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A Concise Route to β-Cyclopropyl Amino Acids Utilizing 1,2-Dioxines and Stabilized Phosphonate Nucleophiles

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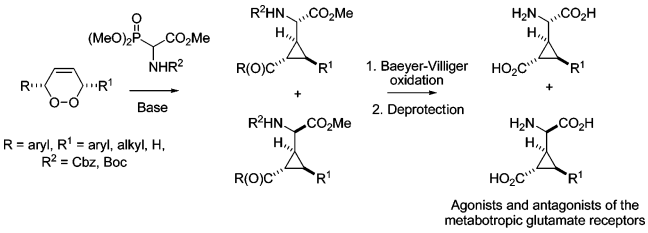
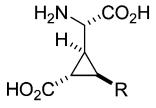


1,2-Dioxines react with glycine-derived phosphonate nucleophiles via a multistep cascade reaction to give β-cyclopropyl amino acid derivatives in good yield with excellent control of the cyclopropane stereocentres. The cyclopropyl ketones were oxidized to the corresponding carboxylic esters using Baeyer−Villiger conditions. Standard deprotection protocols produced a series of known β-cyclopropyl amino acids that are selective and potent agonists or antagonists of the metabotropic glutamate receptors in excellent yields.

Introduction

The cyclopropyl ring is a commonly employed structural motif within drugs and diagnostic chemical tools due to its rigidity and predictable geometry of pendant functional groups.[1] It has been demonstrated that certain cyclopropyl analogues of glutamate selectively bind metabotropic glutamate receptors (mGluR) and can protect against the excitotoxic effects of L-glutamate.[1] Clinically applied, this class of drugs (Figure 1) has the potential to treat neurological disorders such as ischemic stroke,[1] epliepsy,[2] and Parkinson's disease.[3] Substitution at the 3-position of the cyclopropyl ring can modulate the mode of action and affords ligands with significantly higher receptor affinity and specificity.[4−17] Despite recent advances,[18,19] current methodology is not sufficiently versatile to allow for the rapid synthesis of a large and diverse collection of this class of compounds. Consequently, identification of new more subtype selective and higher affinity analogues is advancing slowly.



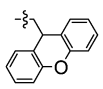
Metabotropic Glutamate Receptor			
Agonists R		Antagonists R	
H	**1**[4,12]	Ph	**6**[8,9]
Me	**2**[6]		**7**[7]
CH_2OH	**3**[5]		
CH_2OMe	**4**[10]		
CO_2H	**5**[11]		

FIGURE 1. Examples of selective agonists and antagonists of the metabotropic glutamate receptors.

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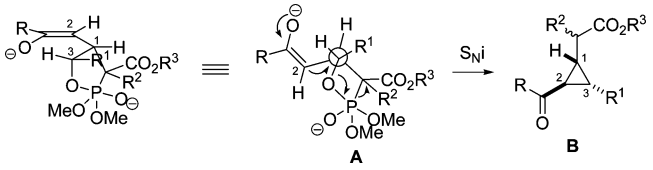
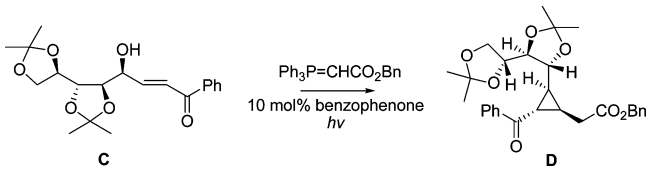
Cascade ring-closing reactions involving phosphine oxides,[20−23] phosphonates,[24−26] and phosphonium salts[27] have been employed by others for the construction of cyclopropanes generally with high stereospecificity and selectivity. We have recently reported that 1,2-dioxines (**8**, Scheme 1) react with stabilized phosphorus ylides[28−32] or phosphonate nucleophiles (**10**)[33] to afford di- and trisubstituted cyclopropyl ketones (**13**). Scheme 1 outlines the manifold common to phosphonates and shows the major cyclopropyl product **13**. In order for the cyclopropanation to occur, the 1,2-dioxine **8** must first undergo base-induced rearrangement to the *cis*-γ-hydroxyenone **9**. Aryl substitution (**8**, R = Ar) allows catalytic amounts of mild bases such as phosphorus ylides[30] or lithiated phosphonates[33] to be used for the isomerization, but Co(II) catalysis[28,30,31] must be used for alkyl substituted 1,2-dioxines. Conjugate addition of the phosphonate nucleophile **10** to the intermediate *cis*-γ-hydroxy enone gives oxaphospholane intermediate **11** which cyclizes intramolecularly to furnish cyclopropane **13** via enolate **12**.[34] However, if the *cis*-γ-hydroxy enone does not react with the phosphonate nucleophile under the reaction conditions a number of side-reactions are possible to give furan **14**, dicarbonyl **15** or *trans*-γ-hydroxy enone **16**. In the presence of hydroxide or alkoxide, both the *cis*-enone **9** and *trans*-enone **16** rapidly dimerize to produce tetrahydrofurans **17**.[35] It is important to note that phosphonate nucleophiles will not add to *trans*-γ-hydroxy enones, presumably due to unfavorable steric interactions.[36]

We envisaged that our methodology would be amenable to the synthesis of β-cyclopropyl amino acid derivatives by inclusion of an amino substituent on the phosphonate nucleophile (**10**, R^2 = NHR, Scheme 1). Protected phosphonoglycinates (**18**, Figure 2) are commonly used for the synthesis of dehydroamino acids[37−41] and are commercially available. This approach would generate all of the required stereogenic centers in a single step and, coupled with subsequent Baeyer−Villiger oxidation of the ketone, would provide the desired protected cyclopropyl amino acids (**20**) in two steps (Figure 2). Standard deprotection chemistry could then be applied to yield the β-cyclopropyl amino acids (**21**). We have previously reported one example of a 1,2-dioxine reacting with an α-substituted phosphonate (**10**, R^2 = Me) to give a trisubstituted cyclopropane with four contiguous stereogenic centers in a low yield (30%) with no selectivity in the formation of the α-stereocenter.[33] We now wish to report the reaction of protected phosphonoglycinates (**18**) with a series of 3,6-disubstituted 1,2-dioxines (**8**)

(34) A reviewer raised the point that if the *cis*-γ-hydroxy enones exist as the alkoxides under the basic reaction conditions then attack by the phosphonate nucleophile may occur from the opposite face to that described in Scheme 1, giving rise to intermediate **A**. Collapse of this intermediate via a S_Ni (frontside) displacement would then give rise to the cyclopropane diastereoisomer **B** in the opposite enantiomeric series.



The following scheme outlines the synthesis of cyclopropane **D** from *trans*-γ-hydroxy enone **C** (reaction of which proceeds via the *cis* γ-hydroxyenone)[36] of known absolute stereochemistry. The absolute stereochemistry of cyclopropane **D** was established by single-crystal X-ray crystallography and supports the mechanism for cyclopropanation shown in Scheme 1 and rules out the alternative depicted above.[52]



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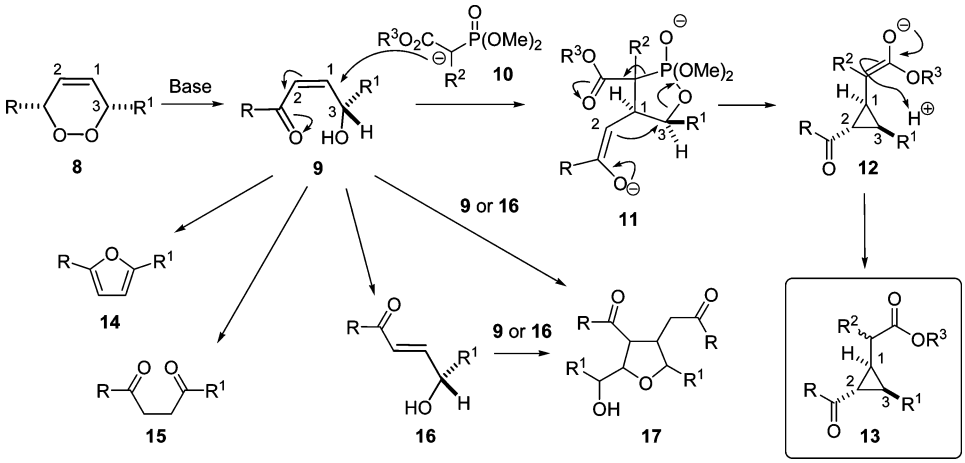
SCHEME 1. Cyclopropanation Cascade Reaction and Alternative Reaction Outcomes



and the conversion of the products into glutamate analogues (**21**) that are potent and selective inhibitors of the metabotropic glutamate receptors.

