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Chiral oxaziridines in the enantioselective synthesis of isoxazolidines

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ABSTRACT

The stereoselective synthesis of oxaziridines with three stereogenic centres is presented in this paper. The chirality is provided by asymmetric induction, and a possible mechanism for the induced stereoselectivity is also discussed. These small heterocycles undergo the [3+2] cycloaddition reaction with aryl ethenes to afford enantiomerically pure isoxazolidines of controlled configurations. This class of heterocycles is present in the structure of various compounds of biological and pharmacological interest, which can undergo further synthetic modifications.

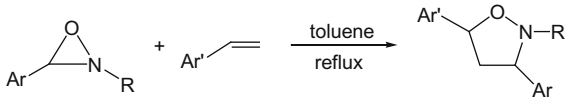
1. Introduction

Oxaziridines are a topic of increasing interest, and their reactivity, stereochemistry, and utility in organic chemistry have been the focus of several studies.[1]

The first described method of oxaziridine preparation, which continues to be the favoured method today, is the oxidation of an imine with *meta*-chloroperbenzoic acid (*m*-CPBA).[2,3] The oxaziridine ring has received considerable attention mainly due to the chirality of the nitrogen atom, which has an inversion barrier of 25–32 kcal/mol in *N*-alkyl substituted oxaziridines.[4] Moreover, the presence of an inherently weak N–O bond, due to the strained ring, makes the molecule unusually highly reactive. As a result, oxaziridines can be used as both oxygenating and aminating agents in reactions with a wide variety of nucleophiles. For example, enolates,[5] alkenes,[6–11] thioethers,[12,13] enamines,[14] organometallic reagents,[15] C–H[16,17] and Si–H[1] bonds, and nitrogen nucleophiles[18] can all be oxygenated by oxaziridines. As aminating agents, the oxaziridines can be involved in the conversion of alcohols into *O*-alkyl oximes,[19] thioethers into sulfimides,[20] enolates into α-amino carbonyl compounds, and structures with C–H bonds into amines.[21,22]

Recently, we identified a novel reactivity of this heterocycle: a cycloaddition reaction performed with alkenes, by selective cleavage of the C–O bond, to afford stable 3,5-diarylisoxazolidines with high regio- and stereoselectivity and interesting yields (Scheme 1).[23]

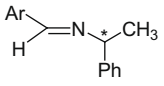
The high level of asymmetric induction observed in the heteroatom transfer to alkenes[24] and sulfides[25,26] by N-protected-oxaziridines suggests that there is also considerable potential for the preparation of chiral isoxazolidines by a [3+2] cycloaddition reaction with a wider range of alkenes. For instance, the extra stereocentre at the nitrogen atom may allow for a good level of stereocontrol. Herein, we report the results of this investigation.



Scheme 1.

2. Results and discussion

The enantiomerically pure imines **1**–**8**[27–32] (Chart 1) were prepared by reacting, in anhydrous diethyl ether, the (*R*)- or (*S*)-1-phenylethylamine (1.0 mmol) with the corresponding aryl aldehydes (1.0 mmol) in the presence of molecular sieves for 2–3 h.[33]



1-8

1: Ar = Ph;
2: Ar = *p*-CH_3-C_6H_4;
3: Ar = *p*-CH_3O-C_6H_4;
4: Ar = *p*-Cl-C_6H_4;
5: Ar = 2-pyridinyl;
6: Ar = 4-pyridinyl;
7: Ar = 2-(4-methylthiazolyl);
8: Ar = 2-benzothiazolyl);

Chart 1.

The oxidation of the obtained imines **1**–**8** was performed according to the known methodology previously reported.[34] The addition of *m*-CPBA (1.1 mmol) to imines (1.0 mmol) in CH_2Cl_2 at 0 °C afforded oxaziridines **9**–**16** in high yields (79–99%). All the reactions proceeded with fairly good stereoselectivity. From each imine, two diastereomeric oxaziridines were generated, both in a

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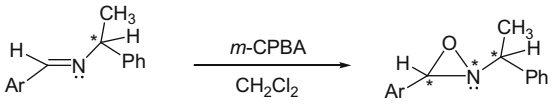
Table 1
Stereoselective synthesis of oxaziridines **9**–**16** by oxidation of imines **1**–**8**



Entry	Imine	Total yield[a] (%)	Isomeric distribution[b] (%) and specific rotation [α]	
1	(*S*)-**1**	95	(1′*S*,2*S*,3*S*)-**9** (23); [α] = −61.1	(1′*S*,2*R*,3*R*)-**9** (77); [α] = +81.5
2	(*R*)-**1**	95	(1′*R*,2*R*,3*R*)-**9** (25); [α] = +60.2	(1′*R*,2*S*,3*S*)-**9** (75); [α] = −79.9
3	(*S*)-**2**	90	(1′*S*,2*S*,3*S*)-**10** (18); [α] = −55.0	(1′*S*,2*R*,3*R*)-**10** (82); [α] = +60.1
4	(*R*)-**2**	90	(1′*R*,2*R*,3*R*)-**10** (19); [α] = +56.7	(1′*R*,2*S*,3*S*)-**10** (81); [α] = −61.1
5	(*S*)-**3**	79	(1′*S*,2*S*,3*S*)-**11** (24); [α] = −41.9	(1′*S*,2*R*,3*R*)-**11** (76); [α] = +90.6
6	(*R*)-**3**	80	(1′*R*,2*R*,3*R*)-**11** (29); [α] = +43.0	(1′*R*,2*S*,3*S*)-**11** (71); [α] = -89.1
7	(*S*)-**4**	85	(1′*S*,2*S*,3*S*)-**12** (19); [α] = −44.1	(1′*S*,2*R*,3*R*)-**12** (81); [α] = +97.3
8	(*R*)-**4**	85	(1′*R*,2*R*,3*R*)-**12** (18); [α] = +44.6	(1′*R*,2*S*,3*S*)-**12** (82); [α] = −96.1
9	(*S*)-**5**	98	(1′*S*,2*S*,3*S*)-**13** (20); [α] = −78.1	(1′*S*,2*R*,3*R*)-**13** (80); [α] = +91.8
10	(*R*)-**5**	98	(1′*R*,2*R*,3*R*)-**13** (22); [α] = +77.3	(1′*R*,2*S*,3*S*)-**13** (78); [α] = −92.2
11	(*S*)-**6**	93	(1′*S*,2*S*,3*S*)-**14** (35); [α] = −103.9	(1′*S*,2*R*,3*R*)-**14** (65); [α] = +37.4
12	(*R*)-**6**	93	(1′*R*,2*R*,3*R*)-**14** (33); [α] = +102.1	(1′*R*,2*S*,3*S*)-**14** (67); [α] = −38.1
13	(*S*)-**7**	99	(1′*S*,2*S*,3*S*)-**15** (24); [α] = −60.2	(1′*S*,2*R*,3*R*)-**15** (76); [α] = +84.6
14	(*R*)-**7**	99	(1′*R*,2*R*,3*R*)-**15** (23); [α] = +58.8	(1′*R*,2*S*,3*S*)-**15** (77); [α] = −84.1
15	(*S*)-**8**	87	(1′*S*,2*S*,3*S*)-**16** (23); [α] = −55.6	(1′*S*,2*R*,3*R*)-**16** (77); [α] = +80.3
16	(*R*)-**8**	87	(1′*R*,2*R*,3*R*)-**16** (23); [α] = +56.0	(1′*R*,2*S*,3*S*)-**16** (77); [α] = −80.7

