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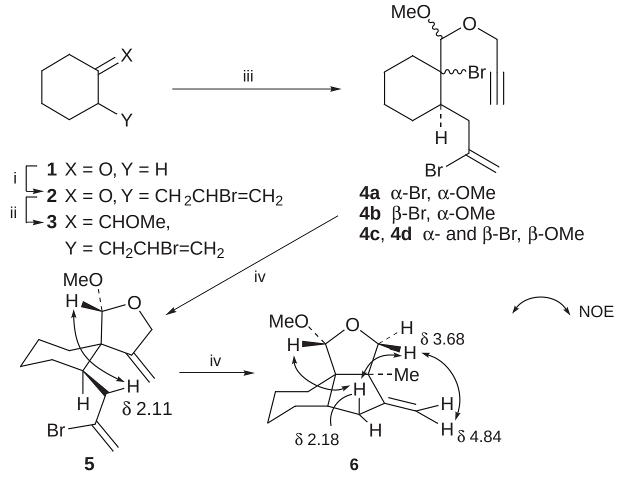
Tandem 5-*Exo*-dig-5-*exo*-trig Radical Cyclization leading to a 6,5-Ring Fused Carbobicycle possessing Two Contiguous Quaternary Carbons at the Bridgehead and its Adjacent Positions†

Hajime Nagano,* Yohko Ohtani, Eiko Odake, Junko Nakagawa, Yukie Mori‡ and Tomoko Yajima

Department of Chemistry, Faculty of Science, Ochanomizu University, Otsuka, Bunkyo-ku, Tokyo 112-8610, Japan

The tin-mediated tandem 5-*exo*-dig-5-*exo*-trig radical cyclization of dibromoacetal **4a** stereoselectively gives the angular 6,5,5-ring fused tricycle **6** *via* spirocyclic acetal **5** in 93% yield.

Tin-mediated tandem radical cyclization has become a powerful method for the construction of complex polycyclic compounds.[1] We now report the tandem 5-*exo*-dig-5-*exo*-trig cyclization of dibromoacetal **4a** yielding the angular 6,5,5-ring fused tricycle **6**, a unique carbon skeleton found in natural products (Scheme 1).[2] The radical precursors **4a**-**d** were prepared from cyclohexanone **1**. The lithium enolate of **1** was allylated with 2,3-dibromopropene to give 2-(2-bromo-2-propenyl)cyclohexanone **2** in 64% yield. The Wittig reaction of **2** with $Ph_3P=CHOMe$ in diethyl ether gave a mixture of enol ethers **3*E*** and **3*Z*** in 83% yield. The *E* geometry of **3*E*** was assigned by NOE between =CBrCH (δ 2.59) and =C*H*OMe (δ 5.78).



Scheme 1 *Reagents*: i, $LiNPr^i_2$, $BrCH_2CBr=CH_2$; ii, $Ph_3P=CHOMe$; iii, NBS, prop-2-yn-1-ol; iv, Bu^n_3SnH, AIBN, *hν*.

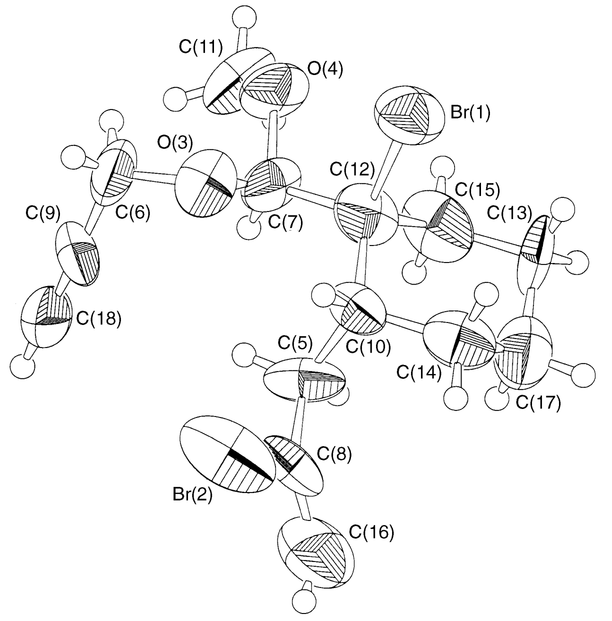
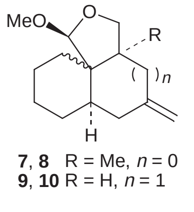


