Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron 63 (2007) 2824–2828
Tetrahedron

Claisen rearrangement/Baylis–Hillman reaction/ring-closing metathesis as bases for the construction of substituted cyanonaphthalenes

Po-Yuan Chen,[a] Hsing-Ming Chen,[b] Liang-Yeu Chen,[c] Jing-Yu Tzeng,[c] Jui-Chi Tsai,[c] Ping-Cheng Chi,[a] Sie-Rong Li[c] and Eng-Chi Wang[a,*]

[a]*Faculty of Medicinal and Applied Chemistry, Kaohsiung Medical University, Kaohsiung City 807, Taiwan*
[b]*Basic Medical Science Education Center, Fooyin University, Kaohsiung County 831, Taiwan*
[c]*Institute of Pharmaceutical Sciences, Kaohsiung Medical University, Kaohsiung City 807, Taiwan*

Received 14 December 2006; revised 24 January 2007; accepted 25 January 2007
Available online 30 January 2007

Abstract—The present paper described how to establish a novel approach for various alkoxycyanonaphthalenes. It was started from isovanillin, and based on the Claisen rearrangement, O-alkylation, the Baylis–Hillman reaction, and ring-closing metathesis in sequence to produce the title compounds in good yield.

1. Introduction

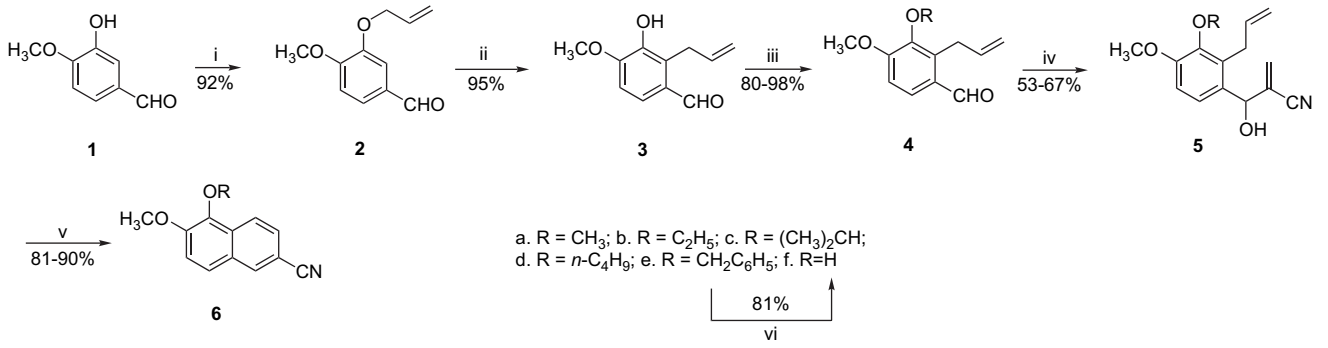
The discovery of the Claisen rearrangement almost a century ago offered a brief and useful tool to give *C*-allyl functionality from *O*-allylphenol.[1] The Baylis–Hillman reaction which offered a simple way to build up an allyl alcohol with α-electron withdrawing substituents has been used at various aspects in organic synthesis.[2] On the other hand, a molecule with two olefinic functionalities can be ring-closed through ring-closing metathesis (RCM), which becomes a powerful and important tool to produce unsaturated cyclic compounds,[3] and also provides distinguished ways to generate arenes with unique mechanisms.[4] However, up to date, to combine those reactions to construct the naphthalenes moiety is still lacking. Naphthalenes, the sub-group of arenes, have intensively attracted the attention of organic chemists for many years due to their occurrence in synthetic and nature products possessing valuable biological activities.[5] The major synthetic naphthalenes, such as nabumetone[6] and naproxen[7] for anti-inflammation, and propranolol[8] for β-blocker to treat tachycardia and angina pectoris, are currently used in medication. Recently, some cyanonaphthalenes were synthesized and reported to exhibit as potential tachykinin antagonists.[9] Furthermore the nitrile can also serve as useful functional group for some biologically potential heterocyclic ring systems such as naphthotetrazoles,[10] naphthotriazines,[11] and so on. Until the present, synthetic methods reported for the preparation of cyanoarenes mainly included the reaction of aryl halides with copper cyanide (Rosenmund–von Braun reaction),[12] and aryldiazonium salts with copper cyanide (Sandmeyer reaction).[13] Instead of copper, some transition metal-catalyzed cyanations of aryl halides have been intensively studied.[14] However, the toxic inorganic metal cyanides, which are required for running those reactions, have disadvantages. Therefore, to develop a unique route for new cyanonaphthalenes with environment concerning is requisite and significant. Herein, we extended our previous study[15] and disclosed a novel route by starting from isovanillin and based on the Claisen rearrangement, Baylis–Hillman reaction, and RCM in sequence to offer various cyanonaphthalenes, which have paid no attention in the reported literatures (Scheme 1).

