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Studies toward the synthesis of arteminolide: [5+2] cycloaddition reaction of allenes with oxidopyrylium ions

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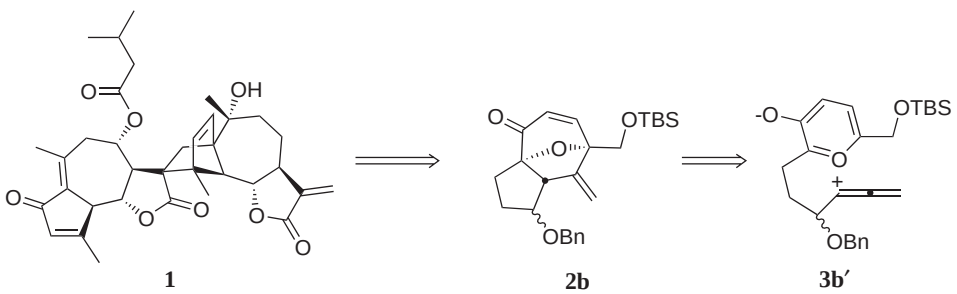
Abstract—The oxidopyrylium cycloaddition reaction of allenes was investigated. Contrary to other cycloaddition reactions, electron deficient allenes were not reactive at all and electron rich allenes were slightly more reactive than neutral allenes. The intermolecular cycloaddition reaction occurred at the terminal position regardless of substitution patterns. For the intramolecular reaction only the perhydroazulene structure was obtained over other possible products.

During the course of our studies on the total synthesis of arteminolide (**1**), a natural product inhibitor of farnesyl transferase,[1] we envisioned a biogenetic type synthetic route[1,2] using a common intermediate, **2b**. The preparation of **2b** could be achieved through an intramolecular [5+2] cycloaddition reaction of the allenyl oxidopyrylium ion **3b′** as the key step (Fig. 1).

Though [5+2] oxidopyrylium ion cycloaddition reactions with alkenes have been studied for more than 20 years[3] and successfully applied to the total synthesis of natural products,[4] the oxidopyrylium cycloaddition reaction of allenes has not been reported yet. Allenes are known to be moderately reactive toward cycloaddition reactions.[5a] Only electron deficient allenes were reported to undergo Diels–Alder reactions unless the reaction was catalysed by transition metals.[6] The nitrile oxide cycloaddition reaction was not strongly affected by the electronic bias of allenes in reactivity and regioselectivity.[5] A systematic investigation of the oxidopyrylium cycloaddition reaction of allenes was necessary to evaluate our synthetic strategy.

The intermolecular oxidopyrylium cycloaddition reaction of various allenes was tested to evaluate reactivity and selectivity of allenes according to the substitution patterns (Scheme 1). When the oxidopyrylium ion precursor **4**[3b] and an electron rich allene, methoxyallene (**5a**),[7] were treated with triethylamine in methylene chloride solution[8] cycloadduct **6a** was obtained as a single diastereomer in low yield. Since the major by-product of the reaction was the dimerization product[3b] of the oxidopyrylium ion of **4**, methoxyallene was used as the solvent of the reaction to minimize by-product formation and to afford a higher yield of **6a**. The cycloaddition reaction of a neutral allene only with



1 **2b** **3b′**

Figure 1.

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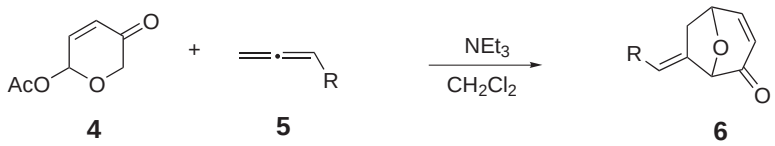
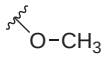
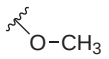
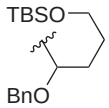
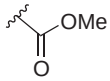
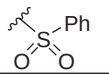
steric bias, **5b** yielded a similar result to the reaction of **5a** as a diastereomeric mixture of **6b** was obtained. The structural integrity of **6a** and **6b** was determined through H–H COSY and NOE experiments. The oxidopyrylium cycloaddition reaction with electron deficient allenes, **5c**[9] or **5d**[10] did not afford any desired products. The current result shows that the oxidopyrylium cycloaddition reaction of allenes proceeds preferentially at the terminal position and the reaction proceeds only with the sterically less encumbered face to give complete diastereoselectivity. Contrary to substituted olefins,[3b] electron deficient allenes are not reactive at all and electron rich allenes are slightly more reactive than neutral ones.

With this result in hand, we turned our attention to the intramolecular cycloaddition reaction. Since it seemed quite possible that **3a–c** could produce **11a–c** instead of **2a–c** as the reaction could occur at the terminal position preferentially, the effect of the length of the tether on the reaction was investigated. Precursors for the cycloaddition reaction **3a**, **3b** and **3c** were prepared from the anion of THP-protected propargyl alcohol **7** in a seven-step sequence (Scheme 2). Addition of **7** to

