JOC*Note*

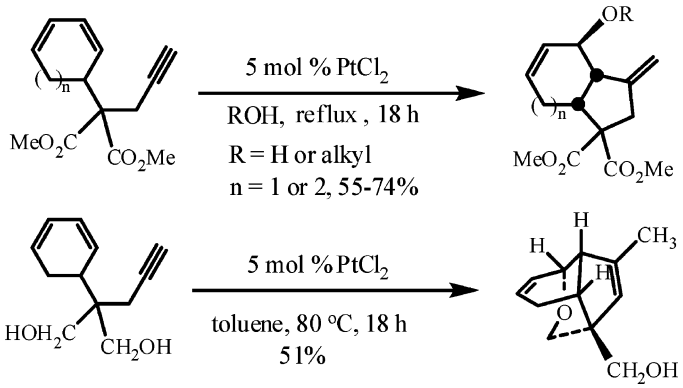
Synthesis of Indenol- and Azulenol Derivatives via Platinum Dichloride-Catalyzed Intramolecular Hydroxy- or Alkoxycyclization of Cyclic Dienynes

Ming-Chang P. Yeh,* Wen-Cheng Tsao, and Sau-Tin Cheng

Department of Chemistry, National Taiwan Normal University, 88 Ding-Jou Road, Section 4, Taipei 11677, Taiwan, Republic of China

cheyeh@scc.ntnu.edu.tw

Received November 11, 2007



Platinum dichloride-catalyzed hydroxy- or alkoxycyclization of cyclohexadienynes gives indenol derivatives, whereas hydroxy- or alkoxycyclization of cycloheptadienynes produces azulenol derivatives. The cyclization reaction proceeds via a cyclopropyl platinacarbene intermediate and allows for the direct stereocontrol of three contiguous stereogenic centers of the fused bicyclic skeletons. The transient reactive intermediate obtained from $PtCl_2$-catalyzed cyclization reaction of a cyclohexadienyndiol can be trapped intramolecularly by a hydroxyl group to afford an oxatricyclo[5.4.0.0^{4,8}]-undecane ring skeleton with extreme diastereoselectivity.

The stereoselective construction of highly functionalized bicyclo[4.3.0] and -[5.3.0] building blocks is an important synthetic goal because such ring skeletons are present in numerous natural products of biological interest.[1] Because the availability of functionalized bicyclo[4.3.0] and -[5.3.0] building blocks could greatly facilitate the elaboration of more complex target molecules, the design of expedient synthetic routes to such intermediates has been actively pursued.[2] Recently, it has been shown that coordination of electrophilic $PtCl_2$ to the alkyne group of enynes generates a (η^2-alkyne)platinum complex, which evolves to form a cyclopropyl platinacarbene complex.[3] Attack of nucleophiles (water or alcohols) at the transient reactive intermediate produced five- or six-membered carbo- or heterocyclic rings.[4] We have now demonstrated that this methodology can be applied toward highly diastereoselective synthesis of indenol derivatives by treatment of cyclohexadienynes with water or an alcohol in the presence of 5 mol % of $PtCl_2$, whereas hydroxy- or alkoxycylization of cycloheptadienynes using the same reaction condition afforded azulenol derivatives.

