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5-Phenylthio-1,3-oxazinan-4-ones via hetero Diels–Alder reactions: synthesis of (*R*)- and (*S*)-Duloxetines and Fluoxetines

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Abstract—The synthesis of 5-phenylthio-1,3-oxazinan-4-ones, through a hetero Diels–Alder strategy, is described. The cycloadducts thus prepared have been shown to be useful intermediates for the synthesis of 1,3-aminoalcohols, valuable intermediates in the preparation of biologically significant molecules, e.g., optically active Duloxetines and Fluoxetines. In the course of this elaboration a novel microwave assisted desulfurization reaction is reported.

1. Introduction

Hetero Diels–Alder cycloaddition is a versatile strategy for the synthesis of natural compounds containing six-membered heterocyclic rings.[1–9] Moreover, this strategy has found important applications through the elaboration of the cyclic adducts thus obtained to acyclic compounds with a well-defined stereo- and regio-control of the present functionalities. Reported herein is the application of hetero Diels–Alder methodology to the synthesis of open-chain compounds containing the 1,3-hydroxy-amino moiety, which is present in a large class of pharmaceutically important compounds such as Duloxetine (Cymbalta®)[10–12] and Fluoxetine (Prozac®).[13,14] Prozac and Cymbalta have been chosen as target compounds being potent and highly selective inhibitors of neutral serotonin-reuptake and among the most important drugs for the treatment of psychiatric disorders and metabolic problems. Last but not the least, their market is very interesting from an industrial point of view.[15] As a matter of fact the establishment of new synthetic protocols, which allow the building-up of small libraries, with an easily obtainable different substitution pattern on the scaffold, is of primary importance for researchers involved in the preparation and the study of this class of compounds. Recent disclosure from these laboratories[16] have demonstrated that 5-unsubstituted perhydrooxazinan-4-ones, obtained via a hetero Diels–Alder strategy, may be adopted as useful intermediates for the preparation of 1,3-aminoalcohols. In continuation of our studies on the use of hetero Diels–Alder strategy in the synthesis of heterocyclic compounds with different substitution pattern and their use for the preparation of acyclic derivatives we would like to present here our recent results on the synthesis and use of the 5-phenylthio-perhydrooxazinan-4-ones in the preparation of racemic and optically active 1,3-aminoalcohols. Compared to the previously reported studies in the same field, we anticipated that the synthesis of the 5-phenylthio-substituted oxazinan-4-ones may have its importance if the position five of the heterocyclic adduct is substituted by an easily removable group, as the thiophenyl one. Moreover, the intrinsic important reactivity of this functionality would allow further elaborations, e.g., introduction of an extra group and/or functionalities. As an example, the parent acyclic β-hydroxy-α-phenylthiocarboxy derivatives[17–20] have been shown to be useful intermediates for the synthesis of 1,3-aminoalcohols.[21,22]

2. Results and discussion

2.1. Synthesis of racemic 5-thiophenyl-1,3-oxazinan-4-ones

5-Phenylthio-1,3-oxazinan-4-ones have been obtained from the easily available 1,3-azadienes,[23–28] prepared from silylimines and ketenes, and using aldehydes as dienophiles. In the present study, the starting azadiene is a neutral

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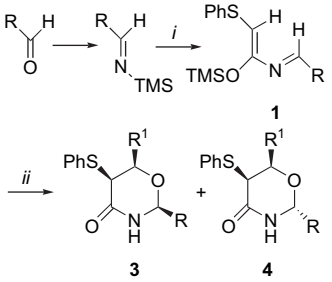
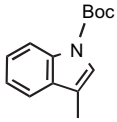
3-trimethylsilyloxy-4-thioaryl-2-aza-1,3-diene, already used in a previous study for the preparation of a β-lactam ring by a 4π-conrotatory electrocyclization.[29]

In detail, reaction of the neutral azadiene **1** with an aldehyde R^1CHO **2**, in the presence of a stoichiometric amount of boron trifluoride etherate in dichloromethane (DCM) at −78 °C, gives rise to the formation of the expected 5-phenylthio-1,3-oxazinan-4-ones **3** and **4** with various substitution patterns at the C_2 and the C_6 carbon atoms (Scheme 1 and Table 1).[30–35] The results shown in Scheme 1 and Table 1 warrant some comments. (1) No traces of azedinones, arising from a 4π-conrotatory electrocyclization, have been detected in the crude reaction mixtures.[29,36] (2) All the reactions are completely regioselective. (3) The use of an excess of Lewis acid does not influence the reaction course since the value of the diastereomeric ratio as well as that of the yield remains substantially untouched (Table 1 entry 2). (4) In all the experiments performed, irrespective of the starting azadiene and the dienophilic aldehyde used, a cis-relationship between the C_5H and C_6H is established, shown by the relative coupling constants (J_{cis}=2–4 Hz) and NOE experiments. Careful analysis of the results reported in Table 1 clearly allows to allocate, from the stereochemical relationship of C_2H–C_5H–C_6H, two groups of cycloadducts: one (compounds **3a**–**3f**) presenting the three ring-protons in a basket conformation and an other group (compounds **4a**–**4f**) presenting the same cis-configuration between the C_5H and C_6H but a trans-relationship between C_2H and C_5H as pointed out by the combined analysis of coupling constants and NOEs. In order to ascertain if this stereo-difference originates from a different cyclization mechanism (hetero Diels–Alder vs a competitive open-chain Mukaiyama mechanism[37]) and taking into account that, as already known,[38–40] an equilibrium between the cyclic perhydrooxazinan-4-ones and the open-chain derivatives may exist (Scheme 2), extra experiments were performed. Treatment of pure **3a** with an excess of BF_3 etherate in methylene chloride for 4 h at room temperature gives rise to a mixture of **3a** and **4a** in 90/10 diastereomeric ratio as evaluated by ^1H NMR spectroscopic analysis. This is, in our opinion, a clear evidence that some degree of isomerization could take place *after* the formation of the Diels–Alder adduct thus suggesting the exclusion of a different reaction mechanism (e.g., a competitive Mukaiyama type addition–cyclization two-step mechanism). A further confirmation of this working hypothesis comes out from the results obtained when a hydroxyalkyl group, which should not favor the formation of a positive charge, is present on the C_2 stereocenter (heterocyclic numbering). As a matter of fact in this case only two products were obtained (vide infra): they have the same basket conformation for the C_2, C_5, and C_6 hydrogen atoms and differ for opposite absolute configuration of these centers. Nevertheless, it must be pointed out that these speculations are interesting from a mechanistic point of view but useless from a practical one since this isomerization is immaterial in our strategic plan because of the loss of the C_2 stereogenic center in the final products (see Schemes 3 and 4). For this reason no more investigations, so far, have been undertaken.

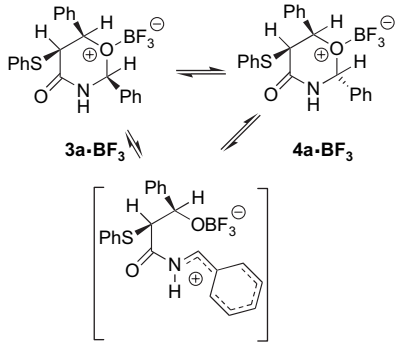


Scheme 1. Reagents and conditions: (i) Ref. 29; (ii) R^1CHO (**2**), DCM, $BF_3 \cdot Et_2O$.

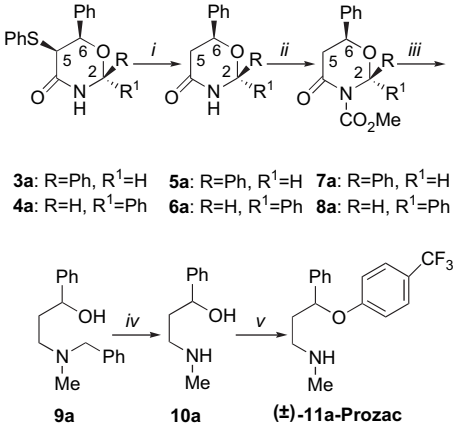
Table 1. Synthesis of perhydrooxazinan-2-ones **3** and **4**

Exps.	R	R^1	Azadiene	Products	Ratio	Ys, %[a]
1	Ph	Ph	**1a**	**3a/4a**	90/10	35
2	Ph	Ph	**1a**	**3a/4a**	74/26	33[b]
3	Ph		**1a**	**3b/4b**	40/60	38
4	*p*-MeO–Ph	Ph	**1b**	**3c/4c**	80/20	55
5	*o*-TIPSO–Ph	Ph	**1c**	**3d/4d**	85/15	48
6	Ph	Me	**1a**	**3e/4e**	50/50	51
7	Ph		**1a**	**3f/4f**	40/60	41

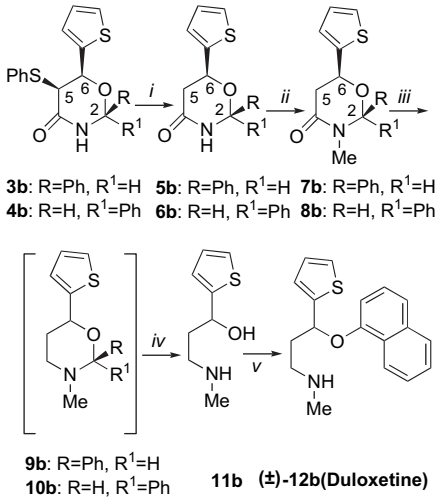
[a] The yields have been calculated on the dienophilic aldehyde.
[b] $BF_3 \cdot Et_2O$ (5 equiv) has been used.



Scheme 2.



Scheme 3. Reagents and conditions: (i) MW, Nickel-Raney/EtOH; (ii) LiHMDS, ClCOOMe, THF; (iii) $LiAlH_4$/THF; (iv) Ref. 40; (v) Ref. 41.



