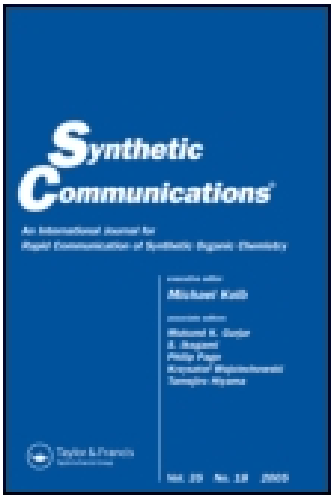

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Diastereoselective Approach to Substituted Oxazolidinones from Morita-Baylis-Hillman Adducts

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DIASTEREOSELECTIVE APPROACH TO SUBSTITUTED OXAZOLIDINONES FROM MORITA–BAYLIS–HILLMAN ADDUCTS

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We disclose herein a new strategy for the diastereoselective preparation of 4- and 4,5-substituted oxazolidinones from Morita–Baylis–Hillman adducts. The strategy is based on an intramolecular cyclization involving a nucleophilic attack of an alkoxide ion to the carbonyl group of a carbamate. The latter is prepared from a Curtius rearrangement having Morita–Baylis–Hillman adduct as substrate. The oxazolidinones were prepared in six steps with an overall yield of 18% and 49%.

Keywords: Curtius rearrangement; heterocycles; Morita–Baylis–Hillman; oxazolidinones

INTRODUCTION

Oxazolidinones (Fig. 1) are five-membered heterocycles that have many synthetic applications and important biological effects. Thanks to the efforts of Evans et al.[1–6] these heterocycles have been successfully used as chiral auxiliaries in many asymmetric organic transformations[7–12] and in aldol condensation reactions,[13–15] Diels–Alder reactions,[16–19] alkylations,[20–23] Michael additions,[24–26] and electrophilic aminations.[27–29]

In addition to the synthetic relevance of oxazolidinones, this type of compound also presents strong antibacterial activity. At present, there is a medical need for the discovery of new classes of antibiotics because of the appearance of several multidrug-resistent microorganisms. Ozaxolidinones are a new class of synthetic antibiotics discovered in the seventies and represent the only new type of antibiotics licensed in the USA by the Food and Drug Administration in the past 30 years.[30–32] Linezolid (Zyvox®) is an example of a successful commercial oxazolidinone antibiotic (Fig. 2).

The combination of synthetic usefulness with the pharmacological activity of the oxazolidinones has stimulated efforts to develop alternatives for the synthesis of this class of compounds.[33–35] Conventionally, oxazolidinones can be synthesized

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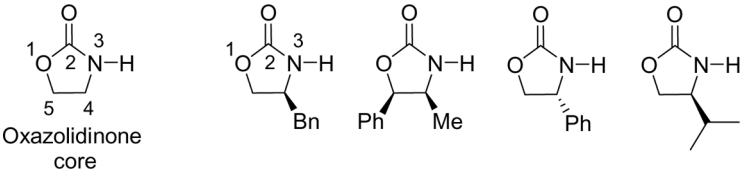


Figure 1. Oxazolidinone core and the most usual oxazolidinone chiral auxiliaries.

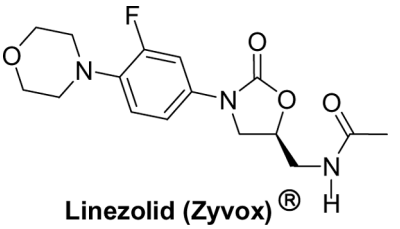


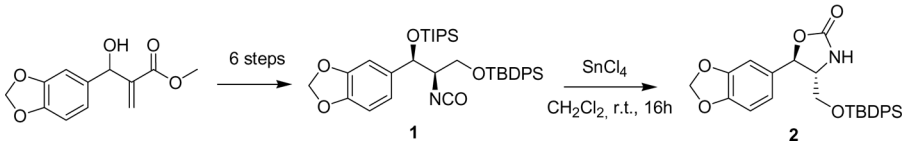
Figure 2. Oxazolidinone-based antibiotic.

by the treatment of α,β-difunctionalized compounds such as β-aminoalcohols, oxiranes, and aziridines with phosgene,[36] carbonates,[33–35] isocyanates,[37–39] or the mixture of carbon monoxide and oxygen via oxidative carbonylation,[40–45] respectively. Strategies based on solid–state chemistry have already been employed for the preparation of oxazolidinones.[46] Despite the great diversity of methodologies, some of them have drawbacks. For example, the use of carbonates and oxidative carbonylations are not ecofriendly because of the risk associated with explosion hazards using CO/O_2 mixtures or the necessity of poisonous phosgene or carbon monoxide involved in the synthesis.[47–49] The synthesis of oxazolidinones from aziridines and carbon dioxide requires high temperatures and has the drawback of polymer formation.[50]

