Synthetic Studies Directed toward Kaitocephalin: A Highly Stereocontrolled Route to the Right-Hand Pyrrolidine Core

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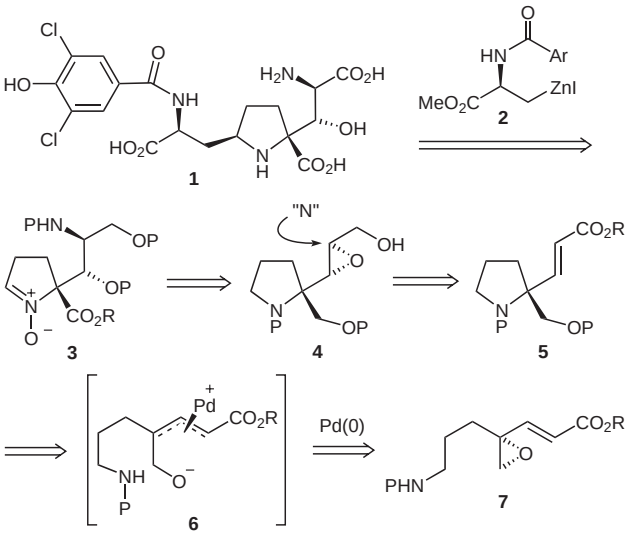
Dedicated to the memory of the late Professor Yoshihiro Matsumura

Abstract: A highly stereocontrolled method for the construction of the right-hand segment of kaitocephalin, an antagonist of AMPA/KA and NMDA glutamate receptors, has been developed employing palladium-catalyzed cyclization of an oxiranylacrylate at the quaternary center as the key step.

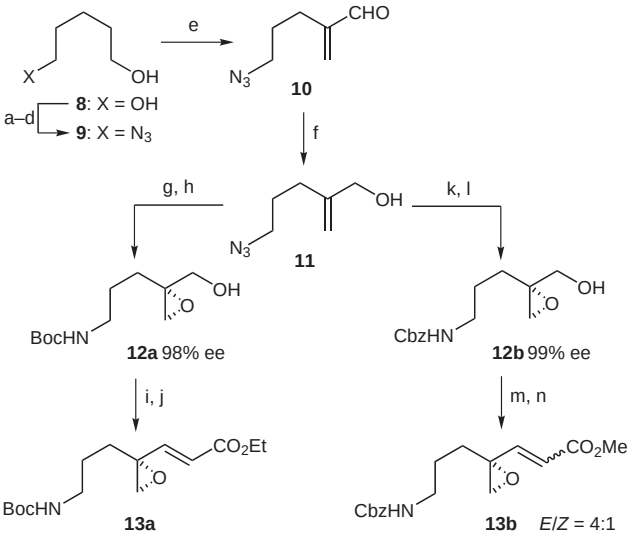
Key words: kaitocephalin, natural products, pyrrolidines, Tsuji–Trost reaction, ring closure

Kaitocephalin (**1**), isolated from *Eupenicillium shearii* PF1191 by Seto and Shin-ya et al.,[1] is known to exhibit potent inhibitory activity against neuronal cell death by the antagonistic action on AMPA [(*S*)-α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid]/KA (kainic acid) as well as NMDA (*N*-methyl-D-asparatic acid) glutamate receptors.[1] This natural product has, therefore, considerable potential as a promising lead compound for developing therapeutic agents against neuronal diseases such as stroke and epilepsy.[2] However, detailed neurobiological studies have become very difficult at present because the fungus has not produced kaitocephalin anymore. Due to such extremely low availability from natural sources as well as the intriguing biological activity and synthetically challenging molecular architecture, kaitocephalin has attracted much attention in the chemical and biological communities. Thus, there have been a number of synthetic studies[3] including two total syntheses[4] of kaitocephalin. However, the reported syntheses are not efficient enough to obtain sufficient quantities of this natural product.[5] The most difficult aspect of its synthesis resides in the stereoselective assembly of the right-hand segment consisting of an α-substituted proline connected to serine with a C–C bond.

