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Intramolecular Diels−Alder Reactions of Optically Active Allenic Ketones: Chirality Transfer in the Preparation of Substituted Oxa-Bridged Octalones

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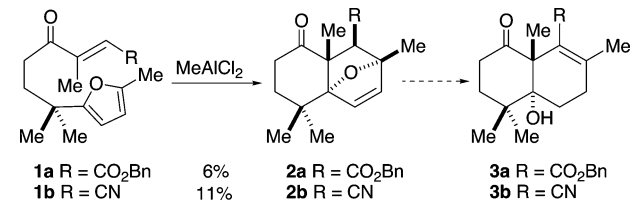
Since their first use in 1929,[1] furans have been employed often as dienes in Diels−Alder reactions.[2] Many groups[2b] have studied the intramolecular Diels−Alder reactions of furans (IMDAF) with various dienophiles since these reactions can generate in a single step with high stereoselectivity oxatricyclic rings, which are useful intermediates for organic synthesis.[3] For example, in the synthesis of the AB ring in arisugacin A, a potent inhibitor of acetylcholinesterase,[4] we examined the use of the IMDAF reaction to build the trans octalone system **3** with the two key AB ring stereocenters, namely the angular methyl and hydroxyl groups (Scheme 1).[5]

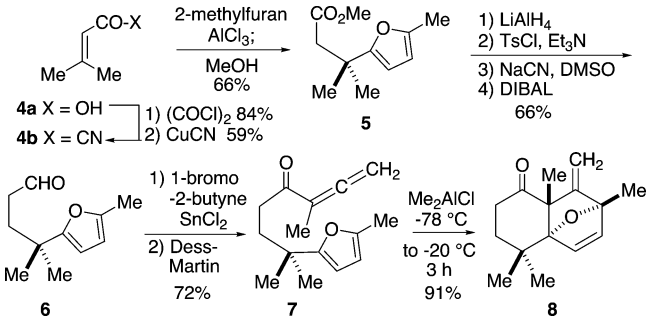
On the basis of previous work, in which we reported that IMDAF reactions of furan dienes with *gem*-dimethyl groups on the ester tether provide oxatricyclic compounds,[6] we initially attempted an IMDAF reaction of the furyl substituted ester and nitrile **1a** and **1b**. Although the IMDAF reactions of these substrates provided the desired Diels−Alder adducts **2a** and **2b** as single diastereomers, the yields were low, owing to a facile retro Diels−Alder reaction to reform the starting materials **1a** and **1b**. We argued that this was presumably due to the severe steric hindrance of the newly formed stereocenters in the products because less substituted systems have been reported to give high yields of similar products.[7] Consequently, we thought that using allenes in this Diels−Alder process would result in greatly reduced steric hindrance of the cycloadducts. Also, since allenes can be made in enantiopure form, we further hypothesized that the absolute stereochemistry of the derived cycloadducts could therefore be controlled. In this contribution, we report the IMDAF reactions of allenic ketones for the stereoselective synthesis of oxatricyclic ring systems, e.g., oxa-bridged octalones.

Although allenes are much more reactive than alkenes as dienophiles,[2b] their utilization as dienophiles in IMDAF reactions is relatively rare despite their exceptional reactivity.[8] Moreover, chirality transfer from optically active allenes to obtain optically pure adducts has not yet been examined. The furyl allenic ketone **7** was synthesized in nine steps from the acid **4a (**Scheme 2). The ester **5**, prepared by the procedure of Keay[7] via the Friedel−Crafts reaction of the acyl nitrile **4b** with 2-methylfuran, was converted in four steps to the aldehyde **6**. Addition of the organostannane derived from 1-bromo-2-butyne to the aldehyde **6**[9] and oxidation of the resulting mixture afforded the desired allenic ketone **7**. Heating the allenic ketone **7** in benzene or toluene for many hours gave no cycloadduct. Microwave heating of **7** in toluene at 160 °C produced the desired oxatricyclic compound **8** as a single diastereomer in 72% yield. Various Lewis acid-promoted reactions[10] of **7** were studied, with dimethylaluminum chloride being the best, giving exclusively the exo cycloadduct **8** in 91% yield. Thus, the allene dienophile greatly facilitates the desired cycloaddition with no starting material being recovered. To prove its structure, we converted **8** into the corresponding alcohol **9** by regioselective diimide reduction of the endocyclic alkene,[11] followed by stereoselective reduction using L-Selectride[12] to give the α-alcohol **9**

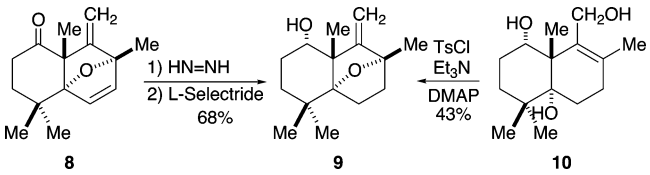
Scheme 1



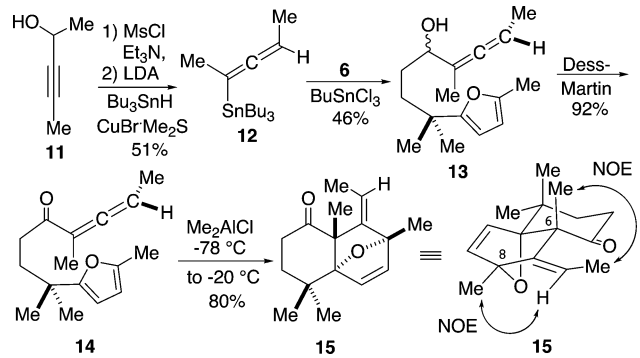
Scheme 2



Scheme 3



Scheme 4



(Scheme 3). The alcohol **9** was also prepared by an intramolecular S_N2'-type reaction of the known compound **10**,[5,13] which was used in the total synthesis of arisugacin A by Hsung.

