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Synthetic studies on bradykinin antagonist martinellines: construction of a pyrrolo[3,2-*c*]quinoline skeleton using silicon-tether RCM reaction and allylic amination

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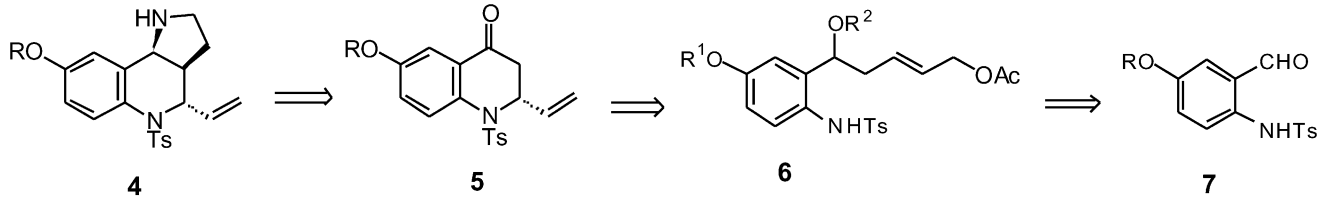
Abstract—The pyrrolo[3,2-*c*]quinoline consisting of a core structure of martinellines, the first naturally occurring heterocycle, was prepared through silicon-tether ring-closing metathesis reaction and intramolecular allylic amination as key steps.

1. Introduction

Heterocycles constitute the core structures of numerous biologically active natural products and have occupied a very important position as lead compounds of medicines. Recently, we have been interested in the unique structure and biological activities of martinelline (**1**) and martinellic acid (**2**), novel bradykinin antagonists, isolated from *Martinella equitosensis* by Witherup et al. in 1995.[1] Especially, the pyrrolo[3,2-*c*]quinoline ring (**3**), which is the structural nucleus of the martinellines and the first naturally occurring ring, has attracted wide attention as a synthetic target. Many research groups have reported not only the synthesis of the core heterocycle but also the synthesis of martinellines.[2,3] We have already demonstrated an asymmetric construction of the tetrahydroquinoline skeleton via asymmetric allylic substitution reaction using our developed chiral ligand, 9-PBN.[4,5] We describe here a new method for construction of the pyrroloquinoline skeleton using the allylic substitution reaction and silicon-tether ring-closing metathesis (RCM) reaction as key reactions. As shown in Scheme 1, pyrroloquinoline **4** would be constructed from tetrahydroquinolinone **5**, which could be synthesized from allyl acetate **6** by using the intramolecular cyclization developed by us (Fig. 1).

2. Results and discussion

In the synthesis of the tetrahydroquinoline ring, we first attempted the preparation of the substrate **6** by introduction of the C_4 unit to aldehyde **7** using methyl 4-bromocrotonate or crotyl reagents. The regioselective introduction using metal reagents with the allyl unit proved difficult. For example, the vinylogous Reformatsky reaction of aldehyde **7b** with methyl 4-bromocrotonate in the presence of zinc and iodine non-regioselectively proceeded to produce an equal mixture of regioisomers **9** and **10**.[4] Alkylation using the crotyl metal type reagent occurred not at the desired α position but at the undesired γ position of the crotyl unit via



Scheme 1.

Keywords: Pyrrolo[3,2-*c*]quinoline; Silicon-tether ring-closing metathesis; Intramolecular allylic amination; Martinelline; Cross-metathesis.
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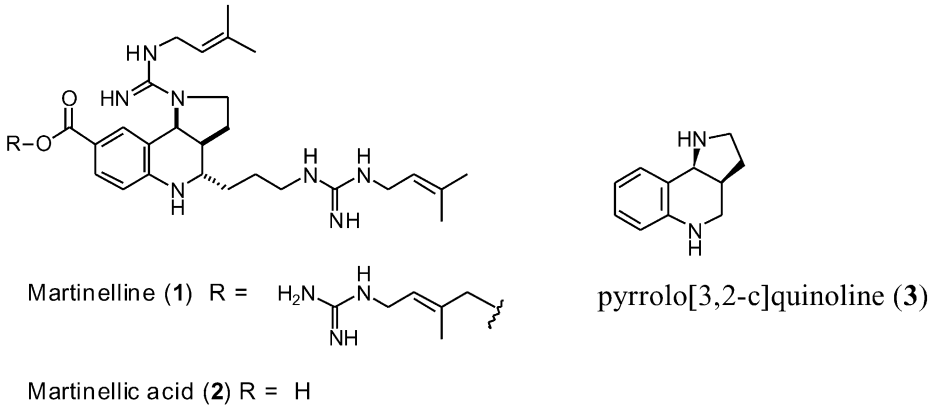
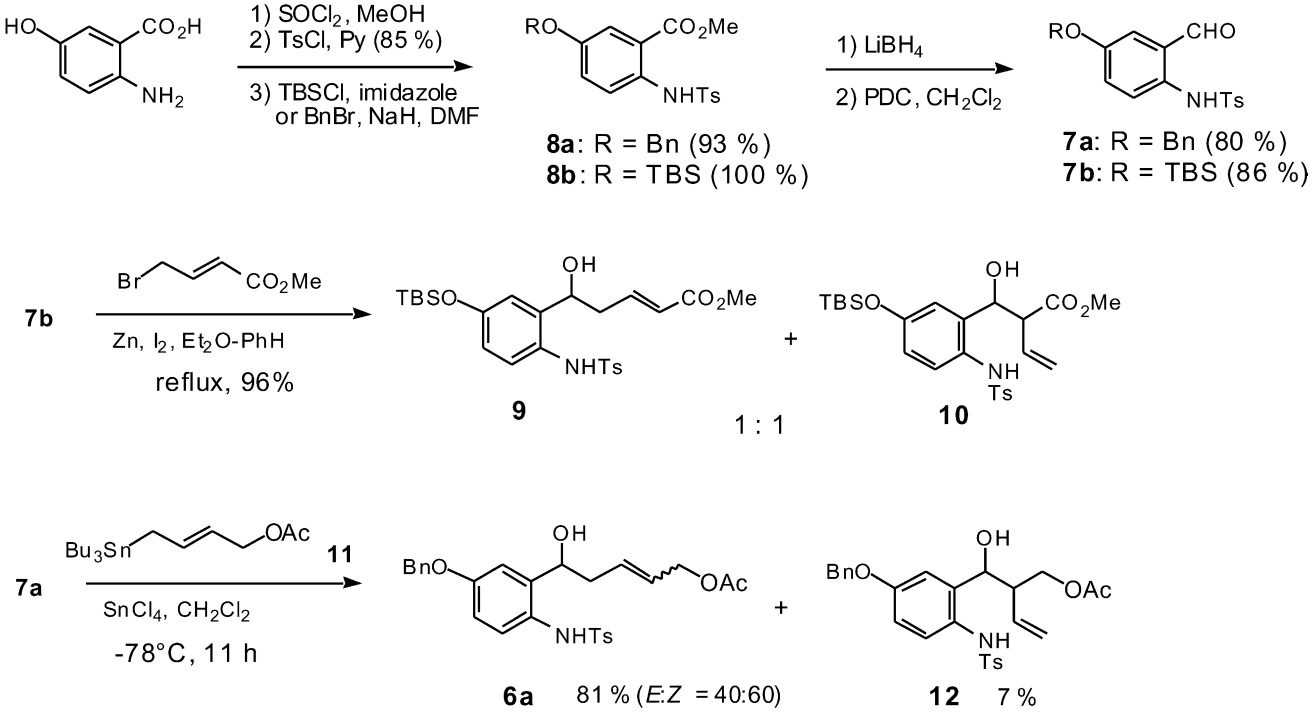


Figure 1.

$S_N 2'$ reaction. Although it appeared difficult to change the regioselectivity from γ to α position, this problem was partly solved by use of the Thomas procedure.[6] Acetoxycrotylstannane **11** was pretreated with stannic chloride in methylene chloride at −78 °C for 5 min and then aldehyde **7a** was added. The reaction proceeded regioselectively to afford an *E*/*Z* mixture of α-product **6a** in 81% yield with a small amount of γ-product **12** (Scheme 2). However, we did not pursue this approach since preparation of the starting stannane **11** was difficult for large-scale production. Recently, olefin metathesis reaction has become a powerful tool for construction of an olefin unit, and has been successfully used for synthesis of many biologically active substances so far. We thought that the olefin metathesis reaction would be able to produce the precursor **6** without contamination of the regioisomer using a cross-metathesis reaction[7] or a RCM reaction[8] (Fig. 2).

First, the cross-metathesis reaction was examined between homoallylic alcohol **13** and allylic acetate. The aldehyde **7** prepared from readily available 5-hydroxyanthranilaldehyde was converted to homoallyl alcohol **13** by reaction with allyl Grignard reagent. The cross-metathesis reactions between the olefin **13** and the donor olefins, allyl acetate and crotyl acetate, are summarized in Table 1. The mixture of olefin **13c** and allyl acetate was treated with 10 mol% of Grubbs reagent **16** to afford cross product **6c** in 15% yield (run 3). The thus-obtained compound **6c** was a mixture of *E* and *Z* olefins in the ratio of 4:1–6:1 (run 3). Since an attempt using an increasing amount of the catalyst and the allyl acetate failed to improve the chemical yield, crotyl acetate was used in place of the allyl acetate. The reaction was similarly carried out in the presence of 10 mol% of the catalyst and 5 equiv of crotyl acetate to give the desired compound in 28% yield (run 4). In this case the substrate disappeared on tlc and a large amount of a side product with the dimeric structure of **13c** generated in 57% yield. An attempt to prevent the production of this dimeric product



Scheme 2.

