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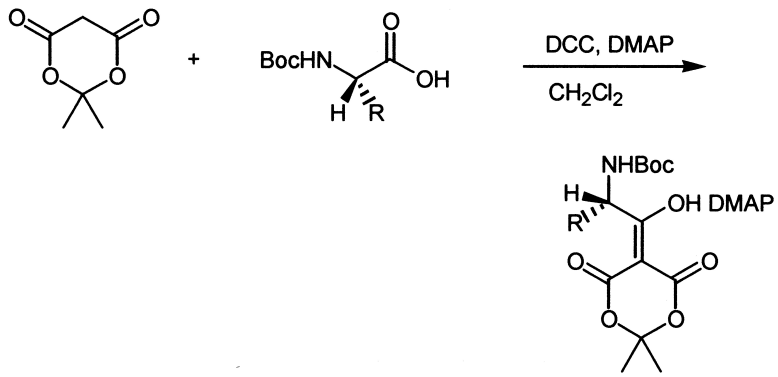

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Preparation and Improved Stability of *N*-Boc-α-amino-5-acyl Meldrum's Acids, a Versatile Class of Building Blocks for Combinatorial Chemistry

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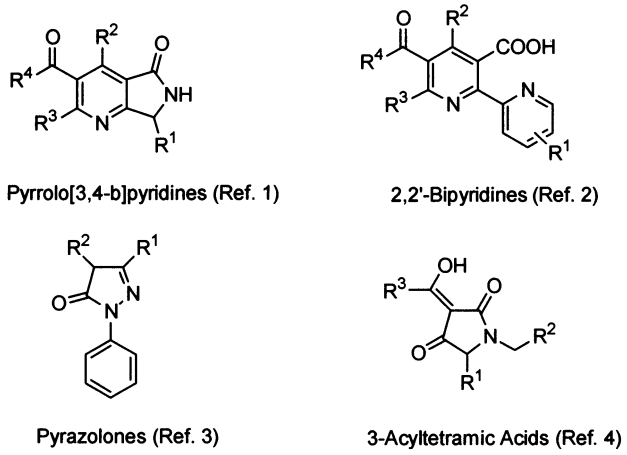
The preparation of novel *N*-Boc-α-amino-5-acyl Meldrum's acids is described. The synthetic inaccessibility and instability of several of these products have led to the development of a protocol that allows the synthesis of their corresponding 4-(dimethylamino)pyridine (DMAP) salts (5-AMA-DMAP's), which exhibit superior stability compared to that of the free 5-AMA. A simple and expedient ion-exchange method was developed for the quantitative removal of DMAP to liberate the synthetically useful DMAP-free form when needed.

The success of every combinatorial chemistry approach is critically dependent on the availability of the necessary building blocks. In recent years, several groups have reported the use of 5-acyl Meldrum's acids (5-AMAs) **3** as key building blocks in the construction of heterocyclic combinatorial libraries by solid-phase chemistry (see Scheme 1).[1−4] However, 5-AMAs are building blocks that are not commercially available, and a search of the literature revealed only a few publications describing the actual preparation of 5-AMAs **3**.[5−8] The majority of reports deal with 5-AMAs primarily as noncharacterized intermediates for the preparation of β-ketoesters and other products.[9−12] The goal of the present work was to develop protocols for the reproducible preparation of 5-AMAs **3** with high purities and good shelf stability.

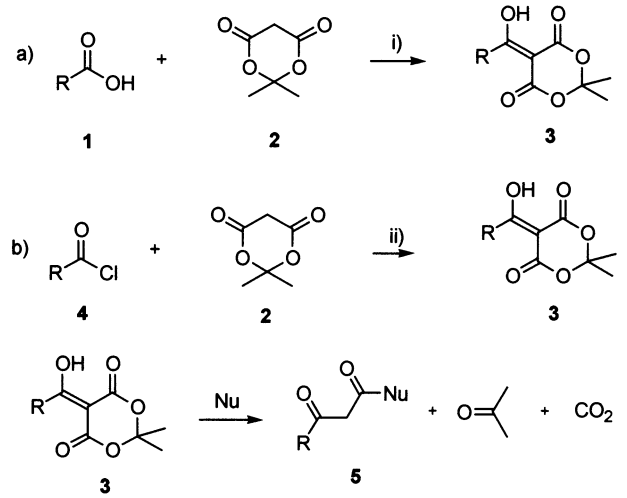
Two general methods for the preparation of 5-AMAs **3** are known and shown in Scheme 2. They are prepared either by (a) the reaction of a carboxylic acid **1** and Meldrum's acid **2** with a condensing agent such as diethylphosphorocyanidate, DCC, or isopropenyl chloroformate together with a base[6−8,14−15] or by (b) the reaction of Meldrum's acid **2** with an acid chloride **4** and a base.[5,13] By use of these methods, a few novel 5-AMAs **3** were obtained in good yields on 100 mmol scales (see Table 1). The basis of the general synthetic utility of five AMAs is through the addition of nucleophiles (Nu), which leads to valuable β-keto compounds **5** (see Scheme 2).

