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A Diels–Alder-Based Total Synthesis of (−)-Kainic Acid

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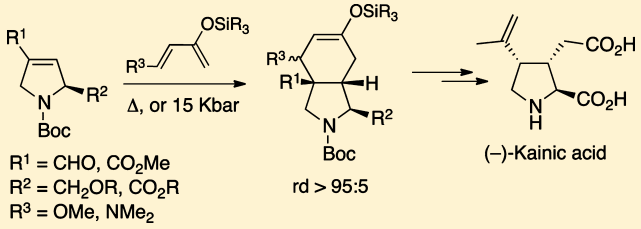
Supporting Information

ABSTRACT: An efficient synthesis of (−)-kainic acid, through a high-pressure-promoted Diels–Alder cycloaddition of a vinylogous malonate derived from 4-hydroxyproline, is described. The bicyclic adduct could be converted into the natural product with complete stereocontrol.



INTRODUCTION

(−)-Kainic acid (**1**, Figure 1) is a naturally occurring pyrrolidine with functionalized substituents at C-2, C-3, and

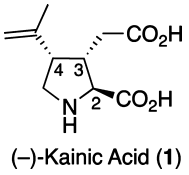


Figure 1. (−)-Kainic acid.

C-4 in a trans-cis relationship. Isolated from *Digenea simplex* in the early 1950s,[1] it was originally used in anthelmintic and insecticide preparations. It is now recognized to be an exceptionally potent glutamate receptor agonist and has become an important tool of biologists for the study of serious neuronal disorders, such as Alzheimer's disease and epilepsy.[2] In 1999, the discontinuance of its commercial extraction from the above alga created concern as to future supply,[3] but this halt in production proved to be only temporary.[4] The supply concern did, however, serve to focus the attention of synthetic chemists on this deceptively simple natural product. Since 2000, there have been numerous total syntheses and many related methodological studies.[5] From this effort, it is evident that the apparent simplicity of the natural product, a pyrrolidine with just three stereogenic centers, belies the difficulty of its synthesis: most syntheses to date require a considerable number of steps.

We have published two total syntheses of (−)-kainic acid from inexpensive *trans*-4-hydroxy-L-proline (**2**, Figure 2), surprisingly the first ones to use this amino acid, which possesses both a structure and absolute stereochemistry seemingly ideal for accessing this target.[6] The first synthesis relied on a crucial, selective alkylation of a 4-oxoproline derivative and a cuprate-mediated isopropenylation,[5hh] whereas the second made effective use of a Diels–Alder reaction, particularly attractive for setting the natural C2–C3–C4

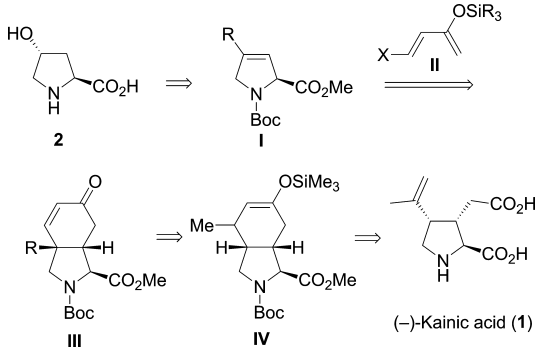


Figure 2. Synthetic strategy.

stereochemical relationship in a straightforward manner.[5oo] The latter synthesis showcased the use of high pressure (15 kbar) to overcome the typical resistance of a trisubstituted olefin to enter into the [4 + 2] cycloaddition. Although it is well-known that high pressure can promote the Diels–Alder reaction in cases of unfavorable diene–dienophile combinations,[7] thereby allowing milder reaction conditions, it has, surprisingly, been scarcely used in the context of total synthesis.[5oo,8] Herein we provide a full account of our Diels–Alder approach to (−)-kainic acid.

RESULTS AND DISCUSSION

First Approach. A Diels–Alder approach with dehydroproline **I** seemed particularly attractive (Figure 2). The functional group at C-2 could be expected to induce effectively the desired face selection in the cycloaddition, which most likely would ultimately lead to the correct stereochemistry of the C3–C4 appendages. The main concern was the reactivity of this type of dienophile. In many, if not most, of the relative few reported examples of [4 + 2] cycloaddition of trisubstituted olefins,[9−12] there is *double* activation as in, for example, α-carbalkoxy

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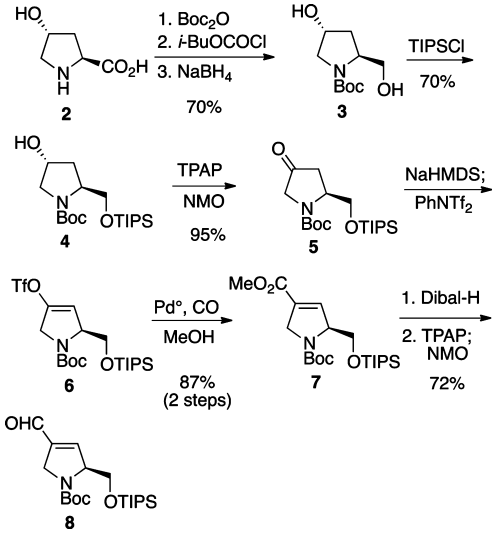
enones. Furthermore, only rarely has the trisubstutituted double bond been incorporated in a five-membered ring (in all successful examples one of the substituents is an activating group).[11−13]

Since pyrroline derivative **I**, R = CO_2R' or CHO, would potentially be chemically and configurationally fragile (vinylogous malonate derivatives), the feasibility of the [4 + 2] cycloaddition and much of the envisioned subsequent chemistry for the synthesis of kainic acid was first studied with the corresponding C-2 TIPS-protected hydroxymethyl derivatives (Scheme 1). The preparation of the cycloaddition

Scheme 1. Synthesis of the Dienophiles

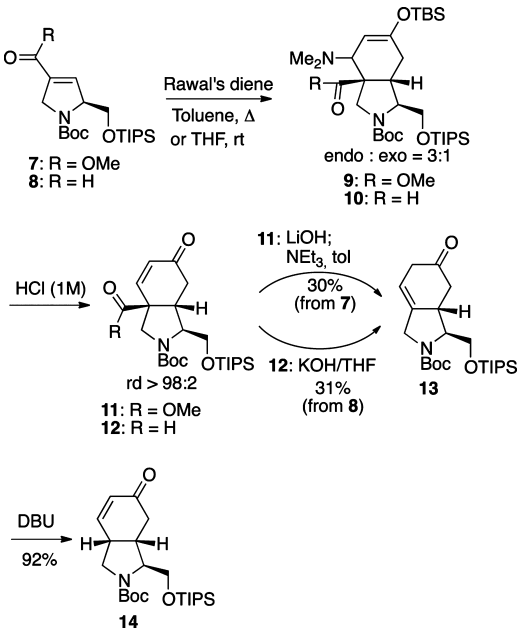


"model" substrates **7** and **8** began by conversion of hydroxyproline **2** into the hydroxymethyl derivative **3** through Boc protection and sodium borohydride reduction of the isobutyl mixed anhydride (70% overall).[14] The newly formed primary hydroxyl was next selectively protected with a triisopropylsilyl group to afford in 70% yield silyl ether **4**, which was then subjected to TPAP oxidation[15] to give cleanly pyrrolidinone **5**. The corresponding enol triflate **6**, formed best from **5** with sodium hexamethyldisilazide and *N*-phenyltriflimide, was converted into unsaturated ester **7** by standard methoxycarbonylation (87%, 2 steps). The corresponding aldehyde **8**, the second potential dienophile we wished to examine, could be secured in 72% yield from ester **7** by using Dibal-H, followed by oxidation with Ley's reagent (TPAP).

The α,β-unsaturated ester **7** and aldehyde **8** showed similar behavior toward electron-rich dienes. No cycloaddition took place thermally with either olefin in the presence of Danishefsky's diene, with only decomposition products and/or recovery of the olefin resulting. In contrast, the more reactive Rawal diene provided the corresponding cycloadduct with each olefin (Scheme 2). As expected, ester **7** was found to be the less reactive of the two, requiring 110 °C (refluxing toluene) for 15 h for complete reaction; aldehyde **8**, in contrast, was completely transformed after 16 h in chloroform at ambient temperature.

The endo/exo ratios of the dimethylamino group in the cycloadducts were, interestingly, nearly identical (ca. 3:1). More importantly, hydrolysis of the cycloadducts **9** and **10** provided *only* diastereomers **11** and **12**. Thus, the cycloadditions were completely face selective, with the stereochemical outcome governed by the silyloxymethyl group, which totally shields the

Scheme 2. Diels−Alder Cycloadditions

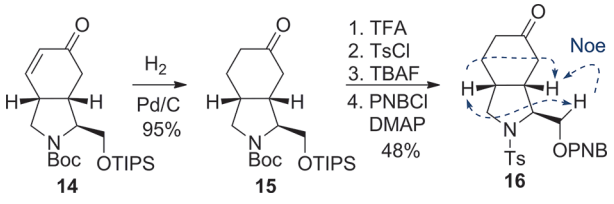


β-face of the molecules. Although both cycloadditions were highly efficient (ca. 90%), the hydrolysis of the cycloadducts **9** and **10** to give enones **11** and **12**, respectively, proceeded at best in only moderate yields, despite considerable effort toward improvement. A reluctant elimination of the pseudoequatorial dimethylamino group in the exo isomers **9** and **10** was undoubtedly at least part of the problem.

Having served their dual purpose of activating the olefin and controlling the regioselectivity of the cycloadditions, the angular functional groups now needed to be excised. The vinylogous β-keto ester **11** on saponification, followed by decarboxylation of the resultant acid with triethylamine in refluxing toluene, provided enone **13** (30%, four steps). The same enone was formed from the vinylogous β-keto aldehyde **12** by decarbonylation with potassium hydroxide (31%, three steps). In both cases, the double bond, surprisingly, suffered translocation to the nonconjugated, ring-junction position; however, fortunately, conjugation could be easily restored with DBU to give the desired enone **14**.

