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Chiral Iminoesters Derived from D-Glyceraldehyde in [3 + 2] Cycloaddition Reactions. Asymmetric Synthesis of a Key Intermediate in the Synthesis of Neuramidinase Inhibitors

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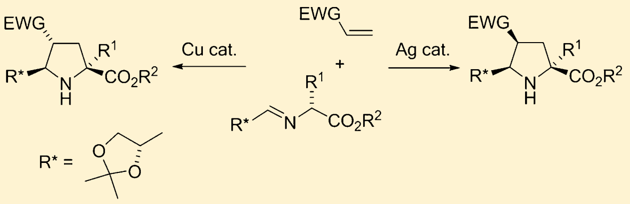
Supporting Information

ABSTRACT: Silver-catalyzed *endo*-selective and copper-catalyzed *exo*-selective asymmetric [3 + 2] cycloadditions of acrylates to chiral iminoesters derived from D-glyceraldehyde have been investigated. The reaction diastereoselectively provides highly functionalized pyrrolidines. This approach was used to develop the first asymmetric synthesis of a key intermediate in the synthesis of pyrrolidine influenza neuramidinase inhibitors.



INTRODUCTION

A wide variety of natural and unnatural biologically active compounds and therapeutics have the pyrrolidine ring as a structural motif. Depending on the substitution pattern and functionality, pyrrolidine-based compounds have found applications as effective antitumor, antidepressant, antihypertensive, antiarthritic, antibacterial, antithrombotic, or analgesic agents, among others.[1] In addition, pyrrolidines are now considered to be privileged ligand architectures,[2] and their use gives rise to excellent results in many useful organocatalyzed transformations.[3] Hence, the synthesis of appropriately substituted enantiopure pyrrolidines is quite a challenging area in organic synthesis.

Among the different approaches for the asymmetric synthesis of pyrrolidines, the diastereoselective 1,3-dipolar cycloaddition reaction of azomethine ylides with electron-deficient alkenes as dipolarophiles provides a straightforward and atom-economical method for the preparation of optically active polyfunctionalized pyrrolidine derivatives.[4]

Imines derived from glyceraldehyde acetonide have proven to be excellent synthetic precursors to obtain bioactive compounds with very different structures in enantiomerically pure form.[5] Starting imines can be obtained from inexpensive D-mannitol,[6] which in turn comes from renewable sources and reacts with different nucleophiles in a highly diastereoselective manner to provide useful and versatile chiral intermediates. Encouraged by this behavior, we decided to investigate the use of chiral iminoesters derived from glyceraldehyde acetonide as azomethine ylide precursors in the synthesis of chiral pyrrolidines. In the only precedent in the literature on the use of glyceraldehyde-derived imines in azomethine ylide cycloadditions Trunkfield et al.[7] describe the reaction of imine prepared by reaction of L-alanine benzyl ester and D-glyceraldehyde acetonide with *N*-phenylmaleimide, dimethyl maleate, or dimethyl fumarate in the presence of silver(I) acetate. With *N*-phenylmaleimide and dimethyl fumarate in each case a single major *endo* diastereoisomer was obtained with 96 and 44% yield, respectively, whereas with dimethyl maleate a 1.2/1 mixture of *endo* and *exo* diastereoisomer was obtained in 94% yield.

RESULTS AND DISCUSSION

Metalation of iminoesters in the presence of a base is a simple and mild procedure for the in situ generation of azomethine ylides, and this approach has clear advantages over other known methods.[8]

The resulting metallo-dipoles have a perfectly controlled geometry that allows the diastereoselective synthesis of *endo* or *exo* adducts depending on the metal employed as cocatalyst. Silver dipoles usually lead to *endo*-cycloadducts in a highly diastereoselective manner,[9] whereas with copper dipoles *exo*-diastereoselectivity is almost complete.[10]

On the basis of these precedents, we began our investigation by testing the reaction of ethyl acrylate and iminoester **1a** with AgOAc (20 mol %) as the catalyst and Et_3N (20 mol %) as the base (Table 1, entry 1). The reaction in CH_3CN at room temperature for 20 h afforded a mixture of two *endo*-pyrrolidines (***endo*-2a-M** and ***endo*-2a-m**) and one *exo*-pyrrolidine (***exo*-2a-M**) from which the major *endo* adduct was obtained in 40% yield.[11] *Endo*/*exo* diastereoselectivity was determined as 75/25, whereas the ratio of *endo* adducts was 77/23.

Adducts were tosylated prior to determination of the absolute configuration. Single-crystal X-ray diffraction studies of crystalline tosylated derivatives **3** and **4**, obtained from ***endo*-2a-M** and ***endo*-2a-m**, respectively as shown in Scheme 1, showed the unequivocal absolute configuration of the major

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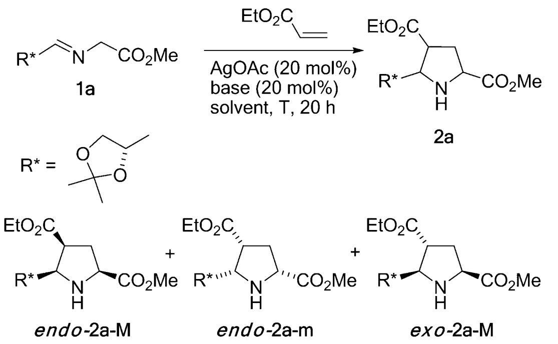
Table 1. Screening Studies on the Catalytic Asymmetric 1,3-Dipolar Cycloaddition of Iminoester 1a with Ethyl Acrylate

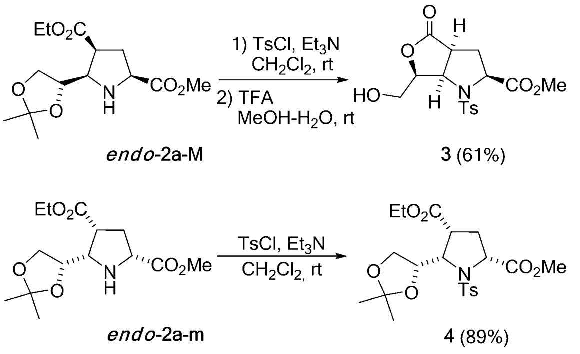


entry	base	solvent	T (°C)	yield^a (%)	endo/exo^b	rd (endo)^b
1	Et_3N	CH_3CN	rt	40	75/25	77/23
2	DIPEA	CH_3CN	rt	41	79/21	75/25
3	K^{t}BuO	CH_3CN	rt	38	78/22	76/24
4	DBN	CH_3CN	rt	41	79/21	76/24
5	DBU	CH_3CN	rt	46	79/21	79/21
6	DBU^c	CH_3CN	rt	33	73/27	80/20
7	DBU	Toluene	rt	60	94/6	83/17
8	DBU	CH_2Cl_2	rt	50	82/18	79/21
9	DBU	Et_2O	rt	49	81/19	79/21
10	DBU	THF	rt	56	90/10	81/19
11	DBU	toluene	0	56	96/4	84/16
12	DBU	toluene	−20	29	94/6	88/12

^{a}Yield of major *endo* adduct determined by ^{1}H NMR spectroscopy using trimethoxybenzene as internal standard. ^{b}Determined by ^{1}H NMR spectroscopy. ^{c}The reaction was performed using 120 mol % of AgOAc and 120 mol % of DBU.

endo product to be (2*S*,4*S*,5*R*) and the minor *endo* adduct to be (2*R*,4*R*,5*S*).

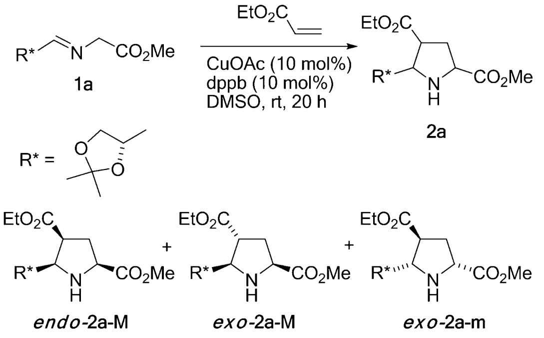
Scheme 1. Synthesis of Tosyl Derivatives 3 and 4 for X-ray Diffraction Studies



A survey of the influence of reaction conditions on yield and stereoselectivity was performed. The nature of the base does not appear to have a dramatic effect on *endo*/*exo* or *endo* stereoselectivity, although a slightly higher yield of the major *endo* adduct was obtained when DBU was used as the base. An increase in the amount of silver salt and base led to a decrease in yield without an improvement in the stereoselectivity (Table 1, entry 6). Evaluation of the impact of the solvent on the reaction revealed that best results were obtained when the reaction was carried out in toluene (Table 1, entry 7). Finally, the effect of temperature was examined in an effort to further improve the stereoselectivity. Similar results were obtained on working at 0 °C (Table 1, entry 11), and an additional decrease in temperature led to a marked decrease in the reaction yield (Table 1, entry 12).

The *exo*-selective 1,3-dipolar cycloaddition of iminoester **1a** with ethyl acrylate was investigated. The reaction of **1a** and ethyl acrylate using 10 mol % of CuOAc and 10 mol % of 1,4-bis(diphenylphosphino)butane (dppb) in DMSO at room temperature for 20 h proceeded smoothly to afford a 95% yield of mainly the adduct ***exo*-2a-M** [*exo*/*endo* = 95/5, rd (*exo*) = 93/7] (Scheme 2).

Scheme 2. CuOAc/dppb-Catalyzed 1,3-Dipolar Cycloaddition of Iminoester 1a with Ethyl Acrylate



Under optimized reaction conditions the generality and substrate scope were assessed, and the results are summarized in Table 2.

The effect of varying the size of the ester moiety of the iminoglycinate was not significant in terms of diastereoselectivity and led to a decrease in yield for both silver dipoles (Table 2, entries 1 and 2) and copper dipoles (Table 2, entries 8 and 9).

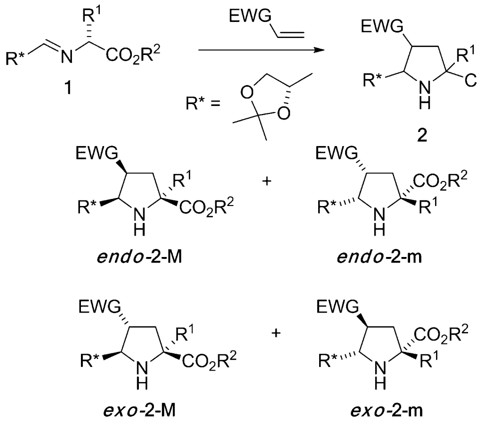
Asymmetric multicomponent reactions have some advantages over other synthetic strategies,[12] and Ag(I)- and Cu(I)-catalyzed [C + NC + CC] coupling processes using chiral glycinesultam have proven useful for the *endo*- and *exo*-selective asymmetric synthesis of functionalized pyrrolidines.[13,14] Thus, the asymmetric multicomponent [C + NC + CC] coupling reaction[15] using D-glyceraldeyde acetonide, *tert*-butyl glycinate, and ethyl acrylate was tested.

In the Cu(I)-catalyzed reaction the yield increased markedly (Table 2, entry 10), whereas the Ag(I)-catalyzed reaction gave pyrazolines **endo-2b-M**, **endo-2b−m**, and **exo-2b-M** in the same yield as in the reaction of *tert*-butyliminoglycinate **1b** with ethyl acrylate (Table 2 entry 3).[16] This result is due to the formation of ca. 27% of oxazolidine **5** (Figure 1) derived from the condensation of *tert*-butyliminoglycinate with D-glyceraldehyde acetonide.

