

52. Diastereo- and Enantiocontrolled Synthesis of (–)-Allosedamine via Cycloaddition of a Chiral Nitrone¹⁾

by Wolfgang Oppolzer*, Jörg Deerberg, and Osamu Tamura

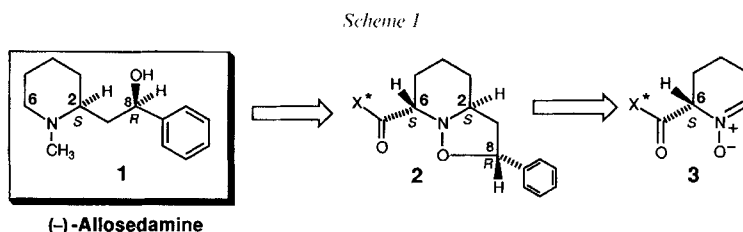
Département de Chimie Organique, Université de Genève, CH-1211 Genève 4

(17.1.94)

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].



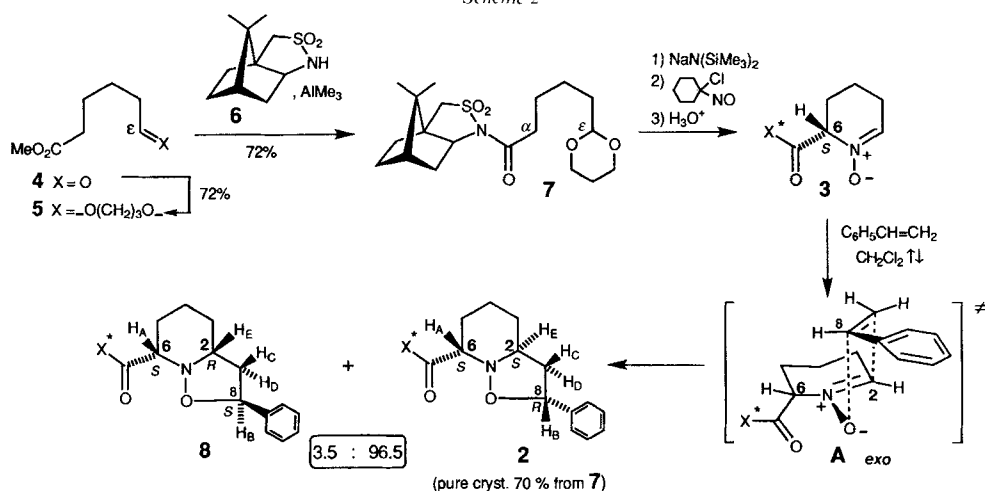
Our strategy (*Scheme 1*) hinges on the assumption that the enantiomerically pure nitrone **3** would undergo an *exo*-selective 1,3-dipolar addition to styrene at the face opposite to the substituent at C(6) with selective generation of the (2*S*)- and (8*R*)-configurations²⁾.

Nitrone **3** should be readily accessible by asymmetric electrophilic α -hydroxyamination of a chiral *N*-acysultam 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 FECHM 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*-acysultam **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 solution³). 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). ^1H -NMR Analysis of this mixture showed no trace of a nitrone dimer³). Flash chromatography and crystallization (EtOH) furnished isoxazolo-pyridine **8** (1.5% from **7**) and the major cycloadduct **2** (m.p. $239\text{--}240^\circ$; 70% from **7**). The depicted structures were readily deduced by means of NOE measurements. Hence, with the minor isomer **8**, NOE enhancements $\text{H}_\text{A}/\text{H}_\text{E}$, $\text{H}_\text{A}/\text{H}_\text{C}$, $\text{H}_\text{B}/\text{H}_\text{D}$, $\text{H}_\text{C}/\text{H}_\text{E}$, and $\text{H}_\text{C}/\text{H}_\text{D}$ were observed, whereas the major product **2** showed the NOE enhancements $\text{H}_\text{A}/\text{H}_\text{B}$, $\text{H}_\text{A}/\text{H}_\text{C}$, $\text{H}_\text{B}/\text{H}_\text{C}$, $\text{H}_\text{D}/\text{H}_\text{E}$, and $\text{H}_\text{C}/\text{H}_\text{D}$.

