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Classical carbonyl reactivity enables a short synthesis of the core structure of acutumine

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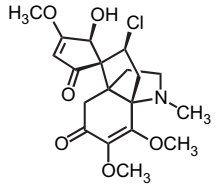
Abstract—The development of a direct synthesis of the complex core topology of the alkaloid acutumine from a simple keto proline derivative is described. An efficient sequence of three carbonyl-dependent reactions is at the heart of this design for synthesis.

1. Introduction

The intrinsic reactivity of the carbonyl group and the special properties it bestows on organic compounds have enabled the development of many types of bond forming strategies that rapidly produce molecular complexity and are of great value to the field of chemical synthesis.[1] In the context of natural products that are both topologically and stereochemically complex, our laboratory has been pursuing strategies for synthesis that are founded on fundamental, carbonyl-dependent reactivity. A synthesis of the tricyclo-[4.3.3.0]dodecane core structure of acutumine featuring an intramolecular rearrangement is the subject of this article.

The unique, chlorine-containing alkaloid acutumine is a minor constituent of the plants *Sinomenium acutum*, *Menispermum canadense*, and *Menispermum dauricum*, the dry rhizome of which (*Rhizoma menispermi*) is part of traditional Chinese medicine and is now officially included in the Chinese Pharmacopoeia as an analgesic and fever reducing agent. In 2002, it was reported that acutumine selectively inhibits human T-cell growth, although with low micromolar potency.[2] In 2004, a patent described that this alkaloid has memory-enhancing properties in experimental animal models.[3]

Acutumine was first isolated in a pure state in 1929 by Goto and Sudzuki from the Kitasato Institute in Tokyo, Japan.[4] Their early structural studies indicated that acutumine contains a ketone, an *N*-methyl, and three *O*-methyl groups, but nearly 40 years passed before the full structure and absolute stereochemistry of this compound became known through the X-ray crystallographic studies of Tomita and co-workers.[5] The remarkable structure of acutumine (**1**) (Fig. 1), with its complex cyclic connectivity and conspicuous chlorine atom, consists of a propellane-like [4.3.3.0] fused tricycle with appended spirocycle core and five contiguous stereocenters, of which three are fully substituted. In the solid state, the nitrogen atom and chlorine-bearing carbon of acutumine are separated by only 3.2 Å.



1: Acutumine

Figure 1. The molecular structure of acutumine (**1**).

In the wake of these studies, Barton and co-workers described their idea that acutumine may originate from a simple benzylisoquinoline alkaloid by a reaction sequence starting with an oxidative coupling of two phenol radicals.[6,7] Two independent efforts to evaluate the experimental feasibility of Barton's creative hypothesis have appeared, and the most recent of these investigations by Wipf and co-workers has led to a slight modification of Barton's proposal.[8] The recent, impressive construction of the propellane-like core structure of acutumine by the Castle laboratory is the only report describing progress toward a chemical synthesis of this natural product.[9]

2. Concepts for synthesis

Our early studies were founded on the idea that we might achieve a synthesis of acutumine (**1**) from *p*-benzoquinone (**2**) (Scheme 1). While it was possible to transform this abundant starting material to enantiomerically enriched alcohol **3**

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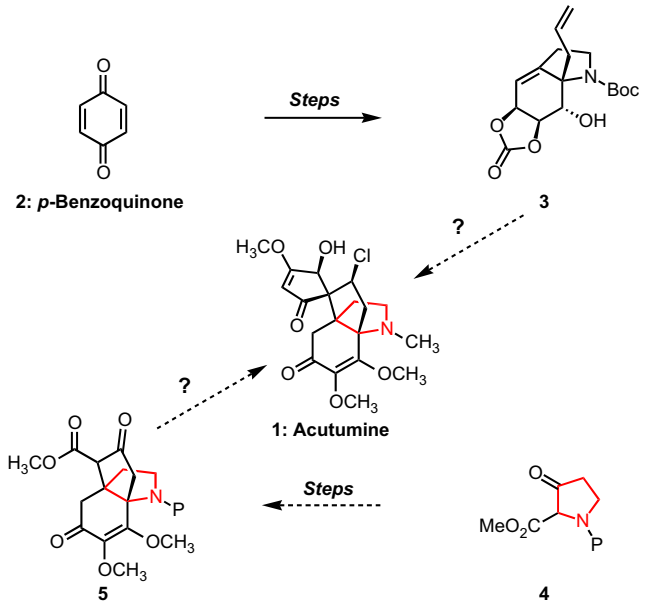
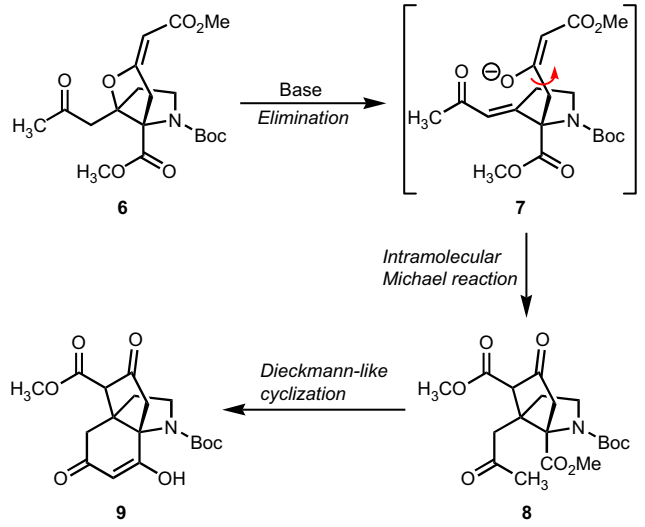
by an efficient reaction sequence, all efforts to move the latter compound closer to acutumine were unsuccessful. With some hesitation, we abandoned the idea that our synthesis should commence from *p*-benzoquinone. Instead of building the acutumine core from a six-membered ring compound, we decided to make the pyrrolidine ring (highlighted in **1**) the foundational element of our synthesis. This new plan had the advantage that keto proline esters of type **4** are readily available by the intramolecular carbenoid insertion chemistry of Rapoport and co-workers[10] and amenable to a range of chemical reactions. From this vantage point, we would attempt a synthesis of tricyclic β-keto ester **5**, which emerged as an attractive subgoal for our effort. The manner in which a compound embodying the architecture of **5** was fashioned from pyrrolidine derivative **4** is described below.



