Stereocontrolled Alkylation of Chiral Pyridinium Salt Toward a Short Enantioselective Access to 2-Alkyl- and 2,6-Dialkyl-1,2,5,6-Tetrahydropyridines

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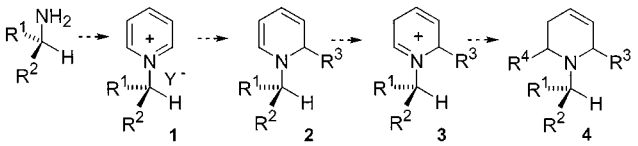
Treatment of salts **1a–b** with Grignard reagents gives, after reduction of the resulting unstable dihydropyridines **7**, the tetrahydropyridines **8a–c**, with modest selectivities but in very few steps and under practical conditions. Higher stereo- and regioselectivities are obtained with salt **1c** which gives the tetrahydropyridines **15a–e**. In addition, the dihydropyridine intermediates **11b** cyclize to give the new oxazolidine derivatives **12a–e**, which turn out to be good precursors of the 2,6-*trans*-disubstituted tetrahydropyridines **21a–e**. Selective syntheses of (–)-lupetidin, (+)-solenopsin, and indolizidines (–)-**5** and (–)-**6** are presented as representative examples of applications.

Introduction

The enantioselective synthesis of six-membered nitrogen heterocycles has been the subject of a large number of studies during the past few years due to the interest of these intermediates in natural alkaloid and medicinal chemistry. As a consequence, efficient methods are now available for preparing chiral 2- and 2,6-substituted piperidines.[1] However, few methods are available concerning the corresponding enantiopure substituted tetrahydropyridines.[2] Therefore, we now present a strategy which is briefly summarized in Scheme 1. The main features of this approach are: (a) selective alkylation with Grignard reagents[3–5] of pyridinium salts **1** (Scheme 1), now readily available from chiral primary amines;[6] (b) protonation of the resulting dihydropyridines **2** to give dihydropyridinium salt equivalents **3**;[7] (c) additional treatment with a Grignard reagent affording the 2,6-disubstituted tetrahydropyridines **4**.



Scheme 1. General strategy for the enantioselective construction of substituted tetrahydropyridines

The interest of this approach is illustrated by the short synthesis from salt **1c** (Scheme 2) of (–)-lupetidin, (+)-solenopsin A and indolizidines (–)-**5** and (–)-**6**, this last synthesis being designed as an example of further ring elaboration of the tetrahydropyridines **4**.

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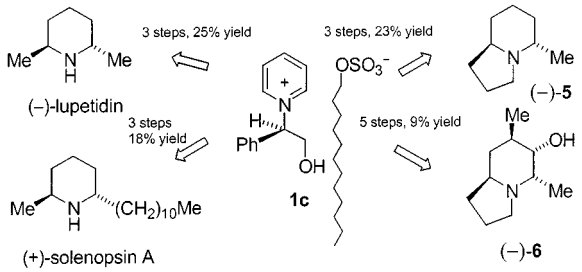

Scheme 2. Representative examples of the syntheses

Results and Discussion

We first investigated the reactions of Grignard reagents with salts **1a–b** (Scheme 3 and Table 1). As reported earlier,[3,4] the use of a lipophilic counter anion (dodecylsulfate, see **1b**) ensures a good solubility of pyridinium salts in organic solvents but was not necessarily required in this particular case. Since the resulting dihydropyridine intermediates **7** were too unstable to be isolated, the crude reaction mixtures were reduced with $NaBH_4$, affording the tetrahydropyridines **8a–c** as major products. As expected, the regioselectivity of the attack at position 2 decreases with relatively hindered Grignard reagents to give predominantly attack at position 4 of the pyridinium ring, resulting, for example, in the formation of major piperidines **10d** and **10e**. In contrast to the 3-substituted series,[3] but in agreement with our recent results in the isoquinoline series,[4] the stereoselectivity of attack at position 2 does not exceed 50%. Despite this modest selectivity, the method constitutes a fairly convenient approach to tetrahydropyridines such as **8a** considering its shortness and simplicity. The absolute configuration of derivative **8c** was confirmed by a correlation with the known alkaloid (+)-coniine (vide infra) and by further elaboration of products from tetrahydropyridine **8a** by epoxidation reactions.[8]

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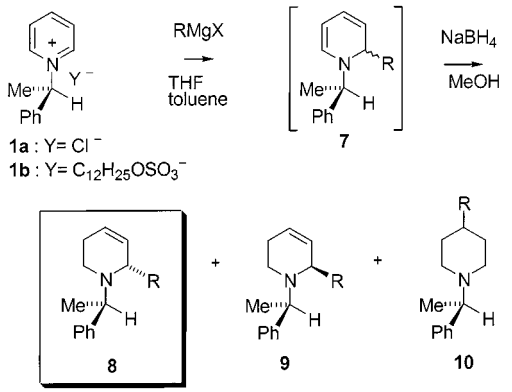
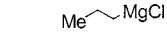
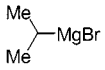
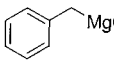


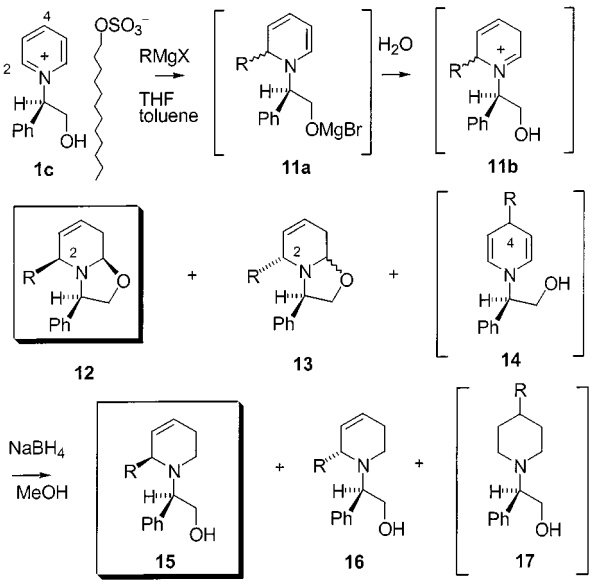
Scheme 3. Two-step access to tetrahydropyridines **8a–d**

Table 1. Two-step access to tetrahydropyridines **8a–d**

RMgX	salt	products (% ratio)	products (% yield)
MeMgCl	**1a**	**8a** (66), **9a** (34), -[a]	**8a** (46), **9a** (24)
	**1a**	**8b** (75), **9b** (25), -[a]	**8b** (33), **9b** (11)
	**1a**	**8c** (52), **9c** (18), **10c** (30)[a]	**8c** (33), **9c** (11)
	**1a**	**8d** (19), **9d** (7), **10d** (74)[b]	**10d** (10)
	**1b**	**8e** (21), **9e** (4), **10e** (75)[b]	**10e** (75)

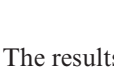
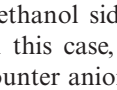
The results of the alkylation of salt **1c**, containing a phenylethanol side chain (Scheme 4), are presented in Table 2. In this case, the presence of the lipophilic dodecylsulfate counter anion is necessary in order to ensure solubility and thus to obtain appreciable yields of products. In view of our previous results,[4,6] the reaction was now expected to give mainly 1,2-dihydropyridines **11a** which, after hydrolysis to **11b**, would afford the oxazolidine isomers **12** and **13**. An attack at position 4 was also possible to give the 1,4-dihydropyridines **14**, which are very unstable products, and which are prone to polymerization rather than to formation of stable oxazolidine derivatives.[6b] In a first series of experiments, the crude reaction mixture was directly reduced with an excess of $NaBH_4$ giving the tetrahydropyridines **15a–d** and piperidine **17e** as the main products.

From the results in Table 2, one can conclude that the derivatives **15a–c** were obtained with an excellent regioselectivity and with a greater selectivity of attack at C-2 than with the series having a phenylethyl auxiliary (compare with results in Table 1). The regioselectivity is also significantly higher (compare yields of **8d** and **15d**) but not yet satisfactory in the benzyl series (poor yield of **15e**). An increase of selectivity can very likely be explained by the formation of an organometallic complex from **1c** which directs the attack at position 2 as we recently reported for the isoquinoline series.[4] The present method thus offers a reasonably efficient approach [three steps from (*R*)-(−)-phenylglycinol, one



Scheme 4. Two-step access to tetrahydropyridines **15a–e**

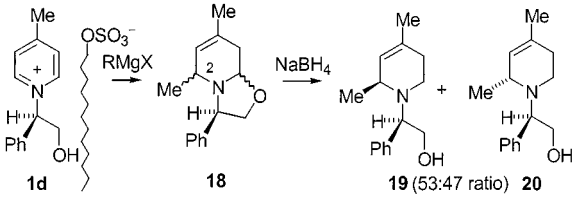
Table 2. Two-step synthesis of tetrahydropyridines **15a–e**

RMgX	**12** (% yield)[a]	products (% ratio)[c]	products (%)[d]	d.e.[e]
MeMgCl	**12a** (70)	**15a** (90), **16a** (10), -	**15a** (40), **16a** (5)	80
	12b (48)	**15b** (90), **16b** (10), -	**15b** (27), **16b** (-)	80
	12c (58)	**15c** (85), **16c** (15), -	**15c** (43), **16c** (10)	70
	**12d** (40)[b]	**15d** (72), **16d** (7), **17d** (21)	**15d** (35), **17d** (15)	82
	**12e** (32)[b]	**15e** (26), **16e** (8), **17e** (66)	**15e** (21), **17e** (39)	54

[a] The product is contaminated with 10–15% epimer at C-2 13 (see Experimental Section). – [b] Isolation by chromatography over alumina. – [c] Determined by integration in the crude ^{1}H-NMR spectrum or GC analysis. – [d] Isolated yield from **1c**, after $NaBH_4$ reduction of the crude reaction mixtures. – [e] Excess of attack at position 2.

