Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron
Tetrahedron 61 (2005) 3473–3481

Convenient synthesis of 2-alkylamino-6-carboxy-5,7-diarylcyclopenteno[1,2-*b*]pyridines via direct acylamination with imidoyl chlorides

Hirobumi Takahashi,* Takehiro Fukami, Hisaki Kojima, Takeru Yamakawa, Hiroyuki Takahashi, Toshihiro Sakamoto, Teruyuki Nishimura, Masayuki Nakamura, Takashi Yosizumi, Kenji Niiyama, Norikazu Ohtake and Takashi Hayama

Tsukuba Research Institute, Banyu Pharmaceutical Co. Ltd, Okubo-3, Tsukuba 300-2611, Ibaraki, Japan

Received 27 December 2004; revised 1 February 2005; accepted 2 February 2005

Abstract—A robust synthetic method for 2-alkylamino-6-carboxy-5,7-diarylcyclopenteno[1,2-*b*]pyridines via acylamination at the alpha position of the functionalized pyridine system has been developed. The key step in this method was achieved by treatment of the corresponding pyridine *N*-oxides with 2.5 equiv of imidoyl chlorides in the presence of triethylamine, thus producing the desired 2-acylaminopyridines in good yields (74–96%).

1. Introduction

Endothelin-1 (ET-1)[1] and its closely related isopeptides (ET-2, ET-3) have been identified as potent vasoconstrictor peptides. The endothelins exert diverse biological actions through distinct cell surface G-protein coupled receptors (GPCR) termed ET_A and ET_B.[2] Elevated levels of endothelins have been observed in numerous disease states including hypertension, congestive heart failure and renal diseases.[3] Therefore, non-peptide endothelin receptor antagonists are currently being evaluated by a number of pharmaceutical companies as potential therapeutic agents for the treatment of these disease states.

Previously, we reported that potent and selective ET_A antagonists (**1** and **2**) were identified in a series of 6-carboxy-5,7-diarylcyclopenteno[1,2-*b*]pyridines.[4,5] It is of significant interest to further clarify the structure–activity relationships (SARs) of the alkylamino group (Fig. 1, R^1) at the 2-position of the pyridine ring and the substituent (Fig. 1, R^2) at the 2′-position of the 7-(4-methoxyphenyl) ring. However, incorporation of the alkylamino group by the previous synthetic method is tedious and the subsequent functionalization on the 7-aryl ring was limited (Route A in Scheme 1). Therefore, the development of a efficient and convenient alternative method for this highly functionalized 2-alkylaminocyclopentenopyridine system is necessary.

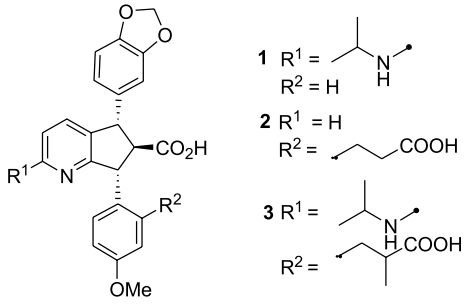
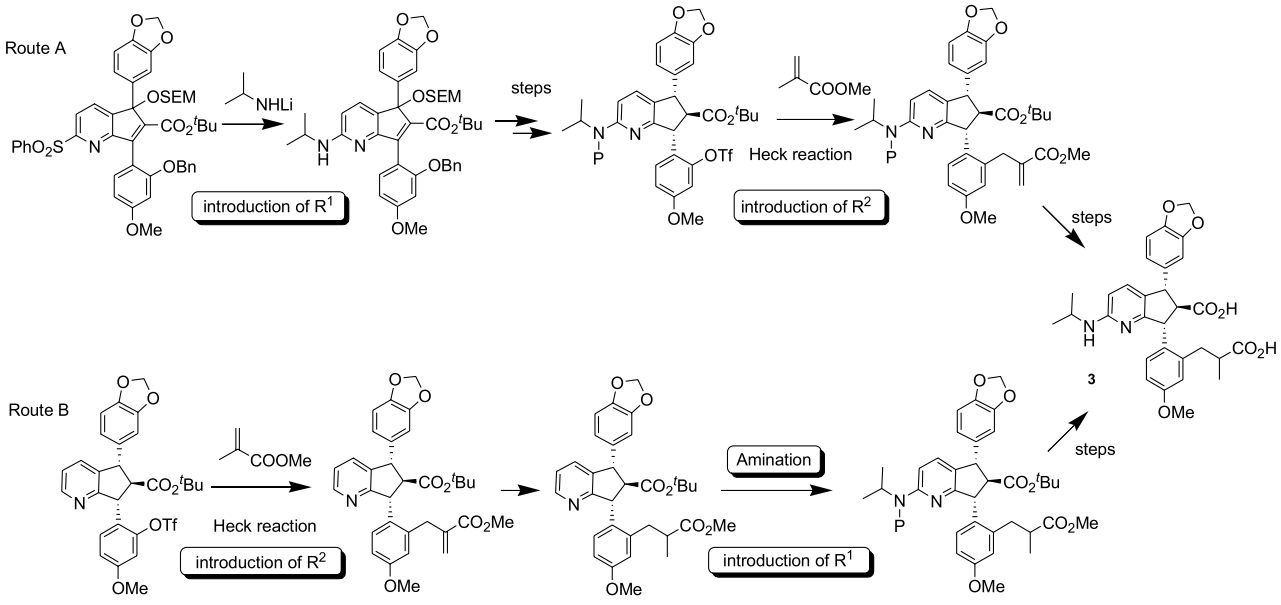


Figure 1.

A number of substituents (Fig. 1, R^2) are easily incorporated in the 7-aryl ring at an early stage in the synthesis,[4] therefore, route B is more available than route A in terms of the synthesis of 2-alkylamino-6-carboxy-5,7-diarylcyclopenteno[1,2-*b*]pyridine derivatives. However, the incorporation of the alkylamino group (Fig. 1, R^1) is a crucial step in this route. A previous work introduced an alkylamino group at the 2-position of a pyridine ring by reacting a readily available pyridine *N*-oxide with an imidoyl chloride.[6] This reaction is thought to be applicable to our highly functionalized pyridine system. Unfortunately, the reaction

Keywords: Acylamination; Imidoyl chloride; Cyclopenteno[1,2-b]pyridines; ETA antagonist.
* Corresponding author. Tel.: +81 29 877 2220; fax: +81 29 877 2027; e-mail: hirobumi_takahashi@merck.com

0040–4020/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2005.02.003



Scheme 1. Possible synthetic route for compound **3**.

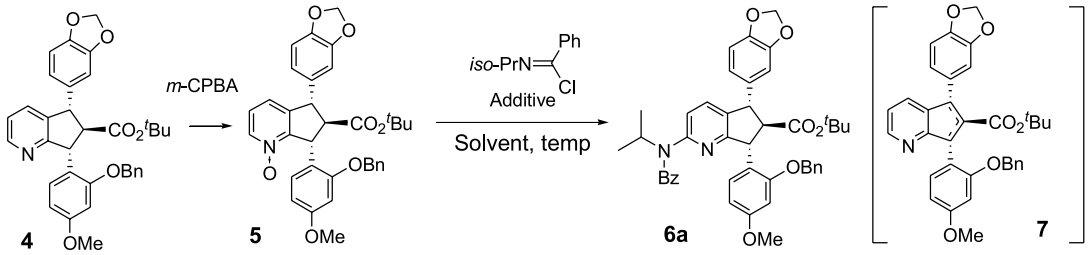
of the pyridine *N*-oxide **5** with one equivalent of *N*-isopropylbenzimidoyl chloride afforded the desired compound **6a** in a very low yield (4.5%). Optimization of the detailed reaction conditions is necessary in order to apply this reaction to the current system.

Herein, we describe the results of the optimization of the direct acylamination at the 2-position of functionalized pyridine derivatives with an imidoyl chloride, as well as a flexible and convenient synthesis of 2-alkylamino-6-carboxy-5,7-diarylcyclopenteno[1,2-*b*]pyridine derivatives.