Results and Discussion

We decided to investigate the cyclopropanation using 1,2-dioxine **8a** (Table 1) and commercially available Cbz- (**22**) and Boc-protected (**23**) phosphonoglycines as well as an acetyl protected phosphonate (**24**), prepared as previously described.[38,39] Initially, the reaction was attempted using methyllithium in ether as reported by Kimber et al. for an α-methyl-substituted phosphonate.[33] However, under the reaction conditions, <10% of the target compound was obtained (entry 1, Table 1) and tetrahydrofurans (**17**, Scheme 1) predominated. We believed that the poor result was due to insufficient basicity of the lithiated phosphonates failing to generate the required *cis*-γ-hydroxy enones **9** in a timely manner. A slightly better outcome was achieved when *n*-butyllithium in hexane was used (entry 2), but again, we suspected that the low yield was due to insufficient basicity of the lithiated phosphonate. From previous work, we knew that the diisopropylamine byproduct from lithiation of the phosphonate with LDA catalyzes ring-opening to *cis*-γ-hydroxy enone,[30] allowing the cyclopropanation cascade reaction to proceed. Rearrangement of 1,2-dioxine to *cis*-γ-hydroxy enone was indeed observed at −78 °C using LDA; however, at this temperature the phosphonate nucleophile did not add to the enone and undesired side reactions predominated if the reaction was left at −78 °C. Nucleophilic addition of the phosphonate initialized at approximately −40 °C, however, the reaction gave higher yields at temperatures ≥-20 °C. To verify these observations and further optimize the reaction we screened a series of bases under three different reaction conditions (Table 1).

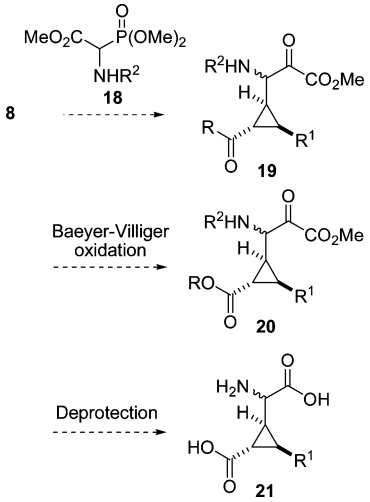
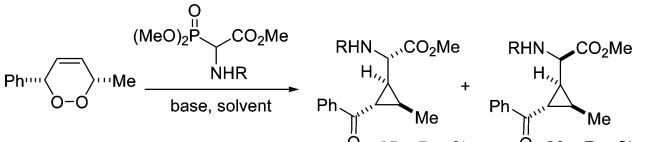


FIGURE 2. Synthetic strategy toward β-cyclopropyl amino acids.

As anticipated, LDA was superior to alkyllithium bases. Maintaining the temperature at −20 °C resulted in moderate yields of the desired cyclopropanes as ∼1:1 mixture of diastereoisomers. The use of LDA as its mono-THF complex in hexane or cyclohexane (entries 7−10) gave better yields of cyclopropane than LDA in THF (entries 4−6). Moreover, yields were significantly improved if the 1,2-dioxine was added to the deprotonated phosphonate and was further improved if the 1,2-

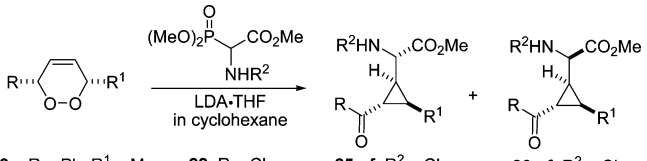
TABLE 1. Development of Cyclopropanation Cascade Reaction



entry	phosphonate	base*method*	yield[d] (%)
1	**22**	MeLi in diethyl ether[a−c]	<10[e]
2	**22**	*n*BuLi in hexane[a]	15
3	**22**	*n*BuLi in hexane[b,c]	23
4	**22**	LDA in THF[a]	38
5	**22**	LDA in THF[b]	39
6	**22**	LDA in THF[c]	20
7	**22**	LDA·THF in cyclohexane[a]	31
8	**22**	LDA·THF in cyclohexane[b]	53
9	**22**	LDA·THF in cyclohexane[c]	48
10[f]	**22**	LDA·THF in hexane[b]	51
11	**22**	LiHMDS in THF[a]	20
12	**22**	NaHMDS in THF[a]	17
13	**22**	DBU in CH_2Cl_2[a]	0
14	**22**	LiTMP in THF[a, c]	0
15	**23**	LDA in THF[b]	0
16	**23**	LDA·THF in cyclohexane[b]	50
17	**24**	LDA in THF[b]	0
18	**24**	LDA·THF in hexane[b]	0

[a] 0 °C for 0.5 h, warm slowly to rt overnight. [b] −20 °C for 0.5 h, warm slowly to rt overnight. [c] −20 °C for 5 h, warm slowly to rt overnight. [d] Combined isolated yield for both diastereoisomers, obtained as ∼1:1 mixture, determined by ^{1}H NMR of the crude reaction mixture. [e] Determined by ^{1}H NMR. [f] Reaction run at both 0.1 and 0.4 M to give the same yield.

TABLE 2. Synthesis of Cyclopropanes from Phosphonates and 1,2-Dioxines



8a, R = Ph, R^1 = Me
8b, R = Ph, R^1 = H
8c, R = R^1 = Ph
8d, R = Ph, R^1 = cyclohexyl
8e, R = Ph, R^1 = CH_2OTBS
8f, R = 2-MeOPh, R^1 = CH_2OTBS

22, R = Cbz
23, R = Boc

25a-f, R^2 = Cbz
27a-f, R^2 = Boc

26a-f, R^2 = Cbz
28a-f, R^2 = Boc

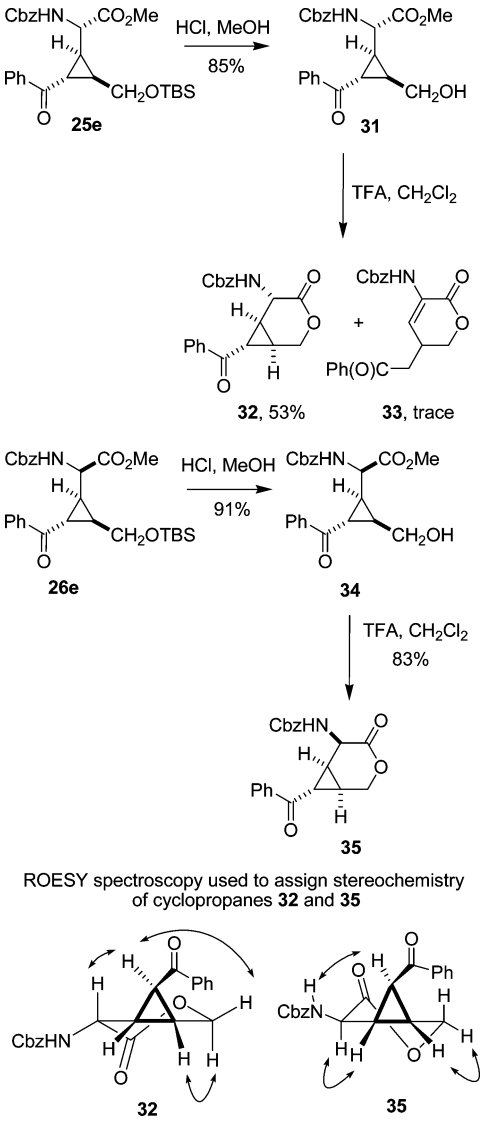
entry	1,2-dioxine	phosphonate	conditions	products	yield[c] (%)
1	**8b**	**22**	*a*	**25b**, **26b**	54
2	**8c**	**22**	*a*	**25c**, **26c**	47
3	**8d**	**22**	*a*	**25d**, **26d**	50
4	**8e**	**22**	*b*	**25e**, **26e**	67
5	**8f**	**23**	*a*	**27f**, **28f**	47
6	**8f**	**23**	*b*	**27f**, **28f**	66