An important class of 5-AMAs for use as building blocks in combinatorial synthesis are the *N*-Boc-α-amino 5-AMAs.[2] Some of these compounds could be generated by DCC-mediated reaction of *N*-Boc-α-amino acids with Meldrum's acid **2** with an excess of pyridine or DMAP. However, this protocol was not always successful. It is known that unprotected α-amino 5-AMAs are themselves susceptible to fast thermal decomposition.[6,17] In our case, often the workup of the reaction mixture led to a complete decomposition of the product, thereby making it impossible to synthesize and

Scheme 1. Heterocycles Prepared by Solid-Phase Synthesis Using 5-Acyl Meldrum's Acids



Scheme 2. Preparation of 5-AMAs and Reaction with Nucleophiles[a]



[a] Reagents: (i) base, condensing agent, solvent; (ii) base, solvent.

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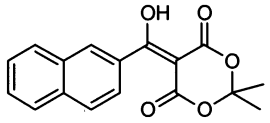
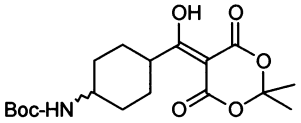
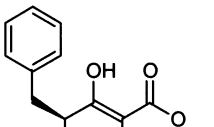
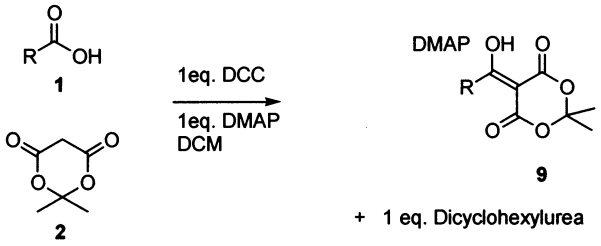
Table 1. Yields and Melting Points of Novel 5-AMAs

Structure	Yield (%)	m.p. (°C)
 **6**	81[a]	118
 **7**	100[b]	118-119
 **8**	100[b]	134-136

[a] Prepared by method B (see Experimental Section). [b] Prepared by method A.

Scheme 3. Preparation of 5-AMA-DMAPs



isolate many of the target molecules. It was speculated that the instability of the products was due to the acidic nature of the compounds, which was responsible for catalyzing the decomposition via cyclization to a tetramic acid or via deprotection of the Boc group with concomitant side reactions. In the condensation of Meldrum's acid with the *N*-Boc-α-amino acid and DCC, the use of 1 equiv of DMAP without an aqueous workup afforded directly the corresponding DMAP salts **9** of the *N*-Boc-α-amino 5-AMAs (see Scheme 3).

The solubility of the DMAP salts **9** in dichloromethane allowed for a simple workup by first filtering off the dicyclohexylurea side product followed by evaporation of the solvent. The DMAP salts **9** could be isolated as solids, whereas many of the free acids **3** had been unstable oils. Several of the DMAP salts **9** were tested for their stability and proved to be superior compounds for storage (see Table 2).

