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Introduction of *cis*-vicinal amino alcohol functionality into the cyclohexane ring employing (1*S*,2*S*)-2-amino-1,2-diphenylethanol: synthesis of enantiopure aminocyclohexitols

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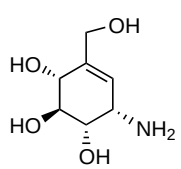
Abstract—Pd(0)-catalyzed allylic amination of 3-bromocyclohexene with (1*S*,2*S*)-2-amino-1,2-diphenylethanol and subsequent intramolecular oxyselenenylation of the resulting allylic amine **6** followed by oxidation–elimination afforded the valuable *cis*-fused bicyclic olefin **10**. Oxyselenenylation of cyclohexene with (1*S*,2*S*)-*N*-(benzyloxycarbonyl)-2-amino-1,2-diphenylethanol and subsequent oxidation–elimination gave the allylic ether **18**. Intramolecular aminoselenenylation of **18** followed by oxidation–elimination provided the *cis*-fused bicyclic olefin **21**, which is the regioisomer of **10**. Further stereoselective transformation of **10** afforded enantiopure aminocyclohexitols. © 2001 Published by Elsevier Science Ltd.

1. Introduction

Various aminocyclohexitols are found to be potent glycosidase inhibitors and also occur as the integral part of important antibiotics, glycosidase inhibitors, and other natural products. For example, the aminocyclohexitol valienamine **1**, which itself is an α-glucosidase inhibitor,[1] is also a structural component of both the antibiotic validmycins[2] and the glycosidase inhibitor arcabose.[3] Aminocyclohexitols validamine **2** and valiolamine **3** were isolated from the same microorganism as that for valienamine and were also found to be glycosidase inhibitors.[4] A characteristic functionality identified in these aminocyclohexitols is the vicinal amino alcohol moiety. Introduction of the *trans*-vicinal amino alcohol functionality is relatively straightforward while introducing the *cis* functionality is considered to be more complicated.[5]



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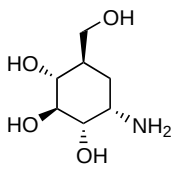

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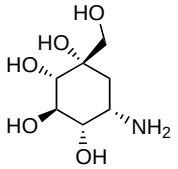

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In fact, valienamine **1**, validamine **2**, and valiolamine **3** all have the *cis* vicinal amino alcohol functionality and many aminoglycoside antibiotics[6] also contain the aminocyclo-hexitol having the *cis*-vicinal amino alcohol functionality. Although several methods are available for the synthesis of aminocyclohexitols,[7] there still remains a need for a new methodology starting from simple starting materials because the aminocyclitols are structurally very diverse and the new methodology could be applied for the synthesis of other highly functionalized cyclic compounds. Herein, we report new methods for the synthesis of aminocyclohexitols by introducing the *cis*-amino alcohol functionality into the cyclohexane ring employing (1*S*,2*S*)-2-amino-1,2-diphenyl-ethanol not only as the nitrogen and oxygen atom source but also as the source of chirality.[8]

2. Results and discussion

Enantiomerically pure (1*S*,2*S*)-2-amino-1,2-diphenylethanol **4**[9] was readily prepared by a two-step sequence: (i) Sharpless asymmetric aminohydroxylation of *trans*-stilbene using sodium benzyl *N*-chlorocarbamate, $K_2OsO_2(OH)_4$, and $(DHQ)_2PHAL$ to afford (1*S*,2*S*)-*N*-(benzyloxycarbonyl)-2-amino-1,2-diphenylethanol **5**;[10] (ii) selective cleavage of the Cbz group of **5** by catalytic hydrogenolysis in the presence of 2,2′-dipyridyl[11] to give the desired compound **4** in 93% yield. Displacement of

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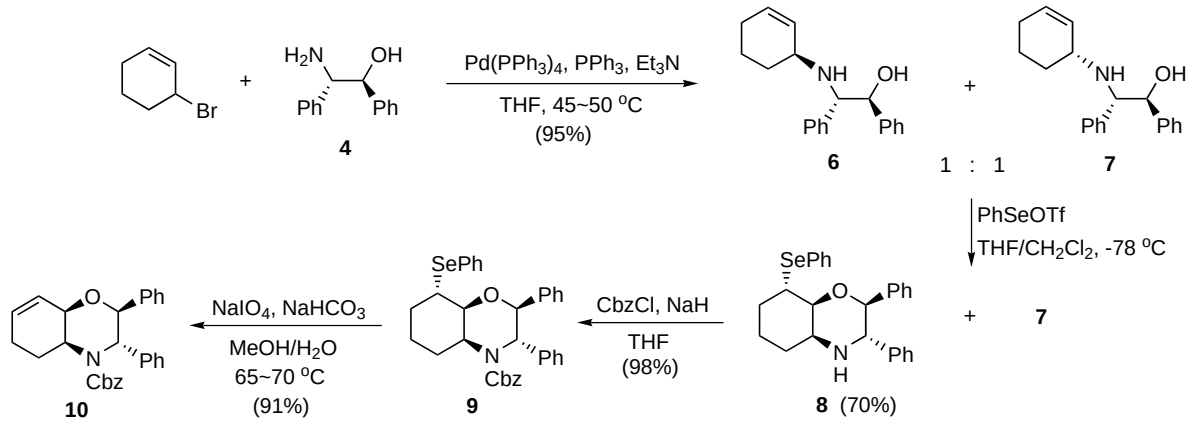


