52. Diastereo- and Enantiocontrolled Synthesis of (−)-Allosedamine *via* Cycloaddition of a Chiral Nitrone[1])

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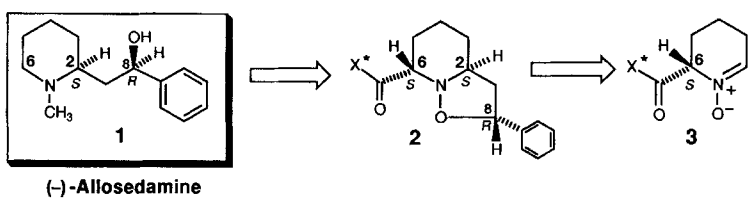
The piperidine alkaloid (−)-allosedamine (**1**) has been synthesized, in 21% overall yield, in nine steps starting from the formyl-ester **4**. The synthesis features the reaction cascade **7** → **3** → **2**, involving asymmetric electrophilic enolate hydroxyamination, hydroxylamine/aldehyde condensation, and nitrone/styrene cycloaddition, as well as the reductive N/O cleavage-decyanation **12** → **1**.

Introduction. – (−)-Allosedamine, isolated from *Lobelia inflata* [1a, b], has been assigned structure **1** [1c, d] (*Scheme 1*).

Several syntheses of the racemic alkaloid **1** are known [2], notably one which features a regio- and diastereoselective 2,3,4,5-tetrahydropyridine 1-oxide/styrene cycloaddition [2d]. On the other hand, enantiospecific approaches to (−)-**1** are rare and lack control of configuration at C(8) [3].

Scheme 1



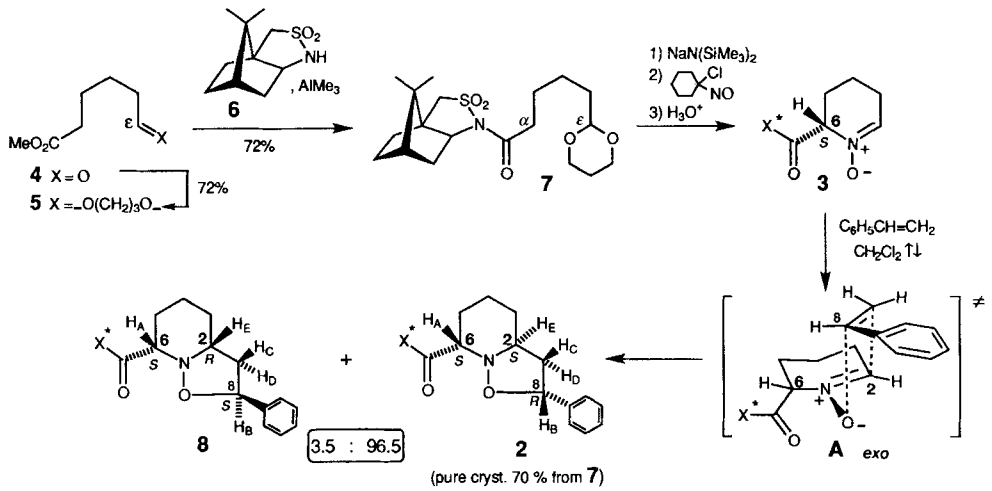
Our strategy (*Scheme 1*) hinges on the assumption that the enantiomerically pure nitrone **3** would undergo an *exo*-selective 1,3-dipolar addition to styrene at the face opposite to the substituent at C(6) with selective generation of the (2*S*)- and (8*R*)-configurations[2]).

Nitrone **3** should be readily accessible by asymmetric electrophilic α-hydroxyamination of a chiral *N*-acylsultam carrying an acetal group in the ε-position, following a protocol recently applied to a synthesis of (−)-pinidine [6].

[1]) Presented by one of us (*W.O.*) at the 'VIIth FECHEM Conference on Heterocycles in Bioorganic Chemistry', Santiago de Compostela, September 1993.

[2]) Reviews on nitrone/alkene cycloaddition reactions: [4]. Cycloadditions of 2-substituted 2,3,4,5-tetrahydropyridine 1-oxides to alkenes afford selectively *trans*-2,6-disubstituted piperidine derivatives [5]. The numbering of **1** corresponds to [1e] and is used also for all intermediates; systematic names are given in the *Exper. Part.*

Scheme 2



Results. – Acetalization of known aldehyde **4** [7] with propane-1,3-diol/pyridinium *p*-toluenesulfonate (72%) followed by Me_3Al-mediated condensation [8] of ester-acetal **5** with sultam **6** provided crystalline *N*-acylsultam **7** (m.p. 85°, 72%; *Scheme 2*).

Deprotonation of **7** with sodium hexamethyldisilazide, electrophilic trapping of the transient (*Z*)-enolate with 1-chloro-1-nitrosocyclohexane at −78°, hydrolysis of the non-isolated nitrone-acetal with 2N aqueous HCl solution (r.t., 12 h) [6], evaporation of the mixture, vigorous stirring of the solid residue with sat. aqueous $NaHCO_3$ solution for 5 min, and extraction (CH_2Cl_2) furnished crude tetrahydropyridine 1-oxide **3**. For characterization, a sample of **3** was purified by flash chromatography (amorphous solid, 63% from **7**, which dimerized slowly in $CDCl_3$ solution)[3]). Crude **3** was directly subjected to the crucial cycloaddition step without further purification. Thus, heating a 0.13M solution of crude nitrone **3** in CH_2Cl_2 with styrene (10 mol-equiv.) under reflux for 2 h and evaporation gave a solid residue containing cycloadducts **2** and **8** in a ratio of 96.5:3.5 (HPLC). ^{1}H-NMR Analysis of this mixture showed no trace of a nitrone dimer[3]). Flash chromatography and crystallization (EtOH) furnished isoxazolo-pyridine **8** (1.5% from **7**) and the major cycloadduct **2** (m.p. 239–240°; 70% from **7**). The depicted structures were readily deduced by means of NOE measurements. Hence, with the minor isomer **8**, NOE enhancements H_A/H_E, H_A/H_C, H_B/H_D, H_C/H_E, and H_C/H_D were observed, whereas the major product **2** showed the NOE enhancements H_A/H_B, H_A/H_C, H_B/H_C, H_D/H_E, and H_C/H_D.

