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Exploiting Quadrupolar Interactions in the Synthesis of the Macrocyclic Portion of Longithorone C

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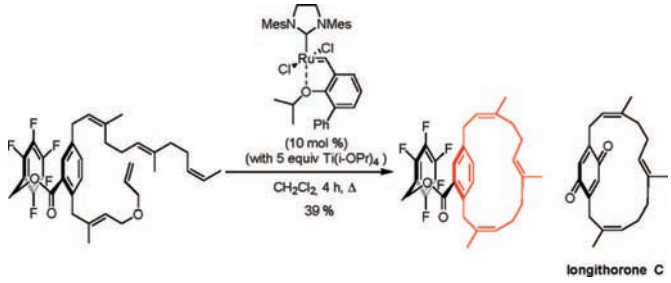
ABSTRACT



2,3,4,5,6-Pentafluorobenzyl and 3,5-bistrifluoromethylbenzyl ester auxiliaries can enable difficult macrocyclizations to afford rigid all-carbon paracyclophanes. The effectiveness of these auxiliaries has been demonstrated in preparing the carbon skeleton of the macrocyclic natural product longithorone C.

Longithorone C, **1**, is a farnesylated quinone and a member of the longithorone family of natural products isolated in 1999 by Schmitz and co-workers from the marine tunicate Aplodium longithorax.[1] Longithorone C, like most members of the family, possesses a macrocyclic [12]paracyclophane skeleton (Figure 1). The macrocycle, which resembles a *cis*-farnesol unit wrapped about a quinone core, exhibits restricted rotation which imparts an element of planar chirality to the structure.[1a] Although no biological activity for longithorone C has been reported, longithorone A has been shown to display cytotoxicity against P388 murine leukemia cells (IC_{50} ~10 μg/mL) and longithorone J has displayed minimal activity in some human cell lines.[2] To demonstrate the rigidity of the skeleton of longithorone C, Schmitz and co-workers refluxed **1** in toluene for 7 days. Some degradation was observed, but the optical rotation remained unchanged.[1a] Few synthetic studies directed toward the synthesis of these macrocyclic natural products have been reported, perhaps denoting the significant synthetic challenge associated with constructing the planar chiral carbon skeleton.

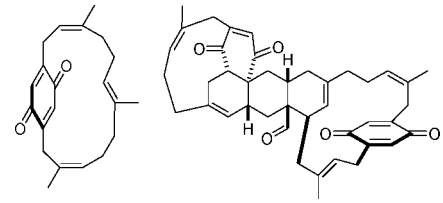


Figure 1. Representative members of the longithorone family of natural products.

(1) For the isolation of longithorone C, see:(a) Fu, X.; Hossain, M. B.; Schmitz, F. J.; van der Helm, D. *J. Org. Chem.* **1997**, *62*, 3810–3819For the isolation of other family members, see: (b) Fu, X.; Ferreira, M. L.; Schmitz, F. J. *J. Nat. Prod.* **1999**, *62*, 1306–1310. (c) Davis, R. A.; Carroll, A. R.; Quinn, R. J. *J. Nat. Prod.* **1999**, *62*, 158–160. (d) Fu, X.; Hossain, M. B.; van der Helm, D.; Schmitz, F. J. *J. Am. Chem. Soc.* **1994**, *116*, 12125–12126.

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Kato et al. have reported on the synthesis of longithorone B,[3] and Shair and co-workers have prepared a dimeric member of the longithorone family, longithorone A.[4] Herein, we report the first application of auxiliaries that engage in quadrupolar interactions in a total synthesis objective: the preparation of the macrocyclic portion of longithorone C.

The synthetic challenge of preparing extremely rigid macrocycles, such as the [12]paracyclophane core of longithorone C, in an efficient and asymmetric fashion encouraged us to develop new methods for enabling difficult macrocyclizations.[5] In 2006, we reported the use of perfluorobenzyl ester auxiliaries as conformational control elements for macrocyclizations using olefin metathesis.[6] In 2007, we reported that 3,5-bistrifluoromethylbenzyl ester auxiliaries were also effective and demonstrated their utility in en-yne metathesis macrocyclizations.[7] The fluoroarene auxiliaries are believed to engage in noncovalent interactions with the macrocyclic precursors, coercing the substrate into a conformation conducive to ring closure.[8]

