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Highly Enantioselective Total Synthesis of (+)-Isonitramine

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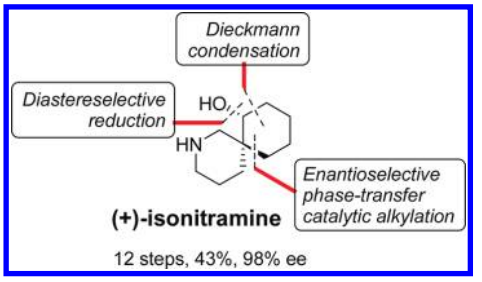
ABSTRACT



A new efficient enantioselective synthetic method of (+)-isonitramine is reported. (+)-Isonitramine was obtained in 12 steps (98% ee and 43% overall yield) from δ-valerolactam *via* enantioselective phase-transfer catalytic alkylation, Dieckman condensation, and diastereoselective reduction as key steps.

There are a number of biologically important natural products[1] containing optically active 2-azaspirocycle structures, such as polyzonimine,[1a] nitropolyzonamine,[1a] horsfiline,[1b] and spirotryprostatin B.[1c] Among these compounds, *Nitraria* alkaloids,[2] (+)-nitramine (**1**), (+)-isonitramine (**2**), and (−)-sibirine (**3**), have chiral quaternary carbon centers on the 2-azaspiro[5,5]undecane-7-ol skeletons. The structural similarity with the neurotoxic (−)-histrionicotoxin has faciliated the development of efficient synthetic routes of *Nitraria* alkaloids (Figure 1). Recently, it was reported that the extracts of *Nitraria* plants have antiproliferative effects on cancer cell lines through the apoptosic pathway.[3]

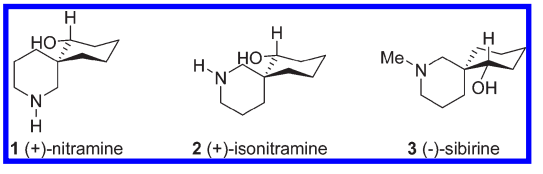


Figure 1. *Nitraria* alkaloids.

Although numerous enantioselective synthetic methods for *Nitraria* alkaloids have been reported thus far,[4] most of these approaches employed chiral auxiliaries,[4a,d,j] chiral substrates,[4b,g] or enzymatic resolution,[4e,f,h,l] which cannot be readily applied to large scale production. In addition,

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(2) For a recent review on *Nitraria* alkaloid, see: Wanner, J. W.; Koomen, G. J. In *Studies in Natural Products Chemistry: Stereoselectivity in Synthesis and Biosynthesis of Lupine and Nitraria Alkaloids*; Atta-ur-Rahman, Ed.; Elsevier: Amsterdam, 1994; p 731 and references therein.

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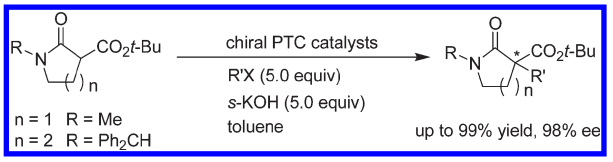
only one reported catalytic method uses an organopalladium catalyst for the establishment of quaternary carbon center (6*R*); however, the enantioselectivity is only 86% ee.[4i] As one of our research programs for the development of new therapeutics for the treatment of cancer, we need to develop very efficient and highly enantioselective synthetic methods for *Nitraria* alkaloids. Herein, we present a novel approach to synthesize (+)-isonitramine (**2**), a representative *Nitraria* alkaloid, via asymmetric phase-transfer catalytic (PTC) alkylation, which is regarded as one of the most efficient synthetic processes for large scale production from the view points of economical and environmental aspects.[5]

Scheme 1. Enantioselective PTC α-Alkylation of Lactams



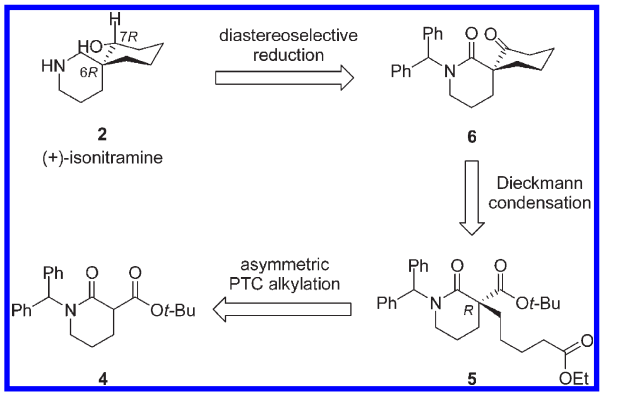
Very recently, we reported on the highly enantioselective PTC alkylations of α-*tert*-butoxycarbonylactams (Scheme 1).[6] The alkylation of *N*(1)-methyl-2-oxo-pyrrolidine-3-carboxylic acid *tert*-butyl ester or *N*(1)-benzhydryl-2-oxo-piperidine-3-carboxylic acid *tert*-butyl ester under PTC conditions in the presence of chiral quaternary ammonium salts successfully afforded the corresponding α-alkylated lactams in high chemical (up to 99%) and optical yields (up to 98% ee), which is potencially applicable to the synthesis of 2-azaspirocycles by further cyclization. Given this, we attempted to apply our novel method to the synthesis of a representative *Nitraria* alkaloid, (+)-isonitramine (**2**).

