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A novel synthesis of substituted naphthalenes via Claisen rearrangement and RCM reaction

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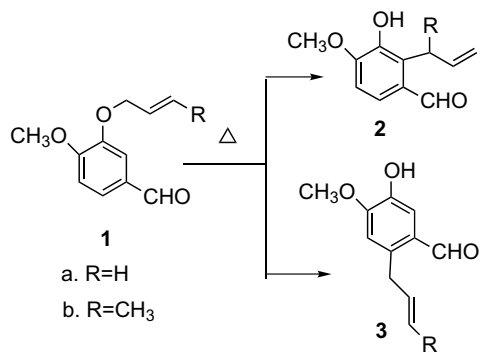
Abstract—A novel synthesis of substituted naphthalenes was studied. Starting from isovanillin, basing on Claisen rearrangement and ring-closing metathesis (RCM), a series of 1-alkoxy-2-methoxynaphthalenes and 1-alkoxy-2-methoxy-8-methylnaphthalenes together with a series of 2-alkoxy-3-methoxynaphthalenes were synthesized.

Naphthalenes, playing an important role as structural units or key intermediates of naturally occurring alkaloids attract the synthetic and natural product chemists for their biological activities. Just as 1,8-dioxygenated 4-aryl-6-methylnaphthalene moiety is a structure unit of anti-HIV agents michellamines A–C,[1] and the related naphthylisoquinoline alkaloids;[2] 1-bromo-4,5-dimethoxy-7-methyl- naphthalene is a key intermediate of antimalarial alkaloids, korupensamine C and ancistrobrevine B;[3] and naphthol is a starting material for propranolol, a β-blocking agent.[4] However, the strategies for the construction of substituted naphthalenes are quite insufficient. In literatures few methods have been described such as cyclization of 2-allyl-3-benzyloxy-4,6-dimethoxyacetophenone with potassium *tert*-butoxide gave 5-methylnaphthalene in 48% yield by a reported procedure,[5] cyclization of 2-(1-propenyl)-benzamides with base resulted in the formation of naphthols.[5] Recently, de Koning et al.[5] reported by heating *O*-allyl substituted acylbenzenes with potassium *tert*-butoxide in DMF with simultaneous irradiation from a high-pressure mercury lamp to afford substituted naphthalenes. However, those methods still have some disadvantages including tedious reaction conditions, low yield, and commercially unavailable key intermediates which are difficult to prepare. Thus, it is necessary to develop more practical and efficient methods for the preparation of multi-substituted naphthalenes. Since Grubbs et al.[6] discovered a novel alkylidene ruthenium complex as a catalyst for ring-closing metathesis (RCM) in 1995, it has been widely applied in organic synthesis for many aspects.[7] Until present only a little attention has been paid to apply this RCM reaction to naphthalene chemistry.[8] Herein we like to report a novel strategy for the synthesis of appropriate naphthalenes such as 1-alkoxy-2-methoxynaphthalenes,



Conditions and % yields of Claisen rearrangement

Compds	△ (°C/solvent)	Reaction time (hr)	product (%yield) 2a	2b	3b
1a	175-180/neat	3	92		
1a	180/decalin	5	95		
1a	217/Diethylanilline	1	95		
1b	175-180/neat	16		48	36
1b	180/decalin	16		71	10
1b	217/Diethylanilline	16		67	20

Scheme 1.

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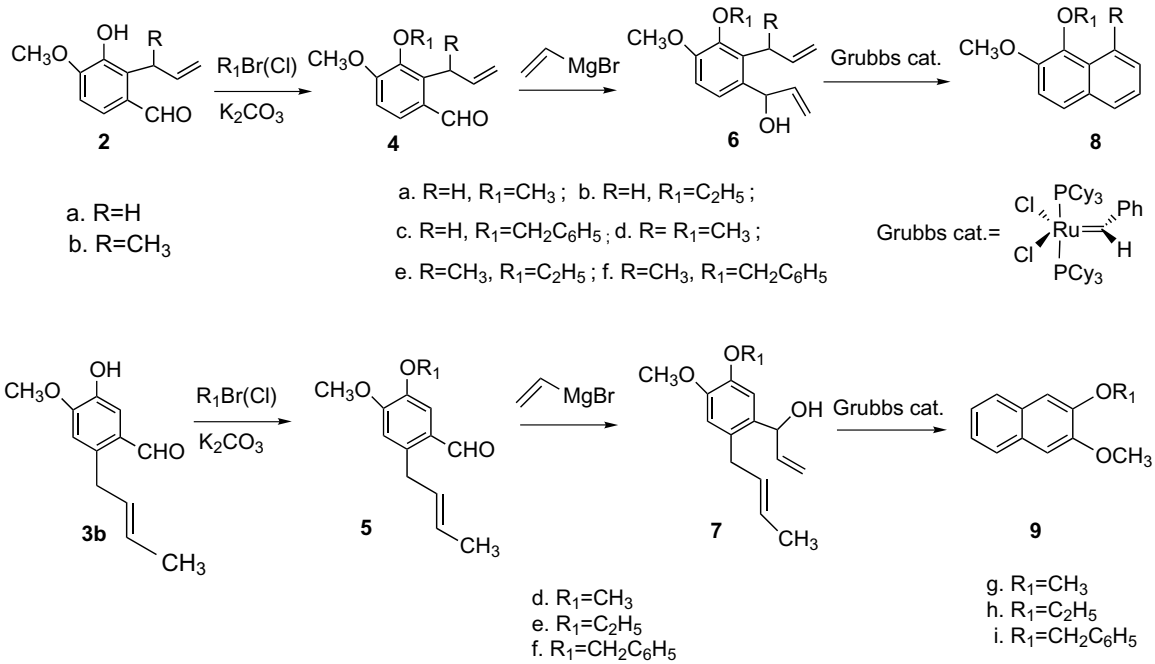
1-alkoxy-2-methoxy-8-methylnaphthalenes, together with a series of 2-alkoxy-3-methoxynaphthalenes starting from isovanillin via Claisen rearrangement (Scheme 1) and RCM reaction (Scheme 2).

