

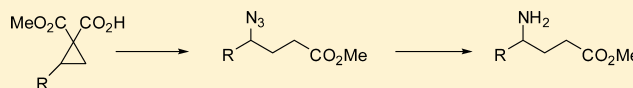
Tandem Ring-Opening Decarboxylation of Cyclopropane Hemimalonates with Sodium Azide: A Short Route to γ -Aminobutyric Acid Esters

Michael R. Emmett, Huck K. Grover, and Michael A. Kerr*

Department of Chemistry, Western University, London, Ontario, Canada N6A 5B7

S Supporting Information

ABSTRACT: Cyclopropane hemimalonates, when treated with sodium azide, undergo a tandem ring-opening decarboxylation to produce γ -azidobutyric acids in good yields. These adducts were hydrogenated to form γ -aminobutyric acid (GABA) methyl esters.



γ -Aminobutyric acid (GABA) is an inhibitory neurotransmitter in the central nervous system.¹ Though the roles of GABA are varied and complex, in humans GABA plays a central part in the regulation of muscle tone. With its many roles in the human body, it is not surprising that many drugs which mimic or interfere with GABA have been investigated. Both pregabalin (Lyrica) and gabapentin (Neurontin) were developed by Pfizer for the treatment of fibromyalgia-related pain and migraine pain, respectively (Figure 1).

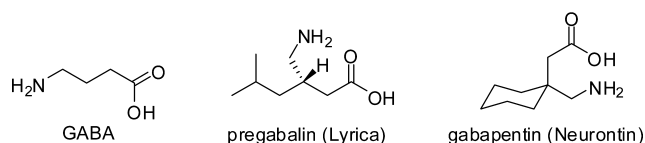
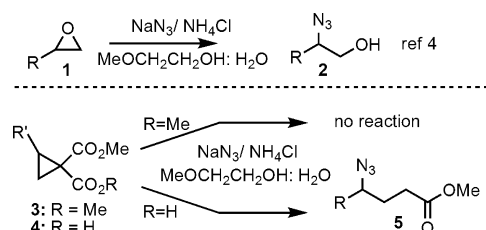


Figure 1. GABA and GABA-inspired drugs.

During our work involving the ring-opening reactions of donor–acceptor cyclopropanes,² specifically the recently discovered special reactivity of cyclopropane hemimalonates,³ we were compelled to attempt the ring-opening of cyclopropane diesters and hemimalonates with the azido anion in order to complement the existing toolbox of nucleophiles for this type of reaction. Herein we report the smooth tandem ring-opening/decarboxylation of cyclopropane hemimalonates in the absence of a Lewis acid catalyst to provide a variety of γ -azidobutyric acid esters (Scheme 1) as well as the reduction to GABA methyl esters.

The reaction conditions which ultimately proved to be the best (after optimization for our substrates) were inspired by Bäckvall,⁴ who reported that a mixture of sodium azide and ammonium chloride in a solvent mixture of 2-methoxyethanol and water was effective in preparing azidoethanols from epoxides (Scheme 1). Table 1 shows the fine-tuning of these conditions for our needs, as well as a brief examination of other conditions. It is of note that the diesters (which were investigated first) were unreactive under these reaction conditions and that the use of Lewis acids in alternative

Scheme 1. Opening of Epoxides and Cyclopropanes with Azide

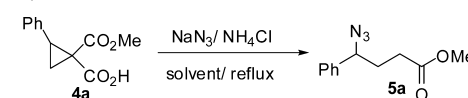


solvents also gave unsatisfactory results. The fact that the diester was unreactive is interesting due to the report that the Meldrum's acid derived cyclopropane underwent ring-opening at subambient temperatures in less than an 1 h.⁵

Entry 1 from Table 1 represents a duplication of the Bäckvall conditions which led to a 70% isolated yield of the azido adduct which had concurrently undergone decarboxylation. In the absence of ammonium chloride (entries 2 and 3), an alternative (and unidentified) product was formed in low yield in the presence of water and the expected adduct was formed in low yield in the absence of water. Other solvents which, in previous work, have been compatible with cyclopropane ring openings (entries 4–6) where unsatisfactory in this instance. A further tuning of the reaction conditions (entries 7–12) revealed our optimal conditions (entry 7).

