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Stereocontrolled Syntheses of Kainoid Amino Acids from 7-Azabicyclo[2.2.1]heptadienes Using Tandem Radical Addition-Homoallylic Radical Rearrangement

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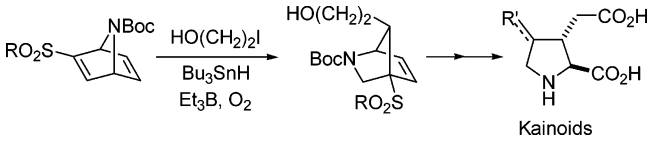
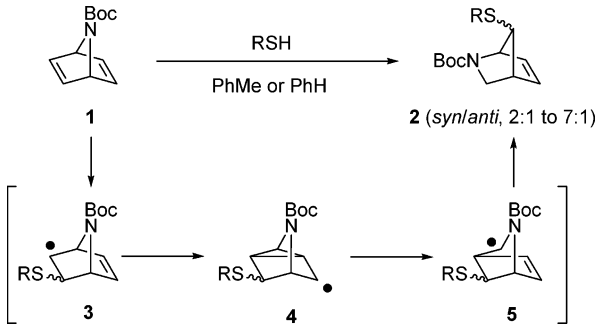


N-Boc *syn*-7-(2-hydroxyethyl)-4-(alkyl or aryl)sulfonyl-2-azabicyclo[2.2.1]hept-5-enes serve as precursors in syntheses of the neuroexcitants 3-(carboxymethyl)pyrrolidine-2,4-dicarboxylic acid **43**, α-kainic acid **12**, α-isokainic acid **14**, and α-dihydroallokainic acid **77**. The key step in these syntheses is the intermolecular radical addition of 2-iodoethanol to a *N*-Boc 2-(alkyl or aryl)sulfonyl-7-azabicyclo[2.2.1]heptadiene **7** to induce nitrogen-directed homoallylic radical rearrangement. Oxidative cleavage of the resulting 2-azabicyclo[2.2.1]hept-5-enes provide straightforward access to polysubstituted pyrrolidines and, in particular, an efficient entry to the kainoid amino acids.

Introduction

Radical cyclizations and rearrangements are versatile processes for the construction of ring systems.[1] We recently demonstrated that the addition of alkyl or aryl thiols to 7-azabicyclo[2.2.1]heptadiene **1** resulted in a tandem intermolecular radical addition-homoallylic radical rearrangement (RA-HRR) reaction, which ultimately led to 7-thio-substituted 2-azabicyclo[2.2.1]hept-5-enes **2** (Scheme 1).[2] This rearrangement (**3** → **5**) is considered to be facilitated by the stabilization imparted to the intermediate radical **5** by the α-nitrogen.[3] The lone pair of electrons on the nitrogen atom can stabilize the adjacent radical via a HOMO−SOMO orbital interaction.[4]

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



In the present paper, we detail a full account of extension and adaptation of the aforementioned methodology to the addition of carbon-based radicals to 7-azabicyclo[2.2.1]heptadienes **7** (Scheme 2).[5] This radical addition process was accompanied by homoallylic radical rearrangement leading to the formation of 2-azabicyclo-[2.2.1]hept-5-enes **10**. The latter could in turn serve as templates for fashioning 2,3,4-trisubstituted pyrrolidines

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(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) For other nitrogen-directed radical rearrangements, see: (a) Rigby, J. H.; Pigge, F. C. *Tetrahedron Lett.* **1996**, *37*, 2201−2204. (b) Hodgson, D. M.; Galano, J.-M. *Org. Lett.* **2005**, *7*, 2221−2224.

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(5) (a) Hodgson, D. M.; Hachisu, S.; Andrews, M. D. *Org. Lett.* **2005**, *7*, 815−817. (b) Hodgson, D. M.; Hachisu, S.; Andrews, M. D. *Synlett* **2005**, 1267−1270.

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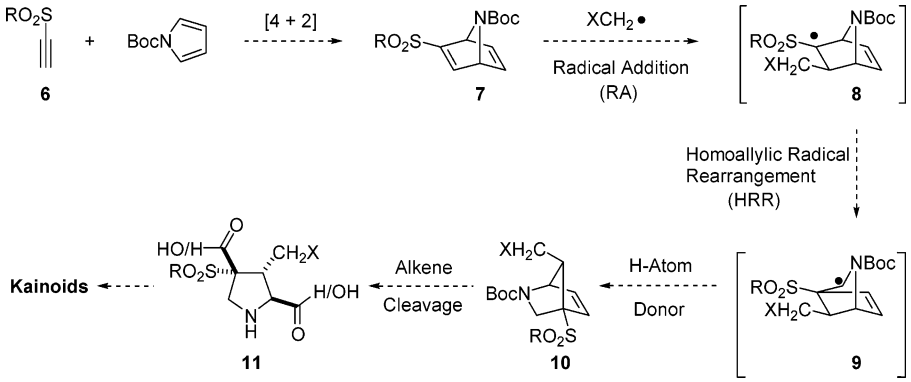
SCHEME 2. Strategy to Trisubstituted Pyrrolidines (Kainoids)



11. To demonstrate the utility of this novel strategy, syntheses of several kainoid amino acids were accomplished.

α-Kainic acid **12**, α-allokainic acid **13**, and α-isokainic acid **14** are members of the kainoid family of natural products (Figure 1).[6] There are also several more complex kainoids, whose structural diversity originates from variation of the C-4 side chain, such as isodomoic acid G **15**.[7] The kainoids have been the focus of considerable synthetic activity, primarily due to their challenging structures combined with the marked excitatory neurotransmitting activities they induce in the mammalian nervous system.[8] In particular, syntheses of α-kainic acid **12** and α-allokainic acid **13** have been accomplished by several approaches;[6,9] however, we considered that our strategy would have the benefit of brevity and enough flexibility to address the various challenging substitution patterns and stereochemical issues found in several kainoid amino acids.

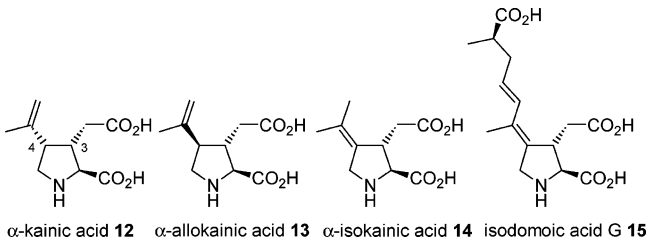
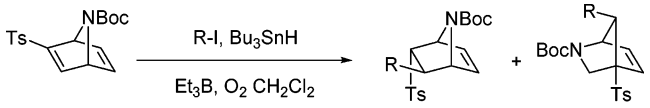


FIGURE 1. Kainoid Amino Acids.

Results and Discussion

Before embarking upon the syntheses of various kainoids, a study of the viability of the key intermolecular RA-HRR reaction was carried out. Dienyl sulfone **16** was chosen as the radical acceptor (Scheme 3) 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.[10] The latter is initiated by exo-selective conjugate addition of (−)-methyl lactate to dienyl sulfone **16** to furnish two diastereomeric Michael adducts that can be separated by an efficient fractional recrystallization. The requisite dienyl sulfone **16** enantiomer can then be liberated by base-induced *β*-elimination of the original (−)-methyl lactate portion (following reduction of the methyl ester with $NaBH_4$).

SCHEME 3. RA-HRR Reaction of Azadiene 16 Using Various Alkyl Iodides



R = *t*-Bu	**17**	(1 : 0.5)	**18**
R = *i*-Pr	**19**	(1 : 2.5)	**20**
R = *n*-Pr	**21**	(1 : 37)	**22**
R = 1-adamantyl	**23**	(1 : 0.5)	**24**
R = 2-hydroxyethyl	**25**	(1 : 13)	**26**

Unlike the symmetrical 7-azabicyclo[2.2.1]heptadiene **1** (Scheme 1), dienyl sulfone **16** could potentially undergo radical addition at four distinct sites at the double bonds. There is also a stereochemical issue (exo vs endo attack) and whether the radical addition would lead on to any homoallylic rearrangement. Consideration of these issues indicates that radical addition to dienyl sulfone **16** could potentially lead to up to 16 distinct products. Hence, it was apparent from the outset that attaining high selectivity in the radical addition and the subsequent rearrangement would be crucial for future synthetic utility.