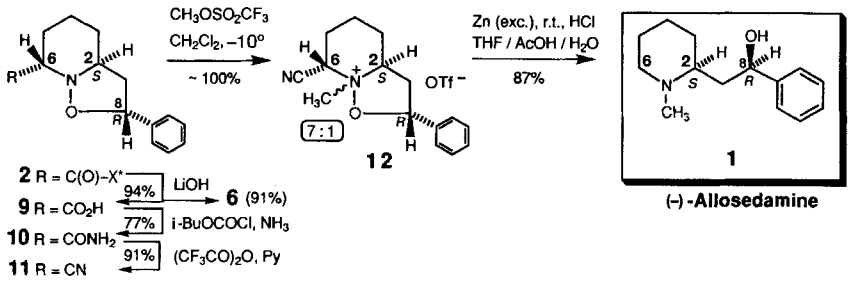
Key cycloadduct **2** was then transformed into alkaloid **1** as depicted in *Scheme 3*.

Mild hydrolysis of **2** (LiOH, THF/H_2O 50:1, 55°, 30 h) and continuous extraction (Et_2O) at pH 7 led to efficient recovery of sultam auxiliary **6** (91% recrystallized). Subsequent continuous extraction (CH_2Cl_2) at pH 1 furnished amino acid **9** (94%).

Attempts to remove the COOH group at C(6) of **9** by *Barton*'s decarboxylation [9] or *Rapoport*'s decarbonylation [10] protocols led to intractable product mixtures. We then

[3]) Competitive formation of a structurally not yet assigned dimer occurred, when the solid residue was suspended in CH_2Cl_2, and the suspension was shaken with sat. aqueous $NaHCO_3$ solution.

Scheme 3



envisaged removal of the substituent at C(6) by a reductive α-aminonitrile decyanation [11]. To this end, we transformed the COOH group of **9** into a CN moiety. Treatment of crude carboxylic acid **9** with i-BuOCOCl/*N*-methylmorpholine and NH_3, followed by dehydration of resulting carboxamide **10** ($(CF_3CO)_2O$/pyridine/dioxane [12]) provided nitrile **11**[4]) (70% from **9**). Disappointingly, all our efforts to achieve reductive decyanation of nitrile **11** yielded nothing but complex mixtures.

It seemed, therefore, preferable to first address the less problematic *N*-methylation/*N,O*-hydrogenolysis. Alkylation of aminonitrile **11** with methyl triflate (1.2 mol-equiv., CH_2Cl_2, $-10°\rightarrow$r.t.) gave ammonium triflates **12** as a 7:1 mixture of *N*-diastereoisomers. Ammonium salts **12** underwent smooth *N,O*-hydrogenolysis with Zn/aqueous AcOH [13] within 5 min.

Even more gratifyingly, *N,O*-cleavage together with reductive decyanation were observed, when ammonium nitriles **12** were stirred with an excess of iron-free activated Zn dust and HCl (4 mol-equiv., THF/AcOH/H_2O 1:1:1, r.t. 20 h). Workup and FC provided (−)-allosedamine (**1**) in 87% yield and > 99.5% e.e. (HPLC, *Daicel Chiralpak AD*). M.p. 80–81°; [1c]: 81–82°. $[\alpha]_D = -29.8$ ($c = 0.2$, MeOH, 20°); [1c]: −31.2 ($c = 5.0$, MeOH, 20°). Synthetic (−)-**1** was identified by comparison (IR and ^{1}H- and ^{13}C-NMR) with a sample of (±)-allosedamine and with published data [1e].

Conclusion. – Enantiomerically and diastereoisomerically pure (−)-allosedamine (**1**) has been prepared from formyl-ester **4** *via* a nine-step reaction sequence in 21% overall yield. The strategic and highly selective tandem hydroxyamination/cycloaddition **7** → **3** → **2** exemplifies again [6] the central role, which chiral cyclic nitrones can play in enantioselective syntheses of molecules containing a piperidine or pyrrolidine nucleus. Further examples will be reported in due course.

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[4]) Aminonitrile **11** shows temperature-dependent ^{1}H- and ^{13}C-NMR spectra probably due to the occurrence of *N*-invertomers.