Scheme 1. The issue of starting material for a synthesis of acutumine (**1**).

Our intention was to achieve a spontaneous conversion of bicyclic vinylogous carbonate **6** to the tricyclic core of acutumine in the presence of a suitable base (Scheme 2).



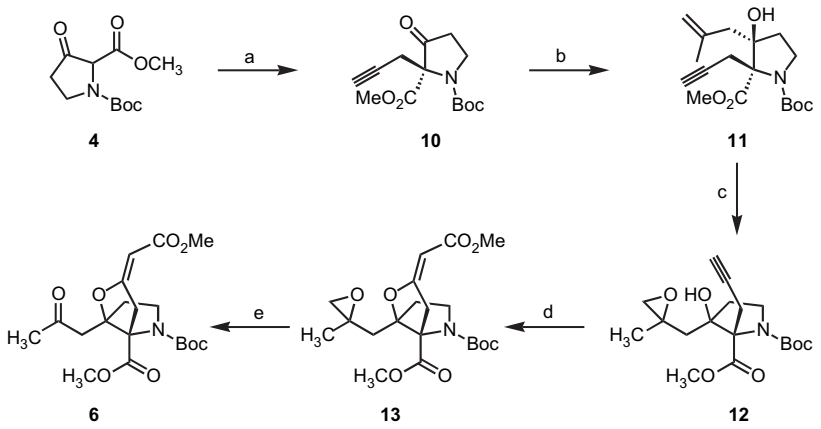
Scheme 2. A concept for generating the acutumine tricyclic core via a cascade of carbonyl-dependent reactions. Boc=*t*-BuOCO.

While such a transformation could well be mechanistically degenerate,[11] we envisioned that it might occur by a sequence of carbonyl-dependent reactions starting with a base-mediated β-elimination (**6**→**7**). This event would leave in its wake a delocalized enolate ion and an electrophilic enone, thus enabling an intramolecular Michael reaction to give compound **8**.[12] An analogous rearrangement carried out by Vorbrüggen and co-workers[13] bolstered our confidence in this type of crowded C–O→C–C bond isomerization. In base, enolization of the newly formed β-keto ester would render this grouping unreactive toward nucleophiles. A subsequent kinetic enolization of the methyl ketone in **8** would then trigger a final Dieckmann-like cyclization[14] to tricyclo[4.3.3.0]dodecane **9**, a compound having key elements of acutumine. The synthesis and reactivity of bicyclic vinylogous carbonate **6** are described below.

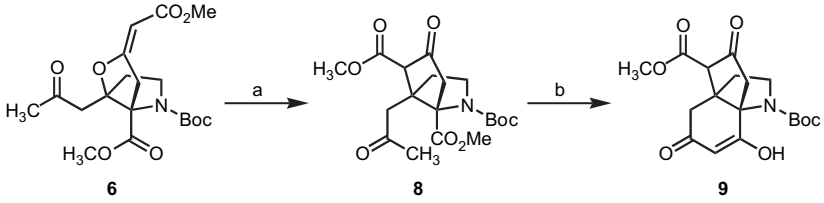
3. Results and discussion

As noted earlier, the functionalized pyrrolidine derivative **4** (wherein P=Boc) is readily available by the method of Rapoport and co-workers;[10] this method was modified slightly[15] and applied to a synthesis of multi-gram quantities of this useful building block. Alkylation of the stabilized sodium enolate derived from **4** with propargyl bromide in a mixed solvent system of THF and DMF afforded compound **10** in racemic form in 71% yield (only one enantiomer is shown for clarity) (Scheme 3). Compound **11** was subsequently produced by a chemoselective addition of 2-methylallylmagnesium chloride to the ketone carbonyl of **10**. This reaction was efficient and highly diastereoselective; nucleophilic addition occurred to the face away from the propargyl chain.[16] A Sharpless, vanadium-based epoxidation[17] of the disubstituted alkene function in **11** was also highly diastereoselective. This oxidation, which was presumably hydroxyl-directed,[18] gave rise to essentially only one diastereoisomer, although we did not establish the configuration of the newly formed stereocenter. This stereochemical matter was ultimately inconsequential because we elected to carry the epoxide function as a direct precursor to the required trigonal keto group after several unsuccessful attempts at achieving a direct oxidative cleavage of the alkene in compound **11**.

