An Enantioselective Access to 1-Alkyl-1,2-Dihydroisoquinolines and 1-Alkyl-, 3-Alkyl-, and 1,3-Dialkyl-1,2,3,4-tetrahydroisoquinolines

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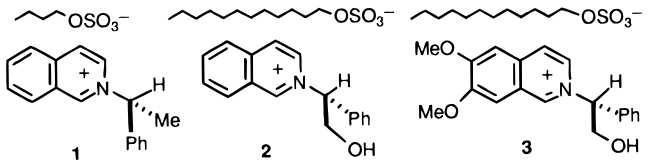
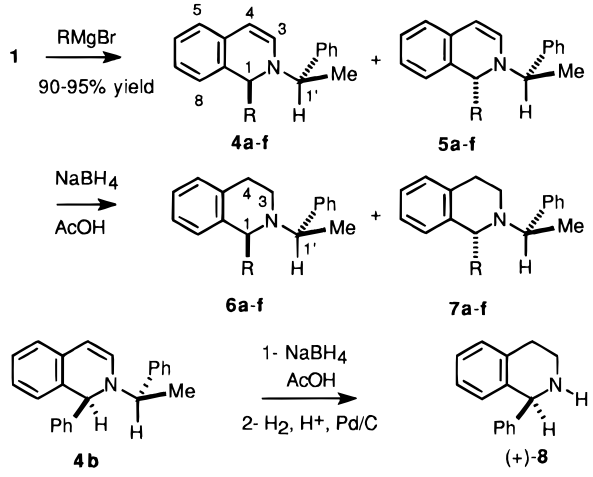
New chiral isoquinolinium salt derivatives **1**, **2** or **3** have been treated with Grignard reagents to give as major products, 1-substituted 1,2-dihydroisoquinolines **4a**−**f**, oxazolidine derivatives **10a**−**f** or **21**, respectively, in good yield and in moderate to good diastereoisomeric excess. The stereochemistry of these new derivatives has been elucidated, in particular, by X-ray crystallographic studies of 1,2-dihydroisoquinoline **4b** and the minor oxazolidine **11b**. Reduction of all these intermediates gave chiral 1-substituted 1,2,3,4-tetrahydroisoquinolines such as base **8**. The enantioselective synthesis of the natural alkaloid (−)-salsonidine in three steps and 38% overall yield from salt **3** is described as an application. Reduction of salt **2** gave a new oxazolidine derivative **15** which is a practical intermediate for the synthesis of 3-alkyl 1,2,3,4-tetrahydroisoquinolines **17a,b**, while oxazolidines such as **10** are convenient precursors of 1,3-disubstituted tetrahydroisoquinolines, as illustrated by a synthesis of 1,3-dimethyl tetrahydroisoquinoline **20**.

Previously, it was demonstrated[1] that the Zincke reaction between chiral primary amines[2] and *N*-(2,4-dinitrophenyl)isoquinolinium salts provided a practical entry to new chiral isoquinolinium salt derivatives such as **1**, **2**, or **3**. The lipophilic sulfate counteranion ensured solubilization of these salts in organic solvents, particularly in toluene or THF, thus allowing further studies of their reactions with Grignard reagents.[3] We now report the results of these studies[4] and the first applications of this strategy to the enantioselective syntheses of 1-substituted 1,2-dihydroisoquinolines, 1- or 3-substituted 1,2,3,4-tetrahydroisoquinolines, and 1,3-disubstituted 1,2,3,4-tetrahydroisoquinolines.



The present approach complements the existing methods reported for the stereoselective synthesis of 1-substituted 1,2,3,4-tetrahydroisoquinolines, an area of research which has generated much interest in the past few years.[5] In addition, it gives an access to chiral 1,2-dihydroisoquinoline derivatives and 1,3-disubstituted tetrahydroisoquinolines which are difficult to obtain otherwise. Indeed, while several methods would now allow synthesis of various 1-substituted chiral tetrahydroisoquinolines, few procedures are available at present for the synthesis of polysubstituted tetrahydroisoquinolines.[6]

Scheme 1



Our attention was first directed to reactions of salt **1** with different Grignard reagents (Scheme 1) in THF under the conditions found appropriate in the corresponding pyridinium series.[3] The results are summarized in Table 1. The yields of rather unstable 1-substituted dihydroisoquinolines **4a**−**f** and **5a**−**f** were practically quantitative, but in most instances the diastereoisomeric excess (de), estimated by the integration of relevant signals in the ^{1}H NMR spectra of the crude

(1) Barbier, D.; Marazano, C.; Das, B. C.; Potier, P. *J. Org. Chem.* **1996**, *61*, 9596−9598.

(2) Génisson, Y.; Marazano, C.; Mehmandoust, M.; Gnecco, D.; Das, B. C. *Synlett* **1992**, 431.

(3) For previous results in pyridinium series, see: Génisson, Y.; Marazano, C.; Das, B. C. *J. Org. Chem.* **1993**, *58*, 2052.

(4) For other examples of the reaction of chiral isoquinolinium salts with Grignard reagents, see: Comins, D. L.; Badawi, M. M. *Heterocycles* **1991**, *32*, 1869.

(5) For a recent review, see: Rozwadowska, M. D. *Heterocycles* **1994**, *39*, 903.

(6) Previous enantiospecific accesses to 1,3-disubstituted tetrahydroisoquinolines: (a) Coote, S. J.; Davies, S. G.; Sutton, K. H. *J. Chem. Soc., Perkin Trans. 1* **1988**, 1481. (b) Richter-Addo, G. B.; Knight, D. A.; Dewey, M. A.; Arif, A. M.; Gladysz, J. A. *J. Am. Chem. Soc.* **1993**, *115*, 11863. (c) Bringmann, G.; Weirich, R.; Reuscher, H.; Jansen, J. R.; Kisinger, L.; Ortmann, T. *Liebigs Ann. Chem.* **1993**, 877. (d) Tietze, L. F.; Burkhardt, O. *Synthesis* **1994**, 1331. (e) Gosmann, G.; Guillaume, D.; Husson, H.-P. *Tetrahedron Lett.* **1996**, *37*, 4369.

