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Just Accepted

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RECEIVED DATE

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R^1 = CHO, CO_2Me
R^2 = CH_2OR, CO_2R
R^3 = OMe, NMe_2

rd > 95:5
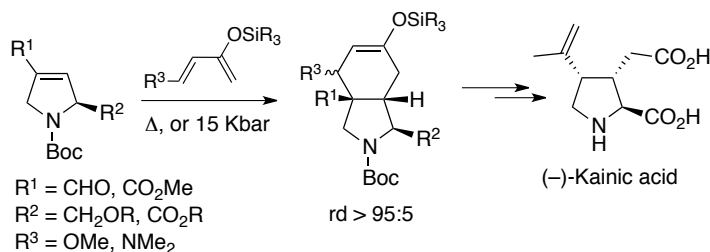
(–)-Kainic acid

ABSTRACT.

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

KEYWORDS. (–)-kainic acid, total synthesis, Asymmetric, Diels-Alder, high pressure

Introduction

(–)-Kainic acid (**1**) is a naturally occurring pyrrolidine with functionalized substituents at C2, C3, and C-4 in a trans-ci*s* relationship. Isolated from *Digenea simplex* in the early fifties,[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 of this natural product 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.
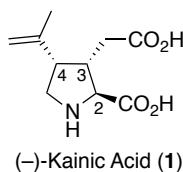
(–)-Kainic Acid (**1**)

FIGURE 1. (–)-Kainic Acid

We have published two total syntheses of (–)-kainic acid from inexpensive *trans*-4-hydroxy-L-proline (2, eq 1), 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-oxo proline derivative and a cuprate-mediate isopropenylation,[5hh] whereas the second made effective use of a Diels-Alder reaction, particularly attractive for setting the natural C2-C3-C4 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.
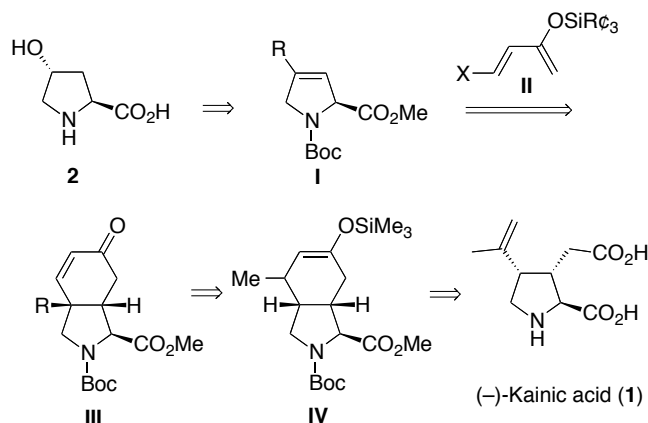
Figure 2. Synthetic strategy

Results and Discussion

First approach

A Diels-Alder approach with dehydroproline **I** seemed particularly attractive (Fig. 2). The functional group at C-2 could be expected to induce effectively the desired face selection to 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,[9,10,11,12] there is "*double* activation" as in, for example, α-carbalkoxy enones. Furthermore, only rarely has the trisubstitituted double bond been incorporated in a five-membered ring (all successful examples have required that one of the substituents be an activating group).[11,12,13]

Since pyrroline derivative **I**, R= CO$_2$R' 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 "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*-phenyl triflimide,

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).

Scheme 1. Synthesis of the dienophiles
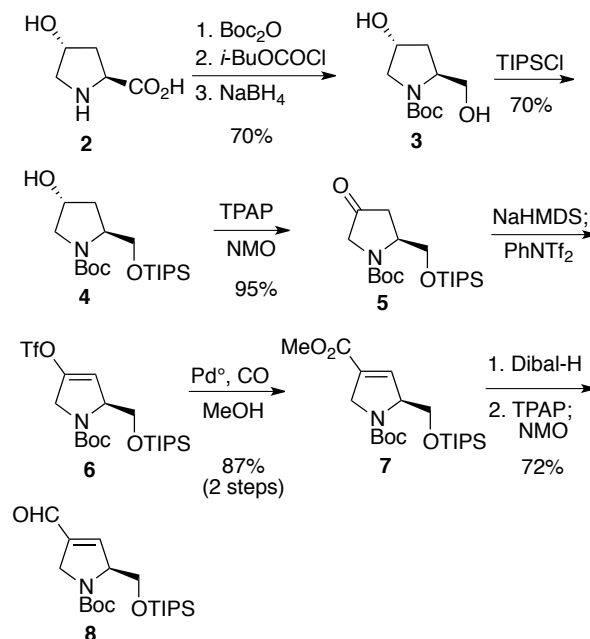
The trisubstituted α,β-unsaturated ester **7** and aldehyde **8** showed similar behavior toward electron-rich

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 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.

