Bisannulation of Platinum-Bound Isochromeno[6,7-*g*]isochromene-2,9-Diium Derived from 3,6-Dialkynylnaphthalen-2,7-Dicarboxaldehyde with Cyclohexene

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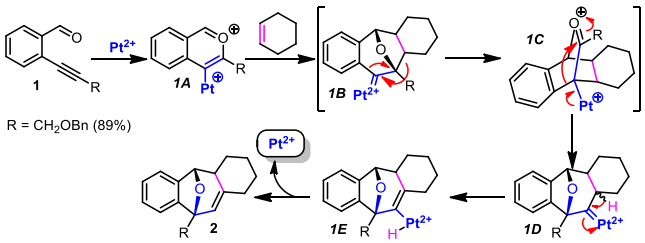
Synthesis of seven-membered carbocycles has been extensively studied especially with transition-metal catalysts. However, its application to natural products has been limited due to its property of having highly substrate-dependent reactivity.[1] The [4 + 3] or [5 + 2] are attractive strategy to prepare these compounds because of its efficient and rapid construction of cycloheptene bicyclic core.[2] Ortho-alkynylbenzaldehydes are frequently used as starting materials for the synthesis of a wide range of important transition-metal activated complex skeleton, which leads to a formation of isochromenylium intermediates that consequently reacts with proper dipolarophiles following the [4 + 2]- and/or [3 + 2]-cycloaddition mechanism.[3] The final product has been obtained from cycloadduct intermediate via a cascade ring-opening/protodemetalation process.[4] There are numerous synthetic applications of this process in the construction of complex bicylic products and detailed mechanistic studies have been reported on this topic.[5]

Although the formation of metal-containing ylide intermediates is now well understood, whether the formation of products is by modes of [3 + 2]- or [4 + 2]-cycloaddition of a Pt-isochromenylium with alkenes are still questionable.[6] For example, the Pt-isochromenylium intermediates, generated from 2-alkynylbenzaldehydes, have underwent [4 + 2] cycloaddition with allylic alcohols as reported by Liu *et al*., while Iwasawa argued a selective [3 + 2] cyclization with electron-rich silyl enol ethers.[7]

In the continuation of our research in [3 + 2]-platinum-catalyzed cyclization which involves the cylcloaddition of a Pt-bound isochromenylium species ***1A***, *in situ* generated from 2-alkynylbenzaldehyde **1**, with an olefin to form intermediate ***1B***. The ***1B*** would undergo isomerization into ***1C*** that might form direct [4 + 2] cycloaddition from ***1A*** with cyclohexene (Scheme 1). The result revealed that the [3 + 2] cycloaddition pathway of Pt-isochromenylium intermediates is more plausible to understand and explain the chemoselectivity of the obtained product. Thus the fast-formed ***1B*** would undergo rearrangement into the more



Scheme 1. Pt-catalyzed cyclization/rearrangement of 2-alkynylbenzaldehyde with cyclohexene

stable ***1C*** and then further migration into ***1D*** by Pt-involving process. The ***1D*** could be tautormerized into ***1E*** and followed by reductive elimination to afford the product **2** with reusable Pt(II). Due to the synthetic application and mechanistic interest of seven-membered ring formation, we would like to extend our process to achieve bisannulation using 3,6-dialkynylnaphthalen-2,7-dicarboxaldehyde with cyclohexene to test its feasibility. We first prepared 3,6-dialkynylnaphthalen-2,7-dicarboxaldehyde **7** as a substrate. The spacer 2,7-naphthalenedicarbaldehyde **5** was prepared in three steps following to reported literature procedures with 2,7-naphthalenediol (**1**) commercially available starting material: bromination, methylation, and formylation.[8] (Scheme 2) The substrate **7** was then obtained in high yield by three steps (59% over three steps) from **5** (Appendix S1, Supporting Information).