The possibility that a trans ring fusion resulted from this DBU-induced transformation was an obvious concern that needed to be addressed. Catalytic hydrogenation of enone **14** afforded ketone **15**, which was converted into its derivative **16** (originally prepared for eventual X-ray crystallographic determination) (Scheme 3). A significant NOE could be observed between the two ring-junction protons and, also, across the ring as shown. Enone **14** was thus cis-fused.[16]

Scheme 3. Determination of the Relative Stereochemistry of Enone 14



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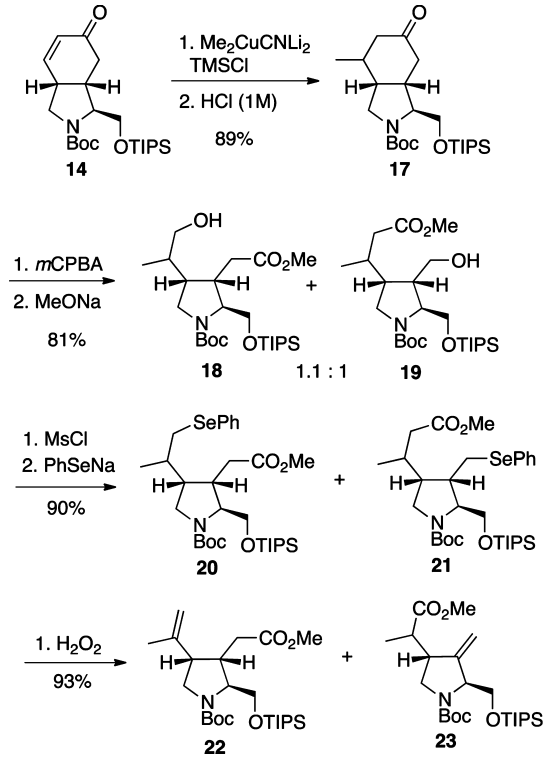
With compound **14** in hand, we were unduly confident of success. The addition of higher order dimethyl cuprate to unsaturated ketone **14** led to compound **17** in excellent yield; however, the closely precedented[17] Baeyer–Villiger oxidation, followed by methanolysis of the inseparable lactones, led, quite unexpectedly, to a nearly equimolar mixture of hydroxy esters **18** and **19** (Scheme 4). We, nevertheless, continued the

Scheme 4. End of the First Route

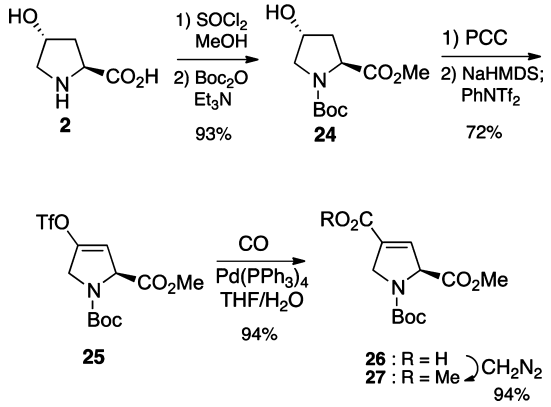


synthesis by conversion of the mixture into the corresponding mesylate esters. Phenylselenide displacement of the mesylates then provided seleno esters **20** and **21**, which on oxidation/elimination afforded a mixture of the potential kainic acid precursor **22** and its isomer **23**.[18]

While at this stage we had essentially completed a Diels–Alder based approach to natural kainic acid,[19] we were not in the least pleased with its efficiency and decided to seek an alternative route. Nonetheless, the work had been instructive: The Diels–Alder reaction had indeed proven useful for the purpose of regio- and stereocontrolling the introduction of the C-3 and C-4 functionalized appendages, but there were too many transformations needed to prepare the dienophiles. The early acid reduction and hydroxyl protection added significantly to these initial steps and would also ultimately require deprotection and oxidation to regenerate the function, thus making the entire synthetic endeavor less than elegant. This required change. The unexpectedly poor regioselectivity in the Baeyer–Villiger oxidation, obviously, also needed to be addressed and a more selective alternative developed. Finally, the introduction of the double bond of the isopropenyl group had to be achieved more directly.

Second Approach. Mindful of the possibility of facile racemization, we nonetheless undertook a study of the behavior of diester **I**, R = CO_2Me (Figure 1), in the Diels–Alder reaction. The preparation of this diester from hydroxyproline **2** began with esterification (thionyl chloride in MeOH), followed by Boc protection of the secondary amine, to give methyl ester **24**[19] (Scheme 5). Oxidation of the hydroxyl group was best

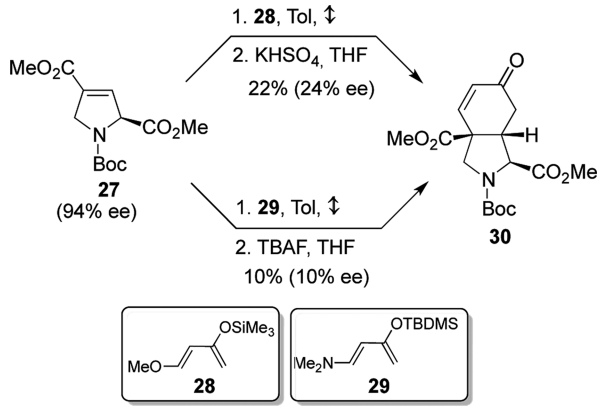
Scheme 5. Synthesis of Diester 27



effected with PCC; other reagents, such as TPAP/NMO, IBX, and Dess–Martin periodinane, proved considerably less amenable to scale up. The enol triflate **25**[20] was then regioselectively formed by using sodium hexamethyldisilazide and $PhNTf_2$. While **25** could not be directly transformed efficiently under palladium catalysis to the corresponding aldehyde **I**, R = CHO, because of competing reduction to **I**, R = H, both the related acid **26** and ester **27** could be secured in high yield through palladium-catalyzed reactions. It was quickly discovered, however, that acid **26** had a much greater configurational stability on storage than did ester **27**, which racemized at room temperature (20% ee after 10 days at 20 °C);[21] hence, ester **27** was prepared from the acid with diazomethane just prior to use.

In refluxing toluene, ester **27** reacted to some extent (57% conversion after 82 h) with Danishefsky's diene (**28**), but after hydrolysis, enone **30** was formed in just 22% yield and, even more discouragingly, in only 24% enantiomeric excess (Scheme 6). With the more reactive Rawal diene (**29**), the cycloaddition was indeed much faster (100% conversion after 6 h), but the hydrolysis was problematic, and enone **30** could be isolated in only less than 10% yield and again with a very low enantiomeric excess (10%). Attempted Lewis acid activation (Et_2AlCl, CuOTf, $AlBr_3/AlMe_3$) of the cycloaddition of ester **27** with diene **29**, unfortunately, led merely to decomposition products.

Scheme 6. Thermal [4 + 2] Cycloadditions with Diester 27



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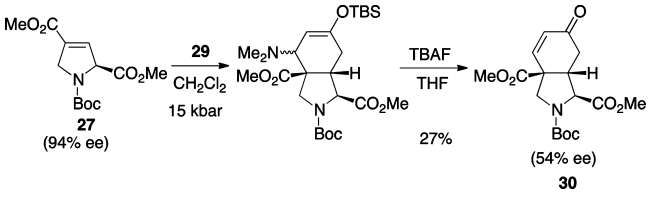
Seeking an alternative that might permit milder reaction conditions, we turned our attention to high pressure. This technique seemed particularly appropriate in the present context: high pressure could be expected to lead to high conversion at lower temperatures and, under the milder conditions, the degree of racemization of the vinyligous malonate should be reduced. Indeed, ester **27** in the presence of Rawal's diene underwent complete reaction at room temperature under 15 kbar in just 52 h; however, hydrolysis produced enone **30** in only 27% yield and 54% ee, considerably better than previously obtained, but nevertheless not synthetically useful (Scheme 7). In view of this problem, Rawal's diene was replaced with Danishefsky's in the hope that it might provide an overall improvement.

Scheme 7. High-Pressure [4 + 2] Cycloaddition with Diester 27



With Danishesfsky's diene, the cycloaddition reached 96% conversion at room temperature under 15 kbar after 82 h (Scheme 8). The cycloadduct **31**, obtained as a 3:1 mixture of endo/exo isomers, could be converted into a mixture of enone **30** and ketone **32** by treatment with $KHSO_4$. The latter could be efficiently converted into the former by treatment with DBU in hot toluene. Thus, high pressure did once again provide the desired gain in reactivity; however, we were both disappointed and puzzled to discover that the enone was essentially racemic! Danishefsky's diene had been purified by rapid distillation, but still contained traces of triethylamine (by ^{1}H NMR). In the belief that this very small amount of triethylamine could be at the origin of the problem, the diene was redistilled, but this time in the presence of trichlorophenol to remove the last traces of the triethylamine contamination. To our satisfaction, with this purified diene, enone **30** could now be secured in both excellent yield (80%) and high enantiomeric excess (90%).[22]

The enormous impact of a minor amount of triethylamine on the resulting enantiomeric excess of the product was completely unexpected. An experiment was therefore conducted with diester **27** in a 5% solution of triethylamine in dichloromethane at room temperature under atmospheric pressure. After 3 h, the enantiomeric excess of the starting diester dropped to 56% (HPLC), and after 17 h, racemization was total (Figure 3, green curve). The result of the same experiment, but under under high pressure, was quite striking in comparison: complete racemization after just 5 min (Figure 3, red curve). To the best of our knowledge, this is the first example of a base-catalyzed high pressure-accelerated racemization, a phenomenon that would seem to warrant further study.

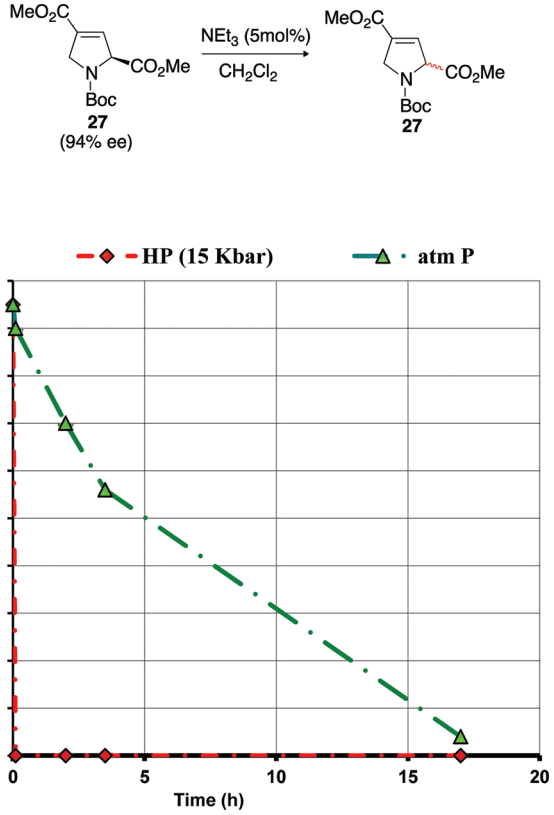
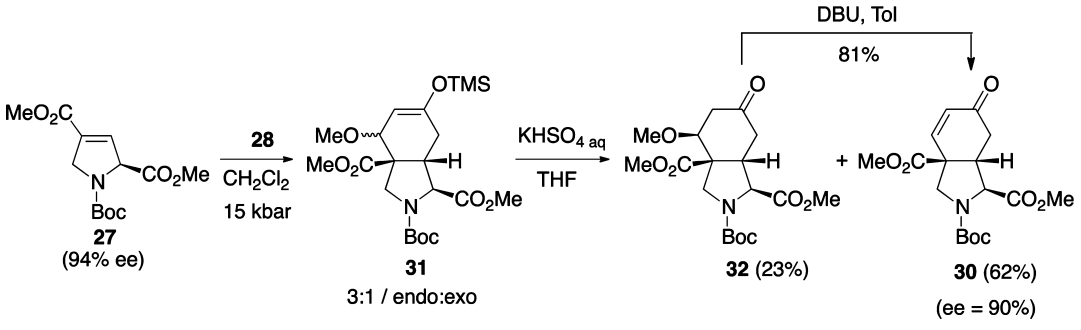


Figure 3. Pressure dependence of racemization rate of diester **27**.

