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ScienceDirect
Tetrahedron
Tetrahedron 63 (2007) 3321–3327

Syntheses of tetrahydropyridin-3-ol and tetrahydroazepin-3-ol from a chiral aziridine-2-carboxylate

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Received 30 December 2006; revised 9 February 2007; accepted 13 February 2007
Available online 15 February 2007

Abstract—A method for the stereoselective preparation of 1,2,3,6-tetrahydropyridin-3-ols and 2,3,4,7-tetrahydro-1*H*-azepin-3-ols, potentially versatile intermediates in the asymmetric synthesis of various piperidine alkaloids and azasugars, has been developed. The routes start with a readily available optically pure aziridine-2-carboxylate. The design strategy relies on four key transformations involving (1) stereoselective reduction of an acyl-aziridine intermediate derived from the aziridine-2-carboxylate, (2) regioselective aziridine ring opening, (3) N-allylation, and (4) ring-closing metathesis. The method developed in this investigation provides ready access to stereochemically defined and highly functionalized 3-hydroxy-substituted tetrahydropyridines and tetrahydroazepines.

1. Introduction

Numerous alkaloids containing piperidine and indolizidine ring systems, are found frequently in nature. Many of these substances display a wide range of interesting biological activities.[1,2] As a result, these alkaloids, which commonly contain a 2-hydroxymethyl-3-piperidinol moiety as a salient structural feature, have become important synthetic targets.[3] In a recent program aimed at uncovering new strategies for the preparation of these alkaloids, we developed a new method for preparing 2-piperidones starting with readily accessible 2-azetidinones.[4c] In addition, we showed that this method can be used in routes for the stereoselective synthesis of indolizidines[4a] and *prosopis* and *cassia* alkaloids.[4b]

This earlier effort provoked an interest in the chemistry of enantiomerically pure aziridines, which has been extensively probed in the context of the synthesis of various nitrogen containing compounds.[5] Owing to ring strain, regioselective and stereoselective ring-opening reactions of aziridines with various nucleophiles take place readily and in a stereochemically predictable manner. Adding to these attractive properties is the fact that ethyl (2*R*)- and (2*S*)-aziridine-2-carboxylate are readily available in optically pure forms.[6] These advantageous features led us to design novel strategies for the synthesis of tetrahydropyridin-3-ols (**A**) and tetrahydroazepin-3-ols (**B**), which are potentially versatile intermediates for asymmetric syntheses of various piperidine alkaloids and azasugars. The key steps in the new approaches we have designed for preparation of these targets involve (1) transformation of the carboxylate group in the aziridine-2-carboxylate **1** to form the olefin appended allyl-aziridines **G** or butenyl-aziridines **H**, (2) nucleophilic aziridine ring opening to form the respective amines **E** and **F**, (3) N-allylation processes to generate the corresponding dienes **C** and **D**, and (4) ring-closing metathesis to construct the six- and seven-membered heterocyclic targets (Scheme 1).

2. Results and discussion

The optically pure aziridine-2-carboxylate **1**, serving as the starting point in the approaches, is prepared via reaction of enantiomerically pure (*R*)-(+)-α-methylbenzylamine and ethyl 2,3-dibromopropionate by using the reported procedure.[6] Aziridine-2-carboxylate (2*R*)-**1** is transformed to the unsaturated ketone **3** by a two-step sequence involving addition of the lithium carbanion of methyl dimethylphosphonate followed by Horner–Wadsworth–Emmons olefination with acetaldehyde and the resulting β-ketophosphonate **2**[7] (Scheme 2). The effort to obtain the unsaturated ketone **3** from the reaction of Weinreb amide **8**[8a,11] and vinyl magnesium bromide was failed affording low yield of **3** and complex by-products.

Studies on the stereoselective reduction of the aziridinyl alkyl or aryl ketones with various reducing agents have been reported earlier by Lee et al.[8] In the current effort in

Keywords: Aziridine-2-carboxylate; Tetrahydropyridin-3-ol; Tetrahydro-1*H*-azepin-3-ol.
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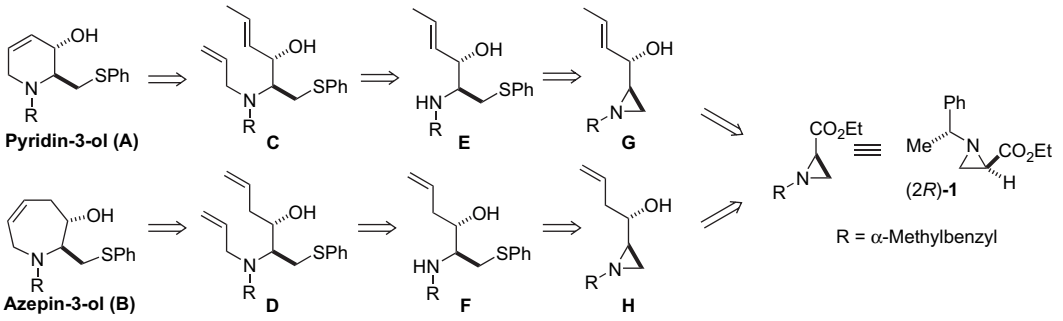
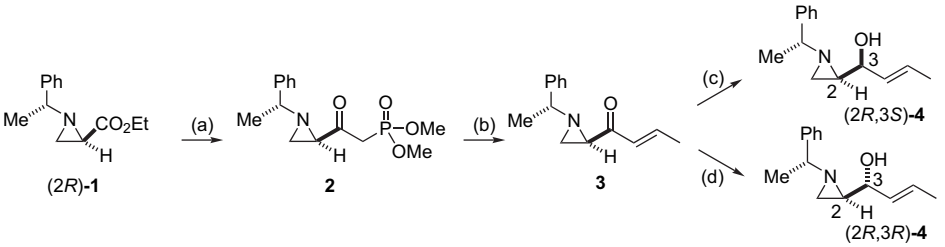
0040–4020/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2007.02.045



Scheme 1. Retrosynthetic analysis of the preparation of tetrahydropyridin-3-ol **A** and tetrahydroazepin-3-ol **B** from chiral aziridine-2-carboxylate **1**.

