Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron Letters
Tetrahedron Letters 47 (2006) 7423–7426

Synthesis of a biphenyl-based axially chiral amino acid as a highly efficient catalyst for the direct asymmetric aldol reaction

Taichi Kano, Osamu Tokuda and Keiji Maruoka*

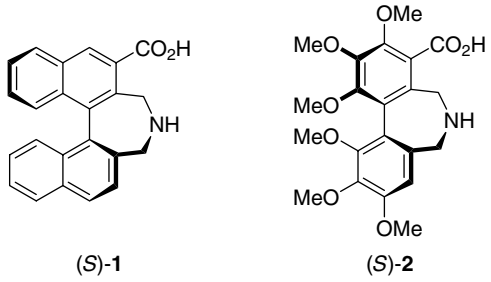
Department of Chemistry, Graduate School of Science, Kyoto University, Sakyo, Kyoto 606-8502, Japan

Received 3 August 2006; revised 12 August 2006; accepted 17 August 2006

Abstract—A biphenyl-based axially chiral amino acid (*S*)-**2** has been designed and synthesized. The new amino acid (*S*)-**2** has been found to be a more efficient catalyst than (*S*)-**1** in the direct asymmetric aldol reaction of acetone with aldehydes. For instance, the use of only 0.1 mol % of (*S*)-**2** was sufficient to complete the reaction between acetone and 4-nitrobenzaldehyde, giving the corresponding aldol adduct in good yield with an excellent enantioselectivity.

Organocatalytic asymmetric synthesis is regarded to be one of the most active areas in the current organic synthesis,[1] and a number of organocatalysts such as proline[2] and proline derivatives[3] including peptides[4] for the direct asymmetric aldol reaction have been successfully developed since the pioneering work of List et al.[2a] However, a substoichiometric amount of catalyst (20–30 mol %) is often required to achieve reasonable yields, and examples of the direct asymmetric aldol reaction at low catalyst loadings (e.g., <1 mol %) are rare. Since one of the main reasons for high catalyst loadings was known to be the degradation of proline under the reaction conditions,[5] we previously designed the binaphthyl-based axially chiral amino acid (*S*)-**1**, which is structurally different from proline.[6] Although the direct asymmetric aldol reaction was efficiently catalyzed by 5 mol % of this new robust amino acid, there is still room for further improvement in terms of catalyst loading. Herein, we report the synthesis of a highly efficient biphenyl-based axially chiral amino acid (*S*)-**2** and its successful application to the direct asymmetric aldol reaction (see Fig. 1).

Although a robust binaphthyl-based amino acid (*S*)-**1** gave a higher yield than the proline catalyst in the direct asymmetric aldol reaction with electron deficient aldehydes, somewhat high catalyst loadings (5 mol %) were still necessary to achieve high yields,[6] presumably due to the low nucleophilicity of the benzylic amine moiety in (*S*)-**1**. Accordingly, we designed a biphenyl-based amino acid of type (*S*)-**2**, which is highly substituted with electron-donating methoxy groups, with the expectation of the increasing nucleophilicity of the amine moiety.



(*S*)-**1** (*S*)-**2**

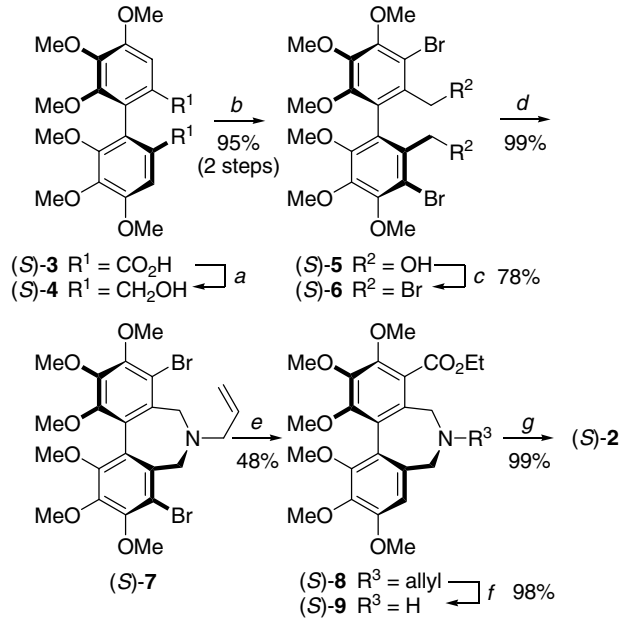
Figure 1. Designer axially chiral amino acids.

