5-*EXO*,5-*EXO* CASCADE CYCLIZATIONS OF HALO-OLEFINS BY ENVIRONMENTALLY FRIENDLY REACTION USING INDIRECT ELECTROLYSIS

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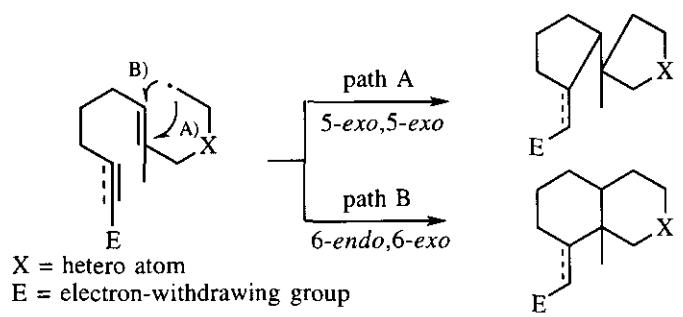
Abstract – [Ni(cyclam)]$(ClO_4)_2$ or vitamin B_{12a}-mediated electroreduction of the 1-bromo-5-ene-10-yne (**4**) and the 1-bromo-5,10-diene (**6**) gave bicyclic five-membered ring compounds in a highly regioselective manner by 5-*exo*,5-*exo* cascade radical cyclizations.

Recently, radical reactions have emerged as useful tools for carbon-carbon bond formation in organic synthesis.[1] The majority of useful radical-mediated addition reactions has been carried out using organostannane[2] or organosilane[3] radical sources. However, the above methods have some drawbacks that a stoichiometric amount of chemical reagents and high dilution conditions are required, and the separation of the cyclized products from byproducts is sometimes a troublesome task.

Previously, we demonstrated the syntheses of six-membered ring compounds by the environmentally friendly cyclization with Ni(II)-mediated electrolysis.[4] As an extension, we applied this methodology for the cascade cyclizations of halo-olefins. Although the cascade radical reactions have been widely studied,[5] most of the cyclizations were performed by treatment with Bu_3SnH. Our previous studies have demonstrated that the substrates having a bromoacetal function as a radical generated group tethered with an electron-withdrawing group as a radical acceptor effectively undergo cyclization under the electrolytic conditions.[4] Accordingly, we designed the reaction system as shown in **Scheme 1**.

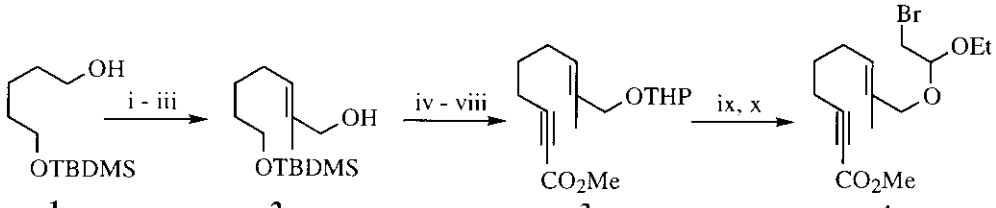


Scheme 1

In this system, we have envisaged the formation of two possible products by competitive cyclization in a 5-*exo*,5-*exo* (path A) and a 6-*endo*,6-*exo* (path B) fashion. Here, we report results of the cascade radical

cyclization by electrolysis.

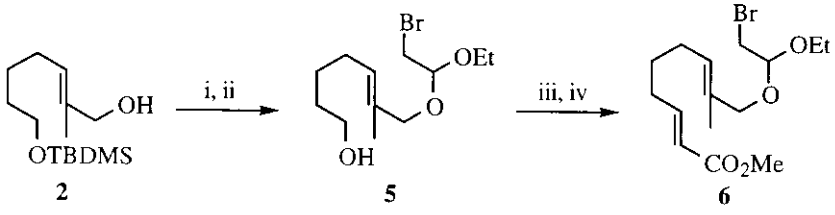
Bromoacetals (**4**) and (**6**) were prepared from 5-(*tert*-butyldimethylsilyloxy)-1-pentanol (**1**)[6] as follows. The allyl alcohol (**2**), which was derived from **1**, was converted into the acetylenic ester (**3**) in five steps; protection with 3,4-dihydro-2*H*-pyran (DHP), deprotection of the TBDMS group with Bu_4NF (TBAF), oxidation with pyridinium dichromate (PDC), dibromoolefination, and elimination with BuLi followed by methyl chloroformate trap.[7] After deprotection of THP group, the treatment of allyl alcohol with 1,2-dibromoethyl ethyl ether, prepared from bromine and ethyl vinyl ether, in the presence of *N,N*-dimethylaniline[2b,8] furnished the bromoacetal (**4**) (**Scheme 2**).