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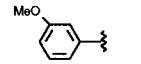
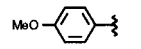
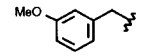
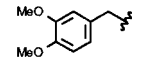
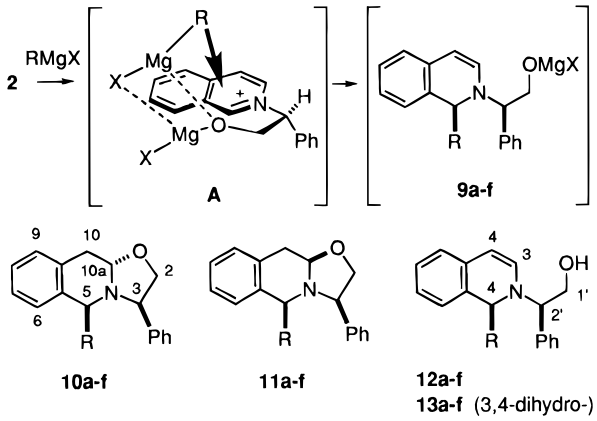
Table 1. Alkylation of Salt 1 with Some Grignard Reagents

R	intermediates (% ratio)[a]	products (%yield)	de[b]
Me	**4a** (64), **5a** (36)	**6a**, **7a**[c]	28
Ph	**4b** (87), **5b** (13)	**6b** (72)[d], **7b**	74
	**4c** (90), **5c** (10)	**6c**, **7c**[c]	80
	**4d** (70), **5d** (30)	**6d**, **7d**[c]	40
	**4e** (62), **5e** (38)	**6e** (42), **7e** (25)	24
	**4f** (65), **5f** (35)	**6f** (39), **7f** (22)	30

[a] Ratio calculated from ^{1}H NMR of the crude mixture. [b] Calculated from ^{1}H NMR of the crude mixture of adducts **6** and **7**. [c] Not separated. [d] Yield from **4b** isolated after crystallization.

Scheme 2

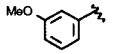
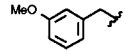


reaction mixture, was modest. Particularly with benzylic Grignard reagents, the observed de's were significantly lower than those observed in the corresponding 3,4-disubstituted pyridinium series (de>80%).[3] Nevertheless, reduction of the crude mixture of unseparable intermediates **4a**−**f** and **5a**−**f** with sodium borohydride in the presence of acetic acid afforded tetrahydroisoquinolines **6a**−**f** and **7a**−**f** which were in general separable by chromatography and thus could be obtained in a few steps, by using simple protocols and inexpensive reagents.

The preparation of base (+)-**8** turned out to be particularly easy since the intermediate **4b** was obtained in good de (74%) and could be isolated after crystallization from dichloromethane-ethanol in 72% yield. The X-ray crystallographic structure of **4b** secured the attribution of the absolute configuration of base (+)-**8** as 1*S* (in a recent paper[7] this configuration was erroneously reported as 1*R* and should therefore be corrected accordingly). The stereochemical preferences in favor of adducts **4a**−**f** are identical to those observed in the corresponding pyridinium series and can be interpreted in a similar way[3].

The reactions of salt **2**, having a chiral phenylethanol auxiliary on the nitrogen, with Grignard reagents were investigated next. The results are depicted in Scheme 2 and Table 2. In this particular case, the intermediate

Table 2. Alkylation of Salt 2 with Some Grignard Reagents

R	intermediates (% ratio)[a]	product (% yield)	de[b]
Me	**10a** (51),**11a** (37), **12a** (12)	**13a** (57)	76
C_6H_5	**10b** (64), **11b** (29), **12b** (7) [**10b** (81), **11b** (12), **12b** (7)][c]	**13b** (58)	90
i-Pr	**10c** (49), **11c** (34), **12c** (17)	**13c** (n. d.)	66
	**10d** (72), **11d** (20), **12d** (8)	–	–
$C_6H_5CH_2$	n. d.	**13e** (45)	42
	n. d.	**13f** (32)	38

[a] Ratio calculated from ^{1}H NMR of the crude mixture at equilibrium. [b] Calculated from ^{1}H NMR of the crude mixture after $NaBH_4$ reduction. [c] Crude mixture obtained immediately after extraction.

1,2-dihydroisoquinolines **9a**−**f** cyclized spontaneously upon hydrolysis, in the same way as previously reported for the analogous 1,2-dihydropyridine derivatives,[8] to give as major products oxazolidines **10a**−**f** and **11a**−**f** [9] accompanied with small amounts (see Table 2) of 1,2-dihydroisoquinolines **12a**−**f** (stereochemistry not determined). Since these intermediates were too unstable to be separated, the de of the reactions were estimated from the ^{1}H NMR analysis of the mixture of diastereoisomers obtained after sodium borohydride reduction, in the presence of acetic acid, of the crude mixture of the Grignard reaction.

A comparison between Table 1 and Table 2 showed that the diastereoselectivities of Grignard addition products were significantly increased in passing from salt **1** having a phenylethyl auxiliary to salt **2** having a phenylethanol auxiliary. This can be readily interpreted if one considers that the alcohol function in salt **2** reacts first to give an organomagnesium complex (see **A** in Scheme 2) which can then direct the alkylation from the face opposite to the phenyl ring. Again, the lowest de were observed with benzylic Grignard reagents.[10]

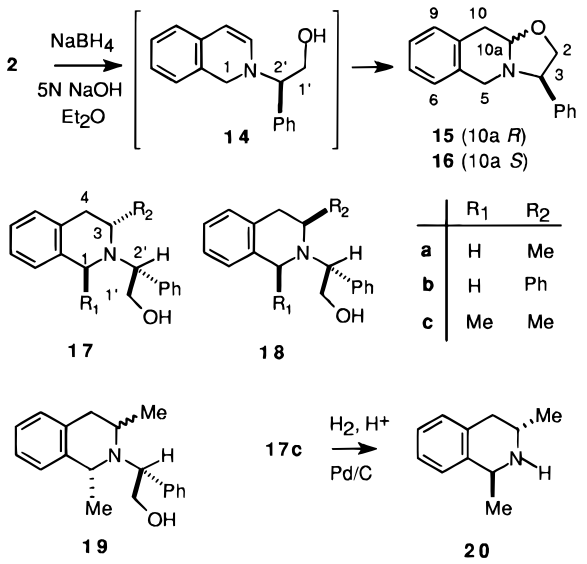
The stereochemistry at the C_{10a} center of oxazolidines **10a**−**f** and **11a**−**f** was easily determined from the ^{1}H NMR chemical shift of the corresponding proton which is deshielded in **10a**−**f** (δ near 5.4 ppm) and shielded in **11a**−**f** (δ near 4.5 ppm). These different chemical shifts can result from a deshielding effect due to the syn relationship between the nitrogen doublet and the proton at C_{10a} in **10a**−**f** compared to the anti arrangement in **11a**−**f**. The predominance of oxazolidines **10a**−**f** over oxazolidines **11a**−**f** can be possibly explained by destabilizing steric interactions between the phenyl group of the oxazolidine ring and the substituents R at C_5. Strong support for these hypotheses as well as confirmation of the stereochemistry at C_{10a} was obtained from an X-ray analysis of the minor oxazolidine **11b** which crystallized out when the crude Grignard reaction mixture was dissolved in Et_2O. We checked by ^{1}H NMR spectroscopy that crystals of oxazolidine **11b** equilibrated very rapidly

(7) Yamato, M.; Hashigaki, K.; Qais, N.; Ishikawa, S. *Tetrahedron* **1990**, *46*, 5909.

