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Total Synthesis of Furanether B. Construction of a Hydroazulene Skeleton via a Novel [5 + 2] Cycloaddition Reaction of Silyloxyallene

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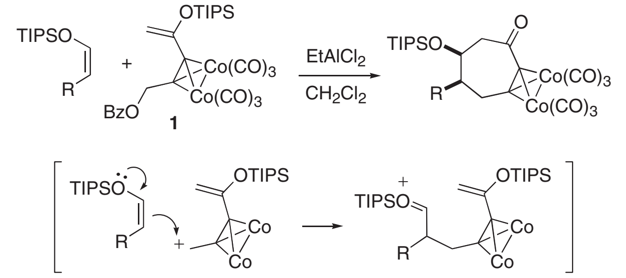
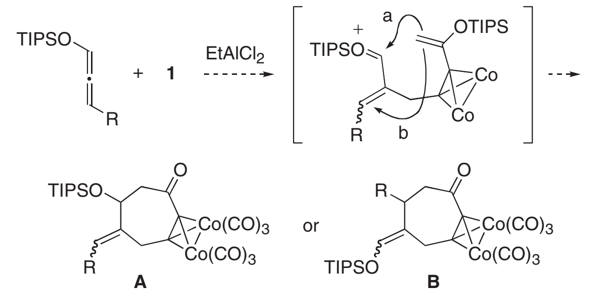
A new synthetic method for cycloheptanone derivatives was developed on the basis of a novel [5 + 2] cycloaddition reaction using a dicobalt hexacarbonyl propargyl cation species and a silyloxyallene. The method can be applied for constructing functionalized hydroazulene skeletons, and a total synthesis of sesquiterpene furanether B was achieved through the reactions involving transformation of the dicobalt acetylene complex into a maleic anhydride derivative and the crucial oxidative transannular ether ring formation.

Cycloaddition reactions provide a straightforward and powerful method for constructing a carbocyclic skeleton of various kinds of natural products. While a significant number of total syntheses have been accomplished by the use of the Diels–Alder reaction,[1] there are relatively few examples involving a [5 + 2] cycloaddition reaction as a key step for construction of a cycloheptane skeleton.[2] We have reported a novel method for cycloheptanone synthesis via an intermolecular [5 + 2] cycloaddition reaction using dicobalt acetylene complex **1** as a five-carbon unit (Scheme 1).[3] The reaction proceeds in a stepwise fashion involving a dicobalt propargyl cation and a silyloxonium ion intermediate as shown in Scheme 1.

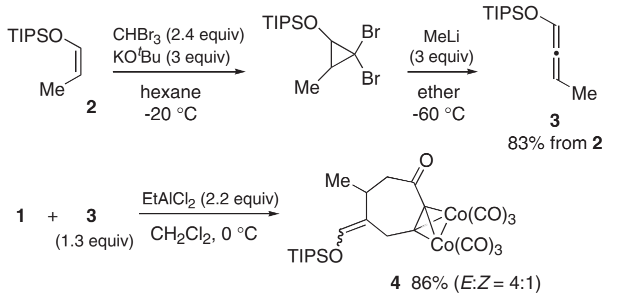
The efficiency of the cycloaddition reaction as well as the utility of the products having a dicobalt acetylene complex moiety led us to explore the reactions with other nucleophilic olefins. Particularly, we were intrigued by a silyloxyallene derivative bearing a highly strained sp carbon atom as a nucleophilic center (Scheme 2). The reaction of a silyloxyallene with **1** would afford a silyloxonium ion conjugated with a double bond that in turn might undergo either a cyclization reaction giving rise to **A** (path a) or a conjugate addition reaction leading to **B** (path b).



Scheme 1. Lewis acid-promoted intermolecular [5 + 2] cycloaddition reaction of dicobalt acetylene complex **1** (TIPSO: triisopropylsilyloxy).



Scheme 2. Intermolecular [5 + 2] cycloaddition reaction of silyloxyallene and dicobalt acetylene complex **1**.

