Stereoselective Synthesis of (±)-α-Kainic Acid Using Free Radical Key Reactions

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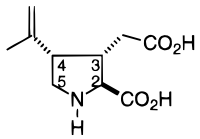
Thiol-mediated free radical isomerization of a deliberately substituted but-3-enyl isocyanide **12a**, and *n*-Bu_3SnH/AIBN-mediated free radical cyclization of a deliberately substituted but-3-enyl isothiocyanate **22**, afforded, respectively, the (ethylthio)pyrroline **13a** and the thiopyroglutamates **5** and **23**. Reduction, protection, and deprotection of these heterocyclic compounds afforded proline derivatives **6** and **25** which contain all the structural elements of α-kainic acid (**1**) except the C-2 acetic acid moiety. These intermediates were stereospecifically converted into (±)-α-kainic acid using a new method of temporary sulfur connection. Accordingly, CH_2CO_2Me is linked to the chiral isopropenyl anchor and then intramolecularly connected to the pyrrolidine ring and eventually disconnected from its anchor by a sequential reductive double elimination process in which the isopropenyl double bond is restored.

Introduction

α-Kainic acid (**1**) is the prototype of a group of neuroexcitatory amino acids which activate a particular subtype of glutamic acid receptors. These amino acids are important substrates in physiological and pharmacological studies of the central nervous system.[1] The synthesis of α-kainic acid continues to challenge organic chemists, providing an arena for developing and testing new strategies and methodologies.[2−11] One of the major obstacles to be overcome in the synthesis of α-kainic acid is the achievement of the 3,4-*cis*-stereochemistry. Most of the reported syntheses are based on the construction of the substituted pyrrolidine system by the stereocontrolled formation of the 3,4-carbon to carbon bond.[2,4,5,7−9] Another commonly employed strategy is to delay to the end of the synthesis the involvement of compounds carrying an acidic C-2 hydrogen atom. Accordingly most authors reported on hydroxy compounds of type **2** as pretargets which are oxidized to carboxylates at an advanced stage of the synthesis.[2,4−9,11]

Synthetic Plan

In contrast to the conventional strategies mentioned above, our synthetic strategy involves the stereocontrolled construction of the substituted heterocyclic system by the formation of the 4,5-carbon to carbon bond and on the use of a starting material which already possesses



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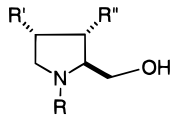

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the carboxylate group designed to occupy position-2 in α-kainic acid (**1**). An early step in this plan entails the generation of a carbon-centered imidoyl radical of type **3**.[12] Such a radical possesses all the building blocks composing the target molecule except for the C-3 acetic acid moiety. The array of substituents and functional groups in **3** was designed to allow, in a single stage, the stereoselective formation of either a pyrroline **4** or a pyrrolidinethione **5**. Reduction of both pyrrolines **4** and thiopyroglutamates **5** to the key intermediate compound **6** was based on conventional methods. The C-2 carboxylate and C-4 isopropenyl groups of pyrrolidine **6** have the same relative stereochemistry as (−)-α-kainic acid **(1)**.[13] The conversion of pyrrolidine **6** into α-kainic acid (**1**) requires the formal substitution of the 3*β*-hydroxyl group by 3α-CH_2COOH. For the introduction of the acetic acid appendage in the desired stereochemistry a new method based on temporary sulfur connection was developed.[14] It was designed with the purpose of securing the prevalence of substitution at position-3 rather then TsOH elimination.

Synthesis of Key Pyrrolidine Derivatives 6 and 25

The *ω*-(ethylthio)dimethylacrylaldehyde **9**, obtained from the bromoacetal **7**,[15] was condensed with lithium enolate of isocyanide **10** to give a separable mixture of the *syn* and *anti* hydroxy esters **11a** and **11b** (Scheme 1). To avoid elimination of H_2O from hydroxy esters **11**,

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(3) Takano, S.; Iwabuhi, Y.; Ogasawara, K. *J. Chem. Soc., Chem. Commun.* **1988**, 1204.
(4) Takano, S.; Sugihara, T.; Satoh, S.; Ogasawara, K. *J. Am. Chem. Soc.* **1988**, *110*, 6467.
(5) Baldwin, J. E.; Moloney, M. G.; Parsons, A. F. *Tetrahedron* **1990**, *46*, 7263.
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(7) Barco, A.; Benetti, S.; Spalluto, G.; Casolari, A.; Pollini, G. P.; Zanirato, V. *J. Org. Chem.* **1992**, *57*, 6279.
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(9) Hatakeyama, S.; Sugawara, K.; Takano, S. *J. Chem. Soc., Chem. Commun.* **1993**, 125.
(10) Monn, J. A.; Valli, M. J. *J. Org. Chem.* **1994**, *59*, 2773.
(11) Yoo, S. E.; Lee, S. H. *J. Org. Chem.* **1994**, *59*, 6968.
(12) Bachi, M. D.; Melman, A. *J. Org. Chem.* **1995**, *60*, 6242.
(13) All chiral compounds in this work are racemic; just one enantiomer of each pair is addressed to in the text and displayed in the structural formulas.
(14) Preliminary report: Bachi, M. D.; Melman, A. *Synlett* **1996**, 60.
(15) Gaonach, O.; Maddaluno, J.; Chauvin, J.; Duhamel, L. *J. Org. Chem.* **1991**, *56*, 4045.

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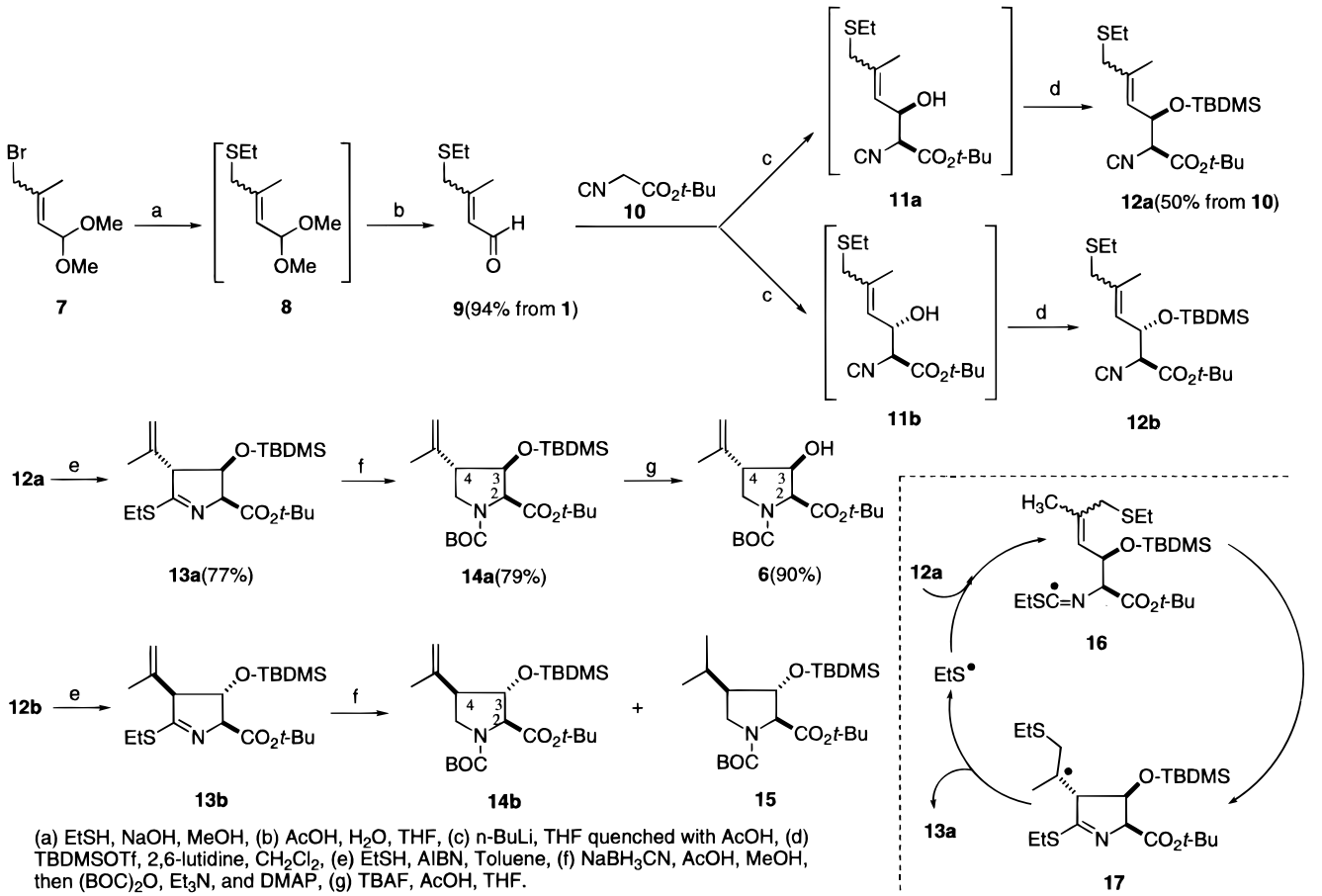
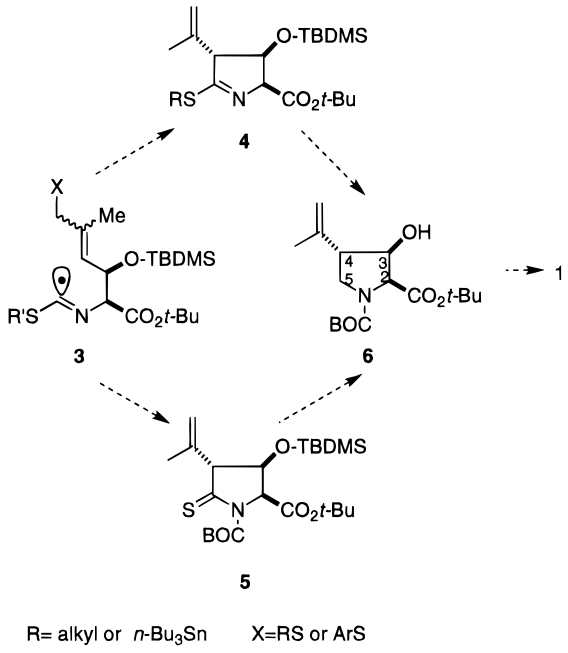
Scheme 1

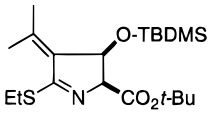


(a) EtSH, NaOH, MeOH, (b) AcOH, H_2O, THF, (c) n-BuLi, THF quenched with AcOH, (d) TBDMSOTf, 2,6-lutidine, CH_2Cl_2, (e) EtSH, AIBN, Toluene, (f) $NaBH_3CN$, AcOH, MeOH, then $(BOC)_2O$, Et_3N, and DMAP, (g) TBAF, AcOH, THF.



