Stereoselective Isoquinoline Alkaloid Synthesis with New Diselenides

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Received 30 June 1997; revised 8 August 1997

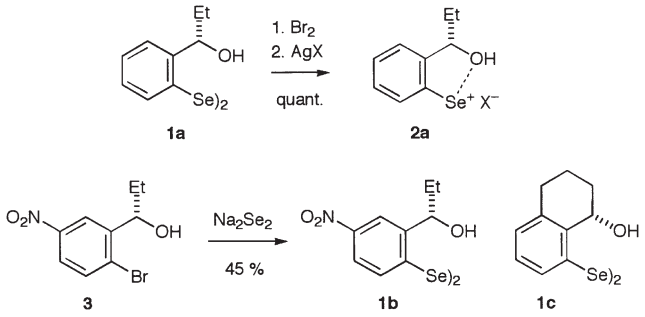
Abstract: The synthesis of improved optically active selenium compounds for electrophilic additions to C=C double bonds is described. These reagents allow the formation of methoxyselenenylated products with high diastereoselectivities (up to 93% de). Intramolecular aminoselenenylations with chiral selenium electrophiles provide a short route to tetrahydroisoquinoline alkaloids.

Key words: asymmetric synthesis, chiral diselenides, chirality, isoquinoline alkaloids, selenium

Synthetic approaches towards the isoquinoline system are almost as old as the discovery of the isoquinoline system itself[1]. Since that time there have been many improvements in the synthesis of these *N*-heterocycles, as a great number of alkaloids are based on 1-substituted tetrahydroisoquinolines. The introduction of a substituent in the 1-position leads to an asymmetric center and is the key problem in the synthesis of these compounds. Some of these compounds exhibit important physiological activities.[2] Therefore, many synthetic methods have been employed to date for the synthesis of either racemic[3] or chiral[4] isoquinolines. An important enantioselective route is performed by asymmetric reduction of 3,4-dihydroisoquinolines with chiral transition metal catalysts yielding the products with high selectivities.[5]

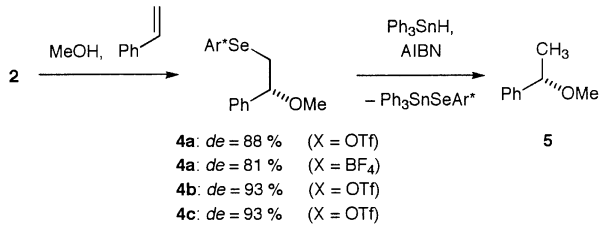
Recently we,[6] and also other research groups,[7] have investigated the use of chiral selenium compounds for the activation of C=C double bonds to perform inter- as well as intramolecular additions. Substrates bearing an internal nucleophile can cyclize to chiral heterocyclic compounds. Many reports describe the selective formation of *O*-heterocycles from unsaturated alcohols or acids. Due to the poor nucleophilicity of the nitrogen atom, only few selective cyclizations of unsaturated amines have been reported to date.[7a,b] The products of intramolecular aminoselenenylation reactions are nitrogen containing heterocycles and, therefore, interesting building blocks for alkaloid synthesis. The selenium functionality is still present in the addition products and can be used for further functionalizations. We applied this strategy to the synthesis of tetrahydroisoquinoline alkaloids and describe herein this new approach in the form of a synthesis of salsolidine (**14**), which was chosen as the synthetic target.

Recently we showed that diselenide **1a** is accessible by a short synthetic sequence and is a versatile reagent for the synthesis of other natural products.[8] It is converted into the selenium cation **2a**, which is used for additions to double bonds. Attachment of substituents at the aromatic ring should change the electrophilicity of the selenium cations and have an influence on reactivity as well as upon the diastereoselectivity of the reaction. Therefore, nitro-substituted diselenide **1b** was prepared from precursor **3** by reaction with sodium diselenide.[9] We have already shown that selenium cations with greater conformational flexibility are less selective in the addition reactions. Therefore, diselenide **1c** with increased rigidity was synthesized from optically active tetralol via *ortho*-lithiation[10] in only one step.



Scheme 1

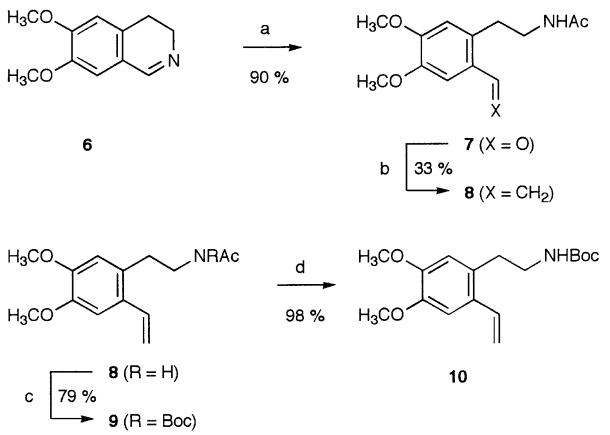
As a test reaction we first investigated the addition of selenium electrophiles **2** to styrene using methanol as nucleophile. The diastereoselectivities of the addition products **4** resulting from this reaction were determined by NMR spectroscopy as well as by GC analysis of the cleavage product **5**. Selenium electrophiles with electron-withdrawing substituents, such as in **2b** or the more rigid bicyclic system in **2c**, show enhanced diastereoselectivities in additions to double bonds compared with the cation **2a**.



