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High-Pressure Diels–Alder Approach to Natural Kainic Acid

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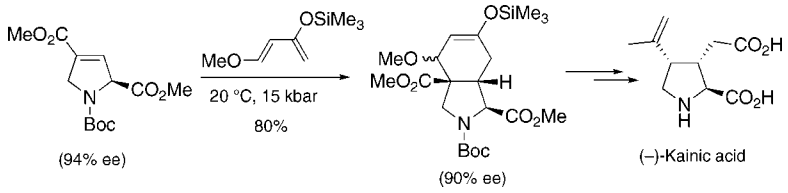
ABSTRACT



The first Diels–Alder based synthesis of (–)-kainic acid is described. Danishefsky's diene and a vinylogous malonate derived from 4-hydroxyproline combine under high pressure to afford a key bicyclic intermediate with virtually no loss of enantiopurity. This adduct can be converted into the natural product with complete stereocontrol.

(−)-Kainic acid (Figure 1**)**, the parent member of the class of marine natural products called kainoids, was first isolated

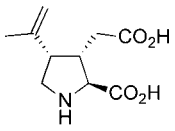


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Figure 1. (−)-Kainic acid.

in 1953 from *Digenea simplex*.[1] Originally used in anthelmintic and insecticide preparations, it has more recently found application in the study of serious neuronal disorders, such as Alzheimer's disease and epilepsy.[2−5a,b] In 1999, the discontinuance of its commercial extraction from the above alga[3] created concern as to future supply, 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. A large number of approaches thus resulted and new syntheses continue to appear.[5]

We recently published a preparation of (−)-kainic acid from *trans*-4-hydroxy-L-proline, which was based on a regioselective alkylation of a keto derivative and an unusual cuprate-mediated tosylate substitution with retention of configuration.[5h] This represented, surprisingly, the first use of 4-hydroxyproline in an approach to kainic acid and led us to consider whether other efficient syntheses might also be possible from this inexpensive starting material. An unprecedented[6] approach based on a Diels−Alder reaction

(1) (a) Murakami, S.; Takemoto, T.; Shimizu, Z. *J. Pharm. Soc. Jpn.* **1953**, *73*, 1026−1028. (−)-Kainic acid has also been isolated from *Centrocerus clavulatum* [(b) Impellizzeri, G.; Mangiafico, G.; Oriente, G.; Piattelli, M.; Sciuto, S.; Fattorusso, E.; Magno, S.; Santacroce, C.; Sica, D. *Phytochemistry* **1975**, *14*, 1549−1557] and from *Alsidum helmithocorton* [(c) Balansard, G.; Pellegrini, M.; Cavalli, C.; Timon-David, P. *Ann. Pharm. Fr.* **1983**, *41*, 77−86].

(2) Since the beginning of 2006, over 300 papers have been published on the use of kainic acid for the study of various neuronal disorders.

(3) Shortage of Kainic Acid Hampers Neuroscience Research. *Chem. Eng. News* **2000**, *78* (1), 14−15.

(4) Producers Strive to Bring Kainic Acid Back on the Market. *Chem. Eng. News* **2000**, *78* (10), 31.

(5) For syntheses prior to 2002, see: (a) Parsons, A. F. *Tetrahedron* **1996**, *52*, 4149−4174. (b) Moloney, M. G. *Nat. Prod. Rep.* **2002**, *19*, 597−616 and references cited therein. For more recent syntheses, see: (c) Trost, B. M.; Rudd, M. T. *Org. Lett.* **2003**, *5*, 1467−1470. (d) Martinez, M. M.; Hoppe, D. *Org. Lett.* **2004**, *6*, 3743−3746. (e) Scott, M. E.; Lautens, M. *Org. Lett.* **2005**, *7*, 3045−3047. (f) Anderson, J. C.; O'Loughlin, J. M. A.; Tornos, J. A. *Org. Biomol. Chem.* **2005**, *3*, 2741−2749. (g) Hodgson, D. M.; Hachisu, S.; Andrews, M. D. *Org. Lett.* **2005**, *7*, 815−817. (h) Poisson, J. F.; Orellana, A.; Greene, A. E. *J. Org. Chem.* **2005**, *70*, 10860−10863.

