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Synthesis of (3′*R*,5′*S*)-3′-hydroxycotinine using 1,3-dipolar cycloaddition of a nitrone

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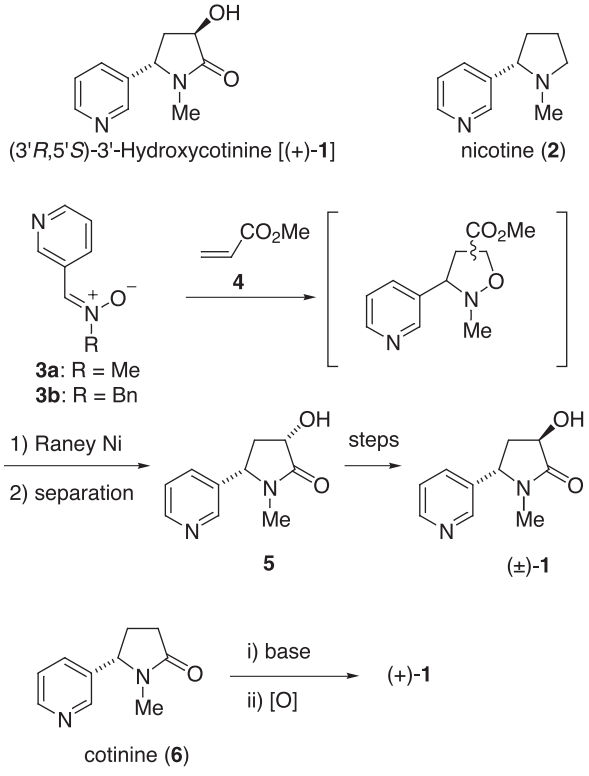
Abstract—To synthesize (3′*R*,5′*S*)-3′-hydroxycotinine [(+)-**1**], the main metabolite of nicotine (**2**), cycloaddition of *C*-(3-pyridyl)nitrones **3a**, **3c**, and **15** with (2*R*)- and (2*S*)-*N*-(acryloyl)bornane-10,2-sultam [(2*R*)- and (2*S*)-**8**] was examined. Among them, L-gulose-derived nitrone **15** underwent stereoselective cycloaddition with (2*S*)-**8** to afford cycloadduct **16**, which was elaborated to (+)-**1**.

1. Introduction

(3′*R*,5′*S*)-3′-Hydroxycotinine [(+)-**1**], which is found in urine of smokers, is one of the main metabolites of nicotine (**2**).[1] Compound (+)-**1** is an important tool for the investigations of the metabolism of nicotine, drug interaction in smokers, and for drug discovery, and many efforts have therefore been made to synthesize (±)-**1** and (+)-**1**, and their derivatives (Scheme 1).[1,2] In 1972, Dagne reported the synthesis of (±)-**1** and revealed that (+)-**1** bears *trans*-stereochemistry.[2a] The synthesis commenced with cycloaddition of nitrone **3a** with methyl acrylate (**4**), which produced a regio- and stereoisomeric mixture of cycloadducts. Hydrogenolysis of the mixture with Raney nickel followed by separation of isomers gave *cis*-hydroxycotinine (**5**), which was elaborated to (±)-**1** in two steps including a Mitsunobu reaction. Since the early 1990s, (3′*R*,5′*S*)-3′-hydroxycotine [(+)-**1**] has been synthesized by using oxidation of natural cotinine (**6**).[2b–e]

Recently, Tejero and co-workers reported reactions of *N*-benzyl-*C*-arylnitrones **7a** and **7b** with (2*R*)-*N*-(acryloyl)-bornane-10,2-sultam [(2*R*)-**8**] (Scheme 2).[3] Thus, *N*-benzyl-*C*-(2-thiazolidinyl)nitrone (**7a**) reacts with (2*R*)-**8** to give only *endo*-addition products **9a** and **10a** with moderate diastereofacial selectivity (78:22) referred to (2*R*)-**8**.[3a] *N*-Benzyl-*C*-(2-furanyl)nitrone (**7b**) also undergoes cycloaddition with (2*R*)-**8** to afford cycloadduct **9b** as the major isomer along with its diastereomer **10b**.[3b] Cycloadditions of acrylate **4** with various *N*-benzyl-*C*-(heteroaryl)nitrones including **3b** and **7b** were also reported.[3c]



Scheme 1.

Keywords: (3′*R*,5′*S*)-3′-Hydroxycotinine; L-Gulose-derived nitrone; Cycloaddition.

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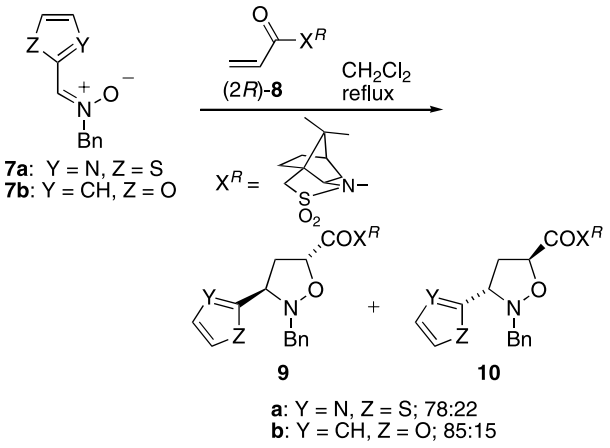


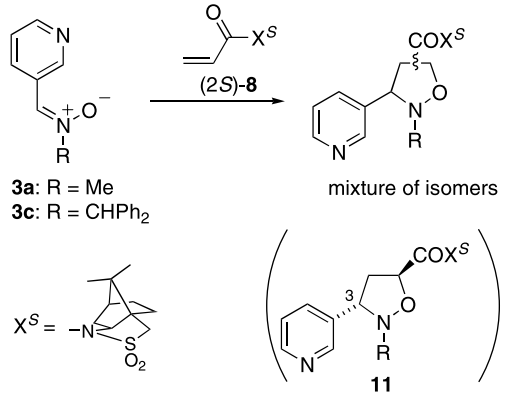
Scheme 2.