Scheme 1.

the bromide in 3-bromohexene by the amino group of **4** was accomplished by Pd(0)-catalyzed allylic substitution as shown in Scheme 1. Thus, to a THF solution of 3-bromocyclohexene, $Pd(PPh_3)_4$ (0.05 equiv.), PPh_3 (0.2 equiv.), and triethylamine (3 equiv.), a THF solution of the compound **4** was slowly added at 45–50°C. The reaction mixture was stirred for a further 5 h at the same temperature to afford an inseparable 1:1 mixture of the diastereomeric allylic amines **6** and **7** in 95% yield. A mixture of compounds **6** and **7** was treated with PhSeOTf at −78°C to give only the *cis*-fused bicyclic phenylselenenyl oxazine **8** in 70% yield along with the unreacted **7**. After protection of the secondary amine **8** with Cbz group, the resultant selenide **9** was treated with $NaIO_4$ in the presence of $NaHCO_3$ to give a valuable intermediate, the bicyclic olefin **10** in high yield.

Attempted direct conversion of the Cbz-protected derivative of the amine **6** into the bicyclic compound **10** by the Pd(II)-mediated oxidative cyclization was not successful.[12] To understand the unreactivity of **7** to cyclization under oxyselenenylation conditions, we considered the transition state model for the intramolecular cyclization. The episelenonium ion, which would be the first intermediate for the cyclization of **7**, could possess either the conformation **A** or **B** as shown in Fig. 1. The conformation **A** would be more favorable over the conformation **B** in which an unfavorable non-bonding interaction would exist between one of the phenyl groups and the pseudoaxial hydrogen at the C(6) position.

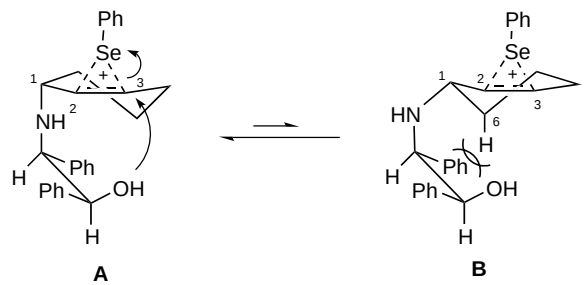
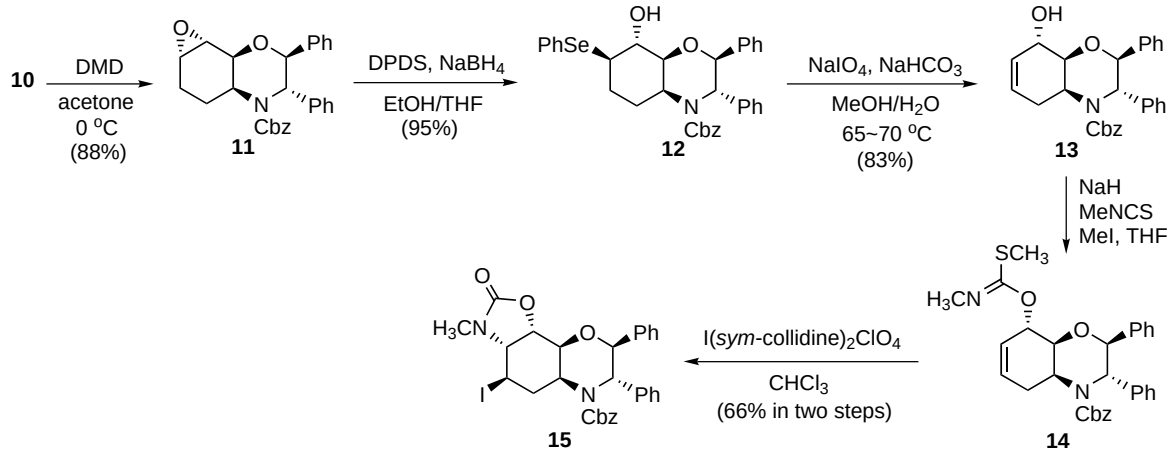


Figure 1. Two half-chair conformation of the episelenonium ion generated from olefin **7**.

