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Asymmetric Intermolecular Conjugate Addition of Amino Acid Derivatives via Memory of Chirality: Total Synthesis of Manzacidin A

Tomoyuki Yoshimura, Tomohiko Kinoshita, Hiroyasu Yoshioka, and Takeo Kawabata*

Institute for Chemical Research, Kyoto University, Uji 611-0011, Japan

kawabata@scl.kyoto-u.ac.jp

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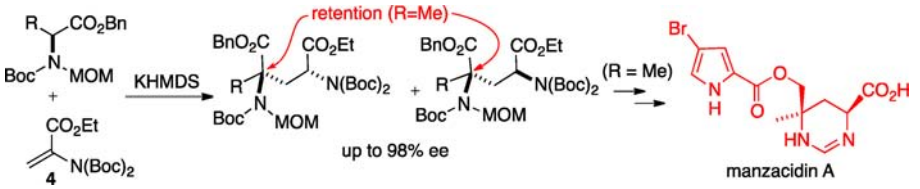
ABSTRACT



Asymmetric intermolecular conjugate addition of α-amino acid derivatives with 4 via memory of chirality has been developed. The reactions proceeded in up to 98% ee with retention of configuration at the newly formed tetrasubstituted carbon center when R = Me. The product (R = Me) was transformed into manzacidin A.

α,α-Disubstituted α-amino acids have been recognized as useful building blocks in the field of medicinal chemistry.[1] They have also been frequently found as structural subunits in biologically active natural products.[2] Several excellent methods have been reported for the asymmetric synthesis of α,α-disubstituted α-amino acid derivatives.[3] We have reported asymmetric syntheses of them by direct alkylation of α-amino acid derivatives, via memory of chirality, without the use of external chiral sources such as chiral catalysts or chiral auxiliaries.[4,5] The reactions have been proposed to proceed via axially chiral enolate intermediates **A** (Scheme 1).[4,5a,5c] Recently, we reported asymmetric aldol reactions of α-amino acid derivatives via memory of chirality.[6] This strategy for asymmetric synthesis is also applicable to intramolecular alkylation,[7,8] intramolecular acyl migration,[9] and intramolecular conjugate addition.[10]

(1) (a) Boyle, S.; Guard, S.; Higginbottm, M.; Horwell, D. C.; Howson, W.; McKnight, A. T.; Martin, K.; Pritchard, M. C.; O'Toole, J.; Raphy, J.; Rees, D. C.; Roberts, E.; Watling, K. J.; Woodruff, G. N.; Hughes, J. *Bioorg. Med. Chem.* **1994**, *2*, 357–370. (b) Ilies, M.; Costanzo, L. D.; Dowling, D. P.; Thorn, K. J.; Christianson, D. W. *J. Med. Chem.* **2011**, *54*, 5432–5443.

(2) For a review on the total synthesis of natural products containing a *tert*-alkylamino hydroxyl carboxylic acid substructure, see: Kang, S. H.; Kang, S. Y.; Lee, H.-S.; Buglass, A. J. *Chem. Rev.* **2005**, *105*, 4537–4558.

(3) For a review, see: Vogt, H.; Braese, S. *Org. Biomol. Chem.* **2007**, *5*, 406–430.

(4) Kawabata, T.; Suzuki, H.; Nagae, Y.; Fuji, K. *Angew. Chem., Int. Ed.* **2000**, *39*, 2155–2157.

(5) For reviews on asymmetric synthesis via memory of chirality, see: (a) Kawabata, T.; Fuji, K. *Top. Stereochem.* **2003**, *23*, 175–205. (b) Zhao, H.; Hsu, D. C.; Carlier, P. R. *Synthesis* **2005**, 1–16. (c) Patil, N. T. *Chem.—Asian J.* **2012**, *7*, 2189–2194. For recent reports related to the memory of chirality, see: (d) Mondal, S.; Nechab, M.; Vanthuyne, N.; Bertrand, M. P. *Chem. Commun.* **2012**, *48*, 2549–2551. (e) Mai, T. T.; Viswambharan, B.; Gori, D.; Kouklovsky, C.; Alezra, V. *J. Org. Chem.* **2012**, *77*, 8797–8801. (f) Fletcher, S. P.; Solá, J.; Holt, D.; Brown, R. A.; Clayden, J. *Beilstein J. Org. Chem.* **2011**, *7*, 1304–1309. (g) MacLellan, P.; Clayden, J. *Chem. Commun.* **2011**, *47*, 3395–3397. (h) Nechab, M.; Campolo, D.; Maury, J.; Perfetti, P.; Vanthuyne, N.; Siri, D.; Bertrand, M. P. *J. Am. Chem. Soc.* **2010**, *132*, 14742–14744. (i) Wanyoike, G. N.; Matsumura, Y.; Kuriyama, M.; Onomura, O. *Heterocycles* **2010**, *80*, 1177–1185. (j) Branca, M.; Pena, S.; Guillot, R.; Gori, D.; Alezra, V.; Kouklovsky, C. *J. Am. Chem. Soc.* **2009**, *131*, 10711–10718.