To develop chemical synthesis of (+)-**1**, we have examined cycloaddition of *C*-(3-pyridyl)nitrones **3a**, **3c**, and **15** with (2*R*)- and (2*S*)-*N*-(acryloyl)bornane-10,2-sultams [(2*R*)- and (2*S*)-**8**], and report here the synthesis of (3′*R*,5′*S*)-3′-hydroxycotinine [(+)-**1**] by regio and stereoselective cycloaddition of L-gulose-derived nitrone **15** with (2*S*)-**8**.

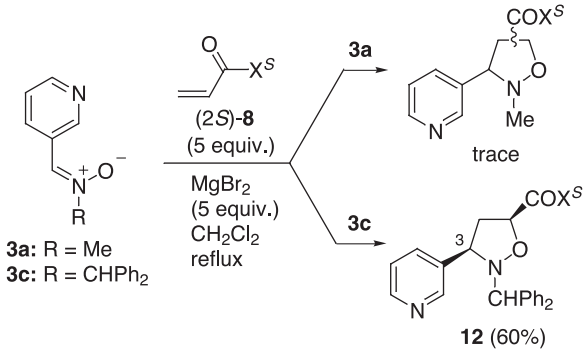
2. Results and discussion

Our investigation began with 1,3-dipolar cycloaddition of *N*-methylnitrone **3a** and *N*-diphenylmethylnitrone **3c** with (2*S*)-**8**,[4] which was expected based on the report by Tejero et al. to afford cycloadduct **11** as the major product having correct stereochemistry at the 3-position of the isoxazolidine ring (Schemes 2 and 3). Nitrone **3a**, on treatment with (2*S*)-**8** in refluxing CH_2Cl_2, underwent 1,3-dipolar cycloaddition to give, however, a complex isomeric mixture of cycloadducts including regio-isomers. Reaction of nitrone **3c** with (2*S*)-**8** again gave a complex mixture of cycloadducts.

These disappointing results prompted us to consider the use of Lewis acid for the cycloaddition (Scheme 4).[4e,5] When *N*-methylnitrone **3a** was heated with (2*S*)-**8** (5 equiv) in the presence of $MgBr_2$ (5 equiv)[6] in refluxing CH_2Cl_2, only trace amounts of cycloadducts were detected. In contrast, reaction of *N*-diphenylmethylnitrone **3b** with (2*S*)-**8** under conditions similar to those for **3a** afforded 60% isolated



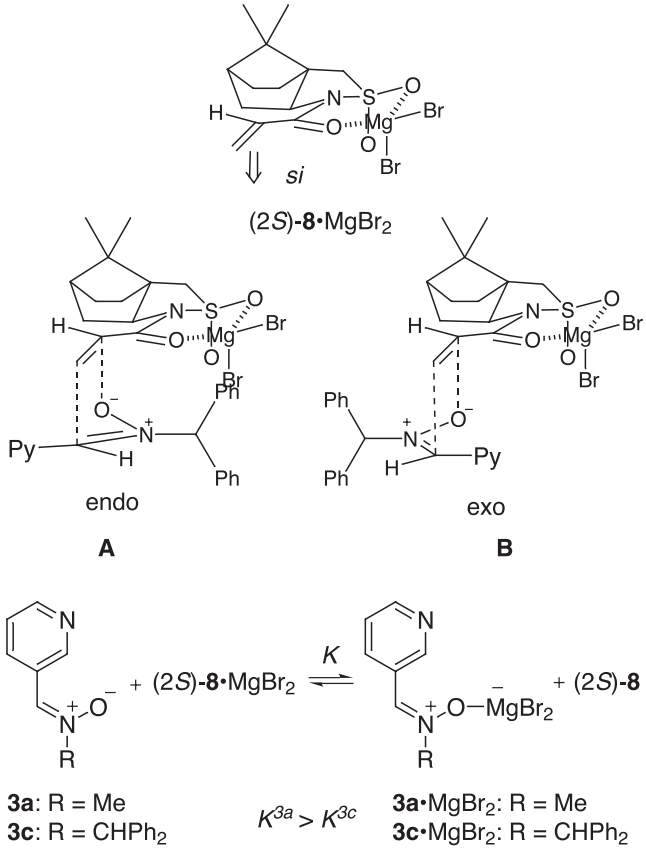
Scheme 3.



Scheme 4.

yield of cycloadduct **12** along with other isomers. The stereochemistry of cycloadduct **12** was determined by X-ray crystallography (Fig. 1),[7] which revealed that cycloadduct **12** had *cis*-relative stereochemistry and (3*R*)-isoxazolidine. To our knowledge, this reaction represents the first example of cycloaddition of *N*-alkyl-*C*-arylnitrone with acryloyl-derivative giving *cis*-isoxazolidine.