With hydroxyl and alkyne groupings in neighboring regions of space, compound **12** was an excellent substrate for a palladium(II)-catalyzed, carbonylative cyclization[19] to mixed, vinylogous carbonate **13**. This transformation was both rapid and highly efficient (consistently >90% crude yield). Finally, on exposure to periodic acid buffered with sodium periodate,[20] the epoxide ring in **13** was cleanly converted to methyl ketone **6**, a compound that was designed to be a direct precursor to the core structure of acutumine (Scheme 2). In fact, it was possible to directly convert bicyclic vinylogous carbonate **6** to tricycle **9** on treatment of **6** with strong, non-nucleophilic bases, although these reactions were inefficient and produced several byproducts. The preferred course of action is shown below in Scheme 4. Under rather gentle reaction conditions,[21] compound **6** was smoothly transformed to bicyclic polycarbonyl **8**, almost certainly via a β-elimination/Michael cyclization mechanism. In relation to compound **6**, which proved to be somewhat sensitive,



Scheme 3. Synthesis of bicyclic vinylogous carbonate **6**: (a) sodium hydride, THF/DMF (9:1), 0 °C→rt, then propargyl bromide, 71% yield; (b) 2-methylallylmagnesium chloride, THF, −78→0 °C, 91% yield; (c) $VO(acac)_2$, *t*-BuOOH, CH_2Cl_2, 0 °C→rt, 80% yield; (d) $(CH_3CN)_2PdCl_2$ (5 mol %), benzoquinone (1.1 equiv), CO (balloon), MeOH, 0 °C, 90% crude yield; (e) $NaIO_4$, H_5IO_6, THF/H_2O, 0 °C→rt. THF=tetrahydrofuran; DMF=*N,N*-dimethylformamide; acac=acetyl acetonate.



Scheme 4. Construction of the core structure of acutumine: (a) *n*-Bu_4NOAc, THF, rt, 64% yield, two steps; (b) $NaN(SiMe_3)_2$ (3.0 equiv), THF, −78 °C→rt, 84% yield.

compound **8** is a stable substance that could be purified by silica gel chromatography.[22] When a solution of **8** in THF was treated with 3.0 equiv of sodium bis(trimethylsilyl)-amide under the conditions shown, the desired Dieckmann-like cyclization occurred and generated compound **9**. The ^1H NMR spectrum of **9** at room temperature in $CDCl_3$ is consistent with the structure and enolic form as drawn. Sharp singlets for the signals corresponding to both the 1,3-dicarbonyl enol hydrogen and the Boc *tert*-butyl hydrogens suggest an intramolecular hydrogen bond between this enol hydrogen and the carbonyl of the Boc group. This results in an overall simplification of the ^1H and ^{13}C NMR spectra consistent with a single *N*-Boc rotamer.

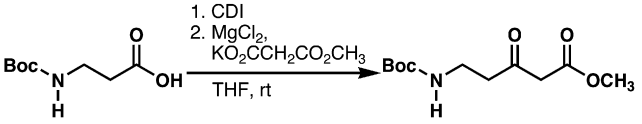
4. Conclusion

It has been our goal to evolve an effective synthesis of the complex topology of the well-known alkaloid acutumine. To this end, we have produced the propellane-like [4.3.3.0] fused tricyclic core of acutumine in only seven transformations from a known and readily available pyrrolidine derivative. Four of these transformations were enabled by the properties and reactivity of the carbonyl group. The concise construction of this rigid, acutumine-like substructural element provides a basis for addressing the larger goal of achieving a stereocontrolled synthesis of the highly challenging full structure of acutumine, as well as many other acutumine-like compounds. These efforts are currently underway and will be described in due course.

5. Experimental

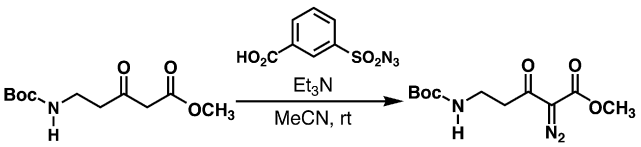
5.1. General

Unless otherwise noted, all reactions were carried out under an atmosphere of argon or nitrogen. Tetrahydrofuran (THF), toluene, diethyl ether, methylene chloride (CH_2Cl_2), and *N,N*-dimethylformamide (DMF) were dried by passing through activated alumina columns. Commercial reagents of high purity were purchased and used without further purification unless otherwise noted. Reactions were monitored by thin-layer chromatography (TLC) carried out on 0.25 mm Merck silica gel plates (60 F_{254}) using UV light as a visualizing agent and aqueous ceric sulfate/phosphomolybdic acid or aqueous potassium permanganate solution and heat as developing agents. E. Merck silica gel 60 (230–400 mesh) was used for flash column chromatography. *Instrumentation*: FTIR spectra were obtained on a Perkin–Elmer Paragon 500 FTIR spectrometer. NMR spectra were obtained on a Varian Inova-500 instrument and calibrated to the residual solvent peak. The multiplicities are abbreviated as follows: s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet, br=broad signal. Mass spectra were obtained on an Agilent ESI-TOF mass spectrometer.