i. PDC, 4Å molecular sieves, CH_2Cl_2
ii. NaH, $(EtO)_2P(O)CH(Me)CO_2Me$, DME (65% for 2 steps)
iii. DIBAL-H, CH_2Cl_2 (91%)
iv. DHP, PPTS, CH_2Cl_2 (92%)
v. TBAF, THF (93%)
vi. PDC, 4Å molecular sieves, CH_2Cl_2
vii. CBr_4, Ph_3P, Zn, CH_2Cl_2 (63% for 2 steps)
viii. BuLi, THF then $ClCO_2Me$ (85%)
ix. PPTS, EtOH (85%)
x. 1,2-dibromoethyl ethyl ether, *N,N*-dimethylaniline, CH_2Cl_2 (96%)

Scheme 2

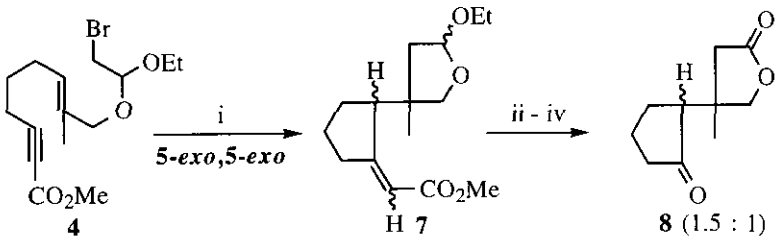
Furthermore, the allyl alcohol (**2**) was transformed into the bromoacetal (**6**) possessing an α,β-unsaturated ester group as a radical acceptor in four steps (**Scheme 3**).



i. 1,2-dibromoethyl ethyl ether, *N,N*-dimethylaniline, CH_2Cl_2
ii. TBAF, THF (93% for 2 steps)
iii. Dess-Martin periodinane, Py, CH_2Cl_2
iv. NaH, $(MeO)_2P(O)CH_2CO_2Me$, DME (61% for 2 steps)

Scheme 3

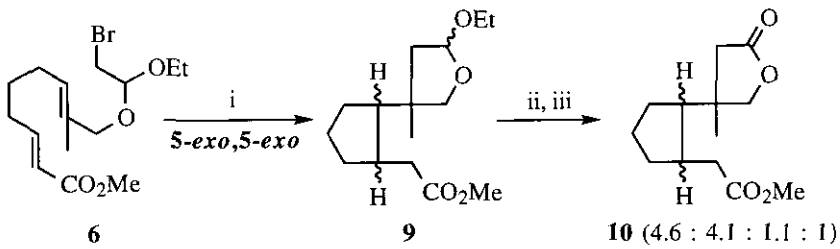
The bromoacetal (**4**) having an acetylenic ester group produced bicyclic five-membered ring compounds (**7**) in a highly regioselective manner by the Ni(II)-mediated electrolysis.[9] However, the reaction did not proceed, when vitamin B_{12a} was used as the mediator. Structures of bicyclic compounds (**7**) were determined after their conversion into keto lactones (**8**) in three steps, whose IR and ^{13}C-NMR spectral data indicated the five-membered ring structure.[10] Two stereoisomers of keto lactones (**8**) were obtained in a ratio of 1.5 : 1 (**Scheme 4**).



i. $[Ni(cyclam)](ClO_4)_2$, NH_4ClO_4, Et_4NClO_4-DMF, –1.5 V (35%)
ii. 10% $HClO_4$, THF
iii. Ag_2CO_3-Celite, benzene (64% for 2 steps)
iv. O_3, CH_2Cl_2 then Me_2S (47%)

