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A Microwave-Assisted Synthesis of (*S*)-*N*-Protected Homoserine γ-Lactones from L-Aspartic Acid

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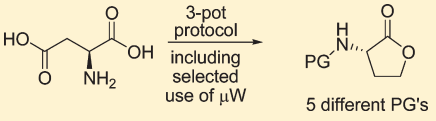
Supporting Information

ABSTRACT: A three-pot preparation of (*S*)-*N*-protected homoserine γ-lactones is presented. Conversion of N-protected L-aspartic acid to an oxazolidinone is followed by selective reduction/acid-catalyzed cyclization to deliver the lactones. Microwave irradiation proved valuable for improving the latter reaction steps in some cases.

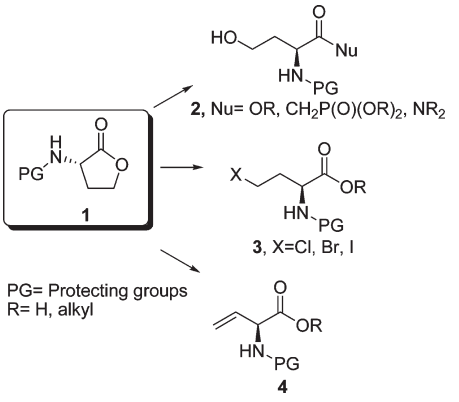


In response to fluctuations in cell-population density, many bacteria regulate a diverse range of physiological actions by a process called quorum sensing. Quorum sensing bacteria release autoinducers to alter gene expression that leads to modification of processes such as competence, conjugation, antibiotic production, and biofilm formation. In general, Gram-negative bacteria (i.e., *Pseudomonas aeruginosa*) use *N*-acylated homoserine γ-lactones (**1**, PG = acylated chain) as autoinducers.[1,2] The study of quorum sensing could find importance in the treatment of several diseases such as cystic fibrosis (CF), which refers to the distinctive fibrosis and cyst formation within the pancreas. Although there is presently no cure for CF, most CF patients survive into adulthood through the extensive use of antibiotics and other medications. Because of the rise of antibiotic-resistant strains of bacteria commonly found in the lungs of CF patients, alternative methods are now sought for the treatment of lung infections of CF patients and also for other diseases which rely on the use of antibiotics.[3] One such alternative therapy, which uses chemicals that interrupt or destroy quorum sensing signals, is called signal interference or quorum quenching. It has been reported that the communication ability of bacteria can be interrupted and thereby its ability to form colonies and to become pathogenic is compromised. Thus, the bacteria can be naturally eliminated by the body through normal immune system functions. It seems plausible that the signal interference approach for the treatment of bacterial infections would replace or complement the use of antibiotics.[4]

N-Protected homoserine γ-lactones (**1**)[5] have been used in numerous biological studies[6] and in the syntheses of several useful organic compounds.[7−10] They also serve as a precursor for a number of synthetically important compounds such as homoserine derivatives (**2**),[8] 2-amino-4-halobutanoic acid derivatives (**3**),[9] and vinylglycine derivatives (**4**) (Scheme 1).[10]

Despite their proven value, *N*-protected homoserine γ-lactones (**1**) are very expensive or not available in their optically pure form. For example, the cost of optically pure (*S*)-*N*- benzyloxycarbonylhomoserine γ-lactones (**1b**) is about US $100/g, while

Scheme 1. Common Organic Reactions of (*S*)-*N*-Protected Homoserine γ-Lactones



the cost of racemic *N*-*tert*-butylcarbonylhomoserine γ-lactone (**1a**) is about US $50/g.[11] Other *N*-protected homoserine γ-lactones (**1**) are not commercially available from any major chemical supplier. Several procedures exist for the synthesis of lactones **1**, but their commercial scarcity may be caused by the lack of an attractive or inexpensive synthetic protocol. Lactones **1** can be obtained from the N-protection of homoserine γ-lactones (**5**) under basic conditions[9a,12] or from homoserine (**6**) via N-protection followed by the cyclization to the lactone (Scheme 2).[12a,13] The drawback in these synthetic schemes is the high cost of L-homoserine γ-lactone (**5**) and L-homoserine.[11] Alternative methods use comparatively less expensive starting materials such as L-methionine (**7**) and L-aspartic acid (**8**).[11] For example, (*S*)-*N*-protected homoserine γ-lactones (**1**) can be synthesized by N-protection of L-methionine (**7**) followed by refluxing with an alkyl iodide under acidic conditions[14a] or by converting it to L-homoserine followed

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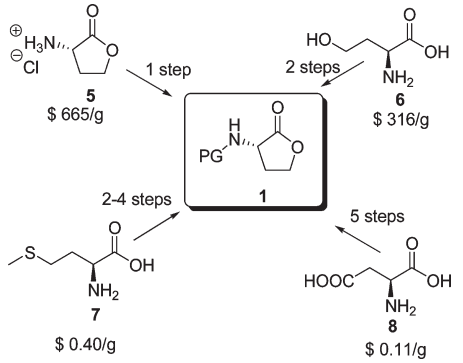
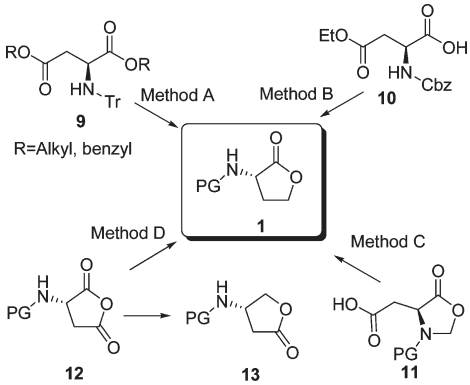
Scheme 2. Comparison of Possible Routes to Synthesize *N*-Protected Homoserine γ-Lactones (1)



