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STEREOSELECTIVE CONSTRUCTION OF FOUR CONSECUTIVE STEREOCENTERS USING [2,3]-WITTIG REARRANGEMENT REACTION#

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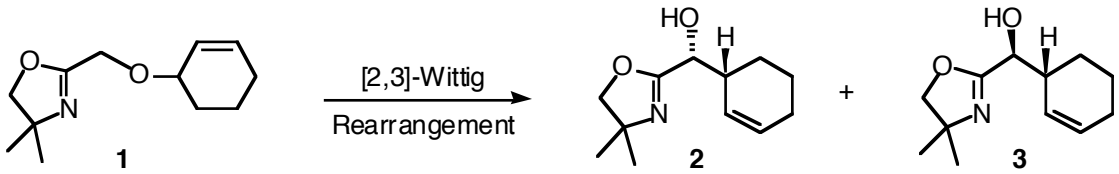
Abstract– A diastereoselective construction of four consecutive stereocenters has been achieved using [2,3]-Wittig rearrangement reactions of oxazoline derivatives.

Construction of consecutive stereocenters in an efficient and shortest possible way continues to remain as a fascinating problem among synthetic organic chemists. Over the past few decades, there has been an intense interest in the development of novel methodology directed to achieve this goal.[1] The [2,3]-Wittig rearrangement reaction was well exploited by others as a powerful tool for the stereoselective construction of carbon-carbon stereocenters.[2] In our effort to develop a novel methodology for the stereoselective construction of consecutive stereocenters, we exploited the characteristics of [2,3]-Wittig rearrangement reaction. Herein we report a diastereoselective construction of four consecutive stereocenters.

Table 1. [2,3]-Wittig Rearrangement of Oxazoline (1)[a]



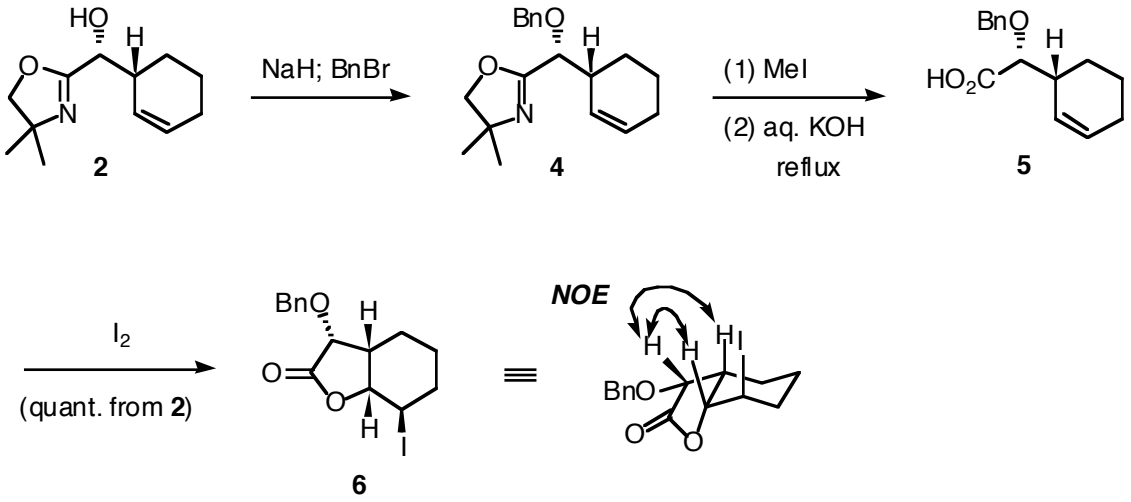
1 **2** **3**

entry	base	solvent	yield (%)	ratio[b] **2** : **3**
1	$LiN(TMS)_2$	THF	0	–
2	BuLi	THF	68	3.7 : 1
3	BuLi	THF–HMPA	69	4.0 : 1
4	LDA	THF	63	4.6 : 1
5	LDA	THF–HMPA	70	4.2 : 1

(a) All reactions were run at –78 °C under argon atmosphere.
(b) Product ratios were determined by ^{1}H NMR spectroscopy.

First of all, [2,3]-Wittig rearrangement reaction of ether (**1**) was investigated. The substrate (**1**) was prepared from cyclohex-2-en-1-ol and 2-chloromethyl-4,4-dimethyl-2-oxazoline.[3] The crucial [2,3]-Wittig rearrangement reaction was attempted under a variety of conditions, and the results are summarized in Table 1. The best result, 70% yield (**2** : **3** = 4.2 : 1), was obtained for the reaction using a 10 : 1 mixture of THF and HMPA as solvent in the presence of LDA. The stereochemistry of the oxazoline (**2**) was determined after the conversion of **2** to iodolactone (**6**) as depicted in Scheme 1. Benzylation of **2** followed by quaternarization of nitrogen in the oxazoline ring, and hydrolysis provided, *via* **4**, carboxylic acid (**5**), which was next subjected to iodolactonization to lead to the iodide (**6**). The relative configuration of **6** was established on the basis of NOESY correlations as shown in Scheme 1.

