57. Synthesis of (−)-Pinidine *via* Asymmetric, Electrophilic Enolate Hydroxyamination/Nitrone Reduction

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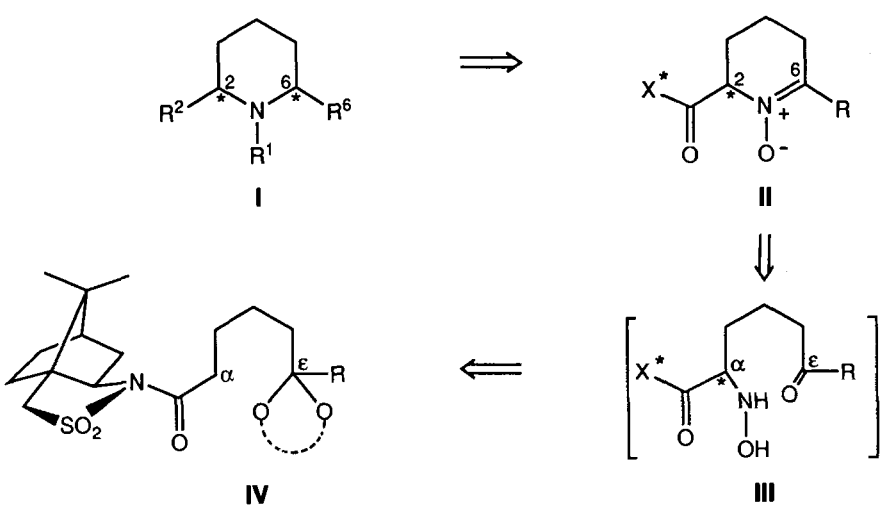
Enantiomerically pure (−)-pinidine (**1**) has been synthesized in 18.5% overall yield by a nine-step sequence starting from keto-ester **2**. The key step **5** → **6** involves an asymmetric, electrophilic enolate hydroxyamination. Diastereoselective hydrogenation of nitrone **6** ensures the *cis*-relation between the substituents at C(2) and C(6) in piperidine **7**.

Introduction. – The piperidine nucleus is a common structural element of numerous naturally occurring alkaloids. This class of compounds has been the subject of notable synthetic efforts not least because of the interesting biological activities shown by many of its representatives [1]. However, general methods to construct variously substituted piperidines in enantiomerically pure form are still scarce[1]).

In this context, we focussed our attention on a versatile approach to piperidines **I** with control of the stereogenic centers at C(2) and C(6) (*Scheme 1*).

Scheme 1



[1]) Review: [2a]. A remarkable example is the employment of a chiral 2-cyano-6-oxazolopiperidine as a pivotal intermediate for the synthesis of various piperidine alkaloids [2b].

Our strategy features enantiomerically pure nitrones **II** as key intermediates[2]). Nitrones **II**, in their turn, should be readily accessible by asymmetric electrophilic α-hydroxyamination [4] of chiral *N*-acylsultams **IV** carrying a protected carbonyl group in the ε-position. The workup using aqueous acid would prompt deprotection and spontaneous condensation of the carbonyl and hydroxylamine moieties of **III**.

As the first example illustrating this concept, we present here an asymmetric synthesis of (−)-pinidine (**1**, *Scheme 2*).

Pinidine, isolated from the leaves of *Pinus sabiniana*, has been assigned structure **1** [5]. Its first synthesis was achieved *via* resolution of racemic **1** [6a]. A further synthesis of (±)-**1** [6b], and three enantiospecific routes to (−)-**1** and (+)-**1**, starting from (*S,S*)-tartaric acid [6c], (*R,R*)-tartaric acid [6c], (*S*)-ethyl lactate [6d], or (*R*)-alanine [6e], have appeared in the literature more recently.

Results. – Me_3Al-mediated acylation [7] of chiral sultam **4**[3]) with the ketal-ester **3**, obtained by acetalization [8] of known keto-ester **2** [9], furnished *N*-acylsultam **5**. Successive treatment of **5** with sodium hexamethyldisilazide, 1-chloro-1-nitrosocyclohexane, and 1N aq. HCl [4] provided the expected diastereoisomerically pure nitrone **6** in 80% yield. Pd-Catalyzed hydrogenation of the C=N bond took place from the less hindered face giving the 2,6-disubstituted *N*-hydroxypiperidine **7** as a single stereoisomer (92%). The *cis*-disposition H_A/H_B in **7** was confirmed by NOE measurements. Alkylation of **7** with pure benzyloxymethyl chloride[4])/$EtN(i\text{-}Pr)_2$ furnished, after crystallization, the *O*-protected piperidine **8** in 78% yield. Reductive cleavage of the amide bond with $(i\text{-}Bu)_2AlH$ afforded the recovered auxiliary **4** (92% after crystallization) and the primary alcohol **9** (88%).