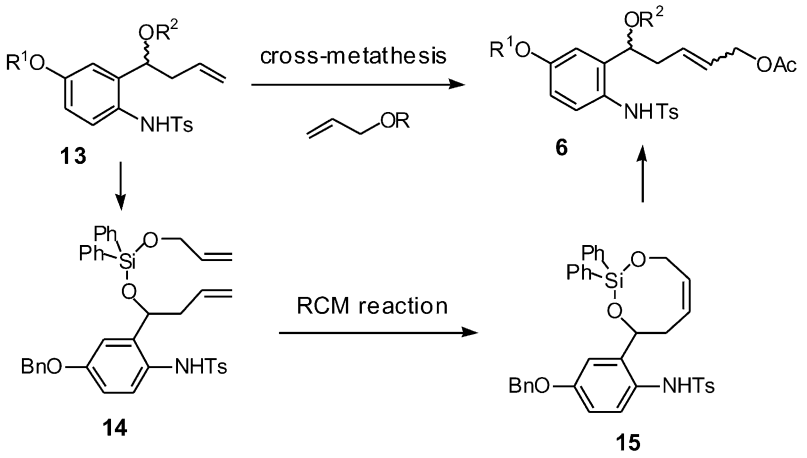
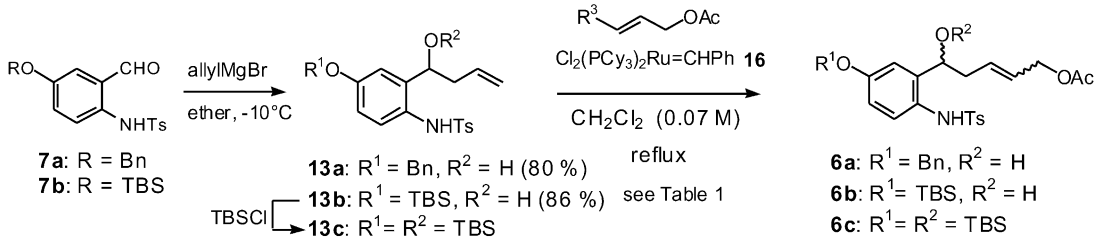


Figure 2.

failed. Next, the influence of the protecting group at the benzylic alcohol was examined because the adjacent functional groups of olefin are known to often prevent the catalytic cycle of olefin metathesis reaction by strong coordination to the ruthenium atom as a ligand. The olefin **13b** bearing a free hydroxy group was reacted with the allylic acetate in the presence of the Grubbs catalyst and the improvement of chemical yield to 42% was observed without recovery of **13b** (run 2). The change of the protecting group on the aromatic ring had no effect on the chemical yield (run 1). As the cross-metathesis gave us unsatisfactory results, we decided to carry out the chain extension of **13** by the RCM reaction. The RCM reaction has been used for the formation of a variety of cyclic compounds including not only macrocyclic compounds but also medium-ring ones. For the silicon-tether RCM reaction,[9] we needed a substrate with the allyl silyl moiety at the benzylic position. The new silicon compound was prepared from commercially available dichlorodiphenylsilane. Dichlorodiphenylsilane was treated with allyl alcohol in the presence of triethylamine in methylene chloride at room temperature to give the desired allyloxychlorodiphenylsilane **17** in 87% yield after distillation under reduced pressure. This compound, however, was very sensitive to moisture and therefore was immediately used for next reaction. Introduction of the silane residue to the hydroxyl group was performed under the general condition. The silane **17** was easily reacted with alcohol **13a** in methylene chloride at room temperature for 5 min to give the precursor **14** for the RCM reaction in 97% yield. The RCM reaction of **14** was carried out with 5 mol% of Grubbs reagent **16** in 0.07 M solution to form the cyclic silyl ether **15** with the eight-membered ring in 40% yield. As the starting material was completely consumed in this reaction, we thought that this low yield might be due to polymerization of the substrate. When the concentration of **14** was diluted to 0.01 M solution, the reaction smoothly took place at reflux for 5 h to afford the desired product **15** in 86% yield. Removal of the silicon-tether from **15** with tetra*n*-butylammonium fluoride (TBAF) gave diol **18** in 84% yield. Acid-catalyzed acetylation of **18** with acetic anhydride furnished allyl acetate **6d** (Scheme 3).

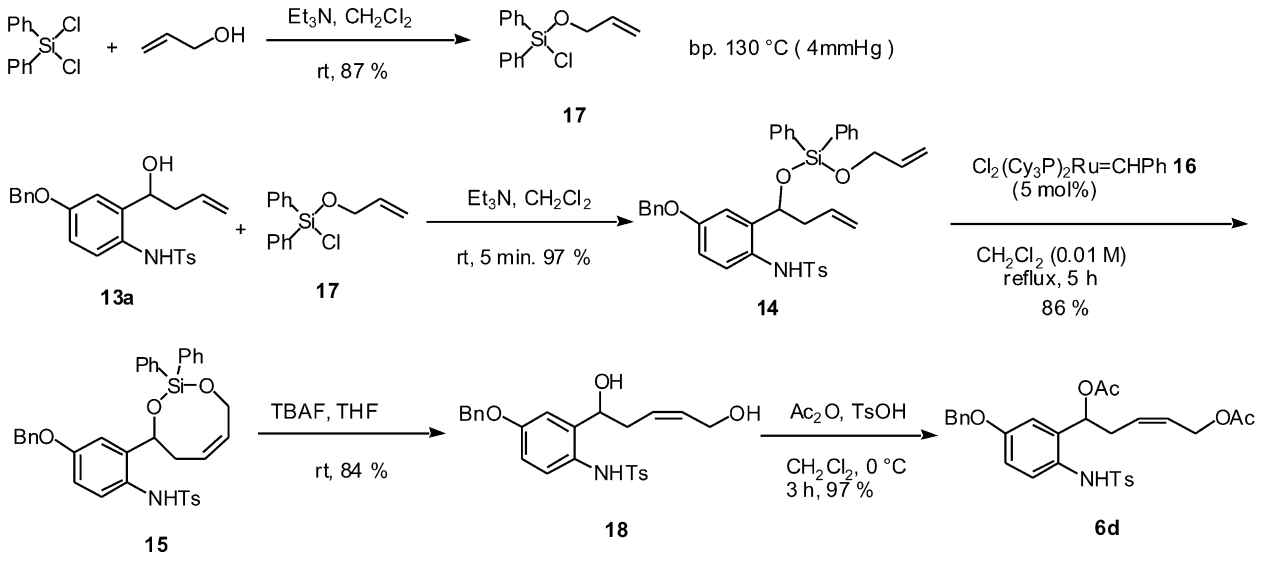
With the substrates for cyclization in hand, we next investigated intramolecular allylic substitution reaction of **6** for construction of the tetrahydroquinoline ring (Table 2). The allyl ester **6c** bearing a hinder TBS group and *E* geometry on the side chain was treated with bis(benzylidene)

Table 1. Cross-metathesis reaction between homoallylic alcohol **13** and allyl acetate



Run	Compounds	R^3	Ru (mol%)	Time (h)	Yield[a]
1	**13a**	H	10	44	38% (56%)
2	**13b**	H	10	23	42%
3	**13c**	H	10	45	15% (85%)
4	**13c**	CH_3	10	20	28%

[a] The product was obtained as a mixture of *E* and *Z* olefins in a ratio of 4:1–6:1. The parentheses are yields based on consumed starting material.

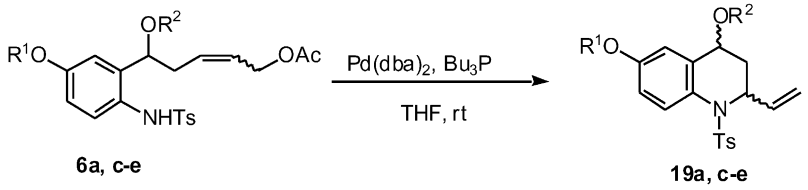


Scheme 3.

palladium ($Pd(dba)_2$) and tri*n*-butylphosphine (Bu_3P) in THF at room temperature to obtain the desired tetrahydroquinoline **19c** with *cis* relationship as a single product in 92% yield (run 1). Even if a mixture of *E* and *Z* olefins was used in this reaction, the reaction proceeded in a similar manner to afford the 2,4-*cis* product in excellent yield (run 2). The relative stereochemistry of **19c** was judged by the coupling constant of the ^1H NMR spectrum. The values of the coupling constants between the C-3 axial proton and the adjacent protons are 11.4 and 11.8 Hz, which show that both the C-4 proton and the C-2 proton are placed on the pseudo-axial position. On the other hand, compounds **6a** and **6d** bearing hydroxyl and acetoxy groups at the benzylic position gave a mixture of *cis* and *trans* diastereomers, respectively, under similar conditions. The observed outcome shows that the hydroxyl and acetoxy substituents adjacent to the π-allyl palladium complex affect the stereoselectivity of the cyclization. With this satisfactory result, the asymmetric cyclization of **6c** using (−)-9-PBN in place of Bu_3P was carried out in the presence of lithium acetate and bis(trimethylsilyl) acetamide (BSA). The reaction somewhat sluggishly proceeded in a reagent-controlled manner and provided a mixture of *cis*-**19c** and *trans*-**19c** with 60%ee each in the ratio of 68:32 (run 3).