Scheme 1

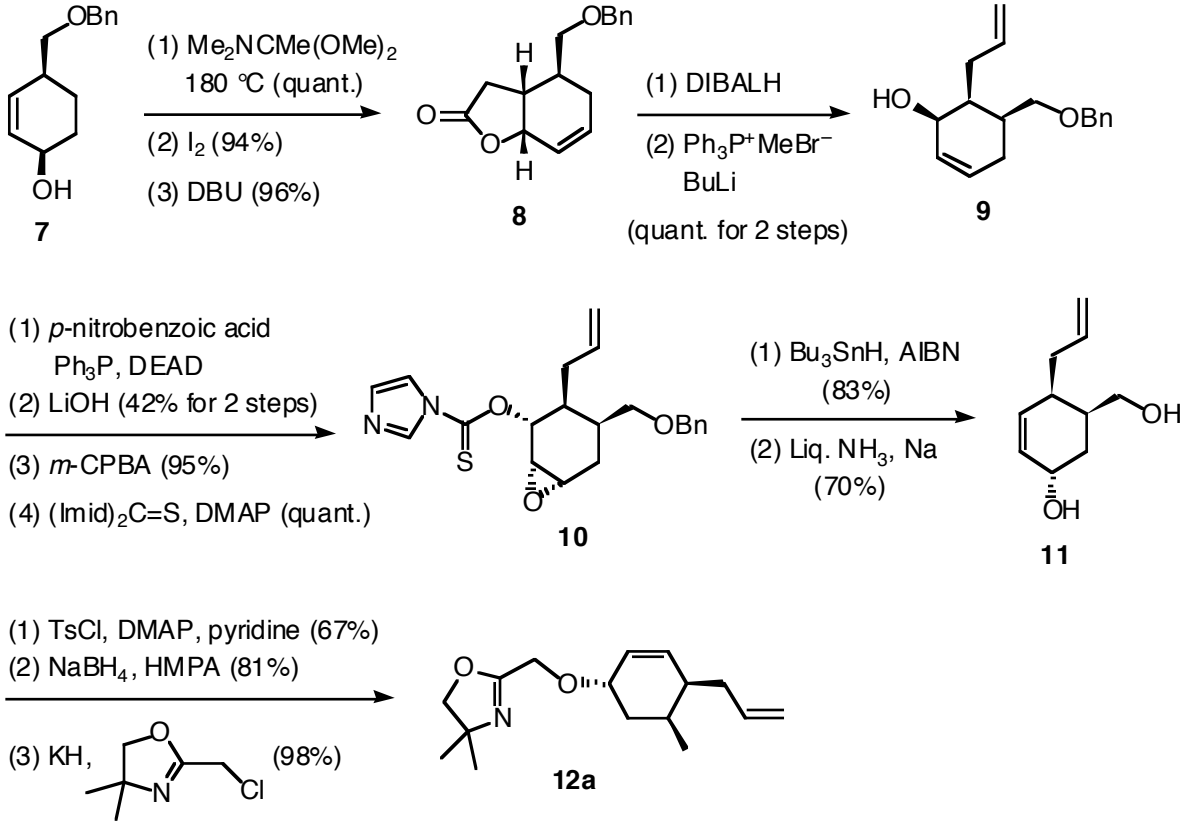


Based on this result, the [2,3]-Wittig rearrangement reaction was next examined employing ethers (**12a**-**c**). The requisite ether (**12a**) was synthesized as described below. An optically active allylic alcohol (**7**)[4] was transformed into lactone (**8**) in the usual manner (1. [3,3]-sigmatropic rearrangement, 2. iodolactonization, 3. elimination of HI, 90% overall yield), which on reduction with DIBALH and Wittig reaction of the resulting lactol provided alcohol (**9**) in quantitative yield. After inversion of the stereochemistry of the hydroxy group of **9** *via* the Mitsunobu protocol, stereoselective epoxidation followed by thioimidazolide formation gave rise to epoxide (**10**). Epoxide ring opening of **10** was conducted under radical conditions to yield the corresponding allylic alcohol, in 83% yield, which was subjected to debenzylation to afford diol (**11**) in 70% yield. Tosylation of the primary hydroxy group of **11**, followed by reduction with $NaBH_4$ (81%) and etherification with 2-chloromethyl-4,4-dimethyl-2-oxazoline furnished **12a** in 98% yield. Other ethers (**12b** and **12c**) were prepared in a similar way as described above (Scheme 2).

With the ethers (**12**) in hand, the [2,3]-Wittig rearrangement reaction was examined. Results of the rearrangement are summarized in Table 2. When the reaction was performed on **12b**, alcohols (**13b** and

14b) were obtained in moderate yield though with low diastereoselectivity (1.2–1.7 : 1). As a next step, the effect of R^2 substituent was evaluated. The rearrangement reaction of **12c** gave alcohols (**13c** : **14c** = 2.6 : 1) in 91% yield in the presence of BuLi. Changing the R^1 substitution from benzyloxymethyl to methyl group gave the desired alcohol (**13a**), in 50% yield, as a major product with a 7.3 : 1 ratio of two diastereomers. The stereochemistry of **13** and **14** could be inferred from their ^{1}H NMR spectra.

Scheme 2

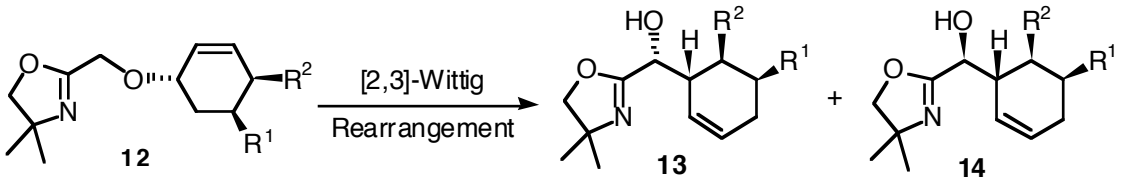


The high selectivity of the present rearrangement may be attributed to the interactions of the substituent on cyclohexene ring with dimethyl group of oxazoline ring in the transition state (**15B**). This non-bonding interaction is absent in the transition state (**15A**), which gives rise to the desired alcohol (**13**) as a major product (Figure 1).[5]

This methodology could be adaptable for the synthesis of some bioactive natural products such as compactin,[6] mevinolin,[7] and their dihydro derivatives.[8,9,10]

In conclusion, a diastereoselective synthesis of four consecutive stereocenters has been achieved by using [2,3]-Wittig rearrangement reaction as the key step.