Experimental Part

General. All reactions were carried out under Ar with magnetic stirring, unless otherwise specified. Solvents were dried by distillation from drying agents as follows: Et_2O, THF, toluene, dioxane (Na metal); pyridine, *N*-methylmorpholine, CH_2Cl_2, DMSO, and Et_3N (CaH_2). Workup denotes extraction with an org. solvent, drying of the org. phase ($MgSO_4$), and evaporation *in vacuo*. Flash chromatography (FC): *Merck 9385* silica gel. GC: *Hewlett-Packard 5790a*, integrator *HP 3390*, capillary column *OV-1* (fused silica, 0.22 mm i.d., 12 m) 10 psi H_2, t_R in min (area-%). HPLC: *Waters ALC/GPC-244*, UV (254 nm) detector, *Mega/Carlo-Erba* integrator, t_R in min (area-%); columns *A*: *Merck Hibar, LiChrosorb Si 60*, 5 μm, 250 × 4 mm; *B*: *DAICEL Chiralpak AD*. M.p.: *Kofler* hot stage, uncorrected. $[\alpha]_D$: *Perkin-Elmer-241* Polarimeter; in $CHCl_3$, unless otherwise specified. IR: *Mattson Instruments Polaris* and *Perkin-Elmer 1600* FT-IR; in KBr, unless otherwise specified; ν_{max} in cm^{-1}. NMR: in $CDCl_3$, unless otherwise specified; standard: TMS ($\delta = 0$ ppm); ^{1}H-NMR: *Bruker AMX 400* (400 MHz) and *Varian XL-200* (200 MHz). ^{13}C-NMR: *Bruker AMX 400* (100 MHz). MS (EI, 70 eV): *m/z* (relative intensity %).

Methyl 5-(1,3-Dioxan-2-yl)pentanoate (**5**). A mixture of *methyl 6-oxohexanoate* (**4**) [7] (28.0 g, 193 mmol), propane-1,3-diol (4.3 g, 583 mmol), pyridinium *p*-toluenesulfonate (PPTS, 9.8 g, 38.8 mmol), and benzene (500 ml) was heated under reflux with azeotropic removal of H_2O (*Dean-Stark* trap) for 1.5 h. Evaporation of the mixture and workup (Et_2O) gave crude acetal **5** (oil, 38.52 g). An aliquot (5 g) was chromatographed (hexane/Et_2O 1:1) to give pure **5** (oil, 3.58 g, 72%). GC (5 min 130°, 10°/min to 270°): 3.58 (97). IR (film): 2920, 2850, 2730, 2660, 1740, 1460, 1435, 1405, 1380, 1240, 1145, 1090, 990. ^{1}H-NMR: 1.34 (*m*, 1 H); 1.37–1.47 (2 H); 1.57–1.68 (4 H); 2.07 (*ddt*, J = 13.5, 12.5, 5.0, 1 H); 2.31 (*t*, J = 7.5, 2 H); 3.66 (*s*, 3 H); 3.71–3.79 (2 H); 4.06–4.12 (2 H); 4.51 (*t*, J = 5.0, 1 H). ^{13}C-NMR: 173.99 (*s*); 101.98 (*d*); 66.81 (*t*, 2 C); 51.39 (*q*); 34.73 (*t*); 33.93 (*t*); 25.76 (*t*); 24.72 (*t*); 23.47 (*t*). MS: 201 (7, $C_{10}H_{17}O_4^+$, $[M-1]^+$), 187 (2), 87 (100, $C_4H_7O_2^+$), 59 (13, $C_2H_3O_2^+$). Anal. calc. for $C_{10}H_{18}O_4$: C 59.39, H 8.97; found: C 59.10, H 8.95.

(2S)-N-[5-(1,3-Dioxan-2-yl)pentanoyl]bornane-10,2-sultam (**7**). A 2M soln. of Me_3Al in hexane (2.47 ml, 4.94 mmol) was added to a soln. of sultam **6**[5] (1.06 g, 4.94 mmol) in toluene (6.0 ml) at r.t. and the mixture was stirred at r.t. for 2 h. Then, ester **5** (1.0 g, 4.94 mmol) was added and the mixture was stirred under Ar at 60° for 40 h. Workup (AcOEt), FC ($CH_2Cl_2 \rightarrow CH_2Cl_2$/AcOEt 10:1) and crystallization (Et_2O/hexane) gave **7** (1.37 g, 72%). M.p. 85°. $[\alpha]_D = +79.8$; $[\alpha]_{578} = +83.4$, $[\alpha]_{546} = +94.8$, $[\alpha]_{436} = +162.8$, $[\alpha]_{365} = +262.8$ (c = 1.00, 20°). IR: 3000, 2990, 2950, 2850, 2735, 2665, 1695, 1455, 1420, 1405, 1380, 1330, 1250, 1210, 1145, 1115, 1090, 1050, 995, 810, 780. ^{1}H-NMR: 0.97 (*s*, 3 H); 1.15 (*s*, 3 H); 1.29–1.49 (5 H); 1.58–1.74 (4 H); 1.84–1.96 (3 H); 1.99–2.16 (3 H); 2.65–2.77 (2 H); 3.42 (*d*, J = 13.8, 1 H); 3.49 (*d*, J = 13.8, 1 H); 3.70–3.78 (2 H); 3.85 (*dd*, J = 5.0, 7.5, 1 H); 4.05–4.11 (2 H); 4.51 (*t*, J = 5.0, 1 H). ^{13}C-NMR: 170.80 (*s*); 102.00 (*d*); 66.82 (*t*, 2 C); 65.17 (*d*); 52.91 (*t*); 48.34 (*s*); 47.70 (*s*); 44.62 (*d*), 38.49 (*t*); 35.39 (*t*); 34.79 (*t*); 32.80 (*t*); 26.41 (*t*); 25.79 (*t*); 24.19 (*t*); 23.37 (*t*); 20.80 (*q*); 19.85 (*q*). MS: 384 (3, $[M-1]^+$), 171 (35, $C_9H_{15}O_3^+$), 113 (8), 95 (9), 87 (100, $C_4H_7O_2^+$), 67 (20), 59 (8). HR-MS: 384.1756 ($C_{19}H_{30}NO_5S^+$, calc. 384.1844). Anal. calc. for $C_{19}H_{31}NO_5S$: C 59.19, H 8.11, N 3.63; found: C 59.21, H 8.11, N 3.72.

