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Inversion of the Direction of Stereoinduction in the Coupling of Chiral γ,δ-Unsaturated Fischer Carbene Complexes with *o*-Ethynylbenzaldehyde

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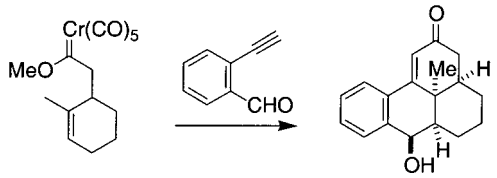
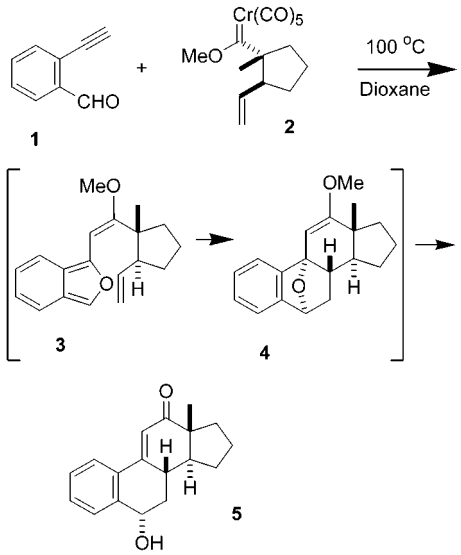
ABSTRACT



A variety of γ,δ-unsaturated carbene complexes that feature a stereogenic center at the β-carbon couple with 2-ethynylbenzaldehyde to afford hydrophenanthrene derivatives with a high degree of stereoinduction. The direction of stereoinduction is opposite for examples where the stereogenic center is acyclic vs examples where it is within a ring.

In a recent publication, stereoselective formation of the steroid ring system (e.g., **5**, Scheme 1) through coupling of 2-alkenylcyclopentylcarbene complexes (e.g., **2**) and 2-ethynylbenzaldyde (**1**) was reported.[1] The stereochemical induction event involves an exo selective intramolecular Diels−Alder reaction of intermediate benzofuran-alkene derivative **3**;[2] subsequent opening of the oxanorbornene ring in **4** followed by hydrolysis leads to the observed product **5**. The transformation in Scheme 1 represents a one-step stereoselective construction of the hydrophenanthrene ring system from simple and readily available components.[3] As a further test of the synthetic utility of this transformation, the coupling of a variety of cyclic and acyclic chiral γ,δ-unsaturated carbene complexes were prepared and tested in their reaction with 2-ethynylbenzaldehyde; these studies are the focus of this Letter.

Scheme 1



(1) Ghorai, B. K.; Herndon, J. W.; Lam, Y. F. *Org. Lett.* **2001**, *3*, 3535−3538.

(2) Intramolecular Diels−Alder reactions of isobenzofurans are generally exo selective. (a) Meegalla, S. K.; Rodrigo, R. *Synthesis* **1989**, 942−944. (b) Yamaguchi, Y.; Yamada, H.; Hayakawa, K.; Kanematsu, K. *J. Org. Chem.* **1987**, *52*, 2040−2046. (c) Tobia, D.; Rickborn, B. *J. Org. Chem.* **1987**, *52*, 2611−2615.

(3) For a discussion of the utility of this class of compounds, see: Nicolaou, K. C.; Zhong, Y. L.; Baran, P. S.; Sugita, S. *Angew. Chem., Int. Ed.* **2001**, *40*, 2145−2149.

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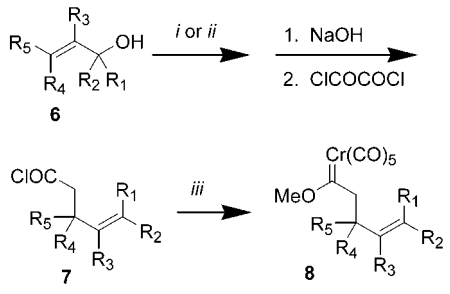
The γ,δ-unsaturated carbene complexes used in this study were prepared from allylic alcohols using the four-step transformation depicted in Scheme 2.[4] The yield for conversion of carboxylic acids to carbene complexes was 52−70% in all cases. The Johnson ortho ester Claisen rearrangement was not successful in more highly substituted systems, and a selenium-based alternative procedure was employed.[5]

