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Selenium-promoted synthesis of enantiomerically pure substituted morpholines starting from alkenes and chiral aminoalcohols

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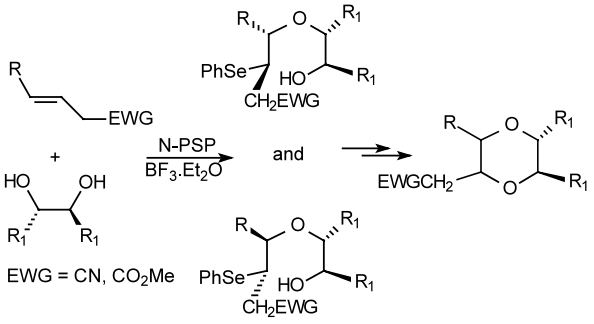
Abstract—Enantiomerically pure 2,3,5-trisubstituted morpholines with two newly created stereocenters have been prepared by a short synthetic sequence having as the key step the selenium-promoted addition of (*R*)-phenylglycinol to a substituted alkene.

1. Introduction

Over the last ten years, we have been engaged in the preparation of heterocyclic compounds using organoselenium reagents. Recently, much attention has been devoted to the synthesis of a variety of heterocycles by asymmetric cyclofunctionalizations. These reactions occur when an alkene, containing a suitably positioned nucleophilic atom, is attached by an enantiomerically pure electrophilic selenium reagent. The addition of the chiral electrophile to the carbon–carbon double bond occurs with high facial selectivity so that the cyclization generates a pair of enantiomerically pure diastereoisomeric heterocycles with excellent stereoselectivity.[1] These versatile processes allow us to synthesize oxygen and/or nitrogen-containing heterocycles such as tetrahydrofurans,[2,3] lactones,[2,3] lactams,[2] substituted pyrrolidines,[2] 1,2-oxazines[4] and isoxazolidines.[5] Multi-step sequences, which have as the key step the selenium-promoted addition of an appropriate nucleophile to an alkene, can also be successfully employed in the preparation of cyclic compounds. Optically active products were obtained either by using a chiral selenium electrophile and an achiral nucleophile[6,7] or an achiral selenium electrophile and a chiral nucleophile.[8] Scheme 1 describes the preparation of several enantiomerically pure tetrasubstituted 1,4-dioxanes using a diol as the chiral source.[8] The synthetic sequence started with the regio and stereospecific *anti* addition of an enantiomerically pure (*R*,*R*) diol to a substituted alkene promoted by *N*-(phenylseleno)phthalimide. After chromatographic separation, the two enantiomerically pure diastereomeric selenoethers were transformed into the corresponding allylic ethers and finally into 1,4-dioxanes by an intramolecular conjugate addition promoted by NaH. Up to four enantiopure isomeric dioxanes, two from each selenoether, were formed.



Scheme 1.

The enantiomers of these four dioxanes were obviously generated by an identical reaction sequence starting from the (*S*,*S*)-diol.

These results encouraged us to examine the feasibility of a similar procedure for the preparation of substituted morpholines. The morpholine skeleton is present in many important biological or therapeutical agents[9–12] and in recent years several asymmetric syntheses of these heterocycles have appeared in the literature.[13–17]

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Starting from an appropriately substituted alkene and an aminoalcohol such as the (*R*)-phenylglycinol as chiral source we expected to obtain 2,3,5-trisubstituted morpholines with two newly created stereocenters.

2. Results and discussion

The first experiments were carried out on 3-pentenenitrile **1**. In order to avoid the negative effects of a free amino group we decided to protect the (*R*)-phenylglycinol as its *N*-Boc derivative by treatment with stoichiometric amounts of triethylamine and di-*tert*-butyl dicarbonate in tetrahydrofuran at room temperature.[18] Then, **1** was treated with *N*-(phenylseleno)phthalimide in the presence of the protected (*R*)-phenylglycinol **2**. The *anti* addition reaction was not only regio- and stereospecific, but also chemospecific.[19] As reported in Scheme 2, the two enantiomerically pure diastereomeric alkoxyselenides **3a** (20%) and **4a** (20%) were isolated by column chromatography. The 4-hydroxy-3-(phenylseleno)pentanenitrile[8] (37% yield) was also isolated. No trace of the aminoselenenylation products could be detected.

The alkoxyselenides **3a** and **4a** were submitted to oxidation with hydrogen peroxide in dichloromethane. The spontaneous elimination of the intermediate selenoxides afforded the Michael acceptors **5a** (86%) and **6a** (93%) in high yields.

Finally, the isomeric morpholines were obtained after treatment of the alkenes **5a** and **6a** with NaH in anhydrous THF overnight. The attack of the nucleophilic nitrogen on both the diastereotopic faces gave **7a** and **8a** from the alkene **5a** and **9a** and **10a** from the alkene **6a**. These latter two isomers were isolated as a mixture (95% yield, **9a**:**10a** = 70:30) which could not be separated.

