An Improved Synthesis of (–)-Martinellic Acid via Radical Addition–Cyclization–Elimination Reaction of Chiral Oxime Ether

Okiko Miyata, Atsushi Shirai, Shintaro Yoshino, Yoshifumi Takeda, Makiko Sugiura, Takeaki Naito*

Kobe Pharmaceutical University, Motoyamakita, Higashinada, Kobe 658-8558, Japan
Fax +81(78)4417556; E-mail: taknaito@kobepharma-u.ac.jp

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Abstract: A concise formal synthesis of (–)-martinellic acid has been accomplished by preparing optically active dipyrroloquinoline as a key synthetic intermediate, which was prepared via the radical addition–cyclization–elimination of oxime ether carrying an unsaturated ester followed by two chemoselective reductions of the carbonyl groups.

Key words: martinellic acid, radical reaction, oxime ether, asymmetric synthesis, pyrroloquinoline

Martinellic acid (**1**) and martinelline (**2**) have attracted considerable interest since they were isolated by Witherup and co-workers[1] in 1995, principally because of their antagonistic activity against some G-protein coupled receptors such as bradykinin B_1 and B_2, α_1-adrenergic, and muscarinic receptors (Figure 1). In addition, both alkaloids contain a pyrroloquinoline ring system, which has not been discovered in natural products so far. Therefore, it is not surprising that these alkaloids have been the object of intense synthetic effort.[2–4]

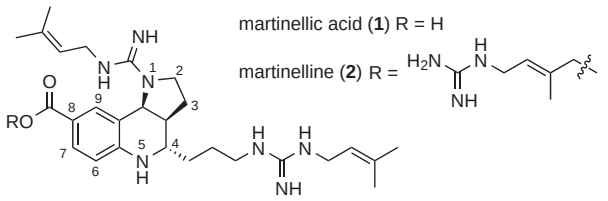
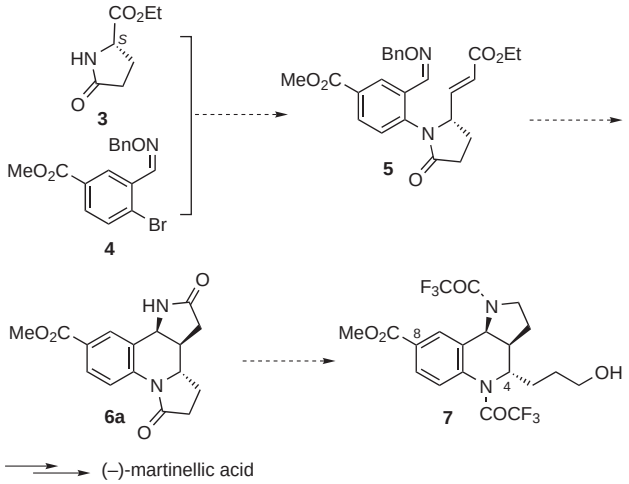


Figure 1 Martinellic acid and martinelline

Recently, we reported a formal synthesis of (±)-martinelline via two types of radical reactions as the key steps.[3d] Those are the radical addition–cyclization–elimination (RACE) of oxime ether and a C–C bond formation through a radical 1,5-hydrogen atom translocation. Though several syntheses of racemic martinelline, martinellic acid and the pyrroloquinoline core have been achieved, to our knowledge, there is only one paper published on the asymmetric synthesis of (–)-martinellic acid by Ma's group.[2a,b] However, their method required many steps (twenty) to achieve the synthesis of (–)-martinellic acid. We have now succeeded in asymmetric formal synthesis of (–)-martinellic acid. Aiming at a short-step synthesis of (–)-martinellic acid, we designed a synthetic strategy for a key intermediate **7** as shown in Scheme 1. Our strategy consists of two key steps: (1) the construction of optically active and requisitely substituted dipyrroloquinoline **6a** using the RACE reaction of the optically active oxime ether **5** bearing a pyrrolidinone ring; (2) chemoselective reduction of two lactam carbonyl groups in dipyrroloquinoline **6a**. Snider and colleagues[3b] reported the synthesis of (±)-martinellic acid via a dipyrroloquinoline as an intermediate, which was prepared by the reaction of aniline with Meldrum's acid-activated vinylcyclopropane followed by [3+2] dipolar cycloaddition. However, it is difficult to apply this method to the preparation of optically active (–)-martinellic acid because the optically active Meldrum's acid activated vinylcyclopropane is rapidly racemized.[5] On the other hand, in our method, the optically active substrate **5** for the RACE reaction used in our synthesis would be efficiently prepared by Cu- or Pd-catalyzed cross-coupling reaction of arylbromide **4** and L-pyroglutamic acid ethyl ester (**3**).