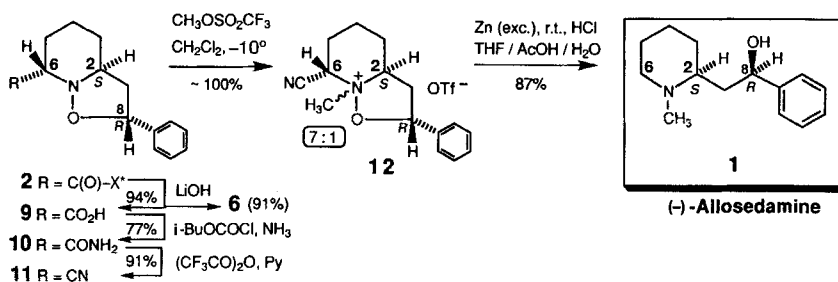
Key cycloadduct **2** was then transformed into alkaloid **1** as depicted in Scheme 3.

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*-BuOCOC(1)/*N*-methylmorpholine and NH_3 , followed by dehydration of resulting carboxamide **10** ($(\text{CF}_3\text{CO})_2\text{O}$ /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 , $-10^\circ \rightarrow \text{r.t.}$) 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 ^1H - 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 $7 \rightarrow 3 \rightarrow 2$ 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 ^1H - 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: Et₂O, THF, toluene, dioxane (Na metal); pyridine, *N*-methylmorpholine, CH₂Cl₂, DMSO, and Et₃N (CaH₂). Workup denotes extraction with an org. solvent, drying of the org. phase (MgSO₄), 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 H₂, *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. [α]_D: Perkin-Elmer-241 Polarimeter; in CHCl₃, 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 CDCl₃, unless otherwise specified; standard: TMS (δ = 0 ppm); ¹H-NMR: Bruker AMX 400 (400 MHz) and Varian XL-200 (200 MHz). ¹³C-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 H₂O (Dean-Stark trap) for 1.5 h. Evaporation of the mixture and workup (Et₂O) gave crude acetal **5** (oil, 38.52 g). An aliquot (5 g) was chromatographed (hexane/Et₂O 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. ¹H-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). ¹³C-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, C₁₀H₁₇O₄⁺, [*M* – 1]⁺), 187 (2), 87 (100, C₄H₇O₂⁺), 59 (13, C₂H₃O₂⁺). Anal. calc. for C₁₀H₁₈O₄: C 59.39, H 8.97; found: C 59.10, H 8.95.

(2*S*)-N-[5-(1,3-Dioxan-2-yl)pentanoyl]bornane-10,2-sultam (7). A 2*M* soln. of Me₃Al 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 (CH₂Cl₂→CH₂Cl₂/AcOEt 10:1) and crystallization (Et₂O/hexane) gave **7** (1.37 g, 72%). M.p. 85°. [α]_D = +79.8; [α]₅₇₈ = +83.4, [α]₅₄₆ = +94.8, [α]₄₃₆ = +162.8, [α]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. ¹H-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). ¹³C-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, C₉H₁₅O₃⁺), 113 (8), 95 (9), 87 (100, C₄H₇O₂⁺), 67 (20), 59 (8). HR-MS: 384.1756 (C₁₉H₃₀NO₅S⁺, calc. 384.1844). Anal. calc. for C₁₉H₃₁NO₅S: C 59.19, H 8.11, N 3.63; found: C 59.21, H 8.11, N 3.72.

(2*S*,2'*S*)-N-(2',3',4',5'-Tetrahydro-1'-oxido-1'-pyridinio-2'-carbonyl)bornane-10,2-sultam (3). An 1*M* 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 2*N* 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. NaHCO₃ soln. (25 ml) for 5 min, addition of CH₂Cl₂ (25 ml), stirring for further 5 min (until complete dissolution of the solid), separation of the org. layer, extraction of the aq. phase with CH₂Cl₂, drying (Na₂SO₄), 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→CH₂Cl₂/MeOH 20:1), giving pure **3** (amorphous solid, 53.4 mg, 63% from **7**). [α]_D = +62.4; [α]₅₇₈ = +65.0, [α]₅₄₆ = +73.0, [α]₄₃₆ = +122.8, [α]₃₆₅ = +191.4 (*c* = 0.50, 20°). IR: 2955, 2880, 1700, 1455, 1395, 1330, 1270, 1235, 1220, 1165, 1135, 1065, 990. ¹H-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). ¹³C-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, [C₁₆H₂₄N₂O₄S + 1]⁺), 136 (12), 119 (15), 98 (100, [C₅H₈NO]⁺), 82 (3, [C₅H₈N]⁺), 55 (65).

