Tetrahedron Letters 55 (2014) 5315–5318

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Rapid construction of polycyclic ring systems from aromatics: stereoselective synthesis of the carbon framework of vinigrol

Yan-Bin Lu [a], Day-Shin Hsu [b,*], Chun-Chen Liao [a,c,*]

[a] Department of Chemistry, National Tsing Hua University, Hsinchu 300, Taiwan
[b] Department of Chemistry and Biochemistry, National Chung Cheng University, Minhsiung 621, Taiwan
[c] Department of Chemistry, Chung Yuan Christian University, Chungli 320, Taiwan

ARTICLE INFO

Article history:
Received 5 June 2014
Revised 11 July 2014
Accepted 17 July 2014
Available online 22 July 2014

Keywords:
Masked *o*-benzoquinones
Oxy-Cope rearrangement
Ene reaction
Tandem reaction
Polycycles

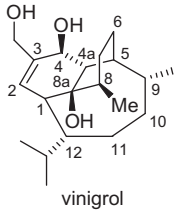
ABSTRACT

The stereoselective syntheses of the tricyclic core structure of vinigrol and highly functionalized polycyclic molecules from 5-bromo-2-methoxyphenol in five synthetic steps are reported. Intramolecular and intermolecular Diels–Alder reactions and tandem oxy-Cope/ene reactions are the key steps in the synthesis.

Vinigrol, which was isolated from *Virgaria nigra* in 1987, is a diterpenoid with a unique tricyclo[4.4.4.0^{4a,8a}]tetradecane framework, involving a *cis*-decalin system bridged by an eight-membered ring (Fig. 1).[1] Vinigrol shows antihypertensive, platelet aggregation-inhibiting, and tumor necrosis factor (TNF) antagonist properties.[2] Owing to its promising biological properties and structural complexity, considerable efforts have been devoted to the synthesis of vinigrol.[3,4] In 2009, Baran[5a] reported the first total synthesis of vinigrol and a few years later Barriault[5b] and Njardarson[5c] published a formal and total synthesis of vinigrol, respectively.

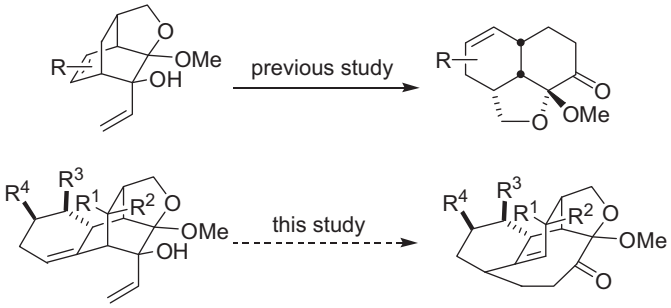
Recently, our laboratory demonstrated that masked *o*-benzoquinones (MOBs), derived from easily accessible 2-methoxyphenol, can be rapidly expanded into complex structural motifs.[6,7] Using this approach, we developed a methodology for constructing *cis*-decalin skeletons from 1,5-dienes using the anionic oxy-Cope rearrangement (Scheme 1).[8,9] Accordingly, we envisioned that the tricyclo[4.4.4.0^{4a,8a}]tetradecane framework in vinigrol could be obtained from another 1,5-diene substrate using the same rearrangement. We reported herein a strategy to construct the core structure of vinigrol along with unexpected polycyclic ring systems, from 1,5-dienes, which were also obtained rapidly from MOBs.

To examine the feasibility of this approach, we first obtained the desired 1,5-dienes. These 1,5-diene substrates were synthesized from 5-bromo-2-methoxyphenol (**1**). The intramolecular



