ORGANIC LETTERS

2003
Vol. 5, No. 9
1467−1470

Ruthenium-Catalyzed Alkyne–Propargyl Alcohol Addition. An Asymmetric Total Synthesis of (+)-α-Kainic Acid

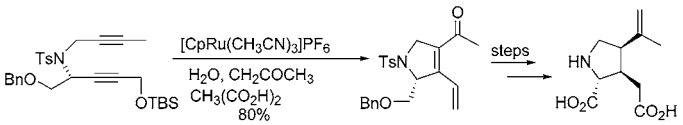
Barry M. Trost* and Michael T. Rudd

Department of Chemistry, Stanford University, Stanford, California 94305-5080

bmtrost@stanford.edu

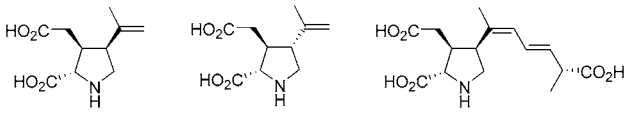
Received February 11, 2003

ABSTRACT



A novel route to the neuroexcitatory amino acid, kainic acid, is developed. The key concept derives from a ruthenium-catalyzed cycloisomerization of a tethered alkyne–propargyl alcohol to form a cylic 2-vinyl-1-acyl compound. A single stereocenter introduced by an asymmetric reduction of a ketone sets the stage for all the other stereocenters. A novel 1,6-addition of silyl cuprate serves to install a hydroxyl group at the diene termines.

Kainic acid is a marine natural product isolated in 1953 that has been shown to have selective interaction with a class of neuroexcitatory amino acid receptors.[1] Kainic acid is the parent member of a large class of structurally related amino acids, two of which are the C-4 epimer allokainic acid and the more structurally complex domoic acid. The selective



recognition by the kainic acid receptors and neuroexcitatory functions are a result of kainic acid's ability to act as a conformationally restricted analogue of L-glutamate.[2] Kainic acid has become especially important in the study of Alzheimer's disease, epilepsy, and other neurological disorders.[3] Recently, a worldwide shortage[4] of kainic acid has stimulated the development of the total syntheses of kainic acid.[5] The biological activity of kainic acid is linked to the *trans*-C2/C3/*cis*-C3/C4 stereochemistry, and thus, any synthesis should result in efficient control of this relative stereochemistry.

Recently, we described an unusual ruthenium-catalyzed dimerization of propargyl alcohols[6] and a related cycloisomerization of alkynes and propargyl alcohol.[7] We believed that extending this methodology to include primary propargyl alcohols would allow a conceptually new entry into the

(1) (a) Murakami, S.; Takemoto, T.; Shimizu, Z. *J. Pharm. Soc. Jpn.* **1953**, *73*, 1026. (b) Impellizzeri, G.; Mangiafico, S.; Oriente, G.; Piatelli, M.; Sciuto, S.; Fattorusso, E.; Magno, S.; Santacroce, C.; Sica, D. *Phytochemistry* **1975**, *14*, 1549. (c) Balansard, G.; Gayte-Sorbier, A.; Cavalli, C. *Ann. Pharm. Fr.* **1982**, *40*, 527.

(2)) Chevliakov, M. V.; Montgomery, J. *J. Am. Chem. Soc.* **1999**, *121*, 11139.

(3) Hollmann, M.; Heinemann, S. *Annu. Rev. Neurosci.* **1994**, *17*, 31.

(4) (a) Tremblay, J.-F. *Chem. Eng. News* **2000**, Jan 3, 14. (b) Tremblay, J.-F. *Chem. Eng. News* **2000**, March 6, 131.