Scheme 2. Diels-Alder cycloadditions

7: R = OMe
8: R = H

endo : exo = 3:1

9: R = OMe
10: R = H

11: LiOH;
NEt$_3$, tol

30%
(from **7**)

HCl (1M)

rd > 98:2

11: R = OMe
12: R = H

12: KOH/THF
31%
(from **8**)

13

DBU
92%

14
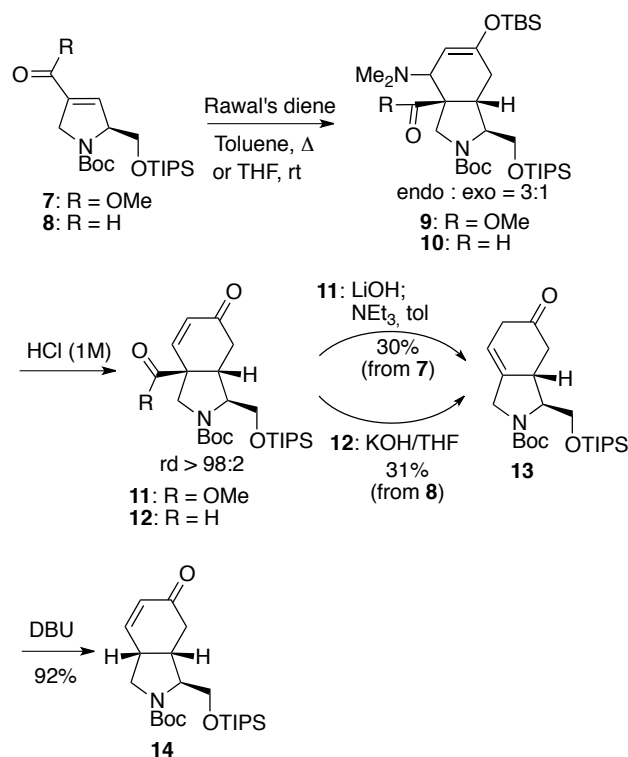
Having served their dual purpose of activating the olefin and controlling the regioselectivity of the cycloadditions, the angular functional groups now needed to be excised. The vinylogous β-keto ester **11** on saponification, followed by decarboxylation of the resultant acid with triethylamine in refluxing toluene, provided enone **13** (30%, 3 steps). The same enone was formed from the vinylogous β-keto aldehyde **12** by decarbonylation with potassium hydroxide (31%, 3 steps). In both cases the double bond, surprisingly, suffered translocation to the non-conjugated, 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) for NOE measurments (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**

14 → **15** → **16**
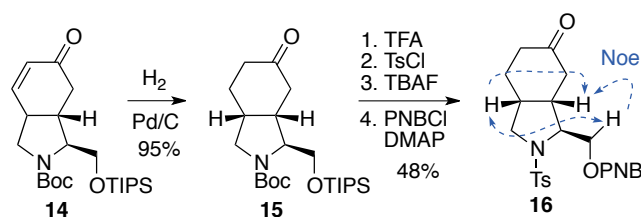
With compound **14** in hand, we were unduly confident of success. The addition of higher-order dimethyl cuprate to unsaturated ketone **14** led to compound **17** in excellent yield, however the closely precedented[17] Baeyer-Villiger oxidation, followed by methanolysis of the unseparable lactones, led, quite unexpectedly, to a nearly equimolar mixture of hydroxy esters **18** and **19** (Scheme 4). We, nevertheless, continued the 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]

