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An efficient approach to bridged-bicyclic rings via intramolecular diazo ketone insertion

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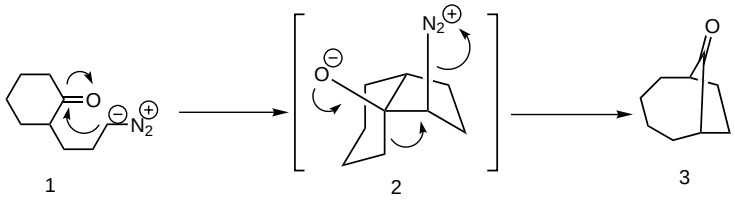
Abstract—A regioselective intramolecular diazo ketone insertion reaction of chiral cyclohexenones is described. The methodology shows potential utility in the syntheses of bicyclo[4.2.1]nonan-9-one, bicyclo[4.3.1]decan-10-one and cyclooctanoid rings.

Bicyclo[4.2.1]nonan-9-one and bicyclo[4.3.1]decan-10-one are two typical bridged-bicyclic rings which constitute key structural units in many natural products. Two recent examples, CP-263,114 and CP-225,917, which are squalene synthase and farnesyl transferase inhibitors, have received increasing attention due to their interesting structures and pharmacological properties.[1] The bridged ketone bonds in bicyclo[4.2.1]nonan-9-one and bicyclo[4.3.1]decan-10-one structures have potentials of cleavage to give eight- and nine-membered rings. These skeletons, especially eight-membered rings, are widely presented in many cyclooctanoid natural products, primarily among terpenoids.[2] The synthetic protocols of cyclooctanoid rings have recently been summarized in a review article.[3] Typically, eight- or nine-membered rings can be formed from appropriate precursors directly by cycloaddition, sigmatropic rearrangement, cyclization and coupling reactions or indirectly through cycloaddition–fragmentation, ring expansion, reductive and oxidative processes. Among all these methods, the process involving diazo ketone insertion and subsequent rearrangement shows high efficiency and generality (Scheme 1).[4] Here we describe an efficient and regioselective method on syntheses of various bicyclo[4.2.1]nonan-9-one, bicyclo[4.3.1]decan-10-one and cyclootanoid rings through diazo ketone insertion process.

Initial studies centered on the chiral cyclohexenones **6**. The preparation of the precursor **6a** was shown in Scheme 2. Birch reduction–alkylation of the benzamide **4** with 1-iodo-3-azido-propane as the alkylating agent followed by the hydrolysis of the corresponding 1,4-diene provided the cyclohexenone **5a** in 75% yield as a single diastereomer. Chemoselective hydrogenation of **5a** using Lindlar catalysis in the presence of acetic anhydride afforded the corresponding acetamide **6a** in 91% yield.[5] Analog syntheses afforded **6b**, **6c**, **6d** and **6e**.[6] Treatment of the acetamide **6a** with N_2O_4 in CH_2Cl_2 gave the nitroso amide intermediate **7a**. Without purification, **7a** were converted into **8a** in ~30% yield and some bridged ketone ring-opened adducts by treatment with a catalytic amount of K_2CO_3 in methanol. The methoxide apparently not only catalyzed



Scheme 1.

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the insertion and rearrangement processes, but also catalyzed the fragmentation of the bridged ketone **8a**. Replacement of K_2CO_3 in MeOH with LiOH in refluxing THF resulted in a much cleaner product **8a** in 80% yield.[7] In this procedure, the acetate ion generated was a much weaker nucleophile than the methoxide so that the bridged ketone **8a** was inactive toward the reaction condition. Table 1 summarized the results of the diazo ketone insertion reactions on various precursors **6a**–**6e**. In all these reactions, only bicyclo[4.2.1]nonan-9-ones **6a**, **6b**, **6d** and bicyclo[4.3.1]decan-10-ones **6c**, **6e** were obtained without any detectable amount of bicyclo[5.2.0]nonan-2-one or bicyclo[5.3.0]decan-2-one isomers,[8] which demonstrated that these reactions proceeded in a highly regioselective manner. This result was also reported from Gutsche and Srikrishna's papers.[4] In the diazonium alkoxide (Scheme 2), electrostatic attraction between the diazonium and the alkoxide maintains a *cis* orientation of two groups. Since the axial C–C bond and the C–N bond are *anti* parallel, the following rearrangement and elimination of N_2 gives the bicyclo[4.2.1]nonan-9-one **8a**.