(6) Watanabe, T.; Yoshimura, T.; Kawakami, S.; Sasamori, T.; Tokitoh, N.; Kawabata, T. *Chem. Commun.* **2012**, *48*, 5346–5348.

(7) (a) Kawabata, T.; Kawakami, S.; Majumdar, S. *J. Am. Chem. Soc.* **2003**, *125*, 13012–13013. (b) Kawabata, T.; Matsuda, S.; Kawakami, S.; Monguchi, D.; Moriyama, K. *J. Am. Chem. Soc.* **2006**, *128*, 15394–15395. (c) Kawabata, T.; Moriyama, K.; Kawakami, S.; Tsubaki, K. *J. Am. Chem. Soc.* **2008**, *130*, 4153–4157.

(8) Asymmetric synthesis of β-lactams by the intramolecular alkylation via memory of chirality has been reported. See: (a) Gerona-Navarro, G.; Bonache, M. A.; Hernz, R.; García-López, M. T.; González-Muñiz, R. *J. Org. Chem.* **2001**, *66*, 3538–3547. (b) Bonache, M. A.; Cativiela, C.; García-López, M. T.; González-Muñiz, R. *Tetrahedron Lett.* **2006**, *47*, 5883–5887.

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On the other hand, *intermolecular* conjugate addition reactions via memory of chirality have yet to be developed. Here we report highly enantioselective *intermolecular* conjugate addition reactions of α-amino acid derivatives via memory of chirality. This method provides a concise access to a new class of glutamic acid derivatives with a tetrasubstituted carbon center. The diastereomeric products obtained by this method were transformed to manzacidin A and *ent*-manzacidin C, members of the biologically active bromopyrrole class of alkaloids (Figure 1).[11]

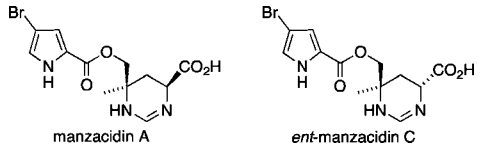
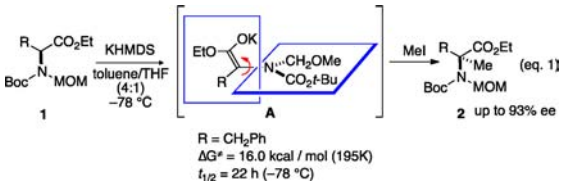


Figure 1. Manzacidin A and *ent*-mazacidin C.

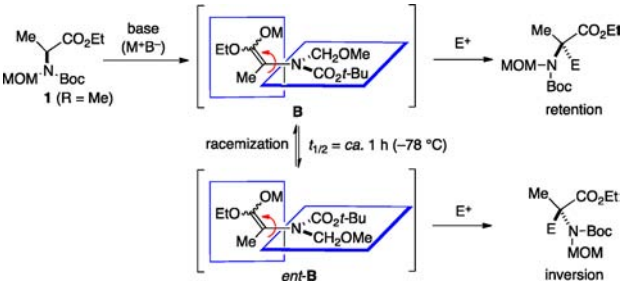
Scheme 1. Asymmetric Methylation via Axially Chiral Enolate **A**



We first focused on the asymmetric conjugate addition of alanine derivatives, since these Michael adducts were expected to be useful intermediates for the synthesis of manzacidin A. However, we anticipated difficulty in the asymmetric intermolecular reactions of alanine derivatives via memory of chirality, because of the shorter half-life of racemization of enolate **B**, derived from L-alanine, than enolate **A** derived from L-phenylalanine (Scheme 2).[12] Since the asymmetric reaction of **B** with an electrophile competes with its own racemization, high enantioselectivity of the reaction is expected only when the reaction of **B** with electrophiles proceeds more rapidly than its racemization (Scheme 2).

