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Hydrazide-catalyzed 1,3-dipolar nitrone cycloadditions

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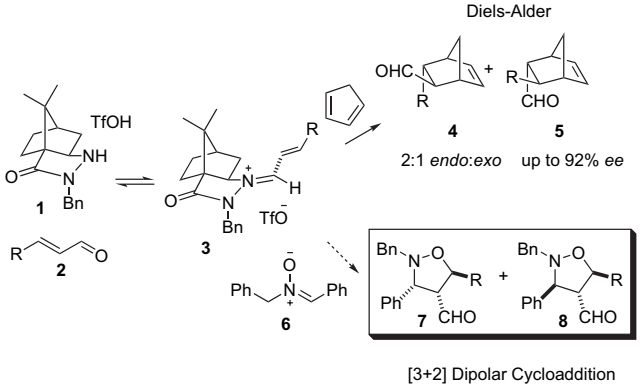
Abstract—The triflate salts of cyclic hydrazides function as asymmetric catalysts for the [3+2]cycloadditions of nitrones with α,β-unsaturated aldehydes. The camphor-derived hydrazides show a preference for the *exo* isomers during these reactions, providing a compliment to other organically catalyzed dipolar cycloadditions. Enantiomeric excesses as high as 93% were realized for the *exo* isomers, while some *endo* products were obtained in 94% ee.

1. Introduction

Using small chiral organic molecules as catalysts, numerous new technologies have recently been developed making enantioselective organocatalysis a viable tool for asymmetric synthesis.[1] Several strategies have emerged, and among these methods, the use of asymmetric secondary amines has received considerable attention. An example of the application of this can be found in the catalytic asymmetric [3+2]dipolar cycloaddition reaction,[2] a powerful method for the enantioselective construction of heterocycles. Of the heterocycles that have been prepared using this chemistry, isoxazolidines are implicated in the assembly of biologically relevant compounds such as amino acids, β-lactams, amino carbohydrates, and alkaloids.[3] Metal-catalyzed asymmetric variations of these [3+2]cycloadditions have enjoyed considerable success,[4,5] however, there have been few developments making use of chiral organocatalysts since the original report from MacMillan.[2a]

The catalytic effect of secondary amine salts has been described as the result of a reversible activation of an α,β-unsaturated aldehyde by iminium ion formation. The LUMO of the alkene moiety is consequently lowered and its interaction with the nitrone is facilitated, leading to increased reaction rates.[6] Recently, our laboratory has been involved in the development of strategies for enantioselective catalysis using chiral hydrazides.[7] In our studies, we have demonstrated that the LUMO-lowering activation of α,β-unsaturated aldehydes by the reversible formation of hydrazonium ions from hydrazides is an efficient platform for the development of enantioselective Diels–Alder cycloadditions. Herein, we demonstrate the efficacy of hydrazide-based catalysts in 1,3-dipolar cycloadditions between nitrones and α,β-unsaturated aldehydes to provide isoxazolidines with high selectivity.



2. Results and discussion

We sought to establish reaction conditions that would furnish the isoxazolidine products in good yield by the reaction with *N*-benzylidenebenzylamine-*N*-oxide (**6**) and *E*-crotonaldehyde (**9**) in the presence of hydrazide catalyst **1**. The products were obtained as mixtures of *exo* and *endo* isomers, generally favoring the *exo* isomer.[8] The choice of solvent was found to have a significant impact on the outcome of the reaction, not only in terms of selectivity, but also with respect to the yield of the process. This was in part a consequence of the formation of an undesired side-product resulting from the hydrolysis of nitrone **6**. During the reaction, the initial nitrone could react with water to release a hydroxylamine, which could then condense with the α,β-unsaturated aldehyde **9** to afford a new nitrone. This new species then

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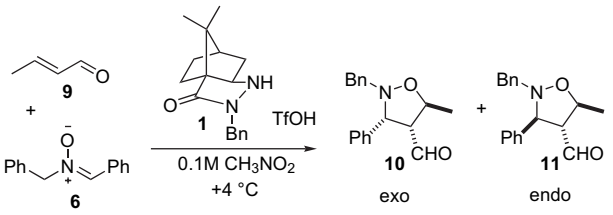
underwent a [3+2]cycloaddition to give the undesired product **12**. Although this type of nitrone exchange is not uncommon,[2b,f] we wished to minimize the production of **12**, which displayed no enantiomeric excess.[9] Most of the solvents investigated gave mixtures that contained significant amounts of this by-product (Table 1, entries 1, 4, and 8–10) making further optimizations in these media impractical. The use of benzene, $CHCl_3$, or CH_3CN resulted in the production of modest amounts of this material (entries 2, 3, and 7) whereas reactions run in CH_2Cl_2 or CH_3NO_2 afforded only minor amounts of **12**. In particular, the reaction run in CH_3NO_2 afforded a 68:32 mixture of *exo* and *endo* isomers (**10** and **11**) in 70% combined yield.[10] The *endo* isomer was formed in 78% enantiomeric excess while the formation of **12** was minimized (entry 6).

The effect of water on the outcome of the cycloaddition was then investigated. When the solvent was dried by the presence of molecular sieves, the yield decreased to 17% consistent with the requirement of water for catalyst turnover (Table 2, entry 2). Unexpectedly, the anhydrous reaction also showed a propensity to generate the *endo* isomer. When excess water was added, the hydrolyzed product **12** became more prevalent and the enantiomeric excess of the *exo* adduct was lowered (entry 3). Reducing the amount of available water to 1 equiv gave not only improved product yields, but also increased the enantioselectivity of both the *exo* and *endo* isomers relative to that realized in entries 1 and 3. No by-product **12** was observed in this reaction, consistent with the observed requirement for excess water during the formation of **12** (entry 4). Further reducing the amount of water available resulted in a slight improvement in enantioselectivity for the *exo* isomer while providing no clear advantage for the *endo* product (entries 5 and 6). The impact of the presence of water on the enantioselectivity is surprising, in that only the enantiomeric ratio of the *exo* isomer was strongly affected. The reasons for this are not clear, but a Brønsted acid-catalyzed background reaction may be implicated for this isomer.

Table 2. Effect of water content on the hydrazide-catalyzed cycloaddition reaction between *E*-crotonaldehyde **9** and nitrone **6**

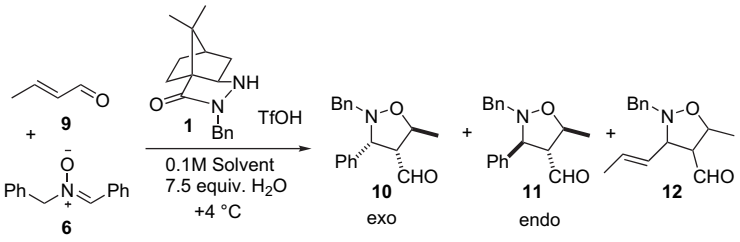


Entry	Water (equiv)	Yield[a] %	*exo*/*endo*[b]	ee *exo*[c]	ee *endo*[c]
1	7.5	70 (6)	68:32	53	78
2	0[d]	17 (0)	18:82	—	—
3	20	62 (12)	68:32	41	78
4	1	82 (0)	62:38	72	80
5	0.2	84 (0)	58:42	79	78
6	0.5	80 (0)	63:37	80	77

[a] Isolated combined yield of **10** and **11**. Value in parentheses refers to the yield of **12**.
[b] Determined by ^{1}H NMR of the crude product.
[c] Determined by HPLC after reduction to the corresponding alcohol.
[d] Molecular sieves of 4 Å were added.

Dipolar cycloadditions catalyzed by organic molecules typically require the presence of a large excess of α,β-unsaturated aldehyde (up to 15 equiv) to assure completion of the reaction.[2] Hydrazide catalysts such as **1** rapidly and completely form iminium ions with the aldehyde components of these processes,[7,11] and so a consistent supply of reactive iminium intermediate is available enabling the reactions to be performed with as little as 5.5 equiv of dipolarophile. Slow addition of the aldehyde component using a syringe-pump did not result in better selectivity but instead reduced the combined yield of the desired cycloadducts from 82% to 59%.

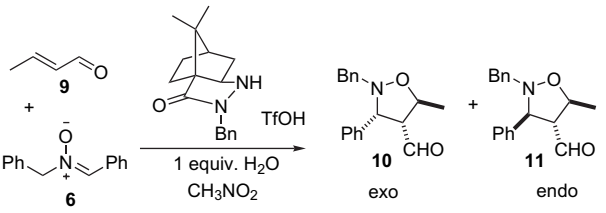
Table 1. Effect of solvent on the hydrazide-catalyzed 1,3-dipolar cycloaddition reaction between *E*-crotonaldehyde **9** and nitrone **6**



Entry	Solvent	Yield %[a]	*exo*/*endo*[b]	ee *exo*[c]	ee *endo*[c]
1	Dioxane	14 (38)	58:42	23	40
2	Benzene	67 (25)	48:52	20	51
3	$CHCl_3$	67 (12)	50:50	13	55
4	THF	5 (48)	62:38	9	46
5	CH_2Cl_2	54 (6)	58:42	21	75
6	CH_3NO_2	70 (6)	68:32	53	78
7	CH_3CN	46 (19)	33:67	29	70
8	DMF	17 (35)	38:62	33	62
9	DMSO	14 (38)	28:72	25	2
10	H_2O	20 (56)	48:52	32	50

[a] Isolated combined yield of **10** and **11**. Value in parentheses refers to the yield of **12**.
[b] Determined by ^{1}H NMR of the crude product.
[c] Determined by HPLC after reduction to the corresponding alcohol.

Table 3. Effect of temperature and concentration on the hydrazide-catalyzed dipolar cycloaddition reaction between *E*-crotonaldehyde **9** and nitrone **6**



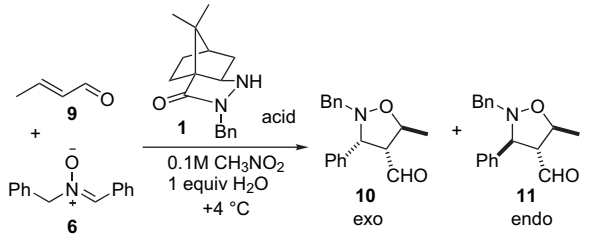
Entry	Concentration (M)	Temperature (°C)	Yield[a] %	*exo*/*endo*[b]	ee *exo*[c]	ee *endo*[c]
1	0.1	+4	82 (0)	62:38	72	80
2	0.1	−20	81 (0)	74:26	63	82
3	1.0	−20	55 (4)	79:21	28	75
4	1.0	+4	55 (11)	72:28	26	71

[a] Isolated combined yield of **10** and **11**. Value in parentheses refers to the yield of **12**.
[b] Determined by ^{1}H NMR of the crude product.
[c] Determined by HPLC after reduction to the corresponding alcohol.

