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Novel Intramolecular (4 + 1) and (4 + 2) Annulations of Halopolyenes by Cascade Radical Reaction

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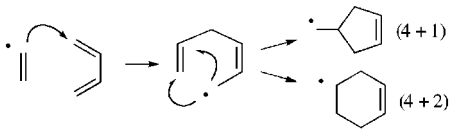
ABSTRACT



Cascade Radical Reaction

Free radical reaction of vinyl iodides having dinenoate function in the presence of tributyltin hydride or tris(trimethylsilyl)silane caused a sequential cyclization reaction to produce (4 + 1) and (4 + 2) annulated compounds by means of a cascade radical reaction. Stereogenic centers of the cascade reaction were highly controlled. On the contrary, the cathodic electrolysis of the vinyl iodides afforded monocyclic compounds.

Intramolecular annulation reactions of polyenes have received much attention as a powerful methodology to construct bi- or polycyclic framework in organic synthesis and have been utilized as key reactions for the total synthesis of natural products.[1] Diels−Alder reaction, 1,3-dipolar addition, and [2 + 2] cycloaddition have been intensely explored. Recently, the annulation methods catalyzed by transition metals,[2,3] for example, cobalt,[3a] rhodium,[3b] and palladium,[3c] have been exceedingly developed. We have been interested in the intramolecular annulation reactions, such as the intramolecular double Michael reaction[4] and the Michael−aldol reaction,[5] to construct polycyclic skeletons. In the above reactions, a nucleophilic function of substrates changes character to that of an electrophile after the initial reaction, and an electrophilic group acts as a nucleophile in a second reaction. That is, the reaction center moves stepwise from one functional group back to the same one via other functional groups. We applied the concept for the cascade radical reactions[6,7] (Figure 1). We envisaged that the vinyl radical can act as both radical donor and acceptor during

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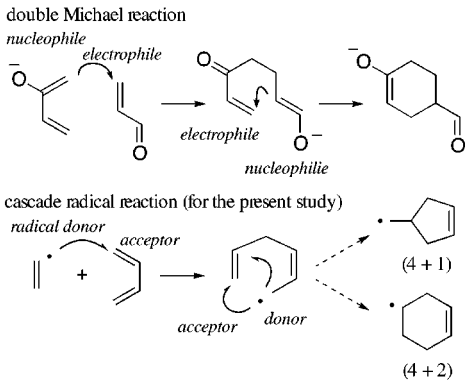
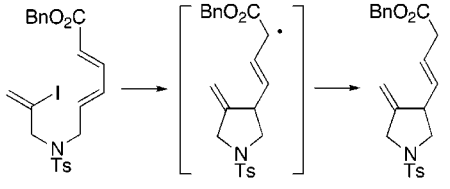


Figure 1.

the same reaction. Recently we reported cascade radical reactions of halopolyenes, which involved (2 + 1) annulation, utilizing this feature.[8] Herein, we describe (4 + 1) and (4 + 2) annulation reactions of iodoolefins tethered with dienoate function as novel radical cascade reactions.

In an initial experiment, we examined the radical reaction of dienoate **1** under two conditions, use of tributyltin hydride (TBTH)−AIBN as a radical generator or cathodic electrolysis[9] mediated by nickel(II) cyclam (Scheme 1). Dienoate **1**

Scheme 1



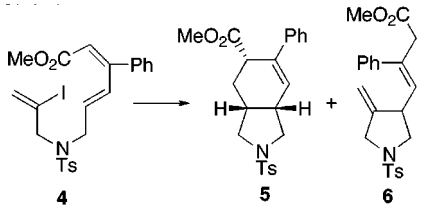
run	conditions	yield (%) of **3**
1	Bu_3SnH, AIBN, benzene, reflux[a]	56
2	$Ni(cyclam)^{2+}$, DMF, −1.5 V, rt	65

[a] Bu_3SnH and AIBN were added dropwise over 1 h.

was chosen as a probe because the radical deiodation of **1** followed by cyclization would generate the intermediate **2** possessing the stabilized captodative radical (acylvinyl radical), which can be expected to introduce succeeding radical cyclization. However, both of the conditions afforded only monocyclic product **3**, which has a *trans*-β,γ-unsaturated ester moiety. The result suggested that the captodative radical intermediate was produced after the first cyclization stage, but the sequential cyclization would be prohibited by the *trans* geometry of the intermediate.

