ORGANIC LETTERS

2009
Vol. 11, No. 20
4664−4667

Efficient Total Synthesis of (−)-Kaitocephalin†

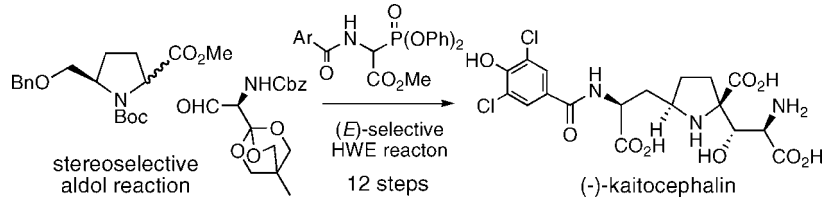
Makoto Hamada, Tetsuro Shinada,* and Yasufumi Ohfune*

Graduate School of Science, Osaka City University, Sugimoto, Sumiyoshi-ku, Osaka 558-8585, Japan

ohfune@sci.osaka-cu.ac.jp; shinada@sci.osaka-cu.ac.jp

Received August 20, 2009

ABSTRACT



A highly diastereoselective total synthesis of (−)-kaitocephalin, a novel antagonist of ionotropic glutamate receptors, was accomplished in 12 steps starting from 5-substituted proline ester via the aldol reaction with OBO-serine aldehyde, (*E*)-selective α,β-dehydroamino acid synthesis using a new HWE reagent, and catalytic hydrogenation.

Glutamate receptors (GluRs), divided into two major types, i.e., ionotropic (iGluRs) and metabotropic (mGluRs), mediate the majority of excitatory signal transmissions at synapses in the mammalian central nervous system and have been implicated in the construction of memory and learning as well as in profound neuron damage by ischemic injury that causes acute and chronic neuronal diseases.[1,2] The iGluRs are divided into three subtypes, i.e., *N*-methyl-D-aspartic acid (NMDA), (*S*)-α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) and kainic acid (KA) receptors. Kaitocephalin (**1**) was isolated from the filamentous fungus *Eupenicillium shearii* PF1191 by Seto et al. by the screening of the novel AMPA/KA antagonist employing chick telencephatic neurons.[3]

Kaitocephalin completely suppressed the kainate toxicity in this assay (EC_{50} = 0.68 μM), which is almost the same concentration as that of 6-cyano-7-nitroquinoxaline-2,3-dione (CNQX), one of the representative antagonists of the AMPA/KA receptors, and is slightly weaker than CNQX using rat hippocampal neurons (2.4 μM). In addition, its cytotoxicity against these neurons is extremely low (>500 μM), whereas that of CNQX is 2−20 μM.[3] Therefore, kaitocephalin has the potential to be a promising lead compound for development of therapeutic agents toward various ischemia-reperfusion injuries such as stroke and epilepsy.[2] However, its detailed neurobiological actions as well as SAR studies have not been sufficiently carried out because of the extremely small amount of samples available from the fungus.

The structure of **1** is characterized by its α-substituted proline as the core assembled by *N*-acylalanine and serine moieties connected by a carbon−carbon bond. Three groups including our group have succeeded in the total synthesis of

† Dedicated to Professor Paul A. Grieco on the occasion of his 65th birthday

(1) (a) Choi, D. W. *Trends Neurosci.* **1988**, *11*, 465–469. (b) Coyle, J. T.; Puttfarcken, P. *Science* **1993**, *262*, 689–695. (c) Meldrum, B. S. *J. Nutr.* **2000**, *130*, 1007S–1015S. (d) Bräuner-Osborne, H.; Engelberg, J.; Nielsen, E. O.; Madsen, U.; Krogsgaard-Larsen, P. *J. Med. Chem.* **2000**, *43*, 2609–2645.

(2) (a) Sheardown, M. J.; Nielsen, E. P.; Hansen, A. J.; Jacobsen, P.; Honore, T. *Science* **1990**, *247*, 571–574. (b) Bleakman, D.; Lodge, D. *Neuropharmacology* **1998**, *37*, 1187–1204. (c) Lees, G. J. *Drugs* **2000**, *59*, 33–78.

(3) (a) Shin-ya, K.; Kim, J.-S.; Furihata, K.; Hayakawa, Y.; Seto, H. *Tetrahedron Lett.* **1997**, *38*, 7079–7082. (b) Kobayashi, H.; Shin-ya, K.; Furihata, K.; Hayakawa, Y.; Seto, H. *Tetrahedron Lett.* **2001**, *42*, 4021–4023. (c) Shin-ya, K. *Biosci. Biotechnol. Biochem.* **2005**, *69*, 867–872.