However, owing to their inert behavior in acylation reactions, the DMAP salts of *N*-Boc-α-amino 5-AMAs **9** had to be converted to the DMAP-free form **3** of the products prior to use as building blocks. Removal of DMAP with aqueous acid followed by evaporation of the extraction solvent proved to be time-consuming and in several cases led to the decomposition of the product. In addition, it was difficult to ensure the complete removal of DMAP without

Table 2. Decomposition of *N*-Boc-α-amino 5-AMAs and Their DMAP Salts on Storage

	decomposition,[b] %	
Boc-amino acid-5-AMA[a]	6 months room temp	preparation method[c]
Boc-Phe-5-AMA	7	A
Boc-Phe-5-AMA-DMAP	0	C
Boc-Ala-5-AMA	12	A
Boc-Ala-5-AMA-DMAP	0	C
Boc-Ser(Ot-Bu)-5-AMA	10	A
Boc-Ser(Ot-Bu)-5-AMA-DMAP	0	C
Boc-Glu(OtBu)-5-AMA	24	A
Boc-Glu(OtBu)-5-AMA-DMAP	0	C

[a] Phe = phenylalanine, Ala = alanine, Glu = glutamic acid, Ser = serine. [b] Calculated as the relative percent of the decomposition product acetone determined in the sample by ^{1}H NMR. [c] See procedures.

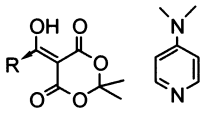
introducing some additional analytical controls. A simple and very effective procedure employing the use of ion-exchange chromatography for the removal of the DMAP was developed. The DMAP salt **9** was dissolved in dichloromethane and mixed for 10 min with 8 equiv of an acidic H^+ cation exchanger. After the ion-exchange resin was decanted off, the resulting dichloromethane solution could then be used directly in subsequent reactions. ^{1}H NMR spectra of the dichloromethane solutions showed no decomposition of the *N*-Boc-α-amino acid 5-AMAs **3** for several hours. Table 3 lists representative novel 5-AMA-DMAP salts **9**.

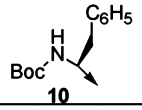
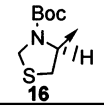
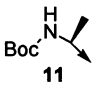
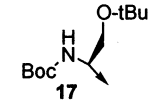
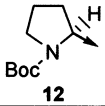
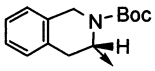
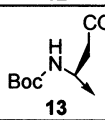
The stereochemical integrity of products with a chiral α carbon was probed with Boc-alanine and Boc-phenylalanine-derived compounds (see Scheme 4). The D,L-products were prepared from racemic Boc-phenylalanine and racemic Boc-alanine, respectively. Compound **10** and the corresponding racemate **22** were then derivatized according to Scheme 4. The sequence consisted of DMAP removal to generate **23** followed by reaction of **23** with benzylamine to give *β*-ketoamide **24**. Removal of the Boc group with TFA yielded the TFA salt **25**. This was treated with Mosher Cl reagent to yield **26**.[18] The products were then analyzed by ^{19}F NMR. The product **26** derived from starting material **22** showed two resonances of similar intensity at 69.147 and 69.309 ppm. The product derived from starting material **10** showed only one resonance, at 69.33 ppm. This result indicates that the procedure used to produce the DMAP salts of Boc-protected amino acids does not result in detectable racemization. Further supporting this finding were two experiments in which Boc-L-alanine was reacted separately at 0 °C and at room temperature to generate Boc-Ala-AMA-DMAP **11**. Both reactions were run overnight and afforded identical optical rotations of −17.5°.

Experimental Section

General. All reagents and solvents were obtained from commercial suppliers and used without further purification. ^{1}H NMR and ^{19}F NMR spectra were recorded on a Varian Gemini 400 MHz instrument. Elemental analyses were carried out at Desert Analytics Laboratories, Tucson, AZ. Optical rotations were measured on a Jasco DIP-370. Melting points are uncorrected.