(5) For recent reviews, see: (a) Parsons, A. F. *Tetrahedron* **1996**, *52*, 4149. Maloney, M. G. *Nat. Prod. Rep.* **2002**, *19*, 597. Selected examples: (b) Clayden, J.; Menet, C. J.; Tchabanenko, K. *Tetrahedron* **2002**, 4727. (c) Xia, Q.; Ganem, B. *Org. Lett.* **2002**, 485. (d) Hirasawa, H.; Taniguchi, T.; Ogasawara, K. *Tetrahedron Lett.* **2001**, 7587; Nakagawa, H.; Sugahara, T.; Ogasawara, K. *Org. Lett.* **2000**, 3181. (e) Miyata, O.; Ozawa, Y.; Ninomiya, I.; Naito, T. *Tetrahedron* **2000**, 6199. (f) Campbell, A. D.; Raynham, T. M.; Taylor, R. J. K. *J. Chem. Soc., Perkin Trans. 1* **2000**, 3194. (g) Chevliakov, M. V.; Montgomery, J. *J. Am. Chem. Soc.* **1999**, 11139. (h) Rubio, A.; Ezquerra, J.; Escribano, A.; Remuinan, M. J.; Vanquero, J. J. *Tetrahedron Lett.* **1998**, 2171. (i) Cossy, J.; Cases, M.; Pardo, D. G. *Synlett* **1998**, 507. (j) Bachi, M. D.; Melman, A. *J. Org. Chem.* **1997**, 18966. (k) Hanessian, S.; Ninkovic, S. *J. Org. Chem.* **1996**, *61*, 8. (l) Yoo, S.; Lee, S. H. *J. Org. Chem.* **1994**, *59*, 8. (m) Monn, J. A.; Valli, M. J. *J. Org. Chem.* **1994**, *59*, 3. (n) Cooper, J.; Knight, D. W.; Gallagher, P. T. *J. Chem. Soc., Chem. Commun.* **1987**, 1220. (o) Oppolzer, W.; Thirring, K. *J. Am. Chem. Soc.* **1982**, *104*, 8.

(6) Trost, B. M.; Rudd, M. T. *J. Am. Chem. Soc.* **2001**, 8862.

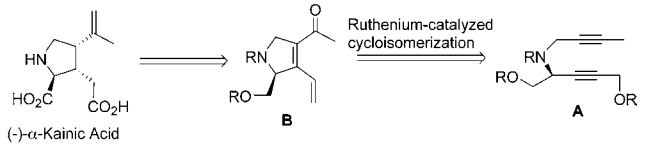
(7) Trost, B. M.; Rudd, M. T. *J. Am. Chem. Soc.* **2002**, 4178

10.1021/ol034241y CCC: $25.00
Published on Web 04/08/2003

kanoid family of amino acids wherein the diversity of alkyne chemistry allows easy access to the required substrate. We report herein our successful realization of an asymmetric total synthesis of kainic acid.

Scheme 1 depicts our retrosynthetic strategy. We planned to introduce the isopropylidene fragment through an olefination of the ketone. This disconnection also enables easy

Scheme 1. Retrosynthetic Analysis



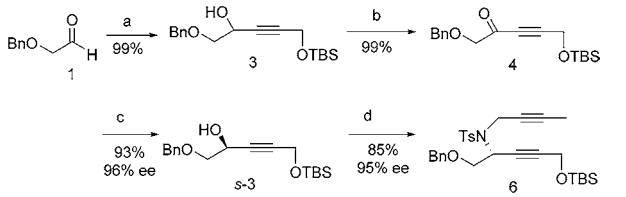
access to domoic acid as well, through use of a different olefination reagent. We envisioned hydroxyl-directed hydrogenation would set the required relative stereochemistry present in the natural product. Introduction of a hydroxyl group or an oxygen equivalent would immediately follow the ruthenium-catalyzed cycloisomerization of the diyne substrate **A**.

