

# A new protocol for benzoannulation by double Claisen rearrangement and ring-closing metathesis reactions as key steps <sup>☆</sup>

Sambasivarao Kotha\* and Kalyaneswar Mandal

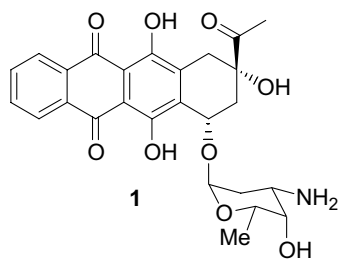
Department of Chemistry, Indian Institute of Technology—Bombay, Powai, Mumbai 400 076, India

Received 15 November 2003; revised 17 January 2004; accepted 30 January 2004

**Abstract**—A new methodology for benzoannulation has been developed by using double Claisen rearrangement followed by a one-pot ring-closing metathesis and DDQ oxidation sequence.

© 2004 Published by Elsevier Ltd.

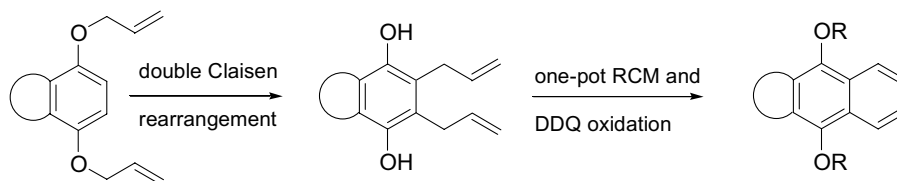
Benzoannulated quinones are useful therapeutic compounds for the treatment of a wide variety of disorders. For example, anthracycline antibiotics<sup>1</sup> such as idarubicin **1**, doxorubicin and daunorubicin have been widely used as clinically effective antitumor agents against acute leukemia, Hodgkin's disease, lymphomas, breast carcinomas and sarcomas.<sup>2</sup> In addition, various naphthoquinones are used as antibiotics.<sup>3</sup>



Benzoannulation reactions are used for appending an aromatic ring to a pre-existing polycyclic structure. There is interest therefore in designing new approaches, which are capable of adding an aromatic moiety for the synthesis of polyaromatic compounds. A variety of synthetic methodologies have been developed for this purpose starting from acyclic or cyclic precursors.<sup>4</sup>

Herein, we report a simple methodology for benzoannulation using a double Claisen rearrangement followed by a one-pot ring-closing metathesis (RCM) and dicyanodichloro-1,4-benzoquinone (DDQ) oxidation reaction sequence (Scheme 1).

In recent times, the RCM reaction using Grubbs' catalysts has become a useful tool for synthetic chemists and has been applied for the preparation of various heterocyclic, carbocyclic and macrocyclic molecules.<sup>5</sup> In the present study, Grubbs' catalysts **2** or **3** have been used for the ring-closing metathesis step (Fig. 1).



**Scheme 1.** Proposed route to benzoannulation sequence.

**Keywords:** Claisen rearrangement; Metathesis; Benzoannulation, Anthracyclines, Quinones.

<sup>☆</sup> A portion of this work was presented at the Group Monitoring Workshop on DST-Funded projects in Organic Chemistry, IIT-Kanpur, October 28, 2002, Kotha, S., Synthesis of novel polycyclics via catalytic metathesis reaction.

\* Corresponding author. Tel.: +91-22-2576-7160; fax: +91-22-2572-3480; e-mail: [srk@chem.iitb.ac.in](mailto:srk@chem.iitb.ac.in)

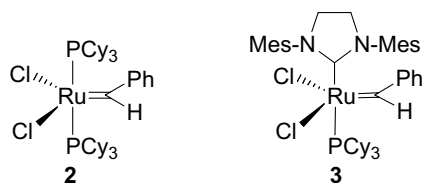


Figure 1. Grubbs' catalysts used for RCM reaction.

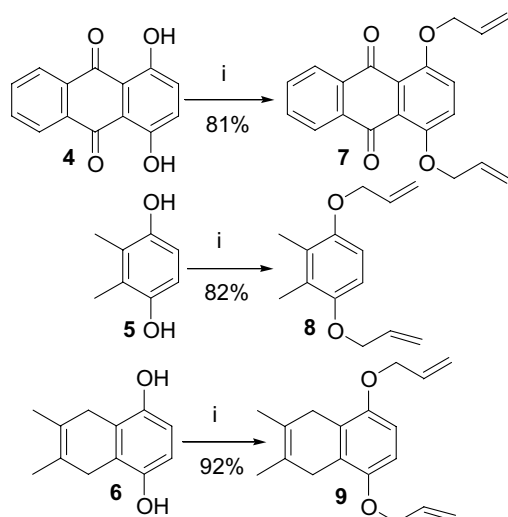
The required precursors for the double Claisen rearrangement were prepared by *O*-allylation of the corresponding 1,4-dihydroxybenzene derivatives following conventional allylation conditions (Scheme 2).