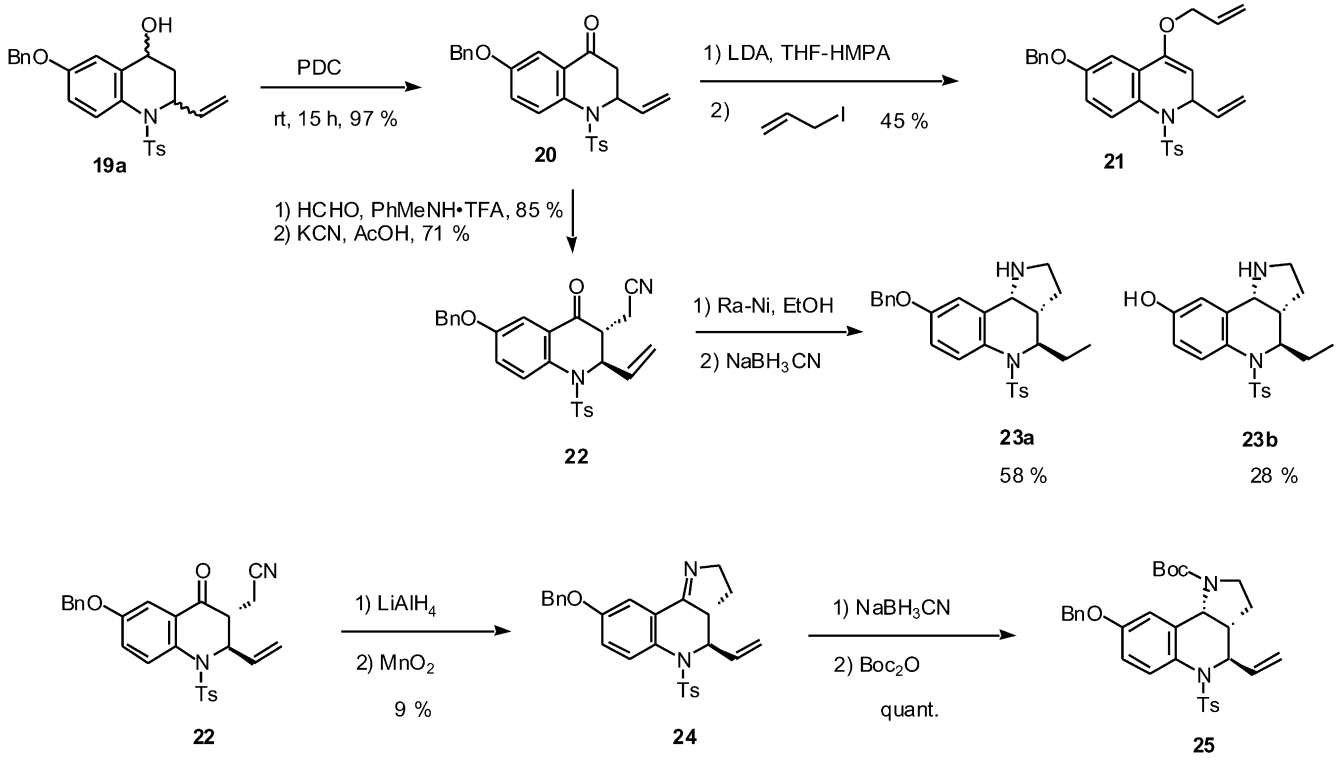
With the tetrahydroquinoline available in large quantities, we then focused our attention on introduction of the pyrrole ring. First, the α-alkylation of tetrahydroquinolone **20** was extensively investigated (Scheme 4). However, we were unable to obtain the corresponding *C*-alkylated product except *O*-alkylated product **21** which was produced by *O*-alkylation of the lithium enolate derived from **20** and lithium diisopropylamide (LDA). After many efforts we found a two-step approach including the Mannich reaction and 1,4-conjugate addition. Tetrahydroquinolone **20** was treated with paraformaldehyde in the presence of *N*-methylaniline trifluoroacetate (TFA·PhNHMe) at reflux for 33 h to provide the *exo*-methylene product in 85% yield. For the introduction of the C_1 unit, 1,4-conjugate addition of the

Table 2. Preparation of tetrahydroquinolines using palladium-catalyzed cyclization



Run	Compound	R^1	R^2	Geometry	Time (h)	Yield (%)	Ratio of *cis*:*trans*
1	**6c**	TBS	TBS	*E* only	20	92	Only *cis*
2	**6c**	TBS	TBS	Mixture of *E* and *Z*			Only *cis*
3[a]	**6c**	TBS	TBS	*E* only	35	42	68:32
4[b]	**6a**	Bn	H	Mixture of *E* and *Z*	17	96	3:1
5	**6d**	Bn	Ac	*Z* only	44	96	3:1
6	**6e**	Bn	*E* only	*E* only	16	96	Only *cis*

[a] This reaction was carried out with the combination of $Pd(dba)_2$ and (−)-9-PBN in the presence of LiOAc ans BSA.
[b] This reaction was carried out in the presence of AcOH.



Scheme 4.

nitrile group was examined. The 1,4-conjugate addition reaction cleanly proceeded by the treatment of potassium cyanide (KCN) in the presence of acetic acid at room temperature to afford *trans* 2,3-disubstituted tetrahydroquinolone **22** as the sole product in 71% yield.

For the construction of pyrroloquinoline, the reduction of nitrile of **22** with lithium aluminum hydride followed by oxidation of benzylic alcohol with manganese dioxide gave an imino product in only poor yield. The resulting imine was reduced with sodium cyanoborohydride ($NaBH_3CN$) at room temperature and then treatment with di-*t*-butyl dicarbonate (Boc_2O) gave pyrroloquinoline **25** in quantitative yield (Scheme 4). As conversion of the nitrile to the corresponding amine was disappointing, the catalytic hydrogenation was employed for the improvement of yields. Among Rh/Al_2O_3, PtO_2, and Raney Ni selected as catalysts for the hydrogenation, Raney Ni gave the best result. Finally, the synthesis of pyrroloquinoline was achieved in a two-step manner: (1) the reduction of nitrile with Raney Ni under hydrogen atmosphere and (2) reduction of the resulting cyclic imine with $NaBH_3CN$. Pyrroloquinoline **23a** and its deprotected product **23b** were obtained in 58 and 28% yields, respectively. The relative stereochemistry of pyrroloquinoline showed the C_{3-4} *cis* relationship, which was confirmed by the NOE experiment.

3. Conclusion

In summary we have established a new access to pyrroloquinolines bearing the martinelline core structure using key reactions, allylic substitution reaction catalyzed by palladium and silicon-tether RCM reaction. Further investigation directed towards total synthesis of martinellines is underway in our laboratories.

4. Experimental

4.1. General

Melting points were measured with a SIBATA NEL-270 melting point apparatus. Infrared spectra were recorded on a JASCO FT/IR-230 Fourier transform infrared spectrophotometer. Optical rotations were measured on a JASCO DIOP-14 polarimeter. ^1H NMR spectra were recorded on a JEOL JNM-GSX 400A (400 MHz), JNM GSX500A (500 MHz), or JNM ECP400 (400 MHz) spectrometer. Chemical shifts are recorded in ppm from tetramethylsilane or chloroform as the internal standard. Analytical thin layer chromatography was performed on Merck Art. 5715, Kieselgel 60F254/0.25 mm thickness plates. Mass spectra were obtained on a JEOL HX-110A spectrometer. Column chromatography was performed with silica gel BW-820MH (Fuji Davision Co.). Solvents for reaction were reagent grade and distilled from the indicated drying agent: tetrahydrofuran (THF), benzene: sodium/benzophenone ketyl; diethyl ether (Et_2O): lithium aluminum hydride ($LiAlH_4$); acetonitrile, dichloromethane (CH_2Cl_2), diisopropylamine, dimethylformamide (DMF), *n*-hexane, toluene, dichloroethane ($C_2H_4Cl_2$): calcium hydride; methanol (MeOH): iodine/magnesium. Dimethylsulfoxide (DMSO) was dried over 4 Å molecular sieves. All other commercially available reagents were used as received.

