

Stereocontrolled Construction of Substituted Pyrrolidines based on Intramolecular Protodesilylation Reaction. Enantiospecific Synthesis of (–)-Kainic Acid and (+)-Allokainic Acid from L-Serine

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Novel stereocontrolled enantiospecific syntheses of (–)-kainic acid and (+)-allokainic acid have been achieved starting from L-serine *via* two modes of C-2 and C-3 side chain-directed intramolecular protodesilylations of 4-(trimethylsilyl-methyl)ethylidenepyrrolidines.

In the course of a search¹ for the synthetic utility of 1-trimethylsilylbuta-2,3-dienes **1**, we have recently found that addition of iodine² to 2-alkyl-1-trimethylsilylbuta-2,3-dienes (**1**; R¹ = alkyl, R² = R³ = H) takes place at the terminal double bond regioselectively and the allylsilane moiety remains intact under the reaction conditions to give *vic*-diiodoallylsilanes **2** in almost quantitative yields.† This finding prompted us to propose a new strategy leading to the kainoid amino acids³ which have attracted considerable interest owing to neuroexcitatory properties.⁴ As outlined in Scheme 1, we envisioned that two modes of protodesilylations⁵ of the allylsilane **3**, possibly accessible from **2**, would be achieved stereoselectively by intramolecular delivery of proton from the suitably functionalized C-2 or C-3 appendage as in **4** and **5**. We report here stereocontrolled enantiospecific syntheses of (–)-kainic acid **6**⁶ and (+)-allokainic acid **7**,⁷ the parent members of the kainoids, from L-serine **8** based upon this strategy.

L-Serine **8** was first converted to the protected 2-amino-propane-1,3-diol **9**,‡ [α]_D²⁷ +5.3 (*c* 0.98, CHCl₃), by a

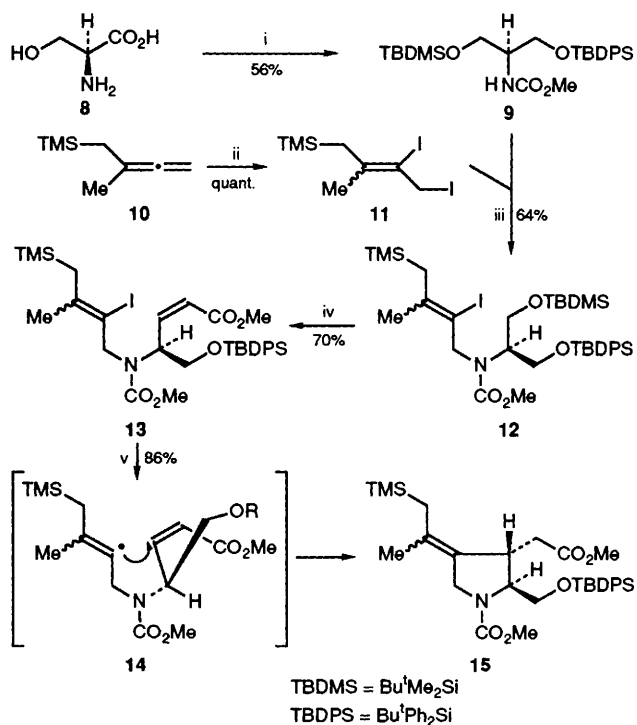
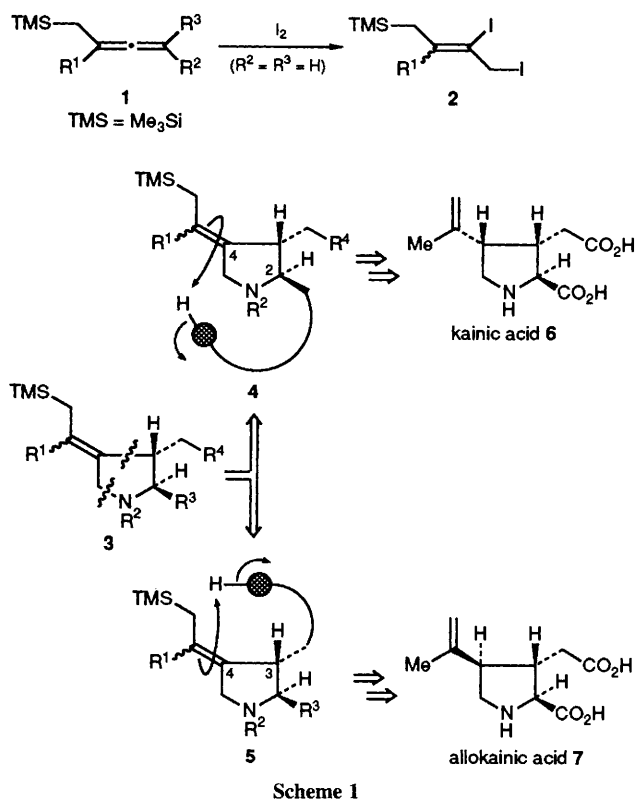
five-step sequence. After reaction of **9** with potassium hydride in dimethylformamide (DMF) at –40 °C for 3.5 h, the resulting anion was allowed to react with the *vic*-diiodoallylsilane **11**, freshly prepared from **10** by quantitative addition of iodine,§ to give the iodoolefin **12** as an inseparable mixture of olefinic geometrical isomers.¶ Upon sequential selective desilylation, Swern oxidation and stereocontrolled olefination,⁸ **12** yielded the *Z*-α,β-unsaturated ester **13** in good overall yield. Treatment of **13** with tributyltin hydride in the presence of a catalytic amount of azoisobutyronitrile (AIBN) in boiling benzene led to highly diastereoselective radical