To assemble the (*E*)-propenyl side chain, alcohol **9** was oxidized ($(COCl)_2$/DMSO) [11] to the aldehyde **10**. Freshly prepared aldehyde **10** was then subjected to various olefination protocols without further purification. *Wittig* [12] (*1*) $Ph_3PEt^+Br^-$, BuLi, THF; *2*) addition to **10** in THF −10°→r.t.) or *Wittig-Schlosser* olefination [13] (*1*) $Ph_3PEt^+Br^-$, LiBr, PhLi, THF, −78°; *2*) **10**, −78°; *3*) PhLi, −78°, *4*) MeOH→r.t.) gave mixtures of (*E*)-alkene **11** and its (*Z*)-isomer in ratios of 11:89 or 83:17 (^{1}H-NMR, ~68% from **9**). A superior (*E*)-selectivity was achieved by *Takai* ethylidenation [14] of **10** (1,1-diiodoethane/$CrCl_2$, DMF, THF, 0°); chromatography of the resulting 95:5 (*E*/*Z*)-mixture on $AgNO_3$-impregnated SiO_2 furnished pure (*E*)-alkene **11** in 70% yield from **9**. *N*/*O*-Hydrogenolysis by stirring (benzyloxy)methyl-protected hydroxylamine **11** with activated Zn powder in aq. AcOH provided volatile (−)-**1**. Treatment with HCl/MeOH and crystallization yielded enantiomerically pure (−)-pinidine hydrochloride salt (**1**·HCl, 71%). M.p. 247–249° ([5a]: 244–246°). $[\alpha]_D = -10.2$ (*c* = 1.1, EtOH, 23°); [6c]: −9.6 (*c* = 0.25, EtOH, 24°). Free (−)-**1** showed $[\alpha]_D$, ^{1}H-NMR, and ^{13}C-NMR data in agreement with published values [6c].

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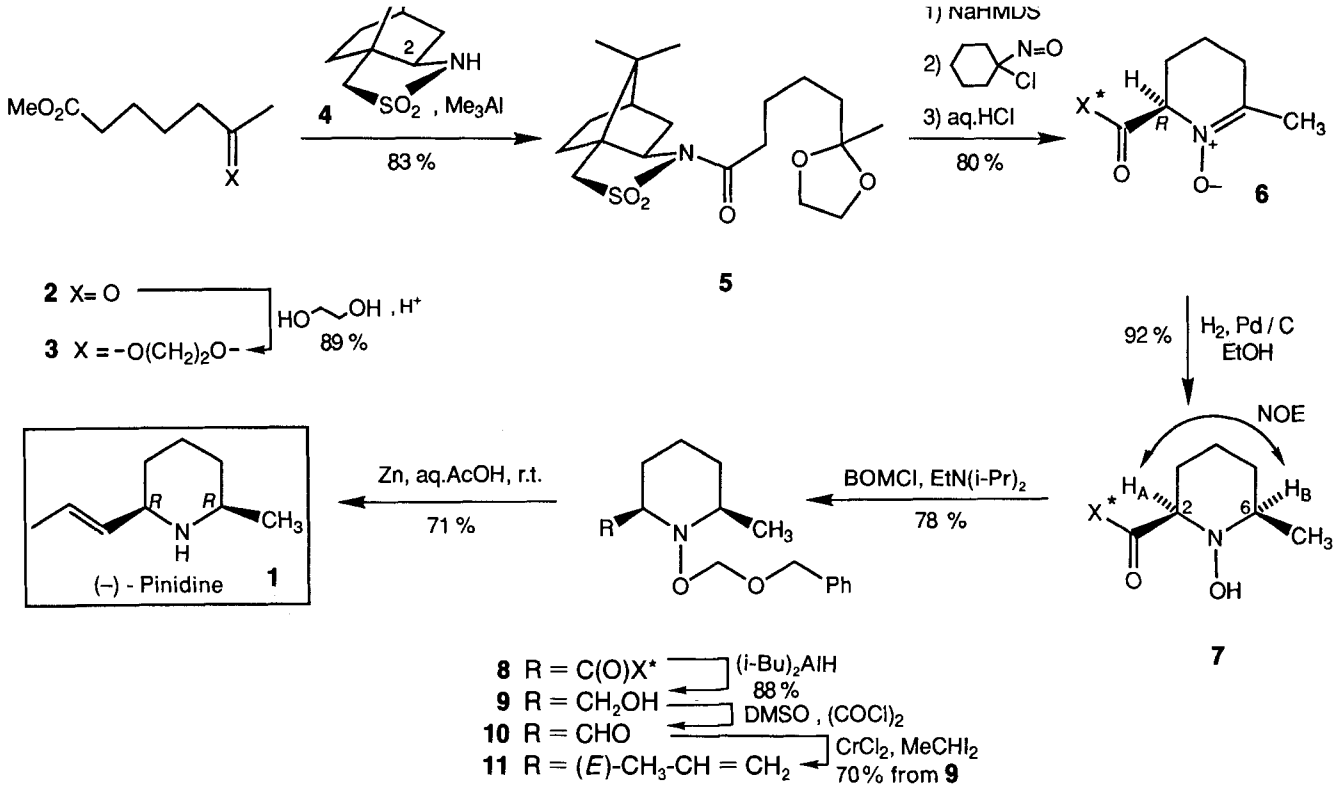
[2]) The use of nitrones in organic synthesis has been reviewed [3].