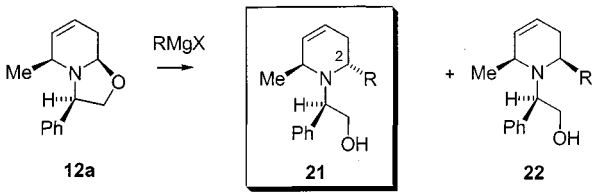
chromatographic separation] to tetrahydropyridines **15** from not too bulky Grignard reagents.

By contrast, it should be noticed that the 4-methyl-substituted pyridinium salt **1d** (Scheme 5) gave surprisingly poor results. Methylmagesium chloride, for example, reacts to give a complex mixture of oxazolidines **18**, affording, after reduction, the tetrahydropyridines **19–20** with no selectivity of attack at C-2, although in 70% yield.



Scheme 5

We next considered the chemistry of the oxazolidine derivatives **12** (Scheme 4). These rather sensitive intermediates can be purified and easily characterized by NMR spectroscopy, but cannot be separated from their minor isomers **13**. In contrast, the 1,4-dihydropyridines **14** are so unstable[6b] that they can be simply eliminated by filtration over alumina, allowing the particularly easy recovery of the oxazolidines **15d–e** which are stable under these conditions. The oxazolidines **12** are potential precursors of 2,6-disubstituted tetrahydropyridines as subsequently illustrated by the results of Grignard additions to the oxazolidine **12a** (Scheme 6 and Table 3).



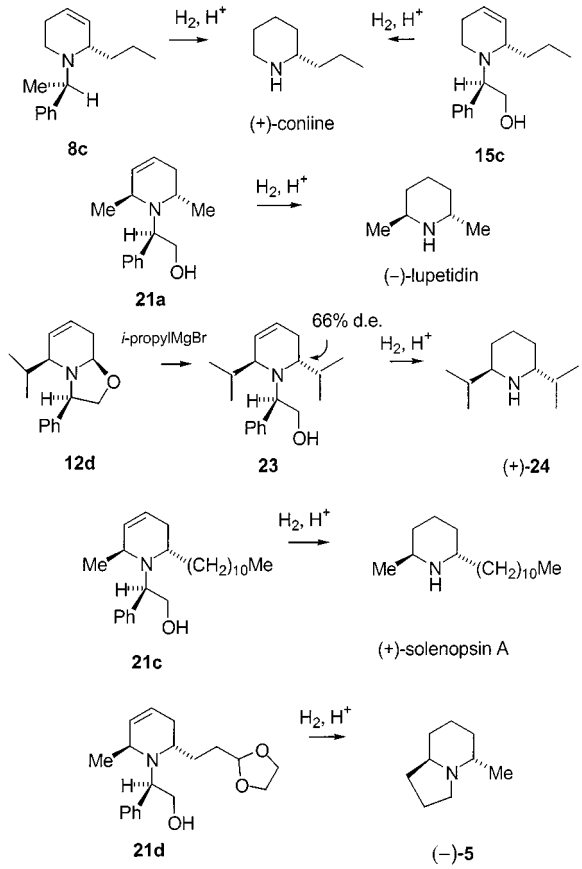
Scheme 6. Two-step synthesis of tetrahydropyridines **21a–e**

Table 3. Syntheses of tetrahydropyridines **21a–e** from **12a**

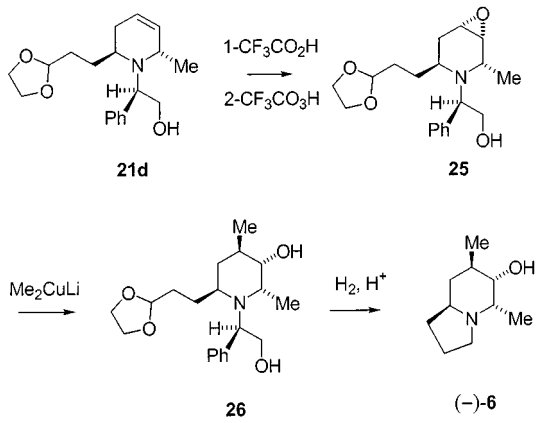
RMgX	products (% ratio)[a]	products (%)[b]	d.e.[c]
MeMgCl	**21a** (75), **22a** (25), -	**21a** (48), **22a** (12)	50
MgCl	**21b** (74), **22b** (26), -	**21b** (53) **22b** (18)	48
n-$C_{11}H_{23}$MgBr	**21c** (66), **22c** (34), -	**21c** (43) **22c** (-)	32
MgBr	**21d** (77), **22d** (23), -	**21d** (47) **22d** (-)	54
Me, Me, Si, Me, MgBr	**21e** (98), **22e** (2), -	**21e** (74) **22e** (-)	96

[a] Determined by integration of protons in the crude ^{1}H-NMR spectra or GC. – [b] Isolated yield after chromatography. – [c] Excess of attack at position 2.

Thus, the results of Grignard addition to these new oxazolidine derivatives (Table 3) showed that, in all cases, the 2,6-*trans*-disubstituted tetrahydropyridines are obtained as major products, albeit with moderate selectivity (32–54% *de*).[9] Noticeable is the contrasting selectivity observed in the case of adduct **21e** (96% *de*) which can thus be obtained in more than 50% yield from salt **1c**. The usefulness of this new approach was illustrated by the syntheses of some piperidine alkaloids as shown in Scheme 7. The hydrogenolysis of both tetrahydropyridines **8c** and **15c** gave the known alkaloid (+)-coniine, while the disubstituted derivative **21a** gave natural (–)-lupetidin. The treatment of oxazolidine **12d** with isopropylmagnesium bromide gave predominantly isomer **23** (66% *de*) which afforded, after hydrogenolysis, piperidine (+)-**24**. The absolute configuration of this new product was assigned by analogy with the results obtained with (–)-lupetidin. Hydrogenolysis of **21c** afforded known (+)-solenopsin,[10] while under the same conditions dioxolane **21d** gave indolizidine (–)-**5**.[11]



Scheme 7. Representative examples of syntheses



Scheme 8

The polysubstituted derivatives can be obtained by epoxidation reactions of tetrahydropyridines[8,12] as illustrated by a three-step synthesis of indolizidine (–)-**6** from **21d** (Scheme 8). Thus the trifluoroacetic salt of **21d** reacts smoothly with pertrifluoroacetic acid to give the rather unstable oxirane **25** as a single diastereoisomer (stereochemistry assigned by comparison with analogous results).[8,12] The treatment of crude **25** with an excess of Me_2CuLi gave diol **26** with complete regioselectivity. Finally, hydrogenolysis in acidic medium afforded the indolizidine **6** in 5 steps with 9% overall yield from salt **1c** (3 steps, 27% yield from **21d**).

Experimental Section

General Remarks: Experiments involving organometallics were carried out in dried glassware under a positive pressure of dry nitrogen. THF and diethyl ether were distilled from sodium benzophenone ketyl. Methylmagnesium chloride, vinylmagnesium chloride and methyllithium were purchased from Aldrich. Column chromatography: silica gel 60, 0.070–0.200 (SDS) or Aluminiumoxid 90, 0.063–0.200 (Merck). NMR spectra were recorded with a Bruker AC-200, AC-AC-250 or AC-300. Mass spectra were recorded with AEI MS-50 (EI) or AEI MS-9 (CI). Optical rotations were measured with a Perkin-Elmer 14.