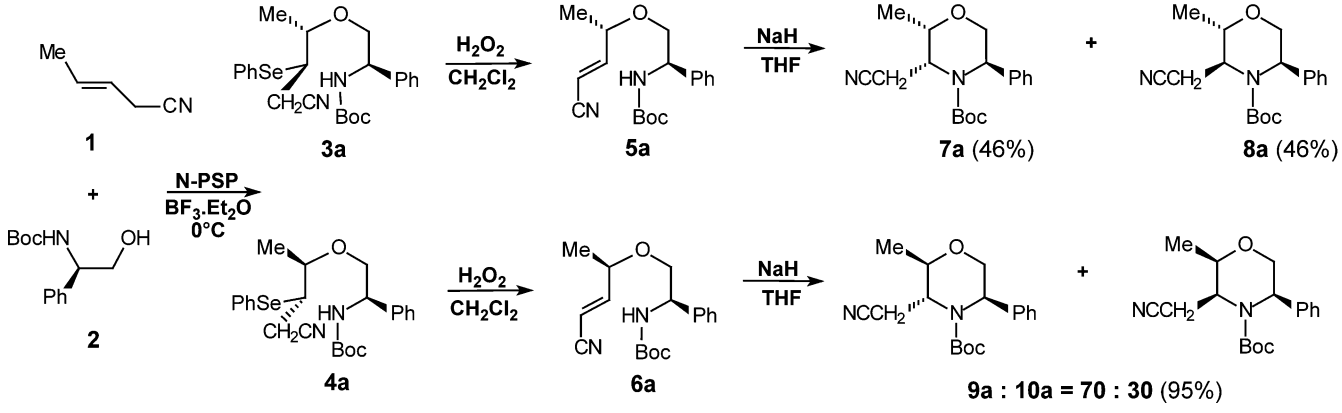
The structural assignment of the four enantiomerically pure morpholines was effected after nitrogen-deprotection, since the broadening of some signals due to the presence of the Boc group caused difficulties in the interpretation of the ^{1}H NMR spectra. The deprotection was effected by treatment with Me_3SiI in acetonitrile at room temperature[20] and proceeded with high yields in every case. Moreover, Boc removal allowed the mixture of **9a** and **10a** to be separated. In particular, after column chromatography, the major morpholine **9′a** was obtained in a pure form, while the minor isomer **10′a**, still contained traces of by-products as demonstrated by ^{1}H and ^{13}C NMR spectra. The absolute configurations of all the morpholines were determined on the basis of ^{1}H and ^{13}C NMR spectra and of some NOESY experiments. The vicinal coupling constants: J_{AB}, $J_{A'B}$, $J_{AA'}$ and J_{CD}, clearly suggest that the conformational equilibrium of the compounds **7′a** (J_{AB} = 10.6 Hz, $J_{A'B}$ = 3.6 Hz, $J_{AA'}$ = 11.1 Hz and J_{CD} = 2.6 Hz), **8′a** (J_{AB} = 10.4 Hz, $J_{A'B}$ = 3.3 Hz, $J_{AA'}$ = 11.2 Hz and J_{CD} = 8.8 Hz), and **10′a** (J_{AB} = 10.0 Hz, $J_{A'B}$ = 4.3 Hz, $J_{AA'}$ = 11.6 Hz and J_{CD} = 3.7 Hz) is completely shifted towards the chair conformations indicated in Scheme 3. The dipolar interactions observed in the NOESY spectra fully confirmed this hypothesis.

For the morpholine **9′a** the indicated conformation is not the most stable because both the methyl and the -CH_2CN groups occupy axial positions. A twist arrangement, which relieves the steric hindrance due to the 1,3-diaxial interactions, is probably more favored. This conformation is also consistent with the observed coupling constants values (J_{AB} = 4.4 Hz, $J_{A'B}$ = 3.4 Hz, $J_{AA'}$ = 11.5 Hz and J_{CD} = 6.3 Hz).

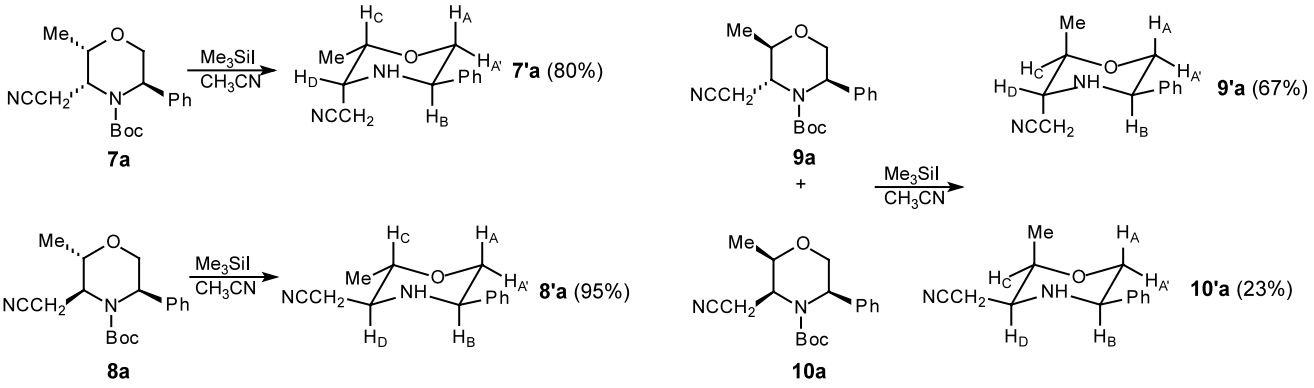
The stereochemical assignments of **3a**, **5a** and **4a**, **6a**, indicated in Scheme 2, were made on the basis of the configurations of the derived compounds **7a**, **8a** and **9a**, **10a**, respectively.

In order to generalize the present procedure, the protected phenylglycinol **2** was also used with other alkenes. Methyl (3*E*)-pent-3-enoate **11** and the methylstyryl acetate **12** were used as the starting materials in synthetic sequences carried out under identical experimental conditions. Table 1 reports the products obtained and the reaction yields.