The requisite cyclohexadienyne **1a** was prepared by addition of sodium dimethylmalonate to the (η^5-cyclohexadienyl)-tricarbonyliron cation salt in THF according to literature procedures.[5] Decomplexation of the resulting complex with cerium ammonium nitrate (CAN) in acetone at 0 °C afforded dimethyl 2-cyclohexa-2,4-dienylmalonate. Treatment of the malonate with sodium hydride followed by addition of propagyl bromide furnished **1a** in 70% overall yield. Compound **1b** was prepared in a similar fashion starting from 2,4-pentanedione and (η^5-cyclohexadienyl)tricarbonyl-iron cation salt. The seven-membered ring substrate **2** was prepared starting from addition of sodium dimethylmalonate to the (η^5-cycloheptadienyl)-tricarbonyliron cation salt following the same procedure as described above for synthesis of **1a**. Our intramolecular hydroxycyclization of cyclic dienynes study began with **1a** (Scheme 1). Addition of 5 mol % $PtCl_2$ to **1a** in refluxing H_2O and acetone (1:1 mixture) for 18 h under nitrogen provided dimethyl 2,3,3a,4,7,7a-hexahydro-4-hydroxy-3-methyleneindene-1,1-dicarboxylate (**3a**) in 72% isolated yield (Scheme 1). The product of the relative stereochemistry as depicted was obtained as a single diastereomer, which is derived from an anti addition of the alkyne and H_2O across the proximal double bond of the conjugated diene. The relative stereochemistry of **3a** was determined as 1,2-*trans*, 2,3-*cis* relationship on the basis of NOSEY (nuclear Overhauser enhancement spectroscopy) measurements. Three contiguous stereogenic centers are created with extreme diastereoselectivity. In general, cis-fused hexahydroindene skeletons are constructed via intramolecular Diels−Alder reaction conditions. However, the Diels−Alder reaction required heating substrates at elevated temperature in toluene in a sealed

(1) (a) Shindo, K.; Kawai, H. *J. Antibiot.* **1992**, *45*, 292. (b) Shindo, K.; Matsuoka, M.; Kawai, H. *J. Antibiot*. **1996**, *49*, 241. (c) Shindo, K.; Iijima, H.; Kawai, H. *J. Antibiot*. **1996**, *49*, 244. (d) Shindo, K.; Sakakibara, M.; Kawai, H. *J. Antibiot*. **1996**, *49*, 249. (e) Molander, G. A. *Acc. Chem. Res.* **1998**, *31*, 603−609.

(2) For bicyclo[4.3.0]compounds see: (a) Gassman, P. G.; Gorman, D. B. *J. Am. Chem. Soc.* **1990**, *112*, 8623. (b) Gassman, P. G.; Gorman, D. B. *J. Am. Chem. Soc.* **1990**, *112*, 8624. (c) Jolly, R. S.; Luedtke, G.; Sheehan, D.; Livinghouse, T. *J. Am. Chem. Soc*. **1990**, *112*, 4965. For bicyclo[5.3.0]-compounds see: (d) Kusama, H.; Onizawa, Y.; Iwasawa, N. *J. Am. Chem. Soc.* **2006**, *128*, 16500. (e) Ni, Y.; Montgomery, J. *J. Am. Chem. Soc.* **2006**, *128*, 2609. (f) Sarpong, R.; Su, J. T.; Stoltz, B. M. *J. Am. Chem. Soc.* **2003**, *125*, 13624. (g) Harvey, D. F.; Lund, K. P. *J. Am. Chem. Soc.* **1991**, *113*, 5066.

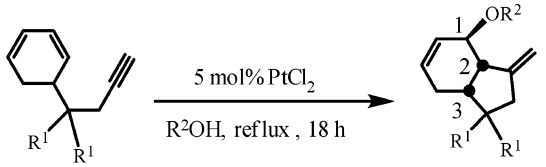
(3) (a) Chatani, N.; Furukawa, N.; Sakurai, H.; Murai, S. *Organometallics* **1996**, *15*, 901. (b) Lloyd-Jones, G. C. *Org. Biomol. Chem*. **2003**, *1*, 215. (c) Méndez, M.; Mamane, V.; Fürstner, A. *ChemTracts-Org. Chem*. **2003**, *16*, 397. (d) Mamane, V.; Gress, T.; Jrause, H.; Fürstner, A. *J. Am. Chem. Soc*. **2004**, *126*, 8654.

(4) (a) Martín-Matute, B.; Nevado, C.; Cárdenas, D. J.; Echavarren, A. M. *J. Am. Chem. Soc*. **2003**, *125*, 5757. (b) Méndez, M.; Paz Muñoz, M.; Nevado, C.; Cárdenas, D. J.; Echavarren, A. M. *J. Am. Chem. Soc*. **2001**, *123*, 10511. (c) Martín-Matute, B.; Cárdenas, D. J.; Echavarren, A. M. *Angew. Chem., Int. Ed*. **2001**, *40*, 4754. (d) Aubert, C.; Buisine, O.; Malacria, M. *Chem. Rev*. **2002**, *102*, 813. (e) Méndez, M.; Echavarren, A. M. *Eur. J. Org. Chem*. **2002**, 15.