2. Results and discussion

2-Allyl-3-alkoxy-4-methoxybenzaldehydes (**4a**–**e**) prepared from isovanillin (**1**) through three steps as our previous report[15] were allowed to react with acrylonitrile in the presence of 1,4-diazabicylo[2.2.2]octane (DABCO) or 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) to undergo the Baylis–Hillman reaction. Two solvent systems were taken for this Baylis–Hillman reaction, when water/dioxane (1:1) was used as solvent and DABCO as base, compound **5a** was obtained in the yield of 50% after stirring for 5 days.

Keywords: Claisen rearrangement; Ring-closing metathesis; Cyanonaphthalenes.
* Corresponding author. Tel.: +886 7 3121101; fax: +886 7 3125339; e-mail: enchwa@kmu.edu.tw

0040–4020/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2007.01.054



Scheme 1. Synthesis of substituted cyanonaphthalenes. Conditions: (i) allyl bromide K_2CO_3, acetone, reflux 8 h; (ii) 180 °C, decalin, 5 h; (iii) (a) methyl iodide, (b) ethyl iodide, (c) isopropyl bromide, (d) *n*-butyl bromide, and (e) benzyl bromide, K_2CO_3, acetone, reflux 8 h; (iv) acrylonitrile, DABCO, H_2O, rt, 3–5 days; (v) 5% second Grubbs' catalyst, 0.05 M CH_2Cl_2, rt, 5–8 h; (vi) 20% $Pd(OH)_2$/C, cyclohexene, ethanol, reflux 10 h.

In contrast, when water was used as sole solvent and DABCO as base, the reaction time is shorter (3 days) and the yield (60%) is higher than that of the mixed solvents. The results giving the Baylis–Hillman adducts (**5a**–**e**) are compiled in Table 1.

The spectral data of **5a**–**e**, for example, the absorption at 3446–3469 and 2230–2253 cm^{-1} in IR spectra was observed indicating the presence of OH and CN functional group, respectively. The signals at δ 6.04–6.09 and 6.07–6.09 with coupling constant J=1.2–1.6 Hz in ^1H NMR revealing the existence of two geminal vinyl protons were also observed in the structures **5a**–**e** proving the work of the Baylis–Hillman reaction. In addition, the carbon signals in ^{13}C NMR, the molecular ion in EIMS, and exact mass in HRMS are all match the structures **5a**–**e**. Finally, the resulting adducts (**5a**–**e**) were respectively subjected to RCM by Grubbs' catalyst (second generation) to undergo cyclization and elimination of water to give the desired cyanonaphthalenes (**6a**–**e**) in the yield of 81–90%. The appearance of typical CN absorption at 2200–2230 cm^{-1} in IR spectrum, no olefinic proton at ^1H NMR, and no sp^3 carbon except for the alkoxy moiety at ^{13}C NMR spectra of giving **6a**–**e** were observed indicating the work of RCM. Moreover, in accordance with NOESY technique, for example, the two key protons, H-3 which neighbored with methoxyl group and H-8 which coupled with H-7 in the structure of compound **6b** can be clarified, respectively. The signal of H-3 at δ 7.39 linking with methoxyl signal at δ 4.02 and H-8 at δ 8.20 linking with H-7 at δ 7.56, which has double doublet splits with coupling constant J=8.8 and 1.4 Hz were observed. Besides, H-4 at δ 7.66, which linked with H-3, and H-5 at δ 8.16, which have a meta-couple, J=1.8 Hz, linked with H-7 are also can be assigned. Furthermore, the ranking of chemical shift, H-3>H-7>H-4>H-5>H-8, from upfield to downfield of those protons on cyanonaphthalenes (**6a**–**e**) is certainly established. In addition, the structures of **6a**–**e** were further confirmed by mass spectra, HRMS, and elemental analysis. Furthermore, the substituted cyanonaphthol, **6f**, was produced from the debenzylation of **6e** with Pd $(OH)_2$/C and cyclohexene in refluxing ethanol.

3. Conclusion

Based on the Claisen rearrangement, Baylis–Hillman reaction, and RCM, we have successfully established a novel, concise, and friendly to the earth way to construct new substituted cyanonaphthalenes (**6a**–**e**). Moreover, compound **6e** was debenzylated to give 1-hydroxy-6-cyano-2-methoxynaphthalene (**6f**) with polyfunctional groups, which can be converted into corresponding compounds in diversity.

