Stereoselective Bifurcating-type Radical Cyclization of *gem*-Dibromocyclopropanes for the Synthesis of Uniquely Fused 5-3-5-Type Tricyclic Compounds

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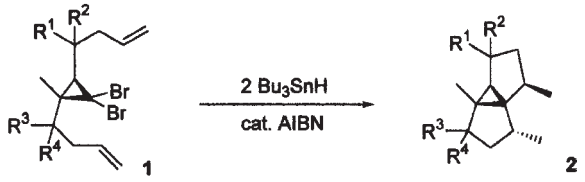
Bifurcating radical cyclization of *gem*-dibromocyclopropane derivatives afforded novel fused 5-3-5 type tricyclic products with high 5-*exo*-*trig* and transannular mode.

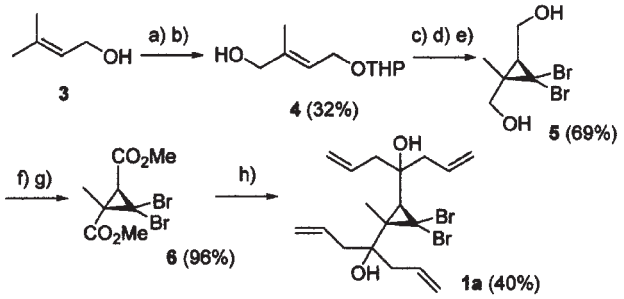
Tandem radical cyclization is a prominent synthetic tool for the construction of polycyclic carbon skeletons.[1] The majority of these cyclizations comprise sequential ring formations through a "cascade" process. Wilcox and co-workers explored a new type (non-cascade) of the reaction, called "bifurcating" cyclization, using acyclic *gem*-dibromo substrates that are transformed into bispentallen skeletons, though with low to moderate stereoselectivities.[2] Dowd and Zhang reported that 3-(3-butenyl)-2,2-dichlorocyclobutanones underwent a related sequential generation of *geminal* radicals to give 2-methyl-bicyclo[3.2.0]heptan-7-ones, wherein cyclization and hydro-dechlorination successively proceeded in a one-pot manner.[3]

There has appeared no report, however, of bifurcating cyclization using the available substrate, *gem*-dihalogenocyclopropanes. As part of a program of synthetic studies on the transformation of *gem*-dihalogenocyclopropanes from many-sided cationic,[4] radical,[5] and anionic[6] approaches, we report herein a new stereoselective bifurcating cyclization of *gem*-dibromocyclopropanes **1** to afford novel, uniquely fused 5-3-5-type tricyclic compounds **2**.[7] Synthetic routes to three types of substrates **1** are as follows.



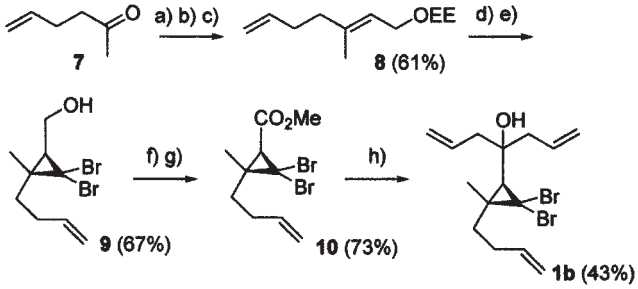
The first entry is tetraene substrate **1a** (Scheme 1). THP protection of 3-methyl-2-buten-1-ol (**3**) followed by stereoselective oxidation with SeO_2-TBHP gave *trans*-half THP-ether **4**. After THP protection of **4**, successive dibromocarbene addition, followed by deprotection of two THP groups gave *gem*-dibromocyclopropyl dimethanol **5**. Jones' oxidation of **5** and CH_2N_2 esterification produced dimethyl ester, which followed by allylation using 4 equiv of allylmagnesium bromide, afforded the desired substrate **1a**.

