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Application of new chiral auxiliaries, *trans*-2-(*N*-arylsulfonyl-*N*-benzyl)cyclohexanols, in an asymmetric radical cyclization

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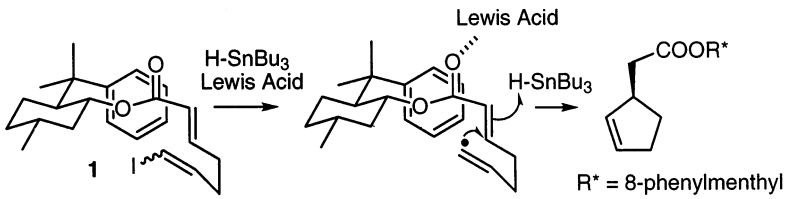
Abstract

New chiral auxiliaries, *trans*-2-(*N*-arylsulfonyl-*N*-benzyl)cyclohexanols, were prepared and applied to an asymmetric radical cyclization. © 2000 Elsevier Science Ltd. All rights reserved.

1. Introduction

There have been important recent advances in radical chemistry, particularly in asymmetric synthesis.[1] We have reported a synthesis of chiral cycloalkenyl acetic acids using diastereoselective radical cyclization with 8-phenylmenthol as the chiral auxiliary (Scheme 1).[2] In this reaction, the presence of a bulky Lewis acid such as methylaluminum bis(2,6-di-*t*-butyl-4-methylphenoxide) (MAD)[3] is essential for high selectivity.



Scheme 1.

8-Phenylmenthol is a cyclohexanol-type chiral auxiliary, and is widely used in asymmetric synthesis. Both enantiomers are now commercially available and the synthesis of 8-phenylmenthol and its analogs have also been reported.[4–6] Although several other cyclohexanol-type chiral auxiliaries are commercially available, we needed a new cyclohexanol-type chiral auxiliary which can be systematically tuned to adjust its asymmetrical circumstances with regard to both steric

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and electronic characteristics. Therefore we designed new chiral cyclohexanols which have a *trans*-amino group at the 2-position. Depending on the two substituents at the amino group, both electronic and steric characteristics can be tuned (Fig. 1).

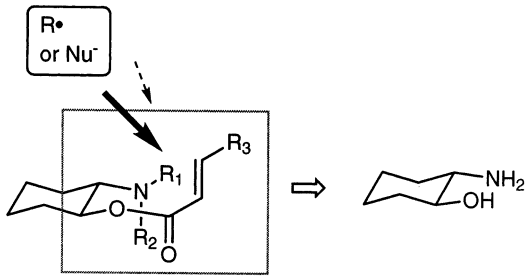
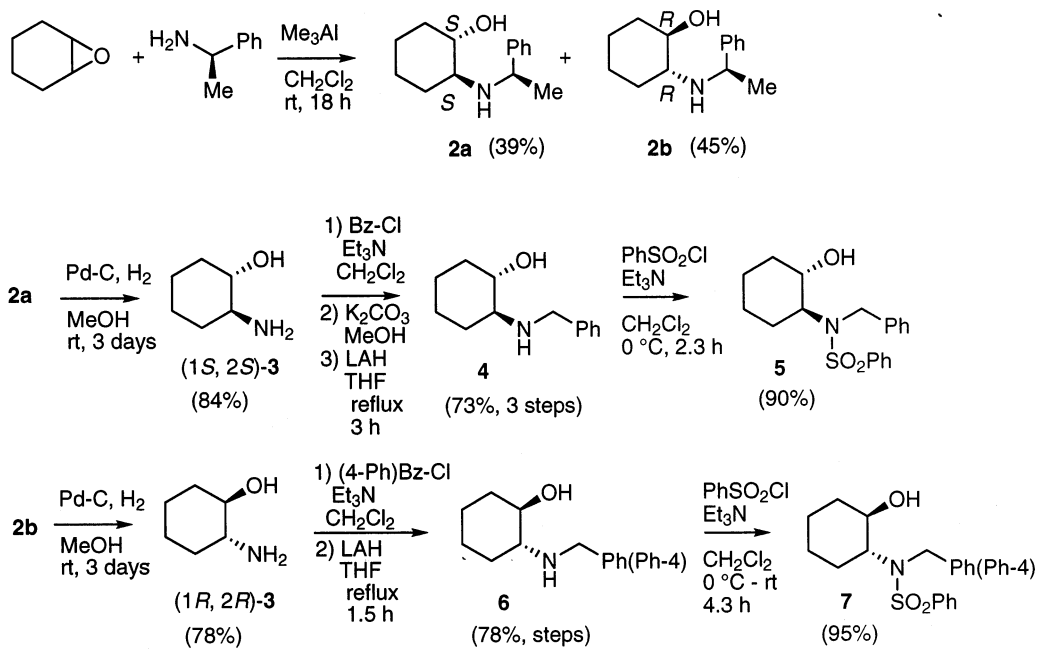


Figure 1. New chiral auxiliary based on *trans*-aminocyclohexanol

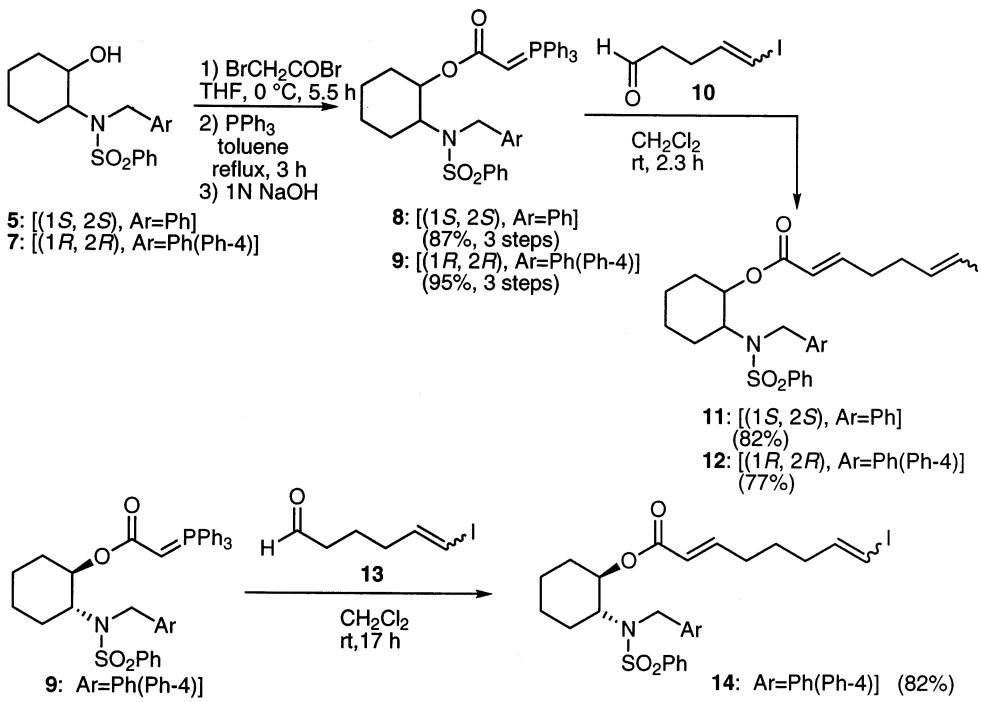
2. Results and discussion

Chiral *trans*-2-aminocyclohexanol can be readily obtained by several methods: (1) resolution of racemic compounds as salts of tartaric acid,[7] (2) ring-opening reaction of cyclohexene oxide by chiral methylbenzylamine resulting in diastereomers that can be separated and debenzylated,[8] and (3) the same ring-opening reaction by TMS-azide in the presence of chiral chromium complex followed by reduction.[9] We chose the second method because it was suitable for synthesizing both enantiomers in enantiomerically pure form (Scheme 2).



Scheme 2.

According to the procedure reported by Overman, cyclohexene oxide was reacted with (+)-*R*-(1-phenylethyl)amine in the presence of trimethylaluminum in dichloromethane to give two diastereomeric *trans*-2-(1-phenylethyl)aminocyclohexanols (**2a** and **2b**), which were easily separated by standard column chromatography. The stereochemistry of both **2a** and **2b** was determined by comparison with reported spectral data. The phenylethyl group of **2a** was removed by hydrogenolysis to give (1*S*,2*S*)-**3**, which was converted to benzenesulfonamide **5** via **4**. Using the same method, **2b** was converted to sulfonamide **7**, which has a 4-phenylbenzyl group on nitrogen and was expected to show higher selectivity. Both **5** and **7** were converted to iodo esters **11**, **12** and **14** as reported previously[2a] (Scheme 3).



Scheme 3.

The conformation of the substrates in solution was studied before the radical reaction. Chemical shifts obtained from ^{1}H NMR studies of **12** and **14** are shown in Fig. 2, in comparison to an achiral substrate. Olefinic protons in **12** and **14** appeared slightly downfield. These results showed that neighboring aromatic rings should be situated near the π-face of an unsaturated ester group.[10] The same conclusion was supported by NOE studies of crotonate of (1*R*,2*R*)-**3** (Fig. 3). Therefore, we expected that this new auxiliary might be effective for diastereoselective radical cyclization through a transition state, as shown in Fig. 1.