§ After the reaction of **10** with iodine was complete (see step ii in Scheme 2), the solvent was evaporated *in vacuo* using a vacuum pump below –20 °C in order to avoid the decomposition of **11**. The compound **10**, b.p. 105–106 °C (760 mmHg), was prepared from but-2-yn-1-ol by two steps in 65% yield: i, BuⁿLi, *p*-Me-C₆H₄SO₂Cl, THF, –78 °C; ii, 6 equiv. Me₃SiCH₂MgCl, 6 equiv. LiCl, 3 equiv. CuCN, THF, 0 °C, then the toluene-*p*-sulfonate was added, –78 °C). Cf.: M. Montury, B. Psaume and J. Gore, *Tetrahedron Lett.*, 1980, 21, 163; A. Yanagisawa, Y. Noritake, N. Nomura and H. Yamamoto, *Synlett*, 1991, 25.

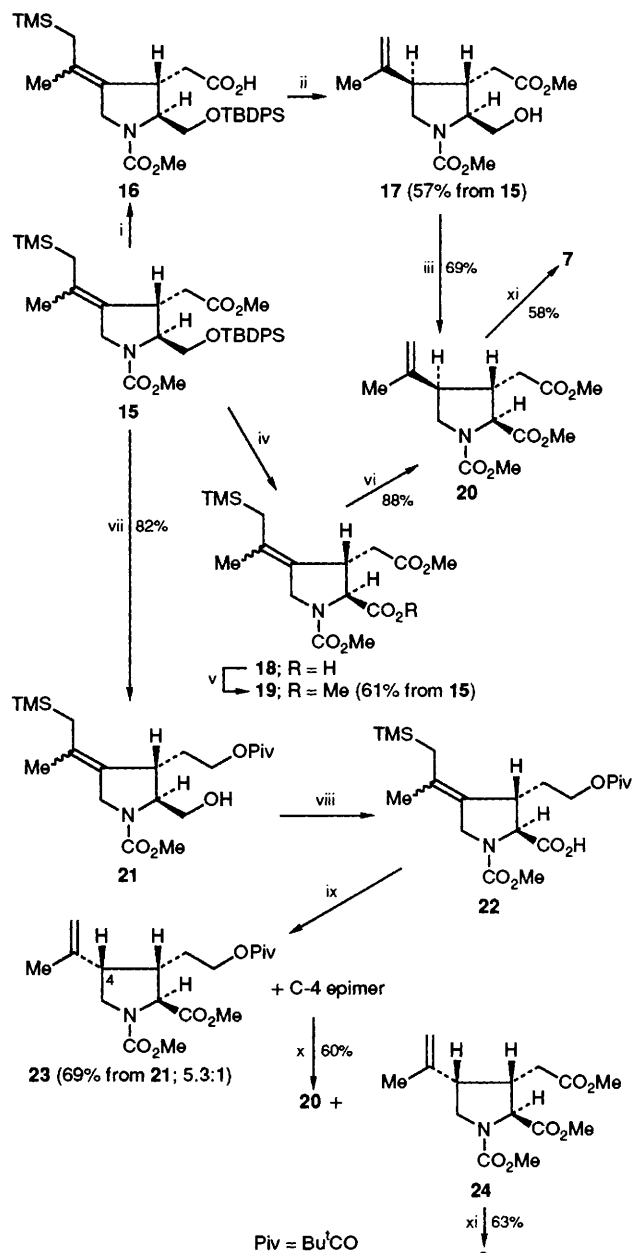
† Details of this finding will be reported in due course.

