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Ring-closing metathesis as a new methodology for the synthesis of monomeric flavonoids and neoflavonoids

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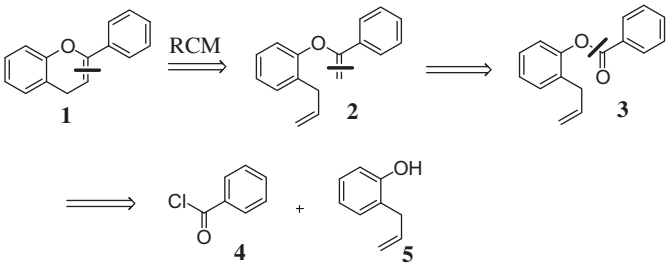
ABSTRACT

Basic flavonoid (flavene) and neoflavonoid (neoflavene) skeletons were successfully synthesized using ring-closing metathesis, showing that this methodology can be used as a central synthetic tool for the synthesis of at least two of the three basic flavonoid classes.

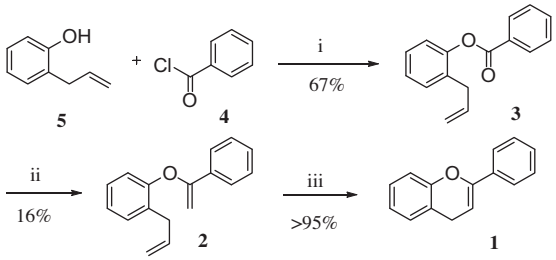
The flavonoids, one of the most abundant groups of naturally occurring polyphenolic compounds, display a wide variety of physiological activities.[1] Difficulties surrounding the isolation of individual flavonoids from plant materials (low yield, inseparable mixtures) and a desire to study the physiological activities of differently substituted compounds have led to extensive investigations into the synthesis of monomeric flavonoids.[2] Existing synthetic methods are often hampered by tedious multistep processes, stoichiometric amounts of sometimes highly poisonous reagents, the use of harsh reaction conditions, and low overall yields.[1,3] Furthermore, though flavonoids and isoflavonoids can be synthesized by using similar methodologies (via chalcones), routes for the synthesis of neoflavonoids are difficult and differ substantially.[4] Following the successful application of ring-closing metathesis (RCM) in the synthesis of 2*H*- and 4*H*-chromenes,[5] it was envisaged that this methodology could give access to all types of flavonoids, that is, flavonoids, isoflavonoids and neoflavonoids, by using appropriately substituted benzene derivatives. This would also allow the direct synthesis of these compounds without the requirement of a carbonyl group at the 2- or 4-positions as is the case in the more classical approaches. We herewith disclose our preliminary results on the synthesis of the flavonoid and neoflavonoid skeletons through the utilization of ring-closing metathesis.

2-Phenyl-4*H*-chromene (flavene) (**1**), as a representative of the flavonoid skeleton, would be accessible from 1-[(1-phenylethenyl)oxy]-2-(prop-2-en-1-yl)benzene (**2**) by ring-closing metathesis according to the retrosynthesis in Scheme 1.

The synthesis of flavene (**1**) started with the esterification of commercially available 2-allylphenol (**5**) with benzoyl chloride (**4**) (Scheme 2). Treatment of a pyridine solution of 2-allylphenol



Scheme 1. Retrosynthetic approach to 2-phenyl-4*H*-chromene (flavene) (**1**).



Scheme 2. Reagents and conditions: (i) 2 M NaOH (aq), rt; (ii) Tebbe reagent, THF, −40 °C; (iii) **7** (5 mol %), CH_2Cl_2, reflux.

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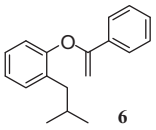
(**5**) with benzoyl chloride (**4**) in the presence of a catalytic amount of dimethylaminopyridine (DMAP), however, led to an inseparable mixture of products. The desired product, 2-allylphenyl benzoate (**3**), could be isolated in 67% yield when 2-allylphenol (**5**) and benzoyl chloride (**4**) were allowed to react in an aqueous 2 M sodium hydroxide solution at room temperature. Methylenation of the ester carbonyl group was subsequently attempted through utilization of the Nozaki–Takai reaction conditions[6] (Zn, CH_2Br_2, $TiCl_4$ and TMEDA in THF at room temperature), but only hydrolysis products, that is, 2-allylphenol (**5**) and benzoic acid, were obtained. Application of the Tebbe methylenation[7] procedure as an alternative was successful in so far as it gave methylenation of the carbonyl moiety. The desired transformation was, however, accompanied by methylation of the propenyl double bond to afford 1-(2-methylpropyl)-2-[(1-phenylethenyl)oxy]benzene (**6**) (63% yield at room temperature).