The requisite catalyst (*S*)-**2** was prepared from (*S*)-4,4′,5,5′,6,6′-hexamethoxybiphenyl-2,2′-dicarboxylic acid (*S*)-**3**,[7] which is readily prepared from commercially available gallic acid derivative or ellagic acid, in a seven-step sequence (Scheme 1).[8]

(*S*)-**2**, the new catalyst thus obtained was applied to the direct asymmetric aldol reaction and the results are summarized in Table 1. As expected, the aldol reaction between 4-nitrobenzaldehyde and acetone with 5 mol % of (*S*)-**2** in DMF was significantly accelerated in comparison with (*S*)-**1** and the reaction was complete within 4 h at room temperature (entry 1 vs 2). Only

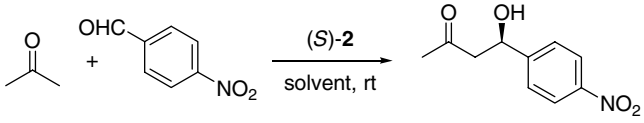
Keywords: Aldol reaction; Amino acid; Organocatalysis.
* Corresponding author. Tel./fax: +81 75 753 4041; e-mail: maruoka@kuchem.kyoto-u.ac.jp

0040-4039/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2006.08.051



Scheme 1. Synthesis of biphenyl-based amino acid (*S*)-**2**. Reagents and conditions: (a) BH_3–SMe_2, $B(OMe)_3$, 0 °C to rt, 5 h; (b) Br_2, pyridine, −20 °C to 0 °C, 1 h; (c) PBr_3, CH_2Cl_2, rt, 5 h; (d) allylamine, CH_3CN, 50 °C, 12 h; (e) *n*-BuLi, THF, −78 °C, 1 h; $(EtO)_2CO$, rt, 1 h; (f) $Pd(OAc)_2$, PPh_3, *N*,*N*-dimethylbarbituric acid, CH_2Cl_2, 35 °C, 12 h; (g) 1 M NaOH, MeOH–THF, reflux, 10 h.

Table 1. Direct asymmetric aldol reaction of 4-nitrobenzaldehyde with acetone catalyzed by (*S*)-**2**[a]



Entry	Catalyst (mol %)	Solvent	Time (h)	Yield[b] (%)	ee[c] (%)
1[d]	5	DMF	24	82	95 (*R*)
2	5	DMF	4	86	96 (*R*)
3	1	DMF	24	91	96 (*R*)
4	1	CH_3CN	24	75	94 (*R*)
5	1	MeOH	24	7	34 (*R*)
6	1	Acetone	24	90	95 (*R*)
7	0.5	DMF	48	58	95 (*R*)
8	0.5	Acetone	44	90	96 (*R*)
9	0.1	Acetone	96	91	96 (*R*)

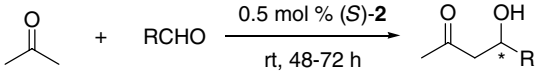
[a] The reaction of 4-nitrobenzaldehyde (0.25 mmol) with acetone (0.5 mL) in solvent (2 mL) was carried out in the presence of (*S*)-**2** at room temperature.
[b] Isolated yield after silica gel chromatography.
[c] The ee was determined by HPLC on a Chiralpak AS column with hexane/2-propanol (2:1).
[d] (*S*)-**1** was used instead of (*S*)-**2**.