With the above assumption in mind, the asymmetric intermolecular conjugate addition of alanine derivatives

Scheme 2. An Expected Stereochemical Course for Asymmetric Intermolecular Reactions of Axially Chiral Enolates Generated from L-Alanine



was examined. *N*-*tert*-butoxycarbonyl(Boc)-*N*-methoxymethyl(MOM)-alanine benzyl ester (**3**) was chosen as a substrate according to our previous results from the asymmetric reactions of the corresponding L-phenylalanine derivatives.[4,5a,5c,6] Attempted asymmetric conjugate addition of **3** with Michael acceptors such as ethyl acrylate or acrylonitrile under various conditions resulted in the low yields and/or low enantioselectivity (data not shown). By further screening of Michael acceptors, **4** was found suitable for the purpose. We first examined potassium hexamethyldisilazide (KHMDS) in toluene/THF (4:1) as a base, because this base/solvent system was critical for high enantioselectivity and yield in the asymmetric methylation of amino acid derivatives **1** via an axially chiral enolate (Scheme 1, R ≠ Me).[4] Since the alanine-derived axially chiral enolate was expected to be readily racemized, a solution of **3** and **4** was added slowly to a solution of KHMDS (Table 1, entry 1, procedure I) in order to minimize racemization of the chiral enolate during the course of intermolecular conjugate addition. Under these conditions, the axially chiral enolate was expected to react with the Michael acceptor immediately after its generation. A 1:1 diastereomeric mixture of **5a** and **5b** was obtained in a combined yield of 68%. The obtained diastereomer **5b** showed 82% ee (entry 1). Use of NaHMDS or LDA in toluene/THF (4:1) resulted in the lower enantioselectivity (63% ee for **5a**) or low yield (25%), respectively (entries 2 and 3). The solvent effects of the reactions using KHMDS as a base were then examined. We had anticipated that use of solvents with low coordinating ability such as toluene would elongate the half-life of racemization of the chiral enolates, but reduce the reactivity of the enolates toward electrophiles due to the higher aggregation state. On the other hand, the use of solvents with high coordinating ability such as THF or DMF would shorten the half-life of racemization of the chiral enolates while enhancing the reactivity of the enolates due to the lower aggregation state.[6] Therefore, the screening of solvents in the asymmetric reactions of chiral enolate intermediates seemed critical. The reaction of **3** and **4** with KHMDS in toluene gave a 1:1 diastereomeric mixture of **5a** and **5b** in a combined yield of 75%, and 92% ee and 92% ee, respectively (entry 4). In contrast, the reaction in THF gave **5** in

(9) Teraoka, F.; Fuji, K.; Ozturk, O.; Yoshimura, T.; Kawabata, T. *Synlett* **2011**, 543–546.

(10) (a) Kawabata, T.; Majumdar, S.; Tsubaki, K.; Monguchi, D. *Org. Biomol. Chem.* **2005**, *3*, 1609–1611. (b) Yoshimura, T.; Takuwa, M.; Tomohara, K.; Uyama, M.; Hayashi, K.; Yang, P.; Hyakutake, R.; Sasamori, T.; Tokitoh, N.; Kawabata, T. *Chem.—Eur. J.* **2012**, *18*, 15330–15336.

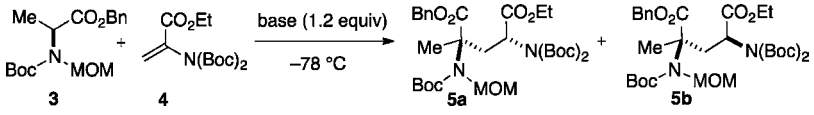
(11) Kobayashi, J.; Kanda, F.; Ishibashi, M.; Shigemori, H. *J. Org. Chem.* **1991**, *56*, 4574–4576.