Scheme 1 illustrates our retrosynthetic analysis of kaitocephalin which starts from the disconnection relying on coupling of nitrone **3**, a right-hand segment, with organozinc reagent **2**, a left-hand segment, tactically devised by Kitahara et al.[3c,4a] It is assumed that nitrone **3** would be accessible from ester **5** via stereo- and regioselective introduction of an amino group to epoxide **4** by taking advantage of the epoxy alcohol functionality. For the construction of the pyrrolidine skeleton with a quaternary



Scheme 1 Retrosynthesis.



Scheme 2 *Reagents and conditions*: (a) DHP, PPTS, CH_2Cl_2; (b) *p*-TsCl, Et_3N, DMAP, CH_2Cl_2; (c) NaN_3, DMF; (d) PPTS, MeOH, 56% (4 steps); (e) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, –78 °C, then *N*,*N*-dimethylmethyleneammonium iodide, Et_3N, CH_2Cl_2, 77%; (f) $NaBH_4$, $CeCl_3·7H_2O$, MeOH, –78 °C, 78%; (g) Ph_3P, H_2O, THF then Boc_2O, $NaHCO_3$, 89% (h) (–)-DIPT, Ti(*i*-PrO)$_4$, TBHP, 4 Å MS, CH_2Cl_2, –40 °C, 61%; (i) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, –78 °C; (j) $Ph_3P{=}CHCO_2Et$, CH_2Cl_2, 97% (2 steps); (k) Ph_3P, H_2O, THF then CbzCl, Na_2CO_3, 89%, (l) (–)-DIPT, Ti(*i*-PrO)$_4$, TBHP, 4 Å MS, CH_2Cl_2, –40 °C, 100%; (m) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, –78 °C; (n) $(MeO)_2POCH_2CO_2Me$, NaH, THF, 69% (2 steps).

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center, we envisioned stereoselective cyclization of oxiranylacrylate **7** through π-allylpalladium complex **6** under Tsuji–Trost reaction conditions.[6] Since, to our knowledge, such a pyrrolidine formation is unprecedented,[7] it is of great interest to probe whether the cyclization takes place via double inversion of stereochemistry even at the quaternary center without significant loss of the enantiomeric purity.

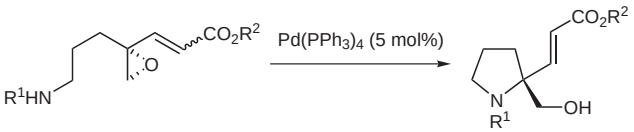
To examine the key pyrrolidine formation, oxiranylacrylate **13a** and **13b** were synthesized in over 98% ee (Scheme 2). Thus, 1,5-pentanediol (**8**) was first converted into azido alcohol **9** by a four-step sequence involving monotetrahydropyranylation, tosylation, azidation, and removal of the tetrahydropyranyl ether protecting group. Swern oxidation of **9** followed by in situ methylenation[8] using Eschenmoser's salt gave aldehyde **10** which was subjected to Luche reduction[9] to afford allyl alcohol **11**. Compound **11** was then converted into epoxy alcohol **12a** and **12b** via Staudinger reaction,[10] N-protection with either *tert*-butoxycarbonyl or benzyloxycarbonyl group, and Katsuki–Sharpless catalytic asymmetric epoxidation.[11] Swern oxidation followed by Wittig reaction converted **12a** into **13a** exclusively. On the other hand, **13b** was obtained as a 4:1 *E*/*Z*-mixture from **12b** by Swern oxidation followed by Horner–Emmons reaction.[12]

Palladium-catalyzed cyclizations of **13a** and **13b** were examined under various conditions using a catalytic amount (5 mol%) of $(Ph_3P)_4Pd$ (Table 1).[13] When the reaction of **13a** was conducted in boiling toluene, the cyclization became competitive with decomposition to give **14a** in poor yield (entry 1). In the reaction in boiling THF, **14a** was formed in 76% ee and in 68% yield (entry 2).[14] This ee value showed that appreciable racemization occurred during the cyclization. Similarly, in DMF and MeCN, the cyclization was also accompanied by racemization to produce **14a** in 73 to 83% ee in moderate yield (entries 3–5). On the other hand, in the reactions using **13b**, better yields were observed in MeCN and DMF than in THF (entries 6–11). It is important to note that *E*-isomer **14b** was produced exclusively in spite of the use of a 4:1 *E*/*Z*-mixture as a substrate. To our delight, addition of 1 equivalent of triethylamine brought about remarkable improvement in both yield and enantiomeric purity (entries 8–11).