With enone **30** now available in high yield and enantiopurity, the synthesis was continued with the removal of the angular methoxycarbonyl group (Scheme 9). This was efficiently accomplished in two stages: first, hydrolysis with lithium hydroxide to afford the crystalline diacid **33**, which, conveniently, could be recrystallized to give an upgraded ee of better than 99%;[23] next, base-induced mono-decarboxylation of this vinylogous β-keto acid and exposure of the product to diazomethane to produce ketone **34**, which, as now expected, was nonconjugated. The desired conjugated enone could,

Scheme 8. High-Pressure Cycloaddition Using Danishefsky Diene



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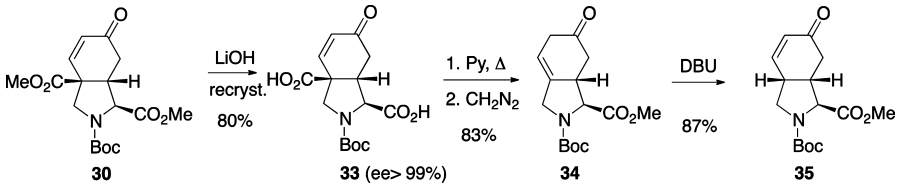
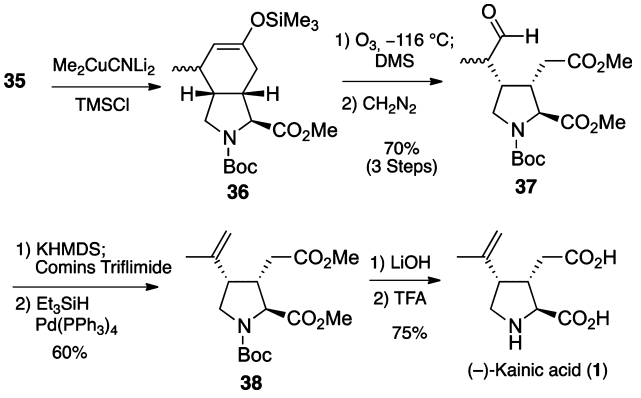
Scheme 9. Decarbomethoxylation of 30



however, once again be regenerated with DBU in high yield.[24] A cis ring fusion in enone **35** was assumed on the basis of both analogy with our earlier results with enone **14** and simple computational studies that indicated the cis isomer to be ca. 6.5 kcal more stable than the trans;[25] this assumption was ultimately shown to be correct through the successful conversion of **35** into kainic acid.

In an attempt to overcome the problem of the poor regioselectivity of the previous Baeyer–Villiger reaction, the possibility of effecting an oxidative cleavage of the enol ether obtained through cuprate 1,4-addition/TMSCl trapping was examined next (Scheme 10). Dimethyl cyanocuprate addition

Scheme 10. Completion of the Synthesis of Kainic Acid



to **35** in the presence of trimethylsilyl chloride served, as planned, to both introduce the final skeletal carbon of kainic acid and generate the enol ether, affording **36**. This unstable product was directly ozonized at low temperature to give, after dimethyl sulfide reduction, the expected aldehyde acid, which on brief exposure to diazomethane smoothly provided aldehyde diester **37**.[26] The overall yield for the three steps was 70%. The problem of regioselectivity resolved, the final challenge was to find an effective means to form the isopropenyl motif from the aldehydic appendage. Rather than reduce the formyl to an hydroxyl group and apply the previous sequence,[27] we opted to try to effect reduction of the corresponding enol triflate, a potentially more direct but surprisingly unprecedented transformation. After some experimentation,[28] it was found that aldehyde **37** could be converted into the enol triflate with KHMDS and the Comins triflimide reagent.[29] Palladium-catalyzed silane reduction of the crude triflate then afforded diester **38** in 60% overall yield.[30] (−)-Kainic acid was easily obtained from this diester in 75% yield by saponification (LiOH), followed by amine deprotection (TFA). The synthetically derived natural product (mp 241–243 °C, $[\alpha]^{20}_{D}$ −14.3 (*c* 0.16, H_2O)) was found to be identical with a commercial sample of the naturally derived material (mp 241–243 °C, $[\alpha]^{20}_{D}$ −13.9 (*c* 0.16, H_2O)).

CONCLUSION

Natural kainic acid has been prepared with nearly total stereocontrol and in approximately 10% overall yield (19 steps). The key features of the synthesis include: a high pressure-promoted Diels–Alder reaction of a sensitive vinylogous malonate that proceeds with a high degree of enantioretention and permits, ultimately, diastereoselective introduction of the C-3 and C-4 substituents of kainic acid; an efficient procedure to cleave regioselectively a bicyclic intermediate and thereby generate appropriately functionalized side chains; a direct method for converting a formyl into a methylene group. Finally, an intriguing effect of pressure on the rate of racemization of a vinylogous malonate has been observed.

EXPERIMENTAL SECTION

General Information. Reactions were carried out under argon in oven-dried glassware. Standard inert atmosphere techniques were used in handling all air- and moisture-sensitive reagents. Dry THF and diethyl ether were obtained by filtration over activated molecular sieves and dry CH_2Cl_2 by filtration through activated aluminum oxide. Thin-layer chromatography was performed on (0.2 mm) silica sheets, which were visualized with ultraviolet light and by heating the plate after treatment, generally with phosphomolybdic acid in ethanol. Silica gel (0.040–0.063 mm) was employed for flash column chromatography. A Fourier transform infrared spectrometer was used to record IR spectra. ^{1}H NMR and ^{13}C NMR spectra were recorded on either a 300, 400, or 500 MHz apparatus. All shifts for ^{1}H spectra were referenced to the residual solvent peak and are reported in ppm. When ambiguous, proton and carbon assignments were established through COSY, HMQC, and/or DEPT experiments. Mass spectra were recorded by using either DCI (ammonia/isobutane 63/37), EI, or ESI techniques. HRMS were recorded on an Orbitrap apparatus (ESI). Microanalyses were performed by an in-house microanalysis service.

(2*S*,4*R*)-*tert*-Butyl 4-Hydroxy-2-(((triisopropylsilyl)oxy)-methyl)pyrrolidine-1-carboxylate (4). A solution of diol **3**[14] (20.1 g, 92.5 mmol) and a catalytic amount of DMAP (2.26 g, 18.6 mmol) in CH_2Cl_2 (200 mL) and triethylamine (14.2 mL, 105.1 mmol) at 0 °C was treated dropwise with TIPSCl (21.8 mL, 101.8 mmol). The reaction mixture was allowed to warm to room temperature and stirred overnight. Water was then added and the organic layer separated. The aqueous layer was extracted with CH_2Cl_2, and the combined organic layers were washed with brine, dried over Na_2SO_4, and filtered. The filtrate was concentrated, and the crude product was purified by column chromatography on silica gel (50:50 EtOAc–pentane) to afford 24.3 g (70%) of alcohol **4** as a colorless liquid: $[\alpha]^{20}_{D}$ −58.6 (*c* 0.42, $CHCl_3$); IR (film) 2944, 2866, 1697, 1673, 1462, 1366, 1256, 1168, 1121, 1014, 882 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$, two rotamers) δ 4.50 (br s, 1H), 4.17–3.92 (m, 2H), 3.86–3.37 (m, 3H), 2.35–2.20 (m, 1H), 2.09–1.86 (m, 1H), 1.84–1.62 (m, 1H), 1.47 (s, 9H), 1.14–0.94 (m, 21H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.8, 154.6, 79.5, 79.1, 70.0, 69.2, 64.4, 63.2, 57.6, 57.5, 55.5, 55.1, 37.0, 36.2, 28.5, 17.98, 17.9, 11.9; MS (DCI, NH_3/isobutane) *m*/*z* 373, 318 (100), 274. Anal. Calcd for $C_{19}H_{39}NO_4Si$: C, 61.08; H, 10.52; N, 3.75. Found: C, 61.42; H, 10.53; N, 3.92.

(*S*)-*tert*-Butyl 4-Oxo-2-(((triisopropylsilyl)oxy)methyl)-pyrrolidine-1-carboxylate (5). To a stirred solution of alcohol **4** (11.7 g, 31.3 mmol) in CH_2Cl_2 (100 mL) at 0 °C were added 4 Å

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molecular sieves (30.0 g) and tetra-*N*-propylammonium perruthenate (0.545 g, 5 Mol %), followed by 4-methylmorpholine *N*-oxide (5.5 g, 46.9 mmol). The reaction mixture was stirred overnight and then filtered through silica gel with ethyl acetate, and the filtrate was concentrated by rotary evaporation under reduced pressure. The residue was purified by silica gel column chromatography (40:60 EtOAc−pentane) to yield 11.1 g (95%) of ketone **5** as a colorless liquid: $[\alpha]^{20}_{D}$ −7.4 (*c* 0.38, $CHCl_3$); IR (film) 2944, 2865, 1716, 1698, 1682, 1463, 1397, 1365, 1253, 1159, 1118, 882 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, two rotamers) δ 4.50−3.62 (m, 5H), 2.83−2.63 (m, 1H), 2.60−2.46 (m, 1H), 1.49 (s, 9H), 1.16−0.95 (m, 21H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 210.8, 153.8, 80.2, 66.0, 65.5, 55.9, 55.4, 54.2, 53.6, 40.7, 40.2, 28.5, 17.9, 11.8; MS (DCI, NH_3/isobutane) *m*/*z* 371, 316 (100), 272. Anal. Calcd for $C_{19}H_{37}NO_4Si$: C, 61.41; H, 10.04; N, 3.77. Found: C, 61.68; H, 10.05; N, 3.82.

(*S*)-*tert*-Butyl 4-(((Trifluoromethyl)sulfonyl)oxy)-2-(((triisopropylsilyl)oxy)methyl)-2,5-dihydro-1*H*-pyrrole-1-carboxylate (6). To a stirred solution of NaHMDS (1.0 M in THF, 41.7 mL, 41.7 mmol) in THF (30 mL) at −78 °C was added slowly a solution of ketone **5** (10.3 g, 27.7 mmol) in THF (25 mL). The reaction mixture was stirred for 30 min and then treated with a solution of $PhNTf_2$ (12.9 g, 36.1 mmol) in THF (25 mL) over 15 min. This mixture was stirred for an additional 1.5 h at −78 °C, warmed to 0 °C, and quenched by slow addition of water (25 mL). The aqueous phase was extracted with Et_2O, and the combined organic layers were washed with brine and dried over Na_2SO_4. Evaporation of the solvent under reduced pressure and filtration of the residue through a short pad of silica gel (15:85 EtOAc−pentane) afforded the sensitive triflate **6** (13.5 g), a small portion of which was further purified (silica gel, 15:85 EtOAc−pentane) for analysis: $[\alpha]^{20}_{D}$ −94.6 (*c* 0.74, $CHCl_3$); IR (film) 2944, 2867, 1711, 1698, 1672, 1431, 1402, 1217, 1140, 1108, 883 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, two rotamers) δ 5.76 and 5.72 (2 s, 1H), 4.61−4.50 (m, 1H), 4.40−4.05 (m, 2H), 4.04−3.82 and 3.78−3.67 (2 m, 2H), 1.49 (s, 9H), 1.20−0.94 (m, 21H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.4, 153.3, 143.6, 143.1, 124.8, 120.6, 116.3, 115.3, 115.2, 112.1, 80.6, 80.3, 64.5, 63.5, 63.0, 51.0, 50.7, 28.3, 17.7, 11.8; MS (DCI, NH_3/isobutane) *m*/*z* 503, 448 (100), 404. Anal. Calcd for $C_{20}H_{36}F_3NO_6SSi$: C, 47.69; H, 7.20; N, 2.78. Found: C, 47.56; H, 7.27; N, 2.54.