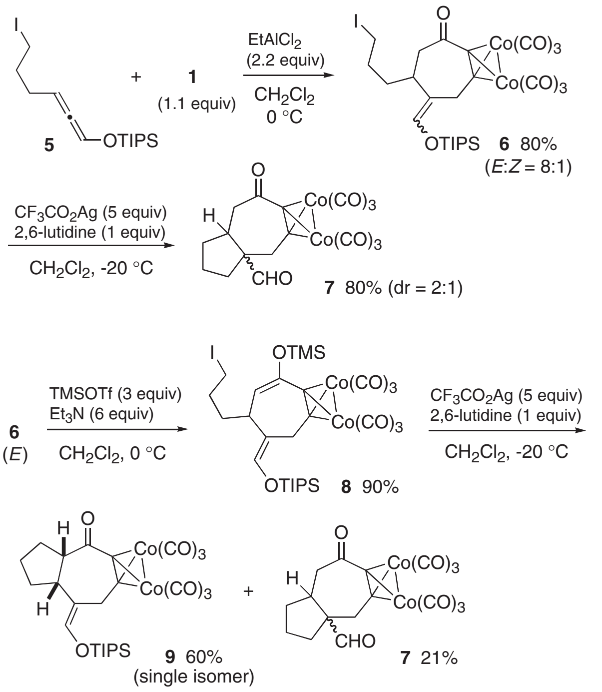


Scheme 3. Preparation and the [5 + 2] cycloaddition reaction of silyloxyallene **3**.

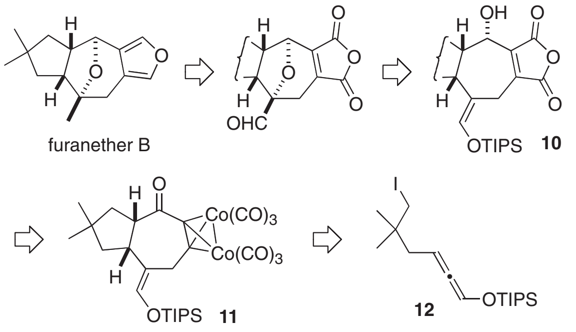
Silyloxyallene **3** was easily prepared from enol silyl ether **2** via cyclopropanation with a dibromocarbene species followed by treatment with MeLi (Scheme 3).[4] Since the silyloxyallene was slightly sensitive to acidic conditions, purification was performed by flash column chromatography using neutralized silica gel. In the presence of $EtAlCl_2$, silyloxyallene **3** smoothly reacted with the five-carbon unit **1** to give cycloheptanone derivative **4**, which indicated that the intramolecular conjugate addition reaction is much more favorable (path b in Scheme 2).

The preliminary result led us to design a new route for constructing a hydroazulene skeleton starting from allene derivative **5** having a terminal iodo group (Scheme 4). The [5 + 2] cycloaddition reaction of **5** with **1** afforded the desired cycloheptanone **6** which was subjected to an intramolecular alkylation reaction mediated by silver(I) trifluoroacetate[5] giving rise to keto aldehyde **7** in high yield. On the other hand, treatment of the corresponding enol silyl ether **8** with the silver salt resulted in the selective formation of ketone **9** as a single product. It is noteworthy that attempts to obtain the ketone **9** through a reaction of **6** with a base led to formation of a complex mixture.

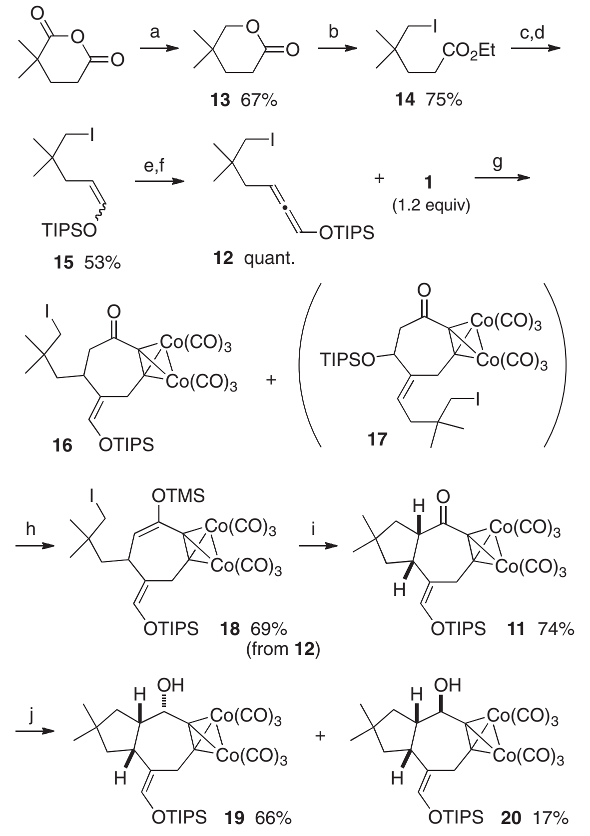
In order to demonstrate the utility of the present method, total synthesis of furanether B,[6,7] a terpenoid isolated from *Lactarius scrobiculetus*, was undertaken (Scheme 5). Since seven-membered dicobalt acetylene complexes are easily trans-



Scheme 4. Synthesis of hydroazulene **9** via sequential [5 + 2] cycloaddition and intramolecular alkylation reactions.



