

Full Paper

## A Simple and Efficient Approach to the Synthesis of *Endo* and *Exo* Bicyclo[6.1.0]nona-3,5-diene-9-carboxaldehyde

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**Abstract:** Monobromination of 1,5-cyclooctadiene, followed by cyclopropanation with ethyl diazoacetate, led to the formation of *endo* and *exo* ethyl 4,5-dibromobicyclo[6.1.0]nonane-9-carboxylates **3a** and **3b**. Bis-dehydrobromination of **3a** and **3b** using 1,8-diazabicyclo[5,4,0]undec-7-ene (DBU) afforded the *endo* and *exo* ethyl bicyclo[6.1.0]nona-3,5-diene-9-carboxylates **4a** and **4b**. Reduction of these compounds to the corresponding alcohols **5a** and **5b** and subsequent oxidation with pyridinium chlorochromate (PCC) resulted in the formation of the target compounds *endo* and *exo* bicyclo[6.1.0]nona-3,5-diene-9-carboxaldehydes **6a** and **6b**.

**Keywords:** Bicyclo[6.1.0]nonanes, cyclopropanation, bromination-debromination, cyclic diene.

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### Introduction

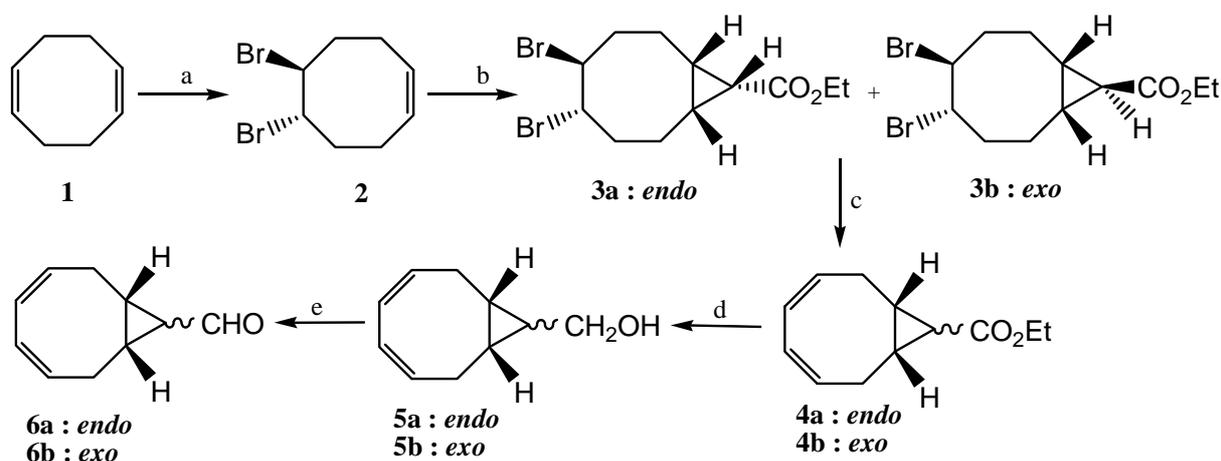
1,5-Cyclooctadiene (**1**) has been used as a starting material to construct complex cyclic and polycyclic compounds [1,2]. As a part of our research program toward the synthesis of some polycyclic compounds, a bicyclo[6.1.0] system containing a diene moiety in the eight-membered ring and an aldehyde functional group in the three-membered ring was needed. The diene part was desired for a Diels-Alder reaction with a suitable acetylenic dienophile in order to initially convert the bicyclic skeleton to a tricyclic system. Transformation of the aldehyde part to the relevant carbene via pyrolysis

of the corresponding tosylhydrazone salt was our next goal to investigate the possibility of the subsequent carbene insertion into the double bond present in the molecule and thus assemble a tetracyclic system. We are pleased to report herein our simple and efficient synthetic route to the title compounds, starting from the commercially available diene **1**. Details of the reaction conditions and spectroscopic characterization of the products will be discussed.