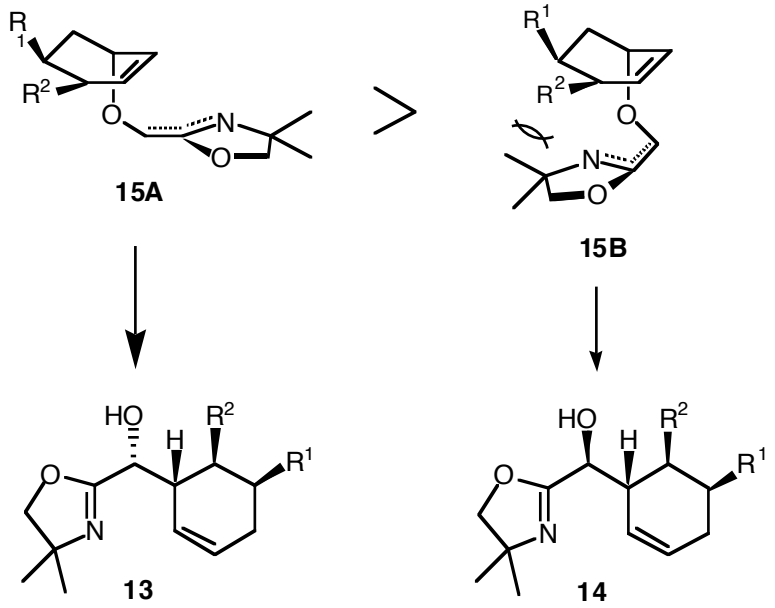
Table 2. [2,3]-Wittig Rearrangement of Oxazolines (12)[a]



entry	substrate	R^1	R^2	base	sovent	yield (%)	ratio[b] **13** : **14**
1	**12b**	CH_2OBn	CH_2CH_2OTr	BuLi	THF	39	1.7 : 1
2	**12b**	CH_2OBn	CH_2CH_2OTr	BuLi	THF–HMPA	53	1.4 : 1
3	**12b**	CH_2OBn	CH_2CH_2OTr	LDA	THF–HMPA	68	1.2 : 1
4	**12c**	CH_2OBn	$CH_2CH=CH_2$	BuLi	THF	91	2.6 : 1
5	**12c**	CH_2OBn	$CH_2CH=CH_2$	BuLi	THF–HMPA	65	2.4 : 1
6	**12c**	CH_2OBn	$CH_2CH=CH_2$	LDA	THF	48	1.7 : 1
7	**12a**	Me	$CH_2CH=CH_2$	BuLi	THF	50	7.3 : 1

(a) All reactions were carried out at –78 °C under argon atmosphere.
(b) Product ratios were determined by ^{1}H NMR spectroscopy.

Figure 1



EXPERIMENTAL

General: All melting points are uncorrected. IR spectra were measured on a JASCO IR-Report 100 spectrometer. ^{1}H NMR spectra were recorded at 300 MHz on a Varian Gemini 200 spectrometer with tetramethylsilane as an internal standard. MS and HRMS spectra were obtained with a JMS AX500 mass

spectrometer and a JMS DX303. The specific rotations were measured using a Horiba SEPA-300 spectrometer.

2-(2-Cyclohexenyl)oxymethyl-4,4-dimethyl-2-oxazoline (1)

To a stirred solution of 2-cyclohexen-1-ol (244 mg, 2.49 mmol) and 2-chloromethyl-4,4-dimethyl-2-oxazoline (800 mg, 5.97 mmol) in anhydrous DME (15 mL) was added dropwise a suspension of KH (30% in oil, 681 mg, 4.98 mmol) in anhydrous DME (5 mL) at 0 °C. After stirring at 0 °C for 2 h, water was added slowly and the resulting mixture was diluted with Et_2O. The mixture was separated, and the organic layer was washed with brine, dried over $MgSO_4$, and evaporated to leave an oil, which was purified by flash chromatography eluting with 2:1 hexane/EtOAc to give oxazoline (**1**) (386 mg, 74%) as a colorless oil. IR (neat) 1660 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.30 (6H, s), 1.42–2.12 (6H, m), 4.00 (2H, s), 4.01 (1H, br s), 4.16 (1H, d, *J*=13.6 Hz), 4.22 (1H, d, *J*=13.6 Hz), 5.77–5.93 (2H, m). ^{13}C NMR ($CDCl_3$) δ 18.9, 24.8, 27.7, 28.0, 28.1, 62.4, 66.9, 73.2, 79.1, 127.0, 131.4, 162.9. MS (EI) 109 (M^+). Anal. Calcd for $C_{12}H_{19}NO_2$: C, 68.87; H, 9.15; N, 6.69. Found: C, 68.72; H, 9.08; N, 6.44.

2-{(*R)-[(1*R**)-2-Cyclohexenyl]hydroxymethyl}-4,4-dimethyl-2-oxazoline (2)**

To a stirred solution of LDA, prepared from *i*-Pr_2NH (36.8 μL, 0.262 mmol) and BuLi (1.60 M in hexane, 0.154 mL, 0.246 mmol), was added dropwise an anhydrous THF solution (1 mL) of the oxazoline (**1**) (34.3 mg, 0.164 mmol) at –78 °C, and the mixture was stirred for 2 h. After addition of saturated aqueous NH_4Cl at –78 °C, the resulting mixture was allowed to warm to rt with stirring. The solution was diluted with Et_2O, and the resulting mixture was separated. The ethereal layer was washed with brine, dried over $MgSO_4$, and evaporated. The residue was purified by flash chromatography eluting with 2:1 hexane/EtOAc to yield oxazoline (**2**) (21.6 mg, 63%), which was crystallized from Et_2O to afford colorless prisms, mp 104 °C. IR (neat) 3175, 1655 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.31 (6H, s), 1.51–1.66 (2H, m), 1.73–1.87 (2H, m), 1.96–2.02 (2H, m), 2.51–2.59 (1H, m), 2.60 (1H, d, *J*=7.0 Hz), 4.03 (3H, s), 4.14 (1H, dd, *J*=7.0, 4.5 Hz), 5.56–5.64 (1H, m), 5.84–5.93 (1H, m). ^{13}C NMR ($CDCl_3$) δ 21.5, 24.9, 25.4, 28.1, 28.3, 39.8, 66.8, 70.5, 79.9, 125.7, 130.6, 167.0. MS (EI) 209 (M^+). Anal. Calcd for $C_{12}H_{19}NO_2$: C, 68.87; H, 9.15; N, 6.69. Found: C, 68.74; H, 9.19; N, 6.50.