(8) Génisson, Y.; Mehmandoust, M.; Marazano, C.; Das, B. C. *Heterocycles* **1994**, *39*, 811.

(9) For the use of other oxazolidine intermediates in the enantioselective syntheses of 1-alkyl 1,2,3,4-tetrahydroisoquinoline series see references 6e, 7, 8 and Carbonelle, A. C.; Gott, V.; Roussi, G. *Heterocycles* **1993**, *36*, 1763.

Scheme 3

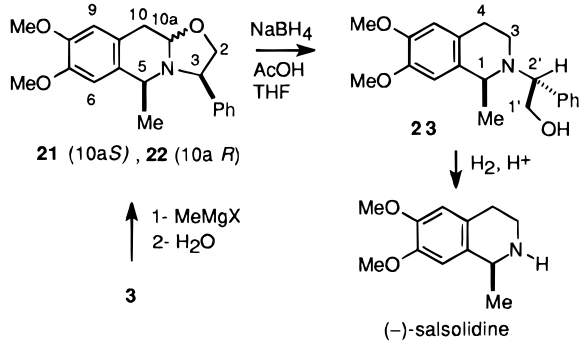


when dissolved in deuteriochloroform to give back isomer **10b** as the major component.

Reduction of salt **2** (Scheme 3) with sodium borohydride in an alkaline medium gave the unstable 1,2-dihydroisoquinoline **14** which could not be isolated since it cyclized spontaneously to oxazolidines **15** and **16** in 4:1 ratio (accompanied with a small amount, ca. 5%, of uncyclized **14**). This result was similar to that obtained in the corresponding 1,2-dihydropyridine series.[8] Thus, in the absence of a substituent at position 1, the 1,2-dihydroisoquinoline **14** prefers to cyclize, as expected, to give the major oxazolidine **15** having a cis relationship between the C_{10a}−O and the C_3−phenyl bonds, while, for steric reasons, the trans relationship is preferred in the presence of a substituent at C_1 to give as major products the trans oxazolidines **10a**−**f**.

The oxazolidine derivatives **15** and **16** are intermediates of interest[11] toward a rapid access to chiral 3-substituted tetrahydroisoquinolines. Thus, for example, they gave adducts **17a,b** (64% and 50% de) and **18a,b** when treated with the appropriate Grignard reagents. These reactions were difficult to bring to completion, significant quantities of starting material being recovered, even when a large excess of the Grignard reagent was used. This was presumably due to the Grignard acting also as a base which deprotonated the starting oxazolidines giving rise to the corresponding dihydroisoquinoline whose hydrolysis gave back the starting oxazolidines **15** and **16**. For these reasons, the reaction was repeated twice in order to give satisfactory yields of the desired alkylated products. Finally, according to this procedure, the major adducts **17a** or **17b** were recovered in about 40−50% yield after chromatography. The enantioselective approach to 1,3-disubstituted tetrahydroisoquinolines starting from chiral isoquinolinium salt derivatives, is illustrated by one example. When the crude mixture of adducts **10a**, **11a**, and **12a** was treated with an excess of methylmagnesium chloride in toluene, a mixture of

Scheme 4



four diastereoisomers **17c**, **18c**, and **19** (two epimers at C_3 in 8:3 ratio) was obtained in 70:17:13 ratio and in a total yield of 95%. Compared to the alkylation of oxazolidine **15** and **16** in THF, the reaction was brought to completion in a single step in toluene. The role of toluene proved to be crucial since the reaction was found to be incomplete when THF was used as solvent.

Finally the utility of this approach was also illustrated by an enantioselective synthesis of the natural alkaloid (−)-salsolidine[7,12] according to Scheme 4. Thus, treatment of salt **3** with methylmagnesium iodide gave a mixture of adducts **21**, **22**, and the corresponding dihydroisoquinoline (undefined stereochemistry) in 40:20:20 ratio and 79% total yield. Reduction of this mixture with sodium borohydride in the presence of acetic acid afforded two diastereoisomers allowing determination of the selectivity (60% de) of the attack by methylmagnesium iodide by ^{1}H NMR spectroscopy. The major isomer **23**, isolated in 45% yield after chromatography over alumina, was hydrogenated in acidic medium to give (−)-salsonidine in 38% overall yield from **3**.

In conclusion, we believe that these new chiral isoquinolinium salts, readily available by the Zincke procedure starting from isoquinolines and chiral primary amines, can be considered as good synthons for the enantioselective syntheses of a number of substituted 1,2-dihydro- or 1,2,3,4-tetrahydroisoquinolines.

Experimental Section

Alkylation of Salt 1 with Grignard Reagents: Preparation of Base (+)-8 as a Typical Procedure. To a solution of salt **1**[1] (7 g, 18.1 mmol) in THF (150 mL) was added dropwise, at 0 °C under an inert atmosphere, an excess of 1 M phenylmagnesium iodide in THF (38.2 mL, 38.2 mmol). After 1 h at 0 °C, the resulting mixture was poured into a 32% NH_4OH solution with strirring and then extracted with cold Et_2O. Removal of solvent left a mixture (5.34 g, 17.16 mmol, 95%) of enamines **4b** and **5b** as an oil in 87:13 ratio. The major isomer **(1*S*,1*R*)-(+)-1-phenyl-2-(1-phenylethyl)-1,2-dihydroisoquinoline (4b)** was isolated by crystallization from CH_2Cl_2−EtOH (4.05 g, 13.02 mmol, 72%): mp 122−124 °C; $[\alpha]_D$ +563 (*c* 1, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.46 (d, J = 7.1 Hz, 3H), 4.24 (q, J = 7.1 Hz, 1H), 5.35 (d, J = 7.6 Hz, 1H), 5.40 (s,1H), 6.64 (ld, J = 7.4 Hz, 1H), 6.70 (d, J = 7.6 Hz, 1H), 6.81 (ddd, J = 1.4, 7.4, 7.4 Hz, 1H), 6.88 (dd, J = 1.4, 7.5 Hz, 1H), 7.01 (ddd, J = 1.4, 7.4, 7.5 Hz, 1H),7.2−7.4 (m, 10H); ^{13}C NMR (75.47 MHz, $CDCl_3$) δ 21.5, 58.9, 64.5, 96.7, 131.9, 122.8, 124.4, 127.0, 127.3, 126.6−128.7 (10C), 132.7, 134.5, 143.8, 144.8; MS (EI) *m*/*z* (rel intensity) 311 ($M^{+\bullet}$, 100), 234 (99), 208 (19), 206 (99), 130 (100), 105 (64), 77 (38). Anal. Calcd for $C_{23}H_{21}N$-0.2 H_2O: C, 87.69; H, 6.84; N, 4.44. Found C, 87.59; H, 6.94; N, 4.31. NMR studies of the mother liquors

(10) Improved selectivities for the alkylation of related 3,4-dihydroisoquinoline equivalents were observed using benzylic titanium reagents: Hashigaki, K.; Kan, K.; Qais, N.; Takeuchi, Y.; Yamato, M. *Chem. Pharm. Bull.* **1991**, *39*, 1126.