Attempts at removal of the chiral auxiliary efficiently from **8a** were unsuccessful except for a few harsh conditions. Thus, we designed and conducted a modified synthetic route for easy removal of the chiral auxiliary (Scheme 3). Birch reduction–alkylation of the MOM protected chiral benzamide **9** with $I(CH_2)_3N_3$, followed by acid-catalyzed acyl migration and subsequent protection of the resulting *s*-amine with chloromethylformate generated the azido β-keto ester **10** in overall 62% yield.[9] Reduction of **10** to the diol by $LiBH_4$ followed by selective protection of the primary alcohol with TBSCl and re-oxidation of the secondary alcohol afforded the cyclohexenone **11** in 64% yield. Sequential reduction of the azide **11** with Lindlar catalysis in the presence of acetic anhydride followed by treatment of the resulting acetamide with N_2O_4 provided the corresponding nitrosoamide. The nitrosoamide was then treated with K_2CO_3 in MeOH to afford the bicyclo[4.2.1]non-9-one **12** in 65% yield.[10] MeLi addition of the bridged ketone **12** occurred from *re* face to afford the *t*-alcohol **13**. Subsequent deprotection of TBS ether with TBAF and oxidation of the alkene with *m*CPBA furnished the epoxide **14**. The stereochemistry of **14** was confirmed by X-ray diffraction analysis (Fig. 1).

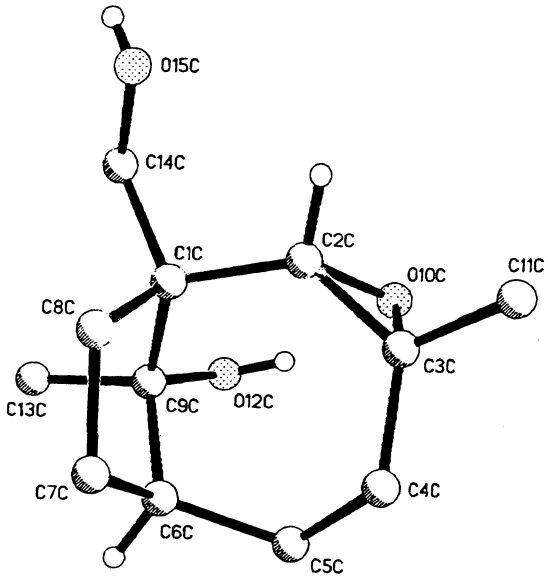
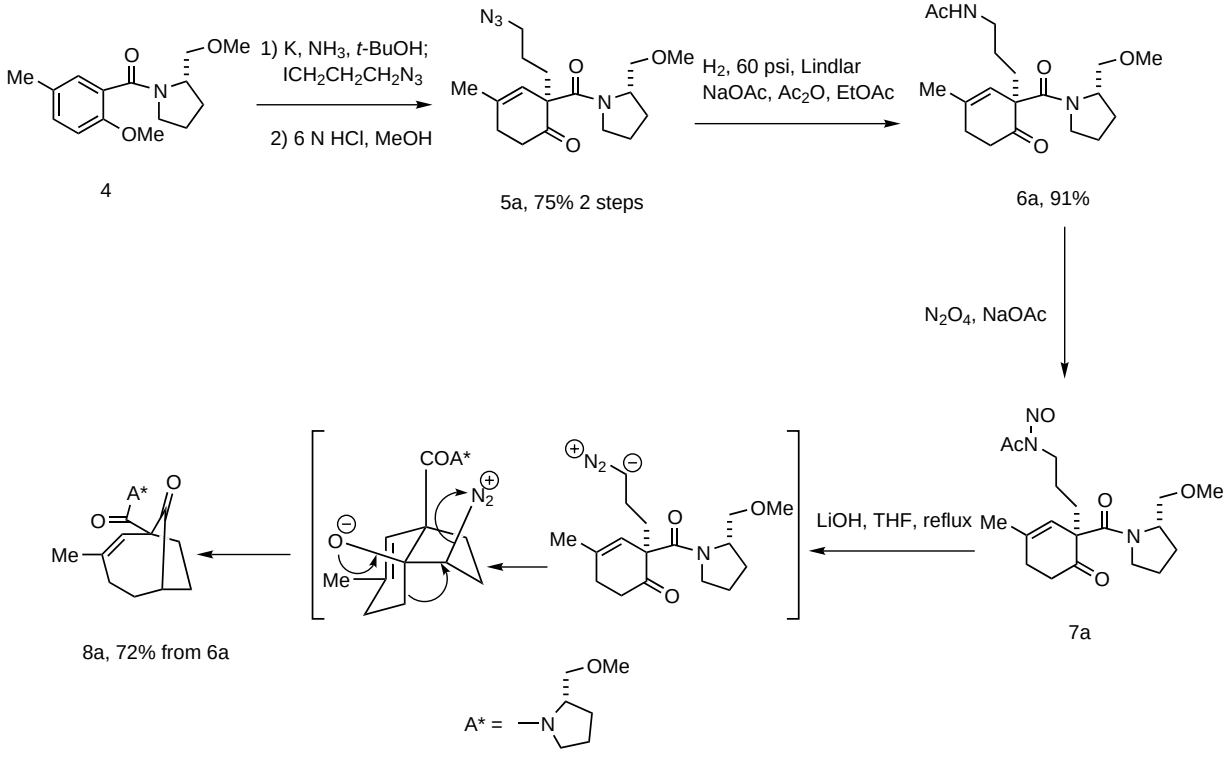
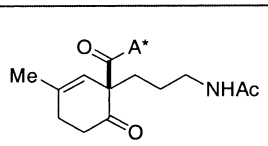
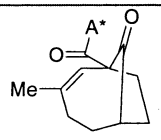
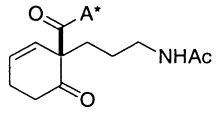
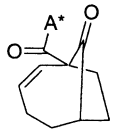
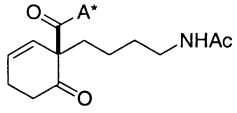
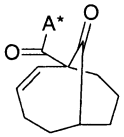
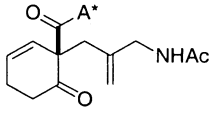
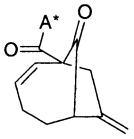
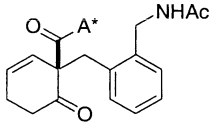
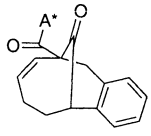