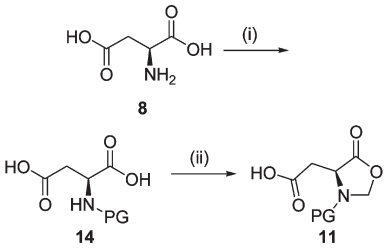
Scheme 3. Synthetic Routes to Lactones 1 from L-Aspartic Acid Based Compounds



by N-protection and cyclization.[14b] While the synthesis from L-methionine can generally be achieved in high yield and in few steps, there is still a scope for improvement in the yield, cost, and amino protecting group choices in these methods.[15] Alternatively, lactones **1** can also be synthesized in a multistep procedure starting with selective esterification of L-aspartic acid (**8**) followed by N-protection, precipitation of the dicyclohexylammonium salts, selective reduction with $LiBH_4$, and cyclization to the corresponding γ-lactones during isolation.[16] Isolated examples of syntheses of compounds **1** from L-aspartic acid based derivatives (**9**−**12**) also exist in the literature; however, these reports did not provide a collective study and appear to be protecting group specific (Scheme 3, method A/B/C).[17−19] For example, the synthetic protocol from **12** to **1** proceeds only with selected protecting groups, whereas formation of lactone **13** occurs in other situations.[20] Most of these methods also require additional steps and use of undesirable reagents (Scheme 3).[19,21] For instance, the synthetic protocol from **11** to **1** requires the use of thionyl chloride, which is not only environmentally damaging but also highly regulated and not easily available. In addition, use of transition-metal catalysis in this protocol is undesirable in the late stages of synthesis of pharmaceutically and biologically relevant compounds.[22]

In light of the above-mentioned difficulties, we report an economical and facile way to synthesize the *N*-protected-L-homoserine

Scheme 4. Synthesis of (*S*)-3-(*N*-Protected)-5-oxo-4-oxazolidineacetic Acid (11)*



Comp.	PG	Yield%
14a	Boc	a
14b	Cbz	75
14c	F-moc	87
14d	Ac	a
14e	Ts	92
14f	Ns	83

Comp.	PG	Yield% Reflux	Yield% MW
11a	Boc	70	60
11b	Cbz	91	87
11c	F-moc	25	85
11d	Ac	0	75
11e	Ts	66	72
11f	Ns	0	86

*Key: (i) solvent, base, PG-Cl, or PG-anhydride (see detail in the Experimental Section); (ii) solvent (toluene, benzene, or EtOAc/Benzene), PTSA (catalytic amount), paraformaldehyde (2 equiv for reflux/7.0 equiv for microwave heating conditions (MW)). [a] **14a,d** were commercially available.

γ-lactones (**1**) in a three-pot process from L-aspartic acids (**8**). Our method involves N-protection of L-aspartic acid (**8**) under basic conditions,[20,23] followed by the acid-catalyzed condensation with paraformaldehyde to yield (*S*)-3-(*N*-protected)-5-oxo-4-oxazolidineacetic acid (**11**) (Scheme 4).[24] While some of the compounds **11a,b,d** could be synthesized in moderate to good yields by refluxing a mixture of **14**, paraformaldehyde, and *p*-toluenesulfonic acid (*p*-TsOH) in toluene or benzene, such a treatment resulted in a low yield of **11c** or did not produce the expected *N*-acetyl or *N*-nosyl-*N*-(2-nitrobenzenesulfonyl)oxazolidinone compounds (**11d**, **f**) at all. Several attempts to obtain **11f** by varying the equivalents of *p*-TsOH (0.06−1.1 equiv) and paraformaldehyde (1−4 equiv), reaction time (1 h to overnight), solvents (benzene, toluene, THF, DMF, acetic anhydride/acetic acid), or temperature (60−100 °C or refluxing) under conventional heating were unsuccessful. The 2-nitrobenzenesulfonyl (nosyl) group, introduced by Fukuyama,[25] is important because it can be removed under very mild conditions with thiolates. *N*-Fmoc protection is also important from a synthetic perspective, whereas *N*-acyl-protected compounds are significant for biological studies related to quorum sensing.

Following the lead of Tantry et al.,[24c] where an unmodified domestic microwave was used for the synthesis of related oxazolidinone derivatives, we attempted to use a microwave reactor for the synthesis of the requisite oxazolidinones. Microwave treatment (300 W, 80−105 °C, benzene or toluene) considerably shortened the reaction time to 5−15 min and resulted in consistently good yields of **11a**−**f**. The optimum reaction conditions standardized for the synthesis of **11a**−**f** are described in the Experimental Section. Oxazolidinones **11d** and **11f** represent new compounds, while full characterization data has not been previously reported for **11c** and **11e**. ^1H and ^{13}C NMR data for **11a** also did not completely match with the reported data. Considerable broadening was observed for the $-CH_2COOH$ protons in the ^1H NMR spectra of **11a** and **11c**, probably due to the presence of rotamers.[26a] Structures of **11a** and **11c** were confirmed by collecting ^1H NMR spectra at higher temperatures (see the Supporting Information). (*S*)-3-Acetyl-5-oxo-4-oxazolidineacetic acid (**11d**) was obtained as a mixture of two rotamers

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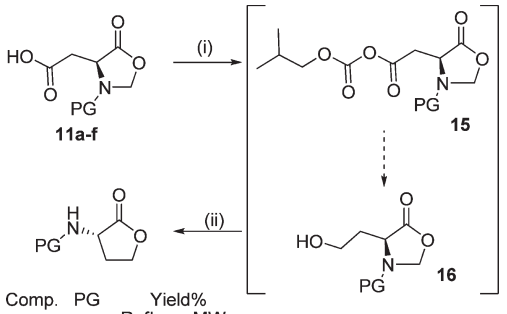
Scheme 5. Synthesis of (*S*)-*N*-Protected Homoserine γ-Lactones[a]



Comp.	PG	Yield% Reflux	Yield% MW
1a	Boc	0	0
1b	Cbz	70	65
1c	F-moc	0	60
1d	Ac	0	84
1e	Ts	68	42
1f	Ns	70	46

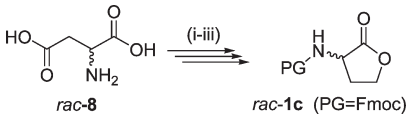
[a] Key: (i) NMM (1.2 equiv)/IBCF (1.2 equiv) in THF −10 to −15 °C, $NaBH_4$ followed by MeOH at 0 °C, quench with acid; (ii) 0.5−1 M citric acid. Method A: refluxing for 2−4 h. Method B: microwave heating (MW), 300 W, 5−15 min, 80−100 °C.