R= alkyl or *n*-Bu_3Sn X=RS or ArS

the conditions described in the Experimental Section should be carefully followed. O-Silylation of **11a** afforded the highly functionalized alkenyl isocyanide **12a** which contains an allylic radical leaving group (EtS). Treatment of **12a** with catalytic amounts of EtSH and AIBN induced a free radical transposition to the isopropenyl-(ethylthio)pyrroline **13a**. The mechanism of this isomerization is shown on the bottom right side of Scheme 1. It involves a sequence of homolytic transformations including intermolecular addition of ethylthiyl radical to the isocyanide group of **12a**, generating the carbon-centered imidoyl radical **16**, ring-closure to radical **17**, and subsequent, or probably concerted, β-elimination leading to the isopropenyl(ethylthio)pyrroline **13a** and EtS$^\bullet$ which continues the chain reaction. The crowded substitution array of **13a** is instrumental in preventing migration of the double bond to the exocyclic position as does occur in the case of a less crowded 4-vinyl(ethylthio)pyrroline which spontaneously isomerizes to the corresponding ethylidene derivative.[16,17] Isomerization of the isopropenyl derivative **13a** to the isopropylidene derivative **18** would induce considerable allylic-1,3 strain on both sides of the isopropylidene group.



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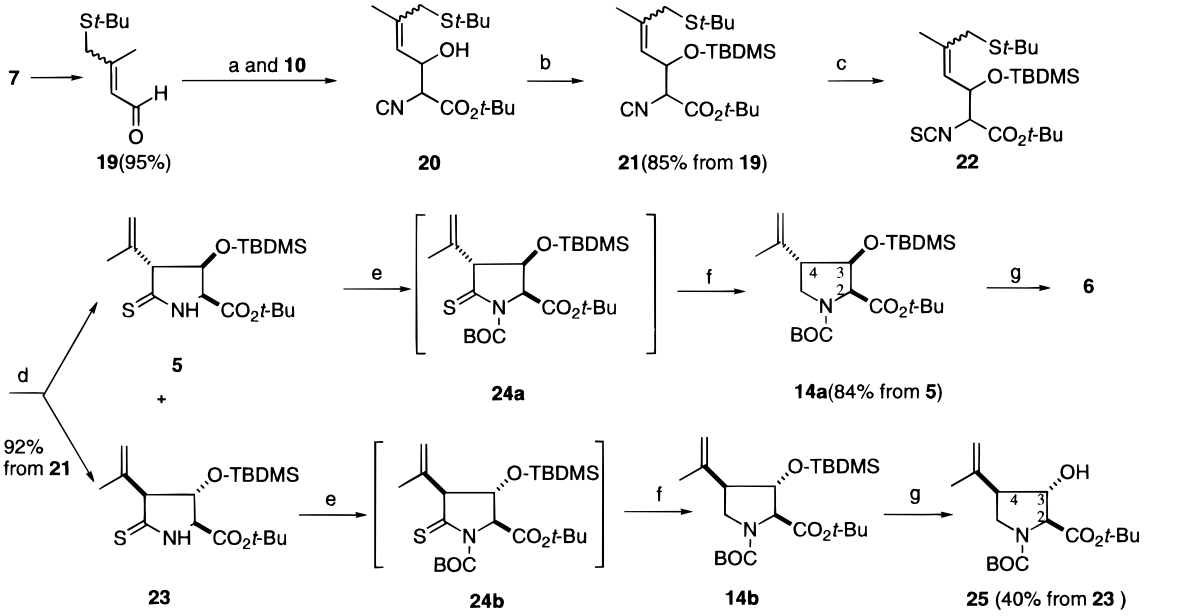
Reduction of the ethylthioimidate function in **13a** with $NaB(CN)H_3$ under mild acidic conditions, followed by nitrogen protection afforded the pyrrolidine **14a** (Scheme 1). Desilylation of **14a** gave the tetrasubstituted pyrrolidine **6**. The assigned relative stereochemistry was corroborated by X-ray diffraction analysis.[18]

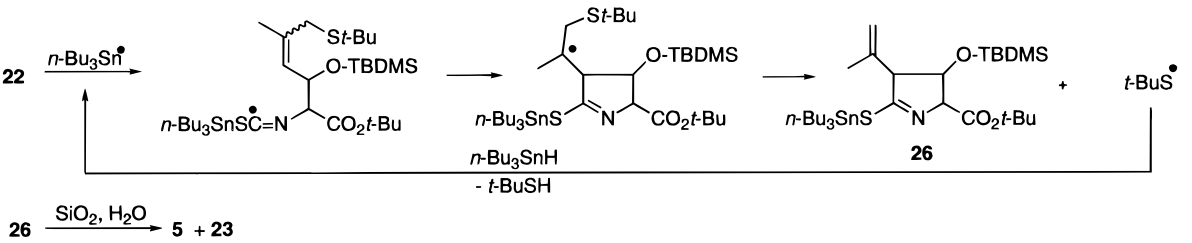
Although the original synthetic plan was based on the use of the tetrasubstituted pyrrolidine **6** as key intermediate we subsequently examined the suitability of its

(16) Bachi, M. D.; Balanov, A.; Bar-Ner, N.; Bosch, E.; Denenmark, D.; Mizhiritskii, M. *Pure Appl. Chem.* **1993**, *65*, 595.
(17) Bachi, M. D.; Balanov, A.; Bar-Ner, N. *J. Org. Chem.* **1994**, *59*, 7752.

Scheme 2



(a) *n*-BuLi, THF,quenched with AcOH, (b) 2,6-lutidine, TBDMSOTf,, (c) *t*-BuSH, ACN, toluene, (d) *n*-Bu_3SnH, ACN, toluene, (e) $(BOC)_2O$, DMAP, THF, (f) *n*-Bu_3SnH, AIBN, toluene, (g) AcOH, TBAF, THF.



diastereoisomer **25** as an additional intermediate for the synthesis of (±)-α-kainic acid. For this purpose the sequence of reactions from the condensation of compounds **9** and **10** up to the formation of (ethylthio)-pyrroline **13a**,**b** was repeated without separation of the acyclic diastereoisomeric mixtures **11a**,**b** and **12a**,**b**. Diastereomerically pure isomers **13a** and **13b** were obtained by chromatography of their mixture. In contrast to the case of isomer **13a**, the $NaB(CN)H_3$ reduction of the ethylthioimidate moiety in isomer **13b** was accompanied by partial reduction of the isopropenyl group leading to the isopropenylpyrrolidine **14b** which contained 15−20% of isopropylpyrrolidine **15**. Pure isopropenylpyrrolidine **14b** was eventually obtained by the alternative method described below which proved to be also an excellent alternative method for the preparation of isopropenylpyrrolidine **14a**.

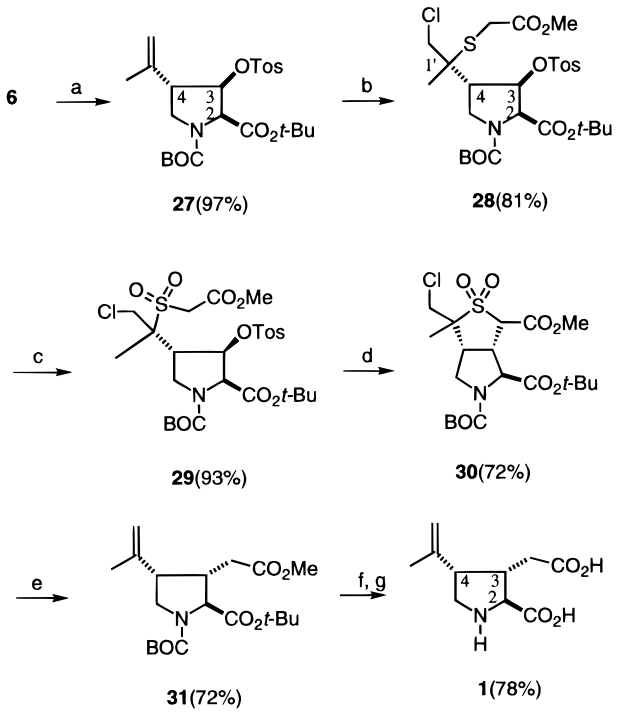
This alternative method required the synthesis of pyrrolidinethiones **5** and **23** (Scheme 2). 4-Alkylpyrrolidinethiones are readily obtained by the *n*-Bu_3SnH/AIBN-mediated cyclization of alk-4-enyl isothiocyanates.[12,16,19] In order to obtain the desired substitution pattern, we designed and synthesized the highly functionalized alkenyl isothiocyanates **22** which carries *t*-BuS as an allylic radical leaving group. While isocyanide **12a** isomerizes to (ethylthio)pyrroline **13a** when treated with EtSH/AIBN, the structurally related isocyanide **21** reacts with *t*-BuSH/ACN (ACN, 1,1′-azobis(cyclohexanecarbonitrile)) to give the corresponding isothiocyanate **22**. A similar difference in reaction selectivity between primary thiols and thiols which may release stabilized radical on the cleavage of their C−S bond was observed also in reactions of other alkenyl isocyanides.[17] *n*-Bu_3SnH/ACN-mediated cyclization of **22**[20] afforded the 4-isopropenylpyrrolidinethiones **5** and **23** (ratio 1.4:1) in excellent yield. This one-pot reaction consists of a sequence of consecutive homolytic steps combining intermolecular addition, intramolecular addition, β-elimination, and intermolecular hydrogen atom transfer as shown at the bottom of Scheme 2. The immediate products of the free radical process are two diastereomeric (stanniothio)-pyrrolines **26** which spontaneously hydrolyze on silica gel to give after chromatography the 4-isopropenylpyrrolidine thiones **5** and **23**. Conversion of **23** into the 2,3-*trans*-hydroxy ester **25** involves N-protection. In order to avoid migration of the double bond in **24b** to the exocyclic position the introduction of the BOC group should be done under mild conditions (see Experimental Section). Crude **24b** was reduced with *n*-Bu_3SnH to give the isopropenylpyrrolidine **14b**, and after desilylation the 2,3-*trans*-hydroxy ester **25**. Following the same procedure 4-isopropenylpyrrolidinethiones **5** was converted

(18) (a) We thank Dr. Felix Frolow for X-ray diffraction analyais of compound **6**. (b) The authors have deposited atomic coordinates for this structure with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 IEZ, U.K. (c) 3D structural formula, ORTEP drawing, and details of X-ray data acquisition are given as supporting information.

