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Facile and selective formation of a linear-triquinane skeleton by a rationally designed round trip radical reaction

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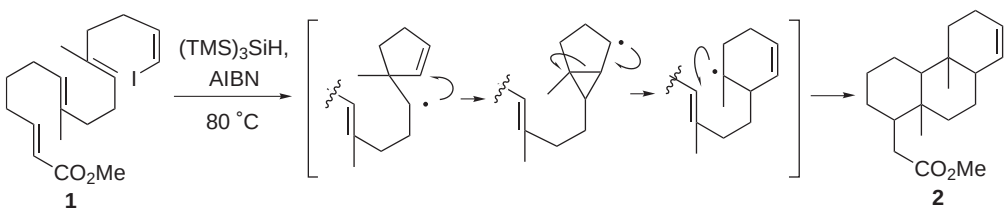
Abstract—The radical reaction of 1-iodo-1,5,10-trienoate afforded a linear fused five-membered carbocycle. Another key feature of this reaction is the remarkable acceleration of the reaction rate and enhancement of selectivity caused by the introduction of a conjugated ester moiety at the terminal olefin. This cascade reaction proceeds through three sequential 5-*exo* cyclizations. The result is in stark contrast with the previously reported radical reaction of 1-iodo-1,5,9,14-tetraenoate, which afforded a linear fused six-membered carbocycle through a 6-*endo*, 6-*endo*, 6-*exo* cyclization.

In nature, cascade (domino) processes are frequently observed during the biosynthetic course of natural products. The processes can effectively build up complex molecules from simple precursors with the formation of several bonds and stereogenic centers. Over the last few decades the biomimetic application of the cascade reaction has been highlighted as a powerful methodology for the total synthesis of natural products.[1,2] Among them, the cascade radical reactions have been developed[3] as alternative approaches to biosynthetic routes, where most of the active intermediates are cationic species. We had reported that the radical reaction of 1-iodo-1,5,9,14-tetraenoate **1** gave tricyclo[8.4.0.0^{2,7}]tetradecene **2** (Scheme 1).[4] The mechanistic studies revealed that the initial 6-*endo* cyclization was thermodynamically caused through a kinetic 5-*exo* cyclization, followed by homoallyl–homoallyl radical rearrangement. This communication documents the radical reaction of 1-iodo-1,5,10-trienoate **3**, which lacks one isoprene unit compared with **1**, to give a tricyclo[6.3.0.0^{2,6}]undecane framework. This reaction gave an easy and regioselective access to a linear-triquinane skeleton using the round trip cascade radical reaction.

Previously, Curran depicted the radical reaction of 1-iodoundeca-1,5,10-triene as a new class of cascade process, '*round trip radical reaction*'.[5,6] However, the reaction resulted in the production of tricyclo-[6.3.0.0^{2,6}]undecane as an inseparable mixture of more than five diastereomers. We had envisaged that the introduction of a conjugated ester moiety at the terminal olefin might accelerate the domino reaction and enhance the regio- and stereoselectivity compared with 1-iodoundeca-1,5,10-triene. The key substrate **3** was prepared by a short sequence of reactions as shown in Scheme 2. Dimethyl malonate was mono-alkylated with geranyl bromide to afford the diene **4** (71% yield), and further alkylation of **4** with methyl 4-bromocroto-



Scheme 1.

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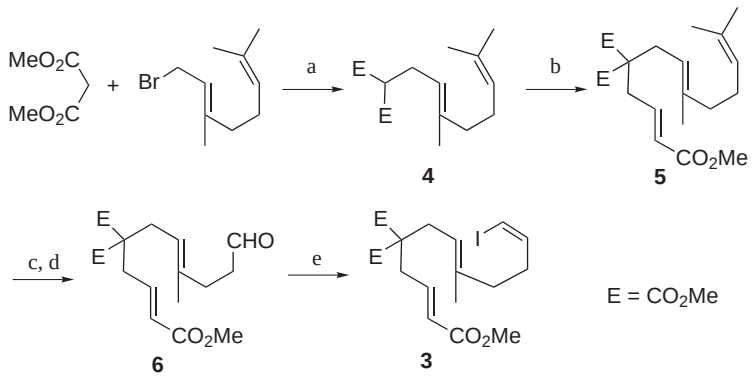
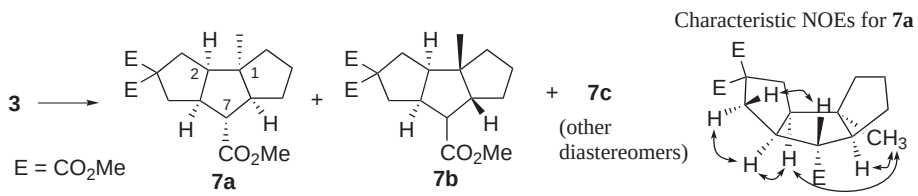