Fig. 1 X-Ray crystal structure of **4a**

The bromoacetalization of the enol ethers **3*E*** and **3*Z*** (14:1) with *N*-bromosuccinimide (NBS) and prop-2-yn-1-ol in dichloromethane gave four diasteromers **4a**–**d** in a ratio of 12.8:2.9:5.7:1. The major product **4a** was isolated from the mixture in 55% yield.[3] The stereochemistry of **4a** was determined by an X-ray crystallographic analysis (Fig. 1).[4] The tandem radical cyclization of **4a** was conducted with 4 equiv. of Bu^n_3SnH in diethyl ether under irradiation with a 100 W tungsten-filament lamp to give the tricyclic 5-*exo*-dig-5-*exo*-trig cyclization product **6** in 94% yield, with neither its stereoisomer nor 5-*exo*-dig-6-(formal)-*endo* trig-cyclization product[5] being detected. The radical reaction performed in the presence of 1 equiv. of Bu^n_3SnH gave spirocyclic compound **5**,[6] which was cyclized with an additional equiv. of Bu^n_3SnH to give **6**.[7] The stereochemistry of compounds **5** and **6** was determined by NOE experiments.[8] Srikrishna *et al.* have reported that the spiroannulation proceeded *via* the less crowded axial radicals.[9] The spiroannulation yielding **5** proceeds *via* either the axial or equatorial radical. However, the axial radical intermediate yielding the diastereomer of **5** is probably less favorable because of the steric repulsion between the OMe and equatorial $CH_2CBr=CH_2$ groups.

Cyclization of the minor dibromoacetal **4c** gave two 5-*exo*-dig-5-*exo*-trig and two 5-*exo*-dig-6-(formal)-*endo*-trig cyclization products **7**–**10** (ratio 1:1.5:3.4:3.4) and spirocyclic intermediates (=stereoisomers of **5**) in 63% yield.[10] Treatment of the inseparable mixture of **4b** and **4d** with Bu^n_3SnH gave **6**,–**9**.[11]



7, **8** R = Me, *n* = 0
9, **10** R = H, *n* = 1

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* To receive any correspondence (*e-mail:* nagano@hososipc.chem.ocha.ac.jp).

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‡ Present address: Molecular Photochemistry Laboratory, The Institute of Physical and Chemical Research (RIKEN), Wako, Saitama, 351-0198, Japan.

Experimental

Allylation of Cyclohexanone **1** *with* 2,3-*Dibromopropene*.—To a solution of the enolate of cyclohexanone, prepared from lithium diisopropylamide and cyclohexanone (1.0 g, 10 mmol) in THF (4 cm^3) cooled to −75 °C, was added a solution of 2,3-dibromopropene (2.0 g, 10 mmol) in THF (4 cm^3). The solution was warmed gradually to room temperature. Column chromatography on silica gel (hexane–ethyl acetate, 50:1) gave ketone **2** (1.4 g, 64% yield), an oil, ^1H NMR ($CDCl_3$) δ 5. 61 (1 H, d, $J = 1.5$ Hz, $=$CH), 5.44 (1 H, t, $J = 0.7$ Hz, =CH), 2.99 (1 H, dd, $J = 14.5$, 4.7 Hz, CHC=), 2.68 (1 H, m, CHC=) and 2.46–1.22 (9 H, m). HRMS: Found *m/z* 137.0929 ($M^+ - Br$). Calc. for $C_9H_{13}O$: (M − Br), 137.0966.

Wittig Reaction of **2**.—To a suspension of Ph_3PCH_2OMeCl (4.6 g, 13.5 mmol) in dry diethyl ether (27 cm^3) cooled to −85°C was added a solution of Bu^nLi (1.6 mol dm^{-3}; 8.4 cm^3, 13.5 mmol). A solution of ketone **2** (1.46 g, 6.7 mmol) in dry diethyl ether (9 cm^3) was then added and the mixture was warmed gradually to room temperature. Column chromatography gave **3*E*** and **3*Z*** in 83% yield and in a ratio of 14:1. **3*E***: ^1H NMR ($CDCl_3$) δ 5.78 (1 H, s,=C*H*OMe), 5.52 (1 H, d, $J = 1.2$ Hz, $=$CH), 5.42 (1 H, d, $J = 1.5$ Hz, =CH), 3.54 (3 H, s, OMe), 2.65–1.95 (5 H, m, CH_2 and CH) and 1.7–1.3 (6 H, m, CH_2). **3*Z*** ^1H NMR ($CDCl_3$) δ 5.79 (1 H, s, =C*H*OMe), 5.56 (1 H, d, $J = 1.5$ Hz, =CH), 5.41 (1 H, d, $J = 1.5$ Hz, =CH), 3.51 (3 H, s, OMe), 3.22 (1 H, m, CH), 2.57 (2 H, m, CH_2) and 2.0–1.2 (8 H, m, CH_2). HRMS (**3*E*+3*Z***): Found *m/z* 212.0198 ($M^+ - MeOH$). Calc. for $C_{10}H_{13}Br$: (M − MeOH), 212.0201.