Reactions were performed at lower temperature in an attempt to increase the selectivity. Although the diastereomeric ratio of *exo* to *endo* products was found to be slightly higher at −20 °C than at +4 °C, there was no significant advantage in terms of the enantioselectivity obtained (Table 3, entries 1 and 2). Reactions performed at a higher concentration at −20 °C (entry 3) reduced the overall yield of the reaction as well as the enantiomeric excess of the *exo* isomer. When a concentrated reaction was performed at +4 °C, decrease in both yields and enantioselectivities was noted. In addition, significant amounts of the unwanted by-product **12** were observed using these conditions (entry 4).

Previously it has been shown that counterion effects may have significant impacts on processes catalyzed by organic catalysts.[1] The present reaction was found to be sensitive to the nature of the Brønsted co-catalyst used. Both triflic and perchloric acids were found to produce the best yields and enantioselectivities (Table 4, entries 1 and 2). Weaker acids provided significantly larger amounts of undesired product **12** (entries 3–5), together with reduced enantiomeric excesses, primarily in the *exo* adduct.

Table 4. Effect of Brønsted acid co-catalyst on the 1,3-dipolar cycloaddition between *E*-crotonaldehyde **9** and nitrone **6**

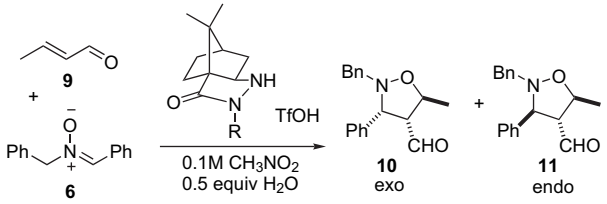


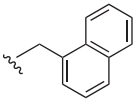
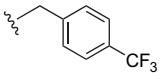
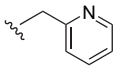
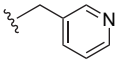
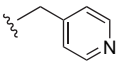
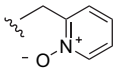
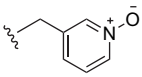
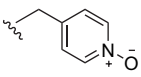
Entry	Acid	Yield[a] %	*exo*/*endo*[b]	ee *exo*[c]	ee *endo*[c]
1	CF_3SO_3H	82 (0)	62:38	72	80
2	$HClO_4$	86 (0)	66:34	76	77
3	HCl	29 (31)	70:30	29	75
4	CH_3SO_3H	39 (24)	71:29	32	79
5	CF_3CO_2H	40 (14)	74:26	31	75

[a] Isolated combined yield of **10** and **11**. Value in parentheses refers to the yield of **12**.
[b] Determined by ^{1}H NMR of the crude product.
[c] Determined by HPLC after reduction to the corresponding alcohol.

Variations in the side chain of the hydrazide catalyst had previously produced significant improvements in reactivity and enantioselectivity. Several hydrazides containing a variety of side chains were therefore prepared and tested as catalysts in the [3+2] process. Incorporating a bulky *tert*-butyl group at this position dramatically reduced the yield of the process and produced no enantiomeric excess (Table 5, entry 2), suggesting that the aromatic residue found in catalyst **1** was essential at this position. We have previously found that

Table 5. Effect of the side chain of the hydrazide catalyst on the dipolar cycloaddition reaction between *E*-crotonaldehyde **9** and nitrone **6**



Entry	R	Yield[a] %	*exo*/*endo*[b]	ee *exo*[c]	ee *endo*[c]
1		80	63:37	80	77
2		24	67:33	2	2
3		72 (3)	34:66	37	90
4		83	68:32	86	85
5		81	64:36	73	76
6		76	63:37	77	63
7		88	78:22	17	53
8		81	74:26	64	65
9		55	76:24	0	18
10		94	83:17	50	59
11		75	75:25	45	68
12		72	71:29	36	57

[a] Isolated combined yield of **10** and **11**. Value in parentheses refers to the yield of **12**.
[b] Determined by ^{1}H NMR of the crude product.
[c] Determined by HPLC after reduction to the corresponding alcohol.

the incorporation of a conformational controlling element onto the benzylic position of the catalyst afforded superior selectivities.[7c] The use of this rigidified catalyst did increase the enantioselectivity of the *endo* isomer but also resulted in a poor ee for the *exo* product (entry 3). The diastereoselectivity was reversed when this catalyst was used, thus giving a slight preference for the *endo* adduct. When an electron withdrawing *p*-CF_3 group was incorporated on the phenyl ring no significant changes were observed suggesting that electronic effects did not offer any advantageous effects relative to the unsubstituted benzyl catalyst. Replacement of the side chain with a bulkier diphenylmethyl group did not improve the enantioselectivity as shown in entry 6. Interestingly, this modification was previously found to be highly deleterious in the Diels–Alder reaction.[7c]

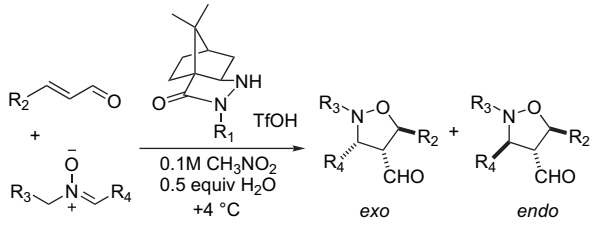
We were pleased to find that a 1-methylnaphthyl moiety did offer a slight advantage relative to the benchmark catalyst **1**, providing better diastereomeric ratios and improved enantioselectivities for both the *exo* and *endo* cycloadducts (entry 4). These improvements were, however, dependent on the nature of the dipole used, and did not translate to all substrates.

The investigation of the effect of the hydrazide catalyst side chain was expanded to include sites for possible hydrogen-bonding. Of the many organic catalysts being used for asymmetric transformations, several incorporate pendant groups that bring the reaction components together in the transition state, often resulting in an increase in selectivity.[1] To investigate this possibility, catalysts bearing picolyl or picolyl-*N*-oxide side chains were synthesized and tested in the [3+2]cycloaddition reaction between *N*-benzylidenebenzylamine-*N*-oxide **6** and *E*-crotonaldehyde **9**. Although all the picolyl-substituted catalysts (entries 7–9) afforded slightly higher diastereoselectivities, in favor of the *exo* isomer, than the catalyst bearing a simple benzyl side chain, the enantiomeric excesses of the products were found to be low, particularly when the 4-picolyl-substituted catalyst was used. The picolyl-*N*-oxide substituted catalysts (entries 10–12) offered somewhat higher *exo*/*endo* ratios (83:17 for entry 10) but afforded lower enantioselectivities than those of catalyst **1**.

Experiments that outline the scope of the present process are given in Table 6. Ortho substituted aryl residues were tolerated on the nitrone component, resulting in a 92% yield of products. In this case, the enantioselectivity of the *endo* product was found to be higher than the enantioselectivity of the same product produced from catalyst **1**, however, a slightly lower ee was noted for the corresponding *exo* material (entry 3). A variety of substituents were tolerated at the *para* position including electron donating and withdrawing substituents (entries 4, 6, 7, and 9). The nitrone substituents (R_3) could also be varied to include smaller groups, giving high ee's for both the *exo* and *endo* products (entries 11–14). In general the use of the catalyst bearing a 1-naphthyl side chain gave small improvements in the enantioselectivities of the *exo* isomers (entries 2, 5, 8, and 12).

We were pleased to find that larger α,β-unsaturated aldehydes such as those bearing *n*-propyl and *iso*-propyl substituents afforded good enantioselectivities and yields (entries 15 and 16). Larger α,β-unsaturated aldehydes such as these are seldom used in nitrone cycloadditions, particularly when catalyzed by Lewis acid.[3] On the other hand, when smaller substrates such as acrolein were employed as the dipolarophile, inseparable mixtures of regioisomers, together with *endo* and *exo* cycloadducts, were obtained.

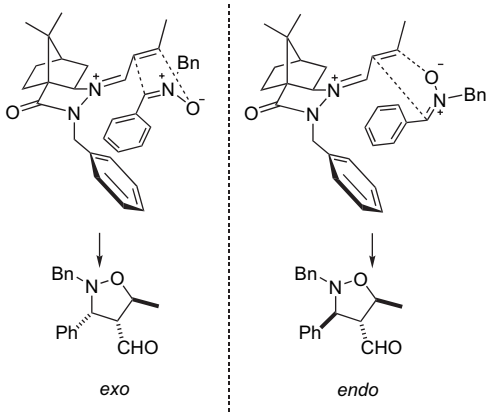
Table 6. Hydrazide-catalyzed 1,3-dipolar cycloaddition reactions between various aldehydes and nitrones



Entry	Catalyst (R_1)	R_2	R_3	R_4	Yield[a] %	*exo*/*endo*[b]	ee *exo*[c]	ee *endo*[c]
1	Bn	Me	Bn	Ph	82	62:38	72	80
2	CH_2-1-naphthyl	Me	Bn	Ph	83	68:32	86	85
3	Bn	Me	Bn	2-ClPh	92	33:67	59	94
4	Bn	Me	Bn	4-OMePh	87	48:52	79	87
5	CH_2-1-naphthyl	Me	Bn	4-OMePh	87	48:52	76	92
6	Bn	Me	Bn	4-MePh	88	57:43	84	80
7	Bn	Me	Bn	4-^{i}PrPh	85	64:36	85	76
8	CH_2-1-naphthyl	Me	Bn	4-^{i}PrPh	89	66:34	90	76
9	Bn	Me	Bn	4-CF_3Ph	67	55:45	61	73
10	Bn	Me	Bn	2-Naphthyl	94	45:55	60	81
11	Bn	Me	Me	4-MePh	71	52:48	92	80
12	CH_2-1-naphthyl	Me	Me	4-MePh	80	52:48	93	79
13	Bn	Me	Me	Ph	61	57:43	80	89
14	Bn	Me	Me	2-Furyl	38	50:50	69	88
15	Bn	*n*-Propyl	Bn	Ph	86	60:40	84	74
16	Bn	Isopropyl	Bn	Ph	68	57:43	66	77

[a] Isolated combined yield of *endo* and *exo* products.
[b] Determined by ^{1}H NMR of the crude product.
[c] Determined by HPLC after reduction to the corresponding alcohol.

Based on calculations and X-ray structures of iminium ions generated by hydrazide catalysts,[7] a model for the facial selectivity observed in the dipolar cycloaddition can be proposed. The preferred *cis*-iminium intermediate leads to the observed diastereoisomers **7** and **8** through bottom-face approach of the nitrone as shown below. Stereochemical bias is provided in this structure by the steric bulk of the camphor bridgehead methyl groups that impair top-side approach of the nitrone. The low diastereoselectivity observed is suggestive of a limited ability of the catalyst to discriminate between *exo* and *endo* pathways. Larger substituents were introduced in place of the benzyl side chain of the catalyst framework to test the effect of a potential increased steric requirement. Only small increases in diastereoselectivity were observed (Table 6, entries 3, 4, and 6) suggesting that other factors may be governing the diastereoisomer selection in this catalytic system.