4.2. Methyl 2-amino-5-hydroxybenzoate

To a stirred solution of precooled (−15 °C) methanol (300 mL) was added dropwise thionyl chloride (26 mL, 204 mmol) over 20 min at the temperature maintaining at below −10 °C and the mixture was stirred at −10 °C for 20 min. 5-Hydroxyanthranilic acid (9 g, 58 mmol) was added to the mixture. The reaction mixture was stirred at room temperature for 2 days and heated to reflux for 4 h. After cooling, the reaction mixture was concentrated in vacuo and the residue was treated with saturated aqueous sodium hydrogen carbonate. The whole was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over magnesium sulfate, and concentrated in vacuo to give methyl 2-amino-5-hydroxybenzoate (8.6 g, 88%) as dark violet crystals: mp 160–162 °C; IR ν_{max}^{KBr} 3380, 3300, 1710 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.86 (3H, s), 6.60 (1H, d, J=8.8 Hz), 6.89 (1H, dd, J=8.8, 2.9 Hz), 7.33 (1H, d, J=2.9 Hz). The solids were used for the next reaction without further purification.

4.2.1. Methyl 5-hydroxy-2-(4-methylbenzenesulfonylamino)benzoate. To a stirred solution of the crude methyl 2-amino-5-hydroxybenzoate (8.6 g, 51.4 mmol) in pyridine (40 mL) at 0 °C was added *p*-toluenesulfonyl chloride (TsCl, 10.3 g, 54 mmol) and the reaction mixture was stirred at room temperature for 5 h. The excess TsCl was destroyed by addition of water (2 mL) and stirred for 30 min. The reaction mixture was diluted with ethyl acetate and washed with 1 N HCl, water, and saturated brine. The organic layer was dried over magnesium sulfate and concentrated in vacuo to give methyl 5-hydroxy-2-(toluenesulfonylamino)benzoate (16 g, 97%) as dark crystals which were used for next reaction without purification. The analytical sample was obtained by purification using column chromatography (silica gel, *n*-hexane/ethyl acetate=2/1) to give brown solids: mp 106–113 °C; IR ν_{max}^{KBr} 3394, 1693, 1405 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.46 (3H, s), 3.86 (3H, s), 4.79 (1H, brs), 7.17–7.71 (7H, m), 9.95 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.4, 52.4, 116.9, 118.4, 121.8, 122.8, 127.2, 129.4, 133.1, 135.9, 143.7, 151.7, 167.5. MS: *m/z* 321 (M^+). HRMS Calcd for $C_{15}H_{15}NO_5S$: 321.0671 (M^+). Found: 321.0684.

4.2.2. Methyl 5-benzyloxy-2-(4-methylbenzenesulfonylamino)benzoate (8a). To a stirred suspension of NaH (60% oil dispersion, 5.22 g, 131 mmol) in DMF (300 mL) at −20 °C was added methyl 5-hydroxy-2-(toluenesulfonylamino)benzoate (20.0 g, 62.2 mmol) and the reaction mixture was stirred at −20 °C for 30 min under argon atmosphere. Benzyl bromide (8.1 mL, 68.4 mmol) was added dropwise to the reaction mixture at 0 °C and the reaction mixture was stirred for 15 h. The reaction mixture was queuched with H_2O at 0 °C and extracted with ethyl acetate /*n*-hexane (8/1). The organic layer was washed with water and saturated brine, dried over sodium sulfate, and concentrated in vacuo. The residue was crystallized from ethyl acetate/*n*-hexane to give the title compound **8a** (23.9 g, 93.3%) as colorless solids: mp 94–96 °C; IR ν_{max}^{KBr} 3160, 1685, 1505, 1288, 1163 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.36 (3H, s), 3.81 (3H, s), 5.00 (2H, s), 7.11 (1H, dd, J=2.9, 9.0 Hz), 7.18 (2H, d, J=8.5 Hz), 7.33–7.38 (5H, m), 7.44 (1H, d, J=2.7 Hz), 7.62 (1H, s), 7.65 (2H, d, J=9.5 Hz), 10.0 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.4, 52.4, 70.4, 115.9, 118.0, 121.6, 122.4, 127.2, 127.5, 128.1, 129.4, 133.6, 136.2, 143.6, 154.5, 167.6. Anal. Calcd for $C_{22}H_{21}NO_5S$: C, 64.22; H, 5.14; N, 3.40. Found: C, 64.11; H, 4.99; N, 3.28.

4.2.3. *N*-(4-Benzyloxy-2-hydroxymethylphenyl)-4-methylbenzenesulfonamide. To a stirred suspension of $LiBH_4$ (1.447 g, 66.4 mmol) in THF (30 mL) at 0 °C was added dropwise a solution of **8a** (18.13 g, 44 mmol) in THF (50 mL) over 20 min and the reaction mixture was heated to reflux for 20 h. The reaction mixture was cooled to room temperature, poured into ice-10% citric acid, and extracted with ethyl acetate. The organic layer was washed with water and saturated brine, dried over magnesium sulfate, and concentrated in vacuo. The residue was crystallized from ethyl acetate/*n*-hexane to give the title compound (17.12 g, quant.) as colorless solids: mp 102–104 °C; IR ν_{max}^{KBr} 3423, 3091, 1499, 1028 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.40 (3H, s), 4.30 (2H, s), 5.02 (2H, s), 6.80 (1H, d, J=2.8 Hz), 6.83 (1H, dd, J=3.1, 8.55 Hz), 7.16 (1H, d, J=8.6 Hz), 7.22 (2H, d, J=8.2 Hz), 7.30–7.39 (5H, m), 7.58 (2H, d, J=8.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.5, 63.2, 70.2, 114.7, 115.6, 127.1, 127.3, 127.4, 128.1, 128.2, 128.6, 129.5, 136.0, 136.5, 136.6, 143.7, 157.6. MS: *m/z* 383 (M^+). HRMS Calcd for $C_{21}H_{21}NO_4S$: 383.1193 (M^+). Found: 383.1188.

4.2.4. *N*-(4-Benzyloxy-2-formylphenyl)-4-methylbenzenesulfonamide (7a). To a stirred solution of *N*-(4-benzyloxy-2-hydroxymethylphenyl)-4-methylbenzenesulfonamide (2 g, 5.21 mmol) in CH_2Cl_2 (25 mL) at room temperature was added pyridinium dichromate (2.35 g, 6.25 mmol) under argon atomsphere and the reaction mixture was stirred at room temperature for 3 h. Magnesium sulfate was added to the reaction mixture and the insoluble material was filtered through silica gel. The filtrate was concentrated in vacuo. The residue was crystallized from ethyl acetate/*n*-hexane to give aldehyde **7a** (1.58 g, 80%) as yellow solids: mp 121–123 °C; IR ν_{max}^{KBr} 3151, 1661, 1497, 1388, 1151 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.35 (3H, s), 5.04 (2H, s), 7.11 (1H, d, J=3.2 Hz), 7.16 (1H, dd, J=3.2, 9.0 Hz), 7.20 (2H, d, J=8.5 Hz), 7.28–7.39 (5H, m), 7.67 (1H, d, J=9.0 Hz), 7.68 (2H, d, J=8.3 Hz), 9.72 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21..5, 70.6, 20.5, 120.8, 122.9, 123.3, 127.1, 127.4, 128.3, 128.7, 129.6, 133.1, 136.0, 136.3, 143.9, 154.7, 194.4. MS: *m/z* 381 (M^+). Anal. Calcd for $C_{21}H_{19}NO_4S$: C, 66.12; H, 5.02; N, 3.67. Found: C, 65.97; H, 4.90; N, 3.55.

4.2.5. 5-[5-(*tert*-Butyldimethylsiloxy)-2-(4-methylbenzenesulfonylamino)phenyl]-5-hydroxypent-2-enoic acid methyl ester (9) and 2-{[5-(*tert*-butyldimethylsiloxy)-2-(4-methylbenzenesulfonylamino)-phenyl]-hydroxymethyl}but-3-enoic acid methyl ester (10). A mixture of **7b** (4.31 g, 10.7 mmol), methyl 3-bromocrotonate (0.6 mL), and activated zinc (1.89 g, 28.9 mmol) in ether (5 mL) and benzene (5 mL) was heated nearly to the boiling point under argon atmosphere. Iodine (254 mg, 1.07 mmol) was added. After a few minute the exothermic reaction began and an additional methyl 3-bromocrotonate (2.8 mL) was slowly added. The reaction mixture was heated to reflux for 3.5 h during which time additional activated zincs (450 mg) were added three times in every 1 h. The completion of the