## Results and Discussion

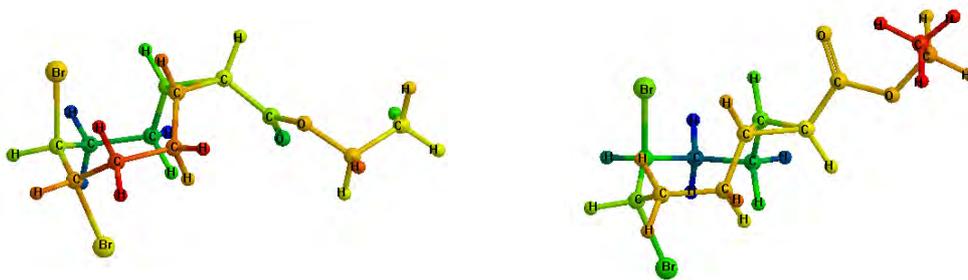
Bromination of olefins followed by bis-elimination of hydrogen bromide has widely been used to prepare symmetrical dienes from olefins [1, 3-5]. Thus, monobromination of 1,5-cyclooctadiene (**1**) was carried out in  $\text{CHCl}_3$  at  $-70\text{ }^\circ\text{C}$ , according to a previously reported procedure [1]. Subsequent cyclopropanation with ethyl diazoacetate in the presence of  $\text{CuSO}_4$  as catalyst [6] was then performed. Based on similar reported reactions [7], we expected to obtain a mixture of two isomers, and indeed column chromatography separation of the reaction products afforded two isomers in a 40:60 ratio, which were identified as the *endo* and *exo* ethyl 4,5-dibromobicyclo[6.1.0]nonane-9-carboxylates **3a** and **3b** (Scheme 1). The stereochemistry of the three-membered ring was established by comparison of coupling constants of H-9 with H-1 and H-8 in the two isomers (8.7 Hz and 4.3 Hz for **3a** and **3b**, respectively), which confirmed the *cis* and *trans* configurations with respect to the cyclopropane ring. As a result of their twisted and unsymmetrical conformations, shown in Figure 1, the isomers **3a** and **3b** exhibited complicated  $^1\text{H-NMR}$  spectra (see Experimental).

**Scheme 1.** Synthetic route to bicyclo[6.1.0]nona-3,5-diene-9-carboxaldehyde (**6**).

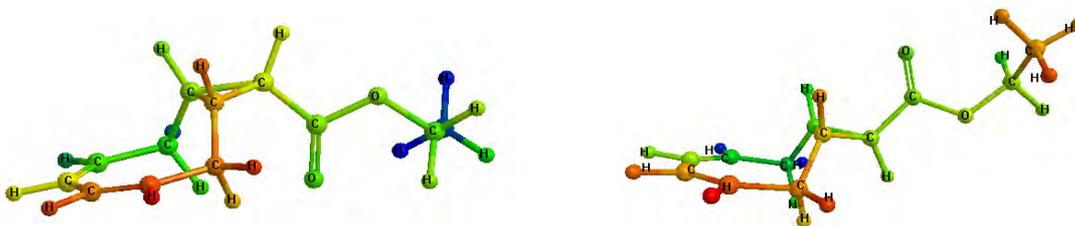


Reagents and conditions: a)  $\text{Br}_2$ ,  $\text{CHCl}_3$ ,  $-70\text{ }^\circ\text{C}$ ; b)  $\text{N}_2\text{CHCO}_2\text{Et}$ ,  $\text{CuSO}_4$ ; n-hexane, reflux; c) DBU,  $\text{CH}_3\text{CN}$  d)  $\text{LiAlH}_4$ , ether; e) PCC,  $\text{CH}_2\text{Cl}_2$

Bis-elimination of hydrogen bromide from the mixture of **3a** and **3b** with DBU in acetonitrile resulted in the formation of ethyl bicyclo[6.1.0]nona-3,5-diene-9-carboxylates **4a,b** in 75% yield, which gave the corresponding **4a** (*endo*) and **4b** (*exo*) isomers after separation by column chromatography.

**Figure 1.** Minimized structures of **3a** (left) and **3b** (right).

As shown in Figure 2, and in contrast to isomers **3a** and **3b**, compounds **4a** and **4b** have a symmetry plane which simplifies the corresponding  $^1\text{H-NMR}$  and  $^{13}\text{C-NMR}$  spectra (see Experimental). Conversion of **4a** and **4b** to 9-(hydroxymethyl)bicyclo[6.1.0]nona-3,5-dienes **5a** (*endo*) and **5b** (*exo*) was carried out by the well known reduction method using lithium aluminum hydride [8]. Due to the difference between the reduction times needed for **4a** and **4b** (the former required 8 h, while reduction of the latter was completed after 12 hr), **4a** and **4b** were reacted separately.

**Figure 2.** Minimized structures of **4a** (left) and **4b** (right).

PCC is well known as a selective and convenient reagent for converting the primary alcohols to the corresponding aldehydes [8-9]. Oxidation of **5a/5b** using PCC successfully gave the bicyclo[6,1,0]-nona-3,5-diene-9-carboxaldehydes **6a** (*endo*) and **6b** (*exo*) in 71% and 64% yields, respectively.