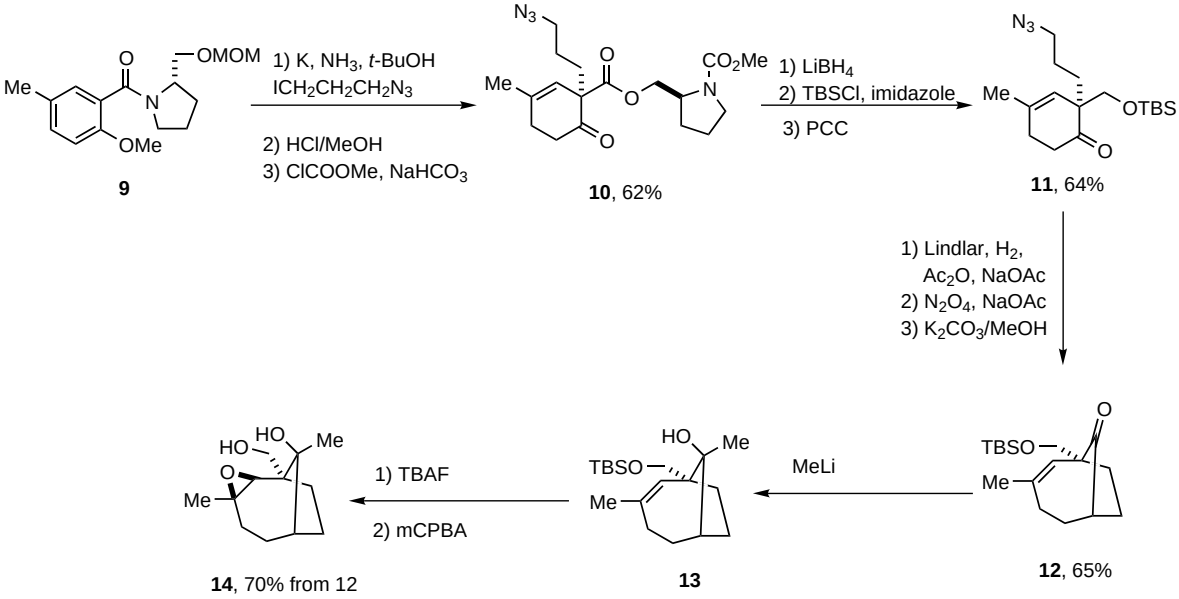
Figure 1. Molecular structure of **14**.



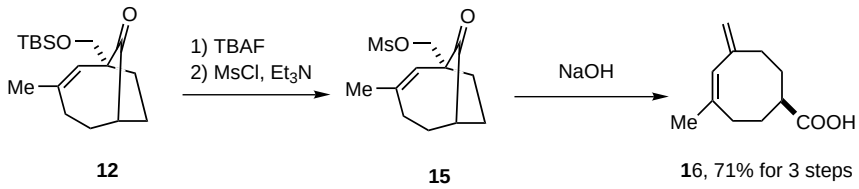
Scheme 2.

Table 1.

entry	precursor	product	yield (%)
a	 **6a**	 **8a**	80
b	 **6b**	 **8b**	75
c	 **6c**	 **8c**	71
d	 **6d**	 **8d**	45
e	 **6e**	 **8e**	51



Scheme 3.



Scheme 4.