Claisen rearrangement with three different reaction conditions: gently boiling and with strongly stirring in neat, in decalin, and in *N*,*N*-diethylanilline were, respectively investigated. When **1a** was treated in all three different conditions, it gave almost *ortho* product, **2a** in 92–95% yields. But, when **1b** was treated with the same conditions, it not only gave *ortho* product, **2b** but also *para* product, **3b** in various ratios (see Scheme 1). When **2a**, **2b**, and **3b** were, respectively treated with some various alkyl halides, it afforded corresponding 2-allyl-3-alkoxy-4-methoxybenzaldehydes (**4a–c**), 3-alkoxy-4-methoxy-2-(1-methylallyl)benzaldehydes (**4d–f**), and 2-(2-butenyl)-5-alkoxy-4-methoxybenzaldehydes (**5d–f**) in excellent yields. Followed by treating these aldehydes with vinyl magnesium bromide, it gave corresponding 1-(2-allyl-3-alkoxy-4-methoxyphenyl)-2-propen-1-ols (**6a–c**), 1-[3-alkoxy-4-methoxy-2-(1-methylallyl)phenyl]-2-propen-1-ols (**6d–f**), and 1-[5-alkoxy-2-(2-butenyl)-4-methoxyphenyl]-2-propen-1-ols (**7d-f**) in good yields. Finally by treating these propen-1-ols with Grubbs' catalyst to undergo RCM reaction, and followed by dehydration in situ in the presence of silica gel, it afforded a series of substituted naphthalenes **8a–f**, and **9g–i** in good yields. The results of percentage yield were compiled in Table 1.

In conclusion with our synthetic strategy starting from isovanillin, basing on Claisen rearrangement and RCM reaction, a novel route to prepare appropriately substituted naphthalenes such as 1-alkoxy-2-methoxynaphthalenes and 1-alkoxy-2-methoxy-8-methylnaphthalenes together with a series of 2-alkoxy-3-methoxynaphthalenes has been established. The synthesis of other substi-



Scheme 2.

Table 1. Yields (%) for compounds **4**, **5**, **6**, **7**, **8** and **9** in Scheme 2

	Substituents	Aldehydes **4**	Aldehydes **5**	Propen-1-ols **6**	Propen-1-ols **7**	Naphthalenes **8**[a]	Naphthalenes **9**[a]
a	$R=H$, $R_1=CH_3$	88		96		86	
b	$R=H$, $R_1=C_2H_5$	80		91[9]		89	
c	$R=H$, $R_1=CH_2C_6H_5$	98		95		83	
d	$R=R_1=CH_3$	92	83	78	83	89	
e	$R=CH_3$, $R_1=C_2H_5$	80	84	82	84	89	
f	$R=CH_3$, $R_2=CH_2C_6H_5$	97	87	80	92	80	
g	$R_1=CH_3$						82
h	$R_1=C_2H_5$						84
i	$R_1=CH_2C_6H_5$						89

[a] All naphthalenes are new compounds except **8a**,[10] **8d**,[11] **9g**,[8] and **9i**.[12] The structural elucidation of these intermediates and all substituted naphthalenes was confirmed by spectral data such as ^1H NMR, ^{13}C NMR, MS and HRMS.

tuted naphthalenes and naphthols via RCM reaction are currently in progress in our laboratory. Furthermore the investigation of the effect of various allyloxy groups on isovanillin to undergo Claisen rearrangement is also currently in progress.