Contrary to what was observed for **3c** and **4c** the diastereomeric selenoadducts **3b** and **4b** could not be

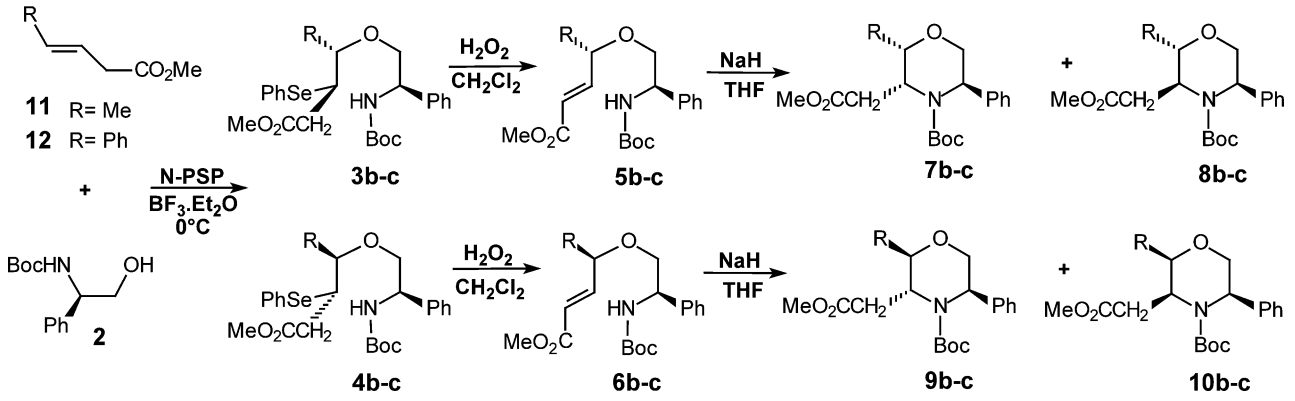


Scheme 2.



Scheme 3.

Table 1.



Alkenes	Selenoethers	Yield (%)	Allylic ethers	Yield (%)	Morpholines	Yield (%)
11	**3b**+**4b**[a] (1:1)	45[b]	**5b**+**6b**[a] (1:1)	73	**7b**+**8b**+**10b**[a,c] (27:13:60)	76
12	**3c**	33	**5c**	70	**7c**	42
	4c	47	**6c**	87		

[a] The products could not be separated by column chromatography. The indicated diastereomeric ratios were determined from the ^{1}H NMR spectra of the crude mixtures.

[b] 5-Methyl-4-(phenylseleno)dihydrofuran-2(3*H*)-one and methyl 4-methoxy-3-(phenylseleno)pentanoate were also isolated.

[c] The three morpholines were separated by column chromatography after Boc-removal.[20]

separated by column chromatography. Thus, their mixture was directly submitted to the oxidative deselenenylation and then to the cyclization. The enantiomerically pure diastereomeric morpholines **7b**, **8b** and **10b** were converted into **7′b**, **8′b** and **10′b** by Boc-removal with Me_3SiI and these diastereomeric morpholines were separated by column chromatography as pure products.

It is interesting to note that in both these experiments some of the possible isomeric morpholines were not formed.

Probably, the high steric requirements of some isomers discourage their formation, as already observed by us in the preparation of dioxanes.[8] The steric constrictions are particularly severe for the morpholines which arise from the alkene **12** in which two phenyl groups are present. As a matter of fact, the cyclization reaction occurs only in the case of compound **5c** which affords **7c** as the sole reaction product.

In summary, we have described a novel synthetic route to enantiomerically pure 2,3,5-trisubstituted morpholines starting from the commercially available (*R*)-phenylglycinol and appropriately substituted alkenes. We are presently investigating possible modifications of this methodology in order to test its potential applications for the preparation of biologically active molecules.

3. Experimental

New compounds were characterized by MS, ^{1}H and ^{13}C NMR spectroscopy. GLC analyses and MS spectra were carried out with an HP 6890 gas chromatograph (25 m dimethyl silicone capillary column) equipped with an HP 5973 Mass Selective Detector; for the ions containing selenium only the peaks arising from the selenium-80 isotope is given.^{1}H and ^{13}C NMR spectra were recorded at 400 and 100.62 MHz, respectively, on

a Bruker DRX 400 instrument; unless otherwise specified, $CDCl_3$ was used as solvent and TMS as standard. Optical rotations were measured with a Jasco DIP-1000 digital polarimeter. Elemental analyses were carried out on a Carlo Erba 1106 Elemental Analyzer.

3.1. Starting products

The starting β,γ-unsaturated nitrile **1** and the esters **11** and **12** are commercial products. The *N*-Boc protected (*R*)-phenylglycinol **2** was prepared from the corresponding aminoalcohol (ee >99%), by treatment with stoichiometric amounts of triethylamine and di-*tert*-butyl dicarbonate in tetrahydrofuran at room temperature according to a standard procedure.[18] The physical and spectral data are reported below.

3.2. *tert*-Butyl (1*R*)-2-hydroxy-1-phenylethylcarbamate 2

Mp 138–140°C; $[\alpha]_D^{24} = -39.2$ (*c* 3.05, $CHCl_3$). ^1H NMR: δ 7.21–7.02 (m, 6H), 5.05 (br s, 1H), 4.84–4.79 (m, 1H), 3.65 (dd, 1H, $J = 4.4$, 10.9 Hz), 3.56 (dd, 1H, $J = 6.4$, 10.9 Hz), 1.45 (s, 9H). ^{13}C NMR: δ 156.9, 140.0, 128.7 (two carbons), 127.7, 126.6 (two carbons), 80.0, 66.6, 57.2, 28.4 (three carbons). Anal. calcd for $C_{13}H_{19}NO_3$: C, 65.86; H, 8.07; N, 5.90. Found: C, 65.84; H, 8.04; N, 5.88%.