[a] −20 °C for 0.5 h, warm slowly to rt overnight. [b] −20 °C for 5 h, warm slowly to rt overnight. [c] Combined isolated yield for both diastereoisomers, obtained as a ∼1:1 mixture, determined by ^{1}H NMR of the crude reaction mixture.

dioxine was added neat rather than as a THF solution. No concentration dependence was observed when the reaction was run at 0.1 M (entry 10) and 0.4 M (entry 10). We also investigated whether we could improve the reaction using amine bases or by replacing the lithium counterion with sodium or potassium. To this end, we chose to screen a wide range of bases commonly employed in the synthesis dehydroamino acids from phosphonoglycines [DBU,[38,41−43] (*i*-Pr)$_2$NEt,[44] tetramethyl guanidine,[45] *t*-BuOK,[38,39,46] NaH,[38,39,47,48] KHMDS,[37] and NaOMe[38]] as well as LiOH, K_2CO_3, DABCO, and LiTMP under a variety of conditions. However, in every case, these failed to give any cyclopropane product. The major products in most cases were THFs **17** (Scheme 1) in a diastereomeric ratio similar to that previously reported.[35] In addition, furan **14**, diketone **15**, and *trans*-γ-hydroxy enone **16** were also observed depending on conditions. LiHMDS (entry 11) and NaHMDS (entry 12) did produce cyclopropane product in low yields and were not pursued further as they were inferior to LDA. Exchanging the Cbz protection group for a Boc group gave a similar result when LDA mono-THF complex in cyclohexane was used (entry 16) but despite repeated attempts completely failed when LDA in THF (entry 15) was employed. The acetyl protected phosphonate **24** (entries 13 and 14) proved insoluble under the reaction conditions and thus no product was obtained.

From the data in Table 1 it is clear that the base used to lithiate the phosphonates is crucial to the reaction outcome. Considering the sensitivity of enone **9** to hydroxide and, in particular, alkoxide,[35] it is likely that even trace amounts of these

SCHEME 2. Stereochemical Determination of Related Cyclopropanes 25e and 26e



contaminants formed during the deprotonation are responsible for the low-yielding reactions and the THF byproducts. Moreover, the lithiated phosphonates generated using alkyllithium reagents (entries 1−3, Table 1) are not sufficiently basic to catalyze the formation of the required *cis*-γ-hydroxy enone as attested to by the presence of a significant amount of 1,2-dioxine starting material in these reactions. Hence, the diisopropylamine generated when using LDA proved essential for the cascade reaction to initiate. To evaluate the scope of the cyclopropanation, a series of 1,2-dioxines **8a**−**f** were allowed to react with *N*-Cbz- and *N*-Boc-protected phosphonoglycines (**22** and **23**) under the optimal conditions (Table 2).

All cyclopropanes were obtained in moderate to good yield with conserved stereochemistry about the cyclopropyl core. The stereogenic center adjacent to the cyclopropane ring was formed with little to no selectivity; however, the diastereomers were separable by column chromatography. It is interesting to note that extended reaction time at −20 °C can be beneficial with certain 1,2-dioxines improving yields significantly (entry 5 vs 6, Table 2).

The stereochemistry of the cyclopropane ring was determined using ^{1}H NMR coupling constants combined with 2D ROESY

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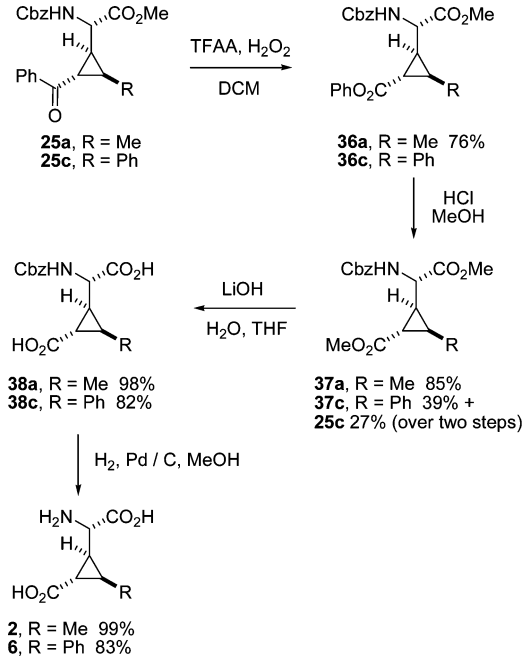
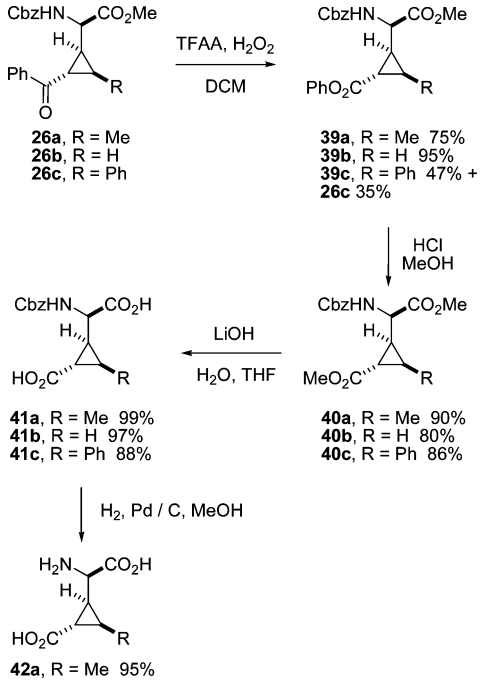
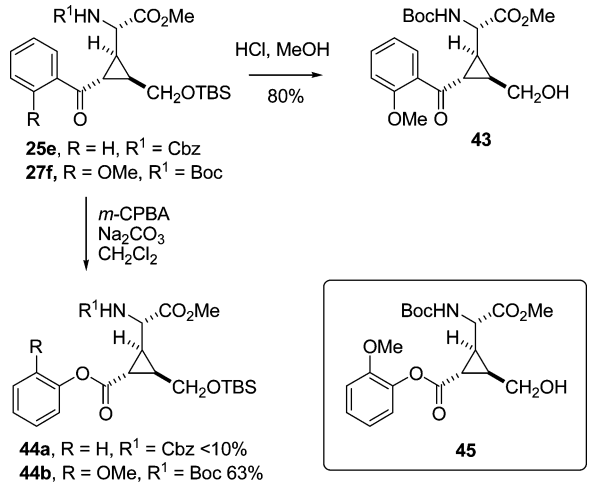
SCHEME 3. Baeyer−Villiger Oxidation of 25a,c and Subsequent Deprotection



SCHEME 4. Baeyer−Villiger Oxidation of 26a−c and Subsequent Deprotection



SCHEME 5. Oxidation and Protecting Group Manipulation of 25e and 27f



NMR. Typically, protons in a *trans* relationship about the cyclopropyl ring showed a coupling of 4.2−4.8 Hz, and a *cis* relationship gave a coupling of around 8.4−9.6 Hz. Assignment of the relative stereochemistry of the α-stereocenter was considerably more challenging. The stereochemistry of cyclopropanes **25e** and **26e** were determined by 2D ROESY NMR on the δ-lactone derivates **32** and **35** (Scheme 2). The initial attempt at preparing δ-lactone **32** by treatment with tetrabutylammonium fluoride only afforded the ring-opened material **33** in 37% yield. However, under acidic conditions, desilylation proceeded smoothly to give alcohol **31,** which subsequently could be lactonized using trifluoroacetic acid giving only trace amounts of ring-opened material **33**. By the same method, cyclopropane **26e** was deprotected and cyclized to give lactone **35** with no observed ring-opening. The stereochemistry of the α-stereocentre of the remaining cyclopropanes was determined unambiguously by single-crystal X-ray crystallography of **26a**, **26b**, **27a, 6**, **25d, 27f**, and **28f**.