(11) For a recent review see: Meyers, A. I.; Brengel G. P. *Chem. Commun.* **1997**, 1.

(12) Battersby, A. R.; Edwards, T. P. *J. Chem. Soc.* **1960**, 1214.

allowed characterization of the minor isomer **(1*R*,1*R*)-1-phenyl-2-(1-phenylethyl)-1,2-dihydroisoquinoline (5b)**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.48 (d, J = 7 Hz, 3H), 4.34 (q, J = 7 Hz, 1H), 5.22 (d, J = 7.4 Hz, 1H), 5.66 (s, 1H), 6.16 (d, J = 7.4 Hz, 1H), 6.6−7.4 (m, 14H); ^{13}C NMR (75.47 MHz, $CDCl_3$) characteristic signals at δ 18.2, 59.3, 63.9, 96.8, 134.5. To a solution of the major isomer **4b** (1.5 g, 4.82 mmol) in THF (50 mL) was added $NaBH_4$ (1.87 g) with stirring. After 0.25 h, a solution of 25% acetic acid in THF (25 mL) was added dropwise with vigorous stirring. After an additional 0.5 h, the resulting mixture was basified with 2 N NaOH and the product extracted with Et_2O to give crude base **6b**. The corresponding hydrochloride **6b,**HCl was dissolved in a minimum of MeOH and precipitated with acetone. Filtration gave a white powder which was extracted in alkaline medium to give **(1*S*,1*R*)-(+)-1-phenyl-2-(1-phenylethyl)-1,2,3,4-tetrahydroisoquinoline (6b)** (1.5 g, 100%)**:** $[\alpha]_D$ +185 (*c* 2.5, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.37 (d, J = 6.9 Hz, 3H), 2.39 (ddd, J = 4, 8.3, 12 Hz, 1H), 2.80 (ddd, J = 4, 5.2, 16.2 Hz, 1H), 2.95 (ddd, J = 5.2, 8.3, 16.2 Hz, 1H), 3.23 (ddd, J = 5.2, 5.2, 12 Hz, 1H), 3.82 (q, J = 6.9 Hz, 1H), 4.79 (s, 1H), 6.74 (ld, J = 7.6 Hz, 1H), 6.94 (ddd, J = 2.5, 6, 7.6 Hz, 1H), 7.01−7.10 (m, 2H), 7.18−7.38 (m, 10H); ^{13}C NMR (75.47 MHz, $CDCl_3$) δ 20.6, 29.0, 41.3, 53.7, 64.6, 125.6, 125.8, 128.7, 129.1, 127.0−129.5 (10C), 135.2, 138.4, 142.3−145.3 (2C); MS (EI) *m*/*z* (rel intensity) 313 ($M^{+\bullet}$, 74), 298 (78), 236 (100), 208 (35), 206 (8), 132 (98), 130 (23), 105 (98), 77 (44); HRMS (EI): calcd for $C_{23}H_{23}N$ *m*/*z* 313.1830, obsd *m*/*z* 313.1836. Base **6b** (1.2 g, 3.83 mmol) was dissolved in EtOAc (5 mL) and EtOH (15 mL) to which an aqueous solution of 2.4 N HCl (2 mL) was added, and the resulting solution was hydrogenated over 10% Pd/C for 15 h with stirring. Filtration over Celite followed by evaporation of solvents left a residue which was dissolved in water and extracted with Et_2O. The aqueous phase was evaporated to give crude salt **8**·HCl which was dissolved in a minimum of MeOH and precipitated with acetone. The precipitate was filtered and dissolved in water to which an excess of sodium bicarbonate was added. Extraction with CH_2Cl_2 gave pure **(1*S*)-(+)-1-phenyl-1,2,3,4-tetrahydroisoquinoline (+)-8** (580 mg, 2.76 mmol, 72%) as a colorless oil: $[\alpha]_D$ +13.5 (*c* 1.15, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.00 (bs, 1H, N*H*), 2.78−2.88 (m, 1H), 3.01−2.88 (m, 2H), 3.23−3.31 (m, 1H), 5.1 (s, 1H), 6.75 (d, J = 7.6 Hz, 1H), 7.05 (m, 1H), 7.15 (m, 2H), 7.2−7.36 (m, 5H); ^{13}C NMR (75.47 MHz, $CDCl_3$) δ 29.9, 42.3, 62.2, 125.8, 126.4, 127.5, 128.2, 128.5, 129.1, 135.5, 138.3, 144.9; MS (EI) *m*/*z* (rel intensity) 209 ($M^{+\bullet}$, 52), 208 (56), 132 (100), 130 (13), 77 (5); HRMS (EI): calcd for $C_{15}H_{15}N$ *m*/*z* 209.1204, obsd *m*/*z* 209.1209.