2-{(*R)-Benzyloxy-[(1*R**)-2-cyclohexenyl]methyl}-4,4-dimethyl-2-oxazoline (4)**

To a stirred suspension of NaH (60% in oil, 2.14 mg, 53.6 μmol, washed with anhydrous hexane) in anhydrous THF (1 mL) was added dropwise an anhydrous THF solution (1 mL) of the alcohol (**2**) (11.1 mg, 53.1 μmol) at 0 °C. After stirring at the same temperature for 20 min, BnBr (6.40 μL, 53.6 μmol) was

added dropwise at 0 °C. The mixture was stirred at 0 °C for 10 min and at rt for 12 h. To the mixture was added water at 0 °C, and the resulting mixture was diluted with Et_2O. After separation, the ethereal layer was washed with brine, dried over $MgSO_4$, and evaporated. The residue was purified by flash chromatography eluting with 10:1 hexane/EtOAc to furnish benzyl ether (**4**) (15.9 mg, 100%) as a colorless oil. IR (neat) 1660 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.28 (3H, s), 1.30 (3H, s), 1.30–1.40 (1H, m), 1.44–1.57 (1H, m), 1.57–1.69 (1H, m), 1.69–1.80 (1H, m), 1.96–2.02 (2H, m), 2.51–2.64 (1H, m), 3.81 (1H, d, *J*=8.0 Hz), 3.91 (1H, d, *J*=7.5 Hz), 3.99 (1H, d, *J*=7.5 Hz), 4.47 (1H, d, *J*=11.0 Hz), 4.64 (1H, d, *J*=11.0 Hz), 5.78 (1H, ddd, *J*=9.5, 6.0, 3.0 Hz), 5.84–5.92 (1H, m), 7.26–7.38 (5H, m). ^{13}H NMR ($CDCl_3$) δ 21.2, 24.9, 25.0, 28.3, 28.4, 38.2, 67.0, 71.9, 78.9, 79.0, 127.4, 127.7, 128.0, 128.3, 128.7, 137.9, 193.8. MS (EI) 249 (M^+). Anal. Calcd for $C_{19}H_{25}NO_2$: C, 76.22; H, 8.42; N, 4.68. Found: C, 76.11; H, 8.40; N, 4.74.

(*R)-Benzyloxy-[(1*R**)-2-cyclohexenyl]acetic acid (5)**

A mixture of the benzyl ether (**4**) (15.9 mg, 53.1 μmol) and MeI (9.9 μL, 0.159 mmol) in DMSO (2 mL) was stirred at rt for 22 h. After removal of the solvent, the residue was dissolved in 2N KOH solution (5 mL), and the resulting mixture was refluxed for 8 h. After washing with Et_2O, the aqueous layer was acidified with 10% HCl solution. The mixture was extracted with Et_2O, and the ethereal layer was washed with brine, dried over $MgSO_4$, and evaporated to yield a crude product (**5**) (13.5 mg, 100%), which was used in the next reaction without further purification. IR (neat) 3200 and 1720 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.46–1.58 (2H, m), 1.68–1.85 (2H, m), 1.95–2.04 (2H, m), 2.60–2.67 (1H, m), 3.80 (1H, d, *J*=6.0 Hz), 4.46 (1H, d, *J*=11.8 Hz), 4.75 (1H, d, *J*=11.8 Hz), 5.70 (1H, br dd, *J*=9.5, 1.5 Hz), 5.83 (1H, ddd, *J*=9.5, 6.0, 3.0 Hz), 7.26–7.99 (5H, m). MS (EI) *m/z* 246 (M^+). HRMS calcd for $C_{15}H_{18}O_3$ (M^+) 246.1255, found: 246.1236.

(3*R,3a*S**,7*S**,7a*R**)-3-Benzyloxy-3a,4,5,6,7,7a-hexahydro-7-iodo-2(3*H*)-benzofuranone (6)**

To a stirred solution of the carboxylic acid (**5**) (9.1 mg, 35.5 μmol) in a 1:1 mixture of DME and water (2 mL) was added I_2 (9.9 mg, 39.1 μmol) at rt, and the mixture was stirred at rt for 6 h. After addition of saturated aqueous $Na_2S_2O_4$, the mixture was diluted with Et_2O. After separation, the ethereal layer was washed with brine, dried over $MgSO_4$, and evaporated to leave an oil, which was purified by flash chromatography eluting with 2:1 hexane/EtOAc to provide **6** (13.2 mg 100%) as a colorless oil. IR (neat) 1790 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.30–1.39 (1H, m), 1.61–1.71 (2H, m), 1.75–1.84 (2H, m), 1.93 (1H, br dd, *J*=15.0, 3.5 Hz), 2.94 (1H, ddd, *J*=15.0, 6.2, 3.3 Hz), 4.23 (1H, d, *J*=6.2 Hz), 4.54 (1H, t, *J*=3.3 Hz), 4.68 (1H, dd, *J*=6.5, 3.3 Hz), 4.72 (1H, d, *J*=12.0 Hz), 4.85 (1H, d, *J*=12.0 Hz), 7.28–7.37 (5H, m). ^{13}C

NMR ($CDCl_3$) □19.9, 21.4, 27.5, 29.9, 36.1, 72.4, 78.3, 78.5, 128.0, 128.2, 128.7, 136.9, 176.7. MS (EI) 245 (M^+). HRMS calcd for $C_{15}H_{17}O_3$ (M^+) 245.1177, found: 245.1173.

(–)-(3a*S*,4*S*,7a*R*)-4-Benzyloxymethyl-3a,4,5,7a-tetrahydro-2(3*H*)-benzofuranone (8)

A mixture of the alcohol (**7**) (1.68 g, 7.72 mmol) and *N,N*-dimethylacetamide dimethyl acetal (2.92 mL, 30.9 mmol) in anhydrous toluene (15 mL) was heated at 180 °C in a strainless sealed tube for 3 h. After removal of the solvent under reduced pressure, the residue was purified by flash chromatography eluting with 2:1 hexane/EtOAc to give rise to the amide (2.22 g, 100%) as a colorless oil. $[□]_D^{22}$ –112.97° (*c* 1.12, $CHCl_3$). IR (neat) 1640 cm^{-1}. ^1H NMR ($CDCl_3$) □1.49 (1H, ddt, *J*=10.5, 10.0, 7.0 Hz), 1.65 (1H, dddd, *J*=9.0, 7.0, 5.0, 3.0 Hz), 2.04 (2H, br t, *J*=6.0 Hz), 2.14 (1H, dd, *J*=14.0, 9.0 Hz), 2.12–2.25 (1H, m), 2.41 (1H, dd, *J*=14.0, 5.0 Hz), 2.83–2.93 (1H, m), 2.89 (3H, s), 2.90 (3H, s), 3.39 (1H, dd, *J*=9.0, 6.0 Hz), 3.46 (1H, dd, *J*=9.0, 7.0 Hz), 4.46 (1H, d, *J*=11.5 Hz), 5.62–5.73 (1H, m), 7.24–7.38 (5H, m). ^{13}C NMR ($CDCl_3$) □22.6, 24.8, 33.3, 35.1, 35.8, 36.8, 37.7, 72.3, 73.4, 127.8, 128.0, 128.1, 128.8, 130.8, 139.1, 172.8. MS (EI) 287 (M^+). Anal. Calcd for $C_{18}H_{25}NO_2$: C, 75.23; H, 8.77; N, 4.87. Found: C, 75.17; H, 8.82; N, 4.90.

