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Total Synthesis of (±)-Kainic Acid: A Photochemical C–H Carbamoylation Approach

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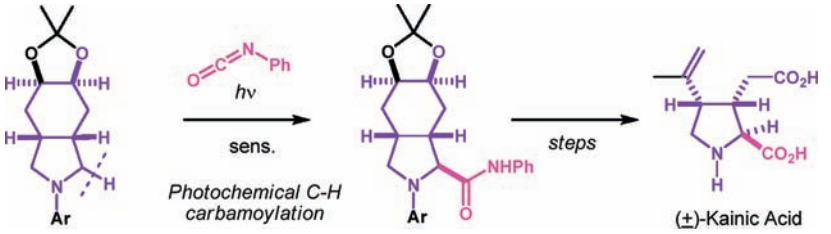
ABSTRACT



A novel photochemical C–H carbamoylation of an octahydroisoindole derivative with PhNCO has allowed the authors to provide a unique access to a highly functionalized proline motif from which total synthesis of (±)-kainic acid, a bioactive marine alkaloid, has been accomplished.

The fact that kainoids exhibit neuroexcitatory effects has stimulated significant efforts to establish chemical access to this class of amino acids.[1,2] Kainic acid (**1**), the first member of this family, was isolated in 1953 from the seaweed *Digenea simplex*.[3] Thereafter, a number of structurally related compounds have been identified in nature, including domoic acid (**2**),[4] acromelic acid (**3**),[5] and isodomoic acid (**4**),[6] all of which share a common trisubstituted proline motif having another carboxylic group and an alkenyl substituent (Figure 1).

Intensive studies on the synthesis of kainoids have culminated in elegant approaches that feature unique synthetic strategies and methodologies.[7] One of the key issues in synthesizing kainoids is the stereoselective construction of the highly functionalized 3,4-*cis*-disubstituted proline motif. In this context, *cis*-fused 6-azabicyclo[4.3.0]nonanes (octahydroisoindole derivative) and their congeners are attractive synthetic scaffolds that have been successfully utilized for the construction of kainoid skeletons. Such bicyclic motifs are accessible by various means,

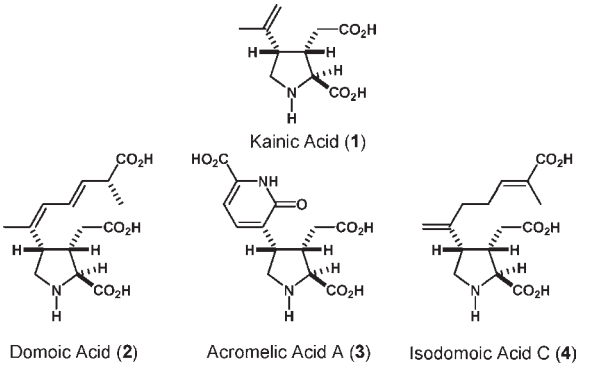


Figure 1. Natural kainoids.

(1) For reviews on the biology of kainoids, see: (a) Monaghan, D. T.; Bridges, R. J.; Cotman, C. W. *Annu. Rev. Pharmacol. Toxicol.* **1989**, *29*, 365–402. (b) Moloney, M. G. *Nat. Prod. Rep* **1998**, 205–219. (c) Moloney, M. G. *Nat. Prod. Rep* **1999**, *16*, 485–498. (d) Chamberlin, R.; Bridges, R. In *Drug Design for Neuroscience*; Kozikowski, A. P., Ed.; Raven Press: New York, 1993; pp 231–259. (e) McGeer, E. G.; Olney, J. W.; McGeer, P. L. *Kainic Acid as a Tool in Neurobiology*; Raven Press: New York, 1978.

(2) For reviews on syntheses of kainoids, see: (a) Parsons, A. F. *Tetrahedron* **1996**, *52*, 4149–4174. (b) Moloney, M. G. *Nat. Prod. Rep.* **2002**, *19*, 597–616. (c) Clayden, J.; Read, B.; Hebditch, K. R. *Tetrahedron* **2005**, *61*, 5713–5724.

(3) Murakami, S.; Takemoto, T.; Shimizu, Z. *J. Pharm. Soc. Jpn.* **1953**, *73*, 1026–1028.