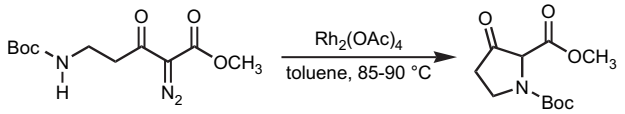
5.1.1. Masamune–Claisen condensation on *N*-Boc-β-alanine. Under a blanket of inert gas, solid *N*-Boc-β-alanine (24.31 g, 128.5 mmol, 1.0 equiv) was added in one portion to a suspension of 1,1′-carbonyldiimidazole (25 g, 154.2 mmol, 1.2 equiv) in 350 mL THF in a 1 L round bottom flask via a powder funnel, which was rinsed with 25 mL THF. The resulting suspension was allowed to stir under a stream of inert gas for 1 h, during which time carbon dioxide evolved and the reaction mixture became a homogeneous, yellow solution, then a septum and argon balloon were placed on the flask. The yellow reaction solution was allowed to stir 3 h further before a mixture of $MgCl_2$ (325 mesh, 12.23 g, 128.5 mmol, 1.0 equiv) and methyl potassium malonate (40.13 g, 257.0 mmol, 2.0 equiv) solids were added under a blanket of inert gas in one portion via a powder funnel, which was rinsed with 25 mL THF. A septum and argon balloon were placed on the flask and the suspension was allowed to stir vigorously overnight (slow gas evolution) before 250 mL water and 150 mL 1 M HCl were added. The resulting yellow, biphasic solution (aqueous layer pH approx 7) was poured into a 2 L separatory funnel, followed by 1 L ethyl acetate, using some to rinse the reaction flask. The aqueous layer was removed and the organic layer was washed with 150 mL 1 M HCl, 150 mL brine, dried with $MgSO_4$, filtered, and concentrated under reduced pressure to give, after azeotropic removal of the remaining ethyl acetate with three 200 mL portions of hexane, 33 g of the desired β-keto ester as a faint yellow liquid, which was taken on without further purification. TLC: R_f=0.24 (SiO_2, 1:2 ethyl acetate/hexane); IR (film) 3397, 2978, 1748, 1714, 1520, 1439, 1367, 1324, 1252, 1170 cm^{-1}; ^1H (500 MHz, $CDCl_3$) δ 5.05 (br s, 1H), 3.62 (s, 3H), 3.38 (s, 2H), 3.26 (q, J=5.9 Hz, 2H), 2.68 (t, J=5.9 Hz, 2H), 1.31 (s, 9H); ^{13}C (125 MHz, $CDCl_3$) δ 202.0, 167.1, 155.6, 79.0, 52.1, 48.8, 42.8, 34.8, 28.1; HRMS (ESI-TOF) $C_{11}H_{19}NO_5$ *m/z* calcd for $[M+Na]^+$ 268.1155; found 268.1151.

5.1.2. 3-Carboxybenzenesulfonyl azide. 3-(Chlorosulfonyl)benzoic acid (50 g, 226 mmol, 1.0 equiv) was added in one portion to 660 mL acetone in a 2 L round bottom flask via a powder funnel, which was rinsed with 50 mL acetone. To the resulting light brown solution was added a solution of sodium azide (18.4 g, 284 mmol, 1.25 equiv) in 120 mL water, followed by approximately 20–30 mL water to make the reaction mixture homogeneous. The light brown solution was allowed to stir for 2 h before most of the acetone was removed under reduced pressure leaving a brown residue. Approximately 1500 mL of water was added to the flask, followed by a few milliliters of concentrated HCl (solution pH <2). The precipitate was collected in a 150 mL sintered glass funnel, rinsed well with water and three portions of hexanes in the funnel, then dried by pulling air through the funnel for 1 h followed by drying under high vacuum overnight to give 41 g of the desired sulfonyl azide as an off-white, powdery solid (80%). IR (film) 3100–2200, 2135, 1913, 1712, 1374, 1265, 1177 cm^{-1}; ^1H (500 MHz, $CDCl_3$/DMSO-d_6) δ 11.41 (br s, 1H), 8.58 (t, J=1.6 Hz, 1H), 8.35 (ddd, J=7.8, 1.5, 1.3 Hz, 1H), 8.07 (ddd, J=7.9, 2.0, 1.2 Hz, 1H), 7.67 (t, J=7.9 Hz, 1H); ^{13}C (125 MHz, $CDCl_3$/DMSO-d_6) δ 166.1, 138.7, 135.6, 132.9, 130.8, 129.8, 128.6; HRMS (ESI-TOF) $C_7H_5N_3O_4S$ *m/z* calcd for $[M-H]^-$ 225.9928; found 225.9926.