vinigrol

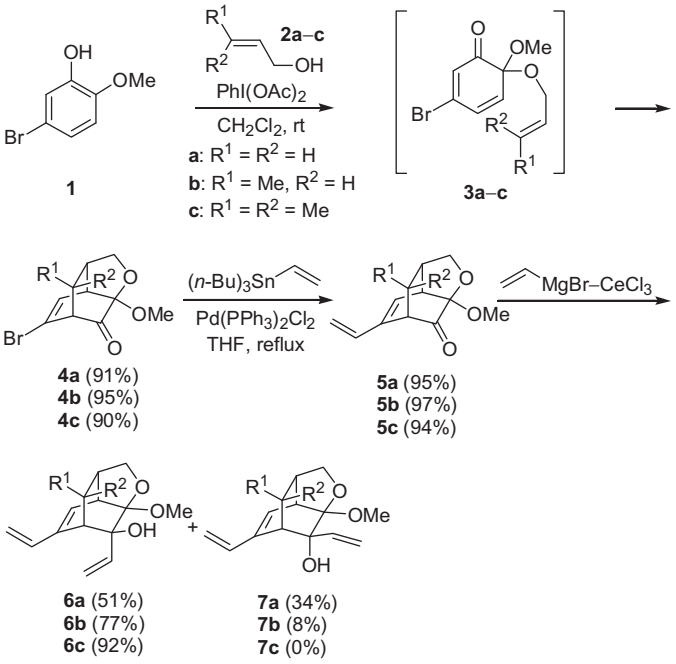
Figure 1. Structure of vinigrol.



Scheme 1. Oxy-Cope rearrangements of 1,5-dienes.

* Corresponding authors. Tel.: +886 5 272 0411x66417; fax: +886 5 272 1040 (D.-S.H.); tel.: +886 3 265 3387; fax: +886 3 265 3389 (C.-C.L.).
E-mail addresses: chedsh@ccu.edu.tw (D.-S. Hsu), ccliao@cycu.edu.tw (C.-C. Liao).

http://dx.doi.org/10.1016/j.tetlet.2014.07.064
0040-4039/



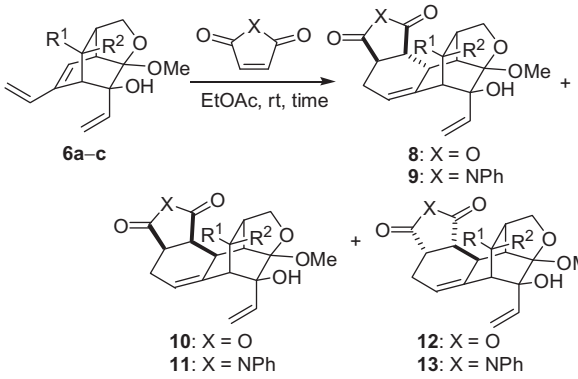
Scheme 2. Preparation of tricyclic 1,3-dienes.

Diels–Alder reaction of MOBs **3a–c** that were generated in situ from **1** in the presence of alkenols **2a–c**, respectively, formed tricyclic ketones **4a–c** in high yields (Scheme 2).[10,11] The bromo group in **4a–c** was then replaced by a vinyl group under Stille conditions to give 1,3-dienes **5a–c**. Addition of a preformed vinylmagnesium bromide–$CeCl_3$ reagent[12] to **5** yielded the two stereoisomers, **6** and **7**. In this reaction, a nucleophilic attack occurred preferentially at the sterically less-hindered endo-face of the ketones **5** to produce *syn*-isomers **6** as the major or exclusive products.[13]

The next step involved the intermolecular Diels–Alder reaction of 1,3-dienes **6** with symmetric dienophiles. Symmetric dienophiles were chosen to avoid the formation of regioisomers in the Diels–Alder reaction. Therefore, maleic anhydride was first used as the dienophile in the Diels–Alder reaction with **6a**. The reaction reached completion after 6 days at room temperature and produced two cycloadducts, **8a** and **10a**, in 57% and 38% yields, respectively (Table 1, entry 1). On the other hand, when *N*-phenylmaleimide reacted with **6a** at room temperature, the reaction was completed after 8 days and produced three cycloadducts **9a**, **11a**, and **13a** (entry 2). In contrast to diene **6a**, dienes **6b**,**c** reacted with maleic anhydride and *N*-phenylmaleimide to give single Diels–Alder adducts (entries 3–6). The Diels–Alder reaction was accelerated under microwave irradiation at 80 °C, and the reactions were completed within 12 h (entries 3–4).