Treatment of Salts 1a–b with Grignard Reagents: 2-Substituted Tetrahydropyridines 8a–c

(1*R*,2*S*)-(+)-2-Methyl-1-(1-phenylethyl)-1,2,5,6-tetrahydropyridine (8a): A commercially available solution of methylmagnesium chloride (21.5 mL, 49.0 mmol) in THF was added dropwise to a solution of pyridinium salt **1a** (7.33 g, 16.3 mmol) in toluene (100 mL) at –20 °C. After 1 h at this temperature, the solution was warmed to 0 °C and then stirred for a further 2 h. The resulting mixture was poured into a vigorously stirred ice-cooled solution of 32% aqueous ammonia saturated with NH_4Cl. This solution was then extracted with cold Et_2O and the extracts were dried with $MgSO_4$, filtered, and concentrated (20 mL) under reduced pressure. After addition of MeOH (90 mL) and H_2O (10 mL), an excess of $NaBH_4$ (3.7 g, 97.8 mmol) was added portionwise. The reaction mixture was refluxed for 1 h, and, after evaporation of solvents under reduced pressure, Et_2O was added. The resulting organic phase was washed with water, dried, filtered, and concentrated to give a mixture of tetrahydropyridines **8a** and **9a** in a ratio 66:34 (determined by GC). The crude product was purified by flash chromatography over silica gel (120 g) with heptane/EtOAc (100:0 to 92:8) as eluent. The major diastereoisomer **8a** (1.51 g, 46% yield) was then obtained as a yellow oil. – $[\alpha]_D$ = +22 (*c* = 1.0, $CHCl_3$). – ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.16 (d, *J* = 6.6 Hz, 3 H), 1.44 (d, *J* = 6.8 Hz, 3 H), 2.07 (m, 2 H), 2.33 (ddd, *J* =11.7, 5.8, 5.8 Hz, 1 H), 2.95 (ddd, *J* = 11.7, 5.3, 5.3 Hz, 1 H), 3.07 (m, 1 H), 4.05 (q, *J* = 6.8 Hz, 1 H), 5.46 (dm, *J* = 9.9 Hz, 1 H), 5.67 (dm, *J* = 9.9 Hz, 1 H), 7.30 (m, 5 H). – ^{13}C NMR (50.32 MHz, $CDCl_3$): δ = 18.2, 20.8, 26.0, 40.8, 51.5, 57.8, 124.4, 126.8, 128.0, 132.5, 142.4. – MS (EI): *m*/*z* (%) = 201 (12) [M^+], 186 (90), 105 (98), 82 (100). – MS (CI): *m*/*z* (%) = 202 (100) [MH^+]. – EI-HRMS ($C_{14}H_{19}N$): calcd. 201.1518; found 201.1539.

Minor Diastereoisomer 9a: Yield 786 mg, 24%; $[\alpha]_D$ = –77 (*c* = 0.9, $CHCl_3$). – ^{1}H NMR (200 MHz, $CDCl_3$) δ = 1.11 (d, *J* = 6.6 Hz, 3 H), 1.32 (d, *J* = 6.6 Hz, 3 H), 1.80 (dm, *J* = 17.3 Hz, 1 H), 2.07 (dm, *J* = 17.3 Hz, 1 H), 2.63 (dd, *J* = 6.7, 4.6 Hz, 2 H), 3.38 (m, 1 H), 3.87 (q, *J* = 6.6 Hz, 1 H), 5.59 (dm, *J* = 9.9 Hz, 1 H), 5.75 (dm, *J* = 9.9 Hz, 1 H), 7.30 (m, 5 H). – ^{13}C NMR (50.32 MHz, $CDCl_3$): δ = 17.6, 17.9, 24.6, 40.4, 51.1, 58.2, 124.9, 126.6, 127.4, 128.2, 132.2, 146.4. – MS (EI): *m*/*z* (%) = 201 (12) [M^+], 186 (94), 105 (100), 82 (96). – EI-HRMS ($C_{14}H_{19}N$): calcd. 201.1518; found 201.1541.

(1*R*,2*S*)-(+)-1-(1-Phenylethyl)-2-vinyl-1,2,5,6-tetrahydropyridine (8b): Salt **1b** (1.5 g, 3.34 mmol) in toluene (100 mL) at –30 °C was treated with vinylmagnesium chloride in THF (24 mmol, 20 mL) and then stirred at 10 °C during 2 h. The resulting solution was reduced with $NaBH_4$ (1.30 g, 34.60 mmol) in MeOH/H_2O (60:7) following the procedure described for the preparation and purification of **8a** to give adduct **8b** (1.1 g, 33% yield) as a pale yellow oil. – $[\alpha]_D$ = +119 (*c* = 2.4, $CHCl_3$). – ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.58 (d, *J* = 7.0 Hz, 3 H), 2.13–2.27 (m, 2 H), 2.29–2.44 (m, 1 H), 3.07–3.25(m, 1 H), 3.62 (m, 1 H), 4.22 (q, *J* = 7.0 Hz, 1 H), 5.27–5.42 (m, 2 H), 5.51 (dm, *J* = 10.0 Hz, 1 H), 5.88 (m, 1 H), 5.98 (ddd, *J* = 10.0, 8.4, 8.4 Hz, 1 H), 7.39 (m, 5 H). – ^{13}C NMR (62.89 MHz, $CDCl_3$): δ = 20.16, 26.32, 40.81, 57.95, 61.36, 116.88, 125.52, 126.88, 127.91, 128.31, 129.71, 140.48, 141.01. – MS (EI): *m*/*z* (%) = 213 (67) [M^+], 198 (71), 186 (100). – MS (CI): *m*/*z* (%) = 214 (100) [MH^+]. – CI-HRMS ($C_{15}H_{20}N$): calcd. 214.1595; found 214.1572.

Minor Diastereoisomer 9b: Yield 367 mg, 11%; $[\alpha]_D$ = –141 (*c* = 1, $CHCl_3$). – ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.48 (d, *J* = 7.0 Hz, 3 H), 2.14 (m, 2 H), 2.73 (m, 2 H), 3.96 (m, 1 H), 4.11 (q, *J* = 7.0 Hz, 1 H), 5.30 (m, 1 H), 5.36 (dm, *J* = 7.5 Hz, 1 H), 5.68 (dm, *J* = 9.0 Hz, 1 H), 5.92–6.10 (m, 2 H), 7.49 (m, 5 H). – ^{13}C NMR (62.89 MHz, $CDCl_3$): δ = 16.0, 25.2, 40.7, 57.9, 60.1, 116.6, 126.2, 126.6, 127.5, 128.2, 129.1, 139.4, 145.8. – MS (EI): *m*/*z* (%) = 213 (67) [M^+], 198 (71), 186 (100).

(1*R*,2*S*)-(+)-1-(1-Phenylethyl)-2-propyl-1,2,5,6-tetrahydropyridine (8c): Salt **1b** (1.418 g, 3.16 mmol) in toluene (20 mL) was treated with *n*-propylmagnesium bromide (6.3 mL, 9.5 mmol) in Et_2O, diluted with toluene (4 mL), and then reduced with $NaBH_4$ (1.19 g, 31.6 mmol) in MeOH/H_2O (9:1) under reflux for 6 h, following the same procedure as for the preparation and purification of adduct **8a**. Tetrahydropyridine **8c** (94 mg, 13% yield) was obtained as a pale yellow oil. – $[\alpha]_D$ = +60 (*c* = 1.5, $CHCl_3$). – ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.93 (t, *J* = 7.5 Hz, 3 H), 1.40 (m, 5 H), 1.54 (m, 2 H), 1.80 (m, 1 H), 2.03 (m, 1 H), 2.30 (ddd, *J* = 12.5, 5.0, 5.0 Hz, 1 H), 2.90 (ddd, *J* = 15.0, 7.5, 5.0 Hz, 1 H), 3.10 (m, 1 H), 3.94 (q, *J* = 7.0 Hz, 1 H), 5.57 (dm, *J* = 10.0 Hz, 1 H), 5.73 (dm, *J* = 10.0 Hz, 1 H), 7.14–7.34 (m, 5 H). – ^{13}C NMR (62.89 MHz, $CDCl_3$): δ = 14.5, 19.2, 21.6, 23.5, 35.8, 40.8, 54.8, 57.7, 125.3, 126.8, 128.0, 128.1, 130.9, 144.1. – MS (EI): *m*/*z* (%) = 229 (12) [M^+], 228 (17), 214 (7), 186 (100), 105 (99). – CI-HRMS ($C_{16}H_{23}N$): calcd. 230.1908; found 230.1904.

Treatment of Salts 1c With Grignard Reagents: Oxazolidines 12a–d

(3*R*,5*S*,8*aR*)-(–)-5-Methyl-3-phenyl-2,3,8,8a-tetrahydro-2*H*-oxazolo[3,2-*a*]pyridine (12a): To an ice-cooled solution of salt **1c** (27.0 g, 58.0 mmol) in dry THF (330 mL) was added dropwise methylmagnesium chloride (290 mL, 290 mmol) in THF. The resulting solution was stirred for 3 h at 0 °C then poured into a vigorously stirred ice-cooled solution of 32% aqueous ammonia saturated with NH_4Cl. This solution was extracted with cold Et_2O, the extract dried with $MgSO_4$, filtered, and concentrated under reduced pressure. Addition of a large amount of pentane allowed the precipitation of the dodecylsulfate salts which were eliminated by filtration through Celite. Removal of the solvents under reduced pressure gave the oxazolidine **12a** [contaminated with a small amount of epimer at C-2 (10%)] as a yellow oil (8.7 g, 70% yield). – $[\alpha]_D$ = –69 (*c* = 1.64, $CHCl_3$). – ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.72 (d, *J* = 6.0 Hz, 3 H), 2.40 (m, 2 H), 3.20 (m, 1 H), 3.70 (dd, *J* = 8.3, 6.8 Hz, 1 H), 3.76 (dd, *J* = 8.3, 6.8 Hz, 1 H), 4.11 (dd, *J* = 8.2, 4.5 Hz, 1 H), 4.22 (dd, *J* =8.3, 6.8 Hz, 1 H), 5.40 (dm, *J* = 10.5 Hz, 1 H), 5.66 (m, 1 H), 7.19–7.48 (m, 5 H). – ^{13}C NMR (62.89 MHz, $CDCl_3$): δ = 21.3, 32.0, 58.2, 67.2, 74.6, 92.4, 122.1, 127.3, 127.5, 128.3, 132.7, 143.4. – MS (EI): *m*/*z* (%) = 215 (100) [M^+], 200 (67), 148 (70), 120 (62), 104 (59), 68 (72). – EI-HRMS ($C_{14}H_{17}NO$): calcd. 215.1310; found 215.1301.