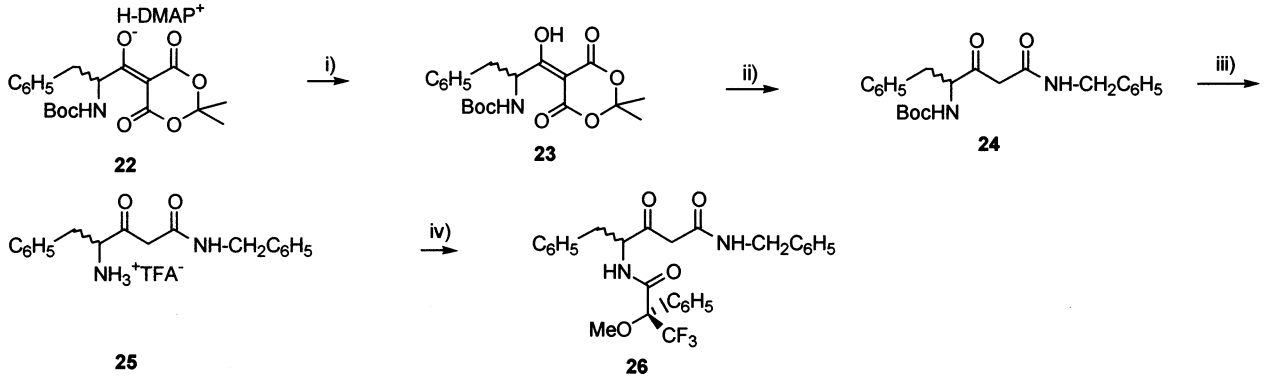
Table 3. Structures, Yields, Melting Points, and Optical Rotations of Novel 5-AMA-DMAPs



R	Yield[a]	m.p.[b]	$[\alpha]_D^{25}$[c]	R	Yield[a]	m.p.[b]	$[\alpha]_D^{25}$[c]
 **10**	95	88-90	+13.5	 **16**	100	64	-69.8
 **11**	98	129-131	-17.5	 **17**	85	117-119	+7.5
 **12**	98	153-154	-57.0	 **18**	100	72-74	+17.4
 **13**	91	50-53	+11.5	 **19**	88	154-156	
 **14**	100	137-139		 **20**	99	136-138	
 **15**	99	153		 **21**	99	63-65	

[a] Yields are in %. [b] Melting points are in °C. [c] Concentration $c = 1$ in $CHCl_3$.

Scheme 4. Stereochemical Analysis of D,L-Boc-Phe-AMA-DMAP[a]



[a] Reagents and conditions: (i) DCM, ion exchange (H^+); (ii) $C_6H_5CH_2NH_2$, toluene 70 °C; (iii) TFA/DCM 1/1; (iv) (*R*)-$C_6H_5C(OCH_3)(CF_3)COCl$, DIEA.

General Procedures. Method A. Via DCC-Mediated Condensation. A mixture of 100 mmol of carboxylic acid and 100 mmol of DCC in 100 mL of dichloromethane was stirred for 30 min with ice-cooling. Then 100 mmol of Meldrum's acid followed by 150 mmol of DMAP were added and the reaction proceeded at room temperature until judged complete by HPLC, in general 3−14 h. The insoluble urea was filtered off and washed with dichloromethane. Then the combined dichloromethane solutions were extracted twice with 1 N HCl (100 mL each), washed twice with water (100 mL each), and once with brine (100 mL). The organic phase was dried with sodium sulfate, and the solvent was evaporated. If an oil was left, trituration with hexane frequently led to a solid. Solid products were dried in a vacuum oven for 16 h at 50 mmHg at 40 °C.

Method B. Via Acid Chloride. A mixture of 165 mmol of Meldrum's acid, 400 mmol of pyridine, and 165 mL of dichloromethane was cooled to 5 °C; 1 equiv of the acid chloride was added at such a rate that the temperature could be kept below 10 °C. The reaction was allowed to stir in the ice bath for 2 h after the addition was complete, then for an additional hour at room temperature. The mixture was extracted with 2 N HCl (100 mL), then washed with water (100 mL twice) and brine (100 mL once). The organic phase was dried with sodium sulfate, and the solvent was evaporated. If an oil was left, trituration with hexane frequently led to a solid. Solid products were dried in a vacuum oven for 16 h at 50 mmHg at 40 °C.

Method C. Preparation of 5-AMA DMAP Salts. A mixture of 100 mmol of carboxylic acid and 100 mmol of

DCC in 100 mL of dichloromethane was stirred for 30 min with ice-cooling. Then 100 mmol of Meldrum's acid followed by 100 mmol of DMAP were added, and the reaction was allowed to proceed at room temperature until judged complete by HPLC, in general 3−14 h. The insoluble urea was filtered off and washed with dichloromethane, after which the combined methylene chloride solutions were concentrated to dryness. This yielded the DMAP salt. Traces of impurities were removed by a wash with the appropriate solvent, and the product was dried in a vacuum oven for 16 h at 50 mmHg at 40 °C.