(19) Bachi, M. D.; Denenmark, D. *J. Org. Chem.* **1990**, *55*, 3442.

(20) For preparative purpose the isothiocyanate **22** was used in the same pot without purification (see Experimental Section)

Scheme 3



(a) *n*-BuLi, *p*-Tos-Cl, THF, (b) $ClSCH_2CO_2Me$, CH_2Cl_2, (c) MCPBA, CH_2Cl_2, (d) MeOK, THF/ MeOH/ methyl formate (40:2:1), (e) SmI_2, THF/MeOH, (f) TFA, CH_2Cl_2, (g) NaOH, H_2O, MeOH.

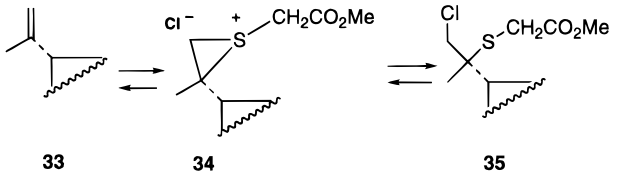
into the 2,3-*cis* silyloxy ester **14a**, identical to the substance obtained from (ethylthio)pyrroline **13a**.

Completion of the Synthesis of 1 by Temporary Sulfur Connection

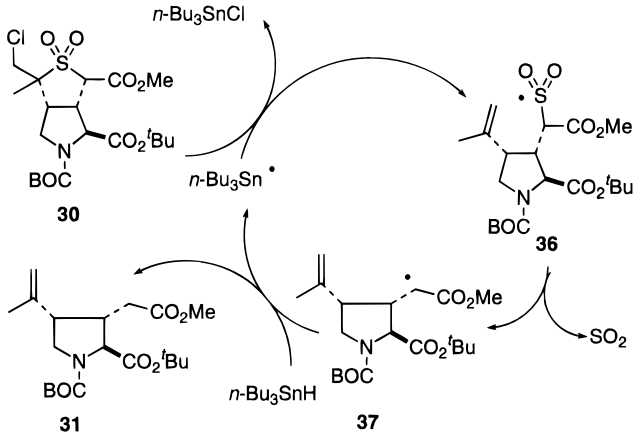
The conversion of key intermediate **6** into α-kainic acid (**1**) requires the formal substitution, with inversion of configuration, of the 3-hydroxy group by an acetic acid residue. For this purpose the hydroxy group in pyrrolidine **6** was converted into its tosyl derivative **27**. An intermolecular S_N2 substitution of the tosyloxy group by a carbon nucleophile was excluded due to the competitive facile elimination involving the acidic hydrogen at C-2. We reasoned that an intramolecular substitution might be feasible, and we investigated the possibility of using the isopropenyl group, which is in the desired α-configuration, as an anchor for the temporary linking of an acetic acid residue. In order to allow a sterically favored substitution of the tosyloxy group the acetic acid residue should be linked to the inner end of the double bond of the isopropenyl anchor by a one-atom linker. Furthermore, this linker should be prone to eventual extrusion with concomitant regeneration of the double bond in its original site. Since silicon, which proved to be an efficient linker in temporary tethered reactions,[21] was deemed unsuitable for solving our particular problems, we were prompted to invent a new type of temporary tethered reactions.

Sulfur was selected as the temporary linking unit in the present work because: (a) of the availability of reactions allowing the regiocontrolled addition of sulfur-compounds to terminal double bonds, (b) of the availability of several efficient processes for selectively cleaving carbon−sulfur bonds, including by reactions which involve the regeneration of the double bond, (c) both thio and sulfonyl substituents on acetic esters increase the acidity of the α-hydrogen atoms and therefore allow the generation of the required nucleophilic center under mild basic conditions.

For adding a methyl mercaptoacetic unit, in the desired regiochemistry, we used the sulfenyl chloride of methyl mercaptoacetate.[22] This reaction afforded in good yield the chloroalkyl sulfide **28** as a single diastereomer as shown in Scheme 3. This remarkable diastereoselectivity derives from shielding of the isopropenyl group by the tosyloxy group, from the *β*-side. This shielding is reflected in the ^1H NMR spectrum of **27**, which exhibits a marked upfield shift of the signal of the vinylic methyl group (*ca.* 0.4) and of the vinylic protons (*ca.* 0.3 ppm). Treatment of the chloroalkyl sulfide **28** with MeOK failed to induce the desired intramolecular substitution of the tosyloxy group as the reaction was reverted to give isopropylene **27**. Addition of alkylsulfenyl chlorides to terminal double bonds is a reversible reaction.[23] Under neutral conditions at room temperature the equilibrium lies in the direction: **33** → **34** → **35**; however, under basic conditions it is reverted and the isopropenyl derivative



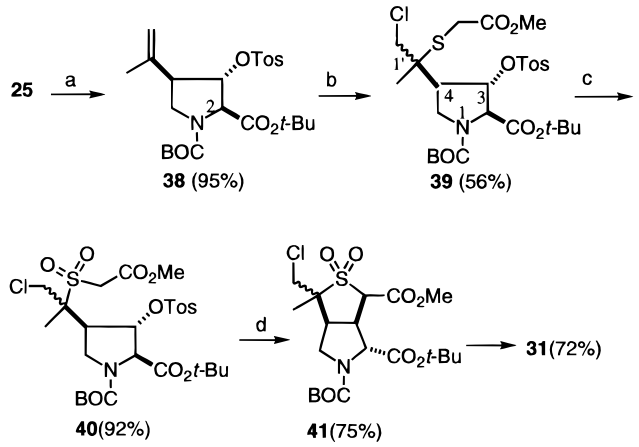
27 is recovered. To overcome this setback we oxidized the chloroalkyl sulfide **28** into the corresponding rather stable chloro-sulfone **29**. Treatment with potassium methylate in THF/methanol afforded the desired chloromethyl bicyclic sulfone **30** which carries the acetic acid residue at the desired site and configuration. The disconnection of the acetic acid moiety from its temporary anchor with concomitant regeneration of the isopropenyl double bond was initially achieved by treatment of chloromethyl bicyclic sulfone **30** with *n*-Bu_3SnH/AIBN. *n*-$Bu_3Sn^{\bullet}$ extrusion of the chlorine atom with concomitant *β*-cleavage generates the sulfonyl radical **36** which presumably undergoes α-elimination of SO_2 giving the stabilized carbon-centered radical **37**, and, after hydrogen atom abstraction from *n*-Bu_3SnH, the protected kainic acid **31**.



However, we were not satisfied with the yield of this process which did not exceed 12% protected α-kainic acid **31** along with 50% recovered starting material **30**. The

(21) Bols, M.; Skrydstrup, T. *Chem. Rev.* **1995**, *95*, 1253.

Scheme 4



(a) *n*-BuLi, *p*-Tos-Cl, THF, (b) $ClSCH_2CO_2Me$, CH_2Cl_2, (c) MCPBA, CH_2Cl_2, (d) MeOK, THF/ MeOH/ methyl formate (40:2:1)

low yield, which could not be improved by modulating temperature, concentration, and stoichiometry, is attributed to the build up of byproducts which inhibit this complex chain reaction and arrest it at low conversion. It was reasoned that a similar process can be induced by employing reducing agents which do not necessarily require a radical chain reaction. The involvement of the C−Cl rather then the weaker C−I bond in **30** limits the arsenal of suitable reagents. However, samarium(II) iodide, which was reported as an efficient reagent for ring scission of cyclic β-chloro ethers,[24] was found as an excellent reagent for the conversion of the chloromethyl sulfone **30** into the protected kainic acid **31**. The *tert*-butyl and BOC groups were removed by TFA and the methyl protecting group by dilute sodium hydroxide to give, after ion exchange resin chromatography, (±)-α-kainic acid (**1**).

On the grounds of the reported easy inversion of configuration at C-2 of some β-kainic acid (all *cis*-kainic acid) derivatives,[3] and of the racemic nature of the compounds used in the present work, it was decided to convert compound **25** into (±)-α-kainic acid (**1**). This was accomplished by following the sequence of reactions described in Scheme 4. It was noted that the diastereoselectivity of $ClSCH_2CO_2Me$ addition to 2,3-*trans*, 3,4-*trans* isopropenyl derivative **38** is lower than that of addition to 2,3-*trans*, 3,4-*trans* isopropenyl derivative **27** as it gives a 5:1 mixture of chloromethyl epimers **39**. This difference may originate from a better directive effect exerted by the CO_2t-Bu group on the TsO group of the 2,3-*cis* oriented isomer **27**.

Treatment of chloroalkyl sulfone **40** with potassium methoxide resulted in substitution of the tosyloxy group accompanied by inversion of configuration at C-2. The resulting cyclic chloromethyl sulfone **41** is identical to compound **30** obtained as shown in Scheme 3 except for being a mixture of two isomers at position 1′.[13]

In summary (±)-α-kainic acid (**1**) was obtained by two routes: (a) from the highly substituted alkenyl isocyanide **11a** in 14% overall yield (series a in Schemes 1 and 3); (b) from isothiocyanate **22** in 20% overall yield (Schemes 2 and 4). In both routes a key heterocyclic intermediate which incorporates the major structural features of the target molecule is obtained by a free radical sequential reaction of a highly functionalized open chain precursor. The lacking structural element, the acetic acid residue, is introduced in a regio- and stereocontrolled manner by a new method based on temporary sulfur connection. The disconnection of the acetic acid from its sulfur linker, with concomitant regeneration of the isopropenyl group, is based on a new reductive sequential double elimination.