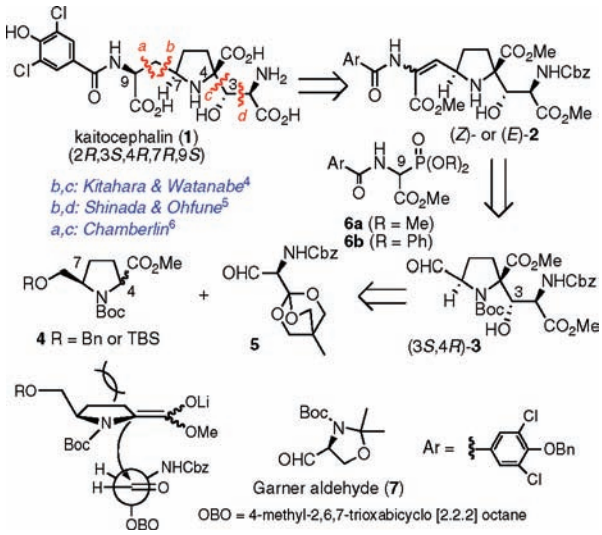
(4) (a) Okue, M.; Kobayashi, H.; Shin-ya, K.; Furihata, K.; Hayakawa, Y.; Seto, H.; Watanabe, H.; Kitahara, T. *Tetrahedron Lett.* **2002**, *43*, 857–860. (b) Watanabe, H.; Okue, M.; Kobayashi, H.; Kitahara, T. *Tetrahedron Lett.* **2002**, *43*, 861–864.

(5) Kawasaki, M.; Shinada, T.; Hamada, M.; Ohfune, Y. *Org. Lett.* **2005**, *7*, 4165–4167.

10.1021/ol9019343 CCC: $40.75
Published on Web 09/18/2009

1.[4−6] These syntheses have been performed by strategically intriguing disconnection approaches as depicted in Scheme 1.[7] However, it still required practical synthetic approaches

Scheme 1. Disconnection Approach to Kaitocephalin (**1**)

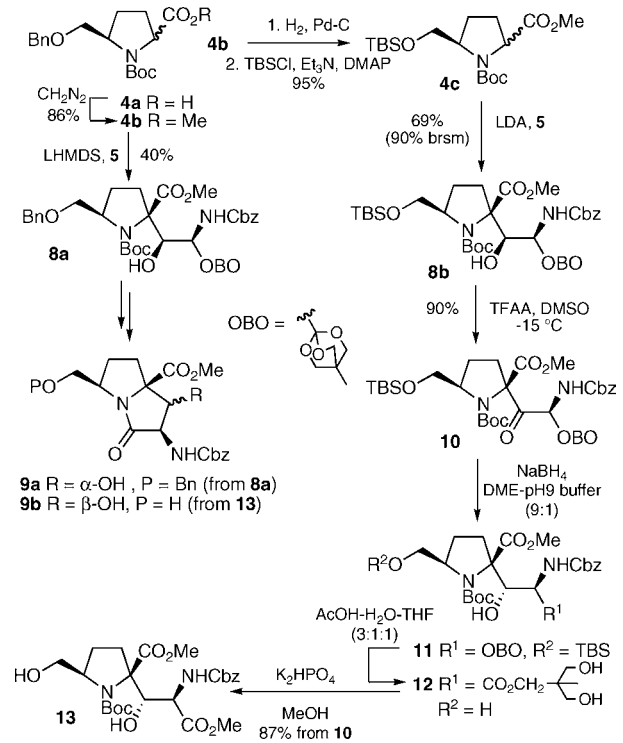


in order to supply sufficient amounts of natural product and its structurally related analogues for the neurobiological assays. We considered that the following aspects are essential to develop a practical synthetic route based on the previous total syntheses and other synthetic studies:[8,9] (1) stereoselective and reproducible reactions on a 1−10 g scale for the construction of the five chiral centers and (2) minimization of the functional group manipulations, in particular, protection−deprotection steps. In this report, we describe a highly efficient total synthesis of **1** based on the stereoselective coupling of each amino acid fragment **4**−**6** in which the oxidation stage of the C2, 4, and 9 carboxyl groups were maintained that minimized functional group manipulations during the synthesis. In addition, a new Horner−Wadsworth−Emmons (HWE) reagent, methyl *N*-acyl-α-(diphenylphosphono)glycinate **6b**, to produce an (*E*)-α,*β*-dehydroamino acid ester that leads to successful installation of the C9 chiral center by a catalytic hydrogenation was developed.