Treatment of the bis-allyloxy anthraquinone **7** with sodium dithionite (1.0 molequiv) in the presence of sodium hydroxide (4 molequiv) in dimethylformamide–water (1:1) with heating for 1 h delivered the desired double double rearranged product **10** in good yields (Scheme 3).<sup>6</sup>

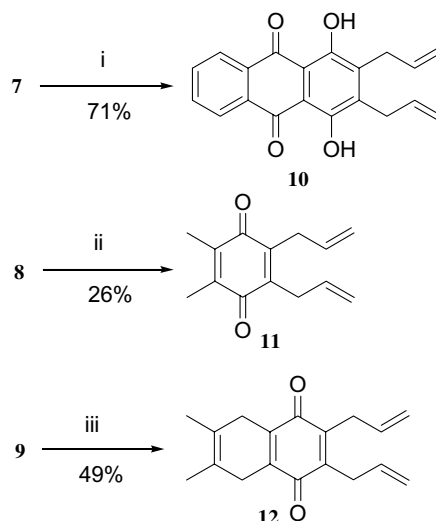
Thermal Claisen rearrangement of the bis-allyloxy 2,3-dimethylbenzene **8** and 5,8-bis-allyloxy-2,3-dimethyl-1,4-dihydronaphthalene **9** gave the corresponding bis-allyl quinones **11** and **12**, respectively. Attempts to improve the yields of the Claisen rearrangement products (**11** and **12**) were unsuccessful. Prolonged heating gave an intractable polymeric material (Scheme 3).

Having the diallylated derivatives in hand, we first tried the RCM reaction with compound **10**. However, Grubbs' catalysts (**2** and **3**) failed to give the required product **13**. The failure could be attributed to the complexation of the phenolic -OH group with the metal catalyst (Scheme 4).

Next, we protected the free hydroxy groups of **10** (Scheme 5) and these protected derivatives successfully underwent the RCM reaction, then on aromatization

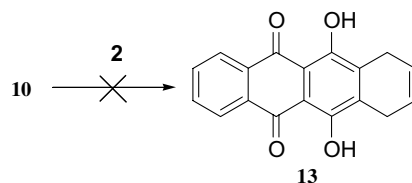


Scheme 2. Reagents and conditions: (i) allyl bromide,  $K_2CO_3$ , acetone,  $\Delta$ .

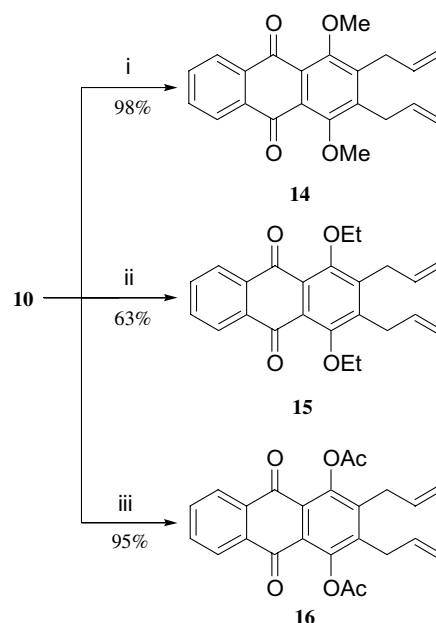


Scheme 3. Reagents and conditions: (i)  $Na_2S_2O_4$ , DMF– $H_2O$  (1:1),  $130^\circ C$ ; (ii) xylene,  $\Delta$ ; (iii) *N,N'*-dimethylaniline,  $\Delta$ .

without isolation by DDQ oxidation, gave moderate overall yields of the benzoannulated products. Various other examples studied are included in Table 1.<sup>7,8</sup>

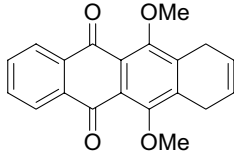
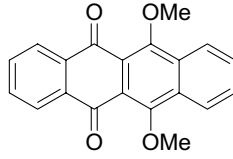
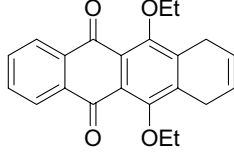
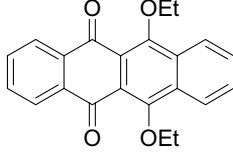
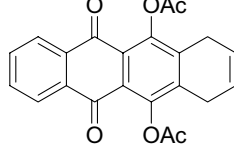
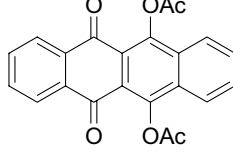
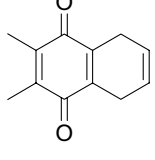
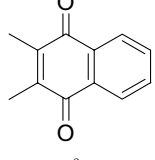
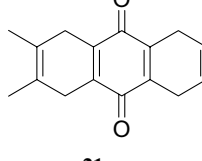
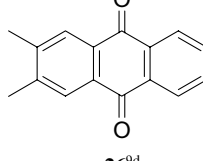


Scheme 4.



