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# Highly stereoselective aziridine ring-opening with phenylselenide anion and selective intramolecular aldol closure for the enantiopure synthesis of γ-aminocyclopentene derivatives

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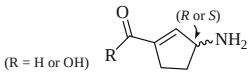
ABSTRACT

A practical and enantiopure synthesis for the preparation of key intermediates of conformationally locked γ-amino acid and nucleoside analogues is described. First, a highly stereoselective aziridine ring-opening reaction with phenylselenide anion was employed for the stereoselective synthesis of the chiral aminoselenide (1*S*,2*S*,1′*S*)-**8**, which after N-benzylation was transformed into the corresponding allyl amine (1*S*,1′*S*)-**7** by oxidation with $H_2O_2$. Then, dihydroxylation–dehomologation of (1*S*,1′*S*)-**7** with ($OsO_4$/NMO, $NaIO_4$) selectively afforded the desired γ-aminocyclopentene aldehyde (*S*)-**1** and its corresponding γ-amino acid (*S*)-**2** via an intramolecular selective aldol-condensation catalyzed by an internal base.



Chiral γ-aminocyclopentene derivatives[1] **A** play an important role as intermediates for the preparation of conformationally locked carbocyclic nucleosides[2] and γ-amino acid[3] analogues, and have been proven to provide very important information about the conformation and puckering of the ribose carbohydrate ring that has permitted to study the outcome of reactions between some prodrugs and specific enzymes,[2b,4] and about the active conformation of GABA at receptors.[3b,5]



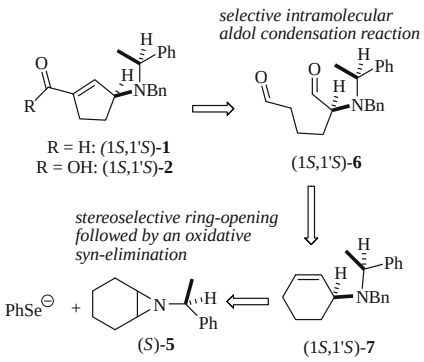

**A**

Since many of the methods reported for the preparation of chiral 3-aminocyclopentene derivatives require resolution into their optical antipodes, the development of new synthetic routes for their selective and stereoselective construction is of great importance.

As result of our continuing investigations on the enantioselective synthesis of biologically important GABA[6] and nucleoside analogues,[7] herein, we report a highly selective and stereoselective synthesis for the optically pure N-protected γ-aminocyclopentene aldehyde (1*S*,1′*S*)-**1** and its corresponding amino acid (1*S*,1′*S*)-**2** using the chiral aziridine (*S*)-**5**[8] as starting material.

Our general strategy for the construction of the chiral γ-aminocyclopentene ring consists of a selective intramolecular aldol-condensation of the chiral amino dialdehyde (1*S*,1′*S*)-**6**, which can be generated via sequential dihydroxylation–dehomologation of allyl amine (1*S*,1′*S*)-**7**. The latter is obtained by a stereoselective aziridine ring-opening reaction with phenylselenide anion[9] followed by an oxidative syn elimination (Scheme 1).

The synthetic route seems to be simple; however, the selective intramolecular aldol-condensation reactions have been proven to be difficult to achieve,[10] and the stereoselective two-step synthesis of allyl amines from aziridines by ring-opening with phenylselenide anion has curiously not been reported yet. Although well-known for epoxides,[11] to the best of our knowledge, this is the first report on a stereoselective synthesis of an allyl amine starting from chiral aziridine.




**Scheme 1.** Strategic plan for the synthesis of (*S*)-**1** and (*S*)-**2**.

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As indicated in Table 1, addition of phenylselenide anion, generated from diphenyldiselenide and $NaBH_4$, to chiral aziridine (*S*)-**5** afforded a mixture of the *trans*-aminoselenides (1*S*,2*S*,1′*S*)-**8** and (1*R*,2*R*,1′*S*)-**9** with high stereoselectivity (91:9) and high yield (95%).[12] During our effort to improve the stereoselectivity of this reaction even more, we noted that the stereoselectivity did not increase neither at lower temperatures (entries 2–7) nor in the presence of Lewis acids (Table 1, entries 4–7). On the contrary, yield and stereoselectivity diminished slightly when using Lewis acids.[13]

The absolute configuration of the major diastereoisomer (1*S*,2*S*,1′*S*)-**8** was determined by single-crystal X-ray diffraction of its corresponding HCl salt[14] (Fig. 1).