Our initial studies into the use of these auxiliaries were conducted using substrates that contained oxygen atoms attached to the arene core that would become part of the formed macrocycle. We had reported that molecular modeling studies suggested that the fluorinated rings of the auxiliaries engage in 1p$-\pi$ interactions with the lone pairs of the oxygen atoms, resulting in a preference for a "closed" conformation that is conducive to ring closure.[6,9] The molecular modeling studies also suggested that the 3,5-bistrifluoromethylbenzyl ester auxiliaries would be more effective in these model substrates. This hypothesis was also proven correct through experiment.[7] However, in the absence of oxygen-containing substrates, like those found in the longithorone family of natural products, the molecular modeling studies suggested that the pentafluorobenzyl auxiliary would be more effective (Figure 2). Molecular modeling suggested that the ester **2** would prefer a conformation **2-S** in which a quadrupolar interaction would be present,

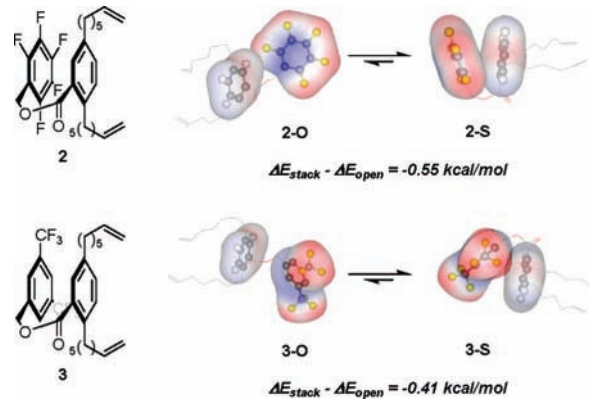

Figure 2. Comparison of pentafluorobenzyl and 3,5-bistrifluoromethylbenzyl ester auxiliaries by molecular modeling.

over the conformation **2-O** by -0.55 kcal/mol.[10] Similarly, the ester **3** would also prefer conformation **3-S** over **3-O**, however, only by -0.41 kcal/mol.[7] To investigate whether the molecular modeling studies could be used to predict which auxiliaries would be more effective for a given substrate, we undertook the synthesis of the carbon skeleton of longithorone C to probe the efficiency of our auxiliaries and the results of the previous molecular modeling study.

Hence, the carbon skeleton of longithorone C, represented by **4** (Figure 3), could arise from a macrocyclic relay ring

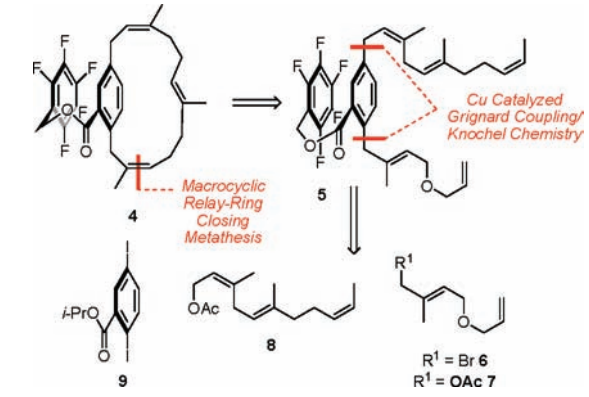

Figure 3. Retrosynthetic analysis of the carbon skeleton of longithorone C.

closing metathesis (RRCM)[11] of ester **5**. The preparation of the macrocyclization precursor **5** required the installation of two carbon$-$arene bonds. We envisioned preparing these bonds through copper-catalyzed Grignard reactions, made possible by combining recent methods for Mg$-$I exchanges

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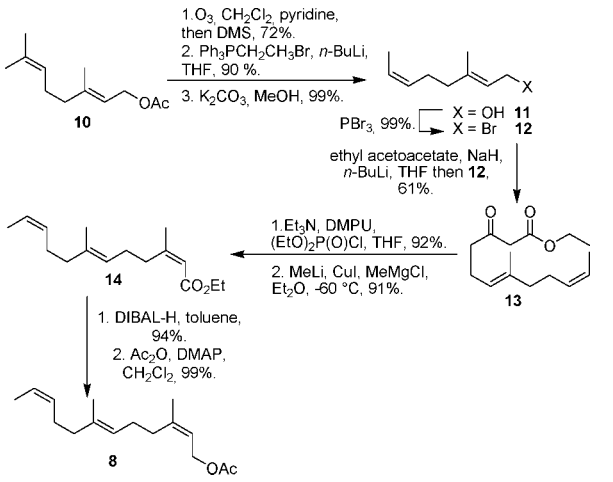
with copper-catalyzed allylic couplings. As such, the three key carbon subunits necessary are the allylic electrophiles **6**, **7**, and **8** and the iso-propyl ester **9**.