(6) See, however: Ohfune, Y.; Tomita, M. *J. Am. Chem. Soc.* **1982**, *104*, 3511−3513.

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seemed particularly attractive for it had the potential to set in a straightforward manner the C2−C3−C4 relationship. The Diels−Alder reaction of a dehydroproline **I** with an electron-rich diene **II** (e.g., Danishefsky's or Rawal's) might lead to enone **III** (Figure 2). This product could then, in

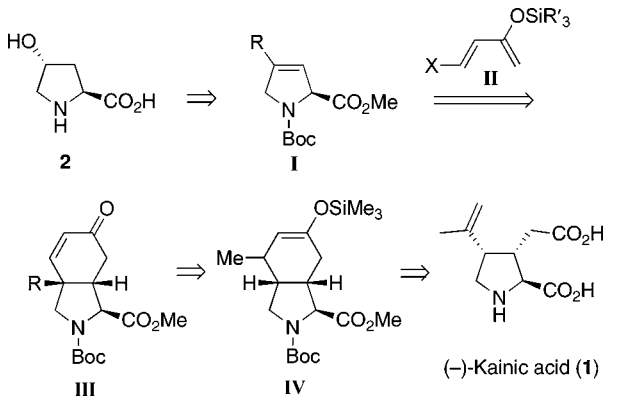


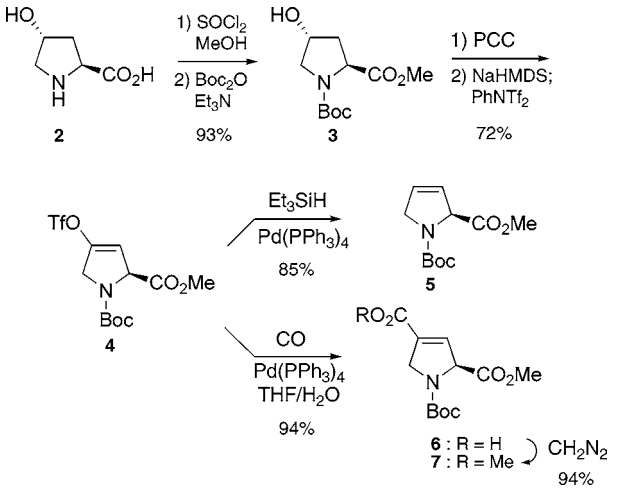
Figure 2. Overview of the projected approach to (−)-kainic acid.

principle, rapidly be converted into kainic acid through a sequence that would include conjugate addition of a methyl group and enolate trapping to produce **IV**, followed by oxidative cleavage, double bond formation, and hydrolysis.

It was obvious that success of the plan would primarily hinge on whether the unactivated disubstituted (R = H) or activated trisubstituted (R = CHO, CO_2H, CO_2Me) olefin **I** could be made to react satisfactorily with diene **II**. It was feared, however, and with some foundation, that the disubstituted olefin, even if reactive, would not undergo cycloaddition regioselectively as desired and, moreover, that an activated trisubstituted olefin would prove nevertheless resistant under normal conditions. The literature contains relatively few examples of trisubstituted olefins as reactive Diels−Alder partners,[7−10] and particularly scarce are examples in which the trisubstituted olefin is incorporated in a five-membered ring: none without activation, only a few with formyl activation,[8] and fewer yet with carboxy, carbalkoxy,[9] or keto activation.[10] These limited examples, furthermore, require in general heating and/or Lewis acid catalysis, *conditions most likely inappropriate in the present context due to facile racemization of chiral (vinylogous) malonate derivatives*.