Having successfully demonstrated that our methodology could produce a variety of densely substituted cyclopropanes, we decided to investigate their potential as useful building blocks for the synthesis of cyclopropane amino acids (Schemes 3 and 4). To this end, it was necessary to convert the pendant ketone to the corresponding carboxylic acid. A Baeyer−Villiger protocol using trifluoroacetic anhydride and hydrogen peroxide worked well giving moderate to excellent yields of the desired carboxylic esters **36a**,**c** (Scheme 3) and **39a**−**c** (Scheme 4).[49] As expected there was no evidence of cyclopropane ring migration onto oxygen due to its lower migratory aptitude compared to phenyl. Synthesis of carboxylic esters **36c** and **39c** using the triflouroacetic anhydride/hydrogen peroxide protocol did not reach completion under a range of conditions and significant amounts of starting material was recovered. As an alternative we tried using *m*-CPBA. This did indeed produce the desired Baeyer−Villiger products (**36c** and **39c**) in high yield; however, reaction times of 4−5 weeks were a considerable drawback making the triflouroacetic anhydride/hydrogen peroxide protocol our preferred method.

Next, we proceeded to fully deprotect the Baeyer−Villiger products through a simple three-step sequence involving a transesterification to give bis-methyl esters **37a**,**c** (Scheme 3) and **40a**−**c** (Scheme 4). Basic hydrolysis using aqueous lithium hydroxide in THF produced bis-carboxylic acids **38a**,**c** and **41a**−**c**. Catalytic hydrogenation of cyclopropanes **38a**,**c** and **41a** gave the known cyclopropane amino acids **2**[6] and **6**[8,9] as well as **42a** that to the best of our knowledge has not been reported previously.

Finally, we turned our attention to silyloxymethyl cyclopropanes **25e** and **27f** (Scheme 5). The Baeyer−Villiger protocol employing triflouroacetic anhydride and hydrogen peroxide unfortunately was not viable in these cases due to the presence

(49) Anastasia, M.; Allevi, P.; Ciuffreda, P.; Fiecchi, A.; Scala, A. *J. Org. Chem.* **1985**, *50*, 321−325.

of an acid sensitive TBS substituent. Moreover, the oxidation of **25e** using *m*-CPBA proved too sluggish only producing <10% of **44a** after 1 week (by ^{1}H NMR). The introduction of an *o*-methoxy substituent on the phenyl ring (**27f**) did, however, increase the rate of the Baeyer−Villiger reaction significantly, producing **44b** (Scheme 5), albeit contaminated with significant amounts of deprotected cyclopropane **45**. Cyclopropane **45** was prone to decomposition, presumably *via* lactonisation; in order to suppress formation of **45** the Baeyer−Villiger oxidation was buffered with Na_2CO_3, allowing formation of **44b** in good yield (63%), with no observed loss of the TBS protecting group. Cyclopropane **44b** is a protected form of the known mGluR agonist **3**.[5]

We also examined the possibility of selectively removing the TBS group in the presence of a Boc group while avoiding lactonization. This was easily accomplished using the conditions previously described for the Cbz-protected cyclopropanes **25e** and **26e** (Scheme 2). The free alcohol in cyclopropane **43** provides a useful handle for further chemical transformations[13] and, hence, synthesis of a diverse collection of β-cyclopropane amino acids after Baeyer−Villiger oxidation and deprotection.

Conclusion

Herein we have described our initial work on a new and mechanistically interesting cyclopropanation cascade reaction producing trisubstituted β-cyclopropyl amino acid precursors with four contiguous stereogenic centers. The stereogenic centers on the cyclopropyl core are formed with excellent selectivity whereas the method at present does not provide any control of the pendant stereogenic center. As a consequence, the method produces two cyclopropane diastereoisomers as a ∼1:1 mixture. The diastereoisomers are however separable and further transformations can be conducted to obtain single diastereoisomers of cyclopropyl glutamic acid analogues in a facile manner and in excellent yields. Work is currently under way to provide further mechanistic insight and to make the process diastereoselective and will be reported in due course.

Experimental Section

General Procedure for the Synthesis of 1,2-Dioxines 8a−f. A solution of the appropriate 1,3-butadiene (1 equiv) in anhydrous dichloromethane (25 mL/g of 1,3-butadiene) was irradiated with light from 3 × 500 W tungsten−halogen lamps at 0 °C in the presence of rose bengal bis(triethylammonium) salt (0.01 equiv) with oxygen bubbled through the solution for 6 h. The solution was concentrated and the resulting residue purified by flash column chromatography using 1:19 ethyl acetate/hexanes as elutent to yield pure 1,2-dioxine **8**. 1,2-Dioxines **8a**,[50] **8b**,[50] **8c**,[50] and **8d**[51]have previously been reported.

(±)-{[(3*R*,6*S*)-3,6-Dihydro-6-phenyl-1,2-dioxin-3-yl]methoxy}-(*tert*-butyl)dimethylsilane (8e): yield 1.55 g, 69%; colorless oil; R_f 0.35 (50% CH_2Cl_2 in hexane, v/v); IR (neat) 2984, 2928, 2857, 1471, 1256, 1129, 837 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.09 (s, 3H), 0.09 (s, 3H), 0.91 (s, 9H), 3.80 (dd, J = 5, 11 Hz, 1H), 3.99 (dd, J = 7, 11 Hz, 1H), 4.55−4.61 (m, 1H), 5.59−5.61 (m, 1H), 6.09−6.18 (m, 2H), 7.36 (s, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ −5.5, −5.2, 18.4, 25.9, 63.8, 79.8, 80.4, 125.3, 128.4, 128.5, 128.7, 129.0, 136.8; HRMS calcd for (M^+ + Na) $C_{17}H_{26}O_3SiNa$ 329.1549, found 329.1541.

(±)-{[(3*R*,6*S*)-3,6-Dihydro-6-(2-methoxyphenyl)-1,2-dioxin-3-yl]methoxy}(*tert*-butyl)dimethylsilane (8f): yield 4.11 g, 52%; colorless oil; R_f 0.45 (10% EtOAc in hexanes, v/v); IR (neat) 1602, 1493, 1463, 1438, 1287, 1250 cm^{-1}; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 0.078 (s, 3H), 0.083 (s, 3H), 0.90 (s, 9H), 3.76 (dd, J = 10.8, 4.8 Hz, 1H), 3.83 (s, 3H), 3.94 (dd, J = 10.8, 6.6 Hz, 1H), 4.60 (ddd, J = 6.6, 4.8, 1.8 Hz, 1H), 6.05 (br s, 1H), 6.07−6.11 (m, 2H), 6.87−6.89 (m, 1H), 6.90−6.94 (m, 1H), 7.27−7.34 (m, 2H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ −5.5, −5.3, 18.4, 25.9, 55.5, 63.8, 74.0, 79.7, 110.7, 120.4, 125.0, 125.4, 128.6, 129.1, 129.8, 157.4; EIMS *m*/*z* 336 (M^+, 4), 304 (32), 290 (55), 163 (96), 135 (54), 115 (30), 89 (100); HRMS calcd for (M + Na^+, ESI) $C_{18}H_{28}O_4Si_1Na_1$ 359.1655, found 359.1660.