Since cycloaddition of nitrones **3a** and **3c** with acrylate-derived dipolarophiles is expected to be controlled by $HOMO_{nitrone}$–$LUMO_{acrylate}$ interaction,[3c] the formation of cycloadduct **12** may involve (2*S*)-**8**·$MgBr_2$ complex having lowered LUMO, which would undergo cycloaddition from the less-hindered *si*-face because of the *s-cis* conformation (Scheme 5).[8,9] Since *endo*-transition state **A** may have severe steric interaction between the bulky diphenylmethyl group and chelated $MgBr_2$, the reaction would mainly



Scheme 5.

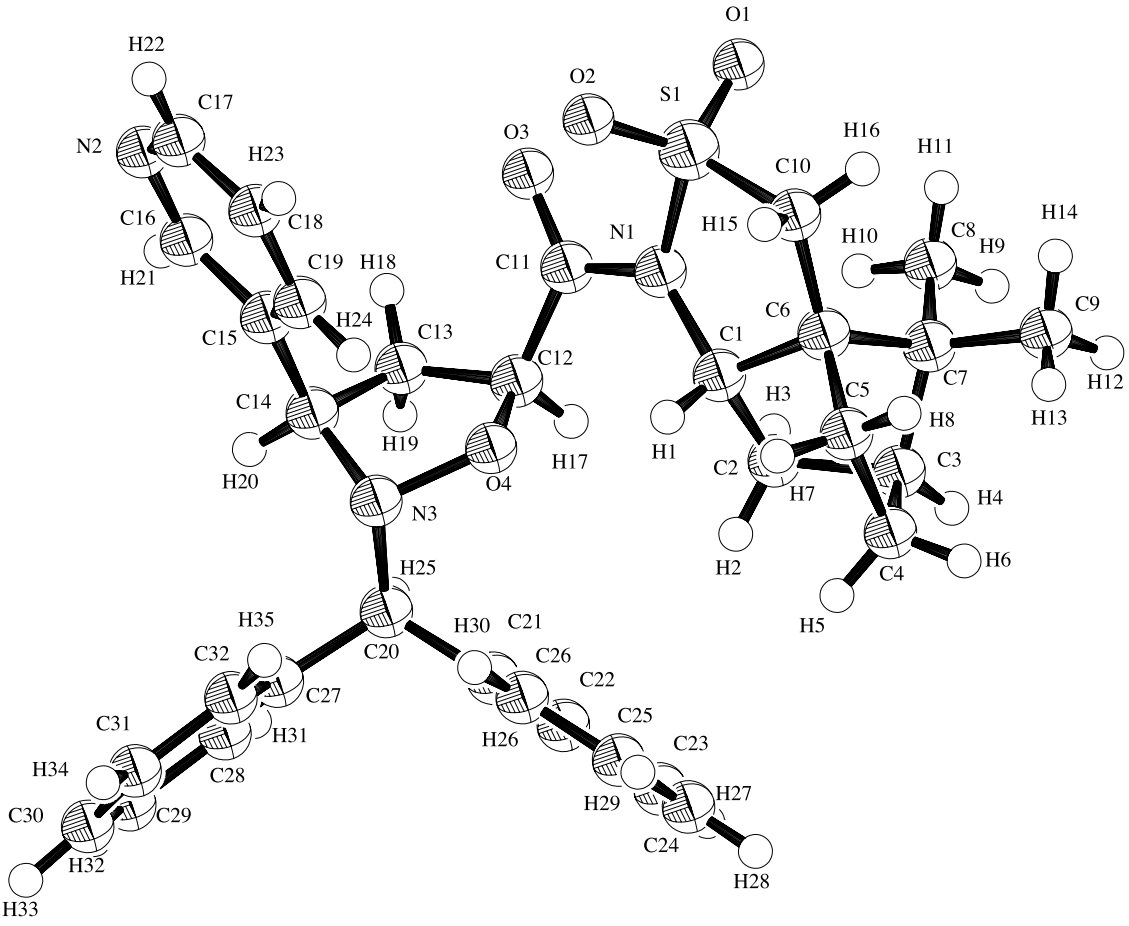


Figure 1. ORTEP drawing of compound **12**.

proceed via *exo*-transition state **B** to afford cycloadduct **12** as the major isomer. The difference in reactivity between nitrones **3a** and **3c** in the presence of $MgBr_2$ may be ascribed to their Lewis basicities. Less bulky nitrone **3a** appears to strongly coordinate with $MgBr_2$ to form non-reactive complex **3a**·$MgBr_2$, whereas sterically more demanding diphenylmethyl group of **3c** would interfere to coordinate with $MgBr_2$. Accordingly, liberated **3b** would react with (2*S*)-**8**·$MgBr_2$ complex to afford adduct **12**.[10]