Scheme 4. End of the first route
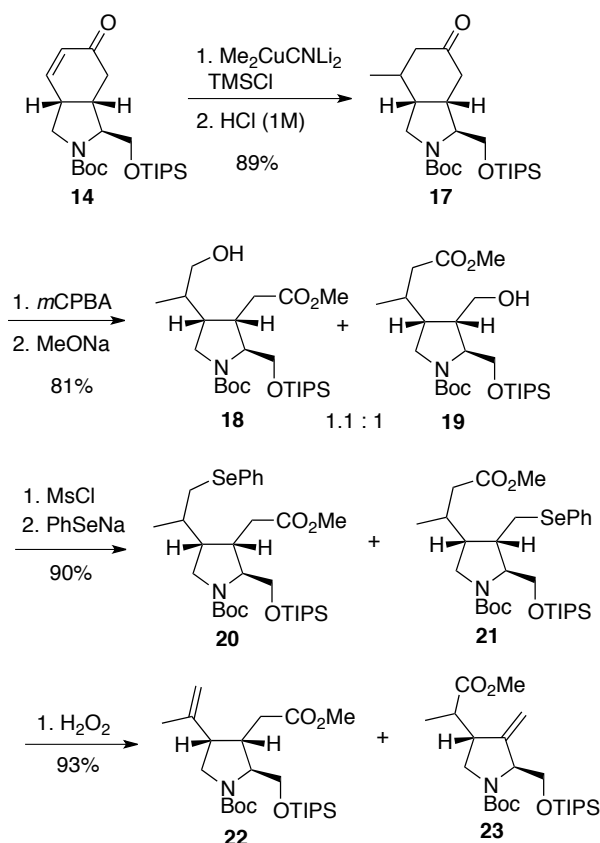
While at this stage we had essentially completed a Diels-Alder based approach to natural kainic acid,[19] we were not in the least pleased with its efficiency and decided to seek an alternative route. Nonetheless, the work had been instructive: The Diels-Alder reaction had indeed proven useful for the 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 (Fig 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**[20] (Scheme 5). Oxidation of the hydroxyl group was best 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 stored acid **26** had a much greater configurational stability than did the 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.

Scheme 5. Synthesis of diester **27**
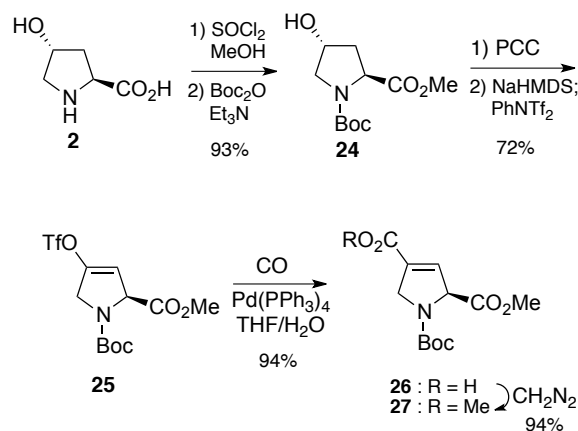
In refluxing toluene, ester **27** reacted to some extent (57% conversion after 82 h) with Danishefsky's diene (**28**) but, after hydrolysis, enone **30** was formed in just 22% yield and, even more discouragingly, in only 24% enantiomeric excess (Scheme 6). With the more reactive Rawal diene (**29**), 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] cycloaddition with diester **27**
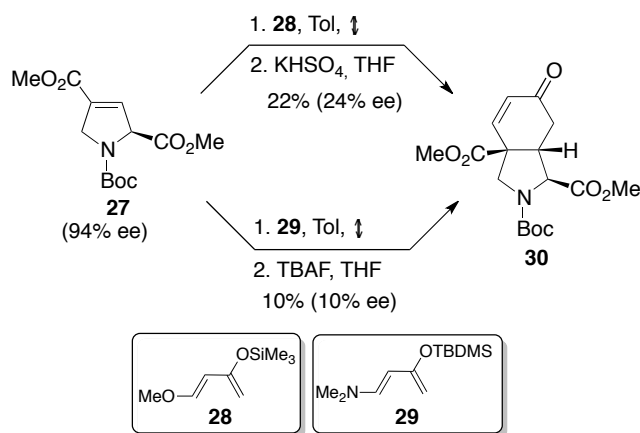
Seeking an alternative that might permit milder reaction conditions, we turned our attention to high pressure. This technique seemed particularly appropriate in present context: high pressure could be expected to lead to high conversion at lower temperatures and at lower temperatures, and, these milder conditions could reduce the degree of racemization of the vinyligous malonate. 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**
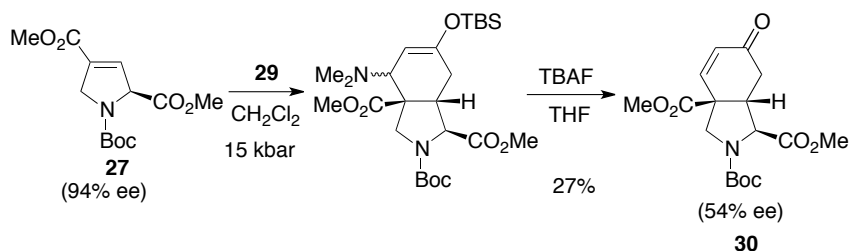
With Danishefsky's diene, the cycloaddition reached 96% conversion at room temperature under 15 kbar after 82 h (Scheme 8). The cycloadduct **31**, obtained as a 3:1 mixture of endo:exo isomers, could be converted into a mixture of enone **30** and ketone **32** by treatment with KHSO$_4$. The latter 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].