Initially, the additions of electrophilic radicals to dienyl sulfone **16** were investigated. These were attempted using ethyl bromoacetate, ethyl iodoacetate, and diethyl bromomalonate by atom transfer (Karasch-type) process and reductive addition employing Bu_3SnH or $Ni(OAc)_2$/

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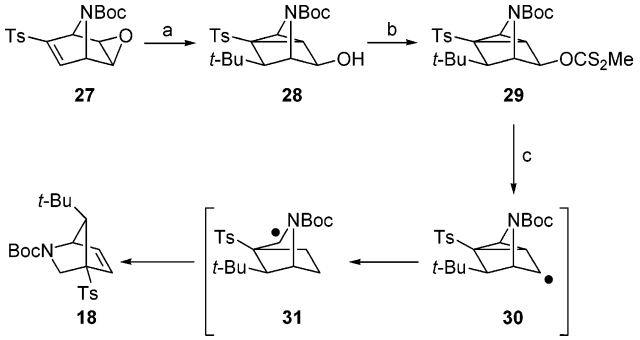
borohydride-exchange resin.[11] All these attempts to effect selective addition at the electron rich (nonsulfone bearing) double bond of dienyl sulfone **16** led to the formation of complex mixtures.

The addition of nucleophilic alkyl radicals to dienyl sulfone **16** was then explored to test selectivity for preferential reaction at the electron poor (tosyl-bearing) double bond. In an effort to maximize facial selectivity (cf. Scheme 1), a tertiary radical was examined. Reductive radical addition using *t*-BuI and Bu_3SnH (3 equiv each) with Et_3B/O_2 as initiator[1c] in CH_2Cl_2 led to the formation of 7-azabicycle **17** and 2-azabicycle **18** in good combined yield (83%, Scheme 3), when the stannane was slowly added to the iodide and dienyl sulfone **16** (0.01 M) at room temperature. Other conditions were found to be less satisfactory. The unrearranged 7-azabicycle **17** predominated 2-fold over the rearranged 2-azabicycle **18**, and this was initially considered to be principally due to a stabilizing effect of the tosyl group on the radical intermediate (cf. **8**, Scheme 2). This stabilizing effect would slow the HRR that ultimately leads to the formation of 2-azabicycle **18**. In support of this argument, radical addition of thiols (better H-atom donors then stannanes) to 7-azabicyclo[2.2.1]heptadiene **1** (initially ~0.1 M in thiol and **1**), which does not contain a potentially radical-stabilizing tosyl group, led to the exclusive formation of rearranged 2-azabicyclo[2.2.1]hept-5-enes **2** (Scheme 1).[2] Importantly, H-atom transfer from Bu_3SnH to the radical precursors of azabicycles **17** and **18** is clearly preferred relative to dienyl sulfone **16** oligimerization; the latter may be disfavored due to severe intermolecular steric interactions in the potential addition steps (and/or capto stabilization for the radical precursor to **17**).

A range of other alkyl iodides was investigated to probe the effect of the differing electronic and steric character of the corresponding alkyl radicals and to establish the scope of the RA-HRR reaction (Scheme 3). In all cases, good yields (70−83%) of radical addition products were obtained. Although addition of the various radicals was efficient, the extent of homoallylic rearrangement varied considerably. The addition of tertiary radicals led to the formation of the unrearranged 7-azabicycles **17** and **23** as the major products, a secondary radical led to the formation of the rearranged 2-azabicycle **20** as the major product, and primary radicals led to the formation of rearranged 2-azabicycles (**22** and **26**) as almost the sole products. Side products due to ethyl radical incorporation from the initiator were not detected in these reactions. Presumably, this process occurs to a small extent (especially with the primary iodides, where the rate of iodine atom transfer is slowest),[12] but propagation of the desired reaction must be efficient relative to ethyl radical generation. It is also noteworthy that exclusive exo-attack of the alkyl radicals on dienyl sulfone **16** was always 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] This novel stereocontrolled entry into 7-substituted 2-azabicyclo-[2.2.1]hept-5-enes is potentially useful due to the current interest in such systems as analogues of the potent nonopioid analgesic nicotinic acetylcholine receptor agonist epibatidine.[13]

To investigate the origins of the selectivity for the isomeric azabicycles in the radical addition reaction, xanthate **29** was synthesized for radical deoxygenation (Scheme 4). Treatment of epoxide **27** (available via regio- and stereoselective epoxidation of dienyl sulfone **16**) with *t*-BuMgCl (3 equiv) led to the formation of tricyclic alcohol **28** (92%).[14] Attempted radical deoxygenation of the derived xanthate **29** at room temperature using Et_3B and Bu_3SnH led only to recovery of the xanthate **29**. Therefore, the deoxygenation was carried out with AIBN and Bu_3SnH at 110 °C, which led to the sole formation of the rearranged 2-azabicycle **18** (45%, Scheme 4).

SCHEME 4. Radical Deoxygenation of Tricyclic Alcohol 28[a]



[a] (a) *t*-BuMgCl, THF, −78−20 °C (92%); (b) KH, CS_2, MeI, THF, 0−20 °C (92%); (c) Bu_3SnH, AIBN, PhMe, 110 °C (45%).

Assuming that radical dexoygenation of xanthate **29** proceeds via tricyclic radical **30** as an intermediate implies that, once the latter is reached in the RA-HRR chemistry, then it can also only lead to rearranged 2-azabicycle rather than (back to) 7-azabicycle. In this analysis of the RA-HRR, the ratio of the 7-aza to 2-aza products (**32**:**33**, Scheme 5) is then determined by the rate of cyclization of the initially formed intermediate from radical addition, **34** to give tricycle **37**, relative to the rate of H-atom transfer to **34**. The origin of the trend in the ratio of products is likely not the electronic nature of the alkyl radicals that are added because the addition of the adamantyl radical gives an essentially identical result to the addition of a standard tertiary (*t*-Bu) radical (Scheme 3). The electronic nature of an adamantyl radical is rather different from that of an ordinary tertiary radical, due to the formers' inability to participate in hyperconjugative radical stabilization.[15] On the other hand, the steric demand of an adamantyl group is similar to that of *t*-Bu group. Hence, it seems reasonable to attribute the unrearranged/rearranged ratio to the steric effect exerted by the alkyl groups once added to 7-azabi-

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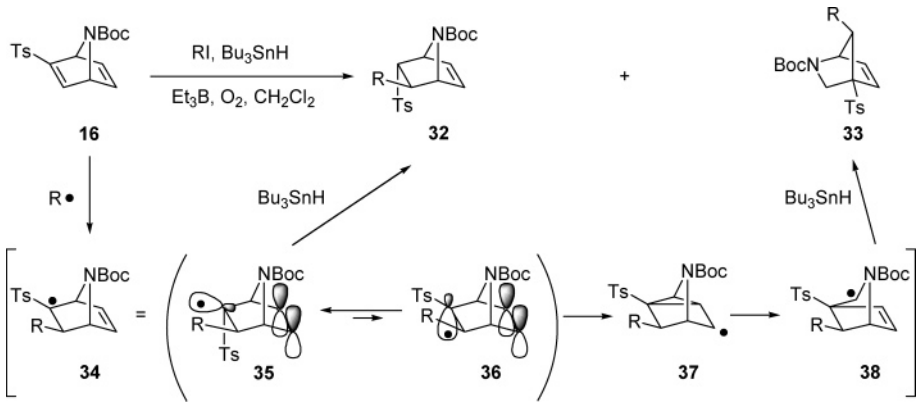
(15) (a) Chick, W. H.; Ong, S. H. *Chem. Commun.* **1969**, 216−217. (b) Humphrey, L. B.; Hodgson, B.; Pincock, R. E. *Can. J. Chem.* **1968**, *46*, 3099−3103.

SCHEME 5. Suggested Reaction Pathway of RA-HRR Reaction



cycle **16**. The addition of alkyl radicals to 7-azabicycle **16** initially leads to the formation of intermediate **34** (Scheme 5), where the radical is likely to be stabilized by the sulfone. The radical in intermediate **34** is unlikely to reside in a sp^2 like hybrid orbital (requiring 120° bond angles), due to the rigidity of the bicyclic system.[16] Instead, the radical is likely to be residing in a more sp^3-like hybrid orbital, as suggested in conformations **35** and **36** (which may be in equilibrium). It is expected that conformation **35** would be preferred, where steric interactions between the sulfone and the alkyl group (R) are minimized; conformation **36** (which possesses the desired SOMO−HOMO overlap for cyclopropane formation) would not be as stable, due to eclipsing of the sulfone and the alkyl group (R), and this effect would be most pronounced for the more sterically demanding alkyl groups. Hence, addition of a sterically demanding tertiary radical leads preferentially to the formation of the unrearranged 7-azabicycle **32**, whereas the addition of sterically less demanding primary radical leads to the formation of rearranged 2-azabicycle **33** as the major product.

Bu_3SnH is a well-established and versatile reducing agent in radical chemistry, but its toxicity, cost, and the problematic removal of byproducts make it less preferable for use in many applications.[17] Therefore, we investigated two alternative hydrogen atom donors: dichlorogallane (Cl_2GaH)[18] and 1-ethylpiperidium hypophosphite (EPHP).[19] Radical addition of *i*-PrI to dienyl sulfone **16** employing Cl_2GaH or EPHP with Et_3B/O_2 as radical initiator led to high yields of products, comparable to using Bu_3SnH (Table 1). Of note was the efficiency of the intermolecular radical addition of *i*-PrI using Cl_2GaH, where just over 1 equiv each of Cl_2GaH and *i*-PrI proved sufficient.