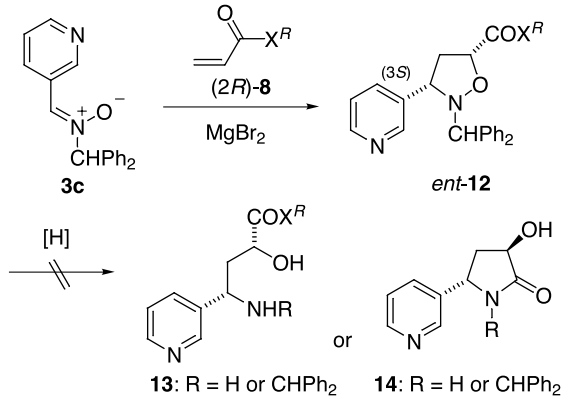
To synthesize (+)-**1** using the present cycloaddition, (3*S*)-isoxazolidine is required. Thus, (3*S*)-isoxazolidine *ent*-**12** was prepared in 58% isolated yield by cycloaddition of nitrone **3c** with (2*R*)-**8** in the presence of $MgBr_2$ (Scheme 6). With *ent*-**12** having correct stereochemistry in hand, we next examined reductive cleavage of the *N–O* bond of *ent*-**12**. However, attempts to obtain 1,3-amino alcohol **13** or lactam **14** by hydrogenolysis of *ent*-**12** with Raney-nickel or 10% Pd–C under various pressures of hydrogen resulted in recovery of *ent*-**12** or a complex mixture probably due to the bulkiness of the diphenylmethyl group of *ent*-**12**.

We then turned our attention to the use of L-gulose-derived nitrone **15**[11–13] because a combination of the chiralities of nitrone **15** and (2*S*)-**8** or (2*R*)-**8** was expected to improve stereoselectivity by double asymmetric induction[14] and because the L-gulosyl group, the chiral auxiliary of nitrone **15**, can be removed under acidic conditions after cycloaddition (Fig. 2).[11] Treatment of nitrone **15** with (2*R*)-**8** in refluxing CH_2Cl_2 caused 1,3-dipolar cycloaddition, however, to give a complex mixture of cycloadducts (Table 1, entry 1). On the other hand, reaction of nitrone **15** with (2*S*)-**8** under conditions similar to those for entry **1** gave cycloadduct **16** as the major product along with small amounts of isomers (entry 2). Moreover, reaction of nitrone **15** with (2*S*)-**8** in refluxing $(CH_2Cl)_2$ still afforded cycloadduct **16** with high selectivity within a shorter reaction time (entry 3).

These results clearly showed a combination of nitrone **15** and (2*R*)-**8** to be a mismatched pair and that of **15** and (2*S*)-**8** to be a matched pair (Scheme 7). In our experience,[11b–e] (*Z*)-*N*-(L-gulosyl)nitrones tend to react from the *si*-face,

Table 1. 1,3-Dipolar cycloaddition of nitrone **15** with (2*R*)- and (2*S*)-**8**

Entry	Dipolarophile	Conditions	Yield (%)	Major product
1	(2*R*)-**8**	CH_2Cl_2 reflux, 9 d	91	Complex mixture of isomers
2	(2*S*)-**8**	CH_2Cl_2 reflux, 7 d	88	**16** (**16**/other isomers=9.3:1)
3	(2*S*)-**8**	$(CH_2Cl)_2$ reflux, 12 h	79	**16** (**16**/other isomers=9.4:1)



Scheme 6.

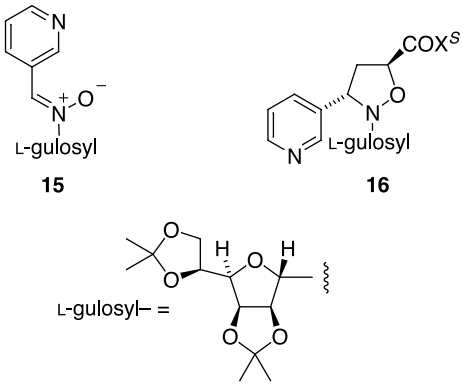
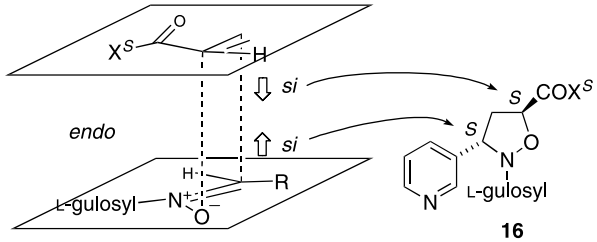


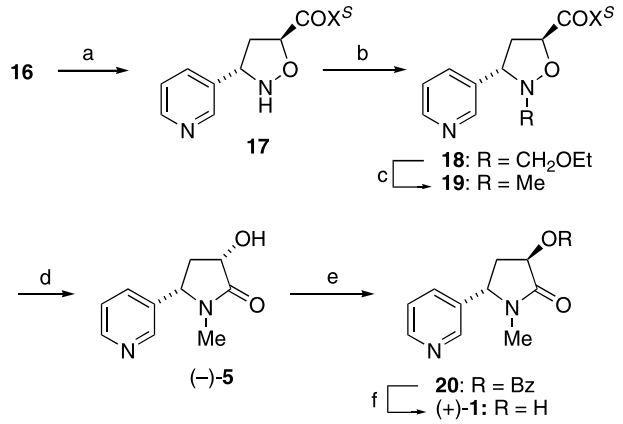
Figure 2. Structures of nitrone **15** and cycloadduct **16**.



Scheme 7.

whereas, as shown in Scheme 2, (2*R*)-**8** reacts mainly from the *e*-face,[9,15] hence of course, (2*S*)-**8** used here should have a tendency to react from the *si*-face. Accordingly, a combination of both selectivities of nitrone **15** and (2*S*)-**8** may exhibit high endo stereoselectivity.