[a] Isolated yields.
[b] Diastereomeric ratios measured by GC and ^{1}H NMR spectroscopy.

trans-configuration, in which the nitrogen atoms became stereocentres because of the high interconversion barrier.[4] The oxaziridines were isolated in enantiomerically pure form after column chromatography on silica gel, and had diastereomeric ratios ranging from 18:82 to 35:65. For example, starting from the (*R*)-**1** imine, the oxaziridines (−)-(1′*R*,2*S*,3*S*)-**9** (75%) and (+)-(1′*R*,2*R*,3*R*)-**9** (25%) were isolated (Table 1, entry 2). Starting, instead, from the (*S*)-**1** imine, diastereomers (+)-(1′*S*,2*R*,3*R*)-**9** (77%) and (−)-(1′*S*,2*S*,3*S*)-**9** (23%) were isolated (Table 1, entry 1). The specific rotation [α] values, together with the ^{1}H and ^{13}C NMR data, clearly showed that the four isomers examined were pairs of enantiomers. In Table 1, the results of the oxidation reactions performed on the remaining imines, (*S*)- and (*R*)-**2**–**8**, are listed (Table 1, entries 3–16). The total yields, specific rotation values, and the product distributions are in agreement with the data observed for oxaziridine **9**.

The observed *trans*-stereoselectivity (*trans:cis* = 100:0) may be due to a synchronous oxygen transfer from the *m*-CPBA to the imine of the *trans*-structure, while the stereoselectivity of the new stereogenic centre (C-3 and N-2) of the oxaziridinic ring is the outcome of asymmetric induction exerted by the closest stereocentre.

In Figure 1, we suggest a possible mechanism for the induced stereoselectivity starting from the (*S*)-imine, which in solution assumes the more stable *trans*-structure. Among the possible *trans*-conformations driven by the closest stereogenic centre, the ones that favour the peroxidic oxygen attack should be those that have the hydrogen atom linked to the stereocentre, up or down with respect to the double bond plane. Moreover, structure **B**, which has a phenyl π system that does not interact with the nitrogen doublet, should be the most favourable for attack by oxygen. Structure **B** should be attacked by the oxygen of the *m*-CPBA from the upper side, with respect to the double bond, affording the major diastereomer (1′*S*,2*R*,3*R*) in yields of 65–82%. On the other hand, structure **A** should be attacked from the bottom, leading to the minor (1′*S*,2*S*,3*S*)-diastereomer in yields of 18–35%.

Another primary goal of this investigation was the application of the enantiomerically pure oxaziridines obtained in the organic synthesis of more complex compounds. We found that by reacting the oxaziridines with aryl ethenes, it was possible to prepare isoxazolidines in a stereoselective manner. This class of heterocycles is

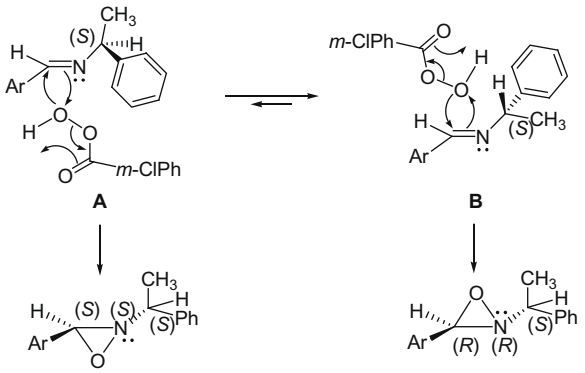
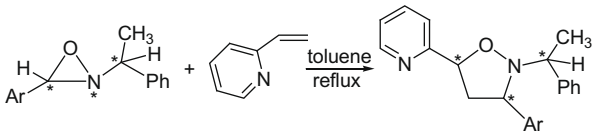


Figure 1.

present in the structures of various compounds of biological and pharmacological interest[35] which can undergo further synthetic modifications. The oxaziridine (+)-(1′*R*,2*R*,3*R*)-**9** (1.0 mmol) was reacted in refluxing toluene with 2-vinylpyridine (2.0 mmol); the reaction was followed by TLC. After 48 h, when the oxaziridine was reacted completely, the reaction mixture was cooled to room temperature and concentrated in vacuo. The crude mixture was purified by column chromatography on silica gel. The isoxazolidines (−)-(1′*R*,3*R*,5*R*)-**17** and (+)-(1′*R*,3*R*,5*S*)-**17** were isolated in a diastereomeric ratio of 70:30 (Table 2, entry 1). The reaction was also monitored by ^{1}H NMR spectroscopy, which showed the progressive decrease of the oxaziridine and the formation of two isoxazolidines **17**, with the same diastereomeric ratio of 70:30. The *trans*- and *cis*-conformations were assigned by ^{1}H NMR spectroscopy by comparing the chemical shift values with those observed for similar known isoxazolidines.[23] The absolute configurations were assigned in a similar way. For instance, considering the synchronous addition by which the [3+2] cycloaddition occurs,[23] the C-3 and the C′ atoms retain the starting absolute configuration; thus, the C-5 will be (*R*) in the *trans*-structure and (*S*) in the *cis*-structure. The same reaction was then performed with the oxaziridine (−)-(1′*S*,2*S*,3*S*)-**9**. The isolated isoxazolidines showed both specific rotation values of opposite sign with respect to those measured for the products observed with the oxaziridine (+)-