The preparation of side chains **6** and **7** has been previously reported.[12] The synthesis of side chain **8** (Scheme 1) was

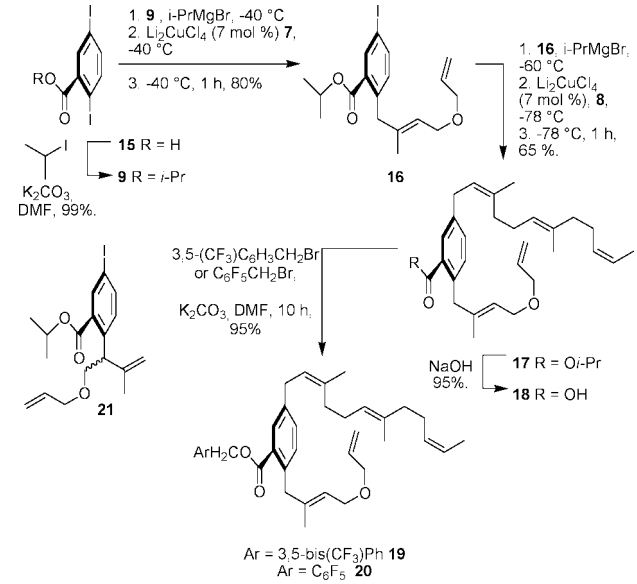
Scheme 1. Synthesis of Side Chain **8**



adapted from a previous report on the synthesis of *cis*-farnesol.[13] Geranyl acetate **10** underwent selective ozonolysis producing the corresponding aldehyde in good yield (72%). Wittig reaction using the ylide generated from *n*-BuLi and ethyltriphenylphosponium bromide followed by cleavage of the acetate protecting group afforded alcohol **11**. The alcohol **11** was subsequently converted to the corresponding bromide **12** in quantitative yield upon treatment with PBr_3. The bromide **12** was reacted with the Weiler dianion of ethyl acetoacetate to afford the β-ketoester **13**. The corresponding phosphonate was formed from the enolate of **13** generated from NEt_3 in the presence of DMPU in 69% yield. Upon treatment of the phosphonate with the cuprate generated from a mixture of MeMgCl, MeLi, and CuI, the ester **14** was obtained in 91% yield, and only the *cis*-isomer was observed by ^{1}H NMR. The reduction of **14** with DIBAL-H and subsequent acetylation afforded the side chain **8**.

The assembly of the carbon skeleton of longithorone C, **4**, began with the esterification of 2,5-diiodobenzoic acid with 2-iodopropanol. The ester **9** was used in the subsequent copper-catalyzed Grignard reactions. The corresponding methyl esters or pentafluorobenzyl esters of **15** were incompatible in the following Mg−I exchange reaction, where the esters normally underwent competitive nucleophilic attack.[14] Treatment of ester **9** with *i*-PrMgBr at −40 °C lead to complete Mg−I exchange in 10 min (Scheme 2). A solution

Scheme 2. Installation of Side Chains



of the newly formed Grignard reagent was added to a solution of acetate **7** and a catalytic amount of Li_2CuCl_4 catalyst.[15] Following workup, the iodide **16** was isolated in 80% yield. The configuration of the benzylic olefin in **16** was confirmed through an NOE study and was found to be identical to the configuration in acetate **7**. Other copper catalysts surveyed (CuI, CuCN·LiCl) resulted in very low yields (<20%) of **16**. The use of an allylic bromide **6** as a coupling partner resulted in a 45% isolated yield of the iodide **16**. All attempts to adjust the reaction conditions using bromide **6** as the coupling partner resulted in inseparable mixtures of **16** and **21**. Consequently, the acetate **8** was used in the second copper-catalyzed coupling reaction.

The Mg−I exchange in **16** was considerably more difficult. The absence of the ester functional group *ortho* to the iodide in **16** necessitated a larger quantity of *i*-PrMgBr and lower temperatures to effect a clean and quantitative Mg−I exchange. Following a similar protocol as described above, the acetate **8** was added, and the product **17** was isolated in 65% yield. It was necessary to keep the reaction mixture as concentrated as possible to maximize the yields. It should be noted that the use of *i*-PrMgCl·LiCl promoted an extremely rapid exchange; however, the yields of **17** were unexplicably low (<10%).