Our plan for the synthesis was disconnection at the C3−C4, and C8−C9 bonds of **1** that provided three amino acid components as the starting material, i.e., substituted proline ester **4** as the central core, *N*-protected (*R*)-serine aldehyde **5** with a 4-methyl-2,6,7-trioxabicyclo [2.2.2] octane (OBO) ester[10] for the serine unit instead of the Garner aldehyde (**7**)[11] previously employed by Kitahara et al.[4] and Ma et al.,[8] and methyl *N*-acyl-α-(dimethylphosphono)glycinate **6a**. The OBO serine aldehyde **5** is known to exhibit a remarkable stability against racemization,[10a] although the aldol condensation of an ester enolate with **5** is unprecedented.[10] Upon aldol condensation of the ester enolate derived from **4** with **5**, we expected that the reaction would produce the requisite (4*R*)-isomer (Scheme 1). Since the nucleophilic addition of an organometallic reagent to (*R*)-**5** is known to produce (2*R*,3*R*)-3-hydroxy-α-amino acids,[10] the product of the aldol reaction would be an inevitable (3*R*)-isomer of **3**, which can be converted into the desired (3*S*)-**3** by an oxidation and reduction sequence.[10b] The HWE olefination using **6a** would produce the (*Z*)-isomer of the α,*β*-dehydroamino acid **2**, which can be hydrogenated to the desired (9*S*)-isomer using a chiral catalyst under the reagent-controlled diastereoselective hydrogenation reactions.

The initial attempt was the aldol reaction of the methyl ester **4b**, prepared from the known carboxylic acid **4a**,[12] with the OBO aldehyde **5** (Scheme 2). The reaction using LHMDS

Scheme 2. Stereoselective Construction of the Pro-Ser **13**



as the base gave the aldol adduct **8a** in 40% yield in which a detectable amount of its diastereomers was observed in its ^{1}H NMR spectrum. The configuration of **8a** was determined by converting it to a bicyclic lactam **9a**, whose ^{1}H NMR data and NOE experiments clearly indicated that the product

(6) Vasawani, R. G.; Chamberlin, R. *J. Org. Chem.* **2008**, *73*, 1661–1681.

(7) Kitahara and co-workers employed Zeebach's protocol for the Pro-Ser unit and nucleophilic addition of the organozinc reagent to a Nitron (14 steps, 1.2% overall yield).[4] We employed a step-by-step method starting from α-formyl pyroglutamate for the core unit. The allylcopper addition to the acyliminium ion at C7 for the construction of the Ala moiety was employed (28 steps, 0.45% overall yield).[5] Chamberlin et al. employed an acylation of the 5-substituted proline derivative for the Pro-Ser moiety followed by an olefin isomerization−diastereoselective hydrogenation of the dehydroalanine for the construction of the C9 chiral center (18 steps, 4.6% overall yield).[6]

(8) Synthesis of 2-epimer of **1**: Ma, D.; Yang, J. *J. Am. Chem. Soc.* **2001**, *123*, 9706–9707.

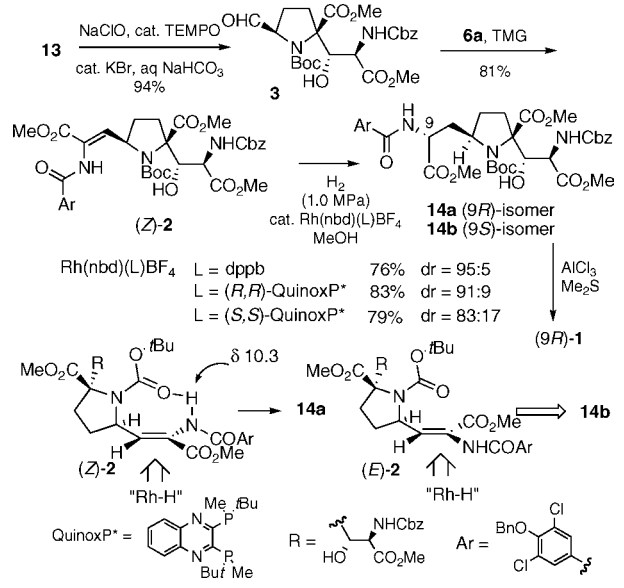
(9) Synthetic approaches to **1**: (a) Takahashi, K.; Haraguchi, N.; Ishihara, J.; Hatakeyama, S. *Synlett* **2008**, 671–674. (b) Loh, T.-P.; Chok, Y.-K.; Yin, Z. *Tetrahedron Lett.* **2001**, *42*, 7893–7897. (c) Kudryavtsev, K. V.; Nukolova, N. V.; Smolin, E. S. *Rus. J. Org. Chem* **2006**, *42*, 412–422.