To achieve the *trans*-1,2-diaxial opening of the episelenonium ion, the hydroxyl group should attack the C(3) position in the conformation **A**. It is, however, supposed that such a cyclization leading to the seven-membered ring would be unfavorable. When commercially available (1*S*,2*R*)-2-amino-1,2-diphenylethanol was used instead of (1*S*,2*S*)-2-amino-1,2-diphenylethanol, the Pd(0)-catalyzed allylic amination of 3-bromocyclohexene proceeded without problems but the subsequent intramolecular oxyselenenylation did not occur at all. The chair conformation of the bicyclic compound **8** would have both phenyl groups equatorial, whereas in the corresponding bicyclic compounds obtained employing (1*S*,2*R*)-2-amino-1,2-diphenylethanol, one of the phenyl groups in the chair form would be in the axial position. Therefore, the energy of the transition state of the intramolecular oxyselenenylation might be high enough to prevent the cyclization. The absolute configuration of the compound **10** was assigned by its conversion into *N*-(*p*-toluenesulfonyl)-(1*R*,2*S*)-2-aminocyclohexanol, of which enantiomer is known,[13] by a three-step sequence: (i) hydrogenation of the double bond and cleavage of the Cbz group in the compound **10** with H_2 and $Pd(OH)_2$, (ii) *N*-tosylation of the resulting amine with *p*-TsCl and triethylamine, and (iii) cleavage of the oxazine ring by hydrogenolysis using Pd/C in the presence of a small amount of *c*-HCl.

The olefin **10** is an ideal intermediate for further stereoselective transformation because the bicyclic ring is *cis*-fused and two bulky phenyl groups are located at the equatorial position. In order to demonstrate the usefulness of the present method for the synthesis of aminocyclitols, we have conducted several more completely stereoselective conversions with **10** as shown in Scheme 2. Indeed, the reaction of **10** with dimethyldioxirane (DMD) afforded exclusively the epoxide **11**, in which the epoxide ring is *trans* to the oxazine ring, in 88% yield. Diaxial ring opening of the epoxide **11** with PhSeNa, obtained from diphenyldiselenide (DPDS) with $NaBH_4$, gave exclusively the hydroxyselenide **12**, whereupon oxidation with $NaIO_4$ followed by elimina-



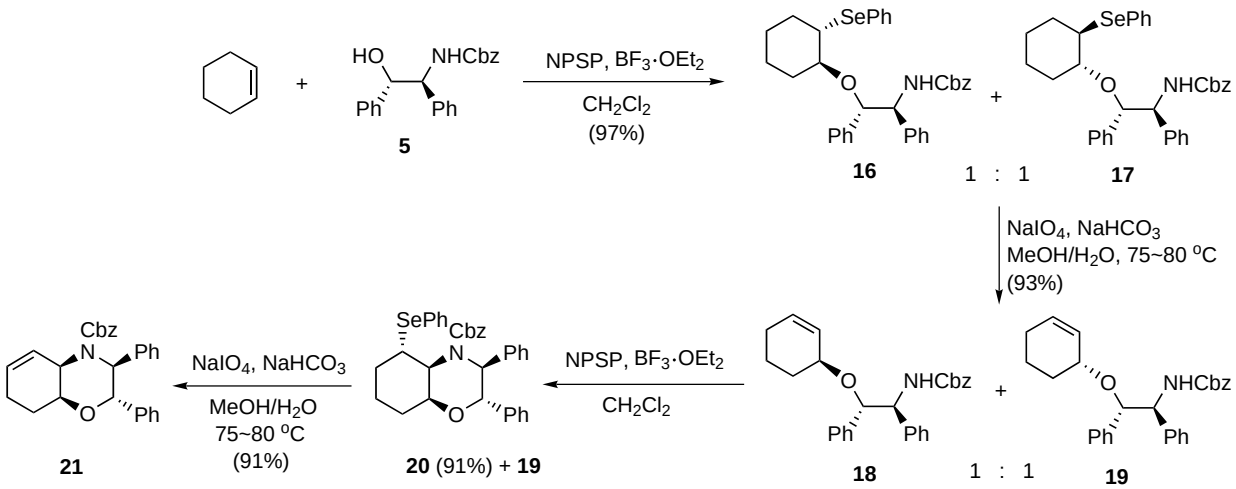
Scheme 2.

tion provided the allylic alcohol **13** in high yield. To generate another vicinal *cis*-aminohydroxyl group, the compound **13** was treated with methyl isothiocyanate and methyl iodide in the presence of sodium hydride to yield **14**. Without purification, the compound **14** was cyclized upon treatment with I(*sym*-collidine)$_2$ClO$_4$ to afford the compound **15**, which contains two vicinal *cis*-amino alcohol functionalities, in 66% yield in two steps.

We could also prepare the regioisomer of the bicyclic olefin **10** starting from cyclohexene and (1*S*,2*S*)-*N*-(benzyloxycarbonyl)-2-amino-1,2-diphenylethanol **5**. To a solution of the compound **5**, *N*-phenyselenophthalimide (*N*-PSP), and cyclohexene in methylene chloride was added slowly $BF_3{\cdot}OEt_2$ (0.1 equiv.) at 0°C. The reaction mixture was stirred for a further 2 h at room temperature to afford the oxyselenide **16** and its diastereomer **17** in about 1:1 ratio in 97% yield as shown in Scheme 3. Oxidation and elimination of the mixture of **16** and **17** followed by the intramolecular aminoselenenylation of the resulting mixture of olefins **18** and **19** provided the bicyclic selenide **20** along with the unreacted **19**. Oxidation of the selenide **20** and the subsequent elimination of the selenoxide gave the bicyclic olefin **21**, which is the regioisomer of **10**. Attempted direct conversion of **18** to **21** mediated by the intramolecular catalytic or stoichiometric aminopalladation of **18** was not successful. The unreactivity of **19** in the intramolecular aminoselenenylation reaction could be explained in the same way as for compound **7**.