The introduction of a larger group in the ester moiety of the acrylate (^{t}Bu) led to a decrease in *endo*/*exo* selectivity and yield for silver dipoles (Table 2, entry 4), whereas for copper dipoles this change led to the formation of ***exo*-2a′-M** as the only adduct in very high yield (Table 2, entry 11). The reaction also works well using phenyl vinyl sulfone instead of ethyl acrylate (Table 2, entries 5 and 12).

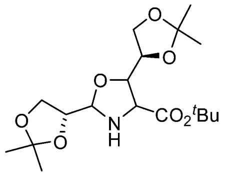
The use of iminoesters derived form other amino acids, alanine and phenylalanine, led to complete *endo*- and *exo*-selectivity in Ag(I)- and Cu(I)-catalyzed reactions, respectively (Table 2 entries 6 and 7 and 13 and 14) and diastereofacial

Table 2. Substrate Scope of the 1,3-Dipolar Cycloaddition of Acrylates with Various Iminoesters 1[a]



entry	cond	R^1/R^2	EWG	product	yield[b] (%)	*endo*/*exo*[c]	rd[c]
1	A	H/Me (**1a**)	CO_2Et	**2a**	60	94/6	83/17
2	A	H/^{t}Bu (**1b**)	CO_2Et	**2b**	49	92/8	87/13
3	A	H/^{t}Bu[d]	CO_2Et	**2b**	50	93/7	85/15
4	A	H/Me (**1a**)	$CO_2{}^tBu$	**2a′**	48	86/14	82/18
5	A	H/Me (**1a**)	SO_2Ph	**2c**	65	81/19	>95/5
6	A	Me/Me (**1c**)	CO_2Et	**2d**	72	>95/5	72/28
7	A	Bn/Me (**1d**)	CO_2Et	**2e**	64	>95/5	67/33
8	B	H/Me (**1a**)	CO_2Et	**2a**	88	5/95	93/7
9	B	H/^{t}Bu (**1b**)	CO_2Et	**2b**	57	<5/>95	93/7
10	B	H/^{t}Bu[d]	CO_2Et	**2b**	86	<5/>95	93/7
11	B	H/Me (**1a**)	$CO_2{}^tBu$	**2a′**	92	<5/>95	90/10
12	B	H/Me (**1a**)	SO_2Ph	**2c**	55	<5/>95	90/10
13	B	Me/Me (**1c**)	CO_2Et	**2d**	75	<5/>95	>95/5
14	B	Bn/Me (**1d**)	CO_2Et	**2e**	55	<5/>95	>95/5

[a] The reaction was carried out using (A) 20 mol % of AgOAc and 20 mol % of DBU in toluene at room temperature; (B) 10 mol % of CuOAc and 10 mol % of (dppb) in DMSO at room temperature. [b] Yield of major *endo* or *exo* adduct determined by ^{1}H NMR spectroscopy using trimethoxybenzene as internal standard. [c] Determined by ^{1}H and/or ^{13}C NMR spectroscopy. [d] [C + NC + CC] coupling reaction using D-glyceraldeyde acetonide *tert*-butyl glycinate and ethyl acrylate.



5

Figure 1. Structures of oxazolidine **5** obtained as byproduct in Ag(I)-catalyzed [C + NC + CC] coupling.

selectivity in the *endo* attack for silver dipoles decreased to some extent.

Neuraminidase (NA) is one of the two surface glycoproteins of the influenza virus, and it is regarded as an attractive target for antiviral drug development.[17] In this context, trisubstituted pyrrolidine derivatives have emerged as new neuraminidase inhibitors with potent activities.[18]

The continuous evolution of antibiotic-resistant influenza strains makes the synthesis of new neuraminidase inhibitors an important target. To this end, racemic aldehyde **12** has proven to be a versatile intermediate for the synthesis of many of these pyrrolidine derivatives,[18c] and it can be used for the synthesis of other new derivatives.

As an example of the potential of the synthetic approach described in this paper for the synthesis of biologically active compounds, we have developed the synthesis of enantiomerically pure aldehyde **12** using 1,3-dipolar cycloaddition of iminoesters derived from D-glyceraldehyde as the key step (Scheme 3). Orthogonally protected 2,4,5-trisubstituted pyrrolidine **6** was obtained in 73% isolated yield by Ag-catalyzed [3 + 2] dipolar cycloaddition of *tert*-butyl iminoester **1b** and methyl acrylate. *N*-Boc protection of compound **6** followed by chemoselective reduction of the methyl ester at C4 in *N*-Boc-derivative **7** with $NaBH_4$–MeOH in the presence of a catalytic amount of $Na(OAc)_3BH$ according to Xie et al.[19] resulted in primary alcohol **8**, which was silylated with *tert*-butyldimethylsilyl chloride to afford **9**. $SnCl_2$-promoted chemoselective deprotection of the acetonide moiety led to **10**, which was oxidized with sodium periodate to produce aldehyde **11** with a 2,5-*cis* disposition.

Finally, DBU-promoted epimerization at C5 provided chiral aldehyde **12** with the required 2,5-*trans* disposition with a 93/7 diastereomeric ratio and in 41% overall yield from pyrrolidine **6**. The use of imines derived from L-glyceraldehyde would give the opposite enantiomer.

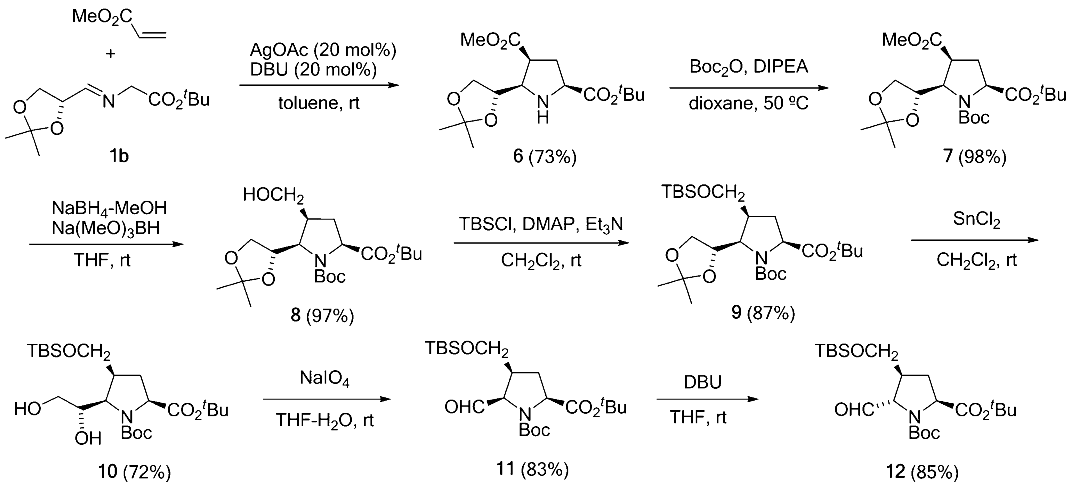
■ CONCLUSION

In summary, we have developed a stereoselective and flexible methodology for the synthesis of 2,4,5-trisubstituted pyrrolidines and 2,2,4,5-tetrasubstituted pyrrolidines with a well-defined stereochemistry from imines derived from glyderaldehyde. Silver-catalyzed [3 + 2] cycloaddition with acrylates was highly *endo*-selective and copper-catalyzed [3 + 2] cycloaddition with acrylates occurred with total *exo*-selectivity. The synthetic utility of the resulting adducts has been demonstrated by the transformation of compound **6** into compound **12**, a key intermediate in the synthesis of neuraminidase inhibitors, in just six steps and in 41% overall yield. This is the first asymmetric synthesis described in the literature for compound **12**.

■ EXPERIMENTAL SECTION

General Procedures. Melting points were determined in open capillary tubes and are not corrected. FT-IR spectra of oils were recorded as thin films on NaCl plates, and FT-IR spectra of solids were recorded as KBr pellets; ν_{max} values expressed in cm^{-1} are given for the main absorption bands. Optical rotations were measured on a digital polarimeter at λ 589 nm and 25 °C in cells with 1 or 10 cm path length, $[\alpha]_D$ values are given in 10^{-1} deg·cm·g^{-1}, and concentrations are given in g/100 mL. ^{1}H NMR and ^{13}C NMR spectra were acquired at room temperature unless otherwise stated at 400 or 300 and 100 or 75 MHz, respectively, using a 5 mm probe. The chemical shifts (δ) are reported in parts per million relative to δH 7.26/δC 77.0 (central line of t) for $CHCl_3/CDCl_3$. Coupling constants (*J*) are reported in hertz. The splitting patterns are reported as: s (singlet), d (doublet), q (quartet), dd (doublet of doublets), m (multiplet), bs (broad singlet),

Scheme 3. Synthesis of Key Intermediate 12



ddd (doublet of doublets of doublets). Attached proton test (APT) spectra were taken to determine the types of carbon signals. Selective ge-1D NOESY experiments were performed with gradient pulses in the mixing time. Spectra were acquired at 300 K with optimized mixing times and 128 transients per spectrum using the Bruker standard selrogp pulse program. Special precautions such as degassing of the sample were not taken. High-resolution mass measurements were made using a microTOF analyzer, and spectra were recorded from methanolic solutions using the positive electrospray ionization mode (ESI+).

Reagents and Materials. All reagents for reactions were of analytical grade and were used as obtained from commercial sources. Reactions were carried out using anhydrous solvents. Reactions were magnetically stirred and whenever possible monitored by TLC. TLC was performed on precoated silica gel polyester plates and products were visualized using UV light (254 nm), ninhydrin, and ethanolic phosphomolybdic acid solution followed by heating. Column chromatography was performed using silica gel (Kiesegel 60, 230–400 mesh).

X-ray Diffraction. The X-ray diffraction data were collected at room temperature on a four-circle diffractometer, using graphite-monochromated Mo Kα radiation (λ = 0.71073 Å). Reflections were measured in the θ /2θ-scan mode in the θ range 2.85 to 29.02°. The structure was solved by direct methods using SHELXLS7, and refinement was performed using SHELXL 97 by the full-matrix least-squares technique with anisotropic thermal factors for heavy atoms. Hydrogen atom bonded to nitrogen was located on the difference Fourier map and refined with an isotropic thermal factor, all other hydrogen atoms were calculated at idealized positions, and during refinement they were allowed to ride on their carrying atom with an isotropic thermal factor fixed to 1.2 times the U_{eq} value of the carrier atom. Colorless single crystals of **3** were obtained by slow evaporation from an ethanol solution. Crystallographic data: crystal size 0.21 × 0.17 × 0.12 mm^3. M = 369.38, crystal system orthorhombic, unit cell dimensions a = 7.0511(2), b = 9.8605(2), c = 24.4965(6) Å, V = 1703.18(7) Å^3, T = 293(2) K, space group P212121, absorption coeficient μ (Mo Kα) = 0.229 mm^{-1}, 12809 reflections collected 3844 unique [R(int) = 0.0334] which were used in all calculations. Final R indices [$I > 2\sigma(I)$] R1 = 0.0412, wR2 = 0.0900,R indices (all data) R1 = 0.0541, wR2 = 0.0969. Colorless single crystals of **4** were obtained by slow evaporation from an ethanol solution. Crystallographic data: crystal size 0.22 × 0.12 × 0.10 mm^3. M = 455.51, crystal system triclinic, unit cell dimensions a = 8.2700(12), b = 9.0465(19), c = 16.281(3) Å, α = 83.342(17)°, β = 77.216(14)°, γ = 87.954(15)°, V = 1179.8(4) Å^3, T = 293(2) K, space group P1, absorption coeficient μ (Mo Kα) = 0.182 mm^{-1}, 8762 reflections collected 0.2320 unique [R(int) = 0.0580] which were used in all calculations. Final R indices [$I > 2\sigma(I)$] R1 = 0.0978, wR2 = 0.0762, R indices (all data) R1 = 0.2437, wR2 = 0.3064.