Scheme 2

For the synthesis of salsolidine an appropriate precursor had to be synthesized. The synthetic sequence started with 6,7-dimethoxy-3,4-dihydroisoquinoline (**6**) which is readily accessible via either a Bischler–Napieralski[11] or a Pictet–Spengler[12] reaction. Compound **6** was converted to the aldehyde **7** by reaction with acetyl chloride.[13] Different methods for the subsequent methylenation were screened because Wittig olefination afforded the styrene derivative **8** in only very low yields. The highest yields in the synthesis of **8** were obtained with Lombardo's reagent.[14]

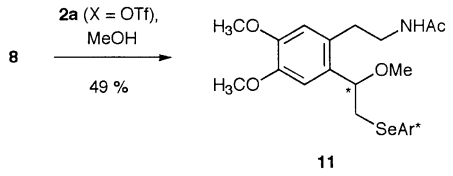
Efforts to cyclize **8** with the electrophilic selenium reagent **2a** to the corresponding tetrahydroisoquinoline derivative were not successful. This property coincides with earlier



Scheme 3

Reagents and Conditions: a) AcCl, sat. $NaHCO_3$, CH_2Cl_2, 1.5 h, 90%. b) Zn, CH_2Br_2, $TiCl_4$, THF, 30 min, 33%. c) DMAP, $(Boc)_2O$, CH_2Cl_2, 15 h, 79%. d) N_2H_4. H_2O . MeOH, 1 h, 98%.

observations of cyclizations using acetamides as nucleophiles.[15] Even in the presence of methanol, which was necessary for selenolactonizations,[6,7a] the cyclization product could not be detected. Probably due to the poor nucleophilicity of the acetamide group the intermolecular methoxyselenenylation is preferred yielding the addition product **11** in 49% yield and a diastereomeric ratio of about 10:1.[16]



Scheme 4

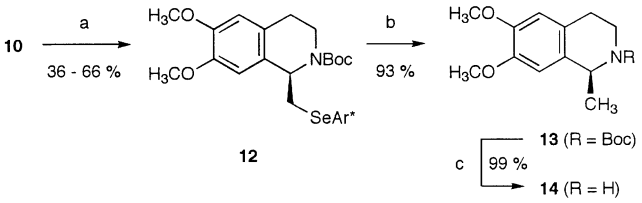
A different precursor for cyclization with an increased nucleophilicity of the nitrogen atom was synthesized. Compound **8** was, therefore, transformed into the carbamate **10** via a sequence of Boc-protection[17] and deacetylation.[18] Now cyclizations using this ε-unsaturated carbamate **10** with different selenium electrophiles (**2a–c**) yielding the tetrahydroisoquinolines **12** are possible. The results are summarized in the Table.

Table. Results of the Cyclization Reaction **10** → **12** Using Different Selenium Electrophiles **2**

Entry	Se Electrophile	Product	Yield (%) of **12**	ee[a] (%) of **13**
1	**2a** (X=OTf)	**12a**	66	79
2	**2a** (X=BF_4)	**12a**	36	59
3	**2b** (X=OTf)	**12b**	64	–[b]
4	**2c** (X=OTf)	**12c**	40	90

[a] Determined by HPLC (Regis Whelk-O1, i-PrOH/hexane 1:5) after cleavage of the Se moiety.
[b] Not determined.

These results show clearly that the counterion of the electrophilic organoselenium species plays a non-negligible role in the addition reaction, having a dramatic influence on yield as well as on selectivity (see entries 1 and 2). In contrast to other examples, in which higher selectivities have been achieved with tetrafluoroborate as a counterion,[7b] we found triflate to be the most suitable counterion. A diastereomeric excess of 79% in the addition product **12a** was obtained. Although the cyclization product **12b** with the nitro-substituted electrophile **2b** was isolated in 64% yield, it was not possible to determine the diastereomeric excess by NMR and the radical cleavage of the carbon–selenium bond was not possible. A further improvement in the selectivity of the cyclization was achieved with the selenium cation **2c**. Cyclization product **12c** was obtained in 40% yield with a diastereoselectivity of 90%.



Scheme 5

Reagents and Conditions: a) **2**, Et_2O, –100°C, 36–66%. b) Ph_3SnH, AIBN, toluene, 120°C, 1 h, 93%. c) TFA, CH_2Cl_2, 3 h, 99%.

The last steps on the way to salsolidine were a radical cleavage of the selenium moiety to Boc-protected salsolidine **13**,[19] which could be converted almost quantitatively into salsolidine (**14**) by treatment with trifluoroacetic acid.[20] The absolute configuration of the stereocenter of salsolidine was confirmed to be *S* by comparison with the optical rotation of the natural product.[21]

In conclusion, the addition to double bonds with chiral selenium electrophiles **2** was further optimized. Electronic as well as steric variations lead to diastereomeric excesses up to 93% in the methoxyselenenylation products **4**. Intramolecular cyclizations of the ε-unsaturated carbamate **10** gave β-amino selenides **12** with tetrahydroisoquinoline structure. By this approach a representative member of the family of isoquinoline alkaloids, (–)-(*S*)-salsolidine (**14**), has been synthesized with an enantiomeric excess of 90%.