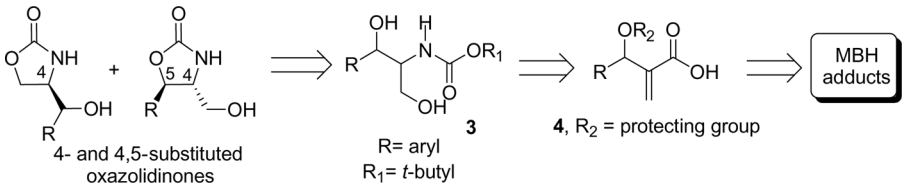
The importance of oxazolidinones in pharmaceutical chemistry and organic synthesis calls for the availability of as many alternative methods to prepare these key compounds as possible. The Morita–Baylis–Hillman reaction (MBH) is an amazing chemical transformation that allows access to a new σ C-C bond.[51–59] This reaction affords multifunctionalized products, which have already been used as starting materials for the synthesis of several advanced synthetic intermediates and natural products.[60–67]

Some years ago, during the synthesis of intermediates for the preparation of alkaloids using MBH adducts, we needed to selectively remove a secondary protecting group in the presence of a primary one. To accomplish this transformation, isocyanate **1** was treated with $SnCl_4$ at room temperature. To our delight, the oxazolidinone **2** was the only product detected (Scheme 1).[68]

Because of the synthetic and biological relevance of oxazolidinones, we decided to evaluate the scope of this synthetic methodology. Oxazolidinones could be promptly prepared using the MBH reaction using the sequence proposed in the retrosynthetic analysis depicted in Scheme 2.



Scheme 1. Synthesis of oxazolidinone **2** from MBH reaction.



Scheme 2. Retrosynthetic analysis for the preparation of oxazolidinones from MBH adducts.

Both oxazolidinones (4- and 4,5-substituted) can be prepared from a common intermediate (**3**) by treatment with NaH in tetrahydrofuran (THF). The alkoxides generated under these experimental conditions can make a nucleophilic attack on the carbonyl group to furnish both regioisomeric oxazolidinones. Carbamate **3** can be prepared from carboxylic acid **4** by a Curtius rearrangement. Finally, acid **4** can be obtained from different MBH adducts.

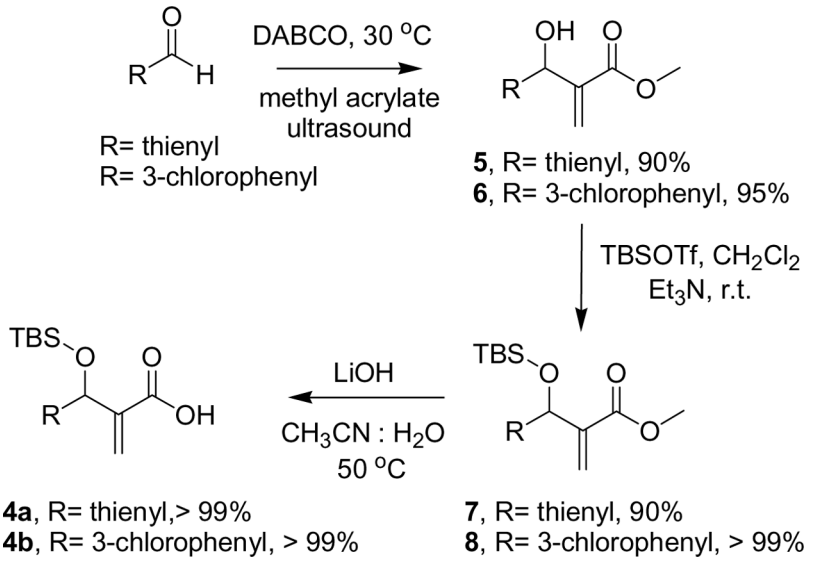
We disclose herein the results achieved in the preparation of 4- and 4,5-substituted oxazolidinones employing the synthetic strategy proposed previously.

RESULTS AND DISCUSSION

Our work begins with the preparation of MBH adducts **5** and **6**, synthesized according a methodology well established in our laboratory (Scheme 3).[69,70] Subsequently, the hydroxyl groups of the adducts were protected by treatment with *tert*-butyldimethylsilyl trifluoromethanesulfonate (TBSOTf) in dichloromethane to furnish the corresponding silyl ethers in 90% and 99% yield, respectively.

The silylated adducts were then treated with LiOH in a mixture of CH_3CN–H_2O (3:1) at 50 °C to afford the corresponding carboxylic acid in almost quantitative yield for both cases. Acids **4a**/**4b** were prepared in three steps with overall yields of 80 and 93%, respectively.

The Curtius rearrangement is an efficient method to add a nitrogen atom to a given compound. An isocyanate is formed as intermediate of this reaction, which in turn can be transformed into several different functional groups (amines, carbamates, etc).[71] Acids **4a/b** were initially treated with ethyl chloroformate at 5 °C in the presence of triethylamine for 5 min. Afterward, a tiny amount of an aqueous solution of NaN_3 was added to the reaction medium to provide the intermediate acylazides, after 2 h of vigorous stirring. The solvent was removed, and the acylazides were thermally rearranged by refluxing them in toluene for 2 h to afford the ene-isocyanates. The entire sequence of reactions was performed without any

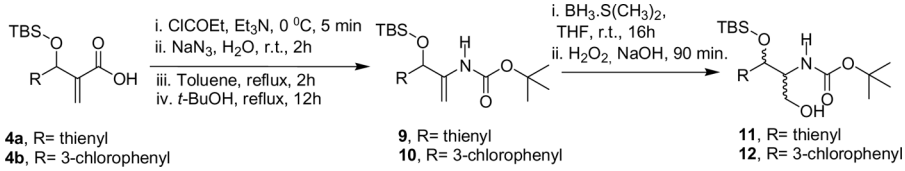


Scheme 3. Preparation of silylated acids from MBH adducts.