(5) (a) Yeh, M. C. P.; Sheu, B. A.; Fu, H. W.; Tau, S. I.; Chuang, L. W. *J. Am. Chem. Soc.* **1993**, *115*, 5941. (b) Yeh, M. C. P.; Sun, M. L.; Lin, S. K. *Tetrahedron Lett.* **1991**, *32*, 113. (c) Yeh, M. C. P.; Tsao, W. C.; Ho, J. S.; Tai, C. C.; Chiou, D. Y.; Tu, L. H. *Organomteallics* **2004**, *23*, 792.

10.1021/jo702424w CCC: $40.75
Published on Web 03/11/2008

SCHEME 1. $PtCl_2$-Catalyzed Indenol Derivatives Synthesis from Cyclohexadienynes



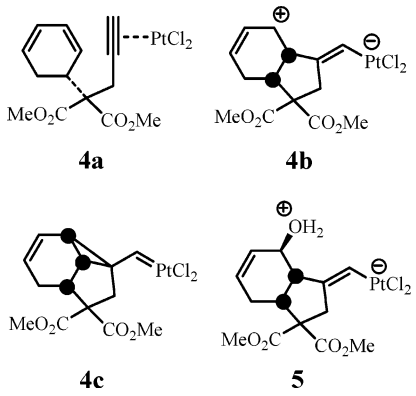
1

a : $R^1 = CO_2Me$
b : $R^1 = COMe$

3

a : $R^1 = CO_2Me$, $R^2 = H$ 72%
b : $R^1 = CO_2Me$, $R^2 = Me$ 68%
c : $R^1 = CO_2Me$, $R^2 = allyl$ 74%
d : $R^1 = CO_2Me$, $R^2 = {}^iPr$ 55%
e : $R^1 = COMe$, $R^2 = {}^iPr$ 40%

tube.[6] The current approach to the synthesis of cis-fused hexahydroindenes is achieved without the use of complex catalysts or critical reaction conditions, only requiring platinum dichloride and alcohols or water. The reaction pathway leading to indenol **3a** was suggested as follows. The catalyst coordinated to the triple bond of **1a** to give **4a** (Figure 1), which was then attacked by the proximal double bond of diene. This generated intermediate **4b** with the newly formed carbon−carbon bond. The 2,3-*cis* relative stereochemistry of the ring juncture of **4b** was fixed by the alkyne moiety aligned to the face of the cyclic diene in which the tethering chain resides. Intermediate **4b** led to the cyclopropyl platinacarbene intermediate **4c** as suggested in the literature.[4] The postulated intermediate **4c** was then attacked by H_2O at the allylic carbon from the convex face to give the bicyclic skeleton **5** containing an η^1-alkenylplatinum bond. Protonation of **5** at the metal center followed by reductive elimination led to **3a** and regenerated $PtCl_2$ catalyst into the catalytic cycle. The postulated mechanism was previously proposed for platinum- and gold-catalyzed cycloisomerization reactions of enynes.[3d]

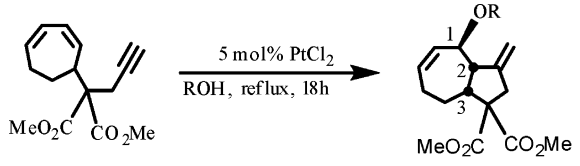


4a **4b** **4c** **5**

FIGURE 1. Reactive Intermediates **4a**−**c** and **5**.