3. Conclusion

We have developed two new methods for the construction of the *cis*-amino alcohol functionality on the cyclohexane ring. Our first method consists of the Pd(0)-catalyzed allylic amination of 3-bromocyclohexene with (1*S*,2*S*)-2-amino-1,2-diphenylethanol and the subsequent intramolecular oxyselenenylation of the resulting allylic amine. We have also shown as the second method that the oxyselenenylation of cyclohexene with (1*S*,2*S*)-*N*-Cbz-2-amino-1,2-diphenylethanol and the subsequent intramolecular aminoselenenylation provided the *cis*-amino alcohol functionality. The present methods could be used not only for the synthesis of enantiopure aminocyclohexitols but may also be



Scheme 3.

applied in the preparation of other important natural products.

4. Experimental

4.1. General

All reactions were conducted under a positive pressure of dry argon with dry, freshly distilled solvents unless otherwise noted. All reagents were purchased from commercial suppliers and used without further purification unless otherwise noted. Flash column chromatography was performed employing 230–400 mesh silica gel. Thin-layer chromatography was performed using silica gel 60 F254 precoated plates (0.25 mm thickness) with a fluorescent indicator. Melting points are uncorrected. IR spectra were recorded on a Nicolet Impact 400 FT-IR spectrometer. NMR spectra were recorded on a Bruker 250, Varian 300, or Bruker 500 NMR spectrometer. Chemical shifts are reported in parts per million (ppm) downfield from tetramethylsilane (TMS) unless otherwise noted. Optical rotations were measured with a Rudolph Autopol III automatic polarimeter.

4.2. (1*S*,2*S*,1′*S*)- and (1*S*,2*S*,1′*R*)-2-(Cyclohex-2′-enylamino)-1,2-diphenylethanol 6 and 7

To a solution of 3-bromocyclohexene (1.46 mL, 11.43 mmol), $Pd(PPh_3)_4$ (661 mg, 0.57 mmol), PPh_3 (600 mg, 2.29 mmol) and triethylamine (4.78 mL, 34.30 mmol) in THF (30 mL) was added slowly a solution of (1*S*,2*S*)-2-amino-1,2-diphenylethanol **4** (2.93 g, 13.72 mmol) in THF (10 mL) at 45–50°C. After stirring for 5 h at the same temperature, the reaction mixture was diluted with ethyl acetate and neutralized with saturated aqueous sodium bicarbonate solution. The organic phase was washed with brine, dried, and evaporated. The residue was purified by flash chromatography (hexane/EtOAc, 2:1) to give a mixture of **6** and **7** as a yellow oil (3.19 g, 95%): R_f=0.30 (hexane/EtOAc, 2:2); ^{1}H NMR ($CDCl_3$, 250 MHz): δ 1.35–1.44 (m, 2H), 1.45–1.58 (m, 1H), 1.69–1.90 (m, 3H), 3.05–3.11 (m, 1H), 3.05 (brs, 1H), 3.69 (dd, J= 8.5, 4.9 Hz, 1H), 4.49 (dd, J=8.5, 4.9 Hz, 1H), 5.40–5.80 (m, 2H), 6.99–7.25 (m, 10H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 19.5, 20.2, 25.3, 29.1, 31.0, 50.3, 51.7, 68.2, 68.4, 77.7, 77.9, 126.9, 127.4, 127.8, 127.9, 128.4, 129.2, 129.3, 129.7, 129.9, 140.7, 141.2, 141.4, 141.5; IR ($CHCl_3$ film) 3378 cm^{-1}. Anal. calcd for $C_{20}H_{23}NO$: C, 81.87; H, 7.90; N, 4.77. Found: C, 81.86; H, 7.94; N, 4.84%.

4.3. (2*S*,3*S*,8*S*,9*S*,10*S*)-2,3-Diphenyl-8-phenylselenenyloctahydrobenzo-1,4-oxazine 8