5.1.3. Diazo transfer reaction on Masamune–Claisen β-keto ester. Under a blanket of inert gas, the above sulfonyl azide (32.11 g, 141.3 mmol, 1.1 equiv) was added in one portion to a solution of the above β-keto ester (33 g, 128.5 mmol, 1.0 equiv) in 450 mL acetonitrile in a 1 L round bottom flask via a powder funnel, which was rinsed with 50 mL acetonitrile. Triethylamine (54 mL, 385.4 mmol, 3.0 equiv) was added dropwise via a pressure equalizing addition funnel over 30 min, and the resulting yellow-orange solution was allowed to stir for 1 h before the solvent was removed under reduced pressure. To the foamy, yellow-orange residue was added a stirbar and 800 mL 1:1 diethyl ether/water. After allowing the mixture to stir well for several minutes, the resulting biphasic solution was poured into a 2 L separatory funnel and the flask was rinsed with 500 mL 4:1 diethyl ether/water and 400 mL diethyl ether. The aqueous layer was removed and the organic layer was washed with 300 mL 2:1 saturated $NaHCO_3$ solution/water and 300 mL 2:1 saturated NH_4Cl solution/water. The organic layer was dried with $MgSO_4$, filtered, and concentrated under reduced pressure to give 35 g of the desired diazo β-keto ester as a viscous yellow liquid that was taken on without further purification. TLC: R_f=0.31 (SiO_2, 1:2 ethyl acetate/hexane); IR (film) 3390, 2978, 2139, 1715, 1652, 1514, 1438 cm^{-1}; ^1H (500 MHz, $CDCl_3$) δ 5.03 (br s, 1H), 3.77 (s, 3H), 3.39 (s, 2H), 3.37 (q, J=5.9 Hz, 2H), 2.97 (t, J=5.9 Hz, 2H), 1.35 (s, 9H); ^{13}C (125 MHz, $CDCl_3$) δ 191.5, 161.4, 155.6, 78.9, 76.0, 52.1, 40.6, 35.3, 28.2; HRMS (ESI-TOF) $C_{11}H_{17}N_3O_5$ *m/z* calcd for $[M+Na]^+$ 294.1060; found 294.1056.

The ^1H and ^{13}C spectra of all compounds below, with the exception of the final compound (**9**), are complicated by *N*-Boc rotamers.



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5.1.4. *N*-Boc-3-keto proline methyl ester 4. $Rh_2(OAc)_4$ (284 mg, 0.642 mmol, 0.005 equiv) was added to a pale yellow solution of the above diazo β-keto ester (34.9 g, 128.5 mmol, 1.0 equiv) in 1300 mL of toluene in a 2 L round bottom flask, which was then fitted with a reflux condenser and placed into a preheated 100 °C oil bath under a stream of inert gas (no septum). The green mixture was allowed to heat at 85–90 °C until nitrogen gas evolution ceased (approximately 30 min) and then was allowed to cool to room temperature. The solvent was removed under reduced pressure, then under high vacuum, and the green residue was then treated with 500 mL hexane and the solvent was again removed under reduced pressure and high vacuum. To remove the $Rh_2(OAc)_4$, the green residue was diluted with diethyl ether and filtered through Celite®, rinsing well

with diethyl ether, and the solvent was evaporated under reduced pressure to give 29 g of a yellow oil (93%), which solidified when azeotroped with hexanes or placed in the freezer. This material is sufficiently pure to be taken on without any further purification, but can be purified by stirring the crude product with 1:1 diethyl ether/hexane, collecting the solid by filtration, evaporation of the filtrate, and repeating the sequence. An analytical sample was obtained by flash column chromatographic purification (SiO_2, 1:3 ethyl acetate/hexane) to give a colorless powder, mp 55–56 °C. TLC: R_f=0.32 (SiO_2, 1:2 ethyl acetate/hexane); IR (film) 2977, 1775, 1746, 1707, 1395, 1239, 1163 cm^{-1}; ^1H (500 MHz, $CDCl_3$) δ 4.55 and 4.47 (2 s, 1H total), 3.93–3.75 (m, 5H), 2.67 (t, J=7.6 Hz, 2H), 1.47 and 1.40 (2 s, 9H total); ^{13}C (125 MHz, $CDCl_3$) δ 204.6, 166.7, 153.7, 81.1, 65.6, 65.2, 52.9, 42.1, 41.5, 37.1, 36.4, 28.1; HRMS (ESI-TOF) $C_{11}H_{17}NO_5$ m/z calcd for $[M+Na]^+$ 266.0999; found 266.0990.

5.1.5. Propargyl keto proline 10. A suspension of sodium hydride (60% dispersion in mineral oil, 181 mg, 4.52 mmol, 1.1 equiv) in 16 mL THF and 2 mL DMF was cooled to 0 °C, then a solution of keto proline **4** (1 g, 4.11 mmol, 1.0 equiv) in 2 mL THF was added over 5–10 min, followed by a rinse with 1 mL THF. The resulting yellow suspension was allowed to stir at 0 °C for 30 min before removing the flask from the ice bath. Propargyl bromide (80 wt % in toluene, 440 μL, 4.93 mmol, 1.2 equiv) was then added dropwise over 5 min and the resulting orange-red suspension was allowed to stir at room temperature for 30 min before adding 5 mL saturated NH_4Cl solution and 10 mL water. The biphasic solution was poured into a 250 mL separatory funnel containing 100 mL water, the organic layer was removed, and the aqueous phase was extracted 4×25 mL diethyl ether. The combined organic extracts were dried with $MgSO_4$, filtered, and the solvent removed under reduced pressure. The residue was purified by flash chromatography (SiO_2, 1:6:1 diethyl ether/hexanes/dichloromethane → 1:4:1 → 1:2:1) to give 820 mg of **10** as small, colorless beads (71%), mp 84–86 °C. TLC: R_f=0.40 (SiO_2, 1:2 ethyl acetate/hexane); IR 3289, 2978, 2360, 1774, 1743, 1706, 1386, 1255, 1147 cm^{-1}; ^1H (500 MHz, $CDCl_3$) δ 3.97–3.89 and 3.89–3.77 (2 m, 2H total), 3.71 (s, 3H), 3.35 and 3.11 (dd and qd, J=17.0, 2.6 Hz, 2H total), 2.86–2.64 (m, 2H), 1.97 and 1.94 (2 t, J=2.6 Hz, 1H total), 1.49 and 1.43 (2 s, 9H total); ^{13}C (125 MHz, $CDCl_3$) δ 206.9, 206.5, 167.4, 154.0, 153.4, 81.6, 81.1, 78.9, 78.2, 71.9, 71.6, 71.5, 70.9, 53.1, 42.8, 42.2, 36.5, 35.7, 28.3, 28.2; HRMS (ESI-TOF) $C_{14}H_{19}NO_5$ m/z calcd for $[M+Na]^+$ 304.1155; found 304.1155.