3.3. Conversion of β,γ-unsaturated nitrile and esters into β-phenylseleno γ-alkoxy derivatives

To a solution of *N*-(phenylseleno)phthalimide (1 mmol) in dichloromethane (6 mL) at 0°C the alkene **1**, **11** or **12** (2.5 mmol) and the *N*-Boc protected (*R*)-phenylglycinol **2** (1.3 mmol) were added. A catalytic amount of $BF_3{\cdot}Et_2O$ was added dropwise. The temperature was allowed to raise to room temperature. The reaction was monitored by TLC, GC–MS and ^1H NMR and worked up after a period of 2–6 h with 5% aqueous NaOH and dichloromethane. The organic layer was dried over Na_2SO_4 and evaporated. Reaction products were obtained in a pure form after column chromatography of the residue on silica gel.

3.4. *tert*-Butyl (1*R*)-2-{[(1*S*,2*R*)-3-cyano-1-methyl-2-(phenylseleno)propyl]oxy}-1-phenylethyl carbamate 3a

Oil (slightly impure, [α] not determined); ^1H NMR (C_6D_6, $T = 328$ K): δ 7.60–7.50 (m, 2H), 7.26–6.95 (m, 8H), 5.30 (br s, 1H), 5.13–5.0 (m, 1H), 3.50 (dd, 1H, $J = 4.6$, 9.3 Hz), 3.26 (dq, 1H, $J = 6.1$, 7.7 Hz), 3.19 (dd, 1H, $J = 5.8$, 9.3 Hz), 2.75 (dt, 1H, $J = 4.8$, 6.7, 7.7 Hz), 2.29 (dd, 1H, $J = 6.7$, 17.1 Hz), 2.14 (dd, 1H, $J = 4.8$, 17.1 Hz), 1.52 (s, 9H) 1.0 (d, 3H, $J = 6.1$ Hz). ^{13}C NMR: δ 155.5, 141.2, 135.4 (two carbons), 129.2 (two carbons), 128.3 (two carbons), 128.1 (two carbons), 127.2, 126.7 (two carbons), 117.6, 79.0, 77.3, 72.3, 54.9, 45.7, 28.2 (three carbons), 20.8, 17.5.

3.5. Methyl (3*R*,4*S*)-4-({(2*R*)-2-[(*tert*-butoxycarbonyl)amino]-2-phenylethyl}oxy)-3-(phenylseleno)pentanoate 3b and methyl (3*S*,4*R*)-4-({(2*R*)-2-[(*tert*-butoxycarbonyl)amino]-2-phenylethyl}oxy)-3-(phenylseleno)-pentanoate 4b

Oil (dr = 1:1); ^1H NMR: δ 7.65–7.52 (m, 4H), 7.42–7.20 (m, 16H), 5.60 (br s, 1H), 5.30 (br s, 1H), 4.80–4.70 (m, 2H), 3.78–3.40 (m, 8H), 3.60 (s, 3H), 3.59 (s, 3H), 2.90–2.70 (m, 2H), 2.70–2.50 (m, 2H), 1.42 (br s, 18H) 1.28 (d, 3H, $J = 6.0$ Hz), 1.18 (d, 3H, $J = 5.9$ Hz). ^{13}C NMR: δ 172.5, 172.4, 155.4 (two carbons), 140.6, 140.4, 135.0 (two carbons), 134.9 (two carbons), 129.1 (four carbons), 128.9, 128.8, 128.3 (two carbons), 128.2 (two carbons), 127.9, 127.8, 127.3, 127.2, 126.8 (two carbons), 126.6 (two carbons), 79.4 (two carbons), 78.3 (two carbons), 72.3, 72.0, 54.6 (two carbons), 51.7 (two carbons), 46.3 (two carbons), 37.0 (two carbons), 28.4 (six carbons), 17.8, 17.5. Anal. calcd for $C_{25}H_{33}NO_5Se$: C, 59.28; H, 6.57; N, 2.77. Found: C, 59.23; H, 6.56; N, 2.73%.

3.6. Methyl (3*R*,4*S*)-4-({(2*R*)-2-[(*tert*-butoxycarbonyl)amino]-2-phenylethyl}oxy)-4-phenyl-3-(phenylseleno)-butanoate 3c

Oil; $[\alpha]_D^{22} = +18.8$ (*c* 1.60, $CHCl_3$). ^1H NMR (C_6D_6, $T = 333$ K): δ 7.50–7.40 (m, 2H), 7.30–6.90 (m, 13H), 5.20 (d, 1H, $J = 7.4$ Hz), 5.05–4.90 (m, 1H), 4.49 (d, 1H, $J = 7.0$ Hz), 3.85 (ddd, 1H, $J = 5.4$, 7.0, 7.8 Hz), 3.51 (dd, 1H, $J = 5.1$, 9.6 Hz), 3.49 (s, 3H), 3.38 (dd, 1H, $J = 6.0$, 9.6 Hz), 2.96 (dd, 1H, $J = 5.4$, 16.3 Hz), 2.87 (dd, 1H, $J = 7.8$, 16.3 Hz), 1.49 (s, 9H). ^{13}C NMR: δ 171.4, 155.0, 140.8, 139.3, 134.8 (three carbons), 129.9, 128.7 (three carbons), 128.1 (two carbons), 128.0 (two carbons), 127.5, 126.9, 126.7 (three carbons), 85.0, 78.6, 72.4, 55.0, 50.7, 47.3, 36.8, 28.1 (three carbons). Anal. calcd for $C_{30}H_{35}NO_5Se$: C, 63.37; H, 6.20; N, 2.46. Found: C, 63.33; H, 6.22; N, 2.43%.

