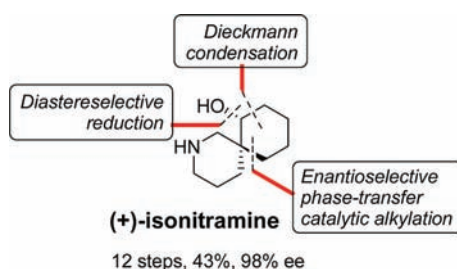


Highly Enantioselective Total Synthesis of
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ABSTRACT



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 products¹ containing optically active 2-azaspirocyclic 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 facilitated 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 apoptotic pathway.³

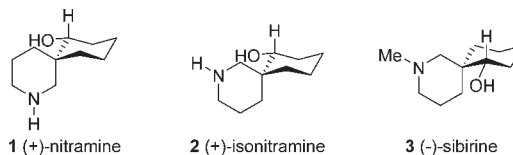


Figure 1. *Nitraria* alkaloids.

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,i} which cannot be readily applied to large scale production. In addition,

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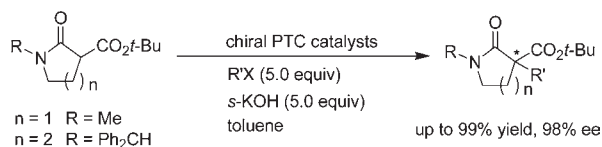
(2) For a recent review on *Nitraria* alkaloid, see: Wanner, J. W.; Koomen, G. J. In *Studies in Natural Products Chemistry: Stereoselectivity in Synthesis and Biosynthesis of Lupine and Nitraria Alkaloids*; Atta-ur-Rahman, Ed.; Elsevier: Amsterdam, 1994; p 731 and references therein.

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only one reported catalytic method uses an organopalladium catalyst for the establishment of quaternary carbon center (6R); 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



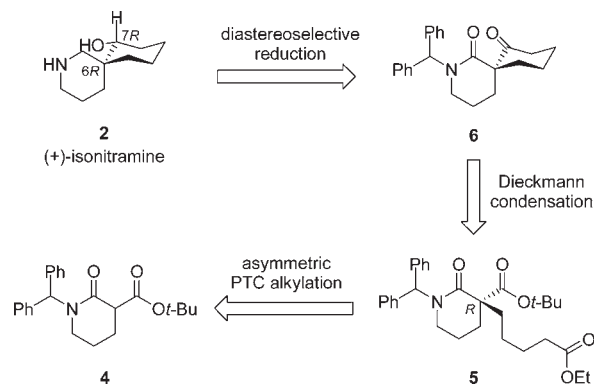
Very recently, we reported on the highly enantioselective PTC alkylations of α -*tert*-butoxycarbonylactams (Scheme 1).⁶ The alkylation of *N*(1)-methyl-2-oxo-pyrrolidine-3-carboxylic acid *tert*-butyl ester or *N*(1)-benzhydryl-2-oxo-piperidine-3-carboxylic acid *tert*-butyl ester under PTC conditions 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 potentially 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(7R) chirality can, in principle, be induced by diastereoselective reduction of **6**, which can be obtained by Dieckmann condensation⁷ 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**).