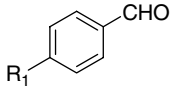
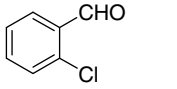
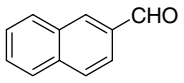
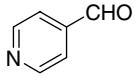
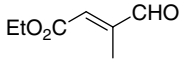
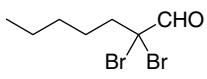
1 mol % of (*S*)-**2** in DMF was sufficient to obtain the desired aldol adduct in 91% yield with 96% ee (entry 3). Encouraged by this result, we next examined the solvent effect with the expectation of further reduction of catalyst loading. Among several solvents examined, acetone, which could not be used as a solvent for (*S*)-**1** due to its poor solubility, was also found to be a suitable solvent (entry 6). While DMF was less efficient with the lower catalyst loading (0.5 mol %) of (*S*)-**2** (entry 7), the reaction in acetone proceeded smoothly with excellent enantioselectivity (entry 8). Upon further investigation of the catalyst loading, it was found that even 0.1 mol % of (*S*)-**2** was sufficient to achieve a high yield and an excellent enantioselectivity (entry 9).

To prove the efficiency of this new catalyst, the aldol reaction of acetone with several other aldehydes was carried out in the presence of 0.5 mol % of (*S*)-**2** (Table 2).[9] Olefinic, heteroaromatic, and aromatic aldehydes with electron withdrawing groups were found to be suitable substrates (entries 1, 2, 5, 7, and 8). With 2 mol % of (*S*)-**2**, even simple aromatic aldehydes such as benzaldehyde and β-naphthylaldehyde gave the corresponding aldol adducts in moderate yields (entries 4 and 6). Furthermore, the reaction of α,α-dibromoheptanal as an aliphatic aldehyde substitute was also found to proceed with a high enantioselectivity (entry 9).[10]

To demonstrate the efficiency of biphenyl-based amino acid (*S*)-**2** in the direct asymmetric aldol reaction, a kinetic study using catalysts (*S*)-**1** and (*S*)-**2** was carried out (Fig. 2). With respect to the reaction rate, the biphenyl-based amino acid (*S*)-**2** was more effective than the binaphthyl-based amino acid (*S*)-**1**, probably due to the higher nucleophilicity of (*S*)-**2**. Furthermore, the reaction catalyzed by only 0.1 mol % of (*S*)-**2** in

Table 2. Direct asymmetric aldol reaction of various aldehydes with acetone catalyzed by (*S*)-**2**[a]



Entry	Aldehyde		Yield[b] (%)	ee[c] (%)
1		$R^1 = NO_2$	90	96 (*R*)
2		$R^1 = CN$	90	94 (*R*)
3		$R^1 = H$	19	95 (*R*)
4[d]		$R^1 = H$	50	95 (*R*)
5			82	96 (*R*)
6[d]			50	94 (*R*)
7			95	95
8			68	96
9			58	91

[a] The reaction of an aldehyde (0.25 mmol) with acetone (0.5 mL) in solvent (2 mL) was carried out in the presence of (*S*)-**2** at room temperature.
[b] Isolated yield after silica gel chromatography.
[c] The ee was determined by HPLC using a chiral column (Chiralpak AS, AD-H, Chiralcel OD-H, Daicel Chemical Industries).
[d] Use of 2 mol % of (*S*)-**2**.

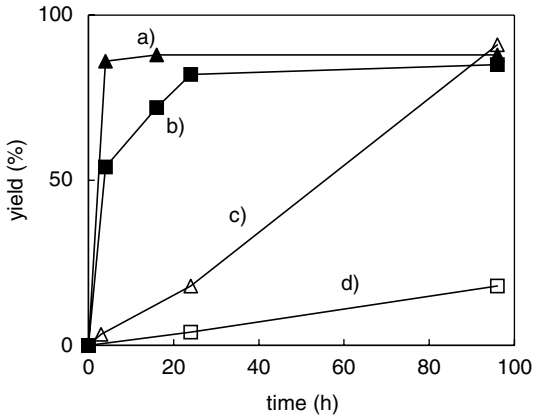


Figure 2. Direct asymmetric aldol reaction of acetone with 4-nitrobenzaldehyde using (a) 5 mol % (*S*)-**2** in DMF (0.125 M), (b) 5 mol % (*S*)-**1** in DMF (0.125 M), (c) 0.1 mol % (*S*)-**2** in acetone (0.10 M), and (d) 0.1 mol % (*S*)-**1** in acetone (0.10 M) at room temperature.

acetone proceeded gradually to completion, indicating the robust nature of (*S*)-**2** under the reaction conditions.