Scheme 5. Retrosynthetic analysis of furanether B.



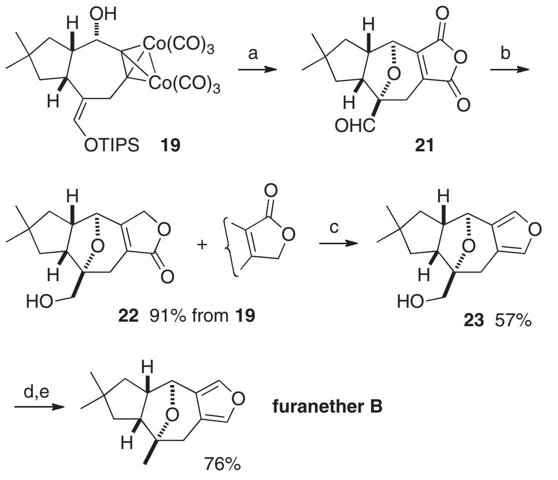
Scheme 6. Synthesis of hydroazulene derivative **19**. Reagents and conditions: (a) i. NaBH$_4$ (3 equiv), THF, rt, 45 h, ii. p-TsOH•H$_2$O (0.1 equiv), benzene, rt, 21 h; (b) TMSI (3 equiv), CCl$_4$, 80 °C, 9 h, then EtOH, rt, 12 h; (c) DIBAL (1.05 equiv), hexane, −78 °C, 30 min then HCl (aq); (d) TIPSOTf (3 equiv), Et$_3$N (9 equiv), CH$_2$Cl$_2$, rt, 1 h; (e) CHBr$_3$ (2.4 equiv), KO^{t}Bu (3 equiv), hexane, −23 °C, 1 h; (f) MeLi (3 equiv), ether, −60 °C, 15 min; (g) EtAlCl$_2$ (2 equiv), CH$_2$Cl$_2$, 0 °C, 30 min; (h) TMSOTf (2.6 equiv), Et$_3$N (5.3 equiv), CH$_2$Cl$_2$, 0 °C, 30 min; (i) CF$_3$CO$_2$Ag (2 equiv), 2,6-lutidine (1 equiv), CH$_2$Cl$_2$, 0 °C, 30 min; (j) DIBAL (2 equiv), ether, −78 °C, 30 min.

formed into the corresponding maleic anhydrides under the influence of ceric ammonium nitrate (CAN),[3,8] we planned to construct the furan moiety by reduction of the corresponding maleic anhydride. The cyclic ether was designed to be constructed via an intramolecular oxidative cyclization reaction of alcohol **10**, which could be prepared from ketone **11** by selective reduction from the convex face followed by treatment with CAN.

Allene **12** was synthesized from lactone **13**,[9] which was prepared from commercially available 2,2-dimethylglutaric anhydride (Scheme 6). The reaction of lactone **13** with TMSI followed by treatment with ethanol afforded iodo ester **14** via cleavage of the C–O bond.[10] Ester **14** was then reduced with DIBAL, and the resulting aldehyde was treated with TIPSOTf and triethylamine giving rise to enol silyl ether **15**. Transformation of **15** into allene **12** was achieved by applying a similar reaction sequence in Scheme 3.

The key [5 + 2] cycloaddition reaction[11] of the allene **12** with **1** afforded an 84:16 mixture of the desired cycloheptanone **16** and its isomer **17** (Scheme 6). Fortunately, the treatment of the inseparable mixture with TMSOTf and triethylamine effected selective conversion of ketone **16** to enol silyl ether **18** in 69% overall yield. The cyclization reaction of **18** mediated by silver(I) trifluoroacetate resulted in selective formation of the desired ketone **11** with no by-product corresponding to the keto aldehyde **7** in Scheme 4. Stereoselective reduction of **11** was performed by using DIBAL in ether to afford alcohol **19** in 66% yield along with its stereoisomer **20**.

It is noteworthy that the bulkiness of the allene **12** having a quaternary carbon atom affected the selectivity of the [5 + 2] cycloaddition reaction in which a small amount of ketone **17** was produced. When the R group in Scheme 2 is bulky, the steric repulsion between the enol silyl ether moiety and the R group slows down path b, which enhances formation of **17** through path a. On the other hand, the bulkiness of the side chain brought about site-selective cyclization of **18** at the less hindered enol silyl ether moiety to afford ketone **11** in good yield.