## Conclusions

In summary, *endo* and *exo* ethyl bicyclo[6.1.0]nona-3,5-diene-9-carboxylates **4a** and **4b** were synthesized via bromination of 1,5-cyclooctadiene, followed by cyclopropanation with ethyl diazoacetate and subsequent dehydrobromination with DBU. Reduction of **4a** and **4b** with lithium aluminum hydride followed by oxidation with PCC finally afforded the *endo* and *exo* bicyclo[6.1.0]nona-3,5-diene-9-carboxaldehydes **6a** and **6b**.

## Experimental

### General

All commercially available chemicals and reagents were purchased from the Merck Chemical Company and used without further purification. Melting points were determined on an Electrothermal model 9100 apparatus and are uncorrected. IR spectra were recorded on a Shimadzu 4300 spectrophotometer. The  $^1\text{H-NMR}$  and  $^{13}\text{C-NMR}$  spectra were recorded in  $\text{CDCl}_3$  using a DRX-500 AVANCE spectrometer at 298 K. Chemical shifts ( $\delta$ ) are reported in ppm and are referenced to the NMR solvent peak. Mass spectra of the products were obtained with a HP (Agilent Technologies) 5937 Mass Selective Detector with Electron Impact (EI) 70eV, and quadrupole analyzer. Column chromatographies were carried out using silica gel 60 (63-200 mesh). All the reactions were carried out under nitrogen atmosphere and reactions progress was monitored by TLC using aluminium sheets precoated with silica gel Merck 60 F254. 5,6-Dibromocyclooct-1-ene (**2**) was prepared using 1,5-cyclooctadiene (**1**) and bromine, according to the previously reported procedure [1].

### *Endo ethyl 4,5-dibromobicyclo[6.1.0]nonane-9-carboxylate (3a) and exo ethyl 4,5-dibromobicyclo-[6.1.0]-nonane-9-carboxylate (3b)*

To a stirred refluxing solution of 5,6-dibromocyclooct-1-ene (**2**, 13.4g, 50 mmol) and anhydrous  $\text{CuSO}_4$  (2 g) in *n*-hexane (150 mL) was added a solution of ethyl diazoacetate (6.27 g, 55 mmol) in *n*-hexane (20 mL) during 30 min. The reaction mixture was then refluxed for one additional hour and filtered while hot in order to remove the  $\text{CuSO}_4$ . The solvent was removed under reduced pressure and the brownish-yellow residue was then recrystallized from methanol to give white crystals (15 g, 85%), consisting of a pair of *endo* and *exo* isomers. The two isomers were separated by column chromatography on silica gel 60 using a 90:10 mixture of petroleum ether/ether as eluent to give **3a** and **3b**. Compound **3a**: m.p. 132-133 °C; IR (KBr): 2970, 1724 (C=O), 1469, 1147, 1082, 790  $\text{cm}^{-1}$ ;  $^1\text{H-NMR}$   $\delta$ : 1.31 (t, 3H,  $J = 7.1$  Hz,  $\text{CH}_3$ ), 1.50-1.65 (m, 2H, H-1 and H-8), 1.79 (m, 1H), 1.83 (t, 1H,  $J = 8.7$  Hz, H-9), 1.90 (m, 1H), 2.20 - 2.41(m, 4H), 2.75 (m, 2H), 4.16 (q, 2H,  $J = 7.1$  Hz,  $\text{OCH}_2$ ), 4.82 (m, 1H, CHBr), 4.88 (m, 1H, CHBr);  $^{13}\text{C-NMR}$   $\delta$ : 14.75, 18.64, 19.70, 22.81, 23.04, 25.66, 35.21, 35.30, 54.72, 56.09, 60.24, 172.14 ppm; MS (EI):  $m/z$  354 ( $\text{M}^+$ ); Compound **3b**: m.p. 123-124 °C; IR (KBr): 2999, 1718 (C=O), 1467, 1174, 981, 783  $\text{cm}^{-1}$ ;  $^1\text{H-NMR}$   $\delta$ : 1.24 (t, 1H,  $J = 4.3$  Hz, H-9), 1.30 (t, 3H,  $J = 7.1$  Hz,  $\text{CH}_3$ ), 1.42 - 1.55 (m, 2H); 1.69, 1.75 (2m, 2H, H-1, H-8), 2.15 (m, 3H), 2.34 (m, 1H), 2.68 (m, 1H), 2.77 (m, 1H), 4.15 (q, 2H,  $J = 7.1$  Hz,  $\text{OCH}_2$ ), 4.82 (m, 1H, CHBr), 4.86 (m, 1H, CHBr);  $^{13}\text{C-NMR}$   $\delta$ : 14.69, 23.45, 24.23, 25.93, 28.18, 28.27, 34.76, 35.21, 52.75, 56.12, 60.64, 173.91 ppm; MS (EI):  $m/z$  354 ( $\text{M}^+$ ).