To a stirred solution of PhSeBr (5.53 g, 23.45 mmol) in CH_2Cl_2 (20 mL) in the presence of 4 Å molecular sieves was added a THF (15 mL) solution of AgOTf (7.412 g, 28.86 mmol) at −78°C and the reaction mixture stirred for further 20 min at the same temperature. To this reaction mixture was slowly added a solution of the mixture of compounds **6** and **7** (5.29 g, 18.04 mmol) in CH_2Cl_2 (10 mL) at −78°C. After stirring for 3 h at −78°C, the reaction mixture was diluted with CH_2Cl_2 and neutralized with saturated aqueous sodium bicarbonate solution. The organic phase was washed with brine, dried, and evaporated. The residue was purified by flash chromatography (hexane/EtOAc, 6:1) to give the title compound **8** as a yellow oil (2.83 g, 70%): R_f=0.29 (hexane/EtOAc, 6:1); $[\alpha]_D$=−32.6 (c=0.54, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 250 MHz): δ 1.52–1.57 (m, 1H), 1.68–1.90 (m, 4H), 2.17–2.27 (m, 1H), 2.47 (ddd, J=24.4, 12.2, 4.6 Hz, 1H), 3.46–3.50 (m, 1H), 3.77 (brs, 1H), 4.08 and 4.37 (ABq, J=9.2 Hz, 2H), 4.24 (brs, 1H), 6.97–7.56 (m, 15H); ^{13}C NMR ($CDCl_3$, 63 MHz): δ 21.7, 26.4, 26.6, 46.3, 50.0, 60.5, 77.7, 86.1, 127.4, 127.7, 127.8, 127.9, 128.1, 128.5, 129.3, 130.1, 133.6, 139.4, 140.2; IR ($CHCl_3$ film) 3311 cm^{-1}. Anal. calcd for $C_{26}H_{27}NOSe$: C, 69.64; H, 6.07; N, 3.12. Found: C, 69.64; H, 6.04; N, 3.18%.

4.4. (2*S*,3*S*,8*S*,9*S*,10*S*)-4-Benzyloxycarbonyl-2,3-diphenyl-8-phenylselenenyloctahydrobenzo-1,4-oxazine 9

A mixture of compound **8** (2.59 g, 5.79 mmol) and NaH (463 mg, 11.57 mmol) in THF (35 mL) was stirred at 0°C for 30 min. Benzyl chloroformate (1.30 mL, 8.68 mmol) was slowly added to this solution at room temperature. The reaction mixture stirred for a further 1 h and diluted with CH_2Cl_2. The organic layer was washed with brine, dried, and evaporated. The residue was purified by flash chromatography (hexane/EtOAc, 8:1) to give the title compound **9** as a yellow oil (3.30 g, 98%): R_f=0.38 (hexane/EtOAc, 6:1); $[\alpha]_D$=−39.6 (c=0.56, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.71–1.75 (m, 3H), 1.86–1.89 (m, 1H), 1.99–2.07 (m, 1H), 2.17–2.24 (m, 1H), 3.77–3.78 (m, 1H), 4.19 (t, J=2.5 Hz, 1H), 4.34 and 4.35 (ABq, J=9.8 Hz, 2H), 4.60–4.63 (m, 1H), 4.88 and 4.92 (ABq, J=12.0 Hz, 2H), 6.84–7.57 (m, 15H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 21.4, 25.0, 26.5, 45.7, 51.5, 61.5, 67.3, 77.3, 85.8, 126.9, 127.3, 127.7, 127.9, 128.2, 128.4, 129.4, 129.9, 133.8, 136.2, 138.7, 140.9, 157.3; IR ($CHCl_3$ film) 1698 cm^{-1}. Anal. calcd for $C_{34}H_{33}NO_3Se$: C, 70.09; H, 5.71; N, 2.40. Found: C, 70.08; H, 5.85; N, 2.44%.

4.5. (2*S*,3*S*,9*R*,10*S*)-4-Benzyloxycarbonyl-2,3-diphenyl-2,3;5,6;9,10-hexahydrobenzo-1,4-oxazine 10

A solution of compound **9** (2.27 g, 3.89 mmol) and $NaIO_4$ (1.98 g, 9.34 mmol) in methanol (50 mL) and water (8 mL) in the presence of $NaHCO_3$ (392 mg. 4.67 mmol) was stirred for 10 min at room temperature and for 48 h at 65–70°C. After removal of some methanol by evaporation, the concentrated solution was diluted with CH_2Cl_2. The organic layer was washed with brine, dried, and evaporated. The residue was purified by flash chromatography (hexane/EtOAc, 6:1) to give the title compound **10** as a white solid (1.51 g, 91%): mp 121–123°C; R_f=0.31 (hexane/EtOAc, 6:1); $[\alpha]_D$=−16.9 (c=0.52, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.76 (brs, 1H), 2.20–2.30 (m,

3H), 4.21 (m, 1H), 4.30 (m, 1H), 4.40 and 4.43 (ABq, $J=9.7$ Hz, 2H), 4.88 (m, 2H), 5.82–5.85 (m, 1H), 6.01–6.03 (m, 1H), 6.87–7.25 (m, 15H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 22.19, 26.10, 53.10, 61.82, 67.34, 71.09, 85.86, 124.70, 126.82, 127.11, 128.05, 128.21, 128.39, 133.31, 136.16, 138.72, 141.20, 157.20; IR ($CHCl_3$ film) 1698 cm^{-1}. Anal. calcd for $C_{28}H_{27}NO_3$: C, 79.03; H, 6.40; N, 3.29. Found: C, 79.04; H, 6.45; N, 3.31%.