When the reaction was carried out under the conditions listed in entry 11,[15] **14b** was obtained in 91% ee and in 86% yield. The absolute configurations of **14a** and **14b** were determined to be *S* by their correlation to an authentic sample.[16] This result clearly showed that the palladium-catalyzed cyclization took place via double inversion of stereochemistry at the quaternary center.

Having obtained key pyrrolidine **14b** in high enantiomeric purity, we then examined the stereoselective assembly of the right-hand segment from **14b** as shown in Scheme 3. Upon silylation and DIBAL-H reduction, **14b** gave allyl alcohol **15**, which was epoxidized with MCPBA at low temperature to give epoxide **17** as the sole product. In this particular case, neither $VO(acac)_2$-catalyzed epoxidation nor Katsuki–Sharpless asymmetric epoxidation conditions turned out to be effective. The stereoselective outcome thus observed can be rationalized by assuming a preferred approach of MCPBA from the less-hindered bottom face of Felkin–Ahn model **16**.[4b]

Table 1 Palladium-Catalyzed Cyclization of **13a** and **13b**



13a: R^1 = Boc, R^2 = Et (*E* only), 98%ee
13b: R^1 = Cbz, R^2 = Me (*E*/*Z* = 4:1), 99% ee

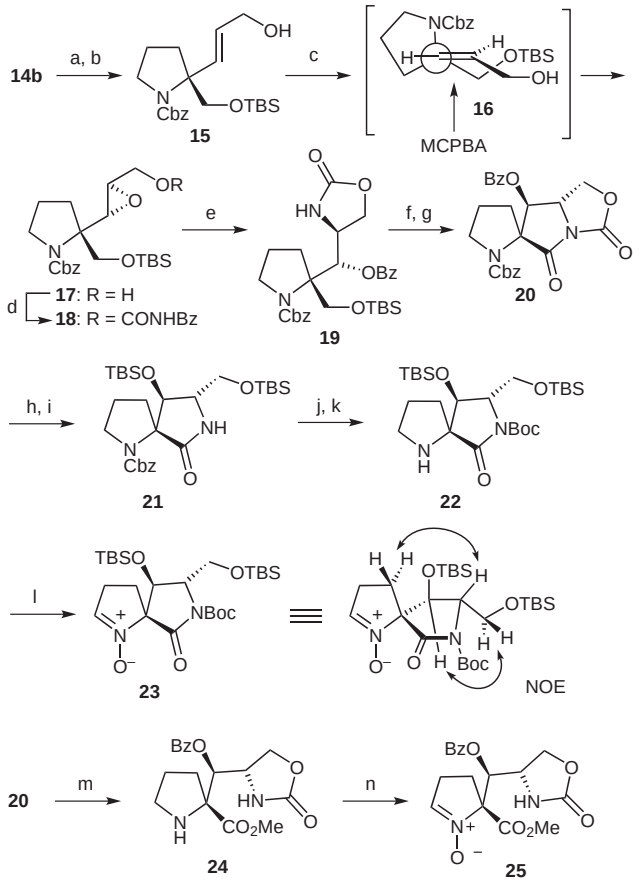
14a: R^1 = Boc, R^2 = Et
14b: R^1 = Cbz, R^2 = Me