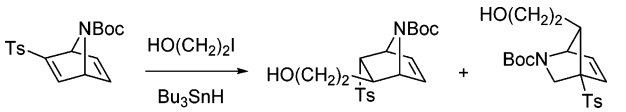
TABLE 1. RA-HRR Reaction of Azadiene 16 Using *i*-PrI and Various Hydrogen Atom Donors

entry	H-donor	H-donor (equiv)	*i*-PrI (equiv)	solvent	*T* (°C)	**19**:**20**	yield (%)
1[a]	Bu_3SnH	3	3	CH_2Cl_2	20	1:2.5	83
2[b]	Cl_2GaH	1.2	1.2	THF	0	1:4.8	63
3[c]	EPHP	9.0	1.0	dioxane	20	1:2.3	67

[a] 0.01 M in **16**. [b] 0.18 M in **16**. [c] 0.16 M in **16**.

The radical addition of 2-iodoethanol (Scheme 3) is a particularly important result in the context of our projected kainoid amino acid syntheses because the resulting 2-azabicyclo[2.2.1]heptene **26** contains a 7-hydroxyethyl substituent that can potentially be converted into carboxymethyl functionality appended at C-3 of the kanoid pyrrolidine core. Therefore, the radical addition of 2-iodoethanol to dienyl sulfone **16** was examined in more detail at different temperatures, and this produced an interesting trend (Table 2). The efficiency of the reaction at −90 °C was excellent (96% yield), but there was a reversal in selectivity in favor of 7-azabicycle **25** at low temperatures (−78 and −90 °C). A reaction carried out at above ambient temperature only resulted in a decrease in yield, with no difference in product ratio being discernible as compared to that at ambient temperature. These results indicate that the presence of sufficient thermal energy is essential for homoallylic rearrangement to occur relative to direct reduction, and that the RA-HRR reaction is most efficiently (and conveniently) carried out at ambient temperature.

TABLE 2. RA-HRR Reaction of Azadiene 16 Using 2-Iodoethanol at Various Temperatures



entry	*T* (°C)	reaction time (min)	**25** + **26** yield (%)	**25**:**26**
1[a]	−90	45	96	1:0.33
2[b]	−78	80	54	1:0.45
3[a]	0	60	67	1:14
4[a]	20	60	78	1:13
5[c]	85	35	53	1:14

[a] Bu_3SnH added over reaction time indicated, Et_3B, dry air (O_2), CH_2Cl_2. [b] Bu_3SnH added in one portion, Et_3B, dry air (O_2), CH_2Cl_2. [c] AIBN and Bu_3SnH in PhMe added over reaction time indicated.

Sulfone functionality is necessary to facilitate the [4 + 2] cycloaddition, giving the starting 7-azadiene **16**,[20] but its presence is not required in the target kainoids; hence, its efficient removal[21] is an important goal. Pleasingly, treatment of the inseparable mixture of sulfones

(16) Kawamura, T.; Koyama, T.; Yonezawa, T. *J. Am. Chem. Soc.* **1973**, *95*, 3220−3228.

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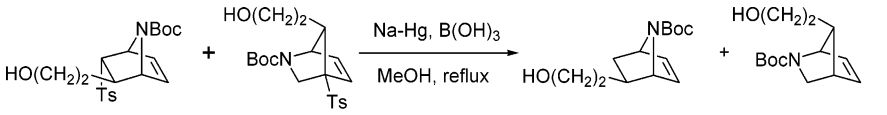
(21) Najera, C.; Yus, M. *Tetrahedron* **1999**, *55*, 10547−10658.

SCHEME 6. Desulfonylation Reactions[a]



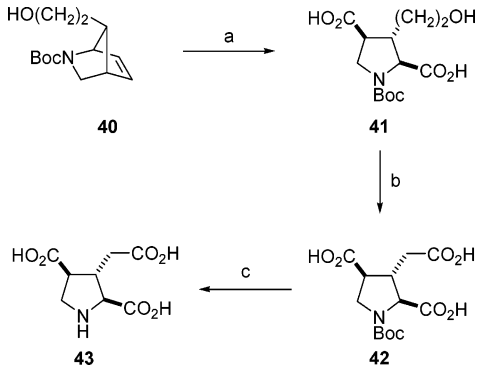
25		26		39	40
1	:	13	74%*	(trace)	(1.34 mmol)
(0.13	:	1.68 mmol)			
1	:	0.33	58%*	(0.32 mmol)	(0.36 mmol)
(0.88	:	0.29 mmol)			

[a] Asterisk: Combined yield of **39** and **40**.

25 and **26** (1:13) with 6% sodium amalgam and boric acid[22] in methanol at reflux gave alkene **40** (74%, Scheme 6) and a trace amount of 7-azabicycle **39**, separable by chromatography. With the aim of definitively identifying 7-azabicycle **39**, desulfonylation was carried out on a mixture of sulfones **25** and **26** in which the 7-aza isomer predominated (1:0.33). Intriguingly, it was observed that the quantity of 2-azabicycle **40** produced from desulfonylation was larger than the quantity of 2-azabicyclic sulfone **26** initially present (Scheme 6). This (fortuitous) enhancement in the yield of 2-azabicycle **40** may be rationalized by recognizing that during desulfonylation of 7-azabicycle **25**, a radical could be generated at C-2 that might undergo partial HRR.[13c]

Having established a viable RA-HRR reaction and subsequent desulfonylation, the stage was set to apply the methodology to kainoid targets. To straightforwardly demonstrate the viability of the synthetic strategy, triacid **43**, which is known to exhibit strong neuroexcitatory activity,[23] was chosen as an initial target (Scheme 7). Oxidative cleavage of alkene **40** was carried out in a biphasic mixture of EtOAc and H_2O containing a catalytic amount of $RuO_2{\cdot}H_2O$ with $NaIO_4$ as the stoichiometric oxidant.[24] Prolonged exposure of the resulting hydroxy diacid **41** to these conditions led to the formation of Boc-protected triacid **42**, but unfortunately, this was accompanied by an unacceptable degree of decomposition. The oxidation of the primary alcohol was therefore carried out in a separate step with Jones' reagent to cleanly yield Boc-protected triacid **42**. The final deprotection was carried out, following literature precedent, by dissolving Boc-protected triacid **42** in formic acid, which gave triacid **43** (77% from alkene **40**) with spectral data in accord with those reported in the literature.[23]

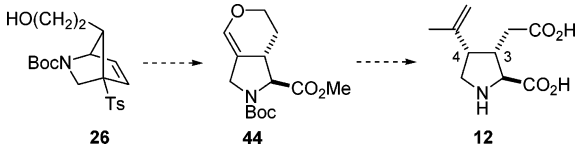
SCHEME 7. Synthesis of Triacid 43[a]



[a] (a) $RuO_2{\cdot}H_2O$, $NaIO_4$ (10% aq), EtOAc, 0 °C; (b) Jones' reagent, acetone, 20 °C; (c) HCO_2H, 20 °C (77% from **40**).

Application of the RA-HRR methodology to the synthesis of α-kainic acid **12** was considered a more challenging target. The RA-HRR reaction was readily applied to the synthesis of triacid **43** (Scheme 7) because oxidative cleavage of the double bond in 2-azabicycle **40** led directly to the desired stereochemistry at the three contigious stereogenic centers, and differentiation between the (originally) alkene termini was not necessary as they were both manipulated into carboxylic acid functionality. In comparison, a successful synthesis of α-kainic acid **12** would necessitate differentiation of the alkene termini to construct an isopropenyl group, and inversion of stereochemistry at C-4 (α-kainic acid numbering). We considered that if differentiation of the originally alkene termini after oxidative cleavage of the double bond could be achieved, then hydration of a derived enol ether **44** (Scheme 8) might furnish the desired cis-stereochemistry between C-3 and C-4, driven by avoidance of the additional ring strain that could result from a trans-fused bicyclic system.