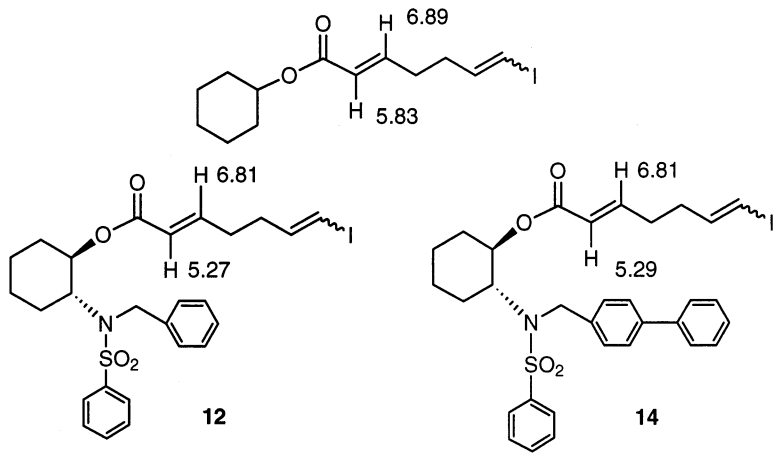


Figure 2. Chemical shifts of chiral and achiral esters in the ^{1}H NMR spectrum

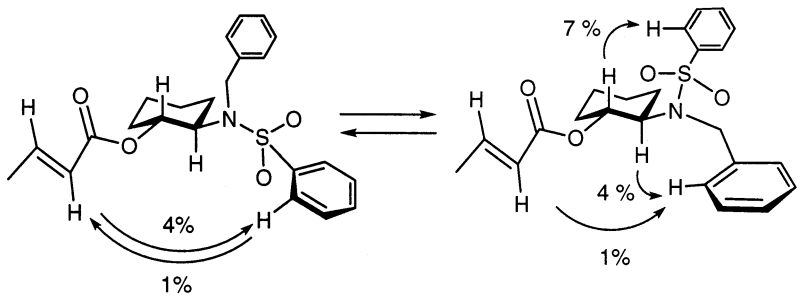
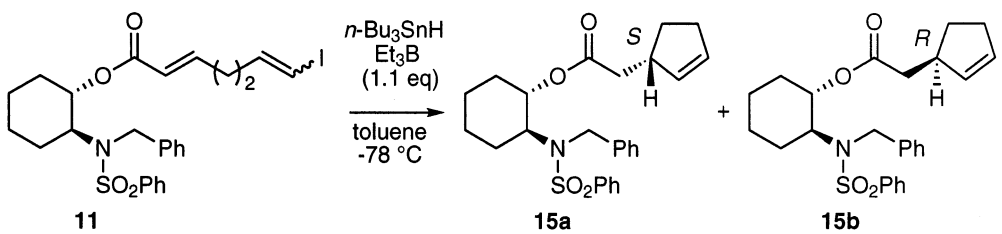


Figure 3. NOE experiments using crotonate of (1*R*,2*R*)-**3**

When **11** was reacted with 1.6 equiv. of *n*-Bu_3SnH in the presence of 1.1 equiv. of Et_3B at −78°C under aerobic conditions for 25 min, cyclized product **15** was obtained in quantitative yield (Table 1, run 1). However, no diastereoselectivity was observed. The diastereoselectivity was determined as discussed below.

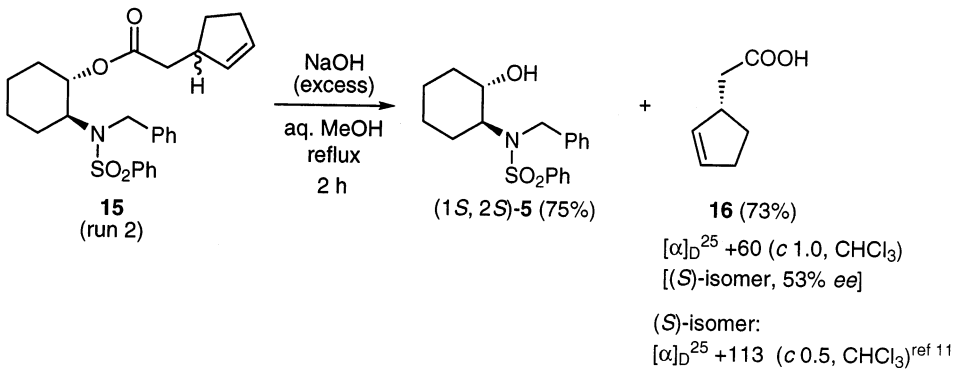
Table 1
Radical cyclization of **11**



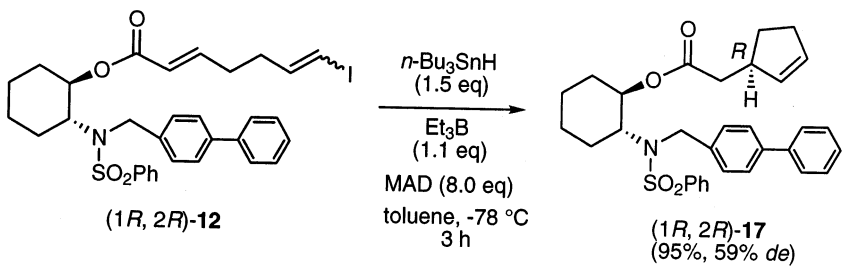
Run	**11** (mmol)	Additive (equiv.)	*n*-Bu_3SnH (equiv.)	Time (min)	Yield (%)	*de* (major isomer, %)
1	0.5	None	1.5	25	100	0
2	0.4	$BF_3{\cdot}Et_2O$ (32)	4.5	30	100	**15b**, 9
3	1.2	MAD (4)	1.6	120	92	**15a**, 53

In our previous study on the diastereoselective radical cyclization of **1**, the presence of a bulky Lewis acid was essential to obtain high selectivity. Therefore, the effect of a Lewis acid was investigated in the radical cyclization of **11**. In contrast to the cyclization of **1**, a large excess of $BF_3{\cdot}Et_2O$ did not improve the selectivity (run 2). However, in the presence of 4 equiv. of methylaluminum bis(2,6-di-*t*-butyl-4-methylphenoxide) (MAD),[3] **15** was obtained in 92% yield with 53% diastereomeric excess (*de*). The *de* value was determined as follows. A mixture of **15a** and **15b** was hydrolyzed to 2-cyclopentenyl acetic acid **16** (75%) and the chiral alcohol **5** (73%). The enantiomeric excess (*ee*) of **16** was determined to be 53% *ee* by comparison of its $[\alpha]_D$ value [$[\alpha]_D$ +60 (*c* 1.0, $CHCl_3$)] to the reported value [$[\alpha]_D$ +113 (*c* 0.5, $CHCl_3$)] for (*S*)-**16**.[11] Therefore, the absolute configuration of the major isomer was **15a** in run 3 (Scheme 4).

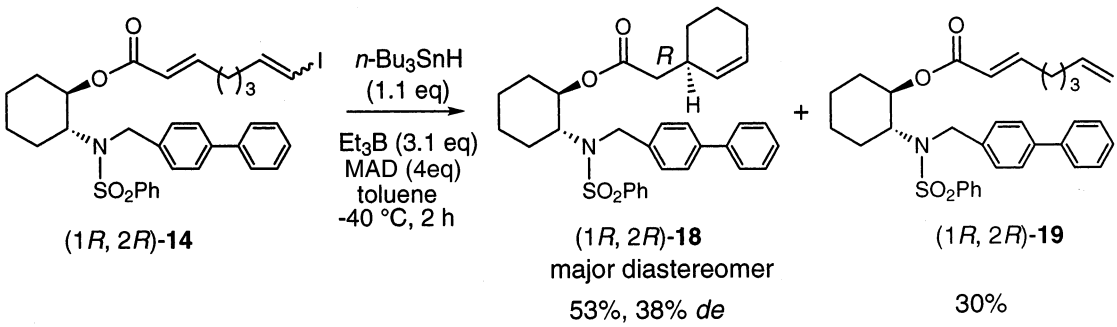
In the presence of 4 equiv. of MAD, phenylbenzyl compound **12** gave **17** in 96% yield with 51% *de*. When the amount of MAD was increased to 8 equiv., the *de* (59% *de*) improved slightly (Scheme 5). As Lewis acids, MgI_2 and $Zn(OTf)_2$ were not effective in the reaction of **12**. Other Lewis acids, such as $EtAlCl_2$ and Et_2AlCl, were also ineffective for obtaining high diastereoselectivity (Scheme 6).



Scheme 4.



Scheme 5.



Scheme 6.

Formation of a six-membered ring was also investigated. When **14** was treated with 1.1 equiv. of n-Bu_3SnH in the presence of 3.1 equiv. of Et_3B and 4 equiv. of MAD at −40°C for 2 h, cyclized product was obtained in 53% yield along with reduced product **19** (30% yield). (*R*)-2-Cyclohexenyl acetic acid ester **18** was obtained as a major diastereomer with 38% *de*. This diastereoselectivity was determined by comparing the $[\alpha]_D$ value of 2-cyclohexenyl acetic acid [$[\alpha]_D$ −30 (*c* 0.8, $CHCl_3$)], which was obtained by hydrolysis of **18**, to the $[\alpha]_D$ value [$[\alpha]_D$ +84 (*c* 2.6, $CHCl_3$)] reported for the (*S*)-isomer.[12]

The diastereoselectivity shown in the reaction of **11** was explained as before, considering the transition state model shown in Fig. 1.

Further tuning of the structure of the auxiliary and its application to other reactions are now underway.

3. Experimental

*3.1. (1*S,*2*S*)*-trans-*2-[(*R*)-(α-Methylbenzyl)amino]cyclohexanol (**2a**) and (1*R,*2*R*)*-trans-*2-[(*R*)-(α-methylbenzyl)amino]cyclohexanol **2b***

To a solution of (+)-(*R*)-α-methylbenzylamine (12.1 mL, 94.1 mmol) in CH_2Cl_2 (80 mL) was added dropwise a solution of Me_3Al in n-hexane (93.2 mL, 94.1 mmol) at 0°C, and the mixture was stirred for 1 h under the same conditions. To this mixture was added a CH_2Cl_2 (80 mL) solution of cyclohexene oxide (10 mL, 98.8 mmol), and the mixture was stirred for 3 h at 0°C and for 18 h at room temperature. The reaction was worked-up as reported to give **2a** (9.7 g, 39%) and **2b** (8.4 g, 45%). **2a**: $[\alpha]_D^{19}$ −23.9 (*c* 1.0, MeOH); IR (neat) ν cm^{-1}: 3408, 3061, 3026, 2929, 2856, 1493, 1448, 1063, 762, 700; ^1H NMR: 400 MHz ($CDCl_3$) δ: 0.78–0.88 (1H, m, C3-H), 1.11–1.35 (4H, m), 1.33 (3H, d, J=6.4, CH_3), 1.63–1.71 (2H, m, C4-H, C5-H), 1.91–2.07 (2H, m, C3-H, C6-H), 2.33 (1H, ddd, J=3.9, 9.3, 11.2, C2-H), 3.09 (1H, ddd, J=4.4, 9.5, 10.4, C1-H), 3.91 (1H, q, J=6.3, CHMe), 7.21–7.34 (5H, m, Ph); ^{13}C NMR: 100 MHz ($CDCl_3$) δ: 23.46 (CH_3), 24.23 (C4), 25.38 (C5), 31.30 (C3), 32.97 (C6), 55.21 (–CHMe), 61.55 (C1), 74.06 (C2), 126.40 (Ph), 127.02 (Ph), 128.46 (Ph), 146.79 (Ph); LR-FABMS m/z: 220 (M^++H), 204. HR-FABMS: calcd for $C_{14}H_{22}NO$ (M^++H), 220.1685; found: 220.1706. **2b**: $[\alpha]_D^{19}$ +90.7 (*c* 1.0, MeOH). IR (neat) ν cm^{-1}: 3298, 3062, 3026, 2931, 2858, 1739, 1493, 1450, 1371, 1271, 1240, 1124, 1066, 760, 702. ^1H NMR: 400 MHz ($CDCl_3$) δ: 0.85–1.28 (4H, m), 1.34 (3H, d, J=6.6, CH_3), 1.63–1.67 (2H, m, C4-H, C5-H), 1.94–2.03 (2H, m, C3-H, C2-H), 2.13–2.18 (1H, m,