[3]) Sultam **4** and its enantiomer are distributed up to a multikg scale by: *NEWPORT Synthesis Ireland Ltd.*; Dublin/Ireland.

[4]) Pure (benzyloxy)methyl chloride (BOMCl) was prepared as described in [10]. The commercial reagent (*Fluka*, *Aldrich*) gave rise to variable amounts of an inseparable impurity.


MeO2C
X
4
NH
SO2 , Me3Al
83 %
SO2
N
O
O
O
5
1) NaHMDS
2)
N=O
Cl
3) aq.HCl
80 %
X*
H
R
N+
O–
CH3
O
6
2 X= O
3 X = -O(CH2)2O-
HO
OH , H+
89 %
92 %
H2, Pd / C
EtOH
NOE
HA
HB
2
6
X*
N
CH3
O
OH
7
BOMCl, EtN(i-Pr)2
78 %
R
N
CH3
O
O
Ph
Zn, aq.AcOH, r.t.
71 %
R
R
N
H
CH3
(–) - Pinidine
1
8 R = C(O)X*
9 R = CH2OH
10 R = CHO
11 R = (E)-CH3-CH = CH2
(i-Bu)2AlH
88 %
DMSO , (COCl)2
CrCl2, MeCHI2
70 % from 9

Conclusion. – In summary, enantiomerically pure (–)-pinidine · HCl (**1** · HCl) has been prepared from the simple keto-ester **2** *via* nine-step sequence in 18.5% overall yield. The key step **5** → **6** illustrates a convenient and efficient route to optically pure tetrahydropyridine *N*-oxides by asymmetric enolate hydroxyamination. The potential of these cyclic nitrones to undergo diastereoselective reductions and cycloaddition reactions may be of value for enantioselective syntheses of various piperidine containing molecules.

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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, dimethoxyethane, and toluene (Na); CH_2Cl_2, DMSO, EtN(i-Pr)$_2$, Et_3N, HMPA (CaH_2); MeOH ($Mg(OMe)_2$). Zn dust (4 g) was activated by stirring in 10% aq. HCl (15 ml) for 3 min, before filtering, washing with H_2O and then acetone and, finally, drying *in vacuo*. 'Workup' denotes extraction with an org. solvent, drying ($MgSO_4$), and evaporation. Column flash chromatography (FC): SiO_2 (*Merck 9385*). GC: *Hewlett-Packard 5790 A*, integrator *HP 3390*, capillary column: *OV*-1, 10 psi H_2, t_R in min (area-%). M.p.: *Kofler* hot stage; uncorrected. $[\alpha]_D$: *Perkin-Elmer-241* polarimeter; in $CHCl_3$ at 20°, unless otherwise specified. IR: *Polaris*, *Matteson Instruments*, in $CHCl_3$, unless otherwise specified. ^{1}H-NMR: *Bruker AMX 400* at 400 MHz in $CDCl_3$, unless otherwise specified; ^{13}C-NMR at 100 MHz in $CDCl_3$, unless otherwise specified; standard $CDCl_3$ (δ = 7.27 ppm), *J* in Hz. MS: *m/z* (rel.-%).

