Pergamon

Tetrahedron Letters 40 (1999) 1941–1944

TETRAHEDRON
LETTERS

# Synthesis of longithorone B, a sixteen-membered farnesylated *p*-benzoquinone[1]

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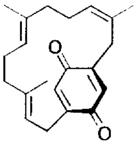
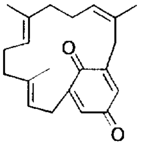
Received 16 November 1998; accepted 28 December 1998

**Abstract**: The intramolecular coupling reactions at the C-1 position of the 10Z-farnesyl moiety appended at the 2'-position of 4'-methoxy phenol derivatives were examined with the aid of $Hf(OTf)_4$ and $LiClO_4$. When the phenol was protected with a TBDMS group, meta coupling predominated while para coupling occurred efficiently when protected with a pivaloyl group. The para-coupled product was transformed to longithorone B, recently isolated from a tunicate. © 1999 Elsevier Science Ltd. All rights reserved.

Recently, a group of farnesylated quinones featuring new macrocyclic skeletons has been isolated from a tunicate, *Aplidium longithorax* by Schmitz and his coworkers.[2] Among the quinones characterized, longithorone B (**1**) is a representative compound containing a 16-membered carbocycle comprised of benzoquinone bridged across the para position by a farnesyl unit having two trans and one cis double bonds. The unique structural features of **1**, which is shown to have an atropisomerism, prompted us to explore an efficient synthetic route to longithorone B. Here we report the preparation of the compounds corresponding to **1** and its position isomer, **2** in *dl*-forms.



**1**



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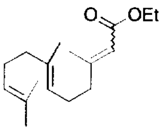
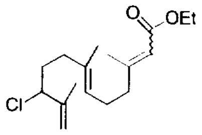


**3**



**4a 2E**
**4b 2Z**

An 8:1 mixture of ethyl farnesate (**3**) was selected as our starting material, which was prepared by Horner-Emmons reaction of *trans* geranyl acetone with diethyl phosphonoacetate and NaH (80% yield). By treatment of **3** with $SO_2Cl_2$ and $Na_2CO_3$,[3] the terminal double bond was selectively chlorinated to give an 8:1 mixture of **4a** and **4b**[4] in 95% yield, which was separated easily by usual silica gel column chromatography. The formation of phenyl ether proceeded smoothly when the allyl chloride (**4a**) was treated wtih *p*-$MeOC_6H_4OK$ in the presence of 18-crown-6, affording **5** in 62% yield (81% conversion yield).

In the Claisen rearrangement of **5**, the formation ratio of **6a** and **6b** depended largely on the reaction

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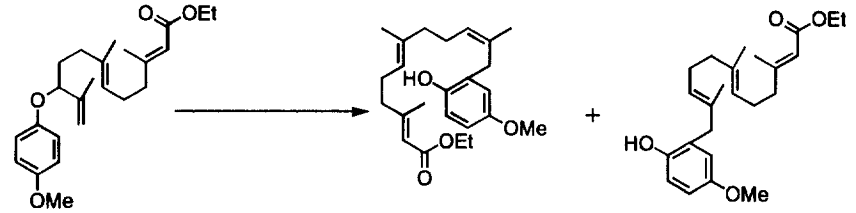
conditions as summarized in Table 1. Reaction of **5** in refluxing xylene for 23 h without any additive (run 1) resulted in a 1:4 ratio of **6a** and **6b** while exclusive formation of **6b** was observed when the Claisen rearrangement was carried out in the presence of $Na_2CO_3$ in refluxing xylene (run 2). These results suggested that the phenolic proton (M = *H*OPh) of the initially formed phenol derivative interacts with the oxygen atom of the phenyl ether (**5**) through the hydrogen bonding as depicted in figure1. In the transition states, the energy difference between Ts-E and Ts-Z may become smaller to permit the formation of the Z isomer (**6a**) in addition to the predominant E isomer (**6b**). In the presence of $Na_2CO_3$, the Claisen rearrangement proceeded exclusively through the energetically more stable Ts-E, in which no interaction between the oxygen atom of the phenyl ether and the phenoxide ion (M = $^-$OPh) may occur. The slower reaction in the presence of $Na_2CO_3$ as compared with that in run 1, in which the Claisen rearrangement is accelerated by the hydrogen bonding, may support the present suggestion.[5] Based on these considerations, the effects of other additives capable of interacting with the oxygen atom in the transition state were explored and we found that the Claisen rearrangement of the phenyl ether (**5**) proceeded in the presence of silica gel (run 3) or activated $Al_2O_3$ (run 4) in refluxing xylene. The latter conditions furnished a 4.3 : 1 mixture of **6a** and **6b** in 71% yield after heating for 36 h. In the transition state, the oxygen atom of the ether linkage may interact with the aluminum atom of $Al_2O_3$ to make the complexes, in which the amount of Ts-E decreases due to the repulsion between M ($Al_2O_3$) and the equatorial R group. The lack of such repulsion in Ts-Z may bring about the predominant formation of **6a**.[6] Both isomers (**6a** and **6b**) were separated by HPLC and the geometry of the double bonds in each compound was deduced from $^{13}C$ chemical shifts of the olefinic methyl groups.[7]