*Synthesis of Crude (S)-Methyl N-[(2,2-Dimethyl-1,3-dioxolan-4-yl)methylidene]glycinate (**1a**).* To a solution of glycine methyl ester hydrochloride (2.52 g, 20.1 mmol) in water (5 mL) at room temperature was added a solution of K_2CO_3 (4.16 g, 30.1 mmol) in water (15 mL). After stirring, the solution was extracted with CH_2Cl_2 (3 × 20 mL), and the combined organic layers were dried over anhydrous $MgSO_4$ and filtered. To the solution containing the glycine methyl ester were added successively 2,3-*O*-isopropylidene-D-glyceraldehyde (1.31 g, 10.0 mmol) and anhydrous $MgSO_4$ (3.0 g), and the resulting suspension was stirred for 2 h at room temperature. The reaction mixture was filtered and evaporated in vacuo to afford 2.20 g of crude imine **1a** of 60% purity (65% yield), as determined by ^{1}H NMR using 1,3,5-trimethoxybenzene as an internal standard.[20] Crude imine **1a** was used without further purification in the next reaction: oil; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.35 (s, 3H), 1.41 (s, 3H), 3.71 (s, 3H), 3.97 (dd, J = 8.6, 6.0 Hz, 1H), 4.12–4.25 (m, 3H), 4.61–4.67 (m, 1H), 7.65 (ddd, J = 5.0, 1.3, 1.3 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 25.2 (CH_3), 26.3 (CH_3), 52.1 (CH_3), 61.1 (CH_2), 67.2 (CH_2), 76.7 (CH), 110.3 (C), 168.1 (C), 169.8 (C).

*Synthesis of Crude (S)-tert-Butyl N-[(2,2-Dimethyl-1,3-dioxolan-4-yl)methylidene]glycinate (**1b**).* To a solution of glycine *tert*-butyl ester hydrochloride (1,68 g, 10.0 mmol) in water (3 mL) at room temperature was added a solution of K_2CO_3 (2.08 g, 15.0 mmol) in water (7 mL). After stirring, the solution was extracted with CH_2Cl_2 (3 × 10 mL), and the combined organic layers were dried over anhydrous $MgSO_4$ and filtered. To the solution containing the glycine methyl ester were added successively 2,3-*O*-isopropylidene-D-glyceraldehyde (1.31 g, 10.0 mmol) and anhydrous $MgSO_4$ (3.0 g), and the resulting suspension was stirred for 2 h at room temperature. The reaction mixture was filtered, and evaporated in vacuo to afford 2.55 g of crude imine **1b** of 50% purity (52% yield), as determined by ^{1}H NMR using 1,3,5-trimethoxybenzene as an internal standard.[20] Crude imine **1b** was used without further purification in the next reaction: oil; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.39 (s, 3H), 1.45 (s, 3H), 1.46 (s, 9H), 3.98 (dd, J = 8.6, 6.1 Hz, 1H), 4.08 (d, J = 16.2, 1H), 4.15 (d, J = 16.2, 1H), 4.22 (dd, J = 8.6, 6.9 Hz, 1H), 4.64 (ddd, J = 6.9, 6.1, 4.8 Hz, 1H), 7.66 (ddd, J = 4.8, 1.3, 1.3 Hz, 1H).

*Synthesis of Crude (S)-Methyl N-[(2,2-Dimethyl-1,3-dioxolan-4-yl)methylidene]alaninate (**1c**).* To a solution of alanine methyl ester hydrochloride (2.79 g, 20.0 mmol) in water (5 mL) at room temperature was added a solution of K_2CO_3 (4.16 g, 30.1 mmol) in water (15 mL). After stirring, the solution was extracted with CH_2Cl_2 (3 × 20 mL), and the combined organic layers were dried over anhydrous $MgSO_4$ and filtered. To the solution containing the alanine methyl ester were added successively 2,3-*O*-isopropylidene-D-glyceraldehyde (1.31 g, 10.0 mmol) and anhydrous $MgSO_4$ (3.0 g), and the resulting suspension was stirred for 2 h at room temperature. The reaction mixture was filtered and evaporated in vacuo to afford 2.70 g of crude imine **1c** of 65% purity (81% yield), as determined by ^{1}H

NMR using 1,3,5-trimethoxybenzene as an internal standard.[20] Crude imine **1c** was used without further purification in the next reaction: oil; ^{1}H NMR (CDCl$_3$, 400 MHz) δ 1.38 (s, 3H), 1.40 (d, J = 6.9 Hz, 3H), 1.43 (s, 3H), 3.72 (s, 3H), 3.93 (dd, J = 8.6, 6.0 Hz, 1H), 3.98 (q, J = 6.9 Hz, 1H), 4.20 (dd, J = 8.6, 6.9 Hz, 1H), 4.63 (ddd, J = 6.9, 6.0, 4.9 Hz, 1H), 7.68 (dd, J = 4.9, 0.5 Hz, 1H).

*Synthesis of Crude (S)-Methyl N-[(2,2-Dimethyl-1,3-dioxolan-4-yl)methylidene]phenylalaninate (**1d**).* To a solution of phenylalanine methyl ester hydrochloride (2.16 g, 10.0 mmol) in water (7 mL) at room temperature was added a solution of K$_2$CO$_3$ (2,08 g, 15.0 mmol) in water (7 mL). After stirring, the solution was extracted with CH$_2$Cl$_2$ (3 × 20 mL), and the combined organic layers were dried over anhydrous MgSO$_4$ and filtered. To the solution containing the alanine methyl ester were added successively 2,3-*O*-isopropylidene-D-glyceraldehyde (1.31 g, 10.0 mmol) and anhydrous MgSO$_4$ (3.0 g), and the resulting suspension was stirred for 2 h at room temperature. The reaction mixture was filtered and evaporated in vacuo to afford 3.05 g of crude imine **1d** of 75% purity (78% yield) as an almost equimolecular E/Z mixture, as determined by ^{1}H NMR using 1,3,5-trimethoxybenzene as an internal standard.[20] Crude imine **1d** was used without further purification in the next reaction: oil; ^{1}H NMR (CDCl$_3$, 400 MHz) δ 1.28 and 1.48 (s, 3H), 1.34 and 1.48 (s, 3H), 3.01 and 3.04 (dd, J = 13.5, 10.0 Hz and J = 13.5, 8.5 Hz, 1H), 3.30 and 3.30 (dd, J = 13.5, 4.0 Hz and J = 13.5, 6.5 Hz, 1H), 3.60 and 3.99 (dd, J = 8.5.5, 6.5 Hz and J = 10.0, 4.3 Hz, 1H), 3.74 and 3.79 (s, 3H), 3.91 and 4.02 (dd, J = 8.6, 5.7 Hz and J = 8.6, 6.8 Hz, 1H), 4.03 and 4.20 (dd, J = 8.6, 5.2 Hz and J = 8.6, 6.9 Hz, 1H), 4.54 and 4.57 (ddd, J = 6.8, 6.7, 5.2 Hz and J = 6.89, 5.7, 4.8 Hz, 1H); 7.09–7.36 (m, 6H).

General Procedure for Silver Acetate Catalyzed 1,3-Dipolar Cycloadditions. To a stirred suspension of crude imine **1** (3.0 mmol) and AgOAc (100 mg, 0.6 mmol) in dry toluene (30 mL) under argon at room temperature were sequentially added the alkene used as dipholarophile (6.0 mmol) and DBU (91 mg, 0.6 mmol). The reaction mixture was stirred in the dark at room temperature for 24 h. The mixture was partitioned between saturated aqueous NH$_4$Cl (30 mL) and CH$_2$Cl$_2$ (3 × 30 mL). The combined organic layers were filtered through a short Celite path, dried over anhydrous MgSO$_4$, filtered, and concentrated under reduced pressure. The crude mixture of cycloadducts was purified by flash chromatography.

General Procedure for Copper(I) Acetate Catalyzed 1,3-Dipolar Cycloadditions. A suspension of CuOAc (37 mg, 0.3 mmol) and 1,4-bis(diphenylphosphino)butane (128 mg, 0,3 mmol) in dry DMSO (20 mL) was stirred at room temperature under argon for 1 h. To this mixture were sequentially added crude imine **1** (3.0 mmol) and the alkene used as dipholarophile (9.0 mmol). The reaction mixture was stirred in the dark at room temperature for 24 h. The mixture was partitioned between saturated aqueous NH$_4$Cl (30 mL) and CH$_2$Cl$_2$ (3 × 30 mL). The combined organic layers were washed with brine, filtered through a short Celite path, dried over anhydrous MgSO$_4$, filtered, and concentrated under reduced pressure. The crude mixture of cycloadducts was purified by flash chromatography.

General Procedure for Silver Acetate Catalyzed Multicomponent [C + NC + CC] Coupling Reaction. To a stirred mixture of *tert*-butyl glycinate (394 mg, 3.0 mmol) and AgOAc (100 mg, 0.6 mmol) in dry toluene (30 mL) under argon and at room temperature were sequentially added 2,3-*O*-isopropylidene-D-glyceraldehyde (390 mg, 3.0 mmol), ethyl acrylate (601 mg, 6.0 mmol), and DBU (91 mg, 0.6 mmol). The reaction mixture was stirred in the dark at room temperature for 24 h. The mixture was partitioned between saturated aqueous NH$_4$Cl (30 mL) and CH$_2$Cl$_2$ (3 × 30 mL). The combined organic layers were filtered through a short Celite path, dried over anhydrous MgSO$_4$, filtered, and concentrated under reduced pressure. The crude mixture of cycloadducts was purified by flash chromatography.

General Procedure for Copper(I) Acetate Catalyzed Multicomponent [C + NC + CC] Coupling Reaction. A suspension of CuOAc (37 mg, 0.3 mmol) and 1,4-bis(diphenylphosphino)butane (128 mg, 0,30 mmol) in dry DMSO (20 mL) was stirred at room temperature under argon for 1 h. To this mixture were sequentially added 2,3-*O*-isopropylidene-D-glyceraldehyde (390 mg, 3.0 mmol), *tert*-butyl glycinate (394 mg, 3.0 mmol), and ethyl acrylate (901 mg, 9.0 mmol). The reaction mixture was stirred in the dark at room temperature for 24 h. Aqueous NH$_4$Cl (30 mL) and CH$_2$Cl$_2$ (3 × 30 mL) were added. The combined organic layers were filtered through a short Celite path, dried over anhydrous MgSO$_4$, filtered, and concentrated under reduced pressure. The crude mixture of cycloadducts was purified by flash chromatography.