Entry	Epoxide	Conditions	Yield (%)[a]	ee (%)
1		Toluene, reflux, 10 min	16	ND
2		THF, reflux, 1 h	68	76[b]
3	**13a**	DMF, 60 °C, 4.5 h	40	72[c]
4		DMF, r.t., 35 h.	46	83[c]
5		MeCN, 70 °C, 45 min	52	83[c]
6		THF, reflux, 45 min	12	ND
7		THF, Et_3N, reflux, 30 min	23	61[b]
8	**13b**	MeCN, 70 °C, 30 min	60	77[d]
9		MeCN, Et_3N, 70 °C, 20 min	72	80[b]
10		DMF, 70 °C, 20 min	54	78[d]
11		DMF, Et_3N, 70 °C, 30 min	86	91[b]

[a] Isolated yields.
[b] Determined by HPLC analysis using a chiral column (see ref. 12).
[c] Calculated by the $[\alpha]_D$ based on that of the sample of entry 2.
[d] Calculated by the $[\alpha]_D$ based on that of the sample of entry 9.

Reaction of **17** with benzoyl isocyanate followed by treatment of the resulting *N*-benzoyl carbamate **18** with K_2CO_3 allowed stereoselective cyclization accompanied by migration of the *N*-benzoyl group to afford cyclic carbamate **19**.[17] Upon desilylation followed by Jones oxidation, **19** afforded tricyclic lactam **20**[18] almost quantitatively. After methanolysis of **20** with Cs_2CO_3 in methanol,[19] the resulting diol was protected as its *tert*-butyldimethylsilyl ether to give **21**. *tert*-Butoxycarbonylation and hydrogenolytic removal of the benzyloxycarbonyl group converted **21** into amine **22**.[20] According to the procedure employed by Kitahara et al.,[3c,4a,21] **22** was cleanly oxidized to nitrone **23**,[22] a right-hand segment, in good yield. The stereostructure of **23** was established by its NOESY spectrum. Consequently, it was unambiguously confirmed that the above-mentioned epoxidation of **15** proceeded with the desired stereoselectivity as depicted in **16**.

Furthermore, it was gratifyingly found that, upon hydrogenolysis of **20** in MeOH, methanolysis of the lactam ring also simultaneously took place to afford amino ester **24**[23] in excellent yield. Oxidation of **24** in the same manner as



Scheme 3 *Reagents and conditions*: (a) *t*-$BuMe_2SiOTf$, 2,6-lutidine, CH_2Cl_2, 88%; (b) DIBAL-H, THF, –78 °C, 96%; (c) MCPBA, CH_2Cl_2, –40 °C, 99%; (d) PhCON=C=O, THF; (e) K_2CO_3, Bu_4NCl, MeCN, 55% (2 steps); (f) TBAF, AcOH, THF; (g) H_2CrO_4, H_2SO_4, acetone, 0 °C, 99% (2 steps); (h) Cs_2CO_3, MeOH, 96%; (i) *t*-$BuMe_2SiOTf$, 2,6-lutidine, CH_2Cl_2, 98%; (j) Boc_2O, Et_3N, MeCN, 81%; (k) H_2, 10% Pd/C, MeOH, 76%; (l) urea·H_2O_2, $MeReO_3$ (20 mol%), MeOH, SiO_2, 81%; (m) H_2, 10% Pd/C, MeOH, 95%; (n) urea·H_2O_2, $MeReO_3$ (11 mol%), MeOH, SiO_2, 64%.

employed for **22** furnished nitrone **25**,[24] another right-hand segment.

In conclusion, we have developed a highly enantio- and stereoselective route to the right-hand segment of kaitocephalin. The key palladium-catalyzed cyclization was proved to occur with double inversion of configuration even at the quaternary center. The present work provides a new methodology for the enantioselective construction of *gem*-substituted pyrrolidines. The synthetic effort toward achieving a total synthesis of kaitocephalin via coupling of **2** with **23** or **25** is currently ongoing.[25]

Acknowledgment

We thank Professor Hidenori Watanabe (The University of Tokyo) for informing us of the detailed coupling reaction conditions. This work is supported by Grant-in-Aid for Scientific Research of Japan Society for the Promotion of Science (JSPS).

