# Synthesis of Polycyclic Coumarin Derivatives by Combined Claisen Rearrangement, Ring-closing Metathesis, and Diels–Alder Reaction

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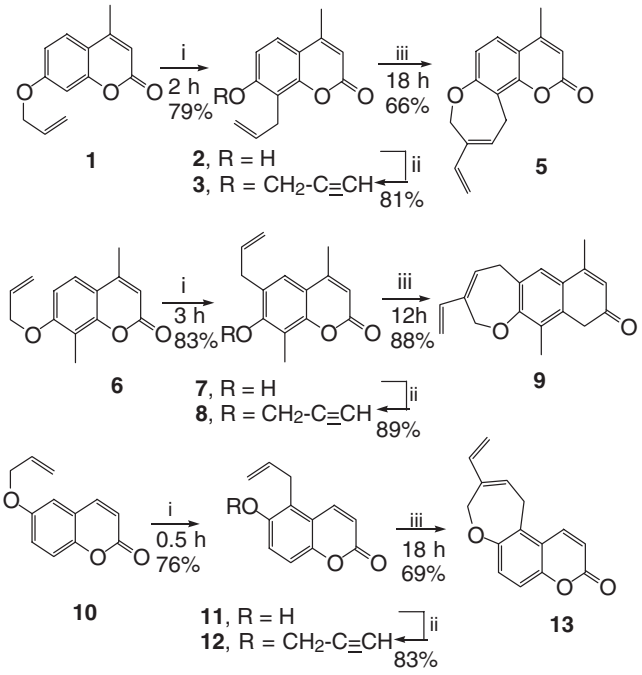
A new route to several hitherto unknown linearly and angularly architectured polycyclic coumarin derivatives has been developed involving tandem applications of three atom economic processes viz. Claisen rearrangement, ring-closing enyne metathesis, and Diels–Alder reactions.

Multiple bond metathesis reactions have emerged[1] as an elegant tool in organic synthesis for the creation of molecular complexity. Of the two types viz. double–double bond and double–triple bond metathesis, the latter version[2] is relatively new but is enjoying increasing attention with regard to further transformations of the resulting conjugate dienes. These tandem transformations have led to synthetic applications in the field of polycycle construction and natural product synthesis.[3]

Various coumarin derivatives are known[4] to display important photophysical and biological activities and, for this and other reasons, interest in the synthesis[5] of derivatives of this important ring system continues to increase. We have recently described[6] tandem applications of Claisen rearrangement and ring-closing metathesis reactions as a route to several carbo- and heterocyclic systems. Herein, we wish to report synthesis of several 6,6,7,6,5- and 6,6,7,6,6,6-ring fused hitherto unknown coumarin derivatives utilizing tandem applications of three atom-economic processes viz. Claisen rearrangement, ring-closing enyne metathesis, and Diels–Alder reaction.

Thus, Claisen rearrangement of 7-allyloxy-4-methylcoumarin (**1**) neatly provided the known[7] 8-allyl-7-hydroxy-4-methylcoumarin (**2**, Scheme 1) under our modified procedure. The latter on alkylation with propargyl bromide under conventional conditions provided the ether **3** in good yield. Ring-closing metathesis of oxygen-tethered enynes leading to oxepin-derivatives is less documented and proved to be erratic in other instances.[8] Pleasingly, metathesis of the enyne derivative **3** with Grubbs' catalyst bis(tricyclohexylphosphine)benzylideneruthenium(IV) dichloride[9] (**4**) in refluxing benzene proceeded smoothly to provide the diene **5** as single isolable product. Similarly, Claisen rearrangement of 7-allyloxy-4,8-dimethylcoumarin[10] under modified conditions neatly provided the rearranged phenol **7** which was alkylated with propargyl bromide to provide the ether **8** in high yield. Ring-closing metathesis of the resulting enyne proved to be even more facile, and the conjugated diene **9** was obtained as a colorless solid, mp 152 °C, in a gratifying yield of 88%. The same sequence of reactions on 6-allyloxycoumarin[11] (**10**) viz. Claisen rearrangement to the phenol **11**, etherification of the latter to the enyne **11** followed by its RCM led to the diene **13** in an overall yield of 43.5% over three steps.