Scheme 4. Reagents and conditions. (i) aluminum amalgam, *i*-PrOH; (ii) LiHMDS, MeI, THF; (iii) Ph_2SiH_2, $RhH(CO)(PPh_3)_3$, THF; (iv) HCl_{aq}; (v) Ref. 49.

2.2. Synthesis of racemic (±)-Prozac and (±)-Duloxetine

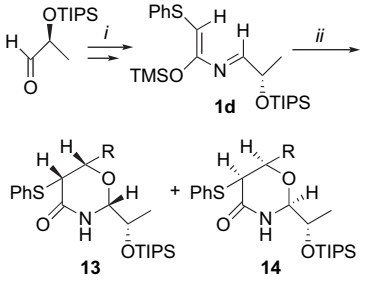
Having the desired perhydrooxazinones in hand, we followed our strategic plan by elaboration of the diastereomeric mixture of compounds **3a/4a** and **3b/4b** to the racemic (±)-Prozac and (±)-Duloxetine, respectively.

The synthetic protocols are outlined in Schemes 3 and 4.

Compounds **3a** and **4a** were easily desulfurated by the use of Nickel-Raney in a novel microwave-mediated[41–45] desulfurization reaction.[18,46–49] Thus treatment of adducts **3a** and **4a** with Raney-Nickel in a microwave oven allows to obtain, in a very short time (2 min) and high yields (80% and 92%, respectively), the corresponding desulfurated derivatives **5a** and **6a**. *N*-Carboxymethyl derivatives **7a** and **8a** were obtained in quantitative yields by treatment of **5a** and **6a** with methyl chloroformate and LiHMDS in THF. Reduction of the amide and carboxymethyl functionalities with lithium aluminum hydride gave rise to open-chain *N*-benzyl derivative **9a**. Following already known procedures, this intermediate was easily converted to the racemic Prozac via hydrogenolysis of the benzyl group and arylation of the hydroxy functionality.[50] It must be stressed that the same synthetic protocol, applied to the diastereomeric mixture of **3a** and **4a**, gave the same results in terms of yields of the overall process. By the same strategy, with slight modifications, (±)-Duloxetine was prepared. Desulfuration of oxazinan-4-ones **3b** and **4b** by the above reported microwave-mediated Nickel-Raney methodology partially failed when applied to these compounds giving rise to low yields of the desired 5-unsubstituted derivatives **5b** and **6b**, probably due to side reactions on the thienyl ring. Different procedures, known in the literature to give good results, failed partially or completely. Finally we have found that desulfuration with aluminum amalgam[51] was the method of choice. Once we prepared the derivatives **5b** and **6b**, their elaboration to the final (±)-Duloxetine was a straightforward task. Methylation by LiHMDS and methyl iodide gave rise, in quantitative yields, to the *N*-methyl intermediates **7b** and **8b**. Reduction of the amide functionality by means of Ph_2SiH_2, in the presence of 1 mol % $RhH(CO)(PPh_3)_3$ in THF,[52] resulted in the production of the partially unstable intermediates **9b** and **10b**. Ring opening by aqueous hydrochloric acid furnished the corresponding aminol **11b**. (±)-Duloxetine was obtained by means arylation of **11b** according to a literature procedure (Scheme 4).[50]

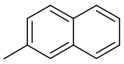
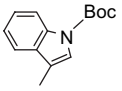
2.3. Synthesis of optically active 5-thiophenyl-substituted oxazinan-4-ones

Owing to the different biological activity exhibited by individual enantiomers of Prozac and Duloxetine, a number of enantioselective syntheses of these important compounds have been developed in recent years.[53–55,50,56] In this section we report the results obtained by our group in the synthesis of optically active aminoalcohols **10a** and **11b** and, therefore, of optically active (*R*)- and (*S*)-Fluoxetines and Duloxetines [(*R*)-**11a**, (*S*)-**11a** and (*R*)-**12b**, (*S*)-**12b**, respectively]. To reach this task and taking advantage of our experience on the synthesis of optically active perhydrooxazinan-4-ones by hetero Diels–Alder strategy, we prepared optically active azadiene **1d** using, in its preparation, the trimethylsilylimine derived from optically active (*S*)-lactic aldehyde and the 2-phenylthioacetylchloride as source of the ketene (Scheme 5). Reaction of the optically active azadiene **1d** with a range of aldehydes furnished two oxazinan-4-ones **13** and **14** in diastereomeric ratios and yields reported in Table 2. The two diastereoisomers presented the same basket conformation for the protons on the heterocyclic ring *but* an opposite absolute configuration of the C_2, C_5, and C_6 stereocenters.



Scheme 5. Reagents and conditions: (i) Ref. 29; (ii) RCHO (**2**), DCM, $BF_3 \cdot Et_2O$.

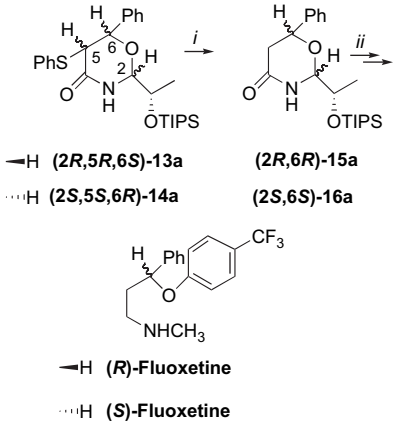
Table 2. Synthesis of oxazinan-4-ones **13** and **14**

Exps.	R	Products	Ratio[a]	Ys, %[b]
1	Ph	**13a/14a**	50/50	81
2		**13b/14b**	60/40	90
3	Me	**13c/14c**	50/50	32
4		**13d/14d**	50/50	41
5		**13e/14e**	63/37	55

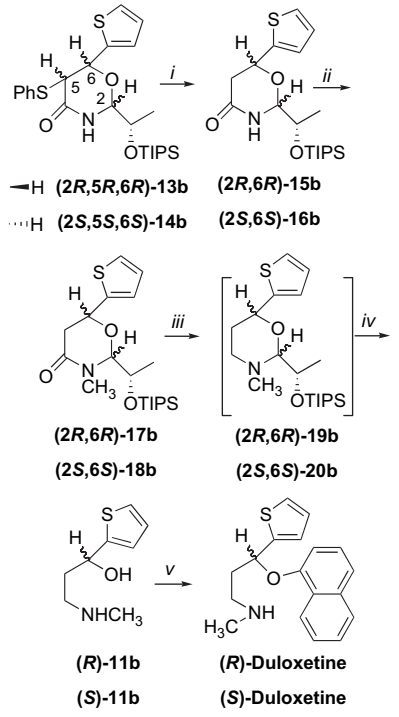
[a] Diastereomeric ratios have been determined on the crude reaction mixtures to avoid enrichments in the course of purification processes.
[b] The yields have been calculated on the dienophilic aldehyde.

2.4. Synthesis of (*R*)- and (*S*)-Fluoxetines and (*R*)- and (*S*)-Duloxetines

Once again, having in hand the desired heterocyclic compounds, we followed our strategic plan, aimed to obtain enantiomerically pure (*S*)- and (*R*)-Fluoxetines and (*S*)- and (*R*)-Duloxetines by elaboration of compounds **13a** and **14a** and compounds **13b** and **14b** to optically active aminoalcohols (1*S*)-**10a**, (1*R*)-**10a** and (1*S*)-**11b**, (1*R*)-**11b**, respectively. Conversion of compounds **13a** and **14a** to the (*S*)- and (*R*)-Fluoxetines proved to be an easy task. Accordingly, compounds **15a** and **16a** were easily obtained in quantitative yields by desulfuration of **13a** and **14a** as already described for the racemic derivatives by means of microwave assisted Raney-Nickel delsufuration. Elaboration of **15a** and **16a** to the target (*S*)- and (*R*)-Fluoxetines has been already described in a previous paper (Scheme 6).[16] On the other hand elaboration of compounds **13b** and **14b** to the (*S*)- and (*R*)-Duloxetines was performed according to the protocol described for the racemic compound. Thus, desulfuration by means of aluminum amalgam followed by N-methylation (LiHMDS, CH_3I), amide functionality reduction, and final arylation with fluoronaphthalene furnished the (*S*)- and (*R*)-Duloxetines (Scheme 7).



Scheme 6. Reagents and conditions: (i) MW, Nickel-Raney/EtOH; (ii) Ref. 16.



Scheme 7. Reagents and conditions. (i) aluminum amalgam, *i*-PrOH; (ii) LiHMDS, MeI, THF; (iii) Ph_2SiH_2, $RhH(CO)(PPh_3)_3$, THF; (iv) HCl_{aq}; (v) Ref. 50.

3. Conclusions

In conclusion we have reported an extra contribution to the applications of azadienes of type **1** in the synthesis of valuable intermediates for the preparation of biologically significant molecules. Moreover, the 5-thio-substituted cyclic adducts thus obtained may be considered as cyclic form of α-thio-carboxylic acid derivatives and, accordingly, may undergo further elaborations. Studies in this vein are currently in progress. Finally, the novel microwave assisted desulfuration herein described, represents a valuable method, alternative to those available for this task (e.g., use of expensive and toxic tributyltin hydride). Its application to other significant classes of compounds is in progress.

4. Experimental

4.1. General procedures

All starting compounds, unless otherwise stated, were purchased. Reactions were run under an atmosphere of dry nitrogen or argon. FT-IR spectra were recorded on a Perkin–Elmer infrared spectrometer, mass spectra on Finnigan MAT instrument, and NMR spectra on a Varian Mercury 400 MHz spectrometer using the residual signal of the solvent as internal standard. Chemical shifts are reported in the δ scale and coupling constants (*J*) in hertz. Optical rotations were recorded on a Perkin–Elmer Polarimeter 343. Solvents were distilled and dried according to standard procedures. All the reactions were performed under a nitrogen atmosphere.