The second entry is tetraene substrate **1b** (Scheme 2). Horner-Emmons-Wadsworth reaction of hexenone **7** with triethyl phosphonoacetate gave α,β-unsaturated ester ($E/Z = 10:1$; after chromatographic separation of major *E* form), which was reduced by LAH, followed by ethoxyethyl (*EE*) protection to afford *EE*-ether **8**. Regioselective dibromocarbene addition[8] of **8**,



a) DHP, cat. CSA / ether; b) SeO_2 (0.5 eq), TBHP (2.0 eq) / CH_2Cl_2; c) DHP, cat. CSA / ether; d) $CHBr_3$, cat. $PhCH_2N^+Et_3 \cdot Cl^-$ / 50%-NaOH aq.; e) cat. CSA / MeOH; f) Jones' reagent / acetone; g) CH_2N_2 / ether; h) $4CH_2=CHCH_2MgBr$ / THF.

Scheme 1.

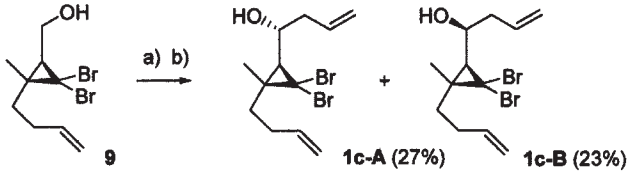


a) $(EtO)_2P(O)CH_2CO_2Et$, NaH / DMF; b) LAH / THF; c) ethyl vinyl ether, cat. CSA / ether; d) $CHBr_3$, cat. $PhCH_2N^+(Me)_2CH_2CH_2OH \cdot Cl^-$ / 50% - NaOH aq.; e) cat. CSA / MeOH; f) Jones' reagent / acetone; g) CH_2N_2 / ether; h) $2CH_2=CHCH_2MgBr$ / THF.

Scheme 2.

followed by *EE* deprotection gave alcohol **9**. Allylation of **9** using 2 equiv of allylmagnesium bromide afforded the desired substrate **1b**.

The third entry is diene substrate. **1c** (Scheme 3). PCC oxidation of **9** followed by allylation with allylmagnesium bromide gave the desired substrates **1c-A** and **1c-B** as separable diastereoisomers. The stereochemistry of **1c-A** and **1c-B** was deduced based on the spectral analogy (^1H NMR) of related *gem*-

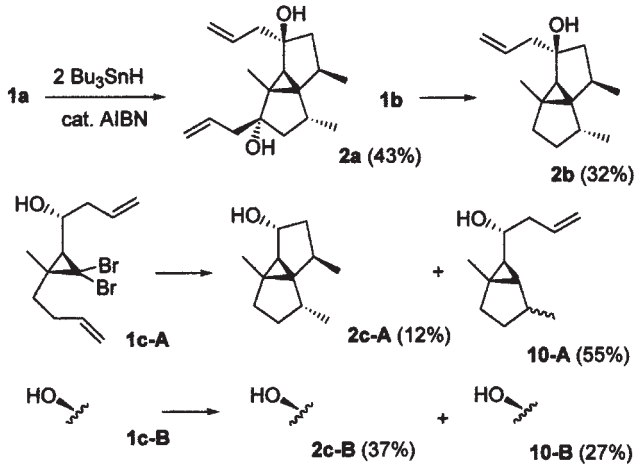


a) PCC / CH_2Cl_2; b) $CH_2=CHCH_2MgBr$ / THF.

Scheme 3.

dihalogenocyclopropanes.[5a]

The stereocontrolled bifurcating cyclization of **1-a** was performed as follows (Scheme 4): Treatment of **1-a** with of Bu_3SnH (3.3 equiv)/cat. AIBN (0.10 equiv) gave nearly C-2 symmetrical 5-3-5 tricyclic compound **2a** as the main product in 43% yield with trace amounts of other stereoisomers.[9] The relative stereochemistry of **2a** was unambiguously determined using X-ray analysis.[10]



Scheme 4.

Triene substrate **1b** also underwent the reaction to give **2b** in 32% yield with trace amounts of other stereoisomers. The stereochemistry of **2b** was deduced on the basis of the spectral analogy (^{1}H and ^{13}C NMR) of **2a**.

