Combined Multiple Claisen Rearrangement and Ring-closing Metathesis as a Route to Naphthalene, Anthracene, and Anthracycline Ring Systems

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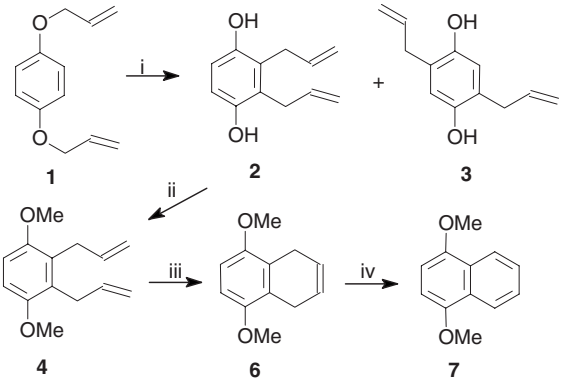
A new route involving double Claisen rearrangement of a suitable 1,4-diallyloxyarene system followed by ring-closing metathesis of the resulting diene has been developed for the synthesis of various benzannulated cyclohexenes. An important demonstration of this methodology is the construction of the tetracyclic quinophenolic ring system of the clinically important anthracyclines.

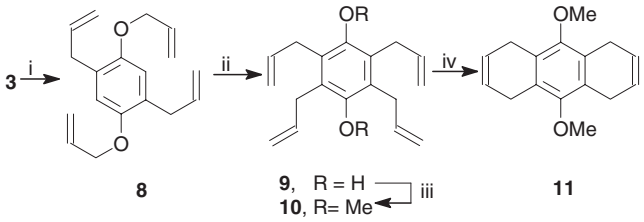
The ring-closing metathesis (RCM) reaction of olefins promoted by metal carbenes has evolved in the last few years as an efficient method for the construction of carbo- and heterocyclic rings of varying size.[1] The synthetic potential of the RCM reaction has been further increased by combining various processes with it, either in tandem or in sequence.[2] We,[3] and others[4] have recently demonstrated that combined Claisen rearrangement and RCM reaction is an efficacious tactic for the synthesis of desired structures. Herein, we wish to report that a combination of multiple Claisen rearrangement and RCM reaction could be successfully exploited for the synthesis of a range of benzannulated cyclohexenes of interest.

Claisen rearrangement of hydroquinone diallyl ether (**1**) was previously[5] carried out in refluxing kerosene. But, isolation of pure products from this solvent was reported to be problematic. We have found that the rearrangement of **1**, prepared following a literature,[5] proceeds effectively in refluxing *N*,*N*-diethylaniline to give the regioisomeric products 2,3-diallylhydroquinone (**2**) and 2,5-diallylhydroquinone (**3**) (Scheme 1) as a 1:1 mixture. The products were separated by chromatography over silica gel using 2% ethyl acetate in petroleum ether as eluent. The isomer **3** eluted first. Distinction between the two regioisomers **2** and **3** could not be made by ^{1}H NMR spectroscopy. The lower melting isomer previously[5] characterised as **2**, was converted into its dimethyl ether **4** under conventional conditions. The RCM of the diene **4** with Grubbs' catalyst[6] bis(tricyclohexylphosphine)benzylideneruthenium(IV) dichloride (**5**) in dichloromethane at ambient temperature proceeded smoothly to provide the dihydronaphthalene derivative **6**. The latter on oxidation with DDQ provided the known 1,4-dimethoxynaphthalene in an overall yield of 47% from **2**.



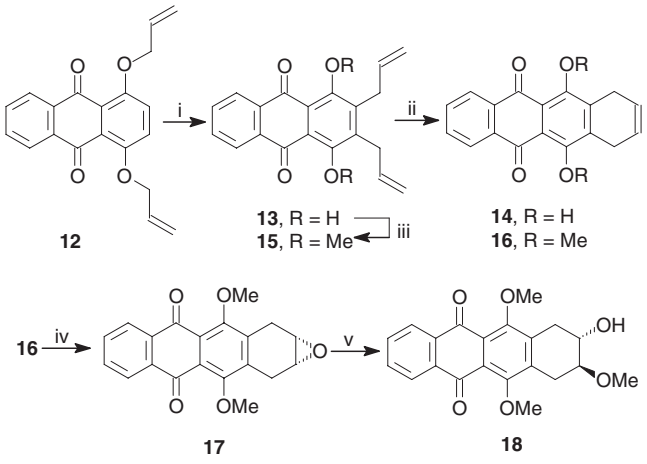
Scheme 1. Reagents and conditions; (i) $PhNEt_2$, reflux, 5 h, 82%; (ii) MeI, K_2CO_3, acetone, reflux, 20 h, 87%; (iii) Grubbs' catalyst **5** (6 mol %), CH_2Cl_2 (**4** : 0.6 M), rt, 20 h, 76%; (iv) DDQ, xylene, reflux, 12 h, 72%.