C6-H), 3.14 (1H, ddd, $J=3.9$, 11.2, 13.0, C1-H), 3.98 (1H, q, $J=6.6$, CHMe), 7.21–7.34 (5H, m, Ph). ^{13}C NMR: 100 MHz ($CDCl_3$) δ: 24.20 (CH_3), 24.96 (C4), 25.67 (C5), 30.43 (C3), 32.97 (C6), 54.05 (–CHMe), 60.00 (C1), 74.16 (C2), 126.64 (Ph), 126.96 (Ph), 128.49 (Ph), 145.30 (Ph). LR-FABMS: 220 (M^++H), 204, 105. HR-FABMS: calcd for $C_{14}H_{22}NO$ (M^++H), 220.1762; found: 220.1684 [lit. **2a**: $[\alpha]_D^{25}$ −15.5 (*c* 1.0, MeOH), **2b**: $[\alpha]_D^{25}$ +86.7 (*c* 1.3, MeOH)].[8]

*3.2. (1*S,*2*S*)*-trans-*2-Aminocyclohexanol (1*S,*2*S*)-**3***

A solution of **2a** in MeOH (160 mL) was stirred for 3 days under a H_2 atmosphere in the presence of 10% Pd carbon (693 mg). Filtration and evaporation of the solvent followed by column chromatography (SiO_2, AcOEt:MeOH:NH_4OH, 10:1:1) gave (1*S*,2*S*)-**3** (1.49 g, 84%): mp 91–92°C (Et_2O), $[\alpha]_D^{26}$ +41.7 (*c* 1.08, MeOH) [lit. mp 88–89°C, $[\alpha]_D^{25}$ +48.2 (*c* 1.0, MeOH)].[8] Using the same procedure, (1*R*,2*R*)-**3** was obtained in 78% yield: mp 91–92°C (Et_2O), $[\alpha]_D^{26}$ −40.9 (*c* 1.01, MeOH) [lit. mp 85–86°C, $[\alpha]_D^{25}$ −48.5 (*c* 1.0, MeOH)].[8]

*3.3. (1*S,*2*S*)*-trans-*2-(*N,O-*Dibenzoyl)aminocyclohexanol*

To a CH_2Cl_2 (95 mL) solution of (1*S*,2*S*)-**3** (1.32 g, 11.5 mmol) was added triethylamine (8.0 mL, 57.4 mmol) and benzoyl chloride (4.0 mL, 34.4 mmol) at 0°C, and the mixture was stirred for 3 h under the same conditions. The reaction was quenched by adding water (20 mL). The aqueous layer was separated and extracted with AcOEt. The combined organic layers were washed with brine, dried and concentrated in vacuo to give a crude product which was purified by column chromatography (SiO_2, AcOEt:*n*-hexane, 1:4) to give (1*S*,2*S*)-*trans*-2-(*N*,*O*-dibenzoyl)aminocyclohexanol (3.81 g, 83%): mp 153–155°C. $[\alpha]_D^{12}$ +60.5 (*c* 1.0, $CHCl_3$). IR (KBr) *v* cm^{-1}: 3068, 2939, 2866, 1718, 1631, 1543, 1491, 1452, 1321, 1286, 1272, 1115, 715, 702. ^{1}H NMR: 400 MHz ($CDCl_3$) δ: 1.29–1.50 (3H, m, CH_2), 1.68–1.78 (2H, m, CH_2), 1.87–1.90 (1H, m, CH_2), 2.15–2.18 (1H, m, C6-H), 2.32–2.35 (1H, m, C3-H), 4.19–4.27 (1H, m, C1-H), 5.05 (1H, ddd, $J=4.4$, 10.5, 10.8, C2-H), 6.46 (1H, d, $J=8.3$, –NH), 7.32–7.52 (6H, m, Ph), 7.65 (2H, d, $J=7.3$, Ph), 8.05 (2H, d, $J=7.8$, Ph). ^{13}C NMR: 100 MHz ($CDCl_3$) δ: 24.24 (C4), 24.26 (C5), 31.26 (C3), 32.15 (C6), 53.71 (C1), 75.40 (C2), 126.77 (Ph), 128.31 (Ph), 128.40 (Ph), 129.70 (Ph), 129.74 (Ph), 129.84 (Ph), 130.02 (Ph), 131.19 (Ph), 133.11 (Ph), 134.47 (Ph), 167.10 (C=O), 167.69 (C=O). LR-FABMS: 324 (M^++H), 202, 154, 105. Anal. calcd for $C_{20}H_{21}NO_3$: C, 74.28; H, 6.55; N, 4.33; found: C, 74.25; H, 6.53; N, 4.26.

*3.4. (1*S,*2*S*)*-trans-*2-(*N-*Benzoyl)aminocyclohexanol*

A mixture of (1*S*,2*S*)-*trans*-2-(*N*,*O*-dibenzoyl)aminocyclohexanol (2.97 g, 9.27 mmol) and potassium carbonate (12.7 g, 92.7 mmol) in 90 mL of MeOH was heated to reflux for 1 h. After the solvent was removed in vacuo, the product was partitioned between AcOEt and aq. $NaHCO_3$. The separated aqueous layer was extracted with AcOEt and the combined organic layers were dried, filtered and concentrated to give a residue which was purified by recrystallization from benzene. The mother liquor was concentrated to give a residue which was further purified by column chromatography (SiO_2, AcOEt:*n*-hexane, 1:1). (1*S*,2*S*)-*trans*-2-(*N*-Benzoyl)aminocyclohexanol was obtained in an overall yield of 98% (1.99 g): mp 173–174°C (benzene). $[\alpha]_D^{24.5}$ +38.6 (*c* 1.1, MeOH). IR (KBr) *v* cm^{-1}: 3305, 3066, 2939, 2858, 1635, 1549, 1491, 1412, 1333, 1039, 860, 800, 694. ^{1}H NMR: 400 MHz ($CDCl_3$) δ: 1.25–1.45 (4H, m, C3-H,

C4-H, C5-H, C6-H), 1.74–1.78 (2H, m, C4-H, C5-H), 2.09–2.11 (2H, m, C3-H, C6-H), 3.40–3.47 (1H, m, C2-H), 3.55 (1H, bs, –OH), 3.80–3.88 (1H, m, C1-H), 6.17 (1H, bs, –NH), 7.41–7.45 (2H, m, Ph), 7.49–7.53 (1H, m, Ph), 7.76–7.78 (2H, m, Ph). ^{13}C NMR: 100 MHz ($CDCl_3$) δ: 24.01 (C4), 24.61 (C5), 31.63 (C3), 34.58 (C6), 56.28 (C1), 75.55 (C2), 127.01 (Ph), 128.31 (Ph), 128.58 (Ph), 131.72 (Ph), 134.13 (Ph), 169.27 (C=O). LR-FABMS: 220 (M^++H), 154, 136, 105. HR-FABMS: calcd for $C_{13}H_{18}NO_2$ (M^++H): 220.1369; found: 220.1329 [lit. mp 168–169°C, $[\alpha]_D^{25}$ +43.5 (*c* 2.0, EtOH)].[7]

3.5. (*1*S,*2*S)-trans-*2-(*N-*Benzyl)aminocyclohexanol (*1S,2S*)-**4**

To a suspension of $LiAlH_4$ (795 mg, 20.9 mmol) in THF (20 mL) was added a THF (200 mL) solution of (1*S*,2*S*)-*trans*-2-(*N*-benzoyl)aminocyclohexanol (1.72 g, 7.84 mmol) at 0°C. The mixture was then heated to reflux for 3 h. The reaction was quenched by adding water (1.6 mL) and 10% aq. NaOH (1.27 mL) at 0°C. The mixture was refluxed for an additional 1 h. The mixture was filtered through a Celite pad and the filtrate was concentrated to give a residue which was purified by column chromatography (SiO_2, AcOEt:*n*-hexane:triethylamine, 1:1:0.1) to give (1*S*,2*S*)-**4** (1.45 g, 90%): mp 70.5–71.5°C (*n*-hexane). $[\alpha]_D^{24.5}$ +83.7 (*c* 1.0, MeOH). IR (KBr) ν cm^{-1}: 3294, 3060, 2937, 2856, 1498, 1450, 1431, 1360, 1338, 1099, 1078, 748, 698. ^{1}H NMR: 400 MHz ($CDCl_3$) δ: 0.93–1.03 (1H, m, CH_2), 1.18–1.33 (4H, m, CH_2, NH), 1.71–1.74 (2H, m, CH_2), 2.00–2.06 (1H, m, CH_2), 2.14–2.20 (1H, m, CH_2), 2.29 (1H, ddd, J=3.6, 3.9, 9.3, NCH), 3.20 (1H, ddd, J=4.6, 9.5, 9.8, OCH), 3.35 (1H, bs, OH), 3.69 (1H, d, J=12.9, $NHCH_2Ph$), 3.95 (1H, d, J=12.9, $NHCH_2Ph$), 7.23–7.35 (5H, m, Ph). ^{13}C NMR: 100 MHz ($CDCl_3$) δ: 24.29 (C4), 25.05 (C5), 30.45 (C3), 33.27 (C6), 50.71 (–CH_2Ph), 63.01 (C1), 73.75 (C2), 126.91 (Ph), 128.02 (Ph), 128.35 (Ph), 140.52 (Ph). LR-FABMS *m*/*z*: 206 (100, M^++H). HR-FABMS: calcd for $C_{13}H_{20}NO$ (M^++H): 206.1568; found: 206.1539.