*(2S,4S,5R)-4-Ethyl 2-Methyl 5-[(S)-2,2-dimethyl-1,3-dioxolan-4-yl]pyrrolidine-2,4-dicarboxylate (**endo-2a-M**).* According to the general procedure for silver acetate catalyzed 1,3-dipolar cycloadditions described above, 415 mg (46% yield) of ***endo*-2a-M** was obtained after column chromatography (first eluent: Et$_2$O, second eluent: Et$_2$O/acetone, 9:1): colorless oil; $[\alpha]^{22}_{D}$ = −34.0 (c 1.00, CHCl$_3$); IR (neat) 3306, 1739; ^{1}H NMR (CDCl$_3$, 400 MHz) δ 1.23 (t, J = 7.2 Hz, 3H), 1.31 (s, 3H), 1.41 (s, 3H), 2.27 (ddd, J = 13.4, 9.5, 7.5 Hz, 1H), 2.35 (ddd, J = 13.4, 6.3, 4.3 Hz, 1H), 2.42–2.62 (bs, 1H), 2.88 (ddd, J = 7.5, 6.9, 4.3 Hz, 1H), 3.26 (dd, J = 6.9, 5.9 Hz, 1H), 3.75 (s, 3H), 3.77 (dd, J = 8.3, 6.9 Hz, 1H), 3.82 (dd, J = 9.5, 6.3 Hz, 1H), 4.04 (dd, J = 8.3, 6.5 Hz, 1H), 4.03–4.13 (m, 2H), 4.19 (ddd, J = 6.9, 6.5, 5.9 Hz, 1H); ^{13}C NMR (CDCl$_3$, 100 MHz) δ 13.8 (CH$_3$), 25.0 (CH$_3$), 26.2 (CH$_3$), 33.1 (CH$_2$), 45.4 (CH), 52.0 (CH$_3$), 59.0 (CH), 60.7 (CH$_2$), 64.3 (CH), 67.2 (CH$_2$), 74.9 (CH), 109.3 (C), 172.5 (C), 173.5 (C); HRMS(ESI$^+$) m/z [M + Na]$^+$ calcd for C$_{14}$H$_{23}$NO$_6$Na 324.1418, found 324.1414; m/z [M + H]$^+$ calcd for C$_{14}$H$_{24}$NO$_6$ 302.1598, found 302.1592.

*(2R,4R,5S)-4-Ethyl 2-Methyl 5-[(S)-2,2-Dimethyl-1,3-dioxolan-4-yl]pyrrolidine-2,4-dicarboxylate (**endo-2a-m**).* According to the general procedure for silver acetate catalyzed 1,3-dipolar cycloadditions described above, 72 mg (8% yield) of ***endo*-2a-m** was obtained after column chromatography (first eluent: Et$_2$O, second eluent: Et$_2$O/acetone, 9:1): colorless oil; $[\alpha]^{22}_{D}$ = +3.8 (c 1.33, CHCl$_3$); IR (neat) 3368, 1735; ^{1}H NMR (CDCl$_3$, 400 MHz) δ 1.25 (t, J = 7.2 Hz, 3H), 1.29 (s, 3H), 1.38 (s, 3H), 2.23 (ddd, J = 13.5, 7.4, 6.5 Hz, 1H), 2.37 (ddd, J = 13.5, 8.8, 7.7 Hz, 1H), 3.06 (ddd, J = 7.7, 6.9, 6.5 Hz, 1H), 3.27 (dd, J = 8.9, 6.9 Hz, 1H), 3.74 (s, 3H), 3.80–3.86 (m, 3H), 4.02 (ddd, J = 8.9, 6.1, 6.1 Hz, 1H), 4.07–4.17 (m, 3H); ^{13}C NMR (CDCl$_3$, 100 MHz) δ 14.2 (CH$_3$), 25.5 (CH$_3$), 26.8 (CH$_3$), 33.6 (CH$_2$), 46.1 (CH), 52.3 (CH$_3$), 59.7 (CH), 60.7 (CH$_2$), 65.0 (CH), 68.3 (CH$_2$), 75.4 (CH), 109.3 (C), 173.1 (C), 173.9 (C); HRMS(ESI$^+$) m/z [M + Na]$^+$ calcd for C$_{14}$H$_{23}$NO$_6$Na 324.1418, found 324.1418; m/z [M + H]$^+$ calcd for C$_{14}$H$_{24}$NO$_6$ 302.1598, found 302.1598.

*(2S,4R,5R)-4-Ethyl 2-Methyl 5-[(S)-2,2-Dimethyl-1,3-dioxolan-4-yl]pyrrolidine-2,4-dicarboxylate (**exo-2a-M**).* According to the general procedure for copper(I) acetate catalyzed 1,3-dipolar cycloadditions described above, 858 mg (95% yield) of ***exo*-2a-M** (dr = 93/7) was obtained after column chromatography (eluent: Et$_2$O): IR (neat) 3366, 1733; ^{1}H NMR (CDCl$_3$, 400 MHz) δ 1.26 (t, J = 7.1 Hz, 3H), 1.36 (s, 3H), 1.46 (s, 3H), 2.18 (ddd, J = 13.1, 9.4, 6.6 Hz, 1H), 2.39 (ddd, J = 13.1, 8.4, 7.3 Hz, 1H), 2.76 (ddd, J = 9.4, 7.9, 7.3 Hz, 1H), 3.35 (dd, J = 7.9, 4.8 Hz, 1H), 3.74 (s, 3H), 3.84 (dd, J = 8.4, 6.7 Hz, 1H), 3.89 (dd, J = 8.4, 6.6 Hz, 1H), 4.05 (dd, J = 8.4, 6.6 Hz, 1H), 4.16 (q, J = 7.1 Hz, 2H), 4.24 (ddd, J = 6.7, 6.6, 4.8 Hz, 1H); ^{13}C NMR (CDCl$_3$, 100 MHz) δ 14.1 (CH$_3$), 25.1 (CH$_3$), 26.3 (CH$_3$), 34.4 (CH$_2$), 45.7 (CH), 52.2 (CH$_3$), 59.3 (CH), 60.9 (CH$_2$), 64.4 (CH), 66.7(CH$_2$), 76.6 (CH), 109.4 (C), 173.5 (C), 173.9 (C); HRMS(ESI$^+$) m/z [M + Na]$^+$ calcd for C$_{14}$H$_{23}$NO$_6$Na 324.1418, found 324.1410; m/z [M + H]$^+$ calcd for C$_{14}$H$_{24}$NO$_6$ 302.1598, found 302.1599.

*(2S,4S,5R)-2-tert-Butyl 4-Ethyl 5-[(S)-2,2-Dimethyl-1,3-dioxolan-4-yl]pyrrolidine-2,4-dicarboxylate (**endo-2b-M**).* According to the silver acetate catalyzed multicomponent [C + NC + CC] coupling reaction described above, 442 mg (43% yield) of ***endo*-2b-M** was obtained after column chromatography (first eluent: Et$_2$O/hexanes, 9:1, second eluent: Et$_2$O, third eluent: Et$_2$O/acetone, 9:1): colorless oil; $[\alpha]^{22}_{D}$ = −49.1 (c 1.03, CHCl$_3$); IR (neat) 3302, 1729; ^{1}H NMR (CDCl$_3$, 400 MHz) δ 1.22 (t, J = 7.2 Hz, 3H), 1.29 (s, 3H), 1.40 (s, 3H), 1.45 (s, 9H), 2.20–2.26 (m, 2H), 2.56–2.79 (bs, 1H), 2.87 (ddd, J = 6.8, 6.2, 6.2 Hz, 1H), 3.22 (dd, J = 6.8, 5.7 Hz, 1H), 3.68 (dd, J =

8.1, 8.1 Hz, 1H), 3.76 (dd, *J* = 8.2, 7.0 Hz, 1H), 4.02 (dd, *J* = 8.2, 6.5 Hz, 1H), 4.00−4.14 (m, 2H), 4.19 (ddd, *J* = 7.0, 6.5, 5.7 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.0 (CH_3), 25.3 (CH_3), 26.4 (CH_3), 28.0 (CH_3), 33.6 (CH_2), 45.9 (CH), 60.1 (CH), 60.8 (CH_2), 64.4 (CH), 67.4 (CH_2), 74.9 (CH), 81.2 (C), 109.4(C), 172.2(C), 172.7(C); HRMS(ESI$^+$) *m*/*z* [M + Na]$^+$ calcd for $C_{17}H_{29}NO_6Na$ 366.1887, found 366.1896; *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{30}NO_6$ 344.2068, found 344.2082.

(2R,4R,5S)-2-tert-Butyl 4-Ethyl 5-[(S)-2,2-Dimethyl-1,3-dioxolan-4-yl]pyrrolidine-2,4-dicarboxylate (***endo*-2b-m**). According to the general procedure for silver acetate catalyzed 1,3-dipolar cycloadditions described above, 62 mg (6% yield) of ***endo*-2b-m** (dr = 80/20) was obtained after column chromatography (first eluent: Et_2O/hexanes, 9:1, second eluent: Et_2O, third eluent: Et_2O/acetone, 9:1): ^{1}H NMR ($CDCl_3$, 400 MHz) 1.26 (t, *J* = 7.1 Hz, 3H), 1.30 (s, 3H), 1.38 (s, 3H), 1.46 (s, 9H), 2.15 (ddd, *J* = 13.5, 8.0, 6.7 Hz, 1H), 2.55 (ddd, *J* = 13.4, 8.7, 8.0 Hz, 1H), 3.06 (ddd, *J* = 8.0, 6.9, 6.7 Hz, 1H), 3.26 (dd, *J* = 8.9, 6.9 Hz, 1H), 3.71 (dd, *J* = 8.7, 8.0 Hz, 1H), 3.83 (dd, *J* = 8.2, 6.1 Hz, 1H), 4.03 (ddd, *J* = 9.0, 6.1, 6.1 Hz, 1H), 4.09−4.17 (m, 3H).

(2S,4R,5R)-2-tert-Butyl 4-Ethyl 5-[(S)-2,2-Dimethyl-1,3-dioxolan-4-yl]pyrrolidine-2,4-dicarboxylate (***exo*-2b-M**). According to the copper(I) acetate catalyzed multicomponent [C + NC + CC] coupling reaction described above, 792 mg (77% yield) of ***exo*-2b-M** was obtained after column chromatography (eluent: Et_2O/hexanes, 9:1): colorless oil; $[\alpha]^{22}_D$ = −28.4 (*c* 1.07, $CHCl_3$); IR (neat) 3296, 1730; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.23 (t, *J* = 7.2 Hz, 3H), 1.33 (s, 3H), 1.42 (s, 9H), 1.43 (s, 3H), 2.06 (ddd, *J* = 13.1, 9.7, 6.7 Hz, 1H), 2.36 (ddd, *J* = 13.1, 8.6, 7.4 Hz, 1H), 2.44−2.56 (bs, 1H), 2.70 (ddd, *J* = 9.7, 8.0, 7.4 Hz, 1H), 3.27 (dd, *J* = 8.0, 4.4 Hz, 1H), 3.71 (dd, *J* = 8.6, 6.7 Hz, 1H), 3.82 (dd, *J* = 8.3, 6.9 Hz, 1H), 4.02 (dd, *J* = 8.3, 6.6 Hz, 1H), 4.12 (q, *J* = 7.1 Hz, 2H), 4.22 (ddd, *J* = 6.9, 6.6, 4.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.1 (CH_3), 25.2 (CH_3), 26.3 (CH_3), 27.9 (CH_3), 34.8 (CH_2), 45.9 (CH), 60.2 (CH), 60.8 (CH_2), 64.4 (CH), 66.7 (CH_2), 76.3 (CH), 81.3 (C), 109.3 (C), 172.7 (C), 173.6 (C); HRMS(ESI$^+$) *m*/*z* [M + Na]$^+$ calcd for $C_{17}H_{29}NO_6Na$ 366.1887, found 366.1888; *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{30}NO_6$ 344.2068, found 344.2092.