(4) Takemoto, T.; Daigo, K. *Chem. Pharm. Bull.* **1958**, *6*, 578–580.

(5) (a) Acromelic acids A and B: Konno, K.; Shirahama, H.; Matsumoto, T. *Tetrahedron Lett.* **1983**, *24*, 939–942. (b) Acromelic acid C: Fushiya, S.; Sato, S.; Kanazawa, T.; Kusano, G.; Nozoe, S. *Tetrahedron Lett.* **1990**, *31*, 3901–3904. (c) Acromelic acids D and E: Fushiya, S.; Sato, S.; Kera, Y.; Nozoe, S. *Heterocycles* **1992**, *34*, 1277–1280.

(6) Maeda, M.; Kodama, T.; Tanaka, T.; Yoshizumi, H.; Takemoto, T.; Nomoto, K.; Fujita, T. *Chem. Pharm. Bull.* **1986**, *34*, 4892–4895.

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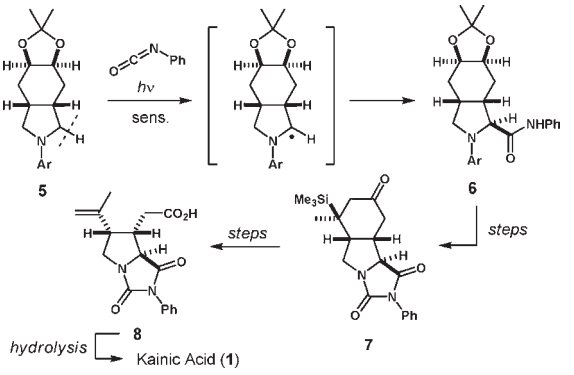
including the Diels–Alder reaction of proline derivatives with dienes,[7ii,8] the dearomatizing cyclization of *N*-benzyl benzamides,[7w,aa] and the stereoselective cyclization of ynone.[7mm] In the present paper, we report the total synthesis of (±)-kainic acid (**1**), which features a novel photochemical C–H carbamoylation of *cis*-fused azabicyclo[4.3.0]nonane derivative **5** to establish a unique entry to the natural amino acid (Scheme 1).

Recently, we developed a means for the synthesis of amino acid anilides from tertiary amines through Et_3B-mediated radical C–H carbamoylation reactions.[9,10] This has enabled us to devise a short access from tertiary amines to bioactive amino acid derivatives, such as the local anesthetic mepivacaine. In this context, it occurred to us that the photolysis of amines in the presence of a photosensitizer that enables hydrogen transfer from nitrogen-substituted C–H bonds would serve as a powerful alternative to the trialkylborane/air system to promote C–H carbamoylation reactions.

Scheme 1. Present Approach to Kainic Acid (**1**) via Direct Radical C–H Carbamoylation of Tertiary Amine **5**



Inspired by pioneering studies of the photochemical transformation of tertiary amines,[11] we envisaged that a carbamoylation reaction would proceed via a hypothetical hydrogen shuttle mediated by excited triplet ketones (Scheme 2). In our hypothesis, a photochemically excited ketone would generate corresponding α-amino alkyl radical **ii** through an electron/proton transfer mechanism. Then, radical **ii** would undergo addition to phenyl isocyanate to produce amidyl radical **iv**, which, by hydrogen atom transfer from ketyl radical **iii**, would eventually generate an anilide and ketone **i**, leading to a catalytic cycle. Our hypothesis on this radical cascade was evaluated for its relevance with *cis*-fused azabicyclo[4.3.0]nonane **5**, which was prepared in four steps from the commercially available tetrahydromaleic anhydride (Table 1).[12] Evaluation of the reaction conditions led to the discovery that, in the presence of a photosensitizer, cyclic amine **5** underwent C–H carbamoylation with phenyl isocyanate to afford anilide **6** along with biscarbamoylated **9**. As far as we know, this is the first example of the intermolecular addition of a photochemically generated α-amino alkyl radical to phenyl isocyanate to furnish amino acid anilides. It has been reported that PhNCO is decomposed by UV irradiation (227 nm) to give phenylnitrene.[13] However, in the present case, most of the unreacted PhCNO could be recovered as methyl phenylcarbamate after quenching the reaction mixture with MeOH. The successful recovery of the unreacted isocyanate is probably attributable to circumvention