at room temperature as evidenced by ^{1}H and ^{13}C NMR spectroscopies which each exhibited two sets of peaks at 295 K. The ^{1}H NMR spectrum of **11d** in pyridine-d_5 was studied further under variable temperature conditions. The two sets of peaks (ratio 1/2.5) began to coalesce as the temperature was raised and the peaks merged completely at 67 °C (see the Supporting Information). This phenomenon is consistent, with the presence of rotamers, as reported previously for *N*-acyl-5-oxazolidinones.[26b]

It is known that the *N*-protected-L-aspartic acid derivatives (**14**) can be selectively reduced;[27] therefore, it was anticipated that selective reduction of the COOH side chain of **11** can be similarly achieved. (*S*)-3-(Benzyloxycarbonyl)-5-oxo-4-oxazolidineacetic acid (**11b**) was chosen for initial experiments due to its higher yields and stability. Treatment of **11b** with *N*-methylmorpholine and methyl chloroformate in dry THF at −15 °C led to the in situ formation of a mixed anhydride (**15b**, PG = Cbz) and was subsequently reacted with $NaBH_4$ and MeOH to reduce the side chain for the formation of (*S*)-(*N*-Cbz)-4-(2-hydroxyethyl)-5-oxo-3-oxazolidine (**16b**, PG = Cbz). The reaction was quenched with an acid (dilute HCl or CH_3COOH) to obtain **16b** in 61% yield.[28] In an attempt to improve this yield, isobutyl chloroformate was used as an alternative to methyl chloroformate,[29] which raised the yield to 71% (Scheme 5). Compound **16b** was further treated with 1.0 M citric acid under refluxing conditions (1 h) to afford **1b** in 55% yield (Scheme 5). The yield could be increased to 70% by subjecting **16b** to the lactone-forming step without workup and by extending the reaction time to 2−4 h. Additional changes to reactions times and reagents did not bring about any further improvements. (*S*)-*N*-Tosyl- and (*S*)-*N*-nosylhomoserine γ-lactones (**1e**,**f**) were also obtained in 68% and 70% yield, respectively, by using a similar two-step protocol.[30] However, this method failed to produce any significant quantities of **1a**,**c**,**d**, presumably because of the acid sensitivity of the starting substrates (**11a**,**c**,**d**) under refluxing temperatures.[31]

To determine at what stage the problem is occurring, the reaction of **11c** was stopped after the reduction step, and formation of **16c** (PG = Fmoc) was observed in the reaction mixture by ^{1}H NMR spectroscopy. However, **16c** further decomposes during

Scheme 6. Synthesis of Racemic (*S*)-*N*-Fmoc-homoserine γ-Lactone (rac-1c)[a]



[a] Key: (i) 10% aq Na_2CO_3, dioxane, Fmoc-Cl (1.1 equiv); (ii) PTSA (0.06 equiv), paraformaldehyde (7 equiv), toluene, MW (300 W, 105 °C, 6 min); (iii) (a) NMM (1.2 equiv)/IBCF (1.2 equiv) in THF, $NaBH_4$ followed by MeOH and 1 M acetic acid; (b) 0.5 M citric acid, MW, 300 W, 10 min, 80 °C.

the cyclization step under conventional heating conditions. When microwave irradiation (300 W, 80 °C) was applied to the crude reaction mixture containing **16c** in 1 M citric acid solution, there was conversion to **1c** within 10 min. Lactone **1c** could be obtained in 60% yield under MW conditions without workup or purification at the reduction stage. Lactone **1d**[32] was similarly obtained in 84% yield under MW conditions, whereas **1b** and **1e**,**f** were obtained in moderate yields. Various acid conditions and the MW treatment could not successfully bring about **1a**; presumably the Boc group is too sensitive to the obligatory acid treatment.

The configuration of the stereocenter of **1b**−**f** was assigned to be *S* by using a variety of methods. Optical rotation values for **1b**, **d**,**e** correlated well with literature values (see the Supporting Information).[14a,18,32b,32c] To confirm the optical purity of **1c**, racemic *N*-Fmoc-homoserine γ-lactone (*rac*-**1c**) was obtained (Scheme 6). HLPC analysis of *rac*-**1c** on a CHIRACEL-*OJ-H* chiral analytical column revealed two peaks at 51.7 and 55.3 min (83/17 hexanes/2-propanol; 1.0 mL/min flow rate), while under similar conditions, a single peak at 56.5 min was observed for **1c**, confirming the optical purity of **1c**. The absolute configuration of previously unknown **1f** was determined to be *S* with the help of single-crystal X-ray analysis.[33]

In summary, we have developed a new and facile method for the synthesis of (*S*)-*N*-protected homoserine γ-lactones. This method is an advancement of the previous methods and uses inexpensive starting materials to produce (*S*)-*N*-protected homoserine γ-lactones of high enantiopurity in moderate to high yields, but is not suitable when the Boc protecting group is used. The use of MW conditions not only reduces the reaction time but also saves significant quantities of organic solvents and the microwaves promote reactions that were unachievable under thermal treatment only.

EXPERIMENTAL SECTION

General Methods. All air- and water-sensitive reactions were carried out in oven-dried glassware under a nitrogen atmosphere using syringe−septum cap techniques. All column chromatography purifications were performed under flash conditions using 200−450 mesh type 60 Å silica gel. Microwave reactions were carried out in a CEM Discover S-class reactor. Microwave reactions were carried out in vessels equipped with a Teflon cap. The temperature of the reaction mixture was monitored using a surface sensor. The dynamic method with maximum power 300 W, 250 psi setting for maximum pressure and without powermax option was used (CAUTION! Cardiac pacemakers require magnets to control their operation during checkout. Some danger exists if a pacemaker is positioned in close proximity to the instrument cavity.)