possessed the (3*R*,4*R*) configuration.[13] The preferential formation of (3*R*,4*R*)-**8a** was in good agreement with Lajoie's nucleophilic addition to **5**[10a] and Ma's aldol reaction of the ester enolate derived from proline ester[8] with **7**. On the basis of these results, we converted **4b** to the TBS ether **4c** since the *N*-Cbz group in the aldol adduct **8a** is incompatible with the benzyl group for its selective removal. The use of LDA for the aldol reaction using **4c** was found to be superior to LHMDS to produce the aldol adduct **8b** in 69% yield (90% based on recovery of the starting material (brsm)).[14]

Next, we examined the inversion of the configuration at the C3 hydroxy group by the oxidation−reduction sequence. Because the C3 hydroxy group of **8b** is highly congested due to the presence of the polar and sterically bulky functional groups at its proximal position, the oxidation using conventional reagents[15] was not successful at all, resulting in the decomposition or recovery of **8b**. After numerous attempts, we found that the treatment with TFAA−DMSO at −15 °C underwent a smooth oxidation to give the desired ketone **10** (90%).[16] The next reduction was again accompanied by difficulty, contrary to the previous studies by Kitahara[4] and Chamberlin[6] groups in which $NaBH_4$ in THF−MeOH or DIBAL−THF was the effective reducing conditions, respectively. The reduction of **10** using these and other reagents, such as $LiBHEt_3$ and $LiBH_4$, did not react at all at low temperature or reduced both the ketone and ester groups at room temperature. During the screening of the solvent system using $NaBH_4$, we found that a trace amount of water in DME affected the desired reduction to give **11**. The yield was increased to 48% when 10 equiv of water was added.[17] The byproduct was a hydrolyzed ester and/or lactam product presumably because the solution was strongly basic, suggesting that the reduced pH would prevent the side reactions. Finally, the reaction condition was optimized using DME and pH 9 phosphate buffer (9:1). The reaction smoothly proceeded to give the crude **11**.[17] The product without chromatographic purification was converted into the methyl ester **13** by the following sequence of reactions: (1) treatment with aqueous AcOH, which produced simultaneous partial hydrolysis of the OBO ester and removal of the TBS group to give **12**, and (2) transesterification of **12** with powdered K_2HPO_4 in MeOH to afford **13** as the sole diastereomer (87%, 3 steps from **10**).[18] The stereochemistry at C3 was determined to be (*S*) by converting it to the bicyclic lactam **9b** and its X-ray crystallographic analysis (Scheme 2).[13,19] The stereochemical outcome of the present reduction was in accord with those of Lajoie's synthesis of β-hydroxy-α-amino acids.[10a]

Installation of the *N*-acyl-α,β-dehydroalanyl moiety was performed by the initial oxidation of **13** and subsequent tetramethylguanidine (TMG)-assisted HWE olefination of the resulting aldehyde **3** with **6a** to give (*Z*)-**2** as the sole product.[20] The hydrogenation of (*Z*)-**2** using the cationic achiral rhodium catalyst under 1.0 MPa hydrogen atmosphere smoothly proceeded to give a mixture of diastereomers at C9 in which the undesired (9*R*)-isomer **14a** was obtained as the major product (**14a**/**14b** = 95:5). Contrary to our initial expectation that the desired (9*S*)-**14b** could be prepared using a chiral catalyst, attempts using the (*R*,*R*)- and (*S*,*S*)-QuinoxP*-Rh complex[21] resulted in the formation of the undesired **14a** as the major isomer, respectively (**14a**/**14b** = 91:9 and 83:17). These results suggested that the product's stereochemistry is attributed to the structure of (*Z*)-**2**. Therefore, the reagent controlled diastereoselective hydrogenation was not applicable in this case. The ^{1}H NMR analysis of (*Z*)-**2** revealed that its vinyl amide proton appeared at relatively low field (δ 10.7)[22] probably as a result of the hydrogen bonding with the proximal Boc group, indicating that the *re* face of (*Z*)-**2** is sterically shielded from attack by the [Rh-H] complex (Scheme 3).[6]