(3*R*,5*S*,8*aR*)-3-Phenyl-(–)-5-vinyl-2,3,8,8a-tetrahydro-2*H*-oxazolo-[3,2-*a*]pyridine (12b): To a cooled (–78 °C) solution of salt **1c** (1.0 g, 2.19 mmol) in dry toluene (20 mL) was added dropwise vinylmagnesium bromide (2.6 mL, 2.19 mmol) in THF. The addition of vi-

nylmagnesium bromide (10.4 mL, 8.76 mmol) was repeated 1 h later at the same temperature. The resulting solution was stirred for 3 h at 0 °C, then poured into a vigorously stirred ice-cooled solution of 32% aqueous ammonia saturated with NH_4Cl. This solution was extracted with cold Et_2O and the extracts dried with $MgSO_4$, filtered, and flash chromatographed over alumina (70 g) with pentane/Et_2O (50:50) as eluent to give oxazolidine **12b** [contaminated with a small amount of epimer at C-2 (10%)] as a pale yellow oil (241 mg, 48% yield). – $[\alpha]_D$ = –53 (*c* = 1.9, $CHCl_3$). – ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.42 (m, 2 H), 3.60 (m, 1 H), 3.75 (m, 2 H), 4.12 (dd, *J* = 10.5, 5.5 Hz, 1 H), 4.22 (dd, *J* = 10.0, 7.5 Hz, 1 H), 4.54 (dd, *J* = 12.5, 2.5 Hz, 1 H), 4.86 (dd, *J* = 20.0, 2.5 Hz, 1 H), 5.16 (dd, *J* = 20.0, 12.5 Hz, 1 H), 5.54 (dm, *J* = 10.5 Hz, 1 H), 5.70 (m, 1 H), 7.12–7.50 (m, 5 H). – ^{13}C NMR (62.89 MHz, $CDCl_3$): δ = 31.9, 67.2, 74.5, 91.7, 115.1, 123.2, 127.2, 128.1, 128.2, 130.4, 139.7, 142.2. – MS (EI): *m*/*z* (%) = 227 (100) [M^+], 226 (29), 200 (16). – EI-HRMS ($C_{15}H_{17}NO$): calcd. 227.1310; found 227.1313.

(3*R*,5*S*,8*aR*)-(–)-3-Phenyl-5-propyl-2,3,8,8a-tetrahydro-2*H*-oxazolo-[3,2-*a*]pyridine (12c): To a cooled (–78 °C) solution of salt **1c** (987 mg, 2.12 mmol) in dry toluene (15 mL) was added dropwise *n*-propylmagnesium bromide (1.0 mL, 2.00 mmol) in Et_2O. The addition of propylmagnesium bromide (4.3 mL, 8.60 mmol) was repeated 1 h later at the same temperature. The resulting solution was then treated under the same conditions described for the extraction and purification of adduct **12a**. Oxazolidine **12c** (302 mg, 58% yield) was obtained as a yellow oil contaminated by minor diastereoisomer (**13c**, 10%). – $[\alpha]_D$ = –26 (*c* = 1.1, $CHCl_3$). – ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.38 (m, 3 H), 0.63–1.27 (m, 4 H), 2.37 (m, 2 H), 3.20 (m, 1 H), 3.65 (ddd, *J* = 7.5, 7.5, 2.5 Hz, 1 H), 3.67 (ddd, *J* = 7.5, 7.5, 2.5 Hz, 1 H), 4.05 (ddd, *J* = 8.7, 5.4, 3.0 Hz, 11 H), 4.21 (ddd, *J* = 7.5, 7.5, 7.5 Hz, 1 H), 5.45 (dm, *J* = 9.6 Hz, 1 H), 5.66 (m, 1 H), 7.02–7.57 (m, 5 H). – ^{13}C NMR (62.89 MHz, $CDCl_3$): δ = 13.8, 16.8, 31.7, 35.1, 62.8, 67.3, 74.7, 92.5, 122.5, 127.3, 127.5, 128.2, 130.7, 143.5. – MS (CI): *m*/*z* (%) = 244 (100) [MH^+]. – CI-HRMS ($C_{16}H_{22}NO$): calcd. 244.1702; found 244.1719.

(3*R*,5*S*,8*aR*)-5-Isopropyl-3-phenyl-2,3,8,8a-tetrahydro-2*H*-oxazolo-[3,2-*a*]pyridine (12d): To a cooled (–78 °C) solution of salt **1c** (10.0 g, 21.60 mmol) in dry toluene (200 mL) was added dropwise isopropylmagnesium bromide (29 mL, 21.60 mmol) in Et_2O. The addition of isopropylmagnesium bromide (115 mL, 86.40 mmol) was repeated 1 h later at the same temperature. The resulting solution was then treated under the same conditions described for the extraction and purification of adduct **12a**. Oxazolidine **12d** (2.10 g, 40% yield) was obtained as a yellow oil contaminated by a minor diastereoisomer (**13d**). – ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.53 (d, *J* = 7.8 Hz, 3 H), 0.76 (d, *J* = 7.8 Hz, 3 H), 2.07 (m, 1 H), 2.34 (m, 2 H), 3.10 (m, 1 H), 3.72 (m, 2 H), 4.10 (dd, *J* = 9.6, 5.0 Hz, 1 H), 4.15 (dd, *J* = 9.6, 7.4 Hz, 1 H), 5.50 (dm, *J* = 10.4 Hz, 1 H), 5.74 (m, 1 H), 7.08–7.62 (m, 5 H). – ^{13}C NMR (50.32 MHz, $CDCl_3$): δ = 15.4, 19.6, 28.7, 31.8, 67.2, 69.0, 75.1, 92.6, 124.0, 126.5, 127.3, 128.3, 144.2. – MS (EI): *m*/*z* (%) = 243 (11) [M^+], 200 (81). – CI-HRMS ($C_{16}H_{22}NO$): calcd. 244.1701; found 244.1705.

Treatment of Salts 1c with Grignard Reagents: 2-Substituted Tetrahydropyridines 15a–d

(2*R*,2*R*)-(+)-2-(2-Methyl-1,2,5,6-tetrahydropyridin-1-yl)-2-phenylethanol (15a): The inseparable mixture of oxazolidines **12a** and **13a** (6.5 g, 30.10 mmol, 90:10) in THF (50 mL) was diluted with MeOH (220 mL) and H_2O (30 mL). $NaBH_4$ (9.0 g, 239.0 mmol) was then added portionwise and the resulting solution was refluxed for 12 h. After evaporation of solvents under reduced pressure, Et_2O was added. The organic phase was washed with H_2O saturated with NH_4Cl, dried, filtered, and concentrated to give a mixture of tetrahydropyridines **15a** and **16a** (90:10 ratio as determined by integration of the ^{1}H-NMR spectrum). The crude product was purified by flash chromatography on silica gel (300 g) with heptane/EtOAc/NEt_3 (100:0:0.1 to 93:7:0.1) as eluent to afford minor diastereoisomer first. The major diastereoisomer **15a** (3.72 g, 57% yield from **12a**, 40% from **1c**) was then obtained as white crystals from which an analytical sample was recrystallised from pentane: m.p. 74 °C. – $[\alpha]_D$ = +75 (*c* = 1.8, $CHCl_3$). – ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.08 (d, *J* = 6.7 Hz, 3 H), 1.84 (m, 1 H), 2.19 (m, 1 H), 2.39 (m, 1 H), 2.85 (m, 2 H), 3.35 (m, 1 H), 3.77–3.87 (m, 3 H), 5.57 (m, 1 H), 5.72 (m, 1 H), 7.34 (m, 5 H). – ^{13}C NMR (50.32 MHz, $CDCl_3$): δ = 17.6, 24.3, 40.6, 51.6, 63.4, 66.3, 124.6, 127.6, 128.5, 131.9, 141.1. – MS (CI): *m*/*z* (%) = 218 (100) [MH^+], 200 (10). – $C_{14}H_{19}NO$ (217.31): calcd. C 77.37, H 8.81, N 6.45, O 7.37; found C 77.49, H 8.77, N 6.46, O 7.51.

Minor Diastereoisomer 16a: Yield 457 mg, 7% from **12a**, 5% from **1c**; $[\alpha]_D$ = +1 (*c* = 1.0, $CHCl_3$). – ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.29 (d, *J* = 6.6 Hz, 3 H), 1.85–2.05 (m, 2 H), 2.13–2.29 (m, 1 H), 2.97 (m, 1 H), 3.11 (m, 1 H), 3.23 (m, 1 H), 3.61 (dd, *J* = 10.5, 5.4 Hz, 1 H), 4.02 (dd, *J* = 10.5, 10.5 Hz, 1 H), 4.22 (dd, *J* = 10.5, 5.4 Hz, 1 H), 5.45 (dm, *J* = 9.6 Hz, 1 H), 5.66 (m, 1 H), 7.14–7.46 (m, 5 H). – ^{13}C NMR (50.32 MHz, $CDCl_3$): δ = 20.3, 26.4, 41.5, 51.8, 59.7, 62.2, 124.4, 128.0, 128.2, 129.1, 132.4, 135.5. – MS (CI): *m*/*z* (%) = 218 (100) [MH^+]. – CI-HRMS ($C_{14}H_{20}NO$): calcd. 218.1545; found 218.1560.