Table 1. The comparison of dioxane/H_2O or H_2O as solvents for aldehydes (**4a**–**e**) with selected bases (DABCO or DBU) to give the Baylis–Hillman adducts (**5a**–**e**)

Compds	Solvents	Reaction time[a] (days)	Product and yields[b] (%)	R_3N
4a	1,4-Dioxane:H_2O (1:1)	5	**5a** (57)	DABCO
	H_2O	3	**5a** (61)	DABCO
	1,4-Dioxane:H_2O (1:1)	5	**5a** (35)	DBU
	H_2O	3	**5a** (42)	DBU
4b	1,4-Dioxane:H_2O (1:1)	5	**5b** (56)	DABCO
	H_2O	3	**5b** (67)	DABCO
	1,4-Dioxane:H_2O (1:1)	5	**5b** (32)	DBU
	H_2O	3	**5b** (25)	DBU
4c	1,4-Dioxane:H_2O (1:1)	5	**5c** (58)	DABCO
	H_2O	3	**5c** (61)	DABCO
4d	1,4-Dioxane:H_2O (1:1)	5	**5d** (48)	DABCO
	H_2O	3	**5d** (60)	DABCO
4e	1,4-Dioxane:H_2O (1:1)	5	**5e** (42)	DABCO
	H_2O	3	**5e** (53)	DABCO

[a] The reaction time is determined by GC–MS until the desired product is no longer increased apparently.
[b] Yield indicated the product which was isolated; the recovery starting material was not calculated.

Besides, we have established all data for those cyanonaphthalenes (**6a–f**).

4. Experimental

4.1. General

Melting points (Yanaco micro melting-point apparatus) were uncorrected. ^{1}H NMR and ^{13}C NMR spectra were obtained on a Varian Gemini-200 or Varian Unity plus 400 spectrometer. Chemical shifts were measured in parts per million with respect to TMS. Elemental analyses were recorded on a Heraeus CHNO rapid analyzer. Mass spectra were recorded on a Chem/hp/middle spectrometer connected to a Hewlett Packard series II model gas–liquid chromatograph. HRMS spectra were performed on a JEOL JMS SX/SX 102A instrument. Elemental analyses were run on Heraeus CHNO rapid analyzer. Silica gel (230–400 mesh) for column chromatography and precoated silica gel plates (60 F-254) for TLC were purchased from E. Merck Co. UV light (254 nm) was used to detect spots on TLC plates after development.

Isovanillin (**1**) was purchased from TCI, Japan. *O*-Allylisovanillin (**2**), 2-allyl-3-hydroxy-4-methoxy-benzaldehydes (**3a–e**), and 3-alkoxy-2-allyl-4-methoxybenzaldehydes (**4a–e**) were prepared as described in the previous report.[15]

4.1.1. General procedure for the preparation of 2-cyano-3-(2-allyl-3-alkoxy-4-methoxy)phenyl-1-propen-3-ol (5a–e). A mixture of **4a–e** (10.0 mmol) and acrylonitrile (0.66 mL, 30 mmol) was added with DABCO (1.23 g, 11.0 mmol) in water (20 mL). The resulting mixture was stirred at room temperature for 3 days. Then, the reaction mixture was extracted with dichloromethane (3×50 mL). The resulting extract was combined, washed with brine, and dried over anhydrous $MgSO_4$. After filtration, the filtrate was concentrated in vacuo to give crude **5a–e**, which was respectively purified with chromatographic column (ethyl acetate/*n*-hexane=1:7).

4.1.1.1. 2-Cyano-3-(2-allyl-3,4-dimethoxy)phenyl-1-propen-3-ol (5a). Compound **5a** (1.58 g, 61%) was obtained as a pale yellow liquid; R_f=0.39 (ethyl acetate/*n*-hexane=1:2); IR (neat) cm^{-1}: 3466 cm^{-1} (OH), 2254 cm^{-1} (CN); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.02 (br s, 1H, O*H*), 3.46 (ddt, *J*=16.4, 5.6, 2.0 Hz, 1H, ArCH_aH$_b$CH=CH$_2$), 3.55 (ddt, *J*=16.4, 5.6, 2.0 Hz, 1H, ArCH$_a$$H_b$CH=CH$_2$), 3.78 (s, OC$H_3$, 3H), 3.85 (s, OC$H_3$, 3H), 4.89 (ddt, *J*=17.2, 2.0, 2.0 Hz, 1H, ArCH$_2$CH=CH_cH$_d$), 5.04 (ddt, *J*=10.4, 2.0, 2.0 Hz, 1H, ArCH$_2$CH=CH$_c$$H_d$), 5.41 (br s, 1H, C*H*OH), 5.98 (ddt, *J*=17.2, 10.4, 5.6 Hz, 1H, ArCH$_2$C*H*=CH$_2$), 6.04 (d, *J*=1.2 Hz, 1H, CH_eH$_f$=C(CN)–), 6.07 (d, *J*=1.2 Hz, 1H, CH$_e$$H_f$=C(CN)–), 6.83 (d, *J*=8.4 Hz, 1H, Ar*H*), 7.11 (d, *J*=8.4 Hz, 1H, Ar*H*); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 29.47, 55.44, 60.75, 69.76, 110.54, 115.49, 117.16, 122.79, 125.75, 129.96, 130.30, 131.62, 136.93, 147.00, 152.80; EIMS (70 eV) *m*/*z* (rel intensity, %) 259 (M$^+$, 67), 242 (32), 208 (34), 207 (100), 189 (43), 176 (28), 174 (34), 173 (31); HRMS calcd for $C_{15}H_{17}NO_3$: 259.1208, found: 259.1207.