Having successfully used an allene dienophile to effect the IMDAF, we next examined (Scheme 4) the cycloadditions of other precursors containing a terminal alkyl-substituted allene. Following the method of Marshall,[14] we prepared the allenyl-stannane **12** by the stannylcuprate S_N2' displacement of the propargylic mesylate,

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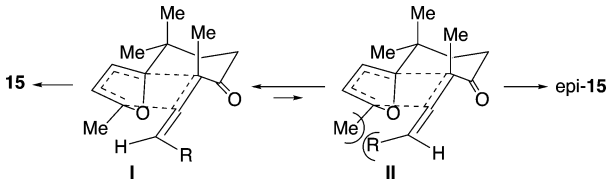
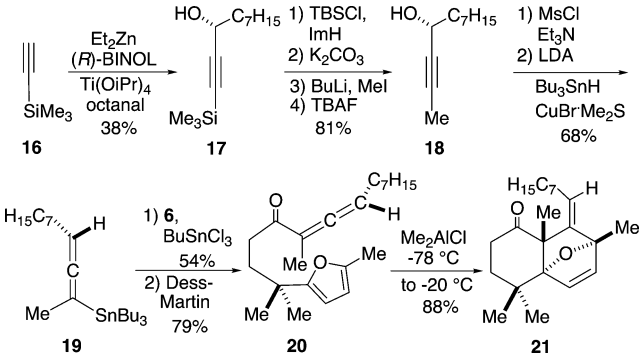
Scheme 5



Scheme 6



which was derived from 3-pentyn-2-ol **11**.[15] The addition of the allenylstannane **12** to the aldehyde **6** provided a mixture of the two diastereomeric allenes **13**, which was oxidized to the IMDAF substrate **14** in 92% yield. The methyl-substituted allenic ketone **14** was smoothly converted, in the presence of dimethylaluminum chloride, to the corresponding oxatricyclic compound **15** at −20 °C for 3 h in 80% yield. The *E* stereochemistry of the methyl group on the exocyclic alkene was determined by NOESY. The methyl group on the exocyclic alkene showed a strong NOE correlation with the C-6 methyl group as did the hydrogen with the C-8 methyl group. This stereochemical outcome can be explained by comparing the two possible exo transition states **I** and **II**. As shown in Scheme 5, the formation of the *E*-isomer **15** is due to the smaller steric interaction between the furan methyl group and terminal hydrogen on the allene in transition state **I** as compared to the greater interaction between the methyl and alkyl groups in **II**. This implies that if the allene were enantiomerically pure, its chirality could be easily transferred to the carbon framework of the cycloadducts and thereby generate these adducts in optically pure form.

To test this idea, we studied the practical synthesis of an optically active propargylic alcohol (Scheme 6). Instead of an optically active 3-pentyn-2-ol, we opted for (*R*)-(−)-2-undecyn-4-ol as the target because it is less volatile and easy to handle, and its spectroscopic data are known.[14a] On the basis of Pu's method,[16] TMS acetylene **16** was treated with diethylzinc, (*R*)-BINOL, and $Ti(OiPr)_4$, followed by addition of octanal to afford the propargylic alcohol **17** in 38% yield. The alcohol **17** was easily converted to the (*R*)-(−)-2-undecyn-4-ol **18** in 81% yield via a four-step sequence: alcohol protection, desilylation, methylation, and a second desilylation. The optical purity of **18** was determined to be 90% ee by ^{1}H NMR analysis of the corresponding (*S*)-*O*-acetyl mandelate.[17] This alcohol **18** was converted into the allenylstannane **19** which was coupled to the aldehyde **6**, and the alcohol was oxidized to give the IMDAF substrate **20**. Treatment of **20** with dimethylaluminum chloride gave the Diels−Alder adduct **21** as a single diastereomer in 88% yield. Thus, complete transfer of the allene chirality of **20** to the oxatricyclic framework in **21** was achieved.

In summary, we have described a stereoselective synthesis of oxatricyclic compounds using IMDAF reactions of substrates having allene dienophiles. In all cases, these IMDAF reactions produced the exo Diels−Alder adducts exclusively. When the allene has a terminal alkyl substituent, the Diels−Alder adduct with the *E* configuration at the exocyclic alkene is formed as the only diastereomer due to the strong steric interaction between the methyl group on the furan and the alkyl group on the allene. Furthermore, we have successfully obtained an optically active oxatricyclic compound from a chiral propargylic alcohol using this protocol. Further studies on the synthesis of arisugacin A using the resulting oxatricyclic intermediate are in progress and will be reported in due course.

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

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