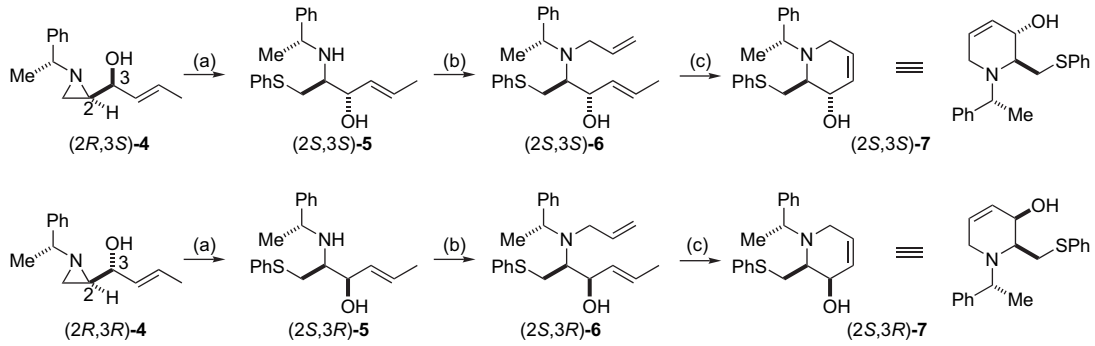


Scheme 2. (a) $CH_3PO(OMe)_2$, *n*-BuLi, −78 °C, 98%; (b) CH_3CHO, K_2CO_3, CH_3CN, rt, 75%; (c) $ZnCl_2$, $NaBH_4$, MeOH, −78 °C, 96%; and (d) L-Selectride, THF, −78 °C, 40%.

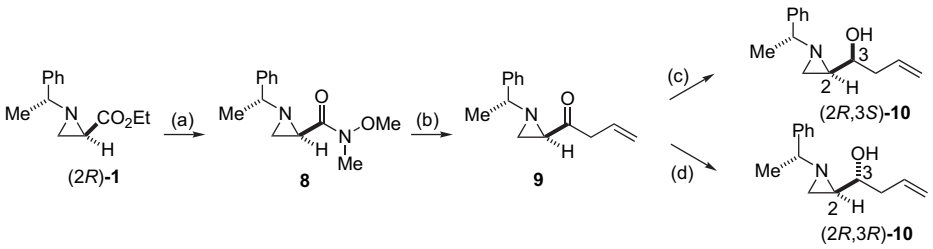
which a number of conditions were probed, we observed that treatment of aziridinyl vinyl ketone **3** with $NaBH_4/ZnCl_2$ in MeOH provides the *erythro* alcohol (2*R*,3*S*)-**4** in excellent yield (96%). The high level of stereochemical control attending this process was rationalized by using a chelation controlled hydride delivery model.[8a] Support for this proposal comes from the observation that reaction of **3** with the non-chelating bulky reducing agent, L-Selectride, provides the *threo* alcohol (2*R*,3*R*)-**4** exclusively. The low 40% yield of this process is due to the formation of over-reduced product that likely arises by initial 1,4-reduction.

A regioselective aziridine ring-opening reaction takes place when (2*R*,3*S*)-**4** is treated with thiophenol at room temperature in CH_2Cl_2. This process smoothly generates the β-amino alcohol **5** through attack of the thiolate at the less sterically hindered C-1 position of the aziridine ring.[9] It is reported that sterically congested amines similar to **5** with bulky substituent α-methylbenzyl group on nitrogen were resistant to intramolecular and intermolecular acylation reaction.[8c] But N-allylation of the resulting amino alcohol **5** with excess (4 equiv) allyl bromide and catalytic amount of $(n\text{-Bu})_4NI$ under reflux condition smoothly affords the bis-olefin **6** in 94% yield. Under the reaction condition no detectable amount of *N*,*O*-diallylated product was obtained. In accord with expectation, ring-closing metathesis[10] reaction of **6** (10 mol % of the first-generation Grubbs catalyst ($(Cy_3P)_2Cl_2Ru{=}CHPh$) in refluxing toluene) produces the desired (2*S*,3*S*)-1,2,3,6-tetrahydropyridin-3-ol (2*S*,3*S*)-**7** in modestly high yield (Scheme 3). The (2*S*,3*R*)-1,2,3,6-tetrahydropyridin-3-ol (2*S*,3*R*)-**7** diastereomer can also be prepared from the diastereomeric *threo* alcohol (2*R*,3*R*)-**4** by employing essentially the same procedure used for the conversion of (2*R*,3*S*)-**4** to (2*S*,3*S*)-**7**.

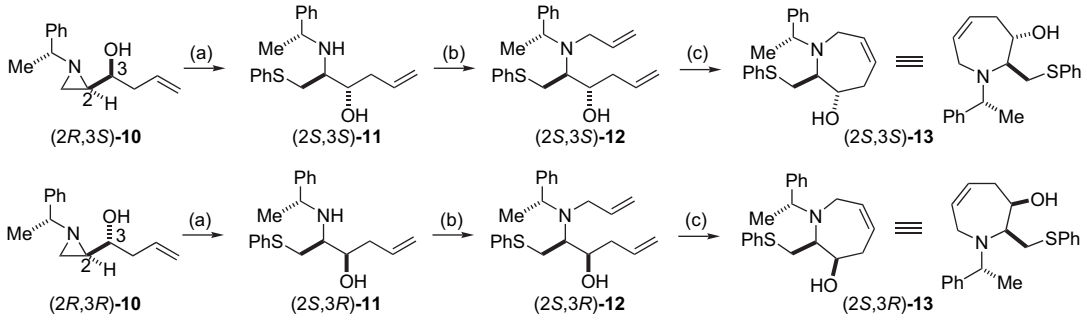
In a conceptually similar manner, we envisaged that the tetrahydroazepin-3-ol **B** could be prepared by a route starting with the allyl-ketone **9**,[8a] prepared from (2*R*)-aziridine-2-carboxylate ethyl ester (2*R*)-**1** by using the corresponding Weinreb amide **8**.[11] In practice, reaction of (2*R*)-**1** with *O*-methylhydroxylamine hydrochloride in the presence $AlMe_3$ provided the Weinreb amide **8** in 92% yield. Reaction



Scheme 3. (a) PhSH, CH_2Cl_2, rt, (2*S*,3*S*)-**5** (95%), (2*S*,3*R*)-**5** (83%); (b) allyl bromide, NaH, THF, cat. $(n\text{-Bu})_4NI$, reflux, (2*S*,3*S*)-**6** (94%), (2*S*,3*R*)-**6** (73%); and (c) $(Cy_3P)_2Cl_2Ru{=}CHPh$ (10 mol %), toluene, reflux, (2*S*,3*S*)-**7** (91%), (2*S*,3*R*)-**7** (74%).