Scheme 5. Reagents and conditions: (i) MeI, acetone, rt; (ii) NaOH, EtBr, NaI, acetone, reflux; (iii)  $Ac_2O$ , Py.

**Table 1.** List of various benzoannulated products prepared by the RCM and DDQ oxidation sequence

Entry	Diallyl substrate	Conditions followed	RCM product	Benzoannulated product	Overall yield (%) <sup>a</sup>
1	14	A			49
			17	22 <sup>9a</sup>	
2	15	A			37
			18	23	
3	16	B			51
			19	24 <sup>9b</sup>	
4	11	A			54
			20	25 <sup>9c</sup>	
5	12	A			85
			21	26 <sup>9d</sup>	

A. (i) Catalyst 2, dry DCM, rt, 24 h.; (ii) DDQ, benzene, reflux.

B. (i) Catalyst 3, dry DCM, rt, 24 h.; (ii) DDQ, benzene, reflux.

<sup>a</sup>Overall yield refers to the yield obtained after the RCM and aromatization sequence.

In summary, a simple protocol involving the double Claisen rearrangement of bis-allyl aryl ethers followed by a one-pot RCM and DDQ oxidation sequence has been developed to generate benzoannulated aromatics. Also, the RCM products **17**, **18** or **19** may be useful as precursors for the synthesis of potent anticancer analogues such as idarubicin **1** using simple transformations.

#### Acknowledgements

We thank the DST for financial support and the RSIC, Mumbai for providing spectral facilities. K.M. thanks the CSIR, New Delhi for the award of a research fellowship.

#### References and notes

- (a) Priebe, W. *Anthracycline Antibiotics: New Analogues, Methods of Delivery, and Mechanisms of Action*; ACS Symp. Ser. No. 574; American Chemical Society: Washington, DC, 1995; (b) Arcamone, F. *Doxorubicin*; Academic: New York, 1980; (c) El Khadem, H. S. *Anthracycline Antibiotics*; Academic: New York, 1982; (d) For related work see: Kotha, S.; Stoodley, R. J. *Bioorg. Med. Chem.* **2002**, *10*, 621, and references therein.
- (a) Weis, R. B.; Sarosy, G.; Clagget-Carr, K.; Russo, M.; Leyland-Jones, B. *Cancer Chemother. Pharmacol.* **1986**, *18*, 185; (b) Weiss, R. B. *Semin. Oncol.* **1992**, *19*, 670; (c) Lown, J. W. *Chem. Soc. Rev.* **1993**, 165; (d) Di Marco, A.; Casazza, A. M.; Giuliani, F.; Pratesi, G.; Arcamone, F.; Bernadi, L.; Franchi, G.; Giradino, P.; Patelli, B.; Penco, S. *Cancer Treat. Rep.* **1978**, *62*, 375.

