The First Asymmetric Synthesis of Optically Active Tropilidenes. Highly Regio- and Diastereo-differentiating Addition of Diazo Ester to Aromatic Ring Using 2,4-Pentanediol as Chiral Linking Bridge

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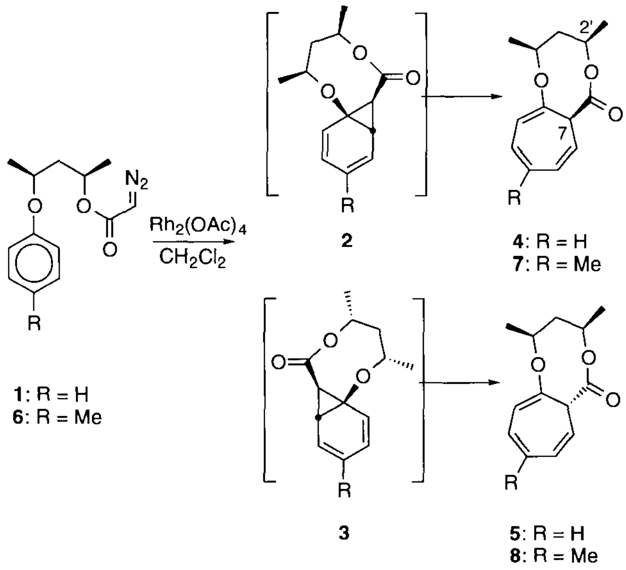
(Received September 11, 1997; CL-970704)

Optically active tropilidenes were prepared by cycloaddition of a diazo ester to an aromatic ring using 2,4-pentanediol as a chiral linking bridge under complete regio- and stereo-differentiations.

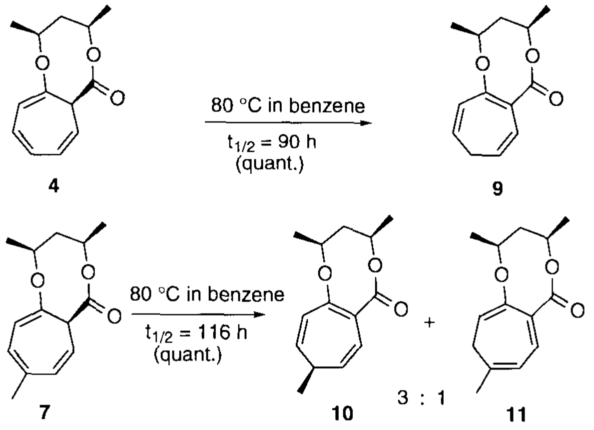
Cycloheptatriene (tropilidene) is a synthetically interesting molecule for the variety of modes of its cycloadditions as 4π and 6π participants including a 4π participant of its norcaradiene tautomer.[1] Because most of those cycloadditions are highly stereoselective, optically active tropilidenes are considered to be promising chiral synthons for various bicyclic and tricyclic compounds. Although optically active chromium(0) complexes of tropilidenes have been prepared as a chiral 6π participant,[2] chiral tropilidenes in optically active forms have not been reported. Chiral tropilidenes can be easily prepared from a diazo ester and a substituted benzene through carbenoid addition catalyzed by a transition metal.[3] Thus, if the regio- and stereochemistries of this addition are fully controlled, optically active tropilidene can be obtained in a straightforward manner. To examine such a possibility, we employed a stereocontrol method where a reagent and a prochiral substrate are linked by optically active 2,4-pentanediol (PD).[4,5] In the reaction of **1**, the PD tether is expected to regulate 1) regioselectivity and *endo*/*exo*-selectivity to give two diastereomeric intermediates, **2** and **3**, and 2) differentiation of the diastereotopic positions closely placed on the phenyl ring in **1**. The stereochemistries of **2** and **3** carry over to chiral tropilidenes of **4** and **5**, respectively. In this communication, we would like to report that the rhodium-catalyzed reaction of **1** (and **6**) afforded only **4** (and **7**) in a quantitative yield. Thermal cycloadditions of the produced tropilidenes without loosing their stereochemical purities under complete stereocontrol were also reported.