Table 2
Synthesis of enantiomerically pure isoxazolidines **17** and **18**



9, 11 **17, 18**

Entry	Oxaziridine	Ar	Total yield[a] (%)	Isomeric distribution[b] (%) and specific rotation [α]	
1	(1′*R*,2*R*,3*R*)-**9** [α] = +60.2	C_6H_5	75	(1′*R*,3*R*,5*R*)-**17** (70); [α] = −50.1	(1′*R*,3*R*,5*S*)-**17** (30); [α] = +70.4
2	(1′*S*,2*S*,3*S*)-**9** [α] = −61.1	C_6H_5	75	(1′*S*,3*S*,5*S*)-**17** (70); [α] = +50.0	(1′*S*,3*S*,5*R*)-**17** (30); [α] = −70.2
3	(1′*R*,2*S*,3*S*)-**9** [α] = −79.9	C_6H_5	69	(1′*R*,3*S*,5*S*)-**17** (72); [α] = +21.2	(1′*R*,3*S*,5*R*)-**17** (28); [α] = −26.0
4	(1′*S*,2*R*,3*R*)-**9** [α] = +81.5	C_6H_5	69	(1′*S*,3*R*,5*R*)-**17** (72); [α] = −21.0	(1′*S*,3*R*,5*S*)-**17** (28); [α] = +26.3
5	(1′*S*,2*S*,3*S*)-**11** [α] = −41.9	*p*-CH_3O–C_6H_4	72	(1′*S*,3*S*,5*S*)-**18** (75); [α] = +55.1	(1′*S*,3*S*,5*R*)-**18** (25); [α] = −65.6
6	(1′*R*,2*R*,3*R*)-**11** [α] = +43.0	*p*-CH_3O–C_6H_4	72	(1′*R*,3*R*,5*R*)-**18** (75); [α] = −55.3	(1′*R*,3*R*,5*S*)-**18** (25); [α] = +64.9
7	(1′*S*,2*R*,3*R*)-**11** [α] = +90.6	*p*-CH_3O–C_6H_4	77	(1′*S*,3*R*,5*R*)-**18** (75); [α] = −15.1	(1′*S*,3*R*,5*S*)-**18** (25); [α] = +30.3
8	(1′*R*,2*S*,3*S*)-**11** [α] = −89.1	*p*-CH_3O–C_6H_4	77	(1′*R*,3*S*,5*S*)-**18** (75); [α] = +15.5	(1′*R*,3*S*,5*R*)-**18** (25); [α] = −31.3

[a] Isolated yields.
[b] Diastereomeric ratios measured by GC and ^{1}H NMR spectroscopy.

(1′*R*,2*R*,3*R*)-**9**, while the ^{1}H and ^{13}C NMR data were the same. These results suggest that compounds (+)-(1′*S*,3*S*,5*S*)-**17** and (−)-(1′*S*,3*S*,5*R*)-**17** were enantiomers of compounds (−)-(1′*R*,3*R*,5*R*)-**17** and (+)-(1′*R*,3*R*,5*S*)-**17**, respectively (Table 2, entries 2 and 1). The utility of this synthetic protocol for the preparation of chiral isoxazolidines of controlled configurations was further supported by the cycloaddition reaction of the remaining two isomers of oxaziridine **9** with 2-vinylpyridine. Starting from (−)-(1′*R*,2*S*,3*S*)-**9**, the isoxazolidines (+)-(1′*R*,3*S*,5*S*)-**17** (72%) and (−)-(1′*R*,3*S*,5*R*)-**17** (28%), respectively, were isolated (Table 2, entry 3), and using the isomer (+)-(1′*S*,2*R*,3*R*)-**9**, compounds (−)-(1′*S*,3*R*,5*R*)-**17** (72%) and (+)-(1′*S*,3*R*,5*S*)-**17** (28%) were observed (Table 2, entry 4).

In Table 2, entries 5–8 serve as other examples of the stereoselective syntheses of isoxazolidines. For instance, enantiomerically pure imines (*S*)- and/or (*R*)-**3** were first transformed into oxaziridines (−)-(1′*S*,2*S*,3*S*)-**11**, (+)-(1′*S*,2*R*,3*R*)-**11**, and (+)-(1′*R*,2*R*,3*R*)-**11**, (−)-(1′*R*,2*S*,3*S*)-**11**, respectively. The subsequent cycloaddition reaction with 2-vinylpyridine led to the enantiomerically pure isoxazolidines in the diastereomeric ratios reported in Table 2, entries 5–8.

3. Conclusion

In this study, we have supported the possibility of preparing enantiomerically pure oxaziridines with three stereogenic centres. Furthermore, using these small heterocycles in the [3+2] cycloaddition reactions with aryl ethenes, enantiomerically pure isoxazolidines were isolated. These results make this contribution extremely interesting for the organic synthesis of biologically active compounds.

4. Experimental

4.1. General

All reactions were performed under a nitrogen atmosphere in oven-dried glassware, using syringe/septum cap techniques. Reagents were generally the best quality commercial grade and used without further purification unless otherwise indicated. Et_2O and THF were purified by distillation from sodium before use. CH_2Cl_2 was distilled from calcium hydride before use. Petroleum ether refers to the 40–60 °C boiling fraction. The ^{1}H and the ^{13}C NMR spectra were recorded on a Bruker Avance 400 apparatus (400.13 and 100.62 MHz, for ^{1}H and ^{13}C, respectively) with $CDCl_3$ as solvent and TMS as an internal standard (δ = 7.26 for ^{1}H spectra; δ = 77.0 for ^{13}C spectra). The IR spectra were recorded with an FT-IR spectrophotometer Digilab Scimitar Series FTS 2000. GC–MS analyses were performed with an Agilent Technologies 6850 series II gas chromatograph (5% phenyl-polymethylsiloxane capillary column, 30 m, 0.25 mm i.d.), equipped with a 5973 Network mass-selective detector operating at 70 eV. The electrospray ionization (HR-ESI-MS) experiments were carried out in a hybrid QqTOF mass spectrometer (PE SCIEX–QSTAR) equipped with an ion spray ionization source. MS (+) spectra were acquired by direct infusion (5 μL/min) of a solution containing the appropriate sample (10 pmol/μL), dissolved in a solution of 0.1% acetic acid, methanol/water 50:50 at the optimum ion voltage of 4800 V. The nitrogen gas flow was set at 30 psi (pounds per square inch) and the potentials of the orifice, the focussing ring and the skimmer were kept at 30, 50 and 25 V relative to ground, respectively. Melting points were determined using an Electrothermal melting point apparatus and are uncorrected. TLC was performed on Merck silica gel plates with F-254 indicator; viewing was by UV light (254 nm). Column chromatographies were performed on silica gel (63–200 mm) using petroleum ether/diethyl ether or petroleum ether/ethyl acetate mixtures as eluents.

4.2. General procedure for the preparation of imines 1–8

The appropriate amine (1 mmol) and the corresponding aldehyde (1 mmol) were dissolved in anhydrous Et_2O (20 mL) in the presence of 7.0 g of molecular sieves (4 Å, 1.6 mm pellets), according to Taguchi's protocol.[33] The imine generation was followed by GC. After 1 h, the molecular sieves were filtered and the reaction mixture was concentrated in vacuo to obtain the pure imine. The spectroscopic data observed were in agreement with those reported in the literature for the same imines.[27–32]

4.3. General procedure for the preparation of oxaziridines 9–16

A small excess of *m*-chloroperbenzoic acid (1.1 mmol) in 3 mL of methylene chloride was added to a solution of imine (1.0 mmol) dissolved in methylene chloride (5 mL) under stirring and cooling (0–5 °C). When the reaction was complete, the excess of *m*-chlorobenzoic acid was removed by filtration. The filtrate was washed twice with a dilute solution of Na_2SO_3 (5%), then with a solution of Na_2CO_3, and finally with water. After drying over $MgSO_4$ (anhydrous), the mixture was concentrated in vacuo and the crude product was purified by column chromatography (silica gel partly deactivated with triethylamine, petroleum ether/diethyl ether = 98:2 for **9**, **10**, **13**; petroleum ether/ethyl acetate = 95:5 for **11**, **12**, **15**, **16**; petroleum ether/ethyl acetate = 7:3 for **14**) to afford the pure oxaziridines **9**–**16** (total yields: 79–99%).