Alkylation of Salt 2 with Grignard Reagents: Preparation of Base (+)-8 as a Typical Procedure. Salt **2**[1] (1.6 g, 3.11 mmol) was treated with an excess of phenylmagnesium iodide under the conditions used for the preparation of enamine **4b** to give a mixture (0.82 g, 2.51 mmol, 81%) of oxazolidines **10b** and **11b** accompanied with a small amount of enamine **12b** in a 69:29:7 ratio at equilibrium. **(3*R*,5*S*,10a*S*)-3,5-Diphenyl-2,3,5,10-tetrahydro-10a*H*-oxazolo[2,3-*b*]isoquinoline (10b)**: ^{1}H NMR (300 MHz, $CDCl_3$) characteristic signals at δ 2.69 (dd, J = 4.8, 15.8 Hz, 1H), 2.89 (dd, J = 2.3, 15.8 Hz, 1H), 3.59 (dd, J = 8.5, 8.5 Hz, 1H), 4.01 (dd, J = 6.4, 8.5 Hz, 1H), 4.11 (dd, J = 6.4, 8.5 Hz, 1H), 4.84 (s, 1H), 5.39 (dd, J = 2.3, 4.8 Hz, 1H); ^{13}C NMR (75.47 MHz, $CDCl_3$) characteristic signals at δ 33.4, 63.2, 68.1, 72.7, 90.9. Crystals of the minor oxazolidine **(3*R*,5*S*,10a*R*)-3,5-diphenyl-2,3,5,-10-tetrahydro-10a*H*-oxazolo[2,3-*b*] isoquinoline (11b)**, suitable for X-ray analysis, were obtained from Et_2O: mp 126−130 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.25 (dd, J = 4.1, 14.7 Hz, 1H), 3.37 (dd, J = 9.1, 14.7 Hz, 1H), 3.76 (dd, J = 6.2, 8.2 Hz, 1H), 3.87 (dd, J = 6.2, 8.2 Hz, 1H), 4.32 (dd, J = 8.2, 8.2 Hz, 1H), 4.45 (dd, J = 4.1, 9.1 Hz, 1Ha), 4.71 (s, 1H), 6.60−7.60 (m, 9 H); ^{13}C NMR (75.47 MHz, $CDCl_3$) δ 35.9, 67.6, 70.4, 75.11, 92.6, 126.1−141.3; MS (IC) *m*/*z* (rel intensity) 328 (MH^+, 100), 206 (28); MS (EI) *m*/*z* (rel intensity) 327 ($M^{+\bullet}$, 53), 326 (18), 296 (4), 250 (21), 206 (8), 180 (100), 130 (15), 103 (8), 77 (9). Anal. Calcd for $C_{23}H_{21}NO$: C, 84.37; H, 6.46: N, 4.28; O, 4.89; found: C, 84.17; H, 6.55: N, 4.11; O, 4.61. The crude mixture of dihydroisoquinolines **10b**, **11b**, and **12b** (680 mg, 2.08 mmol) was reduced with $NaBH_4$ following the procedure used for the preparation of **6b** to give tetrahydroisoquinoline **13b** accompanied with a small amount of the corresponding 1*R* isomer in 95:5 ratio. **(1*S*,2*R*)-(+)-1-Phenyl-2-(1-phenyl-2-hydroxyethyl)-1,2,3,4-tetrahydroisoquinoline (13b)** (396 mg, 1.2 mmol, 58%) was isolated by chromatography on silica gel using EtOAc−pentane as eluent: $[\alpha]_D$ +40.9 (*c* 1.08, EtOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.02 (s, 1H, −O*H*), 2.78 (ddd, J = 4.9, 5.3, 16.7 Hz, 1H), 2.97 (ddd, J = 5.1, 8.7, 16.7 Hz, 1H), 2.97−3.08 (m, 1H), 3.17 (ddd, J = 4.9, 8.7, 14.5 Hz, 1H), 3.88 (dd, J = 4.7, 6.2 Hz, 1H), 3.97 (dd, J = 4.7, 10.8 Hz, 1H), 4.0 (dd, J = 6.2, 10.8 Hz, 1H), 4.90 (ls, 1H), 6.71 (d, J = 7.3 Hz, 1H), 6.98−7.08 (m, 1H), 7.10−7.40 (m, 12H); ^{13}C NMR (62.89 MHz, $CDCl_3$) δ 26.5, 41.7, 62.6, 63.6, 64.8, 125.8, 126.3, 127.0, 127.6, 128.2, 128.5, 128.6, 128.8, 129.3, 134.9, 136.7, 140.4, 144.7; MS (IC) *m*/*z* (rel intensity) 330 (MH^+, 100), 328 (19), 312 (9), 298 (9), 210 (42), 208 (22), 206 (4); HRMS (IC): calcd for $C_{23}H_{24}NO$ *m*/*z* 330.1858, obsd *m*/*z* 330.1859. Minor 1*R* isomer (19 mg): $[\alpha]_D$ −157.6 (*c* 0.36, EtOH); ^{1}H NMR (300 MHz, $CDCl_3$), 2.38 (ddd, J = 3, 11.3, 11.4 Hz, 1H), 2.80 (ddd, J = 2.4, 3, 15.9 Hz, 1H), 3.21 (dddd, J = 1.5, 4.9, 11.4, 15.9 Hz, 1H), 3.38 (ddd, J = 2.4, 4.9, 11.3 Hz, 1H), 3.46 (dd, J = 4.7, 10.2 Hz, 1H), 3.94 (dd, J = 4.7, 10.8 Hz, 1H), 4.08 (dd, J = 10.2, 10.8 Hz, 1H), 4.58 (d, J = 1.5 Hz, 1H), 6.62 (d, J = 7.3 Hz, 1H), 6.92 (ddd, J = 2.1, 6.7, 7.3 Hz, 1H), 6.98−7.09 (m, 2H), 7.20−7.45 (m, 10H); ^{13}C NMR (62.89 MHz, $CDCl_3$) δ 30.4, 42.1, 60.3, 62.8, 65.6, 125.9, 127.8, 128.2, 128.4, 129.0, 129.1, 129.5, 129.7, 134.3, 134.9, 138.9, 144.4; MS (IC) *m*/*z* (rel intensity) 330 (MH^+, 100), 328 (6), 312 (6), 298 (8), 210 (44), 208 (14), 206 (4). Tetrahydroisoquinoline **13b** (120 mg, 0.36 mmol) was hydrogenated under the conditions used for the hydrogenolysis of tetrahydroisoquinoline **6b** to give base (+)-**8** (54 mg, 0.36 mmol, 67%): $[\alpha]_D$ +14.8 (*c* 1.7, $CHCl_3$); ^{1}H NMR, ^{13}C NMR and MS spectra were identical with those of base (+)-**8** obtained from tetrahydroisoquinoline **6b**.