Scheme 4. (a) CH_3NHOCH_3HCl, $AlMe_3$, CH_2Cl_2, rt, 92%; (b) allyl-MgBr, THF, −78 °C, 90%; (c) $ZnCl_2$, $NaBH_4$, MeOH, −78 °C, 90%; and (d) L-Selectride, THF, −78 °C, (70%).



Scheme 5. (a) PhSH, CH_2Cl_2, rt, (2*S*,3*S*)-**11** (85%), (2*S*,3*R*)-**11** (83%); (b) allylbromide, NaH, THF, cat. $(n\text{-Bu})_4NI$, reflux, (2*S*,3*S*)-**12** (90%), (2*S*,3*R*)-**12** (96%); and (c) second-generation Grubbs catalyst (10 mol %), toluene, reflux, (2*S*,3*S*)-**13** (90%), (2*S*,3*R*)-**13** (90%).

of **8** with allyl magnesium bromide affords ketone **9** (90%), which upon stereoselective, chelation controlled reduction with $ZnCl_2/NaBH_4$ in MeOH produces the *erythro* alcohol (2*R*,3*S*)-**10** (Scheme 4).[13] In contrast, reduction of **9** with L-Selectride produces the *threo* alcohol (2*R*,3*R*)-**10** exclusively and in good yield.[8]

Treatment of (2*R*,3*S*)-**10** with thiophenol leads to aziridine ring opening and exclusive formation of the β-amino alcohol **11** by way of attack of the thiolate anion at the less sterically hindered C-1 position.[9] N-Allylation of the amino alcohol **11** with excess allyl bromide and subsequent ring-closing metathesis of the resulting bis-olefin **12** with the second-generation Grubbs catalyst[12] smoothly produces (2*S*,3*S*)-2,3,4,7-tetrahydro-1*H*-azepin-3-ol (2*S*,3*S*)-**13** (Scheme 5). (2*S*,3*R*)-2,3,4,7-Tetrahydro-1*H*-azepin-3-ol (2*S*,3*R*)-**13** can also be generated from the diastereomeric alcohol (2*R*,3*R*)-**10** by using this same general protocol.

The strategies developed in this investigation are highly efficient and they provide ready access to enantiomerically pure, stereochemically defined, and highly functionalized 3-hydroxy-substituted tetrahydropyridines and tetrahydroazepines. Applications of these strategies to the preparation of biologically important piperidine alkaloids and azasugars are currently being pursued.

3. Experimental section

3.1. General

Flash column chromatographies were performed on silica gel (230–400 mesh, Merck). THF and Et_2O were refluxed over sodium in the presence of benzophenone and distilled prior to use. CH_2Cl_2 was distilled from calcium hydride. DMF, benzene, CH_3CN, MeOH, and toluene were dried, distilled, and stored under nitrogen. All other reagent grade chemicals obtained from commercial sources were used as received. Optically pure ethyl (2*R*)-1-[(1*R*)-1-phenylethyl]-aziridine-2-carboxylate [(2*R*)-**1**] was prepared from (*R*)-(+)-α-methyl-benzylamine and racemic ethyl-2,3-dibromopropionate as reported.[6]

3.1.1. {2-Oxo-2-[(2*R*)-1-(1*R*)-(1-phenylethyl)-aziridin-2-yl]ethyl}-phosphonic acid dimethyl ester (2). To a stirred solution of dimethyl methylphosphonate (4.8 ml, 44.62 mmol) in anhydrous THF (28 ml) at −78 °C, under an inert atmosphere of N_2 was added *n*-BuLi (2.5 M, 17.85 ml). After stirring at −78 °C for 30 min, a solution of ethyl (2*R*)-1-[(1*R*)-1-phenylethyl]-aziridine-2-carboxylate[6] [(2*R*)-**1**] (3.9 g, 17.85 mmol) in THF (12 ml) was added slowly. The reaction mixture was then stirred for 1 h at −78 °C and warmed to room temperature and stirred for an additional 15 min before being quenched with 10% acetic acid (25 ml). The reaction mixture was extracted with ethyl acetate (40 ml×2) and the combined organic layers were washed with saturated aqueous $NaHCO_3$ and brine, dried ($MgSO_4$), filtered, and concentrated in vacuo. Purification by flash chromatography afforded **2** as yellow oil (5.18 g, 98%).

Yield: 98%. Bright yellow oil. R_f 0.45 (only EtOAc); $[\alpha]_D^{28}$ +75.60 (*c* 0.79, $CHCl_3$); IR (KBr): 2959, 1711, 1258, 1043, 815, 703 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.40–7.25 (m, 5H), 3.80 (d, 6H, *J*=11.1 Hz), 3.28–3.05 (m, 2H), 2.62 (q, 1H, *J*=6.6 Hz), 2.37 (dd, 1H, *J*=3.0, 6.9 Hz), 2.23 (d, 1H, *J*=2.7 Hz), 1.73 (d, 1H, *J*=6.9 Hz), 1.44 (d, 3H, *J*=6.6 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 200, 143.54, 128.47, 127.42, 126.74, 69.35, 53.19,

53.14, 52.96, 52.91, 45.68, 45.66, 35.75, 34.69, 34.30, 23.22; HRMS (EI): Calcd for $C_{14}H_{20}NO_4P_1$, 297.1130 found, 297.1134.

