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Synthesis of α-Kainic Acid from a 7-Azabicyclo[2.2.1]heptadiene by Tandem Radical Addition–Homoallylic Radical Rearrangement

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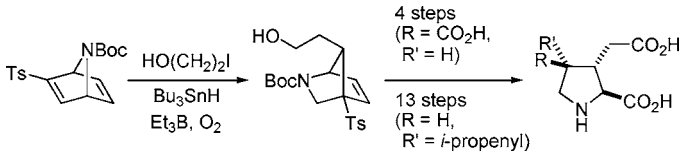
ABSTRACT

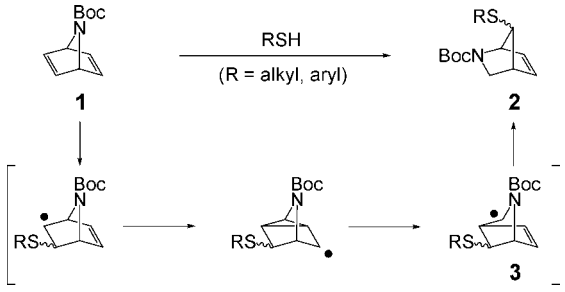


Reductive radical addition of 2-iodoethanol to *N*-Boc 2-tosyl-7-azabicyclo[2.2.1]heptadiene gives *N*-Boc *syn*-7-(2-hydroxyethyl)-4-tosyl-2-azabicyclo-[2.2.1]hept-5-ene, which is converted into the neuroexcitants 3-(carboxymethyl)pyrrolidine-2,4-dicarboxylic acid and α-kainic acid.

Radical cyclizations and rearrangements constitute powerful methodologies for the syntheses of ring systems.[1] We recently reported the reaction of thiols with 7-azabicyclo-[2.2.1]heptadiene **1**, which led exclusively to 7-thio-substituted 2-azabicyclo[2.2.1]hept-5-enes **2**, by tandem intermolecular radical addition−homoallylic radical rearrangement (Scheme 1).[2] A significant factor favoring this rearrangement is probably the stabilization afforded to the intermediate radical **3** by the α-nitrogen.

In the present paper, the results of a related study are presented. This study involved initial intermolecular C−C bond-forming radical addition which, together with oxidative cleavage of the double bond in the resulting 2-azabicyclo-[2.2.1]hept-5-ene, constitute key elements in a new strategy to access 2,3,4-trisubstituted pyrrolidines, specifically kainoid systems.[3]

Scheme 1. Radical Addition of Thiols to 7-Azabicyclo[2.2.1]heptadiene **1**[2]



Triacid **7** is known to exhibit strong neuroexcitatory activity[4] and was selected as an initial target to demonstrate the synthetic strategy (Scheme 2). Dienyl sulfone **4** was used as the radical acceptor substrate, since it is available in one step from commercial materials (*N*-Boc pyrrole and tosyl ethyne) and the enantiomers are also accessible by a straightforward resolution protocol.[5] Preliminary studies

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(1) (a) Beckwith, A. L. J.; Ingold, K. U. In *Rearrangements in Ground and Excited States*; de Mayo, P., Ed.; Academic: New York, 1980: Vol. 1, pp 161−310. (b) Giese, B.; Kopping, B.; Gobel, T.; Dickhaut, J.; Thoma, G.; Kulicke, K. J.; Trach, F. *Org. React.* **1996**, *48*, 301−856. (c) *Radicals in Organic Synthesis*; Renaud, P., Sibi, M. P., Eds.; Wiley-VCH: Weinheim, 2001.

(2) (a) Hodgson, D. M.; Bebbington, M. W. P.; Willis, P. *Chem. Commun.* **2001**, 889−890. (b) Hodgson, D. M.; Bebbington, M. W. P.; Willis, P. *Org. Biomol. Chem.* **2003**, *1*, 3787−3798.

(3) Moloney, M. G. *Nat. Prod. Rep.* **1998**, *15*, 205−219.

(4) Goldberg, O.; Luini, A.; Teichberg, V. I. *Tetrahedron Lett.* **1980**, *21*, 2355−2358.

