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-(trimethylsilylmethyl)ethylidenepyrrolidines.

In the course of a search[1] for the synthetic utility of 1-trimethylsilylbuta-2,3-dienes **1**, we have recently found that addition of iodine[2] to 2-alkyl-1-trimethylsilylbuta-2,3-dienes (**1**; R^1 = alkyl, R^2 = R^3 = 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 acids[3] which have attracted considerable interest owing to neuroexcitatory properties.[4] As outlined in Scheme 1, we envisioned that two modes of protodesilylations[5] 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.

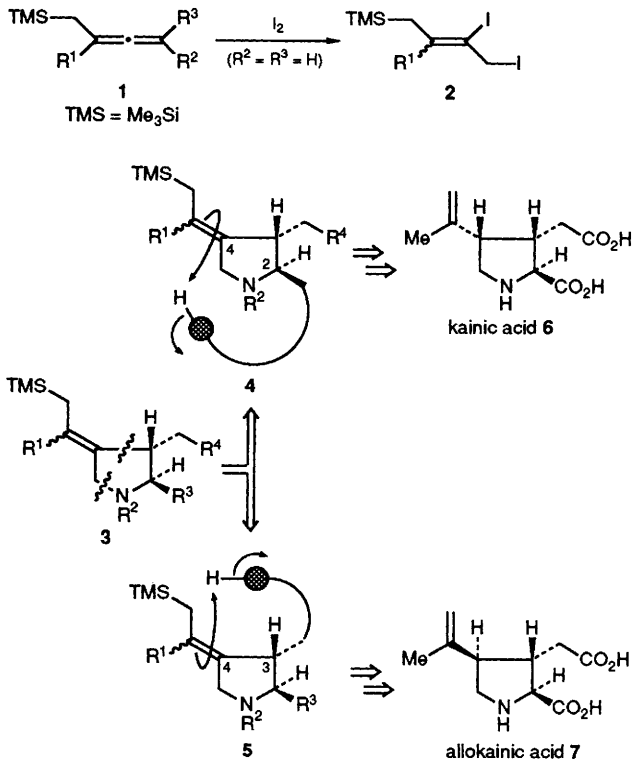
L-Serine **8** was first converted to the protected 2-aminopropane-1,3-diol **9**,‡ $[\alpha]_D^{27}$ +5.3 (*c* 0.98, $CHCl_3$), by a five-step sequence. After reaction of **9** with potassium hydride in dimethylformamide (DMF) at −40 °C for 3.5 h, the resulting anion was allowed to react with the *vic*-diiodoallylsilane **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

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

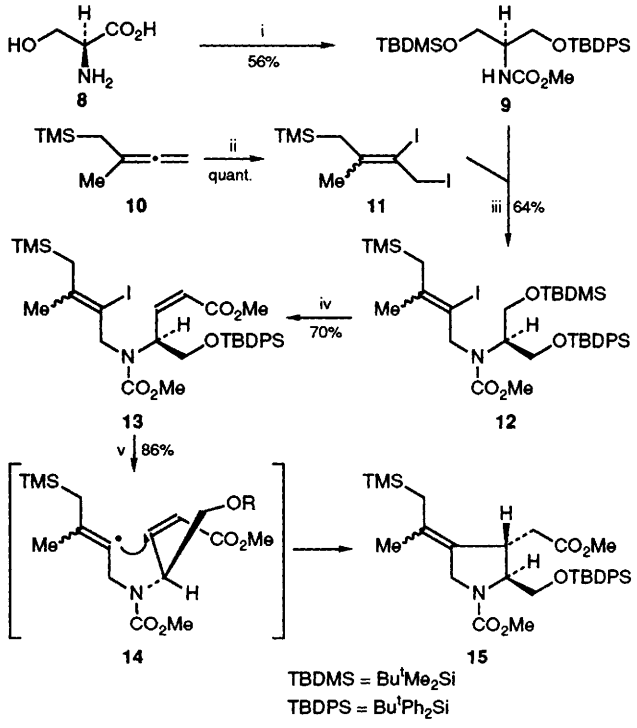
‡ All new compounds exhibited satisfactory spectral (^{1}H NMR, IR) and analytical (high-resolution mass and/or combustion) data.

§ 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, Bu^nLi, *p*-Me-$C_6H_4SO_2Cl$, THF, −78 °C; ii, 6 equiv. Me_3SiCH_2MgCl, 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.