(2*R*,6*S*)-(–)-2-Phenyl-2-(2-vinyl-1,2,5,6-tetrahydropyridin-1-yl)-ethanol (15b): Salt **1c** (585 mg, 1.26 mmol) was treated with an excess of vinylmagnesium bromide under the conditions used for preparation of oxazolidine **12a**, but the crude extracts (containing mixture of oxazolidines **12b** and **13b** in a 90:10 ratio) in THF (10 mL) were reduced with an excess of $NaBH_4$ using the above conditions. The reaction gave a mixture of tetrahydropyridines **15b** and **16b** (90:10, determined by GC). The major diastereoisomer **15b** (78 mg, 27% yield from **1c**) was isolated as a pale yellow oil by flash chromatography over alumina (10 g) with heptane/EtOAc (100:0 to 70:30) as eluent. – $[\alpha]_D$ = –19 (*c* = 1.2, $CHCl_3$). – ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.88–2.30 (m, 3 H), 2.80 (m, 1 H), 3.75 (m, 1 H), 3.88 (m, 3 H), 5.14 (dm, *J* = 13.0 Hz, 2 H), 5.48 (m, 1 H), 5.84 (m, 2 H), 7.32 (m, 5 H). – ^{13}C NMR (62.89 MHz, $CDCl_3$): δ = 24.9, 42.1, 59.8, 62.8, 66.5, 116.6, 125.9, 127.6, 128.5, 128.7, 138.4, 140.1. – MS (CI): *m*/*z* (%) = 230 (100) [MH^+]. – CI-HRMS ($C_{15}H_{20}NO$): calcd. 229.1545; found 229.1537.

(2*R*,2*R*)-(+)-2-Phenyl-2-(2-*n*-propyl-1,2,5,6-tetrahydropyridin-1-yl)ethanol (15c): Salt **1c** (447 mg, 0.96 mmol) was treated with an excess of *n*-propylmagnesium bromide as for the preparation of oxazolidine **12b** but the crude extracts (containing a mixture of oxazolidines **12c** and **13c** in a 90:10 ratio) in THF (10 mL) were reduced with an excess of $NaBH_4$ using the above conditions. The reaction gave a mixture of tetrahydropyridines **15c** and **16c** (85:15, determined by GC). The major diastereoisomer **15c** (100 mg, 43% yield from **1c**) was isolated as a pale yellow oil by flash chromatography over alumina (10 g) with heptane/EtOAc (100:0 to 78:22) as eluent. – $[\alpha]_D$ = +37 (*c* = 1.2, $CHCl_3$). – ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.81 (t, *J* = 7.5 Hz, 3 H), 1.45 (m, 2 H), 1.80 (m, 2 H), 2.01 (m, 2 H), 2.25 (m, 1 H), 2.99 (m, 1 H), 3.07 (m, 1 H), 3.73–3.94 (m, 3 H), 5.59 (dm, *J* = 10.0 Hz, 1 H), 5.74 (m, 1 H), 7.20–7.44 (m, 5 H). – ^{13}C NMR (62.89 MHz, $CDCl_3$): δ = 14.4, 19.7, 22.4, 36.2, 41.0, 55.2, 63.6, 65.7, 125.0, 127.6, 128.5, 128.7, 130.4, 141.4. – MS (EI): *m*/*z* (%) = 245 (6) [M^+], 244 (21), 214

(48), 202 (100). – CI-HRMS ($C_{16}H_{24}NO$): calcd. 246.1858; found 246.1862.

Minor Isomer 16c: Yield 23 mg, 10%; $[\alpha]_D$ = –39 (*c* = 0.9, $CHCl_3$). – ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.96 (t, *J* = 7.5 Hz, 3 H), 1.31–1.76 (m, 5 H), 2.05 (m, 2 H), 2.99 (m, 1 H), 3.20 (m, 1 H), 3.63 (dd, *J*= 10.5, 5.0, 1 H), 4.04 (dd, *J*= 10.5, 10.0, 1 H), 4.20 (dd, *J*= 10.0, 5.0, 1 H), 5.52 (dm, *J* = 10.0 Hz, 1 H), 5.71 (m, 1 H), 7.17–7.46 (m, 5 H). – ^{13}C NMR (62.89 MHz, $CDCl_3$): δ = 14.6, 17.7, 25.9, 35.3, 41.4, 56.0, 60.2, 62.3, 125.3, 128.0, 128.3, 129.3, 130.6, 135.9.

(2*R*,2*S*)-(+)-2-(2-Isopropyl-1,2,5,6-tetrahydropyridin-1-yl)-2-phenylethanol (15d). Salt **1c** (1.106 g, 2.38 mmol) was treated with an excess of isopropylmagnesium bromide as for the preparation of oxazolidine **12a** but the crude extracts in THF (10 mL) were reduced with an excess of $NaBH_4$ using the above conditions. The reaction gave a mixture of tetrahydropyridines **15d**, **16d**, and piperidine **17d** in a 72:7:21 ratio (determined by GC-MS analysis). This crude product was chromatographed over alumina with heptane/EtOAc as eluent. The major diastereoisomer **15d** (204 mg, 35% yield) was obtained as white crystals from which an analytical sample was recrystallised from CH_2Cl_2/pentane for analysis: m.p. 87 °C. – $[\alpha]_D$ = +23 (*c* = 1.3, $CHCl_3$). – ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.78 (d, *J* = 6.6 Hz, 3 H), 0.90 (d, *J* = 6.7 Hz, 3 H), 1.70–1.91 (m, 2 H), 2.15–2.32 (m, 1 H), 2.48 (m, 1 H), 2.94–3.21 (m, 2 H), 3.88 (m, 3 H), 5.64 (dm, *J* = 10.3 Hz, 1 H), 5.79 (dm, *J* = 10.3 Hz, 1 H), 7.18–7.46 (m, 5 H). – ^{13}C NMR (62.89 MHz, $CDCl_3$): δ = 19.4, 20.9, 21.5, 32.7, 41.3, 61.1, 63.6, 65.2, 125.7, 127.47, 128.3, 128.6, 128.9, 141.3. – MS (CI): *m*/*z* (%) = 246 (100) [MH^+], 228 (24). – $C_{16}H_{27}NO$ (245.36): calcd. C 78.32, H 9.45, N 5.71, O 6.52; found C 77.49, H 9.48, N 5.51, O 6.03.

Piperidine 17d was obtained as a colourless oil (95 mg, 15% yield): $[\alpha]_D$ = –15 (*c* = 2.4, $CHCl_3$). – ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.83 (d, *J* = 6.8 Hz, 6 H), 0.91 (m, 1 H), 1.10–1.46 (m, 3 H), 1.64 (m, 3 H), 2.26 (m, 1 H), 2.90 (m, 2 H), 3.66 (m, 2 H), 3.98 (dd, *J* = 8.7, 7.5 Hz, 1 H), 7.09–7.44 (m, 5 H). – ^{13}C NMR (62.89 MHz, $CDCl_3$): δ = 19.8, 29.6, 30.0, 32.4, 42.5, 46.5, 53.4, 60.1, 70.0, 127.8, 128.1, 129.0, 135.7. – MS (CI): *m*/*z* (%) = 248 (100) [MH^+]. – CI-HRMS ($C_{25}H_{26}NO$): calcd. 248.2014; found 248.2012.

Reactions of Oxazolidine 12a with Grignard Reagents: 2,6-Disubstituted Tetrahydropyridines 21a–d

(1*R*,2*S*,6*S*)-(+)-(2,6-Dimethyl-3,6-dihydro-2*H*-pyridin-1-yl)-2-phenylethanol (21a): To an ice-cooled solution of methylmagnesium chloride (98 mL, 98.0 mmol) in THF was added dropwise crude oxazolidine **12a** (7.06 g, 32.8 mmol) in THF (150 mL). When the addition was complete, the solution was stirred for 1 h at 0 °C then warmed to room temperature and stirred overnight. The mixture was poured into a saturated solution of NH_4Cl at 0 °C, extracted with Et_2O, the extract dried with $MgSO_4$, filtered, and evaporated at reduced pressure to give a mixture of tetrahydropyridines **21a** and **21b** in a 75:25 ratio (determined by GC). The diastereoisomers were separated by flash chromatography over silica gel (240 g) with a gradient of heptane/EtOAc/NEt_3 (100:0:0.1 to 90:10:0.1) as eluent. The major diastereoisomer **21a** (3.64 g, 48% yield) was isolated as a pale yellow oil. – $[\alpha]_D$ = +62 (*c* = 1.3, $CHCl_3$). – ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.22 (d, *J* = 7.5 Hz, 3 H), 1.34 (d, *J* = 7.5 Hz, 3 H), 1.70 (m, 2 H), 3.41 (m, 1 H), 3.48 (dd, *J* = 10.0, 6.0 Hz, 1 H), 3.77 (m, 1 H), 3.84 (dd, *J* = 11.0, 10.0 Hz, 1 H), 4.17 (dd, *J* = 11.0, 6.0 Hz, 1 H), 5.30 (m, 1 H), 5.42 (m, 1 H), 7.16–7.36 (m, 5 H). – ^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 19.8, 21.8, 30.8, 47.1, 47.6, 59.8, 61.1, 125.0, 127.5, 127.9, 128.9, 131.5, 140.7. – MS (CI): *m*/*z* (%) = 232 (100) [MH^+], 214 (16). – EI-HRMS ($C_{15}H_{22}NO$): calcd. 232.1701; found 232.1687.