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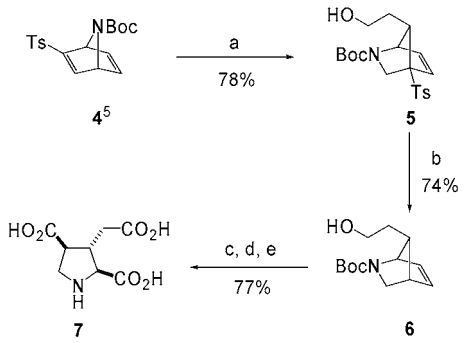
Scheme 2. Synthesis of Triacid **7**[a]



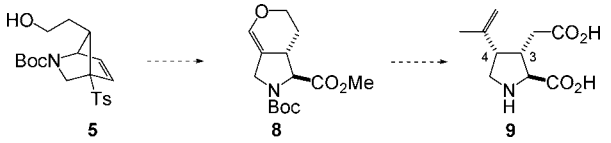
[a] Conditions: (a) $HO(CH_2)_2I$ (4 equiv), Bu_3SnH (4 equiv by syringe pump over 1 h), Et_3B (0.4 equiv), dry air (0.4 equiv O_2 portionwise over 1 h), CH_2Cl_2, 20 °C, 16 h; (b) 6% Na−Hg (27 equiv), $B(OH)_3$ (10 equiv), MeOH, reflux, 12 h; (c) $RuO_2 \cdot H_2O$ (0.06 equiv), $NaIO_4$ (10% aq), EtOAc, 0 °C, 25 min; (d) Jones' reagent (10 equiv), acetone, 20 °C, 40 min; (e) HCO_2H, 20 °C, 4 h.

established 2-iodoethanol as the preferred radical precursor, leading to the desired 2-azabicyclo[2.2.1]hept-5-ene **5** in 78% yield. Only a trace of the adduct arising from simple addition to the sulfone-bearing double bond without rearrangement was detected. This suggests that there is only a modest sulfone-stabilizing effect on the putative α-radical from initial addition (and/or greater steric inhibition to H-atom transfer) relative to the radical precursor of sulfone **5**. This straightforward strategy has the potential to access other 7-substituted 2-azabicyclo[2.2.1]hept-5-enes, which are of current interest as analogues of the potent nonopioid analgesic nicotinic acetylcholine receptor agonist epibatidine.[6] It is also noteworthy that exclusive *exo*-attack of the hydroxyethyl radical on dienyl sulfone **4** was observed, whereas the addition of thiols to diene **1** (Scheme 1) always led to an epimeric mixture of sulfides **2** (favoring the *syn*-isomer from *exo*-attack).[2]

Desulfonylation of sulfone **5** using 6% sodium amalgam with boric acid in methanol[7] at reflux gave alkene **6** (74%), which was oxidatively cleaved using ruthenium tetroxide[8] to obtain the corresponding hydroxy diacid. Prolonged exposure of this hydroxy diacid to the oxidizing conditions resulted in further desired oxidation of the primary alcohol, but an unacceptable level of decomposition was also observed. The primary alcohol was therefore oxidized in a separate step using Jones' reagent, which gave cleanly the known[4] Boc-protected triacid. Boc deprotection using formic acid gave the triacid **7** (77% from alkene **6**), possessing spectral data in accord with those reported in the literature.[4]

In the application of utilizing sulfone **5** to the synthesis of α-kainic acid **9**[9] (Scheme 3), the first significant challenge

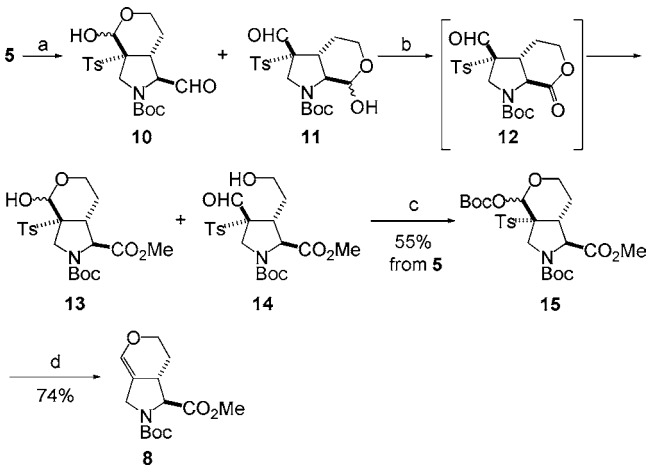
Scheme 3. Synthetic Strategy to α-Kainic Acid **9**



was considered to be achieving efficient differentiation between the (originally) alkene termini, to enable selective manipulation for eventual isopropenyl group construction at C-4 (α-kainic acid numbering). If this could be achieved following double-bond cleavage, then hydration of a derived enol ether **8** was anticipated to provide a conceptually novel way to address the second major challenge, that of controlling *cis*-stereochemistry between C-3 and C-4.[9]

The synthesis of enol ether **8** from sulfone **5** began with ozonolysis followed by Me_2S workup, which led cleanly to the formation of lactols **10** and **11** (**10**:**11**, 1:1 in $CDCl_3$, Scheme 4). Pleasingly, Swern oxidation of lactols **10** and