(12) The half-life of racemization of *N*-*tert*-butoxylcarbonyl-*N*-methoxymethyl alanine ethyl ester was experimentally determined to be *ca.* 1 h at −78 °C in toluene/THF (4:1), while that of the enolate derived from the corresponding phenylalanine derivative has been reported to be 22 h (ref 4).

a quantitative yield with lower enantioselectivity (74% ee) (entry 5). The increase of the ee in the reaction in entry 4 and increase in the yield of the reaction in entry 5 could be attributed to the longer half-life of racemization in toluene and enhanced reactivity of the chiral enolate intermediate in THF, respectively. While the use of toluene/DMF (1:1) as a solvent slightly improved both the diastereoselectivity (**5a:5b** = 1:2) and enantioselectivity (**5a**: 91% ee, **5b**: 94% ee), it diminished the yield (31%; entry 6). Yet, the use of THF/DMF (1:1) improved the diastereoselectivity (**5a:5b** = 1:2), enantioselectivity (**5a**: 93% ee, **5b**: 93% ee), and the yield (83%), compared to the use of toluene/THF (4:1) (entry 1 vs 7). The optimal results were obtained by modification of the reaction procedure (procedure II). Slow addition of KHMDS to a mixture of **3** and **4** in THF/DMF (1:1) gave a 1:2 diastereomeric mixture of **5a** and **5b** in a quantitative yield and 97% ee and 97% ee, respectively (entry 8). The corresponding gram-scale reaction took place smoothly to give a reproducible result (entry 9). The importance of the reaction procedure was confirmed by comparison with our previous procedure for asymmetric methylation of **1** via memory of chirality.[4] A solution of **3** in THF/DMF (1:1) was treated with KHMDS for 30 min before addition of **4**, giving **5a** and **5b** in 70% yield and in 22% ee and 22% ee, respectively (entry 11). This indicates significant racemization of the chiral enolate derived from alanine derivative **3** during the initial 30 min. The absolute and relative configurations of **5a** and **5b** were determined by their conversion to manzacidin A and *ent*-manzacidin C, respectively (Scheme 3). The transformation indicated that the intermolecular conjugate addition proceeded with retention of configuration at the newly formed tetrasubstituted carbon center. We have recently observed that the ee of β-lactam formation by a related intramolecular conjugate addition process decreased following a prolonged reaction time, due to the reversibility of the conjugated addition process.[10b] In order to assess the reversibility of the present asymmetric conjugate addition, the effect of a prolonged reaction time was investigated after the addition of KHMDS. Stirring for 120 min (cf. 10 min in entry 8, procedure II) after the addition of KHMDS to a solution of **3** and **4** in THF/DMF (1:1) resulted in the formation of **5b** with an ee comparable to that in entry 8 (entry 8 vs 10). This suggests that the conjugate addition process of the chiral enolate to Michael acceptor **4** is irreversible.

Intermolecular conjugate addition reactions of various *N*-Boc-*N*-MOM-α-amino acid derivatives **6**–**9** with **4** were performed (Table 2). Reaction of phenylalanine-derived **6** with **4** proceeded smoothly in 20 min at −78 °C to give a 3:2 diastereomeric mixture of **10a** and **10b** in a quantitative combined yield and 97% ee and 97% ee, respectively (entry 1). The reaction of L-valine-derived **7** with **4** was sluggish at −78 °C, and it proceeded at −40 °C to give **11a** as a

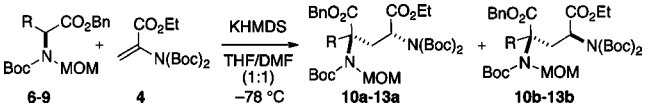
Table 1. Search for the Conditions of Asymmetric Intermolecular Conjugate Addition[a]



entry	base (1.2 equiv)	solvent	procedure[b]	yield	**5a:5b**[c,d]	ee of **5a** (%)[e,f]	ee of **5b** (%)[e,g]
1	KHMDS[h]	toluene/THF (4:1)	I	68%	1:1	–[i]	82
2	NaHMDS[j]	toluene/THF (4:1)	I	quant	1:1	63	–[i]
3	LDA	toluene/THF (4:1)	I	25%	1:1	–[i]	–[i]
4	KHMDS[k]	toluene	I	75%	1:1	92	92
5	KHMDS[h]	THF	I	quant	1:1	74	–[i]
6	KHMDS[k]	toluene/DMF (1:1)	I	31%	1:2	91	94
7	KHMDS[h]	THF/DMF (1:1)	I	83%	1:2	93	93
8	KHMDS[h]	THF/DMF (1:1)	II	quant	1:2	97	97
9[l]	KHMDS[h]	THF/DMF (1:1)	II	98%	1:2	97	98
10	KHMDS[h]	THF/DMF (1:1)	II[m]	90%	1:2	–[i]	97
11	KHMDS[h]	THF/DMF (1:1)	III	70%	1:2	22	22