2. Results and discussion

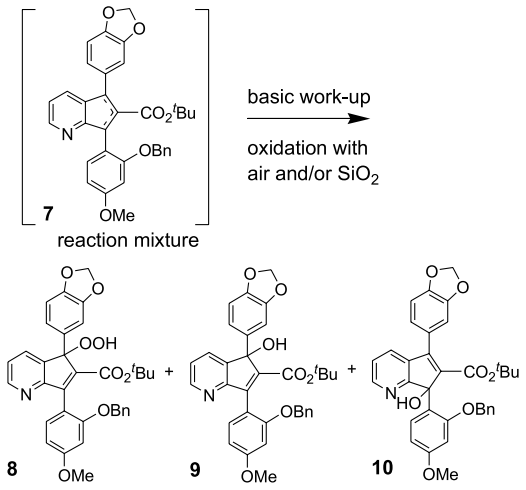
The optimized acylamination reaction conditions utilizing pyridine *N*-oxide **5** and *N*-isopropylbenzimidoyl chloride are shown in Table 1. Pyridine *N*-oxide **5** was readily prepared from **4** by treatment with *m*-CPBA at 0 °C under a nitrogen atmosphere. The initial conditions (entry 1) afforded the desired amide **6a** in a 4.5% yield.[6] Under these conditions, half of the starting material *N*-oxide **5** was recovered together with by-products. The structure of the major by-product was estimated by Mass spectral analysis

Table 1. Acylamination of *N*-oxide **5** with *N*-isopropylbenzimidoyl chloride



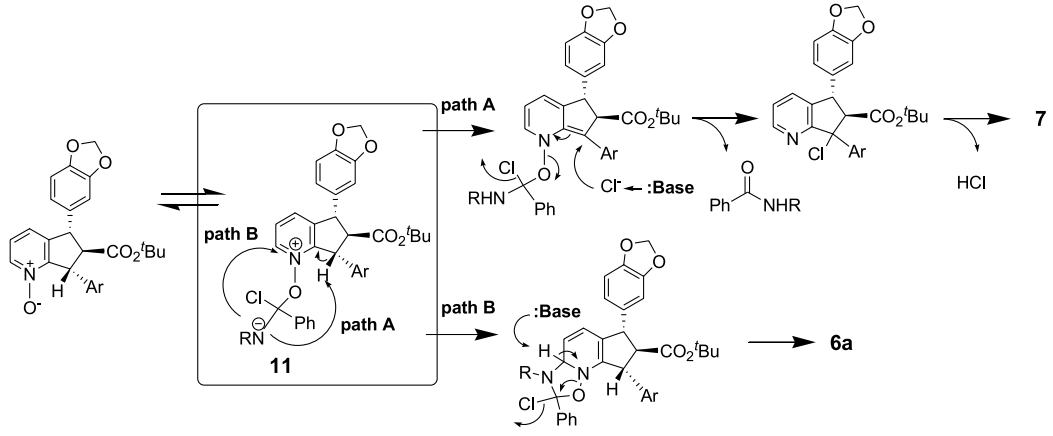
Entry	Imidoyl chloride (equiv)	Solvent	Additive	Temp. (°C)	Results		
					6a	**7**[a]	**5**
1	1	$ClCH_2CH_2Cl$	None	100	4.5%	22%	42%
2	1	$CHCl_3$	None	60	10%	15%	63%
3	10	$CHCl_3$	None	60	13%	21%	40%
4	5	$CHCl_3$	K_2CO_3 (10 equiv)	60	17%	13%	44%
5	5	$CHCl_3$	Cs_2CO_3 (10 equiv)	60	26%	27%	24%
6	5	$CHCl_3$	CsF (10 equiv)	60	69%	6.1%	14%
7	5	$CHCl_3$	Ag_2O (10 equiv)	60	10%	—[b]	19%
8	5	$CHCl_3$	DBU (10 equiv)	60	—	—[b]	79%
9	5	$CHCl_3$	Et_3N (10 equiv)	60	96%	—	—
10	5	Toluene	Et_3N (10 equiv)	60	1.4%	1.2%[b]	75%
11	5	THF	Et_3N (10 equiv)	60	16%	—[b]	39%
12	2.5	$CHCl_3$	Et_3N (5 equiv)	60	94%	—	—

[a] Total yield of **7**, **8**, **9** and **10**.[7]
[b] **4** was isolated as a byproduct



Scheme 2. Identification of side products.

Among the inorganic bases tested, cesium fluoride (CsF) was found to dramatically enhance the desired reaction pathway resulting in a 69% yield of the 2-acylaminated pyridine (**6a**), however the starting material was still recovered (14%). In evaluating the organic bases, unfortunately, DBU was reacted with the imidoyl chloride to produce an ammonium salt rapidly; resulting in a 79% recovery of the starting material (entry 8). In contrast, Et_3N worked very well affording **6a** in an excellent yield (96%, entry 9). With regard to a solvent, chloroform is the best choice for this reaction. Using toluene or tetrahydrofuran instead of chloroform, Et_3N did not work well and a considerable amount of the starting material was recovered (entries 10 and 11). Further experiments around these conditions revealed that 2.5 equiv of imidoyl chlorides in the presence of 5 equiv of Et_3N (entry 12) afforded the product **6a** in 94% yield. These conditions were determined to be the optimal conditions.



Scheme 3. Proposed reaction mechanism.

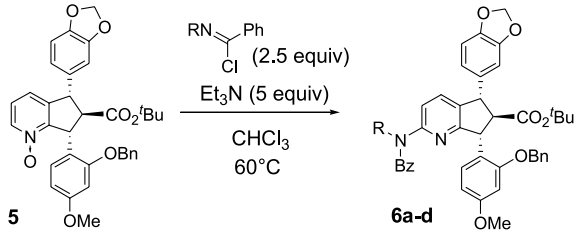
to be **7** in the reaction mixture. However, compound **7** was labile and easily changed by usual work-up and following isolation using silica-gel column chromatography to a mixture of **7**, **8**, **9** and **10** (Scheme 2).[7] Lower reaction temperature with one equivalent of imidoyl chloride (entry 2) or with an excess of imidoyl chloride (entry 3) resulted in an improved yield of **6a**, however, a considerable amount of the starting material and by-products still recovered.

Based on these results, we speculated that the formation of intermediate **11** may be a critical step in this reaction. Further, two reaction pathways were expected to exist for this reaction (Scheme 3). In this reaction, additive(s) are thought to facilitate the formation of the intermediate and the subsequent desired reaction steps, while formation of the by-product **7** can be controlled to trap chloride ions. Moreover, it was reported that addition of a base, such as DBU or triethylamine (Et_3N), increased the yields of 2-acylaminated pyridines in this type of reaction.[6f] However, simple pyridine substrates were used in the optimization of this reaction. Thus, we reexamined the effect of several additional bases in order to accelerate the desired reaction pathway in this highly functionalized pyridine system.

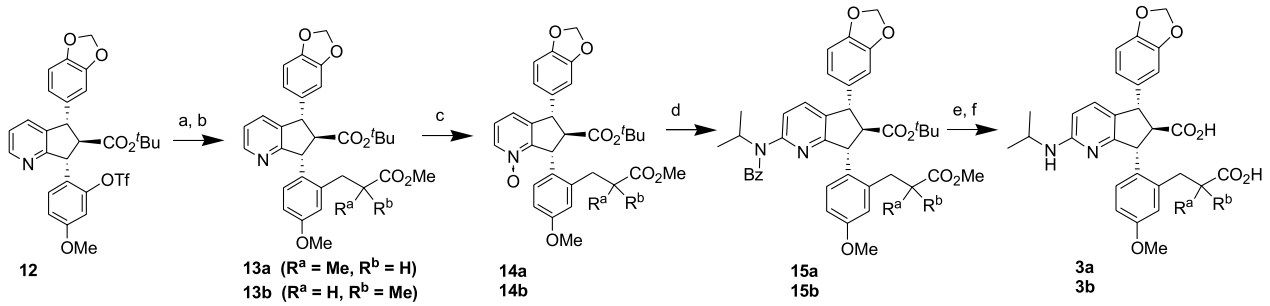
In an effort to examine the applicability of these reaction conditions, pyridine *N*-oxide **5** was reacted with other imidoyl chlorides (Table 2). As expected, the reaction conditions were well tolerated, and the corresponding 2-benzoylaminopyridines (**6a–6d**) were obtained in good to excellent yields.