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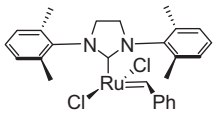

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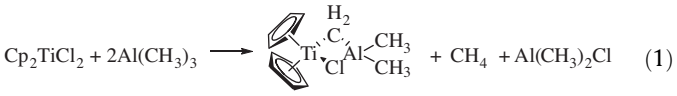
The undesired methylation of the double bond might be explicable in terms of the activation thereof by the Lewis acid, $(CH_3)_2AlCl$, present in the Tebbe reagent (**8**) (Eq. 1),[7] followed by methyl transfer from the aluminium to the incipient carbocation.



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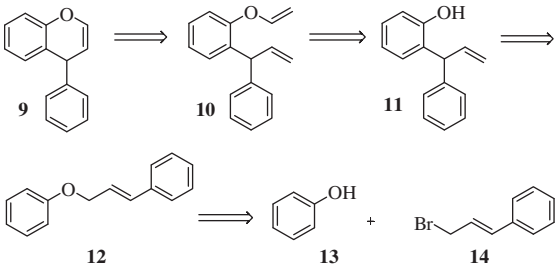
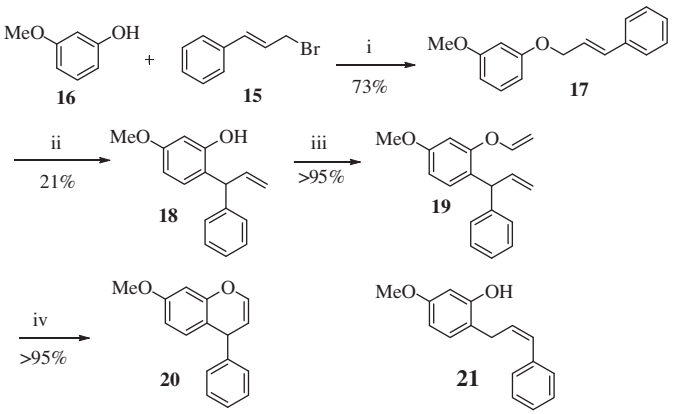
In an attempt to prevent this undesired methylation, the reaction temperature was decreased from 25 to −30 °C in 10 °C increments in a series of reactions. At temperatures of −30 °C and lower, the desired 1-[(1-phenylethenyl)oxy]-2-(prop-2-en-1-yl)benzene (**2**) formed exclusively, albeit in low yield, whereas formation of the isobutyl product **6** was favored at above 0 °C. Ring-closing metathesis of 1-[(1-phenylethenyl)oxy]-2-(prop-2-en-1-yl)benzene (**2**) in the presence of Grubbs' 2nd generation catalyst **7** finally gave flavene **1** in quantitative yield.

Application of the same methodology, that is, allylation, Claisen rearrangement and ring-closing metathesis, was envisaged to also give access to the 4-phenyl-4*H*-chromene skeleton **9**, of the cyclic neoflavonoids (Scheme 3). In order to prepare products that would be easily distinguishable by NMR and thus to facilitate unambiguous structure elucidation, utilization of 3-methoxyphenol (**16**) as the phenolic component in the development of the neoflavene synthetic protocol was decided upon. Standard Williamson etherification methodology, where 3-methoxyphenol (**16**) was reacted with cinnamyl bromide (**15**) in refluxing acetone containing potassium carbonate gave only trace amounts of the desired 1-cinnamyl-



Scheme 3. Retrosynthetic approach to 4-phenyl-4*H*-chromene (neoflavene) (**9**).



Scheme 4. Reagents and conditions: (i) K_2CO_3, DMF, 65 °C; (ii) *N*,*N*-dimethylaniline, reflux; (iii) $Cu(OAc)_2$, $Sn(vinyl)_4$, MeCN, O_2, rt; (iv) **7** (5 mol %), CH_2Cl_2, reflux.

oxy-3-methoxybenzene (**17**). Changing the solvent to DMF afforded product **17** in a high 73% yield (Scheme 4).

