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6-*endo*,6-*endo*,6-*exo* Cascade cyclization starting from vinyl radical; construction of a dodecahydrophenanthrene system

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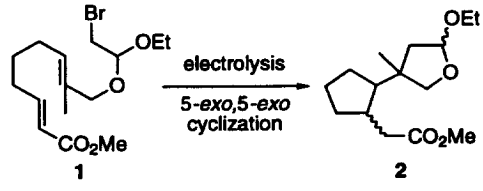
Abstract

Treatment of 1-iodo-1,5-diene **3** with Bu_3SnH at 80°C afforded the 6-*endo* cyclized product **6**. The reaction was extended further to achieve the transformation of 1-iodo-1,5,9,14-tetraene **10** into dodecahydrophenanthrene **11** under one electron reductive conditions via 6-*endo*,6-*endo*,6-*exo* cascade cyclization.

Keywords: radicals; radical reactions; cyclization; alkenyl halides.

In this quarter of the century, cascade radical cyclizations have become one of the most powerful methodologies to construct polycyclic frameworks.[1–4] Since it is well documented that 5-alkenyl radicals undergo cyclization predominantly 5-*exo* mode over 6-*endo*,[5] most of the cascade reactions were designed to afford polycyclic compounds with five-membered rings by 5-*exo* cyclization.[2] For example, recently, we have reported that reductive electrolysis of the bromoacetal **1** gave the 5-*exo*,5-*exo* cyclized compound **2** (Scheme 1).[3]



1 **2**

Scheme 1.

However, a few groups have examined the 6-*endo* cascade cyclization.[4] Zoretic reported that oxidative radical cyclization of a polyolefinic β-keto ester, a precursor of the corresponding ketyl radical, yielded the steroid analogue via consecutive 6-*endo* cyclization.[4b] A similar sequential reaction forming a steroidal skeleton from an acyl radical was demonstrated by Pattenden.[4c]

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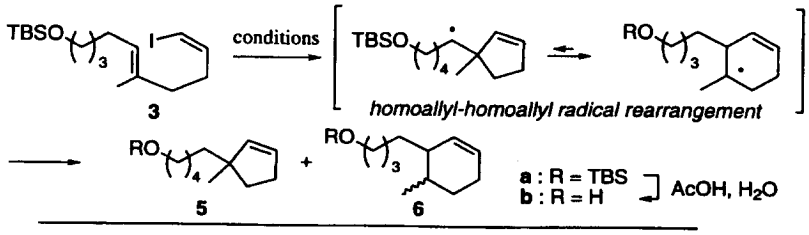
On the other hand, the use of vinyl radicals for ring closure has shown unique behavior indicating an equilibrium between 5-*exo* and 6-*endo* cyclization.[6] We herein report that the 6-*endo*,6-*endo*,6-*exo* cascade radical cyclization starting from a vinyl radical provides the dodecahydrophenanthrene compound.

As a preliminary experiment, we examined the intramolecular radical cyclization of a vinyl iodide with trisubstituted olefin moiety (Scheme 2). The vinyl iodide **3** was readily prepared from 1-(*t*-butyldimethylsiloxy)pentanal (**4**)[3] in four steps. Under refluxing conditions at 80°C in the presence of Bu_3SnH–AIBN, **3** was transformed into the cyclohexene **6a**, which was isolated as **6b** after deprotection of the silyl group, as a diastereomeric mixture in the ratio of 1:3.5 (entry 1). On the contrary, the treatment of **3** with Bu_3SnH–Et_3B at low temperature (–40°C), followed by desilylation, provided the cyclopentene **5b** as a major product (entry 2). The formation of a 6-*endo* adduct under thermodynamic conditions can be explained as follows. The reaction initially proceeds through 5-*exo* cyclization in accordance with Baldwin's rule to give the secondary radical species corresponding to **5a**. Then the homoallyl–homoallyl radical rearrangement provides the thermodynamically stable tertiary radical, which was consequently transformed into the 6-*endo* product **6a**.[6a]



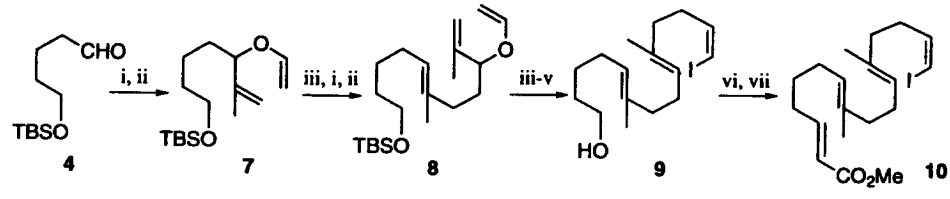
3 **5** **6**

entry	conditions	% yield[a]	ratio[b] (**5b** : **6b**[c])
1	Bu_3SnH, AIBN, benzene (1 mM), reflux	70	0 : 1
2	Bu_3SnH, Et_3B, toluene (1 mM), –40 °C	85	2 : 1

[a] Overall yield in 2 steps. [b] The ratio was determined by ^{1}H-NMR.
[c] **6b** was obtained as a 3.5:1 diastereomeric mixture.

Scheme 2.

Therefore, we planned the construction of the phenanthrene derivative, diterpenoid skeleton, by using the cascade radical cyclization of a suitably functionalized vinyl iodide. The substrate **10** was designed so as to undergo 6-*endo*,6-*endo*,6-*exo* cyclization in a sequential manner. The terminal unsaturated ester moiety was anticipated to act as a good acceptor to accelerate the radical addition.[7] Compound **10** was prepared from **4** in 10 steps (Scheme 3).