3.1.2. (*E*)-1-{(2*R*)-1-[(1*R*)-1-Phenylethyl]-aziridin-2-yl}-2-buten-1-one (3). To a solution of **2** (1.18 g, 3.97 mmol) and powdered K_2CO_3 (1.65 g, 11.91 mmol) in CH_3CN (20 ml) at room temperature was added acetaldehyde (0.27 ml, 4.76 mmol) and stirred for an additional 24 h. The reaction mixture was quenched with 5% aqueous citric acid solution and extracted with methylene chloride (20 ml×3). The combined organic layers were washed with saturated aqueous $NaHCO_3$ and brine, dried ($MgSO_4$), filtered, and concentrated in vacuo. Purification by flash chromatography afforded **3** as colorless oil (0.6 g, 75%).

Yield: 75%. R_f 0.6 (Hexane–EtOAc 3:1); $[\alpha]_D^{21}$ +130.11 (*c* 1.0, $CHCl_3$); IR (KBr): 3060, 2968, 1687, 1628, 1443, 1319, 735 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.42–7.26 (m, 5H), 7.10–7.03 (m, 1H), 6.39 (dd, 1H, *J*=1.5, 15.3 Hz), 2.58 (q, 1H, *J*=6.6 Hz), 2.35 (dd, 1H, *J*=3.0, 6.9 Hz), 2.05 (d, 1H, *J*=2.7 Hz), 1.92 (dd, 3H, *J*=1.8, 6.9 Hz), 1.67 (d, 1H, *J*=6.9 Hz), 1.43 (d, 3H, *J*=6.6 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 197.08, 143.91, 128.40, 128.40, 127.28, 126.82, 126.82, 126.82, 126.68, 69.71, 44.45, 34.33, 23.31, 18.42; HRMS (EI): Calcd for $C_{14}H_{17}NO$, 215.1310 found, 215.1303.

3.1.3. 1-{(2*R*)-1-[(1*R*)-1-Phenylethyl]-aziridine}-2-carboxylic acid methoxy methyl amide (8). To a suspension of *N*,*O*-dimethylhydroxylamine·HCl (1.36 g, 13.68 mmol) in 20 ml of methylene chloride was added $AlMe_3$ (2 M, 6.84 ml, 13.68 mmol) under nitrogen at −10 °C and the solution was stirred for 30 min at room temperature. A solution of ethyl (2*R*)-1-[(1*R*)-1-phenylethyl]-aziridine-2-carboxylate [(2*R*)-**1**)] (1.00 g, 4.56 mmol) in methylene chloride (5 ml) was added slowly at −10 °C. The reaction mixture was stirred for 2 h at room temperature and quenched carefully by water. After extraction with methylene chloride (30 ml×3), the combined organic layers were dried ($MgSO_4$), filtered, and concentrated in vacuo. Purification by fast washing through a short pad of silica gel yielded pure **8** as a white solid.

Yield: 92%. Mp: 72–75 °C. R_f 0.25 (Hexane–EtOAc 1:1); $[\alpha]_D^{21}$ +107.22 (*c* 1.02, $CHCl_3$); IR (KBr): 2973, 1679, 1450, 1329, 1170, 1088, 1007, 766, 702 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.44–7.21 (m, 5H), 3.82 (s, 3H), 3.26 (s, 3H), 2.69–2.67 (m, 1H), 2.62 (q, 1H, *J*=6.6 Hz), 2.19–2.17 (m, 1H), 1.58 (d, 1H, *J*=6.4 Hz), 1.49 (d, 3H, *J*=7.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.42, 143.72, 128.32, 128.15, 127.41, 127.20, 126.99, 70.12, 61.82, 35.89, 33.62, 32.67, 23.31; HRMS (EI): Calcd for $C_{13}H_{18}N_2O_2$, 234.1368 found, 234.1360.

3.1.4. 1-{(2*R*)-1-[(1*R*)-1-Phenylethyl]-aziridin-2-yl}-3-buten-1-one (9). To the solution of **8** (1.98 g, 8.45 mmol) in 40 ml of THF under nitrogen at −78 °C was added Allyl-MgBr (1.0 M, 16.9 ml, 16.9 mmol). The solution was stirred for 30 min at −78 °C. After the solution was warmed to room temperature, 50 ml of aqueous NH_4Cl was added and the organic layer was separated. The aqueous layer was extracted with methylene chloride (40 ml×3) and the combined organic extracts were dried ($MgSO_4$), filtered, and concentrated in vacuo. Purification by flash chromatography afforded **9** as brown oil.

Yield: 90%. R_f 0.4 (Hexane–EtOAc 5:1); $[\alpha]_D^{22}$ +112.4 (*c* 0.99, $CHCl_3$); IR (KBr): 2980, 2384, 2284, 1711, 795, 701, 406 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 7.41–7.26 (m, 5H), 6.05–5.84 (m, 1H), 5.21–5.12 (m, 2H), 3.32 (dd, 1H, *J*=7.0, 17.0 Hz), 3.10 (dd, 1H, *J*=7.0, 17.0 Hz), 2.56 (q, 1H, *J*=6.6 Hz), 2.27 (dd, 1H, *J*=3.0, 6.2 Hz), 2.08 (d, 1H, *J*=3.0 Hz), 1.67 (d, 1H, *J*=7.0 Hz), 1.42 (d, 3H, *J*=6.6 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 207.01, 143.93, 130.65, 128.55, 127.45, 126.89, 126.85, 118.85, 69.67, 53.65, 45.12, 42.35, 34.66, 23.45; HRMS (EI): Calcd for $C_{14}H_{17}NO$, 215.1310 found, 215.1308.

3.2. Representative procedure for $NaBH_4$ reduction of 3 or 9

To the solution of **3** (1.00 g, 4.64 mmol) in MeOH (30 ml) at −78 °C was added $ZnCl_2$ (0.95 g, 6.97 mmol). The solution was stirred for 30 min, and $NaBH_4$ (358 mg, 9.28 mmol) was added at −78 °C. The mixture was stirred for an additional 1 h at −78 °C before being quenched with water (30 ml). The reaction mixture was extracted with methylene chloride (30 ml×3) and the combined organic layers were dried ($MgSO_4$), filtered, and concentrated in vacuo. Purification by flash chromatography afforded (2*R*,3*S*)-**4** (0.96 g, 96%) as colorless oil.