All reactions were performed under anhyd Ar atmosphere. $[\alpha]_D$: Perkin–Elmer-141 polarimeter. IR spectra: Perkin–Elmer-781 spectrophotometer. ^1H and ^{13}C NMR spectra: Varian–Gemini-300 spectrometer (300 and 75 MHz respectively), chemical shifts δ in ppm relative to TMS as internal standard, ^{13}C multiplicities assigned *via* APT pulse sequence. MS spectra: Finnigan-MAT-312 apparatus. Melting points are uncorrected. Et_2O and THF were distilled from sodium/benzophenone, MeCN was distilled from P_2O_5 prior to use.

Addition of Selenium Cations to Alkenes; General Procedures 1 and 2:

The diselenide (0.1 mmol) was dissolved in anhyd Et_2O (4 mL) under Ar, cooled to –78 °C and treated with 1 M bromme in CCl_4 (0.11 mL, 0.11 mmol). After 10 min a solution of silver triflate (72 mg, 0.28 mmol) in MeOH (0.1 mL, **General Procedure 1**) or THF (0.1 mL, **General Procedure 2**) was added and stirred for 10 min at –78 C. The reaction mixture was cooled to –100°C and treated with styrene (0.4 mmol, 0.046 mL). After stirring for 3–4 h at –100 °C, *sym*-collidine (0.3 mmol, 0.04 mL) was added followed by 0.3 M aq citric acid (4 mL). After extraction of the reaction mixture with *t*-BuOMe (3 × 10 mL), drying of the combined organic phases

($MgSO_4$) and removal of the solvent under reduced pressure the residue was purified by flash chromatography on silica gel.

Preparation and characterization of diselenide **1a** see lit.[8a] The diselenides **1b** and **1c**, compound **3** and the addition products **4a–c** are described in lit.[6b] Spectroscopic data are given only for the major diastereomers of **11**, **12a**, **12b**, and **12c.** The Boc-protected tetrahydroisoquinoline derivatives **12a**, **12b**, **12c**, and **13** show some broad signals in the ^{1}H NMR which are due to rotamers of these compounds as described in lit.[20]

***N*-[2-(2-Formyl-4,5-dimethoxyphenyl)ethyl]acetamide (7):**
Compound **6**[22] (1.75 g, 9.16 mmol) was dissolved in a mixture of CH_2Cl_2 (15 mL) and sat. $NaHCO_3$ (15 mL). After the addition of AcCl (1.44 mL, 20 mmol) in CH_2Cl_2 (2 mL) the mixture was stirred at r.t. for 90 min. The layers were separated and the aqueous layer extracted with CH_2Cl_2 (3 × 5 mL). The organic layer was dried ($MgSO_4$) and evaporated to leave a residue which was purified by flash chromatography on silica gel (CH_2Cl_2/acetone 4:1) to afford **7** (2.08 g, 90%) as a colorless solid.
^{1}H NMR ($CDCl_3$): δ = 1.93 (s, 3H, COCH_3), 3.19 (t, *J* = 7.2 Hz, 2H, ArCH_2), 3.48 (q, *J* = 7.0 Hz, 2H, CH_2NH), 3.93 (s, 3H, OCH_3), 3.95 (s, 3H, OCH_3), 5.88 (s, br, 1H, N*H*), 6.76 (s, 1H, arom *H*-6), 7,31 (s, 1H, arom *H*-3), 10.07 (s, 1H, C*H*O).
^{13}C NMR ($CDCl_3$): δ = 23.1 (q, CO*C*H$_3$), 31.5 (t, ArCH$_2$), 41.4 (t, *C*H$_2$NH), 56.0 (q, OCH$_3$), 56.1 (q, O*C*H$_3$), 113.3 (d, arom *C*-3/6), 113.5 (d, arom *C*-3/6), 127.1 (s, arom *C*-2), 136.6 (s, arom *C*-1), 147.8 (s, arom *C*-4), 153.7 (s, arom *C*-5), 170.2 (s, *C*OCH$_3$), 190.7 (d, *C*HO).
IR ($CHCl_3$): ν = 3451, 3368, 3006, 2847, 1672, 1600, 1517, 1464, 1360, 1117, 1049, 1002, 870 cm^{-1}.
MS (EI, 70 eV): *m/z* (%) = 251 (19) [M$^+$], 234 (5), 207 (5), 192 (100), 180 (50), 164 (40), 151(13), 43 (30).
$C_{13}H_{17}NO_4$: calcd C 62.14, H 6.82, N 5.57, O 25.47; found: C 62.15, H 6.99, N 5.52, O 25.52.