Scheme 8. High-pressure cycloaddition using Danishefsky diene
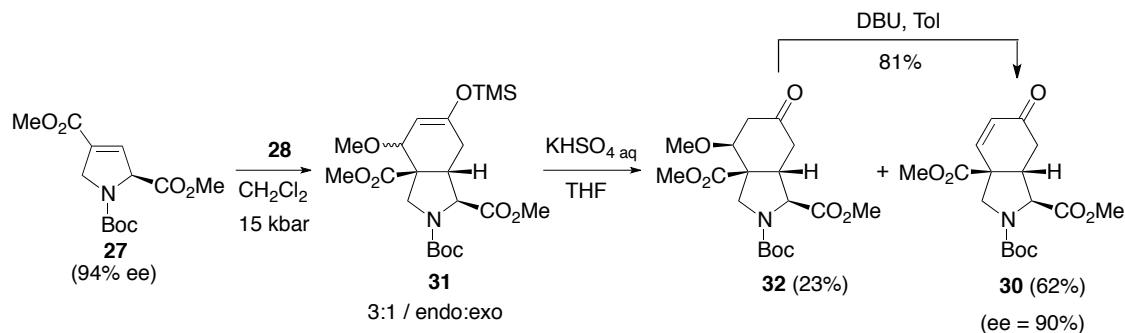
The enormous impact of a minor amount of triethylamine on resulting enantiomeric excess of the product was completely unexpected. An experiment was therefore conducted with diester **27** in a 5% solution of triethylamine in dichloromethane at room temperature under atmospheric pressure. After 3 h, the enantiomeric excess of the starting diester dropped to 56% (HPLC) and after 17 h, racemization was total (Fig 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 (Fig 3, red curve). To the best of our knowledge, this is the first example of a base-catalyze high pressure-accelerated racemization, a phenomenon that would seem to warrent further study.
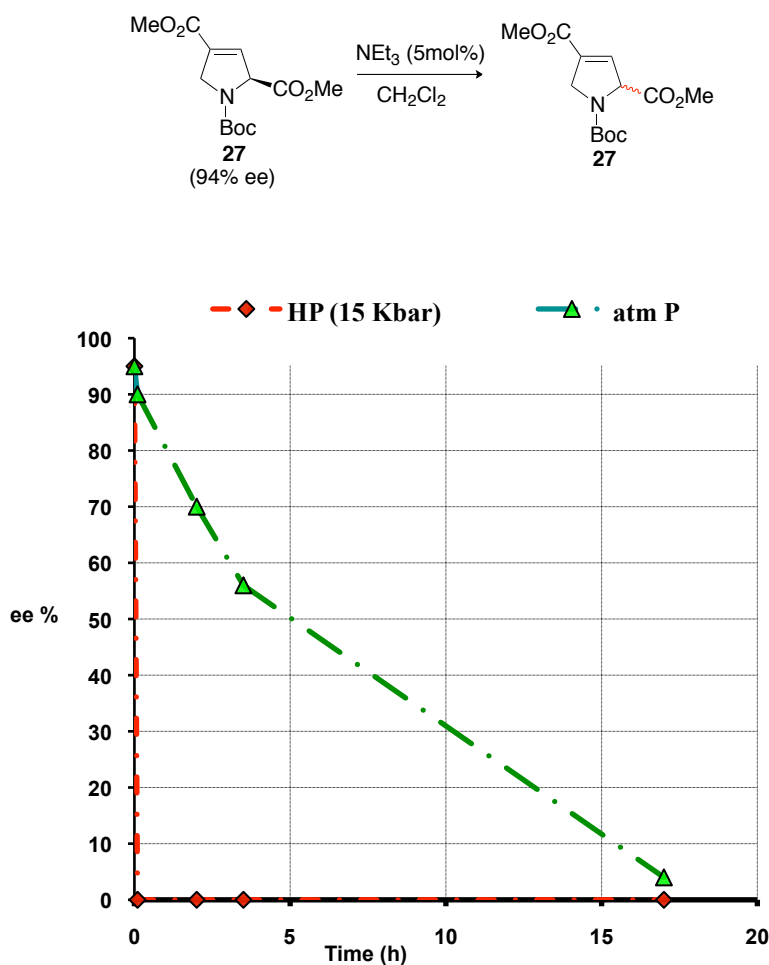
Figure 3. Pressure dependence of racemization rate of diester **27**