Experimental Section

General Procedure. For general procedures see reference 12. MPLC (medium-pressure liquid chromatography) was performed on column l = 40 cm, d = 30 mm, filled with Lichroprep 15−40 μm, flash chromatography on silica gel 60 from Merck. All chiral compounds are racemic.[13]

4-(Ethylthio)-3-methyl-2-butenal (9). To a solution of 1,1-dimethoxy-3-methyl-4-bromobut-2-ene (**7**)[15] (89 mmol) in methanol (50 mL) at −30 °C was added a solution of NaOH (3.6 g, 90 mmol) and ethanethiol (5.6 g, 90 mmol) in methanol (50 mL). The temperature was raised to 20 °C, and water (100 mL) was added. The formed suspension was extracted with hexane (3 × 150 mL), dried, and evaporated, and the residue (dimethylacetal **8**) was dissolved in a mixture of THF (70 mL), water (10 mL), and HCO_2H (5 mL). After 3 h at 20 °C, the reaction mixture was poured into saturated $NaHCO_3$, extracted with hexane (3 × 200 mL), dried ($NaHCO_3$ and Na_2SO_4), and evaporated to afford aldehyde **9** (12 g, 94%) as mixture of *Z* and *E* isomers (*E*/*Z* ratio *ca.* 3:1). IR (neat): 1629, 1675 cm^{-1}. ^1H NMR (δ): 1.10 (t, J = 7.4 Hz, *E*), 1.11 (t, J = 7.4 Hz, *Z*), total 3H; 2.16 (d, J = 1.2 Hz, *E*), 1.98 (d, J = 1.3 Hz, *Z*), total 3H; 2.31 (q, J = 7.4 Hz, *E*), 2.35 (q, J = 7.4 Hz, *Z*), total 2H; 3.11 (d, J = 0.8 Hz, 2H); 5.88 (d, J = 8 Hz, *E*); 5.95 (d, J = 8 Hz, *Z*), total 1H; 9.97 (d, J = 8 Hz, *Z*), 9.90 (d, J = 8 Hz, *E*), total 1H.

***syn-tert*-Butyl 2-Isocyano-3-(*tert*-butyldimethylsiloxy)-5-methyl-6-(ethylthio)hex-4-eneoate (12a).** To a solution of phenanthroline (*ca.* 1 mg) and BuLi (22 mL of 1.6 M solution in hexane, 34.6 mmol) in THF at −72 °C under vigorous stirring was added dropwise *tert*-butyl isocyanoacetate (**10**) (4.88 g, 34.6 mmol) while the temperature was kept below −65 °C. The reaction mixture was stirred for an additional 5 min, a small quantity of butyllithium (*ca.* 1 mL) was added to preserve the deep rose color of Li-phenanthrolide, and 4-(ethylthio)-3-methyl-2-butenal (**9**) (5.23 g, 36.3 mmol) was added in one portion. The reaction mixture was stirred for 5 min at −72 °C and then quenched with acetic acid (7 mL). The resulting suspension was poured into saturated aqueous $NaHCO_3$ (100 mL), and hexane (150 mL) was added. The organic layer was separated, dried (Na_2SO_4 and $NaHCO_3$), and evaporated. The residue was separated by MPLC to afford *syn* hydroxy ester **11a** (6.00 g, 21 mmol, 61%, *E*/*Z* ratio 3:1), R_f 0.28 (EtOAc−hexane, 1:1). ^1H NMR (δ) 1.23 (t, J = 7.4 Hz, *E*), 1.27 (t, J = 7.4 Hz), total 3H; 1.53 (s, *E*), 1.52 (s, *Z*), total 9H; 1.86 (s, *E*), 1.91 (s, *Z*) total 3H; 2.43 (q, J = 7.4 Hz, *E*), 2.52 (m, *Z*), total 2H; 3.13, 3.15 (2d, J = 13.6 Hz, *E*) ,3.24, 3.26 (2d, J = 12.4 Hz, *Z*), total 2H; 4.16 (d, J = 3.7 Hz, *E*), 4.15 (d, J = 3.5 Hz, *Z*) total 1H; 4.84 (m, *E*), 4.83 (m, *Z*), total 1H; 5.44 (d, J = 8.6 Hz, *E*), 5.49 (d, J = 9.6Hz, *Z*), total 1H; and *anti* hydroxy ester **11b** (3.05 g, 11 mmol, 31%, *E*/*Z* ratio *ca.* 10.1), R_f 0.20 (EtOAc−hexane, 1:1), ^1H NMR (δ, major isomer) 1.22 (t, J = 7.2 Hz, 3H); 1.48 (s, 9H); 1.86 (s, 3H); 2.42 (q, J = 7.2 Hz, 2H); 3.13, 3.12 (s, 2H); 4.34 (d, J =5.0 Hz, 1H); 4.82 (dd, J=5 , J=9 Hz, 1H); 5.44 (d, J = 9 Hz, 1H). The *syn* hydroxy ester **11a** was dissolved in methylene chloride (10 mL), the solution was cooled to −72 °C, 2,6-lutidine (3.36 g, 31.4 mmol) and *tert*-butyldimethylsilyl triflate (5.8 g, 22 mmol) were added consequently, and the reaction mixture was stirred for 10 min at −72 °C. Temperature was raised to 20 °C in 20 min, hexane (15 mL) was added, and the resulting mixture was purified by flash chromatography to afford *syn* isocyanide **12a** (6.94 g, 50% from *tert*-butyl isocyanide **10**) as a mixture of *E*/*Z* isomers (*E*/*Z* ratio 3:1). IR (neat): 1745, 2149 cm^{-1}. ^1H

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NMR (δ) 0.07, 0.09 (2s, 6H); 0.89 (s, *E*), 0.88 (s, *Z*), total 9H; 1.24 (t, *J* = 7.4 Hz, *E*), 1.29 (t, *J* = 7.4 Hz), total 3H; 1.50 (s, *E*), 1.49 (s, *Z*), total 9H; 1.82 (s, 3H); 2.44 (q, *J* = 7.4 Hz, *E*), 2.52 (q, *J* = 7.4 Hz, *Z*), total 2H; 3.11 (s, 2H); 4.01 (d, *J* = 4.3 Hz, *E*), 4.15 (d, *J* = 4.5 Hz, *Z*) total 1H; 4.86 (dd, *J* = 4.2, 9 Hz, *E*), 4.82 (m, *Z*), total 1H; 5.40 (d, *J* = 9 Hz, *E*), 5.42 (d, *J* = 9Hz, *Z*), total 1H. Anal. Calcd for $C_{20}H_{37}NO_3SiS$: C, 60.15; H, 9.27; N, 3.51; S, 8.02. Found: C, 59.89; H, 9.56; N, 3.25; S, 7.67.

2β-(*tert*-Butoxycarbonyl)-3β-(*tert*-butyldimethylsiloxy)-4α-isopropenyl-5-(ethylthio)-4*H*-2,3-dihydropyrrole (13a) from Isocyanide 12a. *Syn* isocyanide **12a** (6.25 g, 17.4 mmol), AIBN (0.43 g, 2.6 mmol), ethanethiol (0.27 g, 4.3 mmol), and toluene (250 mL) were stirred for 5 h at 60 °C. The solvent was evaporated, and the residue was purified by flash chromatography (EtOAc−hexane 1:5) to afford the dihydropyrrole **13a** (4.79 g, 77%). IR (film): 1570, 1735 cm^{-1}. ^1H NMR (δ): 0.05, 0.04 (2s, 6H), 0.86 (s, 9H), 1.32 (t, *J* = 7.3 Hz, 3H), 1.47 (s, 9H), 1.70 (s, 3H), 2.96, 3.11 (2dq, *J* = 7.3, 13 Hz, 2H), 3.56 (t, *J* = 3 Hz, 1H), 4.56 (m, 2H), 4.90, 4.99 (2s, 2H). Anal. Calcd for $C_{20}H_{37}NO_3SiS$: C, 60.15; H, 9.27; N, 3.51; S, 8.02. Found: C, 60.14; H, 9.49; N, 3.63; S, 7.88.