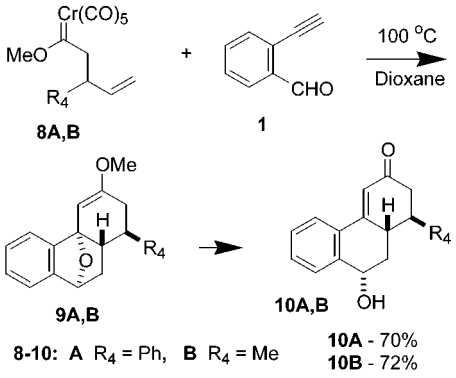
Scheme 2[a]



[a] (i) $CH_3C(OEt)_3/H^+$. (ii) (a) $H_2C{=}CHOEt/PhSeBr$, (b) $NaIO_4$, then 100 °C. (iii) $K_2Cr(CO)_5$, then Me_4NBr, then CH_3OTf.

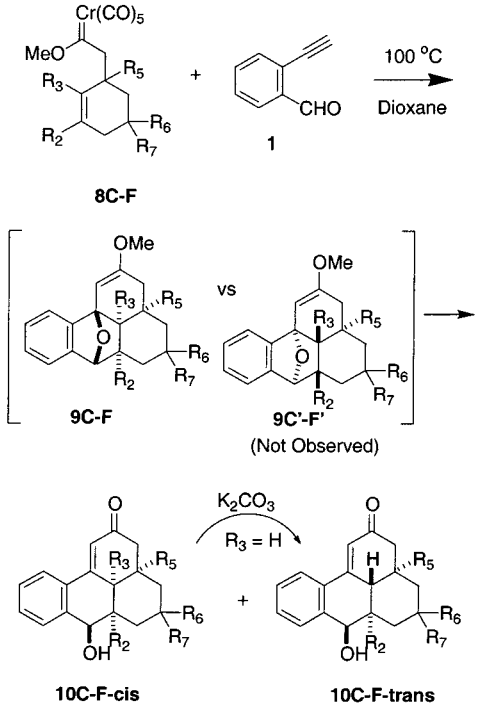
In the first phase of these studies, Fischer carbene complexes containing a single acyclic stereogenic center at the β-carbon (**8A,B**, Scheme 3) were examined. In both cases examined, the reaction was completely stereoselective and led to the compounds **10A** and **10B**. The direction of stereoinduction was identical to that noted in the previous studies involving synthesis of the steroid ring system. Examination of the initial Diels−Alder adducts **9** reveals that the observed stereoisomer is that where the substituent at the stereogenic center is equatorial.[6,7]

Scheme 3



The analogous compound where the alkene is contained within a six-membered ring (**8C**, Table 1) afforded a mixture of two compounds assigned as **10C-cis** (37%) and **10C-trans** (27%).[7] The minor product, **10C-trans**, is obviously an epimerization product since it is formally a Diels−Alder adduct of a *trans* cyclohexene derivative. Major compound **10C-cis** converts to minor compound **10C-trans** upon treatment with potassium carbonate and methanol. Since the products only differ in configuration at an epimerizable stereocenter, they both can ultimately result from a single oxanorbornene derivative, **9C**. Thus the Diels−Alder step of the reactions appears to proceed with complete stereo-

Table 1. Coupling of Cyclohexenylmethylcarbene Complexes with 2-Ethynylbenzaldehyde



entry[a]	R_2	R_3	R_5	R_6 and R_7	yield	cis:trans[b]
C	H	H	H	H	64%	58:42
D[c]	Me	H	H	H	37%	*d*
E	H	Me	H	H	35%	*e*
F[c]	H	H	Me	Me	50%	70:30

[a] Entry letters define substituents for compounds **8**−**10**. [b] The ratio was not consistent over several runs. [c] The selenium-based alternative was employed for formation of **8**. [d] The ratio could not be determined. [e] Only **10E-cis** was obtained.

(4) This carbene-complex-forming step has previously been reported. Moser, W. H.; Hegedus, L. S. *J. Am. Chem. Soc.* **1996**, *118*, 7873−7880.

(5) Pitteloud, R.; Petrilka, M. *Helv. Chim. Acta* **1979**, *62*, 1319−1325.