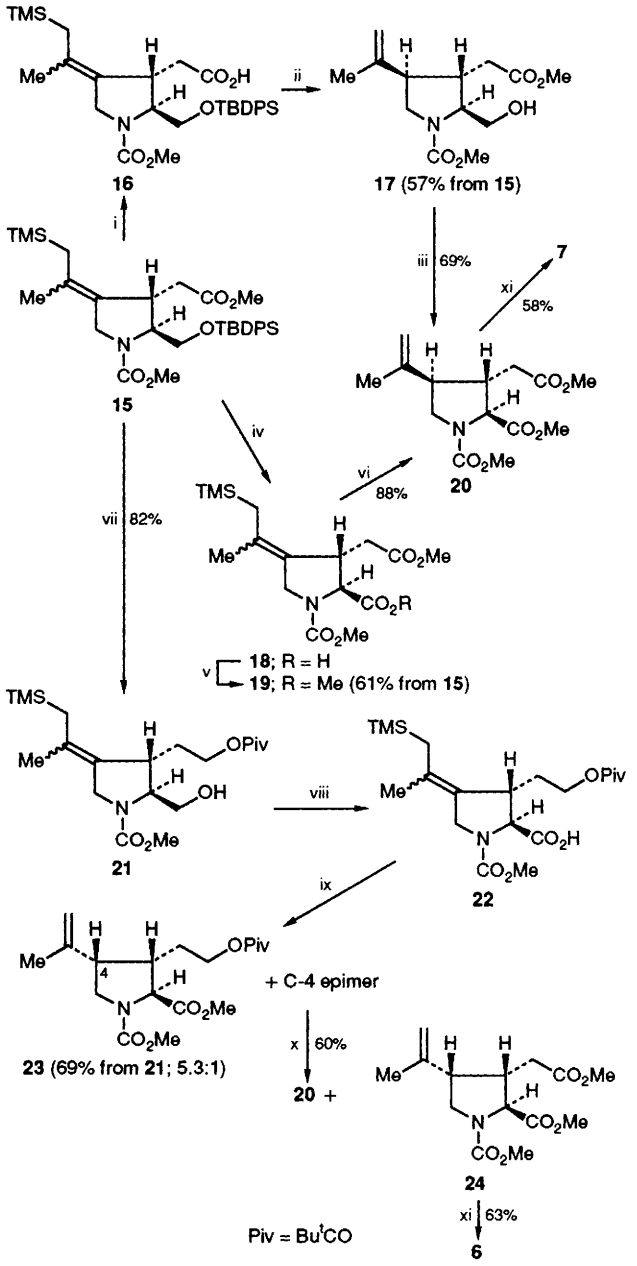
¶ Compounds **11–16**, **18**, **19**, **21** and **22** consist of the olefinic geometrical isomers.



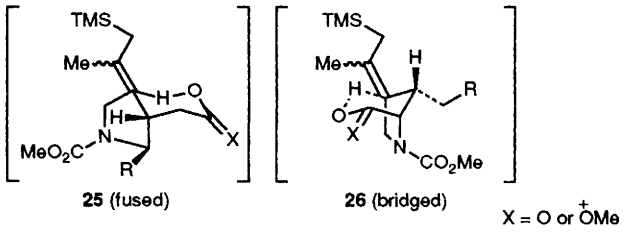
Scheme 1



Scheme 2 *Reagents and conditions*: i, (*a*) MeOCOCl, 1 mol dm^{-3} NaOH, dioxane, (*b*) CH_2N_2, Et_2O, (*c*) TBDMSCl, Et_3N, 4-dimethylaminopyridine (DMAP); catalyst, CH_2Cl_2, (*d*) $NaBH_4$, MeOH, (*e*) TBDPSCl, imidazole, DMF; ii, 0.75 equiv. I_2, CH_2Cl_2, −78 °C; iii, 1.3 equiv. KH, 1.7 equiv. **11**, DMF, −40 °C; iv, (*a*) *p*-TsOH·H_2O (catalyst), MeOH, (*b*) $(COCl)_2$, dimethyl sulfoxide DMSO, CH_2Cl_2, −60 °C then Et_3N, (*c*) $(TMS)_2NK$, 18-crown-6·MeCN $(CF_3CH_2O)_2P(O)CH_2CO_2Me$, THF, −78 to −40 °C; v, Bu_3SnH, AIBN (catalyst), benzene, reflux