2-(*tert*-Butoxycarbonyl)-3-(*tert*-butyldimethylsiloxy)-4-isopropenyl-5-(ethylthio)-4*H*-2,3-dihydropyrroles (13a and 13b), Starting from Isocyanoacetate 10. To a solution of phenanthroline (∼1 g) and BuLi (1.6 M solution in hexane, 66 mL, 104 mmol) in THF (360 mL) at −72 °C under vigorous stirring was added dropwise *tert*-butyl isocyanoacetate (**10**) (15 mL, 103 mmol), while the temperature was kept below −65 °C. The reaction mixture was stirred for additional 5 min. A small quantity of BuLi was added to preserve the deep rose color of Li-phenanthroline, and 4-(ethylthio)-3-methyl-2-butenal (**9**) (14.96 g, 103.2 mmol) was added dropwise to the solution, while the temperature was kept below −68 °C. The reaction mixture was stirred for additional 5 min at −72 °C and quenched with AcOH (17 mL). The resulting suspension was poured into saturated $NaHCO_3$ (260 mL) and extracted with hexane (3 × 360 mL). The hexane layer was dried (Na_2SO_4 and $NaHCO_3$) and evaporated to give a mixture of the four *syn*/*anti*-*cis*/*trans* hydroxy esters **11a**, **11b**. The crude mixture of **11a** and **11b** was dissolved in CH_2Cl_2 (48 mL). The solution was cooled to −72 °C, 2,6-lutidine (19.2 mL, 155 mmol) and *tert*-butyldimethylsilyl triflate (29.2 mL, 113 mmol) were added, and the reaction mixture was stirred for 1 h. The temperature was allowed to rise to 20 °C, hexane (100 mL) was added, the resulting suspension was washed with 1 N HCl (140 mL), saturated $NaHCO_3$ (140 mL), dried ($NaHCO_3$ and Na_2SO_4), and evaporated. Flash chromatography (hexane−EtOAc, 15:1) of the residue afforded a mixture of **12a** and **12b** (29.9 g, 74.9 mmol, 78% yield from isocyanide **10**). Isonitriles **12a**, **12b** were dissolved in toluene (1 L), AIBN (1.8 g, 10 mmol) and ethyl mercaptan (1.4 mL, 27 mmol) were added, and the reaction mixture was refluxed until the reaction was completed (TLC). The solvent was evaporated, and flash chromatography (hexane−EtOAc, 10:1) of the residue afforded dihydropyrrole **13a** (10.2 g, 25.3 mmol) and dihydropyrrole **13b** (11 g, 27.5 mmol). Total yield of the reaction was 51% from isocyanide **10**. Dihydropyrole **13a**: IR,^1H NMR identical to that described above. Dihydropyrole **13b**: IR (film): 1586, 1734 cm^{-1}. ^1H NMR (δ): 0.06, 0.08 (2s, 6H), 0.89 (s, 9H), 1.34 (t, *J* = 7.2 Hz, 3H) 1.49 (s, 9H), 1.67 (s, 3H), 2.96, 3.11 (2dq, *J* = 7.2,13 Hz, 2H), 3.56 (d, *J* = 3.7 Hz, 1H), 4.41 (d, *J* = 3.6 Hz,1H), 4.48 (t, *J* = 3.6 Hz,1H), 4.90, 4.95 (2s, 2H). Anal. Calcd for $C_{20}H_{37}N_3SiS$: C, 60.14; H, 9.49; N, 3.63. Found: C, 60.24; H, 9.02; N, 3.74.

1,2β-Bis(*tert*-butoxycarbonyl)-3β-(*tert*-butyldimethylsiloxy)-4α-isopropenyl-pyrrolidine (14a). To a solution of dihydropyrrole **13a** (4.6 g, 11.5 mmol) and bromocresol green (*ca.* 1 mg) in methanol (15 mL) and AcOH (5 mL) under stirring was added $NaBH_3CN$. The reaction mixture was stirred at room temperature while an additional amount (5 mL) of AcOH was added to preserve the yellow color of solution. Di-*tert*-butyl dicarbonate (5.0 g, 23 mmol) and DMAP (10 mg) were added, and the reaction mixture was stirred for 1 h, neutralized with triethylamine (up to green color of solution), evaporated, poured into water (100 mL), and extracted with EtOAc−hexane mixture (1:5, 2 × 100 mL). The organic layer was dried and evaporated, and the residue was separated by MPLC to afford pyrrolidine **14a** (4.0 g, 9.1 mmol, 79%). IR (neat): 1706, 1741 cm^{-1}. ^1H NMR (two conformers) (δ): 0.06, 0.11 (2s, major), 0.06, 0.10 (2s, minor), total 6H; 0.89 (s, major), 0.88 (s, minor), total 9H; 1.46 (s, major), 1.47 (s, minor), total 9H; 1.50 (s, major), 1.49 (s, minor), total 9H; 1.74 (s, 3H); 3.06 (m, 1H); 3.28 (t, *J* = 9.8 Hz, major), 3.22 (t, *J* = 10.4 Hz, minor), total 1H; 3.68 (dd, *J* = 8.9, 10.7 Hz, major), 3.65 (t, *J* = 8.2 Hz, minor), total 1H; 4.16 (d, *J* = 7.6 Hz, major), 4.27 (m, minor), total 1H; 4.27 (m, 1H; 4.92 (s, major), 4.91 (s, minor), total 2H. Anal. Calcd for $C_{23}H_{43}NO_5Si$: C, 62.59; H, 9.75; N, 3.17. Found: C, 62.30; H, 9.90; N, 2.84.

1,2β-Bis(*tert*-butoxycarbonyl)-3β-hydroxy-4α-isopropenylpyrrolidine (6). To pyrrolidine **14a** (3.0 g, 6.8 mmol) were added AcOH (120 mg, 7 mmol) and a solution of tetrabutylammonium fluoride in THF (15 mL of 1 M solution). The reaction mixture was kept 48 h at 20 °C and then poured into saturated $NaHCO_3$ (50 mL). The formed emulsion was extracted with EtOAc−hexane mixture (1:4, 2 × 50 mL) dried, and evaporated, and the residue was purified by flash chromatography to afford the alcohol **6** (2.0 g, 90%). Mp 109−111 °C. IR (neat): 1679, 1704, 1739, 3437 cm^{-1}. ^1H NMR (two conformers) (δ): 1.41 (s, major), 1.39 (s, minor), total 9H; 1.44 (s, major), 1.45 (s, minor), total 9H; 1.72 (s, 3H); 3.04 (m, 2H); 3.27 (t, *J* = 9.5 Hz, major), 3.15 (t, *J* = 10.3 Hz, minor), total 1H; 3.72 (dd, *J* = 10.6, 8.6 Hz, major), 3.67 (dd, *J* = 10.3, 8.8 Hz, minor), total 1H; 4.21 (d, *J* = 7.8 Hz, major), 4.28 (d, *J* = 7.7 Hz, minor), total 1H; 4.34 (t, *J* = 8.2 Hz, major), 4.33 (t, *J* = 8.2 Hz, minor), total 1H; 4.86 (m, 2H). Anal. Calcd for $C_{17}H_{29}NO_5$: C, 62.36; H, 8.93; N, 4.28. Found: C, 62.35; H, 8.88; N, 4.26.

4-(*tert*-Butylthio)-3-methyl-2-butenal (19). To a cold (−40 °C) solution of 1,1-dimethoxy-3-methyl-4-bromo-2-butene (**7**)[15] (35.9 g, 172 mmol) in methanol (150 mL) was added a solution of NaOH (6.9 g, 172 mmol) and *tert*-butyl mercaptan (19.4 mL, 172 mmol) in methanol (150 mL). The temperature was allowed to rise to room temperature, and the reaction mixture was stirred for 1.5 h. Water (250 mL) was added, and the resultant suspension was extracted with hexane (3 × 250 mL). The combined hexane solution was dried (Na_2SO_4) and evaporated to give (*E*)- and (*Z*)-1,1-dimethoxy-3-methyl-4-(*tert*-butylthio)but-2-enes (*E*/*Z*, 3:1). IR (neat) 1673 cm^{-1}. ^1H NMR *E* isomer (δ) 1.33 (s, 9H), 1.85 (d, *J* = 1.12 Hz, 3H), 3.20 (s, 2H), 3.31 (s, 6H), 5.03 (d, *J* = 6.33 Hz, 1H), 5.48 (dd, *J* = 6.30, 0.79 Hz, 1H); *Z* isomer: (δ) 1.31 (s, 9H), 1.88 (m, 3H), 3.25 (s, 2H), 3.33 (s, 6H), 5.08 (d, *J* = 6.35, 1H), 5.33 (dd, *J* = 6.42, 0.73 Hz, 1H). This compound was dissolved in a mixture of THF (120 mL), H_2O (12 mL), and HCO_2H (6 mL). After 4.5 h at room temperature, the reaction mixture was poured into saturated $NaHCO_3$ (300 mL) and extracted with hexane (3 × 250 mL). The combined hexane solution was dried ($NaHCO_3$ and Na_2SO_4) and evaporated. Flash chromatography (hexane−EtOAc, 8.5:1.5) gave the title compound **19** (29.6 g, 95% yield) as a mixture of two isomers (*E*/*Z*, 3:1). IR (neat) 1677, 1630 cm^{-1}. ^1H NMR *E* isomer: (δ) 1.34 (s, 9H), 2.29 (d, *J* = 1.28 Hz, 3H), 3.31 (d, *J* = 1.04 Hz, 2H), 6.07 (ddd, *J* = 8.0, 2.4, 1.2 Hz, 1H), 9.99 (d, *J* = 7.6 Hz, 1H); *Z* isomer: (δ) 1.37 (s, 9H), 2.11 (d, *J* = 1.36 Hz, 3H), 3.64 (br s, 2H), 6.05 (br d, *J* = 8 Hz, 1H,), 9.98 (d, *J* = 8.0 Hz, 1H). Anal. Calcd for $C_9H_{16}OS$: C, 62.79; H, 9.30; S, 18.60. Found: C, 62.55; H, 9.59; S, 18.33.

***tert*-Butyl 2-Isocyano-3-(*tert*-butyldimethylsiloxy)-5-methyl-6-(*tert*-butylthio)hex-4-eneoate (21).** To a solution of phenanthroline in THF (259 mL) at −40 °C was added a solution of *n*-BuLi (1.6 M in hexane, 50 mL). The temperature was reduced to −72 °C, and *tert*-butyl isocyanoacetate (**10**) (12.2 mL, 0.082 mol) was added dropwise at a rate that kept the temperature below −65 °C. After the addition was completed, more *n*-BuLi (∼2.5 mL) was added until the solution obtained deep rose color. The reaction mixture was cooled to −72 °C, and thioaldehyde **19** (14.4 g, 0.082 mol) was added in one portion. After stirring for 7 min, the reaction mixture was quenched with acetic acid (14 mL), poured into saturated $NaHCO_3$ (210 mL), and extracted with hexane (2 × 300 mL). The organic layer was dried (Na_2SO_4 and $NaHCO_3$)

and evaporated to give alcohol **20** as a mixture of four isomers. To the cold (−60 °C) solution of the alcohol **20** in CH_2Cl_2 (40 mL) were added in rapid succession 2,6-lutidine (16 mL, 0.123 mol) and TBDMSOTf (24.3 mL, 0.09 mol). The reaction mixture was stirred at the same temperature for 1 h. The temperature was allowed to rise to 0 °C, and hexane (250 mL) was added. The emulsion was washed with 1 N HCl (125 mL), saturated $NaHCO_3$ (125 mL), dried ($NaHCO_3$ and Na_2SO_4), and evaporated. The residue was purified by flash chromatography (hexane−EtOAc, 10:1) to afford the silylated alcohol **21** (23.83 g, 85% yield) as a mixture of four isomers. IR (neat) 2149 1747 cm^{-1}. ^1H NMR (δ) 0.05, 0.06, 0.08, 0.09 (s, 6H), 0.88, 0.89 (s, 9H), 1.33, 1.35, 1.37 (s, 9H), 1.49, 1.50, 151 (s, 9H), 1.82, 1,83, 1.84, 1.88 (s, 3H), 3.11−3.26 (m, 2H), 3.99, 4.14, 4.20, 4.23 (four d, J = 4.20 Hz, J = 4.91 Hz, J = 3.29 Hz, J = 4.27 Hz, 1H), 4.78−4.85 (m, 1H), 5.50−5.55 (m, 1H). Anal. Calcd for $C_{22}H_{41}NO_3SSi$: C, 61.82; H, 9.60; N, 3.28; S, 7.49. Found: C, 61.77; H, 9.82; N, 3.20; S, 7.15.