The previously described encouraging results prompted the

Table 2. Acylamination with various imidoyl chlorides



Entry	Imidoyl chloride	Product	Yield (%)
1	R=*iso*-Pr	**6a**	94
2	R=*n*-Pr	**6b**	93
3	R=Benzyl	**6c**	96
4	R=Phenyl	**6d**	74



Scheme 4. Synthetic route for **3**. Reaction conditions: (a) Methyl Methacrylate, $PdCl_2(PPh_3)_2$, $NaHCO_3$, DMF, 130 °C; (b) 10% Pd-C, $HCOONH_4$, EtOH, 80 °C (**13a**, 37%; **13b**, 28% 2 steps); (c) *m*-CPBA, $CHCl_3$, 6 °C (**14a**, 96%; **14b**, 83%); (d) *N*-isopropylbenzimidoyl chloride, Et_3N, $CHCl_3$, 60 °C (**15a**, 72%; **15b**, 74%); (e) TFA, r.t. (f) NaOH, aq-MeOH, 100 °C (**3a**, 74%; **3b**, 67% 2 steps).

synthesis of **3** by route B (Scheme 4). The Heck reaction of triflate **12** with methyl methacrylate [$PdCl_2(PPh_3)_2$, $NaHCO_3$, DMF, 130 °C] followed by subsequent hydrogenation of the resultant olefin afforded a mixture of diastereomers (**13a** and **13b**) in a moderate yield.[5] The diastereomers were easily separated by silica gel column chromatography. Pyridine *N*-oxide **14a** was treated with *N*-isopropylbenzimidoyl chloride (2.5 equiv) in the presence of Et_3N (5.0 equiv) at 60 °C and afforded 2-acylaminated pyridine **15a** in a 72% yield. The stepwise deprotection of the protecting groups (*tert*-butyl ester, methyl ester, benzamide) on **15a** was achieved by treatment with trifluoroacetic acid (TFA), followed by basic hydrolysis (NaOH) to afford the target compound **3a**. The transformation of **13b** to **3b** was successfully achieved in a manner similar to that described above.

3. Conclusions

A novel synthetic method for 2-alkylamino-6-carboxy-5,7-diarylcyclopenteno[1,2-*b*]pyridines via a key acylamination of the corresponding *N*-oxides with imidoyl chlorides has been developed. This mild acylamination is thought to be applicable to the other highly functionalized pyridine derivatives.[8]

4. Experimental

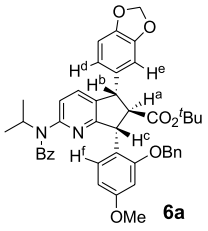
4.1. General

All reagents and solvents were of commercial quality and used without further purification unless otherwise noted. Melting points were determined using a Yanaco MP micromelting point apparatus (Yanaco New Science Inc. Kyoto, Japan) and were not corrected. ^1H NMR and ^{13}C NMR spectra were obtained on a Varian MERCURYvx 400 (Varian, Inc. CA, USA) or JEOL JNM-AL 400 (JEOL Ltd. Tokyo, Japan) instrument at 400 MHz. Chemical shifts were reported in parts per million as δ units relative to tetramethylsilane as an internal standard. Mass spectrometry was performed using micromass Q-Tof 2 (Waters Co. MA, USA) (ESI positive). Analytical and Preparative TLC were preformed using E-Merck Kieselgel F_{254} precoated plates (Merck KGaA. Darmstadt, Germany). Silica gel column chromatography was carried out on Wako gel C-300 (Wako Pure Chemical Industries Ltd, Osaka, Japan.

4.1.1. (5*RS*,6*SR*,7*SR*)-7-(2-Benzyloxy-4-methoxyphenyl)-6-*tert*-butoxycarbonyl-5-(3,4-methylenedioxyphenyl)-cyclopenteno[1,2-*b*]pyridine *N*-oxide (5). To a solution of (5*RS*,6*SR*,7*SR*)-7-(2-Benzyloxy-4-methoxyphenyl)-6-*tert*-butoxycarbonyl-5-(3,4-methylenedioxyphenyl)cyclopenteno[1,2-*b*]pyridine **4** (5.29 g, 9.59 mmol) in $CHCl_3$ (50 ml) was added *m*-CPBA (3.33 g, 19.2 mmol) at 0 °C and the mixture was stirred for 15 h at cold-room temperature (6 °C) under N_2. The reaction was quenched with 1 M $Na_2S_2O_3$ solution while stirring at 6 °C for 30 min and subsequently extracted using EtOAc. The organic layer was washed with saturated $NaHCO_3$ solution, water and brine, dried over Na_2SO_4 and then concentrated. The residue was purified by silica gel column chromatography ($CHCl_3$–MeOH = 100:0 to 30:1) to give **5** as a pale brown amorphous solid (2.89 g, 53%). ^1H NMR ($CDCl_3$) δ 7.99 (d, J = 6.6 Hz, 1H), 7.25–7.19 (m, 4H), 7.15–6.96 (m, 3H), 6.62 (d, J = 7.3 Hz, 1H), 6.55 (d, J = 8.1 Hz, 1H), 6.50–6.43 (m, 2H), 6.38–6.24 (m, 2H), 5.90 (q, J = 1.7 Hz, 2H), 4.98–4.68 (m, 3H), 4.38 (d, J = 8.8 Hz, 1H), 3.76 (s, 3H), 3.27 (t, J = 9.5 Hz, 1H), 1.33 (s, 9H). HRMS calcd for $C_{34}H_{34}NO_7$ (M + 1) 568.2335, found 568.2331.

4.1.2. Preparation of *N*-isopropylbenzimidoyl chloride. A solution of isopropylamine (35.0 ml, 410 mmol) and Et_3N (69.0 ml, 490 mmol) in THF (200 ml) was cooled in an ice bath and benzoyl chloride was added to the solution. After the mixture was stirred at the same temperature for 3 h, the mixture was diluted with water and extracted with EtOAc. The organic layer was washed with 2 N HCl, water, saturated $NaHCO_3$ solution and brine, and subsequently dried over Na_2SO_4 and concentrated to give benzisopropylamide as a white solid (51.9 g, 78%). A mixture of benzisopropylamide (6.09 g, 36.8 mmol) and thionyl chloride (4.50 ml, 61.7 mmol) was stirred at 90 °C under a N_2 atmosphere. After 2.5 h, thionyl chloride was removed in vacuo and distilled under reduced pressure to give *N*-isopropylbenzimidoyl chloride as a colorless liquid (6.08 g, 91% yield). Bp 82–83 °C/5 mmHg. (lit.,[9] 52–54 °C/1 mmHg). d = 1.15 (1.15 g/1.0 ml). ^1H NMR ($CDCl_3$) δ 7.97–7.94 (m, 2H), 7.47–7.34 (m, 3H), 4.14 (sept, J = 6.2 Hz, 1H), 1.27 (d, J = 6.2 Hz, 6H).

4.1.3. Reaction of (5*RS*,6*SR*,7*SR*)-7-(2-Benzyloxy-4-methoxyphenyl)-6-*tert*-butoxycarbonyl-5-(3,4-methylenedioxyphenyl)cyclopenteno[1,2-*b*]pyridine *N*-oxide (5) with *N*-isopropylbenzimidoyl chloride (Table 1). In cases in which inorganic bases were employed as additives, the bases were used before being dried under heat. In cases in which organic bases were used as additives, bases were dried over NaOH. Imidoyl chloride (1, 2.5, 5 or 10 equiv) was added to a mixture of **5** (170 mg, 0.30 mmol) and additive (none, 5 or 10 equiv) in either $ClCH_2CH_2Cl$ or $CHCl_3$ (1.0 ml) and stirred in oil bath at a prescribed temperature under an Ar atmosphere overnight. After cooling the reaction mixture, saturated $NaHCO_3$ solution was added to the mixture and extracted using EtOAc. The organic layer was washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by silica gel column chromatography (Hexane–EtOAc–MeOH as eluent) and if needed, further isolation was performed by preparative TLC ($CHCl_3$–MeOH as eluent). **6a**. ^{1}H NMR ($CDCl_3$) δ 7.27–7.19 (m, 6H), 7.17–7.11 (m, 2H), 7.08–7.04 (m, 2H), 6.97 (d, J=8.2 Hz, 1H), 6.94 (dd, J=7.8, 1.2 Hz, 1H), 6.57–6.53 (m, 2H), 6.53 (d, J=2.3 Hz, 1H), 6.49 (dd, J=8.4, 2.3 Hz, 1H), 6.39–6.35 (m, 2H), 5.89 (br s, 2H), 5.01–4.91 (m, 1H), 4.94 (d, J=11.3 Hz, 1H), 4.90 (d, J=11.3 Hz, 1H), 4.82 (d, J=10.0 Hz, 1H), 4.40 (d, J=10.0 Hz, 1H), 3.82 (s, 3H), 3.40 (t, J=10.0 Hz, 1H), 1.28 (s, 9H), 1.25 (d, J=6.8 Hz, 3H), 1.15 (d, J=6.8 Hz, 3H). The configuration of **6a** were determined by NOE experiments.[7] NOEs were observed between δ 3.40 (H^a) and δ 6.36 (H^d), δ 3.40 (H^a) and δ 6.37 (H^e), δ 4.40 (H^b) and δ 4.82 (H^c), δ 4.40 (H^b) and δ 6.36 (H^d), δ 4.40 (H^b) and δ 6.37 (H^e), δ 4.82(H^c) and δ 6.97 (H^f).