3.6. (*1*S,*2*S)-trans-*2-(*N-*Benzenesulfonyl*-N-*benzyl)aminocyclohexanol (*1S,2S*)-**5**

A mixture of (1*S*,2*S*)-**4** (1.12 g, 5.45 mmol), triethylamine (0.92 mL, 6.54 mmol), and benzenesulfonyl chloride (1.14 mL, 8.93 mmol) in CH_2Cl_2 (25 mL) was stirred at 0°C for 2.3 h. The reaction mixture was partitioned between an aqueous saturated solution of NH_4Cl and AcOEt. The separated aqueous layer was extracted with AcOEt. The combined organic layers were washed successively with 5% HCl, a saturated aqueous solution of $NaHCO_3$, and brine. Dried solvent was removed in vacuo to give a residue which was purified by column chromatography (SiO_2, AcOEt:*n*-hexane, 1:4) to give (1*S*,2*S*)-**5** (1.68 g, 90%): mp 120–121°C (AcOEt/*n*-hexane). $[\alpha]_D^{19}$ +3.2 (*c* 0.99, $CHCl_3$). IR (KBr) ν cm^{-1}: 3531, 3061, 3029, 2942, 2861, 1454, 1445, 1321, 1164, 1149, 1036, 1023, 881, 859, 793. ^{1}H NMR: 400 MHz ($CDCl_3$) δ: 0.98–1.24 (3H, m, CH_2), 1.28–1.38 (1H, m, CH_2), 1.43–148 (1H, m, CH_2), 1.57–1.63 (2H, m, CH_2 and OH), 1.92–1.98 (2H, m, C3-H, C6-H), 3.20 (1H, ddd, J=4.4, 10.1, 14.9, C1-H), 3.50 (1H, ddd, J=3.9, 10.0, 12.1, C2-H), 4.28 (1H, d, J=15.6, $NHCH_2Ph$), 4.63 (1H, d, J=15.6, $NHCH_2Ph$), 7.26–7.33 (3H, m, Ph), 7.38–7.39 (2H, m, Ph), 7.46–7.50 (2H, m, Ph), 7.53–7.57 (1H, m, Ph), 7.82–7.85 (2H, m, Ph). ^{13}C NMR: 100 MHz ($CDCl_3$) δ: 23.98 (C4), 25.37 (C5), 28.98 (C3), 34.46 (C6), 47.87 (CH_2Ph), 64.54 (C1), 69.97 (C2), 126.95 (Ph), 127.84 (Ph), 128.01 (Ph), 128.70 (Ph), 129.08 (Ph), 132.56 (Ph), 137.74 (Ph), 140.77 (Ph). LR-FABMS: 346 (M^++H), 204, 154, 91. Anal. calcd for $C_{17}H_{23}NO_3S$: C, 66.06; H, 6.71; N, 4.05; found: C, 66.07; H, 6.71; N, 3.97.

3.7. (1R,2R)-trans-2-[N-(4-Phenylbenzoyl)]aminocyclohexanol

A mixture of (1*R*,2*R*)-**3** (1.50 g, 13.0 mmol), triethylamine (2.75 mL, 19.5 mmol) and 4-phenylbenzoyl chloride (3.39 g, 15.6 mmol) in CH_2Cl_2 (130 mL) was stirred at 0°C for 1 h. The reaction mixture was partitioned between water and CH_2Cl_2, and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were washed successively with 5% HCl, a saturated aqueous solution of $NaHCO_3$, and brine. Dried solvent was removed in vacuo to give a residue which was purified by recrystallization from benzene. The resulting mother liquor was concentrated to give a residue which was further purified by column chromatography (SiO_2, AcOEt:*n*-hexane:$CHCl_3$, 1:1:0.5). (1*R*,2*R*)-*trans*-2-[*N*-(4-Phenylbenzoyl)]aminocyclohexanol was obtained in an overall yield of 86% (3.30 g): mp 238–239°C (benzene). $[\alpha]_D^{24}$ +1.2 (*c* 0.90, $CHCl_3$). IR (KBr) *v* cm^{-1}: 3235, 3267, 3059, 3033, 2937, 2198, 2854, 1616, 1540, 1486, 1446, 1335, 1061, 1045, 850, 746, 698. ^1H NMR: 400 MHz ($CDCl_3$) δ: 1.26–1.48 (4H, m, C3-H, C4-H, C5-H, C6-H), 1.74–1.84 (2H, m, C4-H, C5-H), 2.08–2.20 (2H, m, C6-H, C3-H), 3.43–3.50 (m, C1-H), 3.53 (1H, d, $J=4.4$, –OH), 3.83–3.92 (1H, m, C2-H), 6.16 (1H, d, $J=7.6$, CONH), 7.36–7.60 (3H, m, Ph), 7.60–7.67 (4H, m, Ph), 7.85–7.86 (2H, m, Ph). ^{13}C NMR: 100 MHz ($CDCl_3$) δ: 23.48 (C4), 23.84 (C5), 30.47 (C3), 33.83 (C6), 55.12 (C1), 70.92 (C2), 125.73 (Ph), 126.25 (Ph), 127.26 (Ph), 127.37 (Ph), 128.34 (Ph), 133.76 (Ph), 139.02 (Ph), 142.08 (Ph), 165.70 (C=O). LR-FABMS: 296 (M^++H), 154. HR-FABMS: calcd for $C_{19}H_{22}NO_2$ (M^++H): 296.1698; found: 296.1631.

3.8. (1R,2R)-trans-2-[N-(4-Phenylbenzyl)]aminocyclohexanol (1R,2R)-6

A mixture of (1*R*,2*R*)-*trans*-2-[*N*-(4-phenylbenzoyl)]aminocyclohexanol (107 mg, 0.36 mmol) and $LiAlH_4$ (61 mg, 1.6 mmol) in THF (12 mL) was heated to reflux for 1.5 h. Excessive reagent was quenched by adding water (0.12 mL) and 10% NaOH (0.01 mL) at 0°C. The mixture was then refluxed for 30 min. Inorganic solid was removed by filtration through a Celite pad and the filtrate was dried over Na_2SO_4. Evaporation of the solvent gave a residue, which was purified by column chromatography (SiO_2, AcOEt:*n*-hexane:triethylamine, 1:1:0.1) to give (1*R*,2*R*)-**6** (93 mg, 91%): mp 137–138.5°C. $[\alpha]_D^{20}$ −54.1 (*c* 0.96, $CHCl_3$). IR (KBr) *v* cm^{-1}: 3294, 3082, 2927, 2848, 1489, 1448, 1429, 1080, 1059, 766, 696. ^1H NMR: 400 MHz ($CDCl_3$) δ: 0.96–1.05 (1H, m, CH_2), 1.18–1.32 (3H, m, CH_2), 1.46 (1H, bs, –NH), 1.70–1.78 (2H, m, C4-H, C5-H), 2.03–2.07 (1H, m, CH_2), 2.13–2.16 (1H, m, CH_2), 2.32 (1H, ddd, $J=3.9$, 9.2, 11.3, C2-H), 3.22 (1H, ddd, $J=4.6$, 9.7, 9.7, C1-H), 3.33 (1H, bs, –OH), 3.74 (1H, d, $J=13.2$, $NHCH_2Ar$), 4.00 (1H, d, $J=12.9$, $NHCH_2Ar$), 7.32–7.35 (1H, m, Ph), 7.40–7.40 (4H, m, Ph), 7.55–7.60 (4H, m, Ph). ^{13}C NMR: 100 MHz ($CDCl_3$) δ: 24.30 (C4), 25.11 (C5), 30.51 (C3), 33.27 (C6), 50.37 (CH_2Ar), 63.06 (C1), 73.82 (C2), 127.00 (Ph), 127.14 (Ph), 128.48 (Ph), 128.69 (Ph), 139.58 (Ph). LR-FABMS *m*/*z*: 282 (M^++H), 167. HR-FABMS: calcd for $C_{19}H_{24}NO$ (M^++H): 282.1845; found: 282.1863.

3.9. (1R,2R)-trans-2-[N-Benzenesulfonyl-N-(4-phenylbenzyl)]aminocyclohexanol (1R,2R)-7

A mixture of (1*R*,2*R*)-**6** (2.11 g, 7.52 mmol), triethylamine (1.6 mL, 11.3 mmol) and benzenesulfonyl chloride (1.95 mL, 15.2 mmol) in CH_2Cl_2 (75 mL) was stirred at 0°C and then at room temperature for 2.3 h. The reaction was quenched by adding water, and the product was extracted with AcOEt. The combined organic layers were washed successively with 5% HCl,

saturated $NaHCO_3$ solution, and brine. Dried solvent was removed in vacuo to give a residue which was purified by recrystallization from AcOEt. The resulting mother liquor was concentrated to give a residue, which was further purified by column chromatography (SiO_2, AcOEt:*n*-hexane, 1:4). The total yield of (1*R*,2*R*)-**7** was 3.02 g (95%): mp 175.0–176.0°C (AcOEt/*n*-hexane). $[\alpha]_D^{23}$ −7.78 (*c* 1.04, $CHCl_3$). IR (KBr) *v* cm^{-1}: 3541, 3059, 3032, 2939, 2862, 1489, 1446, 1410, 1319, 1165, 1149, 1080, 1036, 752, 685. ^1H NMR: 400 MHz ($CDCl_3$) δ: 1.00–1.28 (3H, m, CH_2), 1.30–1.48 (2H, m, CH_2), 1.58–1.65 (2H, m, CH_2, –OH), 1.95–2.00 (1H, m, CH_2), 2.08 (1H, d, $J=3.9$, CH_2), 3.18–3.26 (1H, m, C1-H), 3.55 (1H, ddd, $J=3.9$, 9.8, 11.8, C2-H), 4.30 (1H, d, $J=15.6$, $NHCH_2Ar$), 4.70 (1H, d, $J=15.7$, $NHCH_2Ar$), 7.32–7.37 (1H, m, Ph), 7.42–7.60 (11H, m, Ph), 7.84–7.87 (2H, m, Ph). ^{13}C NMR: 100 MHz ($CDCl_3$) δ: 23.97 (C4), 25.34 (C5), 29.10 (C3), 34.50 (C6), 47.54 (CH_2Ar), 64.55 (C1), 70.00 (C2), 126.94 (Ph), 127.30 (Ph), 128.44 (Ph), 128.71 (Ph), 129.06 (Ph), 132.53 (Ph), 136.72 (Ph), 140.41 (Ph), 140.60 (Ph), 140.75 (Ph). LR-FABMS: 280 (M^++H), 167, 136. Anal. calcd for $C_{25}H_{27}NO_3S$: C, 71.23; H, 6.46; N, 3.32; found: C, 71.36; H, 6.50; N, 3.22.