3. Conclusion

We have developed a highly enantioselective organocatalyzed [3+2]cycloaddition reaction using a range of nitrones and α,β-unsaturated aldehydes. This new system nicely complements other examples of organocatalyzed cycloadditions reactions reported to date.[2] Although the diastereoselectivities observed were lower than some that have been previously observed, the use of hydrazide catalysts allows access to the *exo* cycloadduct, which is otherwise difficult to obtain from acyclic dipolarophiles. Reaction optimization studies suggest that rigorous control of the water content is necessary for good yields in this process. Minimizing the amount of water available prevents the hydrolysis of the nitrone dipole, thus minimizing the amount of by-products such as **12**. The amount of water present also has an impact on the enantioselectivity of the major *exo* isomer, and suggests that a non-asymmetric background reaction may be operative. Further investigations into the mechanism and use of new organocatalysts for this reaction are underway and will be reported in due course.

4. Experimental section

4.1. General

All solvents were used as obtained from commercial suppliers unless otherwise indicated. Standard inert atmosphere techniques were employed in handling air and moisture sensitive reagents. Reactions were monitored by thin layer chromatography (TLC) using commercial aluminum-backed silica gel sheets coated with silica gel 60 F_{254}. TLC spots were visualized under ultraviolet light or developed by heating after treatment with potassium permanganate. Excess solvents were removed in vacuo at pressures obtained by water or air aspirators connected to a rotary evaporator. Trace solvents were removed on a vacuum pump. Product purification by flash chromatography was performed with Silica Gel 60 (230–400 mesh). Infrared (IR) spectra were obtained as neat films on a sodium chloride cell. Chemical shifts are reported downfield from tetramethylsilane (δ scale) in parts per million. Mass spectroscopy (MS), using either electron impact (EI) or chemical ionization (CI), was performed on a mass spectrometer with an electron beam energy of 70 eV (for EI). Electrospray analyses were run on a triple quad mass spectrometer VG QUATTRO. High resolution mass spectroscopy (HRMS) was performed on a mass spectrometer with an electron beam of 70 eV, or a double focusing magnetic sector mass spectrometer. Melting points were measured using a Melt Temp apparatus and are uncorrected.

4.2. General procedure for the preparation of (*S*)-(+)-10,10-dimethyl-3,4-diaza-tricyclo[5.2.1.0^{1,5}]dec-4-en-2-ones

4.2.1. (*S*)-(+)-3-(2-Picolyl)-10,10-dimethyl-3,4-diaza-tricyclo[5.2.1.0^{1,5}]dec-4-en-2-one. Acetic acid (0.19 mL, 3.38 mmol) was added dropwise to a solution of (*S*)-(+)-ketopinic acid[12] (3.08 g, 16.9 mmol) and 2-picolylhydrazine[13] (2.50 g, 20.3 mmol) in anhydrous dichloromethane (150 ml) at room temperature and the reaction mixture was stirred at that temperature until judged complete by TLC analysis. The solution was then passed through a short silica plug and the solvent was removed in vacuo. The crude product was dissolved in mesitylene (120 mL) and the resulting solution was refluxed while water was removed using a Dean–Stark apparatus. Reflux was continued until consumption of the starting material was complete as judged by TLC (46 h). The cooled reaction mixture was directly loaded onto a flash column that was eluted with hexanes followed by 40% EtOAc in hexanes to provide the desired compound as a white solid (3.10 g, 68%). Mp 131–133 °C; $[\alpha]_D$ +24.6 (*c* 1.11, $CHCl_3$); IR (neat) 2967, 1691, 1589 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.57–8.53 (m, 1H), 7.65–7.61 (m, 1H), 7.20–7.14 (m, 2H), 5.00 (d, *J*=16.0 Hz, 1H), 4.97 (d, *J*=16.0 Hz, 1H), 2.60 (ddd, *J*=17.7, 3.4, 3.4 Hz, 1H), 2.32 (ddd, *J*=12.2, 4.4, 4.4 Hz, 1H), 2.26 (t, *J*=4.3 Hz, 1H), 2.19–2.10 (m, 2H), 1.73 (ddd, *J*=13.3, 9.5, 4.4 Hz, 1H), 1.51 (ddd, *J*=13.2, 9.5, 4.4 Hz, 1H), 1.23 (s, 3H), 0.96 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.7 (C), 173.9 (C), 156.7 (C), 149.4 (CH), 136.7 (CH), 122.3 (CH), 121.4 (CH), 63.6 (C), 49.9 (C), 49.7 (CH_2), 49.3 (CH), 32.0 (CH_2), 27.0 (CH_2), 25.5 (CH_2), 19.2 (CH_3), 18.6 (CH_3); MS (EI) 269.2 (M^+); HRMS calcd for $C_{16}H_{19}N_3O$ 269.1528; found 269.1520.

4.2.2. (*S*)-(+)-3-(3-Picolyl)-10,10-dimethyl-3,4-diaza-tricyclo[5.2.1.0^{1,5}]dec-4-en-2-one. Prepared by a procedure similar to that described above for (*S*)-(+)-3-(2-picolyl)-10,10-dimethyl-3,4-diaza-tricyclo[5.2.1.0^{1,5}]dec-4-en-2-one from (S)-(+)-ketopinic acid (3.08 g, 16.9 mmol) and 3-picolylhydrazine (2.50 g, 20.3 mmol). Purification by silica

gel chromatography (hexanes then 50% EtOAc in hexanes) provided the compound as a white solid (2.41 g, 53%). Mp 124–126 °C; $[\alpha]_D$ +27.5 (*c* 1.21, $CHCl_3$); IR (neat) 2971, 1688, 1634 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.57–8.48 (m, 2H), 7.62–7.59 (m, 1H), 7.25–7.21 (m, 1H), 4.83 (d, *J*=15.4 Hz, 1H), 4.79 (d, *J*=15.4 Hz, 1H), 2.54 (ddd, *J*=17.6, 3.5, 3.4 Hz, 1H), 2.30–2.21 (m, 2H), 2.15–2.07 (m, 2H), 1.64 (ddd, *J*=13.3, 9.5, 4.3 Hz, 1H), 1.47 (ddd, *J*=13.1, 9.4, 4.3 Hz, 1H), 1.19 (s, 3H), 0.86 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.9 (C), 173.7 (C), 149.3 (CH), 148.9 (CH), 135.6 (CH), 132.7 (C), 123.4 (CH), 63.7 (C), 50.0 (C), 49.2 (CH), 45.4 (CH_2), 31.9 (CH_2), 26.9 (CH_2), 25.3 (CH_2), 19.1 (CH_3), 18.6 (CH_3); MS (EI) 269.2 (M^+); HRMS calcd for $C_{16}H_{19}N_3O$ 269.1528; found 269.1529.

4.2.3. (*S*)-(+)-3-(4-Picolyl)-10,10-dimethyl-3,4-diaza-tricyclo[5.2.1.0^{1,5}]dec-4-en-2-one. Prepared by a procedure similar to that described above for (*S*)-(+)-3-(2-picolyl)-10,10-dimethyl-3,4-diaza-tricyclo[5.2.1.0^{1,5}]dec-4-en-2-one from (*S*)-(+)-ketopinic acid (2.47 g, 13.5 mmol) and 4-picolylhydrazine (2.00 g, 16.2 mmol). Purification by silica gel chromatography (hexanes then 50% EtOAc in hexanes) provided the compound as a white solid (2.59 g, 71%). Mp 140–142 °C; $[\alpha]_D$ +25.6 (*c* 1.04, $CHCl_3$); IR (neat) 2963, 1692, 1600 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.55–8.52 (m, 2H), 7.19–7.16 (m, 2H), 4.83 (d, *J*=15.9 Hz, 1H), 4.79 (d, *J*=15.9 Hz, 1H), 2.57 (ddd, *J*=17.7, 3.4, 3.3 Hz, 1H), 2.33–2.24 (m, 2H), 2.17–2.09 (m, 2H), 1.68 (ddd, *J*=13.4, 9.5, 4.3 Hz, 1H), 1.50 (ddd, *J*=13.1, 9.5, 4.3 Hz, 1H), 1.21 (s, 3H), 0.91 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.1 (C), 173.8 (C), 150.0 (CH), 146.0 (C), 122.5 (CH), 63.2 (C), 50.0 (C), 49.2 (CH), 46.9 (CH_2), 31.9 (CH_2), 27.0 (CH_2), 25.5 (CH_2), 19.1 (CH_3), 18.6 (CH_3); MS (EI) 269.2 (M^+); HRMS calcd for $C_{16}H_{19}N_3O$ 269.1528; found 269.1549.

4.3. General procedure for the preparation of (*S*)-(+)-3-(picolyl)-10,10-dimethyl-3,4-diaza-tricyclo[5.2.1.0^{1,5}]-decan-2-ones

4.3.1. (*S*)-(+)-3-(2-Picolyl)-10,10-dimethyl-3,4-diaza-tricyclo[5.2.1.0^{1,5}]decan-2-one. To a solution of (*S*)-(+)-3-(2-picolyl)-10,10-dimethyl-3,4-diaza-tricyclo[5.2.1.0^{1,5}]dec-4-en-2-one (300 mg, 1.11 mmol) in a 1:2 mixture of acetic acid and methanol (20 mL) was added sodium cyanoborohydride (700 mg, 10.0 mmol) in small portions over 1 h. The reaction mixture was then stirred at room temperature until TLC indicated that the reaction was complete (29 h). Excess borohydride was quenched by the addition of 10% HCl. The products were extracted using CH_2Cl_2 and the aqueous phase was made basic using sodium hydroxide pellets and then further extracted with CH_2Cl_2. The organic extracts were combined, washed with brine, and dried over sodium sulfate. The solvent was removed in vacuo and the product was purified by flash chromatography (50% EtOAc in hexanes) to afford the desired compound as a white solid (248 mg, 82%). Mp 80–83 °C; $[\alpha]_D$ −4.0 (*c* 1.04, $CHCl_3$); IR (neat) 3241, 2956, 1665 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.52–8.49 (m, 1H), 7.67–7.61 (m, 1H), 7.28–7.24 (m, 1H), 7.19–7.15 (m, 1H), 4.87 (d, *J*=15.7 Hz, 1H), 4.60 (d, *J*=15.6 Hz, 1H), 3.65–3.58 (m, 1H), 2.19–2.05 (m, 2H), 1.94–1.86 (m, 2H), 1.73–1.66 (m, 1H), 1.35–1.20 (m, 2H), 1.17 (s, 3H), 1.06 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.2 (C), 156.4 (C), 149.3 (CH), 136.8 (CH), 122.4 (CH), 122.1 (CH), 65.2 (CH), 58.4 (C), 51.2 (C), 49.1 (CH_2), 46.8 (CH), 36.4 (CH_2), 28.7 (CH_2), 26.7 (CH_2), 21.0 (CH_3), 20.4 (CH_3); MS (EI) 271.2 (M^+); HRMS calcd for $C_{16}H_{21}N_3O$ 271.1685; found 271.1711.