Minor Diastereoisomer 22a: Yield 909 mg, 12%; $[\alpha]_D$ = –132 (*c* = 2.7, $CHCl_3$). – ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.10 (d, *J* = 7.0 Hz, 3 H), 1.20 (d, *J* = 7.0 Hz, 3 H), 1.52 (m, 2 H), 3.18–3.32 (m, 1 H), 3.44–3.67 (m, 1 H), 3.75 (dd, *J* = 8.0, 4.0 Hz, 1 H), 3.88 (dd, *J* = 8.0, 8.0 Hz, 1 H), 3.96 (dd, *J* = 8.0, 4.0 Hz, 1 H), 5.61 (m, 2 H), 7.29 (m, 5 H). – ^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 22.5, 28.8, 44.6, 53.1, 61.4, 67.5, 122.4, 127.4, 128.0, 128.9, 130.1, 140.1. – MS (CI): *m*/*z* (%) = 232 (100) [MH^+], 214 (16). – EI-HRMS ($C_{15}H_{22}NO$): calcd. 232.1701; found 232.1718.

(2*R*,2*R*,6*S*)-(+)-2-(6-Methyl-2-vinyl-3,6-dihydro-2*H*-pyridin-1-yl)-2-phenylethanol (21b): To a cooled (–30 °C) solution of vinylmagnesium chloride (72 mL, 101.3 mmol) was added dropwise crude oxazolidine **12a** (7.26 g, 33.77 mmol) in Et_2O (200 mL). When the addition was complete, the solution was stirred for 2 h at 0 °C then warmed to room temperature and stirred overnight. The resulting solution was treated in the same conditions described for the extraction of adduct **21a**. A mixture of tetrahydropyridines **21b** and **22b** was obtained in a ratio 74:26 (determined by GC). Separation of diastereoisomers was achieved by chromatography over alumina (200 g) with heptane/EtOAc (100:0 to 95:5) as eluent. The major diastereoisomer **21b** (4.31 g, 53% yield) was isolated as a yellow oil. – $[\alpha]_D$ = +58.5 (*c* = 1.38, $CHCl_3$). – ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.25 (d, *J* = 6.8 Hz, 3 H), 1.92 (m, 2 H), 3.35 (broad s, 1 H), 3.48 (dd, *J* = 10.5, 5.4 Hz, 1 H), 3.72–3.90 (m, 3 H), 4.15 (dd, *J* = 10.3, 5.4 Hz, 1 H), 5.30 (m, 2 H), 5.35 (m, 1 H), 5.45 (m, 1 H), 6.15 (m, 1 H), 7.18–7.35 (m, 5 H). – ^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 21.8, 26.7, 47.8, 53.6, 61.4, 61.7, 116.0, 124.2, 127.5, 127.9, 128.8, 131.9, 140.4, 140.6. – MS (CI): *m*/*z* (%) = 244 (100) [MH^+]. – CI-HRMS ($C_{16}H_{22}NO$): calcd. 244.1701; found 244.1718.

Minor Diastereoisomer 22b: Yield 1.51 g, 18%; $[\alpha]_D$ = –15 (*c* = 1.95, $CHCl_3$). – ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.18 (d, *J* = 6.8 Hz, 3 H), 2.10 (m, 2 H), 2.83 (broad s, 1 H), 3.38 (m, 1 H), 3.50 (m, 1 H). – 3.79 (dd, *J* = 10.5, 6.1 Hz, 1 H), 3.92 (dd, *J* = 10.4, 8.3 Hz, 1 H), 4.30 (dd, *J* = 8.3, 6.1 Hz, 1 H), 5.08 (m, 2 H), 5.30 (m, 1 H), 5.65 (m, 1 H), 5.80–6.00 (m, 1 H), 7.20–7.40 (m, 5 H). – ^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 21.8, 31.3, 49.7, 59.1, 62.7, 64.4, 115.6, 122.4, 127.6, 128.5, 128.5, 132.2, 139.1, 141.5. – MS (CI): *m*/*z* (%) = 244 (100) [MH^+]. – CI-HRMS ($C_{16}H_{22}NO$): calcd. 244.1701; found 244.1731.

(1*R*,2*S*,6*S*)-(+)-(6-Methyl-2-undecyl-3,6-dihydro-2*H*-pyridin-1-yl)-2-phenylethanol (21c): To an ice-cooled solution of undecanylmagnesium bromide (5.6 mL, 3.36 mmol) in Et_2O was added dropwise crude oxazolidine **12a** (205 mg, 0.95 mmol) in Et_2O (150 mL). When the addition was complete, the solution was stirred for 1 h at 0 °C then warmed to room temperature and stirred overnight. The mixture was treated in the same conditions described for the extraction of adduct **21a**. A mixture of tetrahydropyridines **21c** and **22c** was obtained in a ratio 66:33 (determined by GC). Separation of the diastereoisomers was achieved by flash chromatography over silica gel (30 g) with heptane/EtOAc (100:0 to 92:8) as eluent. The major diastereoisomer **21c** (153 mg, 43% yield) was isolated as a yellow oil. – $[\alpha]_D$ = +52 (*c* = 1.0, $CHCl_3$). – ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.87 (t, *J* = 7.5 Hz,3 H), 1.29 (m, 22 H), 1.64 (m, 3 H), 3.20 (m, 1 H), 3.44 (dd, *J* = 12.5, 6.3 Hz, 1 H), 3.79 (m, 1 H), 3.85 (dd, *J* = 13.8, 12.5 Hz, 1 H), 4.12 (dd, *J* = 13.8, 6.3 Hz, 1 H), 5.29 (dm, *J* = 12.5 Hz, 1 H), 5.46 (dm, *J* = 12.5 Hz, 1 H), 7.22 (m, 5 H). – ^{13}C NMR (62.89 MHz, $CDCl_3$): δ = 14.1, 21.7, 22.7, 27.0, 29.3, 29.7, 32.0, 33.5, 47.6, 51.8, 60.0, 61.4, 125.5, 127.5,

127.9, 129.0, 131.7, 140.9. – MS (EI): *m*/*z* (%) = 371 (10) [M^+], 370 (28), 340 (100). – EI-HRMS ($C_{25}H_{41}NO$): calcd. 371.3188; found 371.3187.

(2*S*,2*R*,6*S*)-(+)-2-[2-(2-[1,3]-Dioxolan-2-yl-ethyl)-6-methyl-3,6-dihydro-2*H*-pyridin-1-yl]-2-phenylethanol (21d): To an ice-cooled solution of ethyl-1,3-dioxolanmagnesium bromide (44.48 mL, 40.04 mmol) in THF was added dropwise crude oxazolidine **12a** (1.51 g, 7.01 mmol) in THF (45 mL). When the addition was complete, the solution was stirred for 1 h at 0 °C then warmed to room temperature and stirred for 6 h. The mixture was treated in the same conditions described for the extraction of adduct **21a**. A mixture of tetrahydropyridines **21d** and **22a** was obtained in a 77:23 ratio (determined by GC). Separation of the diastereoisomers was achieved by chromatography over silica gel (120 g) with heptane/EtOAc/NEt_3 (100:0:0.1 to 77:13:0.1) as eluent. The major diastereoisomer **21d** (1.036 g, 47% yield) was isolated as a transparent oil. – $[\alpha]_D$ = +51 (*c* = 1.7, $CHCl_3$). – ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.22 (d, *J* = 6.7 Hz, 3 H), 1.53–1.68 (m, 2 H), 1.69–1.94 (m, 4 H), 3.22 (m, 1 H), 3.46 (dd, *J* = 10.5, 5.3 Hz, 1 H), 3.82–3.90 (m, 4 H), 3.93–4.03 (m, 2 H), 4.11 (dd, *J* = 10.5, 5.1 Hz, 1 H), 4.94 (m, 1 H), 5.28 (d, *J* = 10 Hz, 1 H), 5.45 (d, *J* = 10.0 Hz, 1 H), 7.17–7.33 (m, 5 H). – ^{13}C NMR (62.89 MHz, $CDCl_3$): δ = 21.5, 27.1, 29.2, 31.2, 47.5, 51.8, 59.9, 61.4, 64.8, 104.3, 125.1, 127.4, 127.7, 128.8, 131.6, 140.8. – MS (CI): *m*/*z* (%) = 318 (100) [MH^+], 300 (9). – CI-HRMS ($C_{19}H_{28}NO_3$): calcd. 318.2069; found 318.2099.