3.10. 5-Iodo-4-penten-1-ol

To a benzene (85 mL) solution of 4-pentyn-1-ol (2.0 mL, 21.2 mmol) was added tri-*n*-butyltin hydride (5.7 mL, 21.2 mmol) and azobisisobutyronitrile (AIBN, 352 mg, 2.1 mmol), and the mixture was heated to reflux for 1 h. After the reaction was cooled to room temperature, benzene was evaporated to give a residue which was dissolved in CH_2Cl_2 (50 mL). To this solution was added dropwise a CH_2Cl_2 (150 mL) solution of iodine (8.23 g, 63.6 mmol) at 0°C, and the mixture was stirred for 1.3 h. The reaction was quenched by adding a saturated aqueous solution of sodium thiosulfate. The product was extracted with ether and the combined extracts were washed successively with water and brine. The extracts were then dried and concentrated in vacuo to give a residue which was purified by column chromatography (SiO_2, AcOEt:*n*-hexane, 1:2) to give 5-iodo-4-penten-1-ol (4.36 g, 97%). IR (neat) *v* cm^{-1}: 3336, 3047, 2937, 2873, 1606, 1437, 1277, 1219, 1057, 947, 658. ^1H NMR: 400 MHz ($CDCl_3$) δ: 1.35 (1H, bs, –OH), 1.63–1.75 (2H, m, C2-H), 2.17 (1.64H, tdd, $J=1.2$, 7.5, 7.4, C3-H for (*E*)-isomer), 2.25 (0.46H, dt, $J=7.3$, 13.9, C3-H for (*Z*)-isomer), 3.63–3.71 (2H, m, C1-H), 6.05 (0.79H, dt, $J=14.4$, 1.5, C5-H for (*E*)-isomer), 6.18–6.25 (0.42H, m, C4-H and C5-H for (*Z*)-isomer), 6.53 (0.79H, dt, $J=14.4$, 7.1, C4-H for (*E*)-isomer). ^{13}C NMR: 100 MHz ($CDCl_3$) δ: 30.77 (C2 for (*Z*)-isomer), 31.09 (C2 for (*E*)-isomer), 32.26 (C1 for (*E*)-isomer), 61.73 (C3 for (*E*)-isomer), 62.00 (C3 for (*Z*)-isomer), 75.02 (C4 for (*E*)-isomer), 83.01 (C4 for (*Z*)-isomer), 140.52 (C5 for (*Z*)-isomer), 145.69 (C5 for (*E*)-isomer). LR-EIMS: 212 (M^++H), 194, 167, 127, 85, 67. HR-EIMS: calcd for C_5H_9IO: 211.9768; found: 211.9679.

*3.11. (1*S*,2*S*)-*trans*-2-(*N*-Benzenesulfonyl-N-benzyl)aminocyclohexyl bromoacetate*

To a THF (27 mL) solution of (1*S*,2*S*)-**5** (93.5 mg, 2.71 mmol) was added bromoacetyl bromide (1.92 mL, 22.5 mmol) at 0°C, and the mixture was stirred for 5.5 h under the same conditions. The reaction was quenched by adding a saturated aqueous solution of $NaHCO_3$, and the product was extracted with AcOEt. The combined extracts were washed with brine and dried. The solvent was removed in vacuo to give a residue which was purified by column chromatography (SiO_2, AcOEt:*n*-hexane, 1:6) to give (1*S*,2*S*)-*trans*-2-(*N*-benzenesulfonyl-*N*-benzyl)aminocyclohexyl bromoacetate (1.21 g, 96%): mp 85.0–85.5°C (Et_2O/*n*-hexane). $[\alpha]_D^{20}$ −1.9

(*c* 1.0, $CHCl_3$). IR (neat) *v* cm^{-1}: 3087, 3057, 3031, 2935, 2860, 1734, 1446, 1362, 1338, 1277, 1157, 1115, 1091, 1022, 933, 887, 806, 744, 688. ^1H NMR: 400 MHz ($CDCl_3$) δ: 1.06–1.34 (4H, m, C3-H, C4-H, C5-H, C6-H), 1.58–1.68 (2H, m, C4-H, C5-H), 1.74–1.82 (1H, m, C6-H), 2.06–2.14 (1H, m, C3-H), 3.36 (d, $J=12.2$, CH_2Br), 3.60 (d, $J=12.2$, CH_2Br), 3.94–3.88 (1H, m, OCH), 4.18 (1H, d, $J=15.8$, NCH_2Ph), 4.50 (1H, d, $J=15.6$, NCH_2Ph), 4.72 (1H, ddd, $J=4.6$, 10.6, 10.8, NCH–), 7.30–7.24 (5H, m, Ph), 7.46–7.56 (3H, m, Ph), 7.80–7.82 (2H, m, Ph). ^{13}C NMR: 100 MHz ($CDCl_3$) δ: 23.62 (C4), 25.08 (C5), 25.82 (CH_2Br), 31.45 (C3), 31.78 (C6), 48.00 (CH_2Ph), 60.64 (C1), 73.71 (C2), 127.12, 127.75, 128.30, 128.48, 128.94, 132.24, 137.12, 141.39, 166.27 (C=O). LR-FABMS *m*/*z*: 466 (M^+), 328, 91. HR-FABMS: calcd for $C_{21}H_{25}NO_4S^{81}Br$ (M^++H): 468.0710; found: 468.0630.

*3.12. (1*S,*2*S*)*-trans-*2-(*N-*Benzenesulfonyl*-N-*benzyl)aminocyclohexyl (triphenylphosphoranylidene)acetate (1*S,*2*S*)-**8***

A toluene (7.5 mL) solution of (1*S*,2*S*)-*trans*-2-(*N*-benzenesulfonyl-*N*-benzyl)aminocyclohexyl bromoacetate (1.0 g, 2.15 mmol) and triphenylphosphine (567 mg, 2.15 mmol) was heated to reflux for 3 h. After solvent was removed, the product was solidified by adding ether. The product was washed with ether (5 mL, three times) and dissolved in water (10 mL). 1N NaOH was added until the product solution was basic, and the product was extracted with $CHCl_3$. The combined extracts were washed with brine and dried. The solvent was removed in vacuo to give (1*S*,2*S*)-**8** (1.2 g, 91%), which was used in the next step without further purification: $[\alpha]_D^{20}$ −26.7 (*c* 0.97, $CHCl_3$). IR (neat) *v* cm^{-1}: 3059, 2935, 2858, 1612, 1437, 1377, 1333, 1153, 1107, 887, 752, 690, 592, 515. ^1H NMR: 400 MHz ($CDCl_3$) δ: 0.73–1.26 (4H, m, C3-H, C4-H, C5-H, C6-H), 1.41–1.59 (2H, m, C4-H, C5-H), 1.81–1.84 (1H, m, C6-H), 2.05–2.07 (1H, m, C3-H), 3.85–3.91 (1H, m, C1-H, and 1H, d, $J=15.9$, NCH_2Ph), 4.67–4.77 (2H, m, C2-H, NCH_2Ph), 7.03–7.07 (1H, m, CH=PPh_3), 7.20–7.25 (4H, m, Ph), 7.40–7.58 (19H, m, Ph), 7.75 (2H, d, $J=7.3$, Ph). ^{13}C NMR: 100 MHz ($CDCl_3$) δ: 24.03 (C4), 31.69 (C5), 33.35 (C3), 34.29 (C6), 47.23 (CH_2Ph), 61.80 (C1), 68.23 (C2), 127.10, 127.25, 127.57, 128.18, 128.50, 128.62, 128.74, 131.43, 132.03, 132.85, 132.94, 138.56, 141.48, 170.10 (C=O). LR-FABMS: 648 (M^++H), 321, 154, 136. HR-FABMS: calcd for $C_{39}H_{39}NO_4PS$ (M^++H): 648.2339; found: 648.2335.

*3.13. (1*S,*2*S*)*-trans-*2-(*N-*Benzenesulfonyl*-N-*benzyl)aminocyclohexyl (2*E*)-7-iodo-2,6-heptadienoate (1*S,*2*S*)-**11***

A mixture of (1*S*,2*S*)-**8** (2.59 g, 4.00 mmol) and crude 5-iodo-4-penten-1-al **10** (1.42 g, 6.78 mmol), which was prepared by oxidation of 5-iodo-4-penten-1-ol using PCC, in CH_2Cl_2 (15 mL) was stirred at room temperature for 2.3 h. The solvent was removed in vacuo to give a residue which was purified by column chromatography (SiO_2, AcOEt:*n*-hexane, 1:6) to give (1*S*,2*S*)-**11** (770.5 mg, 82%): $[\alpha]_D^{20}$ +15.1 (*c* 1.05, $CHCl_3$). IR (neat) *v* cm^{-1}: 3062, 3028, 2939, 2860, 1714, 1652, 1604, 1495, 1446, 1327, 1269, 1155, 1092, 1028, 754, 690. ^1H NMR: 400 MHz ($CDCl_3$) δ: 1.03–1.27 (4H, m, C3′-H, C4′-H, C5′-H, C6′-H), 1.54–1.62 (2H, m, C4′-H, C5′-H), 1.72–1.74 (1H, m, C6′-H), 2.08–2.10 (1H, m, C3′-H), 2.19–2.32 (4H, m, C4-H, C5-H), 3.90–4.00 (1H, m, C1′-H), 4.11 (1H, d, $J=15.6$, NCH_2Ph), 4.51 (1H, d, $J=15.9$, NCH_2Ph), 4.70 (1H, ddd, $J=4.6$, 10.4, 10.4, C2′-H), 5.27 (1H, d, $J=15.4$, C2-H), 6.12 (0.83H, d, $J=14.4$, C7-H for (*E*)-isomer), 6.21 (0.18H, dt, $J=7.3$, 7.3, C6-H for (*Z*)-isomer), 6.32 (0.17H, d, $J=7.3$, C7-H for (*Z*)-isomer), 6.81 (1H, dt, $J=15.6$, 6.6, C3-H), 7.24–7.28 (2H, m, Ph), 7.33–7.37 (2H, m, Ph), 7.45–7.58 (3H,

m, Ph), 7.80–7.82 (2H, m, Ph). ^{13}C NMR: 100 MHz ($CDCl_3$) δ: 23.73 (C4′), 25.20 (C5′), 30.86 (C5), 31.94 (C3′, C6′), 34.26 (C4), 47.71 (CH_2Ph), 60.74 (C1′), 71.58 (C2′), 76.06 (C7 for (*E*)-isomer), 83.84 (C7 for (*Z*)-isomer), 121.84 (C2), 127.11, 127.60, 128.33, 128.41, 128.86, 131.91, 137.75, 139.35 (C6 for (*Z*)-isomer), 141.59, 144.46 (C6 for (*E*)-isomer), 147.52 (C3 for (*E*)-isomer), 147.78 (C3 for (*Z*)-isomer), 165.30 (C=O). LR-FABMS: 580 (M^++H), 438, 328, 238, 91. HR-FABMS: calcd for $C_{26}H_{32}INO_4S$ (M^++H): 580.1027; found: 580.1008.