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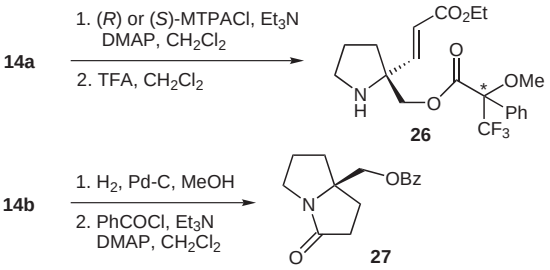
(12) Since the aldehyde derived from **12b** existed as the corresponding aminal, Wittig reaction using $Ph_3P{=}CHCO_2Et$ did not give **13b**.

(13) The ee values of **14a** (entry 2) and **14b** (entries 7, 9, 11) were determined by HPLC analysis [Daicel Chiralcell OJ-H, hexane–*i*-PrOH (20:1)] of **26** and **27**, respectively (Scheme 4).



Scheme 4

(14) **Reaction of 13a Giving 14a (Entry 2)**
To a solution of **13a** (51 mg, 0.17 mmol) in THF (3.3 mL) was added $(Ph_3P)_4Pd$ (10 mg, 0.0583 mmol) under an argon atmosphere, and the mixture was refluxed for 1 h. The reaction mixture was diluted with EtOAc, washed with H_2O

and brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash column chromatography twice [SiO_2 5 g, hexane–EtOAc (3:1); SiO_2 5 g, PhH–EtOAc (10:1)] to give **14a** as a colorless oil (35 mg, 68%, 76% ee): $[\alpha]_D^{24}$ +56.5 (*c* 0.66, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.00 (d, *J* = 15.9 Hz, 1 H), 5.73 (d, *J* = 15.9 Hz, 1 H), 5.43 (d, *J* = 10.2 Hz, 1 H), 4.20 (q, *J* = 7.0 Hz, 2 H), 3.89 (t, *J* = 10.5 H, 1 H), 3.76 (d, *J* = 10.5 Hz, 1 H), 3.56 (br s, 1 H), 3.41 (br s, 1 H), 1.75 (m, 4 H), 1.58 (s, 9 H), 1.29 (t, *J* = 7.0 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.1, 155.8, 148.3, 121.0, 80.8, 69.6, 68.8, 60.5, 48.9, 36.0, 28.3, 20.9, 14.2. FT-IR (neat): 3400, 1702, 1545, 1395, 1170 cm^{-1}. HRMS (EI): *m/z* calcd for $C_{11}H_{25}NO_5$ [M^+]: 299.1733; found: 299.1717.

(15) **Reaction of 13b Giving 14b (Entry 11)**
To a solution of **13b** (8.8 g, 27.6 mmol) and Et_3N (3.87 ml, 27.6 mmol) in DMF (276 mL) was added $(Ph_3P)_4Pd$ (1.6 g, 1.38 mmol) under an argon atmosphere, and the mixture was stirred for 0.5 h at 70 °C. The reaction mixture was diluted with Et_2O, washed with H_2O and brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash column chromatography [SiO_2 600 g, hexane–EtOAc (2:1)] to give **14b** as a colorless oil (7.6 g, 86%, 91% ee): $[\alpha]_D^{26}$ +47.2 (*c* 0.96, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.32 (s, 5 H), 7.02 (d, *J* = 15.9 Hz, 1 H), 5.76 (d, *J* = 15.9 Hz, 1 H), 5.20 (s, 2 H), 4.96 (d, *J* = 10.8 Hz, 1 H), 3.98–3.77 (m, 2 H), 3.74 (s, 3 H), 3.67–3.44 (m, 2 H), 1.87–1.78 (m, 4 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.3, 155.9, 148.1,136.2, 128.8, 128.7, 128.5, 128.1, 127.8, 120.8, 70.5, 68.2, 67.4, 51.6, 48.7, 35.6, 20.9. FT-IR (neat): 3419, 1691, 1412, 1350,1309 cm^{-1}. HRMS (EI): *m/z* calcd for $C_{17}H_{21}NO_5$ [M^+]: 319.1421; found: 319.1420.