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 μ l, 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 μ l, 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 ($^1\text{H-NMR}$). FC (hexane/AcOEt 2:1 $\rightarrow$ 3:2 $\rightarrow$ 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. $^1\text{H-NMR}$: 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). $^{13}\text{C-NMR}$: 170.57 (s); 170.12 (s); 89.25 (d); 88.19 (br. J'); 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, $\text{C}_5\text{H}_8\text{NO}^+$), 82 (100, $\text{C}_5\text{H}_8\text{N}^+$), 67 (13), 55 (30). MS (FAB+): 681 ($[\text{C}_{32}\text{H}_{48}\text{N}_4\text{O}_8\text{S} + 1]^+$).

(2*S*,2'*S*,3*S*,3'*R*,7'*R*)- and (2*R*,2'*R*,3'*S*,7'*S*)-N-(3',3'*a*,4',5',6',7'-Hexahydro-2'-phenyl-2'-isooxazolof[2,3*a*]pyridine-7'-carbonyl)bornane-10,2-sultam (**8** and **2**, resp.). A mixture of crude nitronc **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. $^1\text{H-NMR}$: 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 $\rightarrow$ 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 $\rightarrow$ NOE: 6.8%); 2.61 (m, 1 H, spin saturation at 4.08 $\rightarrow$ 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 $\rightarrow$ NOE: 14%); 5.11 (dd, $J = 3.5$, 9.5, 1 H, spin saturation at 2.47 $\rightarrow$ NOE: 13%); 7.22–7.36 (5 H). $^{13}\text{C-NMR}$: 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, $\text{C}_{24}\text{H}_{32}\text{N}_2\text{O}_4\text{S}^+$), 202 (100, $\text{C}_{13}\text{H}_{16}\text{NO}^+$), 143 (25), 91 (10), 82 (11, $\text{C}_5\text{H}_8\text{N}^+$), 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. $^1\text{H-NMR}$ (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 $\rightarrow$ NOE: 22%, spin saturation at 3.98 $\rightarrow$ NOE: 12%); 2.67 (m, 1 H, spin saturation at 5.46 $\rightarrow$ 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 $\rightarrow$ NOE: 7%, spin saturation at 5.46 $\rightarrow$ NOE: 7%); 5.46 (dd, $J = 3.5$, 9.5, 1 H, spin saturation at 2.67 $\rightarrow$ NOE: 11%, spin saturation at 4.15 $\rightarrow$ NOE: 9%); 7.14–7.23 (5 H). $^1\text{H-NMR}$ (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). $^{13}\text{C-NMR}$ (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, $\text{C}_{24}\text{H}_{32}\text{N}_2\text{O}_4\text{S}^+$), 202 (100, $\text{C}_{13}\text{H}_{16}\text{NO}^+$), 143 (13), 82 (8, $\text{C}_5\text{H}_8\text{N}^+$), 55 (8). HR-MS: 202.1198 ($\text{C}_{13}\text{H}_{16}\text{NO}^+$, calc. 202.1231). Anal. calc. for $\text{C}_{24}\text{H}_{32}\text{N}_2\text{O}_4\text{S}$: C 64.84, H 7.25, N 6.30; found: C 64.80, H 7.32, N 6.34.