With cycloadduct **16** in hand, we elaborated **16** to (3′*R*,5′*S*)-3′-hydroxycotinine [(+)-**1**] (Scheme 8). As expected, adduct **16** underwent hydrolytic removal of the L-gulosyl group by treatment with hydrochloric acid to give *N*-free isoxazolidine **17** in 76% yield. Isoxazolidine **17** was exposed to formaldehyde in EtOH to give *N*-(ethoxymethyl)isoxazolidine **18**, which, without isolation, was reduced with triethylsilane-trifluoroacetic acid to afford *N*-methylisoxazolidine **19** in 88% yield in two steps.[16] Hydrogenolysis of **19** caused cleavage of the *N–O* bond and lactamization to afford (3′*S*,5′*S*)-3′-hydroxycotinine [(−)-**5**]. Finally,



Scheme 8. Reagents and conditions: (a) HCl–EtOH, rt, 5 h, 76%. (b) HCHO, EtOH, rt, 2 h. (c) Et_3SiH, TFA–CH_2Cl_2, reflux, 0.5 h, 88% in two steps. (d) H_2, 10% Pd/C, 95% EtOH, 1.5 h, 54%. (e) $PhCO_2H$, DEAD, Ph_3P, toluene, rt, 5 min. (f) NaOH, MeOH, rt, 15 min, 88% in two steps.

(3′*R*,5′*S*)-3′-hydroxycotinine [(+)-**1**] was obtained by Mitsunobu reaction of (−)-**5** with benzoic acid followed by alkaline hydrolysis of the benzoate **20**.[2a,17]

3. Conclusions

In conclusion, we have synthesized (3′*R*,5′*S*)-3′-hydroxycotine [(+)-**1**], by using cycloaddition of *N*-(L-gulosyl)-*C*-(3-pyridyl)nitrone **15** with (2*S*)-**8**. Since it is known that control of regio and stereoselectivity is difficult with cycloaddition of *C*-(3-pyridyl)nitrone, the present approach will be useful for cycloaddition of a range of nitrones.

4. Experimental

4.1. General

Melting points are uncorrected. IR spectra were recorded with a Shimazu FTIR-8100 spectrophotometer for solutions in $CHCl_3$. ^1H NMR and ^{13}C NMR spectra were measured on a JEOL JNM-EX 270 or a JEOL JNM-GSX 500 spectrometer. δ Values quoted are relative to tetramethylsilane. High resolution mass spectra (HRMS) were obtained with a JEOL JMS-SX 102 instrument. Column chromatography was performed on Silica gel 60 PF_{254} (Nacalai Tesque) under pressure. Compounds **3a**[2a], (2*R*)-**8**[18], and (2*S*)-**8**[18] were prepared by previously reported methods.

4.1.1. (*Z*)-*N*-Diphenylmethyl-(3-pyridyl)methylideneamine *N*-oxide, 3c. A mixture of 3-pyridinecarboaldehyde (0.944 mL, 1.0 mmol) and diphenylmethylhydroxylamine[19] (199 mg, 1.0 mmol) in dry benzene (15 mL) was heated at reflux with azeotropic removal of water using a Dean–Stark trap for 4 h. After cooling, the mixture was concentrated under reduced pressure, and crystalline residue was triturated with Et_2O, and **3c** (267 mg, 94%) was collected by filtration: mp 182–184 °C (EtOH); IR ($CHCl_3$) 3000, 1580 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 6.40 (1H, s), 7.32–7.41 (11H, m), 7.53 (1H, s), 8.60 (1H, m), 8.90 (1H, br s), 9.10 (1H, br d, J=8.3 Hz). Anal. Calcd for $C_{19}H_{16}N_2O$: C, 78.99; H, 5.58; N, 9.75, found: C, 79.14; H, 5.59; N, 9.72.

4.1.2. (2*S*)-*N*-[[(3*R*,5*S*)-2-(Diphenylmethyl)-3-(3-pyridyl)-isoxazolidin-5-yl]carbonyl]bornane-10,2-sultam, 12. To a stirred mixture of (2*S*)-**8** (380 mg, 1.41 mmol) and $MgBr_2$ (318 mg, 1.41 mmol) in CH_2Cl_2 (15 mL) was added nitrone **3c** (80 mg, 0.282 mmol) in CH_2Cl_2 (2 mL), and the mixture was heated at reflux for 3 days. After cooling, the mixture was successively washed with a saturated solution of $NaHCO_3$ and brine, dried (Na_2CO_3), and evaporated under reduced pressure. The residue was chromatographed on silica gel ($CHCl_3$–AcOEt, 30:1) to give **12** (94 mg, 60%) as colorless crystals: mp 224–226 °C (*n*-hexane–AcOEt); $[\alpha]_D^{20}=+89.8$ (*c* 0.32, $CHCl_3$); IR ($CHCl_3$) 1700, 1340 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 0.93 (3H, s), 1.08 (3H, s), 1.1–1.3 (2H, m), 1.75–1.9 (3H, m), 1.9–2.1 (1H, m), 2.1–2.2 (1H, m), 2.7–3.0 (2H, m), 3.35 (1H, d, $J=$ 13.8 Hz), 3.44 (1H, d, $J=13.8$ Hz), 3.76 (1H, br t, $J=$ 6.1 Hz), 3.95 (1H, t, $J=7.9$ Hz), 4.88 (1H, s), 5.01 (1H, br), 7.05–7.10 (3H, m) 7.1–7.35 (6H, m), 7.45 (2H, d, $J=$ 7.2 Hz), 7.90 (1H, br d, $J=7.8$ Hz), 8.23 (1H, br s), 8.39 (1H, dd, $J=4.4$, 1.5 Hz); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 20.4, 21.5, 26.7, 33.3, 38.9, 45.4, 48.1, 49.4, 53.2, 65.2, 65.5, 73.0, 75.4, 77.7, 124.1, 127.8, 127.9, 128.6, 128.7, 128.9, 129.5, 136.1, 136.5, 140.4, 140.7, 149.1, 149.8, 169.8; MS *m*/*z* 557 (M^+); HRMS calcd for $C_{32}H_{35}N_3O_4S$ 557.2349, found: 557.2344.