General Procedure for *N*-Protected L-Aspartic Acids (14). N-Protected L-aspartic acid derivatives (**14a,d**) were purchased from a commercial supplier. Compound **14c** was synthesized from the adaptation of a reported method.[23] Compounds **14b** and **14e** were synthesized using reported protocols, and characterization data including optical rotation for **14b** and **14e** matched literature values.[20,23]

*Synthesis of N-Fmoc-L-aspartic Acid (**14c**).* This protocol was adapted from a previous method.[23b] To a solution of L-aspartic acid (1.00 g, 7.51 mmol, 1.0 equiv) in dioxane (10.0 mL) was added 10% aq Na_2CO_3 (20.5 mL) at rt, and the mixture was cooled to 0 °C with an ice bath. Fmoc-Cl (1.1 equiv) in dioxane (20 mL) was added slowly, and the mixture was stirred at 0 °C for 1 h. The ice bath was removed, and the mixture stirred at rt for 18 h. Water was added to the solution, and the aqueous layer was washed with diethyl ether. The organic layer was extracted with saturated $NaHCO_3$, and the combined aqueous layers were then acidified to pH 1 with 1 M HCl. The aqueous layer was then extracted with EtOAc (3 × 20 mL). The organic layers were then combined, dried over Na_2SO_4, filtered, and concentrated. The resulting Fmoc-protected aspartic acid (**14c**) was chromatographed using EtOAc/*n*-hexanes (1/1) as the eluant: white solid; yield = 2.37 g (87%); mp 172−174 °C; $[\alpha]_D^{27}$ −4.0 (*c* = 1, MeOH); ^{1}H NMR[34] (MeOH-d_4) δ 7.68 (d, *J* = 7.4 Hz, 2H), 7.55 (d, *J* = 7.4 Hz, 2H), 7.27 (t, *J* = 7.2 Hz, 2H), 7.19 (t, *J* = 7.3 Hz, 2H), 4.45 (t, *J* = 6.8 Hz, 1H), 4.27−4.21 (m, 2H), 4.17−4.10 (m, 1H), 2.73 (m, 2H); ^{13}C NMR (MeOH-d_4) δ 174.4, 174.1, 158.4, 145.2, 142.6, 128.8, 128.19, 126.31, 120.94, 68.23, 51.94, 48.35, 37.21; IR (neat, ν max) 3308, 3033, 2990, 2951, 2894, 1708, 1684, 1526, 1451, 1410, 1275, 1194, 1092, 1049, 1007, 906 cm^{-1}.

*Synthesis of N-Nosyl-L-aspartic Acid (**14f**).* To a solution of L-aspartic acid (2.0 g, 15.0 mmol) in aq NaOH solution (16.0 mL, 1.20 g, 30.0 mmol) at 0 °C were added Ns-Cl (3.66 g, 16.5 mmol), $(i\text{-Pr})_2$EtN (2.87 mL, 16.5 mmol), and acetone (16.0 mL). After being stirred for 10 min, the mixture changed from cloudy to clear yellow and was allowed to stir at rt for 18 h. The mixture was then diluted with water, and the aqueous layer was washed with diethyl ether (3 × 10 mL). The aqueous layer was acidified to pH 1 with 1 M HCl and was extracted with EtOAc (3 × 10 mL). The organic layers were combined, dried over Na_2SO_4, filtered, and concentrated. The nosyl-protected aspartic acid, **14f**, (3.18 g, 83%) was obtained as yellow oil after chromatography (70% EtOAc/*n*-hexane). Recrystallization from EtOAc gave **14f** as pale yellow crystals: mp 182−184 °C; $[\alpha]_D^{27.5}$ −92.1 (*c* = 1, MeOH); ^{1}H NMR (MeOH-d_4) δ 8.13−8.10 (m, 1H), 7.91−7.88 (m, 1H), 7.80−7.77 (m, 2H), 4.42 (t, *J* = 5.4 Hz, 1H), 2.85 (m, 2H); ^{13}C NMR (MeOH-d_4) δ 173.8, 173.2, 149.2, 135.4, 135.1, 133.9, 131.7, 126.2, 54.3, 38.5; IR (neat, ν max) 3293, 2990, 2933, 2879, 1706, 1541, 1415, 1404, 1358, 1341, 1298, 1228, 1195, 1160, 1124, 1068, 919 cm^{-1}. Anal. Calcd for $C_{10}H_{10}N_2O_8S$: C, 37.74; H, 3.17. Found: C, 38.00; H, 3.23.

General Procedure for (*S*)-3-(*N*-Protected)-5-oxo-4-oxazolidineacetic Acids (11). *Method A.* To a solution of **14** (1.0 equiv) in EtOAc/benzene (10 mL/mmol (1/13) for **14a**) or toluene (10 mL/mmol for **14b**−**e**) were added paraformaldehyde (2.0 equiv) and *p*-TsOH·H_2O (0.06 equiv). The mixture was heated to 60 °C (for **14a**) or refluxed (for **14b**−**e**) with removal of water using a Dean−Stark trap filled with $MgSO_4$, The reaction was stopped after disappearance of starting material as judged by TLC analysis (approximately 1−2 h, 4 h for **14c**). The reaction mixture of **14a** was cooled to rt, and EtOAc was added. The organic layer was washed with aq K_2CO_3 (0.3 M, 2 mL) and brine and dried over $MgSO_4$. The solution was filtered and concentrated. Recrystallization from diethyl ether provided **11a** as a light yellow solid. For **14b**−**e**, after consumption of starting material the solvent was removed under reduced pressure and the corresponding oxazolidinones (**11b**,**c**,**e**) were immediately chromatographed using EtOAc/hexanes as the eluant.[24] Compounds **11d** and **11f** could not be synthesized using this method.

*Method **B** (Microwave-Assisted Method).* To a solution of **14** (1.0 equiv) in benzene (5 mL/g for **14a**,**b**,**d**−**f**) or toluene (5 mL/mmol for **14c**) were added paraformaldehyde (7.0 equiv) and *p*-TsOH·H_2O (0.06 equiv). The mixture was subjected to microwave irradiation (300 W) at 80 °C (for **14a**,**b**, **d**−**f**) or 105 °C (for **14c**) for 5−15 min. The reaction mixture was concentrated in vacuo, and the corresponding oxazolidinones (**11**) were immediately chromatographed using EtOAc/hexanes as the eluant.

