Tetrahedron Letters 49 (2008) 6327–6329

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Asymmetric synthesis of (−)- and (+)-kainic acid using a planar chiral amide as a chiral building block

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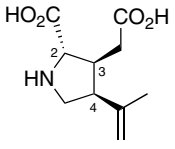
ARTICLE INFO

Article history:
Received 20 July 2008
Revised 16 August 2008
Accepted 19 August 2008
Available online 22 August 2008

ABSTRACT

Both enantiomers of kainic acid have been synthesized from enantioenriched planar chiral cyclic amide **2a**. The C3 and C4 stereocenters in the pyrrolidine ring were constructed by transannular Cope rearrangement of **2a**, and the carboxyl group at the C2 position was introduced through lithiation followed by a carboxylation in the presence of an external chiral ligand.

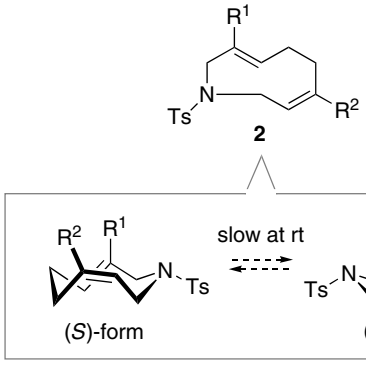
(−)-Kainic acid [(−)-**1**] is a marine natural product that has been first isolated from the Japanese marine alga *Digenea simplex*.[1] (−)-**1** is capable of neurotransmitting activity and therefore has been widely used as a tool in neuropharmacology, especially in the study of epilepsy, Alzheimer's disease, and Huntington's chorea.[2,3]



(−)-kainic acid [(−)-**1**]

The biological activity of (−)-**1** stems from its ability to act as a conformationally restricted analog of L-glutamate, and is linked to the highly functionalized trisubstituted pyrrolidine ring with three contiguous stereocenters. These molecular properties of (−)-**1** have attracted considerable attention from organic chemists.[4]

Recently, we have reported a novel chiral amide **2**, which has only a planar chirality (Scheme 1).[5] The key features of this class of heterocycles are (i) their planar chirality is remarkably stable at ambient temperature, and both enantiomers can be easily obtained via resolution of the racemic one, (ii) the planar chirality can be transferred to the central chirality via both inter- and intramolecular transformations without the loss of stereopurity.[5,6] This means that enantioenriched **2** can serve as a synthetic precursor for a variety of nitrogen-containing chiral compounds with central chirality. We believed that further exploration of this kind of planar chiral heterocycles chemistry will allow a conceptually novel approach to the synthesis of (−)-**1**.



Scheme 1. Planar chirality of amide **2**.

Here, we report the successful asymmetric total synthesis of both enantiomers of **1** using the optically active amide **2a** (R^1 = H, R^2 = Me) as a chiral building block. Scheme 2 depicts the retrosynthetic strategy. We planned to introduce a carboxyl group in the C2 position through lithiation followed by carboxylation, and to introduce the carboxyl group on C3-side chain through hydroboration/oxidation of the olefin followed by further oxidation. For the stereoselective construction of (3*S*,4*S*)-**C**, we planned to perform a transannular Cope rearrangement of (*S*)-**2a**.

The requisite amide **2a** was prepared from the easily available seven-membered lactam **3** by a previously developed method.[5b] The enantiomers were then separated by a semipreparative HPLC with chiral stationary column (see Scheme 3).[7] When maintained at −30 °C in its crystalline form, the enantiopurity of (*S*)-**2a** thus obtained remains unchanged for at least a year.[8]