Methyl 5-(2-Methyl-1,3-dioxolan-2-yl)pentanoate (**3**). A mixture of *methyl 6-oxoheptanoate* (**2**) [9] (1.00 g, 6.3 mmol), ethylene glycol (1.07 ml, 19.5 mmol), and pyridinium *p*-toluenesulfonate (320 mg, 1.3 mmol) in benzene (50 ml) was heated under reflux for 9 h, employing a *Dean-Stark* trap. Addition of a sat. aq. soln. of $NaHCO_3$, extraction with Et_2O, evaporation of the dried ($MgSO_4$) extracts, and FC (hexane/AcOEt 5:1) provided **3** (1.14 g, 89%) as a colorless oil. IR: 3100–2800, 1735, 1440, 1380, 1245, 1200, 1180, 1110, 1070, 955, 860. ^{1}H-NMR: 1.31 (*s*, 3 H); 1.38–1.47 (2 H); 1.60–1.69 (4 H); 2.32 (*t*, *J* = 8, 2 H); 3.67 (*s*, 3 H); 3.89–3.98 (4 H). ^{13}C-NMR: 174.04 (*s*); 109.86 (*s*); 64.58 (*t*); 51.41 (*q*); 38.74 (*t*); 34.00 (*t*); 25.07 (*t*); 23.70 (*q*); 23.59 (*t*). MS: 187 (15, $[C_{10}H_{18}O_4 - CH_3]^+$), 155 (8.1), 111 (6.5), 87 (100), 55 (6.5). HR-MS: 187.0963 ($[C_{10}H_{18}O_4 - CH_3]^+$; calc. 187.0971).

(2R)-N-[5-(2-Methyl-1,3-dioxolan-2-yl)pentanoyl] bornane-10,2-sultam (**5**). A 2M soln. of Me_3Al in hexane (5.0 ml, 10.0 mmol) was added to a soln. of sultam **4** (2.13 g, 9.9 mmol) in toluene (20 ml) at r.t., and the mixture was stirred for 1 h. Then, a soln. of **3** (2.0 g, 9.9 mmol) in toluene (26 ml) was added and the mixture heated to 60° for 40 h. Addition of a sat. aq. soln. of NH_4Cl, extraction with CH_2Cl_2, drying of the extracts, evaporation, and FC (hexane/AcOEt 3:1) gave **5** (3.17 g, 83%) as a colorless, viscous oil. $[\alpha]_D = -79.4$, $[\alpha]_{578} = -82.9$, $[\alpha]_{546} = -94.1$, $[\alpha]_{436} = -161.6$, $[\alpha]_{365} = -261.4$, (*c* = 1.04, $CHCl_3$). IR: 3100–2800, 1700, 1380, 1330, 1270, 1235, 1130, 1110, 1070, 995, 950, 860, 550. ^{1}H-NMR: 0.97 (*s*, 3 H); 1.15 (*s*, 3 H); 1.30 (*s*, 3 H); 1.32–1.50 (4 H); 2.63–1.74 (4 H); 1.85–1.95 (3 H); 2.03–2.16 (2 H); 2.66–2.79 (2 H); 3.42 (*d*, *J* = 14, 1 H); 3.49 (*d*, *J* = 14, 1 H); 3.86 (*dd*, *J* = 8, 5.5, 1 H); 3.90–3.95 (4 H). ^{13}C-NMR: 171.82 (*s*); 109.89 (*s*); 65.18 (*d*); 64.58 (*t*); 52.92 (*t*); 48.34 (*s*); 47.70 (*s*); 44.62 (*d*); 38.73 (*t*); 38.49 (*t*); 35.38 (*t*); 32.80 (*t*); 26.41 (*t*); 24.56 (*t*); 23.76 (*q*); 23.43 (*t*); 20.79 (*q*); 19.84 (*q*). MS: 370 (0.34, $[C_{19}H_{31}NO_5S - CH_3]^+$), 171 (11), 109 (3.6), 99 (4.2), 87 (100), 81 (22), 55 (19).