4.2. General procedure (GP1) for the preparation of 1,3-oxazinan-4-ones 3a–3f and 4a–4f

Compound **1** (2 mmol), prepared according to literature,[29] was dissolved in anhydrous CH_2Cl_2 (20 mL) and cooled at −78 °C. Aldehyde **2** (1 mmol), dissolved in methylene chloride (2 mL), was added followed by a slow addition of BF_3 etherate (1 mmol) in CH_2Cl_2 (10 mL). The solution was stirred overnight while the temperature was allowed to reach room temperature. The mixture was poured into saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2. The organic layers were dried and the solvent was removed in vacuum. The reaction mixture was purified by flash chromatography on silica gel. 5-Phenylthio-perhydrooxazin-4ones **3a**–**3f** and **4a**–**4f** were isolated in combined yields and diastereomeric ratios reported in Table 1.

4.2.1. (2*S,5*S**,6*R**)-2,6-Diphenyl-5-phenylthio-[1,3]oxazinan-4-one 3a; (2*R**,5*S**,6*R**)-2,6-diphenyl-5-phenylthio-[1,3]oxazinan-4-one 4a.** The crude reaction mixture

obtained from azadiene **1a** (2 mmol) and benzaldehyde (0.1 mL, 1 mmol) according to GP1 was subjected to column chromatography (1:1 *EtOAc*/cyclohexane) to give **3a** and **4a** in 90/10 diastereomeric ratio and 35% overall yield.

Compound **3a**: pale yellow solid. Y=32%. Mp 173–174 °C. IR ($CHCl_3$): 1674 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ=7.60–7.10 (m, 15H), 6.30 (br s, 1H), 5.92 (s, 1H), 5.41 (d, J=2.4 Hz, 1H), 3.82 (d, J=2.4 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=169.1, 137.5, 136.9, 134.6, 133.2, 130.0, 128.8, 128.7, 128.1, 127.9, 127.8, 127.1, 125.9, 86.1, 78.6, 55.4. MS (*m*/*z*): 361, 255, 106, 91, 77. E.A. Calcd for $C_{22}H_{19}NO_2S$: C, 73.10; H, 5.30; N, 3.88. Found: C, 73.29; H, 5.33.

Compound **4a**: Pale yellow oil. Y=3%. IR ($CHCl_3$): 1667 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ=7.78–7.00 (m, 15H), 6.53 (br s, 1H), 6.03 (s, 1H), 5.37 (d, J=3.6 Hz, 1H), 4.03 (d, J=3.6 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=169.4, 138.0, 136.1, 134.3, 132.9, 129.4, 128.8, 128.7, 128.3, 128.2, 127.7, 126.7, 126.6, 82.0, 73.6, 53.9. MS (*m*/*z*): 361, 255, 106, 91, 77. E.A. Calcd for $C_{22}H_{19}NO_2S$: C, 73.10; H, 5.30; N, 3.88. Found: C, 73.32; H, 5.31.

4.2.2. (2*S,5*S**,6*S**)-2-Phenyl-6-(thiophen-2-yl)-5-phenylthio-[1,3]oxazinan-4-one 3b; (2*R**,5*S**,6*S**)-2-phenyl-6-(thiophen-2-yl)-5-phenylthio-[1,3]oxazinan-4-one 4b.** The crude reaction mixture obtained from azadiene **1a** (2 mmol) and 2-thiophenecarboxaldehyde (0.093 mL, 1 mmol) according to GP1 was subjected to column chromatography (4:6 *EtOAc*/cyclohexane) to give **3b** and **4b** in 40/60 diastereomeric ratio and 38% overall yield.

Compound **3b**: pale yellow oil. Y=15%. IR ($CHCl_3$): 1676 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ=7.43 (m, 7H), 7.33 (dd, J_1=1.0 Hz, J_2=5.0 Hz, 1H), 7.24 (m, 3H), 7.06 (m, 1H), 7.01 (dd, J_1=3.4 Hz, J_2=5.0 Hz, 1H), 6.54 (br s, 1H), 5.93 (s, 1H), 5.60 (dd, J_1=0.6 Hz, J_2=2.4 Hz, 1H), 3.82 (d, J=2.4 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=168.8, 139.3, 137.1, 134.6, 132.9, 130.0, 128.9, 128.8, 127.8, 127.1, 126.37, 125.9, 125.5, 86.0, 76.3, 55.3. MS (*m*/*z*): 368 (M^++1), 323, 255, 212, 184, 152, 121, 106, 91, 77. E.A. Calcd for $C_{21}H_{19}NOS_2$: C, 69.01; H, 5.24; N, 3.83. Found: C, 70.39; H, 5.34.

Compound **4b**: pale yellow oil. Y=23%. IR ($CHCl_3$): 1675 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ=7.50–7.38 (m, 8H), 7.33 (br s, 1H), 7.26 (m, 4H), 7.14 (m, 1H), 7.05 (dd, J_1=3.2 Hz, J_2=5.2 Hz, 1H), 5.83 (s, 1H), 5.57 (d, J=4.8 Hz, 1H), 4.23 (dd, J_1=3.6 Hz, J_2=4.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=168.6, 137.6, 137.5, 134.4, 133.5, 129.7, 129.0, 128.8, 127.2, 126.8, 126.7, 81.6, 72.1, 53.4. MS (*m*/*z*): 366 (M^+−1), 322, 255, 212, 186, 152, 121, 106, 77. E.A. Calcd for $C_{21}H_{19}NOS_2$: C, 69.01; H, 5.24; N, 3.83. Found: C, 70.39; H, 5.34.

4.2.3. (2*S,5*S**,6*R**)-2-(4-Methoxy-phenyl)-6-phenyl-5-phenylthio-[1,3]oxazinan-4-one 3c; (2*R**,5*S**,6*R**)-2-(4-methoxy-phenyl)-6-phenyl-5-phenylthio-[1,3]oxazinan-4-one 4c.** The crude reaction mixture obtained from azadiene **1b** (2 mmol) and benzaldehyde (0.1 mL, 1 mmol) according to GP1 was subjected to column chromatography (1:1 *EtOAc*/cyclohexane) to give **3c** and **4c** in 80/20 diastereomeric ratio and 55% overall yield.

Compound **3c**: pale yellow solid. Y=44%. Mp 181–183 °C. IR ($CHCl_3$): 1672 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ=7.46–7.16 (m, 12H), 6.93 (d, J=8.8 Hz, 2H), 6.45 (br s, 1H), 5.86 (s, 1H), 5.38 (d, J=2.0 Hz, 1H), 3.83 (s, 3H), 3.80 (d, J=2.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=169.5, 160.8, 140.3, 136.9, 134.6, 133.2, 129.2, 128.8, 128.6, 128.1, 126.4, 125.9, 114.1, 85.8, 78.4, 55.4. MS (*m*/*z*): 392 (M^++1), 334, 316, 299, 285, 187, 162, 136, 105, 91, 77. E.A. Calcd for $C_{24}H_{23}NO_2S$: C, 74.00; H, 5.95. Found: C, 75.48; H, 6.07.

Compound **4c**: pale yellow solid. Y=11%. IR ($CHCl_3$): 1673 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ=7.40–7.20 (m, 12H), 6.90 (d, J=8.6 Hz, 2H), 6.27 (br s, 1H), 5.96 (s, 1H), 5.38 (d, J=3.8 Hz, 1H), 4.08 (d, J=3.8 Hz, 1H), 3.80 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=169.7, 160.7, 136.4, 134.6, 133.1, 130.3, 129.1, 128.5, 128.4, 128.0, 127.9, 127.1, 114.4, 82.1, 73.9, 55.6, 54.1. MS (*m*/*z*): 392 (M^++1), 316, 299, 285, 281, 210, 136, 105, 91, 77. E.A. Calcd for $C_{24}H_{23}NO_2S$: C, 74.00; H, 5.95. Found: C, 75.48; H, 6.07.

4.2.4. (2*S,5*S**,6*R**)-2-(2-Triisopropylsilyloxyphenyl)-6-phenyl-5-(phenylthio)-[1,3]oxazinan-4-one 3d; (2*R**,5*S**,6*R**)-2-(2-triisopropylsilyloxyphenyl)-6-phenyl-5-(phenylthio)-[1,3]oxazinan-4-one 4d.** The crude reaction mixture obtained from azadiene **1c** (2 mmol) and benzaldehyde (0.1 mL, 1 mmol) according to GP1 was subjected to column chromatography (4:6 *EtOAc*/cyclohexane) to give **3d** and **4d** in 85/15 diastereomeric ratio and 48% overall yield.

Compound **3d**: pale yellow oil. Y=41%. IR ($CHCl_3$): 1674 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ=7.62–6.85 (m, 14H), 6.36 (s, 1H), 6.22 (br s, 1H), 5.42 (d, J=2.4 Hz, 1H), 3.84 (d, J=2.4 Hz, 1H), 1.10 (m, 21H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=168.8, 153.0, 137.1, 134.6, 133.2, 130.3, 128.7, 128.1, 127.8, 127.6, 127.5, 127.2, 125.9, 121.5, 118.0, 80.5, 78.5, 55.5, 18.0, 12.9. MS (*m*/*z*): 534, 427, 385, 279, 234. E.A. Calcd for $C_{32}H_{41}NO_2SSi$: C, 72.27; H, 7.77. Found: C, 74.44; H, 8.00.