4.6. (5*S*,6*S*,8*R*,9*S*,10*S*,11*S*)-4-Benzyloxycarbonyl-5,6-diphenyloctahydro-1,7-dioxa-4-azacyclopropa[*a*]naphthalene 11

A solution of compound **10** (232 mg, 0.55 mmol) and dimethyldioxirane (2 equiv., ca. 0.05 M) in acetone (22 mL) was stirred at 0°C for 5 h. The reaction mixture was evaporated to a quarter volume, diluted with methylene chloride, washed with brine. The organic phase was dried and evaporated. The residue was purified by flash chromatography (hexane/EtOAc, 5:1) to give the title compound **11** as an oil (212 mg, 88%): $R_f=0.17$ (hexane/EtOAc, 6:1); $[\alpha]_D=-14.4$ ($c=0.50$, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.39 (brs, 1H), 1.97–2.0 (m, 1H), 2.07–2.17 (m, 2H), 3.25 (brs, 1H), 3.34 (brs, 1H), 4.19–4.22 (m, 1H), 4.39 and 4.42 (ABq, $J=9.78$ Hz, 2H), 4.51 (m, 1H), 4.82–4.93 (m, 2H), 6.87–7.24 (m, 15H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 20.4, 23.0, 41.3, 50.1, 52.2, 54.7, 61.4, 72.8, 86.3, 127.0, 127.1, 128.0, 128.1, 128.3, 128.4, 136.1, 138.3, 140.8, 157.1; IR ($CHCl_3$ film) 1694 cm^{-1}. Anal. calcd for $C_{28}H_{27}NO_4$: C, 76.17; H, 6.16; N, 3.17. Found: C, 76.23; H, 6.10; N, 3.14%.

4.7. (2*S*,3*S*,7*R*,8*R*,9*S*,10*S*)-4-Benzyloxycarbonyl-8-hydroxy-2,3-diphenyl-7-phenylselenenyloctahydrobenzo-1,4-oxazine 12

A solution of diphenyldiselenide (922 mg, 2.95 mmol) and $NaBH_4$ (223 mg, 5.91 mmol) in ethanol (20 mL) was stirred at room temperature for 20 min. To this solution was slowly added a THF (10 mL) solution of compound **11** (652 mg, 1.48 mmol). The reaction mixture was stirred for 30 min, diluted with water, evaporated to a half volume, and diluted again with CH_2Cl_2. The organic layer was washed with brine, dried, and evaporated. The residue was purified by flash chromatography (hexane/EtOAc, 5:2) to give the title compound **12** as an oil (840 mg, 95%): $R_f=0.23$ (hexane/EtOAc, 3:1); $[\alpha]_D=-40.9$ ($c=0.55$, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.61–1.63 (m, 1H), 1.90–1.93 (m, 1H), 2.12 (brs, 1H), 2.31–2.36 (m, 1H), 2.62 (ddd, $J=24.75$, 12.27, 2.28 Hz, 1H), 3.37 (brs, 1H), 4.11 (brs, 1H), 4.34 and 4.37 (ABq, $J=9.8$ Hz, 2H), 4.44–4.46 (m, 1H), 4.52 (brs, 1H), 4.83–4.88 (m, 2H), 6.86–7.57 (m, 20H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 20.7, 25.6, 45.1, 51.0, 62.0, 67.4, 72.5, 77.2, 86.4, 126.9, 127.4, 127.9, 127.9, 128.0, 128.2, 128.3, 128.4, 129.2, 132.3, 133.8, 136.0, 138.3, 140.6, 157.3; IR ($CHCl_3$ film) 1690, 3436 cm^{-1}. Anal. calcd for $C_{34}H_{33}NO_4Se$: C, 68.22; H, 5.56; N, 2.34. Found: C, 68.27; H, 5.54; N, 2.34%.

4.8. (2*S*,3*S*,8*S*,9*S*,10*S*)-4-Benzyloxycarbonyl-8-hydroxy-2,3-diphenyl-2,3;5,10;8,9-hexahydrobenzo-1,4-oxazine 13

Compound **12** (970 mg, 1.62 mmol) was subjected to the same reaction conditions as that for the preparation of **10** from **9**. The reaction mixture was purified by flash chromatography (hexane/EtOAc, 5:2) to afford the title compound **13** as an oil (594 mg, 83%): $R_f=0.15$ (hexane/EtOAc, 3:1); $[\alpha]_D=-3.9$ ($c=0.54$, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.67 (brs, 1H), 2.33–2.37 (m, 1H), 2.53–2.58 (m, 1H), 4.17 (brs, 1H), 4.24 (brs, 1H), 4.39 and 4.46 (ABq, $J=9.7$ Hz, 2H), 4.47–4.51 (m, 1H) 4.87 and 4.93 (ABq, $J=12.2$ Hz, 2H), 5.82–5.84 (m, 1H), 5.94–5.96 (m, 1H), 6.87–7.26 (m, 15H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 24.5, 48.0, 61.6, 67.5, 68.1, 77.1, 86.3, 125.4, 127.0, 127.4, 128.0, 128.1, 128.4, 129.3, 135.9, 138.4, 140.6, 157.3; IR ($CHCl_3$ film) 1694, 3420 cm^{-1}. Anal. calcd for $C_{28}H_{27}NO_4$: C, 76.17; H, 6.16; N, 3.17. Found: C, 76.19; H, 6.16; N, 3.14%.

