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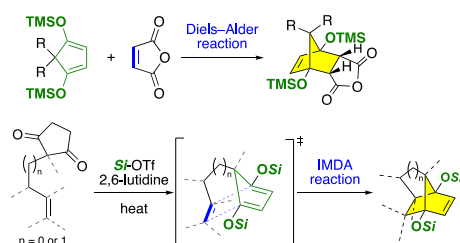
Synthesis of a Bicyclo[2.2.1]heptane Skeleton with Two Oxy-functionalized Bridgehead Carbons via the Diels–Alder Reaction

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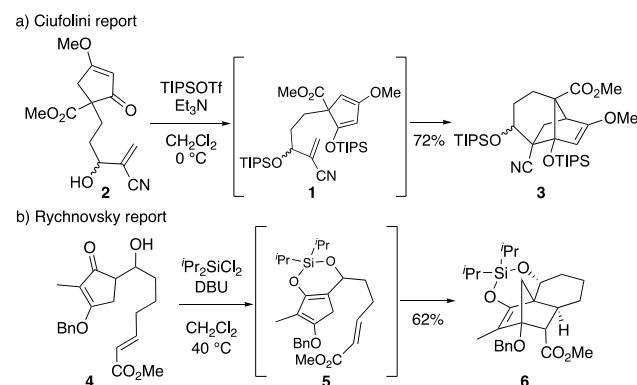
ABSTRACT: We describe a synthetic method for a bicyclo[2.2.1]heptane skeleton with two oxy-functionalized bridgehead carbons. This method involves an intermolecular Diels–Alder reaction using 5,5-disubstituted 1,4-bis(silyloxy)-1,3-cyclopentadienes, the diene structure of which has never been synthesized. Furthermore, the intramolecular Diels–Alder reaction using a diene bearing a dienophile moiety at the 5-position can provide a tricyclic carbon framework including the bicyclo[2.2.1]heptane skeleton. The novel bicyclo[2.2.1]heptane derivatives could be utilized as versatile building blocks for organic synthetic chemistry.

The Diels–Alder (DA) reaction is a powerful tool in organic chemistry because two C–C bonds can be simultaneously formed to provide a cyclohexene ring via a reaction between a diene and a dienophile.¹ This reaction proceeds in a concerted manner; therefore, the generated stereocenters are predictable. In addition, the use of a cyclic diene or application of the intramolecular Diels–Alder (IMDA) reaction enables the synthesis of bicyclic compounds or more complex carbon frameworks.² These advantages accelerate the use of this reaction in the synthesis of natural products.³

Cyclopentadiene derivatives are often used as dienes in the DA reaction to construct a bicyclo[2.2.1]heptane skeleton.⁴ Although the attachment of an oxy-function to the diene moiety enhances the reactivity of the diene for the DA reaction, for examples, the Danishefsky–Kitahara diene,⁵ Brassard diene,⁶ and Rawal diene,⁷ reactions of cyclopentadiene with oxy-functions are limited.⁸ In particular, cyclopentadiene which bears two oxy-functions in the diene moiety is rare.⁹ In 2007, Ciufolini et al. reported the IMDA reaction of **1**, which had a 3-methoxy-1-triisopropylsilyloxycyclopentadiene moiety and was prepared from cyclopentenone **2** with a dienophile, to provide tricyclic compound **3** with an oxy-function at the bridgehead carbon (Scheme 1a).^{9b} Subsequently, their group applied a diene analog to the intermolecular DA reaction.¹⁰ Recently, a similar analogy for constructing a tricyclic skeleton was reported by the Rychnovsky group.^{9c} Specifically, ketoalcohol **4** was transformed into 1,3-bisoxysubstituted cyclopentadiene **5**, the IMDA reaction of which proceeded with high stereoselectivity to give **6** (Scheme 1b). Their group also developed this methodology for natural product synthesis.¹¹ On the other hand, the DA reaction