(6) Related intramolecular Diels−Alder reactions of simple furans afford predominantly the equatorial isomer. (a) Woo, S. Keay, B. A. *Tetrahedron: Asymmetry* **1994**, *5*, 1411−1414. (b) Rogers, C.; Keay, B. A. *Tetrahedron Lett.* **1991**, *32*, 6477−6880. (c) Ferringa, B. L.; Gelling, O. J.; Meesters, L. *Tetrahedron Lett.* **1990**, *31*, 7201−7204. (d) Sader-Bakoumi, L.; Charton, O.; Kunesch, N.; Tillequin, F. *Tetrahedron* **1998,** *54*, 1773−1782. (e) Hudlicky, T.; Butora, G.; Fearnley, S. P.; Gum. A. G.; Persichini, P. J., III; Stabile, M. R.; Merola, J. S. *J. Chem. Soc., Perkin Trans. 1* **1995**, 2393−2398. (f) De Geyter, T.; Cauwberghs, S.; De Clercq, P. J. *Bull. Soc. Chim. Belg.* **1994**, *103*, 433−443. (g) Metz, P.; Stölting, J.; Läge, M.; Krebs, B. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 2195−2197. (h) Meiners, U.; Cramer, E.; Froehlich, R.; Wibbeling, B.; Metz, P. *Eur. J. Org. Chem.* **1998**, 2073−2078. (i) Woo, S.; Keay, B. A. *Synlett* **1996**, 135−137.

(7) The stereochemistry was assigned on the basis of coupling constants between protons at stereogenic centers (see Supporting Information). For stereochemical assignments in similar ring systems, see: Piers, E.; Llinas-Brunet, M.; O'Balla, R. M. *Can. J. Chem.* **1993**, *71*, 1484−1494.

selectivity, followed by partial epimerization at the allylic position. The direction of stereoinduction is *opposite* to that observed in the acyclic case in Scheme 3 and the steroid case in Scheme 1.

The reaction was examined for a variety of cyclohexenylmethylcarbene complexes of varying substitution pattern, and the results are depicted in Table 1. In all cases, the original stereocenter was completely effective in controlling the stereochemistry of the initial Diels−Alder adduct, and only compounds **10-cis** and/or **10-trans** and no other isomers were observed. As predicted, the overall efficiency of the reaction was considerably less as the cyclohexene ring became more hindered, and lower yields were obtained using **10D** and **10E**. In most cases, a mixture of stereoisomers was obtained that could be converted to a single stereoisomer, **10-trans**, upon base treatment. Successful isolation of the pure kinetic product was successful only in entry E, where there is no acidic proton at the three-ring junction.

As noted in Table 1 and Schemes 1 and 3, the original stereogenic center at the β-position of the carbene complex is completely effective in controlling the stereochemistry during the Diels−Alder step. In all cases, two different exo stereoisomers are possible; however, all of the products are derived from a single diastereomer of intermediate oxanorbornene derivative **9**. However, the direction of induction is opposite for the cases of Scheme 3 and the cases in Table 1. In Scheme 3, both the stereogenic center and the alkene are acyclic, while the stereogenic center and the dienophile are both within the same ring for the systems in Table 1. The stereogenic center is part of a ring in the steroidal examples of Scheme 1. However, the dienophile is acyclic; the direction of stereoinduction is the same in these cases as that observed for the examples in Scheme 3. Similar reactions involving cyclohexene dienophiles proceed in the same direction of stereoinduction.[8]

The Diels−Alder step was examined computationally for the reactions of 2-ethynylbenzaldehyde (**1**) with carbene complexes **8B** and **8C**.[9] Comparison of the energies for the most stable conformations of exo Diels−Alder adducts (Figure 1) reveals that the observed products are the more stable products in both cases. Compound **9B**, the equatorial isomer, is considerably more stable than **9B′** and, it is likely that steric interactions between the methyl group and the oxanorbornene bridge are also felt in the transition state. This result is consistent with previous studies of six-membered ring-forming intramolecular Diels−Alder reactions of furans that feature a single stereogenic center in a totally saturated tether;[6] however, highest selectivities were observed in thermodynamic control.[6a,g,i] Since Diels−Alder reactions of isobenzofurans are unlikely to be reversible, the high stereoselectivity is due to kinetic control. Calculations show that **9C** is more stable than **9C′** by 3.0 kcal/mol in the most stable conformation. The relative stereochemistry between the original stereogenic center and the adjacent stereogenic center is opposite for **9B** and **9C**.