‡ All new compounds exhibited satisfactory spectral (¹H NMR, IR) and analytical (high-resolution mass and/or combustion) data.

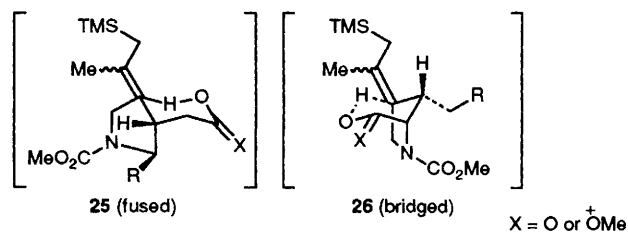
¶ Compounds **11–16**, **18**, **19**, **21** and **22** consist of the olefinic geometrical isomers.



Scheme 2 Reagents and conditions: i, (a) MeOCOC₁, 1 mol dm⁻³ NaOH, dioxane, (b) CH₂N₂, Et₂O, (c) TBDMSCl, Et₃N, 4-dimethylaminopyridine (DMAP); catalyst, CH₂Cl₂, (d) NaBH₄, MeOH, (e) TBDPSCI, imidazole, DMF; ii, 0.75 equiv. I₂, CH₂Cl₂, -78 °C; iii, 1.3 equiv. KH, 1.7 equiv. 11, DMF, -40 °C; iv, (a) *p*-TsOH·H₂O (catalyst), MeOH, (b) (COCl)₂, dimethyl sulfoxide DMSO, CH₂Cl₂, -60 °C then Et₃N, (c) (TMS)₂NK, 18-crown-6·MeCN (CF₃CH₂O)₂P(O)CH₂CO₂Me, THF, -78 to -40 °C; v, Bu₃SnH, AIBN (catalyst), benzene, reflux



Scheme 3 Reagents and conditions: i, 5% KOH in MeOH; ii, (a) 3 equiv. BF₃·Et₂O, CH₂Cl₂ (3–5 × 10⁻² mol dm⁻³), (b) CH₂N₂, Et₂O, (c) 46% HF, MeCN; iii, (a) 8 mol dm⁻³ H₂CrO₄, acetone, (b) CH₂N₂, Et₂O; iv, (a) 46% HF, MeCN; (b) (COCl)₂, DMSO, CH₂Cl₂, -60 °C then Et₃N, (c) NaClO₂, NaHPO₄, 2-methylbut-2-ene, Bu^tOH–H₂O (4:1); v, CH₂N₂, Et₂O; vi, 2 equiv. BF₃·2AcOH, CH₂Cl₂ (3–5 × 10⁻² mol dm⁻³); vii, (a) diisobutylaluminium hydride (DIBAL), CH₂Cl₂, -78 °C, (b) Bu^tCOCl Et₃N, DMAP (catalyst), CH₂Cl₂, -60 °C then Et₃N, (b) NaClO₂, NaHPO₄, 2-methylbut-2-ene, Bu^tOH–H₂O (4:1); ix, (a) 10 equiv. BF₃·Et₂O, CH₂Cl₂ (1.7 × 10⁻³ mol dm⁻³), (b) CH₂N₂, Et₂O; x, (a) 1 mol dm⁻³ NaOH–MeOH (2:1), (b) 8 mol dm⁻³ H₂CrO₄, acetone, (c) CH₂N₂, Et₂O; xi, 40% aq. NaOH–MeOH (1:1), reflux



cyclisation⁹ to give the (trimethylsilylmethyl)ethylidenepyrrolidine **15** exclusively. The stereochemical outcome of this cyclisation can be interpreted by assuming a transition state resembling **14** on the basis of A^{1,3} type of steric interactions.¹⁰