4.1.3. (2*R*)-*N*-[[(3*S*,5*R*)-2-(Diphenylmethyl)-3-(3-pyridyl) isoxazolidin-5-yl]carbonyl]bornane-10,2-sultam, *ent*-12. Mp 224–226 °C (*n*-hexane–AcOEt); $[\alpha]_D^{20}=-89.8$ (*c* 0.31, $CHCl_3$).

4.1.4. (*Z*)-3-Pyridyl-*N*-(2′,3′:5′,6′-*O*-diisopropylidene-α-L-gulofuranosyl)methylideneamine *N*-oxide, 15. A mixture of 3-pyridinecarbaldehyde (0.70 mL, 8.72 mmol) and 2,3:5,6-*O*-diisopropylidene-L-gulofuranose oxime[11d] (2.00 g, 7.26 mmol) in toluene (30 mL) was heated at reflux with azeotropic removal of water by a Dean–Stark trap for 20 h. After cooling to room temperature, precipitated crystals were collected by filtration to give **15** (1.88 g, 71%). The mother liquor was concentrated to give the residue, which was chromatographed on silica gel (AcOEt) to give additional **15** (611 mg, total 94%): mp 177–180 °C (toluene); $[\alpha]_D^{26}=+42.3$ (*c* 2.37, $CHCl_3$); IR ($CHCl_3$) 2990, 1560 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 1.34 (3H, s), 1.41 (3H, s), 1.47 (3H, s), 1.52 (3H, s), 3.74 (1H, dd, $J=8.3$, 7.1 Hz), 4.23 (1H, dd, $J=8.3$, 6.6 Hz), 4.40 (1H, dt, $J=8.3$, 6.6 Hz), 4.60 (1H, dd, $J=8.3$, 4.3 Hz), 4.90 (1H, dd, $J=5.9$, 4.3 Hz), 5.33 (1H, d, $J=5.9$ Hz), 5.60 (1H, s), 7.36 (1H, dd, $J=8.3$, 5.0 Hz), 7.68 (1H, s), 8.63 (1H, dd, $J=4.6$, 1.7 Hz), 8.93 (1H, dt, $J=8.3$, 1.7 Hz), 9.00 (1H, d, $J=2.0$ Hz); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 24.5, 25.4, 25.9, 26.7, 65.8, 75.8, 80.2, 84.4, 87.6, 103.5, 109.9, 113.5, 123.5, 126.0, 130.7, 134.8, 150.1, 151.1. Anal. Calcd for $C_{18}H_{24}N_2O_6$: C, 59.33; H, 6.64; N, 7.69, found: C, 59.61; H, 6.77; N, 7.51.

4.1.5. (2*S*)-*N*-[[(3*S*,5*S*)-2-(2′,3′:5′,6′-*O*-Diisopropylidene-α-L-gulofuranosyl)-3-(3-pyridyl)isoxazolidin-5-yl]carbonyl]bornane-10,2-sultam, 16. (a) (Table 1, entry 2). A solution of (2*S*)-**8** (269 mg, 1.00 mmol) and **15** (73 mg, 0.20 mmol) in CH_2Cl_2 (5 mL) was heated at reflux for 7 days. After concentration of the mixture, the residue was chromatographed on silica gel ($CHCl_3$–AcOEt, 30:1) to give a 9.3:1 mixture (111.5 mg) of **16** and other isomers. The mixture was subjected to preparative TLC on silica gel (Et_2O–AcOEt, 10:1) to give **16** (101 mg, 80%): mp 85–88 °C; $[\alpha]_D^{26}=+72.3$ (*c* 0.32, $CHCl_3$); IR ($CHCl_3$) 1700, 1340 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 0.98 (3H, s), 1.19 (3H, s), 127 (3H, s), 1.28 (3H, s), 1.32 (3H, s), 1.44 (3H, s), 1.2–1.3 (2H, m), 1.8–2.15 (4H, m), 2.24–2.26 (1H, m), 2.70 (1H, ddd, $J=12.7$, 8.3, 4.4 Hz), 3.02 (1H, dt, $J=$ 12.7, 6.4 Hz), 3.43 (1H, d, $J=13.7$ Hz), 3.52 (1H, d, $J=$ 13.7 Hz), 3.61 (1H, dd, $J=8.3$, 6.4 Hz), 3.86 (1H, dd, $J=$ 8.3, 4.4 Hz), 3.92 (1H, dd, $J=7.8$, 4.9 Hz), 4.13 (1H, dd, $J=8.3$, 6.4 Hz), 4.26 (1H, dt, $J=8.3$, 6.8 Hz), 4.66 (1H, dd, $J=6.4$, 4.4 Hz), 4.85 (1H, dd, $J=6.9$, 4.4 Hz), 4.86 (1H, s), 5.06 (1H, d, $J=6.4$ Hz), 5.15 (1H, dd, $J=8.3$, 6.4 Hz), 7.24 (1H, dd, $J=7.8$, 4.9 Hz), 7.71 (1H, br d, $J=7.8$ Hz), 8.50 (1H, br d, $J=4.9$ Hz), 8.61 (1H, br s); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 19.8, 20.9, 24.8, 25.2, 26.0, 26.426.6, 32.9, 38.1, 39.4, 44.7, 47.8, 48.9, 53.0, 62.8, 65.5, 65.8, 75.6, 76.6, 80.2, 83.8, 84.2, 97.3, 109.5, 112.5, 123.4, 134.3, 135.8, 148.7, 148.8, 170.1. HRMS (EI) *m*/*z* Calcd for $C_{31}H_{43}N_3O_9S$ 633.2720, found: 633.2717. (b) (Table 1, entry 3). A solution of (2*S*)-**8** (185 mg, 0.686 mmol) and **15** (50.0 mg, 0.137 mmol) in $(CH_2Cl)_2$ (5 mL) was heated at reflux for 12 h. A work-up similar to that for the reaction in CH_2Cl_2 gave **16** (61.2 mg, 71%) and a mixture of isomers (6.7 mg, 7.7%)