(*S*)-1-*tert*-Butyl 3-Methyl 5-(((triisopropylsilyl)oxy)methyl)-1*H*-pyrrole-1,3(2*H*,5*H*)-dicarboxylate (7). A stirred solution of the above triflate **6** (13.5 g, ca. 26.8 mmol) in MeOH (100 mL) at ambient temperature was treated with $Pd(OAc)_2$ (0.6 g, 2.7 mmol), PPh_3 (1.4 g, 5.3 mmol), and *N*,*N*-diisopropylethylamine (7.0 mL, 40.2 mmol). CO gas was bubbled through the solution for 20 min, after which time a positive pressure of CO was maintained for 1 h. Additional CO was then bubbled through the solution for 5 min and the reaction mixture was stirred for another 2 h, keeping a positive pressure of CO. The solvent was removed under vacuum, and the residue was taken up in water and Et_2O. The ether layer was separated, and the aqueous layer was extracted with ether. The combined ether layers were washed with brine, dried over Na_2SO_4, and filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (30:70 EtOAc−pentane) to afford 10.0 g (87%, two steps) of ester **7** as a colorless liquid: $[\alpha]^{20}_{D}$ −152.7 (*c* 0.44, $CHCl_3$); IR (film) 2942, 2866, 1728, 1702, 1651, 1463, 1438, 1400, 1282, 1234, 1170, 1122, 1068, 882 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, two rotamers) δ 6.80 and 6.75 (2 s, 1H), 4.78−4.57 (m, 1H), 4.48−4.29 (m, 1H), 4.22 and 4.17 (2 dd, *J* = 5.6, 2.0 Hz, 1H), 4.15−3.88 and 3.75−3.67 (2 m, 2H), 3.77 (s, 1H), 1.48 (s, 9H), 1.17−0.95 (m, 21H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.2, 153.7, 153.6, 139.7, 131.8, 79.8, 79.5, 66.7, 66.4, 64.4, 63.1, 52.9, 52.7, 51.5, 28.3, 17.7, 11.8; MS (DCI, NH_3/isobutane) *m*/*z* 413, 358 (100), 314. Anal. Calcd for $C_{21}H_{39}NO_5Si$: C, 60.98; H, 9.50; N, 3.39. Found: C, 61.09; H, 9.84; N, 3.44.

(*S*)-*tert*-Butyl 4-Formyl-2-(((triisopropylsilyl)oxy)methyl)-2,5-dihydro-1*H*-pyrrole-1-carboxylate (8). A solution of ester **7** (10.0 g, 24.2 mmol) in toluene (100 mL) at −78 °C was treated slowly with DIBAL-H (1.5 M in toluene, 35.5 mL, 53.3 mmol). The reaction mixture was stirred for 2 h, quenched by the addition of $Na_2SO_4{\cdot}10H_2O$, and filtered with CH_2Cl_2. The filtrate was concentrated, and the crude product was filtered over silica gel with EtOAc to yield the crude alcohol (9.35 g), which was directly used for the next step. A small portion was purified (silica gel, 50:50 Et_2O−pentane) for analysis: $[\alpha]^{20}_{D}$ −133.1 (*c* 1.5, $CHCl_3$); IR (film) 3444, 2939, 2861, 1702, 1684, 1659, 1460, 1407, 1364, 1258, 1176, 1116, 881 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, two rotamers) δ 5.78 and 5.73 (2 s, 1H), 4.61 and 4.50 (2 br s, 1H), 4.32−4.16 (m, 3H), 4.10−3.85 (2 m, 3H), 1.49 (s, 9H), 1.15−0.93 (m, 21H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.3, 154.1, 139.9, 123.2, 79.7, 79.3, 65.9, 65.8, 65.0, 63.5, 59.7, 59.6, 54.2, 53.9, 53.4, 28.5, 17.9, 11.9; MS (DCI, NH_3/isobutane) *m*/*z* 486, 330 (100), 286. Anal. Calcd for $C_{20}H_{39}NO_4Si$: C, 62.29; H, 10.19; N, 3.63. Found: C, 62.21; H, 9.90; N, 3.51. To a stirred solution of the above alcohol (9.33 g, ca. 24.2 mmol) in CH_2Cl_2 (100 mL) at 0 °C were added 4 Å molecular sieves (20 g) and tetra-*N*-propylammonium perruthenate (0.425 g, 1.2 mmol), followed by 4-methylmorpholine *N*-oxide (4.26 g, 36.4 mmol). The reaction mixture was stirred overnight and then filtered through silica gel with ethyl acetate. The filtrate was concentrated by rotary evaporation under reduced pressure, and the residue was purified by silica gel column chromatography (30:70 Et_2O−pentane) to give 6.70 g, (72%, two steps) of aldehyde **8** as a colorless oil: $[\alpha]^{20}_{D}$ −173.8 (*c* 0.35, $CHCl_3$); IR (film) 2942, 2866, 1703, 1698, 1687, 1397, 1366, 1161, 1114 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz, two rotamers) δ 9.76 (s, 1H), 6.84 (s, 1H), 4.83 and 4.73 (2 br s, 1H), 4.50−4.30 (m, 1H), 4.52 and 4.20 (dd, *J* = 5.4, 2.0 Hz, 1H), 4.13−4.00 and 3.81−3.74 (2 m, 2H), 1.49 (s, 9H), 1.16−0.90 (m, 21H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 187.3, 187.1, 153.8, 153.6, 146.8, 146.6, 142.3, 142.1, 80.1, 79.8, 66.9, 66.6, 64.4, 63.1, 51.2, 51.0, 28.4, 17.8, 11.8; MS (DCI, NH_3/isobutane) *m*/*z* 484, 328 (100), 284; HRMS (LTQ-Orbitrap, ESI) calcd for $C_{20}H_{37}NO_4NaSi$ 406.23841, found 406.23877.

(3*S*,3a*S*)-*tert*-Butyl 5-Oxo-3-(((triisopropylsilyl)oxy)methyl)-3a,4,5,6-tetrahydro-1*H*-isoindole-2(3*H*)-carboxylate (13). Procedure A: A solution of ester **7** (0.019 g, 0.046 mmol) and Rawal's diene (0.045 mL, 0.187 mmol) in toluene (2.0 mL) was refluxed for 15 h, after which the solvent was removed and the residue was dissolved in THF (2.0 mL). The solution was cooled to 0 °C and slowly treated with 1 M HCl (1.0 mL). The reaction mixture was stirred for 1.5 h, and water was then added. The aqueous layer was extracted with AcOEt, and the combined organic layers were washed with aq $NaHCO_3$ and brine, dried over Na_2SO_4, and concentrated to afford 0.0086 g of crude enone **11**. A 0.0077 g sample of crude enone **11** in THF (2.0 mL) was treated with 1 N LiOH (1.0 mL) for 1 h. Et_2O (5 mL) was added, and the organic phase was washed with water. The combined aqueous phases were acidified to pH 2 with HCl and extracted with AcOEt. The combined organic phases were washed with water and brine, dried over Na_2SO_4, and concentrated to give 0.0069 g of crude acid. A solution of a 0.0051 g sample of the crude material and NEt_3 (0.03 mL) in toluene (0.5 mL) was warmed to 80 °C for 3 h. The volatiles were then removed under reduced pressure and the crude product was purified by silica gel column chromatography (25:75 Et_2O−pentane) to afford 0.0037 g (30%, four steps) of enone **13** as a colorless oil. **Procedure B**: A solution of aldehyde **8** (4.49 g, 11.72 mmol) and Rawal's diene (3.97 mL, 15.32 mmol) in THF (10 mL) at ambient temperature was stirred for 24 h, after which the solvent was removed and the residue was dissolved in Et_2O (20 mL). The solution was cooled to 0 °C and slowly treated with 1 M HCl (15.0 mL). The reaction mixture was stirred for 1.5 h and then water was added. The aqueous layer was extracted with Et_2O and the combined organic layers were washed with aq $NaHCO_3$ and brine, dried over Na_2SO_4, and concentrated. The crude material dissolved in Et_2O (150 mL) was then stirred with 1 M KOH (6.0 mL) for 3 h under argon. The mixture was acidified with $NaHSO_4$ and extracted with Et_2O. The combined organic layers were washed with water, dried over Na_2SO_4, and concentrated and the crude product was purified by silica gel column chromatography (25:75 Et_2O−pentane) to afford 1.54 g (31%, three steps) of enone **13** as a colorless oil: $[\alpha]^{20}_{D}$ +9.6 (*c* 0.36, $CHCl_3$); IR (film) 2939, 2861, 1691, 1460, 1389, 1361, 1254, 1165, 1116, 881 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz, two rotamers) δ 5.70 (s, 1H), 4.38−4.06 (m, 2H), 4.03−3.76 (m, 2H),

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3.65 (br s, 1H), 3.32−3.18 (m, 1H), 3.02−2.73 (m, 3H), 2.34 and 2.30 (2 d, J = 12.3 Hz, 1H), 1.48 (s, 9H), 1.18−0.96 (m, 21H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 209.0, 154.0, 139.2, 114.7, 79.7, 65.2, 64.3, 62.7, 51.1, 43.8, 41.9, 40.2, 38.6, 28.4, 17.9, 11.9; MS (DCI, NH_3/isobutane) m/z 424, 368 (100), 324. Anal. Calcd for $C_{23}H_{41}NO_4Si$: C, 65.20; H, 9.75; N, 3.31. Found: C, 64.93; H, 9.87; N, 3.32.

(1*S*,3a*R*,7a*S*)-*tert*-Butyl 6-Oxo-1-(((triisopropylsilyl)oxy)-methyl)-3,3a,7,7a-tetrahydro-1*H*-isoindole-2(6*H*)-carboxylate (14). A solution of enone **13** (0.84 g, 1.98 mmol) and DBU (0.29 mL, 1.97 mmol) in CH_2Cl_2 (5 mL) was stirred for 24 h. Water was then added, and the reaction mixture was extracted with ether. The combined organic layers were washed with aq $KHSO_4$, aq $NaHCO_3$, and brine, dried over Na_2SO_4, and concentrated. The crude product was purified by silica gel column chromatography (30:70 Et_2O−pentane) to give 0.77 g (92%) of **14** as colorless liquid: $[\alpha]^{20}_D$ −115.3 (c 0.97, $CHCl_3$); IR (film) 2943, 2866, 1681, 1462, 1403, 1367, 1264, 1170, 1120, 908 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz, two rotamers) δ 6.82−6.72 (m, 1H), 6.05 (d, J = 9.9 Hz, 1H), 4.10−4.02 and 3.85−3.44 (m, 5H), 3.20−2.96 (m, 2H), 2.65−2.43 (m, 2H), 1.48 (s, 9H), 1.15−0.97 (m, 21H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.8 197.7, 154.2,154.0, 149.4, 148.9,130.7, 130.5, 80.0, 79.6,63.4, 63.3,62.9, 62.3, 51.5, 51.3, 40.3, 39.2, 38.6, 37.5, 37.1, 28.5, 18.0, 11.9; MS(DCI, NH_3/isobutane) m/z 424, 368 (100), 324. Anal. Calcd for $C_{23}H_{41}NO_4Si$: C, 65.20; H, 9.75; N, 3.31. Found: C, 64.99; H, 9.56; N, 3.29.

