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Facile Syntheses of *cis*-Fused Carbobicycles *via* Combination of Claisen Rearrangement of Macrolactone and Nitrile Oxide Cycloaddition

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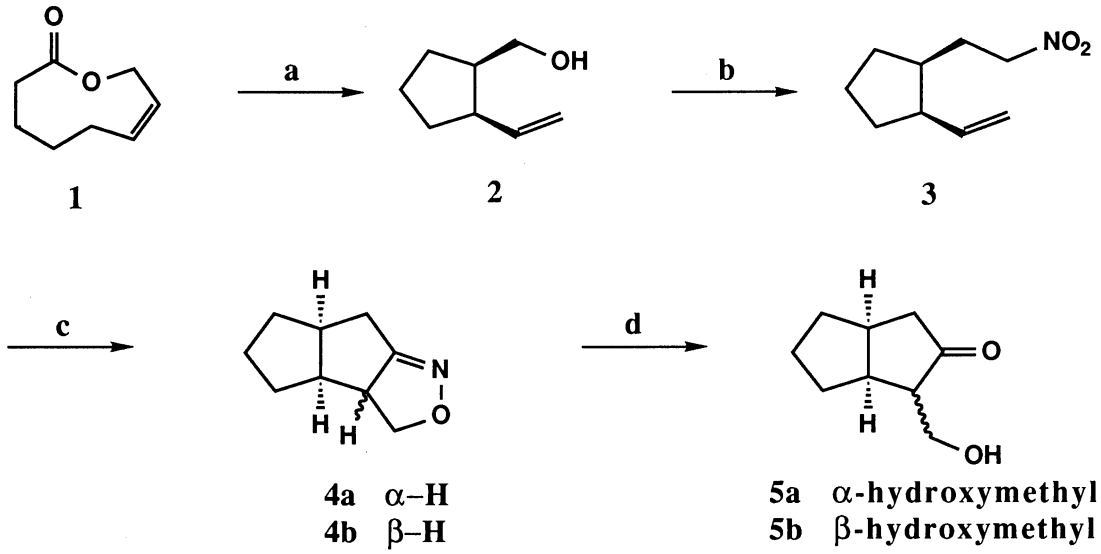
cis-Bicyclo[3.3.0]octanone, *cis*-hydrindanone and *cis*-decalone skeletons have been efficiently constructed by intramolecular nitrile oxide-olefin cycloaddition of 1-ethenyl-2-nitroalkyl cycloalkanes or 1-ethenyl-2-hydroxyiminoalkyl cycloalkane which are readily derived from macrolactone by Funk's Claisen rearrangement.

The methodologies for the construction of carbobicycles have been contineously developed due to their considerable synthetic utilities.[1] Especially, the synthesis of *cis*-fused carbobicyclic systems have recently attracted more interests from organic chemists along with more frequent appearance of *cis*-fused carbobicyclic natural products.[1,2] However, many of the methodologies for the construction of *cis*-fused carbobicycles have been targeted for a particular ring size or have limited availability of the adequate precursors.

Recently, we have looked for the general synthetic route to the potentially bioactive *cis*-fused carbobicycles of various ring size and considered that conversion of the appropriate carbomonocycles into the *cis*-fused carbobicycles by intramolecular nitrile oxide-olefin cycloaddition would be an excellent choice for our purpose. Most of the intramolecular nitrile oxide cycloadditions for the conststruction of carbobicycles, to the best of our knowledge, involve stereoselective conversion of the endo or exo methylene cycloalkanes into *cis*-carbobicyclic systems.[3] However, these applications frequently encounters difficulties in cyclization by the strain energy of the bicyclic systems.[4]