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 2 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 monodecarboxylation of this

vinylogous β-keto acid and exposure of the product to diazomethane produced ketone **34,** which**,** as now expected, was non-conjugated. The desired conjugated enone could, however, once again be regenerated with DBU in essentially quantitative yield.[24] A cis ring fusion in enone **35** was assumed, based on 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.

Scheme 9. Decarbomethoxylation of **30**
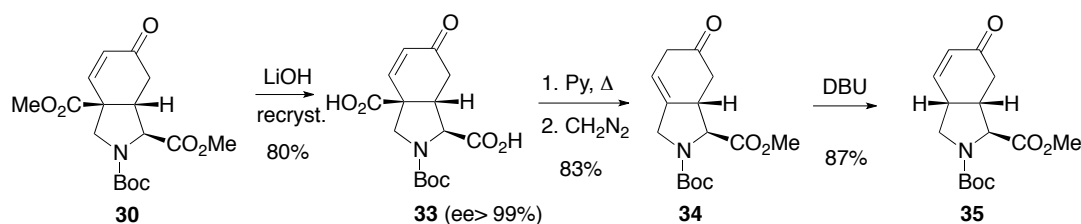
In an attempt to overcome the problem of poor regioselectivity of the previous Baeyer-Villiger reaction, the possibility of effecting an oxidative cleavage of the enol ether obtained through cuprate 1,4-addition/TMSCl trapping was examined next (Scheme 10). Dimethyl cyanocuprate addition to **35** in 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 diester aldehyde **37**.[26] The overall yield for the 3 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, $[a]^{20}_D$ –14.3 (*c* 0.16, H$_2$O)) was found to be identical with a commercial sample of the naturally derived material (mp 241-243 °C, $[a]^{20}_D$ –13.9 (*c* 0.16, H$_2$O)).

Scheme 10. Completion of the synthesis of kainic acid
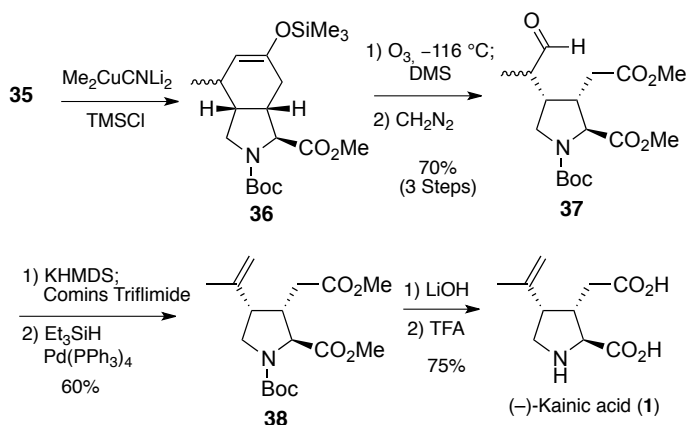
Conclusion

Natural kainic acid has been prepared with nearly total stereocontrol and 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 C3 and C4 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. ^1H NMR and ^{13}C NMR spectra were recorded on either 300, 400, or 500 MHz apparatus. All shifts for ^1H 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,