(7) For selected papers of total synthesis of kainic acid: (a) Oppolzer, W.; Thirring, K. *J. Am. Chem. Soc.* **1982**, *104*, 4978–4979. (b) Cooper, J.; Knight, D. W.; Gallagher, P. T. *J. Chem. Soc., Chem. Commun.* **1987**, 1220–1222. (c) Baldwin, J. E.; Li, C.-S. *J. Chem. Soc., Chem. Commun.* **1987**, 166–168. (d) Takano, S.; Iwabuchi, Y.; Ogasawara, K. *J. Chem. Soc., Chem. Commun.* **1988**, 1204–1206. (e) Takano, S.; Sugihara, T.; Satoh, S.; Ogasawara, K. *J. Am. Chem. Soc.* **1988**, *110*, 6467–6471. (f) Yoo, S.-E.; Lee, S.-H.; Yi, K.-Y.; Jeong, N. *Tetrahedron Lett.* **1990**, *31*, 6877–6880. (g) Barco, A.; Benetti, S.; Pollini, G. P.; Spalluto, G.; Zanirato, V. *J. Chem. Soc., Chem. Commun.* **1991**, 390–391. (h) Kirihata, M.; Kaziwara, T.; Kawashima, Y.; Ichimoto, I. *Agric. Biol. Chem.* **1991**, *55*, 3033–3037. (i) Takano, S.; Inomata, K.; Ogasawara, K. *J. Chem. Soc., Chem. Commun.* **1992**, 169–170. (j) Yoo, S.; Lee, S. H.; Jeong, N.; Cho, I. *Tetrahedron Lett.* **1993**, *34*, 3435–3438. (k) Hatakeyama, S.; Sugawara, K.; Takano, S. *J. Chem. Soc., Chem. Commun.* **1993**, 125–127. (l) Monn, J. A.; Valli, M. J. *J. Org. Chem.* **1994**, *59*, 2773–2778. (m) Hanessian, S.; Ninkovic, S. *J. Org. Chem.* **1996**, *61*, 5418–5424. (n) Bachi, M. D.; Melman, A. *Synlett* **1996**, 60–62. (o) Bachi, M. D.; Barner, N.; Melman, A. *J. Org. Chem.* **1996**, *61*, 7116–7124. (p) Kawamura, M.; Ogasawara, K. *Heterocycles* **1997**, *44*, 129–132. (q) Nakada, Y.; Sugahara, T.; Ogasawara, K. *Tetrahedron Lett.* **1997**, *38*, 857–860. (r) Miyata, O.; Ozawa, Y.; Ninomiya, I.; Naito, T. *Synlett* **1997**, 275–276. (s) Rubio, A.; Ezquerra, J.; Escribano, A.; Remuiñán, M. J.; Vaquero, J. J. *Tetrahedron Lett.* **1998**, *39*, 2171–2174. (t) Cossy, J.; Cases, M.; Pardo, D. G. *Synlett* **1998**, 507–509. (u) Campbell, A. D.; Raynham, T. M.; Taylor, R. J. K. *Chem. Commun.* **1999**, 245–246. (v) Chevliakov, M. V.; Montgomery, J. *J. Am. Chem. Soc.* **1999**, *121*, 11139–11143. (w) Clayden, J.; Tchabanenko, K. *Chem. Commun.* **2000**, 317–318. (x) Nakagawa, H.; Sugahara, T.; Ogasawara, K. *Org. Lett.* **2000**, *2*, 3181–3183. (y) Xia, Q.; Ganem, B. *Org. Lett.* **2001**, *3*, 485–487. (z) Hirasawa, H.; Taniguchi, T.; Ogasawara, K. *Tetrahedron Lett.* **2001**, *42*, 7587–7590. (aa) Clayden, J.; Menet, C. J.; Tchabanenko, K. *Tetrahedron* **2002**, *58*, 4727–4733. (bb) Trost, B. M.; Rudd, M. T. *Org. Lett.* **2003**, *5*, 1467–1470. (cc) Anderson, J. C.; Whiting, M. *J. Org. Chem.* **2003**, *68*, 6160–6163. (dd) Martinez, M. M.; Hoppe, D. *Org. Lett.* **2004**, *6*, 3743–3746. (ee) Hodgson, D. M.; Hachisu, S.; Andrews, M. D. *Org. Lett.* **2005**, *7*, 815–817. (ff) Scott, M. E.; Lautens, M. *Org. Lett.* **2005**, *7*, 3045–3047. (gg) Morita, Y.; Tokuyama, H.; Fukuyama, T. *Org. Lett.* **2005**, *7*, 4337–4340. (hh) Poisson, J.-F.; Orellana, A.; Greene, A. E. *J. Org. Chem.* **2005**, *70*, 10860–10863. (ii) Pandey, S. K.; Orellana, A.; Greene, A. E.; Poisson, J.-F. *Org. Lett.* **2006**, *8*, 5665–5668. (jj) Sakaguchi, H.; Tokuyama, H.; Fukuyama, T. *Org. Lett.* **2007**, *9*, 1635–1638. (kk) Thuong, M. B. T.; Sottocornola, S.; Prestat, G.; Broggini, G.; Madec, D.; Poli, G. *Synlett* **2007**, *10*, 1521–1524. (ll) Chalker, J. M.; Yang, A.; Deng, K.; Cohen, T. *Org. Lett.* **2007**, *9*, 3825–3828. (mm) Jung, Y. C.; Yoon, C. H.; Turos, E.; Yoo, K. S.; Jung, K. W. *J. Org. Chem.* **2007**, *72*, 10114–10122. (nn) Sakaguchi, H.; Tokuyama, H.; Fukuyama, T. *Org. Lett.* **2008**, *10*, 1711–1714. (oo) Tomooka, K.; Akiyama, T.; Man, P.; Suzuki, M. *Tetrahedron Lett.* **2008**, *49*, 6327–6329. (pp) Majik, M. S.; Parameswaran, P. S.; Tilve, S. G. *J. Org. Chem.* **2009**, *74*, 3591–3594. (qq) Farwick, A.; Helmchen, G. *Org. Lett.* **2010**, *12*, 1108–1111. (rr) Kitamoto, K.; Sampei, M.; Nakayama, Y.; Sato, T.; Chida, N. *Org. Lett.* **2010**, *12*, 5756–5759. (ss) Takita, S.; Yokoshima, S.; Fukuyama, T. *Org. Lett.* **2011**, *13*, 2068–2070.