A mixture of the amide (2.22 g, 7.72 mmol) and I_2 (2.16 g, 8.49 mmol) in a 1:1 mixture of DME and water (60 mL) was stirred at rt for 26 h. After addition of saturated aqueous $Na_2S_2O_4$, the resulting mixture was extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, and evaporated to leave a crude product, which was purified by flash chromatography eluting with 5:1 hexane/EtOAc to afford the iodide (2.80 g, 94%) as colorless prisms, mp 126–127 °C. $[□]_D^{23}$ –0.13° (*c* 1.02, $CHCl_3$). IR (neat) 1775 cm^{-1}. ^1H NMR ($CDCl_3$) □1.21 (1H, dq, *J*=12.5, 3.0 Hz), 1.46–1.56 (1H, m), 1.94 (1H, dq, *J*=12.5, 3.0 Hz), 2.10–2.25 (1H, m), 2.20 (1H, dd, *J*=16.0, 7.5 Hz), 2.41 (1H, dd, *J*=16.0, 13.0 Hz), 2.34–2.45 (1H, m), 2.80–2.94 (1H, m), 3.22 (1H, dd, *J*=8.5, 8.0 Hz), 3.36 (1H, dd, *J*=8.5, 5.0 Hz), 3.79 (1H, ddd, *J*=12.5, 9.5, 4.0 Hz), 4.43 (1H, d, *J*=11.0 Hz), 4.50 (1H, d, *J*=11.0 Hz), 4.69 (1H, dd, *J*=9.5, 7.0 Hz), 7.26–7.38 (5H, m). ^{13}C NMR ($CDCl_3$) □25.3, 27.3, 36.0, 36.4, 39.0, 72.2, 73.2, 85.9, 127.7, 127.9, 128.6, 137.9, 175.4. MS (EI) 295 (M^+–91). Anal. Calcd for $C_{16}H_{19}O_3I$: C, 49.76; H, 4.96; I, 32.86. Found: C, 49.59; H, 5.01; I, 32.97.

A mixture of the iodide (83.6 mg, 0.127 mmol) and DBU (0.323 mL, 2.17 mmol) in anhydrous C_6H_6 (5 mL) was heated under reflux for 3 h. After addition of water, the mixture was extracted with Et_2O. The ethereal layer was washed with brine, dried over $MgSO_4$, evaporated to leave an oil, which was purified by flash chromatography eluting with 3:1 hexane/EtOAc to furnish lactone (**8**) (54.0 mg, 96%) as a

colorless oil. $[\alpha]_D^{24}$ –98.15° (*c* 1.38, $CHCl_3$). IR (neat) 1775 and 1650 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.90 (1H, ddt, *J*=17.0, 10.0, 1.0 Hz), 2.12 (1H, dtd, *J*=17..0, 4.5, 1.0 Hz), 2.25 (1H, ddd, *J*=20.0, 9.0, 1.0 Hz), 2.28 (1H, td, *J*=8.0, 1.0 Hz), 2.32 (1H, ddd, *J*=20.0, 10.0, 1.0 Hz), 2.96–3.09 (1H, m), 3.32 (1H, ddd, *J*=8.5, 7.0, 1.0 Hz), 4.46 (1H, d, *J*=11.5 Hz), 4.54 (1H, d, *J*=11.5 Hz), 5.01–5.08 (1H, m), 5.65–5.73 (1H, m), 5.89–5.98 (1H, m), 7.25–7.40 (5H, m). ^{13}C NMR ($CDCl_3$) δ 22.9, 27.6, 33.8, 35.2, 72.4, 73.0, 76.7, 124.7, 127.6, 127.7, 128.4, 130.4, 138.0, 176.8. MS (EI) 258 (M^+). Anal. Calcd for $C_{16}H_{18}O_3$: C, 74.40; H, 7.02. Found: C, 74.36; H, 7.14.

(–)-(1*R*,5*S*,6*S*)-5-Benzyloxymethyl-6-(2-propenyl)-2-cyclohex-1-ol (9)

To a stirred solution of the lactone (**8**) (1.91 g, 7.40 mmol) in anhydrous Et_2O (70 mL) was added dropwise DIBALH (0.95 M in hexane, 8.57 mL, 8.14 mmol) at –78 °C, and then the mixture was stirred at the same temperature for 30 min. After successive addition of water (8.57 mL), Et_2O (20 mL) and hexane (20 mL), the resulting mixture was allowed to warm to rt with stirring. After 12 h of stirring, to the solution were added Celite and $MgSO_4$, and then the mixture was further stirred for 5 min. The mixture was filtered through Celite, the firtrate was concentrated to yield a crude lactol (2.16 g), which was used in the next step without further purification.