Substrate **7**, in hand, was examined for Pt-catalyzed reaction with cyclohexene under three different Pt-based catalytic conditions in Scheme 2. All reactions were performed with 5 mol% loading of platinum catalyst and four equivalents of cyclohexene in toluene or THF as solvent.[9] With THF as solvent at 80 °C, a mixture of **8a** and **8b** in only 35% yield along with some hydration products have been obtained. Platinum chloride in toluene catalyzed this bisannulation to give a mixture with a diastereomeric ratio 1:1 of **8a** and **8b** in 58% yield but only a trace of product was

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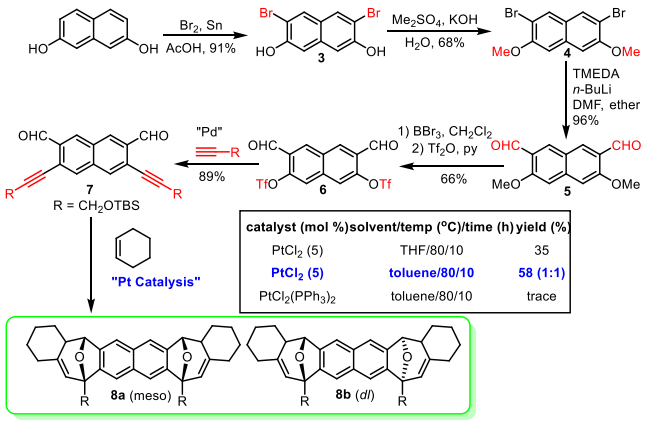


Scheme 2. Pt-catalyzed cyclization/rearrangement of bis (2-alkynylaldehyde) anchoring naphthalene with cyclohexene

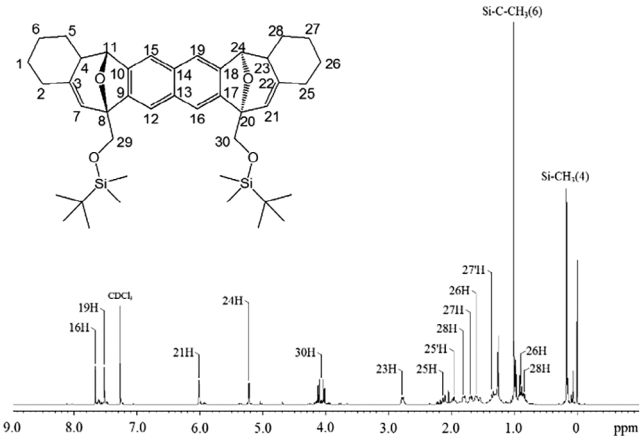


Figure 2. Molecular structure and ^{1}H NMR spectrum of **8b.**

detected with bis(triphenylphosphine)platinum chloride used as a catalyst.

NMR experiments including ^{1}H NMR, ^{13}C NMR, DQFCOSY, TOCSY, and ROESY were carried out by using Varian 500 MHz FT-NMR spectrometer in order to confirm two structures. Samples were dissolved in $CDCl_3$ in 5 mm NMR tube and chemical shifts were referenced to solvent peaks (^{1}H: 7.24 ppm, ^{13}C: 77.23 ppm) at 298 K. ROESY experiment was made with 2 K × 2 K data matrix size with 32 scans per t_1 increment at 300 and 400 ms mixing time for measuring direct NOE connectivity. By using ^{1}H NMR, ^{13}C NMR and homonuclear 2D NMR experiment including DQFCOSY and TOCSY, complete ^{1}H NMR and ^{13}C NMR signal assignments were accomplished for **8a** and **8b** as shown in Figures 1 and 2.