Scheme 3 *Reagents and conditions*: i, 5% KOH in MeOH; ii, (*a*) 3 equiv. BF_3Et_2O, CH_2Cl_2 (3–5 × 10^{-2} mol dm^{-3}), (*b*) CH_2N_2, Et_2O, (*c*) 46% HF, MeCN; iii, (*a*) 8 mol dm^{-3} H_2CrO_4, acetone, (*b*) CH_2N_2, Et_2O; iv, (*a*) 46% HF, MeCN, (*b*) $(COCl)_2$, DMSO, CH_2Cl_2, −60 °C then Et_3N, (*c*) $NaClO_2$, $NaHPO_4$, 2-methylbut-2-ene, But OH–H_2O (4 : 1); v, CH_2N_2, Et_2O; vi, 2 equiv. BF_3·2AcOH, CH_2Cl_2 (3–5 × 10^{-2} mol dm^{-3}); vii, (*a*) diisobutylaluminium hydride (DIBAL), CH_2Cl_2, −78 °C, (*b*) But COCl Et_3N, DMAP (catalyst), CH_2Cl_2, (*c*) 46% HF, MeCN; viii, (*a*) $(COCl)_2$, DMSO, CH_2Cl_2, −60 °C then Et_3N, (*b*) $NaClO_2$, $NaHPO_4$, 2-methylbut-2-ene, But OH–H_2O (4 : 1); ix, (*a*) 10 equiv. BF_3·Et_2O, CH_2Cl_2 (1.7 × 10^{-3} mol dm^{-3}), (*b*) CH_2N_2, Et_2O; x, (*a*) 1 mol dm^{-3} NaOH–MeOH (2 : 1), (*b*) 8 mol dm^{-3} H_2CrO_4, acetone, (*c*) CH_2N_2, Et_2O; xi, 40% aq. NaOH–MeOH (1 : 1), reflux



cyclisation[9] to give the (trimethylsilylmethyl)ethylidenepyrrolidine **15** exclusively. The stereochemcial 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 $BF_3{\cdot}Et_2O$ in methylene chloride at ambient temperature, facile protodesilylation took place with complete diastereoselectivity and the 3,4-*trans*-pyrrolidine **17**, $[\alpha]_D^{29}$ −31.7 (*c* 0.71, $CHCl_3$), was obtained exclusively after esterification followed by desilylation. On the other hand, the $BF_3{\cdot}Et_2O$-mediated protodesilylation of **22** under diluted conditions (1.7×10^{-3} mol dm^{-3} **22** in CH_2Cl_2) 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} CH_2Cl_2 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 $BF_3{\cdot}2AcOH$ in place of $BF_3{\cdot}Et_2O$ 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 $BF_3{\cdot}Et_2O$ 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**, $[\alpha]_D^{29}$ −34.5 (*c* 1.33, $CHCl_3$), obtained from **17** and **19** separately, exhibited spectral properties (^{1}H NMR, IR, mass) in accord with those reported.[8c] Concerning the dimethyl ester **24**, $[\alpha]_D^{29}$ −25.3 (*c* 0.72, $CHCl_3$), its structure was confirmed by spectroscopic (^{1}H NMR, IR, mass) and chromatographic comparisons with authentic material, $[\alpha]_D^{29}$ −25.6 (*c* 0.86, $CHCl_3$).[7c] Both dimethyl esters **20** and **24** were determined to be formed in nearly 100% enantiomeric excess by ^{1}H 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 $LiAlH_4$ 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**, $[\alpha]_D^{29}$ −14.8 (*c* 0.85, H_2O), m.p. 244–247 °C (decomp.) {lit.[7a,b] $[\alpha]_D^{22}$ −14.2 (*c* 0.23, H_2O), m.p. 243–244 °C (decomp.)}, and (+)-allokainic acid **7**, $[\alpha]_D^{27}$ +6.9 (*c* 0.91, H_2O), m.p. 239–242 °C (decomp.) {lit.[8a] $[\alpha]_D^{23}$ +7.4 (*c* 0.7, H_2O), 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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10 *Cf.*: M. Ihara, K. Yasui, N. Taniguchi and K. Fukumoto, *J. Chem. Soc., Perkin Trans. 1*, 1990, 1469.

‖ Determined by ^{1}H NMR (500 MHz) analysis.

** The $BF_3{\cdot}2AcOH$-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.