**5** **6a** **6b**

Table.1 Effect of reaction conditions on Claisen rearrangement of **5**

| Run | Additive | Solv. | Temp. (°C) | Time (h) | **5** : (**6a**+**6b**) (%) | **6a** : **6b** |
|---|---|---|---|---|---|---|
| 1 | - | xylene | 140 | 23 | 28 : 72 | 1 : 4 |
| 2 | $Na_2CO_3$ | xylene | 140 | 24 | 51 : 49 | 0 : 1 |
| 3 | $SiO_2$ | - | 100 | 24 | 43 : 57 | 3 : 1 |
| 4 | $Al_2O_3$ | xylene | 140 | 36 | 29 : 71 | 4.3 : 1 |

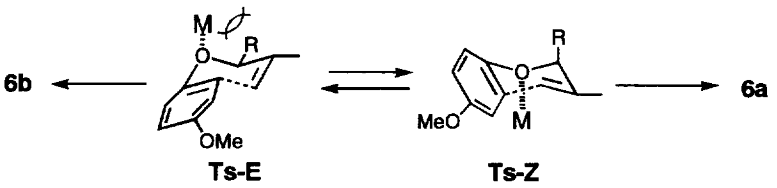
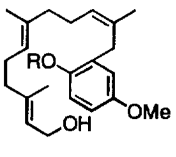


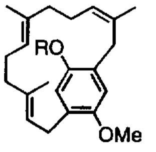
Figure 1 Possible transition states of Claisen rearrangement

The intramolecular coupling reaction was examined using three types of protected allyl alcohols (**7a**, **7b** and **7c**), which were prepared as follows. Protection of **6a** with TBDMS (TBDMSCl, imidazole, DMAP in DMF) or Bn (BnBr, NaH, TBAI in THF) groups followed by DIBAL-H reduction afforded the allyl alcohols **7a** (73 %) and **7b** (81 %), respectively. The pivalate (**7c**) was directly prepared from **7a** in 51% yield by treatment with PivCl and TBAF in THF.[8] When **7a** was treated with Hf(OTf)$_4$ in the presence of LiClO$_4$ in CH$_2$Cl$_2$,[9] a mixture of **8a**, **8b**, and unidentified products (R = TBDMS) were obtained. Due to the difficulty of separation, the mixture was converted to the corresponding pivalates (**8a** and **8b**, R = Piv), from which the pivalate (**8b**) was isolated in 64% yield by HPLC separation.[12] When the pivalate (**7c**) was subjected to the coupling reaction under the same conditions, **8a** (R = Piv) was isolated in 78 % yield.[13] The pivalate (**8a**, R = Piv) was transformed to **1** by the sequential reactions of hydrolysis with KOH/MeOH followed by CAN oxidation in the presence of C$_5$H$_3$NO(CO$_2$H)$_2$ in 58% yield.[14] The meta-coupled product (**8b**) was similarly transformed to the quinone (**2**). The predominant meta coupling of the TBDMS ether (**7a**) may be caused by the electron-donating nature of the TBDMS group overcoming its steric hindrance. In the meantime, steric hindrance as well as electron-withdrawing nature of pivaloyl group of **7c** controlled the coupling reaction, leading to the para-coupled **8a** as the major product. The ortho coupling product corresponding to **8c** was not characterized from either **7a** or **7c**.[15] When the sequential reactions were applied to benzyl ether (**7b**), a complex mixture was detected without formation of any predominant product, suggesting that the benzyl group, in addition to the *p*-hydroquinone skeleton, underwent the coupling reaction.