(2S,4S,5R)-4-tert-Butyl 2-Methyl 5-[(S)-2,2-Dimethyl-1,3-dioxolan-4-yl]pyrrolidine-2,4-dicarboxylate (***endo*-2a′-M**). According to the general procedure for silver acetate catalyzed 1,3-dipolar cycloadditions described above, 444 mg (45% yield) of ***endo*-2a′-M** was obtained after column chromatography (first eluent: Et_2O, second eluent: Et_2O/acetone, 9:1): colorless oil; $[\alpha]^{22}_D$ = −28.8 (*c* 1.08, $CHCl_3$); IR (neat) 3307, 1741; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.31 (s, 3H), 1.40 (s, 9H), 1.41 (s, 3H), 2.21−2.30 (m, 2H), 2.52−2.65 (bs, 1H), 2.78 (ddd, *J* = 6.9, 6.9, 5.3 Hz, 1H), 3.19 (dd, *J* = 6.9, 6.9 Hz, 1H), 3.72 (s, 3H), 3.72−3.81 (m, 2H), 4.08 (dd, *J* = 8.3, 6.5 Hz, 1H), 4.18 (ddd, *J* = 6.5, 6.5, 6.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 25.2 (CH_3), 26.5 (CH_3), 27.9 (CH_3), 33.5 (CH_2), 46.7 (CH), 52.1 (CH_3), 59.2 (CH), 64.8 (CH), 67.5 (CH_2), 75.5 (CH), 81.3 (C), 109.4 (C), 171.7 (C), 173.5 (C); HRMS(ESI$^+$) *m*/*z* [M + Na]$^+$ calcd for $C_{16}H_{27}NO_6Na$ 352.1731, found 352.1740; *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{28}NO_6$ 330.1911, found 330.1920.

(2R,4R,5S)-4-tert-Butyl 2-Methyl 5-[(S)-2,2-Dimethyl-1,3-dioxolan-4-yl]pyrrolidine-2,4-dicarboxylate (***endo*-2a′-m**). According to the general procedure for silver acetate catalyzed 1,3-dipolar cycloadditions described above, 89 mg (9% yield) of ***endo*-2a′-m** was obtained after column chromatography (first eluent: Et_2O, second eluent: Et_2O/acetone, 9:1): colorless oil; $[\alpha]^{22}_D$ = −0.5 (*c* 1.11, $CHCl_3$); IR (Nujol) 3288, 1736, 1712; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.25 (s, 3H), 1.33 (s, 3H), 1.37 (s, 9H), 2.08 (ddd, *J* = 13.4, 7.5, 5.8 Hz, 1H), 2.30 (ddd, *J* = 13.4, 9.0, 8.0 Hz, 1H), 2.75−3.00 (bs, 1H), 2.92 (ddd, *J* = 8.0, 6.9, 5.8 Hz, 1H), 3.14 (dd, *J* = 8.7, 6.9 Hz, 1H), 3.68 (s, 3H), 3.72−3.77 (m, 2H), 3.99−4.10 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 25.4 (CH_3), 26.6 (CH_3), 27.8 (CH_3), 33.9 (CH_2), 46.8 (CH), 52.1 (CH_3), 59.6 (CH), 65.2 (CH), 68.4 (CH_2), 75.1 (CH), 80.8 (C), 109.1 (C), 172.3 (C), 173.5 (C); HRMS(ESI$^+$) *m*/*z* [M + Na]$^+$ calcd for $C_{16}H_{27}NO_6Na$ 352.1731, found 352.1720; *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{28}NO_6$ 330.1911, found 330.1890.

(2S,4R,5R)-4-tert-Butyl 2-Methyl 5-[(S)-2,2-Dimethyl-1,3-dioxolan-4-yl]pyrrolidine-2,4-dicarboxylate (***exo*-2a′-M**). According to the general procedure for copper(I) acetate catalyzed 1,3-dipolar cycloadditions described above, 898 mg (91% yield) of ***exo*-2a′-M** was obtained after column chromatography (eluent: Et_2O): colorless oil; $[\alpha]_D^{21}$ = −22.9 (*c* 1.19, $CHCl_3$); IR (neat) 3363, 1727; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.33 (s, 3H), 1.41 (s, 9H), 1.43 (s, 3H), 2.11 (ddd, *J* = 13.0, 9.5, 6.7 Hz, 1H), 2.34 (ddd, *J* = 13.0, 8.4, 7.2 Hz, 1H), 2.41−2.50 (bs, 1H), 2.62 (ddd, *J* = 9.5, 7.8, 7.2 Hz, 1H), 3.28 (dd, *J* = 7.8, 5.2 Hz, 1H), 3.70 (s, 3H), 3.79 (dd, *J* = 8.3, 6.9 Hz, 1H), 3.84 (dd, *J* = 8.4, 6.7 Hz, 1H), 4.02 (dd, *J* = 8.3, 6.5 Hz, 1H), 4.18 (ddd, *J* = 6.9, 6.5, 5.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 25.2 (CH_3), 26.3 (CH_3), 28.0 (CH_3), 34.4 (CH_2), 46.7 (CH), 52.1 (CH_3), 59.3 (CH), 64.4 (CH), 66.7 (CH_2), 77.0 (CH), 81.1 (C), 109.3 (C), 172.7(C), 174.0(C); HRMS(ESI$^+$) *m*/*z* [M + Na]$^+$ calcd for $C_{16}H_{27}NO_6Na$ 352.1731, found 352.1736; *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{28}NO_6$ 330.1911, found 330.1932.

(2S,4S,5S)-Methyl 5-[(S)-2,2-Dimethyl-1,3-dioxolan-4-yl]-4-(phenylsulfonyl)pyrrolidine-2-carboxylate (***endo*-2c-M**). According to the general procedure for silver acetate catalyzed 1,3-dipolar cycloadditions described above, 664 mg (60% yield) of ***endo*-2c-M** was obtained after column chromatography (first eluent: Et_2O, second eluent: Et_2O/acetone, 9:1): white solid, mp = 208 °C dec; $[\alpha]_D^{21}$ = +34.3 (*c* 1.11, $CHCl_3$); IR (Nujol) 3354, 1735; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.36 (s, 3H), 1.44 (s, 3H), 2.16 (ddd, *J* = 14.2, 8.8, 8.1 Hz, 1H), 2.37 (ddd, *J* = 14.2, 7.2, 6.0 Hz, 1H), 2.86−2.95 (bS, 1H), 3.46 (dd, *J* = 8.5, 6.3 Hz, 1H), 3.53 (ddd, *J* = 8.0, 6.3, 6.0 Hz, 1H), 3.74 (s, 3H), 3.80 (dd, *J* = 8.8, 7.2 Hz, 1H), 3.89 (dd, *J* = 8.9, 5.6 Hz, 1H), 4.35 (dd, *J* = 8.9, 6.5 Hz, 1H), 4.82 (ddd, *J* = 8.5, 6.5, 5.6 Hz, 1H), 7.53−7.59 (m, 2H), 7.62−7.68 (m, 1H), 7.83−7.87 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 24.8 (CH_3), 26.9 (CH_3), 32.0 (CH_2), 52.3 (CH_3), 58.5 (CH), 64.2 (CH), 65.3 (CH), 68.1 (CH_2), 75.0 (CH), 109.4 (C), 128.4 (CH), 129.3 (CH), 133.9 (CH), 138.7(C), 172.4 (C); HRMS(ESI$^+$) *m*/*z* [M + Na]$^+$ calcd for $C_{17}H_{23}NO_6SNa$ 392.1138, found 392.1143; *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{24}NO_6S$ 370.1319, found 370.1325.

(2S,4R,5S)-Methyl 5-[(S)-2,2-Dimethyl-1,3-dioxolan-4-yl]-4-(phenylsulfonyl)pyrrolidine-2-carboxylate (***exo*-2c-M**). According to the general procedure for copper(I) acetate catalyzed 1,3-dipolar cycloadditions described above, 897 mg (81% yield) of ***exo*-2c-M** was obtained after column chromatography (eluent: Et_2O): white solid, mp = 117 °C; $[\alpha]_D^{21}$ = −19.6 (*c* 1.06, $CHCl_3$); IR (Nujol) 3292, 1740; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.31 (s, 3H), 1.43 (s, 3H), 1.96 (ddd, *J* = 13.9, 10.5, 9.0 Hz, 1H), 2.48 (ddd, *J* = 13.9, 7.5, 4.4 Hz, 1H), 2.53−2.63 (bs, 1H), 3.58 (ddd, *J* = 10.5, 6.3, 4.4 Hz, 1H), 3.69 (s, 3H), 3.73−3.79 (m, 1H), 3.83−3.90 (m, 1H), 3.93 (dd, *J* = 8.4, 6.3 Hz, 1H), 4.02 (dd, *J* = 8.4, 6.8 Hz, 1H), 4.29 (ddd, *J* = 6.8, 6.3, 3.0 Hz, 1H), 7.55−7.61 (m, 2H), 7.64−7.70 (m, 1H), 7.89−7.93 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 24.8 (CH_3), 26.1 (CH_3), 33.6 (CH_2), 52.3 (CH_3), 59.3 (CH), 60.9 (CH), 65.3 (CH), 66.6 (CH_2), 75.8 (CH), 109.6 (C), 128.4 (CH), 129.4 (CH), 134.0 (CH), 138.3 (C), 172.8 (C); HRMS(ESI$^+$) *m*/*z* [M + Na]$^+$ calcd for $C_{17}H_{23}NO_6SNa$ 392.1138, found 392.1157; *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{24}NO_6S$ 370.1319, found 370.1354.

(2S,4S,5R)-4-Ethyl 2-Methyl 5-[(S)-2,2-Dimethyl-1,3-dioxolan-4-yl]-2-methylpyrrolidine-2,4-dicarboxylate (***endo*-2d-M**). According to the general procedure for silver acetate catalyzed 1,3-dipolar cycloadditions described above, 661 mg (70% yield) of ***endo*-2d-M** was obtained after column chromatography (first eluent: Et_2O/hexanes, 4:1, second eluent: Et_2O): white solid; mp = 52 °C; $[\alpha]^{22}_D$ = −34.5 (*c* 1.19, $CHCl_3$); IR (Nujol) 3311, 1729; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.22 (t, *J* = 7.2 Hz, 3H), 1.29 (s, 3H), 1.38 (s, 3H), 1.41 (s, 3H), 1.86 (dd, *J* = 13.6, 7.6 Hz, 1H), 2.65 (dd, *J* = 13.6, 4.3 Hz, 1H), 2.93 (ddd, *J* = 7.6, 6.7, 4.3 Hz, 1H), 3.02−3.18 (bs, 1H), 3.36 (dd, *J* = 6.7, 6.4 Hz, 1H), 3.73 (dd, *J* = 8.1, 7.0 Hz, 1H), 3.74 (s, 3H), 4.02 (dd, *J* = 8.1, 6.4 Hz, 1H), 4.02−4.11 (m, 2H), 4.14 (ddd, *J* = 7.0, 6.4, 6.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.0 (CH_3), 25.2 (CH_3), 26.5 (CH_3), 28.1 (CH_3), 40.4 (CH_2), 46.6 (CH), 52.3 (CH_3), 60.8 (CH_2), 63.4 (CH), 65.2 (C), 67.4 (CH_2), 75.3 (CH), 109.4 (C), 172.6 (C), 176.5 (C); HRMS(ESI$^+$) *m*/*z* [M + Na]$^+$ calcd for $C_{15}H_{25}NO_6Na$ 338.1574,

found 338.1593; *m/z* [M + H]$^+$ calcd for $C_{15}H_{26}NO_6$ 316.1755, found 316.1777.