Scheme 3. Synthesis of (*Z*)-**2** and Its Catalytic Hydrogenation



To overcome this problem, we considered that the hydrogenation of the (*E*)-isomer **2** would give the desired

(10) (a) Blaskovich, M. A.; Lajoie, G. A. *J. Am. Chem. Soc.* **1993**, *115*, 5021–5030. (b) Blaskovich, M. A.; Evindar, G.; Rose, N. G. W.; Wilkinson, S.; Luo, Y.; Lajoie, G. A. *J. Org. Chem.* **1998**, *63*, 3631–3646. (c) Hansen, D. B.; Wan, X.; Carroll, P. J.; Joullié, M. M. *J. Org. Chem.* **2005**, *70*, 3120–3126.

(11) Garner, P.; Park, J.-M. *Org. Synth.* **1991**, *70*, 18–28.

(12) Preparation of the antipode of **4a**: Lee, M.; Lee, T.; Kim, E.-Y.; Ko, H.; Kim, D.; Kim, S. *Org. Lett.* **2006**, *8*, 745–748.

(13) For procedures for the conversion of **8a** to **9a** and **13** to **9b** and the NOE correlation of **9a** and X-ray structure of **9b**, see Supporting Information.

(14) A trace amount of the inseparable diastereomers was contaminated. The amount was estimated to be 5−10% from the ^{1}H NMR spectrum of the crude **8b**, but the exact ratio could not be determined because of their broard signals. The contaminated diastereomers were chromatographically removed during its conversion to **11**.

(15) The oxidation of **8b** was attempted using the following reagents: Dess−Martin periodinane, PDC, $(COCl)_2$−DMSO, or 1-Me-AZADO.

(16) Appell, R. B.; Duguid, R. J. *Org. Process Res. Dev.* **2000**, *4*, 172–174.

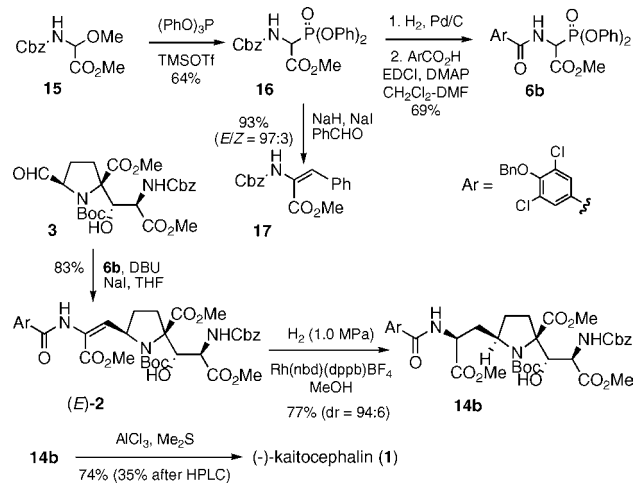
(17) The yield was calculated after conversion to **13** since the OBO ester **11** was labile upon chromatographic isolation or storage under ambient conditions for gradual conversion to the partially hydrolyzed **12**. Contrary to **11**, its C3-epimers **8a,b** are quite stable under these conditions.

(18) Methanolysis of the (3*R*)-isomer of **12** using K_2CO_3 (1.5 equiv) in MeOH gave a sluggish mixture of products containing an N-Cbz group-removed cyclic carbamate (4.9%), and a small amount of the desired 3-epi-**13** was isolated (1.5%). The extremely mild transesterification using K_2HPO_4 is under investigation and will be reported in due course.

(9*S*)-**14b** where the bulky Boc group may shield the *si* face. Several methods for the synthesis of the (*E*)-α,*β*-dehydroamino acids have been reported.[23] However, the presence of the right-half functional groups would not tolerate these methods. Our idea was that the use of methyl *N*-acyl-α-(diphenylphosphono)glycinate **6b**, a new HWE reagent that possesses an Ando-type diphenylphosphonate group,[24] would undergo the desired (*E*)-selective olefination to give (*E*)-**2**. Since the literature procedure for the synthesis of methyl *N*-benzoyl-α-(diphenylphosphono)glycinate was not applicable to the synthesis of *N*-Cbz **16**,[25] the reaction conditions for the phosphite condensation with methyl α-(methoxy)glycinate **15** were screened. As a result, TMSOTf was an effective Lewis acid to give **16** in 64% yield. The HWE olefination of benzaldehyde with **16** was found to be highly stereoselective and produced the (*E*)-α,*β*-dehydroamino acid **17** (93%, *E*/*Z* = 97:3).