3.7. *tert*-Butyl (1*R*)-2-{[(1*R*,2*S*)-3-cyano-1-methyl-2-(phenylseleno)propyl]oxy}-1-phenylethyl carbamate 4a

Oil (slightly impure, [α] not determined); ^1H NMR (C_6D_6): δ 7.60–7.50 (m, 2H), 7.35–7.0 (m, 8H), 5.40 (br s, 1H), 5.15–4.95 (m, 1H), 3.51 (dd, 1H, $J = 5.2$, 9.4 Hz), 3.40–3.34 (m, 2H), 2.85 (dt, 1H, $J = 5.7$, 6.9 Hz), 2.30 (dd, 1H, $J = 6.5$, 17.1 Hz), 2.13 (dd, 1H, $J = 5.2$, 17.1 Hz), 1.45 (s, 9H), 0.92 (d, 3H, $J = 6.1$ Hz). ^{13}C NMR: δ 155.5, 141.2, 135.4 (two carbons), 129.2 (two carbons), 128.3 (two carbons), 128.1 (two carbons), 127.2, 126.8 (two carbons), 117.6, 79.0, 77.7, 72.7, 55.3, 46.1, 28.6 (three carbons), 21.2, 17.9.

3.8. Methyl (3*S*,4*R*)-4-({(2*R*)-2-[(*tert*-butoxycarbonyl)amino]-2-phenylethyl}oxy)-4-phenyl-3-(phenylseleno)-butanoate 4c

Oil; $[\alpha]_D^{27} = -37.7$ (*c* 2.75, $CHCl_3$). ^1H NMR (C_6D_6, $T = 333$ K): δ 7.70–7.51 (m, 2H), 7.25–7.0 (m, 13H),

5.57 (d, 1H, $J=5.6$ Hz), 5.03–4.95 (m, 1H), 4.57 (d, 1H, $J=6.6$ Hz), 3.93 (ddd, 1H, $J=6.0$, 6.6, 7.4 Hz), 3.50 (dd, 1H, $J=4.9$, 9.8 Hz), 3.46 (dd, 1H, $J=4.3$, 9.8 Hz), 3.42 (s, 3H), 2.96 (dd, 1H, $J=6.0$, 16.2 Hz), 2.89 (dd, 1H, $J=7.4$, 16.2 Hz), 1.53 (s, 9H). ^{13}C NMR: δ 171.4, 155.1, 140.9, 139.1, 134.7 (three carbons), 129.9, 128.8 (three carbons), 128.1 (six carbons), 126.8 (three carbons), 84.8, 78.7, 72.5, 54.8, 50.8, 47.4, 36.9, 28.2 (three carbons). Anal. calcd for $C_{30}H_{35}NO_5Se$: C, 63.37; H, 6.20; N, 2.46. Found: C, 63.33; H, 6.19; N, 2.40%.

3.9. Conversion of selenonitriles and selenoesters into allylic ethers

The selenonitriles **3a** and **4a** or the selenoesters **3b–c** and **4b–c** (0.5 mmol) were treated with an excess of hydrogen peroxide 30% (5 mmol) in dichloromethane at room temperature. The progress of the reactions was followed by TLC. After 1–2 h the reaction mixtures were poured into water and extracted with dichloromethane. The organic layers were dried and evaporated. The crude products were purified by column chromatography on silica gel. Physical and spectral data of **5a–c** and **6a–c** are reported below.

3.10. *tert*-Butyl (1*R*)-2-{[(1*S*,2*E*)-3-cyano-1-methylprop-2-enyl]oxy}-1-phenylethylcarbamate 5a

Oil, (slightly impure, [α] not determined); ^{1}H NMR (C_6D_6): δ 7.35–7.10 (m, 5H), 5.82 (dd, 1H, $J=5.1$, 16.4 Hz), 5.20–4.80 (m, 2H), 4.85 (dd, 1H, $J=1.6$, 16.4 Hz), 3.30–3.10 (m, 3H), 1.48 (s, 9H), 0.73 (d, 3H, $J=6.6$). ^{13}C NMR: δ 155.1, 154.2, 139.9, 128.4 (two carbons), 127.4, 126.5 (two carbons), 116.8, 99.3, 79.1, 74.4, 72.0, 54.2, 28.2 (three carbons), 19.4.

3.11. Methyl (2*E*,4*S*)-4-({(2*R*)-2-[(*tert*-butoxycarbonyl)amino]-2-phenylethyl}oxy)pent-2-enoate 5b and methyl (2*E*,4*R*)-4-({(2*R*)-2-[(*tert*-butoxycarbonyl)amino]-2-phenylethyl}oxy)pent-2-enoate 6b

Oil (dr = 1:1); ^{1}H NMR: δ 7.45–7.25 (m, 10H), 6.80 (dd, 1H, $J=6.0$, 15.8 Hz), 6.74 (dd, 1H, $J=6.0$, 15.8 Hz), 5.91 (dd, 1H, $J=1.2$, 15.8 Hz), 5.83 (dd, 1H, $J=1.2$, 15.8 Hz), 5.20 (br s, 2H), 4.83–4.65 (m, 2H), 4.01 (ddq, 1H, $J=1.2$, 6.0, 6.5 Hz), 3.94 (ddq, 1H, $J=1.2$, 6.0, 6.5 Hz), 3.75–3.45 (m, 4H), 3.73 (s, 3H), 3.72 (s, 3H), 1.45 (s, 18H), 1.25 (d, 3H, $J=6.5$ Hz), 1.21 (d, 3H, $J=6.5$). ^{13}C NMR: δ 166.5 (two carbons), 155.2 (two carbons), 148.9, 148.8, 140.3 (two carbons), 128.2 (four carbons), 127.2 (two carbons), 126.5 (two carbons), 126.4 (two carbons), 120.6 (two carbons), 79.5 (two carbons), 75.1, 74.7, 71.7 (two carbons), 54.5, 54.4, 51.4 (two carbons), 28.2 (six carbons), 20.2, 20.1. Anal. calcd for $C_{19}H_{27}NO_5$: C, 65.31; H, 7.79, N, 4.01. Found: C, 65.30; H, 7.83; N, 3.99%.