4.1.1.2. 2-Cyano-3-(2-allyl-3-ethoxyl-4-methoxy)-phenyl-1-propen-3-ol (5b). Compound **5b** (1.83 g, 67%) was obtained as a pale yellow liquid; R_f=0.38 (ethyl acetate/*n*-hexane=1:2); IR (neat) cm^{-1}: 3458 cm^{-1}(OH), 2230 cm^{-1} (CN); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.36 (t, *J*=7.2 Hz, 3H, OCH$_2$CH_3), 2.62 (br s, 1H, O*H*), 3.49 (ddt, *J*=16.4, 5.6, 2.0 Hz, 1H, ArCH_aH$_b$CH=CH$_2$), 3.55 (ddt, *J*=16.4, 5.6, 1.6 Hz, 1H, ArCH$_a$$H_b$CH=CH$_2$), 3.84 (s, 3H, OC$H_3$), 3.98 (m, 2H, OC$H_2CH_3$), 4.91 (ddt, *J*=17.2, 1.6, 1.6 Hz, 1H, ArCH$_2$CH=CH_cH$_d$), 5.05 (ddt, *J*=10.0, 1.6, 1.6 Hz, 1H, ArCH$_2$CHC=CH$_c$$H_d$), 5.44 (m, 1H, C*H*OH), 6.00 (ddt, *J*=16.8, 10.0, 5.6 Hz, 1H, ArCH$_2$C*H*=CH$_2$), 6.07 (d, *J*=1.6 Hz, 1H, CH_eH$_f$=C(CN)–), 6.09 (d, *J*=1.6 Hz, 1H, CH$_e$$H_f$=C(CN)–), 6.83 (d, *J*=8.4 Hz, 1H, Ar*H*), 7.11 (d, *J*=8.8 Hz, 1H, Ar*H*); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 15.58, 29.75, 55.54, 68.99, 69.98, 110.55, 115.53, 117.26, 122.65, 125.76, 130.00, 130.36, 131.86, 137.20, 146.44, 153.09; EIMS (70 eV) *m*/*z* (rel intensity, %) 273 (M$^+$, 69), 244 (29), 221 (100), 193 (43), 185 (27), 184 (75), 143 (54), 115 (27); HRMS calcd for $C_{16}H_{19}NO_3$: 273.1365, found: 273.1366.

4.1.1.3. 2-Cyano-3-(2-allyl-3-isopropyloxy-4-methoxy)-phenyl-1-propen-3-ol (5c). Compound **5c** (1.76 g, 61%) was obtained as a pale yellow liquid; R_f=0.40 (ethyl acetate/*n*-hexane=1:2); IR (neat) cm^{-1}: 3469 m^{-1} (OH), 2230 cm^{-1} (CN); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.27 (d, *J*=6 Hz, 6H, CH(CH_3)$_2$), 2.59 (br s, 1H, O*H*), 3.48 (ddt, *J*=16.4, 5.6, 1.6 Hz, 1H, ArCH_aH$_b$CH=CH$_2$), 3.65 (ddt, *J*=16.4, 5.6, 1.6 Hz, 1H, ArCH$_a$$H_b$CH=CH$_2$), 3.83 (s, 3H, OC$H_3$), 4.51 (sept, *J*=6.0 Hz, 1H, C*H*(CH$_3$)$_2$), 4.92 (ddt, *J*=17.2, 1.6, 1.6 Hz, 1H, ArCH$_2$CH=CH_cH$_d$), 5.05 (ddt, *J*=10.0, 1.6, 1.6 Hz, 1H, ArCH$_2$CH=CH$_c$$H_d$), 5.48 (m, 1H, C*H*OH), 5.98 (ddt, *J*=17.2, 10.0, 5.6 Hz, 1H, ArCH$_2$C*H*=CH$_2$), 6.05 (d, *J*=1.6 Hz, 1H, CH_eH$_f$=C(CN)–), 6.07 (d, *J*=1.6 Hz, 1H, CH$_e$$H_f$=C(CN)–), 6.83 (d, *J*=8.4 Hz, 1H, Ar*H*), 7.09 (d, *J*=8.8 Hz, 1H, Ar*H*); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 22.40, 30.00, 55.46, 69.85, 74.75, 110.49, 110.86, 115.56, 117.28, 122.22, 125.83, 129.86, 130.56, 132.05, 137.13, 144.93, 153.05; EIMS (70 eV) *m*/*z* (rel intensity, %) 287 (M$^+$, 25), 245 (64), 227 (21), 212 (21), 194 (45), 193 (100), 183 (26), 143 (33); HRMS calcd for $C_{17}H_{21}NO_3$: 287.1521, found: 287.1522.