We then focused our attention to the Diels–Alder reaction of the resulting dienes **5**, **9**, and **13**. Thus, when a solution of the diene **5** and *N*-phenylmaleimide was refluxed in benzene for 30 h,

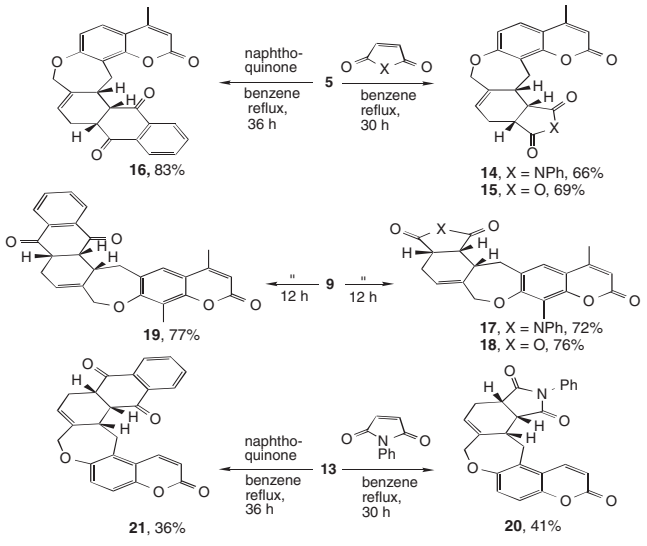



**Scheme 1.** Reagents and conditions; (i) diphenyl ether, reflux; (ii) propargyl bromide, acetone, $K_2CO_3$, reflux, 12 h; (ii) Grubbs' catalyst (**4**, 5 mol %), benzene (0.008 M), reflux.

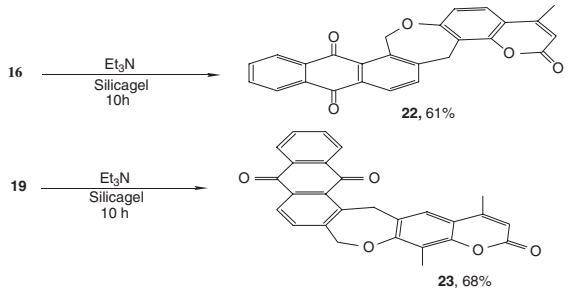
the resulting cycloadduct **14** (Scheme 2) crystallized out of the solution on cooling. It is interesting to note that the cycloadduct was obtained as a single diastereomer and its stereochemistry was assigned to be all *cis* based on precedence[12] and observed coupling constants of the appropriate protons in the $^1$H NMR spectrum. Similarly, reaction of the diene **5** with maleic anhydride and naphthoquinone led exclusively to the cycloadducts **15** and **16**, respectively.

The reaction of the diene **9** with all the three dienophiles tried proceeded uneventfully to provide the cycloadducts **17**–**19** in very good yield. On the other hand, the diene **13** reacted sluggishly with either of *N*-phenylmaleimide and 1,4-naphthoquinone to provide modest yields of the cycloadducts **20** and **21**, respectively. In some instances of application of ring-closing enyne metathesis and Diels–Alder reaction, considerable improvement in yield has been observed when the reaction was carried out in a one-pot manner without isolating the diene. However, controlled experiment with each of the dienes **5**, **9**, and **13** and *N*-phenylmaleimide revealed no significant improvement in yield when the reactions were carried out in a one-pot manner.

In continuation of our earlier studies[6] on sequential RCM-aromatization protocol leading to carbocycles and heterocycles, we further became interested to see whether the cycloadducts with naphthaquinone (**16**, **19**, and **21**) could be aromatized lead-




**Scheme 2.**




**Scheme 3.**

ing possibly to new coumarin–anthraquinone conjugate molecules in view of the known importance of these two ring systems. Thus, when a solution of the cycloadduct **16** in dichloromethane was stirred with triethylamine in the presence of silica gel, smooth oxidative aromatization took place to provide the corresponding anthraquinone derivative **22** (Scheme 3) in good yield. Similar aromatization/oxidation of the cycloadduct **19** provided the conjugate molecule **23** in comparable yield.