3.2.1. (1*S*,2*E*)-1-{(2*R*)-1-[(1*R*)-1-Phenylethyl]-aziridin-2-yl}-2-buten-1-ol [(2*R*,3*S*)-4]. Yield: 96% (colorless oil). R_f 0.2 (Hexane–EtOAc 4:1); $[\alpha]_D^{25}$ +140.40 (*c* 1.0, $CHCl_3$); IR (KBr): 3388, 2970, 1449, 1372, 1078, 973, 701 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.38–7.25 (m, 5H), 5.85–5.78 (m, 1H), 5.45 (dd, 1H, *J*=7.2, 15 Hz), 4.25 (dd, 1H, *J*=3.0, 7.2 Hz), 2.77 (br, 1H), 2.64 (q, 1H, *J*=6.5 Hz), 1.79–1.72 (m, 5H), 1.41 (d, 3H, *J*=6.6 Hz), 1.29 (d, 1H, *J*=6.3 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.59, 130.87, 128.88, 128.54, 127.28, 126.89, 69.93, 68.75, 42.84, 29.11, 23.74, 18.04; HRMS (EI): Calcd for $C_{14}H_{19}NO$, 217.1467 found, 217.1469.

3.2.2. (1*S*,2*E*)-1-{(2*R*)-1-[(1*R*)-1-Phenylethyl]-aziridin-2-yl}-3-buten-1-ol [(2*R*,3*S*)-10]. Yield: 90% (colorless oil). R_f 0.3 (Hexane–EtOAc 5:1); $[\alpha]_D^{19}$ +98.71 (*c* 0.694, $CHCl_3$); IR (KBr): 3442, 2974, 2389, 1641, 1451, 1302, 1075, 914, 772, 735, 700 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.37–7.23 (m, 5H), 5.96–5.87 (m, 1H), 5.21–5.11 (m, 2H), 3.85–3.79 (m, 1H), 2.91 (br, 1H), 2.65 (q, 1H, *J*=6.6 Hz), 2.33 (t, 2H, *J*=7 Hz), 1.78–1.76 (m, 2H), 1.41 (d, 3H, *J*=6.6 Hz), 1.30 (d, 1H, *J*=6 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.56, 134.63, 128.54, 127.28, 126.87, 117.83, 69.01, 68.74, 42.70, 39.62, 29.58, 23.66; HRMS (EI): Calcd for $C_{14}H_{19}NO$, 217.1467 found, 217.1460.

3.3. Representative procedure for L-Selectride reduction of 3 or 9

To the solution of **3** (0.4 g, 1.86 mmol) in anhydrous THF (10 ml) at −78 °C was added dropwise L-Selectride® (1 M in THF, 5.6 ml, 5.6 mmol), and stirred for 4 h at −78 °C.

After the solution was warmed to room temperature, 10 ml of aqueous 10% NaOH solution was added. The reaction mixture was extracted with methylene chloride (10 ml× 3) and the combined organic extracts were dried ($MgSO_4$), filtered, and concentrated in vacuo. Purification by flash chromatography afforded (2*R*,3*R*)-**4** as brown oil (163 mg, 40%).

3.3.1. (1*R*,2*E*)-1-{(2*R*)-1-[(1*R*)-1-Phenylethyl]-aziridin-2-yl}-2-buten-1-ol [(2*R*,3*R*)-4]. Yield: 40% (brown oil). R_f 0.2 (Hexane–EtOAc 4:1); $[\alpha]_D^{23}$ +4.23 (*c* 0.92, $CHCl_3$); IR (KBr): 2969, 1451, 1377, 1219, 1088, 964, 772, 700 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.40–7.19 (m, 5H), 5.58 (dq, 1H, *J*=6.4, 15.0 Hz), 5.19 (dd, 1H, *J*=1.6, 15.0 Hz), 3.89 (t, 1H, *J*=7.8 Hz), 3.78 (q, 1H, *J*=6.4 Hz), 3.29–3.20 (m, 1H), 3.10–2.99 (m, 1H), 2.53–2.43 (m, 1H), 1.61 (dd, 3H, *J*=1.6, 6.4 Hz), 1.21 (d, 3H, *J*=6.4 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) 144.62, 131.02, 128.90, 128.53, 127.33, 126.71, 61.47, 69.06, 44.01, 30.95, 23.89, 18.19; HRMS (EI): Calcd for $C_{14}H_{19}NO$, 217.1467 found, 217.1461.

3.3.2. (1*R*,2*E*)-1-{(2*R*)-1-[(1*R*)-1-Phenylethyl]-aziridin-2-yl}-3-buten-1-ol [(2*R*,3*R*)-10]. Yield: 70% (slightly yellow oil). R_f 0.7 (Hexane–EtOAc 1:1); $[\alpha]_D^{19}$ +65.82 (*c* 0.404, $CHCl_3$); IR (KBr): 3415, 3063, 2974, 2928, 2360, 1451, 1375, 1070, 961, 913, 781, 710, 560 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.38–7.32 (m, 4H), 7.28 (t, 1H, *J*=1 Hz), 5.96–5.87 (m, 1H), 5.20–5.12 (m, 2H), 3.47–3.43 (m, 1H), 2.55 (q, 1H, *J*=6.5 Hz), 2.47–2.36 (m, 3H), 1.76–1.71 (m, 3H), 1.45 (d, 3H, *J*=7 Hz), 1.37 (d, 1H, *J*=3.7 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.59, 134.78, 128.56, 127.29, 126.92, 117.65, 70.54, 69.05, 43.55, 40.79, 31.42, 23.81; HRMS (EI): Calcd for $C_{14}H_{19}NO$, 217.1467 found, 217.1469.