With our best conditions in hand, we set out to survey the range of cyclopropanes⁶ which would effectively undergo this transformation.⁷ Table 2 shows the substrate scope (see ref 3 for preparation of cyclopropanes 4). For the most part, the reaction seems to proceed effectively with aromatic or heteroaromatic substituents on the cyclopropane. Note that electron-withdrawing groups on the phenyl ring attenuated the reactivity and resulted in lower yields (adducts 5g and 5h). Electron-donating groups had the opposite effect, producing

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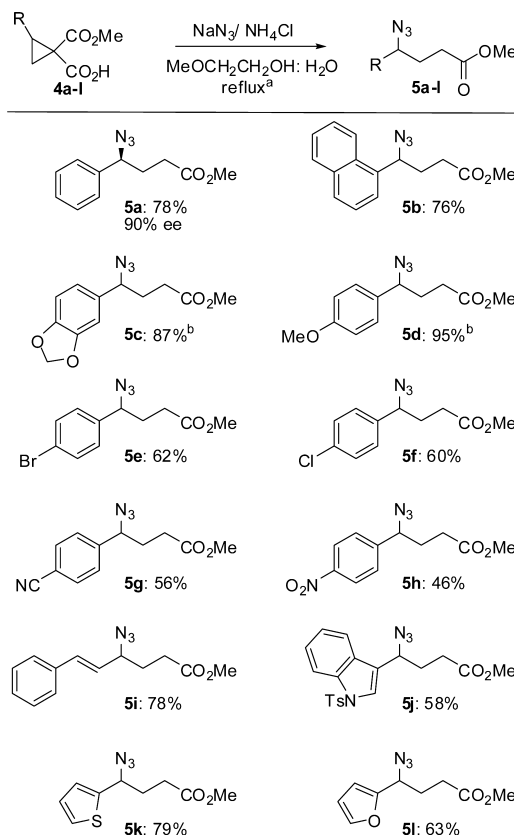
Table 1. Optimization of Tandem Ring-Opening/Decarboxylation


entry	azide (equiv)	NH ₄ Cl (equiv)	solvent ^a	yield ^b (%)
1	1	1.4	2-MeO(CH ₂) ₂ OH/H ₂ O (10:1)	70
2	1	0	2-MeO(CH ₂) ₂ OH/H ₂ O (10:1)	N/A
3	1	0	2-MeO(CH ₂) ₂ OH	30
4	1	1.4	C ₆ H ₆	no reaction
5	1	1.4	CH ₃ CN	no reaction
6	1	1.4	THF	no reaction
7	1.2	1.4	2-MeO(CH ₂) ₂ OH/H ₂ O (10:1)	78
8	2	1.4	2-MeO(CH ₂) ₂ OH/H ₂ O (10:1)	73
9	2	3	2-MeO(CH ₂) ₂ OH/H ₂ O (10:1)	74
10	1.2	1.4	2-MeO(CH ₂) ₂ OH/H ₂ O (10:1)	50 ^c
11	1.2	1.4	2-MeO(CH ₂) ₂ OH/H ₂ O (5:1)	74
12	1.2	1.4	2-MeO(CH ₂) ₂ OH/H ₂ O (1:1)	60
13 ^d	1.2	1.4	2-MeO(CH ₂) ₂ OH/H ₂ O (10:1)	50

^aReactions performed at 125 °C for 2 h. ^bIsolated yield. ^cPerformed in a microwave reactor at 150 °C for 0.5 h. ^d20 mol % of Yb(OTf)₃ was added.