To a stirred suspension of $Ph_3P^+MeBr^-$(5.28 g, 14.8 mmol) in anhydrous THF (70 mL) was added dropwise $NaN(TMS)_2$ (1.0 M in THF, 14.8 mL, 14.8 mmol), and then the resulting mixture was stirred at the same temperature for 15 min. To this solution was added an anhydrous THF solution (10 mL) of the above lactol (2.16 g) at –78 °C. After stirring at –78 °C for 20 min, the mixture was refluxed for 2 h. After addition of water, the mixture was diluted with Et_2O. The resulting mixture was separated, and then the organic layer was washed with brine, dried over $MgSO_4$, and evaporated to give an oil, which was purified by flash chromatography eluting with 4:1 hexane/EtOAc to produce **9** (1.92 g, 100%) as a colorless oil. $[\alpha]_D^{24}$ –41.15° (*c* 1.30, $CHCl_3$). IR (neat) 3350, 1630, 1600 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.97–2.25 (5H, m), 2.30–2.43 (1H, m), 3.00 (1H, br s), 3.42 (1H, dd, *J*=9.6, 4.1 Hz), 3.59 (1H, dd, *J*=9.6, 4.9 Hz), 4.05 (1H, br s), 4.47 (1H, d, *J*=12.1 Hz), 4.52 (1H, d, *J*=12.1 Hz), 4.99 (1H, dd, *J*=9.5, 1.0 Hz), 5.06 (1H, dd, *J*=16.0, 1.5 Hz), 5.75 (2H, br s), 5.86 (1H, ddt, *J*=16.0, 9.5, 7.0 Hz), 7.19–7.42 (5H, m). ^{13}C NMR ($CDCl_3$) δ 28.4, 31.9, 34.6, 40.2, 66.3, 70.7, 73.1, 115.7, 127.5, 127.6, 128.0, 128.3, 129.3, 137.9, 138.2. MS (EI) 240 (M^+–18). Anal. Calcd for $C_{17}H_{22}O_2$: C, 79.03; H, 8.58. Found: C, 79.02; H, 8.68.

(+)-*O*-[(1*R*,2*S*,3*S*,5*S*,6*S*)-5-Benzyloxymethyl-6-(2-propenyl)-2,3-epoxycyclohexanyl]-1-imidazothioate (10)

To a stirred solution of the alcohol (**9**) (980 mg, 3.79 mmol), Ph_3P (1.19 g, 4.56 mmol) and *p*-nitrobenzoic acid (761 mg, 4.56 mmol) in anhydrous THF (30 mL) was added dropwise DEAD (0.717 mL, 4.56 mmol) at 0 °C, and then the mixture was stirred at 0 °C for 20 min and at rt for 17.5 h. After addition of THF (30 mL) and water (60 mL), to the mixture was added $LiOH•H_2O$ (1.59 g, 37.9 mmol) at rt and the resulting solution mixture was stirred at rt for 6.5 h. After removal of the solvent under reduced pressure, the residue was diluted with Et_2O. The ethereal layer was washed with brine, dried over $MgSO_4$, and evaporated to give an oil, which was purified by flash chromatography eluting 4:1 hexane/EtOAc to afford the desired alcohol (409 mg, 42%) as a colorless oil. $[\alpha]_D^{23}$+82.80 ° (*c* 1.07, $CHCl_3$). IR (neat) 3350, 1635 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.80–1.98 (4H, m), 1.99–2.18 (2H, m), 2.29–2.42 (1H, m), 3.95 (1H, br s), 3.41 (1H, dd, *J*=8.5, 7.0 Hz), 3.48 (1H, dd, *J*=8.5, 6.0 Hz), 4.48 (1H, d, *J*=12.0 Hz), 4.53 (1H, d, *J*=12.0 Hz), 4.96–5.05 (2H, m), 5.67–5.88 (3H, m), 7.24–7.38 (5H, m). ^{13}C NMR ($CDCl_3$) δ 26.1, 30.9, 33.4, 41.5, 67.4, 71.3, 72.9, 116.1, 127.5, 128.4, 130.0, 130.4, 137.6, 138.6. MS (EI) 241 (M^+–17). Anal. Calcd for $C_{17}H_{22}O_2$: C, 79.03; H, 8.58. Found: C, 78.99; H, 8.68.

To a stirred solution of the alcohol (177 mg, 0.686 mmol) in anhydrous CH_2Cl_2 (10 mL) was added *m*-CPBA (271 mg, 1.96 mmol) at rt, and then the mixture was stirred at rt for 19 h. After addition of water and Et_2O, the resulting mixture was separated. The organic layer was washed with brine, dried over $MgSO_4$, and evaporated to leave an oil, which was purified by flash chromatography eluting with 3:1 hexane/EtOAc to provide the desired epoxide (118 mg, 95%) as a colorless oil. $[\alpha]_D^{22}$ +54.06° (c 0.97, $CHCl_3$). IR (neat) 3400, 1630 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.66–1.75 (1H, m), 1.78 (1H, ddd, *J*=14.0, 7.0, 3.5 Hz), 1.95–2.11 (5H, m), 3.28–3.45 (4H, m), 3.84–3.93 (1H, m), 4.48 (2H, s), 5.00–5.06 (1H, m), 5.02 (1H, dq, *J*=17.0, 1.5 Hz), 5.75 (1H, ddt, *J*=17.0, 9.0, 7.0 Hz), 7.28–7.39 (5H, m). ^{13}C NMR ($CDCl_3$) δ 24.9, 30.7, 31.2, 39.7, 54.3, 55.2, 67.6, 70.4, 72.9, 116.6, 127.5, 127.7, 128.4, 137.1, 138.4. MS (EI) 256 (M^+–18). HRMS calcd for $C_{17}H_{20}O_2$ (M^+–18) 256.1465, found: 256.1427.

A mixture of the epoxide (175 mg, 0.638 mmol), 1,1'-thiocarbonyldiimidazole (189 mg, 0.958 mmol) and DMAP (171 mg, 1.40 mmol) in anhydrous CH_2Cl_2 (10 mL) was refluxed for 1.5 h. After evaporation of the solvent under reduced pressure, the residue was subjected to flash chromatography eluting with 1:1 hexane/EtOAc to furnish the thioimidazolide (**10**) (245 mg, 100%) as a yellowish oil. $[\alpha]_D^{23}$ +126.78° (*c* 1.59, $CHCl_3$). IR (neat) 1635 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.97 (1H, dt, *J*=15.0, 5.0 Hz), 2.03–2.27 (H, m), 3.39 (1H, t, *J*=3.0 Hz), 3.42 (1H, dd, *J*=9.0, 5.0 Hz), 3.50 (1H, ddt, *J*=14.5, 9.5, 7.0 Hz), 3.54 (1H, t, *J*=3.0 Hz), 4.52 (2H, s), 4.95–5.04 (2H, m), 5.70 (1H, ddt, *J*=14.5, 9.5, 7.0 Hz), 5.97 (1H, dd, *J*=7.0, 3.0 Hz), 7.04 (1H, dd, *J*=1.5, 1.0 Hz), 7.28–7.41 (5H, m), 7.66 (1H, dd, *J*=1.5, 1.0 Hz), 8.38 (1H, t, *J*=1.0 Hz).