To explore the scope of oxygen nucleophiles, a variety of alcohols were examined under the same reaction conditions. Results of alkoxycyclization of dienynes **1a** with 5 mol % of $PtCl_2$ catalyst in various alcohols are listed in Scheme 1. Methanol, allylic alcohol, and isopropyl alcohol were efficient nucleophilic solvents as the yields of desired alkoxycyclization products **3b**−**d** ranged from 55 to 74%. However, indenols

SCHEME 2. $PtCl_2$-Catalyzed Azulenol Deivatives Synthesis from Cycloheptadienynes



2

6

a : R = H 62%
b : R = Me 65%
c : R = Et 55%
d : R = allyl 58%
e : R = ^{i}Pr 53%

formation failed to occur for **1a** in the presence of benzylic alcohols. For example, treatment of **1a** with 5 mol % of $PtCl_2$ using 4-methylbenzyl alcohol or naphthalen-1-ylmethanol as nucleophilic solvents failed to give cyclized products and the reactions led to unidentified mixtures in each case. The reactive benzylic alcohols could add at the Pt-alkyne carbon of the transient intermediate **4a** or various electrophilic sites of **4b** and **4c** and gave a mixture of unidentified compounds. Furthermore, $PtCl_2$-catalyzed isopropoxylation of the diketo substituted dienyne **1b** produced the desired indenol derivative **3e** in 40% yield (Scheme 1). The relative stereochemistry of **3a**−**e** were assigned as the same 1,2-*trans*, 2,3−-*cis* relationship on the basis of their close chemical shift values and similar coupling patterns of the protons at the C-2 position in their ^{1}H NMR spectra.

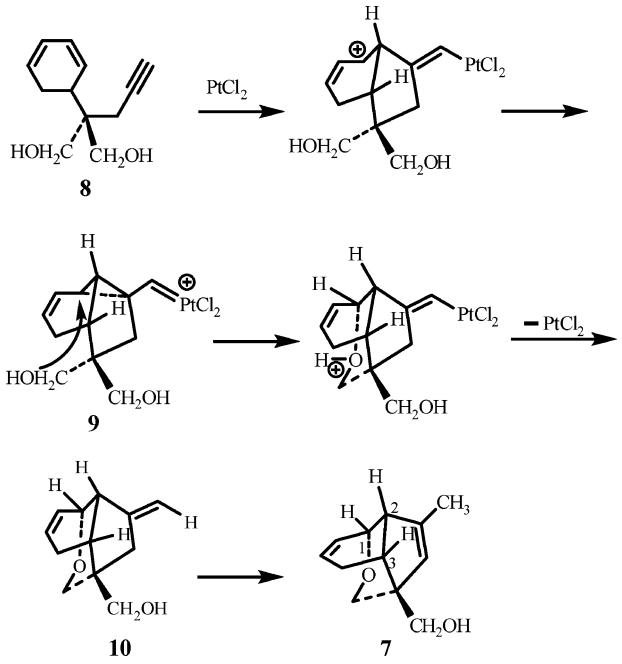
Increasing the ring size by one with cyclohepta-1,3-dienynes **2a**−**e** (Scheme 2) also underwent hydroxy- or alkoxycyclization to afford azulenol derivatives **6a**−**e**, respectively, as the only stereoisomer in each case. ^{1}H NMR studies provided the initial evidence for support of the structure assignments. The hydrogen shift (δ) of 2.94 in **6a** exhibited as a triplet was assigned to H_2. The coupling constant of H_1-H_2 (J_{12}) of 9.0 Hz agrees with the 9−10 Hz coupling constant for the similar *trans* hydrogens found in the literature.[7] Furthermore, the coupling constant of H_2-H_3 (J_{23}) of 9.0 Hz agrees with the 9−10 Hz coupling constant for similar *cis* hydrogens compared to the 11−12 Hz observed when these protons are *trans*.[7] The relative stereochemistry of **6a**−**e** were assigned as the same 1,2-*trans*, 2,3-*cis* relationship on the basis of their close chemical shift values and similar coupling patterns of the proton at the C-2 position in their ^{1}H NMR spectra. The structure elucidation of **6b** and **6c** were finally accomplished by X-ray diffraction analysis. The 1,2-*trans*, 2,3-*cis* relative stereochemistry of **6a**−**e**, derived from an anti addition of the alkyne and H_2O or an alcohol across the proximal double bond of the conjugated diene, further supports the proposed reaction path suggested for the formation of indenols **3a**−**e** (Figure 1).

