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Iodine-Induced Cyclization Reaction of *endo*-Thioester Substituted Norbornenes Followed by Methylthio Group Rearrangement

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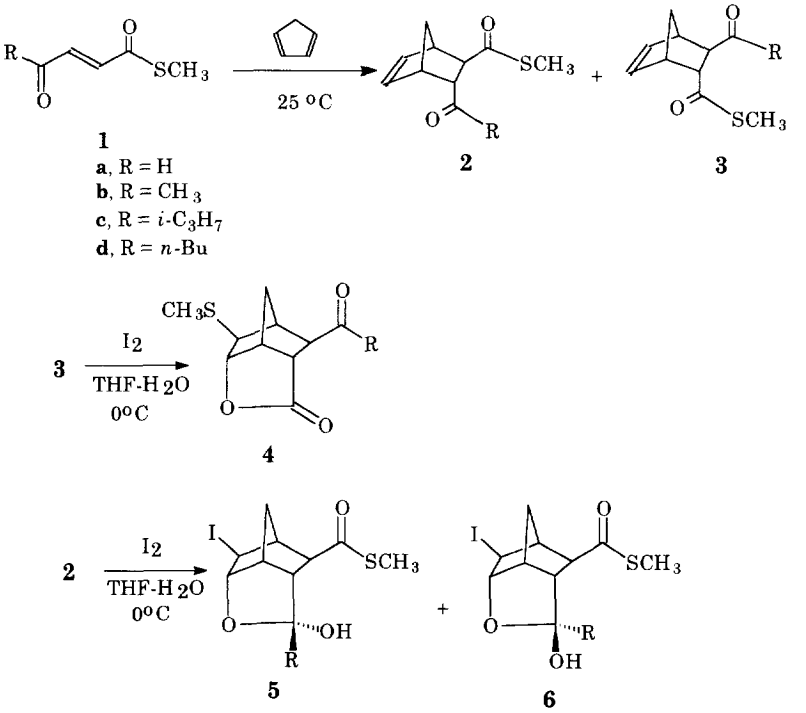
Abstract: Treatment of the *endo*-thioester group substituted norbornenes **3a-3d** with iodine in aqueous tetrahydrofuran at 25°C gave the novel methylthio group rearranged lactonization products **4a-4d** in 80% yields; iodolactonization reaction of **9** was applied to the synthesis of novel diacetal trioxa-cage compound **13**. Copyright © 1996 Elsevier Science Ltd

The halocyclization of an alkene bond is a powerful process in synthetic organic chemistry, especially for regio- and stereoselective functionalization of double bonds.[1] Stereoselective intramolecular lactonization has been used for the synthesis of γ-butyrolactone natural products.[2] Usually, the ring closure takes place with participation of a number of electron-donating groups, such as OH, NHR, COOH, COOR, CONHR, etc. There are some reports regarding the electrophile-induced lactonization of norbornene derivatives.[3] We report here the first example of lactonization of *endo* thioester group substituted norbornenes induced by iodine electrophile, leading to the novel methylthio group rearranged products.

Diels-Alder reaction of the *trans*-γ-oxo-α,β-unsaturated thioesters **1a-1d**, which were obtained by oxidation of the corresponding 2-methylthio-5-alkylfurans[4] with two equivalents of pyridinium chlorochromate (PCC) in dichloromethane for 48 h, with cyclopentadiene at 25 °C for 24 h gave 1 : 1 ratios of the *endo*-acyl isomers **2a-2d** and the *endo*-thioesters **3a-3d** in 90% yields. Reactions of **1a-1d** with cyclopentadiene in the presence of $AlCl_3$ or $BF_3.OEt_2$ at 25°C for 2 h gave high stereoselectivity (ca. 9 :1) in favor of the *endo*-acyl isomers **2a-2d** in 90% yields. The predominant formation of **2a-2d** is readily explained by postulating[5] that the acyl group of the dienophile complexes with the Lewis acid in preference to the thioester group. The

stereoselectivity of the Lewis acid catalyzed Diels-Alder reaction was further enhanced to ca. 49 : 1 in 90% yields when the reaction temperature was lowered to -78℃. The stereochemistry of the cycloadducts **2** and **3** was confirmed by the following chemical transformation (Scheme 1). Reaction of the *endo*-thioester **3a-3d** with I_2 in aqueous THF at 0℃ for 6 h gave the methylthio group rearranged lactones **4a-4d** as the major products in 80% yields.[6] To our knowledge, this is the first example of iodolactonization reaction of norbornene derivatives with *endo*-thioester group and the methylthio group rearrangement is novel.[7] The stereochemistry of the methylthio group of **4** was proven to be *exo* by x-ray analysis of the crystalline compound **4b**.[8] Reaction of the *endo*-acyl isomers **2a-2d** with I_2 in aqueous THF at 0℃ for 6 h gave the isomeric mixture of **5a-5d** and **6a-6d** in 80% yields, respectively.