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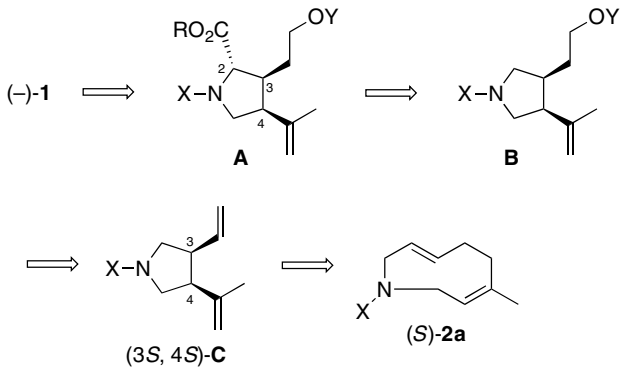
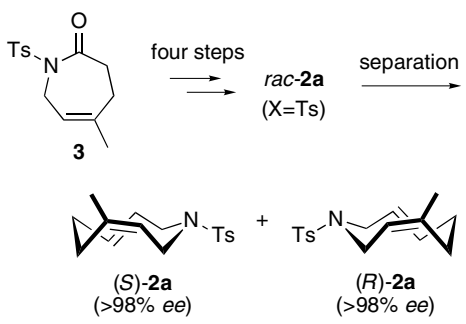
doi:10.1016/j.tetlet.2008.08.058



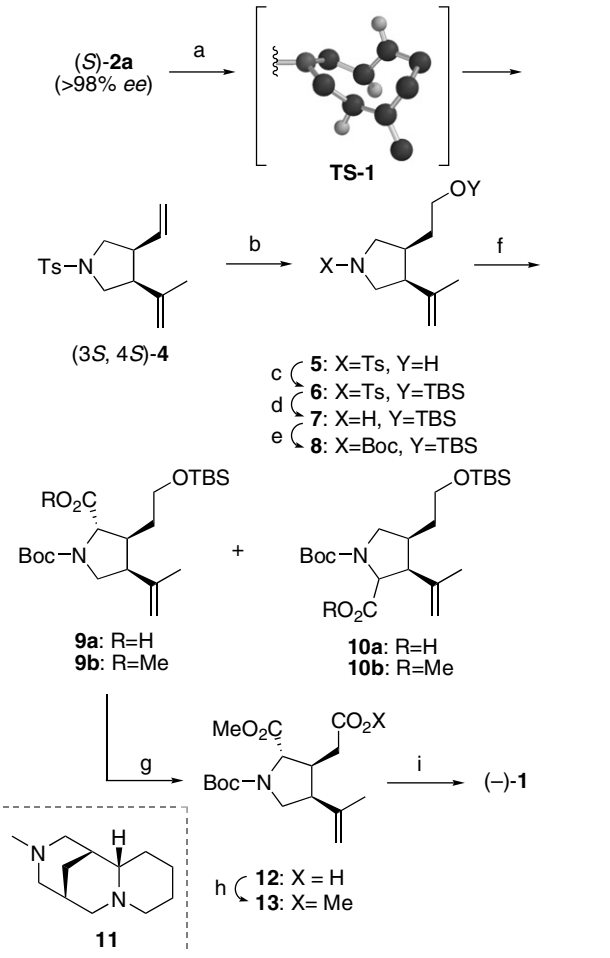
Scheme 2. Retrosynthetic analysis of (–)-**1**.

The Cope rearrangement of (*S*)-**2a** (>98% ee) performed in the presence of a Pd(II) catalyst provided (3*S*,4*S*)-**4** (≡**C**) as the sole product in 87% yield (>98% dr, >98% ee) (see Scheme 4).[9,10] The observed stereoselectivity shows that the reaction most probably proceeds via the TS-1-like transition state.[11] The planar chirality of **2a** was transferred to central chiralities without the loss of stereopurity. Selective hydroboration of the monosubstituted alkene in **4** using disiamylborane,[12,13] followed by protection of the hydroxyl group with TBS, provided **6**.