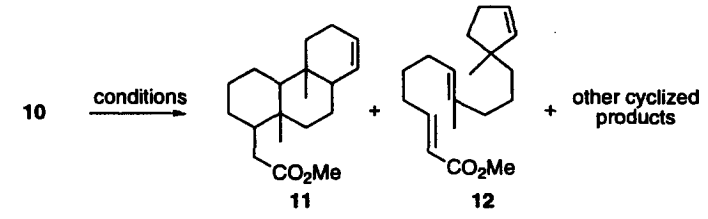


4 **7** **8** **9** **10**

Scheme 3. (i) Li, 2-bromopropene, ultrasound; (ii) ethyl vinyl ether, $Hg(OAc)_2$, $Hg(OCOCF_3)_2$, reflux; (iii) benzene, Δ; (iv) $Ph_3P^+CH_2I(I^-)$, NaHMDS, –78°C; (v) AcOH–H_2O; (vi) Dess–Martin periodate; (vii) $(MeO)_2P(O)CH_2CO_2Me$, NaH

The key reaction was examined under various conditions; reductive electrolysis,[7b,8] the Bu_3SnH method,[9] and the $(TMS)_3SiH$ method[10] (Scheme 4). The electrolysis mediated by Ni(cyclam)$^{2+}$ of **10** at rt yielded the dodecahydrophenanthrene derivative **11**, the cyclopentene derivative **12**, and other cyclized products with a 5:2:3 ratio in low yield (entry 1). The formation of **11** results from the 6-*endo*,6-

endo,6-*exo* cascade cyclization. When the reaction was performed at 100°C, the ratio of **11** increased considerably but the yield was still low (entry 2). On the other hand, when **10** was exposed to thermal conditions by using Bu_3SnH or $(TMS)_3SiH$, the desired cascade cyclization proceeds in high yield to give **11** as a major product (entry 3, 4). Especially, the treatment with $(TMS)_3SiH$–AIBN at 80°C exclusively afforded **11** in 77% yield.[11] The structure of **11** was established by spectral analysis after conversion of the olefin moiety into the carbonyl function,[12] although the stereochemistry was not determined owing to difficulty of separation of each diastereomer. The free radical reaction at –40°C using Bu_3SnH–Et_3B gave only **12** in very high yield (entry 5).[13] This indicates that, at low temperature, only the initial radical cyclization proceeds through 5-*exo* mode, but, further cyclization or homoallyl–homoallyl rearrangement does not take place.



11 **12**

entry	conditions	% yield	ratio[a] (11[b]:12:others[c])
1	Ni(cyclam)$(ClO_4)_2$, NH_4ClO_4, DMF, -1.5 V, rt	22	5 : 2 : 3
2	Ni(cyclam)$(ClO_4)_2$, NH_4ClO_4, DMF, -1.5 V, 100 °C	39	8 : 0 : 2
3	Bu_3SnH, AIBN, benzene (1 mM), reflux	76	8.5 : 0 : 1.5
4	$(TMS)_3SiH$, AIBN, benzene (1 mM), reflux	77	10 : 0 : 0
5	Bu_3SnH, Et_3B, toluene (1 mM), –40 °C	94	0 : 10 : 0

[a] Ratio was determined by ^{1}H-NMR. [b] **11** was obtained as a 4:4:1:1 diastereomeric mixture.
[c] The structures were not determined.

Scheme 4.

In conclusion, dodecahydrophenanthrene derivative **11** was obtained by the radical cyclization of 1-iodo-1,5,9,14-tetraene **10** with a single operation. It is noteworthy that the outcome of the present study is in contrast with the cascade reaction of the bromoacetal **1** mentioned in Scheme 1.

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11. To a solution of **10** (50 mg, 0.12 mmol) in benzene (120 mL) were added $(TMS)_3SiH$ (45 μL, 0.14 mmol) and AIBN (10 mg, 60 μmol) dropwise at rt. After being stirred for 2 h at 80°C, the reaction mixture was concentrated. The residue was chromatographed on silica gel (AcOEt:hexane=1:49 v/v) to afford **11** (24 mg, 77%) as a colorless oil, which was an inseparable diastereomeric mixture (diastereo ratio=1:1:4:4). IR (neat) ν 2950, 2870, 1720, 1600, 1440 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.82–2.46 (m, 25H), 3.65 (s, 1.2H), 3.65 (s, 1.2H), 3.66 (s, 0.3H), 3.67 (s, 0.3H), 5.32–5.36 (m, 0.6H) 5.55–5.57 (m, 0.8H), 5.68–5.72 (m, 0.6H); HRMS calcd for $C_{19}H_{30}O_2$ (M^+) 290.2244, found 290.2242.
12. Compound **11** was converted into the corresponding ketone by the hydroboration-oxidation, followed by CrO_3-oxidation. The formation of the phenanthrene framework was assigned on the basis of 1710 cm^{-1} absorption (C=O) in IR spectrum (neat).
13. Compound **12**: colorless oil. IR (neat) ν 2920, 2850, 1720, 1650, 1450, 1430, 1260, 1200 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.01 (s, 3H), 1.26–1.57 (m, 6H), 1.60 (s, 3H), 1.61–1.72 (m, 2H), 1.92–2.05 (m, 4H), 2.16–2.37 (m, 2H), 2.29–2.35 (m, 2H), 3.73 (s, 3H), 5.08 (m, 1H), 5.49 (dt, 1H, *J*=2.2, 5.5 Hz), 5.59 (dt, 1H, *J*=2.2, 5.8 Hz), 5.82 (dt, 1H, *J*=1.5, 15.7 Hz), 6.98 (dt, 1H, *J*=7.0, 15.7 Hz); HRMS calcd for $C_{19}H_{30}O_2$ (M^+) 290.2244, found 290.2241.