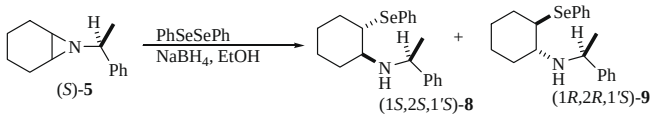
The aminoselenide (1*S*,1′*S*)-**7** was obtained upon treatment of aminoselenide (1*S*,2*S*,1′*S*)-**8** with an excess of $H_2O_2$ in methanol at reflux for 9 h, followed by N-benzylation with BnBr and $Na_2CO_3$ (Scheme 2). It should be mentioned that classical oxidizing agents[15] such as $O_3$, $NaIO_4$, *t*-BuOOH, and *m*CPBA did not work in this case.

Initially, within our strategic plan for the conversion of (1*S*,1′*S*)-**7** into (1*S*,1′*S*)-**1** or (1*S*,1′*S*)-**2**, we postulated the isolation of dialdehyde (1*S*,1′*S*)-**6** followed by the treatment with a chiral/*non*chiral base or another additive;[10d] however, we were very surprised to see that this step was not necessary, since a selective intramolecular aldol-condensation occurred even in the absence of an external base, thus the chiral aminoaldehyde (1*S*,1′*S*)-**1** was obtained in good yield, and its corresponding amino acid (1*S*,1′*S*)-**2** was obtained if Jones reagent was added.[16]

Since 1,4-*non*-symmetric dialdehydes have been proven to be very stable and generally chiral or *non*chiral bases are needed for selective aldol ring-closures,[10] it seems logical to postulate that the N-protected amino group plays a key role in the selective intramolecular aldol-condensation, and a model that accounts for the influence of the internal base is given in Scheme 3.

According to Scheme 3, the amine group acts as an internal base that catalyzes the ring closure. In order to prove the key role of the amine group in this unprecedented intramolecular aldol-condensation, we prepared the amide (*S*)-**11** with the expectation that the nitrogen lone pair is delocalized toward a carbonyl group, so the proposed internal hydrogen bonding will be attenuated and the spontaneous condensation must not occur. The result was as we expected, very high yield of dialdehyde (1*S*,1′*S*)-**12**[17] was obtained when amide (*S*)-**11** was treated with $OsO_4$/NMO and $NaIO_4$ (Scheme 4). However, it is important to mention that

**Table 1**
Stereoselective ring-opening of chiral aziridine (*S*)-**5**[a,b]




| Entry | Conditions | Ratio of **8**:**9** | Yield (%) |
|---|---|---|---|
| 1 | 0 °C, 4 h | 91:09 | 95 |
| 2 | −30 °C, 6 h | 90:10 | 90 |
| 3 | −78 °C, 6 h | 88:12 | 90 |
| 4 | −78 °C, $BF_3{\cdot}OEt_2$, 2 h | 85:15 | 80 |
| 5 | −78 °C, $AlCl_3$, 2 h | 76:24 | 76 |
| 6 | −78 °C, $LiClO_4$, 2 h | 75:25 | 60 |
| 7 | −78 °C, Ti(*i*-PrO)$_4$, 2 h | 75:25 | 70 |

[a] Yield of products determined after purification.
[b] Diastereomeric ratio determined by NMR.