Triflate **4**[11] was prepared to serve as a direct precursor of dehydroproline derivatives **I** (Scheme 1). *trans*-4-Hydroxy-

Scheme 1. Synthesis of Dehydroprolines



L-proline was converted in 93% yield into the *N*-Boc methyl ester derivative **3**, which was smoothly oxidized to the corresponding ketone[11] in 85% yield with PCC in the presence of molecular sieves. This procedure was found to be considerably more efficient and reliable than the others tested (TPAP/NMO, Swern, and Dess−Martin). Triflate **4** was then obtained regioselectively and in high yield from this ketone with NaHMDS−$PhNTf_2$.

Reduction of **4** with triethylsilane in the presence of Pd-$(PPh_3)_4$ led to 3,4-dehydroproline **5** in 85% yield. Unfortunately, however, none of many Diels−Alder reactions attempted with **5** and various diene partners (electron rich and electron poor) was found to be even marginally productive, including those heated in a sealed tube or subjected to high pressure. Since an acceptable means of converting triflate **4** into the corresponding acrolein derivative could not be found,[12] attention was directed toward the preparation of diester **7**. Pleasingly, Pd-catalyzed methoxycarbonylation of **4** afforded the desired acrylate derivative **7** in 60% yield

(7) Six-membered ring dienophiles: (a) Danishefsky, S.; Kitahara, T.; Yan, C. F.; Morris, J. *J. Am. Chem. Soc.* **1979**, *101*, 6996−7000. (b) Jankowski, C. K.; LeClair, G.; Bélanger, J. M. R.; Paré, J. R. J.; VanCalsteren, M.-R. *Can. J. Chem.* **2001**, *79*, 1906−1909. (c) Boger, D. L.; Patel, M. *Tetrahedron Lett.* **1986**, *27*, 683−686. (d) Grieco, P. A.; Lis, R.; Zelle, R. E.; Finn, J. *J. Am. Chem. Soc.* **1986**, *108*, 5908−5919. (e) O'Connor, P. D.; Mander, L. N.; McLachlan, M. M. W. *Org. Lett.* **2004**, *6*, 703−706. Acyclic dienophiles: (f) Paczkowski, R.; Maichle-Mossmer, C.; Maier, M. E. *Org. Lett.* **2000**, *2*, 3967−3969.

(8) Five-membered carbocycles with cyclopentadiene: (a) Ishihara, K.; Yamamoto, H. *J. Am. Chem. Soc.* **1994**, *116*, 1561−1562. (b) Ishihara, K.; Kurihara, H.; Matsumoto, M.; Yamamoto, H. *J. Am. Chem. Soc.* **1998**, *120*, 6920−6930. (c) Ryu, D. H.; Lee, T. W.; Corey, E. J. *J. Am. Chem. Soc.* **2002**, *124*, 9992−9993. (d) Sprott, K. T.; Corey, E. J. *Org. Lett.* **2003**, *5*, 2465−2467. (e) Davies, H. M. L.; Dai, X. *J. Am. Chem. Soc.* **2004**, *126*, 2692−2693. With Rawal's diene: (f) Huang, Y.; Iwama, T.; Rawal, V. H. *J. Am. Chem. Soc.* **2000**, *122*, 7843−7844. Furanoside-type dienophiles: (g) Rehnberg, N.; Sundin, A.; Magnusson, G. *J. Org. Chem.* **1990**, *55*, 5477−5483. (h) Ponten, F.; Magnusson, G. *J. Org. Chem.* **1997**, *62*, 7978−7983. Indole dienophiles: (i) Chataigner, I.; Hess, E.; Toupet, L.; Piettre, S. R. *Org. Lett.* **2001**, *3*, 515−518. (j) Chretien, A.; Chataigner, I.; L'Helias, N.; Piettre, S. R. *J. Org. Chem.* **2003**, *68*, 7990−8002.