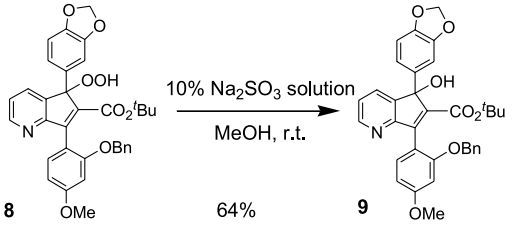


6a

^{13}C NMR ($CDCl_3$) δ 20.6, 21.5, 28.1, 48.9, 51.1, 51.2, 55.4, 61.29, 70.0, 80.7, 99.8, 100.8, 104.5, 108.1, 108.4, 121.3, 121.5, 122.6, 127.1, 127.5, 127.7, 128.2, 128.3, 129.1, 131.4, 133.0, 135.4, 135.9, 136.3, 137.2, 146.3, 147.5, 153.8, 157.3, 159.7, 164.1, 170.0, 172.4. HRMS calcd for $C_{44}H_{45}N_2O_7$ (M+1) 713.3227, found 713.3232. Anal. Calcd for $C_{44}H_{44}N_2O_7$: C, 74.14; H, 6.22; N, 3.93. Found C, 73.93; H, 6.23; N, 3.83.

Compound **7** (mixture of 2 isomers). ^{1}H NMR ($CDCl_3$) δ 8.51 and 8.43 (dd, J=4.9, 1.5 Hz, 1H), 7.06–7.48 (m, 8H), 6.82–6.44 (m, 5H), 5.98 and 5.87 (br s, 2H), 5.18–4.68 (m, 4H), 3.83 and 3.76 (s, 3H), 1.21 and 1.17 (s, 9H). HRMS calcd for $C_{34}H_{32}NO_6$ (M+1) 550.2230, found 550.2229. **8**. ^{1}H NMR ($CDCl_3$) δ 9.44 (s, 1H), 8.47 (dd, J=4.9, 1.6 Hz, 1H), 7.61 (dd, J=7.5, 1.6 Hz, 1H), 7.37 (d, J=9.0 Hz, 1H), 7.23 7.17 (m, 5H), 7.11 (dd, J=7.5, 4.9 Hz, 1H), 6.98 (d, J=1.8 Hz, 1H), 6.85 (dd, J=8.2, 1.8 Hz, 1H), 6.64 (dd, J=7.0, 2.4 Hz, 1H), 6.63 (br s, 1H), 6.56 (d, J=8.2 Hz, 1H), 5.90 (br s, 2H), 5.00 (d, J=11.2 Hz, 1H), 4.95 (d, J=11.2 Hz, 1H), 3.85 (s, 3H), 1.21 (s, 9H). HRMS calcd for $C_{34}H_{32}NO_8$ (M+1) 582.2128, found 582.2134. **9**. ^{1}H NMR ($CDCl_3$) δ 8.46 (dd, J=5.1, 1.5 Hz, 1H), 7.50 (dd, J=7.3, 1.5 Hz, 1H), 7.34 (br s, 1H), 7.24–7.19 (m, 5H), 7.11–7.05 (m, 1H), 7.07 (dd, J=7.3, 5.1 Hz, 1H), 6.94–6.82 (m, 1H), 6.67–6.63 (m, 2H), 5.88 (s, 2H), 5.05 (s, 2H), 4.39 (br s, 1H), 3.84 (s, 3H), 1.17 (s, 9H). HRMS calcd for $C_{34}H_{32}NO_7$ (M+1) 566.2179, found 566.2176. **10**. ^{1}H NMR ($CDCl_3$) δ 8.39 (dd, J=5.1, 1.5 Hz, 1H), 8.01 (d, J=8.8 Hz, 1H), 7.22 (d, J=7.3 Hz, 1H), 7.19–7.12 (m, 3H), 7.07 (dd, J=7.3, 5.1 Hz, 1H), 6.85–6.81 (m, 2H), 6.73 (d, J=8.1 Hz, 1H), 6.65 (dd, J=8.8, 2.2 Hz, 1H), 6.43 (dd, J=8.1, 1.5 Hz, 1H), 6.39 (d, J=1.5 Hz, 1H), 6.36 (d, J=2.2 Hz, 1H), 5.98 (br s, 2H), 4.66 (d, J=11.0 Hz, 1H), 4.57 (d, J=11.0 Hz, 1H), 4.20 (s, 1H), 3.78 (s, 3H), 1.24 (s, 9H). HRMS calcd for $C_{34}H_{32}NO_7$ (M+1) 566.2179, found 566.2182.

4.1.4. Determination of 8 (Scheme 5). To a solution of **8** (32.0 mg, 0.0552 mmol) in MeOH (0.50 ml) was added 10% Na_2SO_3 solution (0.50 ml). After stirring at room temperature for 0.5 h, the mixture was diluted using water and extracted using EtOAc. The organic layer was washed with brine, dried over Na_2SO_4 and then concentrated in vacuo. The residue was purified by silica gel column chromatography (Hexane–EtOAc=10:0 to 3:1) to yield **9** as a white amorphous solid (14.0 mg, 64%).



8 64% **9**

Scheme 5. Conversion of **8** to **9**.

4.1.5. Preparations of imidoyl chlorides (Table 2). All imidoyl chlorides were prepared from the corresponding amines by a procedure similar to that described for the preparation of *N*-isopropylbenzimidoyl chloride. *N*-*n*-propylbenzimidoyl chloride. Colorless liquid. Bp 72–73 °C/1.1 mmHg. ^{1}H NMR ($CDCl_3$) δ 8.03–8.00 (m, 2H), 7.49–7.39 (m, 3H), 3.69 (t, J=7.0 Hz, 2H), 1.78 (qt, J=7.4, 7.0 Hz, 2H), 1.04 (t, J=7.4 Hz, 3H). *N*-benzylbenzimidoyl chloride. Colorless liquid. Bp 139–141 °C/1.1 mmHg. ^{1}H NMR ($CDCl_3$) δ 8.10–8.07 (m, 2H), 7.51–7.27 (m, 8H), 4.95 (s, 2H). *N*-phenylbenzimidoyl chloride. White solid. Bp 120–129 °C/1.1 mmHg. (lit.[6c] 100 °C/0.05 mmHg). Mp 35–37 °C (lit.[6c] 34–35 °C). ^{1}H NMR ($CDCl_3$) δ 8.20–8.17 (m, 2H), 7.59–7.40 (m, 5H), 7.25–7.20 (m, 1H), 7.04–7.01 (m, 2H).

4.1.6. Reaction of (5*RS*,6*SR*,7*SR*)-7-(2-Benzyloxy-4-methoxyphenyl)-6-*tert*-butoxycarbonyl-5-(3,4-methylenedioxyphenyl)cyclopenteno[1,2-*b*]pyridine *N*-oxide (5) with various imidoyl chlorides (Table 2). Imidoyl chloride (0.75 mmol) was added to a mixture of **5** (170 mg, 0.30 mmol) and Et_3N (0.21 ml, 1.50 mmol) in $CHCl_3$ (1.0 ml) and stirred in oil bath (60 °C) under an Ar atmosphere overnight. After cooling the reaction mixture, saturated $NaHCO_3$ solution was added to the mixture and