4.3.2. (S)-(+)-3-(3-Picolyl)-10,10-dimethyl-3,4-diaza-tricyclo[5.2.1.0^{1,5}]decan-2-one. Prepared by a procedure similar to that described above for (*S*)-(+)-3-(2-picolyl)-10,10-dimethyl-3,4-diaza-tricyclo[5.2.1.0^{1,5}]decan-2-one from (*S*)-(+)-3-(3-picolyl)-10,10-dimethyl-3,4-diaza-tricyclo[5.2.1.0^{1,5}]dec-4-en-2-one (200 mg, 0.74 mmol). Purification by silica gel chromatography (EtOAc) provided the title compound as a white solid (175 mg, 87%). Mp 76–78 °C; $[\alpha]_D$ +9.0 (*c* 1.01, $CHCl_3$); IR (neat) 3229, 2957, 1660 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.57–8.51 (m, 2H), 7.67–7.63 (m, 1H), 7.28–7.23 (m, 1H), 4.67 (d, *J*=14.5 Hz, 1H), 4.51 (d, *J*=14.4 Hz, 1H), 3.57–3.50 (m, 1H), 2.21–2.13 (m, 1H), 2.04–1.97 (m, 1H), 1.94–1.86 (m, 2H), 1.71–1.64 (m, 1H), 1.33–1.16 (m, 2H), 1.07 (s, 3H), 1.06 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.4 (C), 149.8 (CH), 149.2 (CH), 136.2 (CH), 131.8 (C), 123.6 (CH), 65.6 (CH), 58.3 (C), 51.3 (C), 46.8 (CH), 45.7 (CH_2), 36.3 (CH_2), 28.6 (CH_2), 26.6 (CH_2), 20.9 (CH_3), 20.3 (CH_3); MS (EI) 271.2 (M^+); HRMS calcd for $C_{16}H_{21}N_3O$ 271.1685; found 271.1689.

4.3.3. (*S*)-(+)-3-(4-Picolyl)-10,10-dimethyl-3,4-diaza-tricyclo[5.2.1.0^{1,5}]decan-2-one. Prepared by a procedure similar to that described above for (*S*)-(+)-3-(2-picolyl)-10,10-dimethyl-3,4-diaza-tricyclo[5.2.1.0^{1,5}]decan-2-one from (*S*)-(+)-3-(4-picolyl)-10,10-dimethyl-3,4-diaza-tricyclo[5.2.1.0^{1,5}]dec-4-en-2-one (300 mg, 1.11 mmol). Purification by silica gel chromatography (EtOAc) provided the title compound as a white solid (236 mg, 78%). Mp 105–106 °C; $[\alpha]_D$ +14.2 (*c* 1.07, $CHCl_3$); IR (neat) 3233, 2957, 1663 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.59–8.53 (m, 2H), 7.23–7.18 (m, 2H), 4.71 (d, *J*=15.6 Hz, 1H), 4.44 (d, *J*=15.6 Hz, 1H), 3.60–3.54 (m, 1H), 2.23–2.14 (m, 1H), 2.05–1.98 (m, 1H), 1.96–1.87 (m, 2H), 1.73–1.66 (m, 1H), 1.36–1.20 (m, 2H), 1.14 (s, 3H), 1.09 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.8 (C), 150.2 (CH), 145.2 (C), 123.0 (CH), 65.8 (CH), 58.2 (C), 51.3 (C), 47.3 (CH_2), 46.8 (CH), 36.2 (CH_2), 28.7 (CH_2), 26.7 (CH_2), 21.0 (CH_3), 20.4 (CH_3); MS (EI) 271.2 (M^+); HRMS calcd for $C_{16}H_{21}N_3O$ 271.1685; found 271.1689.

4.4. General procedure for the preparation of (*S*)-(+)-3-(picolyl-*N*-oxide)-10,10-dimethyl-3,4-diaza-tricyclo-[5.2.1.0^{1,5}]decan-2-ones

4.4.1. (*S*)-(+)-3-(2-Picolyl-*N*-oxide)-10,10-dimethyl-3,4-diaza-tricyclo[5.2.1.0^{1,5}]decan-2-one. A mixture of (*S*)-(+)-3-(2-picolyl)-10,10-dimethyl-3,4-diaza-tricyclo[5.2.1.0^{1,5}]-dec-4-en-2-one (400 mg, 1.49 mmol) and methyltrioxorhenium (1.9 mg, 0.01 mmol) in CH_2Cl_2 (8 mL) was cooled to 0 °C and treated with a 30% solution of aqueous hydrogen peroxide (0.17 mL, 1.78 mmol). The biphasic reaction mixture was stirred until judged complete by TLC (94 h) and filtered over a small pad of Celite using CH_2Cl_2. Removal of the solvent in vacuo afforded crude *N*-oxide-pyrazolone, which was dissolved in a 1:2 mixture of acetic acid and methanol (30 mL). Sodium cyanoborohydride (875 mg,

13.9 mmol) was added in small portions for over 1 h and the reaction mixture was stirred at room temperature until TLC indicated that the reaction was complete. Excess borohydride was quenched by the addition of 10% HCl. The products were extracted using CH_2Cl_2 and the aqueous phase was made basic using sodium hydroxide pellets then further extracted with CH_2Cl_2. The organic extracts were combined, washed with brine, and dried over sodium sulfate. The solvent was removed in vacuo and the product was purified by flash chromatography (2% MeOH in $CHCl_3$) to afford the desired compound as a white solid (277 mg, 65%). Mp 144–145 °C; $[\alpha]_D$ +9.8 (*c* 1.00, $CHCl_3$); IR (neat) 3419, 2959, 1651 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.16 (d, *J*=6.2 Hz, 1H), 7.42 (dd, *J*=7.6, 2.0 Hz, 1H), 7.25–7.15 (m, 2H), 4.81 (d, *J*=15.2 Hz, 1H), 4.56 (d, *J*=15.2 Hz, 1H), 3.57 (dd, *J*=8.3, 4.6 Hz, 1H), 2.08–2.00 (m, 2H), 1.85–1.77 (m, 2H), 1.61 (dd, *J*=12.9, 8.3 Hz, 1H), 1.24–1.13 (m, 2H), 1.10 (s, 3H), 0.96 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.9 (C), 146.6 (C), 139.3 (CH), 127.1 (CH), 126.4 (CH), 125.2 (CH), 64.9 (CH), 58.1 (C), 51.1 (C), 46.6 (CH), 44.4 (CH_2), 36.3 (CH_2), 28.5 (CH_2), 26.6 (CH_2), 20.7 (CH_3), 20.1 (CH_3); MS (EI) 287.2 (M^+); HRMS calcd for $C_{16}H_{21}N_3O_2$ 287.1634; found 287.1652.

4.4.2. (*S*)-(+)-3-(3-Picolyl-*N*-oxide)-10,10-dimethyl-3,4-diaza-tricyclo[5.2.1.0^{1,5}]decan-2-one. Prepared by a procedure similar to that described above for (*S*)-(+)-3-(2-picolyl-*N*-oxide)-10,10-dimethyl-3,4-diaza-tricyclo[5.2.1.0^{1,5}]-decan-2-one from (*S*)-(+)-3-(3-picolyl)-10,10-dimethyl-3,4-diaza-tricyclo[5.2.1.0^{1,5}]dec-4-en-2-one (300 mg, 1.11 mmol). Purification by silica gel chromatography (5% MeOH in $CHCl_3$) provided the title compound as a white solid (173 mg, 54%). Mp 146–148 °C; $[\alpha]_D$ +6.2 (*c* 1.01, $CHCl_3$); IR (neat) 3427, 2958, 1661 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.29–8.11 (m, 2H), 7.34–7.21 (m, 2H), 4.68 (d, *J*=15.1 Hz, 1H), 4.45 (d, *J*=15.0 Hz, 1H), 3.64–3.56 (m, 1H), 2.20–2.04 (m, 2H), 1.96–1.87 (m, 2H), 1.77–1.69 (m, 1H), 1.35–1.17 (m, 2H), 1.10 (s, 3H), 1.06 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.8 (C), 138.9 (CH), 138.3 (CH), 136.1 (C), 126.2 (CH), 125.9 (CH), 65.6 (CH), 58.0 (C), 51.3 (C), 46.7 (CH), 45.0 (CH_2), 36.2 (CH_2), 28.5 (CH_2), 26.6 (CH_2), 20.9 (CH_3), 20.3 (CH_3); MS (EI) 287.2 (M^+); HRMS calcd for $C_{16}H_{21}N_3O_2$ 287.1634; found 287.1620.

4.4.3. (*S*)-(+)-3-(4-Picolyl-*N*-oxide)-10,10-dimethyl-3,4-diaza-tricyclo[5.2.1.0^{1,5}]decan-2-one. Prepared by a procedure similar to that described above for (*S*)-(+)-3-(2-picolyl-*N*-oxide)-10,10-dimethyl-3,4-diaza-tricyclo[5.2.1.0^{1,5}]decan-2-one from (*S*)-(+)-3-(4-picolyl)-10,10-dimethyl-3,4-diaza-tricyclo[5.2.1.0^{1,5}]dec-4-en-2-one (400 mg, 1.49 mmol). Purification by silica gel chromatography (5% MeOH in $CHCl_3$) provided the title compound as a white solid (324 mg, 76%). Mp 186–188 °C; $[\alpha]_D$ +4.7 (*c* 1.01, $CHCl_3$); IR (neat) 3436, 2952, 1642 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.09 (d, *J*=6.9 Hz, 2H), 7.20 (d, *J*=6.7 Hz, 2H), 4.59 (d, *J*=15.4 Hz, 1H), 4.40 (d, *J*=15.4 Hz, 1H), 3.54 (dd, *J*=8.3, 4.6 Hz, 1H), 2.16–2.09 (m, 1H), 2.03–1.97 (m, 1H), 1.92–1.84 (m, 2H), 1.68 (dd, *J*=13.1, 8.4 Hz, 1H), 1.30–1.13 (m, 2H), 1.07 (s, 3H), 1.03 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.9 (C), 139.1 (CH), 135.4 (C), 125.8 (CH), 64.8 (CH), 58.1 (C), 51.3 (C), 46.8 (CH), 46.4 (CH_2), 36.2 (CH_2), 28.6 (CH_2), 26.6 (CH_2), 20.9 (CH_3), 20.4 (CH_3); MS (EI) 287.2 (M^+); HRMS calcd for $C_{16}H_{21}N_3O_2$ 287.1634; found 287.1628.