3.4. Representative procedure for aziridine ring-opening reaction of 4 or 10

To the solution of (2*R*,3*S*)-**4** (225 mg, 1.03 mmol) in methylene chloride (5 ml) was added thiophenol (0.35 ml, 3.11 mmol) and stirred for 24 h at room temperature. After completion of the reaction, the reaction mixture was concentrated in vacuo and the residue was purified by flash chromatography affording (2*S*,3*S*)-**5** as an oil (322 mg, 95%).

3.4.1. (2*S*,3*S*,4*E*)-2-[(1*R*)-1-Phenylethylamino]-1-phenylsulfanyl-4-hexen-3-ol [(2*S*,3*S*)-5]. Yield: 95% (slightly yellow oil). R_f 0.5 (Hexane–EtOAc 4:1); $[\alpha]_D^{21}$ +31.99 (*c* 0.84, $CHCl_3$); IR (KBr): 3422, 3059, 2904, 1480, 1439, 1125, 1087, 970, 738, 703 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.26–7.11 (m, 10H), 5.75–5.63 (m, 1H), 5.34 (dd, 1H, *J*=6.0, 15.6 Hz), 4.30 (br, 1H), 3.86 (q, 1H, *J*=6.6 Hz), 3.30 (br, 1H), 3.03 (dd, 1H, *J*=4.5, 13.8 Hz), 2.79 (dd, 1H, *J*=9.0, 13.8 Hz), 2.64–2.58 (m, 1H), 1.68 (d, 3H, *J*=6.6 Hz), 1.35 (d, 3H, *J*=6.6 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.77, 135.70, 129.22, 129.14, 128.87, 128.52, 128.16, 127.07, 126.45, 126.08, 70.14, 57.06, 54.94, 34.03, 24.48, 17.90; HRMS (ESI, MH^+): Calcd for $C_{20}H_{26}NOS$, 328.1735 found, 328.1731.

3.4.2. (2*S*,3*R*,4*E*)-2-[(1*R*)-1-Phenylethylamino]-1-phenylsulfanyl-4-hexen-3-ol [(2*S*,3*R*)-5]. Yield: 83% (slightly yellow oil). R_f 0.7 (MC–MeOH 10:1); $[\alpha]_D^{24}$ +34.80 (*c* 1.0, $CHCl_3$); IR (KBr): 3356, 2965, 2388, 1488, 1439, 969, 740, 703 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.27–7.18 (m, 10H), 5.66 (dq, 1H, *J*=6.2, 15.0 Hz), 5.42 (dd, 1H, *J*=7.0, 15.0 Hz), 3.88–3.80 (m, 2H), 3.02–2.94 (m, 2H), 2.74 (q, 1H, *J*=6.5 Hz), 1.71 (d, 3H, *J*=6.5 Hz), 1.64 (dd, 1H, *J*=7.2, 15.6 Hz), 1.33 (d, 3H, *J*=6.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 145.60, 136.51, 131.40, 129.81, 129.59, 129.39, 129.35, 129.13, 128.76, 128.73, 127.41, 126.74, 126.41, 72.82, 59.23, 56.63, 36.26, 23.85, 18.10; HRMS (ESI, MH^+): Calcd for $C_{20}H_{26}NOS$, 328.1735 found, 328.1740.

3.4.3. (2*S*,3*S*)-2-[(1*R*)-1-Phenylethylamino]-1-phenylsulfanyl-5-hexen-3-ol [(2*S*,3*S*)-11]. Yield: 85% (slightly yellow oil). R_f 0.5 (Hexane–EtOAc 5:1); $[\alpha]_D^{23}$ +67.08 (*c* 0.6, $CHCl_3$); IR (KBr): 3403, 2917, 2360, 1583, 1480, 993, 911, 780, 689 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.26–7.12 (m, 10H), 5.80–5.63 (m, 1H), 5.10–5.99 (m, 2H), 3.88–3.76 (m, 2H), 3.11 (dd, 1H, *J*=3.6, 2.8 Hz), 2.86–2.74 (m, 1H), 2.58–2.49 (m, 1H), 2.35–2.02 (m, 2H), 1.35 (d, 3H, *J*=6.6 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.79, 135.62, 134.96, 129.65, 129.08, 128.67, 127.21, 126.64, 126.41, 117.41, 68.85, 55.61, 54.85, 37.01, 33.70, 24.75. HRMS (EI): Calcd for $C_{20}H_{25}NOS$, 327.1657 found, 327.1663.

3.4.4. (2*S*,3*R*)-2-[(1*R*)-1-Phenylethylamino]-1-phenylsulfanyl-5-hexen-3-ol [(2*S*,3*R*)-11]. Yield: 83% (colorless oil). R_f 0.7 (Hexane–EtOAc 1:1); $[\alpha]_D^{30}$ +32.22 (*c* 0.69, $CHCl_3$); IR (KBr): 2930, 2373, 1748, 1456, 766, 701 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.29–7.14 (m, 10H), 5.88–5.82 (m, 1H), 5.11 (d, 1H, *J*=1.5 Hz), 5.08 (s, 1H), 3.83 (q, 1H, *J*=6.5 Hz), 3.64–3.60 (m, 1H), 3.02–2.94 (m, 2H), 2.72 (q, 1H, *J*=5.5 Hz), 2.37–2.34 (m, 1H), 2.27–2.23 (m, 1H), 1.32 (d, 3H, *J*=7.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 145.69, 136.29, 135.15, 129.59, 129.17, 128.78, 127.46, 126.76, 126.38, 117.54, 70.72, 57.84, 56.99, 38.97, 36.25, 23.99; HRMS (ESI, MH^+): Calcd for $C_{20}H_{26}NOS$, 328.1735 found, 328.1740.

3.5. Representative procedure for allylation of 5 or 11

To the suspension of NaH (55% in mineral oil, 33 mg, 0.75 mmol) in THF (1 ml) at 0 °C was added slowly (2*S*,3*S*)-**5** (93 mg, 0.28 mmol) in THF (2 ml). After stirring for 30 min at 0 °C, a solution of $(n\text{-}Bu)_4NI$ (21 mg, 0.06 mmol) and allyl bromide (0.097 ml, 1.13 mmol) in THF (4 ml) was added dropwise and the reaction mixture was warmed to room temperature. The reaction mixture was heated to reflux for 5 h and cooled to room temperature. Saturated aqueous NH_4Cl was added to the reaction mixture and extracted with ethyl acetate (10 ml×3). The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated in vacuo. Purification by flash chromatography afforded (2*S*,3*S*)-**6** as an oil (98 mg, 94%).

