



## NMR Signal Assignments of the Stereochemical Cycloadducts of Bicyclolactone via Diels-Alder Reaction

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**Abstract:** Bicyclolactones obtained from the Diels-Alder cycloaddition of 3,5-dibromo-2-pyrone can undergo various palladium catalyzed cross coupling reactions to afford aryl bicyclolactones. The resulting coupled products can be readily converted into various 3-OH cyclohexenes via lactone ring openings, while those bearing dienyl units underwent highly diastereoselective Diels-Alder cycloadditions with selected dienophiles to furnish multiply functionalized polycarbocycles. Bromo-bicyclic diene furnished two different diastereomers *endo-form* (62%) and *exo-form* (38%) upon cycloadditions with N-Et maleimide (NEM), and their stereochemistries were identified with NMR.

### INTRODUCTION

Bicyclolactones prepared from the Diels-Alder (D-A) cycloaddition reaction of 2-pyrone are highly versatile synthetic building blocks that have been used for generations of various structurally diverse natural and unnatural complex molecules including taxol and a series of vitamin D<sub>3</sub> derivatives.<sup>1</sup> As a result of the study on the cycloadditions of 3,5-dibromo-2-pyrone, we have prepared a variety of stereochemically defined and functionally rich bicyclolactones.<sup>2</sup> In the report,<sup>2b</sup> we have shown that the vinyl bromide group in the bicyclolactone could be used as a handle to attach methyl acrylate

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group via conventional Heck reaction. Lactone ring opening reaction of the resulting products of addition of methyl acrylate group would provide the functionally rich and stereochemically defined 3-cyclo-hexenol derivative, potential synthetic precursors to hexahydrobenzofuran and hexahydrobenzopyran types of biologically important natural products including phomactins and candelaides.<sup>3</sup> Realization of its potential synthetic utilities promoted us to investigate other coupling reactions on the cycloadduct. In this paper we wish to report its Pd-catalyzed coupling reactions with various functional groups as well as the synthetic applications of the resulting coupled products. We also wish to report the NMR signal assignments and the elucidation of stereochemistry of products by NMR.

## EXPERIMENTAL

**Synthesis:** All chemicals were purchased from Aldrich Co., and used without further purification in synthesis. The bicyclic lactone carrying the bridgehead bromide group was synthesized by the cycloadditions of 3,5-dibromo-2-pyrone. As shown in Fig. 1, the starting material of the monobromo-bicyclic lactone <sup>2b)</sup> was obtained by removing the bridgehead bromide under typical Bu<sub>3</sub>SnH/AIBN condition with high selectivity over the vinyl bromide. The Pd-catalyzed coupling reactions of **A** turned out to be significantly better than the doubly bridgehead bromide bicyclic lactones, providing the coupled products **B** in 80% isolated yields.

Interestingly, all the D–A cycloadditions were highly diastereoselective, producing virtually a single diastereomer, in each case, out of four possible stereoisomers.

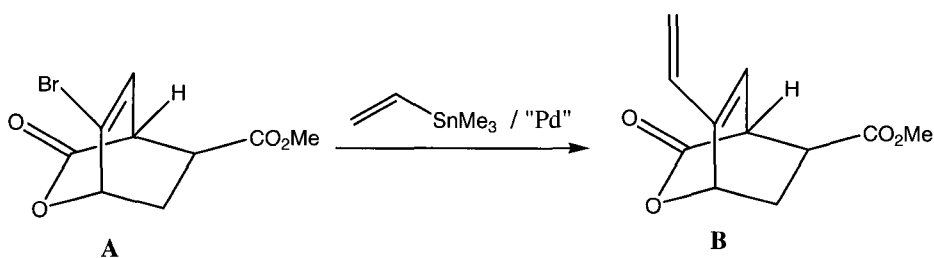


Fig. 1. Pd catalyzed coupling reaction of bromo bicyclic lactones.

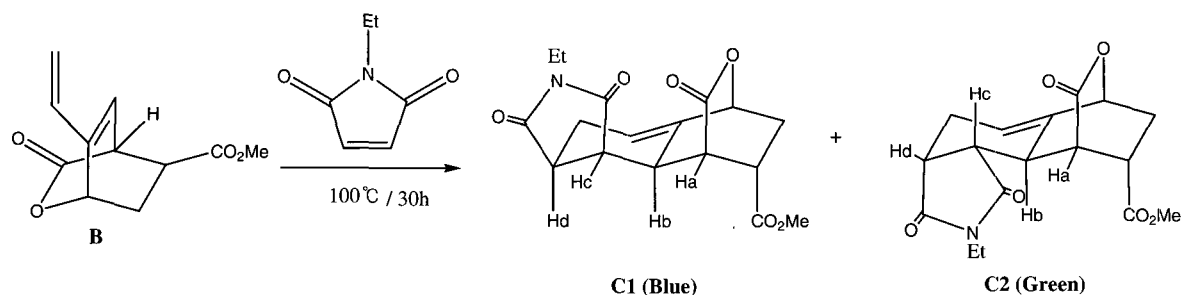


Fig. 2. Diastereomers obtained from Diels-Alder cycloaddition of **B** with N-ethyl maleimide

