Lewis-Acid-Assisted "Tandem Claisen Rearrangement": Application to the Synthesis of a New Type of Macrocycle Containing Phenolic Moieties

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Tandem Claisen rearrangement promoted by Et_2AlCl and 2-methyl-2-butene has produced better results than thermal rearrangement at synthesizing a new type of macrocycles containing phenolic moieties, from the corresponding macrocyclic polyether compound in a dramatically fast reaction with a good yield under mild conditions.

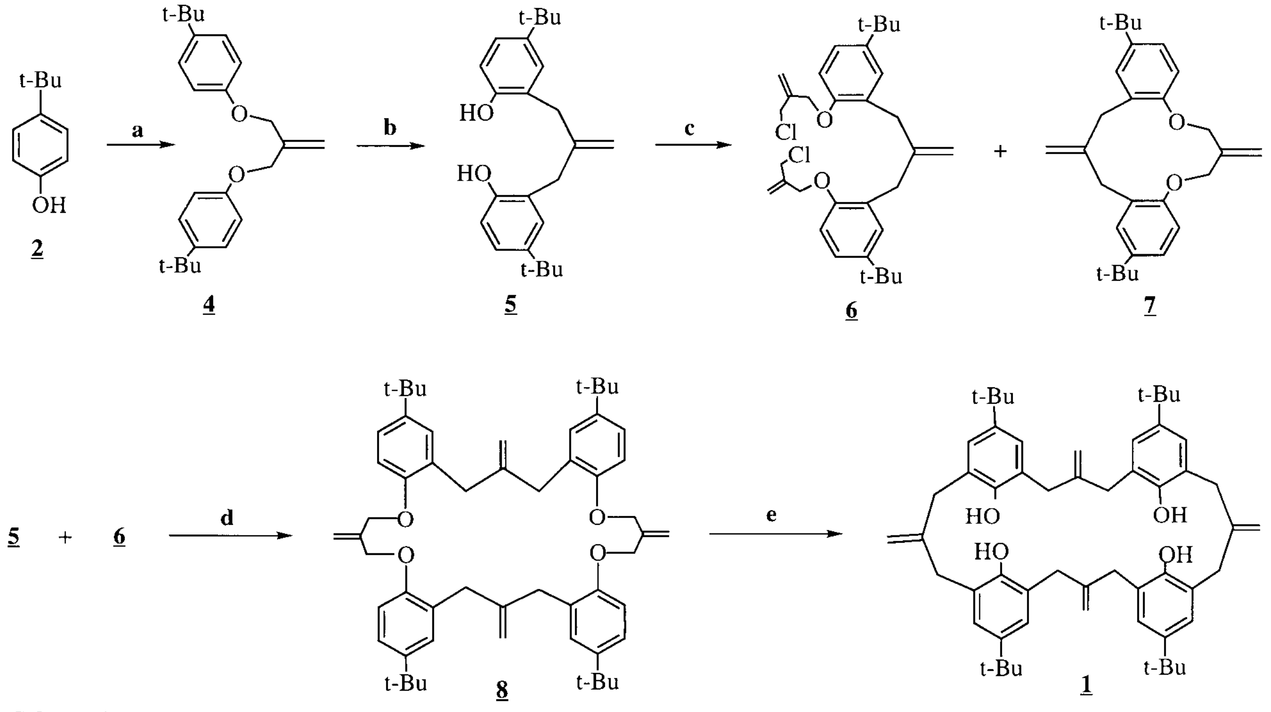
The aromatic Claisen rearrangement[1,2] is a classic reaction for the formation of a phenolic group introduced to an allyl group at the *o*- or *p*-position. This reaction generally requires high temperature (~200 ℃) and several hours' reaction time. Recently, we reported "tandem Claisen rearrangement", in which it is possible to form two new C–C bonds in only one step,[3] and successfully used it to synthesize some crownophanes containing *two* phenolic moieties.[4]

In studies of new potential host molecules and supramolecular building blocks[5] such as calixarenes,[6-8] calixresorcarenes[9,10] and calixnaphthalenes,[11,12] this tandem Claisen rearrangement could become a powerful and attractive tool for preparing host molecules. However, thermal rearrangement is unsuitable for constructing more complicated macrocyclic compounds containing either thermally unstable functional groups or chiral groups. We report in this paper a new synthetic method using Et_2AlCl and 2-methyl-2-butene under mild conditions to promote the tandem Claisen rearrangement instead of the thermal reaction.

