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Asymmetric Total Synthesis of (–)-Epibatidine

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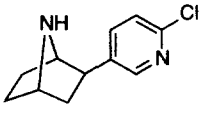
Abstract

An enantioselective approach to (–)-epibatidine based on asymmetric hetero Diels–Alder cycloaddition with an *N*-acylnitroso dienophile bearing 8-(2-naphthyl)menthol as a chiral source, wherein π–π stacking interaction between the naphthyl and nitrosocarbonyl groups may contribute to facial control, is described.

Keywords: Alkaloids; Asymmetric synthesis; Diels–Alder reactions; Nitroso compounds

A new class of amphibian alkaloid epibatidine (**1**), isolated by Daly and co-workers [1] in a trace amount from the skin of the Ecuadorian poison frog, *Epipedobates tricolor*, of the family Dendrobatidae, has been reported to be a highly potent non-opioid analgesic. In preliminary tests on mice, epibatidine proved to be 200 to 500 times as effective as morphine in analgesic effects [1]. Subsequent studies showed that the analgesic activity of epibatidine is attributed to its distinctive property as an extremely potent agonist of the nicotinic acetylcholine receptor [2-4]. The unique feature of this alkaloid is the presence of a strained nitrogen-bridged six-membered carbon ring system (7-azabicyclo[2.2.1]heptane) with an exo-oriented 3-(6-chloropyridyl) substituent, which was first recognized as a component of the natural product.



(–)-epibatidine (**1**)

Due to its unique structure, outstanding pharmacological action, and scarcity in nature, **1** has prompted extensive synthetic efforts toward its total synthesis [5,6]. Of these efforts, however, only two asymmetric syntheses of (–)-epibatidine (**1**), which is the natural enantiomer, have been reported: in one case via Pd-catalyzed desymmetrization reported by Trost [6d], and in the other case via asymmetric protonation reported by Kosugi [6g]. We now report a new enantioselective approach to (–)-epibatidine (**1**) based on asymmetric hetero Diels–Alder cycloaddition with an acylnitroso dienophile bearing 8-(2-naphthyl)menthol as a chiral source.

We have recently recognized [7] efficient asymmetric conjugate allylation of *N*-acyl-2,3-dihydro-4-pyridones using the 8-(2-naphthyl)menthol moiety as a chiral inducer, wherein the presence of π–π stacking interaction between the naphthalene ring and the enamido portion was suggested for control of the facial selectivity. According to this and some other results [8], we envisioned the use of the (1*R*)-8-(2-

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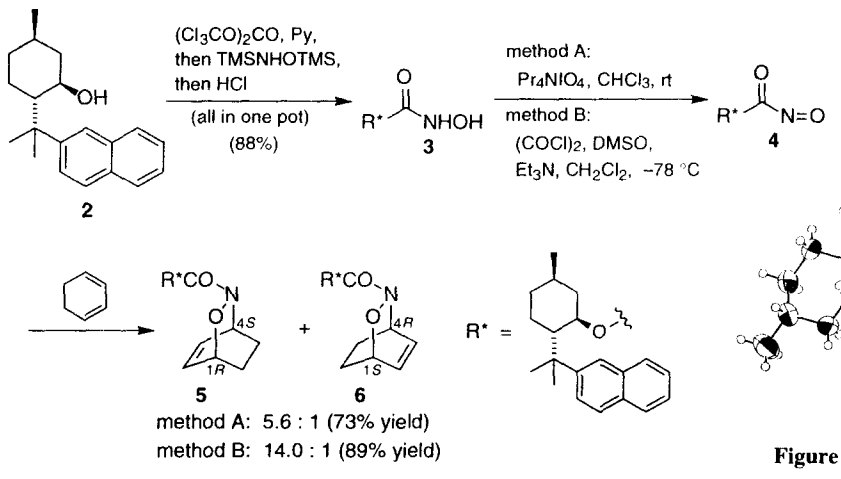
naphthyl)menthol (**2**) as a chiral inducer for asymmetric hetero Diels–Alder cycloaddition with an acylnitroso dienophile [9]. Thus, our initial investigations were designed to evaluate the stereoselectivity in the cycloaddition using the hydroxamic acid **3** incorporating the (1*R*)-8-(2-naphthyl)menthyl group. As shown in Scheme 1, treatment of the (1*R*)-menthol derivative **2** with triphosgen and pyridine in CH_2Cl_2 resulted in the formation of the chloroformate, which immediately underwent reaction with *N*,*O*-bis(trimethylsilyl)hydroxylamine followed by acid treatment in the same reaction vessel, affording **3** in 88% overall yield. In situ oxidation of **3** with periodate in $CHCl_3$ at room temperature (method A) produced the acylnitroso dienophile **4** as a transient intermediate, which reacted at once with 1,3-cyclohexadiene to give the two diastereomeric cycloadducts **5** and **6** with a 5.6:1 ratio in 73% combined yield. When this reaction was performed at −78 °C under Swern oxidation conditions [10] (method B), both the diastereoselectivity and chemical yield were significantly enhanced to 14.0:1 and 89%, respectively. The 2-oxa-3-azabicyclo[2.2.2]oct-5-ene structure with the 1*R*,4*S* absolute configuration of the major cycloadduct **5** was unambiguously established by single crystal X-ray analysis (Figure 1).