1
2 or ESI techniques. HRMS were recorded on an Orbitrap apparatus (ESI). Microanalyses were performed by
3
4 an in-house microanalysis service.
5
6
7 **(2S,4R)-tert-Butyl 4-Hydroxy-2-(((triisopropylsilyl)oxy)methyl)pyrrolidine-1-carboxylate (4)**. A solution
8
9 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
10
11 triethylamine (14.2 mL, 105.1 mmol) at 0 °C was treated dropwise with TIPSCl (21.8 mL, 101.8 mmol). The
12
13 reaction mixture was allowed to warm to room temperature and stirred overnight. Water was then added and
14
15 the organic layer separated. The aqueous layer was extracted with CH_2Cl_2 and the combined organic layers
16
17 were washed with brine, dried over Na_2SO_4, and filtered. The filtrate was concentrated and the crude product
18
19 was purified by column chromatography on silica gel (50:50 EtOAc-pentane) to afford 24.3 g (70%) of
20
21 alcohol **4** as a colorless liquid: $[\alpha]^{20}_D$ –58.6 (c 0.42, $CHCl_3$); IR (film) 2944, 2866, 1697, 1673, 1462, 1366,
22
23 1256, 1168, 1121, 1014, 882 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, 2 rotamers) δ 4.50 (br s, 1H), 4.17-3.92 (m,
24
25 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,
26
27 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,
28
29 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
30
31 $C_{19}H_{39}NO_4Si$: C, 61.08; H, 10.52; N, 3.75. Found: C, 61.42; H, 10.53; N, 3.92.
32
33
34
35 **(S)-tert-Butyl 4-Oxo-2-(((triisopropylsilyl)oxy)methyl)pyrrolidine-1-carboxylate (5)**. To a stirred solution
36
37 of alcohol **4** (11.7 g, 31.3 mmol) in CH_2Cl_2 (100 mL) at 0 °C was added 4 Å molecular sieves (30.0 g) and
38
39 tetra-N-propylammonium perruthenate (0.545 g, 5 Mol %), followed by 4-methylmorpholine N-oxide (5.5 g,
40
41 46.9 mmol). The reaction mixture was stirred overnight and then filtered through silica gel with ethyl acetate
42
43 and the filtrate was concentrated by rotary evaporation under reduced pressure. The residue was purified by
44
45 silica gel column chromatography (40:60 EtOAc-pentane) to yield 11.1 g (95%) of ketone **5** as a colorless
46
47 liquid: $[\alpha]^{20}_D$ –7.4 (c 0.38, $CHCl_3$); IR (film) 2944, 2865, 1716, 1698, 1682, 1463, 1397, 1365, 1253, 1159,
48
49 1118, 882 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, 2 rotamers) δ 4.50-3.62 (m, 5H), 2.83-2.63 (m, 1H), 2.60-2.46
50
51 (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,
52
53 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.
54
55 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.
56
57
58
59
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(S)-tert-Butyl 4-(((Trifluoromethyl)sulfonyl)oxy)-2-(((triisopropylsilyl)oxy)methyl)-2,5-dihydro-1H-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$_2$O and the combined organic layers were washed with brine and dried over Na$_2$SO$_4$. 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}; ^{1}H NMR (300 MHz, CDCl$_3$, 2 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$_3$NO$_6$SSi: 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)-1H-pyrrole-1,3(2H,5H)-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$_2$O. The ether layer was separated and the aqueous layer was extracted with ether. The combined ether layers were washed with brine, dried over Na$_2$SO$_4$ 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}; ^{1}H NMR (300 MHz, CDCl$_3$, 2 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$_5$Si: 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$_2$SO$_4$.10H$_2$O and filtered with CH$_2$Cl$_2$. 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$_2$O-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}; ^{1}H NMR (300 MHz, CDCl$_3$, 2 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$_4$Si: 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$_2$Cl$_2$ (100 mL) at 0 °C was added 4 Å molecular sieves (20 g) and tetra-N-propylammonium perruthenate (425 mg, 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$_2$O-pentane) to give 6.70 g, (72%, 2 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}; ^{1}H NMR (CDCl$_3$, 300 MHz, 2 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$_4$NaSi: 406.23841. Found: 406.23877.

(3S,3aS)-*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 1M 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$_2$SO$_4$, 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 1N LiOH (1.0 mL) for 1 h. Et$_2$O (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$_2$SO$_4$, 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$_2$O-pentane) to afford 0.0037 g (30%, 4 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$_2$O (20 mL). The solution was cooled to 0 °C and slowly treated with 1M 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$_2$O and the combined organic layers were washed with aq. NaHCO$_3$ and brine, dried over Na$_2$SO$_4$, and concentrated. The crude material dissolved in Et$_2$O (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$_2$O. The combined organic layers were washed with water, dried over Na$_2$SO$_4$, and concentrated and the crude product was purified by silica gel column chromatography (25:75 Et$_2$O-pentane) to afford 1.54 g (31%, 3 steps) of enone **13** as a colorless oil: [α]$^{20}_D$ +9.6 (*c* 0.36, CHCl$_3$); IR (film) 2939, 2861, 1691, 1460, 1389, 1361, 1254, 1165, 1116, 881 cm^{-1}; ^{1}H NMR (CDCl$_3$, 300 MHz, 2 rotamers) δ 5.70 (s, 1H), 4.38-4.06 (m, 2H), 4.03-3.76 (m, 2H), 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$_4$Si: C, 65.20; H, 9.75; N, 3.31. Found: C, 64.93; H, 9.87; N, 3.32.