*(2R,4R,5S)-4-Ethyl 2-Methyl 5-[(S)-2,2-Dimethyl-1,3-dioxolan-4-yl]-2-methylpyrrolidine-2,4-dicarboxylate (**endo-2d-m**).* According to the general procedure for silver acetate catalyzed 1,3-dipolar cycloadditions described above, 198 mg (21% yield) of ***endo*-2d-m** was obtained after column chromatography (first eluent: Et_2O/hexanes, 4:1, second eluent: Et_2O): white solid; mp = 64 °C; $[\alpha]^{21}_D$ = +6.9 (*c* 1.00, $CHCl_3$); IR (Nujol) 3300, 1735, 1719; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.23 (t, *J* = 7.1 Hz, 3H), 1.26 (s, 3H), 1.36 (s, 3H), 1.36 (s, 3H), 1.94 (dd, *J* = 13.7, 7.7 Hz, 1H), 2.32−2.50 (bs, 1H), 2.56 (dd, *J* = 13.7, 6.4 Hz, 1H), 3.11 (ddd, *J* = 7.7, 6.7, 6.4 Hz, 1H), 3.35 (dd, *J* = 8.9, 6.7 Hz, 1H), 3.72 (s, 3H), 3.78 (dd, *J* = 8.2, 6.3 Hz, 1H), 3.98 (ddd, *J* = 8.9, 6.3, 6.1 Hz, 1H), 4.04−4.14 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.1 (CH_3), 25.4 (CH_3), 26.7 (CH_3), 27.5 (CH_3), 40.2 (CH_2), 46.4 (CH), 52.4 (CH_3), 60.5 (CH_2), 64.0 (CH), 65.4 (C), 68.2(CH_2), 75.2 (CH), 109.2 (C), 172.8 (C), 176.5 (C); HRMS-(ESI$^+$) *m/z* [M + Na]$^+$ calcd for $C_{15}H_{25}NO_6Na$ 338.1574, found 338.1587; *m/z* [M + H]$^+$ calcd for $C_{15}H_{26}NO_6$ 316.1755, found 316.1770.

*(2S,4R,5R)-4-Ethyl 2-Methyl 5-[(S)-2,2-Dimethyl-1,3-dioxolan-4-yl]-2-methylpyrrolidine-2,4-dicarboxylate (**exo-2d-M**).* According to the general procedure for copper(I) acetate catalyzed 1,3-dipolar cycloadditions described above, 699 mg (74% yield) of ***exo*-2d-M** was obtained after column chromatography (first eluent: Et_2O/hexanes, 4:1, second eluent: Et_2O): colorless oil; $[\alpha]^{21}_D$ = −34.8 (*c* 1.06, $CHCl_3$); IR (neat) 3361, 3306, 1733; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.23 (t, *J* = 7.2 Hz, 3H), 1.32 (s, 3H), 1.40 (s, 3H), 1.42 (s, 3H), 2.02 (dd, *J* = 13.0, 9.7 Hz, 1H), 2.52 (dd, *J* = 13.0, 8.7 Hz, 1H), 2.64−2.82 (bs, 1H), 2.72 (ddd, *J* = 9.7, 8.7, 8.5 Hz, 1H), 3.44 (dd, *J* = 8.5, 5.4 Hz, 1H), 3.70 (s, 3H), 3.74 (dd, *J* = 8.3, 6.9 Hz, 1H), 3.99 (dd, *J* = 8.3, 6.5 Hz, 1H), 4.08−4.16 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.1 (CH_3), 25.2 (CH_3), 26.0 (CH_3), 26.3 (CH_3), 41.3 (CH_2), 46.6 (CH), 52.4 (CH_3), 60.8 (CH_2), 63.5 (CH), 65.3 (C), 66.6 (CH_2), 76.9 (CH), 109.3 (C), 173.2 (C), 176.6 (C); HRMS(ESI$^+$) *m/z* [M + Na]$^+$ calcd for $C_{15}H_{25}NO_6Na$ 338.1574, found 338.1583; *m/z* [M + H]$^+$ calcd for $C_{15}H_{26}NO_6$ 316.1755, found 316.1771.

*(2R,4S,5R)-4-Ethyl 2-Methyl 2-Benzyl-5-[(S)-2,2-dimethyl-1,3-dioxolan-4-yl]-2-methylpyrrolidine-2,4-dicarboxylate (**endo-2e-M**) and (2S,4R,5S)-4-Ethyl 2-Methyl 2-Benzyl-5-[(S)-2,2-dimethyl-1,3-dioxolan-4-yl]-2-methylpyrrolidine-2,4-dicarboxylate (**endo-2e-m**).* According to the general procedure for silver acetate catalyzed 1,3-dipolar cycloadditions described above, 1.07 g (91% yield) of ***endo*-2e-M** and ***endo*-2e-m** was obtained as an unseparable mixture of compounds (***endo*-2e-M**/***endo*-2e-m** = 2/1) after column chromatography (Et_2O/hexanes, 2:3). NMR data for major isomer: ^{1}H NMR δ 1.24 (t, *J* = 7.2 Hz, 3H), 1.32 (s, 3H), 1.44 (s, 3H), 1.57−1.75 (bs, 1H), 2.06 (dd, *J* = 13.7, 7.5 Hz, 1H), 2.69 (dd, *J* = 13.7, 4.1 Hz, 1H), 2.77 (ddd, *J* = 7.5, 6.5, 4.1 Hz, 1H), 2.87 (d, *J* = 13.0, 1H), 3.03 (d, *J* = 13.0, 1H), 3.07 (dd, *J* = 6.5, 5.6 Hz, 1H), 3.73 (s, 3H), 3.77 (dd, *J* = 8.1, 7.0 Hz, 1H), 3.99 (dd, *J* = 8.1, 6.5 Hz, 1H), 4.02−4.18 (m, 3H), 7.18−7.32 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.0 (CH_3), 25.3 (CH_3), 26.4 (CH_3), 38.0 (CH_2), 46.0 (CH_2), 46.2 (CH), 52.1 (CH_3), 60.7 (CH_2), 63.2 (CH), 67.3 (CH_2), 69.3 (C), 75.1 (CH), 109.3 (C), 126.6 (CH), 127.9 (CH), 130.4 (CH), 136.7 (C), 172.7 (C), 175.8 (C). NMR data for minor isomer: ^{1}H NMR δ 1.25 (t, *J* = 7.1 Hz, 3H), 1.30 (s, 3H), 1.38 (s, 3H), 1.57−1.75 (bs, 1H), 2.14 (dd, *J* = 13.9, 7.6 Hz, 1H), 2.63 (dd, *J* = 13.9, 6.1 Hz, 1H), 2.84 (d, *J* = 12.9, 1H), 3.01 (ddd, *J* = 7.6, 6.5, 6.1 Hz, 1H), 3.05 (d, *J* = 12.9, 1H), 3.23 (dd, *J* = 9.0, 6.5 Hz, 1H), 3.71 (s, 3H), 3.81 (dd, *J* = 8.2, 6.3 Hz, 1H), 3.95 (ddd, *J* = 9.0, 6.4, 6.4 Hz, 1H), 4.02−4.18 (m, 3H), 7.18−7.32 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.1 (CH_3), 25.4 (CH_3), 26.7 (CH_3), 38.7 (CH_2), 45.9 (CH_2), 46.1 (CH), 52.2 (CH_3), 60.5(CH_2), 64.1 (CH), 68.1 (CH_2), 69.7 (C), 75.2 (CH), 109.2 (C), 126.8 (CH), 128.0 (CH), 130.0 (CH), 136.5 (C), 172.8 (C), 175.6 (C); HRMS(ESI$^+$) *m/z* [M + Na]$^+$ calcd for $C_{21}H_{29}NO_6Na$ 414.1887, found 414.1903; *m/z* [M + H]$^+$ calcd for $C_{21}H_{30}NO_6$ 392.2068, found 392.2076.

*(2R,4R,5R)-4-Ethyl 2-Methyl 2-Benzyl-5-[(S)-2,2-dimethyl-1,3-dioxolan-4-yl]-2-methylpyrrolidine-2,4-dicarboxylate (**exo-2e-M**).* According to the general procedure for copper(I) acetate catalyzed 1,3-dipolar cycloadditions described above, 528 mg (45% yield) of ***exo*-2e-M** was obtained in 45% yield after column chromatography (Et_2O/hexanes, 2:3): colorless oil; $[\alpha]^{22}_D$ = −33.7 (*c* 1.08, $CHCl_3$); IR (neat) 3360, 3312, 1733; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.28 (t, *J* = 7.2 Hz, 3H), 1.35 (s, 3H), 1.45 (s, 3H), 2.22 (dd, *J* = 12.9, 10.0 Hz, 1H), 2.40−2.80 (bs, 1H), 2.59 (dd, *J* = 12.9, 8.4 Hz, 1H), 2.70 (ddd, *J* = 10.0, 8.5, 8.4 Hz, 1H), 3.04 (d, *J* = 13.8 Hz, 1H), 3.07 (d, *J* = 13.8 Hz, 1H), 3.42 (dd, *J* = 8.5, 5.5 Hz, 1H), 3.66 (s, 3H), 3.78 (dd, *J* = 8.2, 6.8 Hz, 1H), 4.02 (dd, *J* = 8.2, 6.5 Hz, 1H), 4.11 (ddd, *J* = 6.8, 6.5, 5.5 Hz, 1H), 4.17 (q, *J* = 7.2 Hz, 2H), 7.17−7.29 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.1 (CH_3), 25.2 (CH_3), 26.4 (CH_3), 39.4 (CH_2), 45.1 (CH_2), 45.8 (CH), 52.1 (CH_3), 60.9 (CH_2), 63.2 (CH), 66.6 (CH_2), 69.7 (C), 76.9 (CH), 109.3 (C), 126.7 (CH), 128.1 (CH), 129.8 (CH), 136.7 (C), 173.2 (C), 175.6 (C); HRMS(ESI$^+$) *m/z* [M + Na]$^+$ calcd for $C_{21}H_{29}NO_6Na$ 414.1887, found 414.1878; *m/z* [M + H]$^+$ calcd for $C_{21}H_{30}NO_6$ 392.2068, found 392.2066.