### *Endo ethyl bicyclo[6.1.0]nona-3,5-diene-9-carboxylates (4a) and exo ethyl bicyclo-[6.1.0]nona-3,5-diene-9-carboxylate (4b)*

Ethyl 4,5-dibromobicyclo[6.1.0]nonane-9-carboxylates **3a,b** (3.54 g, 10 mmol) were dissolved in acetonitrile (70 mL) and DBU (4.63 g, 30 mmol) was then added in one portion. The solution was

refluxed for 24 h and the solvent was then removed under reduced pressure. Water (50 mL) was added to the brown oily residue and the mixture was extracted with diethyl ether ( $2 \times 50$  mL). The combined organic extracts was washed with HCl (3M,  $2 \times 25$  mL), then with sodium bicarbonate solution (5 %, 25 mL) and finally with distilled water (25 mL). The solution was dried over anhydrous sodium sulfate and the solvent was removed under reduced pressure. A colorless oily liquid was obtained (1.44 g, 75% yield). The two diene isomers were separated by column chromatography on silica gel 60 using a 90:10 mixture of petroleum ether/ether as eluent to give compounds **4a** and **4b** as colorless oily liquids. **4a**: IR (neat): 2937, 1720, 1398, 1355, 1157  $\text{cm}^{-1}$ ;  $^1\text{H-NMR}$   $\delta$ : 1.23 (t, 3H,  $J = 7.1$  Hz,  $\text{CH}_3$ ), 1.58 (t, 1H,  $J = 6.4$  Hz, H-9), 1.61 (m, 2H, H-1, H-8), 2.17 (m, 2H, H-2, H-7), 3.03 (m, 2H, H-2, H-7), 4.08 (q, 2H,  $J = 7.1$  Hz,  $\text{OCH}_2$ ), 5.61 (m, 2H, H-3, H-6), 5.67 (d, 2H,  $J = 11.6$  Hz, H-4, H-5);  $^{13}\text{C-NMR}$   $\delta$ : 14.72, 20.31, 23.05, 24.58, 60.31, 126.32, 130.93, 172.48 ppm; MS (EI):  $m/z$  192 ( $\text{M}^+$ ); **4b**: IR (neat): 2979, 2856, 1722, 1446, 1369, 1163, 995  $\text{cm}^{-1}$ ;  $^1\text{H-NMR}$   $\delta$ : 1.19 (t, 3H,  $J = 7.2$  Hz,  $\text{CH}_3$ ), 1.25 (t, 1H,  $J = 4.6$  Hz, H-9), 1.56 (m, 2H, H-1, H-8), 2.19 (m, 2H, H-2, H-7), 2.50 (m, 2H, H-2, H-7), 4.03 (q, 2H,  $J = 7.2$  Hz,  $\text{OCH}_2$ ), 5.60 (m, 2H, H-3, H-6), 5.88 (d, 2H,  $J = 10.1$  Hz, H-4, H-5);  $^{13}\text{C-NMR}$   $\delta$ : 14.62, 24.63, 25.40, 27.10, 60.60, 129.77, 130.01, 174.45 ppm; MS (EI):  $m/z$  192 ( $\text{M}^+$ ).

*Endo 9-(hydroxymethyl)bicyclo[6.1.0]nona-3,5-dienes (5a) and exo 9-(hydroxymethyl)bicyclo[6.1.0]nona-3,5-diene (5b).*