4.1.6. (2*S*)-*N*-[[(3*S*,5*S*)-3-(3-Pyridyl)isoxazolidin-5-yl]carbonyl]bornane-10,2-sultam, 17. A solution of **16** (39.9 mg, 63.0 μmol) in concentrated HCl–EtOH (1:6, 1 mL) was stirred at room temperature for 5 h. After concentration, the residue was diluted with $CHCl_3$, washed with a saturated solution of $NaHCO_3$, dried ($MgSO_4$), and concentrated. The residue was chromatographed on silica gel ($CHCl_3$–AcOEt, 20:1) to give **17** (18.7 mg, 76%): mp 218–219 °C (AcOEt–MeOH); $[\alpha]_D^{25}=+175.2$ (*c* 0.36, $CHCl_3$); IR ($CHCl_3$) 1690, 1340 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 0.99 (3H, s), 1.18 (3H, s), 1.3–1.5 (2H, m), 1.8–2.0 (3H, m), 2.0–2.3 (2H, m), 2.6–2.8 (1H, m), 2.95 (ddd, $J=13.2$, 8.8, 4.4 Hz), 3.44 (1H, d, $J=13.8$ Hz), 3.53 (1H, d, $J=13.8$ Hz), 3.90 (1H, dd, $J=7.8$, 4.9 Hz), 4.73 (1H, m), 5.26 (1H, dd, $J=8.3$, 4.4 Hz), 7.26 (1H, m), 6.60 (1H, br), 7.76 (1H, d, $J=7.8$ Hz), 8.50 (1H, d, $J=$ 4.9 Hz), 8.59 (1H, br s); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 19.8, 20.8, 26.3, 32.8, 38.2, 38.4, 42.8, 44.4, 44.6, 47.8, 49.0, 53.0, 60.0, 65.1, 123.4, 133.8, 148.2, 148.5, 172.4; HRMS (EI) *m*/*z* Calcd for $C_{19}H_{25}N_3O_4S$ 391.1566, found: 391.1557. Anal. Calcd for $C_{19}H_{15}NO_2$: C, 58.29; H, 6.44; N, 10.73, found: C, 58.03; H, 6.39; N, 10.66.

4.1.7. (2*S*)-*N*-[[(3*S*,5*S*)-2-Methyl-3-(3-pyridyl)isoxazolidin-5-yl]carbonyl]bornane-10,2-sultam, 19. A mixture of **17** (10.8 mg, 27.6 μmol) and a 36% aqueous solution of formaldehyde (0.07 mL) in EtOH (1.5 mL) was stirred at room temperature for 2 h, and then the mixture was concentrated to give crude (2*S*)-*N*-[[(3*S*,5*S*)-2-ethoxymethyl-3-(2-pyridyl)isoxazolidin-5-yl]carbonyl]bornane-10,2-sultam (**18**). The crude **18** was diluted with a 1:1 mixture of CF_3CO_2H and CH_2Cl_2 (3 mL). To the solution was added Et_3SiH (36 μL, 0.41 mmol), and the mixture was heated at reflux for 30 min. After concentration, the residue was diluted with $CHCl_3$, washed with a saturated aqueous solution of $NaHCO_3$, dried ($MgSO_4$), and concentrated. The residue was chromatographed on silica gel (AcOEt–MeOH,