4.5. ((3*R*,4*S*,5*S*)-2-Benzyl-5-methyl-3-phenylisoxazolidin-4-yl)methanol and ((3*S*,4*S*,5*S*)-2-benzyl-5-methyl-3-phenylisoxazolidin-4-yl)methanol

Catalyst **1**[7a] (15 mg, 0.05 mmol) was dissolved in CH_3NO_2 (2.4 mL, 0.1 M), and the resulting solution was cooled to 0 °C. Distilled water (2.1 μL, 0.12 mmol) was added followed by CF_3SO_3H (4.2 μL, 0.05 mmol) and the solution was then stirred for 5 min. (*Z*)-*N*-Benzylidenebenzylamine-*N*-oxide[14] (50 mg, 0.24 mmol) was then introduced followed by freshly distilled (*E*)-crotonaldehyde (59 μL, 0.71 mmol). The reaction was stirred at +4 °C for 48 h, after which time additional (*E*)-crotonaldehyde (50 μL, 0.60 mmol) was added. After a total of 72 h, the reaction mixture was passed through a plug of silica using CH_2Cl_2 as an eluant. Purification by silica gel chromatography (5% EtOAc in hexanes) provided a 68:32 mixture of *exo* and *endo* isoxazolidine aldehydes as a colorless oil (55 mg, 83%). A portion of the aldehyde was dissolved in EtOH (2 mL) and reduced to the primary alcohol using $NaBH_4$ at 0 °C. After 2 h, the reaction was quenched with satd NH_4Cl and stirred for 15 min. The mixture was diluted with brine and extracted twice with CH_2Cl_2. The organic layer was dried with Na_2SO_4, filtered, and concentrated. Purification by silica gel chromatography (15% EtOAc in hexanes) provided the title compound as a clear oil for the determination of enantiomeric purity; *endo* 85%, *exo* 86%. Enantiomeric ratios were determined by HPLC using a Chiralcel OD-H column. λ=220 nm (2% IPA/hexanes, 0.8 mL/min flow rate); *endo* isomers t_R=34.6 min (major enantiomer) and 32.5 min (minor enantiomer); *exo* isomers t_R=20.6 min (major enantiomer) and 22.8 min (minor enantiomer). *exo* isomer $[\alpha]_D$ −118 (*c* 2.87, $CHCl_3$); IR (neat) 3408, 2925, 1602, 1495, 1453 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.45–7.41 (m, 2H), 7.38–7.32 (m, 4H), 7.32–7.27 (m, 3H), 7.25–7.21 (m, 1H), 4.04–3.97 (m, 3H), 3.69 (d, *J*=13.9 Hz, 1H), 3.45–3.35 (m, 2H), 2.47–2.39 (m, 1H), 1.35 (d, *J* 5.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.3 (C), 136.3 (C), 128.8 (CH), 128.7 (CH), 128.2 (CH), 128.1 (CH), 127.9 (CH), 127.2 (CH), 76.8 (CH), 72.1 (CH), 62.3 (CH_2), 59.9 (CH_2), 55.8 (CH), 19.9 (CH_3); MS (EI) 283.2 (M^+); HRMS calcd for $C_{18}H_{21}NO_2$ 283.1572; found 283.1556. *endo* isomer $[\alpha]_D$ −64.8 (*c* 1.29, $CHCl_3$); IR (neat) 3394, 2925, 1599, 1494, 1454 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.45–7.40 (m, 2H), 7.37–7.18 (m, 8H), 4.28–4.27 (m, 1H), 3.98 (d, *J*=14.1 Hz, 1H), 3.83–3.63 (m, 4H), 2.43–2.33 (m, 1H), 1.43 (d, *J*=6.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 139.3 (C), 137.5 (C), 128.7 (CH), 128.5 (CH), 128.1 (CH), 127.9 (CH), 127.0 (CH), 76.3 (CH), 73.6 (CH), 62.3 (CH_2), 61.8 (CH), 59.7 (CH_2), 20.8 (CH_3); MS (EI) 283.2 (M^+); HRMS calcd for $C_{18}H_{21}NO_2$ 283.1572; found 283.1575.

4.6. ((3*R*,4*S*,5*S*)-2-Benzyl-3-(2-chlorophenyl)-5-methylisoxazolidin-4-yl)methanol and ((3*S*,4*S*,5*S*)-2-benzyl-3-(2-chlorophenyl)-5-methylisoxazolidin-4-yl)methanol

Prepared according to the general procedure from (*E*)-crotonaldehyde (100 μL, 1.21 mmol), (*Z*)-*N*-2-chlorobenzylidenebenzylamine-*N*-oxide[15] (50 mg, 0.20 mmol), **1** (11 mg,

0.04 mmol), distilled water (3.7 μL, 0.20 mmol), and CF_3SO_3H (3.6 μL, 0.04 mmol) in CH_3NO_2 (2.0 mL, 0.1 M). Purification by silica gel chromatography (5% ethyl acetate in hexanes) provided a 67:33 mixture of *endo* and *exo* isomers as a colorless oil (59 mg, 92%). Reduction of the aldehydes to the primary alcohols followed by purification by silica gel chromatography (15% EtOAc in hexanes) provided the title compounds as a clear oil for the determination of enantiomeric purity; *endo* 94%, *exo* 59%. Enantiomeric ratios were determined by HPLC using a Chiralcel OD-H column. λ=220 nm (2% IPA/hexanes, 0.8 mL/min flow rate); *endo* isomers t_R=26.8 min (major enantiomer) and 23.5 min (minor enantiomer); *exo* isomers t_R=18.6 min (major enantiomer) and 16.6 min (minor enantiomer). IR (neat) 3389, 2929, 1572, 1441 cm^{-1}. *exo* isomer ^1H NMR (500 MHz, $CDCl_3$) δ 7.66 (d, J=7.6 Hz, 1H), 7.42–7.13 (m, 8H), 4.34–4.28 (m, 2H), 4.13–4.07 (m, 1H), 4.01 (d, J=13.3 Hz, 1H), 3.71 (d, J=15.5 Hz, 1H), 3.35–3.26 (m, 2H), 2.69–2.60 (m, 1H), 1.37 (d, J=6.0 Hz, 3H). *endo* isomer ^1H NMR (500 MHz, $CDCl_3$) δ 7.79 (d, J=7.6 Hz, 1H), 7.41–7.11 (m, 8H), 4.36–4.33 (m, 1H), 3.98–3.91 (m, 2H), 3.85 (dd, J=10.9, 4.4 Hz, 1H), 3.78 (dd, J=10.9, 6.5 Hz, 1H), 2.32–2.25 (m, 1H), 2.31–2.25 (m, 1H), 1.40 (d, J=6.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.7 (C), 137.2 (C), 135.0 (C), 134.6 (C), 133.7 (C), 133.0 (C), 129.6 (CH), 129.4 (CH), 129.3 (CH), 129.3 (CH), 129.1 (CH), 129.0 (CH), 128.8 (CH), 128.7 (CH), 128.2 (CH), 128.1 (CH), 127.5 (CH), 127.2 (CH), 127.1 (CH), 127.0 (CH), 77.4 (CH), 77.1 (CH), 68.7 (CH), 68.4 (CH), 62.6 (CH_2), 62.5 (CH), 61.7 (CH_2), 60.3 (CH_2), 60.1 (CH_2), 53.2 (CH), 20.3 (CH_3), 19.9 (CH_3); MS (EI) 317.1 (M^+); HRMS calcd for $C_{18}H_{20}NO_2Cl$ 317.1183; found 317.1168.

4.7. ((3*R*,4*S*,5*S*)-2-Benzyl-3-(4-methoxyphenyl)-5-methylisoxazolidin-4-yl)methanol and ((3*S*,4*S*,5*S*)-2-benzyl-3-(4-methoxyphenyl)-5-methylisoxazolidin-4-yl)-methanol

Prepared according to the general procedure from (*E*)-crotonaldehyde (102 μL, 1.22 mmol), (*Z*)-*N*-4-methoxybenzylidenebenzylamine-*N*-oxide[4h] (50 mg, 0.21 mmol), **1** (11 mg, 0.04 mmol), distilled water (3.7 μL, 0.21 mmol), and CF_3SO_3H (3.7 μL, 0.04 mmol) in CH_3NO_2 (2.1 mL, 0.1 M). Purification by silica gel chromatography (3% EtOAc in hexanes) provided the compound as a colorless oil (57 mg, 87%, 52:48 *endo*/*exo*). Reduction of the aldehyde to the primary alcohol followed by purification by silica gel chromatography (10% EtOAc in hexanes) provided the title compounds as a clear oil for the determination of enantiomeric purity; *endo* 87%, *exo* 79%. Enantiomeric ratios were determined by HPLC using a Chiralcel AS-H column. λ=210 nm (2% IPA/hexanes, 0.8 mL/min flow rate); *endo* isomers t_R=43.7 min (major enantiomer) and 70.3 min (minor enantiomer); *exo* isomers t_R=37.9 min (major enantiomer) and 48.9 min (minor enantiomer). *exo* isomer $[\alpha]_D$ −127 (*c* 1.47, $CHCl_3$); IR (neat) 3422, 2937, 1614, 1511, 1248 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.43–7.22 (m, 7H), 6.97–6.91 (m, 2H), 4.07–3.95 (m, 3H), 3.84 (s, 3H), 3.69 (d, J=14.5 Hz, 1H), 3.54–3.37 (m, 2H), 2.48–2.36 (m, 1H), 1.37 (d, J=6.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.2 (C), 137.6 (C), 131.5 (C), 129.2 (CH), 128.7 (CH), 128.1 (CH), 127.1 (CH), 114.2 (CH), 76.7 (CH), 71.6 (CH), 62.4 (CH_2), 59.8 (CH_2), 55.8 (CH), 55.2 (CH_3), 19.9 (CH_3); MS (EI) 313.2 (M^+); HRMS calcd for $C_{19}H_{23}NO_3$ 313.1678; found 313.1670. *endo* isomer $[\alpha]_D$ −76.1 (*c* 1.30, $CHCl_3$); IR (neat) 3423, 2928, 1611, 1512, 1248 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.42–7.20 (m, 7H), 6.93–6.88 (m, 2H), 4.20 (dq, J=6.2, 6.1 Hz, 1H), 4.01–3.96 (d, J=14.6 Hz, 1H), 3.83 (s, 3H), 3.80–3.68 (m, 3H), 3.60 (d, J=8.5 Hz, 1H), 2.42–2.30 (m, 1H), 1.46 (d, J=6.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.2 (C), 137.9 (C), 131.2 (C), 129.0 (CH), 128.4 (CH), 128.1 (CH), 126.8 (CH), 114.1 (CH), 76.1 (CH), 73.2 (CH), 62.5 (CH_2), 61.7 (CH), 59.6 (CH_2), 55.3 (CH_3), 21.0 (CH_3); MS (EI) 313.2 (M^+); HRMS calcd for $C_{19}H_{23}NO_3$ 313.1678; found 313.1689.