4.1.1.4. 2-Cyano-3-(2-allyl-3-butoxy-4-methoxy)-phenyl-1-propen-3-ol (5d). Compound **5d** (1.81 g, 60%) was obtained as a pale yellow liquid; R_f=0.39 (ethyl acetate/*n*-hexane=1:2); IR (neat) cm^{-1}: 3458 cm^{-1} (OH), 2230 cm^{-1} (CN); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.97 (t, *J*=7.2 Hz, 3H, CH$_2$CH$_2$CH$_2$CH_3), 1.49 (m, 2H, CH$_2$CH$_2$-CH_2CH$_3$), 1.75 (quint, *J*=7.05 Hz, 2H, CH$_2$CH_2CH$_2$CH$_3$), 2.52 (d, *J*=4.0 Hz, 1H, O*H*), 3.48 (ddt, *J*=16.0, 5.6, 1.6 Hz, 1H, ArCH_aH$_b$CH=CH$_2$), 3.59 (ddt, *J*=16.0, 5.6, 1.6 Hz, 1H, ArCH$_a$$H_b$CH=CH$_2$), 3.84 (s, 3H, OC$H_3$), 3.91 (m, 2H, OC$H_2CH_2CH_2CH_3$), 4.90 (ddt, *J*=17.2, 1.6, 1.6 Hz, 1H, ArCH$_2$CH=CH_cH$_d$), 5.05 (ddt, *J*=10.4, 1.6, 1.6 Hz, 1H, ArCH$_2$CH=CH$_c$$H_d$), 5.44 (s, 1H, C*H*OH), 6.00 (ddt, *J*=17.2, 10.8, 5.6 Hz, 1H, ArCH$_2$C*H*=CH$_2$), 6.07 (d, *J*=1.6 Hz, 1H, CH_eH$_f$=C(CN)–), 6.09 (d, *J*=1.6 Hz, 1H, CH$_e$$H_f$=C(CN)–), 6.83 (d, *J*=8.8 Hz, 1H, Ar*H*), 7.10 (d, *J*=8.8 Hz, 1H, Ar*H*); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.86, 19.08, 29.69, 32.27, 55.54, 69.98, 73.08, 110.61, 115.53, 117.25, 122.60, 125.76, 129.97, 130.39, 131.82, 137.25, 146.55, 153.13; EIMS (70 eV) *m*/*z* (rel intensity, %) 301 (M$^+$, 41), 227 (31), 194 (31), 193 (100), 184 (34),

143 (23), 142 (32), 115 (24); HRMS calcd for $C_{18}H_{23}NO_3$: 301.1678, found: 301.1680.

4.1.1.5. 2-Cyano-3-(2-allyl-3-benzyloxy-4-methoxy)-phenyl-1-propen-3-ol (5e). Compound **5e** (1.77 g, 53%) was obtained as a pale yellow liquid; R_f=0.37 (ethyl acetate/*n*-hexane=1:2); IR (neat) cm^{-1}: 3446 cm^{-1} (OH), 2230 cm^{-1} (CN); ^1H NMR ($CDCl_3$, 400 MHz) δ 2.17 (d, J=4.4 Hz, 1H, O*H*), 3.45 (ddt, J=16.0, 5.2, 1.6 Hz, 1H, ArCH_aH_bCH=CH_2), 3.59 (ddt, J=16.0, 5.2, 1.6 Hz, 1H, ArCH_aH_bCH=CH_2), 3.90 (s, 3H, OCH_3), 4.90 (ddt, J=17.2, 1.6, 1.6 Hz, 1H, ArCH$_2$CH=CH_cH_d), 4.99 (d, J=5.6 Hz, 2H, OCH_2Ph), 5.05 (dd, J=10, 1.6, 1.6 Hz, 1H, ArCH$_2$CH=CH_cH_d), 5.44 (dt, J=4.4, 0.8 Hz, 1H, C*H*OH), 5.98 (ddt, J=17.2, 5.2, 1.6 Hz, 1H, ArCH$_2$C*H*=CH_2), 6.09 (d, J=1.6 Hz, 2H, CH_2=C(CN)–), 6.91 (d, J=8.8 Hz, 1H, Ar*H*), 7.17 (d, J=8.8 Hz, 1H, Ar*H*), 7.32–7.40 (m, 3H, OCH$_2$Ph*H*), 7.44–7.46 (m, 2H, OCH$_2$Ph*H*); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 29.88, 55.70, 70.17, 74.83, 110.81, 115.72, 117.25, 123.04, 125.69, 127.93, 128.06, 128.25, 128.39, 129.97, 130.07, 130.46, 132.15, 137.30, 137.63, 146.19, 153.28; EIMS (70 eV) m/z (rel intensity, %) 335 (M^+, 23), 244 (10), 226 (12), 194 (13), 191 (11), 185 (13), 92 (26), 91 (100); HRMS calcd for $C_{21}H_{21}NO_3$: 335.1521, found: 335.1513.

4.1.2. General procedure for the preparation of 6-cyano-1-alkoxy-2-methoxynaphthalenes (6a–e). A solution of **5a–e** (0.20 g, 0.77 mmol) in dichloromethane (60 mL) was added with Grubbs' catalyst (second generation) (0.03 g, 0.04 mmol) under the protection of dried nitrogen at room temperature. The resulting mixture was stirred for 5 h from the monitoring of TLC, and then concentrated in vacuo. The residue was purified from silica-gel chromatographic column (ethyl acetate/*n*-hexane=1:15) to give pure **6a–e**.