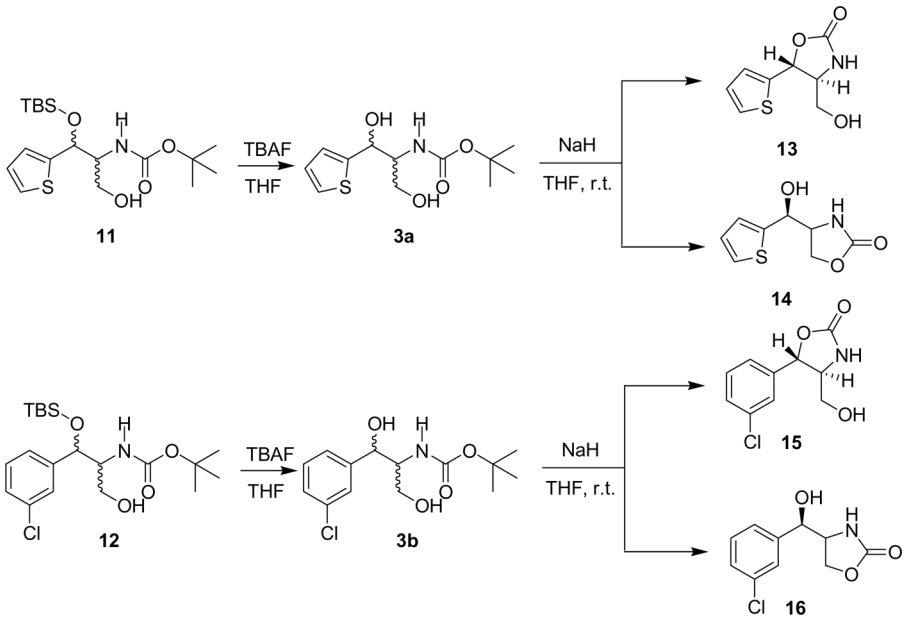
purification steps. The only procedure used between each step was simply solvent removal. After evaporation, the crude ene-isocyanates were refluxed in anhydrous *t*-butanol to give ene-carbamates **9** and **10**. The carbamates were submitted to the next step without purification, since they were demonstrated to be unstable when exposed to silica-gel chromatography. Thus, the crude ene-carbamates were directly treated with borane at 0 °C, and the resulting solution was stirred for 16 h at room temperature. Finally, a solution of NaOH was added, followed by a careful addition of H_2O_2 to give the carbamates **11** and **12**, in 37 and 69% overall yields (Scheme 4).

Because of the presence of the Boc protecting group, the measure of the coupling constants of the carbinolic hydrogen on the ^1H NMR spectra of **11** and **12** was unconclusive, and no data concerning the relative stereochemistry of these compounds could be provided at this stage of our synthetic sequence. This issue forced us to finish the synthesis and determine the relative stereochemistries of **3a** and **3b** indirectly by measurig the coupling constants after cyclization (oxazolidinones).

Compounds **11** and **12** were separatedly treated with tetrabutylammonium fluoride (TBAF) in THF at 0 °C to give the corresponding carbamate-diols **3a** and **3b** in 87 and 98% yields, respectively. Finally, a solution of diols in anhydrous THF was treated with an excess of NaH at room temperature to provide a mixture



Scheme 4. Preparation of carbamates from Curtius rearrangement of MBH adducts.



Scheme 5. Synthesis of 4- and 4,5-substituted oxazolidinones.

of regioisomeric oxazolidinones that were easily separated by silica-gel column chromatography (Scheme 5).

The regioisomeric oxazolidinones **13** and **14** were obtained in 69% yield in a regioisomeric ratio of 1:1.5 (**13:14**), while regioisomeric oxazolidinones **15** and **16** were obtained in 79% yield with a ratio of 1:2 (**15:16**).

To determine the stereochemistry of our oxazolidinones, some nuclear Overhauser effect (nOe) experiments were carried out. The ^{1}H NMR spectrum of **13** does not show a regioisomeric mixture (Fig. 3). A doublet centered at 5.68 ppm ($J = 5.2$ Hz) was atributted to the carbinolic hydrogen. A multiplet centered at

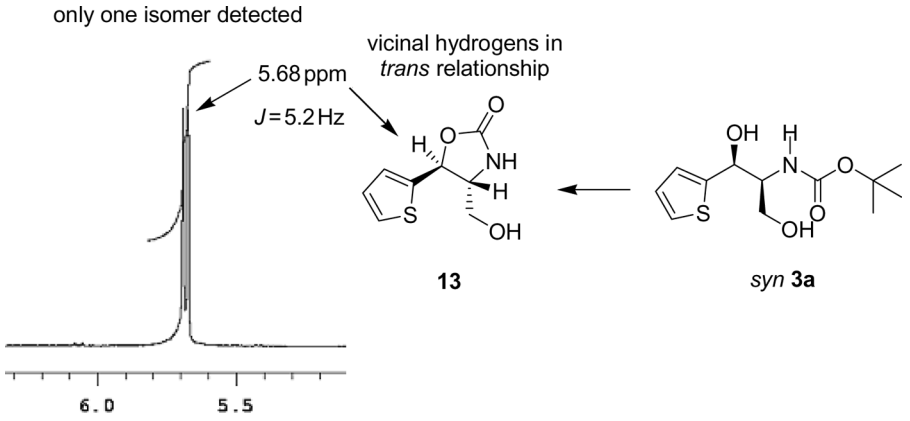


Figure 3. Stereochemical determination of oxazolidinone **13**.