In conclusion, we synthesized a novel biphenyl-based axially chiral amino acid (*S*)-**2** and demonstrated its effectiveness for the direct asymmetric aldol reaction. It is worth noting that the catalyst loading could be decreased to only 0.1 mol % in acetone without loss of yield or enantioselectivity. Further investigations to expand the scope of substrates are currently underway.

Acknowledgments

This work was partially supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science and Technology, Japan.

References and notes

1. For reviews, see: (a) List, B. *Synlett* **2001**, 1675; (b) Dalko, P. I.; Moisan, L. *Angew. Chem., Int. Ed.* **2001**, *40*, 3726; (c) Movassaghi, M.; Jacobsen, E. N. *Science* **2002**, *298*, 1904; (d) List, B. *Tetrahedron* **2002**, *58*, 5573; (e) Alcaide, B.; Almendros, P. *Angew. Chem., Int. Ed.* **2003**, *42*, 858; (f) List, B. *Acc. Chem. Res.* **2004**, *37*, 548; (g) Saito, S.; Yamamoto, H. *Acc. Chem. Res.* **2004**, *37*, 570; (h) Notz, W.; Tanaka, F.; Barbas, C. F., III. *Acc. Chem. Res.* **2004**, *37*, 580; (i) Dalko, P. I.; Moisan, L. *Angew. Chem., Int. Ed.* **2004**, *43*, 5138; (j) Seayad, J.; List, B. *Org. Biomol. Chem.* **2005**, *3*, 719; (k) Berkessel, A.; Gröger, H. *Asymmetric Organocatalysis: From Biomimetic Concepts to Applications in Asymmetric Synthesis*; Wiley-VCH: Weinheim, 2005; Chapter 6, p 130.
2. (a) List, B.; Lerner, R. A.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2000**, *122*, 2395; (b) List, B.; Pojarliev, P.; Castello, C. *Org. Lett.* **2001**, *3*, 573; (c) Notz, W.; List, B. *J. Am. Chem. Soc.* **2000**, *122*, 7386; (d) Sakthivel, K.; Notz, W.; Bui, T.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2001**, *123*, 5260; (e) Bahmanyar, S.; Houk, K. N. *J. Am. Chem. Soc.* **2001**, *123*, 12911; (f) Córdova, A.; Notz, W.; Barbas, C. F., III. *J. Org. Chem.* **2002**, *67*, 301; (g) Bøgevig, A.; Kumaragurubaran, N.; Jørgensen, K. A. *Chem. Commun.* **2002**, 620; (h) Northrup, A. B.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2002**, *124*, 6798; (i) Hoang, L.; Bahmanyar, S.; Houk, K. N.; List, B. *J. Am. Chem. Soc.* **2003**, *125*, 16; (j) Kotrusz, P.; Kmentova, I.; Gotov, B.; Toma, S.; Solcaniova, E. *Chem. Commun.* **2002**, 2510; (k) Córdova, A.; Notz, W.; Barbas, C. F., III. *Chem. Commun.* **2002**, 3024; (l) Loh, T.-P.; Feng, L.-C.; Yang, H.-Y.; Yang, J.-Y. *Tetrahedron Lett.* **2002**, *43*, 8741; (m) Martin, H. J.; List, B. *Synlett* **2003**, 1901; (n) Sekiguchi, Y.; Sasaoka, A.; Shimomoto, A.; Fujioka, S.; Kotsuki, H. *Synlett* **2003**, 1655; (o) Bahmanyar, S.; Houk, K. N.; Martin, H. J.; List, B. *J. Am. Chem. Soc.* **2003**, *125*, 2475; (p) Pidathala, C.; Hoang, L.; Vignola, N.; List, B. *Angew. Chem., Int. Ed.* **2003**, *42*, 2785; (q) Peng, Y.-Y.; Ding, Q.-P.; Li, Z.; Wang, P. G.; Cheng, J.-P. *Tetrahedron Lett.