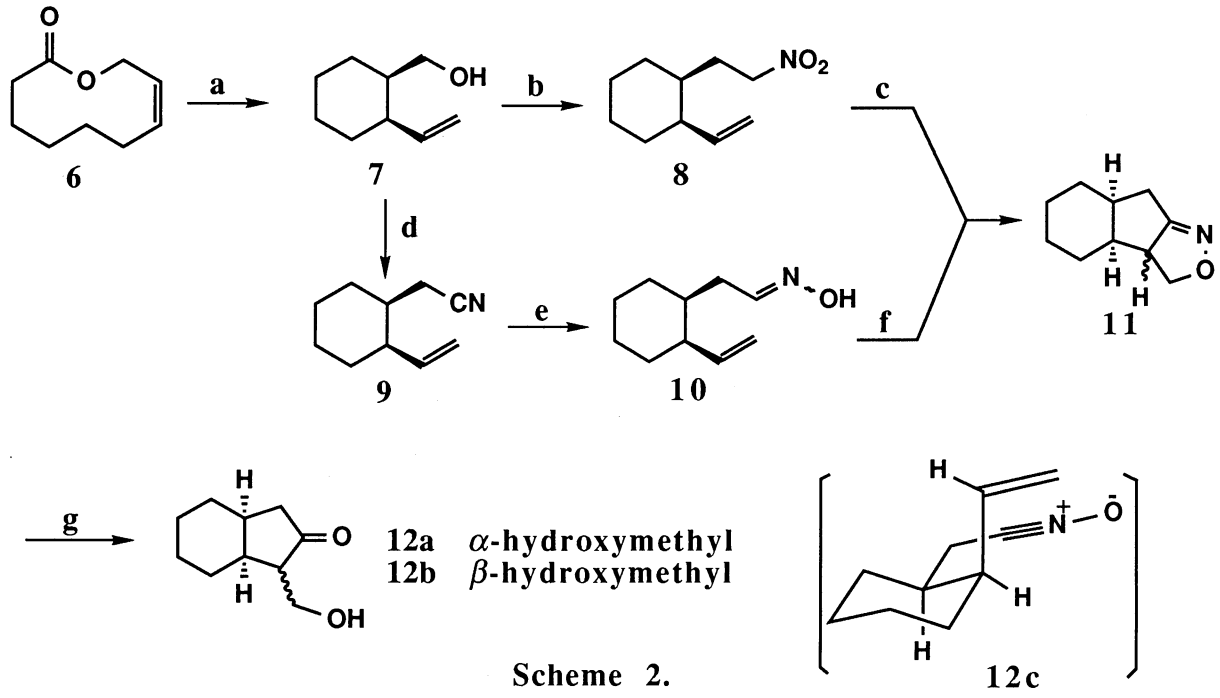
Our basic strategy, shown in Scheme1, involves efficient conversions of *cis*-1-ethenyl-2-hydroxymethyl cycloalkanes into the *cis*-fused carbobicycles of various ring size. The requisite *cis*-disubstituted carbomonocycles are readily available by Funk's ring contraction of lactone[5] and subsequent nitrile oxide cycloaddition of the resultant carbomonocycle provides an easy access to *cis*-carbobicycle although this cyclization step does not directly control the stereochemistry of ring junction.

Here we report the facile synthesis of *cis*-bicyclo[3.3.0]octanone, *cis*-hydrindanone and *cis*-decalone as a part of our ongoing project. First, *cis*-disubstituted cyclopentane **2** was prepared from lactone **1** by Funk's procedure[5] followed by LAH reduction of the resultant ester and conveniently transformed into the *cis*-bicyclooctanone **5** as outlined in Scheme 1. The hydroxymethyl, suitable functional group for the requisite transformation, was converted into the nitrile oxide precursor with one carbon extension. PCC oxidation of alcohol **2** and then Wollenberg homologation[6] afforded nitro-olefin **3**. Treatment of nitro-olefin with 4-chlorophenylisocyanate and then spontaneous cycloaddition[7] of the resultant nitrile oxide yielded the isoxazoline **4a** and **4b** as a 1: 1 mixture of two separable diastereomers. After reduction and subsequent hydrolysis of the



Scheme 1.

(a) i) Ref. 5, ii) LAH. (b) i) PCC, CH_2Cl_2, ii) CH_3NO_2, KF, iii) Ac_2O, DMAP, CH_2Cl_2, iv) $NaBH_4$, EtOH, 38% from 2. (c) *p*-Chlorophenylisocyanate, Et_3N, THF, 92%. (d) H_2, W-2 Raney-Ni, $B(OH)_3$, MeOH-H_2O(5:1), 80%.



Scheme 2.