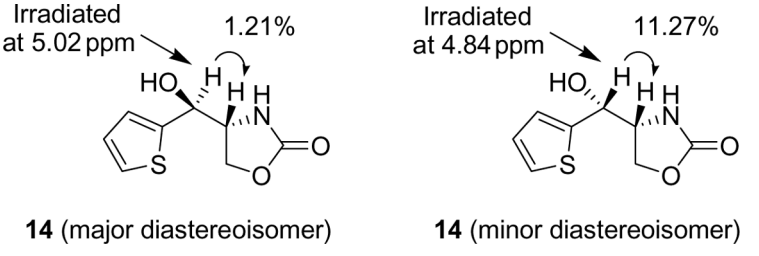
3.94 ppm was attributed to the hydrogen attached to the C-N bond in the five-membered ring. The correlation spectroscopy (COSY) spectrum clearly shows that both hydrogens are coupled, another coupling is centered at 3.94 ppm, and the hydrogen is centered at 3.67 ppm. According Futagawa et al., *trans*-4,5-substituted oxazolidinones have a coupling constant between the vicinal hydrogens ranging from 4 to 6 Hz, while the vicinal coupling constant for the *cis* isomer varies between 9 and 10 Hz.[72] Based on these experimental data, we can unambigously assume that oxazolidinone **13** is *trans* and also that the stereochemistry of diol **3a** should be *syn* (for the major isomer) (Fig. 3).

The ^{1}H NMR spectrum of oxazolidinone **14** shows a mixture of diastereoisomers in a ratio of 5:1. An absorption centered at 5.02 ppm, as a doublet ($J = 4.5$ Hz), was attributed to the carbinolic hydrogen of the major diastereoisomer, and the absorption centered at 4.84 ppm ($J = 6.9$ Hz) was attributed to the minor diastereoisomer. An absorption centered at 4.12 ppm, as a multiplet, was attributed to the hydrogen directly attached to C-N bond. When the doublet centered at 5.02 ppm was irradiated, an increment of 1.21% in the multiplet centered at 4.12 ppm was observed. However, a huge increment of 11.27% was observed when the doublet at 4.84 ppm was irradiated. These data strongly suggest that the hydrogen at 4.84 ppm is on the same side as that appearing at 4.12 ppm and on the opposite side of the hydrogen centered at 5.02 ppm (Fig. 4).

Based on these data, the relative stereochemistry of the major diastereoisomers was determined to be *anti* and that of minor one to be *syn*. Besides, the coupling constant ($J = 6.9$ Hz) of the latter diastereoisomer is compatible with data described by Donohoe et al. for a structurally related *syn*-oxazolidinone.[73]

The same experimental procedure was employed to determine the relative stereochemistries of oxazolidinones **15** and **16**. Oxazolidinone **15** appears as a mixture of diastereoisomers in an 8:1 ratio (measured by ^{1}H NMR from the crude reaction medium; after chromatographic purification, the minor diastereoisomer is no longer detected). The carbinolic hydrogen of the minor isomer appears as doublet centered at 5.72 ppm ($J = 8$ Hz), while this absorption for the major isomer appears also as doublet centered at 5.36 ppm ($J = 5.1$ Hz). According Futagawa, we can assume the relative stereochemistry of the major isomer is *trans*, while that of the minor one is *cis* (Fig. 5).

Unfortunately, oxazolidinone **16** was obtained as a mixture of stereoisomers, without any diastereoselectivity. The relative stereochemistry of both stereoisomers was attributed using the same procedure as already described for **14** and by comparison with data available in literature (Fig. 6).[73]



14 (major diastereoisomer) **14** (minor diastereoisomer)

Figure 4. Determination of the relative stereochemistry of diastereoisomers **14**.

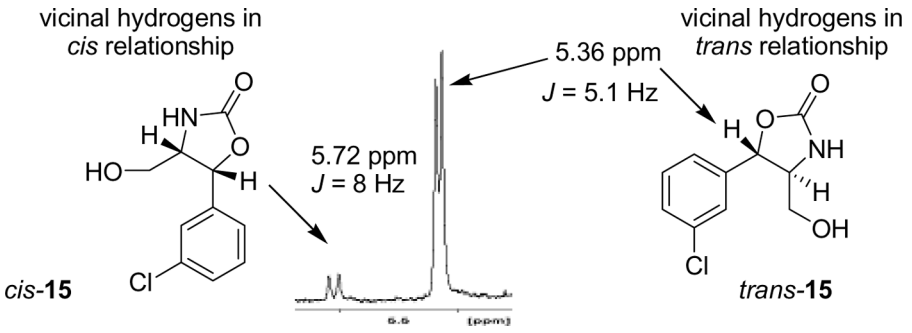


Figure 5. Stereochemical determination of isomers *cis*- and *trans*-**15**.