***tert*-Butyl 2-Isothiocyano-3-(*tert*-butyldimethylsiloxy)-5-methyl-6-(*tert*-butylthio)hex-4-eneoate (22).** A mixture of isocyanide **21** (0.66 g, 1.50 mmol), *tert*-butyl mercaptan (0.28 mL, 1.98 mmol), and ACN (0.066 g, 0.27 mmol) in toluene (18 mL) was refluxed for 10 min. The solvent was evaporated, and flash chromatography (hexane−EtOAc, 12:1) of the residue gave isothiocyanate **22** (0.55 g, 80% yield) as a mixture of four isomers. IR (neat) 2060, 1741 cm^{-1}. ^1H NMR (δ) 0.04, 0.05, 0.06, 0.09 (s, 6H), 0.88, 0.89, 0.90 (s, 9H), 1.33−1.36 (m, 9H), 1.50, 1.51, 1.52 (s, 9H), 1.82, 1.83 1.87 (s, 3H). 3.12−3.27 (m, 2H,), 3.83, 4.02, 4.12, 4.14 (four d, J = 3.27 Hz, J = 2.52 Hz, J = 4.62 Hz, J = 4.60 Hz, 1H), 4.75−5.00 (m, 1H), 4.80−5.52 (m, 1H). Anal. Calcd for $C_{22}H_{41}NO_3S_2Si$: C, 57.52; H, 8.93; N, 3.05; S, 13.94. Found: C, 57.80; H, 9.20; N, 2.98; S, 13.54.

2-(*tert*-Butoxycarbonyl)-3-(*tert*-butyldimethylsiloxy)-4-isopropenyl-5-thioxopyrrolidines 5 and 23. A mixture of isocyanides **21** (12.34 g, 28.9 mmol), *tert*-butyl mercaptan (3.7 mL, 32.9 mmol), and ACN (1.13 g, 4.62 mmol) in toluene (800 mL) was refluxed for about 10 min to give the isothiocyanate **22** (see above). *n*-Bu_3SnH (8.9 mL, 32.9 mmol) was added, and the reaction mixture was boiled for 15 min. The solvent was evaporated, and flash chromatography (hexane−EtOAc, 4:1) of the residue afforded the two isomers of the thiolactam **5** and **23** (9.86 g, 26.6 mmol, 92%; **5**/**23**, 1.4:1). More polar isomer **5**: mp 91.5 °C (hexane). IR (CH_2Cl_2) 3398 , 1739, 1648, 1486 cm^{-1}. ^1H NMR (δ) 0.11 (s, 3H), 0.13 (s, 3H), 0.88 (s, 9H), 1.51 (s, 9H), 1.84 (s, 3H), 3.52 (d, J = 3.04 Hz, 1H), 4.39 (d, J = 5.36 Hz, 1H), 4.61 (dd, J = 5.24, 3.52 Hz, 1H), 4.94 (s, 1H), 5.06 (s, 1H), 7.75 (br s, 1 H). Anal. Calcd for $C_{18}H_{33}NO_3SSi$: C, 58.22; H, 8.89; N, 3.77; S, 8.62. Found: C, 58.51; H, 9.15; N, 3.71; S, 8.34. Less polar isomer **23**: mp 98 °C dec. IR (CH_2Cl_2) 3395, 1739.5, 1650, 1495 cm^{-1}. ^1H NMR (δ) 0.11 (s, 3H), 0.12 (s, 3H), 0.90 (s, 9H), 1.50 (s, 9H), 1.75 (s, 3H), 3.41 (d, J = 3.8 Hz, 1H), 4.17 (dd, J = 3.24, 0.64, Hz, 1H), 4.60 (dd, J = 3.76, 3.32 Hz, 1H), 4.98 (s, 1H), 5.05 (s, 1H), 7.75 (br s, 1 H). Anal. Calcd for $C_{18}H_{33}NO_3SSi$: C, 58.22; H, 8.89; N, 3.77; S, 8.62. Found: C, 58.14; H, 8.96; N, 3.85; S, 8.56.

1,2β-Bis(*tert*-butoxycarbonyl)-3β-(*tert*-butyldimethylsiloxy)-4α-isopropenylpyrrolidine (14a). To a cold (−40 °C) solution of thiolactam **5** (5.74 g, 15.5 mmol) and $(BOC)_2O$ (4 mL, 18.7 mmol) in THF (45 mL) was added a solution of DMAP (0.307 g, 2.5 mmol) in THF (5 mL). The reaction mixture was kept at −40 °C for 10 min (the reaction was monitored by TLC (hexane/EtOAc, 9.5:2) and color (if the reaction starts turning red, it must be stopped) and then was dissolved in hexane (800 mL) and washed with saturated NaH_2PO_4 (2 × 80 mL). The hexane layer was separated, dried (Na_2SO_4), and evaporated under reduced pressure. The residue (thiolactam **24a**) was dissolved in toluene (375 mL). *n*-Bu_3-SnH (9.2 mL, 34.2 mmol) and AIBN (0.394 g, 2.4 mmol) were added, and the reaction mixture was immersed in a hot oil bath (∼200 °C) for 2 h, and then the toluene was evaporated. The residue was dissolved in pentane (40 mL) and extracted with CH_3CN (10 × 250 mL). The combined CH_3CN layers were evaporated and flash chromatography of the residue gave the ester **14a** (5.69 g, 13 mmol, 84% yield). IR; ^1H NMR are described above.

1,2β-Bis(*tert*-butoxycarbonyl)-3α-hydroxy-4β-isopropenylpyrrolidine (25). To a cold (−40 °C) solution of thiolactam **23** (4.73 g, 12.7 mmol) and $(BOC)_2O$ (3.3 mL, 15.2 mmol) in THF (40 mL) was added a solution of DMAP (0.236 g, 1.93 mmol) in THF (4 mL). The reaction mixture was kept at −40 °C. The reaction was monitored by TLC (hexane−EtOAc, 8.5:1.5) and color (reddish color is indicative of double bond migration to exocyclic position). In case reddish color appears the reaction should be immediately quenched. After consumption of starting material, hexane (800 mL) was added and the mixture was washed with saturated NaH_2PO_4 (2 × 80 mL). The hexane layer was separated, dried (Na_2SO_4), and evaporated under reduced pressure. The residue which consisted of crude thiolactam **24b** was dissolved in toluene (300 mL). *n*-Bu_3SnH (7.5 mL, 27.9 mmol) and AIBN (0.32 g, 1.95 mmol) were added, and the reaction mixture was immersed in a hot oil bath (∼200 °C). After the reaction was completed (∼2 h), the toluene was evaporated. The residue was dissolved in pentane (40 mL) and extracted with CH_3CN (10 × 250 mL). The combined CH_3CN layers were evaporated and flash chromatography of the residue gave the ester **14b** (3.48 g, containing ∼10% $(BOC)_2O$). IR (neat) 1739, 1706, 1648 cm^{-1}. ^1H NMR (δ) 0.038, 0.050 (2s, 3H), 0.09, 0.10 (2s, 3H), 0.86, 0.877, 0.882, 0.89 (4s, 9H), 1.74 (br s, 3H), 2.69−2.79 (m, 1H), 3.29−3.37 (m, 1H), 3.65, 3.78 (2 dd, J = 8.14, 13.1 Hz, J = 8.10, 11.02 Hz, 1H), 3.92, 4.00 (2 d, J = 4.08 Hz, J = 4.48 Hz, 1H), 4.25−4.31 (m, 1H), 4.90 (br s, 2H). A mixture of compound **14b** (3.10 g, 7.04 mmol), AcOH (0.4 mL, 7.15 mmol), and TBAF (1 N solution in THF, 15 mL) was stirred at room temperature overnight. The solution was poured into water (30 mL) and extracted with ether (2 × 40 mL). The organic layer was dried (Na_2SO_4), the solvent was evaporated, and flash chromatography (hexane−EtOAc, 6:1) of the residue gave the alcohol **25** (1.62 g, 40% yield from **23**). IR (Nujol) 3354, 1744, 1663 cm^{-1}. ^1H NMR (δ) 1.36, 1.38, 1.41, 1.42 (4s, 18H), 1.69 (br s, 3H), 2.1 (br, OH), 2.59−2.70 (m, 1H), 3.17, 3.20 (2 app t, J = 11.02 Hz, J = 11.20 Hz, 1H), 3.63, 3.78 (2 dd, J = 8.26, 10.7 Hz, J = 7.96, 10.96 Hz, 1H), 3.87, 3.91 (2 d, J = 6.40 Hz and J = 6.36 Hz, 1H), 4.01−4.10 (m, 1H), 4.84, 4.85 (s and t, J = 1.26 Hz, 2H). Anal. Calcd for $C_{17}H_{29}NO_5$: C, 62.36; H, 8.93; N, 4.28. Found: C, 62.54; H, 8.98; N, 4.34.