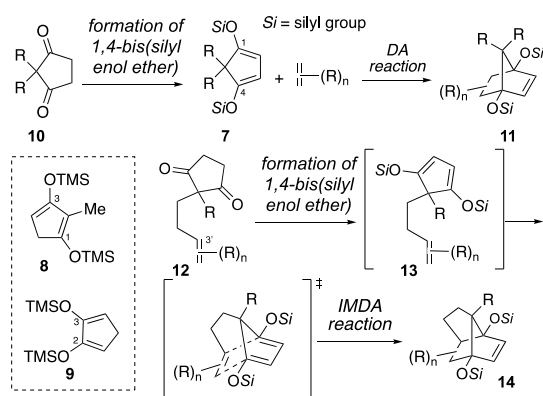
using a cyclopentadiene compound, where the two oxy-functions are located at the C-1 and C-4 positions, is expected to provide bicyclo[2.2.1]heptane compounds with two oxy-functionalized bridgehead carbons. Such compounds can be considered as versatile building blocks for synthesizing complex carbocyclic compounds via a skeletal rearrangement¹² or C–C fragmentation¹³ assisted by an oxy-functionalized group. However, to the best of our knowledge, such compounds have not yet synthesized. Bicyclo[2.2.1]heptane compounds are also widely utilized in medicinal,¹⁴ and polymer chemistry,¹⁵ thus, their production would contribute to the further development of various research fields. Herein, we report a synthetic method for the bicyclo[2.2.1]heptane framework with oxy-functions at the two bridgehead carbons via the DA reaction.

Scheme 1. Examples of the DA reaction using cyclopentadiene derivatives with two oxy-functions on the diene moiety.



The synthetic strategy is illustrated in Scheme 2. Considering the facile formation of an oxy-functionalized vinyl moiety and the removability of the substituted group on the oxygen atom, we planned to use 1,4-bis(silyloxy)-1,3-cyclopentadiene **7** as the diene for the DA reaction. Although the preparation of 1,3-bis(silyl enol ether) **8**¹⁶ and 2,3-bis(silyl enol ether) **9**¹⁷ has been reported, there are no examples of the formation of 1,4-bis(silyl enol ether) on a five-membered ring. We expected that the 1,4-bis(silyl enol ether) could be converted from 1,3-cyclopentadiene **10** via a typical procedure to obtain a silyl enol ether from a carbonyl compound. Silyl enol ether is generally labile, implying that diene **7** is more fragile. Thus, we realized that without purification, the DA reaction of **7**, which produces bicyclic compound **11**, should proceed. Furthermore, if diketone **12**, which has a dienophile moiety at the C3'-position of the side chain in the five-membered ring, is used as the reactant, the IMDA reaction of 1,4-bis(silyl enol ether) **13** generated *in situ* would occur to produce the tricyclic compound **14**.

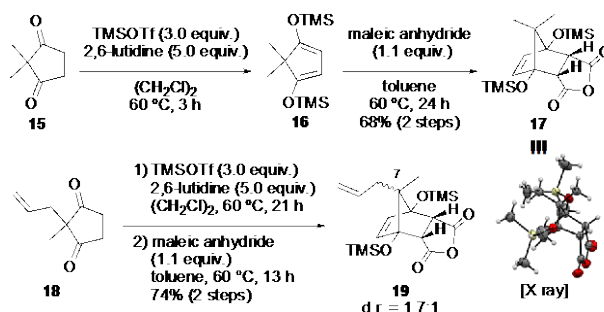
Scheme 2. Synthetic strategy for the DA reaction using 1,4-bis(silyloxy)-1,3-cyclopentadienes.



As expected, 1,4-bis(silyl enol ether) **7** behaved as a diene for the intermolecular DA reaction (Scheme 3). We first exposed 2,2-dimethyl-1,3-cyclopentadione (**15**) to TMSOTf (3.0 equiv.) and 2,6-lutidine (5.0 equiv.) in 1,2-dichloroethane at 60 °C. Bis(silyl enol ether) **16** was detected in the crude ¹H NMR spectrum; however, **16** was unstable in the presence of oxygen, water, and silica gel. Thus, without purification, a DA reaction with maleic anhydride was employed. Notably, the reaction proceeded smoothly in toluene at 60 °C¹⁸ to provide **17** in 68% yield in two steps as the single isomer. X-ray analysis revealed that **17** was the *endo*-isomer. Next, 2-allyl-2-methyl-1,3-cyclopentadione (**18**) was subjected to similar reaction conditions. Although the transformation into the DA product **19** occurred efficiently, facial selectivity did not arise to generate a 1.7:1 diastereomeric mixture corresponding to the C-7 position.