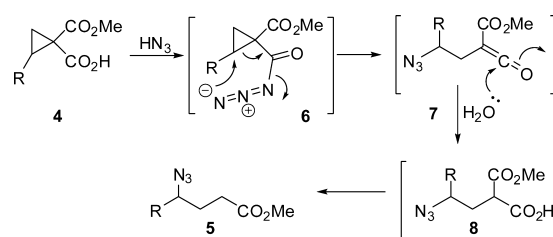
adducts in excellent yields (adducts **5c** and **5d**). While a styrenyl substituent was well tolerated (adduct **5i**), the vinyl cyclopropane (R = CH=CH₂) was not, resulting in the formation of an inseparable mixture of the expected adduct and the product resulting from S_N2' opening. It is of note that the optically enriched phenyl cyclopropane (S)-**4a**⁸ (90% ee) underwent this transformation with full retention of enantiopurity (vide infra) to give (S)-**5a**. Finally, cyclopropanes where R = aliphatic or R = H were unreactive under these conditions, and starting material was recovered intact.

The fact that the hemimalonates are effective substrates and the diesters are not is surprising to us. In our previous report in which we described the nucleophilic opening of these species with indoles,³ we were able to rationalize the results by invoking a high pressure induced intramolecular hydrogen bond between the carboxylic acid and the ester. The effect of this would be to stereoelectronically align the carbonyls for the ring-opening event. It is hard to make such a rationalization in this case since the reaction takes place in a refluxing protic medium. It puzzles us then, why the carboxylic acid moiety is a requirement for this reaction. One explanation (Scheme 2) is that the reaction was proceeding via an acyl azide **6** which could undergo a [3,3]-sigmatropic rearrangement to yield ketene **7**, which in turn would be intercepted by water to regenerate the acid. Decarboxylation of the resulting monoester **8** could then ensue, yielding the observed product **5**. We have attempted to prepare and isolate the acylazide, and subject it to the reaction conditions in order to prove this hypothesis; however, the results were inconclusive due to extensive decomposition.⁹

Table 2. Reaction Scope

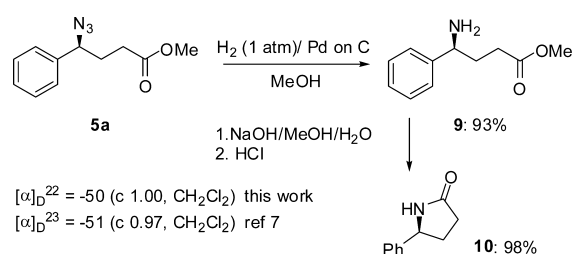
^a For 2 hours ^b For 30 mins

^aFor 2 h. ^bFor 30 min.

Scheme 2. Possible Involvement of an Acyl Azide

As proof that the azidoesters **5** could be viable precursors to GABA esters, a representative example (**5a**) was subjected to reduction under a balloon of hydrogen gas with catalysis by palladium on carbon. GABA ester **9** was produced in 93% yield (Scheme 3).

The conversion of (S)-**5a**, the product of enantioenriched (S)-**4a** (90% ee), to **9** also served to determine the

Scheme 3. Reduction to a GABA Ester and a γ -Lactam

stereochemical course of the cyclopropane ring-opening. Aminoester **9** was derivatized as the Mosher amide (as was the racemate prepared from racemic **4a**). Analysis of the ^{19}F NMR spectrum indicated that no loss of enantiomeric purity had occurred. To rule out a double inversion involving the carboxylic acid moiety (a net retention of configuration), **9** was lactamized to **10** (see the Supporting Information) and the optical rotation compared to the reported value for this known compound.¹⁰ Indeed, **5a** is the result of inversion of configuration upon cyclopropane ring-opening.

In summary, we have reported a technically simple and catalyst-free method for the nucleophilic ring-opening of cyclopropane hemimalonates with azides. The products underwent concomitant decarboxylation to yield 4-azido carboxylic acid esters. Simple reduction yields γ -aminobutyric acid (GABA) methyl esters.

