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Stereocontrolled Syntheses of *cis*-Decalin and Bicyclo[4.2.2]dec-7-en-4-one Derivatives from 2-Methoxyphenols. First Examples of Two-Carbon Ring Expansion of 2-Vinylbicyclo[2.2.2]octenols

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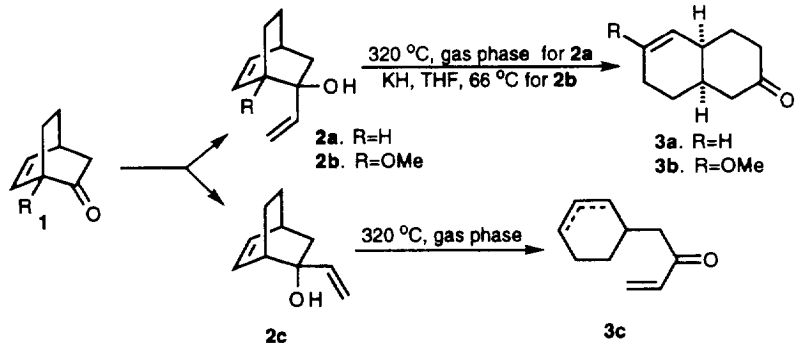
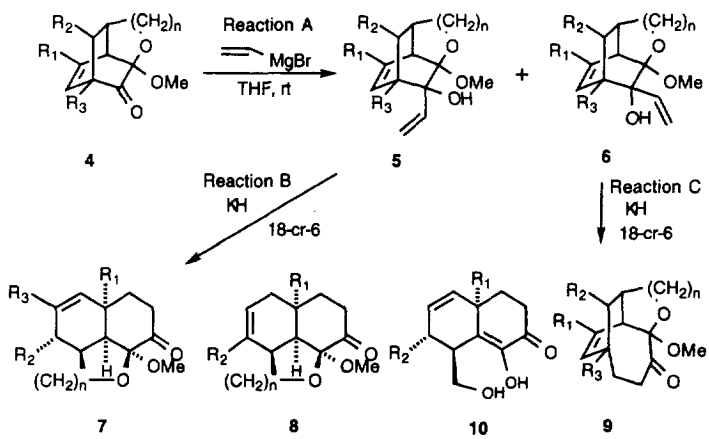
Abstract: Efficient and stereocontrolled four-step preparations of *cis*-decalin and bicyclo[4.2.2]dec-7-en-4-one derivatives from commercially available 2-methoxyphenols are described.

The utilization of the anionic oxy-Cope rearrangements in the syntheses of the polycyclic and medium ring systems present in natural products[1] has received considerable attention because of its exceptional flexibility and broad applicability.[2] In the cases of 2-vinylbicyclo[2.2.2]oct-5-en-2-ols (scheme 1), *syn*-isomer **2a,b** were converted smoothly into bicyclo[4.4.0]octenone **3a,b** *via* thermal[3] or base-catalyzed[4] oxy-Cope rearrangements, whereas *anti*-isomer **2c** failed to undergo rearrangement under base-catalyzed conditions, however gave cyclohexene derivatives **3c** upon gas phase pyrolysis.[3] We wish to report here our studies on [3,3] and [1,3] anionic rearrangements of 2-vinylbicyclo[2.2.2]oct-5-en-2-ols **5a-k** and **6a-k** with dialkoxy substitutents at C-3 position that provide a facile streocontrolled entry to *cis*-decalins and bicyclo[4.2.2]dec-7-en-4-ones from 2-methoxyphenols.



Scheme 1

Addition of vinylmagnesium bromide to tricyclic β,γ-enones[5] **4a-k** (Reaction A), prepared from 2-methoxyphenols *via* a two-step (oxidation with iodobenzene diacetate and intramolecular Diels-Alder reaction) process in one flask, gave the diastereomeric alcohols **5a-k** and **6a-k**, which were readily separated by chromatography. The results are given in Table 1.[6] Exposure of alcohols **5a-i** to excess KH (5 equiv.) in the presence of 18-crown-6 (3 equiv.) (reaction B) afforded the [3,3]-rearrangement products **7a-e**, **8f**, and **7g-i**; **8f** was generated *via* double bond migration of the intial product **7f**. As shown in Table 1, although qualitatively, the substituent and ring size could affect the reactivities. In the cases of **5a-c** (R_1=H), the reaction underwent smoothly at room temperature. But when the R_1 was methyl group (**5d-f**), the reaction temperature had to be raised to 80 °C, and for **5g** (n=2) even more drastic condition (110 °C) was required. A methoxy group at C-1 bridgehead facilitated the reaction (rt); these results were in accordance with that of Evans and Golob.[4] On the other hand, the alcohols **6a-i** under similar conditions (Reaction C) gave rise to the unexpected ring-enlarged [1,3]-rearrangement products **9a-i**. When the R_1 substituent was methoxycarbonyl group, the reaction appeared to be more complex. Treatment of the *syn* (**5j,k**) and *anti* (**6j,k**) alcohols with stoichiometric amounts of potassium hydride (1.1 equiv. of KH, THF, rt) produced both the [3,3] sigmatropic rearrangement products **7j,k** and ring-enlarged products **9j,k**. In contrast, heating **5k** (in xylene at 250 °C) in a sealed tube gave only compound **10k** (72%) which was presumably derived from **7k** upon hydrolysis by trace water, whereas the *anti* alcohol, **6k**, when subjected to same conditions, gave only ring enlarged product **9k** (61%).