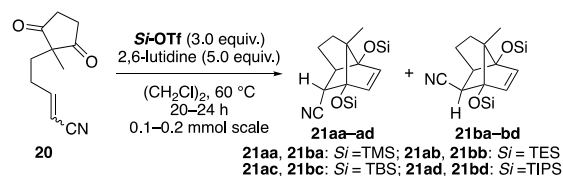
After confirming the reactivity of the novel diene **7**, we investigated the IMDA reaction of **12**, which affords more complex carbon frameworks (Table 1). The reactant selected disubstituted unsaturated nitrile **20**, which was prepared via the Michael addition of 2-methyl-1,3-cyclopentadione to acrolein, followed by the Wittig reaction of the resulting aldehyde with (tri phenylphosphoranylidene)acetonitrile (see Supporting Information (SI) for details).¹⁹ The product was obtained as an inseparable mixture (*E*:*Z* = 3.7–4.0:1); therefore, we subjected the mixture to the same reaction conditions to obtain **16** from **15**, as shown in Scheme 3 (entry 1). The desired reaction proceeded

Scheme 3. Intermolecular DA reaction using 1,4-bis(trimethylsilyloxy)cyclopentadienes.



smoothly to produce tricyclic compounds **21aa** and **21ba** as a 4.8:1 mixture in 78% yield. The structure of **21aa** was confirmed by the X-ray analysis of diol **22a**, where the two TMS groups of the IMDA products were removed and its diastereomer, **22b**, was separated via recrystallization (Scheme 4a). We also showed that the use of TESOTf and TBSOTf gave a mixture of **21ab**/**21bb** and **21ac**/**21bc** in yields comparable to that of the case when TMSOTf was used (entries 2 and 3). Although TIPSOTf induced the desired reaction, the generated 1,4-bis(silyl enol ether) was not completely consumed. In addition, the separation of **21ad**/**21bd** and triisopropylsilanol was difficult; therefore, the calculated yield of **21ad**/**21bd** was designated as the NMR yield (entry 4). In the reactions listed in entries 1–4, the isomeric ratios of the products (**21a**/**21b**) were higher than

Table 1. Optimization of the reaction conditions for the IMDA reaction of **20**.

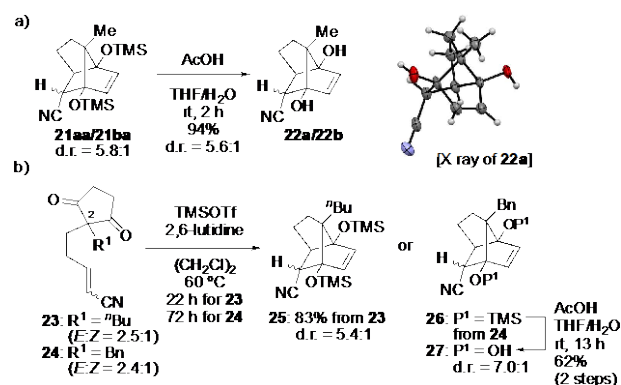


Entry	<i>E</i> : <i>Z</i> ratio of 20	Si-OTf	Yield (%) ^d	21a : 21b ^f
1	3.7:1	TMSOTf	78	4.8:1
2	3.7:1	TESOTf	77	7.1:1
3	3.7:1	TBSOTf	74	5.4:1
4	4.0:1	TIPSOTf	70 ^e	17:1
5	<i>E</i> -only	TMSOTf	93	21aa only
6	<i>Z</i> -only	TMSOTf	55	1:13
7 ^a	3.7:1	TMSOTf	84	3.6:1
8 ^b	3.7:1	TMSOTf	33	11:1
9 ^c	4.0:1	TMSOTf	94	5.8:1

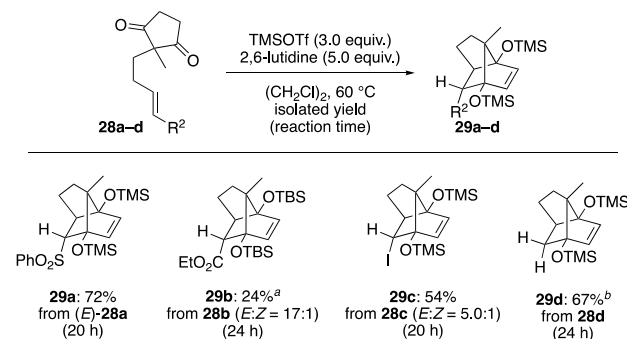
^a Toluene was used as the solvent. ^b Acetonitrile was used as the solvent. ^c 1 mmol scale. ^d Isolated yield. ^e NMR yield. ^f Determined from the ¹H NMR spectrum of the purified product.