(2R,2'R)-N-(2',3',4',5'-Tetrahydro-6'-methyl-1-oxidopyridine-2'-carbonyl)bornane-10,2-sultam (**6**). A 1M soln. of $NaN(TMS)_2$ in THF (2.4 ml, 2.35 mmol) was added dropwise to a stirred soln. of **5** (870 mg, 2.26 mmol) in THF (13 ml) at –78°, and the mixture was stirred at –78° for 45 min. Then, a 1.9M soln. of 1-chloro-1-nitrosocyclohexane [15] in THF (1.34 ml, 2.55 mmol) was slowly added. Stirring the mixture for 30 min at –78°, addition of THF (23 ml) and 10% aq. HCl (15 ml) at –78°, stirring at r.t. for 3 h, evaporation *in vacuo*, shaking of the residue with CH_2Cl_2/sat. aq. $NaHCO_3$, drying of the org. extracts, evaporation, and FC (AcOEt→CH_2Cl_2/MeOH 15:1) provided **6** (641 mg, 80%) as a white solid. A sample was crystallized from CH_2Cl_2/Et_2O. M.p. 171–173°. $[\alpha]_D = -72.5$, $[\alpha]_{578} = -75.8$, $[\alpha]_{546} = -86.0$, $[\alpha]_{436} = -151.5$, $[\alpha]_{365} = -255.4$ (*c* = 1.06, $CHCl_3$). IR: 3050–2800, 1700, 1620, 1400, 1335, 1270, 1240, 1170, 1135, 1070, 995, 885, 660. ^{1}H-NMR: 0.98 (*s*, 3 H); 1.30 (*s*, 3 H); 1.31–1.45 (2 H); 1.70 (*m*, 1 H); 1.84–1.98 (4 H); 2.05 (*dd*, *J* = 14, 8, 1 H); 2.15 (br. *s*, 3 H); 2.17–2.31 (2 H); 2.33–2.62 (3 H); 3.44 (*d*, *J* = 14, 1 H); 3.57 (*d*, *J* = 14, 1 H); 3.92 (*dd*, *J* = 8, 5, 1 H); 5.23 (*m*, 1 H). ^{13}C-NMR: 167.21 (*s*); 147.75 (*s*);

68.01 (*d*); 65.40 (*d*); 53.03 (*t*); 48.94 (*s*); 47.99 (*s*); 44.59 (*d*); 37.94 (*t*); 32.70 (*t*); 30.47 (*t*); 26.51 (*t*); 26.23 (*t*); 20.86 (*q*); 19.91 (*q*); 18.62 (*q*); 16.58 (*d*). MS: 355 (0.84, $[C_{17}H_{26}N_2O_4S + 1]^+$), 354 (0.37), 140 (5.0), 113 (10), 112 (100), 96 (23), 94 (35), 67 (18), 55 (52). HR-MS: 354.1562 ($C_{17}H_{26}N_2O_4S^+$, calc. 354.1614).

(2R,2'R,6'R)-N-(1'-Hydroxy-6'-methylpiperidine-2'-carbonyl)bornane-10,2-sultam (**7**). Nitrone **6** (600 mg, 1.69 mmol) and 10% Pd/C (300 mg) in dry EtOH (40 ml) were stirred under H_2 (1 atm) at r.t. for 2 h. Filtration through *Celite*, washing of the solids with CH_2Cl_2, evaporation of the filtrates, and FC (hexane/AcOEt 1:1) provided **7** (556 mg, 92%) as a colorless solid. A sample was crystallized from hexane/Et_2O. M.p. 171–172° (sintering at 148–150°). $[\alpha]_D = -31.8$, $[\alpha]_{578} = -32.7$, $[\alpha]_{546} = -36.6$, $[\alpha]_{436} = -62.7$, $[\alpha]_{365} = -104.6$ ($c = 1.02$, $CHCl_3$). IR: 3580, 3050–2800, 1700, 1420, 1335, 1270, 1235, 1170, 1135, 1065. ^{1}H-NMR: 0.97 (*s*, 3 H); 1.19 (*s*, 3 H); 1.20 (*d*, $J = 6$, 3 H); 1.30–1.48 (4 H); 1.63–1.75 (3 H); 1.79–1.97 (3 H); 2.03–2.15 (3 H); 2.65 (1 H, spin saturation at $\delta = 3.84 \rightarrow$NOE: 9.8%); 3.44 (*d*, $J = 14$, 1 H); 3.54 (*d*, $J = 14$, 1 H); 3.84 (*dd*, $J = 10$, 3, 1 H, spin saturation at $\delta = 2.65 \rightarrow$NOE: 7.5%); 3.94 (*dd*, $J = 8$, 5, 1 H); 5.14 (br. *s*, 1 H). ^{13}C-NMR: 171.88 (*s*); 71.16 (*d*); 65.66 (*d*); 62.82 (*d*); 53.37 (*t*); 48.59 (*s*); 47.79 (*s*); 44.72 (*d*); 38.51 (*t*); 33.45 (*t*); 32.93 (*t*); 29.05 (*t*); 26.40 (*t*); 22.98 (*t*); 20.92 (*q*); 19.91 (*q*); 19.50 (*q*). MS: 180 (1.1, $[C_{17}H_{28}N_2O_4S - 176]^+$), 151 (1.3), 135 (1.7), 129 (2.0), 114 (100). HR-MS: 114.0915 ($[C_{17}H_{28}N_2O_4S - C_{11}H_{16}NO_3S]^+$; calc. 114.0919).