3.5.1. (2*S*,3*S*,4*E*)-2-Allyl-[(1*R*)-1-phenylethylamino]-1-phenylsulfanyl-4-hexen-3-ol [(2*S*,3*S*)-6]. Yield: 94% (slightly yellow oil). R_f 0.7 (Hexane–EtOAc 5:1); $[\alpha]_D^{24}$ +1.94 (*c* 0.72, $CHCl_3$); IR (KBr): 2977, 2687, 1693, 1572, 1440, 1303, 1084, 744, 703 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.34–7.11 (m, 10H), 5.92–5.81 (m, 1H),

5.70–5.59 (m, 1H), 5.38 (dd, 1H, *J*=7.8 Hz), 5.27–5.13 (m, 2H), 4.04 (dd, 1H, *J*=4.8 Hz), 3.95 (d, 2H, *J*=6.6 Hz), 3.77 (dd, 1H, *J*=4.8, 12.9 Hz), 2.93 (d, 2H, *J*=6.0 Hz), 2.75 (q, 1H, *J*=4.2 Hz), 1.72 (d, 3H, *J*=6.3 Hz), 1.31(d, 3H, *J*=6.6 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 145.99, 137.42, 135.32, 130.56, 129.00, 128.87, 128.75, 128.49, 127.22, 127.02, 125.65, 116.69, 80.18, 69.50, 58.22, 56.31, 35.88, 25.12, 18.11; HRMS (ESI, MH^+): Calcd for $C_{23}H_{30}NOS$, 368.2048 found, 368.2055.

3.5.2. (2*S*,3*R*,4*E*)-2-Allyl-[(1*R*)-1-phenylethylamino]-1-phenylsulfanyl-4-hexen-3-ol [(2*S*,3*R*)-6]. Yield: 73% (slightly yellow oil). R_f 0.7 (Hexane–EtOAc 5:1); $[\alpha]_D^{21}$ −9.99 (*c* 0.08, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.34–7.06 (m, 10H), 5.86–5.81 (m, 1H), 5.69 (dd, 1H, *J*=6.5, 15.4 Hz), 5.46 (ddd, 1H, *J*=1.5, 7.5, 17.0 Hz), 5.22–5.11 (m, 2H), 4.07–3.97 (m, 2H), 3.89 (q, 1H, *J*=6.0 Hz), 3.73 (dd, 1H, *J*=6.1 Hz), 3.09 (dd, 1H, *J*=6.1 Hz), 2.79–2.71 (m, 2H), 1.75 (d, 3H, *J*=6.5 Hz), 1.29 (d, 3H, *J*=6.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 146.04, 137.15, 135.31, 130.13, 128.89, 128.74, 128.67, 128.53, 127.19, 127.11, 125.51, 116.53, 79.93, 69.54, 58.06, 56.99, 35.58, 24.88, 18.16; HRMS (ESI, MH^+): Calcd for $C_{23}H_{30}NOS$, 368.2048 found, 368.2051.

3.5.3. (2*S*,3*S*)-2-Allyl-[(1*R*)-1-phenylethyl]amino-1-phenylsulfanyl-5-hexen-3-ol [(2*S*,3*S*)-12]. Yield: 90%. Yellow oil. R_f 0.6 (Hexane–EtOAc 10:1); $[\alpha]_D^{21}$ +29.96 (*c* 1.19, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.28–7.15 (m, 10H), 5.98–5.61 (m, 2H), 5.29–4.95 (m, 4H), 4.11–3.96 (m, 2H), 3.93–3.83 (m, 1H), 3.61–3.53 (m, 1H), 3.07–3.93 (m, 2H), 2.80–2.72 (m, 1H), 2.61–2.15 (m, 2H), 1.31 (d, 3H, *J*=6.6 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 145.94, 135.23, 135.14, 130.33, 129.17, 128.24, 126.89, 126.72, 116.55, 116.05, 80.27, 72.10, 69.17, 69.07, 57.66, 55.84, 24.87, 17.85; HRMS (EI): Calcd for $C_{23}H_{29}NOS$, 367.1970 found, 367.1978.

3.5.4. (2*S*,3*R*)-2-Allyl-[(1*R*)-1-phenylethyl]amino-1-phenylsulfanyl-5-hexen-3-ol [(2*S*,3*R*)-12]. Yield: 96%. Yellow oil. R_f 0.5 (Hexane–EtOAc 10:1); $[\alpha]_D^{21}$ +37.66 (*c* 0.43, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29–7.25 (m, 5H), 7.23–7.22 (m, 1H), 7.17–7.08 (m, 4H), 5.82–5.76 (m, 2H), 5.18–5.03 (m, 4H), 3.89 (dd, 1H, *J*=7.0, 12.6 Hz), 3.80 (q, 1H, *J*=6.7 Hz), 3.77 (dd, 1H, *J*=5.6, 12.5 Hz), 3.68–3.66 (m, 1H), 3.06 (dd, 1H, *J*=6.7, 13.0 Hz), 2.81 (dd, 1H, *J*=6.6, 13.0 Hz), 2.70 (td, 1H, *J*=2.8, 6.7 Hz), 2.48–2.47 (m, 1H), 2.33–2.30 (m, 1H), 1.27 (d, 3H, *J*=6.6 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 146.01, 136.37, 135.77, 135.25, 129.23, 128.97, 128.60, 127.20, 127.01, 125.91, 117.07, 117.00, 71.45, 56.44, 55.28, 35.06, 34.79, 29.92, 24.66; HRMS (ESI, MH^+): Calcd for $C_{23}H_{30}NOS$, 368.2048 found, 368.2042.