Encouraged by this result, the *N*-Cbz-protected **16** was converted to **6b** in two steps, which, upon HWE reaction with the aldehyde **3**, gave (*E*)-**2** (83%), in which none of the (*Z*)- isomer was observed in its ^{1}H and ^{13}C NMR spectra. Hydrogenation of (*E*)-**2** with an achiral rhodium catalyst furnished the desired **14b** as the major isomer (**14b**/**14a** = 94:6, 77%).[26] The removal of all the protecting groups was performed in one pot according to our previously reported method to give (−)-(**1**) in 74% yield after Dowex-50Wx4 treatment and subsequent reverse-phase chromatography. Diastereomerically pure **1** was obtained as a diethylamine salt in 35% yield by the HPLC separation.[27] The synthetic **1** showed spectroscopic data completely identical to those reported.[5]

Scheme 4. Synthesis of the New HWE Reagent **6b** and Completion of the Total Synthesis of **1**



In summary, we accomplished the total synthesis of (−)-kaitocephalin (**1**) in 12 steps (8.96% overall yield) from the known **4a** via the aldol reaction with the OBO-protected serine aldehyde **5**, (*Z*)-selective α,*β*-dehydroamino acid ester synthesis using the new HWE reagent **6b**, and stereoselective hydrogenation of (*E*)-**2** as the key steps. The present synthetic route not only supplies **1** for a neuropharmacological assay on an in vivo level but also enables synthesis of various types of analogues, e.g., stereoisomers at C3, C9, and/or multiply substituted aromatic acylamide analogues. Further studies of the synthesis of these analogues and their SAR studies are currently underway in our laboratories.

Acknowledgment. This study was supported by Grants-in-Aid (16201045, 19201045, and 1910080) for Scientific Research from the Japan Society for the Promotion of Science (JSPS).

Supporting Information Available: Detailed experimental procedures, spectroscopic data, copies of ^{1}H and ^{13}C NMR spectra, and X-ray strucure of **9b**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL9019343

(19) CCDC 738627 (**9b**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Center via http://www.ccdc.cam.ac.uk/deposit.

(20) Synthesis of (*Z*)-α,*β*-dehydroamino acid ester by HWE reaction: Schmidt, U.; Lieberknecht, A.; Wild, J. *Synthesis* **1984**, 53–60.

(21) Imamoto, T.; Sugita, K.; Yoshida, K. *J. Am. Chem. Soc.* **2005**, *127*, 11934–11935.

(22) The chemical shift of the amide proton in (*E*)-**2** appeared at *δ* 8.1.

(23) For representative examples of the synthesis of α,*β*-dehydroalanine derivatives, see: (a) Stohlmeyer, M. M.; Tanaka, H.; Wandless, T. J. *J. Am. Chem. Soc.* **1999**, *121*, 6100–6101. (b) Bonauer, C.; Walenzyk, T.; Konig, B. *Synthesis* **2006**, 1–20. (c) Humphrey, J. M.; Chamberlin, A. R. *Chem. Rev.* **1997**, *97*, 2243–2246. (d) Schmidt, U.; Lieberknecht, A.; Wild, J. *Synthesis* **1988**, 159–172.

(24) Ando, K. *J. Org. Chem.* **1997**, *62*, 1934–1939.

(25) Ku, B.; Oh, D. Y. *Tetrahedron lett.* **1988**, *29*, 4465–4466.

(26) Asymmetric hydrogenation of (*E*)-**2** using (*R*,*R*)-QuinoxP* did not react at all resulting in the complete recovery of (*E*)-**2**, whereas (*S*,*S*) -QuinoxP* gave a mixture of **14a** and **14b** in 71% yield (**14a**/**14b** = 26:74).

(27) The reverse-phase chromatography afforded a mixture of (9*S*)- and (9*R*)-**1** (94:6) without any other contamination in its ^{1}H NMR. However, the HPLC separation of each isomer was accompanied by a significant loss of the product (see Supporting Informationand ref 5). An improved method for their separation is currently being investigated.