(2S,2'S)-N-(2',3',4',5'-Tetrahydro-1'-oxido-1'-pyridinio-2'-carbonyl)bornane-10,2-sultam (**3**). An 1M soln. of sodium hexamethyldisilazide in THF (4.30 ml, 4.30 mmol) was added dropwise to a stirred soln. of **7** (1.50 g, 3.89 mmol) in THF (80 ml) at −78°, and the mixture was stirred at −78° for 1 h. Then, neat 1-chloro-1-nitrosocyclohexane [14] (500 μl, 3.89 mmol) was added dropwise at −78° with instantaneous decolorization of the blue reagent. Stirring the mixture for 1 h at −78°, addition of 2N aq. HCl soln. (22.5 ml), stirring at r.t. for 12 h, and evaporation *in vacuo* (oil pump) gave a colorless solid residue (2.39 g). Vigorous stirring of this residue with sat. aq. $NaHCO_3$ soln. (25 ml) for 5 min, addition of CH_2Cl_2 (25 ml), stirring for further 5 min (until complete dissolution of the solid), separation of the org. layer, extraction of the aq. phase with CH_2Cl_2, drying (Na_2SO_4), and evaporation of the combined org. layers gave crude **3** as an amorphous solid residue (1.54 g).

For characterization, a sample of crude **3** (100 mg) was chromatographed (AcOEt → CH_2Cl_2/MeOH 20:1), giving pure **3** (amorphous solid, 53.4 mg, 63% from **7**). $[\alpha]_D = +62.4$; $[\alpha]_{578} = +65.0$, $[\alpha]_{546} = +73.0$, $[\alpha]_{436} = +122.8$, $[\alpha]_{365} = +191.4$ (c = 0.50, 20°). IR: 2955, 2880, 1700, 1455, 1395, 1330, 1270, 1235, 1220, 1165, 1135, 1065, 990. ^{1}H-NMR: 0.98 (*s*, 3 H); 1.26 (*s*, 3 H); 1.30–1.47 (2 H); 1.67 (*m*, 1 H); 1.82–1.95 (4 H); 2.06 (*dd*, J = 8.0, 14.0, 1 H); 2.10–2.28 (2 H); 2.32 (*m*, 1 H); 2.39–2.58 (2 H); 3.46 (*d*, J = 14.0, 1 H); 3.58 (*d*, J = 14.0, 1 H); 3.92 (*dd*, J = 4.5, 8.0, 1 H); 5.21 (*m*, 1 H); 7.22 (*m*, 1 H). ^{13}C-NMR: (partially dimerized during acquisition) 166.58 (*s*); 138.04 (*d*); 68.16 (*d*); 65.35 (*d*); 52.95 (*t*); 48.89 (*s*); 47.93 (*s*); 44.49 (*d*); 37.74 (*t*); 32.66 (*t*); 27.97 (*t*); 26.43 (*t*); 25.60 (*t*); 20.70 (*q*); 19.87 (*q*); 15.15 (*t*). MS: 341 (0.35, $[C_{16}H_{24}N_2O_4S + 1]^{+\cdot}$), 136 (12), 119 (15), 98 (100, $[C_5H_8NO]^+$), 82 (3, $[C_5H_8N]^+$), 55 (65).

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[5] Sultam **6** and its enantiomer are available from *NEWPORT Synthesis Ireland*, Dublin, Ireland.

Dimer of **3**. An 1M soln. of sodium hexamethyldisilazide in THF (780 µl, 0.78 mmol) was added dropwise to a stirred soln. of **7** (250 mg, 0.65 mmol) in THF (6.5 ml) at −78°, and the mixture was stirred at −78° for 1 h. Then, neat 1-chloro-1-nitrosocyclohexane [14] (83 µl, 0.65 mmol) was added dropwise at −78° with instantaneous decolorization of the blue reagent. Stirring the mixture for 1 h at −78°, addition of 2N aq. HCl soln. (3.8 ml), stirring at r.t. for 12 h, and evaporation *in vacuo* (oil pump) gave a colorless solid residue. A suspension of this residue in CH_2Cl_2 (15 ml) was stirred at r.t. for 10 min, sat. aq. $NaHCO_3$ soln. (20 ml) was added, and the mixture was stirred for 5 min. Drying (Na_2SO_4) and evaporation of the org. phase gave a colorless oil (318 mg) containing **3** and its dimer in a ratio of 36:64 (^{1}H-NMR). FC (hexane/AcOEt 2:1→3:2→CH_2Cl_2/MeOH 20:1) gave pure dimer (amorphous solid, 39.6 mg, 18% from **7**). IR: 3440, 2960, 2880, 1705, 1450, 1400, 1330, 1270, 1240, 1215, 1135, 1060, 960, 760. ^{1}H-NMR: 0.97 (*s*, 3 H); 0.98 (3 H); 1.17 (*s*, 3 H); 1.18 (*s*, 3 H); 1.25–2.00 (22 H); 2.09 (*dd*, *J* = 7.2, 14.0, 2 H); 2.17 (2 H); 3.42 (*d*, *J* = 14.0, 1 H); 3.46 (*d*, *J* = 14.0, 1 H); 3.53 (*d*, *J* = 14.0, 1 H); 3.55 (*d*, *J* = 14.0, 1 H); 3.92 (2 H); 4.11 (*dd*, *J* = 3.5, 11.0, 1 H); 4.88 (br. *m*, 1 H); 5.00 (*dd*, *J* = 3.4, 9.6, 1 H); 5.46 (*dd*, *J* = 3.0, 3.5, 1 H). ^{13}C-NMR: 170.57 (*s*); 170.12 (*s*); 89.25 (*d*); 88.19 (br. *d*?); 65.47 (*d*); 65.27 (*d*); 65.14 (*d*); 58.56 (*d*); 53.17 (*t*); 53.10 (*t*); 48.57 (*s*); 48.53 (*s*); 47.69 (*s*, 2 C); 44.71 (*d*); 44.68 (*d*); 38.32 (*t*); 38.03 (*t*); 32.78 (*t*); 32.70 (*t*); 28.86 (*t*); 27.94 (*t*, 2 C); 27.34 (*t*); 26.34 (*t*); 26.32 (*t*); 21.28 (*t*); 20.75 (*q*); 20.58 (*q*); 19.80 (*q*); 19.72 (*q*); 17.05 (*t*). MS: 341 (2), 324 (2), 260 (3), 150 (8), 135 (11), 119 (10), 108 (12), 98 (32, $C_5H_8NO^+$), 82 (100, $C_5H_8N^+$), 67 (13), 55 (30). MS (FAB+): 681 ($[C_{32}H_{48}N_4O_8S + 1]^+$).