In order to avoid an undesired *ortho*-lithiation of the Ts group in the following lithiation/carboxylation step, the Ts group of **6** was changed to a Boc group using a standard procedure.[14] Lithiation/carboxylation of **8** was performed in order to introduce a carboxyl group at the C2 position. To gain a basic insight into the regioselectivity and stereoselectivity of this lithiation, we initially examined the reaction of easily available *rac*-**8**[15] with *s*-BuLi in the presence of TMEDA, followed by carboxylation using CO_2 gas. However, the desired (2*S**,3*S**,4*S**)-**9a** was obtained only in 36% yield, along with its epimer (2*R**,3*S**,4*S**)-**9a** (5%) and regioisomer **10a** (38%, dr = 68:32).[16] In order to improve the selectivities, we performed a similar reaction of (3*S*,4*S*)-**8** in the presence of an external chiral ligand (ECL).[17] For the construction of the 2*S*-configuration, we selected O'Brien's chiral amine **11**, which is known as a *pro*-(*R*)-proton-selective ECL in the lithiation of *N*-Boc-pyrrolidine.[18,19] The lithiation of (3*S*, 4*S*)-**8** (>98% ee) using *s*-BuLi/**11** followed by a reaction with methylchloroformate,[20] provided the desired C3-carboxylation product **9b** in excellent stereoselectivity (49%, >98% dr), along with **10b** (35%); and recovered **8** (12%). **9b** and **10b** were easily separated by standard silicagel chromatography. The treatment of **9b** with Jones reagent provided **12** via a sequential deprotection of TBS group and oxidation of the resulting primary alcohol on the C3 side chain. For ease of purification, we converted **12** to its methyl ester **13** by a reaction with $TMSCHN_2$.[21] Finally, alkaline hydrolysis of the ester moieties followed by removal of the Boc group with TFA yielded (–)-**1**, whose spectroscopic data were in excellent agreement with those of a natural sample.



Scheme 3. Synthesis of enantio-enriched **2a**.

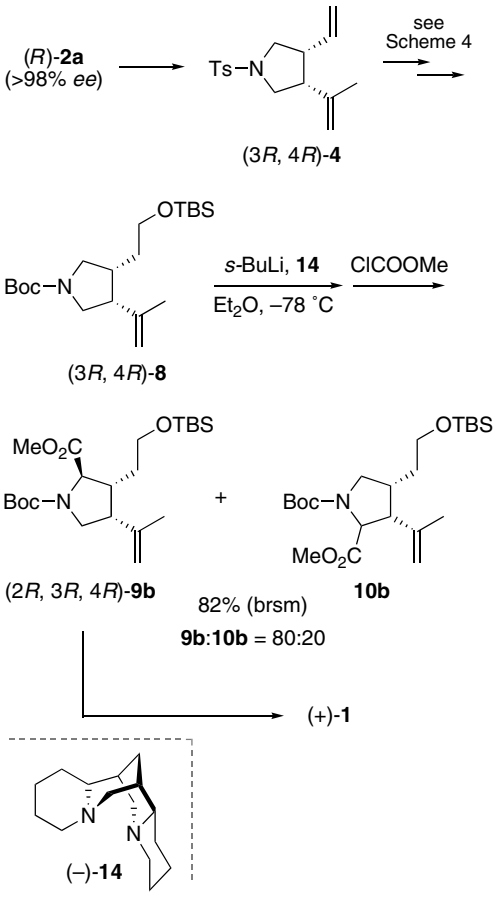


Scheme 4. Synthesis of (–)-**1**. Reagents and conditions: (a) cat. $PdCl_2(PhCN)_2$, CH_2Cl_2, rt, 87%; (b) $(Sia)_2BH$, THF, 0 °C→rt, then H_2O_2, NaOH, MeOH, rt, 82%; (c) TBSCl, imidazole, CH_2Cl_2, 0 °C, 99%; (d) Li naphthalenide, THF, −78 °C; (e) Boc_2O, Et_3N, CH_2Cl_2, 0 °C, 88% for two steps; (f) *s*-BuLi, **11**, Et_2O, −78 °C then ClCOOMe, −78 °C, 84% (**9b**:**10b** = 58:42); (g) Jones reagent, acetone, 0 °C → rt; (h) $TMSCHN_2$, benzene-MeOH, rt, 81% for two steps; (i) aq KOH, THF, rt then TFA, CH_2Cl_2, 57% for two steps.