Scheme 7. Total synthesis of Furanether B. Reagents and conditions: (a) $(NH_4)_2Ce(NO_3)_6$ (12 equiv), CH_3CN–H_2O, rt, 30 min; (b) $NaBH_4$ (5 equiv), THF–H_2O, rt, 30 min then HCl (aq), rt, 30 min; (c) DIBAL (1.8 equiv), CH_2Cl_2, −78 °C, 10 min then HCl (aq); (d) Tf_2O (1.5 equiv), 2,6-di-*tert*-butylpyridine (3 equiv), CH_2Cl_2 −78 °C, 45 min; (e) $LiBHEt_3$ (2.1 equiv), THF, rt, 15 min.

The stage was set for conversion of the dicobalt acetylene complex moiety to a maleic anhydride derivative. Surprisingly, treatment of the alcohol **19** with an excess amount of CAN led to formation of aldehyde **21** having an oxygen bridge in the cycloheptane ring (Scheme 7). The result indicates that the secondary hydroxy group of the substrate underwent transannular oxidative coupling with the enol silyl ether moiety.[12] The unexpected reaction allowed us to accomplish the total synthesis in fewer steps.

Thus, the reaction of the aldehyde **21** with $NaBH_4$ followed by workup under acidic conditions gave rise to hydroxy lactone **22** as a mixture of regioisomers in high overall yield. Conversion of the unsaturated lactones to the furan ring was achieved by DIBAL reduction. Finally, the primary hydroxy group of **23** was removed via reduction of the corresponding triflate with $LiBHEt_3$. The spectral data of the synthetic compound were identical with those of furanether B.

In conclusion, a novel synthetic method for functionalized cycloheptanone derivatives was developed on the basis of a [5 + 2] cycloaddition reaction using a dicobalt hexacarbonyl propargyl cation species and a silyloxyallene. The reaction proceeds through an intermolecular addition followed by an intramolecular conjugate addition. The method can be applied for constructing functionalized hydroazulene skeletons, and a new total synthesis of furanether B was achieved through the reactions involving transformation of dicobalt acetylene complex into the maleic anhydride derivative and the key oxidative transannular ether ring formation.

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11 The experimental procedure for the [5 + 2] cycloaddition reaction: To a mixture of siloxyallene **12** (3.8 g, 9.3 mmol) and cobalt complex **1** (7.2 g, 11 mmol) in CH_2Cl_2 (22 mL) was added a 0.96 M hexane solution of $EtAlCl_2$ (19.3 mL, 18.6 mmol) at 0 °C. After stirring for 30 min, the reaction was quenched with a saturated aqueous solution of Rochelle salt. The mixture was stirred vigorously for 30 min and separated. The aqueous layer was extracted with ether and the combined organic layer was dried over $MgSO_4$. Concentration under reduced pressure followed by flash column chromatography using neutral silica gel afforded 6.3 g of a mixture of cycloadducts **16** and **17**. The mixture was dissolved in CH_2Cl_2 (41 mL), and to this was added triethylamine (6.8 mL, 49 mmol) followed by TMSOTf (4.4 mL, 25 mmol) at 0 °C. After stirring for 30 min, a saturated aqueous solution of $NaHCO_3$ was added, and the mixture was separated. The aqueous layer was extracted with ether, and the combined organic layer was dried over $MgSO_4$. Concentration under reduced pressure followed by purification by flash column chromatography afforded 5.4 g (69% from **12**) of enol silyl ether **18** and 1.1 g (16% from **12**) of cycloadduct **17**. Cobalt complex **18**: ^1H NMR (500 MHz, $CDCl_3$): δ 6.28 (s, 1H), 5.30 (d, $J = 8.0$ Hz, 1H), 4.43 (d, $J = 17.2$ Hz, 1H), 3.31 (d, $J = 17.2$ Hz, 1H), 3.20 (d, $J = 9.7$ Hz, 1H), 3.14 (d, $J = 9.7$ Hz, 1H), 2.85 (td, $J = 8.0$, 4.6 Hz, 1H), 1.64 (dd, $J = 14.3$, 8.0 Hz, 1H), 1.47 (dd, $J = 14.3$, 4.6 Hz, 1H), 1.14 (sept, $J = 6.3$ Hz, 3H), 1.06 (d, $J = 6.3$ Hz, 18H), 1.04 (s, 6H), 0.24 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 199.95 (3C), 199.63 (3C), 147.30, 136.78, 116.88, 115.96, 95.24, 87.81, 44.12, 37.89, 34.27, 29.09, 27.33, 27.30, 24.14, 17.64 (6C), 11.79 (3C), 0.24 (3C). HRMS (EI) m/z; calcd for $C_{31}H_{45}O_8Si_2Co_2I$: 846.0362, found: 846.0316.

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