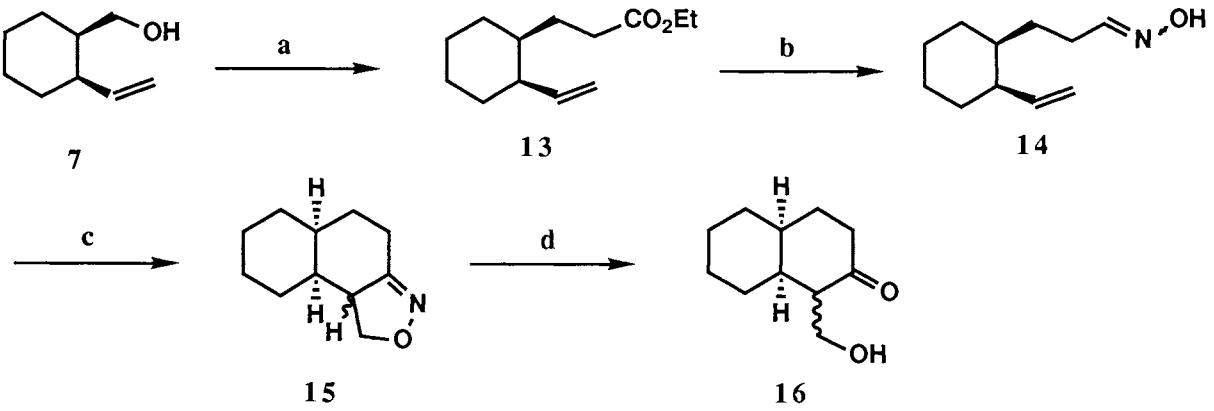
(a) i) Ref. 5, ii) LAH. (b) i) PCC, CH_2Cl_2, ii) CH_3NO_2, KF, iii) Ac_2O, DMAP, CH_2Cl_2, iv) $NaBH_4$, EtOH, 33% from 7. (c) *p*-Chloroisocyanate, Et_3N, THF, 80%. (d) i) TsCl, DMAP, CH_2Cl_2 94%, ii) NaCN, DMPU, 95%. (e) i) DIBAL, CH_2Cl_2, ii) NH_2OH HCl, 50%-NaOH, EtOH-H_2O, 60% from 9. (f) NCS, $CHCl_3$-pyridine, Et_3N, 83%. (g) H_2, W-2 Raney-Ni, $B(OH)_3$, MeOH-H_2O (5:1), 80% from 8.

isoxazolines, NaOMe treatment of the diastereomeric mixture of hydroxymethyl ketone **5a** and **5b** provides a more stable bicyclooctanone **5a** as a single product.[8)]

Secondly, *cis*-disubstituted cyclohexane **7** was prepared from the ten-membered lactone **6** by the same procedure for cyclopentane **2** as shown in Scheme 2. By analogy with the synthesis of bicyclooctanone, *cis*-disubstituted cyclohexane **7** was converted into the *cis*-hydrindanone as a 5 : 2 mixture of two separable diasteromers.[9)] Although the stereochemistry of each isomer has not been confirmed at this stage, the formation of **12a** as a major isomer is expected on the basis of favored approach of dipole and dipolarophile in the preferred chair conformation **12c** corresponding to **12a**.[10)] The isoxazoline **11** is also obtained from the oxime **10**. After one carbon extension of hydroxymethyl sidechain by displacement of alcohol with cyanide, sequential DIBAL reduction and hydroxylamine treatment of the nitrile **9** afforded the oxime **10**. Oxime **10** was finally cyclized by NCS chlorination followed by triethylamine treatment[11)] to give a diastereomeric mixture of isoxazoline **11**.

Conversion of cyclohexane **7** into *cis*-decalone **16** was also achieved by the same procedure for *cis*-hydrindanone **12**. The hydroxymethyl group was transformed into the two-carbon extended ester side chain by sodio malonate treatment of tosylate and decarboxylation of the resultant diester.[12)] DIBAL reduction of ester **13** followed by the standard procedure shown in Scheme 3 provided *cis*-decalone **16** as a 4 : 1 diastereomeric mixture[13)] which are separable by flash column chromatography.

In conclusion, *cis*-fused bicycloalkanone systems have been conveniently constructed *via* combination of Claisen rearrangement of lactone and intramolecular nitrile oxide-olefin cycloaddion. Considering convenient ring fusion of two carbocycles of various ring size and simple manipulation of hydroxy-ketone functionalities, this combination would provide an easy access to the synthesis of many *cis*-fused carbobicyclic analogues. Currently, investigations in extending our methodology to the construction of optically active carbobicycles as well as conversion of *cis*-fused bicycloalkanons to *cis-anti-cis* tricyclic alkanes are in progress. The successful results will be published shortly.