We considered that the introduction of a bulky substituent at the β-position would control the desired configuration of the intermediates to promote sequential cyclization. The radical reactions of β-phenyl-substituted dienoate **4** were summarized in Scheme 2. To a refluxing benzene solution

Scheme 2



run	conditions	yield (%) **5**	yield (%) **6**
1	Bu_3SnH, AIBN, benzene, reflux[a]	40	20
2	Bu_3SnH, AIBN, benzene, reflux[b]	63	0
3	$(TMS)_3SiH$, AIBN, benzene, reflux[b]	66	0
4	benzene, reflux	0	0
5	$Ni(cyclam)^{2+}$, DMF, −1.5 V, rt	0	85
6	$Ni(cyclam)^{2+}$, DMF, −1.5 V, 100 °C	0	86

[a] Bu_3SnH and AIBN were added dropwise over 1 h. [b] Hydride and AIBN were added dropwise over 2 h.

of **4** was slowly added a benzene solution of TBTH (1.2 equiv) and AIBN (0.5 equiv) over 1 h. After an additional 2 h of reflux, bicyclic product **5** and monocyclic **6** were obtained in 40 and 20% yields, respectively (run 1). The slower addition (over 2 h) of the reagents afforded only **5** in 63% yield as a single diastereomer (run 2).[10] When tris(trimethylsilyl)silane (TTMSH) was used as a radical source in the presence of AIBN, a result similar to that above was obtained (run 3). The transformation resulted in a cascade 5-*exo*, 6-*endo* cyclization process to give the isoindole skeleton, that is, an intramolecular (4 + 2) annulation has occurred. No reaction of **4** proceeded without radical sources under reflux conditions in benzene (entry 4), that is, the (4 + 2) annulation is not the result of a Diels−Alder reaction. On the contrary, indirect cathodic electrolysis[11] of **4** provided only **6** in 85 and 86% yields at ambient temperature or at 100 °C, respectively (runs 5 and 6). The structures of **5**[12] and **6**[12] were assigned on the basis of 1D and 2D NMR spectroscopies.

Modification of the substrate in the vicinity of the iodovinyl moiety, however, has induced a different mode of annulation. The treatment of **7**, which has a longer tether

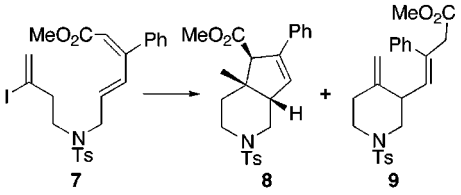
(10) **General procedure for the reaction with TBTH:** To a stirred solution of the vinyl iodide (40 μmol) in degassed benzene (20 mL) were added dropwise a solution of Bu_3SnH (48 μmol) and AIBN (20 μmol) in benzene (4 mL) over 2 h using a syringe pump under reflux. After being stirred for 2 h, the solution was concentrated. The resulting residue was chromatographed on silica gel (4:1 v/v).

(11) The electrolysis was carried out under conditions similar to those of ref 8a.

(12) Spectral data for compound **5**: colorless needles (from Et_2O); mp 176−178 °C; IR (neat) ν 2950, 1730, 1340, 1160, 1090, 660 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.74 (d, J = 8.5 Hz, 2H), 7.34−7.16 (m, 7H), 5.88 (dd, J = 4.9, 1.8 Hz, 1H), 3.69 (m, 2H), 3.53 (dd, J = 10.1, 6.7 Hz, 1H), 3.38 (s, 3H), 3.13 (dd, J = 10.1, 1.8 Hz, 1H), 3.05 (t, J = 9.7 Hz, 1H), 2.81 (m, 1H), 2.43 (s, 3H), 2.36 (m, 1H), 1.92 (dt, J = 13.4, 4.9 Hz, 1H), 1.54 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.1, 143.4, 140.7, 137.8, 133.7, 129.7, 128.3, 127.5, 127.3, 125.5, 53.1, 51.9, 51.7, 44.6, 38.3, 35.1, 28.6, 21.5; MS m/z 411 (M^+). Anal. Calcd for $C_{23}H_{25}NO_4S$: C, 67.13; H, 6.12; N, 3.42; S, 7.79. Found: C, 66.99; H, 6.28; N, 3.36; S, 7.88. Compound **6**: colorless oil; IR (neat) ν 2950, 1730, 1590, 1340, 1160, 1090, 660 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.65 (d, J = 8.0 Hz, 2H), 7.33−7.27 (m, 5H), 7.12 (dd, J = 7.4, 2.2 Hz, 2H), 5.25 (d, J = 9.5 Hz,

than **4**, with TBTH or TTMSH in the presence of AIBN afforded bicyclic product **8**[12] as a sole stereoisomer (runs 1 and 2 in Scheme 3). The reaction of **10**, which has a *cis*-iodovinyl function, under the same conditions gave a diastereomeric mixture of **11** (α:β = 3:2) (runs 1 and 2, Scheme 4). Both of the reactions using TBTH or TTMSH proceeded via a tandem 6-*exo*, 5-*exo* cyclization to furnish (4 + 1) cycloadducts. On the other hand, the electrolysis of **7** and **10** afforded monocyclic products **9** and **12**, respectively (runs 3 in Schemes 3 and 4).