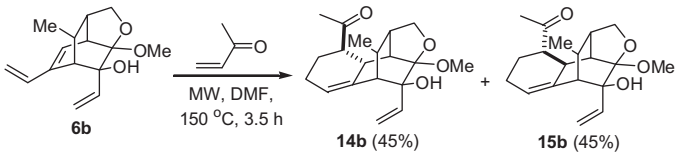
Methyl vinyl ketone, a monosubstituted dienophile, was also examined in the Diels–Alder reaction. As shown in Table 1, excellent stereoselectivity was observed in the Diels–Alder reactions of 1,3-dienes **6b**,**c** (R^1 = Me) with symmetric dienophiles. Thus, **6b** was reacted with methyl vinyl ketone at room temperature; the reaction was sluggish, however microwave conditions significantly accelerated the reaction, and the two diastereomers **14b** and **15b** were obtained in 1:1 ratio (Scheme 3). Surprisingly, in contrast to maleic anhydride and *N*-phenylmaleimide, methyl vinyl ketone showed poor stereoselectivity but excellent regioselectivity in the Diels–Alder reaction with **6b**. The different Diels–Alder adducts, thus obtained, were characterized structurally using IR, NMR, and mass spectral analyses. The stereostructures of **10a**, **11a**, **13a**, **14b**, and **15b** were confirmed by single-crystal X-ray diffraction analyses.[14]

Table 1
Intermolecular Diels-Alder reactions of tricyclic 1,3-dienes **6**



Entry	Diene	Dienophile	Time	Product/yield (%)
1	**6a**	X = O	6 d	**8a**/57 + **10a**/38
2	**6a**	X = NPh	8 d	**9a**/38 + **11a**/38 + **13a**/19
3	**6b**	X = O	7 d (10 h)[a]	**8b**/95 (95)[a]
4	**6b**	X = NPh	10 d (12 h)[a]	**9b**/88 (89)[a]
5	**6c**	X = O	7 d	**8c**/95
6	**6c**	X = NPh	10 d	**9c**/88

[a] Microwave irradiation at 80 °C.



Scheme 3. Intermolecular Diels–Alder reaction of tricyclic 1,3-diene **6b** and methyl vinyl ketone.

With 1,5-dienes **8–15** in hand, we explored suitable conditions for the oxy-Cope rearrangement. First, we used potassium bis(trimethylsilyl)amide (KHMDS) in the presence of 18-crown-6 in THF. Unfortunately, the expected anionic oxy-Cope rearrangement products were not observed at either 0 °C or at the reflux temperature; instead, complex mixtures were formed. The exceptions were two 1,5-dienes: (i) **14b** which gave **18b**, and (ii) **15b**, for which the starting material was recovered. The unexpected product **18b** was formed from **14b** via a tandem anionic oxy-Cope/aldol reaction (Scheme 4).

In order to prevent the undesired intramolecular aldol reaction after the anionic oxy-Cope rearrangement of **14b**, the ketone in **14b** was converted to ketal **19b**.[15] This product was then treated with KHMDS and 18-crown-6 in refluxing THF. The resulting anionic oxy-Cope rearrangement product **20b** was obtained in 85% yield, and it possessed the tricyclic core of vinigrol (Scheme 5). Thus, we believe that our strategy has potential use in the synthesis of vinigrol analogues.

We reasoned that the reaction of 1,5-dienes **8–13** under basic conditions resulted in complex mixtures because of the anhydride and imide moieties. Thus, we turned our attention to the use of neutral conditions. Accordingly, 1,5-diene **8a** was heated to 220 °C in a sealed tube in toluene, and the unexpected polycyclic compound **23a** was obtained in 74% yield (Table 2, entry 1). This polycyclic compound was formed via the sequential oxy-Cope/ene rearrangement reaction[16] of 1,5-diene **8a**. Other 1,5-dienes—**8b**, **9a–b**, **14b**, and **19b**—gave similar results under identical conditions (Table 2, Scheme 6). To our surprise, 1,5-dienes **8c** and **9c**, which cannot undergo the ene reaction after the oxy-Cope