those of the substrates [(*E*)-**20**/(*Z*)-**20**], indicating the higher reactivity of the *E*-isomer over that of the *Z*-isomer. Therefore, we conducted the reactions of each *E*- and *Z*-isomer, which were prepared by an alternative method (see SI for details), with TMSOTf and 2,6-lutidine, separately (entries 5 and 6). As expected, **21aa** was obtained as a single product from (*E*)-**20** in 93% yield, while (*Z*)-**20** underwent slow conversion to **21ba** along with **21aa**, which might be formed through the partial isomerization of (*Z*)-**20** to (*E*)-**20**. The reaction was also conducted in other reaction solvents, and the yield of **21aa/21ba** was found to be similar to that in entry 1 when toluene was used (entry 7); by contrast, the yield of **21aa/21ba** decreased dramatically when acetonitrile was used (entry 8). Notably, this tandem reaction using TMSOTf proceeded smoothly on a 1-mmol scale to give a 5.8:1 diastereomeric mixture of **21aa** and **21ba** in 94% yield (entry 9). Furthermore, reactants **23** and **24**, in which the methyl group at the C-2 position of **20** was replaced with the *n*-Bu and Bn groups, respectively, did not affect the IMDA reaction and afforded **25** and **26** in good yields (Scheme 4b). In the latter reaction, because the isolation of pure **26** was difficult, the two TMS groups were removed by treatment it with aqueous AcOH; thus, **26** was isolated as a diol **27**.

Scheme 4. (a) Transformation of **21** into diol **22**. (b) Application in other reactants.



Scheme 5. Scope of the dienophile moiety.



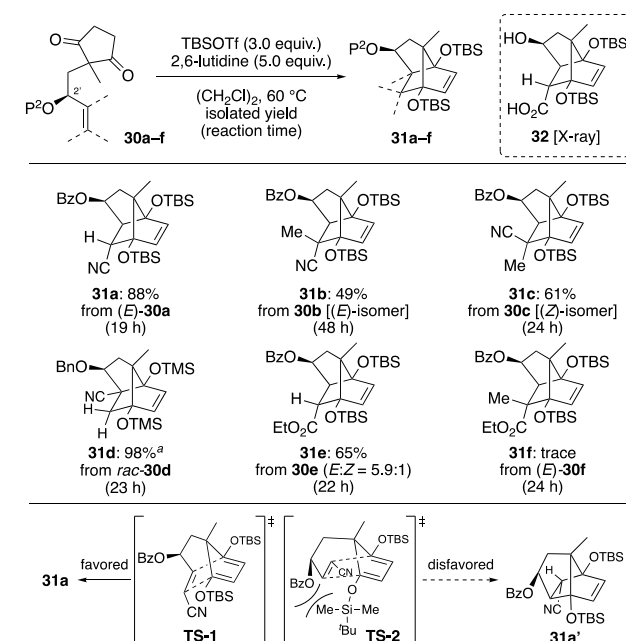
^a TBSOTf was used instead of TMSOTf. ^b at 120 °C.

Next, 1,3-cyclopentadiene **28** with other substituents in the dienophile moiety was exposed to the reaction conditions for entry 1 in Table 1 (Scheme 5). Vinyl sulfone **28a** afforded the tricyclic compound **29a** in 72% yield. By contrast, α,β -unsaturated ester **28b** gave product **29b** in only 17% NMR yield because the intramolecular Michael addition of a silyl enol ether to the unsaturated ester moiety occurred predominately.²⁰ Upon

replacing of TMSOTf with TBSOTf, the yield of **29b** increased, although it was still poor due to the more favorable side reaction. Remarkably, vinyl iodide **28c** (*E*:*Z* = 5.0:1) also underwent the desired reaction, although the yield of **29c** was average; this is because the IMDA product was partially decomposed during the purification process. Moreover, the IMDA reaction of terminal olefin **28d** proceeded at an elevated reaction temperature (120 °C) to afford **29d** in 67% yield.