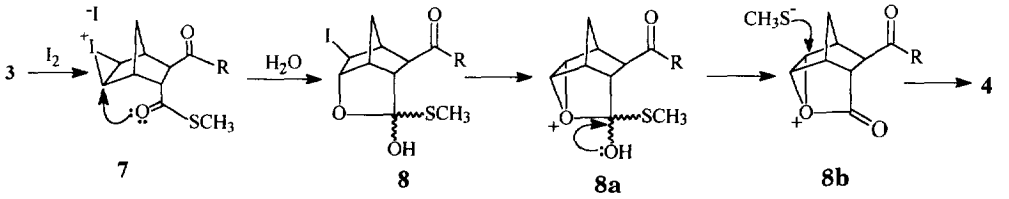
Scheme 1



A mechanism is proposed for the novel methylthio group rearranged iodolactonization (Scheme 2). Electrophilic attack of iodine molecule on the alkene bond of **3** leads to the iodonium ion **7**. Intramolecular nucleophile addition of the *endo* thioester group to the iodonium ion followed by addition of water molecule gives the intermediate **8**. Neighboring oxygen atom displacment for the iodide ion gives the oxonium ion **8a**. Expulsion of the methylthio group of **8a**,

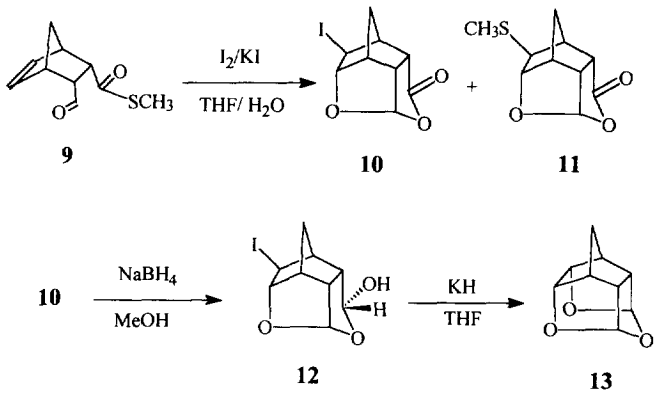
to give **8b**, followed by nucleophilic attack of the methylthio group on the oxonium ion from *exo* face gives the product **4**.

Scheme 2



Oxidation of 2-methylthiofuran with two equivalents of PCC in dichloromethane at 25°C followed by addition of cyclopentadiene gave the *endo* adduct **9** in 50% yield.[4] Treatment of **9** with I_2 in aqueous THF at 0°C for 6 h gave the iodo-cage compound **10** (45%) and the methylthio group rearranged product **11** (40%). Reduction of **10** with sodium borohydride in methanol gave compound **12** in 80% yield. Nucleophilic addition of $NaBH_4$ to the lactone group of **10** from the less hindered *exo* face leads formation of **12**. The stereochemistry of the hydroxy group was confirmed by the following chemical transformation. Treatment of **12** with KH in dry THF at 0 °C gave the parent compound of **13** of diacetal trioxa-cage[9] (Scheme 3). Thus, we have applied the iodine-induced cyclization reaction to the synthesis of novel diacetal trioxa-cage compound.

Scheme 3



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(6). Selected spectral data of **4**. **4c**: IR: 1765, 1715 cm^{-1}; ^1H NMR (300MHz, $CDCl_3$) δ 4.58 (d, J = 4.4 Hz, 1H), 3.25~3.22 (m, 1H), 3.07~3.05 (m, 1H), 2.96 (br s, 1H), 2.89~2.80 (m, 1H), 2.77~2.76 (m, 1H), 2.66 (br s, 1H), 2.31 (s, 3H), 2.01~1.97 (m, 1H), 1.69~1.64 (m, 1H), 1.14 (d, J = 6.6 Hz, 3H), 1.12 (d, J = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 210.33 (C), 178.63 (C), 85.30 (CH), 55.64 (CH), 55.03 (CH), 45.53 (CH), 44.95 (CH), 40.61 (CH), 39.09 (CH), 32.92 (CH_2), 18.90 (CH_3), 18.23 (CH_3), 14.47 (CH_3). MS m/z (rel int.) 254 (M^+, 32), 210 (62), 207(100).

(7). Iodolactonization is usually applied to alkenoic acids or esters, e. g. (a) Dowle, M. D; Davies, D. I. *Chem. Soc. Rev.* **1979**, *8*, 171. (b) Bartlett, P. A.; Myerson, J. *J. Am. Chem. Soc.* **1978**, *100*, 3950. (c) Kallos, J.; Deslongchamps, P. *Can. J. Chem.* **1966**, *44*, 1239. (d) Cambie, R. C.; Ng, K. S.; Rutedge, P. S.; Woodgate, P. D. *Aust. J. Chem.* **1979**, *32*, 2793. (e) Chamberlin, A. R.; Dezube, M.; Dussault, P.; McMills, M. C. *J. Am. Chem. Soc.* **1983**, *105*, 5819.

(8). The X-ray structure will be published in a full paper.

(9). Data for **13**: IR: 2985, 1105cm^{-1} ^1H NMR (300MHz, $CDCl_3$) δ 5.80~5.82 (bs, 2H), 4.33 (s, 2H), 3.04~3.05 (m, 2H), 2.78~2.79 (d, J = 1.5 Hz , 2H), 1.60~1.78 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 108.06 (C), 79.62 (CH), 51.56 (CH), 46.87 (CH), 31.75 (CH_2). MS m/z (rel int.) 166 (M^+, 38), 118 (100).

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