4.9. (4*R*,7*S*,8*S*,10*S*,11*R*,12*S*,13*S*)-6-Benzyloxycarbonyl-4-iodo-3-methyl-2-oxo-7,8-diphenyldecahydro-1,9-dioxa-3,6-diazacyclopenta[*a*]naphthalene 15

A mixture of compound **13** (234 mg, 0.52 mmol) and NaH (42 mg, 1.05 mmol) in THF (3 mL) was stirred at 0°C for 30 min and warmed to room temperature. A THF (1 mL) solution of methyl isothiocyanate (57 mg, 0.79 mmol) was added to this solution and the reaction mixture was stirred for a further 1 h. Then iodomethane (98 μL, 1.57 mmol) was added and the reaction mixture was stirred for further 30 min and evaporated to give crude **14**. A solution of the crude **14** and iodonium di-*sym*-collidine perchlorate (490 mg, 1.05 mmol) in $CHCl_3$ (5 mL) was stirred at room temperature for 20 h. The reaction mixture was diluted with $CHCl_3$ and washed with brine. The organic layer was dried and evaporated. The residue was purified by flash chromatography (hexane/EtOAc, 5:2) to afford the title compound **15** as an oil (215 mg, 66%): $R_f=0.21$ (hexane/EtOAc, 3:1); $[\alpha]_D=-3.3$ ($c=0.51$, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 2.25 (d, $J=12.2$ Hz, 1H), 2.70–2.78 (m, 1H), 3.22 (s, 3H), 3.98–4.07 (m, 2H), 4.34–4.42 (m, 4H), 4.49 (brs, 1H), 4.83 and 4.97 (ABq, $J=12.0$ Hz, 2H), 6.8–7.26 (m, 15H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 21.7, 32.3, 35.0, 51.8, 61.5, 63.9, 67.9, 72.2, 77.5, 86.4, 127.1, 127.3, 127.9, 128.2, 128.2, 128.5, 128.6, 128.8, 135.5, 137.5, 139.9, 156.8; IR ($CHCl_3$ film) 1689, 1766 cm^{-1}. Anal. calcd for $C_{30}H_{29}IN_2O_5$: C, 57.70; H, 4.68; N, 4.49. Found: C, 57.74; H, 4.75; N, 4.45%.

4.10. (1*S*,2*S*,1′*S*,2′*S*)-2-Amino-*N*-benzyloxycarbonyl-*O*-(2′-phenylselenenylcyclohexyl)-1,2-diphenylethanol 16 and 17

To a solution of compound **5** (4 g, 11.6 mmol), cyclohexene (2.8 mL, 27.9 mmol), and NPSP (3.88 g, 12.8 mmol) in CH_2Cl_2 (50 mL) was added slowly $BF_3{\cdot}OEt_2$ (144 μL, 1.1 mmol) at 0°C. The reaction mixture was stirred at room temperature for 2 h, diluted with CH_2Cl_2, neutralized with saturated aqueous sodium bicarbonate solution. The organic layer was washed

with brine, dried, and evaporated. The residue was purified by flash chromatography (hexane/EtOAc, 4:1) to afford a mixture of compounds **16** and **17** (6.6 g, 97%): $R_f = 0.37$ (hexane/EtOAc, 7:1); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.02–2.02 (m, 8H), 3.15–3.28 (m, 2H), 4.55–4.66 (m, 2H), 4.82 (brs, 1H), 4.94–5.00 (m, 2H), 7.01–7.57 (m, 20H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 22.5, 23.0, 24.8, 25.1, 28.4, 31.5, 31.8, 47.4, 48.1, 60.9, 61.8, 66.6, 77.1, 79.3, 80.8, 84.5, 127.0, 127.1, 127.2, 127.5, 127.6, 128.2, 128.3, 128.5, 128.1, 129.4, 133.6, 134.5, 136.8, 138.7, 139.7, 140.3, 140.8, 156.0, 156.1; IR ($CHCl_3$ film) 1713, 1729, 3339, 3434 cm^{-1}. Anal. calcd for $C_{34}H_{35}NO_3Se$: C, 69.85; H, 6.03; N, 2.40. Found: C, 69.89; H, 6.08; N, 2.33%.