(8) Ohfune, Y.; Tomita, M. *J. Am. Chem. Soc.* **1982**, *104*, 3511–3513.

(9) Yoshimitsu, T.; Matsuda, K.; Nagaoka, H.; Tsukamoto, K.; Tanaka, T. *Org. Lett.* **2007**, *9*, 5115–5118.

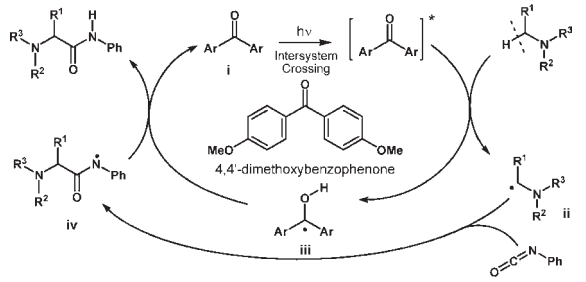
(10) For related studies, see: Yoshimitsu, T.; Arano, Y.; Nagaoka, H. *J. Am. Chem. Soc.* **2005**, *127*, 11610–11611.

(11) (a) Hoffmann, N.; Bertrand, S.; Marinkovic, S.; Pesch, J. *Pure Appl. Chem.* **2006**, *78*, 2227–2246. (b) Hoffmann, N. *Pure Appl. Chem.* **2007**, *79*, 1949–1958 and references cited therein. (c) Griesbeck, A. G.; Hoffmann, N.; Warzecha, K.-D. *Acc. Chem. Res.* **2007**, *40*, 128–140. (d) Cossy, J.; Belotti, D. *Tetrahedron* **2006**, *62*, 6459–6470. (e) Bauer, A.; Westkamper, F.; Grimme, S.; Bach, T. *Nature* **2005**, *436*, 1139–1140. (f) Yoon, U. C.; Mariano, P. S. *Acc. Chem. Res.* **1992**, *25*, 233–240. (g) Cohen, S. G.; Parola, A.; Parsons, G. H., Jr. *Chem. Rev.* **1973**, *73*, 141–161. (h) Jonas, M.; Blechert, S.; Steckhan, E. *J. Org. Chem.* **2001**, *66*, 6896–6904. (i) Kim, S. S.; Mah, Y. J.; Kim, A. R. *Tetrahedron Lett.* **2001**, *42*, 8315–8317.