Scheme 1

We first investigated the RACE reaction of model compound **14** that has no ester group in the benzene ring (Scheme 2). The requisite substrate **14** was readily prepared from 2-bromobenzaldehyde (**9**) as follows. According to the Buchwald–Hartwig cross-coupling method,[6] the optically active L-pyroglutamic acid ethyl ester (**3**),[7] prepared from L-glutamic acid (**8**), was treated with 2-bromobenzaldoxime ether (**10**) in the presence of CuI, K_2CO_3, and a ligand to give *N*-arylpyrrolidinone **11** in 53% yield. When Pd was used as a catalyst, the yield of **11**

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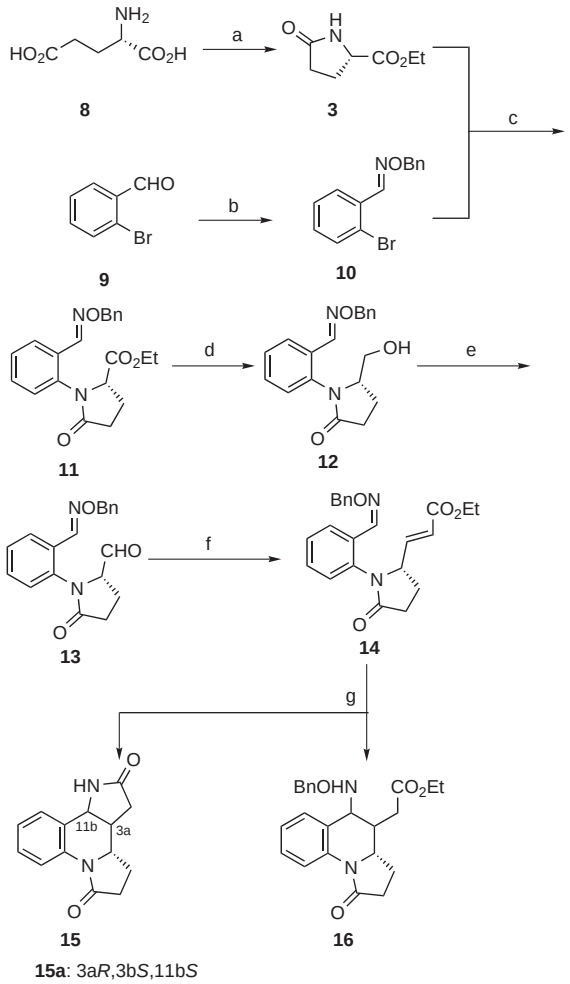


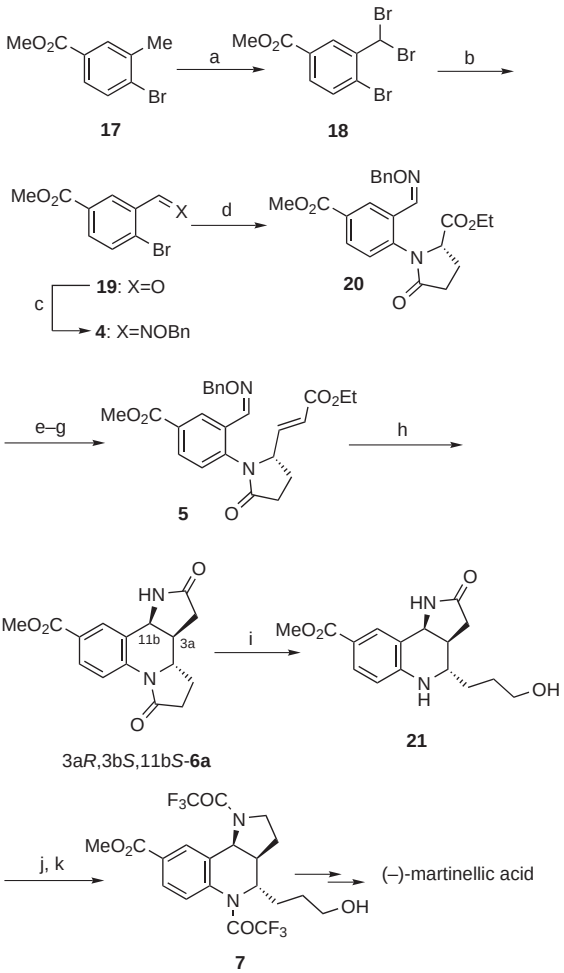
Scheme 2 *Reagents and conditions*: (a) $SOCl_2$, EtOH, reflux, 95%; (b) $BnONH_2$·HCl, NaOAc, MeOH–CH_2Cl_2, r.t., 96%; (c) $Pd_2(dba)_3$, xantphos, Cs_2CO_3, 1,4-dioxane, 100 °C, 99%; (d) $NaBH_4$, MeOH, r.t.; (e) TFAA, DMSO, Et_3N, CH_2Cl_2, –65 °C to r.t.; (f) ethyl (triphenylphosphoranylidene)acetate, THF, r.t., 90% (from **11**); (g) Bu_3SnH, AIBN, benzene, reflux, 60% (**15**); 14% (**16**).

was improved to 99%. The ester **11** was converted to the desired α,β-unsaturated ester **14** via the reduction ($NaBH_4$), Albright oxidation (DMSO–TFAA), and Wittig reaction.