*(2*S*,2'*S*,3'a*R*,7'*R*)- and (2*R*,2'*R*,3'a*S*,7'*S*)-*N*-(3',3'a,4',5',6',7'-Hexahydro-2'-phenyl-2'*H*-isooxazolo[2,3a]pyridine-7'-carbonyl)bornane-10,2-sultam* (**8** and **2**, resp.). A mixture of crude nitrone **3** (1.31 g), styrene (4.5 ml, 39 mmol), and CH_2Cl_2 (30 ml) was heated at reflux for 2 h. Evaporation *in vacuo* furnished a colorless solid residue. HPLC (column *A*, hexane/i-PrOH 96:4, 2 ml/min): 5.20 (3.5), 8.40 (96.5). Chromatography of the residue (CH_2Cl_2/AcOEt 15:1) provided the less polar product **8** admixed with **6** (30 mg). A sample (15.6 mg) was crystallized (EtOH) to give pure minor isomer **8** (11.5 mg, 1.5% from **7**). M.p. 239–240° (dec.). HPLC (column *A*, hexane/i-PrOH 96:4, 2.0 ml/min): 5.20 (99). $[\alpha]_D = -141.6$; $[\alpha]_{578} = -148.0$, $[\alpha]_{546} = -169.2$, $[\alpha]_{436} = -297.4$, $[\alpha]_{365} = -487.8$ (*c* = 0.50, 20°). IR: 3060, 3030, 3005, 2950, 2930, 2885, 1700, 1450, 1330, 1270, 1220, 1165, 1135, 1065, 995, 760, 700. ^{1}H-NMR: 0.93 (*s* (3 H); 1.11 (*s*, 3 H); 1.23–1.61 (4 H); 1.77–1.96 (6 H); 2.02–2.20 (3 H, spin saturation at 2.47→NOE: 24%); 2.06 (*dd*, *J* = 7.5, 13.5, 1 H); 2.47 (*ddd*, *J* = 9.5, 11.0, 11.5, 1 H, spin saturation at 5.11→NOE: 6.8%); 2.61 (*m*, 1 H, spin saturation at 4.08→NOE: 8.3%); 3.45 (*d*, *J* = 14.0, 1 H); 3.55 (*d*, *J* = 14.0, 1 H); 3.85 (*dd*, *J* = 5.0, 7.5, 1 H); 4.08 (*m*, 1 H, spin saturation at 2.60→NOE: 14%); 5.11 (*dd*, *J* = 3.5, 9.5, 1 H, spin saturation at 2.47→NOE: 13%); 7.22–7.36 (5 H). ^{13}C-NMR: 170.68 (*s*); 142.82 (*s*); 128.08 (*d*, 2 C); 126.96 (*d*); 125.72 (*d*, 2 C); 76.92 (*d*); 68.31 (*d*); 65.41 (*d*); 65.19 (*d*); 53.38 (*t*); 48.61 (*s*); 47.77 (*s*); 44.69 (*d*); 42.76 (*t*); 38.13 (*t*); 32.83 (*t*); 28.44 (*t*); 27.68 (*t*); 26.41 (*t*); 23.35 (*t*); 20.70 (*q*); 19.87 (*q*). MS: 444 (0.1, $C_{24}H_{32}N_2O_4S^+$), 202 (100, $C_{13}H_{16}NO^+$), 143 (25), 91 (10), 82 (11, $C_5H_8N^+$), 55 (21).