(12) (a) Otzenberger, R. D.; Lipkowitz, K. B.; Mundy, B. P. *J. Org. Chem.* **1974**, *39*, 319–321. (b) Yasuda, M.; Saito, S.; Arakawa, Y.; Yoshifuji, S. *Chem. Pharm. Bull.* **1995**, *43*, 1318–1324. For details, see Supporting Information.

(13) Waddell, W. H.; Feilchenfeld, N. B. *J. Am. Chem. Soc.* **1983**, *105*, 5499–5500.

Scheme 2. Hypothetical Hydrogen Shuttle in Photochemical C−H Carbamoylation Reaction



of its decomposition by using a Pyrex reaction vessel that filters short-wavelength light (< 300 nm) as well as by the appropriate spectral energy distribution of a high-pressure Hg lamp that has no spectral distribution around 230 nm. Benzophenone, a common sensitizer, was found to be less effective in promoting the carbamoylation of **5** than 4,4′-dimethoxybenzophenone (entries 1 and 2), supporting the superiority of 4,4′-dimethoxybenzophenone over benzophenone.[11a,b,14]

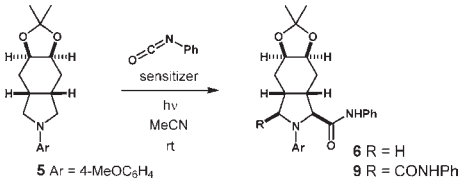
The prolonged reaction time increased the yield of desired anilide **6**, although the undesired production of biscarbamoylated amine **9** was also facilitated (entry 3). The reaction that was performed with 2 g of amine **5** gave a yield comparable to those obtained in smaller scale reactions (entry 2 vs 4). In the absence of the sensitizer, no reaction essentially took place (entry 5).

With suitably functionalized anilide **6** in possession, further synthetic manipulations were performed to yield kainic acid (Scheme 3). Anilide **6** was treated with CAN in aqueous MeCN at room temperature followed by protection of the resultant amine with CDI to furnish tetracyclic **10** in 65% overall yield. Then, acetonide **10** was hydrolyzed with aqueous AcOH at 60 °C to give a diol, which, by treatment with TBSCl and imidazole in DMF, afforded TBS ether **11** selectively in 86% yield (together with regioisomer 7% and bis-ether 4%; for details, see Supporting Information). The ^{1}H NMR analysis of the crude diol obtained by the acid hydrolysis of **10** indicated that the hydroxyl group at C8 was situated in an equatorial position, whereas the C7-hydroxyl group was in an axial position.[15] It is generally accepted that an equatorial hydroxyl group is more reactive toward acylation reactions than a sterically demanding axial one.[16] Therefore, we assume that the observed preference in regioselectivity of the silylation reaction was attributed to the conformational factor associated with the rigid tricyclic skeleton.

Next, the dehydration of resultant **11** with Martin's sulfuran successfully produced alkene **12** in 83% yield. The TBS group of **12** was removed by treatment with in situ generated hydrochloric acid to provide an allylic alcohol, which, by Dess−Martin oxidation, afforded enone **13** in 96% yield over 2 steps. At this stage, it was reasonably assumed that methylation at the C6 position of **13** with Me_2CuLi would provide a β-methylated cyclohexanone, a relevant precursor of the kainic

(14) 4,4-Dimethoxybenzophenone was gradually consumed during the long irradiation to give a complex mixture containing a pinacol coupling product.