3.12. Methyl (2*E*,4*R*)-4-({(2*R*)-2-[(*tert*-butoxycarbonyl)amino]-2-phenylethyl}oxy)-4-phenylbut-2-enoate 5c

Oil; $[\alpha]_D^{22}=+16.3$ (c 1.58, $CHCl_3$). ^{1}H NMR (C_6D_6, $T=328$ K): δ 7.30–7.15 (m, 10H), 7.06 (dd, 1H, $J=5.3$, 15.7 Hz), 6.16 (dd, 1H, $J=1.5$, 15.7 Hz), 5.20–5.0 (m, 2H), 4.62 (dd, 1H, $J=1.5$, 5.3 Hz), 3.55 (dd, 1H, $J=4.9$, 9.8 Hz), 3.50 (dd, 1H, $J=5.4$, 9.8 Hz), 3.49 (s, 3H), 1.50 (s, 9H). ^{13}C NMR: δ 165.8, 155.0, 146.9, 140.7, 139.1, 128.5 (two carbons), 128.2 (two carbons), 128.1, 127.0, 126.8 (two carbons), 126.7 (two carbons), 120.9, 81.3, 78.8, 71.8, 54.8, 50.6, 28.1 (three carbons). Anal. calcd for $C_{24}H_{29}NO_5$: C, 70.05; H, 7.10, N, 3.40. Found: C, 70.07; H, 7.06; N, 3.39%.

3.13. *tert*-Butyl (1*R*)-2-{[(1*R*,2*E*)-3-cyano-1-methylprop-2-enyl]oxy}-1-phenylethylcarbamate 6a

Oil, (slightly impure, [α] not determined); ^{1}H NMR (C_6D_6): δ 7.28–7.03 (m, 5H), 5.80 (dd, 1H, $J=5.1$, 16.3 Hz), 5.20–4.80 (m, 2H), 4.89 (dd, 1H, $J=1.6$, 16.3 Hz), 3.35–3.10 (m, 3H), 1.50 (s, 9H), 0.67 (d, 3H, $J=6.5$). ^{13}C NMR: δ 155.2 (two carbons), 140.0, 128.5 (two carbons), 127.6, 126.5 (two carbons), 117.0, 99.5, 79.9, 75.0, 72.0, 54.4, 28.3 (three carbons), 19.8.

3.14. Methyl (2*E*,4*S*)-4-({(2*R*)-2-[(*tert*-butoxycarbonyl)amino]-2-phenylethyl}oxy)-4-phenylbut-2-enoate 6c

Mp 113–114°C; $[\alpha]_D^{26}=-58.4$ (c 3.48, $CHCl_3$). ^{1}H NMR (C_6D_6, $T=328$ K): δ 7.25–7.08 (m, 10H), 7.07 (dd, 1H, $J=5.4$, 15.7 Hz), 6.17 (dd, 1H, $J=1.6$, 15.7 Hz), 5.15 (d, 1H, $J=7.8$Hz), 5.10–5.0 (m, 1H), 4.69 (dd, 1H, $J=1.6$, 5.4 Hz), 3.57 (dd, 1H, $J=4.8$, 9.8 Hz), 3.50 (s, 3H), 3.47 (dd, 1H, $J=5.8$, 9.8 Hz), 1.50 (s, 9H). ^{13}C NMR: δ 165.8, 155.0, 146.9, 140.6, 139.0, 128.5 (two carbons), 128.2 (two carbons), 128.0, 127.1 (two carbons), 127.0, 126.7 (two carbons), 120.9, 81.0, 78.9, 71.8, 54.6, 50.6, 28.2 (three carbons). Anal. calcd for $C_{24}H_{29}NO_5$: C, 70.05; H, 7.10, N, 3.40. Found: C, 70.05; H, 7.10; N, 3.41%.

3.15. Conversion of allylic ethers into morpholines

The allylic ethers **5a–c** or **6a–c** (0.5 mmol) were treated with sodium hydride (0.55 mmol) in anhydrous THF (4 mL) at 0°C. The reaction mixtures were then allowed to reach room temperature and were stirred overnight. The reactions were worked up in the usual way. Purifications were effected by column chromatography on silica gel. The products **7a–c**, **8a–b**, **9a**, and **10a–b** were fully characterized after removal of the Boc-protection.

3.16. Deprotections of morpholines

The deprotection reactions of compounds **7a–c**, **8a–b**, **9a** and **10a–b** were effected by treatment with Me_3SiI in acetonitrile at room temperature, according to a known procedure.[20] The yields were always high ranging from 80 to 95%. Physical and spectral data of **7′a–c**, **8′a–b**, **9′a** and **10′a–b** are reported below.

3.17. [(2*S*,3*R*,5*R*)-2-Methyl-5-phenylmorpholin-3-yl]acetonitrile 7′a

Oil; $[\alpha]_D^{30}=+20.7$ (c 0.61, $CHCl_3$). ^{1}H NMR: δ 7.50–7.25 (m, 5H), 4.10 (dd, 1H, $J=3.6$, 10.6 Hz), 4.05 (dq, 1H,

$J=2.6$, 6.6 Hz), 3.86 (dd, 1H, $J=3.6$, 11.1 Hz), 3.48 (dd, 1H, $J=10.6$, 11.1 Hz), 3.28 (ddd, 1H, $J=2.6$, 4.3, 10.2 Hz), 3.13 (dd, 1H, $J=10.2$, 16.8 Hz), 2.57 (dd, 1H, $J=4.3$, 16.8 Hz), 2.20 (br s, 1H), 1.16 (d, 3H, $J=6.6$ Hz). ^{13}C NMR: δ 139.9, 128.7 (two carbons), 128.4, 127.4 (two carbons), 118.3, 73.6, 72.9, 53.0, 52.8, 17.7, 15.7. MS m/z (rel. int.): 216 (4), 186 (4), 176 (8), 170 (7), 157 (6), 146 (100), 135 (26), 105 (27), 104, (86), 91 (25), 77 (15), 65 (3), 51 (5). Anal. calcd for $C_{13}H_{16}N_2O$: C, 72.19; H, 7.46, N, 12.95. Found: C, 72.23; H, 7.43; N, 12.90%.