* **2003**, *44*, 3871; (r) Northrup, A. B.; MacMillan, D. W. C. *Science* **2004**, *305*, 1752; (s) Northrup, A. B.; Mangion, I. K.; Hettche, F.; MacMillan, D. W. C. *Angew. Chem., Int. Ed.* **2004**, *43*, 2152; (t) List, B.; Hoang, L.; Martin, H. J. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5839; (u) Storer, R. I.; MacMillan, D. W. C. *Tetrahedron* **2004**, *60*, 7705; (v) Ward, D. E.; Jheengut, V. *Tetrahedron Lett.* **2004**, *45*, 8347; (w) Casas, J.; Engqvist, M.; Ibrahem, I.; Kaynak, B.; Córdova, A. *Angew. Chem., Int. Ed.* **2005**, *44*, 1343; Recently acyclic amino acids were also found to catalyze the direct asymmetric aldol reactions, see: (x) Córdova, A.; Zou, W.; Ibrahem, I.; Reyes, E.; Engqvist, M.; Liao, W.-W. *Chem. Commun.* **2005**, 3586; (y) Bassan, A.; Zou, W.; Reyes, E.; Himo, F.; Córdova, A. *Angew. Chem., Int. Ed.* **2005**, *44*, 7028.
3. For examples, see: (a) Saito, S.; Nakadai, M.; Yamamoto, H. *Synlett* **2001**, 1245; (b) Nakadai, M.; Saito, S.; Yamamoto, H. *Tetrahedron* **2002**, *58*, 8167; (c) Tang, Z.; Jiang, F.; Yu, L.-T.; Cui, X.; Gong, L.-Z.; Mi, A.-Q.; Jiang, Y.-Z.; Wu, Y.-D. *J. Am. Chem. Soc.* **2003**, *125*, 5262; (d) Berkessel, A.; Koch, B.; Lex, J. *Adv. Synth. Catal.* **2004**, *346*, 1141; (e) Hartikaa, A.; Arvidsson, P. I. *Tetrahedron: Asymmetry* **2004**, *15*, 1831; (f) Torii, H.; Nakadai, M.; Ishihara, K.; Saito, S.; Yamamoto, H. *Angew. Chem., Int. Ed.* **2004**, *43*, 1983; (g) Mase, N.; Tanaka, F.; Barbas, C. F., III. *Angew. Chem., Int. Ed.* **2004**, *43*, 2420; (h) Hayashi, Y.; Tsuboi, W.; Shoji, M.; Suzuki, N. *Tetrahedron Lett.* **2004**, *45*, 4353; (i) Tang, Z.; Jiang, F.; Yu, L.-T.; Cui, X.; Gong, L.-Z.; Mi, A.-Q.; Jiang, Y.-Z.; Wu, Y.-D. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5755; (j) Cobb, A. J. A.; Shaw, D. M.; Longbottom, D. A.; Gold, J. B.; Ley, S. V. *Org. Biomol. Chem.* **2005**, *3*, 84; (k) Guo, H.-M.; Cun, L.-F.; Gong, L.-Z.; Mi, A.-Q.; Jiang, Y.-Z. *Chem. Commun.* **2005**, 1450; (l) Tang, Z.; Yang, Z.-H.; Chen, X.-H.; Cun, L.-F.; Mi, A.-Q.; Jiang, Y.-Z.; Gong, L.-Z. *J. Am. Chem. Soc.* **2005**, *127*, 9285; (m) Samanta, S.; Liu, J.; Doddda, R.; Zhao, C.-G. *Org. Lett.* **2005**, *7*, 5321; (n) Chen, J.-R.; Lu, H.-H.; Li, X.-Y.; Chen, L.; Wan, J.; Xiao, W.-J. *Org. Lett.* **2005**, *7*, 4543; (o) Gryko, D.; Lipiński, R. *Adv. Synth. Catal.* **2005**, *347*, 1948; (p) Mase, N.; Nakai, Y.; Ohara, N.; Yoda, H.; Takabe, K.; Tanaka, F.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2006**, *128*, 734.
4. For examples, see: (a) Kofoed, J.; Nielsen, J.; Reymond, J. L. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 2445; (b) Tang, Z.; Yang, Z.-H.; Cun, L.-F.; Gong, L.-Z.; Mi, A.-Q.; Jiang, Y.-Z. *Org. Lett.* **2004**, *6*, 2285; (c) Krattiger, P.; Kovasy, R.; Revell, J. D.; Ivan, S.; Wennemers, H. *Org. Lett.* **2005**, *7*, 1101.
5. The formation of bicyclic oxazolidinones between proline and aldehydes or ketones is also known to lead to the