(*S*)-3-(1,1-Dimethylethoxy)carbonyl)-5-oxo-4-oxazolidineacetic Acid (11a) (Method A/B). To a solution of **14a** (2.00 g for method A or 200 mg for method B) in benzene/EtOAc (65.0/5.00 mL for method A) or benzene (2 mL for method B) were added paraformaldehyde (2.0 equiv, 515 mg for method A or 7.0 equiv, 231 mg for method B) and *p*-TsOH·H_2O (0.06 equiv, 89 mg for method A or 0.06 equiv, 12 mg for method B). The mixture was either refluxed for 2 h (method A) or subjected to microwave irradiation (300 W) at 65 °C for 10 min. Compound **11a** was obtained as white solid after workup as reported earlier.[24a] Recrystallization from diethyl ether: yield = 1.47 g, 70% (method A), 126 mg, 60% (method B); mp 128−129 °C (lit.[24a] mp 132−134 °C); $[\alpha]_D^{26.5}$ +151.3 (*c* = 1, $CHCl_3$) (lit.[24a] $[\alpha]_D^{26.5}$ +153.1 (*c* = 1, $CHCl_3$); ^{1}H NMR(400 MHz, $CDCl_3$) δ (at 328 K) 10.50 (s, 1 H), 5.43 (d, *J* = 2.0 Hz, 1H), 5.23 (d, *J* = 3.6 Hz, 1H), 4.32 (s, 1H), 3.19 (br d, *J* = ca. 17 Hz, 1H), 3.03 (dd, *J* = 17.9, 3.0 Hz, 1H), 1.49 (s, 9H); (at 293 K) 10.00−8.50 (br s, 1 H), 5.50−5.42 (br, 1H), 5.24 (d, *J* = 3.1 Hz, 1H), 4.31 (s, 1H), 3.25−3.02 (m, 2H), 1.49 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (at 328 K) 174.2, 172.0, 152.2, 82.6, 78.5, 51.5, 34.5, 28.1; (at 293 K) 175.3, 172.0, 152.2, 82.6, 78.8, 51.7, 34.7, 28.2; IR (neat, ν max) 3500−2800, 3064, 2980, 2933, 1804, 1712, 1499, 1478, 1398, 1370, 1313, 1290, 1265, 1169, 1141, 1100, 1052, 988 cm^{-1}.

(*S*)-3-(Benzyloxycarbonyl)-5-oxo-4-oxazolidineacetic Acid (11b) (Method A/B). To a solution of **14b** (2.00 g for method A or 200 mg for method B) in benzene (56.0 or 1 mL for method B) were added paraformaldehyde (449 mg, 2 equiv for method A or 157 mg, 7 equiv for method B) and *p*-TsOH·H_2O (77.0 mg, 0.06 equiv or 8 mg, 0.06 equiv for method B). The mixture was either refluxed for 2 h (method A) or subjected to microwave irradiation (300 W) at 80 °C for 6 min (method B). Compound **11b** was obtained as clear oil after chromatography using EtOAc/hexanes (3/7) as the eluant. Recrystallization from EtOAc/*n*-hexane gave **11b** as a clear crystal: yield = 1.90 g, 91% (method A), yield = 182 mg, 87% (method B); mp 82−84 °C (lit.[24b] mp 85−87 °C); $[\alpha]_D^{27.5}$ +124 (*c* = 3.53, MeOH) (lit.[24b] $[\alpha]_D^{23}$ + 125.7 (*c* = 3.53, MeOH)); ^{1}H NMR ($CDCl_3$) δ 9.78 (br s, 1H), 7.34 (s, 5H), 5.48 (br s, 1H), 5.28 (d, *J* = 3.5 Hz, 1H), 5.21−5.11 (m, 2H), 4.34 (s, 1H), 3.30−3.02 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 175.0, 171.7, 152.9, 135.2, 128.8, 128.4, 78.5, 68.3, 51.4, 34.0; IR (neat, ν max) 3500−2600, 3030, 1802, 1721, 1422, 1360 cm^{-1}.

(*S*)-3-[(9*H*-Fluoren-9-ylmethoxy)carbonyl]-5-oxo-4-oxazolidineacetic Acid (11c) (Method B). A mixture of **11c** (300 mg), paraformaldehyde (7.0 equiv, 177 mg), and *p*-TsOH·H_2O (0.06 equiv, 9 mg) in toluene (1 mL) was subjected to microwave irradiation (300 W) at 105 °C for 6 min. The reaction mixture was cooled to rt, and EtOAc was added. The organic layer was washed with water and brine and dried over $MgSO_4$. The solution was filtered and concentrated. Recrystallization from acetone/CH_2Cl_2/hexanes (2/1/3) or EtOAc/*n*-hexane gave **11c** as a white solid. Alternatively, **11c** can also be purified by chromatography using EtOAc/hexanes (5/5) as the eluant: yield = 263 mg, 85% (method B); mp 185−187 °C (lit.[24c] mp 175−177 °C); $[\alpha]_D^{26.5}$ +103.4 (*c* = 1, MeOH); ^{1}H NMR (acetone-d_6, 318 K) δ 7.85 (d, *J* = 7.6 Hz, 2H), 7.66 (d, *J* = 7.3 Hz, 2H), 7.41 (t, *J* = 7.4 Hz, 2H), 7.33 (t, *J* = 7.5 Hz, 2H), 5.41 (d, *J* = 3.5 Hz, 1H), 5.19 (s, 1H), 4.62−4.53 (m, 2H), 4.33 (t, *J* = 5.7 Hz, 1H), 4.26 (m, 1H), 2.84 (br s, 2H); ^{13}C NMR (DMSO-d_6, 318 K) δ 172.1, 171.3, 152.4, 143.6, 140.8, 127.7, 127.2, 127.1, 125.0, 120.1, 77.9, 67.1, 51.4, 46.6, 34.2; IR (neat, ν max) 3300, 3047, 2955, 2923, 1772, 1727, 1692, 1449, 1431, 1411, 1360, 1299, 1260, 1173, 1131, 1053, 1131, 1053, 992 cm^{-1}.

(*S*)-3-[Acetyl]-5-oxo-4-oxazolidineacetic Acid (11d) (Method B). A mixture of **14d** (200 mg), paraformaldehyde (7.0 equiv, 231 mg), and