reaction was judged according to tlc analysis. The mixture was cooled to 23 °C and diluted with ethyl acetate (300 mL) and the partly insoluble product was dissolved by addition of acetic acid. The clear solution was decanted for removal of an excess of zinc metal, washed with water, saturated sodium hydrogen carbonate, water, and saturated brine, and dried over magnesium sulfate. Filtration of the mixture followed by concentration of the filtrate gave the crude product (6.48 g) which was purified by column chromatography (silica gel, *n*-hexane/ethyl acetate=2/1) to give γ-product **9** (2.60 g, 48.3%) as yellow crystals together with α-product **10** (2.55 g, 47.3%) as a slightly yellow oil. **9**: mp 72–75 °C; IR ν_{max}^{neat} 3410, 3136, 1716 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.15 (6H, s), 0.95 (9H, s), 2.39 (3H, s), 2.37 (3H, s), 2.32–2.38 (1H, m), 2.46–2.52 (1H, m), 3.71 (3H, s), 4.83 (1H, td, J=7.0, 2.2 Hz), 5.72 (1H, d, J=15.7 Hz), 6.63–6.68 (2H, m), 6.76 (1H, dt, J=15.7, 7.1 Hz), 7.00 (1H, d, J=8.5 Hz), 7.23 (1H, d, J=8.2 Hz), 7.30 (1H, s), 7.59 (1H, d, J=8.2 Hz); ^{13}C NMR (100 MH, $CDCl_3$) δ −4.5, 18.2, 21.5, 25.6, 39.4, 51.5, 70.6, 119.0, 120.0, 127.3, 127.7, 129.6, 136.4, 137.9, 143.9, 166.5. HRMS Calcd for $C_{24}H_{25}NO_4S$: 505.1954 (M^+). Found: 505.1965. **10**: IR ν_{max}^{neat} 3462, 3273, 2954, 1734 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.14 (6H, s), 0.94 (9H, s), 1.66 (1H, brs), 2.38 (3H, s), 3.33–3.34 (1H, m), 4.69 (1H, d, J=17.1 Hz), 4.83 (1H, d, J=8.1 Hz), 4.94 (1H, d, J=10.3 Hz), 5.33–5.39 (1H, m), 6.52 (1H, d, J=2.9 Hz), 6.66 (1H, dd, J=8.8, 2.92 Hz), 7.18 (1H, d, J=8.8 Hz), 7.23 (2H, d, J=8.1 Hz), 7.66 (2H, d, J=8.1 Hz). HRMS Calcd for $C_{24}H_{25}NO_4S$: 505.1954 (M^+). Found: 505.1958.

4.2.6. *N*-[4-Benzyloxy-2-(1-hydroxybut-3-enyl)phenyl]-4-methylbenzenesulfonamide (13a). To a stirred solution of allylmagnesiumbromide (72.7 mL, 43.6 mmol, 0.6 M) in ether at −20 °C was added dropwise a solution of **7a** (7.922 g, 20.8 mmol) in ether (80 mL) in THF (80 mL) under argon atomsphere and the reaction mixture was stirred at −10 °C for 2 h. The reaction mixture was quenched with saturated NH_4Cl at 0 °C and extracted with ethyl acetate. The organic layer was washed with water and saturated brine, dried over magnesium sulfate, and concentrated in vacuo. The residue was purified by column chromatography (silica gel, *n*-hexane/ethyl acetate=2/1) to give the title compound **13a** (8.76 g, 100%) as a colorless oil: IR ν_{max}^{neat} 3464, 2922, 1499, 1159 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.19–2.30 (2H, m), 2.37 (3H, s), 2.71 (1H, d, J=2.9 Hz), 4.61–4.64 (1H, m), 4.99 (2H, s), 4.99 (1H, dd, J=1.5, 17.1 Hz), 5.05 (1H, d, J=10.1 Hz), 5.55–5.63 (2H, m), 6.77 (1H, dd, J=3.1, 11.0 Hz), 7.78 (1H, s), 7.17 (1H, d, J=9.1 Hz), 7.21 (2H, d, J=7.9 Hz), 7.30–7.36 (5H, m), 7.37 (2H, d, J=6.7 Hz), 7.59 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.4, 41.1, 70.2, 71.4, 114.0, 114.2, 118.8, 125.9, 127.2, 127.4, 127.8, 128.0, 128.5, 129.5, 133.8, 136.5, 136.7, 137.0, 143.6, 156.6. MS: m/z 423 (M^+). HRMS Calcd for $C_{24}H_{25}NO_4S$: 423.1504 (M^+). Found: 423.1476.

4.2.7. 5-[5-Benzyloxy-2-(4-methylbenzenesulfonylamino) phenyl]-5-hydroxypent-2-enyl acetate (6a). A stirred solution of **13a** (1.284 g, 3 mmol) and allylacetate (1.6 mL, 14.8 mmol) in CH_2Cl_2 (40 mL) was degassed by three freeze-thaw cycles under argon atmosphere. Grubbs reagent **16** (271 mg, 0.315 mmol) was added to the reaction mixture at room temperature and the reaction mixture was degassed again by three freeze-thaw cycles. The reaction mixture was heated to reflux for 44 h. The reaction mixture was quenched with 1 M HCl and extracted with ethyl acetate. The organic layer was washed with water and saturated brine, dried over sodium sulfate, and concentrated in vacuo. The residue was purified by column chromatography (silica gel, *n*-hexane/ethyl acetate=3/2 to 1/1) to give the title compound **6a** (577 mg, 38%, E/Z=6:1) as a dark oil and the starting material (726 mg, 56%) as a yellow oil. **6a**: IR ν_{max}^{neat} 2929, 3482, 3255, 3031, 2925, 1733, 1498, 1236, 1159 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.04 (3H, s), 2.17–2.24 (1H, m), 2.33–2.36 (1H, m), 2.39 (3H, s), 2.71 (1H, s), 4.46 (2H, d, J=5.2 Hz), 4.76 (1H, t, J=6.9 Hz), 5.00 (2H, s), 5.47–5.60 (2H, m), 6.75 (1H, dd, J=2.9, 8.9 Hz), 6.83 (1H, d, J=3.0 Hz), 7.03 (1H, d, J=8.9 Hz), 7.31–7.36 (5H, m), 7.37 (2H, d, J=6.7 Hz), 7.48 (1H, s), 7.60 (2H, d, J=8.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.0, 21.5, 39.8, 64.7, 70.2, 71.1, 113.8, 114.4, 126.5, 127.3, 127.4, 127.5, 127.7, 128.1, 128.6, 129.6, 130.8, 136.5, 136.7, 138.4, 143.7, 157.0. MS: m/z 495 (M^+). HRMS Calcd for $C_{27}H_{29}NO_6S$: 495.1716 (M^+). Found: 495.1703.

4.2.8. Allyloxychlorodiphenylsilane (17). To a stirred solution of dichlorodiphenylsilane (8.3 mL, 39.9 mmol) in CH_2Cl_2 (200 mL) at 0 °C was added Et_3N (6.6 mL, 47.5 mmol) and allyl alcohol (2.6 mL, 38.2 mmol) and the reaction mixture was stirred at room temperature. After 24 h, the reaction mixture was concentrated in vacuo. The residue was distilled under reduced pressure to give allyloxychlorodiphenylsilane **17** (7.826 g, 87.0%) as a colorless oil: bp 130 °C (4 mmHg); IR ν_{max}^{neat} 3071, 2864, 1646, 1590, 1428, 1125 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.33 (1H, d, J=4.9 Hz), 4.39 (1H, d, J=4.9 Hz), 5.13 (1H, t, J=10.5 Hz), 5.32 (1H, d, J=15.3 Hz), 5.92–5.99 (1H, m), 7.34–7.72 (10H, m).

4.2.9. *N*-[4-Benzyloxy-2-(1-(allyloxydiphenylsilyloxy)-but-3-enyl)phenyl]-4-methylbenzenesulfonamide (14). To a stirred solution of **13a** (989 mg, 2.35 mmol) and Et_3N (0.68 mL, 4.90 mmol) in CH_2Cl_2 (10 mL) at room temperature was added dropwise allyloxychlorodiphenylsilane (1.267 g, 4.61 mol) in CH_2Cl_2 (2 mL) under argon atmosphere and the reaction mixture was stirred at room temperature. After 5 min, the reaction mixture was quenched with saturated sodium hydrogen carbonate and extracted with ethyl acetate. The organic layer was washed with water and saturated brine, dried over sodium sulfate, and concentrated in vacuo. The residue was purified by column chromatography (silica gel, *n*-hexane/ethyl acetate=6/1 to 2/1) to give the title compound **14** (1.505 g, 97.4%) as a yellow oil: IR ν_{max}^{neat} 3277, 3070, 2919, 1500, 1428, 1161, 1125 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.24–1.52 (1H, m), 2.28–2.36 (1H, m), 2.33 (3H, s), 3.94–3.96 (2H, m), 4.68 (1H, t, J=6.9 Hz), 4.71 (1H, d, J=12.5 Hz), 4.83 (1H, d, J=9.5 Hz), 4.92 (2H, s), 5.05 (1H, d, J=9.9 Hz), 5.19 (1H, d, J=17.0 Hz), 5.21–5.32 (1H, m), 5.72–5.83 (1H, m), 6.52 (1H, d, J=2.9 Hz), 6.78 (1H, dd, J=2.7, 8.8 Hz), 7.12 (2H, d, J=8.05 Hz), 7.30–7.64 (17H, m), 7.81 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.4, 41.7, 64.0, 70.1, 74.6, 114.4, 114.7, 114.8, 117.6, 124.2, 127.0, 127.4, 127.8, 127.8, 127.9, 128.0, 128.5, 129.5, 130.2, 130.4, 130.6, 130.7, 133.7, 134.3, 134.8, 134.9, 135.9, 137.0,

143.4, 155.6. MS: *m/z* 661 (M^+). HRMS Calcd for $C_{39}H_{39}NO_5SSi$: 661.2318 (M^+). Found: 661.2338.