*3.14. (1*R,*2*R*)*-trans-*2-[*N-*Benzenesulfonyl*-N-*(4-phenylbenzyl)]aminocyclohexyl bromoacetate*

To a THF (70 mL) solution of (1*R*,2*R*)-**7** (2.80 g, 6.65 mmol) in an ice bath was added bromoacetyl bromide (4.7 mL, 53.9 mmol), and the mixture was stirred for 2 h under the same conditions. The reaction was quenched by adding a saturated aqueous solution of $NaHCO_3$, and the product was extracted with AcOEt. The combined extracts were washed with brine and dried. The solvent was removed in vacuo to give a residue which was purified by column chromatography (SiO_2, AcOEt:*n*-hexane, 1:10) to give (1*R*,2*R*)-*trans*-2-[*N*-benzenesulfonyl-*N*-(4-phenylbenzyl)]aminocyclohexyl bromoacetate (3.60 g, 99%): $[\alpha]_D^{23}$ −8.0 (*c* 1.04, $CHCl_3$). IR (neat) ν cm^{-1}: 3057, 3030, 2939, 2862, 1736, 1489, 1446, 1333, 1277, 1155, 1090, 1018, 760, 689. ^{1}H NMR: 400 MHz ($CDCl_3$) δ: 1.12–1.34 (4H, m, C3-H, C4-H, C5-H, C6-H), 1.62–1.68 (2H, m, C4-H, C5-H), 1.80–1.82 (1H, m, C6-H), 2.08–2.14 (1H, m, C3-H), 3.36 (d, J=12.4, CH_2Br), 3.42 (d, J=12.4, CH_2Br), 3.94–4.00 (1H, m, C1-H), 4.18 (1H, d, J=15.9, $NCH_2C_6H_4Ph$), 4.55 (1H, d, J=15.8, $NCH_2C_6H_4Ph$), 4.75 (1H, ddd, J=4.6, 10.6, 10.9, C2-H), 7.33–7.38 (3H, m, Ph), 7.42–7.51 (6H, m, Ph), 7.54–7.59 (3H, m, Ph), 7.80–7.83 (2H, m, Ph). ^{13}C NMR: 100 MHz ($CDCl_3$) δ: 23.66 (C4), 25.10 (C5), 25.85 (CH_2Br), 31.49 (C3), 31.96 (C6), 47.74 (CH_2Ph), 60.72 (C1), 73.73 (C2), 127.01, 127.15, 127.34, 128.75, 128.77, 128.93, 132.22, 136.12, 140.55, 141.46, 166.35 (C=O). LR-FABMS m/z: 542 (M^++H). HR-FABMS: calcd for $C_{27}H_{29}NO_4S^{81}Br$ (M^++H): 544.1030; found: 544.0921.

*3.15. (1*R,*2*R*)*-trans-*2-[*N-*Benzenesulfonyl*-N-*(4-phenylbenzyl)]aminocyclohexyl (triphenylphosphoranylidene)acetate (1*R,*2*R*)-**9***

A toluene (60 mL) solution of (1*R*,2*R*)-*trans*-2-[*N*-benzenesulfonyl-*N*-(4-phenylbenzyl)]aminocyclohexyl bromoacetate (3.17 g, 6.00 mmol) and triphenylphosphine (2.05 g, 7.81 mmol) was heated to reflux for 4.5 h. After the solvent was removed, the product was solidified by adding ether. The product was washed with ether (20 mL, three times) and dissolved in water (20 mL). 1N NaOH was added until the product solution was basic, and the product was extracted with $CHCl_3$. The combined extracts were washed with brine and dried. The solvent was removed in vacuo to give (1*R*,2*R*)-**9** (4.0 g, 95%), which was used in the next step without further purification: $[\alpha]_D^{11}$ +10.0 (*c* 1.32, $CHCl_3$). IR (neat) ν cm^{-1}: 3057, 3027, 2936, 2860, 1611, 1485, 1437, 1377, 1333, 1152, 1107, 894, 756, 691. ^{1}H NMR: 400 MHz ($CDCl_3$) δ: 0.85–1.22 (4H, m, C3-H, C4-H, C5-H, C6-H), 1.44–1.60 (2H, m, C4-H, C5-H), 1.86–1.90 (1H, m, C6-H), 2.04–2.13 (1H, m, C3-H), 3.85–3.96 (1H, m, C1-H, and 1H, d, J=15.6, $NCH_2C_6H_4Ph$), 4.70–4.80 (1H, m, C2-H, and 1H, d, J=15.6, $NCH_2C_6H_4Ph$), 7.04–7.07 (1H, m, $CH{=}PPh_3$), 7.21–7.26 (3H, m, Ph), 7.31–7.34 (1H, m, Ph), 7.40–7.48 (12H, m, Ph), 7.53–7.59 (11H, m, Ph), 7.91–7.93 (2H, m, Ph). ^{13}C NMR: 100 MHz ($CDCl_3$) δ: 24.05 (C4), 30.50 (C5), 33.37 (C3), 34.34 (C6), 46.95 (CH_2Ph), 61.86 (C1), 68.30 (C2), 126.85, 127.00, 127.14, 127.60, 128.02, 128.51, 128.64, 128.67, 128.76, 129.18, 131.46, 132.05, 132.85, 132.95, 137.63, 140.03, 140.83, 141.48,

170.27 (C=O). LR-FABMS m/z: 724 (M^++H). HR-FABMS: calcd for $C_{45}H_{44}NO_4PS$ (M^++H): 724.2646; found: 724.2662.

*3.16. (1*R,*2*R*)*-trans-*2-[*N-*Benzenesulfonyl*-N-*(4-phenylbenzyl)]aminocyclohexyl (2*E*)-7-iodo-2,6-heptadienoate (1*R,*2*R*)-**12**

A mixture of (1*R*,2*R*)-**9** (189.2 mg, 0.26 mmol) and crude 5-iodo-4-penten-1-al **10** (54.1 mg, 0.258 mmol), which was prepared by oxidation of 5-iodo-4-penten-1-ol using PCC, in CH_2Cl_2 (3 mL) was stirred at room temperature for 4.5 h. The solvent was removed in vacuo to give a residue which was purified by column chromatography (SiO_2, AcOEt:*n*-hexane, 1:6) to give (1*R*,2*R*)-**12** (130 mg, 77%): $[\alpha]_D^{17}$ −49.1 (*c* 1.05, $CHCl_3$). IR (neat) ν cm^{-1}: 3421, 3059, 3030, 2935, 2860, 1718, 1655, 1604, 1489, 1448, 1340, 1277, 1157, 1092, 1033, 756, 690. ^1H NMR: 400 MHz ($CDCl_3$) δ: 1.10–1.30 (4H, m, C3′-H, C4′-H, C5′-H, C6′-H), 1.60–1.64 (2H, m, C4′-H, C5′-H), 1.78–1.80 (1H, m, C6′-H), 2.10–2.15 (1H, m, C3′-H), 2.16–2.30 (4H, m, C4-H, C5-H), 3.90–4.19 (1H, m, C1′-H), 4.15 (1H, d, J=15.8, $NCH_2C_6H_4Ph$), 4.56 (1H, d, J=15.6, $NCH_2C_6H_4Ph$), 4.70 (1H, ddd, J=4.6, 10.4, 10.4, C2′-H), 5.29 (1H, d, J=15.6, C2-H), 6.10 (0.82H, d, J=15.6, C7-H for (*E*)-isomer), 6.17–6.22 (1H, m, C6-H for (*Z*)-isomer), 6.30 (0.18H, d, J=7.3, C7-H for (*Z*)-isomer), 6.48 (1H, dt, J=15.6, 6.6, C3-H), 7.31–7.59 (12H, m, Ph), 7.80–7.82 (2H, m, Ph). ^{13}C NMR: 100 MHz ($CDCl_3$) δ: 23.75 (C4′), 25.20 (C5′), 30.35 (C5 for (*Z*)-isomer), 30.86 (C5 for (*E*)-isomer), 31.98 (C3′), 32.07 (C6′), 33.05 (C4 for (*Z*)-isomer), 34.25 (C4 (*E*)-isomer), 47.42 ($CH_2C_6H_4Ph$), 60.83 (C1′), 71.59 (C2′), 76.06 (C7 for (*E*)-isomer), 83.85 (C7 for (*Z*)-isomer), 121.66 (C2 for (*Z*)-isomer), 121.82 (C2 for (*E*)-isomer), 127.00, 127.08, 127.14, 128.27, 128.83, 131.89, 136.40, 139.33 (C6 for (*Z*)-isomer), 140.42, 140.65, 141.67, 144.45 (C6 for (*E*)-isomer), 147.56 (C3 for (*E*)-isomer), 147.87 (C3 for (*Z*)-isomer), 166.34 (C=O for (*E*)-isomer), 165.40 (C=O for (*Z*)-isomer). LR-FABMS: 656 (M^++H). HR-FABMS: calcd for $C_{32}H_{35}INO_4S$ (M^++H): 656.1334; found: 656.1298.

3.17. 6-Iodo-5-hexen-1-ol

To a benzene (25 mL) solution of 5-hexen-1-ol (0.5 mL, 4.53 mmol) were added tri-*n*-butyltin hydride (1.25 mL, 4.53 mmol) and AIBN (75.2 mg, 0.45 mmol). The mixture was heated to reflux for 3.5 h. After the reaction was cooled to room temperature, benzene was evaporated to give a residue which was dissolved in CH_2Cl_2 (10 mL). To this solution was added dropwise a CH_2Cl_2 (40 mL) solution of iodine (1.74 g, 13.6 mmol) at 0°C, and the mixture was stirred for 1.3 h. The reaction was quenched by adding an aqueous saturated solution of sodium thiosulfate. The product was extracted with ether and the combined extracts were washed successively with water and brine. The extracts were then dried and concentrated in vacuo to give a residue which was purified by column chromatography (SiO_2, AcOEt:*n*-hexane, 1:2) to give 6-iodo-5-hexen-1-ol (1.07 g, 100%). IR (neat) ν cm^{-1}: 3337, 3048, 2933, 2860, 1604, 1458, 1214, 1066, 949, 660. ^1H NMR: 400 MHz ($CDCl_3$) δ: 1.28–1.39 (1H, m, C2-H), 1.44–1.64 (4H, m, C2-H, C3-H, –OH), 2.13–2.07 (1.6H, m, C4-H for (*E*)-isomer), 2.16–2.21 (0.4H, m, C4-H for (*Z*)-isomer), 3.63–3.69 (2H, m, C1-H), 6.01 (0.74H, dt, J=14.4, 1.4, C6-H for (*E*)-isomer), 6.15–6.23 (0.33H, m, C5-H for (*Z*)-isomer, C6-H for (*Z*)-isomer), 6.51 (0.7H, dt, J=14.4, 7.3, C5-H for (*E*)-isomer). ^{13}C NMR: 100 MHz ($CDCl_3$) δ: 24.12 (C), 24.51 (C), 31.85 (C), 32.01, 34.33 (C), 35.68, 62.50, 62.59, 74.75, 82.65, 140.92, 146.19. LREIMS m/z: 225 (M^++H). HR-EIMS: calcd for $C_6H_{11}IO$: 225.9871; found: 225.9850.