As illustrated in the entire molecular structure and its numbering scheme in Figures 1 and 2, **8a** has symmetric *Meso* compound (*R,S*-configuration) whereas **8b** has a enantiomeric mixture of stereoisomer (*dl* configuration of *R,R* and *S,S*), respectively. These stereoisomers have a rigid ring originated from the sp^{2} hybridization on C22 and the extended ring fusion on C23 carbon. 2D ROESY

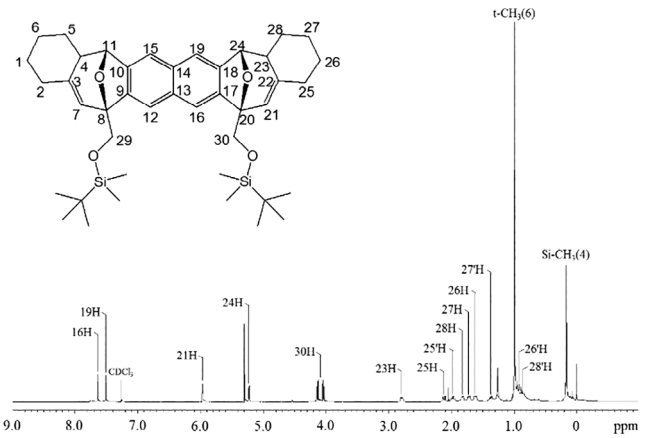


Figure 1. Molecular structure and ^{1}H NMR spectrum of **8a.**

experiments with different mixing times were performed to determine structure and relative conformation of stereoisomers. In addition, coupling constant analyses were carried out to identify geometry of stereogenic carbon atoms.

Figure 3 shows a 2D-ROESY spectrum of **8a** labeled with cross peaks associated with H19, H23, H24, H25 and H28 methylene proton networks. Relative cross peak intensities reflect the direct NOE contacts carrying interatomic proton distance information. Considering a half of molecular structure and a rigid covalent linkage related to C23, C24, C28 atoms, prochiral-*R,S* assignments of H28 germinal protons are an important clue to determine the absolute stereo conformation of C23 chiral carbon. Cross peaks from H23 to H25, H27, H28 (prochiral-R) and cross peaks from H24 to H23, H28 (prochiral-S), H28 (prochiral-R) were observed in Figure 3. In addition, cross peaks from H19 to

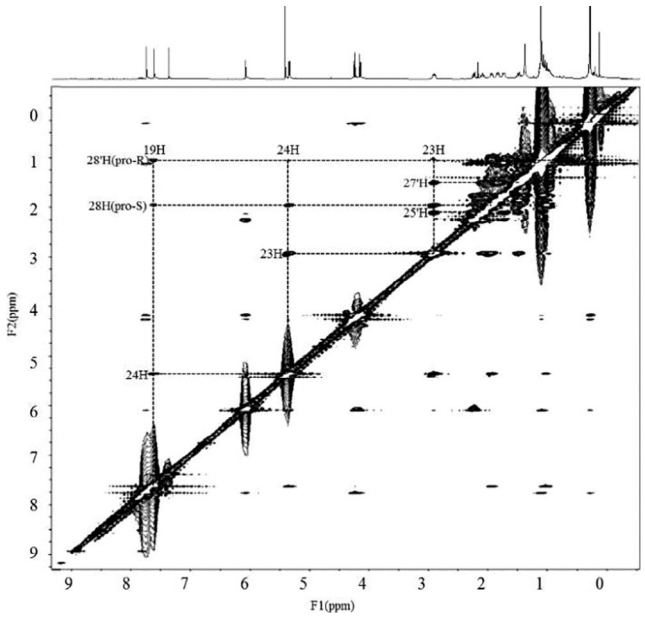


Figure 3. 2D-ROESY spectrum of **8a** with cross peaks associated with H23, H24 and H28 proton networks.