Lithium aluminum hydride (270 mg, 7 mmol) and anhydrous diethyl ether (20 mL) were placed in a three-necked round-bottomed flask fitted with a reflux condenser and an addition funnel. Ethyl bicyclo[6.1.0]nona-3,5-diene-9-carboxylate **4a** (or **4b**) (960 mg, 5 mmol) dissolved in dry ether (5 mL) was added dropwise with magnetic stirring. The addition rate was controlled to maintain gentle reflux. After the addition was complete, the suspension was refluxed for an additional 8 h (in the case of **4a**, 12 h for **4b**). Ammonium chloride solution (10%, 5 mL) was then added slowly to the reaction mixture precooled to 0 °C in an ice bath. The reaction mixture was stirred for another 10 minutes and then filtered. The precipitate was washed with ether (10 mL). The combined ether filtrates were washed with water (10 mL), dried over anhydrous sodium sulfate and the solvent was then removed under reduced pressure to give **5a** (or **5b**) as colorless oily liquids. **5a**: 640 mg (85%); IR (neat): 3400, 2923, 1440, 1400, 1022, 792, 761, 667  $\text{cm}^{-1}$ ;  $^1\text{H-NMR}$   $\delta$ : 1.10- 1.18 (m, 3H, H-1, H-8, H-9), 2.36 (m, 4H, 2H-2, 2H-7), 2.91 (s, 1H, OH), 3.74 (d, 2H,  $J = 7.6$ ,  $\text{CH}_2\text{OH}$ ), 5.67 (m, 2H, H-3, H-6), 5.74 (d, 2H,  $J = 11.3$ , H-4, H-5);  $^{13}\text{C-NMR}$   $\delta$ : 19.14, 21.18, 24.06, 60.00, 127.20, 131.56 ppm; MS (EI):  $m/z$  150 ( $\text{M}^+$ ); **5b**: 600 mg (80%); IR (neat): 3379, 3006, 2858, 1442, 1404, 1033, 790  $\text{cm}^{-1}$ ;  $^1\text{H-NMR}$   $\delta$ : 0.70 (tt, 1H,  $J = 7.0$  Hz,  $J = 4.8$  Hz, H-9), 0.81 (m, 2H, H-1, H-8), 1.60 (s, 1H, OH), 2.15 (m, 2H, H-2, H-7), 2.45 (m, 2H, H-2, H-7), 3.40 (d, 2H,  $J = 7.0$  Hz,  $\text{CH}_2\text{OH}$ ), 5.60 (d, 2H, H-3, H-6), 5.80 (d, 2H,  $J = 10.4$  Hz, H-4, H-5);  $^{13}\text{C-NMR}$   $\delta$ : 20.24, 25.95, 28.14, 67.24, 128.85, 131.21 ppm; MS (EI):  $m/z$  150 ( $\text{M}^+$ ).

*Endo bicyclo[6.1.0]nona-3,5-diene-9-carboxaldehydes (6a) and exo bicyclo[6.1.0]nona-3,5-diene-9-carboxaldehyde (6b)*

To a stirring solution of PCC (430 mg, 2 mmol) in dichloromethane (10 mL) was added a solution of **5a** (or **5b**) (300 mg, 2 mmol) in dichloromethane (2 mL). The mixture was stirred for 22 h at room

temperature and was then refluxed for another 30 min. The reaction mixture was then filtered and the brown polymeric residue was washed with dichloromethane ( $2 \times 10$  mL). The combined dichloromethane solutions were evaporated under reduced pressure. To the residue was then added ether (30 mL) and the mixture was stirred for 10 min. The solution was filtered and the precipitate was washed with ether (5 mL). The combined ether solution was then washed with portions of 5% sodium bicarbonate solution (5 mL) until the ethereal solution became colorless. The solution was then dried over anhydrous sodium sulfate and the ether was removed under reduced pressure to give **6a** (or **6b**) as pale yellow liquids. **6a**: 210 mg (71%); IR (neat): 3014, 2854, 1693, 1458, 1404, 1145, 993  $\text{cm}^{-1}$ ;  $^1\text{H-NMR}$   $\delta$ : 1.77 (m, 3H, H-1, H-8, H-9), 2.32 (m, 2H, H-2, H-7), 2.88 (m, 2H, H-2, H-7), 5.60 (m, 2H, H-3, H-6), 5.76 (d, 2H,  $J = 10.7$  Hz, H-4, H-5), 9.59 (d, 1H,  $J = 4.3$  Hz, CHO);  $^{13}\text{C-NMR}$   $\delta$ : 23.66, 28.07, 30.86, 127.93, 130.69, 202.47 ppm; MS (EI):  $m/z$  148 ( $\text{M}^+$ ); **6b**: 190 mg (64%); IR (neat): 2954, 2850, 1740, 1470, 1193, 719  $\text{cm}^{-1}$ ;  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 1.54 (m, 1H, H-9), 1.71 (m, 2H, H-1, H-8), 2.22 (m, 2H, H-2, H-7), 2.50 (m, 2H, H-2, H-7), 5.59 (m, 2H, H-3, H-6), 5.88 (d, 2H,  $J = 10.1$ , H-4, H-5), 9.03 (d, 1H,  $J = 5.2$  Hz);  $^{13}\text{C-NMR}$   $\delta$ : 25.88, 26.95, 30.08, 129.81, 130.15, 201.56 ppm; MS (EI):  $m/z$  148 ( $\text{M}^+$ ).

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*Sample Availability:* Samples of compounds **3a** and **3b** are available from the authors.

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