(2*R*,3*a*,7*S*)-3,3*a*,4,5,6,7-Hexahydro-2-phenyl-2H-isooxazolo[2,3-*a*]pyridine-7-carboxylic Acid (**9**). A mixture of **2** (445 mg, 1.0 mmol), LiOH $\cdot$ H₂O (420 mg, 10 mmol), THF (20 ml), and H₂O (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 H₂O (10 ml) and neutralization to pH 7 with 1N aq. HCl soln. led to the precipitation of **6**. Continuous extraction with Et₂O 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 ($\text{CH}_2\text{Cl}_2/\text{Et}_2\text{O}$) to give colorless cubes (7.2 mg). M.p. 168–170° (dec.). $[\alpha]_{\text{D}} = -92.4$; $[\alpha]_{578} = -96.6$, $[\alpha]_{546} = -109.5$, $[\alpha]_{436} = -181.7$, $[\alpha]_{365} = -267.7$ ($c = 0.50$, 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. $^1\text{H-NMR}$ (CD_3OD): 1.51–1.66 (3 H); 1.90–2.08 (3 H); 2.04 (*ddd*, $J = 4.0, 7.5, 12.5, 1 \text{ H}$); 2.78 (*m*, 1 H); 3.59 (*m*, 1 H); 3.87 (*m*, 1 H); 5.39 (*dd*, $J = 3.5, 9.5, 1 \text{ H}$); 7.25–7.38 (5 H). $^{13}\text{C-NMR}$ (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 (*r*); 29.66 (*r*); 25.93 (*r*); 18.63 (*r*). MS: 247 (12, $[\text{C}_{14}\text{H}_{17}\text{NO}_3]^+$), 219 (9, $M - \text{CO}]^+$), 202 (100, $\text{C}_{13}\text{H}_{16}\text{NO}^+$), 159 (32), 143 (50, $\text{C}_6\text{H}_9\text{NO}_3^+$), 104 (32, C_8H_8^+ , cycloreversion), 83 (87, $\text{C}_5\text{H}_9\text{N}^+$), 77 (55), 55 (30). HR-MS: 247.1203 ($\text{C}_{14}\text{H}_{17}\text{NO}_3^+$, calc. 247.1210). Anal. calc. for $\text{C}_{14}\text{H}_{17}\text{NO}_3$: C 68.00, H 6.93, N 5.66; found: C 66.84, H 6.67, N 5.72.

(2*R*,3*aS*,7*S*)-3,3*a*,4,5,6,7-Hexahydro-2-phenyl-2H-isoxazolo[2,3-*a*]pyridine-7-carboxamide (**10**). *i*-BuOCOC1 (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 ($\text{Et}_2\text{O}/i\text{-PrOH}/\text{NH}_3$ 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°. $[\alpha]_{\text{D}} = -113.3$; $[\alpha]_{578} = -117.3$, $[\alpha]_{546} = -132.8$, $[\alpha]_{436} = -223.5$, $[\alpha]_{365} = -345.5$ ($c = 0.75$, 20°). IR: 3430, 3180, 3085, 3040, 2970, 2955, 2925, 2900, 2855, 1640, 1495, 1465, 1445, 1420, 1330, 1280, 1250, 1110, 1080, 1055, 760, 700. $^1\text{H-NMR}$: 1.42–1.68 (3 H); 1.90–2.20 (3 H); 2.10 (*ddd*, $J = 4.0, 7.5, 12.5, 1 \text{ H}$); 2.68 (*ddd*, $J = 10.0, 12.0, 12.5, 1 \text{ H}$); 3.33 (*m*, 1 H); 3.93 (*m*, 1 H); 5.32 (*dd*, $J = 4.0, 10.0, 1 \text{ H}$); 5.45 (*br. s*, 1 H); 6.94 (*br. s*, 1 H); 7.26–7.37 (5 H). $^{13}\text{C-NMR}$: 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 (*r*); 29.46 (*r*); 25.13 (*r*); 17.80 (*r*). MS: 246 (2, $\text{C}_{14}\text{H}_{18}\text{N}_2\text{O}_2^+$), 202 (100, $\text{C}_{13}\text{H}_{16}\text{NO}^+$), 143 (42, $\text{C}_6\text{H}_{11}\text{N}_2\text{O}_2^+$), 91 (8), 77 (12), 55 (9). HR-MS: 202.1258 ($\text{C}_{13}\text{H}_{16}\text{NO}^+$, calc. 202.1231).