***N*-[2-(4,5-Dimethoxy-2-vinylphenyl)ethyl]acetamide (8):**
CH_2Br_2 (2.02 mL, 29 mmol) was added to a suspension of activated zinc dust (5.89 g, 89 mmol) in anhyd THF (100 mL). After cooling to –40 °C, $TiCl_4$ (2.4 mL, 22 mmol) was added dropwise over a period of 15 min and the reaction mixture was allowed to stir for 3 d at 5 °C. The resulting slurry was diluted with THF (20 mL) and cooled to 0 °C. Compound **7** (317 mg, 1.26 mmol) in THF (1 mL) was added over a period of 15 min. The reaction mixture was stirred 30 min at r.t.. After addition of pentane (20 mL), sat. Na_2CO_3 (80 mL) was added carefully over 1 h. The organic layer was separated and the residue extracted with CH_2Cl_2 (3 x 50 mL). The organic layer was dried ($MgSO_4$) and evaporated to leave a residue which was purified by flash chromatography on silica gel (CH_2Cl_2/acetone 4:1). Further recrystallization from *t*-BuOMe afforded **8** (105 mg, 33%) as colorless crystals; mp 123–125 °C.
^{1}H NMR ($CDCl_3$): δ = 1.93 (s, 3H, COCH_3), 2.85 (t, *J* = 7.1 Hz, 2H, ArCH_2), 3.42 (q, *J* = 6.6 Hz, 2H, CH_2NH), 3.87 (s, 3H, OCH_3), 3.90 (s, 3H, OCH_3), 5.23 (d, *J* = 11.0 Hz, 1H, CH=CH_{cis}H$_{traa}$), 5.56 (d, *J* = 17.5 Hz, 1H, CH=CH$_{cis}$$H_{trans}$), 5.71 (s, br, 1H, N*H*), 6.64 (s, 1H, arom *H*-6), 6.93 (dd, *J* = 17.3 Hz, *J* = 10.9 Hz, 1H, C*H*=CH$_2$), 7.02 (s, 1H, arom *H*-3).
^{13}C NMR ($CDCl_3$): δ = 23.2 (q, CO*C*H$_3$), 32.3 (t, ArCH$_2$), 40.7 (t, *C*H$_2$NH), 55.8 (q, OCH$_3$), 55.9 (q, OCH$_3$), 108.5 (d, arom *C*-3/6), 112.7 (d, arom *C*-3/6), 113.8 (t, CH= *C*H$_2$), 129.0 (s, 2C, arom *C*-1, *C*-2), 133.7 (d, *C*H=CH$_2$), 147.8 (s, arom *C*-4/5), 148.9 (s, arom *C*-4/5), 170.1 (s, *C*OCH$_3$).
IR ($CHCl_3$): ν = 3451, 3006, 2938, 1666, 1604, 1512, 1464, 1134, 1049, 1016, 910 cm^{-1}.
MS (EI, 70 eV): *m/z* (%) = 249 (35) [M$^+$], 190 (100), 177 (35), 146 (33).
$C_{14}H_{19}NO_3$: calcd C 67.45, H 7.68, N 5.62, O 19.25; found: C 67.27, H 7.53, N 5.47, O 19.24.

***N*-(*tert*-Butoxycarbonyl)-*N*-[2-(4,5-dimethoxy-2-vinylphenyl)ethyl]acetamide (9):**
Compound **8** (247 mg, 0.99 mmol) and DMAP (30 mg, 0.1 mmol) were dissolved in MeCN (7 mL), treated with Boc_2O (273 mg, 1.25 mmol) and stirred for 15 h at r.t.. After addition of CH_2Cl_2 (20 mL) the organic layer was washed with 1 M $KHSO_4$ (2 × 10 mL) and sat. $NaHCO_3$ (2 × 10 mL), dried ($MgSO_4$) and the solvent evaporated in vacuo. The residue was purified by flash chromatography on silica gel (CH_2Cl_2/acetone 50:1) and recrystallized (*t*-BuOMe) to yield **9** (273 mg, 79%) as colorless needles; mp 93–94 °C.
^{1}H NMR ($CDCl_3$): δ = 1.50 [s, 9H, C(CH_3)$_3$], 2.48 (s, 3H, COCH_3), 2.84 (m, 2H, ArCH_2), 3.81 (m, 2H, CH_2N), 3.87 (s, 3H, OCH_3), 3.89 (s, 3H, OCH_3), 5.23 (dd, *J* = 10.9 Hz, *J* = 1.2 Hz, 1H, CH=CH^{cis} H_{trans}), 5.58 (dd, *J* = 17.2 Hz, *J* = 1.2 Hz, 1H, CH=CH$_{cis}$$H_{trans}$), 6.66 (s, 1H, arom *H*-6), 7.03 (s, 1H, arom *H*-3), 7.03 (dd, *J* = 17.3 Hz, *J* = 11.0 Hz, 1H, C*H*=CH$_2$).
^{13}C NMR ($CDCl_3$): δ = 27.0 (q, COCH$_3$), 27.8 [q, 3C, C(*C*H$_3$)$_3$], 31.7 (t, Ar*C*H$_2$), 45.4 (t, *C*H$_2$N), 55.87 (q, OCH$_3$), 55.91 (q, OCH$_3$), 83.0 [s, *C*(CH$_3$)$_3$], 108.1 (d, arom *C*-3/6), 113.0 (d, arom *C*-3/6), 113.4 (t, CH= *C*H$_2$), 129.03 (s, arom *C*-1/2), 129.06 (s, arom *C*-1/2), 133.7 (d, *C*H=CH$_2$), 147.9 (s, arom *C*-4/5), 148.9 (s, arom *C*-4/5), 153.0 [s, *C*OC(CH$_3$)$_3$], 173.1 (s, *C*OCH$_3$).
IR ($CHCl_3$): ν = 3006, 2981, 1730, 1687, 1512, 1370, 1147, 1104, 1049, 909 cm^{-1}.
MS (EI, 70 eV): *m/z* (%) = 349 (39) [M$^+$], 276 (10), 249 (6), 234 (25), 190 (100), 177 (45), 175 (25), 159 (14), 146 (19), 131 (11), 57 (31).
$C_{19}H_{27}NO_5$: calcd C 65.31, H 7.79, N 4.01, O 22.89; found: C 65.29, H 7.59, N 3.98, O 22.92.

