HETEROCYCLES, Vol. 31, No. 2, 1990

ALKYLATIVE LACTONIZATION OF γ,δ-UNSATURATED ESTERS WITH α-CHLORO SULFIDES. A CONCISE SYNTHESIS OF THE MONOTERPENE LACTONE FROM *CHRYSANTHEMUM FLOSCULOSUM* L.

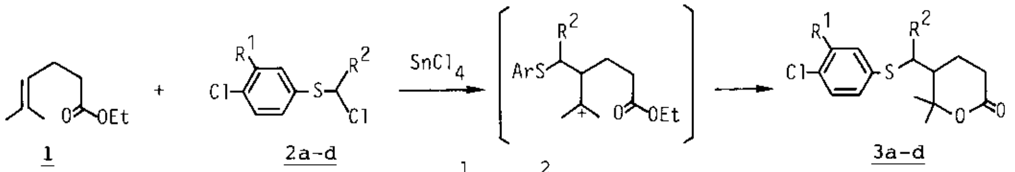
Hiroyuki Ishibashi,* Hiroshi Nakatani, Taru Su So, Toyokazu Fujita, and Masazumi Ikeda

Kyoto Pharmaceutical University, Misasagi, Yamashina, Kyoto 607, Japan

Abstract—The γ,δ-unsaturated ester **1**, on being treated with α-chloro sulfides 2 in the presence of $SnCl_4$, underwent an alkylative lactonization to give the δ-lactones 3. This method was applied to the synthesis of the monoterpene lactone **4** isolated from *Crysanthemum flosculosum* L.

Lactonizations of unsaturated carboxylic acids and esters are important synthetic methods. Halo-lactonization,[1] together with sulfenyl-[2] and selenenyl-lactonization[3] have been widely exploited in the natural products synthesis. However, the corresponding alkylative lactonization has received scant attention.[4] In this paper we wish to report a new synthesis of δ-lactones by Lewis acid promoted alkylative lactonization of γ,δ-unsaturated esters with α-chloro sulfides. Application of this method to the synthesis of the naturally occurring lactone **4** is also described.

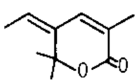
The reactions of ethyl 5-methylhex-4-enoate (**1**) with a series of α-chloro sulfides 2 were examined first. In general, a 1:1 mixture of **1** and **2** was treated with 1.1 equiv. of $SnCl_4$ in dichloromethane at -20°C for 30 min; this gave the expected δ-



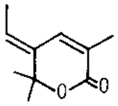
a: R^1=H, R^2=H
b: R^1=Cl, R^2=H
c: R^1=H, R^2=SiMe$_3$
d: R^1=Cl, R^2=SiMe$_3$

lactones **3a** (14%, mp 71-73°C),[5] **3b** (49%, mp 90.5-91.5°C),[5] **3c** (46%, mp 83-85°C), and **3d** (60%, mp 110-111°C), respectively.[6] These results indicate that the 3,4-dichlorophenyl group is superior to the 4-chlorophenyl group as a substituent on the sulfur atom of the chloride **2**. The lactones **3c** and **3d** were obtained as the mixtures of two diastereoisomers in a ratio of ca. 19:1 (by 300 MHz ^{1}H-nmr), which, on exposure to tetrabutylammonium fluoride, gave the desilylated lactones **3a** and **3b** in 98 and 77% yields, respectively.

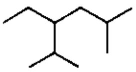
The lactone **4**, isolated from Crysanthemum flosculosum L.,[7] is an irregular monoterpenoid having the santolinyl skeleton **6** which does not conform to the isoprene rule. Uda and co-workers,[8] in the first synthesis of **4**, established unambiguously the geometry of the 5-ethylidene side-chain of the natural lactone to be Z-form as **4** but not (E)-**5**. They also showed that irradiation of **5** yielded the natural lactone **4**.



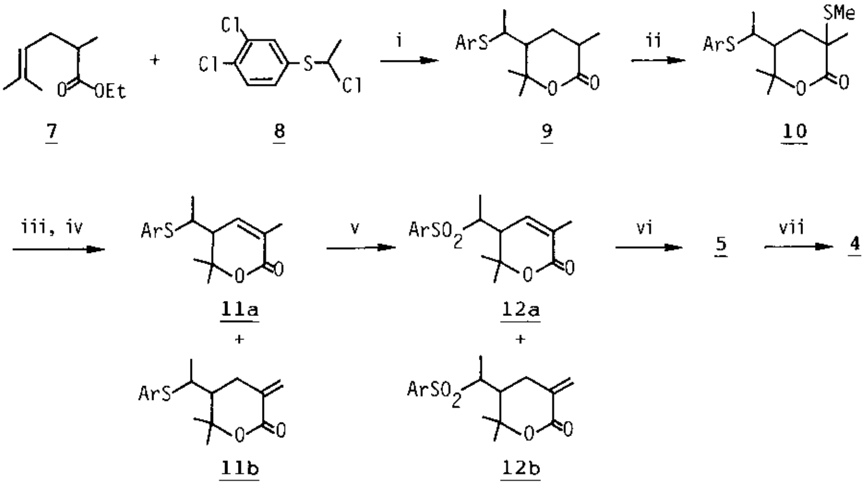
4



5



6



i, $SnCl_4$, CH_2Cl_2, 0°C, 30 min; ii, LDA, THF, -78°C, 30 min then MeSSMe, THF, -78°C, 1.5 h; iii, MCPBA, CH_2Cl_2, room temp., 1 h; iv, $NaHCO_3$, toluene, reflux, 3 h; v, MCPBA, CH_2Cl_2, 0°C, 2 h then room temp. 15 h; vi, DBU, benzene, 150°C, 2 h; vii, hν, benzene, 3 h.