According to our procedure developed in the radical addition–cyclization of oxime ether,[3d] treatment of **14** with Bu_3SnH and AIBN in refluxing benzene gave two types of products, dipyrroloquinoline **15** (60%)[8] and pyrroloquinoline **16** (14%) bearing an amino ester group. The major product was the desired (3a*R*,3b*S*,11b*S*)-dipyrroloquinoline (**15a**)[8] which was isolated in 33% yield. As a possible reaction pathway, **15a** would be formed via consecutive reactions which are addition of a stannyl radical to the oxime ether group to form a benzyl radical, radical cyclization to form a quinoline ring, pyrrolidone ring formation, and finally cleavage of the N–O bond. However, we are unable at the moment to offer a detailed explanation of the reaction pathway in this interesting radical reaction.

We have now succeeded in the preparation of optically active dipyrroloquinoline **15a** using the RACE reaction.

Based on the preliminary results, we next investigated the radical reaction of oxime ether **5** carrying the ester group and selective conversion of dipyrroloquinoline **6a** to the known key intermediate **7** for synthesis of (–)-martinellic acid (Scheme 3). The α,β-unsaturated ester **5** was prepared from commercially available **17** by a similar procedure to form **14**. The benzyl dibromide **18**, prepared from commercially available methyl 4-bromo-3-methylbenzoate (**17**), was treated with $AgNO_3$ in methanolic water to give the aldehyde **19**, which was converted to *O*-benzyloxime ether **4** (80% from **18**) by the usual procedure. The Pd-catalyzed cross-coupling reaction of bromide **4** with L-pyroglutamic acid ethyl ester (**3**) under the Buchwald conditions gave the optically active oxime ether **20** in 98% yield while the coupling reaction using CuI gave **20** in moderate yield. According to the procedure for **14**, the



Scheme 3 *Reagents and conditions*: (a) NBS, AIBN, CCl_4, reflux, quant.; (b)$AgNO_3$, H_2O, MeOH, reflux; (c) $BnONH_2$·HCl, NaOAc, MeOH–CH_2Cl_2, r.t., 80%; (d) L-pyroglutamic acid ethyl ester (**3**), $Pd_2(dba)_3$, xantphos, Cs_2CO_3, 1,4-dioxane,100 °C, 98%; (e) $NaBH_4$, MeOH, r.t.; (f) TFAA, DMSO, Et_3N, CH_2Cl_2, –65 °C to r.t.; (g) ethyl (triphenylphosphoranylidene) acetate, THF, r.t., 82% (from **20**); (h) Bu_3SnH, AIBN, benzene, reflux, 45% (including its stereoisomers); (i) $LiBH_4$, MeOH–THF, reflux, 76%; (j) BH_3·THF, THF, reflux; (k) TFAA, Et_3N, DMAP, CH_2Cl_2, r.t., 79% (from **21**).

ester **20** was converted to the desired α,β-unsaturated ester **5** (82% from **20**). We next carried out the RACE reaction of ester **5** which proceeded smoothly to give the desired 3a*R*,3b*S*,11b*S*-dipyrroloquinoline (**6a**) and its stereoisomers in 45% combined yield.[9]

We next investigated the chemoselective reduction of **6a** carrying three different types of carbonyl groups such as the ester, *N*-arylpyrrolidinone, and *N*-norpyrrolidinone. In order to reduce selectively the carbonyl group of *N*-arylpyrrolidinone, the dipyrroloquinoline **6a** was treated with $LiBH_4$ in the presence of MeOH in THF to afford the desired amino alcohol **21**[10] in 76% yield. Finally, the reduction of lactam **21** with borane–THF followed by acylation of the resulting amine with trifluoroacetic anhydride gave the desired trifluoroacetamide **7**[11] (79% yield from **21**), which is the key intermediate for synthesis of (–)-martinellic acid.

In conclusion, we have newly developed an 11-step synthesis (10% overall yield) of the optically active key intermediate for synthesis of (–)-martinellic acid. Key steps include the RACE reaction of oxime ether and chemoselective reductions of three carbonyl groups.