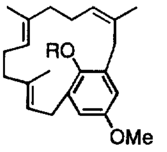
The $^1$H and $^{13}$C chemical shifts and the coupling modes of the synthesized product (**1**) agree approximately with the reported values.[16] Thus, we have developed an efficient route for the construction of the macrocyclic farnesylated quinone derivatives (**1** and **2**).



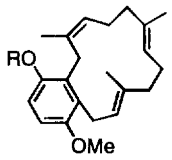
**7a** R=TBDMS
**7b** R=Bn
**7c** R=COCMe$_3$



**8a**



**8b**



**8c**

## Footnotes and References

* E-mail: tkato@ch.kagu.sut.ac.jp (t.kato).

1. This constitutes part 58 of the series of cyclization of polyenes. Part 57, T. Kato, M. Tanaka, M. Hoshikawa and M. Yagi, *Tetrahedron Lett.*, **1998**, *39*, 7553-7556.
2. X. Fu, M. B. Hossain, F. J. Schmitz, and D. van der Helm, *J. Org. Chem.*, **1997**, *62*, 3810-3819.
3. a) Y. Masaki, K. Hashimoto, K. Sakura, and K. Kaji, *Chem Pharm. Bull. Jpn.*, **1984**, *32*, 3952-3958.
   b) M. Bulliard, G. Balme, and J. Gore, *Tetrahedron Lett.*, **1989**, *30*, 5767-5770.
4. The $^{13}$C chemical shifts of C$_3$-methyls (CDCl$_3$); **4a** 16.7 and **4b** 26.3 ppm, respectively.
5. It needed 90 h for the completion of the reaction of run 2.
6. The effect of other Lewis acids is being examined.

7. The $^{13}$C chemical shifts of olefinic methyls ($CDCl_3$); **6a** 16.7, 16.8, and 26.3, and **6b** 16.5, 16.8, and 16.9 ppm, respectively.
8. D. G. Saunders, *Synthesis*, **1988**, 377-379. The formation conditions of **7c** was not optimized.
9. Kobayashi et al succeeded in the intermolecular coupling reaction of allyl chlorides with various types of aromatics with $Hf(OTf)_4$ and $LiClO_4$.[10] In our compound, however, the allyl chloride (**7b**, Cl instead of OH), prepared from **7b** in 90 % yield by the action of MsCl, $Et_3N$, LiCl, 12-crown-4 in $CH_2Cl_2$, afforded no coupling product under these conditions. Fukuzawa et al[11] carried out the intermolecular coupling reactions with $Sc(OTf)_3$ using allyl alcohols and aromatics. In our case, however, application of $Sc(OTf)_3$ to **7b** gave no satisfactory results.