Compound **4d**: pale yellow oil. Y=7%. IR ($CHCl_3$): 1672 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ=7.45–7.05 (m, 14H), 6.33 (br s, 1H), 6.21 (s, 1H), 5.50 (d, J=4.0 Hz, 1H), 4.10 (d, J=4.0 Hz, 1H), 1.05 (m, 21H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=168.4, 153.4, 135.6, 134.4, 132.9, 130.1, 128.8, 128.5, 128.3, 127.7, 127.4, 126.6, 121.1, 118.5, 77.6, 75.1, 53.4, 18.0, 13.0. MS (*m*/*z*): 534, 427, 385, 279, 234. E.A. Calcd for $C_{32}H_{41}NO_2SSi$: C, 72.27; H, 7.77. Found: C, 74.44; H, 8.00.

4.2.5. (2*S,5*S**,6*R**)-6-Methyl-2-phenyl-5-phenylthio-[1,3]oxazinan-4-one 3e; (2*R**,5*S**,6*R**)-6-methyl-2-phenyl-5-phenylthio-[1,3]oxazinan-4-one 4e.** The crude reaction mixture obtained from azadiene **1a** (2 mmol) and acetaldehyde (0.056 mL, 1 mmol) according to GP1 was subjected to column chromatography (6:4 *EtOAc*/cyclohexane) to give **3e** and **4e** in 50/50 diastereomeric ratio and 51% overall yield.

Compound **3e**: pale yellow oil. Y=25%. IR ($CHCl_3$): 1672 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ=7.70 (m, 2H), 7.45–7.23 (m, 8H), 6.69 (br s, 1H), 5.74 (s, 1H), 4.34 (dq, J_1=6.4 Hz, J_2=2.8 Hz, 1H), 3.51 (d, J=2.8 Hz, 1H), 1.57 (d, J=6.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=169.7, 137.8, 135.1, 133.3, 130.2, 129.3, 129.0, 128.0, 127.3, 86.2, 74.2, 54.6, 18.6. MS (*m*/*z*): 299, 255, 122, 106. E.A. Calcd for $C_{17}H_{17}NO_2S$: C, 68.20; H, 5.72; N, 4.68. Found: C, 68.34; H, 5.73.

Compound **4e**: yellow solid. Y=26%. Mp 147–148 °C. IR ($CHCl_3$): 1677 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ=7.61 (m, 2H), 7.50–7.15 (m, 8H), 6.67 (br s, 1H), 5.97 (s, 1H), 4.34 (m, 1H), 3.82 (d, J=3.6 Hz, 1H), 1.48 (d, J=6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=169.0, 138.7, 134.4, 132.8, 129.7, 129.3, 129.1, 128.0, 126.8, 82.0, 69.0, 54.1, 16.8. MS (*m*/*z*): 299, 255, 122, 105, 91, 77. E.A. Calcd for $C_{17}H_{17}NO_2S$: C, 68.20; H, 5.72; N, 4.68. Found: C, 68.30; H, 5.71.

4.2.6. *tert*-Butyl-3-[(2*S,5*S**,6*R**)-4-oxo-2-phenyl-5-(phenylthio)-[1,3]oxazinan-6-yl]-1*H*-indole-1-carboxylate 3f; *tert*-butyl-3-[(2*R**,5*S**,6*R**)-4-oxo-2-phenyl-5-(phenylthio)-[1,3]oxazinan-6-yl]-1*H*-indole-1-carboxylate 4f.** The crude reaction mixture obtained from azadiene **1a** (2 mmol) and *tert*-butyl-3-formyl-1*H*-indole-1-carboxylate (245 mg, 1 mmol) according to GP1 was subjected to column chromatography (4:6 *EtOAc*/cyclohexane) to give **3f** and **4f** in 40/60 diastereomeric ratio and 41% overall yield.

Compound **3f**: yellow oil. Y=16%. IR ($CHCl_3$): 1737, 1673 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ=7.75 (s, 1H), 7.60–7.05 (m, 14H), 6.21 (br s, 1H), 6.00 (s, 1H), 5.63 (dd, J_1=2.0 Hz, J_2=0.8 Hz, 1H), 4.04 (d, J=2.0 Hz, 1H), 1.66 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=169.2, 149.8, 137.7, 134.5, 133.2, 130.3, 129.1, 128.9, 128.0, 127.9, 127.4, 124.8, 124.7, 123.0, 119.0, 118.1, 116.9, 115.7, 86.5, 84.2, 74.7, 54.1, 28.4. MS (*m*/*z*): 399 (M^+-t-Boc), 334, 255, 202, 106, 91, 77. E.A. Calcd for $C_{29}H_{28}N_2O_4S$: C, 69.58; H, 5.64; N, 5.60. Found: C, 69.75; H, 5.62.

Compound **4f**: pale yellow solid. Y=25%. Mp 102–104 °C. IR ($CHCl_3$): 1738, 1673 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ=7.84 (s, 1H), 7.50–7.15 (m, 14H), 6.83 (br s, 1H), 5.78 (s, 1H), 5.67 (dd, J_1=4.8 Hz, J_2=0.8 Hz, 1H), 4.41 (d, J=4.8 Hz, 1H), 1.71 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=168.7, 149.4, 137.7, 135.4, 134.2, 132.4, 129.6, 128.9, 128.8, 128.7, 127.6, 126.8, 125.2, 124.9, 122.9, 119.1, 115.4, 114.4, 84.3, 81.7, 70.0, 52.4, 28.1. MS (*m*/*z*): 456, 422, 399, 334, 255, 202, 186, 131, 107, 91, 77. E.A. Calcd for $C_{29}H_{28}N_2O_4S$: C, 69.58; H, 5.64; N, 5.60. Found: C, 69.77; H, 5.62.

4.3. MW-mediated desulfurization reaction: preparation of 5a as general procedure (GP2)

5-Phenylsulfanyl-perhydrooxazinone **3a** (87 mg, 0.24 mmol), Nickel-Raney (0.6 g), and EtOH (6 mL) were mixed in a 30 mL reaction tube. The tube was sealed and positioned in the reaction cavity. The sealed reaction was irradiated at 150 W for 2 min. The reaction mixture was filtered on Celite, and the solvent evaporated. The crude reaction mixture was purified by flash chromatography (3:7 *EtOAc*/cyclohexane) to give the desired product **5a** in 80% yield.

4.3.1. (2*S,6*S**)-2,6-Diphenyl-[1,3]oxazinan-4-one 5a.** Pale yellow oil. IR (Nujol): 1653 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ=7.51 (m, 2H), 7.43–7.30 (m, 8H), 6.57 (br s, 1H), 5.92 (s, 1H), 5.02 (m, 1H), 2.75 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=168.8, 139.6, 137.7, 129.9, 128.8, 128.7, 128.3, 126.9, 125.6, 85.7, 76.6, 39.1. MS (*m*/*z*): 253, 175, 147, 131, 118, 104, 78. E.A. Calcd for $C_{16}H_{15}NO_2$: C, 75.87; H, 5.97. Found: C, 75.96; H, 5.98.

4.3.2. (2*R,6*S**)-2,6-Diphenyl-[1,3]oxazinan-4-one 6a.** The crude reaction mixture obtained from 5-phenylsulfanyl-perhydrooxazinone **4a**, according to GP2, was subjected to a short column chromatography (3:7 *EtOAc*/cyclohexane) to give **6a** in 92% overall yield.

Pale yellow oil. IR (Nujol): 1653 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ=7.60–7.30 (m, 10H), 6.54 (br s, 1H), 5.95 (s, 1H), 5.05 (dd, 1H, J_1=7.2 Hz, J_2=5.8 Hz), 2.86 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ=169.6, 139.2, 138.4, 129.2, 128.7, 128.6, 128.3, 126.7, 126.1, 81.8, 70.2, 37.6. MS (*m*/*z*): 253, 175, 147, 131, 118, 104, 78. E.A. Calcd for $C_{16}H_{15}NO_2$: C, 75.87; H, 5.97. Found: C, 75.99; H, 5.60.

4.3.3. (2*S,6*S**)-Methyl 4-oxo-2,6-diphenyl-1,3-oxazinane-3-carboxylate 7a.** To a solution of **5a** (253 mg, 1.0 mmol) in THF (10 ml) at 0 °C was added LiHMDS (1 M in THF, 1.0 mmol, 1.0 ml). The reaction mixture was stirred for 20 min, then methyl chloroformate (8 mmol, 0.62 ml) was added. Stirring was maintained for 2 h at the same temperature. A saturated solution of NH_4Cl was added and the mixture was extracted with CH_2Cl_2. The organic phases were dried on Na_2SO_4 and concentrated in vacuum. The carbamate **7a** was obtained in quantitative yield and used as such for the next step.

Compound **7a**: pale yellow oil. IR (Nujol): 1731, 1702 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ=7.50–7.20 (m, 10H), 6.41 (s, 1H), 5.06 (dd, 1H, J_1=7.2 Hz, J_2=5.8 Hz), 3.67 (s, 3H), 2.97 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=167.4, 152.8, 138.4, 138.2, 129.3, 128.5, 128.4, 128.3, 126.8, 125.5, 89.5, 75.2, 53.5, 41.5. MS (*m*/*z*): 311, 234, 223. E.A. Calcd for $C_{18}H_{17}NO_4$: C, 69.44; H, 5.50. Found: C, 70.83; H, 5.61.

4.3.4. (2*R,6*R**)-Methyl 4-oxo-2,6-diphenyl-1,3-oxazinane-3-carboxylate 8a.** The crude reaction mixture obtained from product **6a** according to the procedure used for **7a** gave **8a** in quantitative yield, which was used as such for the next step.