^{13}C NMR ($CDCl_3$) δ 25.6, 32.0, 33.0, 36.4, 51.1, 54.1, 69.9, 73.3, 81.7, 117.2, 118.1, 127.7, 127.8, 128.5, 130.9, 135.8, 137.1, 138.1, 184.1. MS (EI) 384 (M^+). Anal. Calcd for $C_{21}H_{24}N_2O_3S$.: C, 65.50; H, 6.29; N, 7.29. Found: C, 65.14; H, 6.39; N, 7.36.

(–)-(1*S*,4*R*,5*S*)-5-Hydroxymethyl-4-(2-propenyl)-2-cyclohexen-1-ol (11)

To a stirred solution of the thioimidazolide (**10**) (245 mg, 0.638 mmol) in anhydrous toluene (40 mL) was added dropwise, over 30 min, a mixture of Bu_3SnH (0.257 mL, 0.957 mmol) and AIBN (1.0 mg, 6.09 μmol) in anhydrous toluene solution (3 mL) under reflux. After 1 h of refluxing, 10% aqueous NH_3 was added, and then the resulting mixture was stirred at rt for 9 h. After addition of Et_2O, the mixture was separated. The organic layer was washed with brine, dried over $MgSO_4$, and evaporated to give an oil, which was purified by flash chromatography eluting with 2:1 hexane/EtOAc to afford the desired alcohol (136 mg, 83%) as a colorless oil. $[\alpha]_D^{23}$ –153.77° (*c* 1.15, $CHCl_3$). IR (neat) 3350, 1635 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 1.58 (1H, dt, *J*=13.0, 3.0 Hz), 1.78 (1H, ddd, *J*=13.0, 9.0, 4.5 Hz), 1.87 (1H, dt, *J*=13.0, 9.0 Hz), 1.98 (1H, br s), 2.10–2.21 (1H, m), 2.29–2.45 (2H, m), 3.36 (1H, dd, *J*=9.0, 6.5 Hz), 3.46 (1H, dd, *J*=9.0, 7.0 Hz), 4.16 (1H, dd, *J*=7.5, 3.5 Hz), 4.50 (2H, s), 4.99 (1H, d, *J*=10.5 Hz), 5.00 (1H, d, *J*=14.5 Hz), 5.72–5.88 (3H, m), 7.23–7.46 (5H, m). ^{13}C NMR ($CDCl_3$) δ 31.3, 32.9, 33.9, 35.9, 63.9, 70.9, 72.9, 116.0, 127.6, 127.7, 128.4, 128.5, 134.2, 137.1, 138.5. MS (EI) 258 (M^+). Anal. Calcd for $C_{17}H_{22}O_2$: C, 79.03; H, 8.58. Found: C, 78.99; H, 8.63.

To a stirred solution of Na (27.8 mg, 1.12 mmol) in anhydrous NH_3 (20 mL) was added an anhydrous THF solution of the above compound (156 mg, 0.604 mmol) at –78 °C. After 15 min of stirring at –78 °C, NH_4Cl (194 mg, 3.62 mmol) was added at –78 °C, and then the resulting mixture was allowed to warm to rt with stirring. After removal of NH_3, to the mixture was added water and Et_2O. After separation, the organic layer was washed with brine, dried over $MgSO_4$, and evaporated to yield an oil, which was purified by flash chromatography eluting with 1:4 hexane/EtOAc to lead to diol (**11**) (71.3 mg, 70%) as a colorless oil. $[\alpha]_D^{22}$ –253.79 ° (*c* 1.408, $CHCl_3$). IR (neat) 3350, 1635 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 1.65 (1H, dt, *J*=13.0, 3.5 Hz), 1.74 (1H, ddd, *J*=13.0, 10.0, 4.0 Hz), 1.89 (1H, dt, *J*=13.0, 8.5 Hz), 2.10–2.25 (2H, m), 3.48 (1H, dd, *J*=10.0, 7.5 Hz), 3.50 (2H, br s), 3.64 (1H, dd, *J*=10.0, 6.5 Hz), 4.21 (1H, dd, *J*=7.0, 3.5 Hz), 4.98–5.09 (2H, m), 5.73–5.89 (3H, m). ^{13}C NMR ($CDCl_3$) δ 30.7, 33.8, 35.2, 35.9, 63.3, 63.8, 116.2, 128.4, 134.2, 137.0. MS (EI) 150 (M^+–18). HRMS calcd for $C_{10}H_{14}O$ (M^+–18) 150.1045, found: 150.1043.

(–)-2-[(1*S*,4*S*,5*S*)-5-Methyl-4-(2-propenyl)-2-cyclohexenyl]oxymethyl-4,4-dimethyl-2-oxazoline (12a)

A mixture of the diol (**11**) (79.2 mg, 0.276 mmol), TsCl (57.9 mg, 0.303 mmol) and DMAP (13.5 mg, 0.110 mmol) in pyridine (3 mL) was stirred for 40 min. After addition of water and Et_2O, the mixture was separated. The ethereal layer was washed with brine, dried over $MgSO_4$, and evaporated to leave an oil, which was purified by flash chromatography eluting with a gradient of hexane/EtOAc (2 :1 to 1 :4) to provide the desired tosylate (59.9 mg, 67%) as colorless needles, mp 87–88 °C, and the diol (**11**) (8.6 mg). $[\alpha]_D^{24}$ –123.89 ° (*c* 0.944, $CHCl_3$). IR (neat) 3350, 1350, 1175 cm^{-1}. ^1H NMR ($CDCl_3$) δ1.54 (1H, dt, *J*=13.0, 3.0 Hz), 1.70 (1H, br s), 1.68–1.81 (1H, m), 1.86 (1H, ddd, *J*=12.5, 7.5, 1.0 Hz), 1.98–2.10 (1H, m), 2.31–2.45 (2H, m), 2.46 (3H, s), 3.93 (1H, dd, *J*=9.0, 6.5 Hz), 4.04 (1H, dd, *J*=9.0, 7.0 Hz), 4.16 (1H, dd, *J*=6.5, 4.0 Hz), 4.96 (1H, dd, *J*=16.0, 1.5 Hz), 4.98 (1H, dq, *J*=9.0, 1.0 Hz), 5.62–5.79 (1H, m), 5.79 (2H, t, *J*=2.2 Hz), 7.36 (2H, d, *J*=8.5 Hz), 7.80 (1H, d, *J*=8.5 Hz). ^{13}C NMR ($CDCl_3$) δ21.5, 30.6, 32.5, 33.8, 35.3, 63.4, 70.8, 116.7, 128.0, 128.4, 129.9, 132.9, 133.4, 136.0, 145.0. MS (EI) 324 (M^++2). HRMS calcd for $C_{17}H_{24}O_4S$ (M^++2) 324.1395, found: 324.1398.