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(8) In addition to **15a**, three stereoisomers, which are (3a*R*,3b*S*,11b*R*)-**15b** (12%), (3a*S*,3b*S*,11b*S*)-**15c** (9%), and (3a*S*,3b*S*,11b*R*)-**15d** (6%) were obtained after purification of the reaction mixture by column chromatography.
Compound **15a**: mp >260 °C (acetone, MeOH). IR: ν_{max} = 1694, 3433 cm^{-1}. ^1H NMR (500 MHz): δ = 1.72–1.80 (1 H, m), 2.22 (1 H, d, *J* = 17.0 Hz), 2.40–2.71 (4 H, m), 2.80 (1 H, dd, *J* = 17.0, 7.5 Hz), 3.71 (1 H, dt, *J* = 11.5, 7.5 Hz), 4.83 (1 H, d, *J* = 5.5 Hz), 6.48 (1 H, br s), 7.16 (1 H, td, *J* = 8.0, 2.0 Hz), 7.29 (1 H, dd, *J* = 8.0, 2.0 Hz), 7.37 (1 H, td, *J* = 8.0, 2.0 Hz), 8.50 (1 H, dd, *J* = 8.0, 2.0 Hz). ^{13}C NMR (125 MHz): δ = 22.8, 31.2, 34.1, 40.5, 53.4, 55.8, 120.2, 123.8, 124.5, 129.22, 129.24, 135.7, 173.2, 175.1. HRMS: *m/z* calcd for $C_{14}H_{14}N_2O_2$ [M^+]: 242.1055; found: 242.1067; Anal. Calcd for $C_{14}H_{14}N_2O_2$: C, 69.41; H, 5.82; N, 11.56. Found: C, 69.16; H, 5.80; N, 11.48. $[\alpha]_D^{27}$ +44.5 (*c* 0.26, $CHCl_3$).
(9) Column chromatography of the reaction mixture gave (3a*R*,3b*S*,11b*S*)-dipyrroloquinoline **6a** (29%), (3a*R*,3bS,11b*R*)-**6b** (8%), (3a*S*,3b*S*,11bS)-**6c** (4%), and (3a*S*,3b*S*,11b*R*)-**6d** (4%), respectively.
Compound **6a**: mp 165–168 °C (acetone, MeOH). IR: ν_{max} = 1702, 3428 cm^{-1}. ^1H NMR (500 MHz): δ = 1.75–1.83 (1 H, m), 2.26 (1 H, d, *J* = 17.0 Hz), 2.45–2.56 (2 H, m), 2.59–2.74 (2 H, m), 2.82 (1 H, dd, *J* = 17.0, 7.5 Hz), 3.77 (1 H, td, *J* = 11.0, 7.5 Hz), 3.93 (3 H, s), 4.86 (1 H, d, *J* = 5.5 Hz), 5.93 (1 H, br s), 7.99 (1 H, d, *J* = 2.0 Hz) 8.02 (1 H, dd, *J* = 8.5, 2.0 Hz), 8.67 (1 H, d, *J* = 8.5 Hz). ^{13}C NMR (125 MHz): δ = 23.1, 31.4, 34.0, 40.3, 52.3, 53.2, 55.8, 119.6, 123.5, 125.7, 130.7, 131.1, 139.8, 166.2, 173.8, 174.6. HRMS: *m/z* calcd for $C_{16}H_{16}N_2O_4$ [M^+]: 300.1110; found: 300.1128. Anal. Calcd for $C_{16}H_{16}N_2O_4$: C, 63.99; H, 5.37; N, 9.33. Found: C, 63.85; H, 5.25; N, 9.25. $[\alpha]_D^{28}$ +100.7 (*c* 0.235, $CHCl_3$).

(10) Optical purity of **21** was determined to be >93% ee by ^{1}H NMR spectroscopic analysis of the corresponding (–)-MTPA ester which was derived from **21** by esterification using (–)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride.

(11) Compound **7**: IR: ν_{max} = 1695, 3526 cm^{-1}. ^{1}H NMR (300 MHz): δ = 1.56 (4 H, br s), 2.12 (1 H, br s), 2.30 (1 H, m), 2.72 (1 H, m), 3.58 (3 H, m), 3.93 (4 H, br s), 4.75 (1 H, br s), 5.35 (1 H, br s), 7.39 (1 H, br s), 8.03 (1 H, br d, *J* = 8.5 Hz), 8.44 (1 H, br s). ^{13}C NMR (125 MHz): δ = 28.6, 29.7, 30.1, 30.8, 46.0, 52.4, 57.7, 58.6, 61.9, 116.3 (q, CO*C*F$_3$), 125.3, 129.9, 130.4, 133.6, 137.8, 157.1 (q, *C*OCF$_3$), 165.8. HRMS: *m/z* calcd for $C_{20}H_{20}F_6N_2O_5$ [M$^+$]: 482.1276. Found: 482.1273. $[\alpha]_D^{16}$ +64.0 (*c* 0.99, $CHCl_3$) {lit.[2a,2b] $[\alpha]_D^{20}$ +65.1 (*c* 0.97, $CHCl_3$)}.