EXPERIMENTAL SECTION

General Information. All solvents for routine isolation of products and chromatography were reagent grade. Flash chromatography was performed using silica gel (230–400 mesh) with indicated solvents. All reactions were monitored by thin-layer chromatography on 0.25 mm silica plates (60F-254) visualizing with UV light and developed using acidic anisaldehyde. ^1H , ^{19}F , and ^{13}C NMR spectra were recorded either on a 400 MHz or on a 600 MHz NMR spectrometer. Chemical shifts, multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet), coupling constant in hertz (Hz), and number of protons. HRMS were measured with electron impact (EI) ionization and quadrupole mass analyzer.

General Experimental Procedure for the Synthesis of Azidoesters 5a–l. Sodium azide (1.2 equiv) and ammonium chloride (1.4 equiv) were added to a solution of cyclopropane hemimalonate (1.0 equiv) in 2-methoxyethanol:water (5.0 mL:0.5 mL). The mixture was stirred at reflux (125 °C) until the reaction was complete (as determined by TLC analysis). The reaction was then quenched with water and extracted with ether (3 times). The organic layers were then combined and dried with magnesium sulfate. Following filtration, the solvent was removed under reduced pressure and the crude mixture purified by flash chromatography (EtOAc/hexanes, 20:80) to yield the desired products **5a–l**.

Methyl 4-Azido-4-phenylbutanoate (5a). Reagents employed: 1-(methoxycarbonyl)-2-phenylcyclopropanecarboxylic acid (**4a**) (104 mg, 0.47 mmol), sodium azide (37 mg, 0.57 mmol), ammonium chloride (36 mg, 0.66 mmol), 2-methoxyethanol:water: yield 78% (81 mg) as a clear oil. The data for this compound matched that previously reported.¹¹

Methyl 4-Azido-4-(naphthalen-1-yl)butanoate (5b). Reagents employed: 1-(methoxycarbonyl)-2-(naphthalen-1-yl)-cyclopropanecarboxylic acid (**4b**) (119 mg, 0.44 mmol), sodium azide (35 mg, 0.53 mmol), ammonium chloride (33 mg, 0.62 mmol), 2-methoxyethanol:water: yield 76% (90 mg) as a clear oil; R_f = 0.58, 30% EtOAc in hexanes; ^1H NMR (400 MHz, CDCl_3) δ = 8.16 (d, J = 8.6, 1H), 7.90 (dd, J = 7.8, 1.6 Hz, 1H), 7.84 (d, J = 7.8 Hz, 1H), 7.60–7.48 (m, 4H), 5.37 (dd, J = 8.6, 5.8 Hz, 1H), 3.69 (s, 3H), 2.60–2.43 (m, 2H), 2.36–2.16 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ = 173.3, 134.7, 134.0, 130.6, 129.1, 128.95, 126.6, 125.9, 125.3, 124.3, 122.9, 62.0, 51.7, 30.71, 30.6; IR (thin film) 3050, 2953, 2926, 2852, 2101, 1736, 1437, 1364, 1325, 1252, 1201, 1173, 801, 779; HRMS (EI) calcd for $\text{C}_{15}\text{H}_{15}\text{N}_3\text{O}_2$ 269.1164, found 269.1159.

Methyl 4-Azido-4-(benzo[d][1,3]dioxol-5-yl)butanoate (5c). Reagents employed: 2-(benzo[d][1,3]dioxol-5-yl)-1-(methoxycarbonyl)-cyclopropanecarboxylic acid (**4c**) (97 mg, 0.37 mmol), sodium azide (29 mg, 0.44 mmol), ammonium chloride (27 mg, 0.51 mmol), 2-methoxyethanol:water: yield 87% (84 mg) as a clear oil; R_f = 0.58, 30% EtOAc in hexanes; ^1H NMR (400 MHz, CDCl_3) δ = 6.80 (d, J = 1.6 Hz, 1H), 6.78 (s, 1H), 6.76 (d, J = 1.6 Hz, 1H), 5.97 (s, 2H), 4.44 (dd, J = 7.8, 6.25 Hz, 1H), 3.66 (s, 3H), 3.76 (t, J = 7.4, 2H), 2.11–1.94 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ = 173.1, 148.2, 147.7,

132.7, 120.7, 108.3, 106.9, 101.2, 65.1, 51.7, 31.3, 30.5; IR (thin film) 3459, 3323, 2953, 2101, 1739, 1505, 1490, 1443, 1342, 1328, 1252, 1170, 1102, 1042, 933, 863, 813, 661; HRMS (EI) calcd for $\text{C}_{12}\text{H}_{13}\text{N}_3\text{O}_4$ 263.0906, found 263.0905.