((1*S*,3a*R*,7a*S*)-6-Oxo-2-tosyloctahydro-1*H*-isoindol-1-yl)-methyl 4-Nitrobenzoate (16). A mixture of enone **14** (0.062 g, 0.146 mmol) and 10% Pd/C (0.015 g) in EtOAc (2 mL) was stirred under H_2 (1 bar) for 3 h. The reaction mixture was then filtered over Celite, the Celite plug washed with ether, and the filtrate concentrated to afford ketone **15** (0.059 g, 95%) of sufficient purity to be used directly in the next step: ^{1}H NMR ($CDCl_3$, 400 MHz, two rotamers) δ 3.97 (br s, 0.35H), 3.75−3.70 (m, 1.65H), 3.55−3.40 (m, 3H), 2.81 (br s, 0.65H), 2.58 (br s, 1.35H), 2.47−2.24 (m, 3H), 2.05−2.00 (m, 1H), 1.89−1.80 (m, 1H), 1.44 (s, 9H), 1.05−0.95 (m, 21H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 211.3, 154.8, 79.9, 64.2, 63.1, 62.3, 50.8, 49.9, 42.4, 42.1, 41.2, 37.9, 34.9, 34.0, 28.6, 26.3, 18.0, 12.0; MS(ESI) m/z 448 (M + Na)$^+$, 426 (M + H)$^+$; HRMS (LTQ-Orbitrap, ESI) calcd for $C_{23}H_{43}NO_4SiNa$ 448.28536, found 448.28513. A solution of ketone **15** (0.058 g, ca. 0.13 mmol) in CH_2Cl_2 (2 mL) was treated with trifluoroacetic acid (0.25 mL, 3.3 mmol) at room temperature. After being stirred for 3 h, the reaction mixture was concentrated under reduced pressure to yield the crude ammonium trifluoroacetate. This material was dissolved in MeOH (3 mL) at room temperature and treated with NEt_3 (0.76 mL, 5.4 mmol) and TsCl (0.030 g, 0.15 mmol). The reaction mixture was stirred for 12 h and quenched with water. The aqueous phase was extracted with EtOAc, and the combined organic phases were washed with brine, dried over Na_2SO_4, filtered, and concentrated. The resulting crude tosylate was treated with TBAF (1M/THF, 0.41 mL, 0.41 mmol) and stirred for 2 h. The reaction mixture was concentrated and the residue purified by flash chromatography on silica gel (EtOAc/pentane, 50/50 to 80/20) to provide 0.028 g (64%, three steps) of alcohol **16′**: IR (film) 3502, 2926, 2879, 1709, 1323, 1152 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.73 (d, J = 8.2 Hz, 2H), 7.33 (d, J = 8.2 Hz, 2H), 3.85 (dd, = 11.8, 4.1 Hz, 1H), 3.71−3.64 (m, 2H), 3.24−3.17 (m, 2H), 2.61−2.53 (m, 3H), 2.44 (s, 3H), 2.24−2.05 (m, 3H), 1.85−1.78 (m, 1H), 1.65 (dd, J = 14.9, 7.3 Hz, 1H), 1.34−1.25 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 209.3, 144.3, 133.4, 129.9, 127.4, 66.4, 63.9, 52.6, 42.1, 40.3, 37.5, 34.7, 25.1, 21.5; MS(ESI) m/z 346 (M + Na)$^+$, 324 (M + H)$^+$; HRMS (LTQ-Orbitrap, ESI) calcd for $C_{16}H_{21}NO_4SNa$ 346.10835, found 346.10814. A solution of alcohol **16′** (0.011 g, 0.034 mmol), pyridine (0.005 mL, 0.068 mmol), and DMAP (0.004 g, 0.034 mmol) in CH_2Cl_2 (2 mL) was treated at room temperature with p-nitrobenzoyl chloride (0.0095 g, 0.051 mmol). After being stirred for 12 h, the reaction mixture was quenched with HCl (1 N). The aqueous phase was extracted with EtOAc, and the combined organic phases were washed with HCl (1 N), water, and brine, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash chromatography on silica gel (EtOAc/pentane, 4/6 to 6/4) to provide 0.012 g (75%) of ester **16**: IR (film) 2925, 2854, 1719, 1270, 1526, 1159 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.30−8.28 (m, 2H), 8.19−8.16 (m, 2H), 7.76 (d, J = 8.2 Hz, 2H), 7.32 (d, J = 8.2 Hz, 2H), 4.56 (dd, J = 4.6, 11.5 Hz, 1H), 4.49 (dd, J = 7.0, 11.5 Hz, 1H), 3.72−3.68 (m, 1H), 3.65 (dd, J = 7.3, 9.9 Hz, 1H), 3.33 (dd, J = 8.6, 9.7 Hz, 1H), 2.71−2.65 (m, 1H), 2.58−2.51 (m, 1H), 2.41 (s, 3H), 2.21−2.15 (m, 3H), 1.98−1.91 (m, 1H), 1.73−1.68 (m, 1H), 1.56 (dd, J = 10.2, 14.6 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 208.8, 164.3, 150.7, 144.3, 134.9, 134.0, 130.8, 129.9, 127.4, 123.6, 66.0, 63.6, 50.9, 42.7, 40.7, 36.9, 34.6, 24.6, 21.6; MS(ESI) m/z 473 (M + H)$^+$, 495 (M + Na)$^+$; HRMS (LTQ-Orbitrap, ESI) calcd for $C_{23}H_{24}N_2NaO_7S$ 495,12019, found 495.11900.

(1*S*,3a*R*,7a*S*)-*tert*-Butyl 4-Methyl-6-oxo-1-(((triisopropylsilyl)-oxy)methyl)hexahydro-1*H*-isoindole-2(3*H*)-carboxylate (17). Methyllithium (1.6 M in ether, 5.2 mL, 8.32 mmol) was added to a suspension of CuCN (0.374 g, 4.17 mmol) in THF (5 mL) at −78 °C. The solution was stirred for 30 min and allowed to warm to 0 °C. A solution of enone **14** (0.82 g, 1.94 mmol) and TMSCl (1.07 mL, 8.43 mmol) in THF (8 mL) was then added dropwise to the above solution at −78 °C. The resulting mixture was stirred for 3 h and quenched with satd aq NH_4Cl before being allowed to warm to room temperature. The layers were separated, and the aqueous layer was extracted with ether. The combined organic layers were washed with satd aq NH_4Cl and brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude product was then dissolved in THF (15 mL) and stirred overnight with 1 N HCl (5 mL). The solution was extracted with ether, and the combined organic layers were washed with satd aq $NaHCO_3$ and brine, dried over Na_2SO_4, and concentrated under reduced pressure. Purification of the residue by silica gel column chromatography (25:75 Et_2O−pentane) provided 0.76 g (89%) of ketone **17**: $[\alpha]^{20}_D$ −10.0 (c 0.42, $CHCl_3$); IR (film) 2944, 2865, 1716, 1698, 1694, 1682, 1463, 1397, 1365, 1253, 1159, 1118, 882 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz, two rotamers) δ 4.10−3.32 (m, 5H), 2.93−2.80 (m, 1H), 2.50−2.27 (m, 3H), 2.26−2.14 (m, 1H), 2.10 and 2.06 (2 d, J = 9.9 Hz, 1H), 1.98−1.86 (m, 1H), 1.46 (s, 9H), 1.14−0.94 (m, 24H); ^{13}C NMR (75 MHz, $CDCl_3$) δ210.8, 154.5, 79.5, 79.2, 63.3, 63.0, 62.0, 50.3, 49.7, 46.0, 42.8, 42.5, 42.0, 41.6, 40.9, 39.6, 32.4, 28.4, 21.0, 17.9, 11.8; MS(DCI, NH_3/isobutane) m/z 440 (M + H)$^+$, 384 (100%), 340; HRMS (LTQ-Orbitrap, ESI) calcd for $C_{24}H_{45}NO_4SiNa$ 462.30101, found 462.30147.

(2*S*,3*S*,4*S*)-*tert*-Butyl 4-(1-Hydroxypropan-2-yl)-3-(2-methoxy-2-oxoethyl)-2-(((triisopropylsilyl)oxy)methyl)-pyrrolidine-1-carboxylate (18). To a solution of ketone **17** (0.762 g, 1.73 mmol) in CH_2Cl_2 (15 mL) was added m-CPBA (77% purity, 0.777 g, 3.47 mmol), and the solution was stirred for 72 h at room temperature. Sodium sulfite was added, and the mixture was extracted with Et_2O. The combined organic phases were washed with $NaHCO_3$, dried over Na_2SO_4, filtered, and evaporated under reduced pressure. Purification of the residue by flash chromatography afforded 0.698 g (88%) of a 1.1:1 mixture of inseparable isomeric lactones. A solution of the lactones (0.649 g, 1.42 mmol) in THF (15 mL) at −78 °C was treated with a freshly prepared solution of NaOMe (2.9 M in MeOH, 1 mL, 2.9 mmol). After being stirred for 1 h, the reaction mixture was quenched with aqueous NH_4Cl and the aqueous phase extracted with Et_2O. The combined organic phases were washed with brine and dried over Na_2SO_4, and the volatiles were removed under reduced pressure. Purification of the residue by flash chromatography (60:40 Et_2O−pentane) provided 0.642 g (92%) of the regioisomeric esters **18** and **19**. A small amount of pure **18**, obtained in a column fraction, was used for analysis: $[\alpha]^{20}_D$ −42.4 (c 0.33, $CHCl_3$); IR (film) 3053, 2944, 2866, 1731, 1681, 1403, 1366, 1265, 1171, 1120, 1084, 1022, 895 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz, two rotamers) δ 4.02−3.94, 3.80−3.56 and 3.54−3.32 (3 m, 7H), 3.67 (s, 3H), 3.10−2.93 (m, 1H), 2.79−2.66 (m, 1H), 2.60−2.32 (m, 2H), 2.24−2.10 (m, 1H), 1.70−1.56 (m, 1H), 1.44 (s, 9H), 1.15−0.97 (m, 21H), 0.94 (d, J = 6.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ173.2, 154.5, 154.3, 79.5, 79.1, 66.47, 66.40, 64.9, 64.7, 63.7, 51.6, 49.3, 48.9, 41.9, 40.9, 38.9, 38.4, 34.6, 33.2, 33.1, 28.4, 17.9, 17.8, 15.9, 15.8 11.8; MS(DCI, NH_3/isobutane) m/z 487, 432, 400, 388 (100), 356, 200. Anal. Calcd for $C_{25}H_{49}NO_6Si$: C, 61.57; H, 10.13; N, 2.88. Found: C, 61.56; H, 10.13; N, 2.71.