extracted using EtOAc. The organic layer was washed with brine, dried over Na_2SO_4 and then concentrated. The residue was purified by silica gel column chromatography (Hexane–EtOAc as eluent) to give **6b–6d**. **6b**. white amorphous solid (201 mg, 93% yield). ^{1}H NMR ($CDCl_3$) δ 7.32–7.15 (m, 8H), 7.07 (d, J=8.2 Hz, 1H), 6.99–6.95 (m, 2H), 6.90 (dd, J=8.0, 1.2 Hz, 1H), 6.56–6.48 (m, 4H), 6.35 (d, J=1.7 Hz, 1H), 6.31 (dd, J=7.9, 1.7 Hz, 1H), 5.89 (br s, 2H), 4.92 (d, J=11.4 Hz, 1H), 4.85 (d, J=11.4 Hz, 1H), 4.75 (d, J=10.1 Hz, 1H), 4.39 (d, J=10.1 Hz, 1H), 3.98–3.84 (m, 1H), 3.82 (s, 3H), 3.42 (t, J=10.1 Hz, 1H), 1.71–1.45 (m, 2H), 1.29 (s, 9H), 0.79 (t, J=7.4 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ 11.4, 21.2, 28.1, 50.4, 51.3, 51.9, 55.4, 61.2, 70.0, 80.8, 100.0, 100.9, 104.5, 108.2, 108.6, 120.7, 121.1, 121.7, 127.3, 127.9, 128.0, 128.5, 128.6, 129.8, 132.1, 133.4, 135.4, 135.7, 136.4, 136.7, 146.5, 147.7, 155.6, 157.6, 160.2, 164.5, 170.5, 172.8. HRMS calcd for $C_{44}H_{45}N_2O_7$ (M+1) 713.3227, found 713.3226. Anal. Calcd for $C_{44}H_{44}N_2O_7$: C, 74.14; H, 6.22; N, 3.93. Found C, 74.05; H, 6.38; N, 3.75. **6c**. White amorphous solid (219 mg, 96% yield). ^{1}H NMR ($CDCl_3$) δ 7.37–7.05 (m, 14H), 6.76 (d, J=8.0 Hz, 1H), 6.74–6.68 (m, 2H), 6.57–6.52 (m, 2H), 6.48–6.41 (m, 2H), 6.25 (d, J=1.4 Hz, 1H), 6.15 (dd, J=7.9, 1.4 Hz, 1H), 5.86 (s, 2H), 5.23 (s, 2H), 4.77 (d, J=11.0 Hz, 1H), 4.71 (d, J=10.2 Hz, 1H), 4.67 (d, J=11.0 Hz, 1H), 4.34 (d, J=10.2 Hz, 1H), 3.85 (s, 3H), 3.41 (t, J=10.2 Hz, 1H), 1.29 (s, 9H). ^{13}C NMR ($CDCl_3$) δ 28.1, 51.3, 51.7, 52.1, 55.5, 60.9, 70.0, 80.8, 100.0, 100.9, 104.4, 108.3, 108.7, 120.5, 121.1, 121.6, 127.1, 127.6, 127.9, 128.0, 128.3, 128.7, 130.2, 132.2, 133.1 135.1, 135.6, 136.2, 136.2, 138.0, 146.4, 147.6, 155.2, 157.7, 160.3, 164.4, 171.0, 172.9. HRMS calcd for $C_{48}H_{45}N_2O_7$ (M+1) 761.3227, found 761.3214. Anal. Calcd for $C_{48}H_{44}N_2O_7$: C, 75.77; H, 5.83; N, 3.68. Found C, 75.75; H, 5.96; N, 3.55. **6d**. White amorphous solid (167 mg, 74% yield). ^{1}H NMR ($CDCl_3$) δ 7.45–7.41 (m, 2H), 7.31–7.09 (m, 12H), 7.00 (dd, J=8.0, 0.8 Hz, 1H), 6.90–6.85 (m, 3H), 6.52 (d, J=8.0 Hz, 1H), 6.44 (d, J=2.4 Hz, 1H), 6.40 (dd, J=8.2, 2.4 Hz, 1H), 6.33 (d, J=1.7 Hz, 1H), 6.26 (dd, J=8.0, 1.7 Hz, 1H), 5.89 (d, J=1.4 Hz, 1H), 5.89 (d, J=1.4 Hz, 1H), 4.75 (d, J=11.2 Hz, 1H), 4.64 (d, J=10.0 Hz, 1H), 4.63 (d, J=11.2 Hz, 1H), 4.38 (d, J=10.0 Hz, 1H), 3.80 (s, 3H), 3.33 (t, J=10.0 Hz, 1H), 1.27 (s, 9H). ^{13}C NMR ($CDCl_3$) δ 28.1, 51.3, 51.8, 55.4, 61.3, 70.0, 80.7, 99.9, 100.9, 104.5, 108.3, 108.7, 120.1, 121.1, 121.7, 126.7, 127.7, 127.8, 127.9, 128.4, 129.0, 129.0, 130.1, 131.8, 134.2, 135.8, 136.1, 136.4, 136.5, 142.9, 146.5, 147.7, 155.9, 157.6, 160.0, 164.6, 170.9, 172.7. HRMS calcd for $C_{47}H_{43}N_2O_7$ (M+1) 747.3070, found 747.3078. Anal. Calcd for $C_{47}H_{42}N_2O_7$: C, 75.58; H, 5.67; N, 3.75. Found C, 75.26; H, 5.71; N, 3.61.

4.1.7. (5*RS*,6*SR*,7*SR*)-6-*tert*-Butoxycarbonyl-7-[2-(2-methoxycarbonylpropyl)-4-methoxyphenyl]-5-(3,4-methylenedioxyphenyl)cyclopenteno[1,2-*b*]pyridine (13a, 13b). A mixture of $PdCl_2(PPh_3)_2$ (2.37 g, 3.37 mmol), $NaHCO_3$ (5.66 g, 67.4 mmol), methyl methacrylate (90 ml, 841 mmol) and **12**[5] (9.99 g, 16.9 mmol) in DMF (240 ml) was heated with stirring at 130 °C for 15 h under a N_2 atmosphere. After cooling to room temperature, the reaction mixture was diluted with EtOAc (200 ml). Insoluble materials were filtered off using Celite pad and the Celite pad was washed with EtOAc. The combined filtrate was washed with saturated $NaHCO_3$ solution, water and brine, dried over Na_2SO_4 and then concentrated. The residue was purified by silica gel column chromatography (hexane–EtOAc=4:1 to 3:2) to give mixture of *endo* and *exo* olefins (1:5 by ^{1}H NMR) as a pale brown amorphous solid (9.48 g, quant). This solid was used in the subsequent reaction without further separation. Pure samples of each *exo* and *endo* olefins were isolated by further separation with silica gel column chromatography (hexane–EtOAc=3:1 to 2:1). The *exo* olefin. white amorphous solid. ^{1}H NMR ($CDCl_3$) δ 8.42 (d, J=4.9 Hz, 1H), 7.27 (d, J=7.6 Hz, 1H), 7.08 (dd, J=7.6, 4.9 Hz, 1H), 7.04–6.63 (m, 6H), 6.26 (d, J=1.1 Hz, 1H), 5.95 (br s, 2H), 5.46 (br s, 1H), 4.79 (d, J=10.2 Hz, 1H), 4.51 (d, J=10.2 Hz, 1H), 4.00–3.40 (m, 2H), 3.77 (s, 3H), 3.74 (s, 3H), 3.21 (t, J=10.2 Hz, 1H), 1.35 (s, 9H). HRMS calcd for $C_{32}H_{34}NO_7$ (M+1) 544.2335, found 544.2327. The *endo* olefin. Pale brown amorphous solid. ^{1}H NMR ($CDCl_3$) δ 8.42 (d, J=4.9 Hz, 1H), 7.49 (s, 1H), 7.28 (d, J=7.6 Hz, 1H), 7.16–6.67 (m, 6H), 7.10 (dd, J=7.6, 4.9 Hz, 1H), 5.97 (br s, 2H), 4.75 (d, J=10.4 Hz, 1H), 4.53 (d, J=10.4 Hz, 1H), 3.80 (s, 3H), 3.73 (s, 3H), 3.19 (t, J=10.4 Hz, 1H), 1.92 (d, J=1.3 Hz, 3H), 1.32 (s, 9H). HRMS calcd for $C_{32}H_{34}NO_7$ (M+1) 544.2335, found 544.2330.

A quantity of 6.5 g of 10% Pd–C and 20.2 g $HCOONH_4$ was added to a suspension of the olefin (9.48 g, 16.9 mmol) in EtOH (160 ml). After the mixture was heated with stirring at 80 °C for 24 h, insoluble materials were filtered off using a Celite pad and the Celite pad was washed with EtOAc and MeOH. After the combined filtrate was concentrated, the residue was diluted with EtOAc and water and the organic layer was separated. The organic layer was washed with saturated $NaHCO_3$ solution and brine, dried over Na_2SO_4 and then concentrated. The residue was purified by silica gel column chromatography (hexane–EtOAc=9:1 to 2:1) to give the more polar diastereomer **13a** as a colorless oil (3.44 g, 37%) and the less polar diastereomer **13b** as a white amorphous solid (2.54 g, 28%).