(2*R*,2*S*,6*S*)-2-(6-Methyl-2-trimethylsilanylmethyl-3,6-dihydro-2*H*-pyridin-1-yl)-2-phenylethanol (21e): To a cooled (–10 °C) solution of trimethylsilanylmethylmagnesium chloride (72 mL, 101.3 mmol) in Et_2O was added dropwise crude oxazolidine **12a** (962 mg, 4.47 mmol) in Et_2O (45 mL). When the addition was complete, the solution was warmed to room temperature and stirred overnight. The resulting solution was treated under the same conditions described for the extraction of adduct **21a**. A mixture of tetrahydropyridines **21e** and **22e** was obtained in a ratio 98:2 (determined by GC). The major isomer **21e** was isolated after chromatography over alumina with heptane/EtOAc (100:0 to 95:5) as eluent, as a transparent oil (996 mg, 74% yield). – ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.05 (s, 9 H), 0.85 (dd, *J* = 13.9, 2.8 Hz, 1 H), 1.02 (dd, *J* = 13.9, 11.2 Hz, 1 H), 1.20 (d, *J* = 6.8 Hz, 3 H), 1.50–1.75 (m, 2 H), 3.40 (dd and m, *J* = 10.1, 5.3 Hz, 2 H), 3.80 (m, 2 H), 4.30 (dd, *J* = 10.7, 5.3 Hz, 1 H), 5.23 (m, 1 H), 5.40 (m, 1 H), 7.12–7.40 (m, 5 H). – ^{13}C NMR (75.47 MHz, $CDCl_3$): δ = –0.7, 21.8, 22.8, 31.4, 47.9, 49.0, 59.8, 61.2, 125.4, 128.0, 129.1, 131.6, 141.0. – MS (CI): *m*/*z* (%) = 304 (100) [MH^+], 286 (25). – CI-HRMS ($C_{18}H_{30}NOSi$): calcd. 304.2097; found 304.2134.

Examples of Applications of the Enantioselective Synthesis of Alkaloids

(+)-Coniine: Derivative **8c** (220 mg, 0.96 mmol) was dissolved in a mixture of EtOAc (5 mL), EtOH (5 mL), and 3 N HCl (2.5 mL) and stirred overnight in a presence of a catalytic amount of 10% palladium on carbon under hydrogen. The resulting mixture was filtered with Celite and the Celite bed washed with EtOH. After evaporation of solvent, the crude HCl salt was purified over silica gel (4 g) with CH_2Cl_2/MeOH (100:0 to 92:8) as eluent to afford pure (+)-coniineHCl (120 mg, 76% yield) as white crystals. An analytical sample was recrystallised from MeOH/Et_2O for analysis: m.p. 216–217 °C. – $[\alpha]_D$ = +10 (*c* = 1.4, MeOH). – ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.93 (t, *J* = 7.0 Hz, 3 H), 1.30–1.50 (m, 4 H), 1.50–1.71 (m, 3 H), 1.76–1.88 (m, 2 H), 1.90–2.02 (m, 1 H), 2.85–3.11 (m, 2 H), 3.29 (m, 1 H). – ^{13}C NMR (62.89 MHz, $CDCl_3$): δ = 14.1, 19.3, 23.3, 23.7, 29.9, 37.1, 46.1, 58.0. – MS (EI): *m*/*z* (%) = 127 (19) [M^+], 126 (14), 84 (100). – MS (CI): *m*/*z* (%) = 128 (100) [MH^+]. Reduction of derivative **15c** also gave (+)-coniine in identical yield and with the same spectroscopic properties.

(–)-*trans*-Lupetidine: Tetrahydropyridine **21a** (3.64 g, 15.70 mmol) was dissolved in a mixture of EtOAc (20 mL), EtOH (20 mL), and 3 N HCl (10 mL) and stirred for 48 h in the presence of a catalytic amount of 10% palladium on carbon, under hydrogen at a pressure of 4.5 bar. After filtration with Celite and washing with MeOH, the solvents were evaporated at reduced pressure. The residue was dissolved in water, washed with Et_2O, and the aqueous phase evaporated. The resulting gum was dissolved in a minimum volume of hot $CHCl_3$. Crystallisation occurred by addition of a few drops of EtOAc affording (–)-lupetidineHCl (1.64 g, 70% yield) as white crystals: m.p. 252–253 °C. – $[\alpha]_D$ = –11 (*c* = 1.4, EtOH). – ^{1}H NMR (250 MHz, CD_3ODCl): δ = 1.39 (d, *J* = 6.7 Hz, 6 H), 1.59 (m, 2 H), 1.76 (m, 2 H), 1.93 (m, 2 H), 3.59 (qt, *J* = 6.7, 5.0 Hz, 2 H). – ^{13}C NMR (62.89 MHz, CD_3OD): δ = 16.9, 17.6, 29.7, 48.5. – MS (EI): *m*/*z* (%) = 113 (14) [M^+], 112 (21), 98 (100). – $C_7H_{16}ClN$ (149.66): calcd. C 56.17, H 10.78, N 9.36, Cl 23.69; found C 56.14, H 10.64, N 9.21, Cl 23.99.

(+)-(2*S*,6*R*)-2,6-Diisopropylpiperidine [(+)-24]: To an ice-cooled solution of isopropylmagnesium bromide (42 mL, 21.0 mmol) in Et_2O was added dropwise a solution of oxazolidine **12d** (1.45 g, 6.98 mmol) in Et_2O (70 mL). When the addition was complete, the solution was stirred for 1 h at 0 °C then warmed to room temperature and stirred for 8 h. The mixture was treated under the conditions described for the extraction of adduct **15a**. the major tetrahydropyridine **23** was thus obtained along with the corresponding diastereoisomer in an 88:22 ratio (determined by GC). Chromatography over alumina (105 g) with heptane/EtOAc (100:0 to 84:16) as eluent afforded pure base **3** (530 mg, 40% yield) as a pale yellow oil. – $[\alpha]_D$ = +81 (*c* = 2.6, $CHCl_3$). – ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.98 (d, *J* = 5.0 Hz, 3 H), 1.00 (d, *J* = 5.0 Hz, 3 H), 1.09 (d, *J* = 6.0 Hz, 3 H), 1.16 (d, *J* = 6.0 Hz, 3 H), 1.59 (ddd, *J* = 18.0, 11.6, 2.2 Hz, 1 H), 1.80 (m, 1 H), 1.87 (m, 1 H), 2.11 (m, 1 H), 2.70 (td, *J* = 11.6, 4.5 Hz, 1 H), 3.00 (m, 1 H), 3.08 (dd, *J* = 9.3, 4.0 Hz, 1 H), 3.52 (dd, *J* = 10.5, 5.5 Hz, 1 H), 3.97 (t, *J* = 10.5 Hz, 1 H), 4.12 (dd, *J* = 10.5, 5.5 Hz, 1 H), 5.18 (dd, *J* = 9.8, 4.5 Hz, 1 H), 5.63 (ddd, *J* = 9.8, 4.0, 2.2 Hz, 1 H), 7.11–7.38 (m, 5 H). – ^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 20.6, 21.0, 21.1, 21.4, 27.4, 29.6, 33.1, 59.3, 59.6, 60.5, 62.7, 126.0, 127.5, 127.7, 129.4, 130.5, 141.5. – MS (EI): *m*/*z* (%) = 287 (5) [M^+], 286 (16) [M^+ – H], 244 (100) [$M^+ - C_3H_7$]. – MS (CI): *m*/*z* (%) = 344 (29) [M + C_4H_9]$^+$, 288 (100) [M + H]$^+$, 270 (61) [M + H–H_2O]$^+$. – EI-HRMS ($C_{19}H_{29}NO$): calcd. 287.2249; found 287.2240.

Derivative 23 (411 mg, 1.44 mmol) was hydrogenated in the conditions used for the preparation of (–)-*trans*-lupetidine to give **24** · Cl. Addition of K_2CO_3 gave the corresponding base which was purified over alumina (9 g) with heptane/EtOAc (100:0 to 80:20) as eluent. Piperidine **24** (159 mg, 65% yield) was isolated as a transparent oil. – ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.90 (d, *J* = 6.3 Hz, 6 H), 1.10 (d, *J* = 6.3 Hz, 6 H), 1.72–1.93 (m, 6 H), 1.97–2.18 (m, 2 H), 2.99–3.10 (m, 2 H). – ^{13}C NMR (62.89 MHz, $CDCl_3$): δ = 18.1, 19.8, 28.0, 35.9, 58.6. – MS (EI): *m*/*z* (%) = 169 (7) [M^+], 168 (69) [M^+ – H], 126 (100) [$M^+ - C_3H_7$]. – MS (CI): *m*/*z* (%) = 170 (100) [M + H]$^+$. – EI-HRMS ($C_{11}H_{23}N$): calcd. 169.1831; found 169.1816.