Using the same reaction conditions, we were able to construct an oxatricyclo[5.4.0.0^{4,8}]undecane ring skeleton, such as **7**, by intramolecular addition of a hydroxyl group to a postulated reactive cyclopropyl platinacarbene intermediate. Thus, treatment of dienyndiol **8**, obtained by addition of 2.5 molar equiv of diisobutylaluminum hydride to **1a** followed by acid quenching, with 5 mol % $PtCl_2$ in toluene at 80 °C for 16 h furnished

(6) (a) Chang, J.; Paquette, L. A. *Org. Lett.* **2002**, *4*, 253. (b) Munakata, R.; Ueki, T.; Katakai, H.; Takao, K.; Tadano, K. *Org. Lett.* **2001**, *3*, 3029. (b) Dineen, T. A.; Roush, W. R. *Org. Lett.* **2004**, *6*, 2043.

(7) (a) Yeh, M. C. P.; Jou, C. F.; Yeh, W. J.; Chiu, D. Y.; Reddy, N. R. K. *Tetrahedron* **2005**, *61*, 493. (b) Chiba, S.; Kitamura, M.; Narasaka, K. *J. Am. Chem. Soc.* **2006**, *128*, 6931.

SCHEME 3. $PtCl_2$-Catalyzed Synthesis of Oxatri-cyclo [5.4.0.0^{4,8}]undecane Skeleton 7 from Cyclohexa-dienyndiol 8



the heterotricyclic compound **7** in 51% isolated yield (Scheme 3). NOSEY (nuclear Overhauser enhancement spectroscopy) experiments provided the initial evidence for support of all *syn* relationships among hydrogen atoms at C-1, C-2, and C-3 of **7**. The formation of **7** was suggested in Scheme 2. Coordination of the alkyne of **8** to the Pt metal center followed by intramolecular nucleophilic addition of the diene to the Pt-alkyne moiety generated the reactive cyclopropyl platinacarbene intermediate **9**. Due to two fused protons presented on the convex face, the endo hydroxyl group would attack at the cyclopropyl ring from the concave face followed by protonation/reductive elimination of the Pt metal center to afford the oxatricycle **10**, which then underwent double bond migration to furnish **7**.

In summary, a platinum dichloride-catalyzed hydroxy- or alkoxycyclization of dienynes has been successfully developed. The conjugated diene added to the alkyne in the presence of a catalytic amount of $PtCl_2$ and H_2O or an alcohol to afford indenol or azulenol derivatives. Under the same reaction conditions, intramolecular hydroxycyclization of a cyclohexa-dienyndiol generated an oxatricyclo[5.4.0.0^{4,8}]undecane ring skeleton. Due to their numerous reactivities, allylic alcohols and ethers are versatile substrates in a variety of organic transformations including Claisen rearrangements and related processes,[8] epoxidations,[9] cyclopropanations,[10] and palladium-catalyzed allylic substitutions.[11] Therefore, the resulting indenol- and azulenol derivatives containing an allylic alcohol or ether would be expected to demonstrate still higher levels of synthetic utility.

Experimental Section

General Procedure for Platinum Dichloride-Catalyzed Intramolecular Hydroxy- or Alkoxycyclization of Cyclic Dienynes. Cyclic dienyne (1.0 mmol) and $PtCl_2$ (0.05 mmol) were mixed in refluxing H_2O/acetone (1:1, 30 mL) or an alcohol (30 mL) until all dienyne was consumed (typically 16 h). The reaction mixture was diluted with ethyl acetate (50 mL) and washed with water (3 × 50 mL). The organic phase was dried ($MgSO_4$), filtered, and concentrated to give the crude mixture.