The reactions using diene substrates **1c-A** and **1c-B** had a distinctive pattern. *anti*-Diastereoisomer **1c-A** resulted in the formation of the desired tricyclic product **2c-A** in only 12%, mainly with the bicyclic product **10-A** (55%; ca. 1 : 1 diastereo mixtures), whereas *syn*-diastereoisomer **1c-B** provided the desired product **2c-B** in 37% yield, with the bicyclic product **10-B** (27%). Computer-assisted conformation analysis supports the differentiating results; in the most preferential conformations, the olefin part of **1c-B** located in close proximity to the *gem*-dibromo moiety, whereas that of **1c-A** located itself its against position.[11]

It should be noted that all of these reactions uniformly provided 5-*exo*-*trig* and *transannular* stereoisomers, accordingly, the product **2a** possesses of nearly *C*-2 symmetrical structure.

In conclusion, a novel bifurcating radical cyclization of *gem*-dibromocyclopropane analogs was performed. In spite of the inherent steric rigidity, three unique and stereocontrolled 5-3-5 tricyclic products were synthesized using the present method.

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Dedicated to Prof. Teruaki Mukaiyama on the occasion of his 75th birthday.

References and Notes

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7 Throughout this study, methyl substituted cyclopropanes was employed for its convenience of the preparation.[4]

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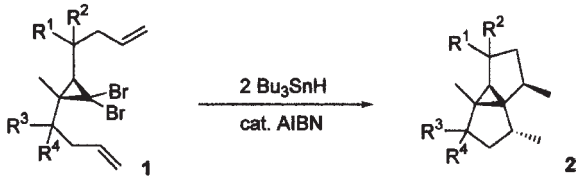
9 Bu_3SnH (633 mg, 2.28 mmol) was added to a stirred mixture of **1a** (342 mg, 0.69 mmol) and AIBN (12 mg, 0.07 mmol) in toluene (1.5 ml) at 65-70 °C under a nitrogen atmosphere, and the mixture was stirred at 105-110 °C for 3 h. After cooled down to room temp., the mixture was stirred with an aqueous 10% KF solution (ca. 10 ml) for 30 min. After Celite filtration, the separated organic phase was washed with water, brine, dried (Na_2SO_4), and concentrated. The obtained crude oil was purified with column chromatography (SiO_2; hexane/AcOEt = 3 : 1 ~ 2 : 1) to give the product **2a** (108 mg, 43%): colorless crystals; 145-150 °C; ^{1}H NMR (400 MHz): δ 0.76 (1H, dd, J = 11.4, 13.7 Hz), 0.86 (3H, d, J = 6.4 Hz), 0.99 (3H, d, J = 6.4 Hz), 1.35 (1H, s), 1.44-1.59 (1H, m), 1.53 (3H, s),1.84 (1H, dd, J = 11.4, 13.7 Hz), 1.92-2.08 (2H, m), 1.98 (1H, d, J = 6.4 Hz), 2.17-2.31 (1H, m), 2,22 (1H, d, J = 6.4 Hz), 2.31-2.54 (4H, m), 5.05-5.22 (4H, m), 5.72-6.08 (2H, m); ^{13}C NMR (100 MHz) with DEPT: δ 10.99 (CH_3), 15.21 (CH_3), 15.51 (CH_3), 31.33 (CH), 31.71 (CH), 33.46 (CH), 38.16 (quaternary), 42.22 (CH_2), 42.66 (CH_2), 45.34 (CH_2), 48.30 (CH_2), 48.67 (quaternary), 80.38 (quaternary), 82.17 (quaternary), 118.11 (CH_2), 118.93 (CH_2), 133.94 (CH), 134.43 (CH); IR(KBr): 3320, 2948, 2880, 1456 cm^{-1}.

10 X-ray crystallographic data: $C_{18}H_{28}O_2$, MW=276.42, colorless, prismatic, monoclinic, space group C2/c (#15), a = 23.505 (3) Å, b = 10.569 (2) Å, c = 17.947 (3) Å, β = 131.473 (7) Å, V = 3340 (1) Å^3, Z = 8, D_c = 1.099 g/cm^3, F_{000} = 1216.00, μ(CuKα) = 5.38 cm^{-1}, T = 24 °C, R = 0.068, Rw = 0.052 for 2025 observations ($I > 3.00\sigma(I)$). The structure was solved by direct method (MITHRIL90).

11 Calculation was performed by SPARTAN version 5.0 (Wavefunction, Inc., Irvine, CA), Ab initio, HF, 3-21G(*).



Additions and Corrections

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Page 31, the scheme below Reference 11 was wrongly displaced on the publishing procedure. Reference 11 should appear as given below.

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