Bromoacetalization of **3**.—To a solution of **3** ($E : Z = 14:1$) (100 mg, 0.4 mmol) in dry CH_2Cl_2 (1.5 cm^3) cooled to −78°C was added a solution of propargyl alcohol (0.5 cm^3) and NBS (73 mg, 0.4 mmol) in CH_2Cl_2 (0.5 cm^3). Column chromatography on silica gel [22 g; hexane–ethyl acetate (50:1)] gave **4a** (86 mg, 55% yield). Compound **4a**, mp 45–46°C (from hexane); ^1H NMR ($CDCl_3$) δ 5.59 (1 H, t, $J = 1.5$ Hz, $=$CH), 5.45 (1 H, s, $=$CH), 4.65 [1 H, s, *H*C(OMe)O], 4.42 (2 H, d, $J = 2.5$ Hz, CH_2O), 3.66 (3 H, s, OMe), 2.93 (1 H, d, $J = 12.0$ Hz, CHC= 2.6–2.4 (2 H, m, CHC= and CH), 2.50 (1 H, t, $J = 2.5$ Hz, C≡CH and 2.2–1.4 (8 H, m, CH_2). HRMS: Found *m/z* 299.0627 ($M^+ - Br$). Calc. for $C_{14}H_{20}BrO_2$: (M − Br), 299.0647.

Radical Cyclization of **4a**.—A solution of **4a** (30 mg, 0.08 mmol), $Bu^n{}_3SnH$ (93 mg, 0.32 mol) and a catalytic amount of AIBN in dry diethyl ether (4 cm^3) was irradiated with 400 W Xe lamp at room temperature for 4.5 h under nitrogen. After treatment of the mixture with potassium fluoride–water, the reaction mixture was chromatographed on silica gel [11 g; hexane–ethyl acetate (100:1)] to give **6** (17 mg, 94%), ^1H NMR ($CDCl_3$) δ 4.93 (1 H, d, $J = 2.7$ Hz, =CH), 4.84 (1 H, d, $J = 2.7$ Hz, $=$CH), 4.79 [1 H, s, *H*C(OMe)O], 3.68 (2 H, s, OCH_2), 3.36 (3 H, s, OMe), 2.18 (1 H, dd, $J = 14.0$, 6.4 Hz, =CH), 2.10 (1 H, tt, $J = 14.0$, 2.7 Hz, =CH), 2.0–1.0 (9 H, m, CH_2 and CH), and 0.98 (3 H, s, Me); ^{13}C NMR ($CDCl_3$) δ 161.1, 107.7, 104.4, 78.8, 57.4, 55.2, 54.5, 46.7, 38.0, 29.4, 27.5, 26.2, 23.7 and 16.6. HRMS: Found *m/z* 222.1623 (M^+). Calc. for $C_{14}H_{22}O_2$: M, 222.1607.

Compound **5**.—^1H NMR ($CDCl_3$) δ 5.52 (1 H, t, $J = 1.5$ Hz, =CH), 5.40 (1 H, t, $J = 2.0$ Hz, =CH), 5.00 (1 H, t, $J = 2.0$ Hz, $=$CH), 4.94 (1 H, t, $J = 2.0$ Hz, =CH), 4.84 [1 H, s, *H*C(OMe)O], 4.43 [1 H, dt, $J = 13.5$, 2.0 Hz, CHO), 4.33 (1 H, dt, $J = 13.5$, 2.0 Hz, CHO), 3.37 (3 H, s, OMe), 2.36 (1 H, d, $J = 14.2$ Hz, CHC=), 2.11 (1 H, dd, $J = 14.2$, 11.2 Hz, CHC=) and 2.05–0.85 (9 H, m, CH_2 and CH). HRMS: Found *m/z* 300.0684 (M^+). Calc. for $C_{14}H_{21}BrO_2$: M, 300.0725.

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4 *Crystal Data for* **4a**: $C_{14}H_{20}Br_2O_2$, $M_r = 380.1$, monoclinic, space group $P2_1$, $a = 10.519(5)$, $b = 12.038(6)$, $c = 6.463(3)$ Å, $\beta = 98.51(4)°$, $V = 809.4(7)$ Å^3, $Z = 2$, Cu-Kα radiation, $\lambda = 1.54184$ Å, $T = 293$ K, $\mu = 63.01$ cm^{-1}, 1338 reflections measured, 1216 unique reflections, 679 observed reflections $[I > 2\sigma(I)]$, $R = 0.089$. Full crystallographic details, excluding structure factors, have been deposited at the Cambridge Crystallographic Data Centre (CCDC). See Instructions for Authors, *J. Chem. Research (S)*, 1998, Issue 1. Any request to the CCDC for this material should quote the full literature citation and the reference number 423/20.

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10 No attempt was made to determine the stereochemistry of the inseparable dibromoacetals and cyclization products.

11 The tandem radical cyclization of the homologous dibromoacetals derived from cycloheptanone gave three 5-*exo*-dig-5-*exo*-trig and two 5-*exo*-dig-6-(formal)-*endo*-trig cyclization products in moderate yield. The reaction of the dibromoacetals derived from cyclopentanone with $Bu^n{}_3SnH$ gave two 5-*exo*-dig-5-*exo*-trig and a 5-*exo*-dig-6-(formal)-*endo*-trig cyclization products.