4.8. ((3*R*,4*S*,5*S*)-2-Benzyl-5-methyl-3-*p*-tolylisoxazolidin-4-yl)methanol and ((3*S*,4*S*,5*S*)-2-benzyl-5-methyl-3-*p*-tolylisoxazolidin-4-yl)methanol

Prepared according to the general procedure from (*E*)-crotonaldehyde (106 μL, 1.27 mmol), (*Z*)-*N*-4-methylbenzylidenebenzylamine-*N*-oxide[16] (50 mg, 0.22 mmol), **1** (12 mg, 0.04 mmol), distilled water (2.0 μL, 0.11 mmol), and CF_3SO_3H (3.9 μL, 0.04 mmol) in CH_3NO_2 (2.2 mL, 0.1 M). Purification by silica gel chromatography (5% EtOAc in hexanes) provided the compound as a colorless oil (58 mg, 88% 43:57 *endo*/*exo*). Reduction of the aldehyde to the primary alcohol followed by purification by silica gel chromatography (15% EtOAc in hexanes) provided the title compound as a clear oil for the determination of enantiomeric purity; *endo* 80%, *exo* 84%. Enantiomeric ratios were determined by HPLC using a Chiralcel OD-H column. λ=210 nm (2% IPA/hexanes, 0.8 mL/min flow rate); *endo* isomers t_R=37.6 min (major enantiomer) and 24.4 min (minor enantiomer); *exo* isomers t_R=17.1 min (major enantiomer) and 18.4 min (minor enantiomer). *exo* isomer $[\alpha]_D$ −122 (*c* 2.07, $CHCl_3$); IR (neat) 3397, 2924, 1602, 1511, 1454 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.40–7.19 (m, 9H), 4.09–3.96 (m, 3H), 3.69 (d, J=14.5 Hz, 1H), 3.55–3.36 (m, 2H), 2.50–2.39 (m, 1H), 2.38 (s, 3H), 1.37 (d, J=6.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.7 (C), 137.7 (C), 133.3 (C), 129.5 (CH), 128.7 (CH), 128.1 (CH), 127.9 (CH), 127.0 (CH), 76.6 (CH), 72.0 (CH), 62.4 (CH_2), 59.9 (CH_2), 55.9 (CH), 21.1 (CH_3), 19.9 (CH_3); MS (EI) 297.2 (M^+); HRMS calcd for $C_{19}H_{23}NO_2$ 297.1729; found 297.1712. *endo* isomer $[\alpha]_D$ −127 (*c* 1.47, $CHCl_3$); IR (neat) 3422, 2937, 1614, 1511, 1248 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.38–7.15 (m, 9H), 4.21 (dq, J=6.1, 6.1 Hz, 1H), 3.99 (d, J=14.5 Hz, 1H), 3.83–3.67 (m, 3H), 3.60 (d, J=8.5 Hz, 1H), 2.42–2.32 (m, 1H), 2.37 (s, 3H), 1.46 (d, J=6.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.9 (C), 137.5 (C), 136.3 (C), 129.4 (CH), 128.4 (CH), 128.1 (CH), 127.8 (CH), 126.8 (CH), 76.1 (CH), 73.5 (CH), 62.5 (CH_2), 61.8 (CH), 59.6 (CH_2), 21.1 (CH_3), 21.0 (CH_3); MS (EI) 297.2 (M^+); HRMS calcd for $C_{19}H_{23}NO_2$ 297.1729; found 297.1725.

4.9. ((3*R*,4*S*,5*S*)-2-Benzyl-3-(4-isopropylphenyl)-5-methylisoxazolidin-4-yl)methanol and ((3*S*,4*S*,5*S*)-2-benzyl-3-(4-isopropylphenyl)-5-methylisoxazolidin-4-yl)methanol

Prepared according to the general procedure from (*E*)-crotonaldehyde (100 μL, 1.20 mmol), (*Z*)-*N*-4-isopropylbenzylidenebenzylamine-*N*-oxide (50 mg, 0.20 mmol), **1** (11 mg,

0.04 mmol), distilled water (1.8 μL, 0.10 mmol), and CF_3SO_3H (3.5 μL, 0.04 mmol) in nitromethane (2.0 mL, 0.1 M). Purification by silica gel chromatography (2% EtOAc in hexanes) provided the compound as a colorless oil (55 mg, 85%, 36:64 *endo*/*exo*). Reduction of the aldehyde to the primary alcohol followed by purification by silica gel chromatography (10% EtOAc in hexanes) provided the title compound as a clear oil for the determination of enantiomeric purity; *endo* 76%, *exo* 85%. Enantiomeric ratios were determined by HPLC using a Chiralcel AS-H column. λ=210 nm (2% IPA/hexanes, 0.8 mL/min flow rate); *endo* isomers t_R=19.2 min (major enantiomer) and 27.3 min (minor enantiomer); *exo* isomers t_R=14.3 min (major enantiomer) and 16.6 min (minor enantiomer). *exo* isomer $[\alpha]_D$ −98.8 (*c* 1.92, $CHCl_3$); IR (neat) 3421, 2961, 1611, 1454 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.36–7.32 (m, 4H), 7.31–7.26 (m, 2H), 7.25–7.19 (m, 3H), 4.05–3.94 (m, 3H), 3.66 (d, *J*=14.5 Hz, 1H), 3.50–3.36 (m, 2H), 2.89 (sept, *J*=6.9 Hz, 1H), 2.45–2.36 (m, 1H), 2.01 (d, *J*=6.1 Hz, 3H), 1.23 (d, *J*=6.9 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.6 (C), 137.7 (C), 133.6 (C), 128.6 (CH), 128.1 (CH), 128.0 (CH), 127.0 (CH), 126.9 (CH), 76.6 (CH), 72.1 (CH), 62.4 (CH_2), 60.0 (CH_2), 56.0 (CH), 33.8 (CH), 23.9 (CH_3), 19.9 (CH_3); MS (EI) 325.2 (M^+); HRMS calcd for $C_{21}H_{27}NO_2$ 325.2042; found 325.2034. *endo* isomer $[\alpha]_D$ −75.3 (*c* 1.29, $CHCl_3$); IR (neat) 3416, 2925, 1602, 1455 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.37–7.29 (m, 4H), 7.28–7.23 (m, 2H), 7.22–7.25 (m, 3H), 4.17 (dq, *J*=6.1, 6.1 Hz, 1H), 3.96 (d, *J*=14.6 Hz, 1H), 3.79–3.65 (m, 3H), 3.56 (d, *J*=8.4 Hz, 1H), 2.88 (sept, *J*=6.6 Hz, 1H), 2.39–2.30 (m, 1H), 1.42 (d, *J*=6.2 Hz, 3H), 1.23 (d, *J*=6.9 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.4 (C), 138.0 (C), 136.7 (C), 128.4 (CH), 128.1 (CH), 127.8 (CH), 126.8 (CH), 126.7 (CH), 76.2 (CH), 73.6 (CH), 62.6 (CH_2), 61.8 (CH), 59.7 (CH_2), 33.8 (CH), 24.0 (CH_3), 21.0 (CH_3); MS (EI) 325.2 (M^+); HRMS calcd for $C_{21}H_{27}NO_2$ 325.2042; found 325.2044.

4.10. ((3*R*,4*S*,5*S*)-2-Benzyl-5-methyl-3-(4-(trifluoromethyl)phenyl)isoxazolidin-4-yl)methanol and ((3*S*,4*S*,5*S*)-2-benzyl-5-methyl-3-(4-(trifluoromethyl)phenyl)isoxazolidin-4-yl)methanol

Prepared according to the general procedure from (*E*)-crotonaldehyde (103 μL, 1.21 mmol), (*Z*)-*N*-4-trifluoromethylbenzylidenebenzylamine-*N*-oxide[17] (50 mg, 0.18 mmol), **1** (9.7 mg, 0.04 mmol), distilled water (1.6 μL, 0.09 mmol), and CF_3SO_3H (3.2 μL, 0.04 mmol) in CH_3NO_2 (1.8 mL, 0.1 M). Purification by silica gel chromatography (5% EtOAc in hexanes) provided the compound as a colorless oil (42 mg, 67%, 45:55 *endo*/*exo*). Reduction of the aldehyde to the primary alcohol followed by purification by silica gel chromatography (10% EtOAc in hexanes) provided the title compound as a clear oil for the determination of enantiomeric purity; *endo* 73%, *exo* 61%. Enantiomeric ratios were determined by HPLC using a Chiralcel AS-H column. λ=210 nm (2% IPA/hexanes, 0.8 mL/min flow rate); *endo* isomers t_R=19.4 min (major enantiomer) and 23.5 min (minor enantiomer); *exo* isomers t_R=16.9 min (major enantiomer) and 18.0 min (minor enantiomer). *exo* isomer $[\alpha]_D$ −76.8 (*c* 1.43, $CHCl_3$); IR (neat) 3422, 2926, 1619, 1455 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.62–7.51 (m, 4H), 7.32–7.20 (m, 5H), 4.09–4.00 (m, 2H), 3.95 (d, *J*=14.3 Hz, 1H), 3.75 (d, *J*=14.3 Hz, 1H), 3.38 (dd, *J*=10.9, 6.9 Hz, 1H), 3.30 (dd, *J*=10.9, 6.4 Hz, 1H), 2.53–2.44 (m, 1H), 1.36 (d, *J*=6.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.1 (C), 137.0 (C), 129.8 (C), 128.8 (CH), 128.6 (CH), 128.2 (CH), 128.2 (CH), 127.3 (CH), 125.5 (q, CF_3, J_{CF}=3.6 Hz) 77.3 (CH), 71.7 (CH), 62.2 (CH_2), 60.3 (CH_2), 55.6 (CH), 19.9 (CH_3); MS (EI) 351.1 (M^+); HRMS calcd for $C_{19}H_{20}NO_2F_3$ 351.1446; found 351.1445. *endo* isomer $[\alpha]_D$ −62.6 (*c* 1.15, $CHCl_3$); IR (neat) 3446, 2925, 1621, 1325 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.59–7.50 (m, 4H), 7.31–7.17 (m, 5H), 4.23 (dq, *J*=6.2, 6.1 Hz, 1H), 3.95 (d, *J*=14.0 Hz, 1H), 3.89 (d, *J*=14.1 Hz, 1H), 3.81–3.69 (m, 3H), 3.34–3.26 (m, 1H), 1.41 (d, *J*=6.13 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.5 (C), 137.2 (C), 129.7 (C), 128.6 (CH), 128.2 (CH), 128.2 (CH), 128.0 (CH), 127.2 (CH), 125.6 (q, CF_3, J_{CF}=3.8 Hz), 76.0 (CH), 72.8 (CH), 62.2 (CH), 62.0 (CH_2), 60.3 (CH_2), 20.4 (CH_3); MS (EI) 351.1 (M^+); HRMS calcd for $C_{19}H_{20}NO_2F_3$ 351.1446; found 351.1436.