4.1.2.1. 6-Cyano-1,2-dimethoxynaphthalene (6a). Compound **6a** (0.14 g, 85%) was obtained as a colorless crystal; mp 98–99 °C, R_f=0.34 (ethyl acetate/*n*-hexane=1:5); IR (KBr) cm^{-1}: 2219 cm^{-1} (CN); ^1H NMR ($CDCl_3$, 400 MHz) δ 4.00 (s, 3H, OCH_3), 4.03 (s, 3H, OCH_3), 7.41 (d, J=9.0 Hz, 1H, H-3), 7.57 (dd, J=1.4, 8.8 Hz, 1H, H-7), 7.67 (d, J=9.0 Hz, 1H, H-4), 8.16 (d, J=1.4 Hz, 1H, H-5), 8.09 (d, J=8.8 Hz, 1H, H-8), ^{13}C NMR ($CDCl_3$, 100 MHz) δ 56.53 (OCH_3), 61.15 (OCH_3), 107.12, 116.18, 119.47, 122.64, 124.89, 126.30, 127.87, 130.26, 133.98, 142.53, 150.78; EIMS (70 eV) m/z (rel intensity, %) 213 (M^+, 71), 198 (61), 191 (71), 170 (94), 167 (28), 152 (22), 150 (25), 149 (100), 147 (29), 127 (22), 91 (38), 71 (27), 55 (37); HRMS calcd for $C_{13}H_{11}NO_2$: 213.0790, found: 213.0790; Anal. Calcd for $C_{13}H_{11}NO_2$: C, 73.23%; H, 5.20%; N, 6.57%. Found: C, 73.26%; H, 5.19%; N, 6.59%.

4.1.2.2. 6-Cyano-1-ethoxy-2-methoxynaphthalene (6b). Compound **6b** (0.15 g, 90%) was obtained as a colorless crystal; mp 78–79 °C, R_f=0.41 (ethyl acetate/*n*-hexane=1:5); IR (KBr) cm^{-1}: 2219 cm^{-1} (CN); ^1H NMR ($CDCl_3$, 400 MHz) δ 1.47 (t, J=7.0 Hz, 3H, OCH$_2$CH_3), 4.02 (s, 3H, OCH_3), 4.21 (t, J=7.0 Hz, 2H, OCH_2CH$_3$), 7.40 (d, J=9.0 Hz, 1H, H-3), 7.56 (dd, J=1.8, 8.8 Hz, 1H, H-7), 7.66 (d, J=9.0 Hz, 1H, H-4), 8.16 (d, J=1.8 Hz, 1H, H-5), 8.20 (d, J=8.8 Hz, 1H, H-8), ^{13}C NMR ($CDCl_3$, 100 MHz) δ 15.76 (OCH$_2$CH$_3$), 56.62 (OCH_3), 69.47 (OCH$_2$CH$_3$), 107.19, 116.24, 119.61, 123.03, 124.79, 126.31, 127.98, 130.88, 134.05, 141.73, 150.95; EIMS (70 eV) m/z (rel intensity, %) 227 (M^+, 62), 199 (100), 185 (23), 184 (81), 170 (44), 156 (39), 128 (14), 115 (17); HRMS calcd for $C_{14}H_{13}NO_2$: 227.0946, found: 227.0948; Anal. Calcd for $C_{14}H_{13}NO_2$: C, 73.99%; H, 5.77%; N, 6.16%. Found: C, 74.03%; H, 5.75%; N, 6.20%.

4.1.2.3. 1-Isopropoxy-2-methoxy-6-cyanonaphthalene (6c). Compound **6c** (0.15 g, 85%) was obtained as a colorless crystal; mp 80–81 °C, R_f=0.42 (ethyl acetate/*n*-hexane=1:5); IR (KBr) cm^{-1}: 2223 cm^{-1} (CN); ^1H NMR ($CDCl_3$, 200 MHz) δ 1.35 (d, J=6.0 Hz, 6H, OCH(CH_3)$_2$), 4.00 (s, 3H, OCH_3), 4.67 (sept., J=6.0 Hz, 1H, OC*H*(CH$_3$)$_2$), 7.39 (d, J=8.8 Hz, 1H, H-3), 7.53 (dd, J=1.4, 8.8 Hz, 1H, H-7), 7.63 (d, J=8.8 Hz, 1H, H-4), 8.13 (d, J=1.4 Hz, 1H, H-5), 8.22 (d, J=8.8 Hz, 1H, H-8); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 22.64 (OCH(*C*H$_3$)$_2$), 56.55 (OCH_3), 75.60 (O*C*H(CH$_3$)$_2$), 107.10, 116.28, 119.52, 123.52, 124.39, 125.96, 127.99, 131.64, 133.85, 140.69,150.94; EIMS (70 eV) m/z (rel intensity, %) 241 (M^+, 26), 199 (100), 186 (21), 185 (82), 156 (31); HRMS calcd for $C_{15}H_{15}NO_2$: 241.1103, found: 241.1101; Anal. Calcd for $C_{15}H_{15}NO_2$: C, 74.67%; H, 6.27%; N, 5.81%. Found: C, 74.69%; H, 6.30%; N, 5.79%.