(2*S*,3*S*,4*S*)-*tert*-Butyl 3-(2-Methoxy-2-oxoethyl)-4-(1-(phenylselanyl)propan-2-yl)-2-(((triisopropylsilyl)-oxy)methyl)-pyrrolidine-1-carboxylate (20) and (2*S*,3*S*,4*R*)-*tert*-Butyl 4-(4-Methoxy-4-oxobutan-2-yl)-3-((phenylselanyl)methyl)-2-(((triisopropylsilyl)oxy)methyl)pyrrolidine-1-carboxylate (21). A solution of esters **18** and **19** (0.376 g, 0.77 mmol) and triethylamine (0.322 mL, 2.3 mmol) in THF (10 mL) at room temperature was treated with methanesulfonyl chloride (0.119 mL, 1.54 mmol) and stirred for 20 h. Water was then added and the organic phase extracted with Et_2O. The combined organic phases were washed with $KHSO_4$, $NaHCO_3$, and brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. To a solution of the residue and PhSeSePh (0.240 g, 1.54 mmol) in MeOH (12 mL) was added $NaBH_4$ (0.060 g, 3.1 mmol), and the solution was heated to 70 °C for 2 h. The reaction mixture was allowed to cool, water was added, and the organic phase was extracted with Et_2O. The combined organic phases were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. Purification of the residue by flash chromatography (30:70 Et_2O–pentane) provided 0.435 g (90%) of an inseparable 1.1:1 mixture of the selenides **20** and **21**: IR (film) 3053, 2943, 2865, 1737, 1691, 1477, 1462, 1400, 1265, 1173, 1121 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.57–7.54 (m, 2H), 7.29–7.25 (m, 3H), 3.98 (dd, J = 10.0, 4.2 Hz, 0.45H), 3.78–3.69 (m, 1.55H), 3.67 and 3.66 (2 s, 3H), 3.61–3.56 (m, 1H), 3.52–3.44 (m, 1H), 3.12 and 3.09 (2 br s, 1H), 2.99 and 2.88 (2 t, J = 10.7 Hz, 1H), 2.76–69 (m, 1H), 2.67–2.53 (m, 1.45H), 2.50–2.40 (m, 0.55H), 2.06–1.95 (m, 2H), 1.63–1.50 (m, 1H), 1.46 (s, 9H), 1.13–1.05 (m, 24H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.9, 154.3, 154.1, 133.4, 130.0, 128.9, 127.1, 127.0, 79.4, 78.9, 64.7, 64.4, 63.7, 51.4, 49.3, 48.9, 44.9, 43.8, 38.7, 38.2, 34.5, 34.4, 33.0, 32.5, 32.3, 28.3, 18.6, 18.5, 17.9, 17.8, 11.75 ; MS(ESI) m/z 650.3 $(M + Na)^+$, 628.4 $(M + H)^+$; HRMS (LTQ-Orbitrap, ESI) calcd for $C_{31}H_{53}NO_5SeSiNa$ 650.27504, found 650.27528.

(2*S*,3*S*,4*S*)-*tert*-Butyl 3-(2-Methoxy-2-oxoethyl)-4-(prop-1-en-2-yl)-2-(((triisopropylsilyl)oxy)methyl)-pyrrolidine-1-carboxylate (22) and (2*S*,4*R*)-*tert*-Butyl 4-(4-Methoxy-4-oxobutan-2-yl)-3-methylene-2-(((triisopropylsilyl)oxy)methyl)-pyrrolidine-1-carboxylate (23). A solution of selenides **20** and **21** (0.415 g, 0.66 mmol) and triethylamine (0.277 mL, 2.0 mmol) in THF (10 mL) was treated with H_2O_2 (8.8 M in water, 0.30 mL, 2.6 mmol) and heated at 65 °C for 4 h. The reaction mixture was allowed to cool, water was added, and the aqueous phase was extracted with Et_2O. The combined organic phases were washed with aqueous $KHSO_4$, $NaHCO_3$, and brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification of the residue by flash chromatography provided 0.155 g (50%) of **22** and 0.135 g (43%) of **23**. Data for **22**: ^1H NMR (300 MHz, $CDCl_3$, two rotamers) δ 4.82 and 4.81 (2 s, 1H), 4.57 and 4.51 (2 s, 1H), 3.99 (dd, J = 10.0, 3.9 Hz, 0.45 H), 3.77–3.67 (m, 1.55H), 3.59 and 3.58 (2 s, 3H), 3.52 (br s, 1H), 3.38–3.25 (m, 2H), 3.28 (app q, J = 9.8 Hz, 0.45H), 3.18 (app q, J = 7.5 Hz, 0.55H), 2.82 –2.76 (m, 1H), 2.20–2.02 (m, 2H), 1.65 (s, 3H), 1.38 (s, 9H), 1.00–0.95 (m, 21H); ^{13}C NMR (75 MHz, $CDCl_3$, two rotamers) 173.2, 142.6, 142.0, 112.3, 111.9, 79.6, 79.2, 64.2, 63.7, 52.5, 48.1, 47.5, 45.7, 44.8, 39.6, 38.8, 33.6, 28.5, 22.5, 18.0, 11.9; MS(ESI) m/z 492.4 $(M + Na)^+$, 470.4 $(M + H)^+$; HRMS (LTQ-Orbitrap, ESI) calcd for $C_{25}H_{47}NO_5SiNa$ 492.31157, found 492.31152. Data for **23**: ^1H NMR ($CDCl_3$, 300 MHz) δ 5.08 (br s, 1H), 4.94 (br s 1H), 4.25–4.05 (m, 1.4H), 3.85–3.65 (m, 1.6H), 3.60 (s, 3H), 3.40–3.25 (m, 2H), 2.72 (br s, 1H), 2.35–2.05 (m, 3H), 1.38 (s, 9H), 1.00–0.95 (m, 21H), 0.81 (d, J = 6.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, two rotamers) 173.2, 154.0, 150.6, 150.1, 112.3, 111.8, 107.5, 107.1, 79.5, 79.2, 65.8, 65.2, 64.2, 63.7, 63.3, 51.5, 51.4, 48.1, 47.6, 47.0, 46.5, 45.7, 44.8, 40.0, 39.6, 38.8, 33.6, 32.4, 28.5, 22.5, 18.1, 17.9, 14.5, 12.2, 11.9, 11.6; MS(ESI) m/z 492.4 $(M + Na)^+$, 470.4 $(M + H)^+$. HRMS (LTQ-Orbitrap, ESI) calcd for $C_{25}H_{47}NO_5SiNa$ 492.31157, found 492.31078.

(*S*)-1-*tert*-Butyl 2-Methyl 4-(Trifluoromethylsulfonyloxy)-2*H*-pyrrole-1,2(5*H*)-dicarboxylate (25).[20] To a stirred solution of NaHMDS (1.0 M in THF, 33.9 mL, 33.9 mmol) in THF (20 mL) at −78 °C was added slowly the ketone[20] derived from **24** (7.50 g, 30.8 mmol) in THF (15 mL). The reaction mixture was stirred for 30 min and then treated over 15 min with a solution of $PhNTf_2$ (12.12 g, 33.9 mmol) in THF (25 mL). The resulting mixture was stirred for 1.5 h at −78 °C, allowed to warm to 0 °C, and then quenched by the addition of water (25 mL). The mixture was extracted with ether, and the organic layer was washed with brine and dried over Na_2SO_4. Evaporation of the solvent under reduced pressure and purification of the residue on silica gel (15:85 EtOAc–pentane) afforded 9.85 g (85%) of triflate **25**:[20] $[\alpha]^{20}_D$ −125.2 (c 1.1, $CHCl_3$); IR (film) 1762, 1720, 1637, 1213, 1140, 1119, 1000 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, two rotamers) δ 5.74–5.72 and 5.69–5.67 (2 m, 1H), 5.05–5.03 and 5.00–4.97 (2 m, 1H), 4.39–4.25 (m, 2H), 3.75 (s, 3H), 1.46 and 1.41 (2 s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$, two rotamers) δ 169.5, 169.2, 153.1, 152.5, 146.2, 145.7, (124.8, 120.5, 116.3, 112.0) CF_3, 111.3, 111.1, 81.4, 81.3, 63.6, 63.1, 52.7, 52.5, 50.3, 50.0, 28.2, 28.1; MS (ESI^+) m/z 398 $(M + Na)^+$, 321, 307 (100); HRMS (LTQ-Orbitrap, ESI) calcd for $C_{12}H_{16}F_3NO_7SNa$ 398.0497, found 398.0492 $(M + Na^+)$.

(*S*)-1-(*tert*-Butoxycarbonyl)-5-(methoxycarbonyl)-2,5-dihydro-1*H*-pyrrole-3-carboxylic Acid (26). To a solution of triflate **25** (11.88 g, 31.65 mmol) in 8:2 THF–H_2O (80 mL) at 20 °C was added $(PPh_3)_4Pd$ (0.915 g, 0.79 mmol), and CO was then bubbled through the solution using a needle attached to a CO-filled balloon for 20 min. A slightly positive pressure of CO was maintained for 1 h, after which CO was again bubbled for 5 min through the solution, which was then stirred for another 2 h under positive pressure of CO. After the CO was replaced with argon, water was added, the mixture was extracted with ether, and the organic layer was extracted with aqueous $NaHCO_3$. This basic aqueous phase was acidified to pH 2 with 2 N HCl and then extracted with ether, which was washed with brine, dried over Na_2SO_4, and concentrated to afford 8.05 g (94%) of acid ester **26** as a white solid: mp 110–112 °C; $[\alpha]^{20}_D$ −202.5 (c 0.7, $CHCl_3$); IR (film) 1737, 1720, 1632, 1175, 1087, 996 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, two rotamers) δ 8.51 (br s, 1H), 6.68–6.66 and 6.63–6.61 (2 m, 1H), 5.23–5.19 and 5.12–5.08 (2 m, 1H), 4.41–4.34 (m, 2H), 3.72 (s, 3H), 1.44 and 1.38 (2 s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$, two rotamers) δ 169.3, 169.0, 165.6, 165.5, 153.8, 153.2, 135.6, 135.4, 134.7, 134.6, 81.1, 67.3, 66.9, 52.7, 52.6, 52.2, 51.9, 28.2, 28.1; MS (DCI, NH_3/isobutane) m/z 270 (100), 224, 133. Anal. Calcd for $C_{12}H_{17}NO_6$: C, 53.13; H, 6.32; N, 5.16. Found: C, 52.79; H, 6.18; N, 5.20.

(*S*)-1-*tert*-Butyl 2,4-Dimethyl 1*H*-Pyrrole-1,2,4(2*H*,5*H*)-tricarboxylate (27). To a solution of the above acid ester **26** (6.26 g, 23.1 mmol) in ether (60 mL) at 0 °C was added ethereal diazomethane (ca. 0.3 M, 88 mL, 26 mmol). After 15 min, the solvent was removed under reduced pressure, and the crude product was purified by chromatography on silica gel (25:75 EtOAc–pentane) to afford 6.20 g (94%) of diester **27** as a white solid: mp 41–43 °C; $[\alpha]^{20}_D$ −214.2 (c 0.6, $CHCl_3$); IR (film) 1762, 1730, 1709, 1245, 1168, 1091, 1003 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, two rotamers) δ 6.64–6.61 and 6.60–6.57 (2 m, 1H), 5.21–5.17 and 5.13–5.09 (2 m, 1H), 4.45–4.37 (m, 2H), 3.78 (s, 3H), 3.76 and 3.75 (2 s, 3H), 1.48 and 1.43 (2 s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$, two rotamers) δ 169.3, 168.9, 162.4, 162.3, 153.4, 152.7, 134.7, 134.6, 134.0, 133.9, 80.5, 80.4, 67.0, 66.7, 52.4, 52.3, 52.2, 52.0, 51.82, 51.80, 28.1, 28.0; MS (ESI^+) m/z 292 $(M + Li)^+$, 239 (100). Anal. Calcd for $C_{13}H_{19}NO_6$: C, 54.73; H, 6.71; N, 4.91. Found: C, 54.84; H, 6.82; N, 4.87.