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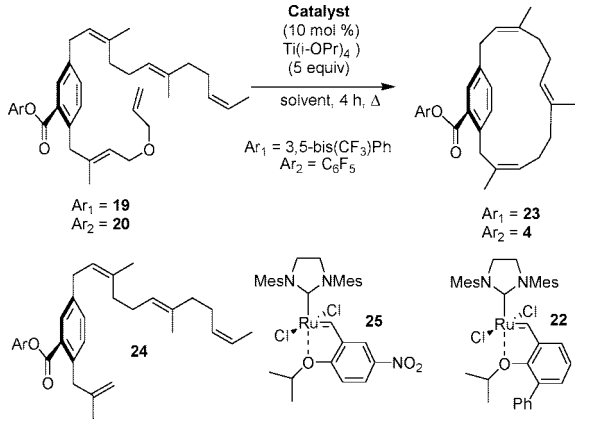
To investigate the macrocyclization with both the pentafluorobenzyl ester and 3,5-bistrifluoromethylbenzyl ester auxiliaries, the esters **19** and **20** were synthesized and their macrocyclization investigated using both the Grela catalyst **25**[16] and the Blechert catalyst **22**.[17] To construct the fluorinated esters, the iso-propyl ester **17** was first saponified using NaOH in refluxing MeOH/PhMe to yield the corresponding carboxylic acid **18** in 95% yield. Alkylation with the corresponding benzyl bromides afforded the esters **19** and **20** in excellent overall yields following purification by chromatography. Some decomposition of **20** was observed over time, and it was usually stored in frozen benzene at −18 °C.

With the two esters **19** and **20** in hand, their macrocyclization was investigated (Table 1). It should be noted that three structural features of **19** and **20** are essential for successful macrocyclization. First, the relay ring closing metathesis strategy was necessary, otherwise only dimerization of the starting material was observed. Second, esters **19** and **20** were prepared with a *cis*-olefin as the metathesis partner. If this olefin was substituted for a terminal olefin, only trace amounts of the desired macrocycle were obtained. Last, the use of any other ester other than the fluoroarenes discussed here resulted in the formation of only dimers and oligomers.

Table 1. Macrocyclization to Form the Carbon Skeleton of Longithorone C



substrate	cat.	solvent	yield (%)[a]
20	25	PhMe	32
20	22	CH_2Cl_2	37
19	25	PhMe	20
19	25	CH_2Cl_2	23

[a] Represents isolated yield after chromatography.

Treatment of the pentafluorophenyl benzyl ester **20** with catalyst **25** in PhMe afforded a 32% isolated yield of the rigid macrocycle **4**. Changing the solvent to CH_2Cl_2 and using the more reactive Blechert catalyst **22** afforded slightly higher yields of the corresponding macrocycle (37−40%). The ester **19** containing a bis-1,3-trifluoromethylbenzyl ester auxiliary did not afford higher yields than the corresponding pentafluorobenzyl ester **20**. Treatment of **19** with catalyst **25** in either CH_2Cl_2 or PhMe afforded 20−23% yields of the isolated macrocycle. In all cases, the reactions afforded **24** as the major product, where the relay ring closing metathesis side chain has been consumed but no productive macrocyclization has occurred. These results are in agreement with the molecular modeling results discussed earlier. The pentafluorobenzyl ester **2** was calculated to have only a slightly higher energetic preference for its "stacked" conformer **2-S** (∼0.1 kcal/mol) compared to the 3,5-bistrifluoromethylbenzyl ester. Although this represents a seemingly small energetic difference, it accounts for approximately 20% higher yields in the formation of macrocyclization products.

In summary, we have synthesized the highly rigid macrocyclic carbon skeleton of the natural product longithorone C. The synthesis of the carbon skeleton **4** highlights the effectiveness of quadrupolar interactions as synthetically useful noncovalent interactions capable of controlling the conformation of molecules for macrocyclization. The combination of Mg−I exchange and copper-catalyzed Grignard reactions allowed the stereocontrolled installation of the olefinic chains for macrocyclization. It is likely that this strategy would be of use in the preparation of other natural products. The success of these auxiliaries opens the way to the development of chiral gearing elements to induce atropisomerism.

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Supporting Information Available: Experimental procedures and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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