4.1.2.4. 1-*n*-Butoxy-2-methoxy-6-cyanonaphthalene (6d). Compound **6d** (0.2 g, 81%) was obtained as a colorless crystal; mp 45–46 °C, R_f=0.39 (ethyl acetate/*n*-hexane=1:5); IR (KBr) cm^{-1}: 2223 cm^{-1} (CN); ^1H NMR ($CDCl_3$, 200 MHz) δ 1.01 (t, J=7.0 Hz, 3H, –CH$_2$CH$_2$CH$_2$CH_3), 1.58 (m, 2H, –CH$_2$CH$_2$CH_2CH$_3$), 1.86 (quint, J=7.0 Hz, 2H, CH$_2$CH_2CH$_2$CH$_3$), 4.01 (s, 1H, OCH_3), 4.12 (t, J=7.0 Hz, 2H, OCH_2CH$_2$), 7.39 (d, J=9.2 Hz, 1H, H-3), 7.55 (dd, J=1.4, 8.8 Hz, 1H, H-7), 7.64 (d, J=9.2 Hz, 1H, H-4), 8.15 (d, J=1.4 Hz, 1H, H-5), 8.19 (d, J=8.8 Hz, 1H, H-8); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 14.02, 19.43, 32.53, 56.80, 73.76, 107.31, 116.58, 119.65, 123.03, 124.70, 126.31, 128.15, 130.85, 134.08, 142.17, 150.95; EIMS (70 eV) m/z (rel intensity, %) 255 (M^+, 31), 199 (100), 185 (30), 184 (39), 156 (14); HRMS calcd for $C_{16}H_{17}NO_2$: 255.1259, found: 255.1263; Anal. Calcd for $C_{16}H_{17}NO_2$: C, 75.27%; H, 6.71%; N, 5.49%. Found: C, 75.30%; H, 5.73%; N, 5.52%.

4.1.2.5. 1-Benzyloxy-6-cyano-2-methoxynaphthalene (6e). Compound **6e** (0.07 g, 81%) was obtained as a colorless crystal; mp 39–40 °C, R_f=0.38 (ethyl acetate/*n*-hexane=1:5); IR (KBr) cm^{-1}: 2219 cm^{-1} (CN); ^1H NMR ($CDCl_3$, 400 MHz) δ 4.01 (s, 3H, OCH_3), 5.15 (s, 2H, OCH_2Ph), 7.32–7.40 (m, 3H, OCH$_2$Ph*H*), 7.38 (d, J=8.8 Hz, 1H, H-3), 7.45 (dd, J=8.8, 1.4 Hz, 1H, H-7), 7.48–7.50 (m, 2H, OCH$_2$Ph*H*), 7.61 (d, J=8.8 Hz, 1H, H-4), 8.08 (d, J=1.4 Hz, 1H, H-5), 8.10 (d, J=8.8 Hz, 1H, H-8); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 56.47, 75.27, 107.00, 116.04, 119.43, 122.85, 124.93, 126.13, 127.74, 128.09, 128.22, 128.37, 130.52, 133.83, 137.14, 141.27, 150.80; EIMS (70 eV) m/z (rel intensity, %) 289 (M^+, 100), 274 (11), 258 (23), 256 (47), 246 (13), 228 (23), 227 (16); HRMS calcd for $C_{19}H_{15}NO_2$: 289.1103, found: 289.1103; Anal. Calcd for $C_{19}H_{15}NO_2$: C, 78.87%; H, 5.23%; N, 4.84%. Found: C, 78.90%; H, 5.21%; N, 4.86%.

4.1.3. Preparation of 1-hydroxy-6-cyano-2-methoxy-naphthalene (6f). A mixture of compound **6e** (0.09 g,

0.31 mmol), $Pd(OH)_2/C$ (20%, 0.05 g, 0.34 mmol), cyclohexene (5.4 mL), and ethanol (30 mL) was refluxed for 10 h. The resulting mixture was concentrated in vacuo to give the residue, which was purified from silica-gel chromatographic column to yield pure **6f**.