3.18. Methyl [(2*S*,3*R*,5*R*)-2-methyl-5-phenylmorpholin-3-yl]acetate 7′b

Oil; $[\alpha]_D^{33}=-7.4$ (c 0.60, $CHCl_3$). ^{1}H NMR: δ 7.48–7.20 (m, 5H), 4.20 (dd, 1H, $J=3.4$, 10.4 Hz), 4.05 (dq, 1H, $J=2.5$, 6.6 Hz), 3.88 (dd, 1H, $J=3.4$, 11.0 Hz), 3.71 (s, 3H), 3.51 (dd, 1H, $J=10.4$, 11.0 Hz), 3.40 (ddd, 1H, $J=2.5$, 3.8, 10.5 Hz), 3.06 (dd, 1H, $J=10.5$, 16.1 Hz), 2.56 (dd, 1H, $J=3.8$, 16.1), 2.52 (br s, 1H), 1.16 (d, 3H, $J=6.6$ Hz). ^{13}C NMR: δ 173.3, 139.5, 128.5 (two carbons), 127.9, 127.4 (two carbons), 74.0, 73.9, 53.2, 52.7, 51.8, 30.1, 17.8. MS m/z (rel. int.): 249 (2), 248 (2), 234 (2), 218 (4), 205 (11), 190 (4), 176 (26), 160 (13), 146 (28), 130 (10), 120 (20), 115 (24), 106 (28), 105 (22), 104 (100), 103 (13), 91 (15), 78 (11), 55 (9). Anal. calcd for $C_{14}H_{19}NO_3$: C, 67.45; H, 7.68, N, 5.62. Found: C, 67.51; H, 7.71; N, 5.59%.

3.19. Methyl [(2*S*,3*R*,5*R*)-2,5-diphenylmorpholin-3-yl]-acetate 7′c

Oil; $[\alpha]_D^{25}=-3.81$ (c 0.83, $CHCl_3$). ^{1}H NMR: δ 7.47–7.35 (m, 2H), 7.35–7.20 (m, 8H), 5.06 (d, 1H, $J=2.8$ Hz), 4.31 (dd, 1H, $J=3.6$, 10.6 Hz), 4.11 (dd, 1H, $J=3.6$, 11.1 Hz), 3.77 (ddd, 1H, $J=2.8$, 3.3, 11.1 Hz), 3.66 (dd, 1H, $J=10.6$, 11.1 Hz), 3.60 (s, 3H), 3.08 (dd, 1H, $J=11.1$, 16.6 Hz), 2.35 (s, 1H), 2.06 (dd, 1H, $J=3.3$, 16.6 Hz). ^{13}C NMR: δ 173.6, 140.3, 139.7, 129.0 (two carbons), 128.8 (two carbons), 128.6, 128.4, 127.8 (two carbons), 125.8 (two carbons), 80.0, 74.9, 54.6, 53.1, 52.0, 30.1. Anal. calcd for $C_{19}H_{21}NO_3$: C, 73.29; H, 6.80, N, 4.50. Found: C, 73.28; H, 6.75; N, 4.48%.

3.20. [(2*S*,3*S*,5*R*)-2-Methyl-5-phenylmorpholin-3-yl]-acetonitrile 8′a

Oil; $[\alpha]_D^{31}=-32.2$ (c 0.60, $CHCl_3$). ^{1}H NMR: δ 7.50–7.25 (m, 5H), 4.06 (dd, 1H, $J=3.3$, 10.4 Hz), 3.87 (dd, 1H, $J=3.3$, 11.2 Hz), 3.44 (dd, 1H, $J=10.4$, 11.2 Hz), 3.41 (dq, 1H, $J=6.2$, 8.8 Hz), 2.96 (ddd, 1H, $J=4.3$, 7.3, 8.8 Hz), 2.54 (dd, 1H, $J=4.3$, 16.8 Hz), 2.46 (dd, 1H, $J=7.3$, 16.8 Hz), 1.75 (br s, 1H), 1.26 (d, 3H, $J=6.2$ Hz). ^{13}C NMR: δ 139.3, 128.6 (two carbons), 128.4, 127.4 (two carbons), 116.9, 75.2, 72.5, 60.1, 56.9, 21.0, 17.6. MS m/z (rel. int.): 216 (2), 186 (3), 172 (6), 157 (5), 146 (88), 135 (29), 134, (27) 105 (27), 104, (100), 103 (13), 91 (23), 77 (16), 65 (3), 51 (6). Anal. calcd for $C_{13}H_{16}N_2O$: C, 72.19; H, 7.46, N, 12.95. Found: C, 72.22; H, 7.45; N, 12.97%.