Compound **8a**: pale yellow oil. IR (Nujol): 1731, 1702 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ=7.50–7.20 (m, 10H), 6.96 (s, 1H), 4.83 (m, 1H), 3.91 (s, 3H), 2.87 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=167.4, 153.0, 139.4, 137.3, 129.13, 128.9, 128.7, 128.4, 126.5, 125.6, 86.1, 69.7, 54.1, 40.9. MS (*m*/*z*): 311, 234, 223. E.A. Calcd for $C_{18}H_{17}NO_4$: C, 69.44; H, 5.50. Found: C, 70.83; H, 5.61.

4.3.5. Procedure for the preparation of aminol 10a.

4.3.5.1. Step 1: 3-(*N*-benzyl-*N*-methylamino)-1-phenyl-propan-1-ol 9a. Carbamate **7a** and/or **8a** (1 mmol) were dissolved in anhydrous Et_2O (10 mL) at 0 °C. Lithium aluminum hydride (LAH, 1 M in Et_2O, 4 mmol) was added and the mixture was stirred for 2 h. NaOH (10 mL, 5 N) was added and the aqueous phase was washed with ethyl acetate. The extracts were treated with HCl 1 N; aqueous phase was neutralized with NaOH 5 N (pH=10–12) and extracted with CH_2Cl_2. The organic phase was dried over Na_2SO_4 and the solvent evaporated. Product **9a** so obtained was used without purification for the next step of the synthesis.

Pale yellow oil. IR (Nujol): 3243, 2946, 2843, 1602 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ=7.0–7.6 (m, 10H), 4.97 (dd, J_1=3.9 Hz, J_2=7.5 Hz, 1H), 3.70 (d, J=12.7 Hz, 1H), 3.53 (d, J=12.7 Hz, 1H), 2.87 (m, 1H), 2.66 (m, 1H), 2.32 (s, 3H), 1.94 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ=144.8, 137.6, 129.0, 128.1, 128.0, 127.2, 126.7, 125.4, 75.4, 62.6, 56.2, 41.6, 34.4. MS (*m*/*z*): 255, 134, 120, 91. Anal. Calcd for $C_{17}H_{21}NO$: C, 79.96; H, 8.29. Found: C, 80.01; H, 8.31.

4.3.5.2. Step 2: hydrogenolysis of 9a. Hydrogenolysis of compound **9a** according to literature procedure furnished aminol **10a** in 78% yield. Spectra are just similar to the literature data.[50]

4.4. Desulfurization reaction by Al/$HgCl_2$ amalgam: preparation of 5b as general procedure (GP3)

Aluminum (4.0 g) and 50 mL of a solution of $HgCl_2$ (1% in H_2O) were stirred for 1 min, the mixture was decanted and the residue was washed with water. The amalgam so prepared was added to a solution of compound **3b** (335 mg, 0.9 mmol) in *i*-PrOH (50 ml) under inert atmosphere. The reaction was stirred overnight until the disappearance of starting materials (TLC test). The mixture was filtered through Celite and the solvent was removed in vacuo. Product **5b** so obtained was used for the next step without any purification. An aliquot of the crude reaction mixture was utilized for identification of **5b** after purification by a short flash chromatography on silica gel (5:3:2 CH_2Cl_2/cyclohexane/*EtOAc*).

4.4.1. (2*S,6*S**)-2-Phenyl-6-(thiophen-2-yl)-[1,3]oxazinan-4-one 5b.** Pale yellow oil. IR ($CHCl_3$): 1670 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ=7.50–6.95 (m, 8H), 6.37 (br s, 1H), 5.93 (s, 1H), 5.27 (dd, J_1=4.0 Hz, J_2=11.2 Hz, 1H), 2.95 (dd, J_1=11.2 Hz, J_2=17.2 Hz, 1H), 2.86 (dd, J_1=4.0 Hz, J_2=11.2 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=168.2, 142.1, 137.3, 130.1, 128.9, 126.9, 126.7, 125.9, 125.0, 85.7, 72.7, 38.9. MS (*m*/*z*): 259, 181, 154, 147, 137, 118, 106, 85, 77. Anal. Calcd for $C_{14}H_{13}NO_2S$: C, 64.84; H, 5.05. Found: C, 64.96; H, 5.06.

4.4.2. (2*S,6*S**)-*N*-Methyl-2-phenyl-6-(thiophen-2-yl)-[1,3]oxazinan-4-one 7b.** To a solution of crude **5b** (0.9 mmol) in THF (10 mL) at 0 °C was added LHMDSA (1 M in THF, 0.9 mL). The reaction was stirred for 20 min, MeI (0.45 mL, 7.2 mmol) was added and the solution warmed to room temperature. Stirring was maintained for 1.5 h at the same temperature. A saturated solution of NH_4Cl was added, the organic solvent removed in vacuo, and the obtained aqueous solution extracted with *EtOAc*. The organic phases were collected, dried on Na_2SO_4, and concentrated in vacuo. The reaction mixture was purified by flash chromatography on silica gel, eluting with CH_2Cl_2/cyclohexane/*EtOAc* 50/30/20. Compound **7b** was obtained in 55% overall yield calculated from product **3b**.

Pale yellow oil. IR ($CHCl_3$): 1644 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ=7.4 (m, 5H), 7.29 (dd, J_1=1.2 Hz, J_2=5.2 Hz, 1H), 7.05 (dd, J_1=1.2 Hz, J_2=4.4 Hz, 1H), 6.97 (dd, J_1=4.4 Hz, J_2=5.2 Hz, 1H), 5.78 (s, 1H), 5.23 (dd, J_1=2.8 Hz, J_2=12.0 Hz, 1H), 3.05 (dd, J_1=12.0 Hz, J_2=16.8 Hz, 1H), 2.90 (dd, J_1=2.8 Hz, J_2=16.8 Hz, 1H), 2.63 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=171.1, 142.0, 136.9, 129.8, 128.8, 127.6, 126.7, 125.9, 125.0, 91.0, 71.9, 39.8, 29.8. MS (*m*/*z*): 273, 259, 196, 167, 137, 118, 110, 91, 77. Anal. Calcd for $C_{15}H_{15}NO_2S$: C, 65.91; H, 5.53. Found: C, 65.81; H, 5.52.

4.4.3. Synthesis of (2*R,6*S**)-2-phenyl-6-(thiophen-2-yl)-[1,3]oxazinan-4-one 6b.** Product **6b**, obtained from **4b** according to GP3, was used for the methylation step without any purification. Identification was performed on an aliquot of the crude reaction mixture prior to purification by a short flash chromatography on silica gel (5:3:2 CH_2Cl_2/cyclohexane/*EtOAc*).

Pale yellow oil. IR ($CHCl_3$): 1671 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ=7.45–7.00 (m, 8H), 6.72 (br s, 1H), 5.84 (s, 1H), 5.34 (t, J=6.0 Hz, 1H), 2.96 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=168.5, 142.0, 137.8, 129.6, 128.9, 126.9, 126.8, 126.5, 125.8, 81.0, 67.8, 37.0. MS (*m*/*z*): 259, 181, 154, 147, 137, 118, 106, 85, 77. Anal. Calcd for $C_{14}H_{13}NO_2S$: C, 64.84; H, 5.05. Found: C, 65.01; H, 5.07.

4.4.4. Synthesis of (2*R,6*S**)-*N*-methyl-2-phenyl-6-(thiophen-2-yl)-[1,3]oxazinan-4-one 8b.** Crude **6b** was methylated, following the procedure used for **7b**, to give **8b**, after a short column chromatography (CH_2Cl_2/cyclohexane/*EtOAc* 50/30/20) in 58% overall yield calculated from product **4b**.

Pale yellow oil. IR ($CHCl_3$): 1645 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ=7.42 (m, 3H), 7.37 (d, J=2.0 Hz, 2H), 7.29 (dd, J_1=1.6 Hz, J_2=5.2 Hz, 1H), 6.95 (dd, J_1=3.2 Hz, J_2=5.2 Hz, 1H), 6.90 (m, 1H), 6.72 (br s, 1H), 5.78 (s, 1H), 5.12 (dd, J_1=6.0 Hz, J_2=8.4 Hz, 1H), 2.94 (m, 2H), 2.85 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=166.6, 142.1, 136.4, 129.5, 128.6, 127.4, 126.7, 125.94, 125.13, 87.6, 66.6, 38.3, 31.1. MS (*m*/*z*): 273, 196, 188, 168, 137, 118, 110, 97, 77. Anal. Calcd for $C_{15}H_{15}NO_2S$: C, 65.91; H, 5.53. Found: C, 68.82; H, 5.51.

4.4.5. Synthesis of aminol *rac*-11b. Ph_2SiH_2 (0.46 mL, 2.5 mmol) and $RhH(CO)(PPh_3)_3$ (1%) were added to a solution of **7b** or **8b** (273 mg, 1.0 mmol) in THF (10 mL) at room temperature and the stirring maintained for 15 h. Disappearance of starting material was verified by TLC (CH_2Cl_2/cyclohexane/*EtOAc* 50/30/20). Aqueous HCl (1 M, 2.50 mL) was added to the crude reaction mixture and the stirring maintained at the same temperature for 4 h. The organic solvent was removed in vacuo and the obtained aqueous

solution extracted with Et_2O. The aqueous phase was basified with NH_4OH (pH=10) and then extracted with CH_2Cl_2. The organic phases were dried over Na_2SO_4 and the solvent evaporated.

Compound *rac*-**11b** was obtained in 95% yield calculated from product **7b**. Spectral data are identical to the product obtained from **19b** or **20b** (see below).