(1*S*)-2-*tert*-Butyl 1,3a-Dimethyl 6-Oxo-3,3a-dihydro-1*H*-isoindole-1,2,3a(6*H*,7*H*,7a*H*)-tricarboxylate (30). A solution of diester **27** (4.72 g, 16.6 mmol) and Danishefsky's diene (4.84 mL, 24.9 mmol, distilled under reduced pressure in the presence of a slight excess of trichlorophenol relative to the remaining triethylamine, estimated by ^1H NMR) in dichloromethane (0.5 mL) was placed in a Teflon ampule, which was then closed (completely filled, no air bubbles). The ampule was subjected to a pressure of 15 kbar for 72 h. After this time, the pressure was released and the reaction mixture was added to THF (25 mL) and saturated aqueous $KHSO_4$ (20 mL). After being stirred for 30 min, the mixture was extracted with ether, and the organic layer was washed with brine and dried over Na_2SO_4. Evaporation of the solvent under reduced pressure and purification of the residue by chromatography on silica gel (35:65 EtOAc–pentane) afforded 1.46 g (23%) of the intermediate β-methoxy ketone

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32 and 3.63 g (62%) of the desired enone diester (**30**). The former was converted in 81% yield to the latter on refluxing in toluene in the presence of a catalytic amount of DBU (0.05 mL, 0.3 mmol) for 7 h. Enone diester **30** (90% ee by HPLC):[22] $[\alpha]^{20}_{D}$ −6.6 (*c* 1.2, $CHCl_3$); IR (film) 1755, 1735, 1701, 1681, 1158, 1128, 1074, 1020 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, two rotamers) δ 6.74−6.67 (m, 1H), 6.16 (d, *J* = 10.0 Hz, 1H), 4.02−3.77 (m, 3H), 3.75 (s, 3H), 3.74 (s, 3H), 3.28−3.23 (m, 1H), 2.88 and 2.82 (2 d, *J* = 5.4 Hz, 1H), 2.71−2.61 (m, 1H), 1.44 and 1.37 (2 s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$, two rotamers) δ 194.6, 194.3, 171.6, 171.3, 169.6, 169.5, 153.1, 152.6, 146.2, 145.8, 131.9, 131.7, 80.6, 62.4, 62.2, 55.5, 55.1, 52.9, 52.8, 52.2, 52.0, 51.8, 51.0, 44.6, 43.7, 35.5, 28.0, 27.8; MS (ESI$^+$) *m*/*z* 376 (M + Na^+, 100), 354 (MH^+). Anal. Calcd for $C_{17}H_{23}NO_7$: C, 57.78; H, 6.56; N, 3.96. Found: C, 57.41; H, 6.57; N, 3.86.

(1*S*)-2-(*tert*-Butoxycarbonyl)-6-oxo-2,3,3a,6,7,7a-hexahydro-1*H*-isoindole-1,3a-dicarboxylic Acid (33). A solution of enone diester **30** (3.10 g, 8.78 mmol) in THF (30 mL) was treated with LiOH (2 N, 20 mL), and the reaction mixture was stirred for 1.5 h, whereupon water and ether were added. The separated aqueous layer was treated with 2 N HCl to pH 2 and then extracted with ether and EtOAc. These organic extracts were combined, washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure to provide 2.80 g (98%) of enone diacid **33**. Recrystallization of this material from hot hexane−EtOAc afforded with 82% recovery the enantiopure (ee >99%)[23] enone diacid **33**: mp 116−117 °C dec; $[\alpha]^{20}_{D}$ −21.7 (*c* 0.5, $CHCl_3$); IR (film) 1737, 1719, 1683, 1675, 1650, 1242, 1162 cm^{-1}; ^1H NMR (300 MHz, CD_3OD, two rotamers) δ 6.93 (app.dd, *J* = 1.8, 10.2 Hz, 1H), 6.20 (d, *J* = 10.2 Hz, 1H), 4.00−3.83 (m, 3H), 3.30−3.24 (m, 1H), 2.98 and 2.96 (2 d, *J* = 17.7 Hz, 1H), 2.71 and 2.66 (2 dd, *J* = 2.3, 17.7 Hz, 1H), 1.49 and 1.43 (2 s, 9H); ^{13}C NMR (75 MHz, CD_3OD) δ 198.3, 175.7, 175.3, 173.0, 156.2, 155.9, 150.2, 150.1, 133.3, 133.2, 83.2, 83.0, 65.1, 64.7, 57.9, 57.4, 54.4, 53.7, 47.2, 46.5, 37.7, 37.6, 29.5, 29.3; MS (DCI, NH_3/isobutane) *m*/*z* 325 (100), 214, 180; HRMS (LTQ-Orbitrap, ESI) calcd for $C_{15}H_{19}NO_7Na$ 348.1059, found 348.1054 (M + Na^+).

(1*S*)-2-*tert*-Butyl 1-Methyl 6-Oxo-5,6,7,7a-tetrahydro-1*H*-isoindole-1,2(3*H*)-dicarboxylate (34). To enone diacid **33** (0.932 g, 2.86 mmol) in toluene (10 mL) was added dry pyridine (1.20 mL, 14.8 mmol). The reaction mixture was refluxed for 2.5 h and then cooled to 0 °C and acidified with 2 N HCl to pH 2. The mixture was extracted with ether, and the organic layer was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure to give 0.782 g of crude enone acid. An analytical sample was obtained from a comparable sample by chromatography on silica gel (80:20:0.5 EtOAc−pentane−AcOH): mp 136 °C dec; $[\alpha]^{20}_{D}$ +53.4 (*c* 0.5, $CHCl_3$); IR (film) 3468, 1730, 1719, 1707, 1683, 1253, 1169, 1028 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, two rotamers) δ 9.24 (br s, 1H), 5.76 (br s, 1H), 4.23−3.98 (m, 3H), 3.20 (br s, 1H), 3.01−2.76 (m, 3H), 2.47−2.27 (m, 1H), 1.46 and 1.42 (2 s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$, two rotamers) δ 207.1, 176.7, 174.8, 153.5, 137.1, 136.4, 116.5, 81.4, 65.4, 50.4, 49.9, 43.8, 42.8, 42.6, 38.4, 28.1; MS (ESI$^+$) *m*/*z* 304 (M + Na^+, 100), 272, 248, 226. Anal. Calcd for $C_{14}H_{19}NO_5$: C, 59.78; H, 6.81; N, 4.98. Found: C, 59.53; H, 6.76; N, 4.99. A solution of crude enone acid (0.782 g) in ether (10 mL) at 0 °C was treated with ethereal CH_2N_2 (ca. 0.3 M, 10 mL). After 20 min, the solvent was removed under reduced pressure and the crude product was purified by chromatography on silica gel (40:60 EtOAc−pentane) to give 0.700 g (83%, two steps) of enone ester **34**: mp 67−69 °C; $[\alpha]^{20}_{D}$ +57.0 (*c* 0.5, $CHCl_3$); IR (film) 1750, 1740, 1719, 1709, 1685, 1160, 1022, 998 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, two rotamers) δ 5.75 (br s, 1H), 4.22−4.12 (m, 2H), 4.05−3.95 (m, 1H), 3.75 (s, 3H), 3.14−2.75 (m, 4H), 2.43 and 2.38 (2 d, *J* = 12.0, 12.3 Hz, 1H), 1.45 and 1.41 (2 s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$, two rotamers) δ 206.7, 171.9, 171.6, 153.0, 152.9, 136.5, 116.2, 116.1, 80.4, 65.4, 65.0, 52.0, 50.0, 49.7, 43.6, 42.8, 42.6, 38.2, 28.0; MS (ESI$^+$) *m*/*z* 318 (M + Na^+, 100). Anal. Calcd for $C_{15}H_{21}NO_5$: C, 61.00; H, 7.17; N, 4.74. Found: C, 60.70; H, 7.18; N, 4.59.

(1*S*,3a*R*,7a*S*)-2-*tert*-Butyl 1-Methyl 6-Oxo-3,3a,7,7a-tetrahydro-1*H*-isoindole-1,2(6*H*)-dicarboxylate (35). A solution of enone ester **34** (0.700 g, 2.37 mmol) and DBU (0.050 mL, 0.33 mmol) in CH_2Cl_2 (5.0 mL) at 20 °C under argon was stirred for 4 h, whereupon at 0 °C 2 N HCl was added to pH 2. The mixture was extracted with CH_2Cl_2, and the organic layer was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. Purification of the residue by chromatography on silica gel (60:40 EtOAc−pentane) afforded 0.607 g (87%) of enone ester **35**: $[\alpha]^{20}_{D}$ −116.1 (*c* 0.5, $CHCl_3$); IR (film) 1755, 1686, 1675, 1122, 1025, 859 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, two rotamers) δ 6.77 and 6.74 (2 dd, *J* = 4.3, 10.2 Hz, 1H), 6.13−6.07 (m, 1H), 4.09 and 3.96 (2 d, *J* = 5.1, 6.6 Hz, 1H), 3.90−3.80 (m, 1H), 3.75 (s, 3H), 3.66, 3.33 and 3.54−3.47 (2 dd + m, *J* = 3.8, 10.7 Hz, 1H), 3.20−3.08 (m, 1H), 2.97−2.85 (m, 1H), 2.65 (d, *J* = 5.3 Hz, 2H), 1.46 and 1.39 (2 s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$, two rotamers) δ 195.2, 171.8, 171.4, 153.2, 152.6, 148.5, 147.8, 130.0, 129.9, 79.6, 62.2, 62.1, 51.6, 51.5, 50.7, 42.0, 41.2, 37.1, 37.0, 36.8, 36.6, 27.6, 27.5; MS (ESI$^+$) *m*/*z* 302 (M + Li^+, 100), 246. Anal. Calcd for $C_{15}H_{21}NO_5$: C, 61.00; H, 7.17; N, 4.74. Found: C, 60.76; H, 7.29; N, 4.59.