4.2.10. *N*-[4-Benzyloxy-2-(2,2-diphenyl-5,8-dihydro-4*H*-[1,3,2]dioxasilocin-4-yl)phenyl]-4-methylbenzenesulfonamide (15). A stirred solution of **14** (39 mg, 0.059 mmol) in CH_2Cl_2 (5.8 mL) was degassed by three freeze-thaw cycles under argon atmosphere and Grubbs reagent **16** (2.4 mg, 0.0029 mmol) was added to the reaction mixture at room temperature. The reaction mixture was degassed again by three freeze-thaw cycles and heated to reflux. After 5 h, the reaction mixture was queuched with 1 M HCl, and extracted with ethyl acetate. The organic layer was washed with water and saturated brine, dried over sodium sulfate, and concentrated in vacuo. The residue was purified by column chromatography (silica gel, *n*-hexane/ethyl acetate=3/1) to give **15** (32 mg, 85.7%) as a yellow oil: IR ν_{max}^{neat} 3273, 1497, 1160, 1125 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.34 (3H, s), 2.53–2.58 (1H, m), 2.66–2.73 (1H, m), 4.47 (1H, dd, J=4.4, 14.9 Hz), 4.58 (1H, dd, J=5.6, 14.6 Hz), 4.83 (1H, dd, J=3.2, 7.3 Hz), 4.88 (2H, s), 5.50 (1H, dd, J=8.5, 19.3 Hz), 5.88 (1H, dt, J=5.6, 11.2 Hz), 6.70 (1H, d, J=2.7 Hz), 6.74 (1H, dd, J=2.7, 8.8 Hz), 7.13 (2H, d, J=8.3 Hz), 7.20–7.66 (17H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.4, 34.7, 61.5, 70.1, 73.2, 113.5, 114.1, 125.0, 127.1, 127.4, 127.6, 127.7, 127.7, 127.9, 128.0, 128.5, 129.4, 130.2, 130.5, 132.6, 134.3, 134.4, 134.5, 134.7, 136.6, 136.7, 136.9, 143.4, 156.2. MS: *m/z* 633 (M^+). HRMS Calcd for $C_{37}H_{35}NO_5Si$: 633.2006 (M^+). Found: 633.1992.

4.2.11. (*Z*)-1,5-Diacetoxy-5-[5-benzyloxy-2-(4-methylbenzenesulfonylamino)phenyl]-2-pentene (6d). To a stirred solution of **15** (709 mg, 1.11 mmol) in THF (7.4 mL) at room temperature was added dropwise TBAF (2.6 mL, 2.6 mmol) under argon atmosphere and the reaction mixture was stirred at room temperature for 5 h. The reaction mixture was quenched with 1 M potassium hydrogen sulfate, and extracted with ethyl acetate. The organic layer was washed with water and saturated brine, dried over sodium sulfate, and concentrated in vacuo. The residue was purified by column chromatography (silica gel, *n*-hexane/ethyl acetate=1/2) to give **18** (427 mg, 84.3%) as a dark oil which was used for the next reaction without further purification.

To a stirred solution of the above diol **18** (335 mg, 0.74 mmol) and *p*-toluenesulfonic acid (295 mg, 1.55 mmol) in methylene chloride (5 mL) at 0 °C was added dropwise acetic anhydride (0.20 mL, 2.13 mmol) and the reaction mixture was stirred at 0 °C for 3 h. The reaction mixture was quenched with water and extracted with ethyl acetate. The organic layer was washed with water and saturated brine, dried over sodium sulfate, and concentrated in vacuo. The residue was purified by column chromatography (silica gel, *n*-hexane/ethyl acetate=2/1) to give **6d** (385 mg, 97%) as a yellow oil: IR ν_{max}^{neat} 3255, 2923, 1735, 1498, 1236, 1162 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.83–1.87 (1H, m), 1.95 (3H, s), 2.06 (3H, s), 2.38 (3H, s), 2.67 (1H, dt, J=8.1, 14.8 Hz), 4.55 (2H, d, J=7.1 Hz), 5.03 (2H, s), 5.07–5.14 (1H, m), 5.29 (1H, dd, J=4.4, 9.5 Hz), 5.54 (1H, dt, J=6.8, 10.9 Hz), 6.92 (1H, d, J=2.9 Hz), 7.23 (1H, d, J=8.1 Hz), 7.29 (2H, dd, J=1.2, 7.8 Hz), 7.32–7.43 (7H, m), 7.61 (1H, s), 7.61 (2H, d, J=8.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.8, 20.9, 21.4, 32.2, 60.1, 70.2, 70.4, 113.8, 115.4, 126.7, 127.1, 127.5, 128.1, 128.6, 128.8, 129.2, 129.6, 135.5, 136.3, 137.0, 143.5, 157.6, 170.8, 171.4. MS: *m/z* 537 (M^+). HRMS Calcd for $C_{37}H_{35}NO_5Si$: 537.1821 (M^+). Found: 537.1803.

4.2.12. 6-Benzyloxy-1-(4-methylbenzenesulfonyl)-2-vinyl-1,2,3,4-tetrahydroquinolin-4-ol (19a). To a stirred solution of $Pd(dba)_2$ (197 mg, 0.34 mmol) in THF (35 mL) was added tri*n*-buthylphosphine (0.17 mL, 0.68 mmol) at 0 °C under argon atmosphere and the reaction mixture was degassed by three freeze-thaw cycles and stirred at 0 °C for 30 min. Allyl acetate **6a** (1.706 g, 3.4 mmol) in THF (10 mL) and AcOH (0.21 mL, 3.7 mmol) were added to the reaction mixture at 0 °C. The reaction mixture was degassed again by three freeze-thaw cycles, warmed to room temperature, and stirred for 17 h. The reaction mixture was quenched with saturated aqueous NH_4Cl and extracted with ethyl acetate. The organic layer was washed with water and saturated brine, dried over sodium sulfate, and concentrated in vacuo. The residue was purified by column chromatography (silica gel, *n*-hexane/ethyl acetate=3/2) to give cyclized product **19a** (1.428 g, 95.7%, *cis*/*trans*=3:1) as a colorless oil. Major product: IR ν_{max}^{neat} 3504, 3032, 1606, 1487 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.60 (1H, dt, J=8.0, 16.0 Hz), 2.14 (1H, ddd, J=4.7, 7.0, 13.3 Hz), 2.37 (3H, s), 3.64–3.76 (1H, m), 4.76–4.81 (1H, m), 5.11 (2H, ABq, J=11.6 Hz), 5.12 (1H, d, J=10.5 Hz), 5.32 (1H, dq, J=1.1, 17.0 Hz), 5.87 (1H, ddd. J=4.8, 10.4, 17.0 Hz), 6.93 (1H, d, J=3.0, 8.9 Hz), 6.98 (1H, d, J=2.2 Hz), 7.15 (2H, d, J=7.9 Hz), 7.33–7.44 (7H, m), 7.66 (1H, d, J=8.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.5, 38.8, 55.3, 64.7, 70.2, 76.7, 77.0, 77.3, 110.9, 114.4, 115.5, 126.7, 127.0, 127.5, 128.0, 128.5, 129.6, 135.8, 136.7, 138.0, 138.1, 143.7, 157.0. MS: *m/z* 435 (M^+). HRMS Calcd for $C_{25}H_{25}O_4NS$: 435.1504. Found: 435.1490.

4.2.13. 4,6-(Di-*tert*-butyldimethylsiloxy)-1-(4-methylbenzenesulfonyl)-2-vinyl-1,2,3,4-tetrahydroquinoline (19c). To a stirred solution of $Pd(dba)_2$ (1 mg, 0.0018 mmol) in THF (1 mL) was added tri*n*-buthylphosphine (0.7 μL, 0.0036 mmol) at −15 °C under argon atmosphere and the reaction mixture was degassed by three freeze-thaw cycles and stirred at −15 °C for 30 min. **6c** (22.2 mg, 0.035 mmol) in THF (1 mL) was added to the reaction mixture at −15 °C. The reaction mixture was degassed again by three freeze-thaw cycles, warmed to room temperature, and stirred for 12 h. After the reaction was completed, the reaction mixture was quenched with saturated aqueous NH_4Cl and extracted with ethyl acetate. The organic layer was washed with water and saturated brine, dried over magnesium sulfate, and concentrated in vacuo. The residue was purified by column chromatography (silica gel, *n*-hexane/ethyl acetate=12/1) to give **19c** (18.5 mg, 92%) as yellow crystals: mp 78–80 °C; IR ν_{max}^{neat} 3448, 2952, 1485 cm^{-1}; ^1H NMR ($CDCl_3$) δ −0.16 (6H, s), 0.19 (6H, s), 0.84 (9H, s), 0.98 (9H, s), 1.42 (1H, dt, J=11.4, 11.8 Hz), 2.19 (1H, ddd, J=4.3, 8.0, 12.5 Hz), 2.37 (3H, s), 3.19 (1H, dd, J=11.6, 4.3 Hz), 4.56–4.62 (1H, m), 5.14 (1H, dd, J=11.5, 1.0 Hz), 5.35 (1H, dd, J=1.0, 17.1 Hz), 5.83–5.88 (1H, m), 6.73 (1H, d, J=2.7 Hz), 6.76 (1H, dd, J=2.7, 8.5 Hz), 7.15 (2H, d, J=8.0 Hz), 7.31 (2H, d, J=8.0 Hz), 7.33–7.44 (2H, m), 7.51 (1H, d, J=8.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ −5.4, −4.5, −4.4, 18.0, 18.3, 21.5, 25.6, 25.7, 41.3, 56.1, 65.5, 114.5, 114.8, 119.1, 126.6, 127.0,

129.5, 135.7, 138.6, 141.5, 143.5, 154.3. MS (FAB): *m/z* 575 ($M+H^+$). Anal. Calcd for $C_{30}H_{47}NO_4SSi_2$: C, 62.78; H, 8.25; N, 2.44. Found: C, 62.49; H, 8.38; N, 2.33.