(2R,2'R,6'R)-N-{1'-[(Benzyloxy)methoxy]-6'-methylpiperidine-2'-carbonyl}bornane-10,2-sultam (**8**). $EtN(i\text{-}Pr)_2$ (0.4 ml, 2.4 mmol) and freshly prepared benzyloxymethyl chloride [10] (165 µl, 1.19 mmol) were added to a soln. of **7** (209 mg, 0.59 mmol) in CH_2Cl_2 (5 ml) at r.t., and the mixture was stirred for 24 h. Addition of CH_2Cl_2 and H_2O, extraction with CH_2Cl_2, drying of the extracts, evaporation, FC (hexane/AcOEt 5:1), and crystallization ($EtOH/CH_2Cl_2$) provided **8** (217 mg, 78%). M.p. 144–146°. $[\alpha]_D = -40.0$, $[\alpha]_{578} = -41.6$, $[\alpha]_{546} = -46.8$, $[\alpha]_{436} = -78.8$, $[\alpha]_{365} = -127.5$ ($c = 1.0$, $CHCl_3$). IR: 3100–2800, 1695, 1460, 1415, 1330, 1270, 1240, 1170, 1135, 1060, 985, 695, 535. ^{1}H-NMR: 0.95 (*s*, 3 H); 1.15 (*s*, 3 H); 1.24 (*d*, $J = 6$, 3 H); 1.28–1.52 (4 H); 1.62–1.79 (4 H); 1.80–1.95 (2 H); 2.02–2.16 (3 H); 2.72 (*m*, 1 H); 3.42 (*d*, $J = 14$, 1 H); 3.53 (*d*, $J = 14$, 1 H); 3.91 (*dd*, $J = 8$, 5, 1 H); 3.94 (*dd*, $J = 12$, 3, 1 H); 4.58 (*d*, $J = 12$, 1 H); 4.71 (*d*, $J = 12$, 1 H); 4.78 (*d*, $J = 7$, 1 H); 4.97 (*d*, $J = 7$, 1 H); 7.26–7.32 (5 H). ^{13}C-NMR: 171.31 (*s*); 138.03 (*s*); 128.20 (*d*); 127.45 (*d*); 127.38 (*d*); 98.89 (*t*); 71.41 (*t*); 70.98 (*d*); 65.48 (*d*); 62.92 (*d*); 53.21 (*t*); 48.40 (*s*); 47.68 (*s*); 44.71 (*d*); 38.58 (*t*); 33.73 (*t*); 32.93 (*t*); 29.33 (*t*); 26.35 (*t*); 22.95 (*t*); 20.86 (*q*); 20.43 (*q*); 19.85 (*q*). MS: 355 (9.7, $[C_{25}H_{36}N_2O_5S - C_8H_9O]^+$), 234 (17), 204 (100), 140 (19), 91 (344). HR-MS: 234.1495 ($[C_{25}H_{36}N_2O_5S - C_{11}H_{16}NO_3S]^+$; calc. 234.1495).