Methyl 4-Azido-4-(4-methoxyphenyl)butanoate (5d). Reagents employed: 1-(methoxycarbonyl)-2-(4-methoxyphenyl)-cyclopropanecarboxylic acid (**4d**) (100 mg, 0.40 mmol), sodium azide (31 mg, 0.48 mmol), ammonium chloride (30 mg, 0.56 mmol), 2-methoxyethanol:water: yield 95% (95 mg) as a clear oil; R_f = 0.54, 30% EtOAc in hexanes; ^1H NMR (400 MHz, CDCl_3) δ = 7.25–7.21 and 6.92–6.89 (m, AA'BB', 4H), 4.47 (dd, J = 7.8, 6.3 Hz, 1H), 3.80 (s, 3H), 3.66 (s, 3H), 2.36 (t, J = 7.4, 2H), 2.15–1.98 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ = 173.1, 159.6, 130.8, 128.1, 114.2, 64.8, 55.2, 51.6, 31.2, 30.5; IR (thin film) 3451, 3319, 2953, 2839, 2482, 2101, 1739, 1611, 1529, 1438, 1245, 1174, 1034, 832, 545; HRMS (EI) calcd for $\text{C}_{12}\text{H}_{15}\text{N}_3\text{O}_3$ 221.1052, found 221.1050 ($M - \text{N}_2$).

Methyl 4-Azido-4-(4-bromophenyl)butanoate (5e). Reagents employed: 2-(4-bromophenyl)-1-(methoxycarbonyl)-cyclopropanecarboxylic acid (**4e**) (95 mg, 0.32 mmol), sodium azide (25 mg, 0.38 mmol), ammonium chloride (24 mg, 0.45 mmol), 2-methoxyethanol:water: yield 62% (59 mg) as a clear oil; R_f = 0.53, 30% EtOAc in hexanes; ^1H NMR (400 MHz, CDCl_3) δ = 7.53–7.50 and 7.20–7.17 (m, AA'BB', 4H), 4.52 (dd, J = 8.2, 6.3 Hz, 1H), 3.66 (s, 3H), 2.37 (ddd, J = 9.8, 7.8, 3.1 Hz, 2H), 2.12–1.97 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ = 173.0, 183.0, 132.0, 128.5, 122.4, 64.6, 51.7, 31.3, 30.3; IR (thin film) 3455, 3319, 2951, 2101, 1737, 1489, 1437, 1250, 1201, 1171, 1044, 1011, 822, 532; HRMS (EI) calcd for $\text{C}_{11}\text{H}_{13}\text{BrN}_3\text{O}_2$ 298.0191, found 298.0185 ($M + \text{H}$).

Methyl 4-Azido-4-(4-chlorophenyl)butanoate (5f). Reagents employed: 2-(4-chlorophenyl)-1-(methoxycarbonyl)-cyclopropanecarboxylic acid (**4f**) (105 mg, 0.41 mmol), sodium azide (32 mg, 0.50 mmol), ammonium chloride (30 mg, 0.58 mmol), 2-methoxyethanol:water: yield 60% (63 mg) as a clear oil; R_f = 0.56, 30% EtOAc in hexanes; ^1H NMR (400 MHz, CDCl_3) δ = 7.38–7.35 and 7.26–7.23 (m, AA'BB', 4H), 4.53 (dd, J = 7.8, 6.3 Hz, 1H), 3.67 (s, 3H), 2.38 (ddd, J = 9.4, 7.4, 2.3 Hz, 2H), 2.13–1.98 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ = 173.0, 137.5, 134.2, 129.1, 128.2, 64.5, 51.7, 31.3, 30.3; IR (thin film) 2952, 2101, 1739, 1493, 1437, 1325, 1249, 1202, 1171, 1092, 1015, 826, 534; HRMS (EI) calcd for $\text{C}_{11}\text{H}_{13}\text{ClN}_3\text{O}_2$ 254.0696, found 254.0710 ($M + \text{H}$).