Ion-Exchange Protocol. The acyl Meldrum's acid DMAP salt (2 mmol) was dissolved in 15 mL of dichloromethane, and 3 g of an acidic polystyrene sulfonic acid cation-exchange resin (Bio Rad AG50W-X2, 5.2 mequiv/g, 16 mmol) was added. The mixture was gently stirred for 20 min, after which the ion-exchanger was filtered off and washed with dichloromethane. The resulting acyl Meldrum's acid dichloromethane solution can be used directly in subsequent reactions.

General Method for the Stereochemical Analysis via Mosher Cl Derivatization, Described for 22. The acyl Meldrum's acid DMAP salt **22** (1 mmol) was dissolved in 20 mL of dichloromethane, and 2 g of an acidic polystyrene sulfonic acid cation-exchange resin (Bio Rad AG50W-X2, 5.2 mequiv/g, 16 mmol) was added. The mixture was gently stirred for 20 min, after which the ion-exchanger was filtered off and washed with dichloromethane. The resulting acyl Meldrum's acid dichloromethane solution of **23** was evaporated under high vacuum. To reconstitute the solution, 20 mL of toluene was added followed by 1.5 mmol of benzylamine. The mixture was reacted for 16 h at 70 °C. An aliquot of the reaction mixture was purified by preparative TLC. This generally yielded 10−20 mg of Boc-protected β-keto amide **24**. Deprotection of the Boc group was achieved by treatment with 5 mL of TFA in dichloromethane (1:1) for 30 min. The reaction mixture was evaporated under high vacuum and treated with 1 equiv of (*R*)-(−)-α-methoxy-α-trifluoromethylphenylacetic acid chloride and 1 equiv of DIEA in chloroform for 2 h. The crude reaction mixture was used directly for ^{19}F NMR analysis.

Characterization of Novel Compounds. 5-(Naphthylhydroxymethylidene)-2,2-dimethyl-1,3-dioxane-4,6-dione 6, prepared by method B: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.88 (s, 6H), 7.53−7.67 (m, 3H), 7.88 (d, 2H, J = 8 Hz), 7.94 (d, 1H, J = 8 Hz), 8.27 (s, 1H). Anal. Calcd for $C_{17}H_{14}O_5$: C, 68.45; H, 4.73. Found: C, 68.49; H, 4.67.

5-[4′(*R*,*S*)-*tert*-Butoxycarbonylaminocyclohexylhydroxymethylidene]-2,2-dimethyl-1,3-dioxane-4,6-dione 7, prepared by method A: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.45 (s, 9H), 1.73 (s, 6H), 1.8−2.2 (br, 8H), 3.9 (br, 2H), 4.88 (br, 1H). Anal. Calcd for $C_{18}H_{27}NO_7 \cdot 0.1$DMAP: C, 58.84; H, 7.40; N, 4.40. Found: C, 58.55; H, 7.66; N, 4.67.

5-[(2*S*)-2-*tert*-Butoxycarbonylamino)-1-hydroxy-3-phenylpropylidene]-2,2-dimethyl-1,3-dioxane-4,6-dione 8, prepared by method A: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.36 (s, 9H), 1.65 (s, 3H), 1.75 (s, 3H), 2.86 (m, 1H), 3.19 (m, 1H), 5.01 (br, 1H), 5.90 (br, 1H), 7.27 (br, 5H). Anal. Calcd for $C_{20}H_{25}NO_7$: C, 61.37; H, 6.44; N, 3.58. Found: C, 61.32; H, 6.49; N, 3.70.

5-[(2*S*)-2-*tert*-Butoxycarbonylamino)-1-hydroxy-3-phenylpropylidene]-2,2-dimethyl-1,3-dioxane-4,6-dione dimethyl-4-pyridylamine 10, prepared by method C: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.40 (s, 9H), 1.68 (s, 6H), 3.24 (s, 6H), 4.48 (m, 1H), 5.5 (m, 1H), 5.81 (m, 1H), 6.63 (d, J = 8 Hz, 2H), 7.2 (m, 5H), 8.13 (d, J = 8 Hz, 2H). Anal. Calcd for $C_{27}H_{35}N_3O_7 \cdot H_2O$: C, 61.00; H, 7.02; N, 7.90. Found: C, 61.46; H, 6.91; N, 8.18.