***N*-(*tert*-Butoxycarbonyl)-2-(4,5-dimethoxy-2-vinylphenyl)ethylamine (10):**
Hydrazine hydrate (26 mg, 0.45 mmol) was added to a solution of **9** (35 mg, 0.1 mmol) in MeOH (0.5 mL) and allowed to stir for 1 h at r.t.. After addition of CH_2Cl_2 (5 mL) the organic layer was washed with 1 M $KHSO_4$ (2 × 5 mL) and sat. $NaHCO_3$ (2 × 5 mL), dried ($MgSO_4$) and the solvent evaporated in vacuo. The residue was recrystallized from MeOH and gave **10** (30 mg, 98%) as colorless crystals; mp 127–129 °C.
^{1}H NMR ($CDCl_3$): δ = 1.46 [s, 9H, C(CH_3)$_3$], 2.84 (m, 2H, ArCH_2), 3.30 (m, 2H, CH_2NH), 3.89 (s, 3H, OCH_3), 3.91 (s, 3H, OCH_3), 4.56 (s, br, 1H, N*H*), 5.24 (dd, *J* = 10.9 Hz, *J* = 1.2 Hz, 1H, CH=CH^{cis} H_{trans}), 5.57 (dd, *J* = 17.3 Hz, *J* = 1.2 Hz, 1H, CH=CH$_{cis}$$H_{trans}$), 6.65 (s, 1H, arom *H*-6), 7.03 (dd, *J* = 17.3 Hz, *J* = 10.9 Hz, 1H, C*H*=CH$_2$), 7.04 (s, 1H, arom *H*-3).
^{13}C NMR ($CDCl_3$): δ = 28.4 [q, 3C, C(*C*H$_3$)$_3$], 33.0 (t, Ar*C*H$_2$), 41.6 (t, *C*H$_2$NH), 55.9 (s, 2C, OCH$_3$), 79.2 [s, *C*(CH$_3$)$_3$], 108.6 (d, arom *C*-3/6), 112.8 (t, CH= *C*H$_2$), 113.8 (d, arom *C*-3/6), 129.03 (s, arom *C*-1/2), 129.06 (s, arom *C*-1/2), 133.7 (d, *C*H=CH$_2$), 147.8 (s, arom *C*-4/5), 148.8 (s, arom *C*-4/5), 155.8 [s, *C*OC(CH$_3$)$_3$].
IR ($CHCl_3$): ν = 3455, 3006, 2937, 1706, 1511, 1464, 1367, 1134, 1103, 1049, 1016 cm^{-1}.
MS (EI, 70 eV): *m/z* (%) = 307 (55) [M$^+$], 251 (39), 234 (17), 206 (8), 190 (76), 177 (100), 146 (22), 57 (57).
$C_{17}H_{25}NO_4$: calcd C 66.43, H 8.20, N 4.56; found C 66.18, H 7.97, N 4.60.

[2-(2-Acetamidoethyl-4,5-dimethoxyphenyl)-2-methoxyethyl] {2-[(*S*)-1-Hydroxypropyl]phenyl} Selenide (11):
Using General Procedure 1 with **1a** (68 mg, 0.15 mmol) and **8** (37 mg, 0.15 mmol). Purification by flash chromatography on silica gel (acetone/CH_2Cl_2 1:4) afforded **11** (36 mg, 49%) as a yellowish oil; $[\alpha]_D^{25}$ –25.4 (*c* = 0.74, $CHCl_3$).
^{1}H NMR ($CDCl_3$): δ = 0.97 (t, *J* = 7.3 Hz, 3H, CH$_2$CH_3), 1.77 (quint, *J* = 7.2 Hz, 2H, CH_2CH$_3$), 1.90 (s, 3H, COCH_3), 2.51–2.63 (m, 2H, ArCH_2), 3.00–3.30 (m, 5H, CH_2Se, CH_2NH, O*H*), 3.21 (s, 3H, CHOCH_3), 3.84 (s, 3H, ArOCH_3), 3.86 (s, 3H, ArOCH_3), 4.48 (dd, *J* = 8.5 Hz, *J* = 4.5 Hz, 1H, C*H*OCH$_3$), 5.06 (t, *J* = 5.0 Hz, 1H, C*H*OH), 5.72 (s, br, 1H, N*H*), 6.59 (s, 1H, arom *H*-6), 6.91 (s, 1H, arom *H*-3), 7.17 (td, *J* = 7.4 Hz, *J* = 1.5 Hz, 1H, arom *H*-5′), 7.32 (td, *J* = 7.5 Hz, *J* = 1.2 Hz, 1H, arom *H*-4′), 7.51 (dd, *J*= 7.7 Hz, *J* = 1.6 Hz, 1H, arom *H*-3′), 7.59 (dd, *J* = 7.7 Hz, *J* = 1.3 Hz, 1H, arom *H*-6′).
^{13}C NMR ($CDCl_3$): δ = 10.4 (q, CH$_2$*C*H$_3$), 23.1 (q, CO*C*H$_3$), 31.4 (t, *C*H$_2$Se), 31.7 (t, *C*H$_2$CH$_3$), 35.4 (t, Ar*C*H$_2$), 40.4 (t, *C*H$_2$NH), 55.99 (q, ArO*C*H$_3$), 56.03 (q, ArO*C*H$_3$), 56.7 (q, CHO*C*H$_3$), 74.2 (d, *C*HOH), 78.0 (d, *C*HOCH$_3$), 109.7 (d, arom *C*-3/6), 112.5 (d, arom *C*-