(2R,6R)-1-[(Benzyloxy)methoxy]-6-methylpiperidine-2-methanol (**9**). A 1M soln. of $(i\text{-}Bu)_2AlH$ in hexane (5.0 ml, 5.0 mmol) was slowly added to a soln. of **8** (789 mg, 1.66 mmol) in THF (25 ml) at r.t., and the mixture was stirred at r.t. for 6 h. Addition of sat. aq. NH_4Cl (20 ml), stirring for 30 min, filtration through *Celite*, washing of the solids with AcOEt, drying, evaporation of the filtrates, and FC (CH_2Cl_2/AcOEt 20:1 → 10:1) provided **4** (329 mg, 92%, after crystallization from hexane/CH_2Cl_2) followed by the more polar alcohol **9** (387 mg, 88%; colorless oil). GC: 5 min 150°, 10°/min to 270°; 9.70 (100). HPLC: (*Chiralcel OD*, hexane/i-PrOH 60:1, 1 ml/min) 7.32 (1.3), 17.65 (98.3). $[\alpha]_D = +83.5$, $[\alpha]_{578} = +87.1$, $[\alpha]_{546} = +98.6$, $[\alpha]_{436} = +164.3$, $[\alpha]_{365} = +251$ ($c = 1.05$, $CHCl_3$). IR: 3600–3300, 3100–2800, 1455, 1380, 1240, 1160, 1110, 1080, 1050, 1025, 1010, 700. ^{1}H-NMR (C_6D_6, 76°): 1.11 (*d*, $J = 7$, 3 H); 1.17 (*m*, 1 H); 1.30–1.52 (4 H); 1.76 (*m*, 1 H); 2.51–2.64 (2 H); 2.68 (br. *s*, exchanges with D_2O, 1 H); 3.60 (*m*, 1 H); 3.96 (br. *s*, 1 H); 4.51 (*d*, $J = 12$, 1 H); 4.61 (*d*, $J = 12$, 1 H); 4.83 (*d*, $J = 7$, 1 H); 4.93 (*d*, $J = 7$, 1 H); 7.10–7.31 (5 H). ^{13}C-NMR: 137.16 (*s*); 128.50 (*d*); 127.90 (*d*); 127.70 (*d*); 99.13 (*t*); 71.12 (*t*); 68.50 (*d*); 63.97 (*d*); 63.90 (*t*); 34.21 (*t*); 29.14 (*t*); 23.71 (*t*); 20.48 (*q*). MS: 266 (3.2, $[C_{15}H_{23}NO_3 + 1]^+$), 265 (0.19), 234 (0.78), 204 (19), 157 (9.9), 114 (100), 91 (84), 55 (23). HR-MS: 265.1888 ($C_{15}H_{23}NO_3^+$; calc. 265.1679).

(2R,6R)-1-[(Benzyloxy)methoxy]-2-methyl-6-[(E)-prop-1'-enyl]piperidine (**11**). A soln. of DMSO (275 µl, 3.87 mmol) in THF (2.6 ml) was added to a soln. of oxalyl chloride (160 µl, 1.86 mmol) in THF (8.5 ml) at −78°. Then, the mixture was stirred at −40° for 5 min and then recooled to −78°. A soln. of **9** (160 mg, 603 µmol) in THF (8.5 ml) was added, the mixture warmed to −40° and stirred for 15 min. Addition of Et_3N (0.54 ml, 3.90 mmol), stirring at −40° for 15 min, then at r.t. for 20 min, pouring of the reaction mixture into sat. aq. NH_4Cl, extraction (AcOEt), drying of the extracts, evaporation, and co-evaporation with toluene (2 × 5 ml) provided crude aldehyde **10** (oil) which was subjected to olefination without further purification.

A mixture of chromium(II) chloride (598 mg, 4.87 mmol) and DMF (370 µl, 4.81 mmol) was stirred in THF (8.0 ml) at r.t. for 30 min. Then, a mixture of **10** and ethylidene iodide (100 µl, 1.21 mmol) in THF (8.0 ml) was added at 0°. The mixture was stirred at 0° for 6 h then allowed to warm slowly to r.t. and stirred for 16 h. Addition of H_2O (5 ml), stirring at r.t. for 10 min, extraction with Et_2O, washing of the extracts with 10% aq. sodium thiosulfate soln. (10 ml) and brine, drying, and evaporation gave a 95:5 mixture (^{1}H-NMR) of (*E*)-olefin **11** and its (*Z*)-isomer. This mixture was separated by FC using a $AgNO_3$-impregnated silica-gel column [16] (hexane/AcOEt 8:1) to provide pure (*E*)-olefin **11** (116 mg, 70%, oil). GC: 5 min 150°, 10°/min to 270°; 8.78 (99.8). $[\alpha]_D = -2.18$, $[\alpha]_{578} = -2.08$, $[\alpha]_{546} = -2.37$, $[\alpha]_{436} = -2.57$ ($c = 1.01$, $CHCl_3$). IR: 3100–2800, 1495, 1460, 1375, 1220, 1160,

J = 7, 3 H); 1.61 (*d*, J = 5, 3 H); 1.24–1.72 (6 H); 2.58 (*m*, 1 H); 2.99 (*m*, 1 H); 4.65 (*s*, 2 H); 4.84 (*d*, J = 7, 1 H); 4.86 (*d*, J = 7, 1 H); 5.50–5.63 (2 H); 7.24–7.35 (5 H). ^{13}C-NMR: 138.31 (*s*); 134.15 (*d*); 128.23 (*d*); 127.32 (*d*); 126.06 (*d*); 98.45 (*t*); 71.04 (*d*); 70.67 (*t*); 62.83 (*d*); 34.24 (*t*); 33.59 (*t*); 23.64 (*t*); 20.79 (*q*); 17.82 (*q*). MS: 276 (0.53, $[C_{17}H_{25}NO_2 + 1]^+$), 245 (2.6), 154 (100), 138 (9.1), 95 (15), 91 (87), 81 (27), 67 (30), 55 (43).

