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Synthesis of cyclic olefins *via* Mitsunobu *C*-alkylation followed by Ramberg-Bäcklund ring contraction

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ABSTRACT

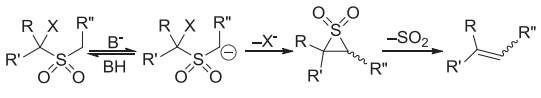
Cyclic olefins were prepared *via* a novel synthetic approach that involves the formation of two C—C bonds in a potentially stereoselective fashion. The first bond is formed by employing a Mitsunobu dehydrative *C*-alkylation; the second C—C bond involves a ring contraction *via* Ramberg-Bäcklund rearrangement.

Introduction

The Mitsunobu reaction is a well-established synthetic tool employed mostly in the formation of esters, thioesters and amides.[1] Another application of the Mitsunobu reaction is the formation of a C—C bond *via* dehydrative *C*-alkylation between an alcohol and a carbon nucleophile.[2] This can be achieved when the acidity of the carbon acting as a nucleophile is enhanced by the presence of electron-withdrawing groups. Bis-sulfonyl methanes are efficient nucleophiles for the Mitsunobu *C*-alkylation because of the acidity that the presence of two sulfones confers to the carbon nucleophile,[3] and the absence of the competitive reactive centers observed in ambident nucleophiles.[4] Furthermore, the bis-sulfone is a versatile functional group that can be employed in a broad variety of transformations.[5] One application of bis-sulfones is the ring or chain contraction *via* a Ramberg-Bäcklund mechanism. The classical Ramberg-Bäcklund rearrangement[6,7] involves the treatment of a halosulfone with a base to yield an olefin, *via* a mechanism that presumably involves the formation of an unstable episulfone intermediate (Scheme 1). The replacement of the halide with a sulfone (X = SO_2R) has been reported in a few cases.[8,9]

Results and discussion

Herein, we report a novel sequence for the preparation of cyclic olefins, which utilizes a Mitsunobu *C*-alkylation, followed by a Ramberg-Bäcklund ring contraction as key steps. In more detail, commercially available sulfanyl alcohols **1** (Scheme 2) were converted into dithioacetals **2** in good yields (60–90%), followed by oxidation to bis-sulfones **3** (typically >90% yield). The Mitsunobu cyclization provided cyclic bis-sulfones **4**, which can be easily alkylated under a variety of reaction conditions. We found that Pd catalyzed allylation[10] of the bis-sulfones **4** to give **5** was particularly effective, with excellent yields (generally >85%). Hydrogenation of the alkene intermediate **5** was necessary to avoid a competitive elimination of benzenesulfinic acid to give a diene system which was observed as the major product when **5** was treated with base.[11] Once the alkene was reduced to **6** (>95%), the ring contraction proceeded in good yield to the cyclic olefin **7**. An analogous ring contraction of bis-sulfones obtained through a different route was described by Fuchs and co-workers.[9]



Scheme 1. Mechanism of the Ramberg-Bäcklund rearrangement.

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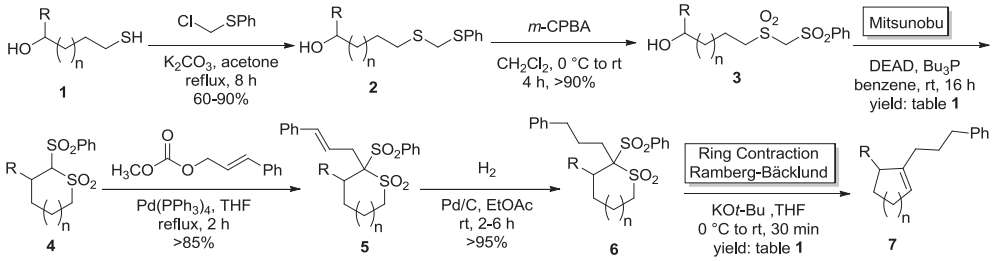


Scheme 2. General scheme for the preparation of cyclic olefins. n = 1, 2; R = H, CH_3.