Scheme 1



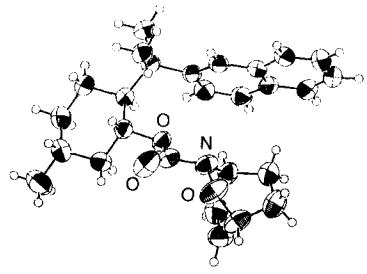
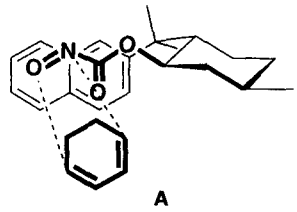


Figure 1. ORTEP drawing of **5**.

The facial diastereoselectivity observed in the cycloaddition is consistent with a transition state model **A**, wherein the naphthyl group shields selectively the face of the nitroso group by π–π stacking interaction between the naphthyl and nitrosocarbonyl groups, forcing the diene to "endo approach" preferentially from the front side. Such an "endo approach" implies that the acylnitroso moiety prefers to be in *s-cis* conformation as indicated [11].

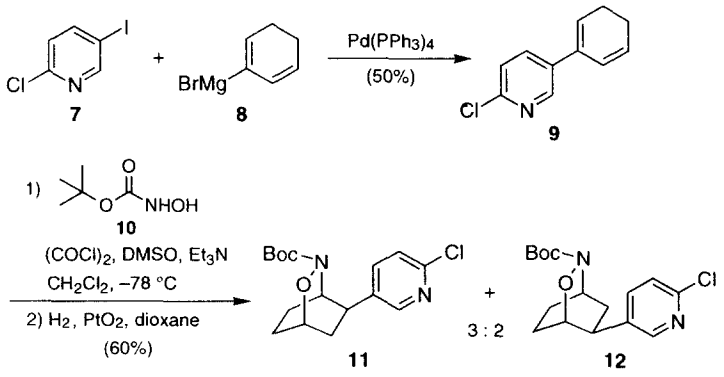


A

Having established the feasibility of the asymmetric cycloaddition with a menthol-based chiral auxiliary, in an attempt to apply this method to the asymmetric synthesis of epibatidine, we next examined the regioselectivity in the cycloaddition using 2-chloro-5-(1,5-cyclohexadienyl)pyridine (**9**) as a diene component. Palladium-catalyzed cross coupling of 2-chloro-4-iodopyridine (**7**) [12,13] with 2-(1,3-cyclohexadienyl)-

magnesium bromide (**8**), prepared from 2-bromo-1,3-cyclohexadiene [14,15] led to **9** in 50% yield. The cycloaddition of **9** with commercially available *tert*-butyl *N*-hydroxycarbamate **10** was performed under Swern conditions. Catalytic hydrogenation of the resulting cycloadducts over PtO_2 reduced the 5,6-double bond to furnish stereoselectively the endo products in 60% yield from **9** as a 3:2 mixture of the regioisomers **11** and **12**. Compound **11** was crystallized, and X-ray crystallographic analysis revealed its regio- and stereochemistry as shown in Figure 2. These results indicate that the *meta-aza* regioisomer favors over the *para-aza* one in this cycloaddition with a strongly electron-withdrawing 2-substituted cyclohexadiene such as **9**. This finding is in contrast to that reported for the cycloaddition with acylnitroso compounds to an electron-deficient 2-substituted-1,3-cyclohexadiene, which predominantly affords *para-aza* adducts consistent with either a normal ($HOMO_{diene}$ controlled) or inverse electron demand ($LUMO_{diene}$ controlled) Diels–Alder reaction [16].