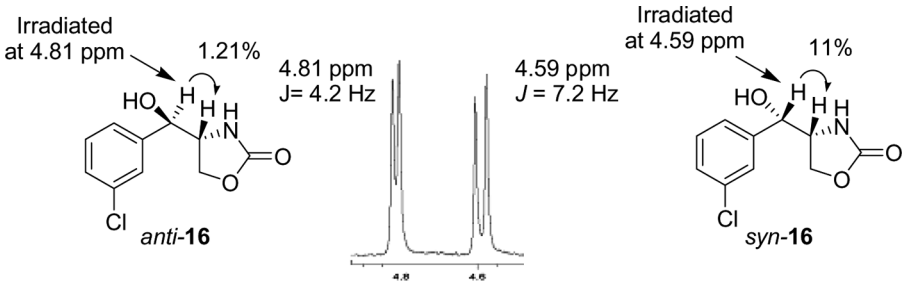


Figure 6. Determination of the relative stereochemistry of **16**.

CONCLUSIONS

In summary, we have described a new approach to synthesize oxazolidinones from MBH adducts. Two new 4-substituted and two new 4,5-substituted oxazolidinones were prepared in six steps with overall yields of 18 and 49%. The diastereoselectivity obtained is very good for most cases. The method allows the preparation of several oxazolidinones with different substitution patterns on the aromatic ring, simply by changing the aldehyde used in the MBH reaction step. We believe that the sequence described herein is a valuable alternative for the preparation of oxazolidinones using an easy-to-handle and easy-to-obtain starting material.

EXPERIMENTAL

The following procedures are representative for all compounds prepared in this work. All the reagents were purchased from specialized suppliers with analytical purity and were utilized without previous purification, unless noted. The ^{1}H and ^{13}C spectra were recorded on a Varian instrument at 250 MHz and 68.5 MHz, respectively, or on an Inova instrument at 500 MHz and 125 MHz, respectively. The mass spectra were recorded using a Micromass (Manchester, UK) QT instrument ESI-QT with 5000 mass resolution and 50 ppm mass accuracy in the turnover frequency (TOF) mass analyzer. Infrared (IR) spectra were obtained with a Nicolet

Impact 410. Manipulations and reactions were not performed under dry atmospheres or employing dry solvents, unless otherwise specified. Purification and separations by column chromatography were performed on silica gel, using normal or flash chromatography. Thin-layer chromatography (TLC) visualization was achieved by spraying with 5% ethanolic phosphomolybdic acid and heating. An ultrasonic cleaner, Unique model GA 1000 (1000 W, 25 kHz), was used to perform MBH reactions. Ice was added occasionally to avoid increasing the temperature of the water bath of the ultrasonic cleaner, which was maintained between 35 and 40 °C.

General Experimental Protocol for the Preparation of the Morita–Baylis–Hillman Adducts

A mixture of 1 mmol of aldehyde, 1.3 mmol of methyl acrylate, and 0.65 mmol of 1,4-diazabicyclo[2.2.2]octane (DABCO) was sonicated (1000 W, 25 kHz) until complete disappearance of starting material (monitoring by TLC). The ultrasound bath temperature was constantly monitored and kept at 30–40 °C during the reaction, through ice addition or by using a refrigerated circulator. After the reaction time, the mixture was evaporated under reduced pressure to remove the excess of acrylate. The residue was diluted with dichlorometane or ethyl acetate (30 mL). The organic solution was washed with 10% aqueous HCl (2×10 mL), saturated $NaHCO_3$ (20 mL), and brine (20 mL) and dried over Na_2SO_4. After filtration and solvent removal, the residue was filtered through a pad of silica gel to afford the corresponding MBH adducts (**5** and **6**) in good to excellent yield, respectively 90 and 95%.

Methyl 2-[hydroxy(2-thienyl)methyl]acrylate (5). A yellow oil; 90% yield; IR (film): ν 3445, 2952, 1715 (C=O), 1632 (C=C) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.25 (1H, *t*, $J = 3.2$ Hz), 6.96 (*d*, 2H, $J = 3.4$ Hz), 6.36 (1H, *s*), 5.96 (1H, *s*), 5.77 (1H, *s*), 3.75 (3H, *s*), 3.48 (1H, *sl*, OH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.4, 145.6, 141.1, 126.7, 126.1, 125.2, 124.6, 69.5, 52.0; HRMS (M^+) calcd. for $C_9H_{10}O_3S$ 198.03507; found 198.03501.

Methyl 2-((3-chlorophenyl)(hydroxy)methyl)acrylate (6). A yellow oil; 95% yield; IR (film): ν 3452, 1711 (C=O), 1624 (C=C), 1433, 1282, 1151, 1041 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$): δ 3.16 (1H, *s*, OH), 3.71 (3H, *s*), 5.49 (1H, *s*), 5.84 (1H, *s*), 6.34 (1H, *s*), 7.24 (3H, *m*), 7.36 (1H, *s*); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 166.6, 143.4, 141.4, 134.3, 129.7, 127.9, 126.7, 124.8, 72.6, 52.1; Anal. calcd. for $C_{11}H_{11}ClO_3$: C, 58.29%; H, 4.89%. Found: C, 58.27%; H, 4.88%.