(±)-(3a*S*,4*R*,7a*R*)-Dimethyl 2,3,3a,4,7,7a-Hexahydro-4-hydroxy-3-methyleneindene-1,1-dicarboxylate (3a). The crude mixture from intramolecular hydroxycyclization of **1a** (0.25 g, 1.0 mmol) was purified by flash column chromatography[12] (silica gel, 10% ethyl acetate/hexanes) to give **3a** (0.19 g, 0.72 mmol, 72%) as a pale-yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.82 (m, 1H), 5.74 (m, 1H), 4.97 (d, J = 1.9 Hz, 1H), 4.90 (d, J = 2.0 Hz, 1H), 4.19 (brs, 1H), 3.73 (s, 3H), 3.72 (s, 3H), 3.28 (dd, J = 17.9, 1.4 Hz, 1H), 3.03 (m, 1H), 2.86 (m, 2H), 2.00 (dt, J = 17.9, 5.8 Hz, 1H), 1.86 (m, 1H), 1.72 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.9, 170.4, 147.4, 127.8, 127.6, 106.9, 65.0, 61.5, 52.8, 52.7, 49.8, 38.8, 38.0, 22.9; IR (CH_2Cl_2) 3554, 2918, 2750, 1710, 1515, 1443, 1372, 1007 cm^{-1}; MS (EI) *m*/*e* 266.3 (M$^+$, 0.3), 197.2 (63), 188.2 (28), 165.2 (43), 145.2 (34), 137.2 (100), 129.2 (64), 128.1 (39), 91.1 (51), 77.1 (62), HRMS (EI) *m*/*e* calcd for $C_{14}H_{18}O_5$ 266.1154, found 266.1153.

(±)-(3a*S*,4*R*,8a*R*)-Dimethyl 2,3,3a,4,8,8a-Hexahydro-4-methoxy-3-methyleneazulene-1,1(7*H*)-dicarboxylate (6b). The crude mixture from intramolecular hydroxycyclization of **2** (0.262 g, 1.0 mmol) was purified by flash column chromatography[7] (silica gel, 5% ethyl acetate/hexanes) to give **6b** (0.191 g, 0.65 mmol, 65%) as a pale-yellow powder: mp 41−43 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.58 (m, 1H), 5.56 (m, 1H), 5.12 (brs, 1H), 4.96 (brs, 1H), 4.04 (brd, J = 8.9 Hz, 1H), 3.69 (s, 3H), 3.68 (s, 3H), 3.33 (s, 3H), 3.19 (dd, J = 17.0, 2.4 Hz, 1H), 3.08 (ddd, J = 9.5, 7.5, 2.1 Hz, 1H), 3.00 (m, 1H), 2.84 (dd, J = 17.0, 1.0 Hz, 1H), 2.32 (m, 1H), 2.18 (m, 1H), 1.51 (qd, J = 14.0, 4.6 Hz, 1H), 1.33 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.7, 170.6, 148.6, 132.2, 129.0, 109.2, 79.1, 63.3, 56.7, 52.7, 52.4, 51.8, 45.5, 39.6, 29.0, 24.1; IR (CH_2Cl_2) : 3475, 3020, 295 3, 2820, 2073, 1733, 1654, 1435, 1396, 1264, 1156 cm^{-1}; MS (EI) *m*/*e* (rel intensity) 294.3 (M$^+$, 8), 234.2 (84), 202.2 (85), 187.2 (10), 170.1 (54), 143.1 (79), 128.1 (44), 117.1 (28), 105.1 (20), 91.1 (100); HRMS (EI) *m*/*e* calcd for $C_{16}H_{22}O_5$ 294.1467, found 294.1462. Crystals suitable for X-ray diffraction analysis were grown from CH_2Cl_2 and hexanes.

Acknowledgment. This work was supported by grants from the National Science Council (NSC 95-2113-M-003-003).

Supporting Information Available: ^{1}H NMR and ^{13}C NMR spectra of compounds **3b**−**e, 6a**, and **6c**−**e** and X-ray crystallographic information files for compounds **6b** and **6c**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO702424W

(8) (a) Corey, E. J.; Lee, D.-H. *J. Am. Chem. Soc.* **1991**, *113*, 4026.(b) Donde, Y.; Overman, L. E. *J. Am. Chem. Soc*. **1999**, *121*, 2933. (c) Metz, P.; Hungerhoff, B. *J. Org. Chem.* **1997**, *62*, 4442.

(9) Johnson, R. A.; Sharpless, K. B. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon Press: Oxford, 1991; Vol. 7, p 389.

(10) (a) Denmark, S. E.; O'Connor, S. *J. Org. Chem*. **1997**, *62*, (584). (b) Charette, A. B.; Marcoux, J. F. *Synlett* **1995**, 1197.

(11) Trost, B. M.; VanVranken, D. L. *Chem. Rev.* **1996**, *96*, 395.

(12) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.