3.18. (1R,2R)-trans-2-[N-Benzenesulfonyl-N-(4-phenylbenzyl)]aminocyclohexyl (2E)-8-iodo-2,7-octadienoate [(1R,2R)-**14**]

A mixture of (1*R*,2*R*)-**9** (1.49 g, 2.06 mmol) and crude 6-iodo-5-hexen-1-al **13** (556 mg, 2.48 mmol), which was prepared by oxidation of 6-iodo-5-hexen-1-ol using PCC, in CH_2Cl_2 (5 mL) was stirred at room temperature for 17 h. The solvent was removed in vacuo to give a residue which was purified by column chromatography (SiO_2, AcOEt:*n*-hexane, 1:10) to give (1*R*,2*R*)-**14** (1.13 g, 82%): $[\alpha]_D^{16}$ −44.4 (*c* 1.03, $CHCl_3$). IR (neat) ν cm^{-1}: 3058, 3029, 2938, 2860, 1717, 1653, 1604, 1489, 1446, 1332, 1154, 1092, 1038, 892, 754, 689. ^1H NMR: 400 MHz ($CDCl_3$) δ: 1.12–1.35 (4H, m, C3′-H, C4′-H, C5′-H, C6′-H), 1.51–1.68 (4H, m, C4′-H, C5′-H, C5-H), 1.79–1.85 (1H, m, C6′-H), 2.06–2.20 (5H, m, C3′-H, C4-H, C6-H), 3.95–4.02 (1H, m, C1′-H), 4.19 (1H, d, J=15.6, NCH_2Ph), 4.53 (1H, d, J=15.6, NCH_2Ph), 4.73 (1H, ddd, J=4.6, 10.3, 10.4, C2′-H), 5.36 (1H, dt, J=15.6, 1.5, C2-H), 6.06 (0.82H, d, J=14.4, C8-H for (*E*)-isomer), 6.18 (0.18H, dt, J=7.0, 7.0, C7-H for (*Z*)-isomer), 6.27 (0.18H, d, J=7.3, C8-H for (*Z*)-isomer), 6.51 (1H, dt, J=14.2, 7.1, C7-H), 6.83 (1H, dt, J=15.6, 7.1, C3-H), 7.30–7.57 (12H, m, Ph), 7.78–7.81 (2H, m, Ph). ^{13}C NMR: 100 MHz ($CDCl_3$) δ: 23.78 (C4′), 25.22 (C5′), 26.58 (C5), 31.17 (C6), 32.03 (C3′, C6′), 35.25 (C4), 47.41 (CH_2Ph), 60.83 (C1′), 71.49 (C2′), 75.40 (C8 for (*E*)-isomer), 83.31 (C8 for (*Z*)-isomer), 121.45 (C2), 127.14, 128.81, 131.92, 136.42, 140.42, 140.68, 141.68, 145.52 (C7 for (*E*)-isomer), 148.72 (C3), 165.51 (C=O). LR-FABMS m/z: 167 (100), 670 (M^++H). HR-FABMS: calcd for $C_{33}H_{38}INO_4S$ (M^++H): 670.1509, found: 670.1447.

3.19. Radical cyclization of (1S,2S)-**11** (a representative procedure for Table 1)

3.19.1. Run 1

To a mixture of (1*S*,2*S*)-**11** (280 mg, 0.49 mmol) and tri-*n*-butyltin hydride (0.2 mL, 0.73 mmol) in toluene (9.7 mL) with stirring at −78°C was added a toluene solution of triethylborane (1.0 M solution, 0.5 mL, 0.5 mmol), and the mixture was stirred for 25 min under the same conditions. The mixture was warmed to room temperature and concentrated in vacuo to give a residue which was treated with 10% aqueous potassium fluoride for 12 h after dissolving in CH_2Cl_2 (15 mL). The resulting suspension was filtered through a Celite pad and the filtrate was extracted with AcOEt. The combined organic layers were washed with an aqueous saturated solution of $NaHCO_3$ and brine. Dried solvent was removed in vacuo to give a residue which was purified by column chromatography (SiO_2, AcOEt:*n*-hexane, 1:6) to give an inseparable mixture of **15a** and **15b** (220 mg, 100%). Spectral data for a mixture of **15a** and **15b**: IR (neat) ν cm^{-1}: 3060, 3032, 2941, 2862, 1734, 1446, 1340, 1259, 1157, 1092, 1026, 930, 887, 741, 690. ^1H NMR: 400 MHz ($CDCl_3$) δ: 1.07–1.40 (6H, m, C3″-H, C4″-H, C5″-H, C6″-H, C2′-H, C5-H), 1.56–1.62 (2H, m, C4′-H, C5′-H), 1.78–1.89 (2H, m, C2′-H, C6″-H), 1.94–2.09 (2H, m, C3″-H, C5-H), 2.24–2.35 (2H, m, C4-H), 2.85–2.92 (1H, m, C1-H), 3.86–3.95 (1H, m, C1′-H), 4.29 (1H, d, J=15.6, NCH_2Ph), 4.56 (1H, d, J=15.9, NCH_2Ph), 4.74 (1H, dddd, J=2.5, 4.6, 10.5, 10.5, C2″-H), 5.55–5.60 (1H, m, C3-H), 5.73–5.76 (1H, m, C2-H), 7.21–7.51 (8H, m, Ph), 7.80 (2H, m, Ph). ^{13}C NMR: 100 MHz ($CDCl_3$) δ: 23.87 (C4″), 25.35 (C5″), 29.58 (C5), 31.83 (C4), 32.17 (C3″), 32.56 (C6″), 40.22 (C2′), 41.86 (C1), 48.06 (CH_2Ph), 61.09 (C1″), 71.62 (C2″), 127.30, 127.67, 128.43, 128.60, 128.81, 131.35 (C3), 131.97, 133.57 (C2), 137.57, 141.90, 171.98 (C=O). LR-FABMS m/z: 454 (M^++H), 328, 312, 238, 154, 91. HR-FABMS: calcd for $C_{26}H_{32}NO_4S$ (M^++H): 454.2041; found: 454.2061.

3.19.2. Run 2

To a mixture of (*1S*,2*S*)-**11** (200 mg, 0.35 mmol) and $BF_3{\cdot}Et_2O$ (1.4 mL, 11.1 mmol) in toluene (3.2 mL) with stirring at −78°C were successively added tri-*n*-butyltin hydride (0.42 mL, 1.56 mmol) and triethylborane (1.01 M solution in *n*-hexane, 0.38 mL, 0.38 mmol). The reaction mixture was stirred under the same conditions for 30 min and worked-up as in run 1 to give a mixture of **15a** and **15b** (157 mg, 100%).

3.19.3. Run 3

To a solution of (1*S*,2*S*)-**11** (695 mg, 1.20 mmol) in toluene (12 mL) with stirring at −78°C was added a toluene solution of MAD (0.4 M solution, 12 mL, 4.8 mmol), which was prepared by adding trimethylaluminum (1 M in *n*-hexane, 5 mL, 5 mmol) to a toluene (7.5 mL) solution of butylhydroxytoluene (2.2 g, 10 mmol) at 0°C. To this mixture were added tri-*n*-butyltin hydride (0.48 mL, 1.80 mmol) and triethylborane (1 M solution in *n*-hexane, 1.25 mL, 1.25 mmol), and the mixture was stirred for 150 min. After adding tri-*n*-butyltin hydride (0.03 mL, 0.12 mmol) and triethylborane (1 M solution in *n*-hexane, 0.12 mL, 0.12 mmol), the mixture was stirred for 30 min. The reaction was quenched and worked-up as in run 1 to give a mixture of **15a** and **15b** (501 mg, 92%).

*3.20. Hydrolysis of **15***

A mixture of **15** (run 3, 457 mg, 0.99 mmol) and NaOH (794 mg, 19.8 mmol) in MeOH:H_2O (4:1, 12.5 mL) was heated to reflux for 2 h. After the mixture was cooled to room temperature, the solvent was removed under reduced pressure and the aqueous layer was extracted with ether. The combined organic layers were washed with brine and dried. The solvent was removed in vacuo to give a residue which was purified by column chromatography (SiO_2, AcOEt:*n*-hexane, 1:4) to give **5** (258 mg, 75%). The aqueous layer was acidified with 1N HCl and extracted with ether. The combined extracts were washed with brine and dried. The solvent was removed in vacuo to give a residue which was purified by column chromatography (SiO_2, ether:*n*-hexane, 1:4, then ether) to give **16** (91 mg, 73%). The enantiomeric excess of **16** was calculated to be 53% *ee* by comparison of the $[\alpha]_D$ value.

$[\alpha]_D^{20}$ +60.0 (*c* 1.01, $CHCl_3$) [lit $[\alpha]_D$ +113 (*c* 0.5, $CHCl_3$)].[11] IR (neat) *v* cm^{-1}: 3053, 2931, 2679, 1707, 1408, 1290, 1217, 928, 723. ^1H NMR: 400 MHz ($CDCl_3$) δ: 1.42–1.53 (1H, m, C5′-H), 2.10–2.19 (1H, m, C5′-H), 2.31–2.46 (4H, m, CH_2COOH, C4′-H), 3.05–3.13 (1H, m, C1-H), 5.67–5.70 (1H, m, C2′-H), 5.77–5.80 (1H, m, C3′-H), 10.4 (1H, m, –COOH). ^{13}C NMR: 100 MHz ($CDCl_3$) δ: 29.62 (C5′), 31.79 (C4′), 40.19 (C2), 41.73 (C1′), 131.74 (C3′), 133.37 (C2′), 179.55 (–COOH). LR-EIMS: 127 (M^++H), 108, 79, 67, 66. HR-EIMS: calcd for $C_7H_{10}O_2$: 126.0607; found: 126.0691.