General Procedure for the Preparation of Silylated MBH Adducts

A mixture of 1 mmol of MBH adduct, 2 mmol of triethylamine, and dichloromethane as solvent was stirred for 10 min. Then, 1.3 mmol of TBSOTf was added at room temperature, under an inert atmosphere, and the resulting mixture was stirred until complete disappearance of starting material (monitoring by TLC). Then, the reaction mixture was diluted with dichloromethane (20 mL), and the organic layer was washed with brine and a saturated solution of $NaHCO_3$ and dried over $MgSO_4$. The solvent was evaporated under reduced pressure. The residue was purified by silica-gel column chromatography using hexane/ethyl acetate as eluent.

Methyl 2-[(*tert*-butyldimethylsilyloxy)(2-thienyl)methyl]acrylate (7). A colorless oil; 90% yield; (film): ν 2954, 2930, 2857, 1723 (C=O), 1632 (C=C), 1256, 1082, 838, 778 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.19 (1H, *dd*, $J = 0.8$ Hz and $J = 5.0$ Hz), 6.95 (1H, *dd*, $J = 0.6$ Hz and $J = 3.0$ Hz), 6.90 (1H, *dd*, $J = 3.5$ Hz and $J = 5.0$ Hz), 6.29 (1H, *s*), 6.14 (1H, *t*, $J = 1.1$ Hz), 5.90 (1H, *s*), 3.74 (3H, *s*), 0.9 (9H, *s*), 0.09 (3H, *s*), 0.01 (3H, *s*); ^{13}C NMR (75 MHz, $CDCl_3$): δ 165.9, 147.1, 143.3, 126.1, 124.4, 124.2, 124.0, 68.4, 51.8, 25.8, 18.3, −2.7, −4.9. HRMS (ESI, *m/z*): calcd. for $C_{15}H_{24}O_3SSi$ $[M + H]^+$ 313.1288; found 313.1280.

Methyl 2-[(*tert*-butyldimethylsilyloxy)(3-chlorophenyl)methyl]acrylate (8). Colorless oil; 99% yield; IR (film): ν 3453, 2954, 2861, 1714 (C=O), 1629 (C=C), 1576, 1475, 1004, 939, 740, 671, 520, 450, 426 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$): δ 7.35 (1H, *s*), 7.26–7.19 (3H, *m*), 6.28 (1H, *t*, $J = 2.6$ Hz), 6.10 (1H, *t*, $J = 3.1$ Hz), 5.58 (1H, *s*), 3.69 (3H, *s*), 0.88 (9H, *s*), 0.06 (3H, *s*), −0.08 (3H, *s*); ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.1, 144.8, 143.4, 133.9, 129.3, 127.5, 127.0, 125.2, 124.4, 72.1, 51.7, 46.7, 25.7, 18.1, −5.0. HRMS (ESI, *m/z*): calcd. for $C_{17}H_{25}ClO_3Si$ $[M + Na]^+$ 366.1153; found 366.1141.

Hydrolysis of MBH Adducts: Preparation of Silylated Acids 4a/b

The silylated MBH adducts were treated with LiOH (10 equiv.) in a mixture of CH_3CN–H_2O (1:1) (1 mmol of adduct / 20 mL of solution), at 50–60 °C. After complete disappearance of starting material (monitoring by TLC), the residue was concentrated under reduced pressure and diluted with ethyl acetate. The organic layer was washed with brine and dried over $NaSO_4$. The solvent was evaporated to afford the crude acids, which are used for the next step without additional purification.

2-[(*tert*-Butyldimethylsilyloxy)(2-thienyl)methyl]acrylic acid (4a). Yellow oil; 99% yield; IR (film): ν 3355 (COOH), 3213, 2959, 2931, 2857, 1691 (C=O), 1627 (C=C), 1459, 1259, 1212, 837 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.21 (1H, *dd*, $J = 0.9$ Hz and $J = 5.1$ Hz), 6.95 (1H, *d*, $J = 3.4$ Hz), 6.91 (1H, *d*, $J = 5.0$ Hz), 6.90 (1H, *d*, $J = 5.0$ Hz), 6.45 (1H, *s*), 6.23 (1H, *s*), 5.87 (1H, *s*), 0.92 (9H, *s*), 0.11 (3H, *s*), 0.03 (3H, *s*); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.4, 146.8, 142.6, 126.8, 126.3, 124.8, 124.5, 68.3, 25.7, 18.2, −5.0. HRMS (ESI, TOF): calcd. for $C_{16}H_{22}O_3SSi$ $[M + Na]^+$ 321.0951; found 321.0883.

2-[(*tert*-Butyldimethylsilyloxy)(3-chlorophenyl)methy])acrylic acid (4b). Colorless oil; 99% yield; IR (film): ν 3056 (COOH), 2953, 2929, 2855, 1695 (C=O), 1629 (C=C), 1470, 1429, 1254, 1074, 837 cm^{-1}; ^1H NMR: δ 7.39 (1H, *s*), 7.35–7.22 (3H, *m*), 6.48 (1H, *s*), 6.26 (1H, *s*), 5.58 (1H, *s*), 0.93 (9H, *s*), 0.11 (3H, *s*), −0.03 (3H, *s*); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.7, 144.4, 142.7, 133.9, 129.4, 127.6, 127.0, 125.1, 71.7, 25.7, 18.1, −5.0. HRMS (ESI, *m/z*): calcd. for $C_{16}H_{23}NO_3ClSi$ $[M + Na]^+$ 349.0918; found 349.1003.