SCHEME 8. Synthetic Strategy to α-Kainic Acid 12



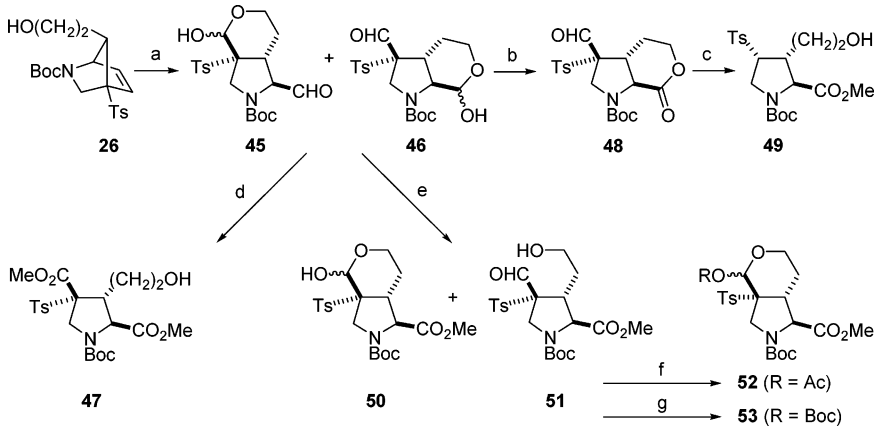
Ozonolysis of 2-azabicycle **26** followed by a reductive (Me_2S) workup cleanly furnished a mixture of lactols **45** and **46** (100% crude yield, unstable to chromatography, Scheme 9). The lactols could potentially interconvert through a transient monocyclic hydroxy dialdehyde. We envisaged that selective oxidation of one of the lactols **45** or **46** to a lactone might be possible, and this could lead to just one oxidation product provided that lactols **45** and **46** readily interconvert (the lactol ratio showed a significant solvent dependence, **45**:**46**, 1:1 in $CDCl_3$, 1:10 in DMSO-d_6). However, Br_2-mediated oxidation[25] of lactols **45** and **46** in a mixture of MeOH and H_2O buffered

(22) 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.

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

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

SCHEME 9. Synthesis of Acetals 52 and 53 from 2-Azabicycle 26[a]



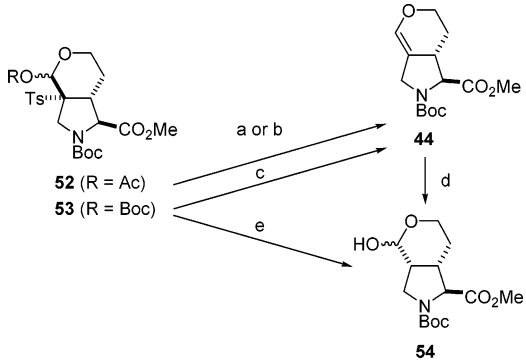
[a] (a) O_3/O_2, Me_2S, CH_2Cl_2, −78 °C (100%, crude yield); (b) $(COCl)_2$, DMSO, NEt_3, CH_2Cl_2, −78−20 °C (97%, crude yield); (c) K_2CO_3, MeOH−CH_2Cl_2 (1:1), 20 °C (42% from **26**); (d) Br_2, $NaHCO_3$, MeOH−H_2O (9:1), 20 °C (24% from **26**); (e) as part b, then AcCl, MeOH, 0 °C; (f) Ac_2O, DMAP, NEt_3, CH_2Cl_2, 20 °C (43% from **26**); (g) Boc_2O, DMAP, NEt_3, CH_2Cl_2, 20 °C (55% from **26**).

with $NaHCO_3$ only gave ring opened diester **47**, in 24% yield from 2-azabicycle **26**. Screening of a variety of other oxidation conditions were studied, but all led to either mixtures of lactones or ring-opened esters/acids. A breakthrough was achieved when lactols **45** and **46** were subjected to Swern oxidation, and lactone **48** was obtained as a single product (97% crude yield, unstable to chromatography). The selectivity in this oxidation is thought to be due to either the larger proportion of lactol **46** present in solution assisted by excess DMSO employed in the reaction and/or the higher reactivity of less-hindered lactol **46** (the hydroxyl group in lactol **45** is adjacent to a quaternary center).

In an effort to establish a bicyclic framework for an eventual elaboration into enol ether **44**, KOMe-catalyzed methanolysis of lactone **48** was carried out. Unfortunately, although this led to methanolysis of the lactone, undesired deformylation was also observed to give alcohol **49** (42% from **26**). The deformylation could occur by a base-catalyzed retro-Claisen-type process. Indeed, the latter is a common problem encountered in Julia-olefination chemistry when the formation of a trisubstituted double bond is desired.[26] An obvious way to try to circumvent such a base-catalyzed deformylation process was to carry out the desired methanolysis under acidic conditions. Addition of anhydrous HCl (generated from the addition of AcCl) in MeOH to the Swern oxidation reaction resulted in the formation of a mixture of lactol **50** and hydroxy aldehyde **51** (**50**:**51**, 1.7:1 in $CDCl_3$, unstable to chromatography). This mixture could be converged into a stable bicyclic acetate **52** or carbonate **53** (in 43 and 55% yields, respectively). The increase in yield when using Boc_2O as compared to Ac_2O to selectively trap and protect lactol **50** is probably due to reprotection of any secondary amine generated during the earlier acid-catalyzed methanolysis of lactone **48**.

Initially, Julia-type elimination to obtain enol ether **44** was attempted on acetate **52** using standard phosphate-buffered conditions with 5% Na amalgam in a mixture of MeOH and THF. Unfortunately, this led to the exclusive formation of alcohol **49** (Scheme 9), which is thought to occur via NaOMe-induced deacetylation, followed by deformylation as discussed previously. To circumvent this problem, the Julia-type elimination was carried out using SmI_2 in a mixture of HMPA and THF.[26] The latter (essentially neutral) conditions with acetate **52** led to formation of the desired enol ether **44**, albeit in low yield (28%, Scheme 10). Further experimentation with sodium amalgam as the reductant was therefore carried out. It was considered essential to decrease the presence of NaOMe that may form in the reaction mixture when employing sodium amalgam in MeOH. To achieve this, $B(OH)_3$ was used as the buffer to decrease the pH of the solution in comparison to phosphate buffers.[22] Pleasingly, Julia-type elimination with sodium amalgam and $B(OH)_3$ led to the formation of enol ether **44** in an improved 48% yield. It was also noted at this point that the yields obtained in these Julia-type reactions were essentially unaffected by the proportion of Na present (5−20%) in the commercially available amalgams, so the more cost-effective 20% Na amalgam was utilized henceforward. The optimized Julia-type reaction conditions (Na amalgam and $B(OH)_3$) were then applied

SCHEME 10. Synthesis of Lactol 54[a]



[a] (a) SmI_2, HMPA, THF (28%); (b) 5% Na−Hg, $B(OH)_3$, MeOH−THF (1:1), 0−20 °C (48%); (c) 20% Na−Hg, $B(OH)_3$, MeOH−THF (1:1), 0−20 °C (74%); (d) HCl, THF (73%); (e) 20% Na−Hg, $B(OH)_3$, MeOH−THF (1:1), 0−20 °C, then HCl (0.4 M, aq) (42%).

(25) Collins, P.; Ferrier, R. *Monosaccharides: Their Chemistry and Their Roles in Natural Products*; Wiley: Chichester, 1995; pp 126−127.

(26) Marko, I. E.; Murphy, F.; Kumps, L.; Ates, A.; Touillaux, R.; Craig, D.; Carballares, S.; Dolan, S. *Tetrahedron* **2001**, *57*, 2609−2619.

to carbonate **53**, and this led to the formation of enol ether **44** in good yield (74%).

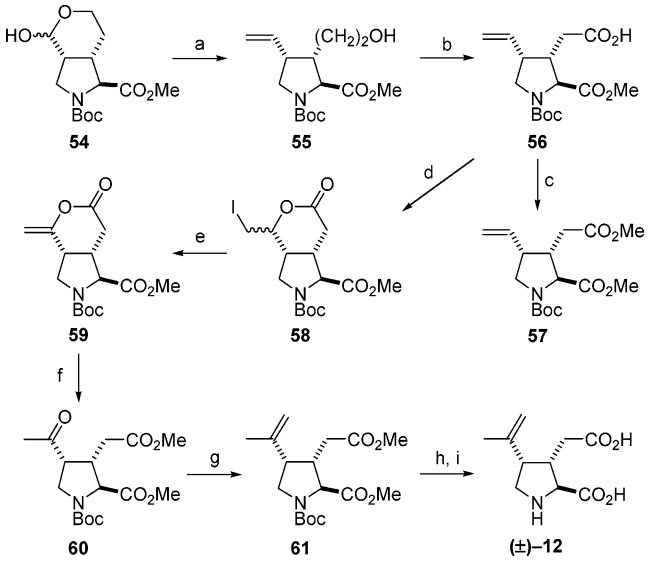
Acid-catalyzed hydration of enol ether **44** gave lactol **54** (73% yield), with the desired cis-configuration between C-3 and C-4. Furthermore, this acid-catalyzed hydration of enol ether **44** could be effected by prolonging exposure to the acidic workup at the end of the Julia-type elimination to directly furnish lactol **54** from Boc-acetal **53**, albeit in modest overall yield (42%). The stereochemistry of the ring fusion was assigned cis by correlation with the known lactone acid,[27] following lactol to lactone oxidation (TPAP/NMO) and methyl ester hydrolysis (aqueous KOH) and, ultimately, by conversion of lactol **54** to α-kainic acid **12**.