3. Wakao, I. JP 2001055326, **2001**; *Chem. Abstr.* **2001**, 134, 188182.
4. (a) Rao, M. S. C.; Rao, G. S. K. *Synthesis* **1987**, 231; (b) Gribble, G. W.; Perni, R. B. *J. Org. Chem.* **1985**, 50, 2935; (c) Rigby, J. H.; Warshakoon, N. C. *J. Org. Chem.* **1996**, 61, 7644; (d) Danheiser, R. L.; Gee, S. K. *J. Org. Chem.* **1984**, 49, 1672; (e) Paquette, L. A.; Melega, W. P.; Kramer, J. D. *Tetrahedron Lett.* **1976**, 45, 4033; (f) Merlic, C. A.; Burns, E. E.; Chen, S. Y. *J. Am. Chem. Soc.* **1992**, 114, 8722; (g) van Otterlo, W. A. L.; Ngidi, E. L.; Coyanis, E. M.; de Koning, C. B. *Tetrahedron Lett.* **2003**, 44, 311; (h) Huang, K. S.; Wang, E. C. *Tetrahedron Lett.* **2001**, 42, 6155; (i) Arisawa, M.; Theeraladanon, C.; Nishida, A.; Nakagawa, M. *Tetrahedron Lett.* **2001**, 42, 8029; (j) Okada, A.; Ohshima, T.; Shibasaki, M. *Tetrahedron Lett.* **2001**, 42, 8023; (k) Chang, S.; Grubbs, R. H. *J. Org. Chem.* **1998**, 63, 864; (l) Harrity, J. P. A.; Visser, M. S.; Gleason, J. D.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1997**, 119, 1488; (m) Ackermann, L.; Fürstner, A.; Weskamp, T.; Kohl, F. J.; Herrmann, W. A. *Tetrahedron Lett.* **1999**, 40, 4787; (n) Kinderman, S. S.; Doodeman, R.; van Beijma, J. W.; Russcher, J. C.; Tjen, K. C. M. F.; Kooistra, T. M.; Mohaselzadeh, H.; van Maarseveen, J. H.; Hiemstra, H.; Schoemaker, H. E.; Rutjes, F. P. J. T. *Adv. Synth. Catal.* **2002**, 344, 736.
5. For review articles on olefin metathesis, see: (a) Kotha, S.; Sreenivasachary, N. *Indian J. Chem.* **2001**, 40B, 763; (b) Trnka, T. M.; Grubbs, R. H. *Acc. Chem. Res.* **2001**, 34, 18; (c) Fürstner, A. *Angew. Chem., Int. Ed.* **2000**, 39, 3012; (d) Phillips, A. J.; Abell, A. D. *Aldrichim. Acta* **1999**, 32, 75; (e) Wright, D. L. *Curr. Org. Chem.* **1999**, 3, 211; (f) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, 54, 4413; (g) Armstrong, S. K. *J. Chem. Soc., Perkin Trans. I* **1998**, 371; (h) Fürstner, A., Ed. *Top. Orgmet. Chem.* **1998**.
6. Boddy, L. K.; Boniface, P. J.; Cambie, R. C.; Craw, P. A.; Larsen, D. S.; McDonald, H.; Rutledge, P. S.; Woodgate, P. D. *Tetrahedron Lett.* **1982**, 45, 4407.
7. Typical procedure for the RCM reaction and one-pot DDQ oxidation reaction: To a solution of compound **11** (56 mg, 0.26 mmol) in dry degassed DCM (12 mL) was added Grubbs' catalyst **2** (11 mg, 5 mol%). The reaction mixture was stirred at rt for 24 h. In the same pot, DDQ (89 mg, 0.39 mmol) dissolved in dry benzene (15 mL) was added and the mixture refluxed for 24 h. Then, the reaction mixture was concentrated and the crude product was purified by silica gel column chromatography. Elution of the column with 1% EtOAc–petroleum ether gave **25** as yellow crystalline solid (26 mg, 54%), mp 130 °C (lit. 127 °C)<sup>9c</sup>.
8. All new compounds were fully characterised by their spectroscopic data. Spectral data for selected compounds: **11** <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 2.03 (s, 6H), 3.27 (dt, 4H, *J* = 6.4, 1.6 Hz), 5.02–5.09 (m, 4H), 5.75–5.85 (m, 2H). **12** <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 1.73 (s, 6H), 3.0 (s, 4H), 3.27 (d, 4H, *J* = 6.0 Hz), 5.03–5.09 (m, 4H), 5.75–5.85 (m, 2H). **15** <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 1.52 (t, 6H, *J* = 7 Hz), 3.59 (dt, 4H, *J* = 5.6, 2 Hz), 4.01 (q, 4H, *J* = 6.8 Hz), 4.92 (d, 2H, *J* = 17.2 Hz), 5.06 (d, 2H, *J* = 10.2 Hz), 5.93–6.03 (m, 2H), 7.69–7.74 (m, 2H), 8.18 (dd, 2H, *J* = 5.6, 3.2 Hz). **23** <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 1.66 (t, 6H, *J* = 6.9 Hz), 4.26 (q, 4H, *J* = 7 Hz), 7.71–7.78 (m, 4H), 8.27 (dd, 2H, *J* = 5.7, 3.3 Hz), 8.43 (dd, 2H, *J* = 6.6, 3.3 Hz).
9. (a) Khanapure, S. P.; Reddy, R. T.; Biehl, E. R. *J. Org. Chem.* **1987**, 52, 5685; (b) Brockmann, H.; Lenk, W. *Chem. Ber.* **1959**, 92, 1880; (c) Smith, L. I.; Webster, I. M. *J. Am. Chem. Soc.* **1937**, 59, 662; (d) Tanaka, K.; Miura, T.; Umezawa, N.; Urano, Y.; Kikuchi, K.; Higuchi, T.; Nagano, T. *J. Am. Chem. Soc.* **2001**, 123, 2530.