General Procedure for the Curtius Rearrangement and Hydroboration

To a solution of 1 mmol of acid in acetone (5 mL) at 0 °C, 1.5 mmol of ethyl chloroformate and 2 mmol of triethylamine were added. After 45 min (analysis by

TLC showed the complete disappearance of starting material), 1.5 mmol of sodium azide dissolved in a small amount of water was added with vigorous stirring, and the resulting mixture was stirred vigorously for 2 h. After that, the mixture was diluted in cold dichloromethane, and the organic layer was washed with cold distilled water and brine and dried over anhydrous Na_2SO_4. The solvent was evaporated, and the residue was dissolved in anhydrous toluene (15 mL) and refluxed for 2 h. Then, the solvent was evaporated, and the residue was dissolved in anhydrous *t*-butanol and refluxed for 12 h. After that, the solvent was evaporated to give the crude ene-carbamates (**9**) and (**10**), which were used immediately in the next step, without purification.

To a stirred solution of 1 mmol of ene carbamates (**9**) and (**10**) in anhydrous THF (10 mL), at 0 °C, under an inert atmosphere, 7 mmol of $BH_3 \cdot S(CH_3)_2$ (1 mol/L^{-1} in THF) were added slowly. After the addition, the reaction medium was warmed to room temperature and stirred for 16 h. The temperature of the resulting solution was then lowered to 0 °C. A solution of NaOH (5 mL, 3 mol L^{-1}) was added, followed by the careful addition (drop by drop) of 30% H_2O_2 (5 mL). The mixture was stirred for 45 min at 0 °C and for 45 min at room temperature. After this time, a saturated solution of $NaHCO_3$ (10 mL) was added, and the mixture was extracted with ethyl acetate. The organic layer was successively washed with a saturated solution of $NaHCO_3$, distilled water, and brine and dried over Na_2SO_4. The solvent was removed under reduced pressure. The products (**11** and **12**) were used in the next steps without purification.

***tert*-Butyl [2-(*tert*-butyl-dimethyl-silanyloxy)-1-(hydroxymethyl)-2-(2-thienyl)-ethyl] carbamate (11).** Colorless oil; 37% overall yield; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.22 (1H, *m*), 6.95 (2H, *m*), 5.4 (1H, *s*, NH), 5.21 (1H, *d*, $J = 3.3$ Hz), 3.96 (1H, *dd*, $J = 2.7$ Hz and $J = 11.7$ Hz), 3.77 (1H, *m*), 3.68 (2H, *d*, $J = 6.0$ Hz), 3.52 (1H, *dd*, $J = 3.6$ Hz and $J = 11.7$ Hz), 1.47 (9H, *s*), 1.42 (9H, *s*), 0.94 (9H, *s*), 0.90 (9H, *s*), 0.12 (3H, *s*), 0.10 (3H, *s*), −0.007 (3H, *s*), −0.08 (3H, *s*); ^{13}C NMR (75 MHz, $CDCl_3$): δ 145.1, 126.7, 126.1, 124.7, 124.1, 123.5, 74.0, 70.0, 62.6, 61.5, 58.3, 57.3, 28.4, 25.8, 18.1, −4.96.

***tert*-Butyl [2-(3-chlorophenyl)-2-*tert*-butyl-dimethyl-silanyloxy-1-(hydroxymethyl)ethyl] carbamate (12).** Colorless oil; 69% overall yield; IR (film): ν 3452 (OH), 3329, 2953, 2937, 2855, 1699 (C=O), 1503, 1474, 1364, 1258, 1127, 1102, 1070, 837, 775 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.37–7.19 (4H, *m*), 5.45 (1H, *d*, $J = 7.7$ Hz), 5.13 (1H, *sl*), 4.91 (1H, *sl*), 3.82 (1H, *dd*, $J = 2.8$ Hz and $J = 11.6$ Hz), 3.73–3.43 (3H, *m*), 1.47 (9H, *s*), 0.90 (9H, *s*), 0.08 (3H, *s*), 0.06 (3H, *s*), −0.08 (3H, *s*), −0.13 (3H, *s*); ^{13}C NMR (75 MHz, $CDCl_3$): δ 155.6, 144.04, 143.3, 134.3, 134.0, 129.6, 129.4, 127.6, 127.5, 126.5, 126.1, 124.4, 124.0, 79.6, 72.7, 62.6, 60.9, 56.6, 28.3, 25.7, 18.1, −4.6, −5.2.

General Procedure for the Desilylation of the Aminoalcohols

To a solution of 1 mmol of protected aminoalcohols in THF (10 mL), 2.5 mmol of tetrabutylamonium fluoride (TBAF) were slowly added under an inert atmosphere, at 0 °C. After that, the reaction medium was stirred for 2 h at room temperature. Then, the solvent was evaporated under reduced pressure, and the residue was

dissolved in ethyl acetate. The organic layer was washed with a saturated solution of amonium chloride (NH_4Cl), distilled water, and brine and dried over Na_2SO_4. Then, the solvent was evaporated to afford the unprotected aminoalcohols **3a** and **3b** in 87% and 98% yields, respectively. Both aminoalcohols were used for the next step without purification.