Initially, attempts to open lactol **54** did not give satisfactory results: direct methylation using MeMgBr and MeTi(*i*-PrO)$_3$ left the lactol moiety intact, and attempted silyl protection of the open aldehyde-alcohol tautomer employing TESCl, TESOTf, TBDMSCl, or TBDMSOTf led to ring-closed silyl-acetals. Opening of the lactol ring was finally accomplished via a Wittig olefination employing PPh$_3$MeBr deprotonated with KHMDS in PhMe, to yield alkene **55** (72%, Scheme 11). Alcohol **55** was converted into diester **57** in two steps via Jones' oxidation to the acid **56**, followed by esterification using TMSCHN$_2$. It was initially conceived that diester **57** could be directly converted into ketone **60** by Wacker oxidation. Terminal olefins generally yield ketones on Wacker oxidation,[28] but unfortunately in the present case, aldehyde formation was observed as the major reaction pathway. The reversal of the usual selectivity in the Wacker oxidation could be due to coordination of the palladium catalyst to the ester at C-3 in diester **57**. This might then cause the palladium associated to the double bond to lie closer to the internal olefinic carbon, leading to a higher concentration of positive charge residing on the terminal carbon. Hence, the terminal carbon would undergo (anti-Markovnikov) nucleophilic attack by water, leading to aldehyde formation.[29]

Because of the failure of the Wacker oxidation to give the desired ketone **60**, an alternative tactic was examined. Iodolactonization of acid **56** gave iodolactone **58**.[30] This lactone proved unstable to silica gel column chromatography, so it was used in crude form in subsequent steps. Nevertheless, an analytical sample of the major iodolactone diastereoisomer could be obtained via recrystallization from CH_2Cl_2 and Et_2O. Treatment of crude iodolactone **58** with a mild base (NMe_4F) in PhH at reflux led to elimination of HI to form enol-lactone **59**, in 51% yield over three steps from alcohol **55**. The use of other more commonly used bases, such as DBU or the Amberlyst A-26 (polymer-supported trimethylammonium) F^- form,[31] gave only decomposition products. Mild methanolysis of enol-lactone **59** using Et_3N in MeOH led to the known ketone **60**[32] in 91% yield. Olefination of ketone **60** to give alkene **61** was carried out using a nonbasic Nozaki reagent. Epimerization at C-4 of ketone **60** is known to be facile, and the employment of a basic Wittig reagent would likely have led to epimerization at this center.[33] The successful generation of alkene **61** constitutes a formal synthesis of α-kainic acid **12**,[34] but deprotection was also carried out in our hands to achieve a total synthesis of α-kainic acid **12**, in 80% yield. The spectroscopic data for our synthetic α-kainic acid **12** was in accord with literature values, and co-mixing of synthetic and authentic samples of α-kainic acid **12** led to a homogeneous ^{1}H NMR spectrum.

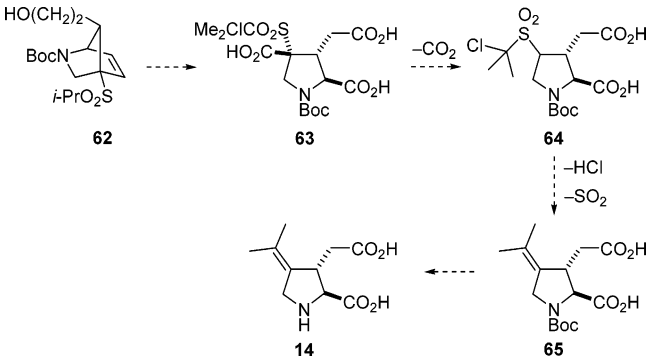
To further develop the present strategy toward other kainoids, specifically α-isokainic acid **14**, we considered utilizing a decarboxylative Ramberg−Bäcklund reaction (RBR)[35] on sulfone **63** to access the isopropylidene unit at C-4 in a direct manner (Scheme 12). We envisaged that

SCHEME 11. Synthesis of α-Kainic Acid 12[a]



(a) PPh$_3$MeBr, KHMDS, PhMe, THF, 20 °C (72%); (b) Jones' reagent, acetone, 20 °C; (c) TMSCHN$_2$, hexane−MeOH (7:2), 20 °C (81% from **55**); (d) I_2, $NaHCO_3$, MeCN, 0 °C; (e) NMe_4F, PhH, reflux (51% from **55**); (f) NEt_3, MeOH, −78 °C (91%); (g) Zn, CH_2I_2, $TiCl_4$, CH_2Cl_2, THF, 20 °C (66%); (h) KOH, H_2O, THF, 20 °C; (i) TFA, CH_2Cl_2, 20 °C (80% from **61**).

SCHEME 12. Synthetic Strategy to α-Isokainic Acid 14



(27) Baldwin, J. E.; Turner, S. C. M.; Moloney, M. G. *Synlett* **1994**, 925−928.
(28) Tsuji, J. *Synthesis* **1984**, 369−384.
(29) (a) Pellissier, H.; Michellys, P.-Y.; Santelli, M. *Tetrahedron* **1997**, *53*, 7577−7586. (b) Pellissier, H.; Michellys, P.-Y.; Santelli, M. *Tetrahedron* **1997**, *53*, 10733−10742.
(30) Goldberg, O.; Luini, A.; Teichberg, V. I. *J. Med. Chem.* **1983**, *26*, 39−42.
(31) Cardillo, G.; Orena, M.; Porzi, G.; Sandri, S.; Tomasini, C. *J. Org. Chem.* **1984**, *49*, 701−703.
(32) (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. Labeled Compd. Radiopharm.* **2002**, *45*, 401−405.
(33) Monn, J. A.; Valli, M. J. *J. Org. Chem.* **1994**, *59*, 2773−2778.
(34) Hanessian, S.; Ninkovic, S. *J. Org. Chem.* **1996**, *61*, 5418−5424.

sulfone **63** could be generated from oxidative cleavage of alkene **62**, which could potentially be obtained from the application of a RA-HRR reaction on an appropriate 7-azabicycle.

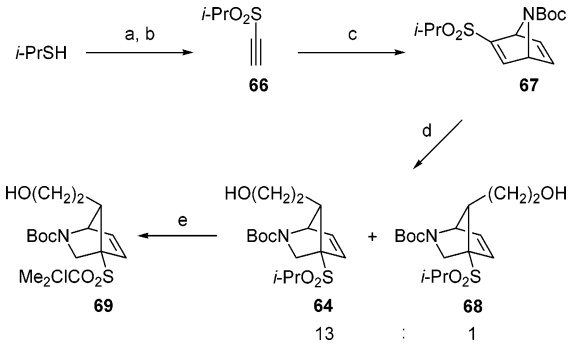
To examine the strategy outlined in Scheme 12, 7-azabicycle **67** was prepared by [4 + 2] cycloaddition of *N*-Boc pyrrole and 2-(ethynylsulfonyl)propane **66** (63%, Scheme 13). 2-(Ethynylsulfonyl)propane **66** has previously been prepared in five steps from acetylene, but it was more conveniently made by following a one-pot protocol for forming *S*-alkyl ynethiol ethers from trichloroethylene, followed by oxidation with peracetic acid.[36] This chemistry uses *i*-PrSK to effect MeOK-catalyzed elimination from trichloroethene to give dichloroacetylene, which undergoes *i*-PrSK-catalyzed addition of *i*-PrSH to give the dichloro enethiol ether. *n*-BuLi (2.2 equiv) is then directly added to generate the lithium acetylide of 2-(ethynylthio)propane, which, on addition of MeOH, gives 2-(ethynylthio)propane. Following an aqueous wash, the resulting solution was treated directly with peracetic acid to give 2-(ethynylsulfonyl)propane **66** (53% from *i*-PrSH), thus avoiding isolation of the intermediate acetylenic thiol. Pleasingly, treatment of 7-azabicycle **67** with 2-iodoethanol, Bu_3SnH, and Et_3B/O_2 led to RA-HRR to give a mixture of 2-azabicycles **64** and **68** in good yield (82%). The radical addition was exoselective, favoring 2-azabicycle **64** (**64**:**68**, 13:1). It is interesting to note that the only minor product obtained from this reaction was 2-azabicycle **68**, the C-7 epimer of **64**, whereas the minor product observed from RA-HRR reaction of 7-azabicycle **16** was the unrearranged 7-azabicycle **25** (Table 2). 2-Azabicycles **64** and **68** are chromatographically separable, but it was more convenient for large-scale preparative purposes to carry the mixture on to the next step. Chlorination of 2-azabicycle **64** to give α-chlorosulfone **69** was achieved by deprotonation α- to the sulfone with *n*-BuLi, followed by trapping of the intermediate α-lithiosulfone with C_2Cl_6.[37] When this reaction is carried out on a large scale with a mixture of 2-azabicycles **64** and **68**, chloride **69** is conveniently isolated by recrystallization.