4.5. General procedure (GP5) for the preparation of 1,3-oxazinan-4-ones 13a–13e and 14a–14e

Azadiene **1d** (2 mmol), prepared according to literature from (2*S*)-triisopropylsilyloxy-propanal and 2-(phenylthio)acetyl chloride[28] **5**, was dissolved in anhydrous CH_2Cl_2 (20 mL) and cooled at −78 °C. Aldehyde **2** (1 mmol) in methylene chloride (2 mL) was added followed by a slow addition of BF_3 etherate (1 mmol) in CH_2Cl_2 (10 mL). The solution was stirred overnight while the temperature was allowed to reach room temperature. The mixture was poured into saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2. The organic layers were dried and the solvent was removed in vacuum. The reaction mixture was purified by flash chromatography on silica gel. 5-Phenylthio-perhydrooxazin-4ones **13a–13e** and **14a–14e** were isolated in combined yields and diastereomeric ratios reported in Table 2.

4.5.1. (2*R*,5*R*,6*S*)-2-[(*S*)-1-Triisopropylsilyloxyethyl]-6-phenyl-5-(phenylthio)-[1,3]oxazinan-4-one 13a; (2*S*,5*S*,6*R*)-2-[(*S*)-1-triisopropylsilyloxyethyl]-6-phenyl-5-(phenylthio)-[1,3]oxazinan-4-one 14a. The crude reaction mixture obtained from azadiene **1f** (2 mmol) and benzaldehyde (0.1 mL, 1 mmol) according to GP5 was subjected to column chromatography (3:7 *EtOAc*/cyclohexane) to give **13a** and **14a** in 50/50 diastereomeric ratio and 81% overall yield.

Compound **13a**: colorless oil. Y=41%. $[\alpha]_D^{20}$ 13.0 (*c* 0.7, $CHCl_3$). IR ($CHCl_3$): 1677 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ=7.45–7.05 (m, 10H), 6.22 (br s, 1H), 5.25 (d, *J*=2.0 Hz, 1H), 5.08 (d, *J*=2.8 Hz, 1H), 4.23 (m, 1H), 3.69 (d, *J*=2.8 Hz, 1H), 1.31 (d, *J*=7.2 Hz, 3H), 1.05 (s, 21H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=169.1, 136.7, 135.0, 132.8, 128.7, 128.0, 127.9, 127.6, 126.0, 85.3, 77.8, 68.8, 56.3, 18.0, 17.9, 15.9, 12.1. MS (*m*/*z*): 486, 442, 399, 379, 336, 239, 211, 188, 135, 77. E.A. Calcd for $C_{27}H_{39}NO_3SSi$: C, 66.76; H, 8.09; N, 2.88. Found: C, 66.86; H, 8.11.

Compound **14a**: colorless oil. Y=40%. $[\alpha]_D^{20}$ −41.5 (*c* 2.0, $CHCl_3$). IR ($CHCl_3$): 1676 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ=7.40–7.07 (m, 10H), 6.35 (br s, 1H), 5.22 (d, *J*=2.4 Hz, 1H), 4.58 (d, *J*=8.0 Hz, 1H), 3.77 (m, 1H), 3.76 (d, *J*=2.4 Hz, 1H), 1.35 (d, *J*=5.6 Hz, 3H), 1.05 (s, 21H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=168.2, 145.4, 137.0, 133.7, 128.9, 128.6, 128.2, 127.8, 125.7, 87.6, 78.0, 71.5, 55.2, 19.5, 18.1, 18.0, 12.6. MS (*m*/*z*): 486, 442, 379, 336, 284, 239, 211, 188, 135, 77. E.A. Calcd for $C_{27}H_{39}NO_3SSi$: C, 66.76; H, 8.09; N, 2.88. Found: C, 66.82; H, 8.10.

4.5.2. (2*R*,5*R*,6*R*)-2-[(*S*)-1-Triisopropylsilyloxyethyl]-6-(thiophen-2-yl)-5-(phenylthio)-[1,3]oxazinan-4-one 13b; (2*S*,5*S*,6*S*)-2-[(*S*)-1-triisopropylsilyloxyethyl]-6-(thiophen-2-yl)-5-(phenylthio)-[1,3]oxazinan-4-one 14b. The crude reaction mixture obtained from azadiene **1d** (2 mmol) and 2-thiophenecarboxaldehyde (0.093 mL, 1 mmol) according to GP5 was subjected to column chromatography (2:8 *EtOAc*/cyclohexane) to give **13b** and **14b** in 60/40 diastereomeric ratio and 90% overall yield.

Compound **13b**: pale yellow oil. Y=54%. $[\alpha]_D^{20}$ +33.5 (*c* 2.9, $CHCl_3$). IR ($CHCl_3$): 1672 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ=7.36 (m, 3H), 7.20 (m, 3H), 7.01 (m, 2H), 6.20 (br s, 1H, NH), 5.46 (d, *J*=2.0 Hz, 1H), 5.09 (d, *J*=3.6 Hz, 1H), 4.19 (dq, J_1=3.6 Hz, J_2=6.0 Hz, 1H), 3.71 (d, *J*=2.0 Hz, 1H), 1.26 (d, *J*=6.0 Hz, 3H), 1.07 (m, 21H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=168.80, 139.61, 135.80, 132.32, 128.84, 127.60, 126.28, 126.03, 125.52, 85.51, 75.69, 68.72, 56.16, 18.02, 15.88, 12.14. MS (*m*/*z*): 492, 448, 379, 336, 187. Anal. Calcd for $C_{25}H_{37}NO_3S_2Si$: C, 61.06; H, 7.58. Found: C, 61.20; H, 7.63.

Compound **14b**: pale yellow oil. Y=36%. $[\alpha]_D^{20}$ −58.6 (*c* 2.5, $CHCl_3$). IR ($CHCl_3$): 1685 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ=7.42–7.20 (m, 6H), 7.02–6.98 (m, 2H), 6.33 (br s, 1H, NH), 5.41 (dd, J_1=1.2 Hz, J_2=2.4 Hz, 1H), 4.60 (d, *J*=8.0 Hz, 1H), 3.77 (d, *J*=2.4 Hz, 1H), 3.68 (m, 1H), 1.31 (d, *J*=6.4 Hz, 3H), 1.08 (m, 21H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=167.68, 139.66, 134.16, 133.56, 128.71, 127.96, 126.51, 125.54, 124.75, 87.66, 76.07, 71.35, 55.16, 19.43, 18.12, 12.58. MS (*m*/*z*): 491, 446, 379, 336, 217, 186. Anal. Calcd for $C_{25}H_{37}NO_3S_2Si$: C, 61.06; H, 7.58. Found: C, 61.18; H, 7.60.

4.5.3. (2*R*,5*R*,6*S*)-2-[(*S*)-1-Triisopropylsilyloxyethyl]-6-methyl-5-(phenylthio)-[1,3]oxazinan-4-one 13c; (2*S*,5*S*,6*R*)-2-[(*S*)-1-triisopropylsilyloxyethyl]-6-methyl-5-(phenylthio)-[1,3]oxazinan-4-one 14c. The crude reaction mixture obtained from azadiene **1f** (2 mmol) and acetaldehyde (0.056 mL, 1 mmol) according to GP5 was subjected to column chromatography (2:8 *EtOAc*/cyclohexane) to give **13c** and **14c** in 50/50 diastereomeric ratio and 32% overall yield.

Compound **13c**: pale yellow oil. Y=16%. $[\alpha]_D^{20}$ 40.0 (*c* 2.1, $CHCl_3$). IR ($CHCl_3$): 1670 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ=7.65 (m, 2H), 7.40–7.18 (m, 3H), 6.10 (br s, 1H), 4.90 (d, *J*=3.2 Hz, 1H), 4.20 (dq, J_1=6.0 Hz, J_2=1.8 Hz, 1H), 4.06 (dq, J_1=6.4 Hz, J_2=3.2 Hz, 1H), 3.46 (d, *J*=1.8 Hz, 1H), 1.50 (d, *J*=6.0 Hz, 3H), 1.11 (d, *J*=6.4 Hz, 3H), 1.05 (s, 21H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=169.4, 135.6, 132.4, 129.0, 127.5, 85.4, 73.2, 68.8, 55.1, 18.0, 17.9, 15.7, 12.1. MS (*m*/*z*): 423, 408, 380, 362, 336, 223, 187, 149, 77. E.A. Calcd for $C_{22}H_{37}NO_3SSi$: C, 62.37; H, 8.80; N, 3.31. Found: C, 62.40; H, 8.83.

Compound **14c**: pale yellow oil. Y=16%. $[\alpha]_D^{20}$ −40.7 (*c* 1.35, $CHCl_3$). IR ($CHCl_3$): 1667 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ=7.65 (m, 2H), 7.25 (m, 3H), 6.25 (br s, 1H), 4.39 (d, *J*=7.2 Hz, 1H), 4.14 (dq, J_1=6.4 Hz, J_2=2.4 Hz, 1H), 3.50 (m, 1H), 3.45 (d, *J*=2.4 Hz, 1H), 1.50 (d, *J*=6.4 Hz, 3H), 1.21 (d, *J*=6.0 Hz, 3H), 1.05 (s, 21H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=168.3, 134.5, 133.4, 128.8, 127.7, 87.5, 73.4, 71.3, 54.5, 19.3, 18.1, 18.0, 12.6. MS (*m*/*z*): 423, 408, 380, 362, 336, 222, 186, 149, 77. E.A. Calcd for $C_{22}H_{37}NO_3SSi$: C, 62.37; H, 8.80; N, 3.31. Found: C, 62.42; H, 8.84.

4.5.4. (2*R*,5*R*,6*S*)-2-[(*S*)-1-Triisopropylsilyloxyethyl]-6-(naphthalen-2-yl)-5-(phenylthio)-[1,3]oxazinan-4-one 13d; (2*S*,5*S*,6*R*)-2-[(*S*)-1-triisopropylsilyloxyethyl]-6-(naphthalen-2-yl)-5-(phenylthio)-[1,3]oxazinan-4-one 14d. The crude reaction mixture obtained from azadiene **1f** (2 mmol) and 2-naphthaldehyde (156 mg, 1 mmol) according to GP5 was subjected to column chromatography (3:7 *EtOAc*/cyclohexane) to give **13d** and **14d** in 50/50 diastereomeric ratio and 41% overall yield.