*tert-Butyl 2,5-Bis[(R)-2,2-dimethyl-1,3-dioxolan-4-yl]oxazolidine-4-carboxylate (**5**).* 302 mg (27% yield of byproduct **5** were isolated in the Ag(I)-catalyzed multicomponent [C + NC + CC] coupling reaction of D-glyceraldeyde acetonide, *tert*-butyl glycinate, and ethyl acrylate: white solid; mp = 78 °C; IR (Nujol) 3288, 1722; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.33 (s, 3H), 1.36 (s, 3H), 1.41 (s, 3H), 1.46 (s, 9H), 1.48 (s, 3H), 3.00−3.18 (bs, 1H), 3.78−3.83 (bs, 1H), 3.84−3.90 (m, 2H), 3.93 (dd, *J* = 8.6, 5.7 Hz, 1H), 4.05 (dd, *J* = 8.6, 6.7 Hz, 1H), 4.09 (dd, *J* = 8.4, 6.9 Hz, 1H), 4.20 (ddd, *J* = 6.7, 5.9, 5.9 Hz, 1H), 4.25 (ddd, *J* = 6.6, 6.6, 3.8 Hz, 1H), 4.53−4.59 (bs, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 25.0 (CH_3), 25.0 (CH_3), 26.2 (CH_3), 26.5 (CH_3), 27.9 (CH_3), 62.5 (CH), 66.3 (CH_2), 66.3 (CH_2), 75.0 (CH), 76.6 (CH), 80.5 (CH), 82.4 (C), 92.6 (CH), 109.7 (C), 110.2 (C), 170,6 (C); HRMS(ESI$^+$) *m/z* [M + Na]$^+$ calcd for $C_{18}H_{31}NO_7Na$ 396.1993, found 396.1991; *m/z* [M + H]$^+$ calcd for $C_{18}H_{32}NO_7$ 374.2173, found 374.2180.

*(2S,3aS,6S,6aR)-Methyl 6-(Hydroxymethyl)-4-oxo-1-tosylhexahydro-1H-furo[3,4-b]pyrrole-2-carboxylate (**3**).* To a solution of the ***endo*-2a-M** (301 mg, 1.0 mmol) in CH_2Cl_2 (10 mL) were sequentially added *p*-toluenesulfonyl chloride (286 mg, 1.5 mmol) and Et_3N (304 mg, 3.0 mmol). The resulting mixture was stirred at room temperature for 24−48 h until complete disappearance of starting material was observed by TLC. The reaction mixture was then washed with water (15 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography (first eluent: Et_2O/hexanes, 1:1, second eluent: Et_2O) to provide the corresponding tosylate (365 mg, 80%) as a white solid. A solution of this tosylate (228 mg, 0.5 mmol) in methanol/water (3:1, 8 mL) was treated with TFA (80 μL) and stirred for 48 h at room temperature. Saturated aqueous $NaHCO_3$ was added until the pH was basic and the solution was concentrated under reduced pressure. The concentrate was partitioned between water (10 mL) and CH_2Cl_2 (3 × 20 mL), and the combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. Purification of the crude product by crystallization in $CHCl_3$ afforded compound **3** (161 mg, 87% yield) as a white solid: mp = 178 °C; $[\alpha]^{21}_D$ = +6.2 (*c* 1.06, $CHCl_3$); IR (Nujol) 3404, 1755, 1739; ^{1}H NMR (CD_3OD, 400 MHz) δ 1.68 (ddd, *J* = 13.7, 9.3, 8.9 Hz, 1H), 2.35 (ddd, *J* = 13.7, 1.2, 1.2 Hz, 1H), 2.47 (s, 3H), 3.41 (ddd, *J* = 8.9, 7.7, 1.2 Hz, 1H), 3.71 (s, 3H), 4.16−4.24 (m, 1H), 4.31 (dd, *J* = 12.8, 2.6 Hz, 1H), 4.51 (dd, *J* = 9.3, 1.2 Hz, 1H), 4.73−4.80 (m, 2H), 7.46−7.51 (m, 2H), 7.80−7.84 (m, 2H); ^{13}C NMR (CD_3OD, 100 MHz) δ 21.6 (CH_3), 32.1 (CH_2), 46.8 (CH), 53.2 (CH_3), 62.7 (CH_2), 63.5 (CH), 64.3 (CH), 85.3 (CH), 129.0 (CH), 131.4 (CH), 135.2 (C), 146.5 (C), 172.5 (C), 178.3 (C); HRMS(ESI$^+$) *m/z* [M + Na]$^+$ calcd for $C_{16}H_{19}NO_7SNa$ 392.0774, found 392.0794.

*(2R,4R,5S)-4-Ethyl 2-Methyl 5-[(S)-2,2-Dimethyl-1,3-dioxolan-4-yl]-1-tosylpyrrolidine-2,4-dicarboxylate (**4**).* To a solution of the ***endo*-2a-m** (301 mg, 1.0 mmol) in CH_2Cl_2 (10 mL) were sequentially added *p*-toluenesulfonyl chloride (286 mg, 1.5 mmol) and Et_3N (304 mg, 3.0 mmol). The resulting mixture was stirred at room temperature for 24−48 h until complete disappearance of starting material was observed by TLC. The reaction mixture was then washed with water

(15 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography (first eluent: Et_2O/hexanes, 1:1, second eluent: Et_2O) to provide the corresponding tosylate (396 mg, 87%) as a white solid: mp = 135 °C; $[\alpha]_D^{21}$ = −36.7 (*c* 1.08, $CHCl_3$); IR (Nujol) 1749, 1734; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.22 (t, *J* = 7.1 Hz, 3H), 1.26 (s, 3H), 1.36 (s, 3H), 2.25−2.37 (m, 2H), 2.43 (s, 3H), 2.38−2.51 (m, 1H), 3.74 (s, 3H), 3.96−4.19 (m, 6H), 4.21−4.28 (m, 1H), 7.32−7.38 (m, 2H), 7.71−7.77 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.9 (CH_3), 21.6 (CH_3), 25.6 (CH_3), 26.7 (CH_3), 30.6 (CH_2), 45.6 (CH), 52.7 (CH_3), 59.7 (CH), 61.1 (CH), 64.3 (CH_2), 67.4 (CH_2), 73.7 (CH), 109.9 (C), 127.5 (CH), 130.1 (CH), 134.2 (C), 144.6 (C), 168.6(C), 171.9 (C); HRMS(ESI^+) *m*/*z* $[M + Na]^+$ calcd for $C_{21}H_{29}NO_8SNa$ 478.1506, found 478.1538.

*(2S,4S,5R)-2-tert-Butyl 4-Methyl 5-[(S)-2,2-Dimethyl-1,3-dioxolan-4-yl]pyrrolidine-2,4-dicarboxylate (**6**).* To a stirred suspension of crude imine **1b** of 50% purity (1.46 g, 3.0 mmol) and AgOAc (100 mg, 0.6 mmol) in dry toluene (30 mL) under argon and at room temperature were sequentially added methyl acrylate (517 mg, 6.0 mmol) and DBU (91 mg, 0.6 mmol). The reaction mixture was stirred in the dark at room temperature for 24 h. The reaction was quenched with saturated aqueous NH_4Cl (30 mL) and the aqueous phase extracted with CH_2Cl_2 (2 × 30 mL). The combined organic layers were filtered through a short Celite path, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The crude cycloadducts were purified by flash chromatography (first eluent: Et_2O, second eluent: Et_2O/acetone, 9:1) to provide compound **6** (721 mg, 73%) as a colorless oil: $[\alpha]^{24}_D$ = −47.8 (*c* 1.07, $CHCl_3$); IR (neat) 3301, 1738, 1728; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.30 (s, 3H), 1.41 (s, 3H), 1.46 (s, 9H); 2.22−2.28 (m, 2H); 2.60−2.85 (bs, 1H); 2.90 (ddd, *J* = 9.9, 6.7, 5.7 Hz, 1H); 3.24 (dd, *J* = 6.7, 5.6 Hz, 1H); 3.62 (s, 3H); 3.69 (dd, *J* = 8.3, 7.8 Hz, 1H); 3.76 (dd, *J* = 8.2, 7.1 Hz, 1H); 4.01 (dd, *J* = 8.2, 6.4 Hz, 1H), 4.19 (ddd, *J* = 7.1, 6.4, 5.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 25.3 (CH_3), 26.4 (CH_3), 28.0 (CH_3), 33.5 (CH_3), 45.7 (CH), 51.7 (CH_3), 60.1 (CH), 64.3 (CH), 67.4 (CH_2), 74.9 (CH), 81.3 (C), 109.4 (C), 172.2 (C), 173.2 (C); HRMS(ESI^+) *m*/*z* $[M + Na]^+$ calcd for $C_{16}H_{27}NO_6Na$ 352.1731, found 352.1706; *m*/*z* $[M + H]^+$ calcd for $C_{16}H_{28}NO_6$ 330.1911, found 330.1890.

*(2S,4S,5R)-1,2-Di-tert-Butyl 4-Methyl 5-[(S)-2,2-Dimethyl-1,3-dioxolan-4-yl]pyrrolidine-1,2,4-tricarboxylate (**7**).* To a solution of compound **6** (659 mg, 2.0 mmol) in dioxane (10 mL) were sequentially added di-*tert*-butyl dicarbonate (873 mg, 4.0 mmol) and *N*,*N*-diisopropylethylamine (26 mg, 0.2 mmol). The resulting mixture was stirred at 50 °C for 18 h until complete disappearance of starting material was observed by TLC. The reaction mixture was concentrated under reduced pressure, and the crude product was purified by flash chromatography (eluent: ether/hexane, 2:1) to give compound **7** (833 mg, 98%) as a white solid: mp = 135 °C; $[\alpha]^{24}_D$ = +28.7 (*c* 1.11, $CHCl_3$); IR (Nujol) 1751, 1731, 1694; ^1H NMR ($CDCl_3$, 300 MHz, 333K) δ 1.24 (s, 3H), 1.35 (s, 3H), 1.44 (s, 9H), 1.47 (s, 9H), 2.37−2.65 (m, 2H), 3.14 (ddd, *J* = 12.6, 7.8, 7.8 Hz, 1H), 3.70 (s, 3H), 3.84 (dd, *J* = 9.2, 7.8 Hz, 1H), 3.97 (dd, *J* = 8.0, 5.3 Hz, 1H), 4.17 (dd, *J* = 10.3, 8.3 Hz, 1H), 4.28 (ddd, *J* = 9.2, 5.3, 3.7 Hz, 1H), 4.38 (dd, *J* = 8.1, 3.7 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz, 333K) δ 26.0 (CH_3), 26.4 (CH_3), 28.2 (CH_3), 28.3 (CH_3), 31.2 (CH_2), 45.7 (CH), 51.5 (CH_3), 57.8 (CH), 59.3 (CH), 66.9 (CH_2), 76.0 (CH), 80.6 (C), 80.8 (C), 108.3 (C), 154.5 (C), 169.9 (C), 170.5 (C); HRMS(ESI^+) *m*/*z* $[M + Na]^+$ calcd for $C_{21}H_{35}NO_8Na$ 452.2255, found 452.2272.

*(2S,4S,5R)-1,2-Di-tert-butyl 4-Hydroxymethyl-5-[(S)-2,2-dimethyl-1,3-dioxolan-4-yl]pyrrolidine-1,2-dicarboxylate (**8**).* To a solution of compound **7** (430 mg, 1.0 mmol) in dry THF (10 mL) were sequentially added $NaBH_4$ (152 mg, 4.0 mmol) and $NaB(OAc)_3H$ (43 mg, 0.2 mmol). To the white slurry was added dry methanol (256 mg, 8 mmol) under argon at room temperature, and the mixture was stirred for 3 days until complete disappearance of starting material was observed by TLC. The resulting reaction mixture was quenched with saturated aqueous NH_4Cl solution (10 mL), and the organic solvents were evaporated under reduced pressure. The aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL), and the combined organic phases were dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by flash chromatography (first eluent: Et_2O/hexanes, 1:1 s eluent: Et_2O) to provide compound **8** (389 mg, 97%) as a colorless oil: $[\alpha]^{24}_D$ = +20.0 (*c* 1.10, $CHCl_3$); IR (neat) 3480, 1754, 1700, 1682; ^1H NMR ($CDCl_3$, 300 MHz, 333K) δ 1.33 (s, 3H), 1.40 (s, 3H), 1.44 (s, 9H), 1.45 (s, 9H), 1.96−2.14 (m, 1H), 2.18−2.40 (m, 2H), 2.42−2.60 (m, 1H), 3.76−3.92 (m, 3H), 4.03 (dd, *J* = 8.2, 5.6 Hz, 1H), 4.14−4.30 (m, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz, 333K) δ 25.9 (CH_3), 26.3(CH_3), 28.2 (CH_3), 28.3 (CH_3), 31.2 (CH_2), 44.6 (CH), 58.1 (CH), 59.9 (CH), 61.2 (CH_2), 67.2 (CH_2), 76.2 (CH), 80.3 (C), 80.5 (C), 108.7 (C), 155.0 (C), 170.1 (C); HRMS(ESI^+) *m*/*z* $[M + Na]^+$ calcd for $C_{20}H_{35}NO_7Na$ 424.2306, found 424.2312.