4.11. (1*S*,2*S*,1′*S*)- and (1*S*,2*S*,1′*R*)-2-Amino-*N*-benzyloxy-carbonyl-*O*-(cyclohex-2′-enyl)-1,2-diphenylethanol 18 and 19

A solution of the mixture of **16** and **17** (6.0 g, 10.3 mmol), $NaIO_4$ (5.3 g, 24.7 mmol), and $NaHCO_3$ (1.73 g. 20.6 mmol) in methanol (120 mL) and water (20 mL) was heated at 75–80°C for 48 h. After removal of some methanol by evaporation, the reaction mixture was diluted with methylene chloride. The organic layer was washed brine, dried, and evaporated. The residue was purified by flash chromatography (hexane/EtOAc, 3:1) to afford a mixture of **18** and **19** (4.10 g, 93%): $R_f = 0.37$ (hexane/EtOAc, 3:1); ^{1}H NMR ($CDCl_3$, 250 MHz): δ 1.26–1.65 (m, 4H), 1.83–2.17 (m, 2H), 3.60 (brs, 1H), 4.62–4.64 (m, 1H), 4.82 (brs, 1H), 4.95 (brs, 2H), 5.47–5.85 (m, 3H), 7.13–7.58 (m, 15H); ^{13}C NMR ($CDCl_3$, 63 MHz): δ 18.7, 19.2, 25.2, 27.4, 29.6, 61.3, 66.8, 71.1, 72.4, 82.2, 82.4, 126.7, 127.0, 127.2, 127.4, 127.9, 128.3, 128.4, 129.1, 132.2, 136.7, 140.2, 141.2, 156.1; IR ($CHCl_3$ film) 1693, 1729, 3359, 3442 cm^{-1}. Anal. calcd for $C_{28}H_{29}NO_3$: C, 78.66; H, 6.84; N, 3.28. Found: C, 78.66; H, 6.83; N, 3.06%.

4.12. (2*S*,3*S*,5*S*,9*S*,10*S*)-4-Benzyloxycarbonyl-2,3-diphenyl-5-phenylselenenyloctahydrobenzo-1,4-oxazine 20

To a solution of the mixture of **18** and **19** (4.5 g, 10.5 mmol) and NPSP (3.5 g, 11.6 mmol) in methylene chloride (60 mL) was slowly added $BF_3{\cdot}OEt_2$ (130 μL, 1.0 mmol) at 0°C. The reaction mixture was stirred at room temperature for 7 h, diluted with methylene chloride, neutralized with saturated aqueous sodium bicarbonate solution. The organic phase was washed with brine, dried, and evaporated. The residue was purified by flash chromatography (hexane/EtOAc, 12:1) to afford the title compound **20** as a colorless solid (2.8 g, 91%): $R_f = 0.37$ (hexane/EtOAc, 7:1); mp 62–64 °C; $[\alpha]_D = -49.6$ ($c = 1.2$, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 250 MHz): δ 1.27–1.53 (m, 4H), 1.76–1.88 (m, 2H), 3.31–3.42 (m, 1H), 3.88–4.26 (m, 2H), 5.01–6.17 (m, 4H), 6.87–7.97 (m, 20H); ^{13}C NMR ($CDCl_3$, 63 MHz): δ 21.4, 31.3, 34.3, 44.5, 56.3, 68.1, 74.8, 125.5, 127.3, 127.5, 127.6, 127.8, 128.3, 128.6, 128.62, 128.8, 129.1, 129.5, 135.0, 136.5, 139.0, 141.7, 156.6; IR ($CHCl_3$ film) 1693 cm^{-1}. Anal. calcd for $C_{34}H_{33}NO_3Se$: C, 70.09; H, 5.71; N, 2.40. Found: C, 70.04; H, 5.79; N, 2.49%.

4.13. (2*S*,3*S*,9*S*,10*R*)-4-Benzyloxycarbonyl-2,3-diphenyl-2,3;7,8;9,10-hexahydrobenzo-1,4-oxazine 21

A solution of **20** (1.5 g, 2.6 mmol), $NaIO_4$ (1.32 g, 6.2 mmol), and $NaHCO_3$ (433 mg. 5.1 mmol) in methanol (60 mL) and water (10 mL) was heated at 75–80°C for 48 h. After removal of some methanol by evaporation, the reaction mixture was diluted with methylene chloride. The organic layer was washed brine, dried, and evaporated. The residue was purified by flash chromatography (hexane/EtOAc, 7:1) to afford the title compound **21** as a colorless oil (1.0 g, 91%): $R_f = 0.35$ (hexane/EtOAc, 7:1); $[\alpha]_D = -141.0$ ($c = 0.5$, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.65–1.78 (m, 1H), 1.91–2.04 (m, 2H), 2.17–2.29 (m, 1H), 4.17 (brs, 1H), 4.72 (brs, 1H), 5.15 (s, 2H), 5.30–5.41 (m, 3H), 5.68 (brs, 1H), 7.19–7.38 (m, 15H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 19.5, 28.3, 49.1, 66.0, 67.5, 76.0, 127.1, 127.6, 127.76, 127.79, 127.9, 128.0, 128.3, 128.4, 128.5, 128.54, 128.9, 139.1, 140.8, 156.1; IR ($CHCl_3$ film) 1654, 1692, cm^{-1}. Anal. calcd for $C_{28}H_{27}NO_3$: C, 79.03; H, 6.40; N, 3.29. Found: C, 79.08; H, 6.26; N, 3.27%.

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