General Procedure for the Reactions of 1,2-Dioxines with Phosphonates. Method A. (±)-Trimethyl-Boc-α-phosphonoglycinate or (±)-trimethyl-Cbz-α-phosphonoglycinate (0.75 mmol) was dissolved in anhydrous THF (3 mL) and cooled to 0 °C. LDA·THF complex (1.5 M in cyclohexane, 0.71 mmol) was added. After 30 min, the appropriate 1,2-dioxine (0.71 mmol) was added, and the reaction was allowed to slowly warm to room temperature overnight. Half-saturated aqueous NH_4Cl (5 mL) was added, and the slurry was transferred to a separatory funnel with water (10 mL) and extracted with EtOAc (25 + 2 × 10 mL). The organic phase was dried (Na_2SO_4), filtered, and concentrated in vacuo and the residue purified by column chromatography.

Method B. (±)-Trimethyl-Boc-α-phosphonoglycinate or (±)-trimethyl-Cbz-α-phosphonoglycinate (0.75 mmol) was dissolved in anhydrous THF (3 mL) and cooled to −78 °C. LDA·THF complex (1.5 M in cyclohexane, 0.71 mmol) was added. After 30 min, the appropriate 1,2-dioxine (0.71 mmol) was added, and the temperature was raised to −20 °C. After 30 min, the reaction mixture was allowed to slowly warm to room temperature overnight and then worked up and purified as described in Method A.

Method C. (±)-Trimethyl-Boc-α-phosphonoglycinate or (±)-trimethyl-Cbz-α-phosphonoglycinate (0.75 mmol) was dissolved in anhydrous THF (3 mL) and cooled to −78 °C. LDA·THF complex (1.5 M in cyclohexane, 0.71 mmol) was added. After 30 min, the appropriate 1,2-dioxine (0.71 mmol) was added, and the temperature was raised to −20 °C. After 5 h, the reaction was allowed to slowly warm to room temperature overnight and then worked up and purified as described in method A.

(±) (*S*)-Methyl 2-[(1*S*,2*S*,3*R*)-2-Benzoyl-3-methylcyclopropyl]-2-{[(benzyloxy)carbonyl]amino}ethanoate 25a: colorless solid; mp 57−60 °C; R_f 0.40 (30% EtOAc in hexanes, v/v); IR (Nujol) 3304, 1747, 1694, 1655, 1550, 1250 cm^{-1}; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 1.41 (d, J = 6.0 Hz, 3H), 1.87 (ddq, J = 9.0, 6.0, 4.2 Hz, 1H), 1.95 (ddd, J = 9.6, 9.0, 4.2 Hz, 1H), 2.75 (dd, J = 4.2, 4.2 Hz, 1H), 3.80 (s, 3H), 4.28 (dd, J = 9.6, 9.0 Hz, 1H), 5.07 (d, J = 12.0 Hz, 1H), 5.13 (d, J = 12.0 Hz, 1H), 5.55 (br d, J = 9.0 Hz, 1H), 7.27−7.29 (m, 5H), 7.42−7.45 (m, 2H), 7.54−7.56 (m, 1H), 7.96−7.98 (m, 2H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 13.2, 25.4, 30.9, 34.0, 52.7, 52.8, 67.1, 127.9, 128.1, 128.5, 128.5, 132.9, 136.0, 137.5, 156.0, 171.4, 198.6, (1 masked aromatic); EIMS *m*/*z* 381 (M^+, 5), 322 (20), 278 (30), 159 (40), 91 (100). Anal. Calcd for $C_{22}H_{23}O_5N_1$: C, 69.28; H, 6.08; N, 3.67. Found: C, 69.28; H, 5.92; N, 3.53.

(±) (*R*)-Methyl 2-[(1*S*,2*S*,3*R*)-2-benzoyl-3-methylcyclopropyl]-2-{[(benzyloxy)carbonyl]amino}ethanoate 26a: colorless solid; mp 137−139 °C (CH_2Cl_2/hexane); R_f 0.36 (30% EtOAc in hexanes, v/v); IR (nujol) 3320, 1753, 1694, 1648, 1539, 1224 cm^{-1}; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 1.30 (d, J = 6.0 Hz, 3H), 1.84−1.89 (m, 2H), 2.66 (dd, J = 4.2, 4.2 Hz, 1H), 3.67 (s, 3H), 4.15 (dd, J = 9.0, 9.0 Hz, 1H), 5.12 (d, J = 12.6 Hz, 1H), 5.14 (d, J = 12.6 Hz, 1H), 5.37 (br d, J = 9.0 Hz, 1H), 7.31−7.37 (m, 5H), 7.47−7.40 (m, 2H), 7.56−7.59 (m, 1H), 7.98−7.99 (m, 2H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 12.4, 23.8, 31.4, 32.0, 52.5, 52.9, 67.2, 128.0, 128.2,

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128.5, 128.5, 133.0, 136.0, 137.5, 155.5, 172.0, 198.1 (1 masked aromatic); EIMS *m*/*z* 381 (M^+, 7), 322 (25), 278 (30), 230 (40), 91 (100). Anal. Calcd for $C_{22}H_{23}O_5N_1$: C, 69.28; H, 6.08; N, 3.67. Found: C, 69.30; H, 6.03; N, 3.53.

(±) (*S*)-Methyl 2-[(1*S*,2*S*,3*R*)-2-benzoyl-3-({[(*tert*-butyl)-1,1-dimethylsilyl]oxy}methyl)cyclopropyl]-2-{[(benzyloxy)carbonyl]-amino}ethanoate 25e: colorless oil; R_f 0.28 (20% EtOAc in hexanes, v/v); IR (neat) 3334, 2953, 2929, 1747, 1723, 1669, 1522, 1452, 1253, 1050, 837 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 0.09 (s, 6H), 0.89 (s, 9H), 1.95−2.11 (m, 2H), 3.05 (dd, J = 4.8, 4.8 Hz, 1H), 3.80 (s, 3H), 3.90−4.07 (m, 2H), 4.54 (dd, J = 9.0, 8.6 Hz, 1H), 5.06 (d, J = 11.9 Hz, 1H), 5.11 (d, J = 11.9 Hz, 1H), 5.74 (d, J = 8.6 Hz, 1H), 7.22−7.59 (m, 8H), 8.00−8.04 (m, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz) −5.43, 18.1, 25.7, 27.2, 31.6, 52.5, 52.6, 60.5, 67.0, 127.9, 128.0, 128.2, 128.3, 128.4, 132.9, 136.1, 137.4, 155.8, 171.5, 198.3; EIMS *m*/*z* 511 (M^+, 7), 496 (25), 454 (65), 105 (80), 91 (100); HRMS calcd for (M + Na^+, ESI) $C_{28}H_{37}O_6N_1SiNa$ 534.2287, found 534.2284.

(±) (*R*)-Methyl 2-[(1*S*,2*S*,3*R*)-2-benzoyl-3-({[(*tert*-butyl)-1,1-dimethylsilyl]oxy}methyl)cyclopropyl]-2-{[(benzyloxy)carbonyl]-amino}ethanoate 26e: colorless oil; R_f 0.25 (20% EtOAc in hexanes, v/v); IR (neat) 3346, 2953, 2929, 2856, 1748, 1725, 1669, 1522, 1452, 1260, 1218 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.03 (s, 3H), 0.55 (s, 3H), 0.88 (s, 9H), 1.95−2.06 (m, 2H), 2.96 (dd, J = 4.8, 4.8 Hz, 1H), 3.68 (s, 3H), 3.80 (dd, J = 11.4, 6.3 Hz, 1H), 3.94 (dd, J = 11.4, 5.1 Hz, 1H), 4.21 (dd, J = 8.7, 6.9 Hz, 1H), 5.06−5.15 (m, 2H), 5.61 (d, J = 6.9 Hz, 1H), 7.30−7.34 (m, 5H), 7.44−7.50 (m, 2H), 7.55−7.60 (m, 1H), 7.99−8.02 (m, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz) −5.48, −5.44, 18.1, 25.7, 27.3, 29.9, 30.0, 52.4, 53.1, 60.1, 67.0, 128.1, 128.1, 128.4, 128.5, 133.1, 136.0, 137.3, 155.6, 171.8, 197.7 (1 masked aromatic); EIMS *m*/*z* 511 (M^+, 5), 495 (30), 453 (50), 105 (60), 91 (100); HRMS calcd for (M + Na^+, ESI) $C_{28}H_{37}O_6N_1SiNa$ 534.2287, found 534.2283.