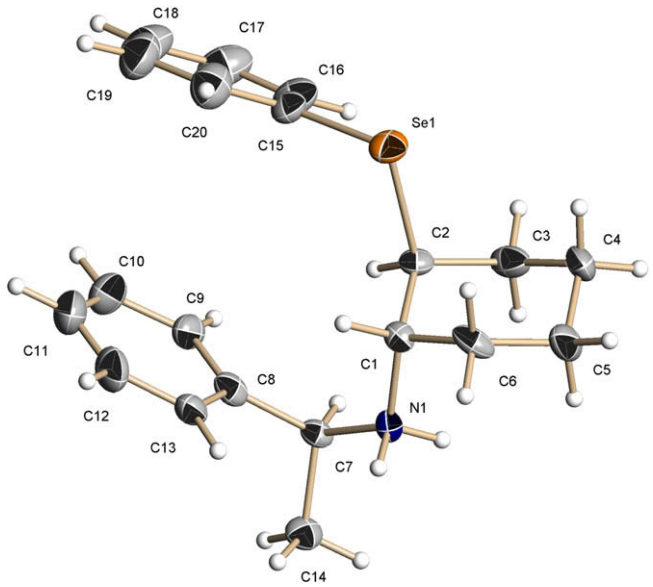
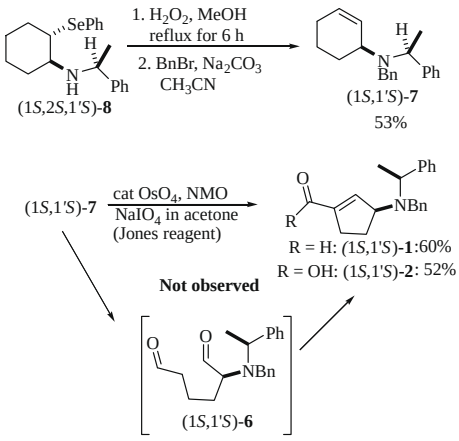
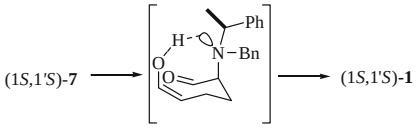


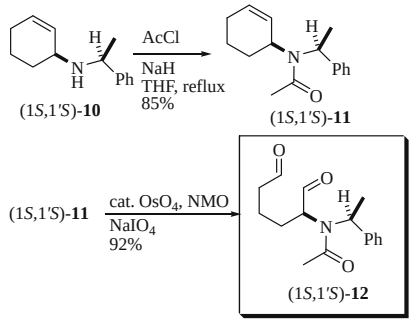

**Figure 1.** Perspective view of the molecular structure of (1*S*,2*S*,1′*S*)-**8** HCl salt.




**Scheme 2.** Selective synthesis of (1*S*,1′*S*)-**1** and (1*S*,1′*S*)-**2**.




**Scheme 3.** Model proposed to account for the influence of the internal base on the selective intramolecular aldol-condensation of (1*S*,1′*S*)-**7**.




**Scheme 4.** Demonstration of amine group acting as an internal base.

keeping the dialdehyde in a chloroform solution for several days at room temperature (inside NMR tube), a small amount of the condensation product is formed.

In conclusion, we are pleased to report the first selective intramolecular aldol-condensation catalyzed by an internal base, which is based on an internal hydrogen bonding. The enormous utility of this reaction was showcased in the synthesis of optically pure N-protected γ-aminocyclopentene aldehyde (1*S*,1′*S*)-**1** and its corresponding γ-amino acid (1*S*,1′*S*)-**2**. Although this route was exclusively designed for the synthesis of the above-mentioned GABA and nucleoside precursors, we expect that these results can also be applied to the synthesis of further complex substituted γ-aminocyclopentene derivatives. Further results on the application of this new route for the synthesis of new GABA, and nucleosides derivatives will be reported soon.