p-TsOH·H_2O (0.06 equiv, 12 mg) in benzene (1 mL) was subjected to microwave irradiation (300 W) at 80 °C for 15 min. The reaction mixture was concentrated in vacuo, and **11d** was chromatographed using EtOAc/hexanes (1/1) as the eluant. Compound **11d** was dissolved in MeOH, and hexanes/diethyl ether was added. This solution was triturated to obtain a white solid after filtration: yield = 160 mg, 75% for two rotamers (1/2.5) (method B); mp 132−133 °C; $[\alpha]_D^{23.5}$ +210.2 (*c* = 1.0, MeOH); ^{1}H NMR (300 MHz, 295 K, MeOH-d_4) δ 5.68 (d, *J* = 4.6 Hz, 1H*), 5.64 (d, *J* = 3.2 Hz, 1H), 5.50 (d, *J* = 3.1 Hz, 1H), 5.25 (d, *J* = 4.5 Hz, 1H*), 4.66 (d, *J* = 3.4 Hz, 1H*), 4.50 (t, *J* = 3.3 Hz, 1H), 3.14 (ABX, *J* = 18.2, 4.1, 2.3 Hz, 2H), 3.12 (d, *J* = 3.1 Hz, 2H*), 2.15 (s, 3H*), 2.07 (s, 3H) *minor rotamer; ^{13}C NMR (100 MHz, MeOH-d_4) δ 174.3, 174.0, 173.5, 172.9, 171.7, 170.5, 80.1, 80.1, 53.7, 52.6, 36.6, 34.7, 21.6, 21.3; IR (neat, νmax) 3500−2600, 2989, 2955, 2926, 2854, 1791, 1716, 1605, 1462, 1455, 1427, 1413, 1350, 1316, 1288, 1253, 1206, 1184, 1107, 1093, 1058, 1031, 994, 940 cm^{-1}. Anal. Calcd for $C_7H_9NO_5$: C, 44.92; H, 4.85. Found: C, 45.11; H, 5.00.

(*S*)-3-[(4-Methylphenyl)sulfonyl]-5-oxo-4-oxazolidineacetic Acid (11e) (Method A/B). A mixture of **14e** (200 mg), paraformaldehyde (2.0 equiv, 42 mg for method A; 7.0 equiv, 146 mg for method B), and *p*-TsOH·H_2O (0.06 equiv, 7 mg) in toluene (6 mL for method A and 1 mL for method B) was refluxed for 3 h or subjected to microwave irradiation (300 W) at 100 °C for 5 min. The reaction mixture was concentrated in vacuo, and **11e** was chromatographed using EtOAc/hexanes (7/3 to 3/7) as the eluant: sticky solid, yield = 137 mg, 66% (method A), 150 mg, 72% (method B); mp 117−118 °C (lit.[24d] 130−131 °C); $[\alpha]_D^{23.5}$ +252 (*c* = 1.0, acetone) (lit.[24d] +252 (*c* = 1.0, acetone)); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.41 (br s, 1H), 7.93 (m, *J* = 8.2 Hz, 2H), 7.40 (m, *J* = 8.0 Hz, 2H), 5.38 (AB pattern, *J* = 5.1 Hz, 2H), 4.06 (t, *J* = 3.6 Hz, 1H), 3.16 (d, *J* = 3.7 Hz, 2H), 2.46 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.0, 170.9, 145.8, 132.0, 130.58, 127.7, 79.6, 52.9, 36.2, 21.6; IR (neat, νmax) 3500−2500, 3241, 3092, 3062, 2986, 2930, 1803, 1718, 1597, 1493, 1401, 1357, 1307, 1293, 1268, 1215, 1165, 1105, 1045, 966 cm^{-1}.

(*S*)-3-[(2-Nitrophenyl)sulfonyl]-5-oxo-4-oxazolidineacetic Acid (11f) (Method B). A mixture of **14f** (200 mg), paraformaldehyde (7.0 equiv, 132 mg), and *p*-TsOH·H_2O (0.06 equiv, 3.2 mg) in benzene (1 mL) was subjected to microwave irradiation (300 W) at 80 °C for 10 min. The reaction mixture was concentrated in vacuo, and **11f** was chromatographed using EtOAc/hexanes (1/1) and EtOAc as the eluant. The solid was recrystallized with EtOAc/diethyl ether to yield a white solid: yield = 178 mg, 86% (method B); mp 180−181 °C; $[\alpha]_D^{23.5}$ +232.4 (*c* = 1.0, MeOH); ^{1}H NMR (400 MHz, MeOH-d_4) δ 8.21−8.19 (m, 1H), 7.93−7.86 (m, 3H), 5.73 (d, *J* = 4.5 Hz, 1H), 5.43 (dd, *J* = 4.5 Hz, *J* = 0.7 Hz, 1H), 4.61 (t, *J* = 3.5 Hz, 1H), 3.04 (ABX, *J* = 18.1 Hz, *J* = 4.2 Hz, *J* = 3.4 Hz, 2H); ^{13}C NMR (400 MHz, MeOH-d_4) δ 173.0, 149.8, 136.7, 133.8, 132.2, 131.4, 126.0, 80.7, 54.6, 36.6; IR (neat, νmax) 3500−2500, 3101, 3024, 2955, 2930, 2854, 1793, 1763, 1726, 1540, 1406, 1372, 1330, 1301, 1223, 1201, 1170, 1127, 1101, 1050, 1041, 971, 852 cm^{-1}. Anal. Calcd for $C_{11}H_{10}N_2O_8S$: C, 40.00; H, 3.05. Found: C, 40.19; H, 3.13.

General Procedure for the Preparation of (*S*)-*N*-Protected-L-homoserine γ-Lactones (1). *Method A.* To a dry THF (40.0 mL/g) solution of **11** (1.0 equiv) at −10 to −15 °C were added *N*-methylmorpholine (1.2 equiv) and isobutyl chloroformate (1.2 equiv). The mixture was allowed to stir under nitrogen for 15−30 min at −15 °C. $NaBH_4$ (3.0 equiv) was then added in one portion, and the reaction was stirred for 5−10 min followed by the dropwise addition of methanol (40.0 mL/g), and the reaction mixture was further stirred for an additional 10−15 min at 0 °C and then neutralized with 1 M acetic acid or citric acid until solution becomes clear (pH = 5−7). The organic solvents were evaporated under reduced pressure while ensuring the water bath temperature did not exceed 35−40 °C. To the concentrate was added 1.0 M citric acid (∼10 mL/g), and the mixture was refluxed for 2−4 h, cooled to rt, and quickly extracted with EtOAc (4×). The organic layers were combined and washed with water, brine, dried over $MgSO_4$, filtered, and concentrated. The corresponding lactones **1** were obtained after chromatography (hexanes/EtOAc).