(±)-(*S*)-Methyl 2-(*tert*-Butoxycarbonylamino)-2-{(1*S*,2*R*,3*R*)-2-[(*tert*-butyldimethylsilyloxy)methyl]-3-(2-methoxybenzoyl)-cyclopropyl}ethanoate 27f: colorless oil; R_f 0.56 (30% EtOAc in hexanes, v/v); IR (neat) 3358, 1747, 1714, 1662, 1598, 1579, 1487, 1463, 1438, 1365, 1326, 1285, 1251 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz) δ 0.02 (s, 3H), 0.04 (s, 3H), 0.85 (s, 9H), 1.39 (s, 9H), 1.98−2.02 (m, 2H), 2.90 (dd, J = 4.8, 4.8 Hz, 1H), 3.75 (s, 3H), 3.84−3.98 (m, 5H), 4.23 (dd, J = 7.8, 7.8 Hz, 1H), 5.32 (br d, J = 7.8 Hz, 1H), 6.95−7.00 (m, 2H), 7.42−7.45 (m, 1H), 7.57−7.59 (m, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ −5.42, −5.39, 18.1, 25.8, 28.3, 31.3, 31.5, 32.2, 52.2, 52.4, 55.6, 60.6, 79.9, 111.5, 120.7, 129.0, 130.1, 133.3, 155.2, 158.4, 172.3, 200.6; EIMS *m*/*z* 507 (M^+, <1), 450 (6), 394 (62), 350 (10), 333 (12), 216 (14), 135 (100), 57 (78). Anal. Calcd for $C_{26}H_{41}O_7Si_1N_1$: C, 61.51; H, 8.14; N, 2.76. Found: C, 61.73; H, 8.18; N, 2.62.

(±) (*R*)-Methyl 2-(*tert*-butoxycarbonylamino)-2-{(1*S*,2*R*,3*R*)-2-[(*tert*-butyldimethylsilyloxy)methyl]-3-(2-methoxybenzoyl)-cyclopropyl}ethanoate 28f: colorless solid; mp 97−98 °C; R_f 0.45 (30% EtOAc in hexanes, v/v); IR (Nujol) 3385, 1749, 1713, 1651, 1598, 1257, 1209, 1157 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz) δ 0.038 (s, 3H), 0.043 (s, 3H), 0.87 (s, 9H), 1.41 (s, 9H), 1.95 (dddd, J = 9.0, 7.8, 5.4, 4.8 Hz, 1H), 2.02 (ddd, J = 9.0, 9.0, 4.8 Hz, 1H), 2.95 (dd, J = 4.8, 4.8 Hz, 1H), 3.61 (dd, J = 9.6, 9.0 Hz, 1H), 3.66 (s, 3H), 3.89 (s, 3H), 3.93−3.96 (m ,2H), 5.39 (br s), 6.94−6.98 (m, 2H), 7.42−7.45 (m, 1H), 7.57−7.58 (m, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ −5.44, −5.41, 18.2, 25.9, 28.3, 29.7, 30.8, 31.8, 52.2, 53.5, 55.5, 60.7, 80.0, 111.6, 120.6, 128.6, 130.1, 133.5, 155.3, 158.6, 172.2, 199.8; EIMS *m*/*z* 507 (M^+, <1), 450 (32), 394 (36), 350 (5), 319 (7), 135 (75), 57 (100). Anal. Calcd for $C_{26}H_{41}O_7Si_1N_1$: C, 61.51; H, 8.14; N, 2.76. Found: C, 61.46; H, 8.07; N, 2.65.

(±)-(*S*)-Methyl 2-[(1*S*,2*S*,3*R*)-2-benzoyl-3-methylcyclopropyl]-2-(*tert*-butoxycarbonylamino)ethanoate 27a: colorless solid; mp 100−101 °C; R_f 0.31 (7% diethyl ether in benzene, v/v); IR (Nujol) 3390, 1744, 1699, 1660, 1598, 1581, 1515, 1259, 1238 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.39−1.50 (m, 12H), 1.88−1.92 (m, 2H), 2.81 (dd, J = 4.8, 4.8 Hz, 1H), 3.81 (s, 3H), 4.25 (dd, J = 9.9, 8.7 Hz, 1H), 5.37 (br d, J = 8.4 Hz, 1H), 7.42−7.47 (m, 2H), 7.53−7.58 (m, 1H), 8.00−8.02 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.2, 25.4, 28.2, 30.8, 35.1, 52.2, 52.6, 80.0, 128.2, 128.5, 132.9, 137.6, 155.4, 171.7, 199.0; EIMS *m*/*z* 347 (M^+, 4), 188 (85), 159 (62), 105 (100), 77 (47); HRMS calcd for (M + Na^+, ESIMS) $C_{19}H_{25}O_5N_1Na_1$ 370.1630, found 370.1622.

(±)-(*R*)-Methyl 2-[(1*S*,2*S*,3*R*)-2-benzoyl-3-methylcyclopropyl]-2-(*tert*-butoxycarbonylamino)ethanoate 28a: colorless solid; mp 152−153 °C; R_f 0.22 (7% diethyl ether in benzene, v/v); IR (Nujol) 3288, 1755, 1744, 1681, 1667, 1598, 1581, 1532, 1297, 1230 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.31 (d, J = 6.0 Hz, 3H), 1.46 (s, 9H), 1.83−1.89 (m, 2H), 2.66 (d, J = 4.5, 4.5 Hz, 1H), 3.68 (s, 3H), 4.07 (dd, J = 8.4, 8.4 Hz, 1H), 5.21 (br d, J = 8.1 Hz, 1H), 7.46−7.51 (m, 2H), 7.55−7.61 (m ,1H), 7.98−8.01 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 12.4, 23.8, 28.2, 31.5, 32.2, 52.4, 80.2, 128.1, 128.5, 133.0, 137.5, 154.9, 172.4, 198.3. Anal. Calcd for $C_{19}H_{25}O_5N_1$: C, 65.69; H, 7.25; N, 4.03. Found: C, 65.91; H, 7.34; N, 4.15.

General Procedure for the Baeyer−Villiger Oxidation of Cyclopropanes 25−28. A solution of cyclopropane in dichloromethane (0.06 M) was added dropwise to trifluoroperacetic acid [prepared by adding trifluoroacetic anhydride (275 equiv) to 30% aqueous hydrogen peroxide (62.5 equiv) in dichloromethane (70 mL per gram of cyclopropane)][49] in dichloromethane at 0 °C, maintaining the reaction temperature at 0 °C. The reaction was allowed to stir (∼5−16 h) at 0 °C until complete (TLC), at which time it was poured into a 2% aqueous potassium carbonate solution and extracted with dichloromethane. The combined extracts were washed with water, dried ($MgSO_4$), filtered, and concentrated in vacuo, and the crude cyclopropane (**36** or **39**) was purified by flash column chromatography.

General Procedure for the Transesterification of Cyclopropanes 36 and 39. To a solution of cyclopropane in anhydrous methanol (0.03 M) was added concd sulfuric acid (1 drop) and the solution refluxed overnight. The volatiles were removed in vacuo, and the crude cyclopropane (**37** or **40**) was purified by column chromatography.

