Evidence for Spontaneous Cycloaromatization of Nine-Membered Monocyclic Enediyne

Takashi Mita, Shinji Kawata, and Masahiro Hirama*
Department of Chemistry, Graduate School of Science, Tohoku University,
and CREST, Japan Science and Technology Corporation (JST), Sendai 980-8578

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Treatment of 2,2-dimethyl-6-nonene-4,8-diynal (**2**) with $CeCl_3$/LiN(TMS)$_2$ at -5~25 °C gave 2,2-dimethyl-1-indanol (**3**) in a moderate yield. In the present study, acyclic (*Z*)-enediyne aldehyde (**2**) was cyclized to afford a nine-membered monocyclic enediyne (**7**), which cycloaromatized spontaneously at room temperature.

Although researches have suggested that a nine-membered monocyclic enediyne (**1**) can undergo Masamune-Bergman cycloaromatization spontaneously at room temperature, no experimental evidence has yet been reported.[1,2] Construction of the highly strained nine-membered core of bicyclo[7.3.0]dodecadiyne system is crucial for synthesizing the enediyne chromophores of extremely potent antitumor chromoprotein antibiotics.[2b,3] Although several methods for constructing those systems have been reported,[4] a $CeCl_3$/LiN(TMS)$_2$ mediated intramolecular acetylide addition to aldehyde has been shown to be most effective.[5,6] All the reaction substrates that lead to cyclononadiyne systems accommodate at least two structural elements which reduce the degree of conformational freedom, i.e., *cis*-olefin or *cis*-epoxide, and an additional five-membered carbocyclic fused ring. We recently demonstrated that the former restriction is not always necessary.[6] Herein, we report that even acyclic (*Z*)-enediyne aldehyde (**2**) without the latter restriction can be cyclized by $CeCl_3$/LiN(TMS)$_2$, resulting in the formation of an indane derivative (**3**).

(*Z*)-enediyne (**2**) was synthesized from **4**[7] and **5**[8] in a straightforward manner: (i) Pd(PPh$_3$)$_4$, CuI, *n*-BuNH$_2$, benzene, r.t., 75%; (ii) LiOH·H$_2$O, THF-H$_2$O (5:1), r.t., 88%; (iii) DIBAL, Et$_2$O, -78 °C, **2**,[9] 49%. Treatment of **2** with $CeCl_3$/LiN(TMS)$_2$ (15 equiv.) in THF (5 mmol/l) at -79 °C for 1 h yielded only a mixture of dimer (**6**) (27%) and oligomeric products. However, the reaction under a higher dilution (1 mmol/l) and higher temperature (-5~25 °C) gave 2,2-dimethyl-1-indanol (**3**)[10] in 14-35% yield. Below -20 °C, even under high dilution conditions, primarily **6** and oligomeric products were produced. The best yield of **3** (35%) was obtained by adding **2** to a THF solution of 15 equiv. of $CeCl_3$/LiN(TMS)$_2$ at 25 °C over a period of 3 h.[11] A large excess of $CeCl_3$/LiN(TMS)$_2$ was necessary to obtain **3** in a yield better than 10%. All attempts to trap the intermediate **7** as a dicobalthexacarbonyl complex using excess $Co_2(CO)_8$ and NMR detection failed. Only **3** was detected in either case. On the other hand, a trapping experiment of putative indane 4,6-biradical with THF-d_8 was attempted but no indane derivative was formed possibly due to a retarded deuterium abstraction.

The present study demonstrates that the intramolecular acetylide-aldehyde condensation reaction with $CeCl_3$/LiN(TMS)$_2$ is applicable to the simple (*Z*)-enediyne aldehyde (**2**) and the resulting nine-membered monocyclic enediyne (**7**) undergoes Masamune-Bergman reaction rapidly at the condensation temperature.

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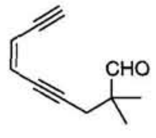

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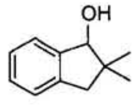

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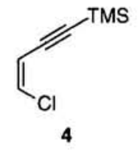

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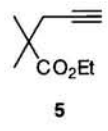

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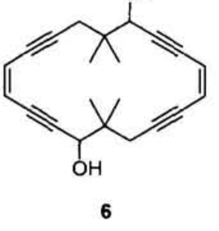

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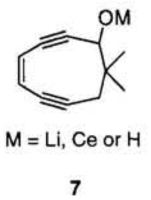

M = Li, Ce or H

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9 **2**: pale yellow oil; ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.19 (6H, s), 2.55 (2H, br d, J=2.2 Hz), 3.29 (1H, dd, J=2.3, 0.9 Hz), 5.75 (1H, ddt, J=10.9, 2.3, 0.6 Hz), 5.87 (1H, dtd, J=10.9, 2.2, 0.9 Hz), 9.57 (1H, s); ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.27, 27.81, 45.56, 80.30, 80.84, 84.13, 94.42, 118.01, 121.80, 204.55; FT-IR (neat) ν 3288, 2972, 2216, 1729, 1468 cm^{-1}; HRMS (EI, 70 eV) Calcd for $C_{11}H_{12}O$ 160.0888 (M^+); Found 160.0884 (M^+).

10 **3**: colorless solid; mp. 87-90°C; ^{1}H NMR (600 MHz, CD_2Cl_2) δ 1.00 (3H, s), 1.16 (3H, s), 2.65 (1H, d, J=15.5 Hz), 2.76 (1H, d, J=15.5 Hz), 4.67 (1H, br s), 7.17-7.22 (3H, m), 7.32-7.34 (1H, m); ^{13}C NMR (150 MHz, CD_2Cl_2) δ 21.88, 27.16, 45.24, 45.48, 84.10, 125.04, 125.74, 127.17, 128.63, 142.78, 145.53; FT-IR (film) ν 3362, 2960, 2930, 2868, 1719, 1611 cm^{-1}; HRMS (EI, 70 eV) Calcd for $C_{11}H_{14}O$ 162.1045 (M^+); Found 162.1050 (M^+).

11 Experimental procedure: To a solution of $(TMS)_2NH$ (0.32 ml, 1.5 mmol) in THF (8 ml) was added a hexane solution of butyllithium (0.8 ml, 1.3 mmol) at 0 °C. After the solution was stirred for 25 min at the same temperature, the solution was cooled down to -45 °C. To this solution was added a suspension of dry $CeCl_3$ (299 mg, 1.2 mmol) in THF (8 ml),[12] and then a solution of **2** (12 mg, 0.076 mmol) in THF (60 ml) was added slowly at room temperature over a period of 3 h. The reaction mixture was further stirred for 1 h and quenched with saturated NH_4Cl aqueous solution.

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