4.2.14. 6-Benzyloxy-4-(*tert*-butyldimethylsiloxy)-1-(4-methylbenzenesulfonyl)-2-vinyl-1,2,3,4-tetrahydroquinoline (19e). To a stirred solution of $Pd(dba)_2$ (127 mg, 0.22 mmol) in THF(15 mL) was added tri*n*-buthylphosphine (0.11 mL, 0.44 mmol) at 0 °C under argon atmosphere and the reaction mixture was degassed by three freeze-thaw cycles and stirred at 0 °C for 30 min. **6e** (1.357 g 2.22 mmol) in THF (7 mL) was added to the reaction mixture at 0 °C. The reaction mixture was degassed again by three freeze-thaw cycles, warmed to room temperature, and stirred for 16 h. The reaction mixture was quenched with saturated aqueous NH_4Cl and extracted with ethyl acetate. The organic layer was washed with water and saturated brine, dried over sodium sulfate, and concentrated in vacuo. The residue was purified by column chromatography (silica gel, *n*-hexane/ethyl acetate=10/1 to 3/1) to give the title compound **19e** (1.169 g, 95.6%) as a yellow oil: IR ν_{max} 2952, 2927, 2856, 1486, 1353, 1159 cm^{-1}; ^1H NMR ($CDCl_3$) δ −0.009 (6H, s), 0.838 (9H, s), 1.43 (1H, dt, J=11.5, 12.9 Hz), 2.19 (1H, ddd, J=4.2, 8.1, 12.4 Hz), 2.36 (3H, s), 3.25 (1H, dd, J=3.9, 11.2 Hz), 4.57–4.63 (1H, m), 5.06 (2H,s), 5.12 (1H, d, J=10.2 Hz), 5.34 (1H, d, J=17.1 Hz), 5.85 (1H, ddd, J=5.4, 10.2, 16.8 Hz), 6.86 (1H, d, J=2.9 Hz), 6.91 (1H, dd, J=2.63, 8.53 Hz), 7.16 (2H, d, J=7.8 Hz), 7.31–7.49 (7H, m), 7.56 (1H, d, J=8.78 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ −5.46, −5.41, 17.9, 21.3, 25.5, 41.1, 55.8, 65.5, 69.9, 108.9, 113.7, 114.7, 126.1, 126.8, 127.3, 127.8, 128.2, 128.2, 128.4, 128.8, 129.4, 135.6, 136.7, 138.4, 141.4, 143.4, 157.2. MS: *m/z* 549 (M^+). HRMS Calcd for $C_{31}H_{39}NO_4SSi$: 549.2369 (M^+). Found: 549.2359.

4.2.15. 6-Benzyloxy-1-(4-methylbenzenesulfonyl)-2-vinyl-2,3-dihydro-1*H*-quinolin-4-one (20). To a stirred solution of **19a** (64 mg, 0.15 mmol) in CH_2Cl_2 (1 mL) at room temperature was added pyridinium dichromate (66.3 mg, 0.176 mmol) under argon atmosphere and the reaction mixture was stirred at room temperature. After 15 h, magnesium sulfate was added to the reaction mixture and the insoluble material was filtered through silica gel. The filtrate was concentrated in vacuo. The residue was purified by column chromatography (silica gel, *n*-hexane/ethyl acetate=3/1) to give quinolone **20** (62 mg, 97.3%) as brown solids: mp 92–96 °C; IR ν_{max}^{KBr} 3032, 1691, 1605 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.37–2.43 (1H, m), 2.39 (3H, s), 2.53 (1H, dd, J=1.8, 17.9 Hz), 5.06 (2H, s), 5.13 (1H, ddd, J=2.2, 6.8 Hz), 5.16 (1H, d, J=2.0 Hz), 5.26–5.29 (1H, m), 5.78 (1H, dd, J=4.2, 10.7, 17.3 Hz), 7.82 (1H, d, J=9.0 Hz), 7.21–7.52 (11H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.5, 391, 56.8, 70.3, 76.7, 77.0, 77.3, 110.1, 118.4, 123.1, 126.7, 126.9, 127.5, 127.9, 128.1, 128.5, 130.0, 133.5, 135.3, 136.1, 136.4, 144.4, 156.5, 191.8. MS: *m/z* 434 (M^+). HRMS Calcd for $C_{25}H_{24}O_4NS$: 434.1426. Found: 434.1434.

4.2.16. 6-Benzyloxy-3-methylene-1-(4-methylbenzenesulfonyl)-2-vinyl-2,3-dihydro-1*H*-quinolin-4-one. To a stirred mixture of paraformaldehyde (7 mg, 0.23 mmol) and *N*-methylaniline trifluoroacetate (TFA·PhNHMe, 19 mg, 0.086 mmol) in 1,4-dioxane (0.5 mL) at room temperature was added **20** (25 mg, 0.057 mmol) in 1,4-dioxane (0.5 mL) under argon atmosphere and the reaction mixture was stirred at reflux for 8 h. A second portion of paraformaldehyde (5.5 mg, 0.18 mmol) and TFA·PhNHMe (38 mg, 0.17 mmol) was added again to the reaction mixture. After stirring the mixture for 25 h, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ and extracted with ethyl acetate. The organic layer was washed with water and saturated brine, dried over sodium sulfate, and concentrated in vacuo. The residue was purified by column chromatography (silica gel, *n*-hexane/ethyl acetate=6/1) to give the title compound (21.7 mg, 84.7%) as yellow solids; mp 104–106 °C; IR ν_{max}^{KBr} 3088, 3032, 2924, 1680, 1602, 1485, 1166 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.33 (3H, s), 5.03 (1H, dd, J=2.2, 17.3 Hz), 5.08 (2H, ABq), 5.12 (1H, dd, J=2.2, 10.5 Hz), 5.33 (1H, s), 5.68 (1H, br), 5.85 (1H, ddd, J=3.4, 10.3, 17.3 Hz), 6.11 (1H, s), 7.07 (2H, d, J=8.0 Hz), 7.24 (2H, d, J=8.3 Hz), 7.25 (1H, dd, J=3.1, 8.8 Hz), 7.35–7.44 (6H, m), 7.74 (1H, d, J=9.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.5, 62.4, 70.3, 110.9, 118.6, 122.8, 125.5, 127.6, 127.8, 128.2, 128.6, 129.0, 129.4, 129.7, 133.3, 134.2, 136.1, 136.2, 138.6, 144.2, 157.5, 181.6. MS: *m/z* 445 (M^+). HRMS Calcd for $C_{26}H_{24}NO_4S$: 446.1426 ($M+H^+$). Found: 446.1416.

4.2.17. [6-Benzyloxy-4-oxo-1-(4-methylbenzenesulfonyl)-2-vinyl-1,2,3,4-tetrahydroquinolin-3-yl]acetonitrile (22). To a stirred solution of 6-benzyloxy-3-methylene-1-(4-methylbenzenesulfonyl)-2-vinyl-2,3-dihydro-1H-quinolin-4-one (147 mg, 0.34 mmol) in ethanol (10 mL) at room temperature was added KCN (43.8 mg, 0.673 mmol) in water (0.4 mL) and acetic acid (0.026 mL, 0.47 mmol). After stirring the reaction mixture at room temperature for 7 h, the reaction mixture was concentrated in vacuo. The residue was diluted with ethyl acetate, washed with water and saturated brine, dried over sodium sulfate, and concentrated in vacuo. The residue was purified by column chromatography (silica gel, *n*-hexane/ethyl acetate=7/2) to give **22** (110 mg, 70.5%) as a brown oil: IR ν_{max}^{neat} 2924, 2250, 1690, 1488, 1164 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.17 (1H, dd, J=10.7, 17.4 Hz), 2.42 (3H, s), 2.70 (1H, ddd, J=4.2, 10.0, 16.5 Hz), 2.97 (1H, dd, J=4.39, 17.3 Hz), 5.03 (1H, dd, J=2.7, 10.2 Hz), 5.07 (2H, s), 5.30–5.36 (2H, m), 5.54–5.62 (1H, m), 7.30 (2H, d, J=8.3 Hz), 7.34–7.48 (7H, m), 7.65 (2H, d, J=8.31 Hz), 7.84 (1H, d, J=9.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.7, 21.5, 44.7, 61.6, 70.3, 110.5, 117.1, 123.0, 123.9, 124.6, 126.8, 127.0, 127.5, 128.2, 128.3, 128.6, 130.3, 133.7, 135.9, 136.5, 144.8, 156.3, 190.3. MS: *m/z* 472 (M^+). HRMS Calcd for $C_{27}H_{24}N_2O_4S$: 472.1457 (M^+). Found: 472.1447.