With the required pivotal pyrrolidine **15** in hand, we then examined the crucial protodesilylation step using various substrates which were prepared from **15**. Upon treatment of **16** with BF₃·Et₂O in methylene chloride at ambient temperature, facile protodesilylation took place with complete diastereoselectivity and the 3,4-*trans*-pyrrolidine **17**, [α]_D²⁹ -31.7 (c 0.71, CHCl₃), was obtained exclusively after esterification followed by desilylation. On the other hand, the BF₃·Et₂O-mediated protodesilylation of **22** under diluted conditions (1.7 × 10⁻³ mol dm⁻³ **22** in CH₂Cl₂) proceeded with opposite diastereoselectivity to give the 3,4-*cis*-pyrrolidine **23** and its C-4 epimer in a ratio of 5.3:1|| after esterification. In this case, the diastereoselectivity turned out to be somewhat concentration dependent. For example, when this reaction was carried out using a 6.8 × 10⁻³ mol dm⁻³ CH₂Cl₂ solution of **22**, the ratio dropped to 2.6:1. These results apparently suggest that the protodesilylations of **16** and **22** preferentially occurred in intramolecular fashion *via* **25** and **26**, respectively. In the case of the dimethyl ester **19**, use of BF₃·2AcOH in place of BF₃·Et₂O was found to cause highly diastereoselective protodesilylation to yield **20** as the sole product. This process is also assumed to be an intramolecular reaction** *via* a transition state resembling **25**. Interestingly, the BF₃·Et₂O mediated reaction of **18** afforded the corresponding protodesilylated products with the 3,4-*trans*-stereochemistry predominating (10:1),|| suggesting the preference of a fused mode transition state rather than a bridged mode transition state in the case where these interventions are competitive.

Without separation, a mixture of **23** and its C-4 epimer obtained from **22** was successively subjected to hydrolysis, Jones oxidation and esterification to give the dimethyl ester **24** which was cleanly separated from its C-4 epimer **20** by silica gel column chromatography. The dimethyl ester **20**, [α]_D²⁹ -34.5 (c 1.33, CHCl₃), obtained from **17** and **19** separately, exhibited spectral properties (¹H NMR, IR, mass) in accord with those reported.^{8c} Concerning the dimethyl ester **24**, [α]_D²⁹ -25.3 (c 0.72, CHCl₃), its structure was confirmed by spectroscopic (¹H NMR, IR, mass) and chromatographic comparisons with authentic material, [α]_D²⁹ -25.6 (c 0.86, CHCl₃).^{7c} Both dimethyl esters **20** and **24** were determined to be formed in nearly 100% enantiomeric excess by ¹H NMR (500 MHz) spectroscopic analysis of the corresponding

N-methyl-diMTPA esters [MTPA = α -methoxy- α -(trifluoromethyl)phenylacetic acid] which were derived from **20** and **24** by LiAlH₄ reduction followed by esterification using (*R*)- or (*S*)- α -methoxy- α -trifluoromethylphenylacetyl chloride. Finally, following the literature precedent,^{7c,8c} syntheses of (-)-kainic acid **6**, [α]_D²⁹ -14.8 (c 0.85, H₂O), m.p. 244–247 °C (decomp.) {lit.^{7a,b} [α]_D²² -14.2 (c 0.23, H₂O), m.p. 243–244 °C (decomp.)}, and (+)-allokainic acid **7**, [α]_D²⁷ +6.9 (c 0.91, H₂O), m.p. 239–242 °C (decomp.) {lit.^{8a} [α]_D²³ +7.4 (c 0.7, H₂O), m.p. 238–242 °C (decomp.)}, were accomplished by alkaline hydrolysis of **24** and **20**.

The present work illustrates a new methodology of general value for the stereocontrol in cyclic system as well as the synthetic utility of 1-trimethylsilylbuta-2,3-dienes.

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|| Determined by ¹H NMR (500 MHz) analysis.

** The BF₃·2AcOH-mediated reaction of the corresponding *p*-methoxyphenyl ether of **21** proceeded with poor diastereoselectivity (3,4-*trans*:*cis* = 2:1; 81% yield) resulting from intermolecular protodesilylation. This result allows us to postulate that the protodesilylation of **19** leading to exclusive formation of **20** should be an intramolecular process.