General Procedure for the Hydrolysis of Cyclopropanes 37 and 40.[5] To a solution of cyclopropane in THF (0.035 M) was added a 2.5 M solution of $LiOH{\cdot}H_2O$ (40 equiv) and the mixture stirred overnight. Brine was added, the aqueous layer was washed with ethyl acetate, and the aqueous layer was then acidified to pH 1 with 1 M HCl and extracted with ethyl acetate. The combined organic fractions were dried ($MgSO_4$), filtered, and concentrated in vacuo to give cyclopropane (**38** or **41**).

(±)-(1*S*,2*S*,3*R*)-Phenyl 2-[(*S*)-1-(benzyloxycarbonylamino]-2-methoxy-2-oxoethyl)-3-methylcyclopropanecarboxylate 36a: yield (351 mg, 76%); colorless oil; R_f 0.6 (30% EtOAc in hexanes, v/v); IR (neat) 3335, 1731, 1715, 1694, 1593, 1331 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.37 (d, J = 5.7 Hz, 3H), 1.77−1.89 (m, 3H), 3.77 (s, 3H), 4.15 (dd, J = 9.9, 8.7 Hz, 1H), 5.09 (d, J = 12.0 Hz, 1H), 5.17 (d, J = 12.0 Hz, 1H), 5.71 (br d, J = 8.7 Hz, 1H), 7.04−7.06 (m, 2H), 7.17−7.37 (m, 8H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 12.8, 23.1, 25.9, 30.5, 52.3, 52.6, 67.1, 121.4, 125.7, 128.0, 128.1, 128.5, 129.2, 136.0, 150.5, 155.9, 171.5, 171.6; EIMS *m*/*z* 397 (M^+, 1), 304 (21), 196 (23), 168 (17), 108 (15), 91 (100); HRMS calcd for (M + Na^+, ESI) $C_{22}H_{23}O_6N_1Na$ 420.1423, found 420.1410.

(±)-(1*S*,2*S*,3*R*)-Methyl 2-[(*S*)-1-(benzyloxycarbonylamino]-2-methoxy-2-oxoethyl)-3-methylcyclopropanecarboxylate 37a: yield (354 mg, 95%); colorless oil; R_f 0.5 (30% EtOAc in hexanes, v/v); IR (neat) 3342, 1750, 1731, 1715, 1526, 1455, 1332 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.30 (d, J = 5.4 Hz, 3H), 1.59−1.75 (m, 3H), 3.65 (s, 3H), 3.78 (s, 3H), 4.06 (dd, J = 9.0, 9.0 Hz, 1H), 5.09 (d, J = 12.0 Hz, 1H), 5.14 (d, J = 12.0 Hz, 1H), 5.53 (br d, J = 9.0 Hz, 1H), 7.27−7.40 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 12.8, 22.3, 25.8, 29.8, 51.9, 52.4, 52.6, 67.1, 128.1, 128.2, 128.5, 136.1, 155.8, 171.6, 173.6; EIMS *m*/*z* 335 (M^+, 1), 276, (11), 232,

(11), 113 (52), 91 (100); HRMS calcd for (M + Na^+, ESI) $C_{17}H_{21}O_6N_1Na$ 358.1267, found 358.1266.

(±)-(1*S*,2*S*,3*R*)-2-[(*S*)-(Benzyloxycarbonylamino)(carboxy)-methyl]-3-methylcyclopropanecarboxylic Acid 38a: yield (289 mg, 98%); colorless solid; mp 201−202 °C; IR (Nujol) 3309, 3092, 1742, 1693, 1681, 1543, 1294, 1244 cm^{-1}; ^1H NMR ($CDCl_3$/DMSO, 300 MHz) δ 1.31 (d, J = 6.0 Hz, 3H), 1.55 (dd, J = 4.2, 4.2 Hz, 1H), 1.65 (ddq, J = 9.6, 6.0, 4.2 Hz, 1H), 1.76 (ddd, J = 9.6, 9.6. 4.2 Hz, 1H), 4.01 (dd, J = 9.6, 9.6 Hz, 1H), 5.04−5.15 (m, 2H), 5.75 (br d, J = 9.6 Hz, 1H), 7.28−7.36 (m, 5H), 10.91 (br s, 2H); ^{13}C NMR ($CDCl_3$/DMSO, 75 MHz) δ 12.8, 22.4, 25.9, 30.1, 52.3, 66.8, 127.87, 127.93, 128.4, 136.2, 155.9, 173.3, 176.1; HRMS calcd for (M + Na^+, ESI) $C_{15}H_{17}O_6N_1Na$ 330.0954, found 330.0952.

(±)-(1*S*,2*S*,3*R*)-2-[(*S*)-Amino(carboxy)methyl]-3-methylcyclopropanecarboxylic Acid 2.[6] To a solution of **38a** (100 mg, 0.33 mmol) in methanol (7 mL) was added 10% Pd/C (18 mg) and the mixture stirred overnight under an atmosphere of hydrogen. Water (10 mL) was added and the solution filtered through Celite, washing with water. The methanol was removed in vacuo and the aqueous solution extracted with ethyl acetate. The aqueous layer was evaporated to give amino acid **2**: yield (56 mg, 99%); colorless solid; dec 213 °C (lit.[6] mp 178−180 °C); IR (solid) 3013, 2606, 1689, 1644, 1601, 1534, 1459, 1446, 1401, 1383, 1364, 1307 cm^{-1}; ^1H NMR (D_2O, 200 MHz) δ 1.26 (d, J = 5.6 Hz, 3H), 1.52 (dd, J = 4.6, 4.6 Hz, 1H), 1.64−1.84 (m, 2H), 3.42−3.54 (m, 1H); ^{13}C NMR (D_2O, 75 MHz) δ 14.1, 24.6, 28.9, 29.8, 55.9, 175.3, 180.3. Anal. Calcd for $C_7H_{11}O_4N_1$: C, 48.55; H, 6.40; N, 8.09. Found: C, 48.40; H, 6.40; N, 8.00.

(±)-(1*S*,2*S*,3*R*)-Methyl 2-[(*S*)-1-(benzyloxycarbonylamino)-2-methoxy-2-oxoethyl]-3-phenylcyclopropanecarboxylate 37c: yield (81 mg, 39% over two steps + **25c** 27% recovered); colorless solid; mp 106−107 °C; R_f 0.4 (30% EtOAc in hexanes, v/v); IR (neat) 3302, 1739, 1722, 1682, 1547, 1456, 1281 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.10 (ddd, J = 9.6, 9.6, 4.8 Hz, 1H), 2.61 (dd, J = 4.8, 4.8 Hz, 1H), 2.93 (dd, J = 9.6, 4.8 Hz, 1H), 3.61 (s, 3H), 3.73 (s, 3H), 3.89 (dd, J = 9.6, 9.6 Hz, 1H), 5.09 (d, J = 12.0 Hz, 1H), 5.14 (d, J = 12.0 Hz, 1H), 5.51 (br d, J = 9.6 Hz, 1H), 7.25−7.42 (m, 10H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 22.7, 31.8 (masked carbon), 51.7, 52.1, 52.4, 67.1, 127.1, 128.0, 128.2, 128.3, 128.5, 128.6, 134.3, 136.1, 155.8, 171.1, 173.1. Anal. Calcd for $C_{22}H_{23}O_6N_1$: C, 66.49; H, 5.83; N, 3.52. Found: C, 66.58; H, 5.87; N, 3.45.