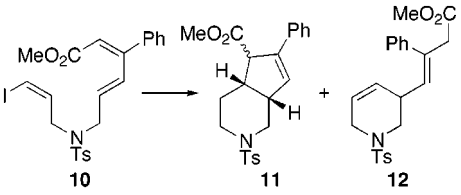
Scheme 3



run	conditions	yield (%) 8	9
1	Bu_3SnH, AIBN, benzene, reflux[a]	45	0
2	$(TMS)_3SiH$, AIBN, benzene, reflux[a]	36	0
3	Ni(cyclam)$^{2+}$, DMF, −1.5 V, rt	0	36

[a] Hydride and AIBN were added dropwise over 2 h.

Scheme 4



run	conditions	yield (%) 11[a]	12
1	Bu_3SnH, AIBN, benzene, reflux[b]	65	0
2	$(TMS)_3SiH$, AIBN, benzene, reflux[b]	70	0
3	Ni(cyclam)$^{2+}$, DMF, −1.5 V, rt	0	47

[a] Diastereomeric ratio; α:β = 3:2. [b] Hydride and AIBN were added dropwise over 2 h.

It was found that the mode of annulation was highly dependent on the substrates. Structural reinforcement of the intermediates that were formed after the first radical cyclization would be important for the regio- and stereoselectivity in the second cyclization step. Although the detailed reaction mechanism must still be clarified, possible conformations of the intermediates can drawn to explain the substrate-controlled selectivity observed (Figure 2). At the second cyclization step in the reaction of **4**, the regioselective 6-*endo* addition was predominant over 5-*exo* addition. On the other hand, the trajectory from **7** and **10** was preferentially 5-*exo*. The difference of the regioselectivity might be caused by the conformational rigidity of the pyrrolidine or piperidine ring. The diastereoselectivity for the reaction of **4** could be induced from the steric repulsion between the phenyl substituent and the ester moiety (see **13A** and **13B**). Thus, the less repulsive conformation **13A** conceded the isoindole **5**. The stereoselective production of **8** from **7** would be mainly derived from the repulsion among the phenyl ring, the ester group, and the axially oriented hydrogen on the piperidine ring (see **14A** and **14B**).

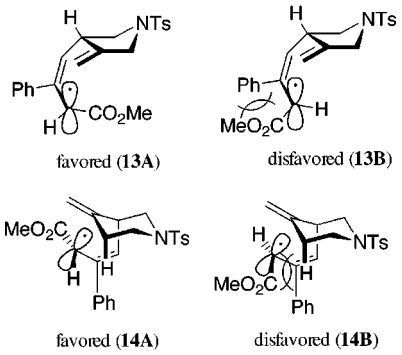


Figure 2. Transition state model.

In summary, we have developed a novel ring formation method based on the cascade radical reaction. The reaction provides (4 + 2) or (4 + 1) annulated compounds, whose regio- and stereoselectivities were highly dependent on the structure of the substrates. Further studies for the generalization of the methodology and the development of more than three-step cascade radical reactions are under investigation.

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Supporting Information Available: Synthetic procedures for key substrates and characterization data for selected compounds **3**−**12**. This material is available free of charge via the Internet at http://pubs.acs.org.

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1H), 4.94 (m, 2H), 3.96 (d, J = 15.0 Hz, 1H), 3.69 (dd, J = 15.0, 1.9 Hz, 1H), 3.60−3.55 (m, 4H), 3.34 (s, 2H), 3.24 (m, 1H), 2.84 (t, J = 9.5 Hz, 1H), 2.42 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.6, 147.4, 143.8, 139.0, 138.2, 132.9, 129.8, 128.6, 128.5, 128.0, 127.8, 127.7, 108.4, 53.4, 51.9, 51.8, 44.2, 43.2, 21.5; MS m/z 411 (M^+); HRMS m/z calcd for $C_{23}H_{25}NO_4S$ 411.1503, found 411.1483. Compound **8**: colorless oil; IR (neat) ν 2950, 1720, 1590, 1330, 1220, 1150, 1090, 750 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.66 (d, J = 8.2 Hz, 2H), 7.38−7.24 (m, 7H), 6.34 (s, 1H), 3.83 (d, J = 12.5 Hz, 1H), 3.66 (s, 3H), 3.55 (m, 1H), 3.41 (s, 1H), 2.94 (br s, 1H), 2.53 (dd, J = 12.5, 4.2 Hz, 1H), 2.43 (s, 3H), 2.46−2.34 (m, 1H), 1.97 (td, J = 12.5, 4.2 Hz, 1H), 1.46 (d, J = 12.5 Hz, 1H), 1.05 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.8, 1435, 140.6, 134.9, 133.5, 132.1, 129.7, 128.5, 127.8, 127.6, 125.4, 63.1, 51.8, 49.4, 44.8, 43.3, 42.7, 34.7, 21.5, 19.2; MS m/z 425 (M^+); HRMS m/z calcd for $C_{24}H_{27}NO_4S$ 425.1659, found 425.1679.