Scheme 4

The bromoacetal (**6**) possessing an α,β-unsaturated ester group gave a stereoisomeric mixture of five-membered ring compounds (**9**) in good yields by Ni(II) or Co(III)-mediated electrolysis. Structures of **9** were proved by their transformation into **10** (**Scheme 5**).[11,12]



i. a) $[Ni(cyclam)](ClO_4)_2$, NH_4ClO_4, Et_4NClO_4-DMF, –1.5 V (72%)
b) vitamin B_{12a}, NH_4Cl, $LiClO_4$-DMF, –1.5 V (65%)
ii. 10% $HClO_4$, THF
iii. Ag_2CO_3-Celite, benzene (86% for 2 steps)

Scheme 5

In conclusion, we have demonstrated the usefulness of radical cyclizations under electrolytic conditions mediated by $[Ni(cyclam)](ClO_4)_2$ or vitamin B_{12a} for effecting the cascade reactions of halo-olefins. Substrates having a bromoacetal unit as a radical generated group and an acetylenic or α,β-unsaturated ester function as a terminal radical acceptor afforded bicyclic five-membered ring compounds according to Baldwin's rule. Thus, the present procedure provides a useful method for a convenient and clean radical cyclization.

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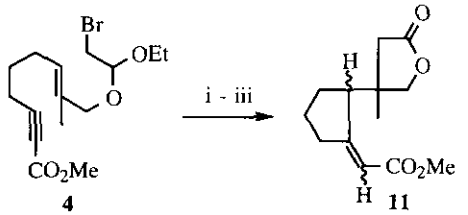
9. General Procedure for Indirect Electrolysis: The electrolysis was carried out in dry DMF (about 15 mL) containing a supporting electrolyte (0.1 M), the substrate, a proton source (200 mol%), and mediator (10 mol%), potentionstatically at –1.5 V (vs Ag/AgCl) using carbon graphite felt (0.5 x 0.5 x 0.5 cm^3) as the working electrode, under N_2 bubbling using an H-type divided cell separated by a cationic exchange membrane (Nafion® 117) at rt. The reaction was monitored by TLC. After the reaction, the mixture was diluted with H_2O and then thoroughly extracted with Et_2O. The combined extracts were washed with brine, dried ($MgSO_4$), and evaporated. The product was purified with column chromatography on silica gel.
10. Compound (**8**): **8** in a ratio of 1.5 : 1 (stereoisomers) as a colorless oil; IR (neat, cm^{-1}) 1770, 1730; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 3.94-4.39 (m, 2H), 2.02-2.73 (m, 7H), 1.64-1.92 (m, 2H), 1.15 (s, 1.2H), 1.13 (s, 1.8H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 218.8, 218.2, 177.0, 176.3, 56.0, 55.0, 41.3, 40.9, 40.7, 40.5, 39.2, 39.1, 26.0, 25.8, 20.9, 20.5, 20.3, 20.2; HRMS calcd for $C_{10}H_{14}O_3$ (M^+) 182.0942, found 182.0934. In general, 1770 cm^{-1} of IR data supports γ-lactone structure, and 218 ppm of ^{13}C-NMR data suggests cyclopentanone unit.
11. Compound (**10**): **10** in a ratio of 4.6 : 4.1 : 1.1 : 1 (stereoisomers) as a colorless oil; IR (neat, cm^{-1}) 1775, 1730; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 3.94-4.18 (m, 2H), 3.69 (s, 2.41H), 3.68 (s, 0.59H), 1.29-2.58 (m, 12H), 1.27 (s, 1.27H), 1.26 (s, 1.14H), 1.16 (s, 0.31H), 1.15 (s, 0.28H); HRMS calcd for $C_{12}H_{17}O_3$ (M^+-OMe) 209.1178, found 209.1212.
12. Lactones (**11**) were obtained from **4** in 55% yield for 3 steps by cyclization using Bu_3SnH, and **10** were produced from **6** in 56% yield for 3 steps by the same procedure.



4 **11**

i. Bu_3SnH, AIBN, benzene, reflux
ii. 10% $HClO_4$, THF
iii. Ag_2CO_3-Celite, benzene (55% for 3 steps)

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