30:1) to give **19** (9.3 mg, 83%): mp 44–47 °C; $[\alpha]_D^{25}=+39.0$ (*c* 0.36, $CHCl_3$); IR ($CHCl_3$) 1700, 1340 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.98 (3H, s), 1.18 (3H, s), 1.30–1.45 (2H, m), 1.90–1.92 (3H, m), 2.10–2.20 (2H, m), 2.63–2.72 (1H, m), 2.71 (3H, s), 2.73–2.90 (1H, m), 3.42 (1H, d, $J=13.8$ Hz), 3.52 (1H, d, $J=13.8$ Hz), 3.90 (1H, br), 3.94 (1H, dd, $J=7.8$, 4.9 Hz), 5.21 (1H, dd, $J=8.8$, 4.4 Hz), 7.28 (1H, dd, $J=8.0$, 4.5 Hz), 7.75 (1H, br d, $J=7.8$ Hz), 8.54 (1H, br d, $J=2.9$ Hz), 8.57 (1H, br s); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 19.9, 20.8, 26.4, 32.9, 38.3, 43.6, 44.7, 47.8, 49.0, 53.0, 65.5, 69.2, 75.5, 123.7, 134.0, 134.1, 149.4, 149.5, 170.3; HRMS (EI) *m/z* Calcd for $C_{20}H_{27}N_3O_4S$ 405.1723, found: 405.1720.

4.1.8. (3′*S*,5′*S*)-3′-Hydroxycotinine, (−)-5. A mixture of **19** (19.0 mg, 46.9 μmol) and 10% Pd–C (30 mg) in 95% EtOH (2 mL) was stirred under a hydrogen atmosphere for 1.5 h. After filtration through a pad of Celite®, the filtrate was concentrated and the residue was chromatographed on silica gel ($CHCl_3$–MeOH, 10:1) to give (−)-**5** (5.8 mg, 54%) and (2*S*)-bornane-2,10-sultam (5.8 mg, 64%). (−)-**5**: mp 134–136 °C (acetone); $[\alpha]_D^{25}=-21.8$ (*c* 0.13, MeOH); IR (CHCl3) 1692 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 1.92 (1H, dt, $J=13.2$, 7.9 Hz), 2.66 (3H, s), 2.90 (1H, ddd, $J=13.2$, 8.3, 7.3 Hz), 4.23 (1H, br), 4.46 (1H, t, $J=7.6$ Hz), 4.50 (1H, t, $J=8.6$ Hz), 7.37 (1H, dd, $J=7.9$, 4.6 Hz), 7.68, (1H, dt, $J=7.9$, 1.8 Hz), 8.56 (1H, d, $J=2.3$ Hz), 8.63 (1H, dd, $J=4.6$, 1.8 Hz); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 28.4, 37.6, 58.9, 69.5, 124.2, 134.6, 135.1, 149.1, 150.2, 175.4. Anal. Calcd for $C_{10}H_{12}N_2O_2$: C, 62.49; H, 6.29; N, 14.57, found: C, 62.53; H, 6.32; N, 14.44

4.1.9. (3′*R*,5′*S*)-3′-Hydroxycotinine, (+)-1. To a stirred solution of (−)-**5** (7.0 mg, 36 μmol), Ph_3P (12.4 mg, 47 μmol), and benzoic acid (8.5 mg, 47 μmol) in toluene (2 mL) was added a 40% solution of DEAD (19 μL, 85 μmol) at room temperature. After 5 min, the mixture was diluted with $CHCl_3$ (20 mL), washed with a saturated aqueous solution of $NaHCO_3$, dried ($MgSO_4$), and concentrated. The residue was purified by preparative TLC on silica gel ($CHCl_3$–MeOH, 10:1) to give (3*R*,5*S*)-1-methyl-3-(benzoyl)oxy-5-(3-pyridyl)pyrrolidin-2-one (**20**); IR ($CHCl_3$) 1710, 1270 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 2.55 (1H, ddd, $J=12.2$, 8.3, 4.0 Hz), 2.61 (1H, ddd, $J=12.2$, 8.3, 6.9 Hz), 2.83 (3H, s), 4.75 (1H, dd, $J=8.3$, 4.0 Hz), 5.70 (1H, dd, $J=8.3$, 6.9 Hz), 7.36–7.62 (5H, m), 8.07 (1H, d, $J=1.7$ Hz), 8.10 (1H, br s), 8.54 (1H, br s), 8.63 (1H, br d, $J=3.3$ Hz). This material was used for the next step without further purification. Compound **20** was dissolved in 10% NaOH–MeOH (1:10, 1 mL), and the solution was stirred at room temperature for 15 min. After concentration, the residue was purified by preparative TLC on silica gel ($CHCl_3$–MeOH, 5:1) to give (+)-**1** (6.0 mg, 88%): mp 108–110 °C (acetone) [lit.[2c] mp 107–108 °C (acetone)]; $[\alpha]_D^{26}=+38.2$ (*c* 0.40, MeOH) [lit.[2d] $[\alpha]_D=+39$ (*c* 0.48, MeOH); IR ($CHCl_3$) 1694 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 2.34 (1H, ddd, $J=13.2$, 8.2, 3.0 Hz), 2.52 (1H, ddd, $J=13.2$, 8.6, 7.5 Hz), 2.78 (3H, s), 4.59 (1H, br t, $J=7.7$ Hz), 4.66 (1H, dd, $J=8.6$, 3.0 Hz), 5.51 (1H, br), 7.35 (1H, dd, $J=7.9$, 4.6 Hz), 7.46 (1H, br d, $J=8.3$ Hz), 8.49 (1H, d, $J=2.0$ Hz), 8.60 (1H, dd, $J=5.0$, 1.3 Hz); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 28.4, 37.1, 59.6, 68.2, 123.9, 133.6, 135.8, 148.1, 149.5, 175.4.

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Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 246606. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk).

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