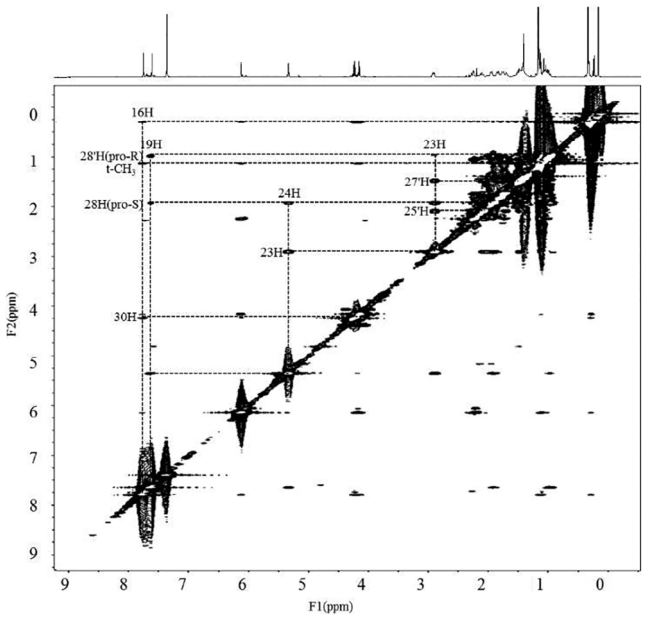


Figure 4. 2D-ROESY spectrum of **8b** with cross peaks associated with H23, H24 and H28 proton networks.

H24, H28 (pro-*S*), H28 (pro-*R*) were observed. These relative cross peak intensities show that C4 and C23 chiral carbons have *R* and *S* configurations, respectively, in **8a**.

A 2D-ROESY spectrum of **8b** is shown in Figure 4. Stereo configuration of **8b** was assigned with similar manner as in **8a**. Interestingly, cross peaks from *tert*-butyl dimethyl silyl ether group to H16, H21 protons were appeared in **8b** and this is due to the chiral change on C24 and the side chain rotation. In addition, new cross peak from H24 to H28 (pro-*R*) was appeared while a cross peak from H19 to H24 was disappeared in comparison with spectrum of **8a**. With all these NMR observations based on comparisons of relative cross peak intensities of ROESY spectra, we were able to elucidate that **8a** has *S,S* configuration whereas **8b** has *R,R* configuration on C23 and C24 carbon atoms with respect to relative C4 and C11 configurations, respectively.

Based on structural confirmation of two products, we became to propose the mechanism of the present bisannulation of **7** to **8a** and **8b** (Scheme 3). As specified in Scheme 1, the same reaction could take place at both side to form the bispyrilium intermediate ***A*** which underwent cycloaddition in both side to give the intermediates ***B1*** and ***B2***. Both ***B1*** and ***B2*** would undergo skeletal rearrangement into ***C1*** and ***C2*** and further into ***D1*** and ***D2***, respectively.

Intermediate ***D1*** and ***D2*** would independently undergo tautomerization and reductive elimination to furnish the product **8a** and **8b** along with Pt(II) for next cycles.

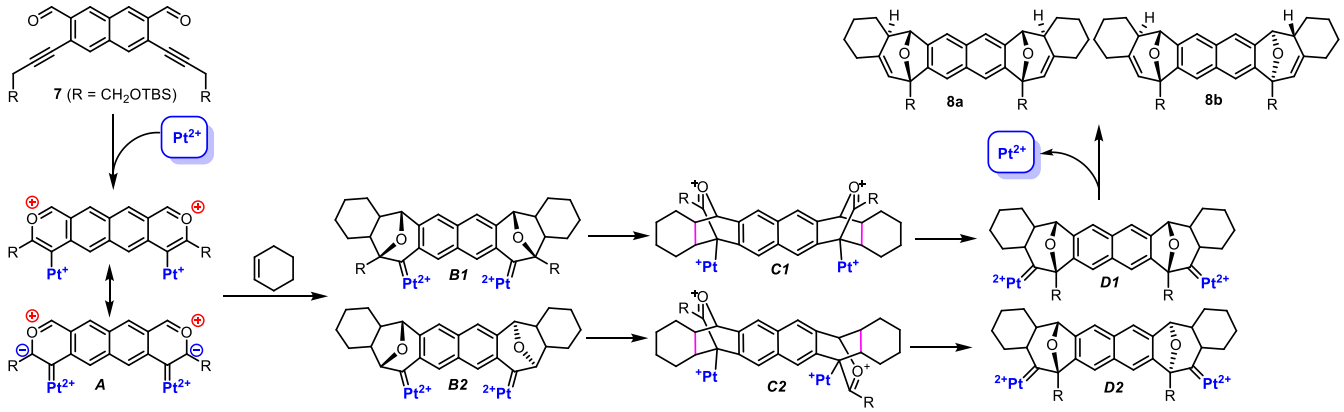
In conclusion, bis(2-alkynylalkenylaldehyde) **7** with cyclohexene under cationic platinum (II) catalysis would undergo at each site a [3 + 2]-cyclization followed by two sequential rearrangement to furnish a very unique molecule, 1,2,3,4,4a,5,8,8a,9,10,11,12,14,17-tetradecahydro-5,17:8,14-diepoxybenzo[4,5]cyclohepta[1,2*b*]benzo[5,6]cyclohepta[1,2-*g*]naphthalene (**8a** and **8b**). Continuing this work with various alkenes is now under study and will be reported in near future.