3/6), 126.7 (d, arom *C*-5′), 127.7 (d, arom *C*-3′), 128.1 (d, arom *C*-4′), 128.4 (s, arom *C*-1′), 128.9 (s, arom *C*-2), 131.0 (s, arom *C*-1), 135.3 (d, arom *C*-6′), 147.1 (s, arom *C*-2′), 148.2 (s, arom *C*-4/5), 148.5 (s, arom *C*-4/5), 170.3 (s, *C*OCH$_3$).
IR ($CHCl_3$): ν = 3449, 3005, 2936, 1663, 1514, 1464, 1135, 1105, 1049, 1016 cm^{-1}.
MS (EI, 70 eV): *m/z* (%) = 495 (5) [M$^+$], 266 (100), 192 (51).

(1*R*)-2-(*tert*-Butoxycarbonyl)-1-{[(*S*)-2-(1-hydroxypropyl)phenyl]selenomethyl}-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (12a):
Using General Procedure 2 with **1a** (64 mg, 0.15 mmol) and **10** (26 mg, 0.085 mmol). Purification by flash chromatography on silica gel (*t*-BuOMe/pentane 1:1) afforded **12a** (29 mg, 66%) as a yellowish oil; $[\alpha]_D^{25}$ + 20.3 (*c*= 1.3, $CHCl_3$).
^{1}H NMR ($CDCl_3$): δ = 0.90 (m, 3H, CH_2CH_3), 1.53 [s, 9H, C(C*H*$_3$)$_3$], 1.57–1.83 (m, 3H, C*H*$_2$CH$_3$, O*H*), 2.45–3.00 (m, 3H, ArC*H2*, CH*H*N), 3.25–3.48 (m, 2H, C*H*HN, CH*H*Se), 3.80–3.90 (m, 1H, C*H*HSe), 3.83 (s, 6H, 2 x OC*H*$_3$), 5.10 (m, 1H, C*H*OH), 5.20–5.30 (m, br, 0.7H, C*H*N), 5.40–5.50 (m, br, 0.3H, C*H*N), 6.60 (s, 2H, arom *H*-5, *H*-8), 7.12 (t, *J* = 8.4 Hz, 1H, arom *H*-5′), 7.28 (t, *J* = 8.4 Hz, 1H, arom *H*-4′), 7.46–7.57 (m, 2H, arom *H*-3′, *H*-6′).
^{13}C NMR ($CDCl_3$): δ = 10.4 (q, CH_2CH_3), 27.9 (t, *C*H$_2$Se), 28.5 [q, 3C, C(*C*H$_3$)$_3$], 29.7 (t, Ar*C*H$_2$), 31.9 (t, *C*H$_2$CH$_3$), 36.5 (t, *C*H$_2$N), 54.2 (d, *C*HN), 55.9 (q, O*C*H$_3$), 56.1 (q, O*C*H$_3$), 73.7 (d, *C*HOH), 80.8 [s, *C*(CH$_3$)$_3$], 110.0 (d, arom *C*-5/8), 110.3 (d, arom *C*-5/8), 126.4 (d, arom *C*-5′), 127.6 (d, arom *C*-3′), 127.8 (d, arom *C*-4′), 128.3 (s, arom *C*-1′), 130.0 (s, 2C, arom *C*-4a, *C*-8a), 133.7 (d, arom *C*-6′), 147.4 (s, arom *C*-2′), 148.0 (s, arom *C*-6/7), 148.1 (s, arom *C*-6/7), 155.1 [s, *C*OC(CH$_3$)$_3$].
IR ($CHCl_3$): ν – 3438, 3063, 3006, 2967, 1682, 1517, 1464, 1367, 1099, 858 cm^{-1}.
MS (FAB, NBA): *m/z* (%) = 520 (2) [M$^+$–H], 464 (2), 446 (5), 420 (1), 292 (39), 248 (35), 236 (100), 192 (16), 57 (81); (FAB, NBA+KCl): *m/z* = 560 [M$^+$+K]; (electron spray) m/z = 544 [M$^+$+Na].