Method B (Microwave-Assisted Method). To a dry THF (40.0 mL/g) solution of **11** (1.0 equiv) at −10 to −15 °C were added *N*-methylmorpholine (1.2 equiv) and isobutyl chloroformate (1.2 equiv). The mixture was left to stir under nitrogen for 15−30 min at −10 °C. $NaBH_4$ (3.0 equiv) was added in one portion, and the reaction was allowed to slowly warm while it stirred for 5−10 min. MeOH (50.0 mL/g) was added dropwise, and the solution was stirred for an additional 10−15 min at 0 °C and then neutralized with 1 M acetic acid (∼ 8 mL/g) until the solution became clear (pH ∼ 7). The reaction mixture was concentrated in vacuo and transferred to a microwave vial with the help of additional methanol and the solvent quickly evaporated in vacuo without exposing it to heat (<40 °C). The reaction mixture was then added to 0.5−1 M citric acid (∼ 4−6 mL/g) solution, and the mixture was exposed to the microwave irradiation (300W) for 5−10 min at 80 °C. The mixture was extracted with EtOAc (4×). The organic layers were combined and washed with water and brine, dried over $MgSO_4$, filtered, and concentrated. The corresponding lactones **1** were obtained after chromatography (hexanes/EtOAc).

(*S*)-*N*-Cbz-homoserine γ-Lactone (1b). A solution of **11b** (200 mg) in dry THF (8.0 mL) was treated with NMM (1.2 equiv, 94 μL) and IBCF (1.2 equiv, 113 μL), followed by the addition of $NaBH_4$ (3.0 equiv, 80 mg), and then quenched with MeOH (10.0 mL) and 1 M acetic acid (1.5 mL). The solvent was evaporated in vacuo, and 1 M citric acid was added (4 mL for method A or 1 mL for method B). The reaction mixture was either refluxed for 2 h (method A) or exposed to microwave irradiation (300W) for 15 min at 80 °C. After the general workup procedure described, **1b** was chromatographed using hexanes/EtOAc (7/3 to 1/1) as eluent. Recrystallization from EtOAc/*n*-hexane gave **11b** as white needles: yield = 118 mg, 70% (method A), 109 mg, 65% (method B); mp 122−124 °C (lit.[18] mp 126−127 °C); $[\alpha]_D^{27.5}$ −32.1 (*c* = 1.0, MeOH) (lit.[18] $[\alpha]_D^{25}$ −30.5 (*c* = 1.0, MeOH)); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 (s, 5H), 5.39 (br s, 1H), 5.11 (s, 2H), 4.44−4.35 (m, 2H), 4.24−4.17 (m, 1H), 2.78−2.70 (m, 1H), 2.26−2.11 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.1, 156.0, 135.8, 128.4, 128.1, 128.0, 67.1, 65.6, 50.2, 29.6; IR (neat, νmax) 3328, 3058, 3029, 2944, 1778, 1695, 1542, 1385, 1298, 1265, 1225, 1180, 1073, 1013, 1007, 946 cm^{-1}; GC−MS (EI) *m*/*z* 235.1(M^+, 1), 191.9 (59), 127.8 (100) .

(*S*)-*N*-Fmoc-homoserine γ-Lactone (1c). A solution of **11f** (200 mg) in dry THF (8.0 mL) was treated with NMM (1.2 equiv, 73 μL) and IBCF (1.2 equiv, 105 μL), followed by the addition of $NaBH_4$ (3.0 equiv, 62 mg), and then quenched with MeOH (10.0 mL). The solvent was quickly evaporated in vacuo, and 0.5 M citric acid (2 mL) was added. The reaction mixture was exposed to the microwave irradiation (300 W) for 10 min at 80 °C. After the general workup procedure, **1f** was chromatographed using hexanes/EtOAc (1/1) as eluent followed by recrystallization from 95% EtOH: white solid; yield = 105 mg, 60% (method B); mp 208−209 °C (lit.[9b] mp 208−209 °C); $[\alpha]_D^{22.0}$ +12.0 (*c* = 0.25, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (d, *J* = 7.5 Hz, 2H), 7.58 (d, *J* = 7.4 Hz, 2H), 7.40 (t, *J* = 7.4 Hz, 2H), 7.31 (t, *J* = 7.4 Hz, 2H), 5.39 (br s, 1H), 4.47−4.41 (m, 4H), 4.26−4.20 (m, 3H), 2.78 (m, 1H), 2.20 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.9, 156.1, 143.7, 143.6, 141.3, 127.8, 127.1, 125.0, 120.0, 67.3, 65.8, 50.5, 47.1, 30.5; IR (neat, νmax) 3328, 3061, 3017, 2948, 2918, 2851, 1789, 1686, 1534, 1461, 1384, 1243, 1285, 1263, 1222, 1187, 1161, 1103, 1081, 1017, 995, 971 cm^{-1}; HPLC (17% iPrOH/hexanes, 1.0 mL/min flow rate, OJ-H chiral analytical column: 250 mm (column length) × 4.6 mm (internal diameter). Packing composition: cellulose tris(4-methylbenzoate) coated on 5 μm silica gel, 56.5 min (pure compound), 51.7 and 55.3 min (racemic mixture).

(*S*)-*N*-Acetylhomoserine γ-Lactone (1d). A solution of **11d** (200 mg) in dry THF (8.0 mL) was treated with NMM (1.2 equiv, 142 μL) and IBCF (1.2 equiv, 121 μL), followed by the addition of $NaBH_4$

(3.0 equiv, 121 mg), and then quenched with MeOH (10.0 mL) and 1 M acetic acid (1.5 mL). The solvent was evaporated in vacuo, and 1 M citric acid (1 mL) was added. The reaction mixture was exposed to the microwave irradiation (300 W) for 15 min at 80 °C. The reaction mixture was cooled to rt, and aq $NaHCO_3$ was added to reach pH ~7. The mixture was extracted with EtOAc (4×), and the combined organic layers were washed with water and brine, dried over $MgSO_4$, filtered, and concentrated. Compound **1d** was chromatographed using EtOAc and EtOAc/MeOH (95/5) as eluent followed by repeated recrystallization from CH_2Cl_2/hexanes, spot detection in I_2 chamber: white solid; yield = 137 mg, 84% (method B); mp 82−84 °C (lit.[32a] mp 82−84 °C); $[\alpha]_D^{27.5}$ −51.0 (c = 1.0, DMF) (lit.[32b] $[\alpha]_D^{27.5}$ −69.0 (c = 1.6, DMF), lit.[32c] −54.7, DMF); ^{1}H NMR (400 MHz, $CDCl_3$)[32d] δ 6.13 (s, 1H), 4.61−4.54 (m, 1H), 4.48 (m, 1H), 4.32−4.25 (m, 1H), 2.89−2.82 (m, 1H), 2.28−2.11 (m, 1H), 2.08 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.8, 170.9, 66.0, 48.8, 29.4, 22.6; IR (neat, ν max) 3305, 3072, 2991, 2920, 1777, 1656, 1542, 1450, 1431, 1379, 1300, 1221, 1180, 1154, 1020, 951 cm^{-1}; GC−MS (CI, MeOH), m/z 143.8 (M^+, 100).