4.1.3.1. 1-Hydroxy-6-cyano-2-methoxynaphthalene (6f). Compound **6f** (0.05 g, 81%) was obtained as a colorless crystal; mp 72–73 °C, R_f=0.40 (ethyl acetate/*n*-hexane=1:5); IR (KBr) cm^{-1}: 3380 cm^{-1} (OH), 2230 cm^{-1} (CN); ^1H NMR ($CDCl_3$, 400 MHz) δ 4.04 (s, 3H, OCH_3), 6.12 (br s, 1H, O*H*), 7.36 (d, *J*=8.6 Hz, 1H, H-3), 7.47 (d, *J*=8.6 Hz, 1H, H-4), 7.53 (dd, *J*=1.8, 8.7 Hz, 1H, H-7), 8.13 (d, *J*=1.8 Hz, 1H, H-5), 8.21 (d, *J*=8.8 Hz, 1H, H-8); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 56.81, 107.37, 114.18, 119.61, 120.46, 122.65, 125.45, 127.79, 128.49, 134.05, 139.59, 143.65; EIMS (70 eV) *m*/*z* (rel intensity, %) 199 (M^+, 77) 184 (100), 157 (14), 156 (99), 128 (54), 101 (33), 77 (15), 75 (25); HRMS calcd for $C_{12}H_9NO_2$: 199.0633, found: 199.0634; Anal. Calcd for $C_{12}H_9NO_2$: C, 72.35%; H, 4.55%; N, 7.03%. Found: C, 72.38%; H, 4.53%; N, 7.01%.

Acknowledgements

We are grateful to NSC (NSC-95-2113-M-037-012), Taiwan for financial support and to Professor Hiroki Takahata, Tohoku Pharmaceutical University, Japan for encouragement.

References and notes

1. Martin Castro, A. M. *Chem. Rev.* **2004**, *104*, 2939–3002.
2. Basavaiah, D.; Rao, A. J.; Satyanarayana, T. *Chem. Rev.* **2003**, *103*, 811–891.
3. Grubbs, R. H. *Angew. Chem., Int. Ed.* **2006**, *45*, 3760–3765 and references cited therein.
4. Donohoe, T. J.; Orr, A. J.; Bingham, M. *Angew. Chem., Int. Ed.* **2006**, *45*, 2664–2670 and references cited therein.
5. (a) Batt, D. G.; Maynard, G. D.; Petraitis, J. J.; Shaw, J. E.; Galbraith, W.; Harris, R. R. *J. Med. Chem.* **1990**, *33*, 360–370; (b) Whiting, D. A. *Nat. Prod. Rep.* **1985**, *2*, 191–211; (c) Ward, R. S. *Nat. Prod. Rep.* **1995**, *12*, 183–205; (d) Eich, E.; Pertz, H.; Kaloga, M.; Schulz, J.; Fesen, M. R.; Mazumder, A.; Pommier, Y. *J. Med. Chem.* **1996**, *39*, 86–95.
6. Goudie, A. C.; Gaster, L. M.; Lake, A. W.; Rose, C. J.; Freeman, P. C.; Hughes, B. O.; Miller, D. *J. Med. Chem.* **1978**, *21*, 1260–1264.
7. (a) Harrison, I. T.; Lewis, B.; Nelson, P.; Rooks, W.; Roszkowski, A.; Tomolonis, A.; Fried, J. H. *J. Med. Chem.* **1970**, *13*, 203–205; (b) Hiyama, T.; Inoue, M. *Synthesis* **1986**, *8*, 689–691.
8. (a) Sasai, H.; Suzuki, T.; Itoh, N.; Shibasaki, M. *Appl. Organomet. Chem.* **1995**, *9*, 421–426; (b) Crowther, A. F.; Smith, L. H. U.S. Patent 3,337,628, 1967.
9. Ashworth, I. W.; Bowden, M. C.; Dembofsky, B.; Levin, D.; Moss, W.; Robinson, E.; Szczur, N.; Virica, J. *Org. Process Res. Dev.* **2003**, *7*, 74–81.
10. (a) Singh, H.; Chawla, A. S.; Kapoor, V. K.; Paul, D.; Malhotra, R. K. *Prog. Med. Chem.* **1980**, *17*, 151–183; (b) Zubarev, V. Yu.; Ostrovskii, V. A. *Chem. Heterocycl. Compd.* **2001**, *36*, 759–774.
11. (a) Hasegawa, Y.; Yanagisawa, T.; Okui, Y.; Sato, T.; Hosaka, K.; Chin, M.; Mitsuhashi, H. *Chem. Pharm. Bull.* **1991**, *39*, 3180–3182; (b) Brzozowski, Z.; Saczewski, F.; Gdaniec, M. *Eur. J. Med. Chem.* **2000**, *35*, 1053–1064; (c) Jensen, N. P.; Ager, A. L.; Bliss, R. A.; Canfield, C. J.; Kotecka, B. M.; Rieckmann, K. H.; Terpinski, J.; Jacobus, D. P. *J. Med. Chem.* **2001**, *44*, 3925–3931.
12. Mowry, D. T. *Chem. Rev.* **1948**, *42*, 189–284.
13. Sandmeyer, T. *Ber. Dtsch. Chem. Ges.* **1884**, *17*, 1633–1635.
14. (a) Schareina, T.; Zapf, A.; Beller, M. *Chem. Commun.* **2004**, 1388–1389; (b) Hatsuda, M.; Seki, M. *Tetrahedron* **2005**, *61*, 9908–9917.
15. Huang, K. S.; Wang, E. C. *Tetrahedron Lett.* **2001**, *42*, 6155–6157.