The most rapid entry into diyne precursors **A** would be the addition of an alkyne fragment to an imine. While this can be done to give racemic product,[9] all attempts to carry out the reaction asymmetrically resulted in either no reaction or very low ee. The new copper-catalyzed methods developed by Li[10] and Knochel[11] show promise but cannot be applied directly to the desired system. A Mitsunobu reaction could also be used to produce the diyne from the corresponding propargyl alcohol. However, the required propargyl alcohol could not be accessed in a high level of enantioselectivity using established methods of direct addition.[12]

An alternative approach starts with the alkyne **4** derived in two steps and 98% from the commercially available aldehyde **1**. The key to the high yield in the addition of the alkynyllithium was raising the temperature to −40 °C. The most convenient oxidation method involves the two-phase TEMPO/bleach oxidation[13] which only requires 1% of the commercially available TEMPO reagent.

Although the asymmetric reduction of alkynyl ketones is a well-developed reaction, none of the standard reduction methods (Noyori ruthenium catalyst,[14] CBS,[15] Alpine-Borane[16]) gave the product in high yield and ee. The optimum reduction method was then found to be the LAH/(*R*)-BINOL[17]/MeOH system developed by Noyori[18] which gave the product in high yield (90%) and excellent ee (96%) (Scheme 2). The major enantiomer, which is in agreement

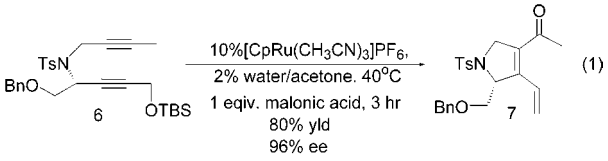
Scheme 2. Synthesis of Cycloisomerization Substrate[a]



[a] Key: (a) $TBSOCH_2C{\equiv}CH$(**2**), ^{n}BuLi, −78 to −40 °C; (b) TEMPO/NaOCl/DCM/KBr/$NaHCO_3$; (c) LAH, (*R*)-BINOL, MeOH, THF, −100 °C; (d) $TsNHCH_2C{\equiv}CCH_3$(**5**), Ph_3P, DIAD, THF, rt.

with the model proposed by Noyori, leads ultimately to the unnatural enantiomer of kainic acid. Of course, the natural enantiomer is equally readily accessible simply by switching the chirality of the BINOL. This reduction is in fact simple to carry out utilizing a filtered, standardized solution of LAH.[19] It is important to conduct the reaction at −100 °C, as raising the temperature to the more convenient −78 °C resulted in lower ee (93%). Also, the reaction mixture must become milky white following addition of LAH, BINOL, and MeOH. If a clear solution with fine particulates results, the yield (∼50%) and ee (83%) are dramatically affected. The Mitsunobu reaction was then carried out using the easily available tosylamine **5**, triphenylphosphine, and diisopropylazadicarboxylate in THF (Scheme 2) to give the diyne **6** in high yield (85%) with nearly perfect chirality transfer.

To carry out the $[CpRu(CH_3CN)_3]PF_6$-catalyzed[20] cyclization, a free propargyl alcohol is preferred; however, the catalyst can deprotect unhindered TBS groups in aqueous acetone. This observation allows **6** to be used directly in the cycloisomerization (eq 1). The formation of **7** is rationalized



through the mechanism depicted in Scheme 3, cycle A. To maximize yields, the reaction is carried out in aqueous

(8) Trost, B. M. *Science* **1991**, *254*, 1471. Trost, B. M. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 259.

(9) Wada, M.; Sakurai, Y.; Akiba, K. Y. *Tetrahedron Lett.* **1984**, 1083. The reaction between lithiated protected progargyl alcohol and the imine derived from benzyloxyacetaldehyde and 1-amino-2-butyne in the presence of $BF_3{\cdot}OEt_2$ gave the expected product in ∼60% yield, which could be subsequently protected.

(10) Wei, C.; Li, C. J. *J. Am. Chem. Soc.* **2002**, *124*, 5638.