(1S,3aR,7aS)-*tert*-Butyl   6-Oxo-1-(((triisopropylsilyl)oxy)methyl)-3,3a,7,7a-tetrahydro-1*H*-isoindole-2(6H)-carboxylate (14). A solution of enone **13** (0.84 g, 1.98 mmol) and DBU (0.29 mL, 1.97 mmol) in CH$_2$Cl$_2$ (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$_2$SO$_4$, and concentrated. The crude product was purified by silica gel column chromatography (30:70 Et$_2$O-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, 2 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$_4$Si: C, 65.20; H, 9.75; N, 3.31. Found: C, 64.99; H, 9.56; N, 3.29.

((1S,3aR,7aS)-6-Oxo-2-tosyloctahydro-1*H*-isoindol-1-yl)methyl 4-Nitrobenzoate (16). A mixture of enone **14** (62 mg, 0.146 mmol) and 10% Pd/C (15 mg, 0.015 mmol) 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** (59 mg, 95%) of sufficient purity to be used directly in the next step. ^{1}H NMR (CDCl$_3$, 400 MHz, 2 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$_4$SiNa : 448.28536; Found : 448.28513. A solution of ketone **15** (58 mg, ca 0.13 mmol) in CH$_2$Cl$_2$ (2 mL) was treated with trifluoroacetic acid (0.25 mL, 3.3 mmol) at room temperature. After stirring 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 (30 mg, 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 provided 28 mg (64 %, 3 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′** (11 mg, 0.034 mmol), pyridine (0.005 mL, 0.068 mmol), and DMAP (4 mg, 0.034 mmol) in CH$_2$Cl$_2$ (2 mL) was treated at room temperature with *p*-nitrobenzoyl chloride (9.5 mg, 0.051 mmol). After stirring for 12 h, the reaction mixture was quenched with HCl (1N). The aqueous phase was extracted with EtOAc and the combined organic phase were washed with HCl (1N), 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 provided 12 mg (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.

(1S,3aR,7aS)-*tert*-Butyl 4-Methyl-6-oxo-1-(((triisopropylsilyl)oxy)methyl)hexahydro-1H-isoindole-2(3H)-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 sat. aq. NH$_4$Cl, 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 sat. aq. NH$_4$Cl and brine, dried over Na$_2$SO$_4$, and concentrated under reduced pressure. The crude product was then dissolved in THF (15 mL) and stirred overnight with 1N HCl (5 mL). The solution was extracted with ether and the combined organic layers were washed with sat. aq. NaHCO$_3$ and brine, dried over Na$_2$SO$_4$, and concentrated under reduced pressure. Purification of the residue by silica gel column chromatography (25:75 Et$_2$O-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, 2 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$_3$) δ 210.8, 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$_4$SiNa : 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** (762 mg, 1.73 mmol) in CH$_2$Cl$_2$ (15 mL) was added *m*-CPBA (77% purity, 777 mg, 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$_2$O. The combined organic phases were washed with NaHCO$_3$, dried over Na$_2$SO$_4$, filtered and evaporated under reduced pressure. Purification of the residue by flash chromatography afforded 698 mg (88%) of a 1.1 :1 mixture of inseparable isomeric lactones. A solution of the lactones (649 mg, 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 stirring for 1 h, the reaction mixture was quenched with aqueous NH$_4$Cl and the aqueous phase extracted with Et$_2$O. The combined organic phases were washed with brine and dried over Na$_2$SO$_4$, and the volatiles were removed under reduced pressure. Purification of the residue by flash chromatography (60:40 Et$_2$O-pentane) provided 642 mg (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, 2 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$_3$) δ 173.2, 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$_6$Si: 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** (376 mg, 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$_2$O. The combined organic phases were washed with KHSO$_4$, NaHCO$_3$, and brine, dried over Na$_2$SO$_4$, filtered, and concentrated under reduced pressure. To a solution of the residue and PhSeSePh (240 mg, 1.54 mmol) in MeOH (12 mL) was added NaBH$_4$ (60 mg, 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 phases was extracted with Et$_2$O. The combined organic phases were washed with brine, dried over Na$_2$SO$_4$, and concentrated under reduced pressure. Purification of the residue by flash chromatography (30:70 Et$_2$O-pentane) provided 435 mg (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}; ^{1}H 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$_5$SeSiNa: 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** (415 mg, 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 155 mg (50%) of **22** and 135 mg (43 %) of **23**. Data for **22** : ^{1}H NMR (300 MHz, CDCl$_3$, 2 rotamers) δ 4.82 and 4.81 (2 s, 1H), 4.51 and 4.57 (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$_3$, 2 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** : ^{1}H 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$_3$, 2 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}; ^{1}H NMR (300 MHz, CDCl$_3$, 2 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$_3$, 2 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$_3$NO$_7$SNa: 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$_2$O (80 mL) at 20 °C was added (PPh$_3$)$_4$Pd (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 replacing the CO with argon, water was added and 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$_2$SO$_4$, 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}; ^{1}H NMR (300 MHz, CDCl$_3$, 2 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$_3$, 2 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}; ^{1}H NMR (300 MHz, CDCl$_3$, 2 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$_3$, 2 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.