(3*R*,10a*R*)-3-Phenyl-2,3,5,10-tetrahydro-10a*H*-oxazolo-[2,3-*b*]isoquinoline (15). Salt **2**[1] (1.08 g, 2 mmol), dissolved in MeOH (4 mL), was added dropwise with vigorous stirring to a two-phase system consisting of 5 N NaOH (2 mL) and Et_2O (10 mL) containing $NaBH_4$ (100 mg, 2.5 mmol). After 0.6 h, the organic phase was collected and filtered over alumina (30 g) with Et_2O as solvent. Removal of solvent under reduced pressure left a pale yellow oil composed of oxazolidine **15** accompanied with isomers **16** and **14** in a 77:18:5 ratio (490 mg, 1.95 mmol, 93%): MS (EI) *m*/*z* (rel intensity) 251 ($M^{+\bullet}$, 78), 250 (27), 220 (36), 130 (21), 104 (100); HRMS (EI): calcd for $C_{17}H_{17}NO$ *m*/*z* 251.1310, obsd *m*/*z* 251.1304. Major oxazolidine **15**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.00−3.23 (m, 2H), 3.46 (d, J = 14.5 Hz, 1H), 3.71 (dd, J = 7.6, 7.6 Hz, 1H), 3.83 (dd, J = 7.6, 7.6 Hz, 1H), 3.95 (d, J = 14.5 Hz, 1H), 4.25 (dd, J = 4, 4 Hz, 1H), 4.32 (dd, J = 7.6 Hz, 1H), 6.90−7.25 (m, 4H), 7.25−7.60 (m, 5H); ^{13}C NMR (75.47 MHz, $CDCl_3$) δ 35.8, 52.0, 68.0, 74.0, 92.2, 126.2−129.9, 127.9−128.9 (5C), 132.9, 134.1, 138.5; MS (EI) *m*/*z* (rel intensity) 251 ($M^{+\bullet}$, 78), 250 (27), 220 (36), 174 (1), 130 (21), 104 (100). Minor oxazolidine **16**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.8−3.15 (m, 2H), 3.55 (m, 1H), 3.6 (m, 1H), 3.71 (dd, J = 7.6, 7.6 Hz, 1H), 3.8 (d, J = 13 Hz, 1H), 4.16 (m, 1H), 5.18 (dd, J = 4.7, 4.7 Hz, 1H); ^{13}C NMR (75.47 MHz, $CDCl_3$) characteristic signals at δ 34.3, 50.9, 67.9, 72.6, 91.0. Dihydroisoquinoline **14**: ^{1}H NMR (300 MHz, $CDCl_3$) characteristic signals at δ 2.43 (m, 2H), 2.82−3.03 (m, 2H), 4.06 (d, J = 12.5 Hz, 2H), 4.19−4.22 (m, 1H), 5.33 (d, J = 7.5 Hz, 1H).

(3*R*,2*R*)-(−)-3-Phenyl-2-(1-phenyl-2-hydroxyethyl)-1,2,3,4-tetrahydroisoquinoline (17b). To a solution of oxazolidine **15**, accompanied with isomers **16** and **14** in a77:18:5 ratio (220 mg, 0.88 mmol), in Et_2O (25 mL) was added dropwise at 0 °C with stirring a 0.8 M solution of phenylmagnesium iodide in Et_2O (3.2 mL, 2.56 mmol). The resulting mixture was stirred for 1 h at 0 °C, followed by 2 h at 20 °C, and then poured into a 32% solution of NH_4OH saturated with NaCl. Extraction with Et_2O left a mixture of the starting materials and adducts **17b** and **18b**. This mixture was again

treated with an excess of phenylmagnesium iodide using the above conditions. Finally, base **17b** and the corresponding 3*S* isomer **18b** were obtained in 75:25 ratio (210 mg, 0.64 mmol). Chromatographic separation on silica gel (50 g) using EtOAc−pentane as eluent (from 0:100 to 30:70) gave major isomer **17b** as a pale yellow oil (130 mg, 0.4 mmol, 45%): $[\alpha]_D$ −20.3 (*c* 1.83, EtOH); ^{1}H NMR (250 MHz, $CDCl_3$) δ 2.05 (s, O*H*), 2.95 (dd, *J* = 4.4, 16.7 Hz, 1H), 3.16 (dd, *J* = 6.1, 16.7 Hz, 1 H), 3.79 (d, *J* = 16 Hz, 1H); 3.87−3.95 (m, 3H), 3.92 (d, *J* = 16 Hz, 1H), 3.98 (dd, *J* = 7.3, 11.8 Hz, 1H), 4.29 (dd, *J* = 4.4, 6.1 Hz, 1H), 6.85−7.55 (m, 14H); ^{13}C NMR (62.89 MHz, $CDCl_3$) δ 32.9, 47.8, 58.5, 62.5, 65.3, 126.0, 126.4, 126.6, 127.3, 127.6, 127.9, 128.5, 134.3, 135.3, 139.9, 143.0; MS (IC) *m*/*z* (rel intensity) 330 (MH^+, 44), 328 (100), 312 (4), 298 (4), 210 (24), 208 (74), 144 (56); HRMS (IC): calcd for $C_{23}H_{24}NO$ *m*/*z* 330.1857 (MH^+), obsd *m*/*z* 330.1849. Isomer **18b** (43 mg, 0.13 mmol, 15%) was isolated as an oil: $[\alpha]_D$ −63.3 (*c* 1.03, EtOH); ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.28 (s, 1H, −O*H*), 3.0 (dd, *J* = 5.2, 16.6 Hz, 1H), 3.11 (dd, *J* = 8.7, 16.6 Hz, 1H), 3.58 (dd, *J* = 3.6, 9.2 Hz, 1H), 3.59 (d, *J* = 15 Hz, 1), 3.87 (dd, *J* = 5.2, 8.7 Hz, 1H), 3.98 (d, *J* = 15 Hz, 1H), 4.12 (dd, *J* = 9.2, 10.2 Hz, 1H), 4.19 (dd, *J* = 3.6, 10.2 Hz, 1H), 7.00−7.50 (m, 14H); ^{13}C NMR (62.89 MHz, $CDCl_3$) δ 39.5, 47.5, 60.6, 62.0, 62.6, 125.9, 126.3, 126.5, 127.7, 127.9, 128.0, 128.3, 128.6, 129.0, 129.3, 134.2, 134.7, 135.5, 142.8; MS (IC) *m*/*z* (rel intensity) 330 (MH^+, 100), 328 (43), 312 (5), 298 (5), 210 (22), 208 (26), 144 (13).