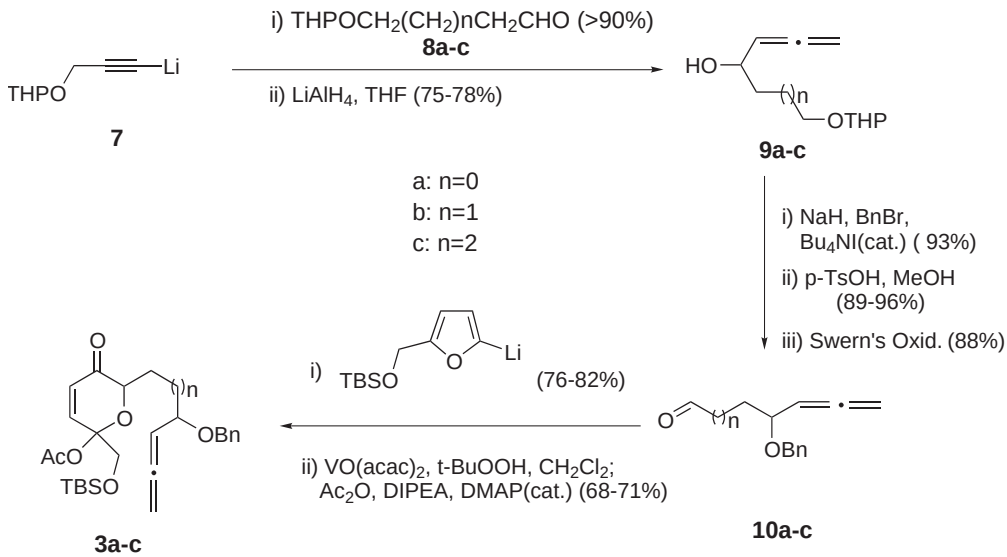


4 **5** **6**

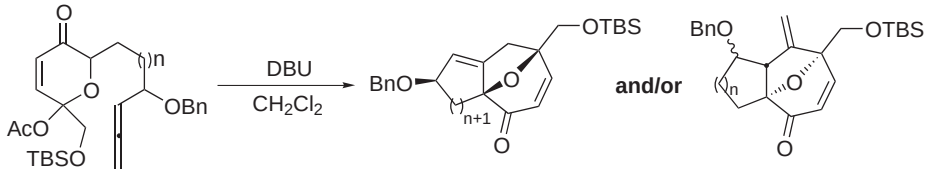
Allene	R	Product	Yield[a]
5a		**6a**	**25%**
5a		**6a**	**46%[b]**
5b		**6b**	**10%**
5c		no cycloadduct observed	
5d		no cycloadduct observed	

a: yields are isolated and purified yields.
b: methoxyallene was used as the solvent.

Scheme 1.



Scheme 2.



3a-c 11a-c 2a-c

Substrate	n	product (yield)
3a	0	**11a (81%)**
3b	1	**2b (45%);** diastereoselectivity(α:β=1:2)
3c	2	**no cycloadduct obtained**

Scheme 3.

8a–c, followed by $LiAlH_4$ reduction[11] afforded allene **9a–c**. Protection of the secondary alcohol as the benzyl ether, followed by deprotection of the primary alcohol and subsequent oxidation gave allenyl aldehyde **10a–c** in good yield. After the addition of the furfuryl moiety, selective oxidation of the furan ring with $VO(acac)_2$/*t*-BuOOH,[12] followed by acetylation of the hydroxy pyranones afforded **3a–c** in 68–71% yield.

Intramolecular oxidopyrylium-allene cycloaddition of **3a–c** with DBU[8] produced an interesting result (Scheme 3). As anticipated, the intramolecular cycloaddition reaction proceeded more efficiently than the intermolecular reaction. In the case of **3a**, the cycloadduct **11a** was obtained in 81% yield as a single diastereomer.[13] The cycloaddition reaction of substrates substituted at the 2′-position of the tether have not been reported yet and it turned out that the diastereoselectivity is as good as substrates substituted at the 1′-position of the tether.[3] The complete diastereoselectivity can be explained through conformational preference of the benzyl ether located at the *pseudo*-equatorial position to avoid eclipsing interaction with the pyrylium ring. The cycloaddition reaction of **3b** produced **2b**, the desired compound for the total synthesis of arteminolide, in 45% yield as a separable mixture of two diastereomers (**2b**α/**2b**β = 2/1). The relative stereochemistry of the two isomers was determined by ^1H NMR coupling constants of the proton at the epimeric center. When **3c** was subjected to the same reaction conditions none of the possible cycloadduct was produced.

The preferential formation of the five-membered rings in the intramolecular allenic oxidopyrylium cycloaddition reaction was quite different from the outcome of the corresponding intramolecular Diels–Alder reaction where six-membered ring formations were favored.[6a]

In summary, the oxidopyrylium cycloaddition reaction of allenes proceeded preferentially at the terminal position and electron-withdrawing groups deactivate allenes for the cycloaddition reaction. The intramolecular cycloaddition reaction was sensitive to the length of the tether. With the desired product **2b** in hand, we are currently pursuing the total synthesis of arteminolide using **2b** as the stereochemistry of benzyl ether in **2b** is not relevant to arteminolide.

Acknowledgements

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8. General reaction procedure (a) for the intermolecular reaction: To a 1.0 M solution of **4** with **5** (3 equiv.) in CH_2Cl_2, was added Et_3N (1.5 equiv.) dropwise at 0°C. After the reaction was stirred for 20 h at ambient temperature the reaction mixture was diluted with Et_2O, washed subsequently with 0.5N HCl, saturated $NaHCO_3$, and brine. The product was purified by flash chromatography; (b) for the intramolecular reaction: DBU (2 equiv.) was used instead of Et_3N and the concentration of the reac-

tion was 0.02 M. Other reaction conditions were the same as the intermolecular reaction.
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13. The stereochemistry was assigned with the DIBAL reduction product of **9a** through NOE experiment.