The other isomer **3** on further alkylation with allyl bromide provided the bisallyl ether **8** (87%) (Scheme 2). The compound **8** underwent smooth double Claisen rearrangement in refluxing *N*,*N*-diethylaniline to provide the hexasubstituted benzene derivative **9** in moderate yield (63%). For convenience, **9** was converted into its dimethyl ether **10** using conventional conditions. Recently, the use of multiple RCM reactions of polyenes has been exploited to deliver spirocyclic, annulated and other bicyclic systems from acyclic precursors in a single step.[7] However, few benzannulated constructs have appeared. We were pleased to see that RCM of the tetraene **10** gave the tetrahydroanthracene derivative **11** directly in good yield.



Scheme 2. Reagents and conditions; (i) Allyl bromide, K_2CO_3, acetone, reflux, 20 h, 87%; (ii) $PhNEt_2$, reflux, 10 h, 63%; (iii) MeI, K_2CO_3, acetone, reflux, 20 h, 77%; (iv) Grubbs' catalyst **5** (6 mol %), CH_2Cl_2 (**10** : 0.7 M), rt, 20 h, 69%.

We are further interested in seeing whether the tetracyclic quinophenolic ring system of the clinically important anthracyclines could be prepared through the application of this tandem double Claisen rearrangement and RCM methodology. With this aim, 1,4-diallyloxyanthraquinone **12** (Scheme 3) was prepared by allylation of commercially available 1,4-dihydroxyanthraquinone as reported.[8] Claisen rearrangement of **12** to **13** was previously effected using sodium dithionite as the reducing agent[9] which possibly in situ reduces the deactivating carbonyl groups to anthraquinone radical anion. We have found that the rearrangement of **12** to **13** also proceeds effectively in the presence of the organic reducing agent glucose in aqueous DMF thereby avoiding the need of using unpleasant smelling dithionite. Although the rearranged product **13** is known, it has not so far been utilized in anthracycline synthesis. A ring-closing metathe-



Scheme 3. Reagents and conditions; (i) Glucose, DMF–H_2O, 120 °C, 12 h, 66%; (ii) Grubbs' catalyst **5** (5–10 mol %), CH_2Cl_2 (**13** or **15** : 0.01 M), rt, 4 h, 63–86%; (iii) MeI, K_2CO_3, acetone, reflux, 20 h, 77%; (iv) *m*-CPBA, CH_2Cl_2, 0–4 °C, 12 h, 95%; (v) *p*-TsOH, methanol, reflux, 4 h, 87%.

sis of the diene **13** was then considered for such an application. Pleasingly, the diene **13** underwent smooth RCM in the presence of the catalyst **5** to afford the tetracycle **14** in an acceptable yield of 63%. The RCM of the dimethyl ether **15**, prepared by straightforward methylation of the bis-phenol **13**, proved to be more efficient under identical conditions and the tetracyclic compound **16** was obtained (86%) as a yellow crystalline solid, mp 135 °C.[10]

We reasoned that the olefinic unit in **16** should serve as an effective handle for the installation of functionalities relevant to anthracycline synthesis, and we considered a few options along this direction. The attempted dihydroxylation[11] of **16** (OsO_4/NMO) proved to be problematic due to its poor solubility in the usual solvents. However, it could be successfully epoxidised to **17** using *m*-chloroperbenzoic acid as oxidant. Acid catalysed opening of the *meso*-epoxide **17** with methanol smoothly afforded the racemic product **18**.

Although various routes are available,[12] development of new synthetic routes to the anthracyclines continues to be of current interest.[13] The simplicity of our methodology may make the route complementary to those existing in the literature and the compounds **14** and **16**–**18** may prove to be valuable intermediates for the synthesis of drug candidates belonging to the anthracycline family.

In short, we have demonstrated that tandem multiple Claisen rearrangement and ring-closing metathesis is an effective route for the preparation of 1,4-dioxygenated naphthalene derivatives, 9,10-dioxygenated anthracene derivatives and the tetracyclic quinophenolic ring system of the anthracyclines. The methodology developed may become useful for accessing other related products of interest.

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10 All new compounds reported gave satisfactory spectroscopic and/or analytical data. Preparation of **16**: To a stirred solution of **15** (175 mg, 0.5 mmol) in dry and degassed dichloromethane (50 mL), Grubbs' catalyst **5** (20 mg) was added under argon atmosphere and the solution was stirred for four hours at room temperature. The reaction mixture was then concentrated in vacuo and chromatographed over silica gel using a mixture of toluene and petroleum ether (2:3) as eluent to give the product **16** (136 mg, 86%) as an yellow crystalline solid. mp 135 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.19 (2H, m), 7.74 (2H, m), 5.93 (2H, s), 3.92 (6H,s), 3.49 (4H, s). ^{13}C NMR (75 MHz, $CDCl_3$) δ 182.9 (s), 154.8 (s), 138.9 (s), 134.1 (s), 133.4 (d), 126.5 (d), 124.3 (s), 123.0 (d), 61.3 (q), 24.8 (t). Elemental analyses: C, 75.06%; H, 5.11%; calcd. for $C_{20}H_{16}O_4$ C, 74.99%; H, 5.03%. Mass (EI, 70 eV): m/z, 321 ($M^+ + 1$).
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