitroketones. Current efforts focus on other reactions of bicyclic nitrones related to **4**.

Acknowledgment. These investigations were supported by the Natural Sciences and Engineering Research Council of Canada and the Canada Foundation for Innovation.

Supporting Information Available: Experimental methods, spectroscopic data, ^1H and ^{13}C data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(28) Synthesis of (−)-pancracine : (a) Jin, J.; Weinreb, S. M. *J. Am. Chem. Soc.* **1997**, *119*, 2050. (b) Jin, J.; Weinreb, S. M. *J. Am. Chem. Soc.* **1997**, *119*, 5773. (c) Overman, L. E.; Shim, J. *J. Org. Chem.* **1993**, *58*, 4662. Formal synthesis of (−)-pancracine: (d) Anada, M.; Tanaka, M.; Shimada, N.; Nambu, H.; Yamawaki, M.; Hashimoto, S. *Tetrahedron* **2009**, *65*, 3069. Formal synthesis of (+)-pancracine: (e) Chang, M.-Y.; Chen, H.-P.; Lin, C.-Y.; Pai, C.-Li. *Heterocycles* **2005**, *65*, 1999. Synthesis of racemic pancracine: (f) Banwell, M. G.; Edwards, A. J.; Jolliffe, K. A.; Kemmler, M. *J. Chem. Soc., Perkin Trans. 1* **2001**, 1345. (g) Ishizaki, M.; Kurihara, K.-I.; Tanazawa, E.; Hoshino, O. *J. Chem. Soc. Perkin Trans. 1* **1993**, 101. (h) Ishizaki, M.; Hoshino, O.; Iitaka, Y. *J. Org. Chem.* **1992**, *57*, 7285. (i) Ishizaki, M.; Hoshino, O.; Iitaka, Y. *Tetrahedron Lett.* **1991**, *32*, 7079. (j) Overman, L. E.; Shim, J. *J. Org. Chem.* **1991**, *56*, 5005. Formal synthesis of racemic pancracine: (k) Pandey, G.; Banerjee, P.; Kumar, R.; Puranik, V. G. *Org. Lett.* **2005**, *7*, 3713. (l) Ikeda, M.; Hamada, M.; Yamashita, T.; Ikegami, F.; Sato, T.; Ishibashi, H. *Synlett* **1998**, 1246. Also see ref 23.