As shown in a retrosynthetic analysis (Scheme 2), the C(7*R*) chirality can, in principle, be induced by diastereoselective reduction of **6**, which can be obtained by Dieckmann condensation[7] of **5**. Optically active (*R*)-**5** can be derived from the enantioselective phase-transfer catalytic alkylation of *N*(1)-benzhydryl-2-oxo-piperidine-3-carboxylic acid *tert*-butyl ester (**4**).

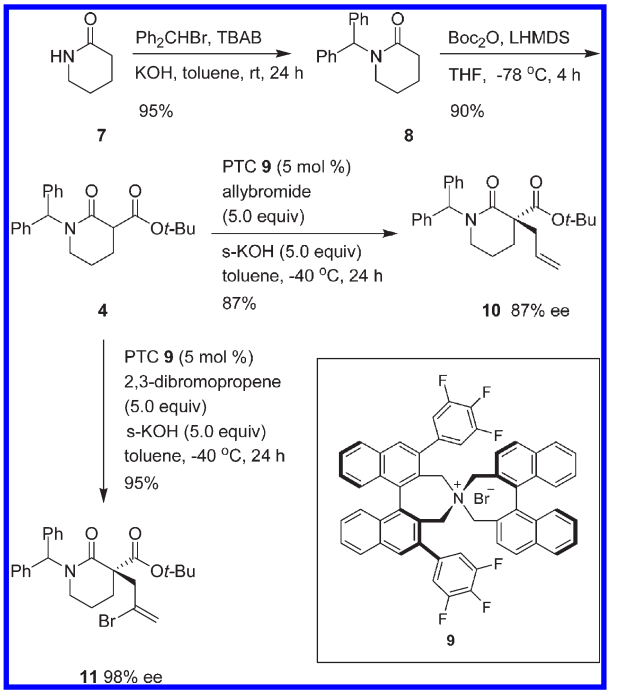
First, the substrate (**4**) for PTC alkylation was prepared from δ-valerolactam (**7**) in two steps (Scheme 3). *N*-Diphenylmethylation of **4** under PTC reaction conditions in the presence of TBAB as a catalyst, followed by *tert*-butylcarboxylation using Boc_2O under LiHMDS basic conditions, provided lactam **4** in good yield.

Since the phase-transfer catalytic alkylation of **4** with unactivated alkyl halides usually produced poor chemical

Scheme 2. Retrosynthetic Analysis



Scheme 3. Enantioselective PTC Alkylation



yields, we changed the synthetic route of **5** through allylation, followed by chain elongation. However, the allylation still resulted in unsatisfactory enantioselectivity (87% ee) as reported previously; thus, we attempted to improve the enantioselectivity. We previously improved the enantioselectivity in the monoallylation of the *N*,*N*-diphenylmalonamide ester system during the total synthesis of (−)-paroxetine by switching the "allyl bromide" with "2-bromoallyl bromide".[8] Therefore, we used bromoallyl bromide as an alternative electrophile. The phase-transfer catalytic allylation of **4** was carried out with 2-bromoallyl

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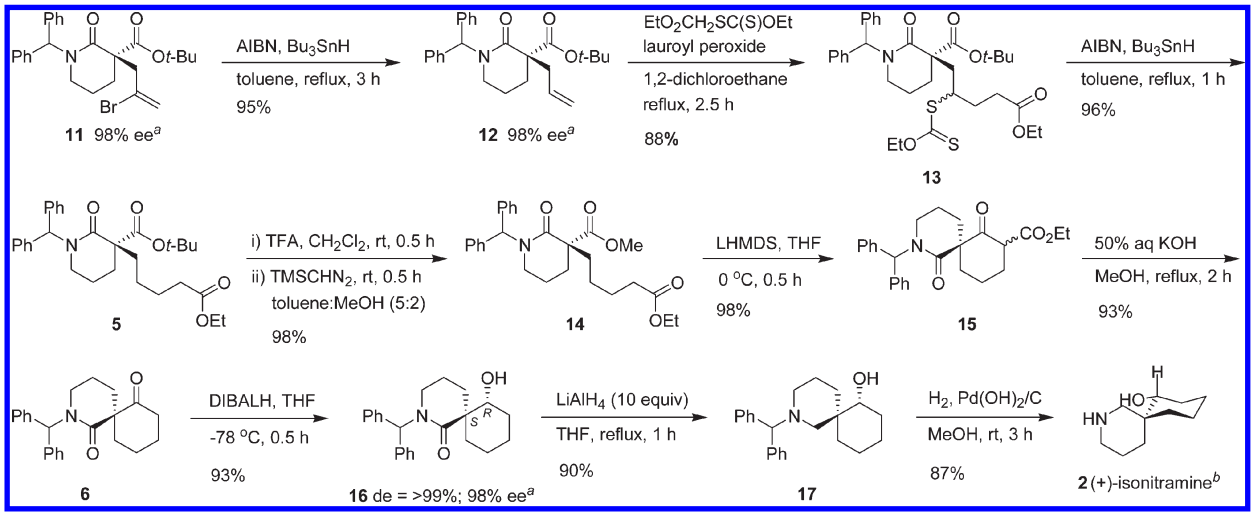
(8) Kim, M.-h.; Park, Y.; Jeong, B.-S.; Park, H.-g.; Jew, S.-s. *Org. Lett.* **2010**, *12*, 2826.