4.11. ((3*R*,4*S*,5*S*)-2-Benzyl-5-methyl-3-(naphthalen-2-yl)isoxazolidin-4-yl)methanol and ((3*S*,4*S*,5*S*)-2-benzyl-5-methyl-3-(naphthalen-2-yl)isoxazolidin-4-yl)methanol

Prepared according to the general procedure from (*E*)-crotonaldehyde (97 μL, 1.17 mmol), (*Z*)-*N*-2-naphthylbenzylidenebenzylamine-*N*-oxide[18] (50 mg, 0.19 mmol), **1** (10 mg, 0.04 mmol), distilled water (1.7 μL, 0.10 mmol), and CF_3SO_3H (3.4 μL, 0.04 mmol) in CH_3NO_2 (1.9 mL, 0.1 M). Purification by silica gel chromatography (5% EtOAc in hexanes) provided the compound as a colorless oil (59 mg, 94%, 55:45 *endo*/*exo*). Reduction of the aldehyde to the primary alcohol followed by purification by silica gel chromatography (15% EtOAc in hexanes) provided the title compound as a clear oil for the determination of enantiomeric purity. *endo* 81%, *exo* 60%. Enantiomeric ratios were determined by HPLC using a Chiralcel OD-H column. λ=210 nm (2% IPA/hexanes, 0.8 mL/min flow rate); *endo* isomers t_R=39.1 min (major enantiomer) and 46.3 min (minor enantiomer); *exo* isomers t_R=33.4 min (major enantiomer) and 42.9 min (minor enantiomer). *exo* isomer $[\alpha]_D$ −73.5 (*c* 1.93, $CHCl_3$); IR (neat) 3408, 2925, 1599, 1447 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.91–7.80 (m, 4H), 7.57–7.52 (m, 1H), 7.52–7.45 (m, 2H), 7.37–7.33 (m, 2H), 7.32–7.26 (m, 2H), 7.25–7.20 (m, 1H), 4.17 (d, *J*=8.2 Hz, 1H), 4.11–4.03 (m, 2H), 3.75 (d, *J*=14.5 Hz, 1H), 3.43 (d, *J*=6.5 Hz, 2H), 2.56–2.47 (m, 1H), 1.38 (d, *J*=6.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.5 (C), 134.1 (C), 133.2 (C), 133.0 (C), 128.8 (CH), 128.4 (CH), 128.2 (CH), 127.9 (CH), 127.7 (CH), 127.1 (CH), 127.0 (CH), 126.4 (CH), 126.2 (CH), 126.0 (CH), 77.1 (CH), 72.3 (CH), 62.4 (CH_2), 60.1 (CH_2), 56.0 (CH), 19.9 (CH_3); MS (EI) 333.2 (M^+); HRMS calcd for $C_{22}H_{23}NO_2$ 333.1729; found 333.1708. *endo* isomer $[\alpha]_D$ −47.4 (*c* 2.57, $CHCl_3$); IR (neat) 3420, 2924, 1599, 1454 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.86–7.78 (m, 4H), 7.63 (dd, *J*=8.4, 1.7 Hz, 1H), 7.50–7.43 (m, 2H), 7.36–7.30 (m, 2H), 7.28–7.16 (m, 3H), 4.25 (dq, *J*=6.2, 5.9 Hz, 1H), 4.00 (d, *J*=14.1 Hz, 1H), 3.86–3.70 (m, 4H), 2.48–2.40 (m, 1H), 1.46 (d, *J*=5.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.8 (C), 137.1 (C), 133.3 (C),

133.1 (C), 128.6 (CH), 128.5 (CH), 128.3 (CH), 128.1 (CH), 127.7 (CH), 127.7 (CH), 127.0 (CH), 126.9 (CH), 126.2 (CH), 126.0 (CH), 125.4 (CH), 76.1 (CH), 73.8 (CH), 62.3 (CH_2), 61.9 (CH), 60.0 (CH_2), 20.9 (CH_3); MS (EI) 333.2 (M^+); HRMS calcd for $C_{22}H_{23}NO_2$ 333.1729; found 333.1715.

4.12. ((3*R*,4*S*,5*S*)-2,5-Dimethyl-3-phenylisoxazolidin-4-yl)methanol and ((3*S*,4*S*,5*S*)-2,5-dimethyl-3-phenylisoxazolidin-4-yl)methanol

Prepared according to the general procedure from (*E*)-crotonaldehyde (142 μL, 1.7 mmol), (*Z*)-*N*-benzylidenemethylamine-*N*-oxide (50 mg, 0.34 mmol), **1** (20 mg, 0.07 mmol), distilled water (3.3 μL, 0.18 mmol), and $HClO_4$ (6.2 μL, 0.07 mmol) in CH_3NO_2 (3.7 mL, 0.1 M). Purification by silica gel chromatography (10% EtOAc in hexanes) provided the compound as a colorless oil (46 mg, 61%, 43:57 *endo*/*exo*). Reduction of the aldehyde to the primary alcohol followed by purification by silica gel chromatography (20% EtOAc in hexanes) provided the title compound as a clear oil for the determination of enantiomeric purity; *endo* 89%, *exo* 80%. Enantiomeric ratios were determined by HPLC using a Chiralcel OD-H column. λ=210 nm (2% IPA/hexanes, 0.8 mL/min flow rate); *endo* isomers t_R=33.6 min (major enantiomer) and 27.0 min (minor enantiomer); *exo* isomers t_R=18.7 min (major enantiomer) and 20.3 min (minor enantiomer). *exo* isomer $[\alpha]_D$ −203 (*c* 0.79, $CHCl_3$); IR (neat) 3385, 2925, 1558, 1456 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.36–7.32 (m, 4H), 7.31–7.26 (m, 1H), 4.01 (dq, *J*=6.1, 6.0 Hz, 1H), 3.74 (d, *J*=8.6 Hz, 1H), 3.42–3.32 (m, 2H), 2.61 (s, 3H), 3.47–3.40 (m, 1H), 1.38 (d, *J*=6.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.2 (C), 128.8 (CH), 128.8 (CH), 127.9 (CH), 76.9 (CH), 74.9 (CH), 62.4 (CH_2), 55.4 (CH), 43.5 (CH_3), 19.8 (CH_3); MS (EI) 207.1 (M^+); HRMS calcd for $C_{12}H_{17}NO_2$ 207.1259; found 207.1234. *endo* isomer $[\alpha]_D$ −100 (*c* 0.75, $CHCl_3$); IR (neat) 3420, 2921, 1652, 1455 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.40–7.25 (m, 5H), 4.21 (dq, *J*=18.4, 6.3 Hz, 1H), 3.78–3.65 (m, 2H), 3.40–3.25 (m, 1H), 2.56 (s, 3H), 2.42–2.32 (m, 1H), 1.44 (d, *J*=6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.8 (C), 127.8 (CH), 128.1 (CH), 127.9 (CH), 76.2 (CH), 74.9 (CH), 62.4 (CH), 62.2 (CH_2), 43.5 (CH_3), 21.4 (CH_3); MS (EI) 207.1 (M^+); HRMS calcd for $C_{12}H_{17}NO_2$ 207.1259; found 207.1238.

4.13. ((3*R*,4*S*,5*S*)-3-(Furan-2-yl)-2,5-dimethylisoxazolidin-4-yl)methanol and ((3*S*,4*S*,5*S*)-3-(furan-2-yl)-2,5-dimethylisoxazolidin-4-yl)methanol

Prepared according to the general procedure from (*E*)-crotonaldehyde (200 μL, 1.8 mmol), (*Z*)-*N*-fur-2-ylmethylidenemethylamine-*N*-oxide[19] (50 mg, 0.40 mmol), **1** (22 mg, 0.08 mmol), distilled water (3.6 μL, 0.20 mmol), and $HClO_4$ (6.7 μL, 0.08 mmol) in CH_3NO_2 (4.0 mL, 0.1 M). Purification by silica gel chromatography (10% EtOAc in hexanes) provided the compound as a colorless oil (29 mg, 38%, 50:50 *endo*/*exo*). Reduction of the aldehyde to the primary alcohol followed by purification by silica gel chromatography (20% EtOAc in hexanes) provided the title compound as a clear oil for the determination of enantiomeric purity; *endo* 88%, *exo* 69%. Enantiomeric ratios were determined by HPLC using a Chiralcel OD-H column. λ=220 nm (2% IPA/hexanes, 0.8 mL/min flow rate); *endo* isomers t_R=29.4 min (major enantiomer) and 37.8 min (minor enantiomer); *exo* isomers t_R=27.9 min (major enantiomer) and 33.8 min (minor enantiomer). IR (neat) 3392, 2933, 1656, 1500, 1458 cm^{-1}. *exo* isomer ^1H NMR (500 MHz, $CDCl_3$) δ 7.43–7.40 (m, 1H), 6.39–6.33 (m, 2H), 4.13–4.04 (m, 1H), 3.87–3.77 (m, 1H), 3.53 (d, *J*=6.0 Hz, 2H), 2.63 (s, 3H), 2.48–2.38 (m, 1H), 1.36 (d, *J*=5.7 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 150.0 (C), 142.6 (CH), 110.4 (CH), 108.8 (CH), 77.1 (CH), 74.9 (CH), 62.2 (CH_2), 55.4 (CH), 43.7 (CH_3), 19.4 (CH_3). *endo* isomer ^1H NMR (500 MHz, $CDCl_3$) δ 7.43–7.35 (m, 1H), 6.36–6.26 (m, 2H), 4.19 (dq, *J*=18.1, 5.9 Hz, 1H), 3.83–3.66 (m, 2H), 3.55–3.40 (m, 1H), 2.72–2.42 (m, 4H), 1.42 (d, *J*=5.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.0 (C), 142.7 (CH), 110.3 (CH), 108.1 (CH), 77.5 (CH), 74.9 (CH), 62.2 (CH), 61.9 (CH_2), 43.9 (CH_3), 20.7 (CH_3); MS (EI) 197.1 (M^+); HRMS calcd for $C_{10}H_{15}NO_3$ 197.1052; found 197.1047.