General procedure for the preparation of naphthalenes (8a–f) and (9g–i)

Compound **6a–f** or **7d–f** (1 mmol) dissolved in anhydrous CH_2Cl_2 (15 mL), was added with Grubbs catalyst (0.05 mmol). The mixture was stirred for 2 h at ambient temperature under dry argon. And then the solution was added with silica gel (0.25 g) and continually stirred for overnight at room temperature. Finally the solvent was removed under reduced pressure, and the residue was subjected to a silica gel column (1:1 hexane/MTBE) or to distill under vacuum to give **8a–f** and **9g–i**, respectively. The selected spectral data was given as follows: Compound **8f** was obtained as colorless crystals, mp 67–68°C; bp 120–121°C (3 mmHg); ^{1}H NMR ($CDCl_3$, 600 MHz) δ: 2.89 (s, 3H, $C\underline{H}_3$), 3.99 (s, 3H, $OC\underline{H}_3$), 5.07 (2H, $OC\underline{H}_2C_6H_5$), 7.20 (d, J=7.2 Hz, 1H), 7.21 (t, J=7.2 Hz, 1H), 7.31 (d, J=8.4 Hz, 1H), 7.35 (t, J=7.2 Hz, 1H), 7.42 (t, J=7.2 Hz, 1H), 7.57 (d, J=7.2 Hz, 2H), 7.61 (d, J=7.2 Hz, 1H), 7.62 (d, J=8.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 24.05 ($\underline{C}H_3$), 56.85 ($O\underline{C}H_3$), 75.56 ($O\underline{C}H_2C_6H_5$), 114.61, 123.64, 125.26, 126.49, 127.71, 127.93, 128.36, 128.65, 129.10, 130.92, 133.35, 137.92, 144.12, 149.81. EI–MS (70 eV) m/z 278 (M^+, 100), 263 (23.67), 245 (21.23), 235 (12.02), 202 (28.02), 145 (25.08), 129 (14.52), 115 (22.90), 91 (20.30); HRMS: calcd. for $C_{19}H_{18}O_2$: 278.1307. Found: 278.1307. Compound **9h** was obtained as colorless crystals, mp 77–78°C; ^{1}H NMR ($CDCl_3$, 600 MHz) δ: 1.54 (t, J=6.8 Hz, 3H, $OCH_2C\underline{H}_3$), 3.98 (s, 3H, $OC\underline{H}_3$), 4.21 (q, J=6.8 Hz, 2H, $OC\underline{H}_2CH_3$), 7.11 (s, 2H, H-1 and H-4), 7.33 (dt, J=9.6 Hz, J=3.6 Hz, 2H, H-6, H-7), 7.68 (ddd, J=9.6 Hz, J=5.7 Hz, J=3.6 Hz, 2H, H-5, H-8); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 14.61 ($\underline{C}H_3$), 55.80 ($O\underline{C}H_3$), 64.09 ($O\underline{C}H_2CH_3$), 106.36, 107.27, 124.04, 126.20, 129.07, 129.19, 148.72, 149.65; EI-MS (70 eV) m/z 202 (M^+, 79.17), 174 (100), 159 (58.71), 131 (91.91), 115 (31.07), 102 (33.21), 77 (13.06); HRMS: calcd for $C_{13}H_{14}O_2$: 202.0994. Found: 202.0992.

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9. Data for **6b**: colorless liquid, ^{1}H NMR ($CDCl_3$, 600 MHz) δ: 1.36 (t, J=7.2 Hz, 3H, $OCH_2C\underline{H}_3$), 2.11 (br s. 1H, OH, D_2O exchangeable), 3.50 (ddt, J=15.6 Hz, J=5.4 Hz, J=1.8 Hz, 1H, CH_2=CH $C\underline{H}_2$), 3.60 (ddt, J=15.6 Hz, J=5.4 Hz, J=1.8 Hz, 1H, CH_2=CH $C\underline{H}_2$), 3.82 (s, 3H, OCH_3), 3.98 (q, J=7.2 Hz, 2H, $OC\underline{H}_2CH_3$), 4.91 (dd, J=16.8 Hz, 1.8 Hz, 1H), 5.01 (dd, J=9.9 Hz, 1.8 Hz, 1H), 5.17 (dt, J=10.2 Hz, 1.2 Hz, 1H), 5.31 (dt, J=16.8 Hz, 1.2 Hz, 1H), 5.35 (br. s, 1H), 6.02 (m, 2H), 6.80, 7.13 (each d, J=8.4 Hz, 2H, H-5 and H-6); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 15.43 ($OCH_2\underline{C}H_3$), 29.69 (CH_2=$CH\underline{C}H_2$), 55.35 ($O\underline{C}H_3$), 68.58 ($O\underline{C}H_2CH_3$), 70.58 ($\underline{C}$HOH), 110.23, 114.07, 122.17, 131.23, 137.43, 139.95, 146.05, 151.97; HRMS, calcd for $C_{15}H_{20}O_3$: 248.1412. Found: 248.1414.
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