3.6. Representative procedure for RCM reaction of 6

To the solution of (2*S*,3*S*)-**6** (48 mg, 0.13 mmol) in toluene (3 ml) was added first-generation Grubbs catalyst (10 mol %) and refluxed for 3 h with stirring. After completion of the reaction by TLC, the reaction mixture was cooled to room temperature and concentrated in vacuo and the residue was purified by flash chromatography affording (2*S*,3*S*)-**7** (39 mg, 91%) as an oil.

3.6.1. (2*S*,3S)-1-[(1*R*)-1-Phenylethyl]-2-phenylsulfanylmethyl-1,2,3,6-tetrahydropyridin-3-ol [(2*S*,3*S*)-7]. Yield: 91%. Yellow oil. R_f 0.45 (Hexane–EtOAc 10:1); $[\alpha]_D^{25}$ +40.25 (*c* 0.77, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31–7.11 (m, 10H), 6.00–5.98 (m, 1H), 5.74–5.71 (m, 1H), 5.12–5.09 (m, 1H), 4.69–4.64 (m, 2H), 3.99 (q, 1H, *J*=6.6 Hz), 2.95–2.86 (m, 2H), 2.78–2.75 (m, 1H), 1.33 (d, 3H, *J*=6.6 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 145.53, 136.75, 128.94, 128.77, 128.37, 128.14, 127.08, 126.90, 125.69, 86.35, 75.70, 57.13, 55.81, 35.41, 25.02; HRMS (ESI, MH^+): Calcd for $C_{20}H_{23}NOS$, 326.1573 found, 326.1585.

3.6.2. (2*S*,3*R*)-1-[(1*R*)-1-Phenylethyl]-2-phenylsulfanylmethyl-1,2,3,6-tetrahydropyridin-3-ol [(2*S*,3*R*)-7]. Yield: 74%. Brown oil; $[\alpha]_D^{22}$ +94.21 (*c* 0.66, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31–7.22 (m, 5H), 7.14–7.07 (m, 3H), 7.02 (d, 2H, *J*=7.3 Hz), 6.01–5.99 (m, 1H), 5.88–5.87 (m, 1H), 5.16 (s, 1H, br), 4.72–4.70 (m, 1H), 4.68–4.64 (m, 1H), 3.87 (q, 1H, *J*=6.5 Hz), 2.99 (dd, 1H, *J*=7.0, 13.6 Hz), 2.84 (dd, 1H, *J*=6.8, 13.6 Hz), 2.74 (td, 1H, *J*=3.1, 6.9 Hz), 1.72 (s, 1H, br), 1.28 (d, 3H, *J*=6.6 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 145.83, 136.60, 128.99, 128.60, 128.30, 128.14, 127.69, 127.17, 127.10, 125.54, 87.03, 76.05, 57.29, 56.81, 35.79, 25.06; HRMS (ESI, MH^+): Calcd for $C_{20}H_{23}NOS$, 326.1573 found, 326.1581.

3.7. Representative procedure for RCM reaction of 12

To the solution of (2*S*,3*S*)-**12** (48 mg, 0.13 mmol) in toluene (5 ml) was added second-generation Grubbs catalyst (10 mol %) and refluxed for 3 h with stirring. After completion of the reaction by TLC, the reaction mixture was cooled to room temperature and concentrated in vacuo and the residue was purified by flash chromatography affording (2*S*,3*S*)-**7** (40 mg, 90%) as an oil.

3.7.1. (2*S*,3*S*)-1-[(1*R*)-1-Phenylethyl]-1-phenylsulfanylmethyl-2,3,4,7-tetrahydro-1*H*-azepin-3-ol [(2*S*,3*S*)-13]. Yield: 90%. yellow oil. R_f 0.5 (Hexane–EtOAc 10:1); $[\alpha]_D^{25}$ −8.80 (*c* 0.2, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30–7.7.12 (m, 10H), 5.83–5.79 (m, 1H), 5.71–5.69 (m, 1H), 4.18–4.07 (m, 2H), 3.89 (q, 1H, *J*=6.5 Hz), 3.68–3.64 (m, 1H), 3.08 (dd, 1H, *J*=6.8, 13.5 Hz), 3.00 (dd, 1H, *J*=4.7, 13.7 Hz), 2.77–2.74 (m, 1H), 2.18–2.15 (m, 1H), 1.96–1.91 (m, 1H), 1.33 (d, 3H, *J*=6.6 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 146.01, 136.97, 129.45, 128.97, 128.54, 127.10, 127.04, 126.47, 125.99, 124.54, 73.81, 66.49, 57.78, 56.05, 35.41, 29.90, 27.47, 24.63; HRMS (ESI, MH^+): Calcd for $C_{21}H_{25}NOS$, 340.1730 found, 340.1726.

3.7.2. (2*S*,3*R*)-1-[(1*R*)-1-Phenylethyl]-1-phenylsulfanylmethyl-2,3,4,7-tetrahydro-1*H*-azepin-3-ol [(2*S*,3*R*)-13]. Yield: 90%. Brown oil. R_f 0.25 (Hexane–EtOAc 5:1); $[\alpha]_D^{23}$ −24.21 (*c* 0.64, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.35–7.04 (m, 10H), 5.87–5.82 (m, 1H), 5.71–5.69 (m, 1H), 4.20–4.05 (m, 2H), 3.87–3.82 (m, 2H), 3.05 (dd, 1H, *J*=7.8, 13.5 Hz), 2.87 (dd, 1H, *J*=5.1, 13.2 Hz), 2.73–2.67 (m, 1H), 1.31 (d, 3H, *J*=6.6 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 128.98, 128.65, 128.58, 127.18, 127.10, 126.42, 73.44, 66.50, 60.58, 58.11, 34.81, 21.81, 21.24, 14.39;

HRMS (ESI, MH^+): Calcd for $C_{21}H_{25}NOS$, 340.1730 found, 340.1728.

Acknowledgements

We would like to thank the Ministry of Science and Technology of Korea for financial support of these studies.

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13. Stereoselective reduction of the diastereomeric (2*S*)-**9** was reported under the same reaction condition.[8a]