Subsequently, we studied the IMDA reaction of **30** with an oxy-function at the C-2' position (Scheme 6). This reaction has the possibility of generating regioisomers because two transition states in the IMDA reaction can be formed. Thus, for the reaction of (*E*)-unsaturated nitrile **30a** bearing a BzO group, **TS-1** and **TS-2** can be considered to give **31a** and **31a'**, respectively. However, the TBSOTf-mediated reaction produced only tricyclic product **31a** in good yield. The formation of transition state **TS-2** appears unfavorable due to the steric repulsion between the BzO group and the TBS group, thus predominately generating **31a** from **TS-1**. The same regioselectivity was observed for the other reactions. (*E*)- and (*Z*)-trisubstituted unsaturated nitriles, **30b** and **30c**, were transformed into **31b** and **31c** without isomerization in average yields; the yield of **31c** was higher. The reaction of α -substituted acrylonitrile **30d** proceeded efficiently even when TMSOTf was used, producing **31d** in 98% yield. Surprisingly, ester **30e** also delivered **31e** in 65% yield, although the conversion of **28b** (lacking a BzO group) into **29b** was very low. We presume that the Thorpe-Ingold effect²¹ of the BzO group enhanced the occurrence of the desired reaction. Unfortunately, the use of trisubstituted ester **30f** provided a trace amount of **31f**. The structures of **31a**–**31e** were confirmed based on the X-ray structure of **32**, which is a hydrolysis product of **31e** (see SI for details).

Scheme 6. IMDA reaction using **30** with an oxy-function at the C-2' position.



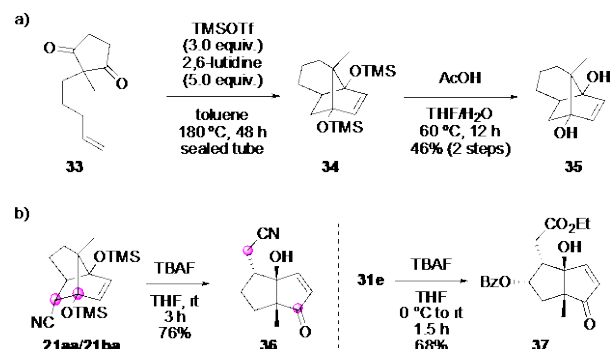
^a TMSOTf was used instead of TBSOTf.

Our IMDA reaction system was also applicable to another reactant, **33**, where a one-methylene unit was incorporated into the side chain on **29d** (Scheme 7a). The IMDA reaction proceeded using TMSOTf and 2,6-lutidine in toluene at 180 °C in

a sealed tube. The removal of the two TMS groups of the obtained tricyclic compound **34** via acidic hydrolysis afforded diol **35** in 46% isolated yield in two steps.

The tricyclic skeleton of the two IMDA products was easily transformed into the *cis*-fused 5,5-ring skeleton via the retroaldol reaction (Scheme 7b). Thus, treatment of nitrile **21aa/21ba** in THF with TBAF produced bicyclic compound **36** in 76% yield. A similar reaction occurred when using ester **31e**, which afforded **37** in 68% yield. The obtained bicyclic skeletons contain multiple functional groups, suggesting that these compounds are useful as building blocks for the synthesis of natural products.

Scheme 7. Development of our reaction system.



In summary, we revealed that 5,5-disubstituted 1,4-bis(silyloxy)-1,3-cyclopentadienes can behave as dienes in the DA reaction. Furthermore, the cyclopentadiene derivatives with a dienophile moiety at the C-5 position induce the IMDA reaction, providing a tricyclic carbon framework including a bicyclo[2.2.1]heptane skeleton with two oxy-functions at the bridgehead carbons in acceptable yields. We believe that these compounds will attract attention in various research fields.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Experimental procedures, analytical data, and crystallographic information for **17**, **22a**, and **32**, copies of the ^1H and ^{13}C NMR spectra for all new products (PDF).

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- (20) In fact, the Michael addition product underwent further transformation *in situ* to provide another compound, the structure of which has not been determined yet because the NMR analysis results were ambiguous. The creation of single crystal of the product or its derivative also failed. The structure determination is in progress.
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