5-[(2*S*)-2-*tert*-Butoxycarbonylamino)-1-hydroxypropylidene]-2,2-dimethyl-1,3-dioxane-4,6-dione dimethyl-4-pyridylamine 11, prepared by method C: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.34 (d, J = 6 Hz, 3H), 1.45 (s, 9H), 1.70 (s, 6H), 3.22 (s, 6H), 5.28 (q, J = 6 Hz, 1H), 6.67 (d, J = 8 Hz, 2H), 8.31 (d, J = 8 Hz, 2H). Anal. Calcd for $C_{21}H_{31}N_3O_7$: C, 57.65; H, 7.14; N, 9.6. Found: C, 57.75; H, 7.57; N, 9.93.

5-[1-Hydroxy-(2*S*)-[1-*tert*-butoxycarbonylaminopyrrolidine-2-yl]methylidene]-2,2-dimethyl-1,3-dioxane-4,6-dione dimethyl-4-pyridylamine 12, prepared by method C: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.30 (s, 9H), 1.60 (s, 6H), 1.7−1.9 (m, 2H), 2.45−2.55 (m, 2H), 3.20 (s, 6H), 3.4−3.6 (m, 2H), 5.49 (dxd, J_1 = 3.3 Hz, J_2 = 9.8 Hz, 1H), 6.66 (d, J = 8 Hz, 2H), 8.36 (d, J = 8 Hz, 2H). Anal. Calcd for $C_{23}H_{33}N_3O_7$: C, 59.60; H, 7.18; N, 9.07. Found: C, 59.67; H, 7.13; N, 9.40.

5-[(2*S*)-2-*tert*-Butoxycarbonylamino)-1-hydroxy-3-*tert*-butoxycarbonylpropylidene]-2,2-dimethyl-1,3-dioxane-4,6-dione dimethyl-4-pyridylamine 13, prepared by method C: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.37 (s, 9H), 1.43 (s, 9H), 1.67 (s, 6H), 2.6−2.8 (br, 1H), 3.26 (s, 6H), 5.80 (br, 1H), 5.90 (br, 1H), 6.68 (d, J = 8 Hz, 2H), 8.35 (d, J = 8 Hz, 2H). Anal. Calcd for $C_{26}H_{39}N_3O_9$: C, 58.09; H, 7.31; N, 7.82. Found: C, 57.58; H, 7.55; N, 8.20.

5-(1-Hydroxy-3,3-dimethylbutylidene)-2,2-dimethyl-1,3-dioxane-4,6-dione dimethyl-4-pyridylamine 14, prepared by method C: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.06 (s, 9H), 1.69 (s, 6H), 3.03 (s, 2H), 3.17 (s, 6H), 6.64 (d, J = 8 Hz, 2H), 8.33 (d, J = 8 Hz, 2H). Anal. Calcd for $C_{19}H_{28}N_2O_5$: C, 62.62; H, 7.74; N, 7.69. Found: C, 62.23; H, 7.78; N, 7.80.

5-(Phenylhydroxymethylidene)-2,2-dimethyl-1,3-dioxane-4,6-dione dimethyl-4-pyridylamine 15, prepared by method C: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.69 (s, 6H), 3.16 (s, 6H), 6.64 (d, J = 8 Hz, 2H), 7.25−7.6 (m, 4H), 8.1 (d, J = 8 Hz, 1H), 8.37 (d, J = 8 Hz, 2H). Anal. Calcd for $C_{20}H_{22}N_2O_5 \cdot 0.25H_2O$: C, 64.07; H, 6.05; N, 7.47. Found: C, 64.15; H, 6.06; N, 7.80.

5-[1-Hydroxy-(2*S*)-[3-*tert*-butoxycarbonylaminothiazolidine-4-yl]methylidene]- 2,2-dimethyl-1,3-dioxane-4,6-dione dimethyl-4-pyridylamine 16, prepared by method C: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.45 (s, 9H), 1.68 (s, 6H), 3.12 (dxd, J_1 = 3 Hz, J_2 = 12 Hz, 1H), 3.22 (s, 6H), 3.72 (dxd, J_1 = 8 Hz, J_2 = 12 Hz, 1H), 4.62 (d, J = 8 Hz, 1H), 4.69 (d, J = 8 Hz, 1H), 5.85 (dxd, J_1 = 3 Hz, J_2 = 8 Hz, 1H), 6.67 (d, J = 8 Hz, 2H), 8.34 (d, J = 8 Hz, 2H). Anal. Calcd for $C_{22}H_{31}N_3O_7 \cdot 0.5H_2O$: C, 53.86; H, 6.57; N, 8.56. Found: C, 53.70; H, 6.68; N, 8.58.