In short, we have demonstrated that combined Claisen rearrangement, ring-closing enyne metathesis, and Diels–Alder reaction is an efficacious strategy for the preparation of several hitherto unknown linearly and angularly architectured polycyclic complex coumarin derivatives. The advantage of the methodology lies in its true atom-economic nature, operational simplicity, predetermined mode of cyclization and high level of stereocontroll. The prepared compounds[13] may find biological applications.

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13 All new compounds reported gave satisfactory spectroscopic and analytical data. Data for **17**: mp 296–298 °C. $\lambda_{max}$: 328 nm. IR (KBr, $cm^{-1}$): 1716, 1698, 1610, 1387, 1114. $^1$H NMR ($CDCl_3$, 500 MHz) $\delta$ 7.48–7.45 (2H, m), 7.41–7.38 (1H, m), 7.20–7.17 (3H, m), 6.18 (1H, app. t, $J = 3.4$ Hz), 6.11 (1H, s), 5.19 (1H, d, $J = 12.6$ Hz), 4.52 (1H, d, $J = 12.6$ Hz), 4.24 (1H, app. t, $J = 14.8$ Hz), 3.43 (1H, dd, $J = 8.9$, 5.9 Hz), 3.40–3.37 (1H, m), 3.01 (1H, dd, $J = 15.0$, 2.5 Hz), 2.92 (1H, dd, $J = 16.3$, 6.8 Hz), 2.78 (1H, brd, $J = 12.8$ Hz), 2.34 (3H, s), 2.23–2.18 (1H, m), 2.14 (3H, s). $^{13}$C NMR ($CDCl_3$, 75 MHz) $\delta$ 178.2 (s), 176.6 (s), 161.6 (s), 157.3 (s), 152.3 (s), 151.6 (s), 139.7 (s), 131.6 (s), 129.1 (d), 128.8 (d), 127.1 (d), 126.3 (d), 124.7 (d), 121.7 (s), 115.4 (s), 113.4 (s), 112.1 (d), 70.1 (t), 44.4 (d), 40.2 (d), 38.7 (t), 34.4 (d), 24.8 (t), 18.6 (q), 8.9 (q). Elemental analyses: Found: C, 73.70; H, 5.46; N, 3.04%. Calcd for $C_{27}H_{23}NO_5$: C, 73.46; H, 5.25; N, 3.17%. $m/z$ (EI, 70 eV): 441 (100%), 268 (63%), 203 (81%). Data for **14**: mp 218–220 °C. $\lambda_{max}$: 326 nm. IR (KBr, $cm^{-1}$): 1707, 1595, 1494, 1389, 1265. $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 7.48–7.40 (4H, m), 7.35 (1H, d, $J = 8.5$ Hz), 7.19 (1H, d, $J = 7.8$ Hz), 6.77 (1H, d, $J = 8.8$ Hz), 6.15 (2H, brs), 5.25 (1H, d, $J = 12.5$ Hz), 4.44 (1H, d, $J = 12.6$ Hz), 3.94 (1H, d, $J = 2.7$ Hz), 3.91 (1H, s), 3.52 (1H, dd, $J = 8.9$, 5.6 Hz), 3.38 (1H, t, $J = 8.3$ Hz), 2.93–2.86 (2H, m), 2.39 (3H, s), 2.33–2.30 (1H, m). $^{13}$C NMR ($CDCl_3$, 75 MHz) $\delta$ 178.3 (s), 176.5 (s), 161.2 (s), 159.7 (s), 152.9 (s), 152.8 (s), 140.1 (s), 131.7 (s), 129.1 (d), 128.6 (d), 126.9 (d), 126.4 (d), 123.4 (d), 115.9 (s), 114.0 (s), 113.8 (s), 111.6 (d), 70.3 (t), 44.8 (d), 40.3 (d), 38.9 (d), 25.2 (t), 22.9 (t), 18.8 (q). Elemental analyses: Found: C, 73.19; H, 5.12; N, 3.41%. Calcd for $C_{26}H_{21}NO_5$: C, 73.06; H, 4.95; N, 3.28%. $m/z$ (EI, 70 eV): 427 (100%), 307 (22%), 254 (61%).

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