*3.21. Radical cyclization of (1*R,2R*)-**12***

To a mixture of (1*R*,2*R*)-**12** (263 mg, 0.40 mmol) and MAD (0.8 M solution in toluene, 4 mL, 3.2 mmol) were successively added tri-*n*-butyltin hydride (0.16 mL, 0.6 mmol) and triethylborane (1.0 M solution in *n*-hexane, 0.42 mL, 0.42 mmol), and the mixture was stirred for 3 h at −78°C. The reaction was quenched by adding 1N HCl (3 mL) and worked-up as above to give (1*R*,2*R*)-**17** (201 mg, 95%): IR (neat) *v* cm^{-1}: 3057, 2935, 2862, 1718, 1489, 1448, 1340, 1020, 891, 862, 806, 688. ^1H NMR: 400 MHz ($CDCl_3$) δ: 1.05–1.44 (6H, m, C3″-H, C4″-H, C5″-H, C6″-H, C2′-H,

C5-H), 1.58–1.63 (2H, m, C4′-H, C5′-H), 1.75–1.87 (2H, m, C2′-H, C6″-H), 2.02–2.09 (2H, m, C3″-H, C5-H), 2.27–2.35 (2H, m, C4-H), 2.83–2.91 (1H, m, C1-H), 3.92–3.96 (1H, m, C1′-H), 4.04 (1H, d, $J=15.9$, NCH_2Ph), 4.63 (1H, d, $J=15.9$, NCH_2Ph), 4.77 (1H, ddd, $J=4.4$, 10.4, 10.5, C2″-H), 5.54–5.59 (1H, m, C3-H), 5.72–5.76 (1H, m, C2-H), 7.32–7.36 (1H, m, Ph), 7.39–7.51 (9H, m, Ph), 7.57–7.59 (2H, m, Ph), 7.79–7.81 (2H, m, Ph). ^{13}C NMR: 100 MHz ($CDCl_3$) δ: 23.75 (C4″), 25.19 (C5″), 29.38 (C5), 31.80 (C4), 32.59 (C3″), 32.66 (C6″), 40.01 (C2′), 41.74 (C1), 47.45 (CH_2Ph), 60.89 (C1″), 71.42 (C2″), 126.97, 127.04, 127.15, 127.30, 128.72, 128.81, 128.90, 128.81, 131.41 (C3), 131.99, 133.45 (C2), 136.43, 140.46, 140.60, 141.53, 172.02 (C=O). LR-FABMS: 530 (M^++H). HR-FABMS: calcd for $C_{32}H_{36}NO_4S$: 530.2370; found: 530.2359.

A mixture of (1*R*,2*R*)-**17** (201 mg, 0.381 mmol) and NaOH (93 mg, 2.34 mmol) in MeOH:water (4:1, 4 mL) was refluxed for 1.5 h. The usual work-up gave 2-cyclopentenyl acetic acid (31 mg, 64%) with $[\alpha]_D^{19}$ −67.1 (*c* 0.86, $CHCl_3$), 59% *ee*. IR (neat) ν cm^{-1}: 3053, 2931, 2679, 1707, 1408, 1290, 1217, 928, 723. ^1H NMR: 400 MHz ($CDCl_3$) δ: 1.42–1.53 (1H, m, C5′-H), 2.10–2.19 (1H, m, C5′-H), 2.31–2.46 (4H, m, CH_2COOH, C4′-H), 3.05–3.13 (1H, m, C1-H), 5.67–5.70 (1H, m, C2′-H), 5.77–5.80 (1H, m, C3′-H), 10.4 (1H, m, –COOH). ^{13}C NMR: 100 MHz ($CDCl_3$) δ: 29.62 (C5′), 31.79 (C4′), 40.19 (C2), 41.73 (C1′), 131.74 (C3′), 133.37 (C2′), 179.55 (–COOH). LR-EIMS: 127 (M^++H), 108, 79, 67. HR-EIMS: calcd for $C_7H_{10}O_2$: 126.0607; found: 126.0691.

*3.22. Radical cyclization of (1*R*,2*R*)-**14***

To a mixture of (1*R*,2*R*)-**14** (268 mg, 0.40 mmol) and MAD (0.4 M solution in toluene, 4 mL, 1.6 mmol) with stirring at −78°C were successively added tri-*n*-butyltin hydride (0.21 mL, 0.78 mmol) and triethylborane (1.0 M solution in *n*-hexane, 0.93 mL, 0.93 mmol), and the mixture was stirred for 2 h at −78°C. The reaction was quenched by adding 1N HCl (3 mL). The reaction was worked-up as above to give (1*R*,2*R*)-**18** (85 mg, 39%) and (1*R*,2*R*)-**19** (76 mg, 35%). (1*R*,2*R*)-**18**: IR (neat) ν cm^{-1}: 3027, 2934, 2861, 1730, 1489, 1447, 1340, 1156, 1092, 891, 759, 716, 689. ^1H NMR: 400 MHz ($CDCl_3$) δ: 0.85–1.26 (6H, m, C3″-H, C4″-H, C5″-H, C6″-H, C2′-H, C5-H), 1.48–1.80 (4H, m, C4′-H, C5′-H), 1.81–1.89 (3H, m, C2′-H, C6″-H), 1.96–1.97 (1H, m), 2.09–2.12 (1H, m, C3″-H, C5-H), 2.39–2.43 (1H, m, C4-H), 3.93 (1H, ddd, $J=4.6$, 10.9, 10.9, C1′-H), 4.10 (1H, d, $J=15.8$, –N–CH_2–Ph), 4.61 (1H, d, $J=15.6$, –N–CH_2–Ph), 4.80 (1H, ddd, $J=4.6$, 10.3, 10.4, C2″-H), 5.44 (1H, dd, $J=2.2$, 10.1, C3-H), 5.69 (1H, ddd, $J=3.4$, 10.0, 5.9, C2-H), 7.30–7.34 (1H, m, Ph), 7.38–7.58 (11H, m, Ph), 7.79–7.81 (2H, m, Ph). ^{13}C NMR: 100 MHz ($CDCl_3$) δ: 20.90 (C6), 23.74 (C4″), 24.95 (C5), 25.17 (C5″), 28.66 (C4), 31.88 (C3″), 32.04 (C1), 32.59 (C6″), 40.34 (C2′), 47.45 (CH_2Ph), 60.86 (C1″), 71.45 (C2″), 126.96, 127.03, 127.14, 127.28, 128.07, 128.71, 128.81, 128.90, 129.83, 132.01 (C2), 136.45, 140.44, 140.57, 141.50, 171.92 (C=O). LR-FABMS *m*/*z*: 544 (M^++H). HR-FABMS: calcd for $C_{33}H_{38}NO_4S$ (M^++H): 544.2553; found: 544.2484. (1*R*,2*R*)-**19**: $[\alpha]_D^{16}$ −42.1 (*c* 1.0, $CHCl_3$). IR (neat) ν cm^{-1}: 3061, 3029, 2935, 2860, 1714, 1654, 1489, 1446, 1331, 1264, 1155, 1092, 1038, 892, 760, 689. ^1H NMR: 400 MHz ($CDCl_3$) δ: 1.20–1.29 (4H, m, C3′-H, C4′-H, C5′-H, C6′-H), 1.51–1.65 (4H, m, C4′-H, C5′-H, C5-H), 1.80–1.85 (1H, m, C6′-H), 2.06–2.18 (5H, m, C3′-H, C4-H, C6-H), 3.93–4.00 (1H, m, C1′-H), 4.16 (1H, d, $J=15.6$, NCH_2Ph), 4.56 (1H, d, $J=15.8$, NCH_2Ph), 4.76 (1H, ddd, $J=4.6$, 10.5, 10.5, C2′-H), 4.99–5.07 (2H, m, C8-H), 5.33 (1H, dt, $J=15.6$, 1.5, C2-H), 5.81 (1H, ddt, $J=10.2$, 17.1, 6.6, C7-H), 6.83 (1H, dt, $J=15.9$, 6.8, C3-H), 7.32–7.34 (1H, m, Ph), 7.38–7.57

(11H, m, Ph), 7.79–7.81 (2H, m, Ph). ^{13}C NMR: 100 MHz ($CDCl_3$) δ: 20.90 (C4′), 23.75 (C5′), 25.19 (C5), 31.44 (C6′), 32.01 (C3′), 32.26 (C6′), 33.07 (C4), 47.41 (CH_2Ph), 60.86 (C1′), 71.38 (C2′), 115.14 (C8), 121.02 (C2), 126.97, 127.04, 127.13, 127.23, 128.68, 128.80, 13188, 136.48, 137.90 (C7), 140.38, 140.65, 141.60, 149.44 (C3), 165.65 (C=O). LR-FABMS: 544 (M^++H), 167. HR-FABMS: calcd for $C_{33}H_{38}NO_4S$ (M^++H): 544.2546; found: 544.2491.

A mixture of (1*R*,2*R*)-**18** (85 mg, 0.16 mmol) and NaOH (91 mg, 2.28 mmol) in MeOH:water (4:1, 1.6 mL) was refluxed for 6 h. The usual work-up gave 2-cyclohexenyl acetic acid (15.1 mg, 68%) with $[\alpha]_D^{14}$ −30 (*c* 0.76, $CHCl_3$), 35% *ee* [lit. $[\alpha]_D^{27}$ +84 (*c* 2.6, $CHCl_3$) for (*S*)-isomer].[12]

3.22.1. 2-Cyclohexenyl acetic acid

IR (neat) ν cm^{-1}: 2927, 1707, 1410, 1292, 1202, 941, 721, 680. ^{1}H NMR: 400 MHz ($CDCl_3$) δ: 1.35–1.26 (1H, m, C5′-H), 1.52–1.62 (1H, m, C5′-H), 1.68–1.73 (1H, m, C6′-H), 1.83–1.90 (1H, m, C6′-H), 1.95–2.02 (2H, m, C4′-H), 2.30 (1H, dd, J=8.0, 15.2, CH_2COOH), 2.37 (1H, dd, J=6.8, 15.1, CH_2COOH), 2.55–2.62 (1H, m, C1′-H), 5.57 (1H, dd, J=2.2, 9.9, C2′-H), 5.74 (1H, ddd, J=3.4, 5.8, 9.8, C3′-H), 10.6–12.0 (1H, bs, –COOH). ^{13}C NMR: 100 MHz ($CDCl_3$) δ: 20.90 (C5′), 24.96 (C6′), 28.73 (C4′), 32.01 (C1′), 40.57 (C2), 128.39 (C3′), 129.79 (C2′), 179.25 (–COOH). LR-EIMS: 140 (M^++H), 122, 80, 79, 67. HR-EIMS: calcd for $C_8H_{12}O_2$: 140.0782; found: 140.0846.

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