Ozonolysis of 2-azabicycle **69** with a reductive workup (Me_2S) led cleanly to the formation of lactols **70** and **71** (Scheme 14), which are likely in equilibrium (cf. lactols **45** and **46**, Scheme 9). The latter was supported by the fact that in $CDCl_3$, the two lactols are present in a 1:1 mixture, whereas in DMSO-d_6, only lactol **71** was present, as determined by ^{1}H NMR spectroscopy. Subjection of lactols **70** and **71** to oxidation with Br_2 buffered by $NaHCO_3$ in MeOH−H_2O led to the formation of monoester **72**. Thus, decarboxylation (or deformylation) at C-4 had occurred spontaneously under the reaction conditions. This result contrasts with the bromine oxidation of lactols **45** and **46**, which led to the formation of diester **47** (Scheme 9). The difference in these Br_2 mediated oxidations is likely due to the more electron-withdrawing nature of the α-chlorosulfonyl functionality, which strongly enhances the vicinal decarboxylation (or deformylation) relative to the tosyl functionality. Deformylation for the latter required more basic conditions (K_2CO_3, MeOH) for the formation of monoester **49** from lactone **48** (Scheme 9). Pleasingly, treatment of sulfone **72** with *t*-BuOK at −78 °C led to RBR to produce alkene **73** in 45% yield. Alkene **73** could potentially be transformed into α-isokainic acid **14** after an oxidation, hydrolysis, and Boc-deprotection sequence, but it was decided to carry out further work on the earlier bromine oxidation step. It was envisaged that simultaneous oxidation of the primary alcohol (masked as lactol) and aldehydes in **70/71** would considerably shorten the synthesis. Furthermore, if the oxidation could be carried out in basic media, then the RBR might also occur concurrently. This global oxidation and concurrent RBR was realized when lactols **70** and **71** were treated with 4-AcNH-TEMPO and Br_2 under basic conditions (aq KOH)[38] to give diacid **65**. Under these conditions, heating was necessary for the RBR to proceed at a useful rate. To facilitate purification, the resulting diacid **65** was esterified using $TMSCHN_2$ to form protected α-isokainic acid **74** in 72% yield from 2-azabicycle **69**. α-Isokainic acid **14** was finally obtained after hydrolysis of the methyl esters (THF and aq KOH), and deprotection of the Boc group (TFA in CH_2Cl_2),[34] in 81% yield over two steps.

Spectroscopic (^{1}H and ^{13}C NMR) data for α-isokainic acid **14**, required to ratify the present synthesis of α-isokainic acid **14**, do not exist in the literature. Therefore, our sample of (±)-α-isokainic acid **14** was compared to material obtained from treatment of (−)-α-kainic acid **12** with refluxing aqueous HBr (20%) for 3 h, which is known to give α-kainic acid δ-lactone **75** and α-isokainic acid **14** (Scheme 15).[39] The mixture of α-kainic acid δ-lactone **75** and α-isokainic acid **14** were purified with Dowex-50H$^+$ and then with Amberlite CG-50, and pleasingly, the ^{1}H NMR spectrum of this mixture showed peaks with identical chemical shifts and coupling constants to synthetic (±)-α-isokainic acid **14**.

Additional evidence was sought to further support the synthesis of α-isokainic acid **14**, which was via the

SCHEME 13. Synthesis of 2-Azabicycle 69[a]



[a] (a) KH, THF, 20 °C, then Cl_2C=CHCl, cat. MeOH, −50−20 °C, then *n*-BuLi, −70 to −40 °C; (b) $MeCO_3H$, MeOH, THF 0−20 °C (53% from *i*-PrSH); (c) *N*-Boc pyrrole, 85 °C (63%); (d) $HO(CH_2)_2I$, Bu_3SnH, Et_3B, dry air (O_2), CH_2Cl_2, 20 °C (82%); (e) *n*-BuLi, C_2Cl_6, THF, −78 to 20 °C (86%).

(35) (a) Wladislaw, B.; Marzorati, L.; Russo, V. F. T.; Zim, M. H.; Di Vitta, C. *Tetrahedron Lett.* **1995**, *36*, 8367−8370. (b) Taylor, R. J. K.; Casy, G. *Org. React.* **2003**, *62*, 357−475.

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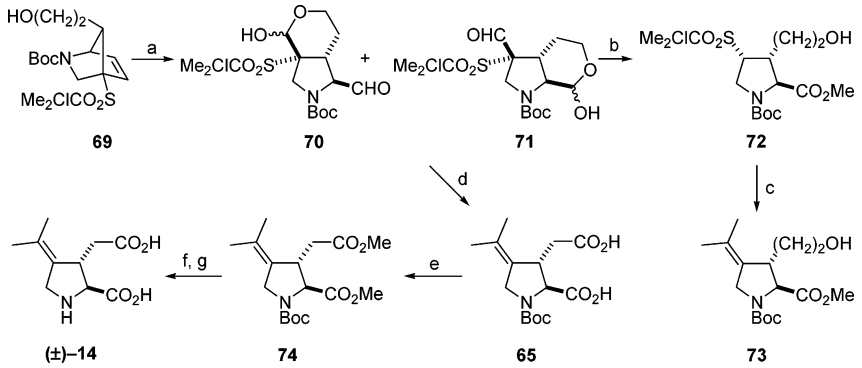
(37) Vacher, B.; Samat, A.; Allouche, A.; Laknifli, A.; Baldy, A.; Chanon, M. *Tetrahedron* **1988**, *44*, 2925−2932.

(38) Merbouh, N.; Bobbitt, J. M.; Brückner, C. *J. Carbohydr. Chem.* **2002**, *21*, 65−77.

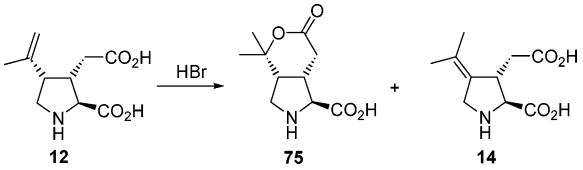
(39) Morimoto, H. *Yakugaku Zasshi* **1955**, *75*, 916−919; ibid. *Chem. Abstr.* **1956**, *50*, 24089.

SCHEME 14. Synthesis of α-Isokainic Acid 14[a]



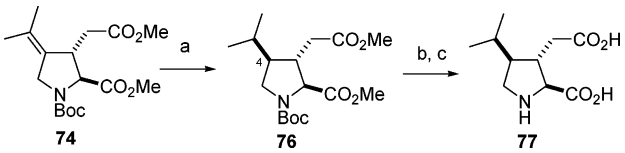
(a) O_3/O_2, then Me_2S, CH_2Cl_2, −78 to 20 °C (100%, crude yield); (b) Br_2, $NaHCO_3$, MeOH−H_2O (9:1), 20 °C (61% from **69**); (c) *t*-BuOK, THF, −78 °C (45%, 10% recovered **72**); (d) 4-AcNH-TEMPO, Br_2, KOH (added to maintain pH at 11.5), $Na_2S_2O_5$, MeCN/H_2O (1:1), 0−95 °C; (e) $TMSCHN_2$, PhMe/MeOH (7:2), 20 °C (72% from **69**); (f) KOH, H_2O, THF, 20 °C; (g) TFA, CH_2Cl_2, 20 °C (81% from **74**).

SCHEME 15. Synthesis of α-Kainic Acid *δ*-Lactone 75 and α-Isokainic Acid 14



synthesis of α-dihydroallokainic acid **77** (Scheme 16). Catalytic hydrogenation of protected α-isokainic acid **74** using Adams' catalyst gave protected α-dihydroallokainic acid **76** in 98% yield. Hydrogenation occurred highly stereoselectively, without observation of protected-α-dihydrokainic acid (C-4 epimer). Hydrolysis (aqueous KOH) followed by Boc deprotection (TFA in CH_2Cl_2) of protected-α-dihydroallokainic acid **76** gave α-dihydroallokainic acid **77**[40] in 91% yield. This latter result provided further supporting evidence for our synthesis of α-isokainic acid **14** (as all possible diastereomers of dihydrokainic acid are known)[41] and establishes a divergent approach to α-dihydroallokainic acid **77**.

SCHEME 16. Synthesis of α-Dihydroallokainic Acid 77[a]



[a] (a) PtO_2, H_2 (1 atm), MeOH, 20 °C (98%); (b) KOH, H_2O, THF, 20 °C; (c) TFA, CH_2Cl_2, 20 °C (91% from **76**).