5-[(2*S*)-2-*tert*-Butoxycarbonylamino)-1-hydroxy-3-*tert*-butoxypropylidene]-2,2-dimethyl-1,3-dioxane-4,6-dione dimethyl-4-pyridylamine 17, prepared by method C: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.1 (s, 9H), 1.42 (s, 9H), 1.66 (s, 6H), 3.21 (s, 6H), 3.7−3.8 (br, 2H), 5.6 (m, 1H), 6.65 (d, J = 8 Hz, 2H), 8.32 (d, J = 8 Hz, 2H). Anal. Calcd for $C_{25}H_{39}N_3O_8$: C, 58.92; H, 7.71; N, 8.25. Found: C, 58.88; H, 7.73; N, 8.42.

5-[1-Hydroxy-(3*S*)-[2-*tert*-butoxycarbonylaminotetrahydroisoquinoline-3-yl]methylidene]- 2,2-dimethyl-1,3-dioxane-4,6-dione dimethyl-4-pyridylamine 18, prepared by method C: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.39 (s, 9H), 1.65 (s, 6H), 3.11 (dxd, J_1 = 4 Hz, J_2 = 16 Hz, 1H), 3.20 (s, 6H), 3.34 (dxd, J_1 = 4 Hz, J_2 = 16 Hz, 1H), 4.72 (s, 2H), 6.09 (q, J = 4 Hz, 1H), 6.50 (d, J = 8 Hz, 2H), 7.05−7.2 (m, 4H), 7.88 (d, J = 8 Hz, 2H). Anal. Calcd for $C_{28}H_{35}N_3O_7 \cdot 0.5H_2O$: C, 62.90; H, 6.78; N, 7.86. Found: C, 62.57; H, 6.70; N, 7.98.

***N*-(2-((2,2-Dimethyl-4,6-dioxo(1,3-dioxane-5-ylidene))-2-hydroxyethyl)-*tert*-butoxy-*N*-methylcarboxamide dimethyl-4-pyridylamine 19, prepared by method C:** ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.44 (s, 9H), 1.65 (s, 6H), 2.90 (s, 3H), 3.22 (s, 6H), 4.55 (s, 2H), 6.67 (d, J = 8 Hz, 2H), 8.37 (d, J = 8 Hz, 2H). Anal. Calcd for $C_{21}H_{31}N_3O_7 \cdot 0.25H_2O$: C, 57.06; H, 7.18; N, 9.51. Found: C, 57.16; H, 7.50; N, 9.69.

5-[2-*tert*-Butoxycarbonylamino-*N*-methyl)-1-hydroxyethylidene]-2,2-dimethyl-1,3-dioxane-4,6-dione dimethyl-4-pyridylamine 20, prepared by method C: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.46 (s, 9H), 1.67 (s, 6H), 3.24 (s, 6H), 4.46 (d, J = 5 Hz, 2H), 5.83 (br, 1H), 6.70 (d, J = 8 Hz, 2H), 8.32 (d, J = 8 Hz, 2H). Anal. Calcd for $C_{20}H_{29}N_3O_7$: C, 56.73; H, 6.90; N, 9.92. Found: C, 56.67; H, 6.89; N, 9.90.

5-(Benzylhydroxymethylidene)-2,2-dimethyl-1,3-dioxane-4,6-dione dimethyl-4-pyridylamine 21, prepared by method C: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.64 (s, 6H), 3.18 (s, 6H), 4.35 (s, 2H), 6.58 (d, J = 8 Hz, 2H), 7.17 (t, J = 7 Hz, 1H), 7.26 (t, J = 7 Hz, 2H), 7.34 (d, J = 7 Hz, 1H), 8.14 (d, J = 8 Hz, 2H). Anal. Calcd for $C_{21}H_{24}N_2O_5$: C, 65.61; H, 6.29; N, 7.29. Found: C, 65.67; H, 6.35; N, 7.44.

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