Methyl 4-Azido-4-(4-cyanophenyl)butanoate (5g). Reagents employed: 2-(4-cyanophenyl)-1-(methoxycarbonyl)-cyclopropanecarboxylic acid (**4g**) (116 mg, 0.47 mmol), sodium azide (37 mg, 0.57 mmol), ammonium chloride (35 mg, 0.66 mmol), 2-methoxyethanol:water: yield 56% (65 mg) as a clear oil; R_f = 0.46, 30% EtOAc in hexanes; ^1H NMR (400 MHz, CDCl_3) δ = 7.69–7.66 and 7.44–7.41 (m, AA'BB', 4H), 4.63 (dd, J = 7.0, 7.0 Hz, 1H), 3.66 (s, 3H), 2.46–2.32 (m, 2H), 2.07–2.02 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ = 172.7, 144.4, 132.7, 127.5, 118.2, 112.3, 64.4, 51.7, 31.3, 30.0; IR (thin film) 2953, 2230, 2100, 1734, 1609, 1438, 1417, 1308, 1252, 1200, 1174, 1019, 835, 566; HRMS (EI) calcd for $\text{C}_{12}\text{H}_{13}\text{N}_4\text{O}_2$ 245.1039, found 245.1045 ($M + \text{H}$).

Methyl 4-Azido-4-(4-nitrophenyl)butanoate (5h). Reagents employed: 1-(methoxycarbonyl)-2-(4-nitrophenyl)-cyclopropanecarboxylic acid (**4h**) (116 mg, 0.44 mmol), sodium azide (34 mg, 0.53 mmol), ammonium chloride (33 mg, 0.61 mmol), 2-methoxyethanol:water: yield 46% (53 mg) as a clear oil; R_f = 0.44, 30% EtOAc in hexanes; ^1H NMR (400 MHz, CDCl_3) δ = 8.26–8.23 and 7.52–7.49 (m, AA'BB', 4H), 4.71 (dd, J = 7.0, 7.0 Hz, 1H), 3.68 (s, 3H), 2.49–2.34 (m, 2H), 2.08 (q, J = 7.0 Hz, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ = 172.7, 147.8, 146.4, 127.7, 124.1, 64.3, 51.8, 31.5, 30.0; IR (thin film) 2953, 2926, 2100, 1735, 1607, 1522, 1437, 1348, 1253, 1200, 1172, 853, 700; HRMS (EI) calcd for $\text{C}_{11}\text{H}_{13}\text{N}_4\text{O}_4$ 265.0937, found 265.0935 ($M + \text{H}$).

(E)-Methyl 4-Azido-6-phenylhex-5-enoate (5i). Reagents employed: (E)-1-(methoxycarbonyl)-2-(4-styrylphenyl)-cyclopropanecarboxylic acid (**4i**) (101 mg, 0.41 mmol), sodium azide (32 mg, 0.49 mmol), ammonium chloride (30 mg, 0.57 mmol), 2-methoxyethanol:water: yield 78% (78 mg) as a clear oil; R_f = 0.50, 30% EtOAc in hexanes; ^1H NMR (400 MHz, CDCl_3): δ = 7.37 (d, J =

7.4 Hz, 2H), 7.31 (t, J = 7.4 Hz, 2H), 7.26–7.22 (m, 1H), 6.60 (d, J = 15.6 Hz, 1H), 6.06 (dd, J = 16.0, 8.2 Hz, 1H) 4.08 (dd, J = 14.9, 7.4 Hz, 1H), 3.64 (s, 3H), 2.41 (t, J = 7.4 Hz, 2H), 1.94–1.88 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ = 173.2, 135.7, 133.9, 128.6, 128.2, 126.7, 126.1, 63.9, 51.7, 30.2, 29.8; IR (thin film) 3027, 2952, 2105, 1739, 1493, 1437, 1239, 1170, 1112, 1071, 969, 888, 751, 694; HRMS (EI) calcd for $\text{C}_{13}\text{H}_{14}\text{NO}_2$ 216.1030, found 216.1030 ($M - \text{N}_2$, H).