Although, the Claisen rearrangement is commonly catalyzed by Lewis acids,[8] 1-cinnamyloxy-3-methoxybenzene (**17**) when treated with Et_2AlCl in THF at temperatures even as low as −40 °C, gave a mixture of numerous products of which only 2-cinnamyl-5-methoxyphenol (**21**) (63% at room temperature) could be identified.

A thermal Claisen rearrangement could however be achieved in *N*,*N*-dimethylaniline at ca. 190 °C to give 5-methoxy-2-(1′-phenylallyl)phenol (**18**) in 21% yield. Vinylation of the latter gave 4-methoxy-1-(1′-phenylallyl)-2-(vinyloxy)benzene (**19**) in quantitative yield by applying the procedure described by Van Otterlo et al.[5] utilizing $Cu(OAc)_2$ and tetravinyl tin in acetonitrile under positive oxygen pressure. Finally, ring-closing metathesis in the presence of Grubbs' 2nd generation catalyst (**7**) led to the target compound, 4-phenyl-4*H*-7-methoxychromene (**20**) in quantitative yield.

Although Van Otterlo et al.[5] established that ring-closing metathesis can be applied in the synthesis of both 2*H*- and 4*H*-chromenes, application of this method was never extended to the synthesis of the phenyl substituted chromenes. Successful synthesis of the basic flavonoid (flavene) **1** and neoflavonoid (neoflavene) **20** skeletons, with the latter being very difficult to synthesize by any other means, has shown that ring-closing metathesis can be used as a central synthetic tool for the synthesis of at least two of the three basic flavonoid classes.[9] The versatility of the new methodology has also been demonstrated by the potential of introducing oxygenation into other positions than those possible by classical synthetic routes. Application of this methodology to the synthesis of isoflavonoid derivatives as well as improvements to the low yielding intermediate steps will be investigated and disclosed in a follow-up Letter.