4.1.8. More polar diastereomer 13a. ^{1}H NMR ($CDCl_3$) δ 8.43 (d, J=5.0 Hz, 1H), 7.29 (d, J=7.6 Hz, 1H), 7.09 (dd, J=7.6, 5.0 Hz, 1H), 6.92–6.65 (m, 6H), 6.37 (s, 1H), 5.97 (br s, 2H), 4.91 (d, J=10.1 Hz, 1H), 4.53 (d, J=10.1 Hz, 1H), 3.76 (s, 3H), 3.66 (s, 3H), 3.20 (t, J=10.1 Hz, 1H), 3.19–2.79 (m, 3H), 1.34 (s, 9H), 1.22 (d, J=6.6 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ 17.1, 27.9, 36.5, 41.2, 49.5, 51.5, 51.9, 55.0, 64.4, 81.0, 100.8, 108.1, 108.1, 112.6, 115.0, 121.6, 121.7, 129.4, 132.0, 132.3, 135.5, 137.6, 139.6, 146.4, 147.7, 149.2, 157.7, 164.6, 172.1, 176.3. HRMS calcd for $C_{32}H_{36}NO_7$ (M+1) 546.24292, found 546.2488.

4.1.9. Less polar diastereomer 13b. ^{1}H NMR ($CDCl_3$) δ 8.41 (d, J=4.9 Hz, 1H), 7.29 (d, J=7.6 Hz, 1H), 7.08 (dd, J=7.6, 4.9 Hz, 1H), 6.94–6.86 (m, 1H), 6.80 (d, J=7.9 Hz, 1H), 6.79–6.67 (m, 4H), 5.97 (br s, 2H), 4.94 (d, J=9.7 Hz, 1H), 4.55 (d, J=9.7 Hz, 1H), 3.77 (s, 3H), 3.63 (s, 3H), 3.48–3.24 (m, 1H), 3.24 (t, J=9.7 Hz, 1H), 2.95–2.50 (m, 2H), 1.34 (s, 9H), 1.28–1.15 (m, 3H). ^{13}C NMR ($CDCl_3$) δ 17.1, 28.1, 37.3, 41.0, 49.1, 51.7, 52.0, 55.2, 64.6, 81.1, 101.0, 108.2, 108.3, 112.7, 115.6, 121.8, 129.6, 132.2, 132.4, 135.8, 137.7, 139.6, 146.6, 147.9, 149.4, 157.7, 164.9, 172.2, 176.5. HRMS calcd for $C_{32}H_{36}NO_7$ (M+1) 546.2492, found 546.2485.

4.1.10. (5*RS*,6*SR*,7*SR*)-6-*tert*-Butoxycarbonyl-7-[2-(2-methoxycarbonylpropyl)-4-methoxyphenyl]-5-(3,4-methylenedioxyphenyl)cyclopenteno[1,2-*b*]pyridine *N*-oxide (14a). To a solution of **13a** (3.63 g, 6.65 mmol) in $CHCl_3$ (50 ml) was added *m*-CPBA (2.47 g, 14.3 mmol) at 0 °C and the mixture was stirred for 15 h at cold room temperature (6 °C) under a N_2 atmosphere. The reaction was quenched with 1 M $Na_2S_2O_3$ solution, stirred at 6 °C for 30 min and then extracted with EtOAc. The organic layer was washed with saturated $NaHCO_3$ solution, water and brine, dried over Na_2SO_4 and then concentrated. The residue was purified by silica gel column chromatography ($CHCl_3$–MeOH=30:1) to give **14a** as a pale brown amorphous solid (3.58 g, 96%). ^{1}H NMR ($CDCl_3$) δ 8.02 (d, J=6.2 Hz, 1H), 7.14 (dd, J=7.7, 7.0 Hz, 1H), 6.92 (d, J=7.7 Hz, 1H), 6.82–6.60 (m, 6H), 5.96 (br s, 2H), 5.05 (d, J=7.0 Hz, 1H), 4.56 (d, J=7.7 Hz, 1H), 3.73 (s, 3H), 3.64 (s, 3H), 3.40–2.98 (m, 4H), 1.42 (s, 9H), 1.31 (d, J=7.0 Hz, 3H). HRMS calcd for $C_{32}H_{36}NO_8$ (M+1) 562.2441, found 562.2444.

4.1.11. A diastereomer of 14a (14b). *Compound* **14b** was prepared from **13b** (starting material) in a similar procedure to that described for the preparation of **14a**. White amorphous solid (83% yield); ^{1}H NMR ($CDCl_3$) δ 8.01 (d, J=6.4 Hz, 1H), 7.15 (t, J=7.1 Hz, 1H), 6.94 (d, J=7.9 Hz, 1H), 6.80–6.66 (m, 6H), 5.96 (s, 2H), 5.09 (d, J=7.3 Hz, 1H), 4.61 (d, J=8.2 Hz, 1H), 3.73 (s, 3H), 3.65 (s, 3H), 3.52 (dd, J=13.9, 4.6 Hz, 1H), 3.40–3.29 (m, 1H), 3.15 (dd, J=8.2, 7.3 Hz, 1H), 2.64 (dd, J=13.9, 10.4 Hz, 1H), 1.42 (s, 9H), 1.20 (d, J=6.8 Hz, 3H). HRMS calcd for $C_{32}H_{36}NO_8$ (M+1) 562.2441, found 562.2441.

4.1.12. (5*RS*,6*SR*,7*SR*)-2-(1-Benzoyl-1-*iso*-propylamino)-6-*tert*-butoxycarbonyl-7-[2-(2-methoxycarbonylpropyl)-4-methoxyphenyl]-5-(3,4-methylenedioxyphenyl)cyclopenteno[1,2-*b*]pyridine (15a). To a solution of **14a** (3.40 g, 6.05 mmol) and Et_3N (2.7 ml, 19.4 mmol) in $CHCl_3$ (30 ml) was added *N*-isopropylbenzoylimidoyl chloride (2.97 ml, 18.9 mmol) at room temperature. After stirring overnight at 60 °C under N_2, the mixture was cooled to room temperature and diluted with saturated $NaHCO_3$ solution. The mixture was extracted with ethyl acetate and the organic layer was washed with brine, dried over Na_2SO_4 and then concentrated. The residue was purified by silica gel column chromatography (hexane–EtOAc=10:0 to 4:1) to give **15a** as a pale brown amorphous solid (3.20 g, 72% yield). ^{1}H NMR ($CDCl_3$) δ 7.27–7.12 (m, 5H), 7.02–6.97 (m, 1H), 6.79–6.48 (m, 7H), 5.94 (br s, 2H), 4.98 (sept, J=6.8 Hz, 1H), 4.89 (d, J=9.8 Hz, 1H), 4.46 (d, J=9.8 Hz, 1H), 3.81 (s, 3H), 3.67 (s, 3H), 3.14 (t, J=9.8 Hz, 1H), 3.07–2.96 (m, 2H), 2.92–2.82 (m, 1H), 1.34 (s, 9H), 1.25 (d, J=7.0 Hz, 3H), 1.13 (d, J=7.0 Hz, 6H). ^{13}C NMR ($CDCl_3$) δ 17.0, 20.8, 21.1, 28.0, 36.6, 41.8, 48.2, 49.0, 51.3, 51.7, 55.2, 64.7, 81.3, 101.1, 108.1, 108.3, 113.0, 114.4, 121.8, 123.5, 127.6, 128.4, 129.2, 129.4, 133.0, 133.6, 135.9, 136.3, 137.5, 140.0, 146.8, 148.0, 154.3, 158.0, 164.6, 170.2, 172.4, 176.8. HRMS calcd for $C_{42}H_{47}N_2O_8$ (M+1) 707.3332, found 707.3325. Anal. Calcd for $C_{42}H_{46}N_2O_8$: C, 71.37; H, 6.56; N, 3.96. Found C, 71.09 H, 6.59; N, 3.83.

4.1.13. A diastereomer of 15a (15b). *Compound* **15b** was prepared from **14b** (starting material) in a similar procedure to that described for the preparation of **15a**. White amorphous solid (74% yield). ^{1}H NMR ($CDCl_3$) δ 7.25–7.12 (m, 5H), 7.01 (dd, J=7.7, 1.1 Hz, 1H), 6.79–6.69 (m, 4H), 6.64 (dd, J=7.8, 2.0 Hz, 1H), 6.58–6.51 (m, 2H), 5.96 (br s, 2H), 4.96 (septet, J=6.8 Hz, 1H), 4.90 (d, J=9.8 Hz, 1H), 4.49 (d, J=9.8 Hz, 1H), 3.82 (s, 3H), 3.68 (s, 3H), 3.52–3.43 (m, 1H), 3.21 (t, J=9.8 Hz, 1H), 2.99–2.89 (m, 1H), 2.63–2.53 (m, 1H), 1.34 (s, 9H), 1.18 (d, J=7.0 Hz, 3H), 1.12 (d, J=7.0 Hz, 3H), 1.10 (d, J=7.0 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ 16.4, 20.7, 21.2, 28.0, 37.4, 40.6, 48.2, 48.8, 51.0, 51.7, 55.3, 64.3, 81.3, 101.1, 108.2, 108.4, 112.8, 115.7, 121.8, 123.4, 127.6, 128.4, 129.3, 129.4, 132.9, 133.7, 136.1, 136.2, 137.4, 139.6, 146.8, 148.0, 154.4, 157.7, 164.7, 170.2, 172.3, 176.8. HRMS calcd for $C_{42}H_{47}N_2O_8$ (M+1) 707.3332, found 707.3329. Anal. Calcd for $C_{42}H_{46}N_2O_8$: C, 71.37; H, 6.56; N, 3.96. Found C, 71.15 H, 6.57; N, 3.83.