Preparation of the 4- and 4,5-Substituted Oxazolidinones

A solution of 1 mmol of aminoalcohol **3a** in THF (10 mL) was added to a suspension of 2.5 mmol of NaH under an inert atmosphere. After that, the reaction medium was stirred for 16 h at room temperature. After this time, a solution of ammonium chloride (NH_4Cl) was added, and the resulting solution was extracted with ethyl acetate. The organic layer was washed with a 5% solution of HCl (10 mL), a saturated solution of $NaHCO_3$(10 mL), and brine and dried over Na_2SO_4. The solvent was evaporated under reduced pressure to afford a mixture of regioisomers in 69% yield. The regioisomers were separated on silica gel to afford the oxazolidinones **13** and **14** in a proportion of 2:3, respectively.

(4-(Hydroxymethyl)-5-(2-thienyl)-1,3-oxazolidin-2-one (13). Colorless oil; IR (film): ν 3378, 2955, 2929, 2856, 1735, 1522, 1347, 1112, 704 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.5 (1H, *dd*, $J = 1.1$ Hz and $J = 6.1$ Hz), 7.22 (1H, *d*, $J = 3.3$ Hz), 7.06 (1H, *dd*, $J = 3.6$ Hz and $J = 5.2$ Hz), 5.68 (1H, *d*, $J = 5.2$ Hz), 3.94 (1H, *m*), 3.67 (2H, *m*); ^{13}C NMR (75 MHz, $CDCl_3$): δ 161.0, 143.1, 128.2, 127.8, 127.6, 77.5, 63.5; HRMS (ESI, *m/z*): calcd. for $C_8H_9NO_3S$ 199.0303; found 200.0308 $[M + H]^+$.

4-[Hydroxy(2-thienyl)methyl]-1,3-oxazolidin-2-one (14). Colorless oil; IR (film): ν 3319, 2922, 2852, 1736, 1475, 1415, 1240, 1036 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.28 (1H, *dd*, $J = 4.2$ Hz and $J = 7.2$ Hz), 6.99 (2H, *m*), 6.80–6.60 (1H, *s*, NH, diastereoisomers), 5.02 (1H, *d*, $J = 4.5$ Hz, major diastereoisomer), 4.84 (1H, *d*, $J = 6.9$ Hz, minor diastereoisomer), 4.5–4.3 (1H, *m*, HC-N, OH), 4.12 (2H, *m*, CH_2); ^{13}C NMR (75 MHz, $CDCl_3$): δ 160.5, 142.6, 127.5, 125.5, 124.7, 70.3, 66.2, 57.8; HRMS (ESI, *m/z*): calcd. for $C_8H_9NO_3S$ 199.0303; found 200.0421 $[M + H]^+$.

A solution of 1 mmol of aminoalcohol **3b** in THF (10 mL) was added to a suspension of 2.5 mmol of NaH, under an inert atmosphere. After that, the reaction medium was stirred for 16 h at room temperature. After this time, a solution of ammonium chloride (NH_4Cl) was added, and the resulting solution was extracted with ethyl acetate. The organic layer was washed with a 5% solution of HCl (10 mL), saturated solution of $NaHCO_3$(10 mL), and brine and dried over Na_2SO_4. The solvent was evaporated under reduced pressure to afford a mixture of regioisomers with 79% yield. The regioisomers were separated in silica gel to afford the oxazolidinones **15** and **16** in a proportion of 1:2, respectively.

4-(Hydroxymethyl)-5-(3-chlorophenyl)-1,3-oxazolidin-2-one (15). Colorless oil; IR (film): 3305, 2970, 2937, 2913, 2876, 1740, 1601, 1572, 1433, 1041, 739 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.28 (4H, *m*), 6.63 and 6.24 (1H, s*l*, NH, diastereoisomers), 5.72 (1H, *d*, $J = 8.0$ Hz, minor diastereoisomer), 5.36 (1H, *d*, $J = 5.1$ Hz,

major diastereoisomer), 3.83 (3H, *m*, N-CH and CH_2); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 164.3, 140.6, 130.5, 129.2, 79.2, 63.0, 61.9. HRMS (ESI, *m/z*) calcd. for $C_{10}H_{10}ClNO_3$ 227.0349; found $[M+H]^+$ 228.0344.

4-[Hydroxy(3-chlorophenyl)methyl]-1,3-oxazolidin-2-one (16). Colorless oil; IR (film): ν 3423, 3309, 2958, 2921, 2859, 1736, 1593, 1568, 1474, 1417, 1237, 1029, 730 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) (diastereoisomers): δ 7.28 (4H, *m*), 6.45 and 6.27 (1H, *s*, NH); 4.81 (1H, *d*, $J=4.2$ Hz), 4.59 (1H, *d*, $J=7.2$ Hz), 4.40 (1H, *m*), 4.25 (2H, *m*), 4.05 (3H, *m*); ^{13}C NMR (75 MHz, $CDCl_3$) (diastereoisomers): δ 160.7, 160.0, 141.2, 134.9, 130.2, 130.09, 128.9, 128.4, 126.8, 126.2, 124.8, 124.1, 75.3, 72.6, 66.6, 65.9, 58.2, 57.8. HRMS (ESI, *m/z*) calcd. for $C_{10}H_{10}ClNO_3$ 227.0349; found $[M+H]^+$ 228.0344.

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