In summary, a tandem intermolecular radical addition−homoallylic radical rearrangement reaction has been developed to access 2-azabicyclo[2.2.1]hept-5-enes that are not readily accessible by other means. These 2-azabicycles can be used as templates to form 2,3,4-trisubstituted pyrrolidines with excellent stereocontrol. This methodology has been exemplified in racemic syntheses of a known biologically active kainoid analogue **43**, α-kainic acid **12**, α-isokainic acid **14**, and α-dihydroallokainic acid **77**.

Experimental Procedures

General experimental details are described in the Supporting Information.

Synthesis of α-Isokainic Acid 14. 2-(Ethynylsulfonyl)-propane 66. 2-Propanethiol (6.97 mL, 75.0 mmol) in THF (100 mL) was added dropwise to a suspension of KH (15.1 g, 30% in mineral oil, 113 mmol) in THF (100 mL) over 10 min and allowed to stir for 17 h. The reaction mixture was cooled to −50 °C, and trichloroethylene (7.50 mL, 83.5 mmol) in THF (75 mL) was added dropwise over 5 min, followed by MeOH (0.2 mL, 4.9 mmol). The reaction mixture was warmed to 20 °C and stirred until gas evolution was complete. After 4 h, the reaction mixture was cooled to −70 °C, and *n*-BuLi (138 mL, 1.2 M in hexane, 166 mmol) was added dropwise over 15 min. After 30 min at −70 °C, the mixture was warmed to −40 °C over 30 min and then treated dropwise with MeOH (9 mL) over 10 min. The mixture was allowed to warm to 20 °C, and after 10 min, further MeOH (15 mL) was added. The reaction mixture was washed with saturated aqueous NH_4Cl (300 mL) and H_2O (4 × 100 mL). Peracetic acid (37.2 mL, 36−40% in acetic acid) was added to the organic layer at 0 °C, and the mixture was allowed to warm to 20 °C. After 15 h, the organic phase was separated from the acidic phase and washed with saturated aqueous $NaHCO_3$ (4 × 300 mL) and H_2O (3 × 100 mL). The organic layer was dried and concentrated in vacuo. The residue was purified by column chromatography (30% Et_2O-petroleum ether) to give ethynyl sulfone **66**[36a] as a colorless liquid (5.25 g, 53%); R_f (50% Et_2O-petroleum ether) 0.3; ν_{max}/cm^{-1} 3236, 2984, 2940, 2067, 1467, 1332, 1262, 1132; δ_H (400 MHz, $CDCl_3$) 3.44 (1H, s), 3.25 (1H, sept, J = 6.9 Hz), 1.48 (6H, d, J = 6.9 Hz); δ_C (100 MHz, $CDCl_3$) 81.6, 76.5, 57.6, 15.6; *m/z* (CI) 150 (M + NH_4^+, 100%) (Found: M + NH_4^+, 150.0588. $C_5H_{12}NO_2S$ requires *M*, 150.0589).

***N*-Boc 2-[(1-Methylethyl)sulfonyl]-7-azabicyclo[2.2.1]-heptadiene 67.** Ethynyl sulfone **66** (1.32 g, 9.99 mmol) and *N*-*t*-butoxycarbonylpyrrole (8.51 mL, 49.9 mmol) were mixed neat at 85 °C under Ar and protected from light. After 27 h, the reaction mixture was cooled to 20 °C and subjected directly to purification by column chromatography (gradient elution: 10−40% Et_2O-petroleum ether) to give 7-azabicycle **67** as a yellow solid (1.88 g, 63%); R_f (50% Et_2O-petroleum ether) 0.2; mp 65−66 °C; ν_{max}/cm^{-1} 2978, 2935, 1710, 1369, 1338, 1309, 1257, 1163, 1136; δ_H(250 MHz, DMSO-d_6, 90 °C) 7.87−7.84 (1H, m), 7.27−7.22 (1H, m), 7.12−7.08 (1H, m), 5.39−5.36 (1H, m), 5.31−5.28 (1H, m), 3.29 (1H, sept, J = 6.8 Hz), 1.39 (9H, s), 1.25−1.20 (6H, m); δ_C (63 MHz, DMSO-d_6, 90 °C) 156.3,

(40) Sugawa, T. *Yakugaku Zasshi* **1957**, *77*, 332−333; ibid. *Chem. Abstr.* **1957**, *51*, 62288.

(41) Hashimoto, K.; Konno, K.; Shirahama, H. *J. Org. Chem.* **1996**, *61*, 4685−4692.

155.2, 152.8, 143.0, 142.0, 80.3, 67.7, 66.6, 52.5, 27.4, 14.4, 14.0; *m/z* (CI) 317 ($M + NH_4^+$, 100%) (Found: $M + NH_4^+$, 317.1533. $C_{14}H_{25}N_2O_4S$ requires *M*, 317.1535).

***N*-Boc *syn*-7-(2-Hydroxyethyl)-4-[(1-methylethyl)sulfonyl]-2-azabicyclo[2.2.1]hept-5-ene 64 and *N*-Boc *anti*-7-(2-Hydroxyethyl)-4-[(1-methylethyl)sulfonyl]-2-azabicyclo[2.2.1]hept-5-ene 68.** 7-Azabicycle **67** (956 mg, 3.19 mmol) was dissolved in CH_2Cl_2 (320 mL), and Ar was bubbled through the solution for 15 min. 2-Iodoethanol (1.50 mL, 19.2 mmol) and Et_3B (1.91 mL, 1.0 M in hexane, 1.91 mmol) were added to the degassed solution. Bu_3SnH (5.16 mL, 19.2 mmol) was added via a syringe pump over 100 min, and dry air (10 mL portions) was injected into the reaction mixture in parallel at 5 min intervals. The reaction mixture was then washed with saturated aqueous NaH_2PO_4 (400 mL), and the aqueous layer was extracted with CH_2Cl_2 (3 × 200 mL). The organic extracts were combined and dried and then concentrated in vacuo. Purification of the resulting residue by column chromatography (Et_2O) gave a mixture of azabicycles **64** and **68** (906 mg, 82%) as colorless oil. Further chromatographic purification (Et_2O) led to the isolation of **64** (842 mg, 76%) and **68** (58 mg, 5%) as colorless oils. *syn*-**64**: R_f (Et_2O) 0.1; ν_{max}/cm^{-1} 3468, 2977, 2936, 2359, 1338, 1689, 1393, 1368, 1303, 1259, 1161, 1119, 1051; δ_H (500 MHz, DMSO-d_6, 90 °C) 6.61−6.57 (2H, m), 4.56 (1H, s), 4.25 (1H, s), 3.66 (1H, d, J = 9.2 Hz), 3.51−3.40 (3H, m), 2.85 (1H, d, J = 9.2 Hz), 2.31 (1H, dd, J 3.1, J = 9.8 Hz), 1.90−1.84 (1H, m), 1.42 and 1.41 (9H, s), 1.42−1.26 (1H, m), 1.32 and 1.32 (3H, d, J = 6.8 Hz), 1.31 and 1.31 (3H, d, *J* = 6.8 Hz); δ_C(125 MHz, DMSO-d_6, 90 °C) 155.9, 137.0, 136.9, 80.4, 74.8, 63.9, 59.8, 59.5, 51.8, 43.7, 28.4, 27.6, 15.3, 14.1; m/z (CI) 363 (25%), 346 ($M + H^+$, 100%) (Found: $M + H^+$, 346.1687. $C_{16}H_{28}NO_5S$ requires M, 346.1688). *anti*-**68**: R_f (Et_2O) 0.2; ν_{max}/cm^{-1} 3469, 2976, 2361, 2342, 1696, 1394, 1368, 1302, 1163, 1133, 1052, 872; δ_H (500 MHz, DMSO-d_6, 90 °C) 6.49 (1H, dd, J = 5.8, 2.4 Hz), 6.41 (1H, d, J 5.8), 4.66 (1H, s), 4.18 (1H, s), 3.64 (1H, d, *J* = 8.9 Hz), 3.48−3.39 (3H, m), 2.92 (1H, d, *J* = 8.9 Hz), 2.68−2.65 (1H, m), 1.83−1.77 (1H, m), 1.43−1.36 (1H, m), 1.41 (9H, s), 1.34 and 1.34 (3H, d, *J* = 6.7 Hz), 1.32 and 1.32 (3H, d, *J* = 6.7 Hz); δ_C (125 MHz, DMSO-d_6, 90 °C) 153.8, 133.7, 130.2, 78.9, 76.0, 62.5, 59.5, 59.0, 52.2, 48.5, 27.8, 27.6, 15.5, 14.4; *m/z* (CI) 713 ($2M + Na^+$, 100%), 368 ($M + H^+$, 50%) (Found: $M + H^+$, 346.1684. $C_{16}H_{28}NO_5S$ requires *M*, 346.1688).