Scheme 4. Synthesis of (+)-Isonitramine[a,b]



[a] The enantiopurity was determined by HPLC analysis of **11**, **12**, and **16** using a chiral column (Chiralpak AD-H) with hexanes/2-propanol as the eluent. [b] Absolute configuration was assigned by comparison of the specific optical rotation value of the (+)-isonitramine (**2**) with the literature value.[4f]

bromide under the previously reported optimal reaction conditions[6] [(*S*,*S*)-3,4,5-Trifluorophenyl-NAS bromide (**9**, 5 mol %), and solid KOH (5.0 equiv) in toluene at −40 °C] to afford **11**. Surprisingly, the enantioselectivity was dramatically increased (87% ee to 98% ee), as well as the chemical yield (87% to 95%). These findings indicate that the bulkier electrophile was better able to selectively approach the *re*-face of the enolate of **4** when complexed with quaternary ammonium catalyst **10**, resulting in C(6*R*) chirality with higher enantioselectivity. The debromination of **11** using tributyltin hydride in the presence of a catalytic amount of AIBN in toluene gave **12** (95%) (Scheme 4).[9] For the elongation of the carbon chain, ethyl ethoxythiocarbonylsulfanylacetate was successfully added to the allylic moiety of **12** under radical conditions to provide **13** (88%).[10,11] The xanthate was then removed using tributyltin hydride and AIBN, which afforded diester **5** (96%). Since the direct Dieckmann condensation of **5** for the construction of the spirocyclic skeleton failed, the *tert*-butyl ester of **5** was transformed to afford the corresponding methyl ester **14** by the removal of *tert*-butyl ester with TFA in methylene chloride, followed by methylation with an excess of diazomethane (98%). Dieckmann condensation of **14** was then successfully accomplished under LiHMDS base conditions in THF at 0 °C, resulting in the production of spirocyclic β-ketoester **15** (98%). The hydrolysis of **15** with 50% aqueous KOH in MeOH, followed by decarboxylation, afforded ketone **6** (93%).

Next, the C(7*R*) chirality of **2** was introduced by the diastereoselective reduction of **6**. The reduction of **6** using DIBAL in THF at −78 °C afforded **16** as a single diastereomer of the desired 7*R*-form in 93% chemical yield. Notably, the diastereoselectivity was much higher than that in the reduction of the free amide analogue of **6** under the same reaction conditions, which was reported previously (87% de).[4f] The bulky benzhydryl group seems to play important roles in not only the high enantioselectivity of C(6*R*) in the PTC alkylation of **4** but also the high enantioselectivity of C(7*R*) in the diastereoselective reduction of **6**. The reduction of the lactam **16** using excess $LiAlH_4$ in THF readily afforded piperidine **17** (90%). Finally, (+)-isonitramine {**2**, $[\alpha]_D^{23}$ = +6.22 (*c* 1.16, $CHCl_3$); $[\alpha]_D^{23}$ = +5.8 (*c* 1.4, $CHCl_3$)[4f]} could be obtained by the catalytic hydrogenation of **17** with $Pd(OH)_2$ in methanol (87%).

In conclusion, a new efficient synthetic approach toward (+)-isonitramine (**2**) was developed. (+)-Isonitramine (**2**) was synthesized in 12 steps (43% overall yield, 98% ee) by enantioselective phase-transfer catalytic alkylation, Dieckmann condensation, and diastereoselective reduction from δ-valerolactam (**7**). Both the high enantioselectivity and chemical yield make this approach a practical route for the large scale synthesis of 2-azaspirocycles. Structure−activity relationship studies of (+)-isonitramine derivatives are now in progress.

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Supporting Information Available. Spectroscopic characterizations of compounds **2**, **4**−**6**, **8**, and **10**−**17**. This material is available free of charge via the Internet at http://pubs.acs.org.

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