5.1.6. Homoallylic alcohol 11. To a solution of propargyl keto proline **10** (1 g, 3.55 mmol, 1.0 equiv) in 10.5 mL THF cooled to −78 °C was added 2-methylallylmagnesium chloride (0.5 M in THF, 7.11 mL, 1.0 equiv) dropwise over 15–20 min via syringe pump. The resulting colorless solution was allowed to slowly warm to between −10 °C and 0 °C over 90 min, after which 30 mL saturated NH_4Cl solution was added and the mixture was allowed to warm to room temperature. The biphasic solution was poured into a 125 mL separatory funnel, 10 mL diethyl ether was added, and the organic layer was removed. The aqueous phase was extracted 4×15 mL diethyl ether, the combined organic extracts dried with $MgSO_4$, and the solvent evaporated under reduced pressure. The residue was purified by flash chromatography (SiO_2, 1:4:1 diethyl ether/hexanes/dichloromethane → 1:3:1 → 1:2:1 → 1:1:1) to give 1.09 g of **11** as a colorless solid (91%), mp 77–79 °C. TLC: R_f=0.45 (SiO_2, 1:2 ethyl acetate/hexane); IR (film) 3462, 3308, 2977, 2250, 2122, 1739, 1694, 1394, 1258, 1172 cm^{-1}; ^1H (500 MHz, $CDCl_3$) δ 4.90 (s, 1H), 4.74 (s, 1H), 3.82–3.72 and 3.72–3.58 (2 m, 4H total), 3.67 (s, 3H), 3.56–3.39 (m, 1H), [3.16 and 3.04 (2 dd, J=17.0, 2.3 Hz), 3.02 and 2.95 (2 dd, J=17.0, 2.6 Hz) 2H total], 2.72 (d, J=15.5 Hz, 1H), 2.56 and 2.46 (2 d, J=13.4 Hz, 1H total), 2.14–2.02 (m, 2H), 1.99–1.91 (m, 1H), 1.88 (d, J=13.7 Hz, 1H), 1.79 (s, 3H), 1.40 and 1.37 (2 s, 9H total); ^{13}C (125 MHz, $CDCl_3$) δ 172.5, 172.3, 154.2, 153.4, 141.6, 141.4, 116.3, 116.1, 84.9, 83.9, 82.1, 81.6, 80.8, 80.2, 73.7, 73.5, 71.2, 71.0, 52.5, 45.9, 45.6, 44.2, 36.1, 35.5, 28.6, 28.4; HRMS (ESI-TOF) $C_{18}H_{27}NO_5$ m/z calcd for $[M+Na]^+$ 360.1781; found 360.1778.

5.1.7. Epoxide 12. To a solution of homoallylic alcohol **11** (1 g, 2.96 mmol, 1.0 equiv) in 30 mL CH_2Cl_2 was added $VO(acac)_2$ and the resulting green solution was cooled to 0 °C before ^{t}BuOOH (5.5 M in decane, 1.62 mL, 8.89 mmol, 3.0 equiv) was added dropwise. After allowing the reddish purple solution to stir at 0 °C for 15 min, the solution was allowed to warm to room temperature and stir there overnight. The resulting yellow-orange solution was poured into a 125 mL separatory funnel, the flask was rinsed with 30 mL of CH_2Cl_2, 20 mL brine was added, the pale yellow organic layer was removed, and the aqueous layer was extracted 2×10 mL CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, filtered, and the solvent removed under reduced pressure. The residue was purified by flash chromatography (SiO_2, 1:4:1 diethyl ether/hexanes/dichloromethane → 1:3:1 → 1:2:1 → 1:1:1) to give 832 mg of **12** as a colorless oil (80%). When this oil was treated with a small amount of diethyl ether a colorless solid formed, which gave way to a colorless foam upon evaporation of the solvent. By scratching the sides of the flask, **12** could be isolated as a colorless powder, mp 83–88 °C. TLC: R_f=0.38 (SiO_2, 1:1 ethyl acetate/hexane); IR (film) 3461, 3307, 2977, 1737, 1696, 1394, 1256, 1172 cm^{-1}; ^1H (500 MHz, $CDCl_3$) δ 3.89–3.82, 3.76–3.64 and 3.62–3.42 (3 m, 6H total), 3.25–2.91 (m, 2H), 2.76–2.54 (m, 2H), 2.34–1.95 (m, 4H), 1.48–1.28 (m, 12H); ^{13}C (125 MHz, $CDCl_3$) δ 172.4, 154.2, 153.4, 85.4, 84.3, 81.9, 81.4, 80.9, 80.3, 73.9, 73.7, 71.1, 70.8, 56.0, 55.6, 52.6, 46.1, 45.8, 41.7, 36.5, 35.9, 28.6, 28.4; HRMS (ESI-TOF) $C_{18}H_{27}NO_6$ m/z calcd for $[M+Na]^+$ 376.1730; found 376.1716.