Table 1. Photochemical C−H Carbamoylation of Tertiary Amine **5**

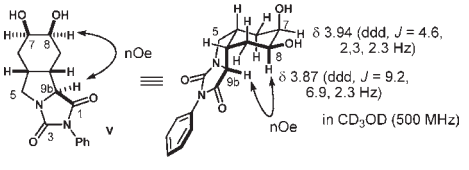


			products (%)[b]	
entry[a]	sensitizer	time (h)	**6**	**9**
1	benzophenone	3.5[c]	20 (31)	7 (11)
2	4,4′-dimethoxybenzophenone	3.5[c]	37 (49)	13 (17)
3	4,4′-dimethoxybenzophenone	8.5[c]	44 (47)	28 (30)
4	4,4′-dimethoxybenzophenone	9[d]	39 (54)	8 (11)
5	no	15	not observed[e]	

[a] The mixture of **5** (1 equiv), PhNCO (1.5 equiv), and sensitizer (0.2 equiv) in MeCN was degassed prior to the irradiation by a Hg high-pressure lamp. [b] Yields in parentheses are based on recovered **5**. [c] 150 mg of **5** were used. [d] 2 g of **5** were used. [e] Determined by NMR analysis.

acid motif, as reported by the Clayden group.[7w,17] Clayden and co-workers have demonstrated that the β-substitution of a pyroglutamate-fused cyclohexanone derivative causes severe steric interaction with a hemiperoxyacetal moiety in the Baeyer−Villiger oxidation, allowing regioselective oxygenation of the bond between C7 and C8. We envisioned that a quaternalization at the β-position of enone **14** with a silyl substituent would enable a high degree of regiocontrol in the Baeyer−Villiger oxidation because of the steric demand caused by the hindered substituent, and allow facile desilylative olefination at a later stage to efficiently deliver the isopropenyl unit of kainic acid. Thus, enone **13** was first converted into α,β-unsaturated enone **14** through Me_2CuLi-mediated methylation followed by silylation with TMSCl and $Pd(OAc)_2$-mediated oxidation of the resultant silyl enol ether.[18] Then,

(15) The ^{1}H NMR spectra of diol **v** showed similar coupling patterns of the H(7) and H(8) protons in either CD_3OD or $CDCl_3$, indicating the conformational rigidity of the tricyclic molecule in various solvents. Furthermore, NOE was observed between the H(8) and H(9b) protons, suggesting that the diol possesses the conformation indicated below. Therefore, we currently assume that diol **v** in DMF has a similar conformation to those in the above solvents and that the silylation of diol **v** in DMF with TBSCl occurred regioselectively at the reactive equatorial C8 hydroxyl group. For details, see Supporting Information.

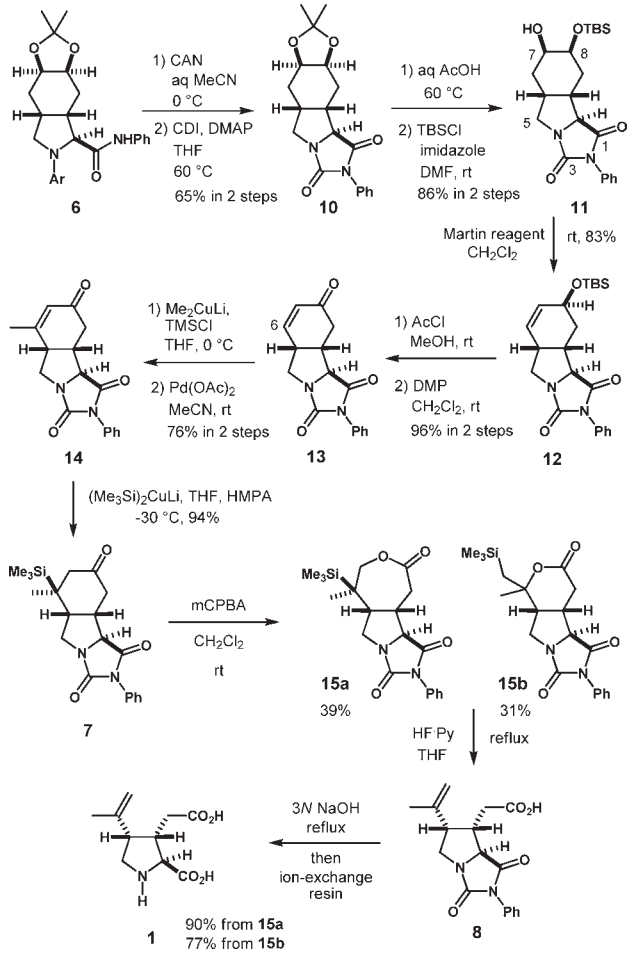


(16) (a) Barton, D. H. R. *Exper.* **1950**, *6*, 316–320. (b) Eliel, E. L.; Biros, F. J. *J. Am. Chem. Soc.* **1966**, *88*, 3334–3343.