Our synthesis of **5** as a pivotal relay to **4** was begun by applying the above alkylative lactonization process to the direct construction of its santolinyl skeleton.

Thus, treatment of the ester **7** with the chloride **8** under similar conditions to those above, and successive chromatographic separation afforded, in 35% yield, the less polar lactone **9** and a trace amount of the polar lactone **9**.[9] The former was found to be a mixture of three of possible four diastereoisomers in a ratio of 62:32:6 (by 300 MHz ^{1}H-nmr), and the latter to be the fourth stereoisomer. Further experimentation has revealed that the use of molar ratio of **7**:**8**:$SnCl_4$=1:2:3 at 0°C raised the yield of **9** to 73% (the less polar lactone: 56% and the polar lactone: 17%).

The next stage of the synthesis required the introduction of two olefinic bonds into **9**. Sequential treatment of the less polar lactone **9** with lithium diisopropylamide (LDA) and then with dimethyl disulphide afforded the methylthio derivative **10** in 52% yield, along with the recovered **9** (16%). Oxidation of **10** with m-chloroperbenzoic acid followed by heating of the resultant sulfoxide in refluxing toluene gave a mixture (ca. 1:1) of the unsaturated lactone **11a** (δ 6.54, m) and its exo-methylene isomer **11b** [δ 5.66 (br s) and 6.50 (m)] in 74% total yield. This mixture was then oxidized (66% yield) with 2 equiv. of m-chloroperbenzoic acid, and the resultant mixture of the sulfones **12a** and **12b** was heated with DBU in benzene in a sealed tube at 150°C to give the lactone **5**[8] in 64% yield. Interestingly, no corresponding exo-methylene lactone derived from **12b** was detected in the crude reaction mixture. This might be a result of an isomerization of the exo-methylene sulfone **12b** to **12a** under the basic conditions used. *Finally, irradiation of* **5** *in benzene* with 300 W high-pressure mercury lamp through Pyrex for 3 h furnished the lactone **4**, mp 61.5-62.5°C, lit[8] 63.5-64.5°C, in 53% yield, along with the recovered **5** (35%). Thus, we succeeded in a concise total synthesis of the monoterpenoid **4** by using the alkylative lactonization of the unsaturated ester **7** with α-chloro sulfide **8** as a key step, by seven chemical operations.

The preliminary results reported herein demonstrate clearly the viability of our approach to δ-lactones by alkylative lactonization of unsaturated esters. We are continuing in our studies of the synthetic potential of this methodology.

ACKNOWLEDGEMENT

The authors thank Professor Hisashi Uda, Tohoku University, for providing spectra of compound **4**.

REFERENCES AND NOTES

1. M. D. Dowle and D. I. Davies, Chem. Soc. Rev., 1979, **8**, 171; G. W. Holbert and B. Ganem, J. Am. Chem. Soc., 1978, **100**, 352; P. Kočovský and F. Tureček, Tetrahedron, 1983, **39**, 3621.

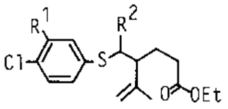
2. K. C. Nicolaou and Z. Lysenko, J. Chem. Soc., Chem. Commun., 1977, 293.

3. D. L. J. Clive and G. Chittattu, J. Chem. Soc., Chem. Commun., 1977, 484; C. Paulmier,'Selenium Reagents and Intermediates in Organic Synthesis,' Pergamon Press, 1986, pp. 232-238.

4. For an intramolecular version, see R. B. Ruggeri, K. F. McClure, and C. H. Heathcock, J. Am. Chem. Soc., 1989, **111**, 1530.

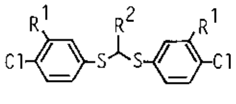
5. **3a**: Ir (ν, cm^{-1}, CCl_4) 1740. ^{1}H-Nmr (δ, ppm, 60 MHz, $CDCl_3$) 1.29 (3H, s, Me), 1.42 (3H, s, Me), 1.5-2.7 (6H, m), 3.13 (1H, dd, J=13, 3 Hz, one of SCH_2), 7.22 (4H, s, ArH). **3b**: Ir (ν, cm^{-1}, CCl_4) 1740. ^{1}H-Nmr (δ, ppm, 60 MHz, $CDCl_3$) 1.33 (3H, s), 1,45 (3H, s), 1.6-2.9 (6H, m), 3.22 (1H, dd, J=13, 3 Hz, one of SCH_2), 7.1-7.6 (3H, m).

6. The side products isolated in these reactions were the unsaturated esters I and the dithioacetals II.



(I)

$R^1=R^2=H$: 38%
$R^1=Cl$, $R^2=H$: 15%



(II)

7. F. Bohlmann and M. Grenz, Tetrahedron Lett., 1969, 2413.

8. S. Yamagiwa, H. Kosugi, and H. Uda, Bull. Chem. Soc. Jpn., 1978, **51**, 3011. For another synthesis of **4**, see D. V. Banthorpe and P. N. Christou, J. Chem. Soc., Perkin Trans. 1, 1981, 105.

9. Ir (ν, cm^{-1}, CCl_4) 1730. ^{1}H-Nmr (δ, ppm, 60 MHz, $CDCl_3$) 1.2-1.5 (12H, m), 1.6-2.8 (4H, m), 3.52 (1H, dq, J=2, 7 Hz, SCH), 7.2-7.6 (3H, m).

Received, 7th November, 1989