Further elution afforded more polar, major cycloadduct **2** (1.05 g) which was crystallized (EtOH) to give pure **2** (1.01 g, 70% from **7**). M.p. 239–240° (dec.). $[\alpha]_D = -71.1$ (*c* = 0.35, CH_2Cl_2); $[\alpha]_D = -53.4$; $[\alpha]_{578} = -55.8$, $[\alpha]_{546} = -63.9$, $[\alpha]_{436} = -110.0$, $[\alpha]_{365} = -172.5$ (*c* = 1.00, 20°). HPLC (column *A*, hexane/i-PrOH 96:4, 2.0 ml/min): 8.40 (100). IR: 3085, 3060, 3025, 3000, 2960, 2930, 2905, 2885, 2865, 1700, 1455, 1410, 1320, 1295, 1270, 1235, 1220, 1165, 1135, 1070, 1035, 995, 760, 700. ^{1}H-NMR: (CD_3COOD): 0.86 (*s*, 3 H); 1.03 (*s*, 3 H); 1.20 (*m*, 1 H); 1.34 (*m*, 1 H); 1.40–1.56 (2 H); 1.56–1.69 (2 H); 1.69–2.10 (8 H, spin saturation at 2.67→NOE: 22%, spin saturation at 3.98→NOE: 12%); 2.67 (*m*, 1 H, spin saturation at 5.46→NOE: 5%); 3.47 (*d*, *J* = 14.0, 1 H); 3.58 (*d*, *J* = 14.0, 1 H); 3.85 (*dd*, *J* = 5.0, 7.5, 1 H); 3.98 (*m*, 1 H); 4.15 (br. *d*, *J* = 10.0, 1 H, spin saturation at 2.67→NOE: 7%, spin saturation at 5.46→NOE: 7%); 5.46 (*dd*, *J* = 3.5, 9.5, 1 H, spin saturation at 2.67→NOE: 11%, spin saturation at 4.15→NOE: 9%); 7.14–7.23 (5 H). ^{1}H-NMR ($CDCl_3$): 0.95 (*s*, 3 H); 1.14 (*s*, 3 H); 1.25–2.18 (13 H); 2.05 (*dd*, *J* = 7.5, 14.0, 1 H); 2.75 (*m*, 1 H); 3.46 (*d*, *J* = 14.0, 1 H); 3.55 (*d*, *J* = 14.0, 1 H); 3.94 (*dd*, *J* = 4.5, 7.5, 1 H); 3.95 (*m*, 1 H); 4.13 (br. *d*, *J* = 11, 1 H); 5.53 (*dd*, *J* = 3.5, 9.5, 1 H); 7.24–7.34 (5 H). ^{13}C-NMR ($CDCl_3$): 171.18 (*s*); 142.25 (*s*); 128.34 (*d*, 2 C); 127.55 (*d*); 126.76 (*d*, 2 C); 79.25 (*d*); 65.50 (*d*); 62.44 (*d*); 60.93 (*d*); 53.41 (*t*); 48.67 (*s*); 47.80 (*s*); 44.65 (*d*); 38.76 (*t*); 38.18 (*t*); 32.79 (*t*); 27.34 (*t*); 26.41 (*t*); 24.68 (*t*); 20.72 (*q*); 19.89 (*q*); 17.47 (*t*). MS: 444 (1, $C_{24}H_{32}N_2O_4S^+$), 202 (100, $C_{13}H_{16}NO^+$), 143 (13), 82 (8, $C_5H_8N^+$), 55 (8). HR-MS: 202.1198 ($C_{13}H_{16}NO^+$, calc. 202.1231). Anal. calc. for $C_{24}H_{32}N_2O_4S$: C 64.84, H 7.25, N 6.30; found: C 64.80, H 7.32, N 6.34.

*(2*R*,3a*S*,7*S*)-3,3a,4,5,6,7-Hexahydro-2-phenyl-2*H*-isoxazolo[2,3-a]pyridine-7-carboxylic Acid* (**9**). A mixture of **2** (445 mg, 1.0 mmol), LiOH·H_2O (420 mg, 10 mmol), THF (20 ml), and H_2O (0.4 ml) was stirred at 55° (oil bath) until complete disappearance (TLC) of **2** (30 h). Careful evaporation of the THF *in vacuo* addition of H_2O (10 ml) and neutralization to pH 7 with 1N aq. HCl soln. led to the precipitation of **6**. Continuous extraction with Et_2O for 3 h and evaporation of the dried ($MgSO_4$) org. layer gave crystalline **6** (196.8 mg, 91%), m.p. 181–182°. Acidification of the aq. layer with 10% aq. HCl soln. (2.5 ml to pH 1) and continuous extraction with CH_2Cl_2 for 3 h,

drying, and evaporation of the org. layer furnished **9** (231.7 mg, 94%) as a solid residue. A sample of crude **9** (10 mg) was crystallized (CH_2Cl_2/Et_2O) to give colorless cubes (7.2 mg). M.p. 168–170° (dec.). $[\alpha]_D = -92.4$; $[\alpha]_{578} = -96.6$, $[\alpha]_{546} = -109.5$, $[\alpha]_{436} = -181.7$, $[\alpha]_{365} = -267.7$ ($c = 0.50$, MeOH, 20°). IR: 3020, 3000, 2955, 2930, 2895, 2860, 2735, 2670, 2600, 2530, 2480, 1745, 1715, 1495, 1450, 1285, 1265, 1205, 1110, 1065, 770, 710. ^{1}H-NMR (CD_3OD): 1.51–1.66 (3 H); 1.90–2.08 (3 H); 2.04 (*ddd*, $J = 4.0, 7.5, 12.5$, 1 H); 2.78 (*m*, 1 H); 3.59 (*m*, 1 H); 3.87 (*m*, 1 H); 5.39 (*dd*, $J = 3.5, 9.5$, 1 H); 7.25–7.38 (5 H). ^{13}C-NMR (CD_3OD): 175.74 (*s*); 143.32 (*s*); 129.50 (*d*, 2 C); 128.82 (*d*); 127.59 (*d*, 2 C); 80.35 (*d*); 63.75 (*d*); 61.34 (*d*); 39.90 (*t*); 29.66 (*t*); 25.93 (*t*); 18.63 (*t*). MS: 247 (12, $[C_{14}H_{17}NO_3]^{+\cdot}$), 219 (9, $M - CO]^{+\cdot}$), 202 (100, $C_{13}H_{16}NO^+$), 159 (32), 143 (50, $C_6H_9NO_3^+$), 104 (32, $C_8H_8^+$, cycloreversion), 83 (87, $C_5H_9N^+$), 77 (55), 55 (30). HR-MS: 247.1203 ($C_{14}H_{17}NO_3^{+\cdot}$, calc. 247.1210). Anal. calc. for $C_{14}H_{17}NO_3$: C 68.00, H 6.93, N 5.66; found: C 66.84, H 6.67, N 5.72.