Scheme 3.

(a) i) TsCl, DMAP, CH_2Cl_2, 94%, ii) NaI, $NaCH(CO_2Et)_2$, DMF, 89%, iii) LiCl, DMSO, 160°, 97%. (b) i) DIBAL, toluene, ii) PCC, CH_2Cl_2, iii) NH_2OH, 50%-NaOH, EtOH-H_2O, 85% from 13. (c) NCS, $CHCl_3$-pyridine, Et_3N, 96%. (d) H_2, W-2 Raney-Ni, $B(OH)_3$, MeOH-H_2O (5:1), 86%.

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7) Exomethylene-cyclopentane does not undergo intramolecular nitrile oxide cycloaddition for the conversion to the carbocycle. Refer to the Ref. 4.

8) The less stable isomer **4b** is slowly epimerized even at room temperature to give more stable isomer **4a**. Spectral data of **5a**: IR (neat) 3400, 1740 Cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.78 (dd, 1H, J=11.0, 4.8 Hz), 3.70 (dd, 1H, J=11.0, 7.6 Hz), 2.61-2.51 (m, 1H), 2.48 (dd, 1H, J=19.1, 9.2 Hz), 2.50-2.33 (m, 1H), 2.19 (dd, 1H, J=19.1, 4.4 Hz), 2.12 (dd, 1H, J=13.6, 7.6 Hz), 1.99-1.31 (m, 6H); MS(EI) m/e 154 (M^+).

9) NaOMe or LiOH treatment of the minor isomer, for the conversion of it to the major isomer, did not afford the epimerization product but an unidentified elimination product. Spectral data of major isomer: IR (neat) 3400, 1730 Cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.87 (dd, 1H, J=11.4, 8.1 Hz), 3.62 (dd, 1H, J=11.4, 6.2 Hz), 2.55-2.46 (m, 1H), 2.49-2.11 (m, 4H), 1.81-1.64 (m, 5H), 1.43-1.02 (m, 2H), 0.88 (dq, 1H, J=12.8, 3.3 Hz); MS(EI) m/e 168 (M^+). Spectral data of minor isomer: IR (neat) 3400, 1730 Cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.81 (dd, 1H, J=11.0, 4.4 Hz) , 3.64 (dd, 1H, J=11.0, 7.0 Hz), 2.44-2.01 (m, 5H), 1.77-1.49 (m, 5H), 1.45-1.01 (m, 3H); MS(EI) m/e 168 (M^+). Stereochemical determination of each diastereomer by further spectroscopic analysis was not successful. The stereochemistry of each isomer will be reported shortly after completion of ongoing natural product synthesis which is closely related to this work.

10) The transition model **12c** for the formation of **12a** reveals the best parallel approach of dipole and dipolarophile which can be achieved without significant distortion of the cyclohexane ring: A. P. Kozikowski, and P. D. Stein, *J. Org. Chem.*, **49**, 2301 (1984).

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13) The ratio was determined by 400 MHz ^1H NMR and gas chromatography; The carbon adjacent to hydroxymethyl group was not epimerized under the conditions employed for *cis*-bicyclo[3.3.0]octanone system; The stereochemistry of these two diastereomers has not been confirmed yet. They will be reported with those of **12a** and **12b** in due courses. Spectral data of major isomer: IR (neat) 3400, 1710 Cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.06-3.97 (m, 1H), 3.52-3.32 (m, 1H), 2.74-2.64 (m, 1H), 2.54-2.31 (m, 2H), 2.31-2.06 (m, 3H), 1.77-0.93 (m, 9H); MS(EI) m/e 182 (M^+). Spectral data of minor isomer: IR (neat) 3400, 1710 Cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.88-3.77 (m, 1H), 3.74-3.64 (m, 1H), 2.76-2.66 (m, 1H), 2.65-2.48 (m, 1H), 2.52-2.43 (m, 1H), 2.32-2.22 (m, 1H), 2.12-2.01 (m, 1H), 1.97-1.35 (m, 10H); MS(EI) m/e 182 (M^+).

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