Except for the C2-carboxylation step, we synthesized the unnatural enantiomer of **1** from (*R*)-**2a** in a similar manner (Scheme 5).

The Cope rearrangement of (*R*)-**2a** provided (3*R*,4*R*)-**4** (>98% dr, >98% ee), which was converted to (3*R*,4*R*)-**8** by the above-mentioned steps. For the synthesis of (+)-**1**, it is required to have a 2*R*-selective carboxylation at the C2 position. We accomplish this by using (–)-sparteine (**14**), a *pro*-(*S*)-proton-selective ECL.[17,22] The lithiation of (3*R*,4*R*)-**8** with *s*-BuLi/(–)-**14** followed by carboxylation gave the desired (2*R*,3*R*,4*R*)-**9b** [36%, 66% (br s m)] along with its regioisomer **10b** [9%, 16% (br s m), >95% dr], and recovered **8** (45%). The observed regioselectivity shows that sparteine is a more efficient coordinating agent for the C2-selective lithiation than amine **11**. In analogy to the synthesis of (–)-**1** from (2*S*,3*S*,4*S*)-**9b**, (2*R*,3*R*,4*R*)-**9b** was then converted to the desired (+)-**1**.

In summary, an asymmetric total synthesis of both enantiomers of kainic acid has been accomplished. The main feature of the synthesis is the stereoselective construction of C3 and C4 central chiralities by conversion of the planar chirality of the enantioenriched cyclic amide. Research on further synthetic applications of the planar chiral heterocycles is in progress.



Scheme 5. Synthesis of (+)-**1**.

Acknowledgments

This research was supported in part by a Grant-in-Aid for Scientific Research in Priority Areas (A) 'Creation of Biologically Functional Molecules' from the Ministry of Education, Culture, Sports, Science and Technology, Japan, and The Naito Foundation.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.08.058.

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7. Analytical and semipreparative-scale HPLC were performed with a chiral stationary column [CHIRALCEL OD-H (4.6 × 250 mm or 20 × 250 mm)], which was equipped with a UV detector and a CD spectropolarimeter.
8. The half-life of the optical activity of **2a** in hexane at 25 °C is 290 h, see Ref. 5b.
9. Pd(II)-catalyzed Cope rearrangement, see: Overman, L. E.; Jacobsen, E. J. *J. Am. Chem. Soc.* **1982**, *104*, 7225–7231.
10. Diastereopurity and enantiopurity were determined by the ^{1}H NMR and HPLC analyses.
11. Calculation of TS-1 was performed by PM3 using Spartan.
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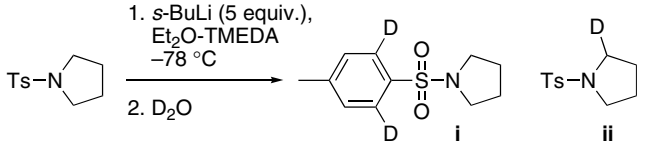
13. The hydroboration of **4** was found to result in the exclusive formation of **5**, without any detectable formation of the isoprene-moiety-reacted product.
14. We examined a lithiation/deuteration reaction of 1-tosylpyrrolidine as a model compound, in which only the *ortho*-deuterated product **i** was obtained without any α-nitrogen-deuterated product **ii**, as shown below.



15. *Rac*-**8** was prepared from *rac*-**2a** by the above-mentioned method.
16. Yields were determined after methyl esterification ($TMSCHN_2$/MeOH). Regio- and diastereoselectivities were determined by ^{1}H NMR and HPLC analyses of the methyl esters.
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19. A similar approach for carboxylation at the C2 position in the asymmetric synthesis of (–)-kainic acid has been reported by Fukuyama and Tokuyama's group, see Ref. 4c.
20. A similar reaction using CO_2 instead of methylchloroformate gave the corresponding carboxylic acids with comparable yields and selectivities.
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