4.1.14. (5*RS*,6*SR*,7*SR*)-7-[2-(2-Carboxypropyl)-4-methoxyphenyl]-5-(3,4-methylenedioxyphenyl)-2-*iso*-propylaminocyclopenteno[1,2-*b*]pyridine-6-carboxylic acid (3a). *Compound* **15a** (3.40 g, 4.81 mmol) were dissolved with TFA (50 ml) and stirred for 4 h at room temperature. After TFA was removed in vacuo, water was added to the residue and the compound was extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4 and then concentrated. The residue was purified by silica gel column chromatography ($CHCl_3$ to $CHCl_3$–MeOH=10:1) to yield the monoester as a white amorphous solid (2.94 g, 94%). ^{1}H NMR ($CDCl_3$) δ 7.25–7.09 (m, 5H), 7.01 (d, J=7.9 Hz, 1H), 6.76–6.53 (m, 7H), 5.94 (br s, 2H), 4.95 (septet, J=6.8 Hz, 1H), 4.93 (d, J=9.6 Hz, 1H), 4.52 (d, J=9.6 Hz, 1H), 3.79 (s, 3H), 3.61 (s, 3H), 3.28 (t, J=9.6 Hz, 1H), 3.09–2.78 (m, 3H), 1.22 (d, J=6.8 Hz, 3H), 1.12 (d, J=6.8 Hz, 3H), 1.11 (d, J=6.8 Hz, 3H). HRMS calcd for $C_{38}H_{39}N_2O_8$ (M+1) 651.2706, found 651.2699. A quantity of 50 ml (200 mmol) of 4 M NaOH solution was added to a solution of monoester (2.94 g, 4.52 mmol) in MeOH (70 ml) and the mixture was stirred under reflux overnight. After cooling to room temperature, 4 N HCl was added drop-wise to the mixture until it reached pH 2–3. The mixture was then extracted with EtOAc and the organic layer was washed with brine, dried over Na_2SO_4 and then concentrated. The residue was purified by silica gel column chromatography (hexane–EtOAc=1:2 to $CHCl_3$–MeOH=10:1) to give **3a** as a white solid (1.79 g, 74%). Mp 158–160 °C. ^{1}H NMR (acetone-d^6) δ 7.08 (d, J=8.5 Hz, 1H), 7.05 (d, J=8.3 Hz, 1H), 6.88–6.72 (m, 5H), 6.38 (d, J=8.5 Hz, 1H), 6.00 (s, 2H), 5.20 (br s, 1H), 4.90 (d, J=9.5 Hz, 1H), 4.47 (d, J=8.9 Hz, 1H), 3.87–3.75 (m, 1H), 3.75 (s, 3H), 3.29 (dd, J=9.5, 8.9 Hz, 1H), 3.17–3.10 (m, 1H), 3.00–2.80 (m, 2H), 1.22 (d, J=6.5 Hz, 3H), 1.13 (d, J=6.3 Hz, 3H), 1.10 (d, J=6.3 Hz, 3H). ^{13}C NMR (acetone-d^6) δ 17.8, 22.8, 22.9, 38.6, 42.6, 43.4, 50.3, 52.0, 55.2, 63.7, 101.8, 106.8, 108.7, 108.9, 113.3, 115.8, 122.2, 125.7, 130.3, 133.8, 135.0, 138.4, 140.7, 147.2, 148.6, 158.6, 159.6, 162.8, 174.9, 176.7. HRMS calcd for $C_{30}H_{33}N_2O_7$ (M+1) 533.2288, found 533.2282. Anal. Calcd for $C_{30}H_{32}N_2O_7 \cdot 0.5\ H_2O$: C, 66.53; H, 6.14; N, 5.17. Found C, 66.55 H, 6.28; N, 5.01.

4.1.15. A diastereomer of 3a (3b). A volume of 2 ml of 6 M NaOH solution (12 mmol) was added to a solution of **15b** (85 mg, 0.120 mmol) in MeOH (4 ml) and the mixture was

stirred under reflux overnight. After cooling to room temperature, 6 N HCl was added to the mixture until it reached pH 2–3. Insoluble material was collected by filtration and the filtrate was extracted using EtOAc. The organic layer was washed with brine, dried over Na_2SO_4 and then concentrated. The residue and the insoluble material were combined and purified by silica gel column chromatography ($CHCl_3$–MeOH=10:0 to 9:1) to give **3b** as a pale brown solid (43 mg, 67%). Mp 137–141 °C. ^{1}H NMR (CD_3OD) δ 7.33 (d, J=8.8 Hz, 1H), 6.94 (d, J=7.8 Hz, 1H), 6.83–6.75 (m, 5H), 6.68 (d, J=8.8 Hz, 1H), 5.92 (s, 2H), 5.16–5.05 (m, 1H), 4.48 (d, J=8.4 Hz, 1H), 3.90–3.80 (m, 1H), 3.76 (s, 3H), 3.28–3.20 (m, 1H), 3.14–3.06 (m, 1H), 2.85 (dd, J=14.6, 7.0 Hz, 1H), 2.73–2.62 (m, 1H), 1.30–1.23 (m, 3H), 1.21 (d, J=6.3 Hz, 3H), 1.14 (d, J=6.3 Hz, 3H). ^{13}C NMR (CD_3OD) δ 18.3, 22.3, 22.6, 37.5, 43.2, 45.1, 52.8, 55.7, 65.4, 102.4, 109.1, 109.2, 110.6, 114.0, 116.0, 122.4, 127.8, 130.3, 132.6, 137.2, 139.9, 141.8, 148.2, 149.4, 156.0, 156.2, 159.9, 176.1, 180.5. HRMS calcd for $C_{30}H_{33}N_2O_7$ (M+1) 533.2288, found 533.2295. Anal. Calcd for $C_{30}H_{32}N_2O_7 \cdot 0.5\ H_2CO_3$: C, 65.00; H, 5.90; N, 4.97. Found C, 64.99 H, 6.04; N, 4.94.

Acknowledgements

We thank Dr. Shigeru Nakajima and Mr. Hirokazu Ohsawa for analytical support (NMR and Mass spectra). We also thank Toray Research Center, Inc. for elemental analysis.