Stereochemically pure substrate **1** was prepared in three steps; the Mitsunobu reaction with phenol and (2*R*,4*R*)-PD to give the (2*S*,4*R*)-monophenyl ether (81.7%),[4j] introduction of acetoacetate ester to the other side of the hydroxyl group (99.3%), and conversion of the ester group to diazoacetate (82.5%).[4k,6] The reaction of **1** in dichloromethane (10 mM) in the presence of Rh$_2$(OAc)$_4$ catalyst (1% mol) proceeded smoothly at room temperature. Analyses of the reaction mixture by NMR and HPLC indicated that a single isomer of the tropilidene was produced in a quantitative yield.[7] The resulting tropilidene was isolated by silica gel chromatography (79.5%), and the structure was determined to be (7*S*)-**4** based on its NMR spectra where a 10% NOE between H-7 and H-2' was observed. The conformation of **4** calculated by the PM3 method consists of a relatively planer tropilidene ring, an axial ester group, and closely placed H-7 and H-2' at 1.847 Å distance, which agrees with the observed strong NOE. In the same way, the methyl-substituted substrate **6** was prepared (64.9% in 3 steps) and converted to (7*S*)-**7** without any accompanying detectable (7*R*)-**8** in a quantitative yield (97.9% after isolation). Thus, the reactions proceeded predominantly through **2** under complete regiocontrol, *endo*/*exo*-control and diastereocontrol.



Scheme 1.

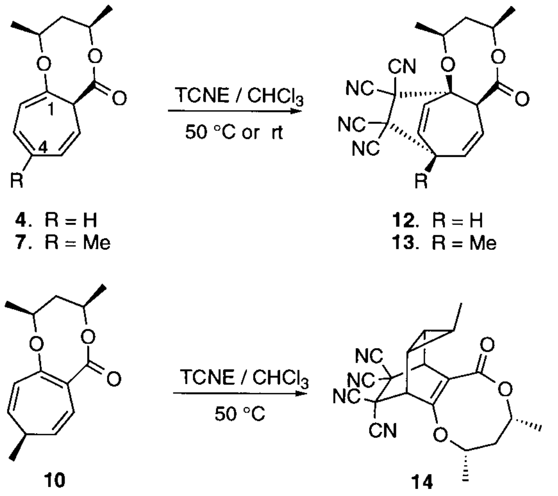
The thermal stability of **4** under neutral conditions was studied in [d]$_6$-benzene monitored by ^{1}H NMR. At 80 °C, a first-order rate, regiospecific and quantitative [1.5]-hydrogen shift to give **9** was observed in a 90.8 h half-lifetime ($k = 2.29 \times 10^{-6}$ s^{-1}). The thermal [1.5]-shift of **7** at 80 °C occurred at a similar rate ($k = 1.62 \times 10^{-6}$ s^{-1}) affording **10** with its regioisomer **11** in a ratio of 3 to 1. The new chiral tropilidene (7*R*)-**10** was



Scheme 2.

isolated by chromatography (58% yield). The results indicated that **4** and **7** are stable chiral synthons below 80 °C.

Cycloadditions to the obtained chiral tropilidenes were studied with tetracycanoethylene (TCNE). When a mixture of **4** and TCNE (3 equivalents) was heated to 50 °C in $CDCl_3$, Diels-Alder reaction proceeded by full regio- and diastereo-differentiation to give **12** in a quantitative yield (51% after recrystallization).[8] The addition between **7** and TCNE at room temperature in $CDCl_3$ yielded **13** (55.1% after recrystallization), also as a single diastereomer with a trace amount of a regioisomer of **13**.[8,9] Because the norcaradiene form of **4** (**2** in Scheme 1) was not expected to have extra strain,[10] the [4+2] cycloaddition of the tropilidene form could be attributed to the nature of the electron-rich and relatively planer trienes in **4** and **7**. On the other hand, the addition of **10** to TCNE occurred through the norcaradiene form. The reaction in $CDCl_3$ proceeded smoothly at 50 °C and afforded **14** as a single diastereomer in an almost quantitative yield.



Scheme 3.

In conclusion, the first asymmetric synthesis of tropilidenes was succeeded and the products were proved to be potent chiral synthons for optically active polycyclic compounds.

References and Notes

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5 For a recent example of the intramolecular cycloadditions with diazo esters forming medium size rings, see: M. P. Doyle, M. N. Protopopova, C. S. Peterson, and J. P. Vitale, *J. Am. Chem. Soc.*, **118**, 7865 (1996).

6 J. B. Hendrickson and W. A. Wolf, *J. Org. Chem.*, **33**, 3610 (1968).

7 When the reaction was carried out at higher concentration (50 mM), the fumaric diester by intermolecular diazo homo-coupling was also obtained in 2.4% yield.

8 The structures of the cycloadducts were assigned based on ^{1}H NMR analysis using the NOE technique and a shift reagent.

9 When the addition was carried out in acetonitrile, the ratio of **14** and the regioisomer was 1 to 1. The cycloaddition of **4** in acetonitrile also gave a regioisomer as 20% of the adduct. In all cases, the regioisomer was the TCNE adduct at the 3,6-positions and diastereomerically pure.

10 Heats of formation calculated by PM3 were -72.57 kcal/mol for **4** and -70.04 kcal/mol for **2** (R = H).