[a] All reactions were run at substrate concentration of 0.1 M. [b] I: A solution of **3** (0.25 mmol) and **4** (2.0 equiv) was added to a solution of the base (1.2 equiv) during a period of 60 or 15 min for entries 1, 4, 6, and 7 or entries 2, 3, and 5, respectively, at −78 °C. The resulting mixture was stirred at the same temperature for 10 min. II: A KHMDS solution (1.2 equiv) was added to a solution of **3** (0.25 mmol) and **4** (2.0 equiv) during a period of 35 min at −78 °C. The resulting mixture was stirred at the same temperature for 10 min. III: A KHMDS (1.2 equiv) solution was added to a solution of **3** (0.29 mmol) in THF/DMF during a period of 5 min at −78 °C, and the mixture was stirred at the same temperature for 30 min. A solution of **4** (2.0 equiv) was added to the solution, and the resulting mixture was stirred for 10 min. [c] Diastereomeric ratio was determined by ^{1}H NMR of the diastereomeric mixture (see Supporting Information). [d] The relative configuration was determined by NOESY spectrum (see Supporting Information). [e] Enantiomeric excess was determined by HPLC analysis with a chiral stationary phase (see Supporting Information). [f] Absolute configuration was determined by the conversion to *ent*-manzacidin C (see text). [g] Absolute configuration was determined after the conversion to manzacidin A (see text). [h] A KHMDS solution in THF (0.5 M) was used. The solvent ratio shown in the table indicates the final solvent ratio. [i] Not determined. [j] A NaHMDS solution in THF (1.85 M) was used. The solvent ratio shown in the table indicates the final solvent ratio. [k] A KHMDS solution in toluene (0.5 M) was used. The solvent ratio shown in the table indicates the final solvent ratio. [l] A 3.4 mmol scale reaction. [m] After the addition of KHMDS, the solution was stirred for 120 min at −78 °C.

Table 2. Asymmetric Intermolecular Conjugate Addition of Amino Acid Derivatives **6**–**9** with **4**[a]



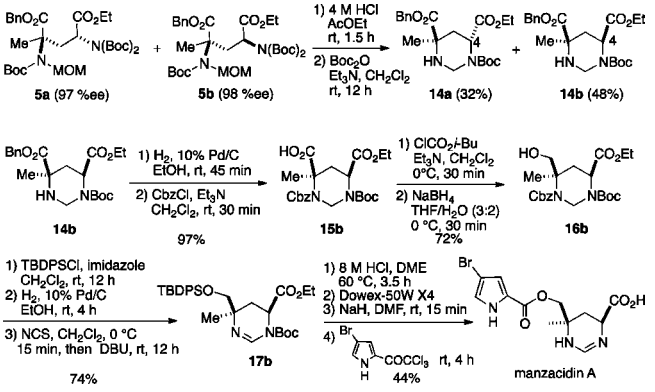
entry	R	time (h)	product (yield)	a:b[b–d]	ee (%)[e,f] a, b
1	$PhCH_2$ (**6**)	0.3	**10** (quant)	3:2	97, 97
2[g]	*i*-Pr (**7**)	24	**11** (50%)	1:0	87
3	*i*-Bu (**8**)	2	**12** (62%)	1:2	97, 97
4	$MeS(CH_2)_2$ (**9**)	0.2	**13** (quant)	1:2	91, 92

[a] Reactions were run in 0.39, 0.26, 0.34, and 0.52 mmol scale for entries 1, 2, 3, and 4, respectively, at substrate concentration of 0.1 M. [b] A KHMDS solution (1.2 equiv, 0.5 M in THF) was added to a solution of **6**–**9** and **4** (2.0 equiv) in THF/DMF during a period of 50, 30, or 25 min for entries 1, 2 and 3, or 4, respectively at −78 °C (final ratio of THF/DMF = 1:1). The resulting mixture was stirred at −78 °C for the time indicated in the table. [c] See footnote c in Table 1. [d] See footnote d in Table 1. [e] See footnote e in Table 1. [f] Absolute configuration was tentatively assigned by analogy with **5a** and **5b**. [g] Run at −40 °C.

single diastereomer in 50% yield and 87% ee (entry 2). The reactions of leucine-derived **8** and methionine-derived **9** with **4** took place at −78 °C to give **12** and **13**, respectively, in 91−97% ee (entries 3 and 4).