We attempted to synthesize a new type of macrocycles **1**, with *four* phenolic hydroxyl groups, from the corresponding macrocyclic polyether **8**. Compound **8** was synthesized as shown in Scheme 1. Compound **4** was readily prepared from *tert*-butylphenol (**2**) and 3-chloro-2-chloromethyl-1-propene (**3**) in the usual manner. The key compound **5**[13] was prepared from **4** by pyrolysis in 61% yield. Compound **6** was prepared from **5** and excess **3**, together with cyclic compound **7** as a by-product. The 24-member macrocyclic polyether **8**[13] was synthesized at high dilution from 1:1 reaction of **5** with **6** in 50% yield.

Thermal rearrangement of **8** did not proceed in decahydronaphthalene (decalin; *trans* and *cis* mixture, bp 189-191℃) at refluxing temperature under a nitrogen atmosphere as reported.[3,4] It is reported that some Lewis acids proceed Claisen rearrangements under mild conditions.[2,14] Thus, the conversion of **8** into **1** was achieved in the presence of Et_2AlCl to give only 4% of **1**.

As the yields of rearrangements were so low, we tried to improve the above method. Considering that the terminal olefins of **8** and **1** might be labile[15] to Lewis acids, addition of large



Scheme 1. Reagents and Conditions: (a) NaH, DMF, 3-chloro-2-chloromethyl-1-propene (**3**, 0.47mol eq. of **2**) (97%); (b) decahydronaphthalene (decalin), reflux, 8h (61%) ; (c) NaH, DMF, **3** (6 mol eq. of **5**) (**6**; 45%, **7**; 37%); (d) NaH, DMF (50%) ; (e) Et_2AlCl, 2-methyl-2-butene (46%).

amount of 2-methyl-2-butene resulted in the formation of 24-membered macrocyclic compound **1**[13] as a main product at room temperature within 10 min (46%). Furthermore, conversion of **4** to **5** was also successfully performed using the above method. Addition of Et_2AlCl alone at room temperature gave a yield of 86% of **5** after only 10 min, much better than the 61% yield by the much longer thermal reaction. Addition of a large amount of 2-methyl-2-butene with Et_2AlCl also gave a good result (81%). The yields and reaction rates have been dramatically improved under these conditions.

The structure of **1** was characterized by ^{1}H-NMR, mass spectroscopy, and so on. In the ^{1}H-NMR spectrum of **1**, all signals showed singlet peaks.[13] In the FAB mass spectrum, the molecular weight of **1** was confirmed to be the same as the starting material **8**. From these spectroscopic results, it was concluded that **1** was produced from **8** by the successive four times of Claisen rearrangement.

In summary, we developed a new strategy for the tandem Claisen rearrangement by using Et_2AlCl and 2-methyl-2-butene under mild conditions. This method could have wide application in the synthesis of novel macrocyclic calixarene analogs and related compounds.

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13 **5**: ^{1}H-NMR (400 MHz, $CDCl_3$) δ 2.11 (s,*tert*-butyl), 4.24 (s, Ar-CH_2–C(=CH_2)–), 5.69 (s, Ar-CH_2–C(=CH_2)–), 7.5–8.0 (m, aromatics). Elemental analysis calculated for $C_{24}H_{32}O_2$: C, 81.77; H, 9.15; found: C, 81.80; H, 9.28.
8: ^{1}H-NMR (300 MHz, $CDCl_3$) δ 3.40 (s, Ar-CH_2–C(=CH_2)–), 4.36 (s, O–CH_2–C(=CH_2)–), 4.61 (s, Ar-CH_2C(=CH_2)–), 5.13 (s, –O–CH_2C(=CH_2)–), 6.6-7.2 (m, aromatics). Elemental analysis calculated for $C_{56}H_{72}O_4 \cdot 0.5H_2O$: C, 82.21; H, 8.99; found: C, 82.42; H, 9.25. FAB MS (positive mode) m/z 808.
1: m.p. 222–223 ℃, ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.29 (s,*tert*-butyl), 3.36 (s, Ar-CH_2–C(=C)–), 4.70 (s, C=CH_2), 7.01 (s, aromatics). Elemental analysis calcd for $C_{56}H_{72}O_4 \cdot 0.5H_2O$: C, 82.21; H, 8.99; found: C, 82.50; H, 8.79. FAB MS (positive mode) m/z 808.

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