Scheme 2. (a) NaH, 0°C (71%); (b) NaH, methyl 4-bromocrotonate, 0°C (92%), (c) cat. OsO_4, NMO, rt (85%); (d) $NaIO_4$, rt (98%); (e) $Ph_3P^+CH_2I(I)^-$, NaHMDS, rt (57%).

nate gave trienoate **5** in 92% yield. The treatment of **5** with a catalytic amount of osmium tetroxide in the presence of *N*-methylmorpholine oxide (NMO), followed by oxidative cleavage of the corresponding diol by sodium periodate, provided the desired aldehyde **6** (78% overall yield in two steps). Vinyl iodide **3** was prepared by Wittig reaction of **6** in 57% yield as a single isomer having only *Z* configuration with respect to the iodo olefinic double bond.

The radical cyclization reactions of **3** were conducted under several conditions, such as tributyltin hydride (TBTH) method, tris(trimethylsilyl)silane (TTMSH) method and cathodic electrolysis[7] (Scheme 3, Table 1). The hydride source, TBTH or TTMSH, was introduced by slow addition using a syringe pump (runs 1–5), otherwise uncyclized reductants were obtained as by-products. The reaction with AIBN–TBTH under refluxing conditions afforded tricyclo[6.3.0.$0^{2,6}$]undecanes **7** in 80% yield as a mixture of more than four isomers (run 1). The desired round trip radical reaction proceeded to give a linear-triquinane framework,[5,8] but unselective formation of several diastereomers was observed. At room temperature the number of stereoisomers was reduced; treatment with Et_3B–TBTH at room temperature afforded only two isomers, **7a** and **7b**, in 83% yield with a ratio of 4:3 (run 2).[9] However, when the temperature was further lowered (–40°C), the yields of mono- and double-cyclized products were increased (run 3). The TTMSH method gave almost similar results to the TBTH method (runs 4 and 5). On the contrary, the cathodic electrolysis mediated by Ni(cyclam)$^{2+}$ afforded the poor production of **7** (runs 6 and 7).

After a careful purification using column chromatography on silica gel, only **7a** was separated from a mixture of **7a** and **7b** (run 2 in Table 1).[10] The structural assignment of **7a** was achieved on the basis of detailed 2D NMR (COSY, HETCOR, HMBC and NOESY) experiences. Its framework was determined as a *cis–syn–cis* linear-triquinane and the methoxycarbonyl group at C(7) was located on the convex side of the skeleton. Additional experiments supported its stereochemistry. The acidic proton at C(7) of **7a** would be sterically hindered, and accordingly, no deprotonation could be performed by treatment with DBU under



Scheme 3.

Table 1. Radical reaction of **3** using the TBTH method, the TTMSH method and electrolysis

Run	Conditions	Total yield of **7** (%)	Ratio[a] (**7a**:**7b**:**7c**)
1	Bu_3SnH, AIBN, benzene (2 mM), reflux	80	4:3:4
2	Bu_3SnH, Et_3B, benzene (2 mM), rt	83	4:3:0
3	Bu_3SnH, Et_3B, toluene (2 mM), −40°C	54	Nd[b]
4	$(TMS)_3SiH$, AIBN, benzene (2 mM), reflux	80	4:3:7
5	$(TMS)_3SiH$, Et_3B, benzene (2 mM), rt	74	4:3:0
6	Ni(cyclam)$(ClO_4)_2$, NH_4ClO_4, DMF, −1.5 V, 100°C	54	Nd[b]
7	Ni(cyclam)$(ClO_4)_2$, NH_4ClO_4, DMF, −1.5 V, rt	29	Nd[b]

[a] Ratio of **7a**, **7b** and **7c** was determined by ^1H NMR.
[b] Nd means 'not determined'.

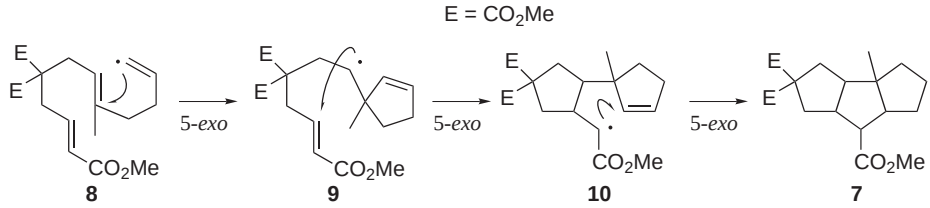


Figure 1. Pathways for the cascade reaction.

thermodynamic conditions or by LDA under kinetic conditions. Based on mechanistic aspect, the framework of **7b** might have *cis–anti–cis* configuration.