4.3.1. 3-Phenyl-2-(1-phenylethyl)oxaziridine 9

(−)-(1′*S*,2*S*,3*S*)-**9**: Yield 49 mg, 21.8%, yellow oil; $[\alpha]_D^{21.0} = -61.1$ (*c* 0.02, $CHCl_3$); FT-IR ($CHCl_3$) 3060, 3037, 2984, 2933, 1495, 1454, 1402 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.51 (d, *J* = 6.9 Hz, 3H), 3.38 (q, *J* = 6.9 Hz, 1H), 4.66 (s, 1H), 7.33–7.43 (m, 5H), 7.47–7.54 (m, 5H); ^{13}C NMR (100.62 MHz, $CDCl_3$) δ 19.7, 70.3, 80.3, 127.0, 127.6, 128.5, 128.6, 129.1, 130.0, 134.8, 141.8; GC–MS *m/z* 225 [M^+] (15), 121 (16), 105 (100), 77(50); HRMS-ESI calcd for $C_{15}H_{16}NO$ 226.12328; found 226.12330. (+)-(1′*S*,2*R*,3*R*)-**9**: Yield 164 mg, 73.1%, yellow oil; $[\alpha]_D^{21.0} = +81.5$ (*c* 0.01, $CHCl_3$); FT-IR ($CHCl_3$) 3060, 3037, 2984, 2930, 1492, 1450, 1405 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.67 (d, *J* = 6.5 Hz, 3H), 3.29 (q, *J* = 6.5 Hz, 1H), 4.61 (s, 1H), 7.27–7.35 (m, 10H); ^{13}C NMR (100.62 MHz, $CDCl_3$) δ 21.7, 71.3, 80.2, 127.1, 127.5, 127.9, 128.4, 128.7, 129.8, 134.7, 140.1; GC–MS *m/z* 225 [M^+] (16), 121 (17), 105 (100), 77(49); HRMS-ESI calcd for $C_{15}H_{16}NO$ 226.12328; found 226.12326. (+)-(1′*R*,2*R*,3*R*)-**9**: Yield 53.3 mg, 23.7%, yellow oil; $[\alpha]_D^{21.0} = +60.2$ (*c* 0.01, $CHCl_3$). (−)-(1′*R*,2*S*,3*S*)-**9**. Yield 160.2 mg, 71.2%, yellow oil; $[\alpha]_D^{21.0} = -79.9$ (*c* 0.02, $CHCl_3$).

4.3.2. 2-(1-Phenylethyl)-3-*p*-tolyloxaziridine 10

(−)-(1′*S*,2*S*,3*S*)-**10**: Yield 39 mg, 16.2%, yellow oil; $[\alpha]_D^{21.3} = -55.0$ (*c* 0.02, $CHCl_3$); FT-IR ($CHCl_3$) 3065, 3030, 2985, 2930, 1490, 1452 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.49 (d, *J* = 6.9 Hz, 3H), 2.36 (s, 3H), 3.36 (q, *J* = 6.9 Hz, 1H), 4.62 (s, 1H), 7.19 (d, *J* = 8.0 Hz, 2H), 7.24–7.39 (m, 5H), 7.48 (d, *J* = 8.0 Hz, 2H); ^{13}C NMR (100.62 MHz, $CDCl_3$) δ 19.6, 21.3, 70.2, 80.4, 126.9, 127.5, 128.5, 129.2, 129.8, 131.9, 140.1, 141.9; GC–MS *m/z* 239 [M^+] (40), 224 (5), 119 (100), 104 (18), 91 (25); HRMS-ESI calcd for $C_{16}H_{18}NO$ 240.13894; found 240.13890. (+)-(1′*S*,2*R*,3*R*)-**10**: Yield 176 mg, 73.8%, white solid, mp 68–69 °C, *n*-hexane; $[\alpha]_D^{21.3} = +60.1$ (*c* 0.01, $CHCl_3$); FT-IR ($CHCl_3$) 3063, 3033, 2984, 2931, 1491, 1450 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.66 (d, *J* = 6.5 Hz, 3H), 2.32 (s, 3H), 3.28 (q, *J* = 6.5 Hz, 1H), 4.57 (s, 1H), 7.13 (d, *J* = 7.9 Hz, 2H), 7.20–7.40 (m, 7H); ^{13}C NMR (100.62 MHz, $CDCl_3$) δ 21.3, 21.8, 71.2, 80.2, 127.1, 127.4, 127.9, 128.7, 129.1, 131.7, 139.9, 140.2; GC–MS *m/z* 239 [M^+] (38), 224 (5), 119 (100), 104 (20), 91 (20); HRMS-ESI calcd for $C_{16}H_{18}NO$ 240.13894; found 240.13898. (+)-(1′*R*,2*R*,3*R*)-**10**: Yield 41 mg, 17%, yellow oil; $[\alpha]_D^{21.3} = +56.7$ (*c* 0.03, $CHCl_3$). (−)-(1′*R*,2*S*,3*S*)-**10**. Yield 174.5 mg, 73%, yellow oil; $[\alpha]_D^{21.3} = -61.1$ (*c* 0.01, $CHCl_3$).

4.3.3. 3-(4-Methoxyphenyl)-2-(1-phenylethyl)oxaziridine 11

(−)-(1′*S*,2*S*,3*S*)-**11**: Yield 48 mg, 19%, yellow oil; $[\alpha]_D^{25.0} = -41.9$ (*c* 0.02, $CHCl_3$); FT-IR ($CHCl_3$) 3065, 3012, 2981, 2936, 1614, 1494, 1454, 1305, 1252 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.49 (d, *J* = 6.9 Hz, 3H), 3.35 (q, *J* = 6.9 Hz, 1H), 3.81 (s, 3H), 4.61 (s, 1H), 6.91 (d, *J* = 8.7 Hz, 2H), 7.18–7.41 (m, 7H); ^{13}C NMR (100.62 MHz, $CDCl_3$) δ 19.6, 55.3, 70.1, 80.2, 113.9, 126.9, 127.5, 128.4, 129.0, 129.4, 141.9, 161.1; GC–MS *m/z* 255 [M+] (18), 151 (6), 135 (100), 77 (20); HRMS-ESI calcd for $C_{16}H_{18}NO_2$ 256.13384; found 256.13379. (+)-(1′*S*,2*R*,3*R*)-**11**: Yield 153 mg, 60%, yellow oil; $[\alpha]_D^{25.0} = +90.6$ (*c* 0.02, $CHCl_3$); FT-IR ($CHCl_3$) 3065, 3011, 2981, 2937, 1615, 1518, 1454, 1395, 1305, 1250 cm^{-1}; ^1H NMR (400 MHz, CDCl3) δ 1.66 (d, *J* = 6.6 Hz, 3H), 3.27 (q, *J* = 6.6 Hz, 1H), 3.77 (s, 3H), 4.56 (s, 1H), 6.83 (d, *J* = 8.7 Hz, 2H), 7.25–7.34 (m, 7H); ^{13}C NMR (100.62 MHz, $CDCl_3$) δ 21.7, 55.2, 71.1, 80.1, 113.8, 126.8, 127.0, 127.8, 128.6, 128.8, 140.2, 160.9; GC–MS *m/z* 255 [M+] (18), 151 (6), 135 (100), 77 (20); HRMS-ESI calcd for $C_{16}H_{18}NO_2$ 256.13384; found 256.13389. (+)-(1′*R*,2*R*,3*R*)-**11**. Yield 59 mg, 23%, yellow oil; $[\alpha]_D^{25.0} = +43.0$ (*c* 0.01, $CHCl_3$). (−)-(1′*R*,2*S*,3*S*)-**11**: Yield 145 mg, 57%, yellow oil; $[\alpha]_D^{25.0} = -89.1$ (*c* 0.01, $CHCl_3$).