(11) Koradin, C.; Polborn, K.; Knochel, P. *Angew. Chem., Int. Ed. Engl.* **2002**, *41*, 2535.

(12) The method developed by Carreira only gave a moderate level of enatioselectivity (∼60%) in the applicable case. (a) Frantz, D. E.; Fassler, R.; Carreira, E. M. *J. Am. Chem. Soc.* **2002**, *122*, 1806. (b) Anand, N. K.; Carreira, E. M. *J. Am. Chem. Soc.* **2001**, *123*, 9687. Other methods also resulted in low yields or poor ee.

(13) For a general review, see: de Nooy, A. E. J.; Besemer, A. C.; van Bekkum, H. *Synthesis* **1996**, 1153.

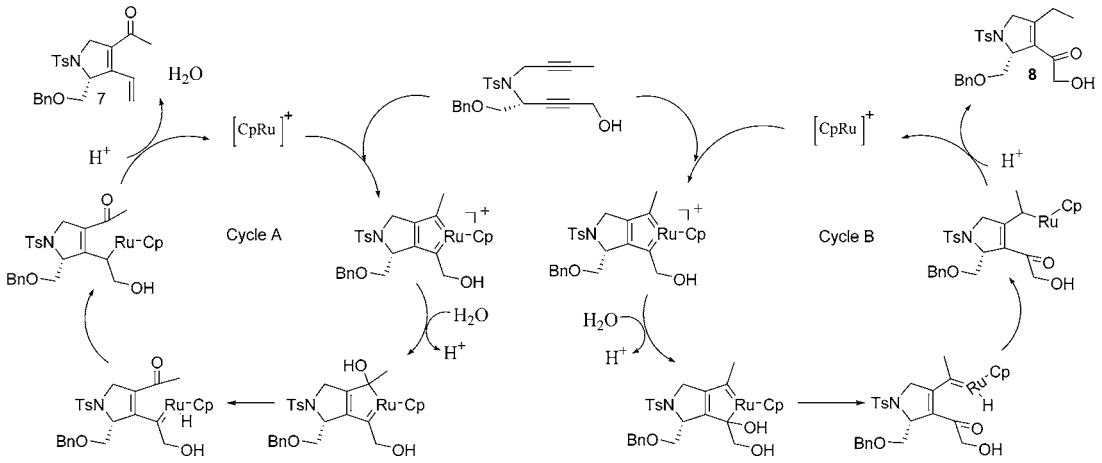
(14) Matsumura, K.; Hashiguchi, S.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1997**, *119*, 8738. The ee was good (90%), but the conversion was low for **4** and related substrates.

(15) (a) Helal, C. J.; Magriotis, P. A.; Corey, E. J. *J. Am. Chem. Soc.* **1996**, *118*, 10938. (b) Parker, K. A.; Ledeboer, M. W. *J. Org. Chem.* **1996**, *61*, 3214. The ee here was 67%.

(16) Midland, M. M.; McDowell, D. C.; Hatch, R. L.; Tramontano, A. *J. Am. Chem. Soc.* **1980**, *102*, 7. The ee here was 86%.

(17) The ligand can be recovered and reused through precipitation and/or column chromatography.

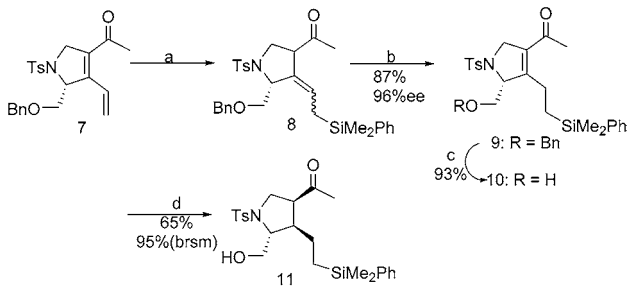
Scheme 3. Mechanistic Rationale for Cycloisomerization and Formation of Side Product



acetone; however, if a larger percentage of water is utilized side product **8**, resulting from addition of a molecule of water to the substrate (Scheme 3, cycle B), becomes a larger component of the reaction mixture.[21] This mechanistic proposal differs from the one proposed in the tertiary and secondary propargyl alcohol examples.[7] The isolation of products similar to **8**, along with other data, led us to propose that a different mechanism operates with primary propargyl alcohol substrates. While the addition of malonic acid is not required, an increase in yield from 75% to 80% occurred upon its addition.