*(2R,3aS,7S)-3,3a,4,5,6,7-Hexahydro-2-phenyl-2*H*-isoxazolo[2,3-a]pyridine-7-carboxamide* (**10**). i-BuOCOCl (169 µl, 1.3 mmol) was added slowly to a mixture of crude **9** (320 mg), *N*-methylmorpholine (285 µl, 2.6 mmol), and THF (25 ml) at −15°. The resulting colorless suspension was stirred for 10 min at −15°. Then, a stream of gaseous dry NH_3 was passed into the suspension for 30 min, and the mixture was allowed to warm to r.t. Evaporation, workup (AcOEt), and FC (Et_2O/i-PrOH/NH_3 20:1:0.04) gave **10** (241 mg, 77%). A sample (11 mg) was crystallized (Et_2O) giving colorless needles (6 mg). M.p. 192–194°. $[\alpha]_D = -113.3$; $[\alpha]_{578} = -117.3$, $[\alpha]_{546} = -132.8$, $[\alpha]_{436} = -223.5$, $[\alpha]_{365} = -345.5$ ($c = 0.75$, 20°). IR: 3430, 3180, 3085, 3040, 2970, 2955, 2925, 2900, 2855, 1640, 1495, 1465, 1445, 1420, 1330, 1280, 1250, 1110, 1080, 1055, 760, 700. ^{1}H-NMR: 1.42–1.68 (3 H); 1.90–2.20 (3 H); 2.10 (*ddd*, $J = 4.0, 7.5, 12.5$, 1 H); 2.68 (*ddd*, $J = 10.0, 12.0, 12.5$, 1 H); 3.33 (*m*, 1 H); 3.93 (*m*, 1 H); 5.32 (*dd*, $J = 4.0, 10.0$, 1 H); 5.45 (br. *s*, 1 H); 6.94 (br. *s*, 1 H); 7.26–7.37 (5 H). ^{13}C-NMR: 175.37 (*s*); 141.38 (*s*); 128.59 (*d*, 2 C); 127.97 (*d*); 126.65 (*d*, 2 C); 78.64 (*d*), 63.36 (*d*); 60.18 (*d*), 38.98 (*t*); 29.46 (*t*); 25.13 (*t*); 17.80 (*t*). MS: 246 (2, $C_{14}H_{18}N_2O_2^{+\cdot}$), 202 (100, $C_{13}H_{16}NO^+$), 143 (42, $C_6H_{11}N_2O_2^+$), 91 (8), 77 (12), 55 (9). HR-MS: 202.1258 ($C_{13}H_{16}NO^+$, calc. 202.1231.

*(2R,3aS,7S)-3,3a,4,5,6,7-Hexahydro-2-phenyl-2*H*-isoxazolo[2,3-a]pyridine-7-carbonitrile* (**11**). $(CF_3CO)_2O$ (135 µl, 0.97 mmol) was added dropwise to a stirred mixture of **10** (217 mg, 0.88 mmol), freshly dist. 1,4-dioxane (4 ml), and pyridine (142 µl, 176 mmol) at 7 to 10°. Stirring of the clear soln. at r.t. for 1 h, addition of H_2O, workup, and FC (hexane/AcOEt 7.5:2) afforded **11** (184 mg, 91%). A sample (10.2 mg) was crystallized (Et_2O/hexane) to give colorless crystals (7.3 mg). M.p. 70°. $[\alpha]_D = +52.0$; $[\alpha]_{578} = +54.5$, $[\alpha]_{546} = +62.5$, $[\alpha]_{436} = +110.0$, $[\alpha]_{365} = +181.8$ ($c = 0.40$, 20°). IR: 3070, 3040, 2990, 2960, 2930, 2895, 2865, 2850, 2230, 1600, 1495, 1455, 1440, 1365, 1330, 1315, 1290, 1260, 1240, 1120, 1070, 1010, 870, 760, 705. ^{1}H-NMR (+55°): 1.48 (*m*, 1 H); 1.59–1.80 (2 H); 1.94–2.10 (3 H); 2.19 (*ddd*, $J = 4.0, 6.5, 11.0$, 1 H); 2.38 (*ddd*, $J = 9.5, 10.0, 11.0$, 1 H); 3.07 (*m*, 1 H); 4.39 (br. *m*, 1 H); 5.07 (*dd*, $J = 4.0, 9.5$, 1 H); 7.24–7.42 (5 H); the ^{1}H-NMR spectrum showed at +25° only br. signals and at −30° two groups of sharp signals (~ 16:1-ratio). ^{13}C-NMR (+55°): 141.53 (*s*); 128.58 (*d*, 2 C); 127.88 (*d*); 126.52 (*d*, 2 C); 116.72 (*s*); 78.16 (*d*); 60.64 (*d*); 53.17 (*d*); 42.58 (*t*); 28.57 (*t*); 28.22 (*t*); 20.35 (*t*); at +25°, br. peaks for most C signals were observed. MS: 228 (35, $C_{14}H_{16}N_2O^{+\cdot}$), 211 (23, $C_{14}H_{15}N_2^+$), 104 (100, $C_8H_8^+$, cycloreversion), 91 (17), 77 (16). HR-MS: 228.1245 ($C_{14}H_{16}N_2O^{+\cdot}$, calc. 228.1262), 211.1230 ($C_{14}H_{15}N_2^+$, calc. 211.1235).