***N*-Boc 4-[(1-Chloro-1-methylethyl)sulfonyl]-7-(2-hydroxyethyl)-2-azabicyclo[2.2.1]hept-5-ene 69.** 2-Azabicycle **64** (829 mg, 2.40 mmol) was dissolved in THF (20 mL), and the temperature was lowered to −78 °C. *n*-BuLi (3.52 mL, 1.5 M in hexane, 5.28 mmol) was added dropwise over 10 min, and then C_2Cl_6 (1.70 g, 7.20 mmol) dissolved in THF (15 mL) and precooled to −78 °C was added over 15 min by cannula. The resulting mixture was stirred for 75 min, warmed to 20 °C, and stirred for a further 50 min. The mixture was then diluted with Et_2O (200 mL) and washed with aqueous HNO_3 (200 mL, 0.10 M). The aqueous layer was extracted with Et_2O (3 × 100 mL), and the combined organic extracts were dried and concentrated in vacuo. The residue was purified by column chromatography (Et_2O) to give chloride **69** (784 mg, 86%) as a white solid. Recrystallization from Et_2O/CH_2Cl_2 gave an analytically pure sample (recrystallization at this point is recommended for large scale preparation, as this makes the separation of azabicycles **64** and **68** unnecessary in the previous step); R_f (Et_2O) 0.3; mp 115−116 °C; ν_{max}/cm^{-1} 3446, 2977, 2935, 1698, 1393, 1368, 1310, 1167, 1108; δ_H (500 MHz, DMSO-d_6, 90 °C) 6.70 (1H, d, *J* = 6.1 Hz), 6.60 (1H, dd, *J* = 6.1, 2.7 Hz), 4.58 (1H, s), 3.76 (1H, d, *J* = 9.2 Hz), 3.52−3.40 (2H, m), 2.98 (1H, d, *J* = 9.2 Hz), 2.49−2.48 (1H, m), 2.02−1.95 (1H, m), 1.97 (6H, s), 1.42 (9H, s), 1.34−1.26 (1H, m); δ_C (125 MHz, DMSO-d_6, 90 °C) 154.4, 135.6, 134.9, 83.5, 79.1, 74.7, 61.9, 59.1, 58.4, 44.8, 28.4, 27.6, 26.7, 26.4; *m/z* (ES) 675 (68%), 402 ($M + Na^+$, 55%), 380 ($M + H^+$, 100%) (Found: $M + H^+$, 380.1293. $C_{16}H_{27}{}^{35}ClNO_5S$ requires *M*, 380.1303).

***N*-Boc 3-(Carboxymethyl)-4-(*i*-propylidene)-2-pyrrolidinecarboxylic Acid Dimethyl Ester 74.** 2-Azabicycle **69** (270 mg, 0.711 mmol) was dissolved in CH_2Cl_2 (200 mL), and the temperature was lowered to −78 °C. A mixture of O_3/O_2 was bubbled through the solution until it turned blue, followed by O_2 until the solution became colorless. Then, Ar was passed through the solution for 5 min, and Me_2S (5 mL, 68 mmol) was added dropwise. The mixture was warmed to 20 °C and stirred for 1 h. The mixture was then concentrated in vacuo, and the residue was dissolved in Et_2O (50 mL, the dissolution aided by a small amount of CH_2Cl_2). This solution was washed with H_2O (2 × 30 mL), dried ($MgSO_4$), and concentrated in vacuo to give a crude mixture of lactols **70** and **71** as a white foam. This crude mixture was dissolved in MeCN/H_2O (17 mL, 1:1 MeCN/H_2O), and the temperature was lowered to 0 °C. 4-Acetamido-2,2,6,6-tetramethylpiperidine-1-oxyl (14 mg, 0.066 mmol) was added, followed by aqueous KOH (7.5 M) until the pH was 11.5. A mixture of Br_2 (0.21 mL, 4.10 mmol) and MeCN (6 mL) was added dropwise over 30 min, together with aqueous KOH (7.5 M) to maintain the pH at 11.5. Residual Br_2 was washed into the reaction using MeCN/H_2O (6 mL, 1:1 MeCN/H_2O), and the reaction was further stirred at pH 11.5 and 0 °C for 2 h. $Na_2S_2O_5$ (1.35 g, 7.10 mmol) was then added, and the mixture was stirred vigorously until it turned colorless. Aqueous KOH (6 mL, 7.5 M, 45.0 mmol) was now added, and the temperature was raised to 95 °C for 2 h. The mixture was cooled to 20 °C and acidified to pH 1 with aqueous HCl (2.0 M). The aqueous layer was extracted with EtOAc (4 × 20 mL), and the combined organic extracts were washed with brine (100 mL), dried ($MgSO_4$), and concentrated in vacuo. The residue was dissolved in PhMe/MeOH (18 mL, 7:2 PhMe/MeOH), (trimethylsilyl)diazomethane (5 mL, 2.0 M in hexane, 10.0 mmol) was added, and the mixture was stirred at 20 °C for 16 h. AcOH (0.6 mL) was then added, and the mixture was concentrated in vacuo. Purification of the residue by column chromatography (25% Et_2O-pentane) gave protected α-isokainic acid **74** (174 mg, 72%) as a colorless oil; R_f (25% Et_2O-pentane) 0.3; ν_{max}/cm^{-1} 2976, 1742, 1706, 1394, 1256, 1175, 1104, 1108, 897; δ_H (400 MHz, $CDCl_3$) 4.33 and 4.23 (1H, s), 4.09−3.85 (2H, m), 3.67 and 3.64 (3H, s), 3.67 and 3.64 (3H, s), 3.27 (1H, dd, *J* = 9.4, 5.5 Hz), 2.45−2.32 (2H, m), 1.60 (3H, s), 1.56 (3H, s), 1.43 and 1.37 (9H, s); δ_C (100 MHz, $CDCl_3$) 172.5 and 172.3, 172.0 and 171.8, 155.1 and 154.6, 130.0 and 129.1, 126.4 and 126.3, 80.2 and 80.2, 64.4 and 63.9, 52.4 and 52.3, 51.9 and 51.9, 48.6, 42.7 and 41.9, 38.5, 28.5 and 28.3, 21.1 and 21.1, 20.5 and 20.5; *m/z* (ES) 705 ($2M + Na^+$, 14%), 364 ($M + Na^+$, 100%), 308 (22%), 242 ($M - Boc + H^+$, 39%) (Found: $M + H^+$, 342.1927. $C_{17}H_{28}NO_6$ requires *M*, 342.1917).

α-Isokainic Acid 14. Protected α-isokainic acid **74** (51 mg, 0.15 mmol) was dissolved in a mixture of THF (1.2 mL) and aqueous KOH (4.6 mL, 2.5%). The reaction mixture was stirred for 15 h, and then aqueous HCl (2.0 M) was added until pH ∼2. The aqueous layer was extracted with EtOAc (4 × 10 mL), dried, and concentrated in vacuo. The residue was redissolved in CH_2Cl_2 (10 mL), TFA (0.5 mL, 6.5 mmol) was added dropwise, and the reaction mixture was stirred for 28 h. The mixture was then concentrated in vacuo, and the residue was purified by column chromatography (Dowex-50H^+, WX8-200, 8% cross linking, 100−200 wet mesh), eluting with NH_4OH (2.0 M). The resulting solution was concentrated in vacuo, redissolved in H_2O, and stirred with Amberlite CG-50 (100−200 dry mesh) for 1 h, and then filtered. The filtrate was concentrated in vacuo to give α-isokainic acid **14**[42] (26 mg, 81%) as a white solid; mp 240−245 °C (dec) [Lit.[42] 237−240 °C (dec)]; ν_{max}/cm^{-1} 2927, 2361, 2342, 1564, 1557, 1373, 1297, 1043, 859; δ_H (250 MHz, D_2O) 4.15 (1H, d, *J* = 1.2 Hz), 4.06 (1H, d, *J* = 14.9 Hz), 3.94 (1H, d, *J* = 14.9 Hz), 3.55 (1H, td, *J* = 6.8, 1.2 Hz), 2.54 (1H, dd, *J* = 14.8, 6.8 Hz), 2.46 (1H, dd, *J* = 14.8, 6.8 Hz), 1.71 (3H, s), 1.62 (3H, s); δ_C(126 MHz, D_2O) 178.1, 174.1, 131.0, 126.0, 66.7, 47.4, 42.2, 39.8, 21.2, 20.9; *m/z* (ES)

(42) Honjo, M. *Yakugaku Zasshi* **1957**, *77*, 598−603. ibid. *Chem. Abstr.* **1957**, *51*, 90648.

212 ($M - H^+$, 100%), 168 (35%) (Found: $M + H^+$, 214.1074. $C_{10}H_{16}NO_4$ requires *M*, 214.1079).

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Supporting Information Available: Full experimental details of syntheses and characterization of compounds not described in the Experimental Procedures. Copies of ^1H and ^{13}C spectra for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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