Attempts to introduce a hydroxyl group at the γ position of **7** with hydroboration−oxidation led to either decomposition or various products resulting from 1,6 or 1,2 reduction depending on conditions. Protecting the ketone as a cyclic acetal alleviated this problem but was less desirable as added steps were required. If a hydroxyl group cannot be introduced directly, an oxygen equivalent could be used in its place. Silicon can be used as a stable oxygen surrogate that can be oxidized at the appropriate time. Owing to the conjugated nature of **7**, it is feasible to introduce the silicon moiety through a 1,6 addition of silicon. While much work has been done on the 1,4-addition of silyl cuprates,[22] the 1,6-addition is unknown. When the standard phenyldimethylsilyl cuprate was added to **7**, no reaction occurred at −78 °C; however, when the temperature was raised to 0 °C, 1,6-addition took place smoothly to yield **8** as a mixture of α-diastereomers (in a 2.8:1 ratio). The olefin could be easily isomerized into conjugation with DBU in refluxing benzene to give the desired product **9** in 87% yield over two steps (Scheme 4).

Scheme 4. Setting the Relative Stereochemistry[a]



[a] Key: (a) Li[Si(Me)$_2$Ph], CuCN, THF, −78 to 0 °C; (b) DBU, PhH, reflux; (c) Pd/C, rt, 1:1 formic acid/MeOH; (b) 20% [Ir(cod)Py(PCy$_3$)]PF$_6$, 2000 psi H_2, 1 equiv of B(O-^{i}Pr)$_3$ 24 h.

The relative stereochemistry was then set by a directed hydrogenation of the α,β-unsaturated alkene. Various functional groups are known to direct reduction including methyl ethers; however, with the benzyl ether moiety in **9** intact, no reaction occurred with Crabtree's catalyst[23] [Ir(cod)Py(PCy$_3$)]PF$_6$. Removal of the benzyl group to reveal the more powerfully directing free hydroxyl group was then carried out with 1:1 formic acid/methanol and Pd/C. Use of other Pd sources or direct hydrogen pressure led to either no reaction or over-reduction of the double bond as well. Even with the strong directing effects of the free hydroxyl group, high pressure and extended reaction times were required to maximize the yield of **11** (Scheme 4). We found that addition of triisopropyl borate increased turnover to give an isolated yield of **11** of 65%, 95% based on recovered **10**.

After the initial step of the Peterson olefination,[24] it was envisioned that the elimination and the oxidation of the

(18) (a) Noyori, R.; Tomino, I.; Yamada, M.; Nishizawa, M. *J. Am. Chem. Soc.* **1984**, *106*, 6717. (b) Noyori, R.; Tomino, I.; Tanimoto, Y.; Nishizawa, M. *J. Am. Chem. Soc.* **1984**, *106*, 6709.

(19) Refer to the Experimental Section (Supporting Information) for details.

(20) The catalyst is readily available through an improved procedure: Trost, B. M.; Older, C. M. *Organometallics* **2002**, *21*, 2544.

(21) Changes in the temperature, concentration, and substrate (ring size formed or alkyl group on the alkyne) can also alter the ratio of these type of products.

(22) (a) Fleming, I.; Winter, S. B. D. *J. Chem. Soc., Perkin Trans. 1* **1998**, 2687. (b) Fleming, I.; Roberts, R. S.; Smith, S. C. *J. Chem. Soc., Perkin Trans. 1* **1998**, 1209.