(2*R*,3*aS*,7*S*)-3,3*a*,4,5,6,7-Hexahydro-2-phenyl-2H-isoxazolo[2,3-*a*]pyridine-7-carbonitrile (**11**). $(\text{CF}_3\text{CO})_2\text{O}$ (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 ($\text{Et}_2\text{O}/\text{hexane}$) to give colorless crystals (7.3 mg). M.p. 70°. $[\alpha]_{\text{D}} = +52.0$; $[\alpha]_{578} = +54.5$, $[\alpha]_{546} = +62.5$, $[\alpha]_{436} = +110.0$, $[\alpha]_{365} = +181.8$ ($c = 0.40$, 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. $^1\text{H-NMR}$ ($+55^\circ$): 1.48 (*m*, 1 H); 1.59–1.80 (2 H); 1.94–2.10 (3 H); 2.19 (*ddd*, $J = 4.0, 6.5, 11.0, 1 \text{ H}$); 2.38 (*ddd*, $J = 9.5, 10.0, 11.0, 1 \text{ H}$); 3.07 (*m*, 1 H); 4.39 (*br. m*, 1 H); 5.07 (*dd*, $J = 4.0, 9.5, 1 \text{ H}$); 7.24–7.42 (5 H); the $^1\text{H-NMR}$ spectrum showed at $+25^\circ$ only br. signals and at -30° two groups of sharp signals ($\sim 16:1$ -ratio). $^{13}\text{C-NMR}$ ($+55^\circ$): 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 (*r*); 28.57 (*r*); 28.22 (*r*); 20.35 (*r*); at $+25^\circ$, br. peaks for most C signals were observed. MS: 228 (35, $\text{C}_{14}\text{H}_{16}\text{N}_2\text{O}^+$), 211 (23, $\text{C}_{14}\text{H}_{15}\text{N}_2^+$), 104 (100, C_8H_8^+ , cycloreversion), 91 (17), 77 (16). HR-MS: 228.1245 ($\text{C}_{14}\text{H}_{16}\text{N}_2\text{O}^+$, calc. 228.1262), 211.1230 ($\text{C}_{14}\text{H}_{15}\text{N}_2^+$, calc. 211.1235).

(2*R*,3*aS*,7*S*)-2-Cyano-3,3*a*,4,5,6,7-hexahydro-8-methyl-2-phenyl-2H-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. $^1\text{H-NMR}$ (CD_2Cl_2): 1.85–2.70 (6 H, **12a + 12b**); 2.75 (*dd*, $J = 4.0, 8.0, 14.0, 1 \text{ H}$, **12a**); 2.75 (*m*, 1 H, **12b**); 3.09 (*ddd*, $J = 9.5, 13.0, 13.5, 1 \text{ H}$, **12b**); 3.46 (*ddd*, $J = 9.5, 12.5, 14.0, 1 \text{ H}$, **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*, $J = 3.0, 9.5, 1 \text{ H}$, **12b**); 6.00 (*dd*, $J = 4.0, 9.5, 1 \text{ H}$, **12a**); 7.40–7.47 (5 H, **12a + 12b**). $^{13}\text{C-NMR}$ (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 ((2*S*,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), 2*N* 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 $\rightarrow$ 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, $\text{C}_6\text{H}_6 \rightarrow \text{C}_6\text{H}_6/i\text{-PrOH}/\text{NH}_3$ 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% Et₃NH, 1.0 ml/min): 9.46 (100); no trace of the antipode was detected; (±)-allosedamine: 6.34 (50), 9.46 (50). IR (CHCl₃): 3270, 3080, 3060, 3030, 2935, 2855, 2800, 2725, 1450, 1445, 1280, 1275, 1060, 1030, 755, 700. ¹H-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). ¹³C-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, C₁₄H₂₁NO⁺), 98 (100, C₆H₁₂N⁺), 70 (12, C₄H₈N⁺). HR-MS: 219.1600 (C₁₄H₂₁NO⁺, calc. 219.1623).