Stereochemical assignments of the cycloadducts would have been difficult. Fortunately, bromo-bicyclic diene **B** furnished two different diastereomers **C-endo** (**C1**, 62%) and **C-exo** (**C2**, 38%) upon cycloadditions with N-Et maleimide (NEM) as shown in Fig. 2.<sup>4,5</sup>

**NMR experiments:** NMR signal assignment of each isomer was completely accomplished with COSY, TOCSY and ROESY. All NMR spectra were recorded in CDCl<sub>3</sub> at 25 °C on a Varian Unity 500MHz and Mercury 300MHz. In order to analyze the signal assignment of specific proton attached to carbon, H, C-COSY and DEPT experiments were also executed. NOESY and ROESY experiments were executed for three-dimensional structure information of each isomer. All 2D NMR spectra were recorded with 2048 data points and 256 t1 increments. NOESY spectra were obtained with a mixing time of 200ms and ROESY spectra were obtained with spin lock pulses of 100, 200, 300, 400 ms. Homonuclear correlated spectra were zero-filled to final matrix sizes of 2048 × 2048 real points. The delay time between scans was 1.5s. Gaussian line broadening of 2 Hz was used in the t2 dimension before Fourier transformation. A 90°shifted sinebell squared filtering was used in the t1 dimension before Fourier transformation.

## RESULT and DISCUSSION

Fresh column chromatography enabled us to separate two stereoisomers of endo-form(62%) and exo-form(38%), respectively. Complete NMR signal assignments

were accomplished by modern homonuclear and heteronuclear 2D-NMR techniques.<sup>6-7</sup> Adjacent scalar coupling and long range J-networks were obtained by using COSY and TOCSY spectra, respectively. Complete <sup>1</sup>H-NMR signal assignments were made and summarized in Table 1. Major difference in the chemical shift change was observed in H2, H3, H4, H5 (axial) and H5(equatorial) protons associated with the stereo conformation as shown in Fig. 3.

Molecular stereo conformations were identified with NOESY spectrum and ROESY spectrum, respectively. The NOE restraints were obtained via qualitative assessment of NOE cross peak volumes in the NOESY spectra. The identification of relay peaks based on the NOE volume integration and ROESY spectra. Direct NOE contacts from H2 to H1, H3, H4, H5(equatorial), H9(axial), H10 protons, and relay NOE contacts from H2 to H5(axial) and H9(equatorial) were observed for the endo-form of stereoisomer(C1).

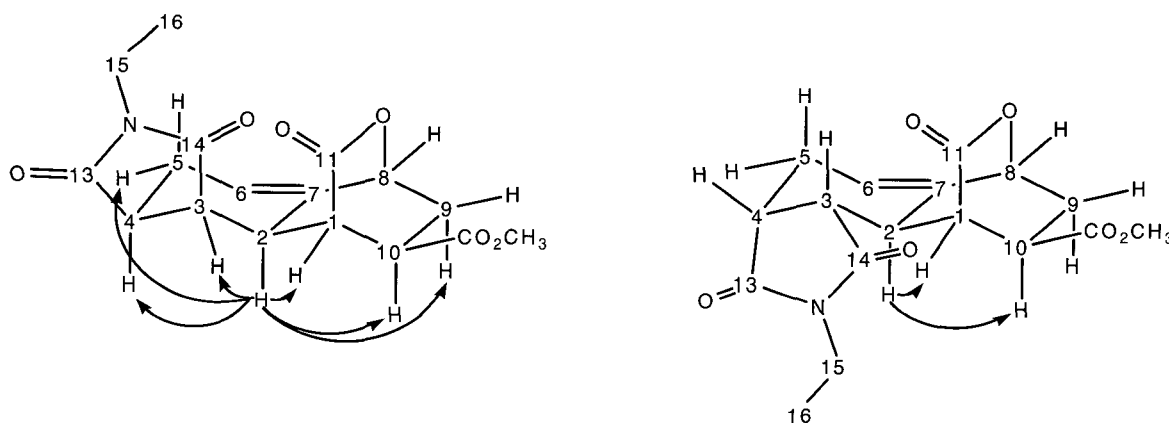


Fig. 3. Endo-form (left) and exo-form (right) of diastereomers exhibiting direct NOE contacts with arrows.