4.3.4. 3-(4-Chlorophenyl)-2-(1-phenylethyl)oxaziridine 12

(−)-(1′*S*,2*S*,3*S*)-**12**: Yield 41 mg, 16%, yellow oil; $[\alpha]_D^{22.1} = -44.1$ (*c* 0.01, $CHCl_3$); FT-IR ($CHCl_3$) 3060, 3055, 2980, 2930, 1494, 1454, 1402 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.50 (d, *J* = 6.9 Hz, 3H), 3.39 (q, *J* = 6.9 Hz, 1H), 4.63 (s, 1H), 7.18–7.53 (m, 9H); ^{13}C NMR (100.62 MHz, $CDCl_3$) δ 19.6, 70.2, 79.5, 127.0, 127.4, 127.7, 128.3, 128.5, 128.8, 129.0, 129.4, 141.6; GC–MS *m/z* 259 [M^+] (41), 244 (10), 139 (100), 104 (32); HRMS-ESI calcd for $C_{15}H_{15}ClNO$ 260.08336; found 260.08330. (+)-(1′*S*,2*R*,3*R*)-**12**: Yield 179 mg, 69%, white solid, mp = 88–89 °C, *n*-hexane; $[\alpha]_D^{22.1} = +97.3$ (*c* 0.01, $CHCl_3$); FT-IR ($CHCl_3$) 3062, 3055, 2982, 2933, 1495, 1455, 1403 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.66 (d, *J* = 6.5 Hz, 3H), 3.28 (q, *J* = 6.5 Hz, 1H), 4.57 (s, 1H), 7.24–7.33 (m, 9H); ^{13}C NMR (100.62 MHz, $CDCl_3$) δ 21.7, 71.3, 79.4, 124.3, 127.1, 128.1, 128.8, 128.9, 129.5, 133.3, 135.9, 140.0; GC–MS *m/z* 259 [M^+] (39), 244 (11), 139 (100), 104 (31); HRMS-ESI calcd for $C_{15}H_{15}ClNO$ 260.08336; found 260.08341. (+)-(1′*R*,2*R*,3*R*)-**12**: Yield 39 mg, 15%, yellow oil; $[\alpha]_D^{22.1} = +44.6$ (*c* 0.01, $CHCl_3$). (−)-(1′*R*,2*S*,3*S*)-**12**: Yield 181 mg, 70%, yellow oil; $[\alpha]_D^{22.1} = -96.1$ (*c* 0.01, $CHCl_3$).

4.3.5. 2-[2-(1-Phenylethyl)oxaziridin-3-yl]pyridine 13

(−)-(1′*S*,2*S*,3*S*)-**13**: Yield 44 mg, 19.6%, yellow oil; $[\alpha]_D^{24.0} = -78.1$ (*c* 0.03, $CHCl_3$); FT-IR ($CHCl_3$) 3062, 3030, 2976, 2930, 1591, 1439, 1392, 1218 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.47 (d, *J* = 6.9 Hz, 3H), 3.37 (q, *J* = 6.9 Hz, 1H), 4.80 (s, 1H), 7.22–7.43 (m, 7H), 7.64 (t, *J* = 7.3 Hz, 1H), 8.53 (d, *J* = 4.6 Hz, 1H); ^{13}C NMR (100.62 MHz, $CDCl_3$) δ 19.4, 70.3, 80.4, 121.4, 124.6, 127.0, 127.6, 128.4, 136.9, 141.6, 149.0, 154.8; GC–MS *m/z* 226 [M^+] (20), 197 (90), 105 (78), 78 (100); HRMS-ESI calcd for $C_{14}H_{15}N_2O$ 227.11855; found 227.11861. (+)-(1′*S*,2*R*,3*R*)-**13**: Yield 177 mg, 78.4%, yellow oil; $[\alpha]_D^{24.0} = +91.8$ (*c* 0.02, $CHCl_3$); FT-IR ($CHCl_3$) 3063, 3030, 2977, 2930, 1592, 1442, 1392, 1219 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.61 (d, *J* = 6.5 Hz, 3H), 3.29 (q, *J* = 6.5 Hz, 1H), 4.76 (s, 1H), 7.14–7.30 (m, 7H), 7.58 (t, *J* = 7.6 Hz, 1H), 8.43 (d, *J* = 4.7 Hz, 1H); ^{13}C NMR (100.62 MHz, $CDCl_3$) δ 21.4, 71.1, 80.4, 121.5, 124.4, 127.3, 128.0, 128.7, 136.7, 139.5, 148.9, 154.5; GC–MS *m/z* 226 [M^+] (22), 197 (88), 105 (75), 78 (100); HRMS-ESI calcd for $C_{14}H_{15}N_2O$ 227.11855; found 227.11850. (+)-(1′*R*,2*R*,3*R*)-**13**: Yield 50 mg, 22%, yellow oil; $[\alpha]_D^{24.0} = +77.3$ (*c* 0.01, $CHCl_3$). (−)-(1′*R*,2*S*,3*S*)-**13**: Yield 172 mg, 76%, yellow oil; $[\alpha]_D^{24.0} = -92.2$ (*c* 0.02, $CHCl_3$).