5.1.8. Vinylogous carbonate 13. To a three-neck 250 mL round bottom flask containing 80 mL of anhydrous methanol was added freshly sublimed yellow needles of 1,4-benzoquinone (475 mg, 4.39 mmol, 1.1 equiv), followed by $(MeCN)_2PdCl_2$ (52 mg, 0.199 mmol, 0.05 equiv) under a stream of inert gas delivered via a three-way adapter attached to the central neck of the flask. A balloon of carbon monoxide was attached to the three-way adapter and the flask was evacuated and refilled with carbon monoxide three times. While maintaining the reaction under 1 atm of carbon monoxide, the orange solution was allowed to cool to 0 °C before a solution of epoxide **12** (1.41 g, 3.99 mmol, 1.0 equiv) in 36 mL

methanol was added dropwise over several minutes, followed by a rinse with 4 mL methanol. The resulting solution was allowed to stir at 0 °C for 30 min before pouring the orange solution into a 2 L separatory funnel. The flask was rinsed 3×200 mL CH_2Cl_2, and then 800 mL 5% NaOH was added. The organic layer was removed, and the brown/black aqueous layer was extracted 3×100 mL CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, filtered, and the solvent removed under reduced pressure to give 1.48 g of the desired product as an off-white foam (90%). This material was taken on without further purification as it partially decomposed when subjected to purification by flash chromatography on silica gel. However, an analytical sample was obtained by flash column chromatographic purification (SiO_2, 1:1 diethyl ether/hexane → 1:1:1 diethyl ether/hexane/dichloromethane) to give a colorless foam. TLC: R_f=0.42 (SiO_2, 1:1 ethyl acetate/hexane); IR (film) 3482, 2980, 2953, 1747, 1699, 1652, 1437, 1394 cm^{-1}; ^1H (500 MHz, $CDCl_3$) δ 5.32 (m, 1H), 3.96–3.69 (m, 3H), 3.71 (s, 3H), 3.64 (s, 3H), 3.43–3.22 (m, 2H), 2.71 (d, J=4.6 Hz, 1H), 2.61 (d, J=4.6 Hz, 1H), 2.41–1.97 (m, 2H), 1.49–1.36 (m, 12H); ^{13}C (125 MHz, $CDCl_3$) δ 172.6, 172.4, 169.7, 168.4, 168.2, 153.5, 152.6, 98.1, 97.0, 92.3, 92.0, 81.5, 81.0, 78.7, 76.5, 54.8, 53.5, 53.2, 51.1, 45.6, 45.4, 41.1, 40.8, 39.4, 38.8, 33.5, 32.9, 28.5; HRMS (ESI-TOF) $C_{20}H_{29}NO_8$ m/z calcd for $[M+H]^+$ 412.1966; found 412.1951.

5.1.9. Ketone 6. A solution of crude vinylogous carbonate **13** (276 mg, 0.671 mmol, 1.0 equiv) in 6.7 mL THF and 670 μL water was cooled to 0 °C, then $NaIO_4$ (86 mg, 0.402 mmol, 0.6 equiv) and H_5IO_6 (184 mg, 0.805 mmol, 1.2 equiv) were added. The resulting solution was allowed to stir at 0 °C for 15 min, then at room temperature overnight, during which time sodium iodate precipitated. The resulting suspension was poured into a 60 mL separatory funnel, followed by 3.5 mL saturated $NaHCO_3$ solution, 7 mL water, and 10 mL diethyl ether. The organic layer was removed and the aqueous layer was extracted 3×10 mL diethyl ether. The organic extracts were dried over $MgSO_4$, filtered, and the solvent removed under reduced pressure to give 270 mg of an off-white foam. This material was taken on without further purification as it significantly decomposed when subjected to purification by flash chromatography on silica gel. However, an analytical sample was obtained by flash column chromatographic purification (SiO_2, 1:1:1 diethyl ether/hexane/dichloromethane → 2:1:1 → diethyl ether) to give a colorless foam. TLC: R_f=0.39 (SiO_2, 1:1 ethyl acetate/hexane); IR (film) 3472, 2979, 2954, 2901, 2254, 1780–1650 cm^{-1}; ^1H (500 MHz, $CDCl_3$) δ 5.18 (m, 1H), 3.89–3.53 (m, 6H), 3.50 (s, 3H), 3.24–3.11 (m, 1H), 2.78 and 2.74 (2 d, J=14.2 and 14.9 Hz, 1H total), 2.36 (dd, J=13.9, 5.9 Hz, 1H), 2.14 and 2.13 (2 d, J=15.1 and 15.3 Hz, 1H total), 2.10–1.97 (m, 4H), 1.28 and 1.26 (2 s, 9H total); ^{13}C (125 MHz, $CDCl_3$) δ 203.3, 203.0, 171.9, 169.1, 167.7, 153.0, 152.0, 96.7, 95.6, 91.8, 91.5, 80.9, 80.4, 75.5, 75.3, 52.8, 50.5, 45.9, 45.8, 45.0, 44.7, 39.2, 38.5, 32.7, 32.1, 31.5, 27.9; HRMS (ESI-TOF) $C_{19}H_{27}NO_8$ m/z calcd for $[M+Na]^+$ 420.1629; found 420.1622.