REFERENCES

- [1] a) H. Wieland, K. Koschara, E. Dane, J. Renz, W. Schwarze, W. Linde, *Liebigs Ann. Chem.* **1939**, 540, 103; b) C. Schöpf, T. Kauffmann, P. Berth, W. Bundschuh, G. Dummer, H. Fett, G. Habermehl, E. Wieters, W. Wüst, *ibid.* **1957**, 608, 88; c) C. Schöpf, G. Dummer, W. Wüst, *ibid.* **1959**, 626, 134; d) C. Schöpf, W. Wüst, *ibid.* **1959**, 626, 150; e) C. Hootelé, F. Halin, S. Thomas, *Tetrahedron* **1985**, 41, 5563.
- [2] a) H. C. Beyerman, W. Eveleens, Y. M. F. Muller, *Recl. Trav. Chim. Pays-Bas* **1956**, 75, 63; b) R. Lukes, J. Kovar, K. Blaha, *Collect. Czech. Chem. Commun.* **1956**, 21, 1475; c) H. C. Beyerman, J. Eenshuistra, W. Eveleens, A. Zweistra, *Recl. Trav. Chim. Pays-Bas* **1959**, 78, 43; d) J. J. Tufariello, S. A. Ali, *Tetrahedron Lett.* **1978**, 4647; e) T. Shono, Y. Matsumura, K. Tsubata, *J. Am. Chem. Soc.* **1981**, 103, 1172; f) C. Hootelé, W. Ibebeke-Bomangwa, F. Driessens, S. Sabil, *Bull. Soc. Chim. Belg.* **1987**, 96, 57; g) A. Liguori, R. Ottanà, G. Romeo, S. Sindona, N. Uccella, *Chem. Ber.* **1989**, 122, 2019; h) N. Ozawa, S. Nakajima, K. Zaoya, F. Hamaguchi, T. Nagasaka, *Heterocycles* **1991**, 32, 889.
- [3] a) T. Wakabayashi, K. Watanabe, Y. Kato, M. Saito, *Chem. Lett.* **1977**, 223; b) K. Irie, K. Aoe, T. Tanaka, S. Saito, *J. Chem. Soc., Chem. Commun.* **1985**, 633; c) T. Kiguchi, Y. Nakazono, S. Kotera, I. Ninomiya, T. Naito, *Heterocycles* **1990**, 31, 1525.
- [4] J. J. Tufariello, *Acc. Chem. Res.* **1979**, 12, 396; P. N. Confalone, E. M. Huie, *Org. React.* **1988**, 36, 1.
- [5] a) E. Gössinger, *Tetrahedron Lett.* **1980**, 21, 2229; *Mh. Chem.* **1981**, 112, 1017; b) D. Lathbury, T. Gallagher, *Tetrahedron Lett.* **1985**, 26, 6249; c) W. Carruthers, M. J. Williams, *J. Chem. Soc., Chem. Commun.* **1986**, 1287; d) J. J. Tufariello, J. M. Puglis, *Tetrahedron Lett.* **1986**, 27, 1489; e) W. Carruthers, P. Coggins, J. B. Weston, *J. Chem. Soc., Perkin Trans. 1* **1990**, 2323.
- [6] W. Oppolzer, E. Merifield, *Helv. Chim. Acta* **1993**, 76, 957.
- [7] E. Bosone, P. Farina, G. Guazzi, S. Innocenti, V. Marotta, *Synthesis* **1983**, 942.
- [8] W. Oppolzer, J.-P. Barras, *Helv. Chim. Acta* **1987**, 70, 1666; W. Oppolzer, G. Poli, A. J. Kingma, C. Starkemann, G. Bernardinelli, *ibid.* **1987**, 70, 2201.
- [9] D. H. R. Barton, Y. Hervé, P. Potier, J. Thierry, *Tetrahedron* **1988**, 44, 5479.
- [10] R. T. Dean, H. C. Padgett, H. Rapoport, *J. Am. Chem. Soc.* **1976**, 98, 7448; H. A. Bates, H. Rapoport, *ibid.* **1979**, 101, 1259; I. G. Csendes, Y. Y. Lee, H. C. Padgett, H. Rapoport, *J. Org. Chem.* **1979**, 44, 4173.
- [11] a) S. Yamada, H. Akimoto, *Tetrahedron Lett.* **1969**, 3105; b) G. Stork, R. M. Jacobson, R. Levitz, *ibid.* **1979**, 771; c) G. Massiot, T. Mulamba, *J. Chem. Soc., Chem. Commun.* **1983**, 1147; d) D. S. Grierson, J. Royer, L. Guerrier, H.-P. Husson, *J. Am. Chem. Soc.* **1986**, 108, 4475; e) K. Ogura, Y. Shimamura, M. Fujita, *J. Org. Chem.* **1991**, 56, 2920.
- [12] F. Campagna, A. Carotti, G. Casini, *Tetrahedron Lett.* **1977**, 1813.
- [13] A. S. Amarasekara, A. Hassner, *Tetrahedron Lett.* **1987**, 28, 3151.
- [14] E. Müller, H. Metzger, D. Fries, *Chem. Ber.* **1954**, 87, 1449.