4.2.18. 8-Benzyloxy-4-ethyl-5-(4-methylbenzenesulfonyl)-2,3,3a,4,5,9b-hexahydro-1*H*-pyrrolo[3,2-*c*]quinoline (23a) and 8-hydroxy-4-ethyl-5-(4-methylbenzenesulfonyl)-2,3,3a,4,5,9b-hexahydro-1*H*-pyrrolo[3,2-*c*]quinoline (23b). To a stirred solution of **22** (9 mg, 0.019 mmol) in ethanol (2 mL) at room temperature was added Raney Ni (300 mg) and the reaction mixture was stirred under hydrogen atmosphere. After 48 h, the reaction mixture was filtered through celite and concentrated in vacuo to afford the crude cyclic imine (11 mg). The crude imine was dissolved in MeOH (2 mL) and sodium cyanoborohydride (3 mg, 0.048 mmol) was added at room temperature under

argon atmosphere. The reaction mixture was acidified to pH 4 with 2 N HCl. After stirring the mixture for 3 h, the reaction mixture was concentrated in vacuo, quenched with 0.1 N KOH, and extracted with ether. The organic layer was washed with water and saturated brine, dried over sodium sulfate, and concentrated in vacuo. The residue was purified by column chromatography (silica gel, $CHCl_3$/MeOH=20/1 containing 1% triethylamine) to give pyrroloquinoline **23a** (5 mg, 56.7%) as a colorless oil and debenzylated pyrroloquinoline **23b** (2 mg, 28.2%) as a colorless oil. **23a**: IR ν_{max}^{neat} 2926, 1491, 1162 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.88–0.96 (3H, m), 1.25–1.31 (1H, m), 1.37–1.47 (1H, m), 1.85–1.88 (1H, m), 2.33–2.41 (1H, m), 2.37 (3H, s), 2.75 (1H, dt, J=5.3, 10.7 Hz), 2.95–3.04 (1H, m), 3.29 (1H, d, J=8.1 Hz), 4.24–4.30 (1H, m), 5.04 (2H, s), 6.92 (1H, dd, J=2.4, 8.8 Hz), 7.06 (1H, br), 7.15 (2H, d, J=9.0 Hz), 7.31–7.46 (6H, m), 7.62 (2H, d, J=9.0 Hz). MS: m/z 462 (M^+). HRMS (FAB, NBA) Calcd for $C_{27}H_{30}N_2O_3S$: 463.2065 ($M+H^+$). Found: 463.2070. **23b**: ^1H NMR ($CDCl_3$) δ 0.81–0.94 (3H, m). 1.25–1.35 (1H, m), 1.45–1.53 (1H, m), 1.70–1.80 (1H, m), 1.95–2.04 (1H, m), 2.37 (3H, s), 2.91–3.01 (1H, m), 3.13–3.20 (1H, m), 3.66 (1H, d, J=8.5 Hz), 4.21–4.24 (1H, m), 6.79 (1H, dd, J=2.7, 9.0 Hz), 7.10 (1H, br), 7.14 (2H, d, J=8.1 Hz), 7.38 (2H, d, J=8.3 Hz), 7.55 (1H, d, J=8.8 Hz). MS: m/z 372 (M^+). HRMS (FBA, NBA) Calcd for $C_{20}H_{25}N_2O_3S$: 373.1586 ($M+H^+$). Found: 373.1594.

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References and notes

1. Witherup, K. M.; Ransom, R. W.; Graham, A. C.; Bernard, A. M.; Salvature, M. J.; Lumma, W. C.; Anderson, P. S.; Pitzewberger, S. M.; Verga, S. L. *J. Am. Chem. Soc.* **1995**, *117*, 6682–6685.
2. (a) Ma, D.; Xia, C.; Jiang, J.; Zhang, J. *Org. Lett.* **2001**, *3*, 2189. (b) Hadden, M.; Nieuwenhuyzen, M.; Osborne, D.; Stevenson, P. J.; Thompson, N. *Tetrahedron Lett.* **2001**, *42*, 6417. (c) Snider, B. B.; Ahn, Y.; O'Hare, S. M. *Org. Lett.* **2001**, *3*, 4217. (d) Powell, D. A.; Batey, R. A. *Org. Lett.* **2002**, *4*, 2913–2916. (e) Xia, C.; Heng, L.; Ma, D. *Tetrahedron Lett.* **2002**, *43*, 9405–9409. (f) Ma, D.; Xia, C.; Jiang, J.; Zhang, J.; Tang, W. *J. Org. Chem.* **2003**, *68*, 442–451.
3. (a) Ho, T. C. T.; Jones, K. *Tetrahedron* **1997**, *53*, 8287–8294. (b) Gurjar, M. K.; Pal, S.; Rama Rao, A. V. *Heterocycles* **1997**, *45*, 231–234. (c) Kim, S. S.; Cheon, H. G.; Kang, S. K.; Yum, E. K.; Choi, J. K. *Heterocycles* **1998**, *48*, 221–226. (d) Hadden, M.; Stevenson, P. J. *Tetrahedron Lett.* **1999**, *40*, 1215–1218. (e) Batey, R. A.; Simoncic, P. D.; Lin, D.; Smyj, R. P.; Lough, A. J. *Chem. Commun.* **1999**, 651–652. (f) Lovely, C. J.; Mahmud, H. *Tetrahedron Lett.* **1999**, *40*, 2079–2082. (g) Snider, B. B.; Ahn, Y.; Foxman, B. M. *Tetrahedron Lett.* **1999**, *40*, 3339–3342. (h) Frank, K. E.; Aube, J. *J. Org. Chem.* **2000**, *65*, 655–666. (i) Nieman, J. A.; Ennis, M. D. *Org. Lett.* **2000**, *2*, 1395–1397. (j) Nyerges, M.; Fejes, I.; Toke, L. *Tetrahedron Lett.* **2000**, *41*, 7951–7954. (k) Mahmud, H.; Lovely, C. J.; Dias, H. V. R. *Tetrahedron* **2001**, *57*, 4095–4105. (l) Hadden, M.; Nieuwenhuyzen, M.; Potts, D.; Stevenson, P. J.; Thompson, N. *Tetrahedron* **2001**, *57*, 5615–5624. (m) Hadden, M.; Nieuwenhuyzen, M.; Osborne, D.; Stevenson, P. J.; Thompson, N. *Tetrahedron Lett.* **2001**, *42*, 6417–6419. (n) Batey, R. A.; Powell, D. A. *Chem. Commun.* **2001**, 2362–2363. (o) He, Y.; Mahmud, H.; Wayland, B. R.; Dias, H. V. R.; Lovely, C. J. *Tetrahedron Lett.* **2002**, *43*, 1171–1174. (p) Malassene, R.; Sanchez-Bajo, L.; Toupet, L.; Hurvois, J.; Moinet, C. *Synlett* **2002**, 1500–1504. (q) Nyerges, M.; Fejes, I.; Toke, L. *Synthesis* **2002**, 1823–1828.
4. Hamada, Y.; Kunimune, I.; Hara, O. *Heterocycles* **2002**, *56*, 97–100.
5. (a) Hamada, Y.; Seto, N.; Ohmori, H.; Hatano, K. *Tetrahedron Lett.* **1996**, *37*, 7565–7568. (b) Hamada, Y.; Seto, N.; Takayanagi, Y.; Nakano, T.; Hara, O. *Tetrahedron Lett.* **1999**, *40*, 7791–7794.
6. (a) McNeill, A. H.; Thomas, E. J. *Tetrahedron Lett.* **1990**, *31*, 6239. (b) Mortlock, S. V.; Thomas, E. J. *Tetrahedron Lett.* **1988**, *29*, 2479–2482.
7. (a) Cannon, S. J.; Blechert, S. *Angew. Chem., Int. Ed.* **2003**, *42*, 1900–1923. (b) Joelle, P. *Angew. Chem., Int. Ed.* **2003**, *42*, 2826–2830.
8. (a) Fu, G. C.; Grubbs, R. H. *J. Am. Chem. Soc.* **1992**, *114*, 5426–5427. (b) Fu, G. C.; Grubbs, R. H. *J. Am. Chem. Soc.* **1992**, *114*, 7324–7325.
9. Hoye, T. R.; Promo, M. A. *Tetrahedron Lett.* **1999**, *40*, 1429–1432.
10. Gillard, J. W.; Fortin, R.; Morton, H. E.; Yoakim, C.; Quesnelle, C. A.; Daignault, S.; Guindon, Y. *J. Org. Chem.* **1988**, *53*, 2602–2608.
11. (a) Gras, J. *Org. Synth.* **1982**, *60*, 88–91. (b) Gras, J. *Tetrahedron Lett.* **1978**, *24*, 2111–2114.