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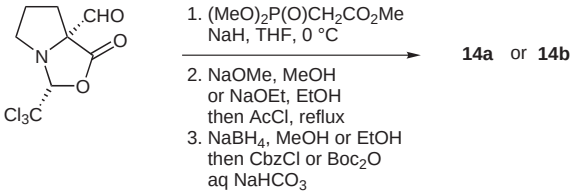

Scheme 5

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(18) Compound **20**: $[\alpha]_D^{27}$ +103.6 (*c* 0.87, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$, ca 2:3 mixture of rotamers): δ = 7.99 (d, *J* = 7.0 Hz, 2 H), 7.92 (d, *J* = 7.0 Hz, 2 H), 7.65 (m, 1 H), 7.38 (m, 5 H), 5.65 (d, *J* = 7.0 Hz, 0.6 H), 5.24 (d, *J* = 7.5 Hz, 0.4 H), 5.14 (s, 1 H), 5.14 (d, *J* = 11.0 Hz, 0.4 H), 4.96 (d, *J* = 11.0 Hz, 0.6 H), 4.81 (dd, *J* = 8.0 Hz, 0.6 H), 4.73 (dd, *J* = 8.0 Hz, 0.6 H), 4.46 (dd, *J* = 8.0 Hz, 0.4 H), 4.43 (m, 0.6 H), 4.30 (m, 0.4 H), 4.10 (m, 0.4 H), 3.73 (m, 1 H), 3.67 (m, 1 H), 2.75 (m, 1 H), 2.17 (m, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 180.0, 167.2, 154.4, 148.8, 135.8, 134.2, 131.2, 129.6, 129.1, 129.0, 128.9, 128.8, 128.5, 128.2, 128.0, 78.1, 71.3, 68.7, 67.6, 58.6, 47.7, 31.1, 24.5. FT-IR (film): 1835, 1738, 1565 cm^{-1}. HRMS (EI): *m/z* calcd for $C_{24}H_{22}N_2O_7$ [M^+]: 450.1425; found: 450.1427.

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(20) Compound **22**: $[\alpha]_D^{23}$ +32.0 (*c* 1.14, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 4.18–4.12 (m, 1 H), 4.06 (d, *J* = 3.9 Hz, 1 H), 3.75 (dd, *J* = 10.4, 2.0 Hz, 1 H), 3.68 (br s, 1 H), 3.22–3.16 (m, 1 H), 2.93–2.89 (m, 1 H), 2.22–2.17 (m, 1 H), 1.90–1.74 (m, 3 H), 1.53 (s, 9 H) 0.92–0.83 (m, 18 H), 0.07–0.01 (m, 12 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 176.8, 150.2, 83.1, 73.1, 72.1, 64.7, 59.8, 47.0, 29.3, 28.0, 25.7, 25.6, 17.9, –4.8, –5.4; FT-IR (film): 1754, 1719, 1489 cm^{-1}. HRMS (EI): *m/z* calcd for $C_{25}H_{50}N_2O_5Si_2$ [M^+]: 514.3260; found: 528.3258.

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(22) **Oxidation of 22 to 23**
To a solution of urea·H_2O_2 (1.54 g, 16.4 mmol) in MeOH (5 mL) was added $MeReO_3$ (47 mg, 0.16 mmol) under an argon atmosphere, and the mixture was stirred at r.t. for 10 min. A solution of **22** (449 mg, 0.82 mmol) in MeOH (8 mL) and SiO_2 (1.35 g) were added and the mixture was stirred at r.t. for 1.5 h. The reaction was quenched with sat. $Na_2S_2O_3$ and the reaction mixture was extracted with EtOAc. The extract was washed with H_2O and brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography [SiO_2 20 g, hexane–EtOAc (3:2)] to give **23** (350 mg, 81%) as a colorless viscous oil. $[\alpha]_D^{23}$ +39.2 (*c* 1.01, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$): δ = 7.17 (s, 1 H), 5.33 (d, *J* = 7.0 Hz, 1 H), 4.37 (d, *J* = 10.5 Hz, 1 H), 3.74 (d, *J* = 10.5 Hz, 1 H), 3.61 (m, 1 H), 2.87 (m, 1 H), 2.76–2.71 (m, 1 H), 2.64–2.59 (m, 1 H) 2.08 (t, *J* = 10.5 Hz, 1 H), 1.52 (s, 9 H), 0.84 (s, 18 H), 0.16–0.14 (m, 12 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 168.5, 149.6, 136.0, 84.7, 83.9, 65.4, 63.3, 59.6, 28.2, 26.0, 25.7, 22.8, 17.4, 17.1, 4.0, –5.6. FT-IR (neat): 1764, 1725, 1304, 1254 cm^{-1}. HRMS (EI): *m/z* calcd for $C_{25}H_{48}N_2O_6Si_2$ [M^+]: 528.3035; found: 528.3051.

