Novel Acid-Catalyzed Rearrangement of Alkoxycarbonylcycloheptatriene Assisted by Alkoxy Substitution

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(Received October 29, 2001; CL-011061)

Methoxy substitution was found to promote acid-catalyzed rearrangement of alkoxycarbonylcycloheptatriene in two different ways depending on the catalyst employed.

A cycloheptatriene unit has a useful synthetic function not only as a cyclic seven-carbon unit but also as a precursor for bicyclic and tricyclic systems.[1] Recently, we have developed a versatile method for the synthesis of optically active alkoxycarbonylcycloheptatrienes such as **1**.[2] Since most reactions of cycloheptatrienes are those with electrophilic reagents, we thought that more reactive and regioselective chiral synthons could be obtained by introducing an electron-donating methoxy group at a proper position of **1**. During the synthetic study of such compounds,[3] we found that 8-methoxy derivative **2** undergoes two different types of acid-catalyzed rearrangements, which are completely switchable by the acid employed.

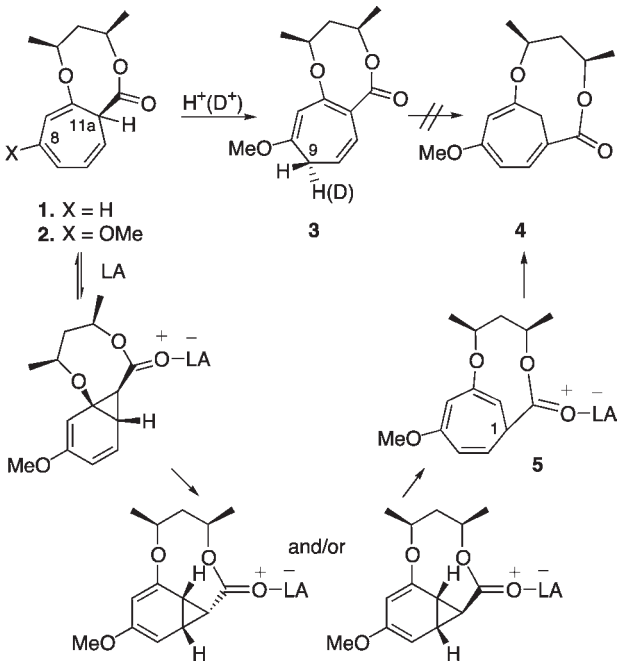
When **2** was treated with catalytic or stoichiometric amounts of *p*-TsOH in dry ether, **3** was obtained regioselectively in a quantitative yield (at rt, reaction time: 2–10 h). The same results were obtained with wet ether as a solvent. In contrast, **1** and other derivatives including the 9- and 11-methoxy derivatives[3] remained unchanged under similar acidic conditions (*p*-TsOH or BF_3 in ether at rt). By using a deuterated acid *p*-TsOD, a deuterium was incorporated stereoselectively at the 9-position to give (9*S*)-9-^{2}H-**3**.[4]

When Lewis acids were used, the mode of rearrangement changed completely. The reaction with BF_3 (in ether at rt, 0.5 h), $SnCl_4$ (in CH_2Cl_2, 0.5 h), or ZnI_2 (in ether, 13.5 h) resulted in skeletal rearrangement; irrespective of the Lewis acid employed, **4** was obtained in a quantitative yield.[5] Formation of **4** via **3** was experimentally discarded.

Since the most basic site of the substrate **2** is the carbonyl group, both Brϕnsted and Lewis acids should first coordinate to this position. In the case of Brϕnsted acid, protonation can occur at the electron rich 9-position, and this is followed by deprotonation at the 11a-position, which is promoted by the carbonyl protonation.

In contrast, the Lewis acids cannot add to the 9-position, and thus the skeletal rearrangement to give **4** take place. This kind of rearrangement pathway through norcaradiene tautomers shown in Scheme 1 is called ''walk rearrangement'' in thermal reaction of cycloheptatrienes.[6] The methoxy group should assist the rearrangement by stabilizing the cationic transition state due to the electron-donation. Since an intermediate **5** was not isolated and its stereochemical information is lost during its conversion to **4**, stereospecificity of the acid-catalyzed walk rearrangement could not be determined.[7]

The observed rearrangements are novel not only for the cycloheptatriene chemistry but also for the biological formation



Scheme 1.

mechanism of ω-cycloheptyl fatty acids.[8]

References and Notes

1 For a review, see: J. H. Rigby, in ''Comprehensive Organic Synthesis,'' ed. by L. A. Paquette, Pergamon, Oxford (1991), Vol. 5, pp 617–643.
2 a) T. Sugimura, S. Nagano, and A. Tai, *Chem. Lett.*, **1998**, 45. b) T. Sugimura, K. Hagiya, Y. Sato, T. Tei, A. Tai, and T. Okuyama, *Org. Lett.*, **3**, 37 (2001).
3 The $Rh_2(OAc)_4$ catalyzed reaction of the precursor diazo compound in dichloromethane at room temperature gave **2** in 75% yield under strict regio- and stereocontrols. The 9- and 11-methoxy derivatives were also prepared by the same procedure. See Ref. 2b for related syntheses.
4 The H/D exchange of **2** or **3** was not observed under the reaction conditions. The stereochemistry of 9*S* could be determined since the NMR spectrum of 9-^{2}H-**3** was identical with a thermal 1,5-shift product of 11a-^{2}H-**2**, which was prepared by base-catalyzed H/D exchange. For the 1,5-shift reactions, see: T. Sugimura, H. Kohno, S. Nagano, F. Nishida, and A. Tai, *Chem. Lett.*, **1999**, 1143.
5 Structure of **4** was determined by ^{1}H NMR and confirmed after reduction with $LiAlH_4$.
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7 When 11a-^{2}H-**2** (see Ref. 4) was treated with BF_3, the deuterium distributed only at the 13-position of **4** in a diastereomeric ratio of 3 : 1. This result may suggest the stereospecificity of the acid-catalyzed walk rearrangement if the final hydride shift is stereospecific.

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