Michael adducts **5a** and **5b** were transformed into *ent*-manzacidin C and manzacidin A, respectively[11,13] (Scheme 3). Treatment of a diastereomeric mixture of **5a** (97% ee) and **5b** (98% ee) with 4 M HCl in ethyl acetate followed by regioselective introduction of an *N*-Boc group gave **14a** and **14b** in 32% and 48% yield, respectively as a diastereomerically pure form.[14] The pyrimidine ring was formed via an iminium intermediate generated from the *N*-MOM group under acidic conditions. Hydrogenolysis of the benzyl ester of **14b** followed by *N*-benzyloxycarbonylation gave **15b** in 97% yield. Chemoselective reduction of the carboxyl group of **15b** was accomplished via its mixed anhydride to give alcohol **16b** in 72% yield. Protection of the primary alcohol and hydrogenolysis of the Cbz group, followed by treatment with NCS and DBU, gave **17b** in 74% yield. Global deprotection of **17b** under acidic conditions followed by esterification with 4-bromo-2-trichloroacetylpyrrole[13a] gave manzacidin A in 44% yield, $[\alpha]^{20}_D = -24.2$ (*c* 0.7, MeOH) {lit.[11] $[\alpha]^{27}_D = -28$ (*c* 0.67, MeOH), lit.[13a] $[\alpha]^{27}_D = -22.4$ (*c* 0.52, MeOH)}. The spectral data of synthetic manzacidin A were identical to those of the natural product. *ent*-Manzacidin C was obtained from **14a** by a similar route to that shown in Scheme 3. The spectral data of synthetic *ent*-manzacidin C were identical to those of the natural product except for the sign of the optical rotation.

Scheme 3. Total Synthesis of Manzacidin A



In summary, we have developed a method for asymmetric intermolecular conjugate addition of α-amino acid derivatives via memory of chirality and achieved total syntheses of manzacidin A and *ent*-manzacidin C. The Michael adducts obtained by the present method will provide chiral building blocks for the synthesis of the manzacidin family and the related natural products.[2] The Michael adducts may also have potential utilities in the field of medicinal chemistry because they provide a new class of glutamic acid derivatives.[15]

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Supporting Information Available. Experimental procedures and spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

(13) For total syntheses of manzacidin A, see: (a) Namba, K.; Shinada, T.; Teramoto, T.; Ohfune, Y. *J. Am. Chem. Soc.* **2000**, *122*, 10708–10709. (b) Wehn, P. M.; Du Bois, J. *J. Am. Chem. Soc.* **2002**, *124*, 12950–12951. (c) Kano, T.; Hashimoto, T.; Maruoka, K. *J. Am. Chem. Soc.* **2006**, *128*, 2174–2175. (d) Wang, Y.; Liu, X.; Deng, L. *J. Am. Chem. Soc.* **2006**, *128*, 3928–3930. (e) Sibi, M. P.; Stanley, L. M.; Soeta, T. *Org. Lett.* **2007**, *9*, 1553–1556. (f) Hashimoto, T.; Maruoka, K. *Org. Biomol. Chem.* **2008**, *6*, 829–835. (g) Ichikawa, Y.; Okumura, K.; Matsuda, Y.; Hasegawa, T.; Nakamura, M.; Fujimoto, A.; Masuda, T.; Nakano, K.; Kotsuki, H. *Org. Biomol. Chem.* **2012**, *10*, 614–622. (h) Ohfune, Y.; Oe, K.; Namba, K.; Shinada, T. *Heterocyles* **2012**, *85*, 2617–2649.

(14) Attempted epimerization at the C(4) position of **14a** was unsuccessful under the basic conditions using DBU or KO*t*-Bu.

(15) (a) O'Neal, R. M.; Chen, G.-H.; Reynolds, C. S.; Meghal, S. K.; Koeppe, R. E. *Biochem. J.* **1968**, *106*, 699–706. (b) Thomas, H. A.; Ling, N.; Wei, E. T.; Berree, F.; Cobas, A.; Rapoport, H. *J. Pharmcol. Exp. Ther.* **1993**, *267*, 1321–1326. (c) Gumpena, R.; Kishor, C.; Ganji, R. J.; Addlagatta, A. *ChemMedChem* **2011**, *6*, 1971–1976.