4.14. ((3*R*,4*S*,5*S*)-2,5-Dimethyl-3-*p*-tolylisoxazolidin-4-yl)methanol and ((3*S*,4*S*,5*S*)-2,5-dimethyl-3-*p*-tolylisoxazolidin-4-yl)methanol

Prepared according to the general procedure from (*E*)-crotonaldehyde (134 μL, 1.6 mmol), (*Z*)-*N*-4-methylbenzylidenemethylamine-*N*-oxide (50 mg, 0.33 mmol), **1** (18 mg, 0.07 mmol), distilled water (3.0 μL, 0.17 mmol), and CF_3SO_3H (5.9 μL, 0.07 mmol) in CH_3NO_2 (3.4 mL, 0.1 M). Purification by silica gel chromatography (10% EtOAc in hexanes) provided the compound as a colorless oil (53 mg, 71%, 48:52 *endo*/*exo*). Reduction of the aldehyde to the primary alcohol followed by purification by silica gel chromatography (20% EtOAc in hexanes) provided the title compound as a clear oil for the determination of enantiomeric purity; *endo* 80%, *exo* 92%. Enantiomeric ratios were determined by HPLC using a Chiralcel OD-H column. λ=210 nm (2% IPA/hexanes, 0.8 mL/min flow rate); *endo* isomers t_R=14.9 min (major enantiomer) and 16.3 min (minor enantiomer); *exo* isomers t_R=34.7 min (major enantiomer) and 21.8 min (minor enantiomer). *exo* isomer $[\alpha]_D$ −192 (*c* 1.42, $CHCl_3$); IR (neat) 3416, 2925, 1540, 1515 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.22 (d, *J*=8.0 Hz, 2H), 7.15 (d, *J*=8.0 Hz, 2H), 3.98 (dq, *J*=18.4, 6.2 Hz, 1H), 3.70 (d, *J*=8.7 Hz, 1H), 3.45–3.31 (m, 2H), 2.59 (s, 3H), 2.44–2.35 (m, 1H), 2.32 (s, 3H), 1.37 (d, *J*=6.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.6 (C), 133.1 (C), 129.5 (CH), 127.8 (CH), 76.7 (CH), 74.7 (CH), 62.4 (CH_2), 56.5 (CH), 43.4 (CH_3), 21.1 (CH_3), 19.8 (CH_3); MS (EI) 221.1 (M^+); HRMS calcd for $C_{13}H_{19}NO_2$ 221.1416; found 221.1394. *endo* isomer $[\alpha]_D$ −98.9 (*c* 1.41, $CHCl_3$); IR (neat) 3397, 2925, 1653, 1515 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.24 (d, *J*=7.9 Hz, 2H), 7.13 (d, *J*=8.0 Hz, 2H), 4.19 (dq, *J*=18.1, 6.0 Hz, 1H), 3.75–3.63 (m, 2H), 3.34–3.19 (m, 1H), 2.54 (s, 3H), 2.39–2.33 (m, 1H), 2.32 (s, 3H), 1.43 (d, *J*=6.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.8 (C), 135.5 (C), 129.4 (CH), 127.8 (CH), 76.1 (CH), 74.8 (CH), 62.4 (CH), 62.1 (CH_2), 43.5 (CH_3), 21.4 (CH_3), 21.1 (CH_3); MS (EI) 221.1 (M^+); HRMS calcd for $C_{13}H_{19}NO_2$ 221.1416; found 221.1390.

4.15. ((3*R*,4*S*,5*S*)-2-Benzyl-3-phenyl-5-propylisoxazolidin-4-yl)methanol and ((3*S*,4*S*,5*S*)-2-benzyl-3-phenyl-5-propylisoxazolidin-4-yl)methanol

Prepared according to the general procedure from (*E*)-hex-2-enal (93 mg, 0.95 mmol), (*Z*)-*N*-benzylidenebenzylamine-*N*-oxide (50 mg, 0.24 mmol), **1** (13 mg, 0.05 mmol), distilled water (1.4 μL, 0.11 mmol), and CF_3SO_3H (4.2 μL, 0.05 mmol) in CH_3NO_2 (2.0 mL, 0.1 M). Purification by silica gel chromatography (5% EtOAc in hexanes) provided the compound as a colorless oil in 86% yield (63 mg, 86%, 40:60 *endo*/*exo*). Reduction of the aldehyde to the primary alcohol followed by purification by silica gel chromatography (15% EtOAc in hexanes) provided the title compound as a clear oil for the determination of enantiomeric purity; *endo* 74%, *exo* 84%. Enantiomeric ratios were determined by HPLC using a Chiralcel OD-H column. λ=210 nm (2% IPA/hexanes, 0.8 mL/min flow rate); *endo* isomers t_R=26.1 min (major enantiomer) and 23.6 min (minor enantiomer); *exo* isomers t_R=15.3 min (major enantiomer) and 17.4 min (minor enantiomer). *exo* isomer $[\alpha]_D$ −115 (*c* 2.40, $CHCl_3$); IR (neat) 3420, 2930, 1599, 1454 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.44–7.20 (m, 10H), 4.02 (d, *J*=14.4 Hz, 1H), 3.96 (d, *J*=8.1 Hz, 1H), 3.89 (dd, *J*=12.2, 5.7 Hz, 1H), 3.68 (d, *J*=14.4 Hz, 1H), 3.47 (dd, *J*=11.3, 6.7 Hz, 1H), 3.38 (dd, *J*=11.3, 5.3 Hz, 1H), 2.51–2.43 (m, 1H), 1.70–1.56 (m, 2H), 1.52–1.35 (m, 2H), 0.93 (t, *J*=7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.4 (C), 136.4 (C), 128.9 (CH), 128.8 (CH), 128.1 (CH), 128.0 (CH), 127.9 (CH), 127.1 (CH), 80.0 (CH), 72.0 (CH), 62.5 (CH_2), 59.9 (CH_2), 55.5 (CH), 37.1 (CH_2), 19.2 (CH_2), 14.2 (CH_3); MS (EI) 311.2 (M^+); HRMS calcd for $C_{20}H_{25}NO_2$ 311.1885; found 311.1873. *endo* isomer $[\alpha]_D$ −90.0 (*c* 1.38, $CHCl_3$); IR (neat) 3421, 2930, 1652, 1455 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.44–7.39 (m, 2H), 7.36–7.29 (m, 4H), 7.29–7.23 (m, 3H), 7.22–7.16 (m, 1H), 4.01–3.90 (m, 2H), 3.79–3.67 (m, 2H), 3.56 (d, *J*=7.2 Hz, 1H), 2.43–2.35 (m, 1H), 1.95–1.84 (m, 1H), 1.66–1.54 (m, 1H), 1.52–1.30 (m, 3H), 0.92 (t, *J*=7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.6 (C), 138.0 (C), 128.7 (CH), 128.4 (CH), 128.0 (CH), 127.9 (CH), 127.8 (CH), 126.8 (CH), 79.9 (CH), 73.8 (CH), 62.9 (CH_2), 60.7 (CH), 59.5 (CH_2), 37.7 (CH_2), 19.4 (CH_2), 14.1 (CH_3); MS (EI) 311.2 (M^+); HRMS calcd for $C_{20}H_{25}NO_2$ 311.1885; found 311.1858.

4.16. ((3*R*,4*S*,5*S*)-2-Benzyl-5-isopropyl-3-phenylisoxazolidin-4-yl)methanol and ((3*S*,4*S*,5*S*)-2-benzyl-5-isopropyl-3-phenylisoxazolidin-4-yl)methanol

Prepared according to the general procedure from (*E*)-4-methylpent-2-enal (93 mg, 0.95 mmol), (*Z*)-*N*-benzylidenebenzylamine-*N*-oxide (50 mg, 0.24 mmol), **1** (13 mg, 0.05 mmol), distilled water (1.4 μL, 0.11 mmol), and CF_3SO_3H (4.2 μL, 0.05 mmol) in CH_3NO_2 (2.0 mL, 0.1 M). Purification by silica gel chromatography (5% EtOAc in hexanes) provided the compound as a colorless oil (50 mg, 68%, 43:57 *endo*/*exo*). Reduction of the aldehyde to the primary alcohol followed by purification by silica gel chromatography (15% EtOAc in hexanes) provided the title compound as a clear oil for the determination of enantiomeric purity; *endo* 77%, *exo* 66%. Enantiomeric ratios were determined by HPLC using a Chiralcel OD-H column. λ=220 nm (2% IPA/hexanes, 0.8 mL/min flow rate); *endo* isomers t_R=24.7 min (major enantiomer) and 22.1 min (minor enantiomer); *exo* isomers t_R=13.0 min (major enantiomer) and 15.0 min (minor enantiomer). *exo* isomer $[\alpha]_D$ −134 (*c* 1.40, $CHCl_3$); IR (neat) 3442, 2958, 1652, 1454 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.45–7.21 (m, 10H), 4.05 (d, *J*=14.4 Hz, 1H), 3.87 (d, *J*=7.6 Hz, 1H), 3.68–3.61 (m, 2H), 3.56 (dd, *J*=11.5, 7.4 Hz, 1H), 3.36 (dd, *J*=11.5, 4.1 Hz, 1H), 2.57–2.49 (m, 1H), 1.89–1.77 (m, 1H), 0.96 (s, 3H), 0.95 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.2 (C), 136.2 (C), 129.2 (CH), 129.0 (CH), 128.1 (CH), 128.0 (CH), 127.2 (CH), 84.4 (CH), 72.2 (CH), 62.8 (CH_2), 59.6 (CH_2), 52.1 (CH), 18.5 (CH_3), 18.4 (CH_3); MS (EI) 311.2 (M^+); HRMS calcd for $C_{20}H_{25}NO_2$ 311.1885; found 311.1867. *endo* isomer $[\alpha]_D$ −82.7 (*c* 1.01, $CHCl_3$); IR (neat) 3461, 2921, 1652, 1454 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.46–7.41 (m, 2H), 7.36–7.30 (m, 4H), 7.30–7.23 (m, 3H), 7.22–7.16 (m, 1H), 3.92 (d, *J*=14.7 Hz, 1H), 3.80–3.70 (m, 2H), 3.65 (d, *J*=14.6 Hz, 1H), 3.60–3.56 (m, 2H), 2.57–2.48 (m, 1H), 2.16–2.03 (m, 1H), 0.94 (d, *J*=6.6 Hz, 3H), 0.90 (d, *J*=6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.8 (C), 138.2 (C), 128.7 (CH), 128.3 (CH), 128.3 (CH), 128.0 (CH), 127.8 (CH), 126.8 (CH), 85.2 (CH), 74.6 (CH), 63.7 (CH_2), 59.4 (CH), 58.7 (CH_2), 32.7 (CH), 19.1 (CH_3), 18.5 (CH_3); MS (EI) 311.2 (M^+); HRMS calcd for $C_{20}H_{25}NO_2$ 311.1885; found 311.1888.

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Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2007.08.110.

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