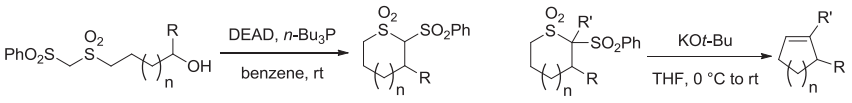
The Mitsunobu cyclization[12] gave access to six and seven membered rings (Table 1). The reaction worked with primary as well as secondary alcohols. Attempts at the preparation of rings larger than seven following this methodology were not successful. Although five membered rings could be easily prepared in high yield *via* the Mitsunobu reaction, they were of no synthetic utility since efforts at ring contraction to obtain cyclobutene systems failed. After alkylation of the cyclic bis-sulfones the cyclic olefins were obtained in good yield by treatment with a base.[13]

The Mitsunobu reaction proceeds *via* complete inversion of configuration at the alcohol center, and this important feature can be utilized for the preparation of optically active cyclic olefins *via* the above described approach. Thus alcohol **10** (Scheme 3), which was purchased with 9:1 enantiomeric ratio, was protected to give the silyl ether **11** (85% yield) and then converted to the γ-thionolactone **12** in 72% yield using Lawesson's reagent.[14] Reductive ring opening of **12** with $LiBH_4$ provided the 1,4-sulfanylalcohol **13** (64%), which was converted to the dithioacetal **14** in 67% yield. Oxidation of **14** to the bis-sulfone **15** (92%) was followed by ring closure *via* dehydrative alkylation under Mitsunobu conditions to obtain **16** (68%) as an 85:15 mixture of diastereomers. The two diastereomers could be separated by column chromatography for analysis purposes. Alternatively, **16** could be used directly in the next step as a diastereomeric mixture. When the Pd-catalyzed allylation was performed on the mixture, compound **17** was isolated in 95% as a 1:1 diastereomeric mixture. Hydrogenation of **17** provided **18** (>95%), which was employed in the next step without separating the two diastereomers. The ring contraction reaction of **18** to obtain **19** was performed in good yield (74%) using *n*-BuLi. When KO*t*-Bu was employed the transformation required longer reaction time and the product **19** was obtained in low yield due to partial loss of the silyl protecting group.