4.3.6. 4-[2-(1-Phenylethyl)-oxaziridin-3-yl]pyridine 14

(−)-(1′*S*,2*S*,3*S*)-**14**: Yield 74 mg, 32.5%, yellow oil; $[\alpha]_D^{22.3} = -103.9$ (*c* 0.01, $CHCl_3$); FT-IR film 3060, 3033, 2974, 2929, 1603, 1495, 1421, 1324 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.52 (d, *J* = 6.9 Hz, 3H), 3.40 (q, *J* = 6.9 Hz, 1H), 4.63 (s, 1H), 7.30–7.48 (m, 7H), 8.66 (d, *J* = 4.9 Hz, 2H); ^{13}C NMR (100.62 MHz, $CDCl_3$) δ 19.5, 70.2, 78.8, 122.1, 126.9, 127.7, 128.5, 141.2, 143.5, 150.0;

GC–MS *m/z* 226 [M$^+$] (23), 105 (100), 78 (50); HRMS-ESI calcd for $C_{14}H_{15}N_2O$ 227.11855; found 227.11860. (+)-(1′*S*,2*R*,3*R*)-**14**: Yield 136 mg, 60.4%, yellow oil; $[\alpha]_D^{22.3} = +37.4$ (*c* 0.01, $CHCl_3$); FT-IR film 3060, 3033, 2974, 2929, 1603, 1495, 1421, 1324 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.67 (d, *J* = 6.5 Hz, 3H), 3.30 (q, *J* = 6.5 Hz, 1H), 4.58 (s, 1H), 7.23–7.34 (m, 7H), 8.58 (d, *J* = 5.8 Hz, 2H); ^{13}C NMR (100.62 MHz, $CDCl_3$) δ 21.6, 71.2, 78.2, 121.8, 126.9, 127.8, 128.6, 139.4, 143.2, 149.8; GC–MS *m/z* 226 [M$^+$] (24), 105 (100), 78 (48); HRMS-ESI calcd for $C_{14}H_{15}N_2O$ 227.11855; found 227.11863. (+)-(1′*R*,2*R*,3*R*)-**14**: Yield 70 mg, 31%, yellow oil; $[\alpha]_D^{22.3} = +102.1$ (*c* 0.01, $CHCl_3$). (−)-(1′*R*,2*S*,3*S*)-**14**: Yield 140 mg, 62%, yellow oil; $[\alpha]_D^{22.3} = -38.1$ (*c* 0.01, $CHCl_3$).

4.3.7. 4-Methyl-2-[2-(1-phenylethyl)oxaziridin-3-yl]thiazole 15

(−)-(1′*S*,2*S*,3*S*)-**15**: Yield 58 mg, 23.8%, yellow oil; $[\alpha]_D^{23.0} = -60.2$ (*c* 0.02, $CHCl_3$); FT-IR film 3107, 3063, 3033, 2974, 2926, 1528, 1447, 1348 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.53 (d, *J* = 6.9 Hz, 3H), 2.46 (s, 3H), 3.43 (q, *J* = 6.9 Hz, 1H), 5.05 (s, 1H), 6.97 (s, 1H), 7.30 (t, *J* = 7.2 Hz, 1H), 7.36 (t, *J* = 7.2 Hz, 2H), 7.44 (d, *J* = 7.0 Hz, 2H); ^{13}C NMR (100.62 MHz, $CDCl_3$) δ 16.8, 19.3, 70.0, 76.8, 116.4, 126.9, 127.7, 128.4, 140.9, 153.2, 165.0; GC–MS *m/z* 246 [M$^+$] (8), 142 (23), 105 (100), 77 (48); HRMS-ESI calcd for $C_{13}H_{15}N_2OS$ 247.09065; found 247.09064. (+)-(1′*S*,2*R*,3*R*)-**15**: Yield 185 mg, 75.2%, yellow oil; $[\alpha]_D^{23.0} = +84.6$ (*c* 0.02, $CHCl_3$); FT-IR film 3107, 3063, 3033, 2974, 2926, 1528, 1447, 1348 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.65 (d, *J* = 6.5 Hz, 3H), 2.37 (s, 3H), 3.30 (q, *J* = 6.5 Hz, 1H), 5.01 (s, 1H), 6.91 (s, 1H), 7.26–7.40 (m, 5H); ^{13}C NMR (100.62 MHz, $CDCl_3$) δ 16.9, 21.5, 71.2, 76.7, 117.3, 121.1, 127.1, 129.2, 149.9, 154.5, 166.2; GC–MS *m/z* 246 [M$^+$] (9), 142 (22), 105 (100), 77 (49); HRMS-ESI calcd for $C_{13}H_{15}N_2OS$ 247.09065; found 147.09059. (+)-(1′*R*,2*R*,3*R*)-**15**: Yield 57 mg, 23%, yellow oil; $[\alpha]_D^{23.0} = +58.8$ (*c* 0.01, $CHCl_3$). (−)-(1′*R*,2*S*,3*S*)-**15**: Yield 187 mg, 76%, yellow oil; $[\alpha]_D^{23.0} = -84.1$ (*c* 0.01, $CHCl_3$).

4.3.8. 2-[2-(1-Phenylethyl)oxaziridin-3-yl]benzothiazole 16

(−)-(1′*S*,2*S*,3*S*)-**16**: Yield 56 mg, 20%, yellow oil; $[\alpha]_D^{21.0} = -55.6$ (*c* 0.02, $CHCl_3$); FT-IR ($CHCl_3$) 3068, 3038, 2993, 2931, 1603, 1523, 1496, 1354, 1317 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.59 (d, *J* = 7.0 Hz, 3H), 3.52 (q, *J* = 7.0, 1H), 5.19 (s, 1H), 7.32–7.52 (m, 7H), 7.91 (d, *J* = 7.7 Hz, 1H), 8.08 (d, *J* = 8.3 Hz, 1H); ^{13}C NMR (100.62 MHz, $CDCl_3$) δ 19.4, 70.2, 77.3, 122.1, 123.6, 126.1, 126.3, 127.0, 127.9, 128.6, 135.6, 140.8, 167.0, 170.1; GC–MS *m/z* 282 [M$^+$] (8), 267 (23), 162 (70), 135 (50), 120 (100); HRMS-ESI calcd for $C_{16}H_{15}N_2OS$ 283.09065; found 283.09061. (+)-(1′*S*,2*R*,3*R*)-**16**: Yield 189 mg, 67.0%, yellow oil; $[\alpha]_D^{21.0} = +80.3$ (*c* 0.01, $CHCl_3$); FT-IR ($CHCl_3$) 3068, 3038, 2993, 2931, 1603, 1523, 1496, 1354, 1317 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.70 (d, *J* = 6.6 Hz, 3 H), 3.38 (q, *J* = 6.6 Hz, 1H), 5.14 (s, 1H), 7.33–7.53 (m, 7H), 7.90 (d, *J* = 7.8 Hz, 1H), 8.08 (d, *J* = 8.2 Hz, 1H); ^{13}C NMR (100.62 MHz, $CDCl_3$) δ 18.8, 69.2, 77.2, 121.4, 124.3, 126.3, 126.9, 128.3, 129.4, 133.1, 137.1, 152.8, 167.1, 170.1. GC–MS *m/z* 282 [M$^+$] (10), 267 (22), 162 (68), 135 (51), 120 (100); HRMS-ESI calcd for $C_{16}H_{15}N_2OS$ 283.09065; found 283.09058. (+)-(1′*R*,2*R*,3*R*)-**16**: $[\alpha]_D^{21.0} = +56.0$ (*c* 0.01, $CHCl_3$). (−)-(1′*R*,2*S*,3*S*)-**16**: $[\alpha]_D^{21.0} = -80.7$ (*c* 0.01, $CHCl_3$).