(±)-(1*S*,2*S*,3*R*)-2-[(*S*)-(Benzyloxycarbonylamino)(carboxy)-methyl]-3-phenylcyclopropanecarboxylic acid 38c: yield (211 mg, 82%); colorless solid; mp 184−185 °C; IR (nujol) 3304, 3090, 1738, 1694, 1682, 1538, 1218, 1066 cm^{-1}; ^1H NMR ($CDCl_3$/DMSO, 300) δ 2.15 (ddd, J = 9.0, 9.0, 5.7 Hz, 1H), 2.50 (dd, J = 5.7, 5.7 Hz, 1H), 2.93 (dd, J = 9.0, 5.7 Hz, 1H), 3.81 (dd, J = 9.0, 9.0 Hz, 1H), 4.83−5.32 (m, 2H), 5.82 (br d, J = 9.0 Hz, 1H), 7.16−7.44 (m, 5H), 10.55 (br s, 2H); ^{13}C NMR ($CDCl_3$/DMSO, 75 MHz) δ 22.7, 31.9 (masked carbon), 51.4, 66.6, 126.6, 127.7, 127.8, 128.0, 128.3, 128.8, 134.8, 136.1, 155.9, 172.5, 175.0. Anal. Calcd for $C_{20}H_{19}O_6N_1$: C, 65.03; H, 5.18; N, 3.69; Found: C, 64.63; H, 5.12; N, 3.69.

(±)-(1*S*,2*S*,3*R*)-2-[(*S*)-Amino(carboxy)methyl]-3-phenylcyclopropanecarboxylic Acid 6.[8] To a solution of **38c** (81 mg, 0.22 mmol) in methanol (5 mL) was added 10% Pd/C (10 mg) and the mixture stirred overnight under an atmosphere of hydrogen. Dilute HCl solution (10 mL) was added and the mixture filtered through Celite, washing with dilute HCl. The solution was taken to dryness in vacuo, and then anhydrous methanol (2 mL) and propylene oxide (5 mL) were added and the mixture stirred over night at ambient temperature. The precipitated amino acid **6** was filtered, washed with methanol, and dried in vacuo to give pure cyclopropane **6**: yield (43 mg, 83%); colorless solid; dec 200 °C (lit.[8] mp 217−218 °C). All data were consistent with that reported in the literature.[8]

(±)-(1*S*,2*S*,3*R*)-Phenyl 2-[(*R*)-1-(benzyloxycarbonylamino]-2-methoxy-2-oxoethyl)-3-methylcyclopropanecarboxylate 39a: yield (156 mg, 75%); colorless oil; R_f 0.4 (30% EtOAc in hexanes, v/v); IR (neat) 3351, 1746, 1724, 1709, 1593, 1524, 1494, 1454, 1436, 1327 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.29 (d, J = 5.7 Hz, 3H), 1.68−1.86 (m, 3H), 3.81 (s, 3H), 4.06 (dd, J = 8.7, 8.4 Hz, 1H), 5.08−5.17 (m, 2H), 5.46 (br d, J = 8.4 Hz, 1H), 7.03−7.10 (m, 2H), 7.18−7.25 (m, 1H), 7.31−7.41 (m, 7H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 12.17, 21.8, 26.7, 29.4, 52.5, 52.7, 67.2, 121.4, 125.8, 128.1, 128.2, 128.5, 129.4, 136.0, 150.6, 155.5, 171.4, 172.1; EIMS m/z 397 (M^+, 3), 355 (8), 305, (42), 261 (15), 171 (16), 91 (100); HRMS calcd for (M + Na^+, ESI) $C_{22}H_{23}O_6N_1Na$ 420.1423, found 420.1420.

(±)-(1*S*,2*S*,3*R*)-Methyl 2-[(*R*)-1-(benzyloxycarbonylamino]-2-methoxy-2-oxoethyl)-3-methylcyclopropanecarboxylate 40a: yield (201 mg, 90%); colorless oil; R_f 0.3 (30% EtOAc in hexanes, v/v); IR (neat) 3349, 1744, 1731, 1714, 1525, 1454, 1332, 1278, 1216 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.20 (d, J = 5.7 Hz, 3H), 1.52−1.71 (m, 3H), 3.66 (s, 3H), 3.76 (s, 3H), 3.96 (dd, J = 9.0, 9.0 Hz, 1H), 5.45 (br d, J = 9.0 Hz, 1H), 7.31−7.40 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 12.1, 21.0, 26.4, 28.5, 51.9, 52.5, 52.6, 67.1, 128.0, 128.2, 128.5, 136.0, 155.4, 172.1, 173.2; EIMS m/z 335 (M^+, 31), 291 (59), 231 (100), 181 (56. Anal. Calcd for $C_{17}H_{21}O_6N_1$: C, 60.89; H, 6.44; N, 4.18. Found: C, 61.02; H, 6.44; N, 4.22.

(±)-(1*S*,2*S*,3*R*)-2-[(*R*)-(Benzyloxycarbonylamino)(carboxy)-methyl]-3-methylcyclopropanecarboxylic acid 41a: yield (354 mg, 99%); colorless solid; mp 179−180 °C; IR (nujol) 3331, 1711, 1683, 1533, 1309, 1274, 1233 cm^{-1}; ^1H NMR ($CDCl_3$, 300) δ 1.22 (d, J = 5.7 Hz, 3H), 1.56−1.74 (m, 3H), 3.91 (dd, J = 9.0, 8.4 Hz, 1H), 5.04−5.13 (m, 2H), 5.79 (br d, J = 8.4 Hz, 1H), 7.25−7.31 (m, 5H), 10.72 (br s, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 12.0, 21.9, 26.6, 28.9, 52.5, 67.3, 128.1, 128.2, 128.5, 135.9, 155.8, 177.3, 179.2; EIMS m/z 307 (M^+, 2), 289 (19), 218 (28), 153 (40), 127 (66), 44 (100). Anal. Calcd for $C_{15}H_{17}O_6N_1$: C, 58.63; H, 5.58; N, 4.56; Found: C, 58.58; H, 5.54; N, 4.60.

(±)-(1*S*,2*S*,3*R*)-2-[(*R*)-Amino(carboxy)methyl]-3-methylcyclopropanecarboxylic Acid 42a. To a solution of **41a** (110 mg, 0.36 mmol) in methanol (7 mL) was added 10% Pd/C (18 mg) and the mixture stirred overnight under an atmosphere of hydrogen. Water (10 mL) was added and the solution filtered through Celite, washing with water. The methanol was removed in vacuo and the aqueous solution extracted with ethyl acetate. The aqueous layer was evaporated to give amino acid **42a**: yield (59 mg, 95%); colorless solid; dec 216 °C; IR (solid) 3054, 2587, 1682, 1604, 1511, 1401, 1359, 1332, 1240 cm^{-1}; ^1H NMR (D_2O, 200 MHz) δ 1.24 (d, J = 5.4 Hz, 3H), 1.63−1.79 (m, 3H), 3.44 (br d, J = 9.8 Hz, 1H); ^{13}C NMR (D_2O, 75 MHz) δ 13.1, 22.9, 28.8, 29.4, 54.8, 175.8, 179.5. Anal. Calcd for $C_7H_{11}O_4N_1$: C, 48.55; H, 6.40; N, 8.09. Found: C, 48.27; H, 6.61; N, 7.79.

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Supporting Information Available: Experimental details for compounds **25b**, **26b**, **25c**, **26c**, **25d**, **26d**, **31**−**35**, **39b**, **40b**, **41b**, **39c**, **40c**, **41c**, **43**, and **44b**; ^{13}C NMR spectra for compounds **8f**, **25a**, **26a**,**b**, **26c**, **25e**, **26e**, **27f**, **28f**, **27a**, **28a**, **31**−**34**, **36a**, **38a**, **2**, **38c**, **39a**, **40a**, **41a**, **42a**, **39b**, **40b**, **41b**, **40c**, **41c**, **43**, and **44b**; and ^1H NMR spectra for compounds **8e**, **25b**−**d**, **26d, 35, 37a,c**, and **39c**. Crystallographic data and CIF files for **26a**, **26b**, **27a, 6**, **25d, 27f**, and **28f**. This material is available free of charge via the Internet at http://pubs.acs.org.

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