(9) (a) Strunz, G. M.; Bethell, R.; Dumas, M. T.; Boyonoski, N. *Can. J. Chem.* **1997**, *75*, 742−753. (b) Martin, C.; Mailliet, P.; Maddaluno, J. *J. Org. Chem.* **2001**, *66*, 3797−3805. (c) Pichon, N.; Harrison-Marchand, A.; Mailliet, P.; Maddaluno, J. *J. Org. Chem.* **2004**, *69*, 7220−7227.

(10) (a) Reddy, T. J.; Rawal, V. H. *Org. Lett.* **2000**, *2*, 2711−2712. (b) Jung, M. E.; Davidov, P. *Angew. Chem., Int. Ed. Engl.* **2002**, *41*, 4125−4128. (c) Jung, M. E.; Ho, D.; Chu, H. V. *Org. Lett.* **2005**, *7*, 1649−1651.

(11) (a) Oba, M.; Terauchi, T.; Miyakawa, A.; Kamo, H.; Nishiyama, K. *Tetrahedron Lett.* **1998**, *39*, 1595−1598. (b) Honda, T.; Takahashi, R.; Namiki, H. *J. Org. Chem.* **2005**, *70*, 499−504.

(12) Surprisingly, no aldehyde was obtained on treatment of triflate **4** with Pd(0) and tributyltin hydride in DMF under carbon monoxide (only the reduced product **5** was formed). Other approaches to the conjugated aldehyde were low yielding and/or too long.

Scheme 2. Diels−Alder Reactions

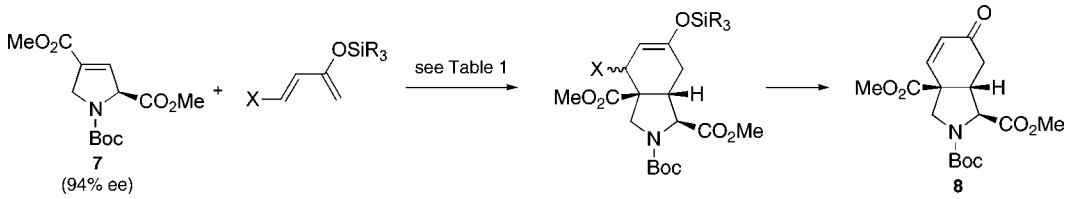


Table 1. Diels−Alder Reactions of Diester **7** with Electron-Rich Dienes

entry	diene[a]	solvent	activation method	time (h)	conversion (%)[b]	yield of **8** (%)[c]	ee[d]
1	Danishefsky	toluene	115 °C	82	57	22	24
2	Rawal	toluene	120 °C	6	100	<10, 40[e]	10
3	Rawal	toluene	Et_2AlCN, CuOTf, or $AlBr_3/AlMe_3$	24	0		
4	Rawal	CH_2Cl_2	15 kbar	52	100	27	54
5	Danishefsky[f]	CH_2Cl_2	15 kbar	82	96	79	2
6	**Danishefsky**[g]	**CH_2Cl_2**	**15 kbar**	**72**	**100**	**80**	**90**

[a] Danishefsky's diene: (4-methoxy-2-trimethylsilyloxybutadiene); Rawal's diene: (4-dimethylamino-2-*tert*-butyldimethylsilyloxybutadiene). [b] Based on unreacted diester (^{1}H NMR of crude product). [c] Isolated yield. [d] By HPLC: Chiralcel OD-H, isopropanol:hexane = 20:80, 0.5 mL/min. t_R of minor enantiomer = 18.13 min; t_R of major enantiomer = 24.44 min. [e] Yield of purified cycloadducts. [f] Contains a small amount of triethylamine. [g] Distilled from trichlorophenol.

and with an enantiomeric excess of 94%. As anticipated, however, racemization of this compound occurred quite readily: after 10 days at 20 °C, the ee was only 20%. Fortunately, it was discovered that hydroxycarbonylation could be accomplished in yet higher yield and that the resultant acid-ester **6**, which was obtained pure (94% ee) by simple base-acid extraction, was significantly less prone than the diester to racemization. It was more effective, therefore, to prepare the diester **7** via the acid-ester **6** (diazomethane, just prior to use).