(1*R*)-2-(*tert*-Butoxycarbonyl)-1-{[(*S*)-2-(1-hydroxypropyl)-4-nitrophenyl]selenomethyl}-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (12b):
Using General Procedure 2 with **1b** (28 mg, 0.054 mmol) and **10** (22 mg, 0.072 mmol). Purification by flash chromatography on silica gel (*t*-BuOMe/pentane 1:1) afforded **12b** (26 mg, 64%) as a yellowish oil; $[\alpha]_D^{25}$ + 8.3 (*c* = 0.19, $CHCl_3$).
^{1}H NMR ($CDCl_3$): δ = 0.98 (t, *J* = 7.4 Hz, 3H, CH_2CH_3), 1.52 [s, 9H, C(C*H*$_3$)$_3$], 1.50–1.80 (m, 3H, C*H*$_2$CH$_3$, O*H*), 2.60–2.85 (m, 3H, ArC*H2*, CH*H*N), 3.30–3.50 (m, 3H, C*H*HN, C*H*$_2$Se), 3.87 (s, 6H, 2 × OC*H*$_3$), 5.06 (t, 5.8 Hz, 1H, C*H*OH), 5.22–5.35 (m, 0.7H, C*H*N), 5.35–5.47 (m, 0.3H, C*H*N), 6.60 (s, 2H, arom *H*-5, *H*-8), 7.55 (m, 1H, arom *H*-6′), 7.95 (dd, *J* = 8.6 Hz, *J* = 2.7 Hz, 1H, arom *H*-5′), 8.38 (m, 1H, arom *H*-3′).
^{13}C NMR ($CDCl_3$): δ = 10.7 (q, CH_2CH_3), 28.0 (t, *C*H$_2$Se), 28.4 [q, 3C, C(*C*H$_3$)$_3$], 31.2 (t, *C*H$_2$CH$_3$), 36.3 (t, Ar*C*H$_2$), 39.3 (t, *C*H$_2$N), 53.8 (d, *C*HN), 55.9 (q, O *C*H$_3$), 56.1 (q, O*C*H$_3$), 72.9 (d, *C*HOH), 80.5 [s, *C*(CH$_3$)$_3$], 110.7 (d, arom *C*-5/8), 111.7 (d, arom *C*-5/8), 121.1 (d, arom *C*-5′), 126.5 (d, arom *C*-3′), 127.5 (s, arom *C*-4a/8a), 131.0 (s, arom *C*-4a/8a), 131.4 (d, arom *C*-6′), 140.0 (s, arom *C*-1′), 146.0 (s, 2C, arom *C*-6, *C*-7), 147.6 (s, arom *C*-4′), 148.7 (s, arom *C*-2′), 155.2 [s, *C*OC(CH$_3$)$_3$].
IR ($CHCl_3$): ν = 3685, 3009, 2931, 2855, 1682, 1601, 1573, 1464, 1366, 1342, 1134, 1050, 1036, 858 cm^{-1}.
MS (FAB+KCl): *m/z* (%) = 605 (2) [M$^+$+K], 493 (3), 292 (16), 236 (65), 57 (100).

(1*R*)-2-(*tert*-Butoxycarbonyl)-1-{[(*S*)-8-hydroxy-5,6,7,8-tetrahydro-1-naphthyl]selenomethyl}-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (12c):
Using General Procedure 2 with **1c** (39 mg, 0.086 mmol) and **10** (20 mg, 0.065 mmol). Purification by flash chromatography on silica gel (*t*-BuOMe/pentane 1:1) afforded **12c** (14 mg, 40%) as a yellowish oil; $[\alpha]_D^{25}$ + 21.0 (*c* = 0.70, $CHCl_3$).
^{1}H NMR ($CDCl_3$): δ = 1.46 [s, 9H, C(C*H*$_3$)$_3$], 1.70–1.80 (m, 2H, $CH_2CH_2CH_2$), 1.90–2.05 (m, 1H), 2.10–2.20 (m, 1H), 2.50–2.90 (m, 5H), 3.25–3.40 (m, 3H, C*H*$_2$N, CH*H*Se), 3,86 (s, 6H, 2 × OC*H*$_3$), 3.80–3.90 (m, 1H, C*H*HSe), 5.00–5.10 (m, 1H, C*H*OH), 5.25–5.45 (m, 1H, C*H*N), 6.59 (s, 1H, arom *H*-5/8), 6.65 (s, 1H, arom *H*-5/8), 7.00 (d, *J* = 7.4 Hz, 1H, arom *H*-4′), 7.09 (t, *J* = 7.5 Hz, 1H, arom *H*-3′), 7.30–7.55 (m, 1H, arom *H*-2′).
^{13}C NMR ($CDCl_3$): δ = 28.0 (t, *C*-6′), 28.4 [q, 3C, C(*C*H$_3$)$_3$], 29.7 (t, CH_2), 30.1 (t, CH_2), 31.4 (t, CH_2), 34.1 (t, CH_2), 37.3 (t, CH_2), 53.9 (d, *C*HN), 55.9 (q, O*C*H$_3$), 56.1 (q, O*C*H$_3$), 66.0 (d, *C*HOH), 80.0 [s, *C*(CH$_3$)$_3$], 110.2 (d, arom *C*-5/8), 111.5 (d, arom *C*-5/8), 126.5 (s, 2C, arom *C*-4a, *C*-8a), 127.9 (d, arom *C*-2′/3′/4′), 128.4 (d, arom *C*-2′/3′/4′), 130.5 (d, arom *C*-2′/3′/4′), 133.3 (s, arom *C*-l′), 138.6 (s, arom *C*-4a′/8a′), 139.0 (s, arom *C*-4a′/8a′), 147.5 (s, arom *C*-6/7), 148.1 (s, arom *C*-6/7), 154.5 [s, *C*OC(CH$_3$)$_3$)].
IR ($CHCl_3$): ν = 3671, 3460, 3006, 2935, 2856, 1683, 1516, 1465, 1367, 1134, 1050, 1015, 859 cm$^{-1.}$
MS (FAB+KCl): *m/z* (%) = 572 (8) [M$^+$+K], 516 (3), 460 (5), 416 (5), 292 (45), 236 (100), 57 (98).