(23) Compound **24**: $[\alpha]_D^{23}$ +19.2 (*c* 1.05, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 8.03 (d, *J* = 7.2 Hz, 2 H), 7.60 (t, *J* = 7.3 Hz, 1 H), 7.47 (t, *J* = 7.5 Hz, 2 H), 6.37 (br s, 1 H), 5.24 (d, *J* = 5.7 Hz, 1 H), 4.53 (dd, *J* = 11.6, 3.6 Hz, 1 H), 4.26 (dd, *J* = 12.0, 8.1 Hz, 1 H), 3.81 (m, 1 H), 3.79 (s, 3 H), 3.29–2.15 (m, 1 H), 3.10–2.92 (m, 1 H), 2.38–2.31 (m, 1 H), 1.92–1.79 (m, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 179.4, 165.6, 155.4, 133.6, 129.7, 129.1, 128.6, 77.6, 69.6, 68.1, 56.0, 55.1, 47.7, 29.9, 26.5. FT-IR (neat): 3240, 2262, 2875, 1720, 1448 cm^{-1}. HRMS (EI): *m/z* calcd for $C_{17}H_{20}N_2O_6$ [M^+]: 348.1306; found: 348.1321.

(24) **Oxidation of 24 to 25**
Compound **24** (139 mg, 0.40 mmol) was oxidized using urea·H_2O_2 (827 mg, 8.80 mmol), $MeReO_3$ (11 mg, 0.044 mmol), and SiO_2 (580 mg) in MeOH (5 mL) in the same manner as described in ref. 22. Purification of crude product by column chromatography [SiO_2 7 g, MeOH–EtOAc (0:1 to 1:10)] gave **25** (92 mg, 64%) as a colorless viscous oil: $[\alpha]_D^{23}$ +65.9 (*c* 0.83, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 8.04 (d, *J* = 7.2 Hz, 2 H), 7.64 (t, *J* = 7.2 Hz, 1 H), 7.49 (t, *J* = 7.2 Hz, 2 H), 7.07 (s, 1 H), 6.95 (br s, 1 H), 5.99 (d, *J* = 3.9 Hz, 1 H), 4.79 (dd, *J* = 11.1, 4.8 Hz, 1 H), 4.48 (dd, *J* = 11.1, 4.8 Hz, 1 H), 4.04–3.96 (m, 1 H), 3.78 (s, 3 H), 2.97, 2.91 (m, 1 H), 2.69–2.61 (m, 1 H), 2.56–2.51 (m, 2 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.4, 165.1, 155.2, 133.9, 129.8, 128.7, 128.5, 128.3, 82.8, 72.0, 68.4, 57.0, 55.1, 26.9, 23.7. FT-IR (neat): 3230, 2922, 1724, 1373, 1277,1176, 1109 cm^{-1}. HRMS (EI): *m/z* calcd for $C_{17}H_{18}N_2O_7$ [M^+]: 362.1104; found: 362.1114.

(25) Coupling reactions of **2** (Ar = 4-benzyloxy-3,5-dichlorophenyl) with **23** and **25** were preliminarily examined following the procedure reported by Kitahara et al.,[3c,4a] but the desired coupling products were obtained in <10% yield, respectively. To improve the yield, these coupling reactions are now being examined under various conditions.