With these results in hand, we carried out several simple steps to cleave the bridged ketone bond of **12** (Scheme 4). Deprotection of the hydroxy group of **12** followed by mesylation of the resulting alcohol afforded the mesylate **15**. Grob-type fragmentation of **15** by treatment with NaOH gave eight-membered ring acid **16** in overall 71% yield.[11]

In summary, we have developed a regioselective diazo ketone insertion method to synthesize bicylo[4.2.1]-nonan-9-one and bicyclo[4.3.1]decanan-10-one rings. The bridged ketone bonds can be efficiently cleaved to afford eight-membered rings. The method should be useful for the syntheses of bridged-bicyclic rings and cyclooctanoid natural products.

Acknowledgements

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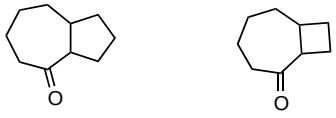
6. For preparation of α-iodo-ω-azido alkane, see: Khoukhi, M.; Vaultier, M.; Carrie, R. *Tetrahedron Lett*. **1986**, *27*, 1031.
7. *Typical procedure for preparation of bicyclo[4.2.1]non-9-one or bicyclo[4.3.1]decan-10-one compounds, from* **6a** *to* **8a**: To a cooled (−30°C) solution of amide **6a** (1.252 g, 3.572 mmol) in CH_2Cl_2 (50 mL) was added NaOAc (0.967 g, 1.20 mmol). Dinitrogen tetraoxide was bubbled into the amide solution until the dark blue color was maintained for 30 min. The solution, upon warming to −10°C, was stirred at −10 to 0°C over a period of 20–30 min. During this time the initial blue color changed into a bright yellow color. The reaction mixture was washed with an ice-cooled 10% K_2CO_3 solution and then brine. After drying with anhydrous Na_2SO_4, the solvent was removed to leave the nitroso amide **7a** as a yellow oil (∼1.28 g), which was used in the next step without further purification. To the solution of **7a** (1.28 g, 3.373 mmol) in THF (100 mL) was added $LiOH·H_2O$ (0.141 g, 3.373 mmol) and the resulting solution was refluxed overnight. A saturated NH_4Cl solution (∼50 mL) was added to quench the reaction. The mixture was extracted with ether (25 mL×3), dried over Na_2SO_4 and concentrated to give crude **8a** as a yellow oil. Chromatography (silica gel, 2:1 hexane/EtOAc) purification gave **8a** (0.776 g, 80%) as a light yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.87 (1H, s), 4.31–4.29 (1H, m), 2.28–2.20 (2H, m), 2.14–2.06 (3H, m), 3.34 (3H, s), 2.70–2.69 (1H, m), 2.50 (1H, m), 2.28–2.20 (2H, m), 2.14–2.06 (3H, m), 1.96–1.84 (3H, m), 1.81 (3H, s), 1.80–1.69 (3H, m). ^{13}C NMR (125 MHz, $CDCl_3$) δ 214.1, 168.8, 154.8, 138.0, 124.4, 72.2, 59.2, 57.9, 47.1, 46.9, 33.1, 33.0, 28.7, 27.7, 27.0, 24.9, 24.7. CI-MS, m/z (relative intensity) 292 (M^++1, 100%). IR (film, cm^{-1}) 2929 1736, 1631, 1400. Anal. calcd for $C_{17}H_{25}NO_3$: C, 70.07; H, 8.65; N, 4.81. Found: C, 69.89; H, 8.66; N, 4.86. $[\alpha]_D^{25}$ −236 ($CDCl_3$, c 1.2).
8. These two skeletons were not detected from the diazo ketone insertion reactions.



bicyclo[5.3.0]decan-2-one bicyclo[5.2.0]nonan-2-one

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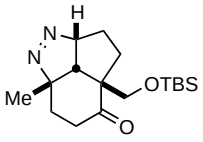
10. Treatment of the nitroso amide precursor with 1.0 equiv. of LiOH in refluxing THF resulted in a tricyclic pyrazoline, which was derived from intramolecular dipolar cycloaddition of azide to alkene.



11. *Spectrographic data of* **16**. ^{1}H NMR (500 MHz, $CDCl_3$) δ 11.0 (1H, br), 6.10 (1H, s), 4.84 (1H, s), 4.78 (1H, s), 3.06–2.99 (1H, m), 2.93–2.86 (1H, m), 2.69–2.64 (1H, m), 2.39–2.35 (1H, m), 2.00–1.93 (3H, m), 1.86–1.74 (2H, m), 1.81 (3H, s). ^{13}C NMR (125 MHz, $CDCl_3$) δ 146.2, 135.5, 130.2, 116.7, 76.6, 40.4, 32.9, 30.8, 30.0, 28.7, 27.6. CI-MS, m/z (relative intensity) 181 (M^++1, 100%). Anal. calcd for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95. Found: C, 72.93; H, 8.93%.