   The authors are indebted to Professor S. Kobayashi for his kind gift of qualified $Hf(OTf)_4$.
10. a) I. Hachiya, M. Moriwaki, and S. Kobayashi, *Tetrahedron Lett.*, **1995**, *36*, 409-412.
    b) I. Hachiya, M. Moriwaki, and S. Kobayashi, *Bull. Chem. Soc. Jpn.*, **1995**, *68*, 2053-2060.
11. T. Tsuchimoto, K. Tobita, T. Hiyama, and S. Fukuzawa, *J. Org. Chem.*, **1997**, *62*, 6997-7005.
12. After deprotection of TBDMS group with TBAF in THF (90% yield), the resultant phenolic mixture was treated with PivCl, pyr., DMAP in $CH_2Cl_2$ to give the pivalates. The HPLC analysis showed an 8 : 1 ratio of **8b** and **8a** (R = Piv).
13. The HPLC analysis indicated a 6 : 1 ratio of **8a** and **8b** (R = Piv).
14. As reported by Schmitz et al,[2] the quinones (**1** and **2**) were fairly unstable, particularly in oxygen atmosphere.
15. The preliminary MM2 calculation shows the molecular energies of **1**, **2** and quinone derived from **8c** are 15.34, 17.06, and 23.12 kcal/mol, respectively, reflecting the sterically crowded nature of **8c**.
16. Some efforts to resolve the *dl*-form into the optically active compounds were unsuccessful using chiral columns. The synthetic compound (**1**) has the following physical data. $^1$H-NMR(500MHz, $C_6D_6$); 6.37(t, *J*=1.5Hz, Δ-0.08; H-21), 6.23(d, *J*=1.0Hz, Δ0; H-18), 5.45(t, *J*=7.5Hz, Δ+0.05; H-2), 5.18(dm, *J*=9.5Hz, Δ+0.08; H-10), 4.71(br m, Δ-0.02; H-6), 3.38(dd, *J*=18.0, 1.5Hz, Δ-0.08; H-12), 3.34(dd, *J*=10.5, 7.5Hz, Δ+0.01; H-1), 2.44(dd, *J*=11.5, 9.5Hz, Δ-0.01; H-1), 2.42(dd, *J*=17.9, 1.2Hz, Δ-0.02; H-12), 1.97(m, Δ+0.03; H-4, H-5), 1.87(m, Δ-0.02; H-9a), 1.86(m, Δ-0.01; H-8a), 1.71(m, Δ-0.02; H-8b), 1.64(s, Δ+0.01; H-15), 1.54(s, Δ+0.16; H-14), 1.45(m, Δ0; H-9b), 1.38(s, Δ+0.05; H-13) $^{13}$C-NMR(125MHz, $C_6D_6$); 187.2(s, Δ-0.9; C-20), 187.1(s, Δ-0.7; C-17), 147.3(s, Δ-1.0; C-16), 147.3(s, Δ-0.5; C-19), 140.1(s, Δ-1.6; C-3), 135.0(s, Δ-0.2; C-7), 132.5(d, Δ+0.1; C-21), 130.3(s, Δ-0.6; C-11), 129.7(d, Δ-0.5; C-18), 128.3(d, Δ+0.9; C-10), 123.2(d, Δ+0.6; C-6), 121.3(d, Δ-0.8; C-2), 39.3(t, Δ-0.2; C-8), 38.4(t, Δ-0.6; C-4), 31.8(t, Δ-0.3; C-12), 29.5(t, Δ+0.4; C-11), 28.3(t, Δ-0.9; C-9), 26.2(q, Δ-0.3; C-15), 24.7(t, Δ+0.6; C-5), 16.1(q, Δ+0.5; C-14), 14.4(q, Δ-0.2; C-13).

    The Δ values in the above chemical shifts are the deviation of the synthetic compound (**1**) from the reported values.[2] Some of the chemical shifts in both $^1$H- and $^{13}$C-NMR spectra are obviously inconsistent beyond experimental deviation. The chemical shifts of $^1$H and $^{13}$C NMR spectra of the synthetic compound (**1**) were almost same when measured under two different concentrations in 0.5 ml $C_6D_6$ solutions, the sample being 7 mg and 2 mg, respectively. We have independently carried out the NMR analysis of our synthetic compound (**1**) using H-H COSY, C-H COSY and NOESY spectra, leading the synthetic compound to the several structures including the formula (**1**).

    At present, the reason of the inconsistency remains obscure.