(1*S*,2*R*,3*S*)-(+)-1,3-Dimethyl-2-(1-phenyl-2-hydroxyethyl)-1,2,3,4-tetrahydroisoquinoline (20). A crude mixture (860 mg, 3.24 mmol) of oxazolidines **10a**, **11a** and dihydroisoquinoline **12a**, resulting from the treatment of salt **2** with methylmagnesium chloride, was dissolved in toluene (50 mL). To this solution was added dropwise at 0 °C with stirring a 0.9 M solution of methylmagnesium chloride in toluene (11 mL, 9.8 mmol). After stirring for 1 h at 0 °C, the resulting mixture was poured into a 32% solution of NH_4OH saturated with NH_4Cl. Extraction with Et_2O left a gum (849 mg) containing adducts **17c**, **18c**, and **19** (two epimers at C_3 in 8:3 ratio) in a 76:11:13 ratio as shown by ^{1}H NMR spectroscopy. Chromatography over silica gel using EtOAc−pentane gave major isomer **17c** as a colorless oil (560 mg, 2 mmol, 65%): $[\alpha]_D$ +48.3 (*c* 4, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.43 (d, *J* = 6.8 Hz, 3H); 1.51 (d, *J* = 6.9 Hz, 3H), 2.33 (dd, *J* = 11.1, 16.8 Hz, 1H), 2.45 (dd, *J* = 4.8, 16.8 Hz, 1H), 3.50 (dd, *J* = 5.3, 10.5 Hz, 1H), 3.71 (ddq, *J* = 4.8, 6.8, 11.1 Hz, 1H), 3.92 (dd, *J* = 10.5, 10.5 Hz, 1H), 4.23 (dd, *J* = 5.3, 10.5 Hz, 1H), 4.45 (qdd, *J* = 6.9 Hz, 1H), 6.62 (d, *J* = 7.6 Hz, 1H), 6.80−7.25 (m, 8H); ^{13}C NMR (62.89 MHz, $CDCl_3$) δ 20.1, 24.8, 34.0, 47.0, 51.1, 60.2, 61.5, 125.4, 125.5, 126.5, 127.4, 127.6, 128.5, 128.9, 134.6, 139.5, 139.9; MS (IC) *m*/*z* (rel intensity) 282 (MH^+, 100), 280 (19), 264 (20), 250 (4), 162 (4), 160 (15); HRMS (IC): calcd for $C_{19}H_{24}NO$ *m*/*z* 282.1858, obsd *m*/*z* 282.1849. Minor isomer **18c**: ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.05 (d, *J* = 6.6 Hz, 3H), 1.50 (d, *J* = 6.8 Hz, 3H), 2.32−2.43 (m, 2H), 3.43 (m, 1H), 3.72 (dd, *J* = 5.4, 10.5 Hz, 1H), 3.95 (dd, *J* = 8.3, 10.5 Hz, 1H), 4.09 (dd, *J* = 5.4, 8.3 Hz, 1H), 4.10 (q, *J* = 6.8 Hz, 1H), 6.95−7.35 (m, 9H); ^{13}C NMR (62.89 MHz, $CDCl_3$) δ 23.2, 23.7, 35.0, 47.2, 54.4, 61.5, 66.6. Tetrahydroisoquinoline **17c** (150 mg, 0.53 mmol) was hydrogenated under the conditions used for the hydrogenolysis of tetrahydroisoquinoline **13b**. The resulting salt **20**·HCl was isolated by crystallization from acetone (78 mg, 0.4 mmol, 74): mp 232−240 °C; $[\alpha]_D$ +25.1 (*c* 0.8, MeOH); ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.48 (d, *J* = 6.4 Hz, 3H), 1.69 (d, *J* = 6.9 Hz, 3H), 2.88 (dd, *J* = 10.2, 17.4 Hz, 1H), 3.29 (dd, *J* = 4.8, 17.4 Hz, 1H), 3.83 (ddq, *J* = 4.8, 6.4, 10.2 Hz, 1H), 4.7 (q, *J* = 6.9 Hz, 1H), 7.27−7.32 (m, 4H); ^{13}C NMR (62.89 MHz, $CDCl_3$) δ 18.6, 20.8, 34.2, 46.2, 51.8, 127.6, 128.3, 129.1, 130.2, 131.9, 134.3; HRMS (IC): calcd for $C_{11}H_{16}N$ *m*/*z* 162.1283, obsd *m*/*z* 162.1278.