(+)-Solenopsine A: Tetrahydropyridine **21c** (108 mg, 0.3 mmol) was hydrogenated under the conditions used for (–)-lupetidineHCl. The

crude salt was purified over silica gel (2 g) with CH_2Cl_2/MeOH (100:0 to 93:7) as eluent to afford pure (+)-solenopsineHCl (52 mg, 60% yield) as white crystals. An analytical sample was recrystallised from MeOH/H_2O for analysis: m.p. 145–146 °C. – $[\alpha]_D$ = +5 (*c* = 1.0, $CHCl_3$). – ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.88 (t, *J* = 6.8 Hz, 3 h), 1.07 (d, *J* = 6.5 Hz, 3 H), 1.26 (s, 18 H), 1.49–1.73 (m, 8 H), 2.07 (m, 1 H), 2.91 (m, 1 H), 3.10 (m, 1 H). – ^{13}C NMR (62.89 MHz, $CDCl_3$): δ = 14.3, 19.5, 21.0, 22.8, 26.6, 29.77, 30.6, 32.0, 32.8, 34.0, 46.2, 51.1. – MS (CI): *m*/*z* (%) = 254 (100) [MH^+]. – CI-HRMS ($C_{17}H_{36}N$): calcd. 254.2847; found 254.2865.

(5*S*,8*aR*)-(–)-5-Methyloctahydroindolizidine [(–)-5]: Tetrahydropyridine **21d** (1.29 g, 4.07 mmol) in solution in EtOAc/EtOH/3 N HCl (20:20:10) was stirred for 48 h in the presence of a catalytic amount of palladium on carbon (10%) under hydrogen. The resulting mixture was treated as described previously for (–)-*trans*-lupetidine to give crude (–)-**5** · Cl. Addition of H_2O and K_2CO_3, followed by extraction with CH_2Cl_2 afforded the corresponding base, after the usual treatment. Purification by chromatography over alumina (28 g) with heptane/EtOAc (100:0 to 95:5) as eluent gave indolizidine (–)-**5** (397 mg, 75% yield) as a transparent oil. – $[\alpha]_D$ = –3 (*c* = 1.9, $CHCl_3$). – ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.98 (d, *J* = 7.0 Hz, 3 H), 1.08–1.40 (m, 3 H), 1.43–1.63 (m, 3 H), 1.68–1.91 (m, 4 H), 2.30–2.47 (m, 1 H), 2.54 (ddd, *J* = 8.8, 8.8, 8.8 Hz, 1 H), 2.82 (ddd, *J* = 8.8, 8.8, 2.8 Hz, 1 H), 3.24 (m, 1 H). – ^{13}C NMR (62.89 MHz, $CDCl_3$): δ = 10.0, 19.4, 20.9, 30.6, 31.5, 49.2, 50.1, 54.6. – MS (EI): *m*/*z* (%) = 139 (18) [M^+], 138 (13), 124 (100). – EI-HRMS ($C_9H_{17}N$): calcd. 139.1361; found 139.1346.

Synthesis of Substituted Indolizidine (–)-6

(2*S*,2*R*,4*S*,5*R*,6*S*)-(+)-2-{2-[2-(1,3)-Dioxolan-2-yl-ethyl]-6-methyl-4,5-epoxy-3,6-dihydro-2*H*-pyridin-1-yl}-2-phenylethanol (25): To an ice-cooled water solution of 50% hydrogen peroxide (0.3 mL) in CH_2Cl_2 (12 mL) was added dropwise trifluoroacetic anhydride (1.6 mL, 11.3 mmol). This solution was stirred for 1.5 h at 0 °C. The resulting solution of pertrifluoroacetic acid was then added dropwise to a solution (at 0 °C) of the trifluoroacetate salt of tetrahydropyridine **21d**, previously prepared from base **21d** (173 mg, 0.55 mmol) and excess trifluoroacetic acid (0.24 mL) in CH_2Cl_2 (2 mL). This mixture was warmed to room temperature, stirred for 30 min, and poured into an ice-cooled saturated solution of Na_2SO_3. After neutralisation by a solution of $NaHCO_3$ and extraction with CH_2Cl_2, the organic phase was dried with $MgSO_4$ and evaporated at reduced pressure to give crude epoxide **25** (131 mg, 71%) as a pale yellow oil. – $[\alpha]_D$ = +9 (*c* = 2.3, $CHCl_3$). – ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.24 (d, *J* = 6.9 Hz, 3 H), 1.34–1.62 (m, 2 H), 1.63–1.91 (m, 4 H), 2.61 (m, 1 H), 2.90 (t, *J* = 4.4 Hz, 1 H), 2.93–3.07 (m, 1 H), 3.45 (dd, *J* = 10.6, 5.4 Hz, 1 H), 3.76–3.92 (m, 4 H), 3.93–4.09 (m, 3 H), 4.90 (m, 1 H), 7.10–7.60 (m, 5 H). – ^{13}C NMR (62.89 MHz, $CDCl_3$): δ = 16.8, 26.7, 28.0, 30.8, 44.6, 48.1, 52.5, 54.1, 59.6, 61.7, 64.9, 104.1, 128.0, 128.6, 128.9, 140.8. – MS (EI): *m*/*z* (%) = 333 (4) [M^+], 302 (100). – EI-HRMS ($C_{19}H_{28}NO_4$): calcd. 334.2019; found 334.2011.

(1*R*,2*S*,3*S*,4*R*,6*S*)-(–)-6-[2-[1,3]-Dioxolan-2-ylethyl]-1-(2-hydroxy-1-phenylethyl)-2,4-dimethylpiperidin-3-ol (26): To an ice-cooled solution of copper iodide (864 mg, 4.54 mmol) in Et_2O (2 mL) was added dropwise methyllithium (5.7 mL, 9.12 mmol) in Et_2O. Addition of the first equivalent gave an intense yellow colour followed by decolouration to give a transparent solution after the second equivalent. The resulting solution was stirred for 30 min at 0 °C and then added dropwise, at 0 °C, to the crude epoxide **25** (302 mg, 0.91 mmol) in a mixture of Et_2O and THF (5:5). After 1 h, the solution was warmed to room temperature and stirred overnight. The resulting mixture was poured into a saturated solution of NH_4Cl, extracted with CH_2Cl_2, and the extract dried with $MgSO_4$, filtered, and evaporated at reduced pressure. The crude product was purified by chromatography over alumina (10 g) with CH_2Cl_2/MeOH (100:0 to 99:1) as eluent. Diol **26** (181 mg, 57% yield) was thus isolated as a pale yellow oil. – $[\alpha]_D$ = –6 (*c* = 3.2, $CHCl_3$). – ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.69 (d, *J* = 6.3 Hz, 3 H), 0.81–1.06 (m, 1 H), 1.15 (d, *J* = 7.3 Hz, 3 H), 1.41–1.59 (m, 2 H), 1.62–1.93 (m, 4 H), 2.44 (dd, *J* = 10.5, 5.6 Hz, 1 H), 3.13–3.26 (m, 1 H), 3.30 (dd, *J* = 7.3, 5.6 Hz, 1 H), 3.58 (dd, *J* = 10.6, 5.5 Hz, 1 H), 3.72–3.91 (m, 2 H), 3.92–4.06 (m, 3 H), 4.20 (dd, *J* = 9.5, 5.5 Hz, 1 H), 4.93 (m, 1 H), 7.08–7.50 (m, 5 H). – ^{13}C NMR (62.89 MHz, $CDCl_3$): δ = 12.6, 18.6, 27.7, 31.3, 32.8, 38.9, 51.1, 53.1, 59.5, 60.4, 65.1, 73.9, 104.5, 127.8, 128.6, 128.8, 141.1. – MS (CI): *m*/*z* (%) = 350 (100) [MH^+], 332 (98), 318 (79). – CI-HRMS ($C_{20}H_{31}NO_4$): calcd. 350.2332; found 350.2317.

(5*S*,6*S*,7*R*,8*aS*)-(–)-5,7-Dimethyloctahydroindolizidin-6-ol [(–)-6]: Diol **26** (181 mg, 0.52 mmol), in solution in a mixture of EtOAc/EtOH/3N HCl (8:8:4), was stirred overnight in a presence of a catalytic amount of palladium on carbon (10%) under hydrogen. The resulting mixture was treated as described previously for (–)-lupetidine. The salt obtained was dissolved in H_2O, and washed with Et_2O. The aqueous phase was made basic with K_2CO_3 and extracted with CH_2Cl_2. The organic phase was dried, filtered, and evaporated to give the indolizidinol **(–)-6** (60 mg, 68% yield) as a pale rose oil. – $[\alpha]_D$ = –46 (*c* = 2.2, $CHCl_3$). – ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.92 (m, 1 H), 0.95 (d, *J* = 6.6 Hz, 3 H), 1.01 (d, *J* = 6.4 Hz, 3 H), 1.19–1.36 (m, 1 H), 1.52–1.73 (m, 2 H), 1.74–1.90 (m, 3 H), 2.44–2.55 (m, 1 H), 2.63 (dd, *J* = 17.3, 8.7 Hz, 1 H), 2.79 (dt, *J* = 8.7, 2.6 Hz, 1 H), 3.33 (qd, *J* = 6.6, 6.0 Hz, 1 H), 3.48 (dd, *J* = 10.0, 6.0 Hz, 1 H). – ^{13}C NMR (62.89 MHz, $CDCl_3$): δ = 3.5, 18.6, 21.7, 30.3, 31.9, 38.7, 48.5, 53.5, 55.6, 76.0. – MS (EI): *m*/*z* (%) = 169 (24) [M^+], 168 (27), 154 (100). – EI-HRMS ($C_{10}H_{19}NO$): calcd. 169.1467; found 169.1464.

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