Scheme 2



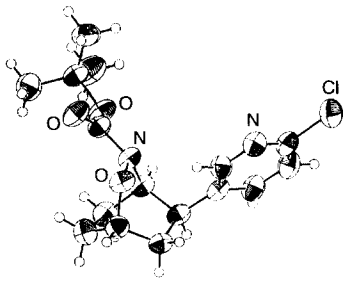
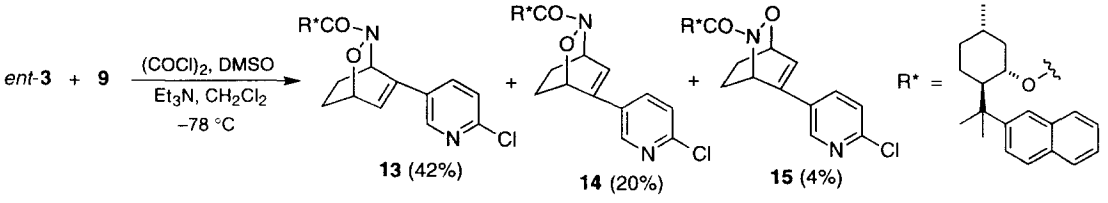


Figure 2. ORTEP drawing of **11**.

Considering the diastereo- and regioselectivities observed in these cycloadditions with the hydroxamic acids **3** and **10**, respectively, we designed an enantioselective approach to (–)-epibatidine (**1**) based on asymmetric hetero Diels–Alder reaction with an acylnitroso dienophile involving the (1*S*)-menthyl auxiliary. Thus, the chiral hydroxamic acid *ent*-**3**, prepared from (1*S*)-8-(2-naphthyl)menthol (*ent*-**2**), was reacted with the diene **9** under Swern conditions to produce the cycloadducts **13** (42%), **14** (20%), and **15** (4%) (Scheme 3).

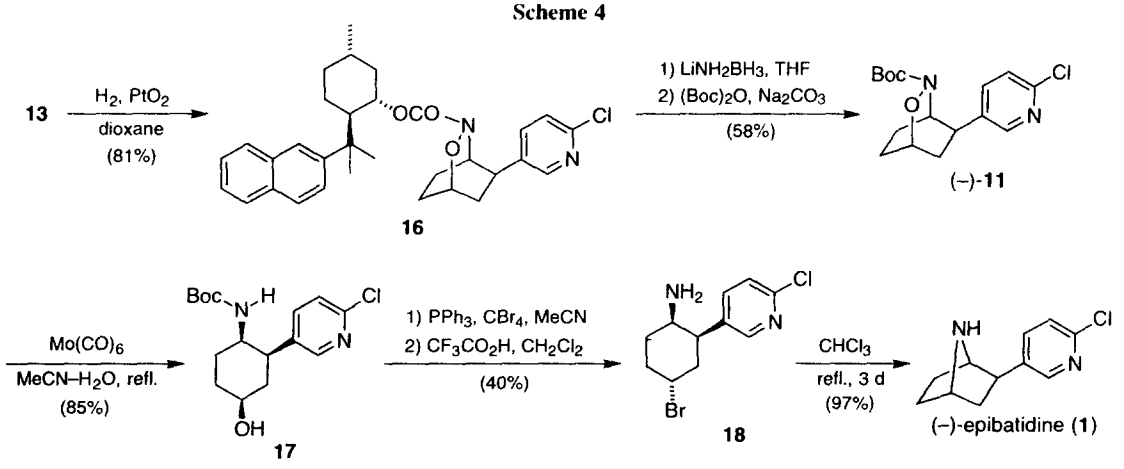
Scheme 3



The major *meta-aza* regioisomer **13** was hydrogenated to give the exo product **16** as a single diastereomer (81%), which underwent removal of the chiral auxiliary with LiH_2NBH_3, prepared from $BH_3{\bullet}NH_3$ and BuLi [17], followed by *tert*-butoxycarbonylation to give (–)-**11** (58% from **16**) identical with the above-described compound **11**, except for the optical rotation. After cleavage of the N–O bond with $Mo(CO)_6$ (85%), the resulting *N*-Boc aminoalcohol **17** was brominated with PPh_3 and CBr_4 with inversion of configuration and then deprotected with trifluoroacetic acid to give the bromoamine **18** in 40% overall yield. Finally, refluxing of **18** in $CHCl_3$ for 3 days provided (–)-epibatidine (**1**), mp 61–62 °C; $[\alpha]^{27}_D$ –6.26 (*c* 0.80, $CHCl_3$), in 97% yield, which was identical with the spectral data (^1H and ^{13}C NMR) reported in the literature [5a].

In conclusion, the enantioselective synthesis of (−)-epibatidine (**1**) has been accomplished by an eight-step route based on asymmetric hetero Diels–Alder cycloaddition with an acylnitroso dienophile incorporating (1*S*)-8-(2-naphthyl)menthol as a chiral inducer, wherein π–π stacking interaction between the naphthyl and nitrosocarbonyl groups may contribute to facial control.

Scheme 4



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