Scheme 4. Synthesis of Enol Ether **8**[a]



[a] Conditions: (a) O_3/O_2, Me_2S (143 equiv), CH_2Cl_2, −78 °C; (b) $(COCl)_2$ (1.5 equiv), DMSO (3 equiv), NEt_3 (5 equiv), CH_2Cl_2, −78 to 20 °C, 20 h, then AcCl (25 equiv), MeOH, 0 °C, 30 min; (c) Boc_2O (6 equiv), DMAP (0.3 equiv), NEt_3 (6 equiv), CH_2Cl_2, 20 °C, 13 h; (d) 20% Na−Hg (15 equiv), $B(OH)_3$ (10 equiv), MeOH−THF (1:1), 20 °C, 1 h.

11 resulted in selective reaction through the less hindered lactol **11** to give lactone **12**. The efficiency of this reaction

(5) Leung-Toung, R.; Liu, Y.; Muchowski, J. M.; Wu, Y.-L. *J. Org. Chem.* **1998**, *63*, 3235−3250.

(6) Malpass, J. R.; White, R. *J. Org. Chem.* **2004**, *69*, 5328−5334. See also: Hodgson, D. M.; Maxwell, C. R.; Wisedale, R.; Matthews, I. R.; Carpenter, K. J.; Dickenson, A. H.; Wonnacott, S. *J. Chem. Soc., Perkin Trans. 1* **2001**, 3150−3158.

(7) Suh, Y.-G.; Jung, J.-K.; Seo, S.-Y.; Min, K.-H.; Shin, D.-Y.; Lee, Y.-S.; Kim, S.-H.; Park, H.-J. *J. Org. Chem.* **2002**, *67*, 4127−4137.

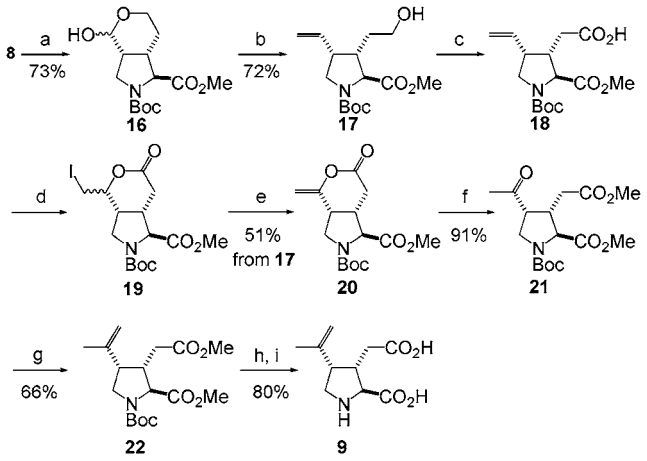
(8) Arakawa, Y.; Yasuda, M.; Ohnishi, M.; Yoshifuji, S. *Chem. Pharm. Bull.* **1997**, *45*, 255−259.

(9) (a) For a review of α-kainic acid syntheses, see: Parsons, A. F. *Tetrahedron* **1996**, *52*, 4149−4174. For selected recent syntheses, see: (b) Chevliakov, M. V.; Montgomery, J. *J. Am. Chem. Soc.* **1999**, *121*, 11139−11143. (c) Campbell, A. D.; Raynham, T. M.; Taylor, R. J. K. *J. Chem. Soc., Perkin Trans. 1* **2000**, 3194−3204. (d) Xia, Q.; Ganem, B. *Org. Lett.* **2001**, *3*, 485−487. (e) Clayden, J.; Menet, C. J.; Tchabanenko, K. *Tetrahedron* **2002**, *58*, 4727−4733. (f) Trost, B. M.; Rudd, M. T. *Org. Lett.* **2003**, *5*, 1467−1470. (g) Martinez, M. M.; Hoppe, D. *Org. Lett.* **2004**, *6*, 3743−3746.

suggests lactol **10** can convert to lactol **11** through a transient monocyclic hydroxy dialdehyde. Acid-catalyzed methanolysis of lactone **12**, to give a mixture of lactol **13** and hydroxy aldehyde **14** (**13**:**14**, 1.7:1 in $CDCl_3$), was then effected by addition of HCl in MeOH directly to the Swern oxidation reaction. It was envisaged that selective reaction through lactol **13** by conversion of the hydroxyl moiety to a suitable leaving group could be followed by Julia-type elimination to give enol ether **8**. After some experimentation, activation as carbonate **15** (55% overall yield from sulfone **5**)[10] was found to be optimal for this sequence. The unusual use of a carbonate group in the Julia elimination evolved from the need to maintain a good leaving group at the anomeric center under the desulfonylation conditions, together with reprotection of any secondary amine generated during the earlier acid-catalyzed methanolysis of lactone **12**.