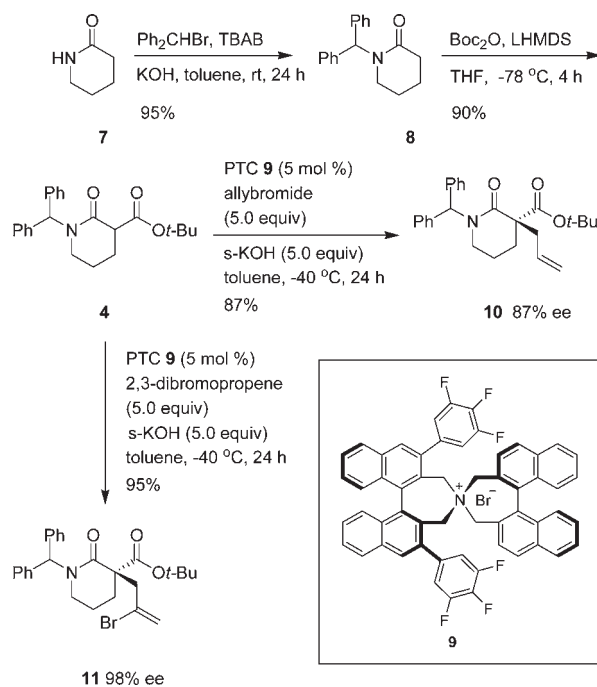
First, the substrate (**4**) for PTC alkylation was prepared from δ -valerolactam (**7**) in two steps (Scheme 3). *N*-Diphenylmethylation of **7** under PTC reaction conditions in the presence of TBAB as a catalyst, followed by *tert*-butylcarboxylation using Boc_2O under LiHMDS basic conditions, provided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

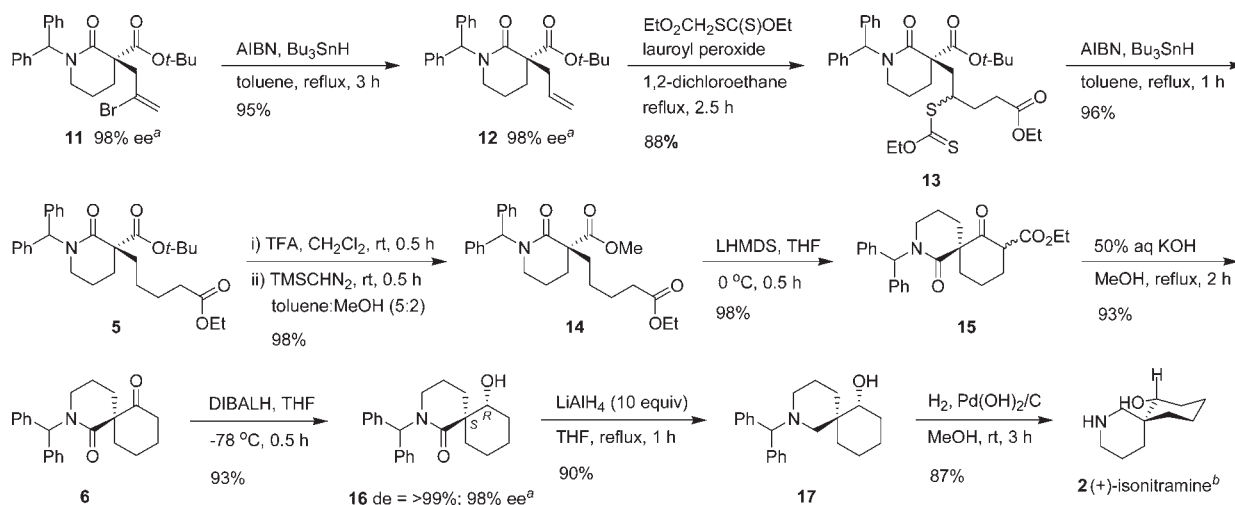
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Scheme 4. Synthesis of (+)-Isonitramine^{a,b}



^aThe 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. ^bAbsolute 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 conditions⁶ [(*S,S*)-3,4,5-Trifluorophenyl-NAS bromide (**9**, 5 mol %), and solid KOH (5.0 equiv) in toluene at $-40\text{ }^{\circ}\text{C}$] 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 $0\text{ }^{\circ}\text{C}$, 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 $-78\text{ }^{\circ}\text{C}$ 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 LiAlH₄ in THF readily afforded piperidine **17** (90%). Finally, (+)-isonitramine {**2**, [α]_D²³ = +6.22 (*c* 1.16, CHCl₃); [α]_D²³ = +5.8 (*c* 1.4, CHCl₃)^{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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