(2*R*,3*S*,4*S*)-1-*tert*-Butyl 2-Methyl 3-(2-Methoxy-2-oxoethyl)-4-(1-(trifluoromethylsulfonyloxy)prop-1-en-2-yl)pyrrolidine-1,2-dicarboxylate (37′). An argon-flushed flask was charged with CuCN (0.495 g, 5.53 mmol) and THF (10 mL) was added. The flask was cooled to −78 °C, and MeLi (1.6 M in ether, 6.9 mL, 11.0 mmol) was added slowly. Stirring was continued for 30 min at −78 °C, and then a mixture of enone ester **35** (0.544 g, 1.84 mmol) and TMSCl (1.42 mL, 11.11 mmol) in THF (6 mL) was added. After 45 min at −78 °C, the reaction mixture was quenched by the addition of an aqueous solution of NH_4Cl−NH_4OH. The mixture was extracted with ether, and the organic layer was washed with brine and dried over Na_2SO_4. The solvent was removed under reduced pressure to give the crude enol ether (0.683 g), which was used directly for the next reaction. Enol ether **36**: ^1H NMR (300 MHz, $CDCl_3$, two rotamers) δ 4.75−4.70 (m, 1H), 4.02 and 3.89 (2 d, *J* = 5.8, 7.6 Hz, 1H), 3.74 and 3.73 (2 s, 3H), 3.85−3.52 (m, 1H), 3.44−3.37 and 3.27−3.22 (2 m, 1H), 2.58 and 2.48 (2 m, 1H), 2.32−2.21 (m, 1H), 2.16−1.80 (m, 3H), 1.45 and 1.39 (2 s, 9H), 1.01 (d, *J* = 6.6 Hz, 3H), 0.19 and 0.18 (2 s, 9H). A stream of O_3 in O_2 was bubbled through a solution of 0.675 g of the above crude enol ether in CH_2Cl_2−MeOH (3:1, 10 mL) at −116 °C. When the blue color persisted (ca. 10 min), dimethyl sulfide (1.5 mL) was added, and reaction mixture was allowed to warm to 20 °C and was stirrred for 2 h. The solvents were then removed under reduced pressure, the residue was taken up in ether, and the organic layer was washed with brine and dried over Na_2SO_4. The solvent was removed under reduced pressure to give the crude aldehyde acid (0.712 g), which was used directly for the next step. A solution of the above crude aldehyde acid (0.712 g) in ether (10 mL) was cooled to 0 °C and treated with ethereal CH_2N_2 (ca. 0.3 M, 8.3 mL). After 15 min, the solvent was removed under reduced pressure and the crude product was purified by chromatography on silica gel (40:60 EtOAc−pentane) to afford 0.453 g (70%, three steps) of unstable aldehyde ester **37**: IR (film) 1740, 1697, 1206, 1167, 1002, 898 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, two rotamers) δ 9.56 (br s, 1H), 4.22−4.12 (m, 1H), 3.87−3.63 (m, 2H), 3.74 (s, 3H), 3.69 (s, 3H), 3.37−3.30 and 3.16−3.04 (2 m, 1H), 2.97−2.87 and 2.72−2.58 (2 m, 1H), 2.50−2.18 (m, 3H), 1.45 and 1.39 (2 s, 9H), 1.13 (d, *J* = 7.1 Hz, 3 H). To a stirred solution of KHMDS (0.065 g, 0.33 mmol) in THF (3 mL) at −78 °C was added aldehyde ester **37** (0.053 g, 0.15 mmol) in THF (2 mL). After 15 min, the reaction mixture was treated with a solution of 2-[*N*,*N*-bis(trifluoromethylsulfonyl)amino]-5-chloropyridine (0.128 g, 0.33 mmol) in THF (3 mL), stirred for 1.5 h, and then allowed to warm to 0 °C. An aqueous solution of NH_4Cl−NH_4OH was added, the mixture was extracted with ether, and the organic layer was washed with brine and dried over Na_2SO_4. The solvents were removed under reduced pressure to yield the crude product, which was purified by chromatography on silica gel (15:85 EtOAc-pentane) to afford the 0.046 g (63%) of enol triflate **37′** and 0.005 g of the starting aldehyde ester. Enol triflate **37′**: $[\alpha]^{20}_{D}$ −37.8 (*c* 1.1, $CHCl_3$); IR (film) 3100, 1751, 1730, 1704, 1686, 1140, 1057, 1018 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, two rotamers) δ 6.49, 6.36 (2 s, 1H), 4.00−3.90 (m, 1H), 3.76−3.55 (m, 9H), 3.13−2.87 (m, 1H), 2.58−2.27 (m, 2H), 1.71 and 1.61 (2 d, *J* = 1.5 Hz, 3H), 1.45 and

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1.39 (2 s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$, two rotamers) δ 172.2, 172.0, 171.6, 171.1, 153.6, 153.0, 132.6, 132.5, 125.6, 125.5, (124.8, 120.6, 116.3, 112.1) CF_3, 80.76, 80.71, 63.5, 63.4, 63.14, 63.0, 52.42, 52.37, 52.26, 52.20, 51.92, 51.89, 48.7, 48.3, 43.0, 42.9, 42.13, 42.10, 38.7, 37.8, 33.2, 33.1, 32.9, 32.8, 28.3 28.1; MS (ESI$^+$) m/z 496 (M + Li^+, 100), 344; HRMS (LTQ-Orbitrap, ESI) calcd for $C_{18}H_{26}F_3NO_9SNa$ 512.1178, found 512.1173 (M + Na^+).

(2*S*,3*S*,4*S*)-1-*tert*-Butyl 2-Methyl 3-(2-Methoxy-2-oxoethyl)-4-(prop-1-en-2-yl)pyrrolidine-1,2-dicarboxylate (38). A mixture of enol triflate **37′** (0.105 g, 0.21 mmol), LiCl (0.027 g, 0.64 mmol), $(PPh_3)_4Pd$ (0.050 g, 0.04 mmol), and triethylsilane (0.075 g, 0.64 mmol) in DMF (3.0 mL) was stirred at 55 °C for 2 h, whereupon it was allowed to cool to 20 °C, and ether and water were added. The aqueous phase was separated and extracted with ether, and the combined organic phases were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by chromatography on silica gel (15:85 EtOAc−pentane) to give 0.070 g (96%) of olefin **38**: $[\alpha]^{20}_D$ −20.0 (*c* 0.7, $CHCl_3$); IR (film) 3085, 1737, 1701, 1206, 1169, 1130, 1007, 898 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$, two rotamers) δ 4.91 and 4.69 (2 s, 2H), 4.16 and 4.06 (2 d, J = 3.3, 3.8 Hz, 1H), 3.79−3.62 (m, 7H), 3.52−3.38 (m, 1H), 3.07−2.97 and 2.89−2.79 (2 m, 2H), 2.40−2.21 (m, 2H), 1.69 (s, 3H), 1.46 and 1.40 (2 s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$, two rotamers) δ 172.6, 172.4, 172.3, 172.2, 153.7, 153.6, 141.3, 141.2, 113.3, 113.1 80.2, 63.9, 63.6, 52.2, 52.1, 51.7, 47.8, 47.5, 45.9, 45.2, 41.8, 40.9, 32.9, 28.3 28.1, 22.2, 22.1; MS (ESI$^+$) m/z 348 (M + Li^+, 100), 303, 261; HRMS (LTQ-Orbitrap, ESI) calcd for $C_{17}H_{27}NO_6Na$ 364.1736, found 364.1731 (M + Na^+).

(2*S*,3*S*,4*S*)-3-(Carboxymethyl)-4-(prop-1-en-2-yl)pyrrolidine-2-carboxylic Acid (Kainic Acid) (1). A solution of olefin **38** (0.0360 g, 0.105 mmol) in THF (1.5 mL) at 0 °C was treated with 2 N LiOH (15 mL) and then stirred for 10 h at 20 °C. The reaction mixture was acidified with 2 N HCl to pH 3 and extracted with ethyl acetate. The combined organic phases were dried over Na_2SO_4 and concentrated. Dichloromethane (2 mL) and TFA (0.106 mL, 1.43 mmol) were added to the residue, and the resulting reaction mixture was stirred for 10 h. After removal of the solvent, the crude product was purified on Dowex-50 (WX8-200, H^+ form), eluting with NH_4OH (0.1−0.5 N), to afford 0.0206 g of slightly impure kainic acid. Recrystallization of this material from MeOH−H_2O provided the analytical sample (0.0168 g, 75%): mp 241−243 °C; $[\alpha]^{20}_D$ −14.3 (*c* 0.16, H_2O); ^{1}H NMR (300 MHz, D_2O) δ 5.11 (s, 1H), 4.82 (s, 1H), 4.15 (d, J = 3.1 Hz, 1H), 3.70 (dd, J = 11.7, 7.4 Hz, 1H) 3.50 (dd, J = 11.7, 10.5 Hz, 1H), 3.18−3.03 (m, 2H), 2.45 (dd, J = 15.6, 6.4 Hz, 1H), 2.34 (dd, J = 15.6 8.2 Hz, 1H), 1.83 (s, 3H); ^{13}C NMR (75 MHz, D_2O) δ 179.8, 174.0, 140.6, 113.3, 66.2, 46.7, 46.2, 42.1, 36.2, 22.5. This material was spectroscopically and chromatographically indistinguishable from a commercial sample of the natural product.

■ ASSOCIATED CONTENT

Supporting Information

^{1}H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(16) Simple computational studies revealed that the cis isomer is 2.4 kcal/mol more stable than the trans.

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(18) Attempts to form the olefins more directly from the alcohols by using Grieco's procedure were unsuccessful: Grieco, P. A.; Gilman, S.; Nishizawa, M. *J. Org. Chem.* **1976**, *41*, 1485−1486.

(19) Intermediates closely related to **22** have been converted into kainic acid. See: refs 5o and 5w.

(20) Honda, T.; Takahashi, R.; Namiki, H. *J. Org. Chem.* **2005**, *70*, 499−504.

(21) The enantiomeric excess of diester **27** was determined by HPLC: Chiracel AD-H, 5 mm, hexane/2-propanol, 9:1, 1.0 mL/min t_R 12.0 min; t_R (enantiomer) 16.5 min.

(22) The enantiomeric excess of diester enone **30** was determined by HPLC: Chiracel OD-H, 5 mm, hexane/2-propanol, 9:1, 1.0 mL/min t_R 16.9 min; t_R (enantiomer) 22.0 min.

(23) The enantiomeric excess was determined by HPLC of diester **30**, obtained by treatment of diacid **33** with diazomethane.

(24) All attempts to effect the decarbomethoxylation/decarboxylation and reconjugation in fewer operations, unfortunately, led to unsatisfactory results. For example, treatment of diester **30** with 1 N KOH in refluxing THF led only to diacid **33**, without any decarboxylated product; a catalytic amount of DBU in pyridine did not effect decarboxylation−reconjugation of diacid **33**.

(25) Additional support was obtained through NOE experiments on the dihydro *N*-tosyl derivative from **35**.

(26) For an alternative preparation of this aldehyde (for a synthesis of domoic acid), see: Ohfune, Y.; Tomita, M. *J. Am. Chem. Soc.* **1982**, *104*, 3511−3513.

(27) Sodium borohydride did provide the corresponding alcohol, but neither Grieco's one-step procedure nor the Burgess reagent yielded the desired olefin.

(28) Tf_2O in combination with 2,6-di-*tert*-butyl-4-methylpyridine (DTMB) in refluxing 1,2-dichloroethane failed to produce the desired enol triflate; the use of potassium hydride as the base in combination with *N*-phenyltriflimide in THF led to only traces of the enol triflate; KHMDS in lieu of potassium hydride with *N*-phenyltriflimide in THF afforded the expected product, but in lower (46%) yield than that obtained using the Comins reagent.

(29) Comins, D. L.; Dehghani, A. *Tetrahedron Lett.* **1992**, *33*, 6299−6302.

(30) For other examples, see: Pandey, S. K.; Greene, A. E.; Poisson, J.-F. *J. Org. Chem.* **2007**, *72*, 7769−7770.