(1S)-2-$tert$-Butyl   1,3a-Dimethyl   6-Oxo-3,3a-dihydro-1H-isoindole-1,2,3a($6H,7H,7aH$)-tricarboxylate

(30). A solution of diester 2**7** (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 ^{1}H NMR) in dichloromethane (0.5 mL) was placed in a teflon ampoule, which

was then closed (completely filled, no air bubbles). The ampoule was then 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 minutes, the mixture was extracted with ether,

and the organic layer was washed with brine and dried over Na$_2$SO$_4$. 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 **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}; ^{1}H NMR (300 MHz, CDCl$_3$, 2

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$_3$, 2 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.

(1S)-2-($tert$-Butoxycarbonyl)-6-oxo-2,3,3a,6,7,7a-hexahydro-1H-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}; ^{1}H NMR (300 MHz, CD_3OD, 2 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}; ^{1}H NMR (300 MHz, $CDCl_3$, 2 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, $CDCl_3$, 2 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%, 2 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}; ^{1}H NMR (300 MHz, $CDCl_3$, 2 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, $CDCl_3$, 2 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, CHCl₃); IR (film) 1755,

1686, 1675, 1122, 1025, 859 cm⁻¹; ¹H NMR (300 MHz, CDCl₃, 2 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); ¹³C NMR (75 MHz, CDCl₃, 2 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 NH₄Cl–NH₄OH. 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, CDCl₃, 2 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 O₃ in O₂ 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 and 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 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%, 3 steps) of unstable

aldehyde ester **37**:   IR (film) 1740, 1697, 1206, 1167, 1002, 898 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$, 2

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

and 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 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′**: [α]$^{20}_D$ –37.8 (*c* 1.1, CHCl$_3$); IR (film) 3100, 1751,

1730, 1704, 1686, 1140, 1057, 1018 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$, 2 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 1.39 (2 s, 9H); ^{13}C NMR (75 MHz, CDCl$_3$, 2 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$_3$)$_4$Pd (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 mixture was extracted with ether, and the organic layer was washed with brine, dried over Na$_2$SO$_4$, 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$_3$, 2 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$_3$, 2 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$_6$Na: 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, which was dried over Na$_2$SO$_4$ 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$_4$OH (0.1-0.5 N), to afford 0.0206 g of slightly impure kainic acid. Recrystallization of this material from MeOH-H$_2$O provided the analytical sample (0.0168 g, 75%): mp 241-243 °C; $[\alpha]^{20}_D$ –14.3 (*c* 0.16, H$_2$O); ^{1}H NMR (300 MHz, D$_2$O) 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$_2$O) 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.

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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[21] The enantiomeric excess of diester **27** was determined by HPLC: Chiracel AD-H, 5 mm, hexane/isopropanol, 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/isopropanol, 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 a single operation, unfortunately, led to unsatisfactory results. For example, treatment of diester **30** with 1N KOH in refluxing THF led only to the 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**.

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[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$_2$O 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.

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