3.21. Methyl [(2*S*,3*S*,5*R*)-2-methyl-5-phenylmorpholin-3-yl]acetate 8′b

Oil; $[\alpha]_D^{29}=-65.6$ (c 0.60, $CHCl_3$). ^{1}H NMR: δ 7.45–7.25 (m, 5H), 4.04 (dd, 1H, $J=3.3$, 10.5 Hz), 3.84 (dd, 1H, $J=3.3$, 11.1 Hz), 3.65 (s, 3H), 3.48 (dd, 1H, $J=10.5$, 11.1 Hz), 3.47–3.35 (m, 1H), 3.05 (dt, 1H, $J=3.1$, 9.3 Hz), 2.55 (dd, 1H, $J=3.1$, 16.3 Hz), 2.44 (dd, 1H, $J=9.3$, 16.3 Hz), 2.40 (br s, 1H), 1.21 (d, 3H, $J=6.2$ Hz). ^{13}C NMR: δ 172.5, 139.9, 128.5 (two carbons), 127.9, 127.3 (two carbons), 75.3, 73.1, 60.2, 57.9, 51.8, 36.4, 17.8. MS m/z (rel. int.): 249 (3), 248 (3), 234 (2), 205 (9), 176 (30), 160 (8), 146 (34), 130 (12), 120 (13), 115 (21), 106 (25), 105 (20), 104, (100), 103 (12), 91 (14), 78 (13), 77 (12), 55 (7). Anal. calcd for $C_{14}H_{19}NO_3$: C, 67.45; H, 7.68, N, 5.62. Found: C, 67.42; H, 7.69; N, 5.59%.

3.22. [(2*R*,3*R*,5*R*)-2-Methyl-5-phenylmorpholin-3-yl]-acetonitrile 9′a

Oil; $[\alpha]_D^{32}=-14.1$ (c 0.53, $CHCl_3$). ^{1}H NMR: δ 7.53–7.48 (m, 2H), 7.30–7.25 (m, 3H), 4.14 (dd, 1H, $J=4.4$, 11.5 Hz), 4.08 (dd, 1H, $J=3.4$, 4.4 Hz), 3.89 (dd, 1H, $J=3.4$, 11.5 Hz), 3.62 (quint, 1H, $J=6.3$ Hz), 3.0 (ddd, 1H, $J=4.9$, 6.3, 7.4 Hz), 2.63 (dd, 1H, $J=7.4$, 16.8 Hz), 2.54 (dd, 1H, $J=4.9$, 16.8 Hz), 2.0 (br s, 1H), 1.35 (d, 3H, $J=6.3$ Hz). ^{13}C NMR: δ 140.8, 128.6 (two carbons), 127.6, 127.5 (two carbons), 117.5, 74.1, 67.9, 54.2, 51.7, 21.7, 17.5. MS m/z (rel. int.): 216 (2), 185 (3), 172 (4), 157 (4), 146 (72), 139 (24), 135 (26), 134 (24), 117 (5), 105 (28), 104 (100), 103 (15), 91 (22), 78 (17), 77 (17), 65 (9), 51 (7). Anal. calcd for $C_{13}H_{16}N_2O$: C, 72.19; H, 7.46, N, 12.95. Found: C, 72.24; H, 7.44; N, 12.99%.

3.23. [(2*R*,3*S*,5*R*)-2-Methyl-5-phenylmorpholin-3-yl]-acetonitrile 10′a

Oil; (slightly impure, [α] not determined). ^{1}H NMR: δ 7.48–7.25 (m, 5H), 4.02 (dd, 1H, $J=4.3$, 10.0 Hz), 4.01 (dq, 1H, $J=3.7$, 6.6 Hz), 3.61 (dd, 1H, $J=10.0$, 11.6 Hz), 3.56 (dd, 1H, $J=4.3$, 11.6 Hz), 3.55 (ddd, 1H, $J=3.7$, 6.3, 8.3 Hz), 2.40 (dd, 1H, $J=6.3$, 16.6 Hz), 2.34 (dd, 1H, $J=8.3$, 16.6 Hz), 2.0 (br s, 1H), 1.39 (d, 3H, $J=6.6$ Hz). ^{13}C NMR: δ 139.3, 128.5 (two carbons), 127.9, 127.1 (two carbons), 117.1, 69.8, 65.5, 60.1, 53.1, 21.7, 10.9. MS m/z (rel. int.): 216 (2), 186 (3), 176 (5), 157 (6), 146 (100), 135 (25), 134 (19), 117 (6), 105 (26), 104, (91), 103 (14), 91 (21), 78 (13), 77 (14), 65 (3), 51 (5).

3.24. Methyl [(2*R*,3*S*,5*R*)-2-methyl-5-phenylmorpholin-3-yl]acetate 10′b

Oil; $[\alpha]_D^{30}=-89.1$ (c 2.10, $CHCl_3$). ^{1}H NMR: δ 7.45–7.39 (m, 2H), 7.35–7.24 (m, 3H), 4.01 (dd, 1H, $J=3.8$, 10.4 Hz), 3.88 (dq, 1H, $J=3.6$, 6.6 Hz), 3.66 (s, 3H), 3.60 (dd, 1H, $J=10.4$, 11.4 Hz), 3.58 (ddd, 1H, $J=3.6$, 5.2, 8.5 Hz), 3.53 (dd, 1H, $J=3.8$, 11.4 Hz), 2.34 (dd, 1H, $J=5.2$, 16.1 Hz), 2.30 (dd, 1H, $J=8.5$, 16.1 Hz), 2.20 (br s, 1H), 1.35 (d, 3H, $J=6.6$ Hz). ^{13}C NMR: δ 172.2, 140.6, 128.4 (two carbons), 127.7, 127.3 (two carbons),

70.6, 65.8, 63.6, 54.5, 51.7, 36.9, 11.4. MS *m*/*z* (rel. int.): 249 (1), 248 (2), 234 (2), 205 (7), 176 (16), 160 (9), 146 (24), 130 (10), 120 (11), 115 (20), 106 (24), 105 (17), 104 (100), 103 (12), 91 (14), 78 (11), 77 (12), 55 (9). Anal. calcd for $C_{14}H_{19}NO_3$: C, 67.45; H, 7.68, N, 5.62. Found: C, 67.51; H, 7.67; N, 5.60%.

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