Simulation of the entire Diels−Alder step was undertaken in order to understand the factors favoring **9C** over **9C′** (Figure 2). The simulation was performed using Hartree−Frock calculations using the 6-31G* basis set. The reaction profile was established by taking the energy-minimized conformations of **9C** (solid line) and **9C′** (dashed line) and lengthening the C−C bonds formed in the Diels−Alder step to 3 Å in 10 steps. Although the calculated reaction profile is based on the retro-Diels−Alder reaction, the graph in Figure 2 is presented as the forward reaction (the final points on the right represent **9C** and **9C′**). The transition state for **9C′** is 5.6 kcal/mol less stable than the transition state for **9C**. The cyclohexene ring in the transition state precursor to **9C′** deviates substantially from the ideal half-chair

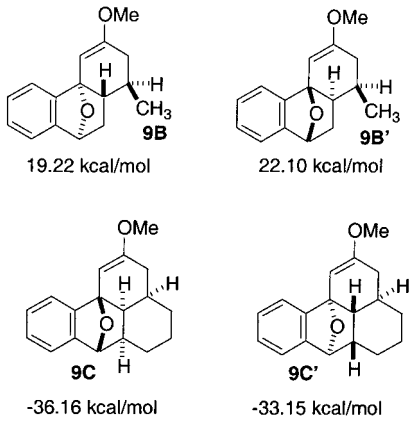


Figure 1. Heats of formation for compounds **9B**, **9B′**, **9C**, **9C′**.

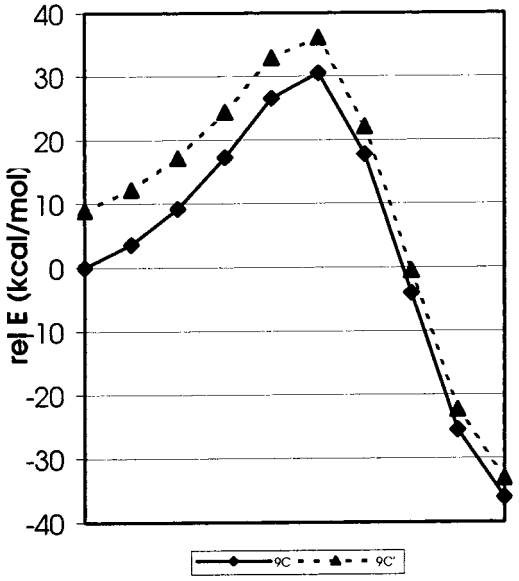


Figure 2. Calculated reaction profile for the Diels−Alder reactions leading to **9C** and **9C′**.

(8) (a) Grieco, P. A.; Kaufman, M. D.; Daeuble, J. F.; Saito, N. *J. Am. Chem. Soc.* **1996**, *118*, 2095−2096. (b) Blond, A.; Paltzer, N.; Guy, A.; D'Hotel, H.; Serva, L. *Bull. Soc. Chim. Fr.* **1996**, *133*, 283−293.

(9) The program MacSaprtan Pro v. 1.04 was utilized in this study.

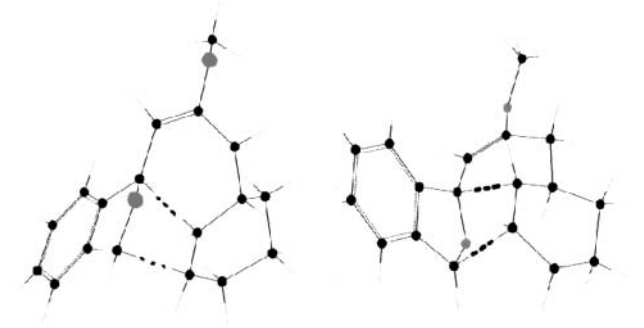


Figure 3. Calculated transition states for formation of **9C** (left) and **9C′** (right).

conformation. The cyclohexene ring of the transition state precursor to **9C** is in the desired half-chair conformation. The energy differences are even greater in earlier points along the reaction pathway. For the first point on the graph, the conformation of the isobenzofuran leading to **9C′** is 9.0 kcal/mol higher in energy for the reaction producing **9C′** than that leading to **9C**.

In summary, stereoselective construction of the hydrophenanthrene ring system has been realized through coupling of β-substituted γ,δ-unsaturated carbene complexes and 2-ethynylbenzaldehyde. A high degree of asymmetric induction was observed in the critical step, intramolecular Diels−Alder reaction of an isobenzofuran intermediate. The direction of asymmetric induction was opposite for complexes where the stereogenic center is acyclic and those where the β,γ, and δ-carbons of the carbene complex are in a ring system.

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Supporting Information Available: Experimental procedures and compound characterization data for reactions producing compounds **8** and **10** and discussion of stereochemical assignments. This material is available free of charge via the Internet at http://pubs.acs.org.

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