Experimental

Typical procedure platinum-catalyzed bisannulation of **7** to **8a** and **8b** is shown below.

To a solution of 3,6-dialkynylnaphthalen-2,7-dicarboxaldehyde (**7**, 0.10 mmol) and cyclohexene (0.20 mmol) in toluene was added platinum chloride (5 mol%) and the reaction mixture was heated at 80 °C and stirred for 10 h under argon atmosphere.

After the reaction was complete by TLC analysis, the reaction mixture was cooled down to room temperature and concentrated under reduced pressure. The concentrated residue was then rapidly purified by flash silica gel chromatography to give a 1:1 mixture of **8a** and **8b** (39.7 mg, 58%), which was further separated by HPLC for analysis. **8a**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.64 (s, H16), 7.51 (s, H19), 5.97 (s, H21), 5.23 (d, J = 5.86 Hz, H24), 4.09 (m, J = 9.76 Hz, H30), 2.79 (m, J = 6.35 Hz, H23), 2.12 (d, H25), 1.98 (m, H25′), 1.83 (d, H28), 1.72 (d, H27), 1.62 (d, H26), 1.37 (m, H27′), 0.94 (m, H26′), 0.87 (m, H28′), 0.99 (s, t-CH_3), 0.17–0.16 (s, Si-CH_3); ^{13}C NMR (500 MHz $CDCl_3$) δ 151.74, 142.13, 139.97, 135.03,



Scheme 3. Proposed mechanism for this bisannulation of Pt-catalyzed reaction of **7** with cyclohexene to **8a** and **8b**

133.98, 126.02, 124.20, 119.35, 85.32, 83.50, 67.99, 43.28, 36.68, 32.36, 30.54, 29.43, 28.65, 27.98, 21.00, 2.66, −2.67, −2.82; IR (cm^{-1}) 2928, 2858, 1737, 1465, 1255, 1102; HRMS(ESI) exact mass calculated for $[C_{42}H_{60}O_4Si_2Na]^+$ requires m/z 707.3922, found m/z 707.3922. **8b**: ^1H NMR (500 MHz, $CDCl_3$) δ 7.66 (s, H16), 7.52 (s, H19), 6.01 (s, H21), 5.22 (d, J = 5.86 Hz, H24), 4.07 (m, J = 9.76 Hz, H30), 2.79 (m, J = 5.86 Hz, H23), 2.12 (d, H25), 1.97 (m, H25′), 1.81 (d, H28), 1.70 (d, H27), 1.61 (d, H26), 1.34 (m, H27′), 0.91 (m, H26′), 0.85 (m, H28′), 1.02 (s, t-CH_3), 0.18–0.16 (s, Si-CH_3); ^{13}C NMR (500 MHz $CDCl_3$) δ 151.94, 142.13, 139.98, 135.15, 133.87, 125.95, 124.08, 119.41, 85.16, 83.55, 68.20, 43.22, 36.72, 32.35, 30.53, 29.48, 28.68, 27.95, 21.06, 2.65, −2.70, −2.83;; IR (cm^{-1}) 2930, 2857, 1727, 1465, 1256, 1105; HRMS(ESI) exact mass calculated for $[C_{42}H_{60}O_4Si_2Na]^+$ requires m/z 707.3922, found m/z 707.3923.

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Supporting Information. Additional supporting information is available in the online version of this article.

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