The cascade reaction of **3** occurred even at room temperature, and consequently improved the selectivity. The acceleration of the cascade could be explained by the introduction of an ester function at the terminal olefin (Fig. 1). The vinyl radical **8**, which was generated from **3** by iodine abstraction, easily cyclized in a 5-*exo*-*trig* manner to give the alkyl radical intermediate **9**. Although there are several possible pathways for the second cyclization, 5-*exo*-*trig* addition to provide α-carboxy radical intermediate **10** is kinetically predominant,[11] because alkyl radicals are widely accepted to act as nucleophilic radicals.[12] Final cyclization of **10** would be expedited because α-carboxy radicals (electrophilic species) tend to preferentially react with electron-rich olefins.[12] As a consequence, three sequential 5-*exo*-*trig* cyclizations to afford **7** could be completed at room temperature with good efficiency.

It is quite interesting to observe that the radical reactions of acyclic isoprenoid analogs **1** and **3** proceed through different pathways. The reaction of geranylgeranyl analog **1** produced tricyclo[8.4.0.$0^{2,7}$]tetradecane **2**, which is a linear fused six-membered ring carbocycle, through a sequential 6-*endo*, 6-*endo*, 6-*exo* cyclization (Scheme 1).[4,13] Whereas a 5-*exo*, 5-*exo*, 5-*exo* cyclization proceeded in the case of farnesyl analog **3** to give tricyclo[6.3.0.$0^{2,6}$]undecane **7**, which is a linear fused five-membered ring carbocycle[8] (Scheme 3). The cascade sequences were firmly dependent on the regioselectivity at the second stage of the radical reaction. In the former case, 3-*exo*-*trig* cyclization, followed by rearrangement to result in formal 6-*endo*-*trig* cyclization, kinetically preceded over 5-*endo*-*trig* addition to another olefin. However, in the latter, 5-*exo*-*trig* cyclization was much preferred to 3-*exo*-*trig* cyclization. These complementary results might be attributed to the characteristic features of radical cascades.

In summary, tricyclo[6.3.0.$0^{2,6}$]undecane **7**, which resembles a linear-triquinane skeleton, was obtained by the round trip radical cyclization of 1-iodo-1,5,10-triene **3** with a single operation. The reactivity and selectivity of the cascade reaction could be controlled by the rational design of the substrate, such as the introduction of ester function. We believe the further studies would pave way for the facile total syntheses of various linear-triquinanes.

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9. Procedure for run 2 in Scheme 2: To a solution of **3** (0.10 mmol) in benzene (50 mL) was added a 1 M solution of Et_3B in hexane (0.05 mmol) at rt. To the mixture was slowly added a solution of Bu_3SnH (0.12 mmol) in benzene (5 mL) over 3 h. After being stirred for 1 h at rt, the solution was concentrated. The resulting residue was chromatographed on silica gel.
10. Spectral data for **7a**: Colorless oil, IR (neat) ν 1732 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.66 (s, 3H), 3.65 (s, 3H), 3.60 (s, 3H), 2.84–2.76 (m, 1H), 2.51 (dd, $J=14.2$, 8.2 Hz, 1H), 2.34 (t, $J=8.0$ Hz, 1H), 2.30 (t, $J=8.0$ Hz, 1H), 2.27–2.24 (m, 1H), 2.20 (t, $J=10.3$ Hz, 1H), 1.97 (dd, $J=14.2$, 5.3 Hz, 1H), 1.93–1.90 (m, 1H), 1.69–1.58 (m, 4H), 1.51–1.46 (m, 1H), 1.15 (dt, $J=13.3$, 6.6 Hz, 1H), 1.01 (s, 3H); HRMS m/z calcd for $C_{19}H_{27}O_6$ (M^++1) 339.1808, found 339.1790.
11. In the second cyclization of **3**, the rate of 5-*exo* cyclization might be $\sim$100 times faster than 3-*exo* cyclization, which can lead to homoallyl–homoallyl radical rearrangement. On the other hand, in the second cyclization of **1**, 3-*exo* cyclization is predominant against 5-*endo* cyclization. For a review of kinetics of radical cyclizations, see: Griller, D.; Ingold, K. U. *Acc. Chem. Res.* **1980**, *13*, 317–323.
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