4.4. General procedure for the synthesis of isoxaziridines 17 and 18

A solution of alkene (1.5 mmol) and oxaziridine **9** or **11** (1.0 mmol) in toluene (10 mL) was refluxed under magnetic stirring overnight. Afterwards, TLC showed the reaction to be complete. The solution was cooled to rt, and concentrated in vacuo to dryness. The crude product was purified by flash chromatography (silica gel, petroleum ether/ethyl acetate = 9:1) to afford the pure isoxazolidines **17** and **18** (total yields: 69–77%).

4.4.1. 2-[3-Phenyl-2-(1-phenylethyl)isoxazolidin-5-yl]pyridine 17

(−)-(1′*R*,3*R*,5*R*)-*trans*-**17**: Yield 175 mg, (53%), yellow oil; $[\alpha]_D^{24.0} = -50.1$ (*c* 0.01, $CHCl_3$); FT-IR ($CHCl_3$) 3063, 3025, 2960, 2928, 1590, 1220 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.46 (d, *J* = 6.4 Hz, 3H), 2.63–2.67 (m, 1H), 2.75 (dt, *J* = 7.8, 12.4 Hz, 1H), 3.87–3.93 (m, 2H), 5.26 (t, *J* = 7.8 Hz, 1H), 7.12–7.38 (m, 11H), 7.43 (d, *J* = 7.8 Hz, 1H), 7.60 (t, *J* = 7.8 Hz, 1H), 8.47 (d, *J* = 4.5 Hz, 1H); ^{13}C NMR (100.62 MHz, CDCl3) δ 20.2, 43.5, 65.4, 66.8, 80.2, 121.4, 122.4, 126.9, 127.1, 127.2, 127.5, 127.7, 127.9, 136.5, 141.6, 143.1, 149.1, 161.1; GC–MS *m/z* 330 [M$^+$] (>1), 209 (20), 194 (19), 105 (100), 77 (12); HRMS-ESI calcd for $C_{22}H_{23}N_2O$ 331.18119; found 331.18121. (+)-(1′*R*,3*R*,5*S*)-*cis*-**17**: Yield 73 mg, (22%), yellow oil; $[\alpha]_D^{24.0} = +70.4$ (*c* 0.02, $CHCl_3$); FT-IR ($CHCl_3$) 3064, 3028, 2961, 2928, 1592, 1221 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.47 (d, *J* = 6.5 Hz, 3H), 2.40–2.47 (m, 1H), 3.10 (dt, *J* = 8.1, 12.5 Hz, 1H), 3.87–3.93 (m, 2H), 5.12 (dd, *J* = 6.5, 8.1 Hz, 1H), 7.10–7.40 (m, 11H), 7.43 (d, *J* = 7.8 Hz, 1H), 7.58 (t, *J* = 7.8 Hz, 1H), 8.46 (d, *J* = 4.4 Hz, 1H); ^{13}C NMR (100.62 MHz, $CDCl_3$) δ 20.0, 45.4, 64.5, 67.5, 79.6, 120.4, 122.3, 126.5, 127.0, 127.3, 127.9, 128.0, 128.2, 136.7, 142.4, 142.7, 148.8, 161.1; GC–MS *m/z* 330 [M$^+$] (>1), 209 (19), 194 (21), 105 (100), 77 (10); HRMS-ESI calcd for $C_{22}H_{23}N_2O$ 331.18119; found 331.18115. (+)-(1′*S*,3*S*,5*S*)-*trans*-**17**: $[\alpha]_D^{24.0} = +50.0$ (*c* 0.01, $CHCl_3$). (−)-(1′*S*,3*S*,5*R*)-*cis*-**17**: $[\alpha]_D^{24.0} = -70.2$ (*c* 0.01, $CHCl_3$).

(+)-(1′*R*,3*S*,5*S*)-*trans*-**17**: Yield 165 mg, (50%), yellow oil; $[\alpha]_D^{24.0} = +21.2$ (*c* 0.01, $CHCl_3$); FT-IR ($CHCl_3$) 3065, 3020, 2960, 2930, 1590, 1222 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.52 (d, *J* = 6.4 Hz, 3H), 2.72–2.78 (m, 1H), 2.94 (dt, *J* = 7.9, 12.5 Hz, 1H), 4.03 (q, *J* = 6.3 Hz, 1H), 4.25 (dd, *J* = 4.2, 7.6 Hz, 1H), 5.24 (t, *J* = 7.9 Hz, 1H), 7.10–7.38 (m, 11H), 7.51 (d, *J* = 7.8 Hz, 1H), 7.68 (t, *J* = 7.8 Hz, 1H), 8.57 (d, *J* = 4.6 Hz, 1H); ^{13}C NMR (100.62 MHz, $CDCl_3$) δ 20.3, 43.5, 65.5, 66.8, 80.2, 121.3, 122.4, 126.8, 127.1, 127.2, 127.6, 127.7, 128.0, 136.5, 141.6, 143.0, 149.1, 161.0; GC–MS *m/z* 330 [M$^+$] (>1), 209 (16), 194 (18), 105 (100), 77 (14); HRMS-ESI calcd for $C_{22}H_{23}N_2O$ 331.18119; found 331.18124. (−)-(1′*R*,3*S*,5*R*)-*cis*-**17**: Yield 63 mg, (19%), yellow oil; $[\alpha]_D^{24.0} = -26.0$ (*c* 0.02, $CHCl_3$); FT-IR ($CHCl_3$) 3065, 3020, 2961, 2934, 1593, 1222 cm^{-1}; ^{1}H NMR (400 MHz, CDCl3) δ 1.58 (d, *J* = 6.5 Hz, 3H), 2.43–2.50 (m, 1H), 3.27 (dt, *J* = 8.3, 12.7 Hz, 1H), 4.11(q, *J* = 6.5 Hz, 1H), 4.26 (dd, *J* = 5.9, 8.1 Hz, 1H), 5.41 (t, *J* = 8.3 Hz, 1H), 7.11–7.25 (m, 9H), 7.29–7.33 (m, 2H), 7.40 (d, *J* = 7.8 Hz, 1H), 7.59 (t, *J* = 7.8 Hz, 1H), 8.49 (d, *J* = 4.4 Hz, 1H); ^{13}C NMR (100.62 MHz, CDCl3) δ 20.1, 45.5, 64.4, 67.5, 79.5, 120.4, 122.2, 126.6, 127.1, 127.3, 127.9, 128.1, 128.2, 136.7, 142.4, 142.7, 148.7, 161.2; GC–MS *m/z* 330 [M$^+$] (>1), 209 (22), 194 (17), 105 (100), 77 (9); HRMS-ESI calcd for $C_{22}H_{23}N_2O$ 331.18119; found 331.18117. (−)-(1′*S*,3*R*,5*R*)-*trans*-**17**: $[\alpha]_D^{24.0} = -21.0$ (*c* 0.02, $CHCl_3$). (+)-(1′*S*,3*R*,5*S*)-*cis*-**17**: $[\alpha]_D^{24.0} = +26.3$ (*c* 0.02, $CHCl_3$).