Initial Diels−Alder results with diester **7** were not at all encouraging (Scheme 2 and Table 1). Reaction with Danishefsky's diene, incomplete after 82 h at 115 °C, provided after elimination enone **8** in only 22% yield, and worse, with an enantiomeric excess of just 24% (entry 1). In an attempt to improve both the yield and the enantiomeric excess, Rawal's diene, known to be substantially more reactive than Danishefsky's,[13] was tested. Indeed, after just 6 h at 120 °C, the diester was completely consumed; however, the combined yield of the purified diastereomeric cycloadducts (NMe_2 epimers) was only 40%, their conversion to enone **8** problematic, and the enantiomeric excess of **8** extremely low (entry 2). The use of Lewis acids at ambient temperature, furthermore, failed to improve the situation (entry 3). These initial results confirmed the expected low reactivity and the facile racemization of diester **7** and suggested that another reaction parameter should be examined: pressure. It was hoped that high pressure[14] might allow the reaction to proceed at room temperature, and thereby limit the degree of attendant racemization.

Diester **7** indeed underwent cycloaddition with the Rawal diene at 20 °C under 15 kbar to yield after dimethylamine elimination enone **8**, still in modest yield, but now with a much improved 54% ee (entry 4). Even better were the results obtained with Danishefsky's diene: a complete, totally face-selective reaction was achieved at 20 °C under 15 kbar to provide a ca. 3:1 mixture of cycloadducts (OMe epimers). This mixture on treatment with aqueous $KHSO_4$ was partially (major diastereomer) converted into enone **8**; the recovered material (methoxy ketone from minor diastereomer) could also be transformed into the enone by reaction with DBU in toluene. While the enone was found to be essentially racemic with simply distilled Danishefsky diene (which contained residual triethylamine, entry 5), strikingly, when triethylamine-free diene (by distillation from trichlorophenol) was used, a 90% ee was produced (80% yield, entry 6). *Thus, the enantiopurity of the highly racemization-prone vinylogous malonate could be transferred to the cycloadduct virtually undiminished through the use of high pressure*.

With the key enone in hand, the removal of the angular methoxycarbonyl group was next addressed. While rhodium-mediated decarbonylation of a formyl derivative would have been expected to proceed with retention of configuration,[15] the stereochemical outcome of demethoxycarbonylation of **8** was expected to reflect product stability. AM1 calculations, encouragingly, indicated the desired cis-fused product to be ca. 6.5 kcal/mol more stable than the trans.[16] Saponification of **8**, followed by a single recrystallization of the crude

(13) Kozmin, S. A.; Green, M. T.; Rawal, V. H. *J. Org. Chem.* **1999**, *64*, 8045−8047.

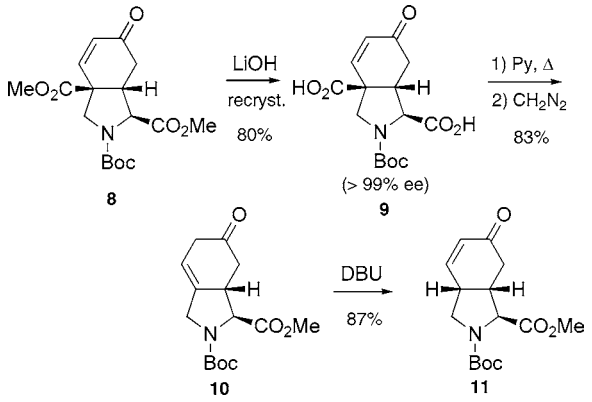
(14) For a review, see: *High Pressure Chemistry*, van Eldik, R., Klärner, F-G., Eds.; Wiley: Weinheim, 2002.