Methyl 4-Azido-4-(1-tosyl-1H-indol-3-yl)butanoate (5j). Reagents employed: 1-(methoxycarbonyl)-2-(4-(1-tosyl-1H-indol-3-yl)phenyl)-cyclopropanecarboxylic acid (**4j**) (98 mg, 0.24 mmol), sodium azide (18 mg, 0.28 mmol), ammonium chloride (18 mg, 0.33 mmol), 2-methoxyethanol/water: yield 58% (57 mg) as a clear oil; R_f = 0.54, 30% EtOAc in hexanes; ^1H NMR (400 MHz, CDCl_3) δ = 7.99 (d, J = 8.2 Hz, 1H), 7.75 (d, J = 8.6 Hz, 2H), 7.61 (d, J = 1 Hz, 1H), 7.58 (s, 1H), 7.35 (ddd, J = 8.6, 7.4, 1.2 Hz, 1H), 7.26 (ddd, J = 8.2, 8.2, 0.8 Hz, 1H), 7.23–7.21 (m, 2H), 4.76 (dd, J = 7.0, 7.0 Hz, 1H), 3.68 (s, 3H), 2.51–2.38 (m, 2H), 2.33 (s, 3H), 2.27–2.17 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ = 173.0, 145.2, 135.5, 134.8, 129.9, 128.4, 126.8, 125.3, 124.0, 123.5, 120.2, 120.0, 113.9, 57.8, 51.7, 30.4, 29.4, 21.5; IR (thin film) 2953, 2925, 2109, 1735, 1448, 1372, 1256, 1178, 1123, 1089, 749, 669, 574, 538; HRMS (EI) calcd for $\text{C}_{20}\text{H}_{20}\text{N}_4\text{O}_4\text{S}$ 412.1205, found 412.1190.

Methyl 4-Azido-4-(furan-2-yl)butanoate (5k). Reagents employed: 2-(4-(furan-3-yl)phenyl)-1-(methoxycarbonyl)cyclopropanecarboxylic acid (**4k**) (126 mg, 0.60 mmol), sodium azide (47 mg, 0.72 mmol), ammonium chloride (45 mg, 0.84 mmol), 2-methoxyethanol/water: yield 63% (79 mg) as a clear oil; R_f = 0.54, 30% EtOAc in hexanes; ^1H NMR (400 MHz, CDCl_3) δ = 7.42 (d, J = 1 Hz, 1H), 6.36 (dd, J = 3.1, 1.8 Hz, 1H), 6.33 (d, J = 3.1 Hz, 1H), 4.53 (dd, J = 7.2, 7.2 Hz, 1H), 3.68 (s, 3H), 2.43 (ddd, J = 7.6, 7.6, 0.8 Hz, 2H), 2.25–3.12 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ = 172.9, 151.5, 143.0, 110.2, 108.1, 57.9, 51.7, 30.2, 27.8; IR (thin film) 2954, 2102, 1736, 1438, 1338, 1239, 1210, 1173, 1013, 745; HRMS (EI) calcd for $\text{C}_9\text{H}_{11}\text{NO}_3$ 181.0739, found 181.0739 ($M - \text{N}_2$).