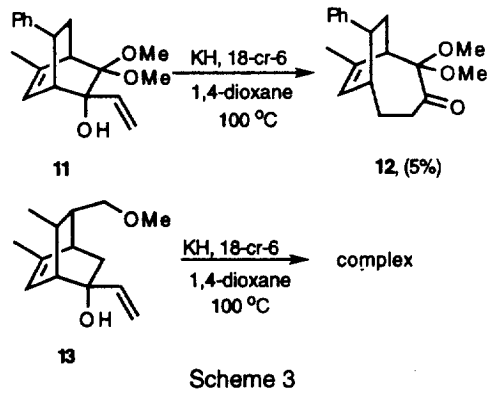
a R_1=H, R_2=H, R_3=H, n=1
b R_1=H, R_2=Me, R_3=H, n=1
c R_1=H, R_2=Ph, R_3=H, n=1
d R_1=Me, R_2=H, R_3=H, n=1
e R_1=Me, R_2=Me, R_3=H, n=1
f R_1=Me, R_2=Ph, R_3=H, n=1
g R_1=Me, R_2=H, R_3=H, n=2
h R_1=Me, R_2=H, R_3=OMe, n=1
i R_1=Me, R_2=Ph, R_3=OMe, n=1
j R_1=CO_2Me, R_2=H, R_3=H, n=1
k R_1=CO_2Me, R_2=Me, R_3=H, n=1

Scheme 2

Table 1 Yields of Products of Reactions A, B and C

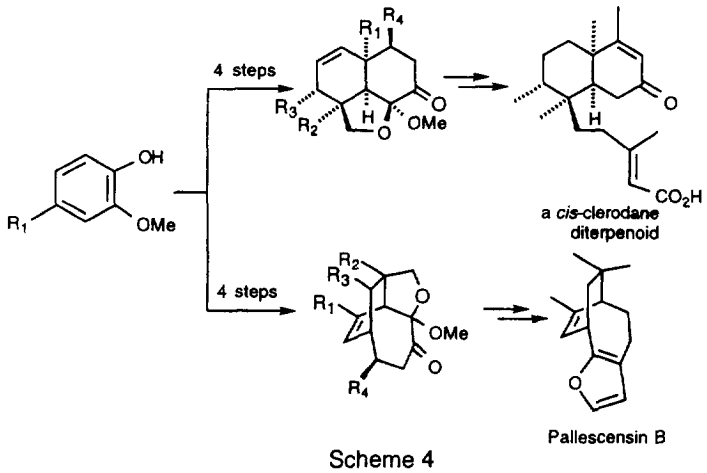
Entry	Product of Reaction A	Reaction Condition for Reactions B and C	Product of Reaction B	Product of Reaction C
1	**5a** (35%); **6a** (47%)	THF, rt, 12h	**7a** (79%)	**9a** (76%)
2	**5b** (23%); **6b** (36%)	THF, rt, 12h	**7b** (87%)	**9b** (90%)
3	**5c** (50%); **6c** (34%)	THF, rt, 12h	**7c** (70%)	**9c** (88%)
4	**5d** (29%); **6d** (46%)	1,4-dioxane, 80 °C, 50min	**7d** (82%)	**9d** (73%)
5	**5e** (30%); **6e** (51%)	1,4-dioxane, 80 °C, 50min	**7e** (83%)	**9e** (81%)
6	**5f** (28%); **6f** (45%)	1,4-dioxane, 80 °C, 50min	**8f** (63%)	**9f** (53%)
7	**5g** (50%); **6g** (25%)	1,4-dioxane, 110 °C, 50min	**7g** (81%)	**9g** (70%)
8	**5h** (18%); **6h** (45%)	THF, rt, 5h	**7h** (72%)	**9h** (77%)
9	**5i** (23%); **6i** (63%)	THF, rt, 30 min	**7i** (67%)	**9i** (90%)
10	**5j** (43%); **6j** (22%)	THF, rt, 1h then CH_2N_2	**7j** (64%); **9j** (8%)	**7j** (46%); **9j** (23%)
11	**5k** (54%); **6k** (16%)	THF, rt, 1h then CH_2N_2	**7k**(57%); **9k** (7%)	**7k** (41%); **9k** (20%)

In order to probe the role of the dialkoxy group at C-3 position, we have subjected the *anti*-alcohol **11**[7] to similar rearrangement conditions to obtain only 5% of ring-enlarged [1,3] rearrangement product **12**. In contrast, under similar reaction conditions, *anti*-alcohol **13**,[7] which was no dialkoxy group at C-3 position, could not undergo this reaction. Thus the cyclic acetals at C-3 positions seemed to be essential for such rearrangements. The structures of the products were assigned from their IR, NMR and mass spectra. In addition, the structure of **9f** was substantiated by X-ray diffraction analysis.[8]



Scheme 3

In summary, we have developed an efficient and stereocontrolled four-step preparation of tricyclic dodecenone derivatives, which possess synthetic potential for *cis*-clerodane diterpenoids[9] and pallescensin B[10] from commercially available 2-methoxyphenols (scheme 4). Applications of these adducts in the synthesis of natural products are under active investigation.



Scheme 4

Acknowledgment:

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6. The reaction conditions have not yet been optimized to increase stereoselectivities.
7. Both the *syn* isomers of **11** and **13** underwent [3,3] anionic oxy-Cope rearrangement.
8. The result will be published in a full paper in the future. We thank professor Shie-Ming Peng and Mr. Gene-Hsiang Lee for the X-ray diffraction study.
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