Pleasingly, acid-catalyzed hydration of enol ether **8** gave lactol **16** in 73% yield with the desired *cis*-configuration between C-3 and C-4 for α-kainic acid synthesis (Scheme 5). The stereochemistry was initially assigned by chemical

Scheme 5. Synthesis of α-Kainic Acid **9**[a]



[a] Conditions: (a) HCl (6 equiv, aqueous), THF, 20 °C, 5 h; (b) PPh_3MeBr (11 equiv), KHMDS (11 equiv), PhMe, THF, 20 °C, 2 h; (c) Jones' reagent (10 equiv), acetone, 20 °C, 40 min; (d) I_2 (5 equiv), $NaHCO_3$ (30 equiv), MeCN, 0 °C, 4 h; (e) NMe_4F (15 equiv), PhH, reflux, 4 h; (f) NEt_3 (1.2 equiv), MeOH, −78 °C, 30 min; (g) Zn (18 equiv), CH_2I_2 (10 equiv), $TiCl_4$ (2 equiv), CH_2Cl_2, THF, 20 °C, 18 h; (h) KOH (175 equiv), H_2O, THF, 20 °C, 12 h; (i) TFA (12 equiv), CH_2Cl_2, 20 °C, 12 h.

correlation with the known[11] corresponding lactone acid, following lactol to lactone oxidation (TPAP/NMO) and methyl ester hydrolysis (aqueous KOH), and, ultimately, by conversion of lactol **16** to α-kainic acid. With the desired stereochemistry established, completion of the synthesis now required construction of the isopropenyl group at C-4, oxidation at the C-3 side-chain, and deprotection. Wittig methylenation of lactol **16** gave unsaturated alcohol **17** (72%) without epimerization at C-4[12] and was followed by Jones' oxidation to give the unsaturated acid **18**. The known ketone **21**[13] was then obtained by iodolactonization,[14] subsequent elimination of HI from the resulting iodolactone **19** using azeotropically dried NMe_4F in benzene[15] to give enol lactone **20** (51% from unsaturated alcohol **17**), and finally methanolysis (91%). Methylenation of ketone **21** under nonbasic conditions gave unsaturated diester **22** (66%), which has previously been converted into α-kainic acid **9** by Hanessian and Ninkovic.[16] In our hands, deprotection of unsaturated diester **22** gave α-kainic acid **9** (80%), with spectroscopic data in full accord with an authentic sample.[17]

In summary, a new stereocontrolled route to trisubstituted pyrrolidines possessing the biologically important kainoid motif has been established using a novel tandem intermolecular C−C bond-forming radical addition−homoallylic radical rearrangement sequence. The presence of the sulfone substituent is crucial to several stages of the α-kainic acid synthesis: (i) facilitating the initial [4 + 2] cycloaddition to provide dienyl sulfone **4**,[18] (ii) allowing efficient addition of a nucleophilic radical to occur on this substrate and with high regio- and stereocontrol (and yet not preventing the subsequent homoallylic rearrangement), and (iii) being constructively removed in a Julia elimination. Extension of the process to other targets of biological interest is under investigation.

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

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(10) Aldehydic compounds **10**−**14** were unstable to chromatography and were used without further purification to prepare carbonate **15**.

(11) Baldwin, J. E.; Turner, S. C. M.; Moloney, M. G. *Synlett* **1994**, 925−928.

(12) Krafft, M. E.; Cheung, Y. Y.; Abboud, K. A. *J. Org. Chem.* **2001**, *66*, 7443−7448.

(13) (a) Baldwin, J. E.; Fryer, A. M.; Pritchard, G. J. *J. Org. Chem.* **2001**, *66*, 2588−2596. (b) Ahern, D. G.; Seguin, R. J.; Filer, C. N. *J. Labelled Compd. Radiopharm.* **2002**, *45*, 401−405.

(14) Goldberg, O.; Luini, A.; Teichberg, V. I. *J. Med. Chem.* **1983**, *26*, 39−42.

(15) Cardillo, G.; Orena, M.; Porzi, G.; Sandri, S.; Tomasini, C. *J. Org. Chem.* **1984**, *49*, 701−703.

(16) Hanessian, S.; Ninkovic, S. *J. Org. Chem.* **1996**, *61*, 5418−5424.

(17) Mixing of synthetic and an authentic sample of α-kainic acid **9** led to a homogeneous ^1H NMR spectrum.

(18) Chen, Z.; Trudell, M. L. *Chem. Rev.* **1996**, *96*, 1179−1193.