(−)-Pinidine Hydrochloride (**1**·HCl). A mixture of **11** (74.6 mg, 271 µmol), activated Zn powder (382 mg, 5.8 mmol), and AcOH/H_2O 1:1 (9.0 ml) was stirred at r.t. for 2 h. Filtration through *Celite*, washing of the solids with AcOH, addition of TsOH·H_2O (52.5 mg, 276 µmol) to the filtrate, evaporation *in vacuo*, shaking of the residue with H_2O/Et_2O, basification of the separated aq. phase with 1M aq. NaOH (5 ml), extraction with Et_2O, drying of the extracts, addition of a freshly prepared dry 1.9M soln. of HCl in MeOH (0.21 ml), evaporation, co-evaporation of the residue with MeOH/toluene 1:4, and crystallization from Et_2O/i-PrOH 5:3 afforded **1**·HCl (34.0 mg, 71%) as colorless needles. M.p. 247–249° ([5a]: 244–246°). $[\alpha]_D = -10.2$, $[\alpha]_{578} = -10.6$, $[\alpha]_{546} = -12.2$, $[\alpha]_{436} = -20.0$, $[\alpha]_{365} = -29.9$ (c = 1.09, EtOH, 23°); [6c]: $[\alpha]_D = -9.6$ (c = 0.25, EtOH, 24°). IR: 3050–2600, 2540, 1595, 1460, 1435, 1240, 1020, 970, 665. ^{1}H-NMR: 1.49 (*m*, 1 H); 1.59 (*d*, J = 6, 3 H); 1.68 (*dd*, J = 6, 2, 3 H); 1.73–1.95 (5 H); 3.1 (*m*, 1 H); 3.44 (*m*, 1 H); 5.75 (*m*, 1 H); 5.90 (*dq*, J = 6, 15, 1 H); 9.1–9.7 (br., 2 H). ^{13}C-NMR: 132.38 (*d*); 126.92 (*d*); 59.84 (*d*); 54.24 (*d*); 30.22 (*t*); 28.77 (*t*); 22.78 (*t*); 19.47 (*q*); 17.75 (*q*). MS: 139 (21, $C_9H_{17}N^+$), 124 (64), 110 (19), 96 (75), 82 (69), 68 (100), 55 (53).

(−)-Pinidine (= *(−)-(2R,6R)-2-Methyl-6-[(E)-prop-1-enyl]piperidine*; **1**). Aq. NaOH (5M, 0.5 ml) was added to a soln. of **1**·HCl (11.1 mg, 63 µmol) in H_2O. Extraction with Et_2O, drying of the extracts, and careful evaporation at low temp. provided free **1** (6.2 mg, 71%) as a colorless oil. IR: 3050–2750, 1455, 1400, 1425, 1380, 1320, 1300, 1115, 1040, 970, 940, 820, 640. ^{1}H-NMR: 1.02 (*tdd*, J = 13, 11, 4, 1 H); 1.07 (*d*, J = 6, 3 H); 1.15 (*tdd*, J = 13, 11, 4, 1 H); 1.36 (*qt*, J = 12.5, 4, 1 H); 1.47–1.64 (3 H); 1.66 (br. *d*, J = 6, 3 H); 1.77 (*m*, 1 H); 2.66 (*m*, 1 H); 3.05 (*ddd*, J = 11, 7, 2, 1 H); 5.46 (*m*, 1 H); 5.58 (*dq*, J = 6, 15, 1 H). ^{13}C-NMR: 135.12 (*d*); 124.90 (*d*); 59.42 (*d*); 52.20 (*d*); 33.84 (*t*); 32.39 (*t*); 24.68 (*t*); 23.06 (*q*); 17.78 (*q*). MS: 139 (54, $C_9H_{17}N^+$), 124 (100), 110 (26), 96 (77), 82 (52), 68 (48), 55 (24).

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