1,2β-Bis(*tert*-butoxycarbonyl)-3β-(*p*-toluenesulfonyloxy)-4α-isopropenylpyrrolidine (27). To a solution of alcohol **6** (2.0 g, 6.1 mmol) and phenanthroline (*ca.* 1 mg) in THF (20 mL) at −72 °C was added BuLi (4 mL of 1.6 M solution, 6.1 mmol) until deep rose color of phenanthroline was obtained. A solution of *p*-toluenesulfonyl chloride (2.34 g, 12.3 mmol) in THF (2 mL) was added, the reaction mixture was stirred 15 min at −72 °C, and the temperature was slowly raised to 20 °C (30 min). The reaction mixture was evaporated and the residue was dissolved in EtOAc−hexane (1:5 mixture, 30 mL), washed with water, dried, and evaporated. The residue was separated by flash chromatography to afford the tosylate **27** (2.85 g, 97%). IR (neat): 1702, 1738 cm^{-1}. ^1H NMR (two conformers) (δ): 1.36 (s, major), 1.48 (s, minor), total 3H, 1.42 (s, major), 1.43 (s, minor), total 9H, 1.52 (s, major), 1.47 (s, minor), total 9H, 2.46 (s, 3H), 3.09 (m, 1H), 3.22 (dd, J = 8.5, 10.7 Hz, major), 3.22 (m, minor), total 1H, 3.69 (dd, J = 8.8, 10.7 Hz, major), 3.69 (m, minor), total 1H, 4.49 (d, J = 7.6 Hz, 1H), 4.43 (d, J = 7.5 Hz, minor), total 1H, 4.66, 4.68 (2s, major), 4.73 (m, minor), total 2H, 4.84 (t, J = 8 Hz, major), 4.87 (m, minor), total 1H, 7.33 (d, J = 8.2 Hz, 2H); 7.77 (d, J = 8.2 Hz, 2H). Anal. Calcd for $C_{24}H_{35}NO_7S$: C, 59.88; H, 7.28; N, 2.91; S, 6.65. Found: C, 59.60; H, 7.52; N, 2.78; S, 6.54.

1,2β-Bis(*tert*-butoxycarbonyl)-3β-(*p*-toluenesulfonyloxy)-4α-[2′-chloro-1′-[[(methoxycarbonyl)methyl]thio]-1′-methylethyl]pyrrolidine (28). To a solution of $(SCH_2CO_2Me)_2$ (0.31 g, 1.5 mmol), methyl mercaptoacetate (1.06 g, 10 mmol), and pyridine (0.87 g, 11 mmol) in dry CH_2Cl_2 (8 mL) at −70 °C was added sulfuryl chloride (1.35 g, 10 mmol). The reaction mixture was warmed to 0 °C and kept 10 min at 0 °C. The resulting solution of crude $ClSCH_2CO_2Me$ was added dropwise to precooled (−70 °C) solution of tosylate **27** (4.60 g, 9.56 mmol) in CH_2Cl_2 (20 mL). The reaction mixture was

stirred for 10 min at −70 °C, warmed to 0 °C, neutralized to pH 6 with several drops of pyridine, and evaporated. The residue was triturated with EtOAc−hexane (1:9, 5 mL), and the precipitate crude crystals were collected and extracted with EtOAc−hexane (1:1). Pyridine hydrochloride was filtered off, and the filtrate was evaporated to afford the crystalline chloroalkyl sulfide **28** (4.81 g, 7.7 mmol, 81%), mp 119−120 °C. IR (neat): 1705, 1737 cm^{-1}. ^1H NMR (two conformers) (δ): 1.24 (s, major), 1.35 (s, minor), total 3H; 1.42 (m, 18H); 2.47 (s, 3H); 3.16−3.31 (m, 4H); 3.50−3.78 (m, 6H); 4.57 (d, J = 7.7 Hz, major), 4.46 (d, J = 7.7, minor), total 1H; 5.36 (dd, J = 7.8, 9 Hz, major), 5.35 (m, minor), total 1H; 7.37 (d, J = 8.1 Hz, 2H); 7.86 (d, J = 8.3 Hz, 2H). Anal. Calcd for $C_{27}H_{40}ClNO_9S_2$: C, 52.36; H, 6.41; N, 2.24; S, 10.25. Found: C, 52.13; H, 6.69; N, 2.02; S, 9.85.

1,2β-Bis(*tert*-butoxycarbonyl)-3β-(*p*-toluenesulfonyloxy)-4α-[2′-chloro-1′-[[(methoxycarbonyl)methyl]sulfonyl]-1′-methylethyl]pyrrolidine (29). To a solution of chloroalkyl sulfide **28** (2.14 g, 3.45 mmol) in methylene chloride (5 mL) at −20 °C was added MCPBA (2.23 g of 80% reagent, 3 equiv), and the reaction mixture was slowly warmed to 20 °C and stirred 30 min at 60 °C. The resulting suspension was poured into EtOAc−hexane (1:1 mixture, 50 mL), washed with saturated $NaHCO_3$ solution, dried (Na_2SO_4), and evaporated. The residue was purified by flash chromatography to afford the chloroalkyl sulfone **29** (2.1 g, 93%). IR (neat): 1702, 1743 cm^{-1}. ^1H NMR (two conformers) (δ),1.39 (s, 9H); 1.44 (s, major), 1.43 (s, minor), total 9H; 1.45 (s, 3H), 2.49 (s, major), 2.48 (s, minor), total 3H; 3.58 (m, 2H); 3.78−4.31 (m, 8H), 4.51 (d, J = 7.7 Hz, major), 4.35 (d, J = 7.8 Hz, minor), total 1H ; 5.22 (m, 1H), 7.40 (d, J = 8.3 Hz, 2H), 7.88 (d, J = 8.3 Hz, 2H). Anal. Calcd for $C_{27}H_{40}ClNO_{11}S_2$: C, 49.81; H, 6.09; N, 2.13; S, 9.75. Found: C, 49.84; H, 6.33; N, 2.01; S, 9.32.

1-(Chloromethyl)-1-methyl-2,2-dioxo-3-(methoxycarbonyl)-4β,5-bis(*tert*-butoxycarbonyl)-hexahydrothieno-[3α,4α-*c*]pyrrolidine (30). To a solution of chloroalkyl sulfone **29** (1.48 g, 2.28 mmol), methanol (3 mL), and methyl formate (1.5 mL) in THF (60 mL) was added potassium methylate (350 mg, 5 mmol). The reaction mixture was stirred at 20 °C for 3 h, neutralized with AcOH, and evaporated. The residue was dissolved in EtOAc−hexane (3:7 mixture, 50 mL), washed with water, dried, and evaporated. The residue was purified by flash chromatography to afford the title cyclic sulfone **30** (779 mg, 72%). IR (neat): 1702, 1748 cm^{-1}. ^1H NMR (δ): 1.43, 1.48, 1.49 (3s, 18H), 1.60 (s, 3H), 3.06 (m, 1H), 3.43 (t, J = 8.7 Hz, 1H), 3.68 (m, 2H), 3.80−4.01 (m, 6H), 4.07, 4.19 (2s, 1H). Anal. Calcd for $C_{20}H_{32}ClNO_8S$: C, 49.84; H, 6.69; N, 2.90; S, 6.65. Found: C, 50.14; H, 6.53; N, 3.14; S, 6.33.

1,2β-Bis(*tert*-butoxycarbonyl)-3α-[(methoxycarbonyl)-methyl]-4α-isopropenylpyrrolidine (31). Cyclic sulfone **30** (0.74 g, 1.5 mmol) was mixed with a solution of SmI_2 (50 mL of 0.1 M in THF, 5 mmol) and methanol (2 mL). The reaction mixture was left for 20 min at 20 °C and quenched with aqueous $NaHCO_3$ (10 mL). The resulting suspension was extracted with EtOAc−hexane (1:1 mixture, 2 × 100 mL) and EtOAc (2 × 50 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated, and the residue was purified by flash chromatography to afford the title pyrrolidine **31** (413 mg, 72%). IR (neat): 1705, 1742 cm^{-1}. ^1H NMR (two conformers) (δ): 1.43 (s, major), 1.47 (s, minor), total 9H, 1.49 (s, major), 1.48 (s, minor), total 9H; 1.69 (s, 3H); 2.26 (dd, J = 8.7, 16.5 Hz, major), 2.33 (dd J = 5.9, 16.5 Hz, major), 2.30 (m, minor), total 2H; 2.80 (m, 1H); 2.97 (m, 1H); 3.49 (dd, J = 8.2, 10.8 Hz, major), 3.42 (dd, J = 7.9, 10.7 Hz, minor), total 1H; 3.67 (dd, J = 7.3, 10.8 Hz, major), 3.61 (dd, J = 7.2, 10.7 Hz, minor), total 1H; 3.70 (s, major), 3.68 (s, minor), total 3H; 3.93 (d, J = 3.5 Hz, major), 4.01 (d, J = 3.7 Hz, minor), total 1H; 4.69 (s, 1H), 4.91 (s, 1H). Anal. Calcd for $C_{20}H_{33}NO_6$: C, 62.66; H, 8.62; N, 3.66. Found: C, 62.87; H, 8.90; N, 3.53.

2β-Carboxy-4α-isopropenyl-3α-pyrrolidineacetic Acid, (±)-Kainic Acid (1). To a solution of pyrrolidine **31** (300 mg, 0.79 mmol) in methylene chloride (2 mL) was added trifluoroacetic acid (2 mL). The reaction mixture was left for 2 h at 20 °C, toluene (10 mL) was added, the mixture was evaporated, the residue was dissolved in methanol (0.5 mL), and aqueous NaOH (1 M, 2mL) was added. After 2 h the reaction mixture was neutralized with AcOH, washed with ether (5 mL), and chromatographed on an anion-exchange column (Dowex 1 × 8, charged with acetate-ion, eluent water → 5% aqueous AcOH) to afford racemic kainic acid (**1**) as monohydrate (142 mg, 78%). IR (KBr): 1617, 1720, 3450 cm^{-1}. ^1H NMR (D_2O, δ): 1.75 (s, 3H); 2.38 (dd, J = 16.8, 8.3 Hz, 1H); 2.47 (dd, J = 6.3, 16.8 Hz, 1H); 3.05 (m, 2H); 3.42 (t, J = 11.6 Hz, 1H); 3.62 (dd, J = 7.2, 11.9 Hz, 1H); 4.09 (d, J = 3.3 Hz, 1H); 4.75 (s, 1H); 5.04 (s, 1H), all identical to authentic sample from Sigma. Anal. Calcd for $C_{10}H_{15}NO_4 \cdot H_2O$: C, 51.95; H, 7.36; N, 6.06. Found: C, 51.73; H, 7.33; N, 5.73.