Methyl 4-Azido-4-(thiophen-2-yl)butanoate (5l). Reagents employed: 1-(methoxycarbonyl)-2-(4-(thiophen-3-yl)phenyl)-cyclopropanecarboxylic acid (**4l**) (135 mg, 0.60 mmol), sodium azide (47 mg, 0.72 mmol), ammonium chloride (45 mg, 0.84 mmol), 2-methoxyethanol/water: yield 79% (106 mg) as a clear oil; R_f = 0.47, 30% EtOAc in hexanes; ^1H NMR (400 MHz, CDCl_3) δ = 7.30 (dd, J = 5.0, 1.2 Hz, 1H), 7.04–7.03 (m, 1H), 7.01–6.98 (m, 1H), 4.9 (dd, J = 7.0, 7.0 Hz, 1H), 3.67 (s, 3H), 2.44 (dd, J = 7.4, 1.2 Hz, 2H), 2.23–2.10 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ = 172.8, 141.7, 126.8, 125.8, 125.6, 60.3, 51.6, 31.6, 30.4; IR (thin film) 2952, 2099, 1736, 1437, 1367, 1328, 1240, 1173, 854, 835, 707; HRMS (EI) calcd for $\text{C}_9\text{H}_{11}\text{NO}_3\text{S}$ 197.0510, found 197.0511 ($M - \text{N}_2$).

Experimental Procedure for the Azide Reduction to GABA Esters 9. To a solution of azide (1 equiv) in MeOH was added 10% palladium on activated carbon. The solution was stirred under a balloon of hydrogen for two hours. The mixture was then passed through Celite, and the solvent was removed under reduced pressure to give GABA ester **9**.

Methyl 4-Amino-4-phenylbutanoate (9). Reagents employed: methyl 4-azido-4-phenylbutanoate (**5a**) (66 mg, 0.30 mmol), 10% palladium on activated carbon (3 mg): yield 93% (54 mg) as a yellow oil. The data for this compound matched that previously reported.¹²

Lactamization Procedure. To a solution of optically enriched methyl 4-amino-4-phenylbutanoate **9** (0.26 mmol) in MeOH, was added 1.7 M NaOH (0.39 mmol) dropwise. The solution was stirred for 2 h and then diluted with EtOAc and water to separate layers. The aqueous layer was then acidified with 5% HCl to reach pH 2, then extracted three times with EtOAc. The combined organic layers were washed with brine, dried of MgSO_4 , filtered and concentrated.

(S)-5-Phenylpyrrolidin-2-one (10). Reagents employed: methyl 4-amino-4-phenylbutanoate (**9**) (50 mg, 0.26 mmol), 1.7 M NaOH (0.5 mL, 0.39 mmol): yield 98% (40 mg) as a yellow oil. The data for this compound matched that previously reported.⁷

Mosher's Amide Procedure. To a solution of methyl 4-amino-4-phenylbutanoate (**9**) (0.068 mmol) in THF (1 mL) was added Mosher's Acid (0.071 mmol), DCC (0.081 mmol) and DMAP

(0.0041 mmol). The solution was stirred at room temperature overnight. The solution was filtered and the solvent was removed under reduced pressure, to which the mixture was purified by flash chromatography (EtOAc/hexanes, 20:80) to yield Mosher's amide.

Mosher's Amide. Reagents employed: methyl 4-amino-4-phenylbutanoate (**9**) (13 mg, 0.068 mmol), Mosher's acid (17 mg, 0.071 mmol), DCC (17 mg, 0.081 mmol), DMAP (1 mg, 0.0041 mmol): yield 61% (17 mg); ^1H NMR (400 MHz, CDCl_3) δ = 7.56–7.54 (m, 2H), 7.42–7.41 (m, 3H), 7.37–7.34 (m, 2H), 7.31–7.29 (m, 3H), 7.19 (d, J = 8.2 Hz, 1H), 5.01 (br dd J = 15.2, 7.8 Hz, 1H), 3.67 (s, 0.19H), 3.59 (s, 3H), 3.40 (s, 0.22H), 3.37 (s, 3H), 2.30–2.26 (m, 3H), 2.17–2.11 (m, 2H); ^{19}F NMR (376 MHz, CDCl_3) δ = –68.8 (s, 3F), –68.9 (s, 0.16F). The enantiomeric excess was determined to be 90% by Mosher's amide (^1H , ^{19}F NMR).

■ ASSOCIATED CONTENT

● Supporting Information

Complete experimental procedures as well as ^1H NMR and ^{13}C NMR, IR, MS, data for all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: makerr@uwo.ca.

Notes

The authors declare no competing financial interest.

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