## Acknowledgments

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12. *Stereoselective ring-opening of N-[(S)-1-phenylethyl]cyclohexyl aziridine (1S)-**5** with phenylselenide anion*: To a solution of diphenyldiselenide (2.33 g, 7.45 mmol) and sodium borohydride (1.13 g, 19.84 mmol) in methanol (50 mL) at 0 °C, *N*-[(*S*)-1-phenylethyl]cyclohexyl aziridine (*S*)-**5**[8] (1 g, 4.96 mmol) dissolved in methanol (15 mL) was added. The resulting solution was stirred for 6 h. When the consumption of the starting aziridine was completed (monitored by TLC), the reaction mixture was quenched with water (50 mL) and the organic phase was extracted with ethyl acetate (3 × 50 mL). The combined organic layers were dried with anhydrous $Na_2SO_4$ and concentrated under reduced pressure. The yellow oil residue was purified by flash silica gel chromatography (eluent:hexane/ethyl acetate 30:1). *(1S,2S,1′S)-[(1′-Phenylethyl)-(2-phenylselenyl-cyclohexyl)amine]; (1S,2S,1′S)-**8***: Yield 86%; $[\alpha]_D^{20}$ = +69.23 (*c* = 2.0, $CHCl_3$); $^1$H NMR ($CDCl_3$, 400 MHz) *δ*: 1.01 (m, 1H), 1.16 (m, 2H), 1.33 (d, 3H, *J* = 6.8 Hz), 1.53 (m, 3H), 1.81 (m, 1H), 2.08 (m, 2H), 2.53 (td, 1H, *J* = 9.6, 4.0 Hz), 3.01 (m, 1H), 3.82 (q, 1H, *J* = 6.4 Hz), 7.14–7.29 (m, 8H), 7.54 (m, 2H); $^{13}$C NMR ($CDCl_3$, 100 MHz) *δ*: 24.2, 24.4, 26.7, 33.7, 33.8, 50.8, 56.5, 59.4, 126.3, 126.4, 127.3, 128.7, 135.1, 146.8; HRMS (EI) *m*/*z* found 359.1140, calcd. for $C_{20}H_{25}NSe$ 359.1152. *(1R,2R,1′S)-[(1′-Phenyl-ethyl)-(2-phenylselenyl-cyclohexyl)]amine; (1S,2S,1′S)-9*: Yield 8%; $[\alpha]_D^{20}$ = −82.72 (*c* = 1.8, $CHCl_3$); $^1$H NMR ($CDCl_3$, 400 MHz) *δ*: 1.10 (m, 1H), 1.17–1.33 (m, 2H), 1.35 (d, 3H, *J* = 6.9 Hz), 1.53–1.63 (m, 2H), 2.03 (m, 2H), 2.13–2.26, (m, 2H) 2.43(s, 1H), 3.04 (ddd, 1H, *J* = 11.7, 9.9, 3.9 Hz), 3.93 (q, 1H, *J* = 6.6 Hz), 7.15–7.42 (m, 10H); $^{13}$C NMR ($CDCl_3$, 100 MHz) *δ*: 24.3, 24.9, 27.1, 32.2, 34.1, 51.0, 54.1, 56.8, 126.6, 126.8, 127.4, 128.4, 128.8, 135.3, 145.2. HRMS (EI) *m*/*z* found 359.1151, calcd. for $C_{20}H_{25}NSe$ 359.1152.
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14. *Crystal data*: $C_{20}H_{26}ClNSe$, $M_r$ = 394.83 gmol$^{-1}$, 0.10 × 0.28 × 0.60 mm$^3$, triclinic, space group *P*-1, *T* = 293(2) K, *a* = 7.5474(9), *b* = 9.0498(11) *c* =16.145(2) Å, *α* = 99.491(2), *β* = 97.620(2), *γ* = 113.462(2) °, *V* = 973.5(2) Å$^3$, *Z* = 2, $\rho_{calcd}$ = 1.347, *μ* = 2.066 mm$^{-1}$, $2\theta_{max}$ = 25.00, 9488 measured and 6734 independent reflections ($R_{int}$ = 0.038), $R_1$ = 0.075 for 6002 reflections with *I* >2 σ(*I*) and $wR_2$ = 0.173 for all data, 411 parameters, *GOF* = 1.16 (CCDC 723281).