4.4.2. 2-[3-(4-Methoxyphenyl)-2-(1-phenylethyl)isoxazolidin-5-yl]pyridine 18

(+)-(1′*S*,3*S*,5*S*)-*trans*-**18**: Yield 194 mg, (54%), yellow oil; $[\alpha]_D^{21.0} = +55.1$ (*c* 0.02, $CHCl_3$); FT-IR ($CHCl_3$) 3065; 3004; 2959; 2935; 1510; 1247; 1108 cm^{-1}; ^{1}H NMR (400 MHz, CDCl3) δ 1.56 (d, *J* = 6.3 Hz, 3H), 2.50–2.58 (m, 1H), 2.71–2.77 (m, 1H), 3.80 (s, 3H), 4.10 (q, *J* = 6.3 Hz, 1H), 4.21 (dd, *J* = 7.6 Hz, 1H), 5.27 (t, *J* = 7.7 Hz, 1H), 6.90 (d, *J* = 8.5 Hz, 2H), 7.17–7.40 (m, 8H), 7.57 (d, *J* = 7.6 Hz, 1H), 7.71 (t, *J* = 7.6 Hz, 1H), 8.49 (d, *J* = 4.5 Hz, 1H); ^{13}C NMR (100.62 MHz, $CDCl_3$) δ 20.2, 43.6, 54.8, 65.3, 65.5, 79.8, 113.8, 121.3, 121.9, 127.4, 128.1, 128.2, 128.8, 133.8, 136.8, 143.1, 149.1, 158.5, 162.1; GC–MS *m/z* 360 [M$^+$] (<1), 240 (5), 239 (24), 238 (17), 224 (30), 134 (10), 105 (100), 77 (32); HRMS-ESI calcd for $C_{23}H_{25}N_2O_2$ 361.19175; found 361.19169. (−)-(1′*S*,3*S*,5*R*)-*cis*-**18**: Yield 65 mg, (18%), yellow oil; $[\alpha]_D^{21.0} = -65.6$ (*c* 0.01, $CHCl_3$); FT-IR ($CHCl_3$) 3063, 3003, 2967, 2931, 1513,

1248, 1109 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.48 (d, J = 6.9 Hz, 3H), 2.36–2.43 (m, 1H), 3.06 (dt, J = 8.0, 12.5 Hz, 1H), 3.79 (s, 3H), 3.82–3.88 (m, 2H), 5.10 (dt, J = 7.4, 8.0 Hz, 1H), 6.83 (d, J = 8.4 Hz, 2H), 7.13–7.40 (m, 8H), 7.70 (d, J = 4.0 Hz, 2H), 8.48 (d, J = 4.7 Hz, 1H); ^{13}C NMR (100.62 MHz, $CDCl_3$) δ 21.4, 47.2, 55.2, 63.1, 66.8, 78.0, 113.9, 120.1, 121.9, 126.9, 127.2, 127.9, 128.8, 132.3, 136.6, 141.3, 148.7, 158.9, 163.3; GC–MS m/z 360 [M^+] (<1), 239 (20), 238 (15), 134 (7), 105 (100), 77 (29); HRMS-ESI calcd for $C_{23}H_{25}N_2O_2$ 361.19175; found 361.19178. (−)-(1′*R*,3*R*,5*R*)-*trans*-**18**: $[\alpha]_D^{21.0} = -55.3$ (c 0.01, $CHCl_3$). (+)-(1′*R*,3*R*,5*S*)-*cis*-**18**: $[\alpha]_D^{21.0} = +64.9$ (c 0.01, $CHCl_3$).

(−)-(1′*S*,3*R*,5*R*)-*trans*-**18**: Yield 209 mg, (58%), yellow oil; $[\alpha]_D^{21.0} = -15.1$ (c 0.01, $CHCl_3$); FT-IR ($CHCl_3$) 3064, 3004, 2958, 2934, 1512, 1247, 1110 cm^{-1}; ^1H NMR (400 MHz, CDCl3) δ 1.51 (d, J = 6.3 Hz, 3H), 2.71–2.77 (m, 1H), 2.86–2.92 (m, 1 H), 3.78 (s, 3H), 4.0 (q, J = 6.3 Hz, 1H), 4.21 (dd, J = 4.2, 7.6 Hz, 1H), 5.25 (t, J = 7.8 Hz, 1H), 6.78 (d, J = 8.3 Hz, 2H), 7.14–7.30 (m, 8H), 7.51 (d, J = 7.6 Hz, 1H), 7.70 (t, J = 7.6 Hz, 1H), 8.57 (d, J = 4.5 Hz, 1H); ^{13}C NMR (100.62 MHz, $CDCl_3$) δ 20.0, 43.7, 55.2, 65.1, 66.1, 80.1, 113.7, 121.3, 122.4, 127.1, 127.7, 128.2, 128.4, 128.8, 133.5, 136.5, 143.2, 149.1, 161.9; GC–MS m/z 360 [M^+] (<1), 240 (5), 239 (25), 238 (19), 224 (30), 134 (8), 105 (100), 77 (33); HRMS-ESI calcd for $C_{23}H_{25}N_2O_2$ 361.19175; found 361.19173. (+)-(1′*S*,3*R*,5*S*)-*cis*-**18**: Yield 68 mg, (19%), yellow oil; $[\alpha]_D^{21.0} = +30.3$ (c 0.01, $CHCl_3$); FT-IR ($CHCl_3$) 3065, 3005, 2966, 2930, 1512, 1248, 1110 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.59 (d, J = 6.6 Hz, 3H), 2.41–2.48 (m, 1H), 3.25 (dt, J = 8.2, 12.6 Hz, 1H), 3.74 (s, 3H), 4.09 (q, J = 6.6 Hz, 1H), 4.22 (dd, J = 6.0, 8.1 Hz, 1H), 5.39 (t, J = 8.2 Hz, 1H), 6.70 (d, J = 8.4 Hz, 2H), 7.15–7.30 (m, 8H), 7.50 (d, J = 7.8 Hz, 1H), 7.62 (t, J = 7.8 Hz, 1H), 8.50 (d, J = 4.4 Hz, 1H); ^{13}C NMR (100.62 MHz, $CDCl_3$) δ 21.0, 46.5, 55.1, 63.3, 65.8, 78.1, 114.2, 120.1, 121.3, 126.3, 127.1, 127.5, 128.3, 132.3, 136.8, 141.3, 148.9, 158.8, 162.1; GC–MS m/z 360 [M^+] (<1), 240 (6), 239 (19), 238 (16), 224 (25), 134 (9), 105 (100), 77 (30). HRMS-ESI calcd for $C_{23}H_{25}N_2O_2$ 361.19175; found 361.19167. (+)-(1′*R*,3*S*,5*S*)-*trans*-**18**: $[\alpha]_D^{21.0} = +15.5$ (c 0.01, $CHCl_3$). (−)-(1′*R*, 3*S*,5*R*,)-*cis*-**18**: $[\alpha]_D^{21.0} = -31.3$ (c 0.01, $CHCl_3$).

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