consumption of proline, see: Hartikka, A.; Arvidsson, P. I. *Eur. J. Org. Chem.* **2005**, 4287, and references therein.
6. Kano, T.; Takai, J.; Tokuda, O.; Maruoka, K. *Angew. Chem., Int. Ed.* **2005**, *44*, 3055.
7. Han, Z.; Yamaguch, Y.; Kitamura, M.; Maruoka, K. *Tetrahedron Lett.* **2005**, *46*, 8555, and references therein.
8. *Analytical data for* (*S*)-**2**: $[\alpha]_D^{30}$ −32.1 (*c* 0.46, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$/MeOD = 2:1) δ 6.87 (1H, s, Ar*H*), 4.00–4.04 (2H, m, ArC*H*H), 3.87 (3H, s, OCH_3), 3.85 (3H, s, OCH_3), 3.84 (3H, s, OCH_3), 3.79 (3H, s, OCH_3), 3.58 (3H, s, OCH_3), 3.57 (3H, s, OCH_3), 3.51 (1H, d, J = 12.4 Hz, ArCH*H*), 3.32 (1H, d, J = 13.2 Hz, ArCH*H*) ppm; ^{13}C NMR (100 MHz, $CDCl_3$/MeOD = 2:1) δ 173.8, 154.5, 152.3, 151.2, 150.1, 147.6, 143.6, 133.9, 126.4, 126.3, 123.4, 121.3, 109.5, 61.9, 61.4, 61.3, 61.24, 61.18, 56.5, 46.5, 43.8 ppm; IR (neat) 3404, 2988, 1582, 1458, 1387, 1325, 1096, 1030, 802 cm^{-1}; HRMS (ESI-TOF) Calcd for $C_{21}H_{26}NO_8$: 420.1653 ($[M+H]^+$), Found: 420.1653 ($[M+H]^+$).
9. *General procedure for the aldol reaction of acetone and aldehydes with* (*S*)-**2**: To a mixture of amino acid (*S*)-**2** (0.52 mg, 1.25 μmol) in anhydrous acetone (2.5 mL) was added an aldehyde (0.25 mmol) at room temperature. After stirring for 24–96 h at room temperature, the reaction mixture was then treated with saturated ammonium chloride solution and extracted with ethyl acetate. The organic layer was dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by flash column chromatography on silica gel (hexane/ethyl acetate as eluent) to give the corresponding aldol adduct.
10. *5,5-Dibromo-4-hydroxydecan-2-one (Table 2, entry 9)*: $[\alpha]_D^{29}$ 35.1 (*c* 1.30, $CHCl_3$; 91% ee); ^1H NMR (400 MHz, $CDCl_3$) δ 4.26 (1H, ddd, J = 9.3, 4.8, 2.0 Hz, C*H*OH), 3.32 (1H, d, J = 4.8 Hz, CHO*H*), 3.26 (1H, dd, J = 17.7, 2.0 Hz, C*H*H), 2.96 (1H, dd, J = 17.7, 9.3 Hz, CH*H*), 2.32–2.44 (2H, m, CH_2), 2.26 (3H, s, COCH_3), 1.69–1.74 (2H, m, CH_2), 1.34–1.39 (4H, m, CH_2), 0.92 (3H, t, J = 6.8 Hz, CH_3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 207.7, 81.1, 75.4, 47.4, 46.3, 31.0, 30.8, 26.9, 22.4, 13.9 ppm; IR (neat) 3423, 2955, 2926, 1715, 1362, 1080, 692 cm^{-1}; HRMS (ESI-TOF) Calcd for $C_{10}H_{18}Br_2O_2Na$: 350.9566 ($[M+Na]^+$). Found: 350.9669 ($[M+Na]^+$). HPLC analysis: Daicel Chiralpak AD-H, hexane/isopropanol = 9:1, flow rate = 1.0 mL/min, λ = 210 nm, retention time—11.7 min (major) and 13.1 min (minor).