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16. *Sequential dihydroxylation–dehomologation-aldol-condensation of allyl amine (1S,1′S)-7*: To a solution of allyl amine (1*S*,1′*S*)-**7** (0.050 g, 0.17 mmol) in 10 mL of a mixture of acetone/$H_2O$ (10/1), 4-methylmorpholine *N*-oxide (0.060 g, 0.51 mmol) and osmium tetroxide (0.0034 mmol, 0.034 mL of a 0.1 M *tert*-butanol solution) were added. The resulting solution was stirred for 16 h at room temperature. When the consumption of the starting amine was completed (monitored by TLC), the reaction mixture was quenched with water (20 mL) and the organic phase was extracted with $CH_2Cl_2$ (3 × 30 mL). The combined organic layers were dried with anhydrous $Na_2SO_4$, filtered, and the solvent was evaporated carefully under reduced pressure. The residue was dissolved in ethanol (10 mL) and sodium periodate (0.07 g, 0.32 mmol) was slowly added at 0 °C. The reaction mixture was allowed to react for 2 h and filtered, whereupon the solvent was evaporated carefully under reduced pressure and the residue extracted with $CH_2Cl_2$ (50 mL). The organic layer was washed with water and brine, dried with $Na_2SO_4$, and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel (eluent:hexane/ethyl acetate 5:1) to afford the γ-aminocyclopentene aldehyde (1*S*,1′*S*)-**1** in 60% yield; $[\alpha]_D^{20}$ −84.66 (*c* 0.03, $CHCl_3$); $^1$H NMR *δ*: 1.40 (d, 3H, *J* = 6.6 Hz), 1.90–2.00 (m, 1H), 2.07–2.18 (m, 1H), 2.28–2.39 (m, 1H), 2.55 (m, 1H), 3.67 (q, 2H, *J* = 15.0 Hz), 3.91 (q, 1H, *J* = 6.9 Hz), 4.28 (m, 1H,), 6.42 (s, 1H), 7.23 (m, 4H), 7.24–7.42 (m, 6H), 9.62 (s, 1H); $^{13}$C NMR ($CDCl_3$, 100 MHz) *δ*: 6.1, 16.7, 26.9, 50.9, 57.6, 64.2, 126.8, 126.9, 127.6, 128.2, 128.3, 154.9, 158.1, 189.8; HRMS (FAB+) *m*/*z* found 305.1887, calcd. for $C_{21}H_{23}NO$, 305.1780. The corresponding γ-aminocyclopentene acid (1*S*,1*S*′)-**2** is obtained when 2 equiv of Jones reagent is added into the flask containing the (1*S*,1′*S*)-**1** reaction crude. Purification by flash chromatography on silica gel (eluent:hexane/ethyl acetate 3:1) afforded the γ-aminocyclopentene acid (1*S*,1′*S*)-**2** in 52% yield. White solid, mp 127–128 °C; $[\alpha]_D^{20}$ −171.6 (*c* 1.0, $CHCl_3$). $^1$H NMR *δ*: 1.25 (s, 2H), 1.35 (d, 3H, *J* = 6.6 Hz), 1.88–2.00 (m, 1H), 2.04–2.17 (m, 1H), 2.35–2.45 (m, 1H), 2.57 (m, 1H), 3.67 (q, 2H, *J* = 15 Hz), 3.88 (q, 1H, *J* = 6.6 Hz), 4.19 (m, 1H,), 6.57 (s, 1H), 7.23 (m, 4H), 7.28–7.42 (m, 6H); $^{13}$C NMR *δ*: 16.6, 27.4, 29.9, 50.7, 57.5, 64.4, 126.7, 126.8, 127.6, 128.1, 128.2, 128.3, 135.9, 141.2, 143.9, 148.8, 170.1 HRMS (EI) *m*/*z* found 322.1804, calcd. for $C_{21}H_{23}NO_2$, 322.1807.
17. (1*S*,1′*S*)-[(*N*-1,4-Diformylbutyl)-*N*-(1′ phenylethyl)]acetamide; (1*S*, 1′*S*)-**12**: $^1$H NMR *δ*: 1.55–1.82 (m, 2H), 1.67 (d, 3H, *J* = 7.2 Hz), 2.29 (m, 2H), 2.36 (s, 3H), 2.48 (q, 2H, *J* = 6.4 Hz), 2.99 (dd, 1H, *J* = 8.0, 4.4 Hz), 5.22 (q, 1H, *J* = 7.2 Hz), 7.37 (m, 5H), 9.06 (s, 1H), 9.77 (s, 1H); $^{13}$C NMR ($CDCl_3$, 100 MHz) *δ*: 18.2, 20.0, 29.2, 43.7, 56.3, 61.6, 127.0, 128.4, 129.0, 139.2, 170.6, 198.6, 202.1.