Compound **13d**: pale yellow oil. Y=20%. $[\alpha]_D^{20}$ −39.7 (*c* 1.40, $CHCl_3$). IR ($CHCl_3$): 1678 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ=7.82 (m, 5H), 7.50 (m, 2H), 7.38 (m, 1H), 7.05 (m, 5H), 6.26 (br s, 1H), 5.41 (d, *J*=2.6 Hz, 1H), 5.15 (d, *J*=3.6 Hz, 1H), 4.29 (dq, J_1=6.4 Hz, J_2=3.6 Hz, 1H), 3.83 (d, *J*=2.6 Hz, 1H), 1.36 (d, *J*=6.4 Hz, 3H), 1.08 (s, 21H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=169.1, 134.8, 134.1, 132.9, 132.8, 132.7, 128.6, 128.1, 127.8, 127.7, 127.6, 126.2, 126.1, 125.2, 123.4, 85.5, 78.0, 68.8, 56.0, 18.1, 18.0, 16.0, 12.1. MS (*m*/*z*): 535, 379, 336, 289, 261, 187. E.A. Calcd for $C_{31}H_{41}NO_3SSi$: C, 69.49; H, 7.71; N, 2.61. Found: C, 69.63; H, 7.73.

Compound **14d**: pale yellow oil. Y=21%. $[\alpha]_D^{20}$ −14.2 (*c* 1.70, $CHCl_3$). IR ($CHCl_3$): 1677 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ=7.85 (m, 5H), 7.55 (m, 2H), 7.38 (m, 1H), 7.22–7.05 (m, 5H), 6.42 (br s, 1H), 5.37 (d, *J*=2.2 Hz, 1H), 4.65 (d, *J*=7.6 Hz, 1H), 3.90 (d, *J*=2.2 Hz, 1H), 3.85 (m, 1H), 1.43 (d, *J*=6.4 Hz, 3H), 1.12 (s, 21H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=168.1, 134.3, 134.1, 133.7, 132.9, 132.8, 128.5, 128.1, 127.9, 127.8, 127.7, 127.6, 126.2, 126.1, 124.9, 123.2, 87.6, 78.2, 71.5, 55.0, 19.6, 18.1, 18.0, 12.6. MS (*m*/*z*): 535, 379, 336, 289, 261, 187. E.A. Calcd for $C_{31}H_{41}NO_3SSi$: C, 69.49; H, 7.71; N, 2.61. Found: C, 69.62; H, 7.71.

4.5.5. *tert*-Butyl-3-[(2*R*,5*R*,6*S*)-2-[(*S*)-1-triisopropylsilyloxyethyl]-4-oxo-5-(phenylthio)-[1,3]oxazinan-6-yl]-1*H*-indole-1-carboxylate 13e; *tert*-butyl-3-[(2*S*,5*S*,6*R*)-2-[(*S*)-1-triisopropylsilyloxyethyl]-4-oxo-5-(phenylthio)-[1,3]oxazinan-6-yl]-1*H*-indole-1-carboxylate 14e. The crude reaction mixture obtained from azadiene **1d** (2 mmol) and *tert*-butyl-3-formyl-1*H*-indole-1-carboxylate (245 mg, 1 mmol) according to GP2 was subjected to column chromatography (3:7 *EtOAc*/cyclohexane) to give **13e** and **14e** in 63/37 diastereomeric ratio and 55% overall yield.

Compound **13e**: pale yellow oil. Y=35%. $[\alpha]_D^{20}$ +24 (*c* 0.5, $CHCl_3$). IR ($CHCl_3$): 1738, 1674 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ=7.70 (s, 1H), 7.42–6.98 (m, 9H), 6.23 (br s, 1H), 5.46 (dd, J_1=2.2 Hz, J_2=1.2 Hz, 1H), 5.14 (d, *J*=3.2 Hz, 1H), 4.23 (dq, J_1=3.2 Hz, J_2=6.4 Hz, 1H), 3.92 (d, *J*=2.2 Hz, 1H), 1.68 (s, 9H), 1.30 (d, *J*=6.4 Hz, 3H), 1.08 (s, 21H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=168.7, 149.5, 135.2, 134.4, 132.4, 128.5, 127.4, 124.6, 122.6, 118.6, 116.5, 115.4, 85.6, 83.9, 73.7, 68.8, 54.5, 28.1, 18.0, 17.9, 15.9, 12.1. MS (*m*/*z*): 567 (M^+−*t*-Bu), 525, 473, 379, 336, 230, 188, 77. E.A. Calcd for $C_{34}H_{50}N_2O_5SSi$: C, 65.14; H, 8.04; N, 4.47. Found: C, 65.41; H, 8.07.

Compound **14e**: pale yellow oil. Y=20%. $[\alpha]_D^{20}$ −42.8 (*c* 1.12, $CHCl_3$). IR ($CHCl_3$): 1737, 1671 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ=7.65 (s, 1H), 7.40–7.00 (m, 9H), 6.38 (br s, 1H), 5.41 (dd, J_1=2.4 Hz, J_2=1.2 Hz, 1H), 4.66 (d, *J*=7.2 Hz, 1H), 3.97 (d, *J*=2.4 Hz, 1H), 3.76 (m, 1H), 1.68 (s, 9H), 1.35 (d, *J*=6.4 Hz, 1H), 1.11 (s, 21H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=167.8, 149.6, 135.3, 133.8, 133.5, 132.5, 128.5, 127.8, 127.7, 124.6, 124.1, 122.7, 118.7, 116.8, 115.4, 87.8, 83.9, 74.1, 71.4, 53.6, 28.2, 19.5, 18.1, 18.0, 12.6. MS (*m*/*z*): 567 (M^+−*t*-Bu), 379, 336, 230, 188, 77. E.A. Calcd for $C_{34}H_{50}N_2O_5SSi$: C, 65.14; H, 8.04; N, 4.47. Found: C, 65.41; H, 8.07.

4.5.6. (2*R*,6*R*)-2-[(*S*)-1-Triisopropylsilyloxyethyl]-6-phenyl-[1,3]oxazinan-4-one 15a. The crude reaction mixture obtained from desulfurization of **13a**, according to GP2, was subjected to column chromatography (3:7 *EtOAc*/cyclohexane) to give **15a** in 98% overall yield. Spectroscopic data are superimposable with the published ones.[16]

4.5.7. (2*S*,6*S*,)-2-[(*S*)-1-Triisopropylsilyloxyethyl]-6-phenyl-[1,3]oxazinan-4-one 16a. The crude product obtained from desulfurization of **14a** according to GP2 was subjected to column chromatography (3:7 *EtOAc*/cyclohexane) to give **16a** in 90% overall yield. Spectra are just similar to literature data.[16]

4.5.8. (2*R*,6*R*)-2-[(*S*)-1-Triisopropylsilyloxyethyl]-6-(thiophen-2-yl)-[1,3]oxazinan-4-one 15b. Product **15b**, obtained from **13b** according to GP3 was used for the next step without any purification. An aliquot of the crude reaction mixture was utilized for identification of **15b** after purification by flash chromatography on silica gel (2:8 *EtOAc*/cyclohexane).

Compound **15b**: pale yellow oil. $[\alpha]_D^{20}$ +1.9 (*c* 1.3, $CHCl_3$). IR ($CHCl_3$): 1666 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ=7.33 (d, *J*=5.2 Hz, 1H), 7.05 (d, *J*=3.6 Hz, 1H), 7.00 (dd, J_1=3.6 Hz, J_2=5.2 Hz, 1H), 6.38 (br s, 1H, NH), 5.11 (dd, J_1=6.0 Hz, J_2=9.6 Hz, 1H), 5.07 (d, *J* =3.6 Hz, 1H), 4.19 (dq, *J*=3.6 Hz, 6.4 Hz, 1H), 2.77 (m, 2H), 1.19 (d, *J*=6.4 Hz, 3H), 1.07 (m, 21H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=168.18, 142.26, 126.77, 125.88, 124.88, 84.91, 72.13, 68.61, 39.66, 18.01, 15.69, 12.14. MS (*m*/*z*): 384, 340, 322, 202, 187. Anal. Calcd for $C_{19}H_{33}NO_3SSi$: C, 59.49; H, 8.67. Found: C, 60.68; H, 8.84.

4.5.9. (2*S*,6*S*)-2-[(*S*)-1-Triisopropylsilyloxyethyl]-6-(thiophen-2-yl)-[1,3]oxazinan-4-one 16b. Product **16b**, obtained from **14b** according to GP3 was used for the next step without any purification. An aliquot of the crude reaction mixture was utilized for identification of **16b** after purification by flash chromatography on silica gel (2:8 *EtOAc*/cyclohexane).

Compound **16b**: pale yellow oil. $[\alpha]_D^{20}$ −1.3 (*c* 2.1, $CHCl_3$). IR ($CHCl_3$): 1666 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ=7.32 (dd, J_1=1.6 Hz, J_2=4.8 Hz, 1H), 6.99 (m, 2H), 6.53 (br s, NH), 5.05 (dd, J_1=6.4 Hz, J_2=8.4 Hz, 1H), 4.62 (d, *J*=6.4 Hz, 1H), 3.87 (m, 1H), 2.78 (m, 2H), 1.32 (d, *J*=6.0 Hz, 3H), 1.07 (m, 21H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=167.52, 142.48, 126.70, 125.72, 124.36, 87.33, 72.32, 71.20, 38.95, 19.61, 18.06, 12.59. MS (*m*/*z*): 384, 340, 322, 202, 187. Anal. Calcd for $C_{19}H_{33}NO_3SSi$: C, 59.49; H, 8.67. Found: C, 60.68; H, 8.84.