Synthesis of (−)-Salsonidine: To a solution of salt **3**[1] (560 mg, 0.97 mmol) in THF (20 mL) was added dropwise with stirring at −78 °C a 1 M solution of methylmagnesium chloride in THF (5 mL, 5 mmol). Applying the procedure utilized for the preparation of enamine **4b** gave an unseparable mixture (250 mg, 3.4 mmol, 79%) of oxazolidines **21**, **22** and the corresponding dihydroisoquinoline, in a 40:20:20 ratio at equilibrium, as a pale yellow oil: MS (EI) *m*/*z* (rel intensity) 325 ($M^{+\bullet}$, 30), 310 (100), 190 (73), 178 (100), 163 (15); HRMS (EI): calcd for $C_{20}H_{23}NO_3$ *m*/*z* 325.1678, obsd *m*/*z* 325.1662. **(3*R*,5*S*,10a*S*)-7,8-Dimethoxy-5-methyl-3-phenyl-2,3,5,10-tetrahydro-10a*H*-oxazolo[2,3-*b*]isoquinoline (21):** ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.33 (d, *J* = 6.9 Hz, 3H), 2.92 (dd, *J* = 4.3, 16 Hz, 1H), 3.10 (dd, *J* = 4.9, 16 Hz, 1H), 3.51 (dd, *J* = 8.1, 9 Hz, 1H), 3.74 (q, *J* = 6.9 Hz, 1H), 3.84 (s, 3H), 3.87 (s, 3H), 4.04 (dd, *J* = 6.7, 9 Hz, 1H), 4.18 (dd, *J* = 6.7, 8.1 Hz, 1H), 5.27 (dd, *J* = 4.3, 4.9 Hz, 1H), 6.62 (s, 1H), 6.65 (s, 1H); ^{13}C NMR (62.89 MHz, $CDCl_3$) δ 21.6, 32.8, 55.3, 55.9, 56.0, 68.0, 73.0, 90.2, 108.9, 112.1. **(3*R*,5*S*,10a*R*)-7,8-Dimethoxy-5-methyl-3-phenyl-2,3,5,10-tetrahydro-10a*H*-oxazolo[2,3-*b*]isoquinoline (22):** ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.06 (d, *J* = 6.5 Hz, 3H), 3.07−3.18 (m, 2H), 3.75−3.9 (m, 1H), 3.84 (s, 3H), 3.87 (s, 3H), 3.75−3.95 (m, 1H), 3.80−4.00 (m, 1H), 4.27 (dd, *J* = 4.4, 8.7 Hz, 1H), 4.33 (dd, *J* = 6.2, 6.2 Hz, 1H), 6.62 (s, 1H), 6.75 (s, 1H), 7.20−7.50 (m, 5H); ^{13}C NMR (62.89 MHz, $CDCl_3$) δ 22.0, 35.6, 55.9, 56.0, 59.5, 67.0, 72.2, 92.4, 109.7, 112.0. **(2*R*)-6,7-Dimethoxy-1-methyl-2-(1-phenyl-2-hydroxyethyl)-1,2-dihydroisoquinoline:** ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.17 (d, *J* = 6.5 Hz, 3H), 1.6 (ls, 1H, −O*H*), 2.87−2.91 (m, 1H), 2.93−2.97 (m, 1H), 3.84 (s, 3H), 3.87 (s, 3H), 4.53 (dq, *J* = 1.5, 6.5 Hz, 1H), 4.75 (dd, *J* = 4, 8.9 Hz, 1H), 5.37 (d, *J* = 7.4 Hz, 1H), 6.18 (dd, *J* = 1.5, 7.4 Hz, 1H), 6.45 (s, 1H), 6.51 (s, 1H); ^{13}C NMR (62.89 MHz, $CDCl_3$) δ 21.0, 55.9, 56.0, 57.3, 73.8, 85.1, 98.2, 109.3, 110.2, 130.4) The crude mixture of oxazolidines **21** and **22** and the corresponding dihydroisoquinoline (200 mg, 0.62 mmol) was reduced with $NaBH_4$ according to the procedure used for the preparation of **6b** to give tetrahydroisoquinoline **23** accompanied with the corresponding 1*R* isomer in 80:20 ratio. Chromatography over alumina using EtOAc−pentane as eluent gave **(1*S*,2*R*)−(−)-6,7-dimethoxy-1-methyl-2-(1-phenyl-2-hydroxyethyl)-1,2,3,4-tetrahydroisoquinoline (23)** as an oil (135 mg, 0.41 mmol, 66%): $[\alpha]_D$ −5.8 (*c* 1.28, EtOH); ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.31 (d, *J* = 6.8 Hz, 3H), 2.23 (ls, 1H, −O*H*), 2.49 (ddd, *J* = 1.8, 3.9, 16 Hz, 1H), 2.90 (ddd, *J* = 6.2, 11.8, 16 Hz, 1H), 3.04 (ddd, *J* = 1.8, 6.2, 13.1 Hz, 1H), 3.12 (ddd, *J* = 3.9, 11.8, 13.1 Hz, 1H), 3.81 (s, 3H), 3.83 (dd, *J* = 4, 12 Hz, 1H), 3.84 (s, 3H), 3.84 (dd, *J* = 4, 6.9 Hz, 1H), 3.93 (dd, *J* = 6.9, 12 Hz, 1H), 3.95 (q, *J* = 6.8 Hz, 1H), 6.43 (s, 1H), 6.56 (s, 1H), 7.25−7.40 (m, 5H); ^{13}C NMR (62.89 MHz, $CDCl_3$) δ 20.1, 26.2, 39.8, 54.2, 55.9, 56.0, 63.8, 66.2, 110.5, 111.5, 125.9, 127.6−128.6, 132.2, 141.2, 147.3, 147.5.MS (IC) *m*/*z* (rel intensity) 328 (MH^+, 100), 326 (35), 312 (5), 310 (8), 296 (5), 208 (42), 206 (56), 204 (59), 194 (3), 192 (14), 190 (28), 121 (10); HRMS (IC): calcd for $C_{20}H_{26}NO_3$ *m*/*z* 372.1964, obsd *m*/*z* 372.1954. Minor 1*R* isomer was obtained as an oil (25 mg, 0.08 mmol, 13%): $[\alpha]_D$ −38 (*c* 0.8, EtOH); ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.58 (d, *J* = 6.4 Hz, 3H), 2.40 (ddd, *J* = 4, 8.1, 11.7 Hz, 1H), 2.63 (ddd, *J* = 4, 5.7, 15.8 Hz, 1H), 2.76 (ddd, *J* = 4.5, 8.1, 15.8 Hz, 1H), 3.12 (ddd, *J* = 4.5, 5.7, 11.7 Hz, 1H), 3.78 (dd, *J* = 5.1, 10.5 Hz, 1H), 3.82 (s, 3H), 3.83 (s, 3H), 3.97 (q, *J* = 6.4 Hz, 1H), 3.98 (dd, *J* = 8.3, 10.5 Hz, 1H), 4.12 (dd, *J* = 5.1, 8.3 Hz, 1H), 6.43 (s, 1H), 6.56 (s, 1H), 7.25−7.4 (m, 5H); ^{13}C NMR (62.89 MHz, $CDCl_3$) δ 22.3, 28.9, 41.0, 53.9, 56.0, 56. 1, 61.3, 64.1, 110.4, 111.3, 126.9, 128.0−129.2, 132.0, 137.2, 147.4, 147.5. Tetrahydroisoquinoline **23** (80 mg, 0.24 mmol) was hydrogenated under the conditions used for the hydrogenolysis of tetrahydroisoquinoline **6b** to give (−)-salsolidine base (37 mg, 0.18 mmol, 73%): $[\alpha]_D$ −57.4 (*c* 1.4, EtOH) [lit.[11] $[\alpha]_D$: −59.5 (*c* 4.39, EtOH)]; ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.44 (d, *J* = 6.7 Hz, 3H), 1.67 (ls, 1H, N-*H*), 2.64 (ddd, *J* = 4.7, 4.7, 16 Hz, 1H), 2.79 (ddd, *J* = 5.4, 8.6, 16 Hz, 1H), 3 (ddd, *J* = 4.7, 8.6, 12.6 Hz, 1H), 3.25 (ddd, *J* = 4.7, 5.4, 12.6 Hz, 1H), 3.85 (s, 3H), 3.86 (s, 3H), 4.04 (qd, *J* = 1, 6.7 Hz, 1H), 6.57 (s, 1H), 6.63 (s, 1H); ^{13}C NMR (62.89 MHz, $CDCl_3$) δ 23.0, 29.7, 42.0, 51.3, 55.9−56.1, 109.2, 111.9, 127.0, 132.7, 147.3, 147.4; MS (EI) *m*/*z* (rel intensity) 207 ($M^{+\bullet}$, 12), 206 (11), 205 (10), 204 (4), 192 (100), 190 (8); HRMS (IC): calcd for $C_{12}H_{18}NO_2$ *m*/*z* 208.1337 (MH^+), obsd *m*/*z* 208.1357.

Supporting Information Available: X-ray data for intermediates **4b** and **11b**, copies of ^{1}H and ^{13}C NMR spectra of compounds **4b**, **6b**, **6e**−**f**, **7e**−**f**, **8**, **10b**, **13a,b**, **13e,f**, **17b,c**, **18b**, **20**·HCl, **23**, (−)-salsolidine, and mixtures of **4a**−**5a**, **10a**−**12a**, **10b**−**11b**, **15** and **16** with attribution of signals (59 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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