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

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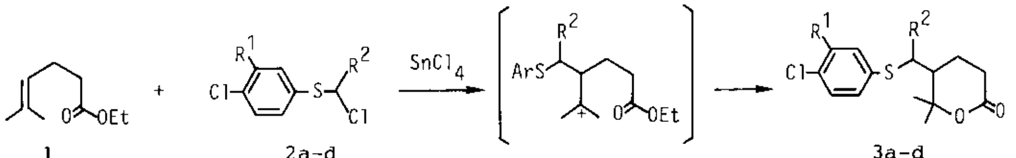
Abstract—The γ,δ-unsaturated ester **1**, on being treated with α-chloro sulfides 2 in the presence of $SnCl_4$, underwent an alkylative lactonization to give the δ-lactones 3. This method was applied to the synthesis of the monoterpene lactone **4** isolated from *Crysanthemum flosculosum* L.

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-

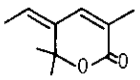


1 2a-d 3a-d

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**.



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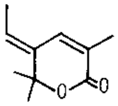

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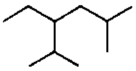

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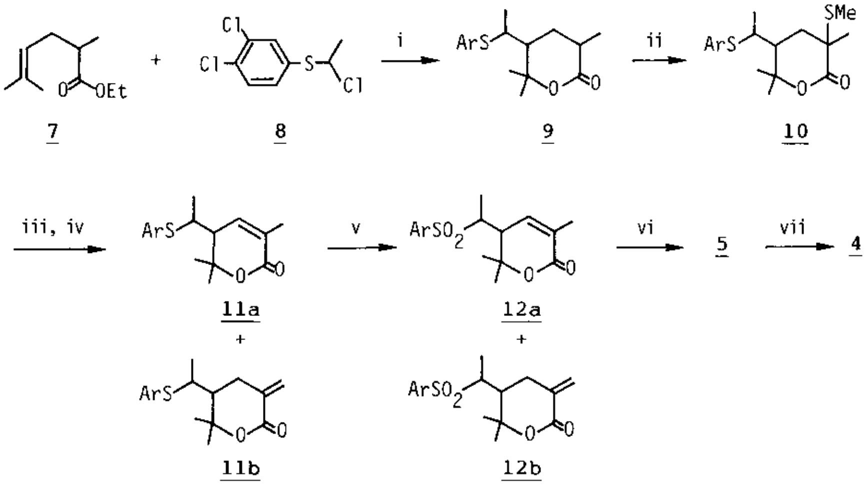

i, $SnCl_4$, CH_2Cl_2, 0°C, 30 min; ii, LDA, THF, -78°C, 30 min then MeSSMe, THF, -78°C, 1.5 h; iii, MCPBA, CH_2Cl_2, room temp., 1 h; iv, $NaHCO_3$, toluene, reflux, 3 h; v, MCPBA, CH_2Cl_2, 0°C, 2 h then room temp. 15 h; vi, DBU, benzene, 150°C, 2 h; vii, hν, benzene, 3 h.

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.

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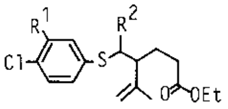
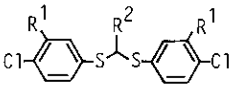
REFERENCES AND NOTES

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.



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

(I)



(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).

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