(17) A nice approach employing the direct Baeyer−Villiger lactonization of a cyclohexenone derivative has also been reported. See ref 7mm.

(18) (a) Toyooka, N.; Okumura, M.; Nemoto, H. *J. Org. Chem.* **2002**, *67*, 6078–6081. (b) Ito, Y.; Hirao, T.; Saegusa, T. *J. Org. Chem.* **1978**, *43*, 1011–1013.

Scheme 3. Total Synthesis of (±)-Kainic Acid (**1**)

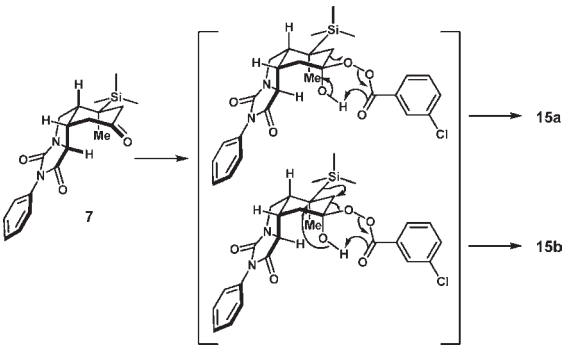


14 was subjected to 1,4-silylation with a silylcopper reagent[19] to produce **7** as a single detectable isomer whose stereochemistry was established by NOE analysis.[20] The next task was to oxidize the silylated ketone with mCPBA, which led to the production of desired seven-membered lactone **15a** along with silyl-migrated product **15b**.[21] Although the mechanism of the formation of silyl lactone **15b** is still unclear, it is likely that the cationic stabilization of the β-carbon by the silyl group enabled the unique migration (Scheme 4). The Baeyer–Villiger oxidation of ketone **16** that lacks the silyl substituent gave a mixture of regioisomeric lactones **17a** and **17b** in a ratio of ca. 3:2. This result indicates the importance of quaternalization at the C6 position in achieving a high degree of regiocontrol (Scheme 5).

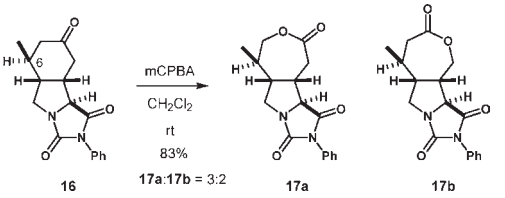
Then, the desilylative olefinations of **15a** and **15b** each with HF·Py in THF under heating conditions delivered olefin **8**, respectively, as a single product that possessed all the functionalities necessary for accessing kainic acid (**1**). Hydrolysis of **8** with 3 N NaOH took place smoothly, giving rise to kainic acid (**1**) as the sole product. The NMR spectra of synthesized **1** exactly matched those reported in the literature.[7ff,ss]

(19) Fleming, I.; Newton, T. W. *J. Chem. Soc., Perkin Trans. 1* **1984**, 1805–1808.

Scheme 4. Rationale for Formation of **15a** and **15b**



Scheme 5. Baeyer–Villiger Oxidation of Ketone **16**



In conclusion, we have accomplished the total synthesis of (±)-kainic acid (**1**), which features the novel photochemical C–H carbamoylation reaction of octahydroisoindole derivative **5** with PhNCO. Further work is ongoing to explore the scope of the present radical C–H carbamoylation method through its application to the synthesis of various bioactive nitrogen-containing natural products.

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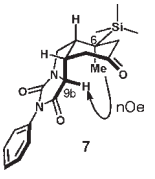
Supporting Information Available. Experimental procedures, characterization data, and $^1H/^{13}C$ NMR spectra of products. This material is available free of charge via the Internet at http://pubs.acs.org.

(20) The relative stereochemistry of **7** was determined by an NOE correlation that showed the proximity between the methyl substituent at C6 and the proton at C9b.



(21) The stereochemistry of the newly created quaternary stereocenter of **15b** has yet to be determined.