4.5.10. (2*R*,6*R*)-*N*-Methyl-2-[(*S*)-1-triisopropylsilyloxyethyl]-6-(thiophen-2-yl)-[1,3]oxazinan-4-one 17b. Crude **15b** was methylated according to the procedure described for **7b**. After column chromatography (3:7 *EtOAc*/cyclohexane) **17b** was obtained in 65% overall yield calculated from product **13b**.

Compound **17b**: pale yellow oil. $[\alpha]_D^{20}$ +36.3 (*c* 2.7, $CHCl_3$). IR ($CHCl_3$): 1644 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ=7.31 (dd, J_1=1.6 Hz, J_2=4.8 Hz, 1H), 7.00 (m, 2H), 5.03 (dd, J_1=5.6 Hz, J_2=8.4 Hz, 1H), 4.96 (d, J=0.8 Hz, 1H), 4.16 (dq, J_1=0.8 Hz, J_2=6.4 Hz, 1H), 3.06 (s, 3H), 2.76 (m, 2H), 1.17 (d, J=6.4 Hz, 3H), 1.06 (m, 21H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=167.45, 142.42, 126.66, 125.63, 124.53, 90.83, 71.14, 70.44, 40.26, 29.65, 18.03, 16.70, 12.19. MS (*m*/*z*): 397, 354, 216, 137. Anal. Calcd for $C_{20}H_{35}NO_3SSi$: C, 60.41; H, 8.87. Found: C, 62.22; H, 9.14.

4.5.11. (2*S*,6*S*)-*N*-Methyl-2-[(*S*)-1-triisopropylsilyloxyethyl]-6-(thiophen-2-yl)-[1,3]oxazinan-4-one 18b. Crude **16b** was methylated according to the procedure described for **7b**. After column chromatography (3:7 *EtOAc*/cyclohexane) **18b** was obtained in 54% overall yield calculated from product **14b**.

Compound **18b**: pale yellow oil. $[\alpha]_D^{20}$ −67.4 (*c* 2.2, $CHCl_3$). IR ($CHCl_3$): 1646 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ=7.29 (dd, J_1=2.4 Hz, J_2=3.6 Hz, 1H), 6.98 (m, 2H), 5.02 (dd, J_1=3.6 Hz, J_2=10.0 Hz, 1H), 4.87 (d, J=2.4 Hz, 1H), 4.25 (dq, J_1=2.4 Hz, J_2=6.4 Hz, 1H), 2.94 (s, 3H), 2.81 (m, 2H), 1.19 (d, J=6.4 Hz, 3H), 1.08 (m, 21H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=167.32, 142.87, 126.60, 125.48, 123.93, 90.84, 70.56, 68.87, 39.90, 29.43, 18.05, 16.57, 12.46. MS (*m*/*z*): 397, 354, 216, 137. Anal. Calcd for $C_{23}H_{41}NO_3SSi$: C, 62.82; H, 9.40. Found: C, 62.70; H, 9.38.

4.5.12. Synthesis of optically pure aminoalcohols (*R*)-11b and (*S*)-11b.

4.5.12.1. Step 1: (2*R*,6*R*)-[(*S*)-1-(triisopropylsilyloxy)ethyl]-3-methyl-6-(thiophen-2-yl)-1,3-oxazinane 19b. Ph_2SiH_2 (0.46 mL, 2.5 mmol) and $RhH(CO)(PPh_3)_3$ (1%) were added to a solution of **17b** (1.0 mmol) in THF (10 mL) at room temperature and the stirring maintained for 15 h. Disappearance of starting material was verified by TLC (CH_2Cl_2/cyclohexane/ethyl acetate 50/30/20). An aliquot of the solution was utilized for identification of the reduction product **19b** after removing the solvent and fast purification by a short flash chromatography eluting with cyclohexane/ethyl acetate 90:10 (saturated with NH_3 (g)).

Compound **19b**: pale yellow oil. $[\alpha]_D^{20}$ +35.7 (*c* 1.0, $CHCl_3$). IR ($CHCl_3$): 2944, 2865, 1463 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ=7.23 (dd, J_1=1.6 Hz, J_2=4.8 Hz, 1H), 6.96 (m, 2H), 4.75 (dd, J_1=2.0 Hz, J_2=11.2 Hz, 1H), 3.99 (m, 1H), 3.92 (d, J=5.2 Hz, 1H), 3.06 (ddd, J_1=2.0 Hz, J_2=4.4 Hz, J_3=12.8 Hz, 1H), 2.88 (dt, J_1=2.8 Hz, J_2=12.8 Hz, 1H), 2.40 (s, 3H), 2.13 (m, 1H), 1.64 (m, 1H), 1.28 (d, J=6.8 Hz, 3H), 1.06 (m, 21H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=145.80, 126.12, 124.35, 123.43, 97.06, 75.38, 70.46, 54.80, 36.62, 30.51, 18.78, 18.12, 12.27. MS (*m*/*z*): 383, 340, 235, 182, 123. Anal. Calcd for $C_{20}H_{37}NO_2SSi$: C, 62.61; H, 9.72. Found: C, 64.49; H, 9.99.

4.5.12.2. Step 2: (*R*)-3-(methylamino)-1-(thiophen-2-yl)propan-1-ol (*R*)-11b. Aqueous HCl (1 M, 2.50 mL) was added to the crude THF solution of **19b** and the stirring maintained at the same temperature for 4 h. The organic solvent was removed in vacuo and the obtained aqueous solution extracted with Et_2O. The aqueous phase was basified with NH_4OH (pH=10) and then extracted with CH_2Cl_2. The organic phases were dried over Na_2SO_4 and the solvent evaporated.

The crude reaction mixture was subjected to column chromatography (ethyl acetate/MeOH/NH_4OH 80/19/1) to give (*S*)-**11b** in 68% overall yield calculated on **17b**.

Compound (*R*)-**11b**: pale yellow oil. $[\alpha]_D^{20}$ +13.7 (*c* 2.5, EtOH) [lit. $[\alpha]_D$ +13.3 (*c* 1.05, MeOH)[57]]. IR ($CHCl_3$): 3302, 3103, 2939, 2853, 2793, 1473, 1315 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ=7.20 (dd, J_1=1.2 Hz, J_2=4.8 Hz, 1H), 6.96 (dd, J_1=4.0 Hz, J_2=5.2 Hz, 1H), 6.91 (d, J=1.2 Hz, 1H), 5.19 (dd, J_1=2.8 Hz, J_2=8.4 Hz, 1H), 2.94 (m, 1H), 2.89 (m, 1H), 2.44 (s, 3H), 1.95 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=149.64, 126.53, 123.70, 122.31, 71.92, 50.12, 36.73, 35.88. MS (*m*/*z*): 170, 153, 138, 127, 110, 97, 88. Anal. Calcd for $C_8H_{13}NOS$: C, 56.11; H, 7.65. Found: C, 56.21; H, 7.66.

The same procedure was applied for the preparation of (*S*)-**11b** via reduction product **20b**. (*S*)-**11b** was obtained in 60% overall yield from **18b**.

4.5.12.3. Step 1: (2*S*,6*S*)-[(*S*)-1-(triisopropylsilyloxy)ethyl]-3-methyl-6-(thiophen-2-yl)-1,3-oxazinane 20b. Compound **20b**: pale yellow oil. $[\alpha]_D^{20}$ −17.8 (*c* 2.3, $CHCl_3$). IR ($CHCl_3$): 2944, 2865, 1463 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ=7.23 (dd, J_1=2.8 Hz, J_2=3.6 Hz, 1H), 6.96 (m, 2H), 4.73 (dd, J_1=2.8 Hz, J_2=11.6 Hz, 1H), 4.15 (m, 1H), 3.92 (d, J=4.0 Hz, 1H), 3.07 (ddd, J_1=1.6 Hz, J_2=4.4 Hz, J_3=14.4 Hz, 1H), 2.88 (dt, J_1=3.2 Hz, J_2=13.2 Hz, 1H), 2.37 (s, 3H), 2.13 (m, 1H), 1.71 (m, 1H), 1.28 (d, J=6.0 Hz, 3H), 1.06 (m, 21H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=146.17, 126.24, 124.31, 122.89, 96.83, 75.32, 68.14, 54.65, 37.22, 29.81, 18.77, 18.17, 12.60. MS (*m*/*z*): 383, 340, 235, 182, 123. Anal. Calcd for $C_{20}H_{37}NO_2SSi$: C, 62.61; H, 9.72. Found: C, 64.49; H, 9.99.

4.5.12.4. Step 2: (*S*)-3-(methylamino)-1-(thiophen-2-yl)propan-1-ol (*S*)-11b. $[\alpha]_D^{20}$ −12.0 (*c* 3.0, EtOH). IR ($CHCl_3$): 3302, 3103, 2939, 2853, 2793, 1473, 1315 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ=7.20 (dd, J_1=1.2 Hz, J_2=4.8 Hz, 1H), 6.96 (dd, J_1=4.0 Hz, J_2=5.2 Hz, 1H), 6.91 (d, J=1.2 Hz, 1H), 5.19 (dd, J_1=2.8 Hz, J_2=8.4 Hz, 1H), 2.94 (m, 1H), 2.89 (m, 1H), 2.44 (s, 3H), 1.95 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=149.64, 126.53, 123.70, 122.31, 71.92, 50.12, 36.73, 35.88. MS (*m*/*z*): 170, 153, 138, 127, 110, 97, 88. Anal. Calcd for $C_8H_{13}NOS$: C, 56.11; H, 7.65. Found: C, 57.23; H, 7.88.

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