*(2R,3aS,7S)-2-Cyano-3,3a,4,5,6,7-hexahydro-8-methyl-2-phenyl-2*H*-isoxazolo[2,3-a]-1-pyridinium Trifluoromethanesulfonate* (**12**). Methyl triflate (52 µl, 0.47 mmol) was added slowly to a stirred soln. of **11** (90 mg, 0.40 mmol) in CH_2Cl_2 (1.5 ml) at −10°. Stirring of the mixture at −10° for 20 min, then at r.t. for 30 min, evaporation, repeated co-evaporation with CH_2Cl_2, and drying of the residue *in vacuo* gave **12** (solid, 158 mg) consisting of two diastereoisomers **12a**/**12b** in a 7:1 ratio. IR (film): 3045, 2955, 2880, 1460, 1260, 1225, 1165, 1030, 760, 700, 640. ^{1}H-NMR (CD_2Cl_2): 1.85–2.70 (6 H, **12a** + **12b**); 2.75 (*dd*, $J = 4.0, 8.0, 14.0$, 1 H, **12a**); 2.75 (*m*, 1 H, **12b**); 3.09 (*ddd*, $J = 9.5, 13.0, 13.5$, 1 H, **12b**); 3.46 (*ddd*, $J = 9.5, 12.5, 14.0$, 1 H, **12a**); 3.68 (*s*, 3 H, **12b**); 3.83, (*s*, 3 H, **12a**); 4.34 (*m*, 1 H, **12b**); 4.66 (*m*, 1 H, **12a**); 5.66 (*m*, 1 H, **12a** + **12b**); 5.84 (*dd*, $J = 3.0, 9.5$, 1 H, **12b**); 6.00 (*dd*, $J = 4.0, 9.5$, 1 H, **12a**); 7.40–7.47 (5 H, **12a** + **12b**). ^{13}C-NMR (CD_2Cl_2): 136.68 (*s*, **12a**); 135.40 (*s*, **12b**); 130.52 (*d*, **12b**); 130.39 (*d*, **12a**); 129.79 (*d*, 2 C, **12b**); 129.69 (*d*, 2 C, **12a**); 127.17 (*d*, 2 C, **12a**); 127.04 (*d*, 2 C, **12b**); 112.66 (*s*, **12a**); 112.28 (*s*, **12b**); 85.12 (*d*, **12a**); 84.15 (*d*, **12b**); 77.12 (*d*, **12a**); 74.59 (*d*, **12b**); 64.14 (*d*, **12b**); 61.63 (*d*, **12a**); 49.55 (*q*, **12a**); 45.95 (*q*, **12b**); 36.69 (*t*, **12a**); 36.07 (*t*, **12b**); 27.99 (*t*, **12a**); 26.68 (*t*, **12b**); 24.56 (*t*, **12b**); 23.24 (*t*, **12a**); 19.64 (*t*, **12b**); 15.79 (*t*, **12a**).

(−)-Allosedamine (*(2S,2′R)-1,2,3,4,5,6-Hexahydro-2-(2′-hydroxy-2′-phenylethyl)-1-methylpyridine*, **1**). Iron-free Zn dust (10 g) was treated with 10% aq. HCl soln. for 5 min, filtered, washed with H_2O (150 ml) then with acetone (150 ml), and dried *in vacuo* for 16 h. A mixture of this activated Zn dust (1.29 g), freshly prepared crude **12** (*N*-diastereoisomer mixture, 158 mg), AcOH (4 ml), H_2O (4 ml), THF (4 ml), 2N aq. HCl soln. (810 µl, 1.62 mmol) was vigorously stirred at r.t. for 20 h. Addition of sat. aq. $NaHCO_3$ soln. (160 ml→pH 8, formation of a colorless precipitate), extraction (AcOEt), and evaporation yielded a solid residue (88.4 mg). A sample (30 mg) was chromatographed on Al_2O_3 (activity II, C_6H_6→C_6H_6/i-PrOH/NH_3 40:1:0.04) providing pure **1** (25.4 mg, 87%

from **11**). M.p. 80–81° ([1c]: 81–82°). $[\alpha]_D = -29.8$ ([1c]: −31.2 ($c = 5.0$, MeOH, 20°)); $[\alpha]_{578} = -31.0$, $[\alpha]_{546} = -35.0$, $[\alpha]_{436} = -61.7$, $[\alpha]_{365} = -100.0$ ($c = 0.20$, MeOH, 20°). HPLC (column *B*, hexane/i-PrOH 15:1, containing 0.2% Et_2NH, 1.0 ml/min): 9.46 (100); no trace of the antipode was detected; (±)-allosedamine: 6.34 (50), 9.46 (50). IR ($CHCl_3$): 3270, 3080, 3060, 3030, 2935, 2855, 2800, 2725, 1450, 1445, 1280, 1275, 1060, 1030, 755, 700. ^{1}H-NMR: 1.32 (*m*, 1 H); 1.55–1.75 (4 H); 1.78–1.95 (2 H); 2.10 (*ddd*, $J = 3.5$, 11.0, 11.5, 1 H); 2.17 (*ddd*, $J = 3.5$, 10.5, 15.0, 1 H); 2.34 (*m*, 1 H); 2.46 (*s*, 3 H); 3.01 (*m*, 1 H); 5.13 (*dd*, $J = 3.5$, 10.5, 1 H); 7.24–7.40 (5 H). ^{13}C-NMR: 145.51 (*s*); 128.23 (*d*, 2 C); 126.914 (*d*); 125.58 (*d*, 2 C); 71.75 (*d*); 62.61 (*d*); 56.90 (*t*); 43.76 (*q*); 39.39 (*t*); 29.17 (*t*); 25.33 (*t*); 24.23 (*t*). MS: 219 (2, $C_{14}H_{21}NO^{+\cdot}$), 98 (100, $C_6H_{12}N^+$), 70 (12, $C_4H_8N^+$). HR-MS: 219.1600 ($C_{14}H_{21}NO^{+\cdot}$, calc. 219.1623).

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