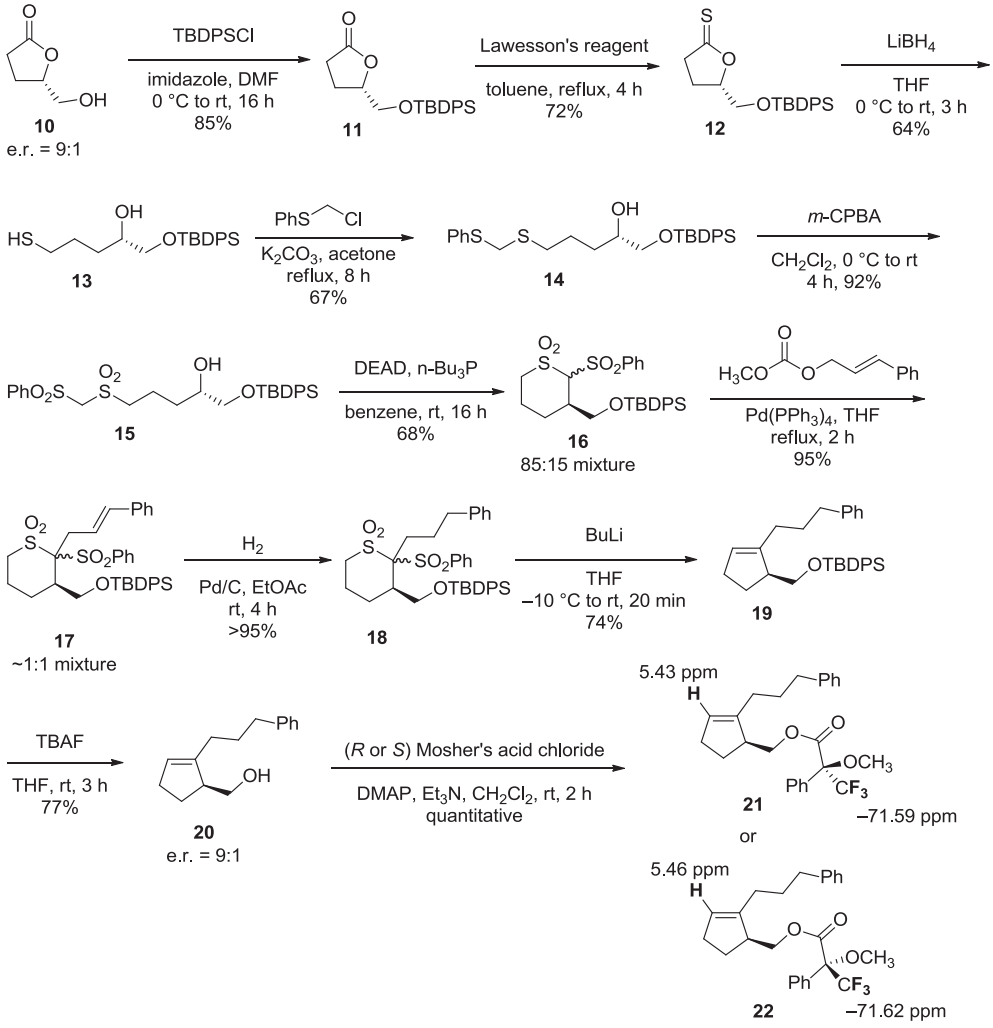
Compound **19** was isolated with no loss of optical purity, as determined, after cleavage of the silyl ether (**20**, >95%), by preparing the Mosher's esters[15] **21** and **22**. Integration of the ^{1}H and ^{19}F NMR diagnostic peaks of **21** and **22** confirmed that the 9:1 enantiomeric ratio of the starting material **10** was maintained through the reaction sequence.

In conclusion, we explored a novel synthetic sequence based on the use of Mitsunobu *C*-alkylation, followed by ring contraction *via* a Ramberg-Bäcklund mechanism. This approach provided the means for the preparation of cyclic olefins, potentially in a stereospecific fashion when readily available optically active alcohol starting materials are employed.

Table 1
Mitsunobu *C*-alkylation and Ramberg-Bäcklund ring contraction.



3	4	6	7
3a	**4a** 92%	**6a**	**7a** 69%
		8	**9** 72%
3b	**4b** 59%	**6b**	**7b** 86%
3c	4:1 **4c** 68%	**6c**	**7c** 73%



Scheme 3. Synthesis of cyclic olefins from optical pure alcohols.

A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.tetlet.2018.06.014.

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12. General procedure for the Mitsunobu reaction to prepare compounds **4**: To a solution of the bis-sulfonyl alcohol **3** (1 equiv) in benzene (0.05 M) at 0 °C (ice bath) under nitrogen was added *n*-Bu_3P (1.5 equiv), followed by DEAD (1.5 equiv). The ice bath was removed and the mixture was stirred at room temperature overnight (16 h). The mixture was concentrated and the residue was purified by column chromatography (silica, gradient 0–25% EtOAc, hexanes) to provide the desired product **4**.
13. General procedure for the ring contraction reaction via Ramberg-Bäcklund rearrangement to prepare compounds **7**: To a solution of bis-sulfone **6** (1 equiv) in THF (0.05 M) at 0 °C (ice bath) and under nitrogen was added dropwise a solution of KO*t*-Bu (1 M in THF, 1.5 equiv). Typically the reaction mixture turned from colorless to pale yellow. After 10 min the ice bath was removed and the mixture was stirred at room temperature until completion of the reaction as per TLC analysis (normally the reaction was complete within 30 min). The mixture was diluted with hexanes and washed with water and brine. The organic extract was dried over Na_2SO_4, filtered, and concentrated. The residue was purified by column chromatography (silica, gradient 0–25% EtOAc, hexanes) to provide the desired product **7**.
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