(15) (a) Walborsky, H. M.; Allen, L. E. *J. Am. Chem. Soc.* **1971**, *93*, 5465−5468. (b) Andrews, M. A.; Gould, G. L.; Klaeren, S. A. *J. Org. Chem.* **1989**, *54*, 5257−5264. (c) O'Connor, J. M.; Ma, J. *J. Org. Chem.* **1992**, *57*, 5075−5077.

(16) See: Clayden, J.; Menet, C. J.; Tchabanenko, K. *Tetrahedron* **2002**, *58*, 4727−4733.

product, conveniently provided in 80% yield the enantiopure (>99% ee) diacid **9**, which was monodecarboxylated in hot pyridine and then esterified with diazomethane to give the deconjugated enone **10** in 83% yield (two steps, Scheme 3).

Scheme 3. Decarbomethoxylation of **8**



Transformation of **10** into the conjugated enone was next effected with DBU in dichloromethane, which produced a single isomer. Gratifyingly, the relative stereochemistry in this isomer, determined by NOE experiments on the dihydro *N*-tosyl derivative, was the expected cis.

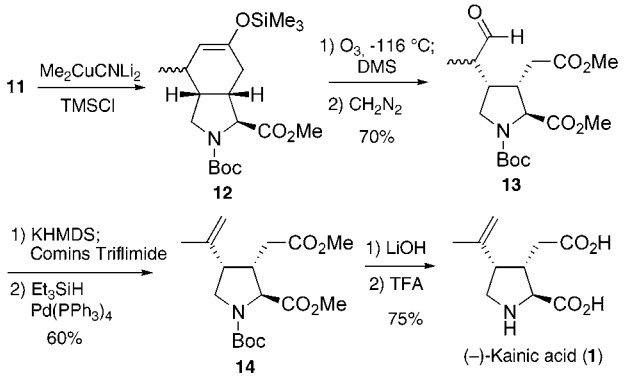
Conjugate addition of a methyl group to enone **11** through the use of a higher-order cyanocuprate in the presence of trimethylsilyl chloride afforded the trimethylsilyl enol ether derivative **12**, which was subjected to ozonolysis to give, following treatment with dimethyl sulfide and diazomethane, aldehyde **13**[17] in 70% overall yield (Scheme 4). Conversion of this aldehyde into the desired olefin **14** was next achieved in 60% yield through palladium-catalyzed triethylsilane reduction of the enol triflate, formed with KHMDS and Comins triflimide.[18] This approach was found to be far superior to others examined, such as dehydration of the corresponding alcohol and selenoxide elimination.[19]

(17) For an alternative preparation of this aldehyde (for the synthesis of (−)-domoic acid), see ref 6.

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

(19) Grieco, P. A.; Gilman, S.; Nishizawa, M. *J. Org. Chem.* **1976**, *41*, 1485−1486.

Scheme 4. Final Steps of the Synthesis



Saponification of **14** and then removal of the Boc group with TFA afforded kainic acid in 75% yield after recrystallization. The synthetically derived material (mp 241−243 °C, $[\alpha]^{20}_D$ −14.3 (*c* 0.16, H_2O)) was spectroscopically and chromatographically indistinguishable from an authentic sample of the natural product (mp 241−243 °C, $[\alpha]^{20}_D$ −13.9 (*c* 0.16, H_2O)).

In summary, enantiopure (−)-kainic acid has been prepared from 4-hydroxyproline in nearly 10% overall yield. High-pressure activation in the crucial Diels−Alder reaction of the chiral vinylogous malonate **7** with Danishefsky's diene was found to provide a unique solution to the connected problems of reactivity and enantioretention and should prove useful for related transformations.

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Supporting Information Available: Complete experimental procedures and spectral data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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