(*S*)-*N*-Tosylhomoserine γ-Lactone (1e). A solution of **11f** (250 mg) in dry THF (10.0 mL) was treated with NMM (1.2 equiv, 111 μL) and IBCF (1.2 equiv, 134 μL), followed by the addition of $NaBH_4$ (3.0 equiv, 95 mg), and then quenched with MeOH (12.5 mL) and 1 M acetic acid (2 mL). The solvent was evaporated in vacuo, and 1 M citric acid was added (5 mL for method A or 1.5 mL for method B). The reaction mixture was either refluxed for 2 h (method A) or exposed to microwave irradiation (300 W) for 10 min at 65 °C. After the general workup procedure, **1f** was chromatographed using hexanes/EtOAc (7/3 to 1/1) as eluent followed by recrystallization from CH_2Cl_2/hexanes, white crystals: yield = 145 mg, 68% (method A), 100 mg, 46% (method B); mp 129−130 °C (lit.[14a] mp 130−133 °C); $[\alpha]_D^{22.0}$ +8.0 (c = 1.0, MeOH) (lit.[32c] $[\alpha]_D^{25}$ +8.0 (c = 1.0, MeOH); GC−MS (CI) m/z 256.0 ($(M + 1)^+$,100); ^{1}H NMR, ^{13}C NMR, and IR matched with the literature.[30]

(*S*)-*N*-Nosylhomoserine γ-Lactone (1f). A solution of **11f** (200 mg) in dry THF (8.0 mL) was treated with NMM (1.2 equiv, 81 μL) and IBCF (1.2 equiv, 97 μL), followed by the addition of $NaBH_4$ (3.0 equiv, 69 mg), MeOH (10.0 mL) and 1 M acetic acid (1.5 mL). The solvent was evaporated in vacuo, and 1 M citric acid (4 mL for method A or 1 mL for method B) was added. The reaction mixture was either refluxed for 2 h (method A) or exposed to microwave irradiation (300 W) for 5−10 min at 80 °C. After the general workup procedure, **1f** was chromatographed using hexanes/EtOAc (1/1) as eluent followed by recrystallization from $CHCl_3$ to afford transparent crystals (121 mg, 70%, method A), (73 mg, 42%, method B): mp 131−132 °C; $[\alpha]_D^{22.0}$ −350 (c = 0.1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 (m, 1H), 7.97 (m, 1H), 7.80−7.75 (m, 2H), 6.16 (d, J = 5.7 Hz, 1H), 4.47 (d, J = 9.0 Hz, 1H), 4.30−4.23 (m, 2H), 2.77−2.83 (m, 1H), 2.34−2.45 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.8, 147.8, 134.1, 133.8, 133.2, 130.8, 125.9, 66.0, 52.7, 31.0; IR (neat, ν max) 3345, 3089, 2998, 2960, 2924, 2883, 1782, 1593, 1539, 1442, 1376, 1355, 1221, 1167, 1124, 1058, 1021, 999 cm^{-1}. Anal. Calcd for $C_{10}H_{10}N_2O_6S$: C, 41.96; H, 3.52. Found: C, 41.89; H, 3.63.

Synthesis of (*S*)-(*N*-Cbz)-4-(2-hydroxyethyl)-5-oxo-3-oxazolidine (16b).[28] This protocol was adapted from a previous method.[27b] A solution of **11b** (1.0 equiv, 500 mg, 1.78 mmol) in dry THF (20.0 mL) at −15 °C was treated with NMM (1.2 equiv, 235 μL, 2.14 mmol) and IBCF (1.2 equiv, 282 μL, 2.14 mmol), followed by the addition of $NaBH_4$ (3.0 equiv, 203 mg, 5.35 mmol) and MeOH (20.0 mL), and the mixture was neutralized with 1 M HCl (1 mL). EtOAc (25 mL) was added to the mixture, and the organic layer was washed consecutively with 0.1 M HCl (2 mL), H_2O (5 mL), 5% aq $NaHCO_3$ (5 mL), and H_2O (2 × 5 mL), dried over $MgSO_4$, and concentrated. The product was chromatographed (50% EtOAc/hexane) leaving the product as a clear oil (335 mg, 72% yield): ^{1}H NMR ($CDCl_3$) δ (mixture of rotational isomers) 7.32 (s, 5H), 5.15 (s, 2H), 4.88 (br s, 1H), 4.80 (d, J = 11.2 Hz, 1H), 4.57−4.47 (m, 3H) 4.24−4.21 (m, 2H), 3.61 (br s, 1H), 2.49 (br s, 2H); ^{13}C NMR ($CDCl_3$) δ (mixture of rotational isomers) 175.2, 174.7, 154.8, 135.6, 135.2, 128.4, 128.2, 128.1, 127.9, 72.3, 71.8, 68.1, 67.8, 65.9, 65.4, 56.0, 55.3, 27.4, 26.9; IR (neat, ν max) 3446 (br), 2956, 1779, 1705, 1482, 1436, 1355, 1258, 1184, 1024 cm^{-1} MS, ESI, m/z 288 ($[M + Na]^+$, 100); HRMS, CI (+ve), m/z calcd for $C_{12}H_{13}NO_4$ $[M - H_2CO]^+$ 235.0845, found 235.0836.

■ ASSOCIATED CONTENT

Supporting Information. ^{1}H and ^{13}C NMR spectra for compounds **14b−c,e−f**, **11a−f**, **16b**, and **1a−f**, a variable-temperature ^{1}H NMR spectrum of **11d** in $CDCl_3$ and d_5-pyridine-d_5, ORTEP diagram, and X-ray data for the crystal of **1f** (CIF) (CCDC no. 807944). This material is available free of charge via the Internet at http://pubs.acs.org.

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