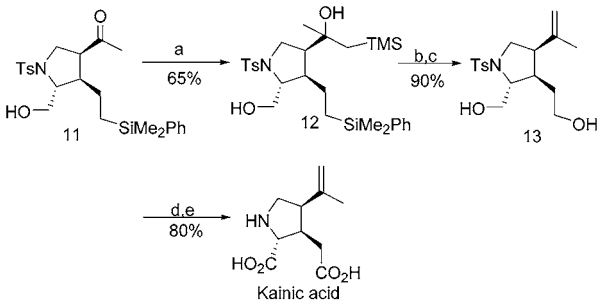
(23) (a) Crabtree, R. H.; Davis, M. W. *Organometallics* **1983**, *2*, 681. (b) Crabtree, R. H.; Davis, M. W. *J. Org. Chem.* **1986**, *51*, 2655.

phenyldimethylsilyl group could be carried out simultaneously. This in fact was possible using the Woerpel modification of the Tamao−Fleming oxidation.[25] The standard Tamao−Fleming conditions require strong acids to oxidize phenyldimethylsilyl groups, which were expected to be incompatible with the olefin present in the molecule. The addition of (trimethylsilylmethyl)lithium proceeded smoothy to give **12**, which could be directly converted to **13** using the Woerpel KH/^{t}BuOOH/TBAF conditions.

However, some amount of a protodesilyated product was also isolated under these conditions, and modifications to minimize this undesired product resulted in lower yields of **13**. Higher yields were obtained if the elimination was carried out with HF/acetonitrile first, followed by the Woerpel oxidation to diol **13** without any prior purification (Scheme 5). Both primary alcohols were then oxidized simultaneously with the Jones reagent[26] to give a quantitative yield of the diacid. The tosyl group was then removed in a known step[27] with Li/NH_3 to give kainic acid in 80% yield over two steps.

In conclusion, we have successfully carried out the stereoselective synthesis of the unnatural enantiomer of kainic acid in 14 linear steps. Since the initially introduced stereogenic center dictates all the remaining ones, this route provides equal access to the natural enantiomer by simply switching the chirality of the BINOL in the enantioselective reduction of ketone **4**. The ring structure was formed through a novel ruthenium-catalyzed cycloisomerization and was functionalized through an unprecedented 1,6-addition of a silyl cuprate. The relative stereochemistry was set by directed hydrogenation, and the endgame was carried out expeditiously through the use of two different types of silicon−carbon reactivity.

Scheme 5. Adjusting the Oxidation Level[a]



[a] Key: (a) (trimethylsilylmethyl)lithium, THF, −78 °C; (b) HF/CH_3CN, rt; (c) KH, ^{t}BuOOH, TBAF, DMF, 65 °C; (d) 8 N Jones reagent, acetone, rt, 1.5 h; (e) Li/NH_3, THF, −78 °C.

Acknowledgment. We thank the National Science Institutes of Health, General Medical Science (GM 13598), and the National Science Foundation for their generous support of our programs. Mass spectra were provided by the Mass Spectrometry Regional Center of the University of California—San Francisco supported by the NIH Division of Research Resources.

Supporting Information Available: Experimetal procedures for the preparation of new compounds as characterization data are included. This material is available free of charge via the Internet at http://pubs.acs.org.

OL034241Y

(24) Johnson, C. R.; Tait, B. D. *J. Org. Chem.* **1987**, *52*, 281. For a recent review, see: van Staden, L. F.; Gravestock, D.; Ager, D. J. *Chem. Soc Rev.* **2002**, *31*, 195.

(25) Smitrovich, J. H.; Woerpel, K. A. *J. Org. Chem.* **1996**, *61*, 6044.

(26) See the Experimental Section (Supporting Information) for preparation.

(27) Yoo, S.; Lee, S. H *J. Org. Chem.* **1994**, *59*, 6968.