Table 1.  $^1\text{H}$ -NMR Chemical Shift of endo- and exo-form of stereoisomers

Protons	endo-form	exo-form
H1	3.699	3.844
H2	2.660	2.354
H3	3.277	2.568
H4	3.126	2.804
H5a	2.128	1.906
H5e	2.912	2.823
H6	5.972	6.097
H8	4.845	4.998
H9a	2.229	2.328
H9e	2.422	2.447
H10	3.178	3.186
H15	3.482	3.556
H16	1.078	1.160
H18	3.783	3.761

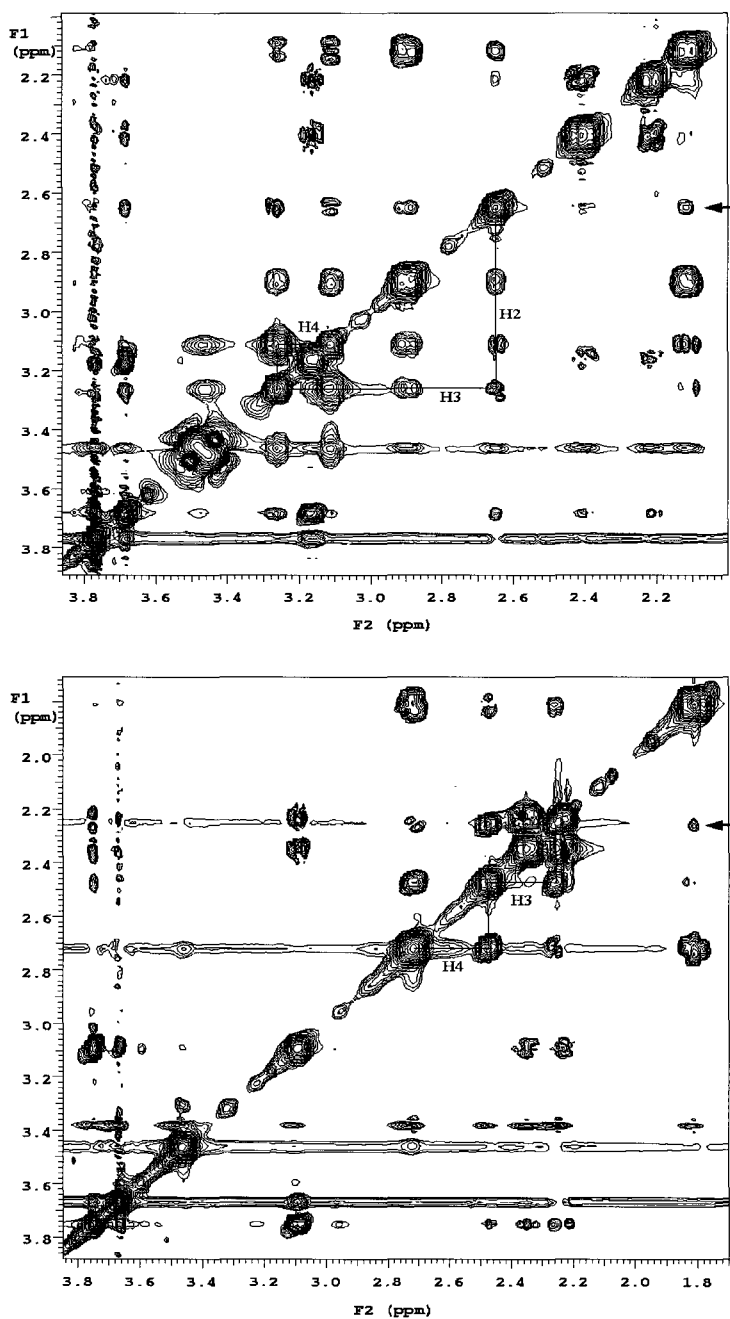


Fig. 4. ROESY spectra recorded at 200 ms mixing time. Important direct ROE connectivities are labeled for endo-isomer (up) and exo-isomer, respectively.

<sup>1</sup>H-NMR signal overlap was severe so that the direct NOE contact from H2 to H3 could not be resolved very well in the other stereoisomer. Only a strong COSY type coupling was observed between H2 and H3 while there was a strong NOE contact between H3 and H4. These results of correlations of J-coupling and dipolar coupling associated with H3 proton indicated that it has an exo-form of stereoisomer. Important direct NOE contacts confirming each stereoisomer were assigned and represented in the ROESY spectra (Fig. 4).

As a result of coupling constant analysis,  $J_{H2-H3}$  was observed to be 8.8Hz and 9.7Hz for the endo- and exo-form of isomer, respectively. Eclipsed and anti-form of Newman projection for H2 and H3 protons are possible for two stereoisomers. In order to compare experimental and theoretical value of coupling constant, molecular geometry optimization has been made by using HyperChem with MM+ force field. Dihedral angles of 32.7 degree and 142.7 degree were obtained for the eclipsed form and anti-form, respectively. 8.24 Hz for eclipsed form (endo-stereoisomer) and 9.13 Hz for anti-form (exo-stereoisomer) were calculated by utilizing the Karplus equation,  ${}^3J_{HH} = (7 - \cos\theta + 5\cos2\theta)$  Hz, exhibiting that the relation between dihedral angle and coupling constants are also consistent with experimental results.

In summary, the Diels–Alder cycloaddition reaction of bromo-bicyclic diene obtained from bridgehead dibromide bicyclic lactone with N-ethyl maleimide were highly diastereoselective, producing stereoisomers of endo-form (62%) and exo-form (38%). By utilizing homonuclear and heteronuclear 2D-NMR experiments, complete <sup>1</sup>H-NMR signal assignments and the identification of stereochemistry of diastereomer were made. NOE-restrained molecular dynamic computation or other quantum mechanical computation will be made for the atomic level structure determination and their energetics.

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