Reduction of 1-(Chloromethyl)-1-methyl-2,2-dioxo-3-(methoxycarbonyl)-4β,5-bis(tert-butoxycarbonyl)-hexahydrothieno[3α,4α-*c*]pyrrolidine (30) with *n*-Bu_3SnH. To the solution of chloroalkyl sulfone **30** (425 mg, 0.89 mmol) and ACN (86 mg, 0.35 mmol) in toluene (50 mL) under reflux was added by syringe pump a solution of *n*-Bu_3SnH (0.52 g, 1.77 mmol). The addition was complete within 2 h, the reaction mixture was refluxed for an additional 30 min and evaporated. The residue was dissolved in 50 mL of MeCN and extracted with 20 mL of pentane, and the pentane solution was extracted with 30 mL of MeCN. The combined MeCN solutions were evaporated, the residue was separated by flash chromatography to afford kainate **31** contaminated with 30% of *n*-Bu_3SnCl (64 mg, *ca.* 12% yield) and recovered starting material (242 mg, contaminated with 10% of *n*-Bu_3SnCl, *ca.* 50% yield).

1,2β-Bis(*tert*-butoxycarbonyl)-3α-(*p*-toluenesulfonyloxy)-4β-isopropenyl pyrrolidine (38). To a solution of alcohol **25** (2.5 g, 7.7 mmol) and phenanthroline (*ca.* 1 mg) in THF (20 mL) at −72 °C was added BuLi (4.8 mL of 1.6 M solution, 7.7 mmol) until deep rose color of phenanthroline was reached. Solution of *p*-toluenesulfonyl chloride (2.9 g, 15 mmol) in THF (2 mL) was added, the reaction mixture was stirred for 15 min at −72 °C, and the temperature was slowly (30 min) raised to 20 °C. The reaction mixture was evaporated, and the residue was dissolved in EtOAc−hexane (1:5 mixture, 100 mL) washed with water, dried, and evaporated. The residue was separated by MPLC to afford the tosylate **38** (3.52 g, 7.3 mmol, 95%). IR (neat): 1706, 1745 cm^{-1}. ^1H NMR (two conformers) (δ): 1.41 (s, major), 1.43 (s, minor), total 9H; 1.46 (s, 9H); 1.59 (s, major), 1.67 (s, minor), total 3H; 2.46 (s, 3H); 2.83 (m, major), 2.95 (m, minor), total 1H; 3.46 (dd, J = 7.0, 11.2 Hz, major), 3.22 (m, minor), total 1H; 3.69 (dd, J = 8.2, 11.2 Hz, major), 3.69 (m, minor), total 2H; 4.23 (d, J = 2.7 Hz, 1H); 4.78 (d, J = 4.3 Hz, major), 4.78 (d, J = 4.6 Hz, minor), total 2H; 5.05 (dd, J = 2.9, 4.6 Hz, 1H); 7.35 (d, J = 8.0 Hz, 2H); 7.81 (m, 2H). Anal. Calcd for $C_{24}H_{35}NO_7S$: C, 59.88; H, 7.28; N, 2.91; S, 6.65. Found: C, 59.58; H, 7.50; N, 2.75; S, 7.01.

1,2β-Bis(*tert*-butoxycarbonyl)-3α-(*p*-toluenesulfonyloxy)-4β-[2′-chloro-1′-[[(methoxycarbonyl)methyl]thio]-1′-methylethyl]pyrrolidine (39). To a solution of ($SCH_2CO_2Me)_2$ (0.31 g, 1.5 mmol), methyl mercaptoacetate (1.06 g, 10 mmol), and pyridine (0.87 g, 11 mmol) in dry methylene chloride (8 mL) at −70 °C was added sulfuryl chloride (1.35 g, 10 mmol). The reaction mixture was warmed to 0 °C and kept 10 min at 0 °C. The resulting solution of crude $ClSCH_2CO_2Me$ (7 mL, 1.02 equiv) was added dropwise to a precooled (−70 °C) solution of tosylate **38** (3.3 g, 6.9 mmol) in methylene chloride (20 mL). The reaction mixture was stirred 10 min at −70 °C, warmed to 0 °C, neutralized to pH 6 with pyridine, and evaporated. The residue was dissolved with EtOAc−hexane (1:5 mixture, 50 mL), washed with saturated aqueous NaH_2PO_4 (2 × 10 mL), dried, and evaporated. The residue was triturated with 10% EtOAc−hexane mixture (5 mL), and the formed crystals of chloroalkyl sulfide **39** (1.50 g, 2.4 mmol) were filtered. The filtrate was evaporated, and the residue was separated by MPLC to afford more of the title chloroalkyl sulfide **39** (0.87 g, 1.4 mmol) and starting material **38** (1.24 g, 2.6 mmol). Yield 2.37 g (56%, the product consists of two diastereomers with 5:1 ratio), and 1.24 g (37%) of starting material was recovered. IR (neat): 1707, 1742 cm^{-1}. ^1H NMR, Major product (two conformers) (δ): 1.30 (s, major), 1.29 (s, minor), total 3H; 1.39−1.53 (m, 18H); 2.47 (s, 3H); 3.16−3.40

(m, 4H); 3.48−3.92 (m, 6H); 4.40 (s, major), 4.38 (s, minor), total 1H; 5.44 (d, J = 3.7 Hz, major), 5.49 (d, J = 3.7 Hz, minor), total 1H; 7.38 (d, J = 8.4 Hz, 2H); 7.92 (d, J = 8.1 Hz, 2H). ^{1}H NMR of minor product shows different peaks at 4.30 (s, major), 4.28 (s, minor), total; 5.28 (d, J = 3.7 Hz, major), 5.31 (m, minor), total 1H. Anal. Calcd for $C_{27}H_{40}NO_9S_2Cl$: C, 52.36; H, 6.41; N, 2.24; S, 10.25; Cl, 5.68. Found: C, 52.35; H, 6.60; N, 2.21; S, 10.22; Cl, 6.00.

Back Conversion of 1,2*β*-Bis(*tert*-butoxycarbonyl)-3α-(*p*-toluenesulfonyloxy)-4*β*-[2′-chloro-1′-[[(methoxycarbonyl)methyl]thio]-1′-methylethyl]pyrrolidine (39) into 1,2*β*-Bis(*tert*-butoxycarbonyl)-3α-(*p*-toluenesulfonyloxy)-4*β*-isopropenylpyrrolidine (38). To a solution of chloroalkyl sulfide **39** (44 mg, 0.07 mmol) in THF (1 mL) at −40 °C was added a solution of MeOK in THF (0.1 M, 0.5 mL, 0.05 mmol). The reaction mixture was warmed to room temperature and evaporated, and the residue was purified by flash chromatography to afford tosylate **38** (12 mg, 50% yield based on MeOK). The product was TLC identical to a sample of tosylate **38**.

1,2*β*-Bis(*tert*-butoxycarbonyl)-3α-(*p*-toluenesulfonyloxy)-4*β*-[2′-chloro-1′-[[(methoxycarbonyl)methyl]sylfonyl]-1′-methylethyl]pyrrolidine (40). To the solution of chloroalkyl sulfide **39** (1.4 g, 2.3 mmol) in methylene chloride (5 mL) at −20 °C was added MCPBA (1.46 g of 80% reagent, 3 equiv), and the reaction mixture was slowly warmed to 20 °C and stirred 20 min at 50 °C. The resulting suspension was poured into 50 mL of 20% EtOAc−hexane mixture, washed with saturated $NaHCO_3$ solution, dried (Na_2SO_4), and evaporated. The residue was purified by flash chromatography to afford the chloroalkyl sulfone **40** (1.38 g, 93%). IR (neat): 1707, 1748 cm^{-1}. ^{1}H NMR (δ, two diastereomers, two conformers): 1.40−1.54 (m, 21H, 2 × t-Bu, CH_3); 2.47 (s, 3H, $ArCH_3$);3.00−3.50 (m, 2H); 3.80−4.30 (m, 6H); 5.45−5.60 (m, 1H); 7.38 (m, 2H); 7.90 (m, 2H). Anal. Calcd for $C_{27}H_{40}ClNO_{11}S_2$: C, 49.81; H, 6.09; N, 2.13; S, 9.75; Cl, 5.41. Found: C, 49.52; H, 6.31; N, 1.97; S, 9.31; Cl, 5.79.

1-(Chloromethyl)-1-methyl-2,2-dioxo-3-(methoxycarbonyl)-4*β*,5-Bis(*tert*-butoxycarbonyl)-hexahydrothieno-[3a,4a-c]pyrrolidine (41). To a solution of chloroalkyl sulfone **40** (1.32 g, 2.0 mmol) in THF (250 mL) at −70 °C was added potassium methylate (1.15 g, 10 mmol). The reaction mixture was stirred 5 min at −70 °C, 2 h at 20 °C, neutralized with AcOH, and evaporated. The residue was purified by flash chromatography to afford title cyclic sulfone **41** (730 mg, 75%). IR (neat): 1702, 1748 cm^{-1}. ^{1}H NMR (δ): 1.43, 1.48, 1.49 (3s, 18H), 1.60 (s, 3H), 3.06 (m, 1H), 3.43 (t, J = 8.7 Hz, 1H), 3.68 (m, 2H), 3.80−4.01 (m, 6H), 4.07, 4.19 (2s, 1H). Calcd for $C_{20}H_{32}ClNO_8S$: C, 49.84; H, 6.69; N, 2.90; Cl, 7.35. Found: C, 50.14; H, 6.93; N, 2.73; Cl, 7.63.

Supporting Information Available: A copy of the ^{1}H NMR spectrum of compound **9,** 3D structural formula, ORTEP drawing, and details of X-ray data aquisition for 1,2β-bis(*tert*-butoxycarbonyl)-3β-hydroxy-4α-isopropenylpyrrolidine (**6**) (4 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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