To a stirred solution of the tosylate (43.4 mg, 0.135 mmol) in anhydrous HMPA (2 mL) was added $NaBH_4$ (21.4 mg, 0.539 mmol) at 0 °C, and then the mixture was heated at 70 °C for 1 h. After addition of water and Et_2O, the mixture was separated. The ethereal layer was washed with brine, dried over $MgSO_4$, and evaporated to give an oil, which was purified by flash chromatography eluting with 2:1 hexane/EtOAc to yield the desired compound (16.6 mg, 81%) as a colorless oil. $[\alpha]_D^{24}$ –237.17 ° (*c* 1.08, $CHCl_3$). IR (neat) 3350, 1635 cm^{-1}. ^1H NMR ($CDCl_3$) δ0.92 (3H, d, *J*=7.0 Hz), 1.50 (1H, br s), 1.57 (1H, ddd, *J*=13.0, 6.5, 3.0 Hz), 1.86 (1H, ddd, *J*=12.5, 7.5, 5.0 Hz), 1.90–2.00 (1H, m), 2.06–2.20 (2H, m), 2.20–2.30 (1H, m), 4.24 (1H, t, *J*=5.5 Hz), 4.99–5.12 (2H, m), 5.69–5.90 (1H, m), 5.73 (2H, s). ^{13}C NMR ($CDCl_3$) δ 15.2, 28.7, 35.1, 37.9, 37.8, 64.9, 116.0, 128.7, 133.6, 137.2. MS (EI) 151 (M^+–1). HRMS calcd for $C_{10}H_{15}O$ (M^+–1) 151.1123, found: 151.1131.

To a stirred solution of the above alcohol (9.4 mg, 61.8 μmol) and 2-chloromethyl-4,4-dimethyl-2-oxazoline (18.2 mg, 0.124 mmol) in anhydrous DME (1 mL) was added an anhydrous DME solution (1 mL) of KH (30% in oil, 42.3 mg, 0.309 mmol) at 0 °C, and then the mixture was stirred at 0 °C for 1 h. After addition of water and Et_2O, the mixture was separated. The ethereal layer was washed with brine, dried over $MgSO_4$, and evaporated to leave an oil, which was purified by flash chromatography eluting with 2:1 hexane/EtOAc to furnish oxazoline (**12a**) (15.9 mg, 98%) as a colorless oil. $[\alpha]_D^{19}$ –142.65 ° (*c* 1.32, $CHCl_3$). IR (neat) 1660, 1635 cm^{-1}. ^1H NMR ($CDCl_3$) δ0.90 (3H, d, *J*=6.8 Hz), 1.29 (6H, s), 1.69 (1H, ddd, *J*=12.5, 6.0, 3.2 Hz), 1.82 (1H, ddd, *J*=12.5, 7.5, 5.0 Hz), 1.86–1.98 (1H, m), 2.06–2.20 (2H, m), 2.20–2.30 (1H, m), 3.99 (2H, s), 4.00–4.07 (1H, m), 4.15 (1H, d, *J*=12.5 Hz), 4.20 (1H, d, J=12.5 Hz),

4.99–5.09 (2H, m), 5.72–5.88 (3H, m). ^{13}C NMR ($CDCl_3$) 15.0, 15.2, 28.2, 28.8, 33.9, 35.2, 38.7, 62.7, 67.1, 72.9, 79.3, 116.0, 125.8, 134.5, 137.2, 163.0. MS (EI) 263 (M^+). HRMS calcd for $C_{16}H_{25}NO_2$ (M^+) 263.1885, found: 263.1866.

(–)-2-{(*R*)-[(1*S*,5*S*,6*S*)-5-Methyl-6-(2-propenyl)-2-cyclohexenyl]hydroxymethyl}-4,4-dimethyl-2-oxazoline (13a)

To a stirred solution of **12a** (13.9 mg, 0.164 mmol) in anhydrous THF (1 mL) was added dropwise BuLi (1.52 M in hexane, 38.0 L, 58.1 mol) at –78 °C, and then the mixture was stirred at –78 °C for 2 h. After addition of saturated aqueous NH_4Cl and Et_2O, the mixture was separated. The ethereal layer was washed with brine, dried over $MgSO_4$, and evaporated to yield an oil, which was purified by flash chromatography eluting with 2:1 hexane/EtOAc to lead to **13a** (6.9 mg, 50%) as a 7.3 : 1 mixture of diastereomers. $[]_D^{21}$ –38.92 ° (*c* 0.52, $CHCl_3$). IR (neat) 3300, 1655 cm^{-1}. ^{1}H NMR ($CDCl_3$) 0.86 (2.64H, d, *J*=7.0 Hz), 0.89 (0.36H, d, *J*=7.0 Hz), 1.31 (6H, s), 1.56–1.92 (3H, m), 1.92–2.20 (3H, m), 2.24–2.40 (1H, m), 2.50–2.66 (1H, m), 4.04 (2H, s), 4.13 (0.88H, br s), 4.29 (0.12H, br s), 4.98–5.11 (2H, m), 5.42–5.92 (3H, m). MS (EI) 263 (M^+). HRMS calcd for $C_{16}H_{25}NO_2$ (M^+) 263.1885, found: 2631896.

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