5.1.10. Bicyclic β-keto ester 8. Bu_4NOAc (405 mg, 1.34 mmol, 2.0 equiv) was added to a solution of crude ketone **6** (270 mg, 0.671 mmol, 1.0 equiv) in 13 mL THF and the resulting yellow suspension was allowed to stir at room temperature for 30 min before removing most of the solvent under reduced pressure. To the residue was added 13 mL water, 2.6 mL 1 M NaOH, and 3 mL hexane. The resulting biphasic solution was poured into a 30 mL separatory funnel, the organic layer was removed, and the aqueous layer was washed 3×3 mL hexane. To the aqueous layer was then added 10% HCl until the solution was acidic and the aqueous layer was then extracted 5×15 mL diethyl ether. The combined diethyl ether extracts were dried over $MgSO_4$, filtered, and the solvent removed under reduced pressure. The residue was purified by flash chromatography (SiO_2, 30% diethyl ether/hexane → 40% → 50% → 60% → 70%, all eluant containing 1% AcOH) to give 171 mg of **8** as a colorless oil (64%, two steps). TLC: R_f=0.34 (SiO_2, 1:1 ethyl acetate/hexane+1% AcOH); IR (film) 2978, 2954, 1749, 1701, 1663, 1618, 1448, 1393 cm^{-1}; ^1H (500 MHz, $CDCl_3$) δ 10.76 (br s, 1H), 3.83–3.63 (m, 9H), 3.22–3.13 (m, 2H), 2.98 (d, J=18.8 Hz, 0.4H), 2.82 (d, J=18.5 Hz, 0.6H), 2.78 and 2.77 (2 d, J=15.9 and 15.8 Hz, 1.5H total), 2.53 and 2.49 (2 d, J=15.8 and 15.9 Hz, 1H total), 2.41–2.32 (m, 1H), 2.13–1.96 (m, 5H), 1.41 and 1.38 (2 s, 9H total); ^{13}C (125 MHz, $CDCl_3$) δ 205.4, 205.2, 176.6, 175.8, 171.4, 168.9, 168.7, 153.4, 152.5, 99.3, 80.6, 80.2, 73.8, 73.6, 60.0, 58.7, 52.4, 52.3, 51.1, 51.0, 47.6, 47.5, 45.6, 45.4, 41.5, 40.4, 33.1, 32.6, 31.4, 28.2; HRMS (ESI-TOF) $C_{19}H_{27}NO_8$ m/z calcd for $[M+H]^+$ 398.1809; found 398.1799.

5.1.11. Tricycle 9. A solution of β-keto ester **8** (100 mg, 0.252 mmol, 1.0 equiv) in 5 mL THF was cooled to −78 °C, then NaHMDS (0.6 M in toluene, 1.26 mL, 0.755 mmol, 3.0 equiv) was added dropwise. The resulting yellow solution was allowed to stir at −78 °C for 15 min, then at room temperature for 90 min. At room temperature, 3 mL 1 M $NaHSO_4$ was slowly added to the yellow-orange suspension, the organic layer was removed, and the aqueous layer (pH <2) was extracted 4×1 mL ethyl acetate. The combined organic extracts were washed 3×1 mL brine, dried over Na_2SO_4, filtered, and the solvent removed under reduced pressure. The residue was purified by flash chromatography (SiO_2, 30% diethyl ether/hexane → 40% → 50% → 60% → 70%, all eluant containing 1% AcOH) to give, after azeotropic removal of AcOH with three portions of hexanes, 77 mg of **9** (84%) as a colorless powder, mp 135–139 °C. TLC: R_f=0.34 (SiO_2, 1:1 ethyl acetate/hexane+1% AcOH); IR (film) 2980, 2716, 2360, 2341, 1772, 1734, 1717, 1661, 1447, 1406 cm^{-1}; ^1H (500 MHz, $CDCl_3$) δ 11.41 (s, 1H), 10.65 (br s, 1H), 5.38 (s, 1H), 3.79 (s, 3H), 3.65 (d, J=18.7 Hz, 1H), 3.46 (dd, J=10.7, 8.3 Hz, 1H), 3.19 (ddd, J=12.2, 10.7, 6.3 Hz, 1H), 2.96 and 2.93 (2 d, J=18.7 and 16.5 Hz, 2H total), 2.41 (dd, J=13.0, 6.2 Hz, 1H), 2.37 (d, J=16.5 Hz, 1H), 1.82 (dt, J=12.7, 12.6, 8.3 Hz, 1H), 1.47 (s, 9H); ^{13}C (125 MHz, $CDCl_3$) δ 196.1, 173.0, 172.7, 169.0, 158.5, 103.5, 103.3, 83.6, 67.7, 56.2, 51.6, 47.0, 44.6, 38.7, 31.0, 28.2; HRMS (ESI-TOF) $C_{18}H_{23}NO_7$ m/z calcd for $[M+H]^+$ 366.1547; found 366.1533.

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21. We also found sodium hydroxide, tetrabutylammonium fluoride, and cesium carbonate suitable to effect this and related transformations. Surprisingly, amine bases (e.g., triethylamine, DBU, etc.) were ineffective under identical conditions without the addition of a mild Lewis acid such as lithium chloride.

22. Compounds containing the vinylogous carbonate moiety (**13** and **6**) proved sensitive toward purification on silica gel, though they were of sufficient purity after aqueous workup to be taken on into the next reaction. Purification via silica gel chromatography was carried out on compound **8**.