(*S*)-*N*-(*tert*-Butoxycarbouyl)salsolidine (13):
Compound **12a** (29 mg, 0.056 mmol), triphenyltin hydride (45 mg, 0.128 mmol) and AIBN (10 mg, 0.061 mmol) were dissolved in toluene (0.4 mL) and refluxed for 1 h. The reaction mixture was separated via preparative TLC (*t*-BuOMe/pentane 1:1) to give **13** (16 mg, 93%); $[\alpha]_D^{25}$ + 72.1 (*c* = 0.69, $CHCl_3$).
^{1}H NMR ($CDCl_3$): δ = 1.42 (d, *J* = 6.7 Hz, 3H, CHC*H*$_3$), 1.49 [s, 9H, C(C*H*$_3$)$_3$], 2.58–2.70 (m, 1H, ArCH*H*), 2.77–2.90 (m, 1H, ArC*H*H), 3.07–3.25 (m, 1H, CH*H*N), 3.85 (s, 3H, OC*H*$_3$), 3.86 (s, 3H, OC*H*$_3$), 3.95–4.25 (m, 1H, C*H*HN), 5.06–5.23 (m, 1H, C*H*N), 6.59 (s, 2H, arom *H*-5, *H*-8).
^{13}C NMR ($CDCl_3$): δ = 21.8 (q, CH*C*H$_3$), 28.5 [q, 3C, C(*C*H$_3$)$_3$], 28.8 (t, 2C, Ar*C*H$_2$, *C*H$_2$N), 50.2 (d, *C*HN), 55.9 (q, O*C*H$_3$), 56.0 (q, O*C*H$_3$), 79.6 [s, *C*(CH$_3$)$_3$], 109.8 (d, arom *C*-5/8), 111.4 (d, arom *C*-5/8), 126.2 (s, 2C, arom *C*-4a, *C*-8a), 147.5 (s, 2C, arom *C*-6, *C*-7), 154.5 [s, *C*OC(CH$_3$)$_3$].
IR ($CHCl_3$): ν = 3006, 2978, 2935, 1681, 1518, 1421, 1366, 1106, 1053, 992, 859 cm$^{-1.}$
MS (EI, 70 eV): *m/z* (%) = 307 (9) [M$^+$], 292 (4), 250 (78), 236 (100), 234 (20), 192 (45), 57 (50).

(–)-(*S*)-Salsolidine (14):
To a solution of **13** (12 mg, 0.039 mmol) in CH_2Cl_2 (0.4 mL) was added,I.FA (0.04 mL, 0.53 mmol). The reaction mixture was allowed to stir for 3 h at r.t.. After addition of 1 N NaOH (5 mL) the aqueous layer was extracted with CH_2Cl_2. The organic layer was dried ($MgSO_4$) and evaporated to afford salsolidine **14** (7 mg, 99%); $[\alpha]_D^{25}$ – 29.5 (*c* = 0.325, EtOH).
^{1}H NMR ($CDCl_3$): δ = 1.44 (dd, *J* = 6.5 Hz, *J* = 1.8 Hz, 3H, CHC*H*$_3$), 1.78 (s, br, 1H, N*H*), 2.60–2.83 (m, 2H, ArC*H*$_2$), 2.85–3.03 (m, 1H, CH*H*NH), 3.20–3.50 (m, 1H, C*H*HNH), 3.848 (s, 3H, OC*H*$_3$), 3.853 (s, 3H, OC*H*$_3$), 4.05 (q, *J* = 6.4 Hz, 1H, C*H*NH), 6.57 (s, 1H, arom *H*-8), 6.63 (s, 1H, arom *H*-5).
^{13}C NMR ($CDCl_3$): δ = 22.9 (q, CH*C*H$_3$), 29.6 (t, Ar*C*H$_2$), 41.9 (t, *C*H$_2$N), 51.3 (d, *C*HNH), 55.9 (q, O*C*H$_3$), 56.1 (q, O*C*H$_3$), 109.2 (d, arom *C*-5), 111.9 (d, arom *C*-8), 126.8 (s, arom *C*-8a), 132.5 (s, arom *C*-4a), 147.3 (s, arom *C*-6/7), 147.4 (s, arom *C*-6/7).

This work was supported by the Stipendienfonds der Basler Chemischen Industrie (scholarship for G. F.), by the Deutschen Forschungsgemeinschaft, by the Schweizer Nationalfonds and by the Treubel-Fonds (scholarship for T. W.). We thank Prof. B. Giese for his continuous generous support.

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