References and notes

1. Yanagisawa, M.; Kurihara, H.; Kimura, S.; Tomobe, Y.; Kobayashi, M.; Mitsui, Y.; Yazaki, Y.; Goto, K.; Masaki, T. *Nature* **1988**, *332*, 411–415.
2. Hosoda, K.; Nakao, K.; Arai, H.; Nagakawa, O.; Hosoda, K.; Suga, S.; Nakanishi, S.; Imura, H. *FEBS Lett.* **1991**, *287*, 23–26.
3. For ET_A selective antagonist. (a) Winn, M.; Geldern, T. W.; Opgenorth, T. J.; Jae, H.; Tasker, A. S.; Boyd, S. A.; Kester, J. A.; Mantei, R. A.; Bal, R.; Sorensen, B. K.; Wu-Wong, J. R.; Chiou, W. J.; Dixon, D. B.; Novosad, E. I.; Hernadez, L.; Marsh, K. C. *J. Med. Chem.* **1996**, *38*, 1039–1048. (b) Wu, C.; Chan, M. F.; Stavros, F.; Okun, I.; Mong, S.; Keller, K. M.; Brock, T.; Kogan, T. P.; Dixon, R. A. F. *J. Med. Chem.* **1997**, *40*, 1690–1697. (c) Liu, G.; Henry, K. J., Jr.; Szczepankiewicz, B. G.; Winn, M.; Kozmina, N. S.; Boyd, S. A.; Wasicak, J.; von Geldern, T. W.; Wu-Wong, J. R.; Chiou, W. J.; Dixon, D. B.; Nguyen, B.; Marsh, K. C.; Opgenorth, T. J. *J. Med. Chem.* **1998**, *41*, 3261–3275. (d) Astles, P. C.; Brown, T. J.; Halley, F.; Handscombe, C. M.; Harris, N. V.; Majid, T. N.; McCarthy, C.; McLay, A.; Porter, B.; Roach, A. G.; Sargent, C.; Smith, C.; Walsh, R. J. A. *J. Med. Chem.* **2000**, *43*, 900–910. (e) Wu, C.; Decker, E. R.; Blok, N.; Li, J.; Bourgoyne, A. R.; Bui, H.; Keller, K. M.; Knowles, V.; Li, W.; Stavros, F. D.; Holland, G. W.; Brock, T. A.; Dixon, R. A. F. *J. Med. Chem.* **2001**, *44*, 1211–1216. (f) Morimoto, H.; Ohashi, N.; Shimadzu, H.; Kushiyama, E.; Kawanishi, H.; Hosaka, T.; Kawase, Y.; Yasuda, K.; Kikkawa, K.; Yamauchi-Kohno, R.; Yamada, K. *J. Med. Chem.* **2001**, *44*, 3369–3377. (g) Ishizuka, N.; Matsumura, K.; Sakai, K.; Fujimoto, M.; Mihara, S.; Yamamori, T. *J. Med. Chem.* **2002**, *45*, 2041–2055. (h) Murugesan, N.; Gu, Z.; Spergel, S.; Young, M.; Chen, P.; Mathur, A.; Leith, L.; Hermsmeier, M.; Liu, E. C.-K.; Zhang, R.; Bird, E.; Waldron, T.; Marino, A.; Koplowitz, B.; Humphreys, W. G.; Chong, S.; Morrison, R. A.; Webb, M. L.; Moreland, S.; Trippodo, N.; Barrish, J. C. *J. Med. Chem.* **2003**, *46*, 125–137. For ET_B selective antagonist. (a) Balwierczak, J. L.; Bruseo, C. W.; Del Grande, D.; Jeng, A. Y.; Savage, P.; Shetty, S. S. *J. Cardiovasc. Pharmacol.* **1995**, *26*(Suppl. 3), S393–S396. (b) Chan, M. F.; Kois, A.; Verner, E. J.; Raju, B. G.; Castillo, R. S.; Wu, C.; Okun, I.; Stavros, F. D.; Balaji, V. N. *Bioorg. Med. Chem.* **1998**, *6*, 2301–2316. (c) Liu, G.; Kozmina, N. S.; Winn, M.; von Geldern, T. W.; Chiou, W. J.; Dixon, D. B.; Nguyen, B.; Marsh, K. C.; Opgenorth, T. J. *J. Med. Chem.* **1999**, *42*, 3679–3689. (d) Mederski, W. W. K. R.; Osswald, M.; Dorsch, D.; Christadler, M.; Schmitges, C.-J.; Wilm, C. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 619–622. For ET_A/ET_B balanced antagonist. (a) Clozel, M.; Breu, V.; Gray, G. A.; Kalina, B.; Loffler, B.; Burri, K.; Cassal, J.; Hirth, G.; Muller, M.; Neidhart, W.; Ramuz, H. *J. Pharmacol. Exp. Ther.* **1994**, *270*, 228–235. (b) Elliot, J. D.; Lago, M. A.; Cousins, R. D.; Gao, A.; Leber, J. D.; Erhard, K. F.; Nambi, P.; Elshourbagy, N. A.; Kumar, C.; Lee, J. A.; Bean, J. W.; Debrosse, C. W.; Eggleston, D. S.; Brooks, D. P.; Feuerstein, G.; Ruffolo, R. R.; Weinstock, J.; Gleason, J. G.; Peishoff, C. E.; Ohlstein, E. *J. Med. Chem.* **1994**, *37*, 1553–1557. (c) Walsh, T. F.; Fitch, K. J.; Chakravarty, P. K.; Williams, D. L.; Murphy, K. A.; Nolan, N. A.; O'Brien, J. A.; Lis, E. V.; Pettibone, D. J.; Kivlighn, S. D.; Gabel, R. A.; Zingaro, G. J.; Krause, S. M.; Siegl, P. K. S.; Clineschmidt, B. V.; Greenlee, W. J. Abstracts of American Chemical Society National Meeting, Washington, DC, August 21-25, 1994, American Chemical Society: Washington, DC, 1994; MEDI 145. (d) Jae, H.-S.; Winn, M.; Dixon, D. B.; Marsh, K. C.; Nguyen, B.; Opgenorth, T. J.; von Geldern, T. W. *J. Med. Chem.* **1997**, *40*, 3217–3227. (e) Amberg, W.; Hergenröder, S.; Hillen, H.; Jansen, R.; Kettschau, G.; Kling, A.; Klinge, D.; Raschack, M.; Riechers, H.; Unger, L. *J. Med. Chem.* **1999**, *42*, 3026–3032.
4. Niiyama, K.; Takahashi, H.; Nagase, T.; Kojima, H.; Amano, Y.; Katsuki, K.; Yamakawa, T.; Ozaki, S.; Ihara, M.; Yano, M.; Fukuroda, T.; Nishikibe, M.; Ishikawa, K. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 3041–3045.
5. Niiyama, K.; Mase, T.; Takahashi, H.; Naya, A.; Katsuki, K.; Nagase, T.; Ito, S.; Hayama, T.; Hisaka, A.; Ozaki, S.; Ihara, M.; Yano, M.; Fukuroda, T.; Noguchi, K.; Nishikibe, M.; Ishikawa, K. *Bioorg. Med. Chem.* **2002**, *10*, 2461–2470.
6. (a) Abramovitch, R. A.; Singer, G. M. *J. Am. Chem. Soc.* **1969**, *91*, 5672–5673. (b) Abramovitch, R. A.; Rogers, R. B. *Tetrahedron Lett.* **1971**, *22*, 1951–1954. (c) Abramovitch, R. A.; Singer, G. M. *J. Org. Chem.* **1974**, *39*, 1795–1802. (d) Abramovitch, R. A.; Rogers, R. B. *J. Org. Chem.* **1974**, *39*, 1802–1807. (e) Abramovitch, R. A.; Rogers, R. B.; Singer, G. M. *J. Org. Chem.* **1975**, *40*, 41–47. (f) Abramovitch, R. A.; Bailey, T. D. *J. Heterocycl. Chem.* **1975**, *12*, 1079–1080. (g) Abramovitch, R. A.; Abramovitch, D. A.; Tomasik, P. *J. Chem. Soc., Chem. Commun.* **1979**, *21*, 956–957. (h) Abramovitch, R. A.; Pilski, J.; Konitz, A.; Tomasik, P. *J. Org. Chem.* **1983**, *48*, 4391–4393. Recently, one pot method for the generation of imidoyl chloride and in situ reaction with pyridine *N*-oxide was described. Manley, P. J.; Bilodeau, M. T. *Org. Lett.* **2002**, *4*, 3127–3129.
7. Compound **7** and **9** was synthesized or determined in previous

literature. Niiyama, K.; Yoshizumi, T.; Takahashi, H.; Naya, A.; Ohtake, N.; Fukami, T.; Mase, T.; Hayama, T.; Ishikawa, K. *Bioorg. Med. Chem.* **2002**, *10*, 3437–3444. Compound **10** was synthesized in the unpublished SAR study of 7-aryl part. The structure of **8** was elucidated by conversion of **8** to **9** (10% aqueous Na_2SO_3 solution, Scheme 5).

8. (a) Takahashi, H.; Ohtake, N.; Sakamoto, T.; Iino, T.; Kawanishi, N.; Nakamura, M.; Yoshizumi, T.; Niiyama, K.; Ozaki, S.; Okada, H.; Kano, A.; Takahashi, H.; Ishii, Y.; Okada, M.; Saito, M.; Sawazaki, Y.; Hayama, T.; Nishikibe, M. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 1503–1507. (b) Yoshizumi, T.; Takahashi, H.; Ohtake, N.; Jona, H.; Sato, Y.; Kishino, H.; Sakamoto, T.; Ozaki, S.; Takahashi, H.; Shibata, Y.; Ishii, Y.; Saito, M.; Okada, M.; Okada, M.; Hayama, T.; Nishikibe, M. *Bioorg. Med. Chem.* **2004**, *12*, 2139–3150.
9. Brindly, J. C.; Caldwell, J. M.; Meakins, G. D.; Plackett, S. J.; Price *J. Chem. Soc., Perkin Trans. 1* **1987**, 1153–1158.