Acknowledgement

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9. *Physical characterization*: *Compound* **1**: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.70–7.67 (2H, m, H2′ and H6′), 7.40–7.37 (2H, m, H3′ and H5′), 7.33 (1H, ddd, J = 7.31, 3.80, 1.14 Hz, H4′), 7.18 (1H, ddd, J = 8.22, 8.12, 1.59 Hz, H7), 7.10–7.07 (1H, m, H5), 7.04–6.99 (2H, m, H6 and H8), 5.51 (1H, t, J = 3.90 Hz, H3), 3.60 (2H, d, J = 3.85 Hz, H4); ^{13}C NMR (151 MHz, $CDCl_3$) δ 128.98 (C-5), 128.72 (C-4′), 128.31 (C-7), 127.51, 124.50, 123.29 (C-6), 116.61 (C-8), 96.43 (C-4), 62.67 (C3); MS m/z 208.10 (M^+, 65%), 207.10 (100), 178.05 (22), 131.10 (29), 89.05 (17), 77.00 (13); *Compound* **2**: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.78–7.75 (2H, m, H2′ and H6′), 7.42–7.37 (3H, m, H3′-H5′), 7.29 (1H, dd, J = 7.53, 1.58 Hz, H3), 7.23 (1H, ddd, J = 7.64, 7.86, 1.58 Hz, H5), 7.14 (1H, ddd, J = 7.53, 7.64, 1.16 Hz, H4), 7.07 (1H, dd, J = 7.86, 1.16 Hz, H6), 6.01 (1H, ddt, J = 20.34, 10.16, 6.74 Hz, H8), 5.12–5.07 (2H, m, H9a and H9b), 4.93 (1H, d, J = 2.60 Hz, Hβa), 4.18 (1H, d, J = 2.60 Hz, Hβb), 3.45 (1H, dd, J = 19.75, 6.68 Hz, H7a), 3.42 (1H, dd, J = 19.75, 6.68 Hz, H7b); ^{13}C NMR (151 MHz, $CDCl_3$) δ 136.75 (C-8), 135.43, 132.32, 130.57, 128.96, 127.68, 125.54, 124.65, 121.17, 116.11 (C-9), 89.24 (C-β), 34.25 (C-7); MS m/z 134.15 (-C_8H_7, 100%), 133.10 (36), 119.10 (36), 117.10 (11), 115.10 (31), 107.10 (19), 105.10 (24), 91.10 (50), 79.05 (18), 78.05 (16), 77.05 (33), 51 (18); HRMS (AP+) m/z Calcd for $C_{17}H_{17}O$ $[M+1]^+$ 237.1279. Found 237.1277. *Compound* **3**: ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.32 (2H, dd, J = 7.90, 1.27 Hz, H2 and H6), 7.71–7.67 (1H, m, H4), 7.59–7.56 (2H, dd, J = 7.90, J = 1.96, H3 and H5), 7.40–7.35 (2H, m, H3′ and H5′), 7.33–7.26 (2H, m, H4′ and H6′) 6.03 (1H, ddt, J = 16.96, 10.20, 6.65 Hz, H2″), 5.15–5.10 (2H, m, H3″a and H3″b), 3.48 (1H, dd, J = 19.90, 6.60 Hz, H1″a), 3.45 (1H, dd, J = 19.90, 6.60 Hz, H1″b); ^{13}C NMR (151 MHz, $CDCl_3$) δ 164.93 (C-α) 135.82 (C-2″), 133.59 (C-4), 132.13, 130.42 (C-3′), 130.14 (C-2 and C-6), 129.52, 128.62 (C-3 and C-5), 127.49 (C-5′), 126.22 (C-6′), 122.51 (C-4′), 116.32 (C-3″), 34.70 (C-1″); MS m/z 238.10 (M^+, 9%), 106.05 (8), 105.05 (100), 77.05 (34); HRMS (ES+) m/z Calcd for $C_{16}H_{15}O_2$ $[M+1]^+$ 239.1072. Found 239.1075. *Compound* **6**: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.79–7.75 (2H, m, H-2′, H-6′), 7.44–7.36 (3H, m, H3′, H4′ and H5′), 7.25 (1H, dd, J = 7.53, 1.51, H3), 7.22–7.19 (1H, m, H5), 7.13–7.09 (1H, m, H4), 7.06 (1H, dd, J = 7.96, 0.95, H6), 4.91 (1H, d, J = 2.57, Hβa), 4.16 (1 H, d, J = 2.53, Hβb), 2.52 (2H, d, J = 7.24, H1″a and H1″b), 2.01 (1H, m, H2″), 0.93 (6 H, d, J = 6.66, H3″a-c and H4″a-c); *Compound* **17**: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.47–7.45 (2H, m, H2″ and H6″), 7.39–7.36 (2H, m, H3″ and H5″), 7.31 (1H, tt, J = 7.31, 2.04 Hz, H4″), 7.27–7.23 (1H, m, H5), 6.77 (1H, br d, J = 16.0 Hz, H3′), 6.64–6.58 (3H, m, H2, H4 and H6), 6.46 (1H, dt, J = 11.68, 5.85 Hz, H2′), 4.71 (2H, dd, J = 5.85, 1.22 Hz, H1′a and H1′b), 3.83 (s, 3H, -OMe); ^{13}C NMR (151 MHz, $CDCl_3$) δ 133.10 (C-3′), 130.04 (C-5), 128.68, 127.98, 126.67, 124.50 (C-2′), 107.00 (C-4), 106.58 (C-2), 101.41 (C-6), 68.71 (C-1′), 55.32 (-OMe); MS m/z 240.15 (M^+, 5%), 118.10 (10), 117.10 (100), 116.15 (7), 115.10 (30), 91.10 (14); HRMS (AP+) m/z Calcd for $C_{16}H_{17}O_2$ $[M+1]^+$ 241.1229. Found 241.1228. *Compound* **18**: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.32 (2H, t, J = 15.15, 7.57 Hz, H2″ and H6″), 7.23 (3H, dd, J = 14.64, 7.35 Hz, H3″–H5″), 6.95 (1H, d, J = 8.48 Hz, H3), 6.47 (1H, dd, J = 8.48, 2.51 Hz, H4), 6.41 (1H, d, J = 2.51 Hz, H6), 6.32 (1H, ddd, J = 16.97, 10.17, 6.55 Hz, H2'), 5.28 (1H, d, J = 10.17 Hz, H3′b), 5.03 (1H, br s, OH), 5.02 (1H, d, J = 16.97 Hz, H3′a), 4.87 (1H, d, J = 6.50 Hz, H1′), 3.76 (3H, s, -OMe); ^{13}C NMR (151 MHz, $CDCl_3$) δ 141.92, 139.84 (C-2′), 130.39 (C-3), 128.78, 128.72, 126.87, 121.36, 116.96 (C-3′), 106.39 (C-4), 102.59 (C-6), 55.43 (-OMe), 48.95 (C-1′); MS m/z 241.15 (17%), 240.15 (M^+, 100), 239.15 (54), 225.10 (13), 223.10 (15), 213.10 (15), 211.10 (16), 209.10 (13), 165.15 (10), 163.10 (19), 152.10 (14), 149.10 (14), 137.10 (14), 136.10 (12), 117.10 (11), 116.10 (13), 115.05 (37); HRMS (ES-) m/z Calcd for $C_{16}H_{15}O_2$ $[M-1]^-$ 239.1072. Found 239.1074. *Compound* **19**: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.30–7.27 (2H, m, H2″ and H6″), 7.21–7.18 (3H, m, H3″, H4″ and H5″), 7.07 (1H, d, J = 8.54 Hz, H6), 6.62 (1H, dd, J = 8.53, 2.54 Hz, H5), 6.55 (1H, d, J = 2.51 Hz, H3), 6.52 (1H, dd, J = 13.77, 6.08 Hz, H1‴), 6.28 (1H, ddd, J = 17.11, 10.20, 6.63 Hz, H2′), 5.21 (1H, br d, J = 10.20 Hz, H3′b), 5.06 (1H, br.d, J = 6.63 Hz, H1′), 4.94 (1H, br d, J = 17.11 Hz, H3′a), 4.66 (1H, dd, J = 13.75, 1.56 Hz, H2‴a), 4.36 (1H, dd, J = 6.08, 1.56 Hz, H2‴b), 3.79 (s, 3H, -OMe); ^{13}C NMR (151 MHz, $CDCl_3$) δ 140.18 (C-2′), 130.11 (C-6), 128.58, 128.17 (C-2″ and C-6″), 126.08, 116.13 (C-3′), 108.52 (C-5 and C-1‴), 103.80 (C-3), 94.58 (C-2‴), 55.40 (-OMe), 47.19 (C-1′); MS m/z 266.10 (M^+, 95%), 238.10 (52), 224.05 (100), 211.10 (15), 209.05 (34), 189.05 (29), 178.05 (42), 165.10 (34), 161.10 (79), 152.05 (38), 148.05 (26), 142.10 (20), 137.05 (33), 128.10 (18), 115.00 (84), 91.05 (89); *Compound* **20**: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.28 (2H, m, H2′ and H6′), 7.22–7.16 (3H, m, H3′–H5′), 6.77 (1H, d, J = 8.53 Hz, H5), 6.59 (1H, dd, J = 6.23, 1.56 Hz, H2), 6.48 (1H, dd, J = 8.53, 2.60 Hz, H6), 6.45 (1H, d, J = 2.54 Hz, H8), 4.98 (1H, dd, J = 6.23, 3.49 Hz, H3), 4.58 (1H, br d, J = 3.49, H4), 3.73 (s, 3H, -OMe); ^{13}C NMR (151 MHz, $CDCl_3$) δ 139.23 (C-6), 130.65 (C-5), 128.55, 128.12, 126.51, 110.33 (C-2), 105.44 (C-3), 101.08 (C-8), 53.28 (-OMe), 39.18 (C-4); MS m/z 238.15 (M^+, 38%), 237.10 (23), 162.15 (11), 161.15 (100), 118.10 (14); *Compound* **21**: ^{1}H NMR (600 MHz, CDC_3) δ 7.36–7.33 (2H, m, H2″ and H6″), 7.31–7.27 (2H, m, H3″ and H5″), 7.23–7.19 (1H, m, H4″), 7.05 (1H, d, J = 8.33 Hz, H3), 6.50 (2H, br d, J = 13.92 Hz, H3′), 6.47 (1H, dd, J = 8.33, 2.50 Hz, H5), 6.43 (1H, d, J = 2.50 Hz, H6), 6.37 (1H, dt, J = 13.92, 6.50 Hz, H2′), 3.78 (3H, s, -OMe), 3.50 (2H, dd, J = 6.50, 1.31 Hz, H1′a and H1′b); HRMS (AP-) m/z Calcd for $C_{16}H_{15}O_2$ $[M-1]^-$ 239.1072. Found 239.1075.