*(2S,4S,5R)-1,2-Di-tert-butyl 4-(tert-Butyldimethylsilanyloxymethyl)-5-[(S)-2,2-dimethyl-1,3-dioxolan-4-yl]pyrrolidine-1,2-dicarboxylate (**9**).* A solution of compound **8** (321 mg, 0.8 mmol), *tert*-butyldimethylsilyl chloride (603 mg, 4.0 mmol), Et_3N (810 mg, 8.0 mmol), and DMAP (49 mg, 0.4 mmol) in dry CH_2Cl_2 (10 mL) was stirred at room temperature for 24 h. The reaction was diluted with CH_2Cl_2 (20 mL), washed with water (10 mL), dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The residual oil was purified by flash chromatography (eluent: ether/hexane, 1:4) to afford compound **9** (360 mg, 87%) as a colorless oil: $[\alpha]^{22}_D$ = +21.8 (c = 0.98 in $CHCl_3$); IR (neat) 1754, 1700; ^1H NMR ($CDCl_3$, 300 MHz, 333K) δ 0.06 (s, 6H), 0.91 (s, 9H), 1.31 (s, 3H), 1.38 (s, 3H), 1.45 (s, 9H), 1.46 (s, 9H), 2.01 (ddd, *J* = 12.7, 11.8, 10.5 Hz, 1H), 2.20 (ddd, *J* = 11.8, 7.8, 6.8 Hz, 1H), 2.39−2.55 (m, 1H), 3.75 (dd, *J* = 10.1, 6.4 Hz, 1H), 3.81−3.93 (m, 2H), 3.97 (dd, *J* = 8.0, 5.3 Hz, 1H), 4.07−4.24 (m, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz, 333K) δ −5.5 (CH_3), −5.4 (CH_3), 18.3 (C), 25.9 (CH_3), 26.3 (CH_3), 26.5 (CH_3), 28.3 (CH_3), 28.4 (CH_3), 32.1 (CH_2), 45.0 (CH), 58.3 (CH), 60.1 (CH), 62.4 (CH_2), 67.4 (CH_2), 76.1 (CH), 80.1 (C), 80.2 (C), 108.4 (C), 155.2 (C), 170.0 (C); HRMS(ESI^+) *m*/*z* $[M + Na]^+$ calcd for $C_{26}H_{49}NO_7SiNa$ 538.3171, found 538.3218; *m*/*z* $[M + H]^+$ calcd for $C_{26}H_{50}NO_7Si$ 516.3351, found 516.3352.

*(2S,4S,5R)-1,2-Di-tert-butyl 4-(tert-Butyldimethylsilanyloxymethyl)-5-(1,2-dihydroxyethyl)pyrrolidine-1,2-dicarboxylate (**10**).* Compound **9** (258 mg, 0.5 mmol) and $SnCl_2$ (237 mg, 1.25 mmol) were mixed in anhydrous CH_2Cl_2 (25 mL), and the mixture was stirred under argon for 24 h until complete disappearance of starting material was observed by TLC. The undissolved $SnCl_2$ was removed by filtration and the filtrate washed with saturated aqueous $NaHCO_3$ solution (10 mL). The organic layer was dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The resulting residue was purified by flash chromatography (eluent: ether/hexane, 1:2) to afford compound **10** (171 mg, 72%) as a white solid: mp = 78 °C; $[\alpha]^{23}_D$ = +9.7 (*c* 1.07, $CHCl_3$); IR (Nujol) 3429, 1710, 1685; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.03 (s, 3H); 0.03 (s, 3H); 0.86 (s, 9H); 1.43 (s, 9H); 1.46 (s, 9H); 1.95 (ddd, *J* = 12.5, 12.5, 9.8 Hz, 1H), 2.32 (ddd, *J* = 12.5, 8.4, 7.7 Hz, 1H), 2.48−2.60 (m, 1H), 3.56 (ddd, *J* = 11.7, 9.5, 5.8 Hz, 1H), 3.43 (d, *J* = 12.4 Hz, 1H), 3.61 (ddd, *J* = 11.6, 9.6, 5.7 Hz, 1H), 3.69−3.78 (m, 2H), 3.85 (dd, *J* = 10.0, 7.6 Hz, 1H), 4.20 (dd, *J* = 9.5, 8.7 Hz, 1H), 4.23−4.29 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ −5.5 (CH_3), −5.4 (CH_3), 18.1 (C), 25.8 (CH_3), 27.9 (CH_3), 28.2 (CH_3), 33.1 (CH_2), 43.8 (CH), 58.9 (CH), 60.1 (CH), 62.1 (CH_2), 63.7(CH_2), 71.0 (CH), 81.4 (C), 82.5 (C), 155.9 (C), 174.7 (C); HRMS(ESI^+) *m*/*z* $[M + Na]^+$ calcd for $C_{23}H_{45}NO_7SiNa$ 498.2858, found 498.2858.

*(2S,4S,5R)-1,2-Di-tert-butyl 4-(tert-Butyldimethylsilanyloxymethyl)-5-formylpyrrolidine-1,2-dicarboxylate (**11**).* Compound **10** (143 mg, 0.3 mmol) and $NaIO_4$ (129 mg, 0.6 mmol) in a mixture of THF (3 mL) and water (0.5 mL) were reacted at room temperature for 24 h. The reaction mixture was diluted with CH_2Cl_2 (30 mL), washed with water (10 mL), dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The resulting residue was purified by flash chromatography (eluent: ether/hexane, 1:2), to give compund **11** (110 mg, 83%) as a white solid: mp = 70 °C; $[\alpha]^{22}_D$ = −18.5 (*c* 1.19, $CHCl_3$); IR (neat) 2745, 1732, 1705; ^1H NMR ($CDCl_3$, 400 MHz, compound exists as a 1.2:1 mixture of rotamers) δ 0.01 (s, 6H rotamer A), 0.01 (s, 6H rotamer B), 0.86 (s, 9H rotamer A), 0.87 (s, 9H

rotamer B), 1.40 (s, 9H rotamer B), 1.44 (s, 9H rotamer A), 1.47 (s, 9H rotamer B), 1.49 (s, 9H rotamer A), 2.04–2.22 (m, 1H), 2.24–2.38 (m, 1H), 2.56–2.74 (m, 1H), 3.62–3.72 (m, 2H), 4.03 (dd, *J* = 9.0, 4.4 Hz, 1H rotamer B), 4.10 (dd, *J* = 8.8, 3.9 Hz, 1H rotamer A), 4.22 (dd, *J* = 8.4, 8.4 Hz, 1H rotamer A), 4.27 (dd, *J* = 8.4, 8.4 Hz, 1H rotamer B), 9.67 (d, *J* = 4.4 Hz, 1H rotamer B), 9.71 (d, *J* = 3.7 Hz, 1H rotamer A); ^{13}C NMR ($CDCl_3$, 100 MHz, compound exists as a 1.2:1 mixture of rotamers) δ −5.8 (CH_3 rotamer A), −5.7 (CH_3 rotamer B), −5.7 (CH_3 rotamer B), −5.6 (CH_3 rotamer A), 18.1 (C), 25.7 (CH_3), 27.8 (CH_3 rotamer B), 28.0 (CH_3 rotamer A), 28.1 (CH_3 rotamer B), 28.2 (CH_3 rotamer A), 31.9 (CH_2 rotamer B), 32.4(CH_2 rotamer A), 44.3 (CH rotamer A), 45.5 (CH rotamer B), 59.5 (CH_2 rotamer A), 59.8 (CH_2 rotamer B), 60.3 (CH rotamer A), 60.6 (CH rotamer B), 67.3 (CH rotamer A), 67.6 (CH rotamer B), 81.0 (C rotamer A), 81.1 (C rotamer B), 81.4 (C), 153.5 (C rotamer B), 154.0 (C rotamer A), 171.2 (C rotamer B), 171.6 (C rotamer A), 201.0 (CH rotamer B), 201.1 (CH rotamer A); HRMS(ESI$^+$) *m/z* [M + Na]$^+$ calcd for $C_{22}H_{41}NO_6SiNa$ 466.2595, found 466.2562.

*(2S,4S,5S)-1,2-Di-tert-butyl 4-(tert-Butyldimethylsilanyloxymethyl)-5-formylpyrrolidine-1,2-dicarboxylate (**12**).* A solution of compound **11** (89 mg, 0.2 mmol) in THF (3 mL) was treated with DBU (61 mg, 0.4 mmol) and stirred at room temperature for 24 h. The reaction mixture was diluted with dichloromethane (30 mL), washed with saturated aqueous NH_4Cl solution (5 mL), dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The resulting residue was purified by flash chromatography (Eluent: ether/hexane, 1:2), to afford a mixture of diastereoisomers **12**/**11** in a ratio 93/7 (75 mg, 85%) as a white solid: IR (Nujol) 2728, 1737, 1721 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz, compound **12** exists as a 1:1 mixture of rotamers) δ 0.032 and 0.034 (s, 3H), 0.042 and 0.044 (s, 3H), 0.87 and 0.88 (s, 9H), 1.41 and 1.43 (s, 9H), 1.45 and 1.46 (s, 9H), 1.87–1.98 (m, 1H), 2.25–2.40 (m, 2H), 3.54–3.59 (m, 1H), 3.60–3.67 (m, 1H), 4.03 and 4.17 (dd, *J* = 6.3, 3.2 Hz and *J* = 5.7, 2.6 Hz, 1H), 4.22–4.33 (m, 1H), 9.42 and 9.52 (d, *J* = 3.2 Hz and *J* = 3.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz, compound exists as a 1:1 mixture of rotamers) δ −5.5 (CH_3), −5.5 (CH_3), 18.1 and 18.2 (C), 25.8 (CH_3), 27.9 and 28.0 (CH_3), 28.1 and 28.2 (CH_3), 30.7 and 31.5 (CH_2), 41.6 and 42.9 (CH), 59.9 and 60.4 (CH), 62.3 and 62.4 (CH_2), 67.5 and 67.6 (CH), 81.0 and 81.3 (C), 81.4 and 81.4 (C), 153.4 and 154.2 (C), 171.2 and 171.6 (C), 198.5 (CH); HRMS(ESI$^+$) *m/z* [M + Na]$^+$ calcd for $C_{22}H_{41}NO_6SiNa$ 466.2595, found 466.2593.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Crystallographic data (CIF) of tosyl derivatates **3** and **4**, copies of ^{1}H and ^{13}C NMR spectra for all compounds, and X-ray ORTEP diagrams of tosyl derivatates **3** and **4**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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