Tetrahedron Letters, Vol. 34, No. 28, pp. 4527-4530, 1993
Printed in Great Britain

0040-4039/93 $6.00 + .00
Pergamon Press Ltd

Gem-Dimethyl Effect in the Formation of Seven to Eleven-membered Ring Lactones by Iodolactonisation

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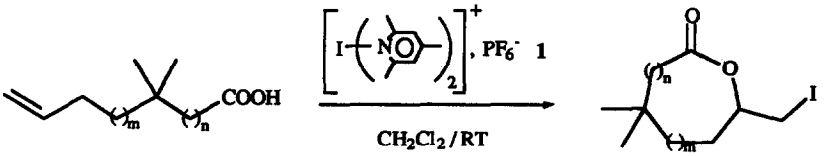
***Abstract** : The influence of a gem-dimethyl group on an iodine-induced cyclisation of ω-alkenoic acids, leading to seven-membered and medium ring lactones was studied.*

It is well established that β-, γ- and δ-lactones are formed during the reaction of ω-ethylenic hydrocarbon chain acids with iodine.[1] We have recently shown that this reaction could be extended to the formation of seven-membered lactones using bis(*sym*-collidine)iodine (I) hexafluorophosphate **1**.[2] Only traces of medium ring lactones (5% or less) were observed under these conditions. However, introduction of an oxygen atom in the hydrocarbon chain allowed the formation of corresponding medium ring lactones. These results can be considered as the first general examples of an electrophilic induced cyclisation leading to these sized ring compounds.

Other structural factors can affect the ease of ring formation from acyclic precursors. Alkyl substitution has been recognised in some cases to favour cyclisations,[3] the most common effect is however, the *gem*-dialkyl effect.[3a,4] From recent results concerning intramolecular Diels-Alder reactions,[5] it has been shown that this effect stems from an increase in reactive rotamer population [6] rather than a Thorpe-Ingold effect.[7]

The *gem*-dialkyl effect is well known in the formation of five and six-membered ring compounds however, few results are reported in the range of seven to eleven-membered ring compounds.[8,9] We decided to carry out a study of the *gem*-dimethyl effect for the formation of seven-membered and medium ring lactones using the iodolactonisation reaction. Required n,n-dimethyl-ω-alkenoic acids were prepared as followed. 2,2-Dimethylacids were obtained by the alkylation of 2-methylpropanoic acid dianion by the desired bromide. 3,3-Dimethylacids were prepared by 1,4-addition of the corresponding alkenyl organocuprate to methyl 3,3-dimethylacrylate,[10] followed by hydrolysis of the ester function. 4,4-Dimethylacids were synthetised from 3,3-dimethylacids by the Arndt-Eistert homologation procedure.[11] Reactions of acids **2** with complex **1** (2 equiv., 0.07M solution) were conducted in methylene chloride at room temperature and the results are reported Table I. The structures shown are supported by ^{1}H and ^{13}C NMR, IR, CI-MS, as well as elemental analysis.[12]

Table 1. Iodolactonisation of n,n-Dimethyl-ω-alkenoic Acids 2 using Bis(*sym*-collidine)iodine(I) Hexafluorophosphate 1.

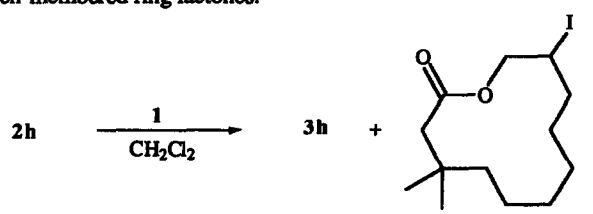


2 3

alkenoic acid			reaction	ring	yield [a]
m	n	no.	time (h)	size	%
2	0	**2a**	1	7	57
1	1	**2b**	2	7	70
0	2	**2c**	1	7	81
3	0	**2d**	2	8	23
2	1	**2e**	17	8	41
1	2	**2f**	5	8, 9	43[b]
3	1	**2g**	5	9	19
5	1	**2h**	14	11, 12	27[c]

[a] Isolated yield after column chromatography. [b] 60-40 mixture of 8- and 9-membered iodolactones [c] 84-16 mixture of 11- and 12-membered iodolactones.

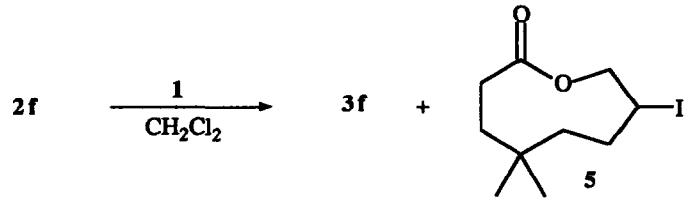
Comparison of the yields in iodolactones obtained from acid **2a** and 6-heptenoic acid (76%) [2] showed that the introduction of a *gem*-dimethyl group in the 2 position induced a slight negative effect (in yield), while no special effect can be appreciated with acids **2b** and **2c**. However, a sensitive positive *gem*-dimethyl effect was observed for the formation of medium ring lactones **3d-3h**, since no reaction was observed with corresponding non-substituted hydrocarbon chain acids. These results show the generality of the *gem*-dimethyl effect for this type of *exo* mode cyclisation in the range of medium ring lactones. Comparison of results obtained in the reaction of acids **2a**, **2b** and acids **2d**, **2e** demonstrates the influence of the *gem*-dimethyl position in the ease of cyclisation. During the formation of the eleven-membered lactone **3h**, we observed also a competitive *endo* mode cyclisation which led to a small amount of the twelve-membered lactone **4**. Such a competition had been observed during the cyclisation of n-oxa-ω-alkenoic acids leading to nine- to eleven-membered ring lactones.[2]



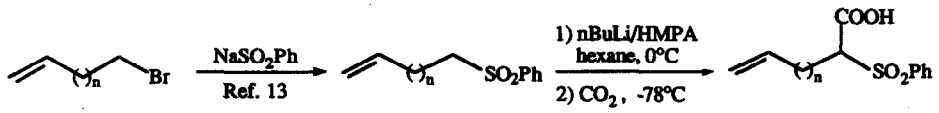
4

This *endo-exo* mode competitive cyclisation was also observed during the reaction of acid **2f** to lactones **3f** and **5**. We can explain this result by the fact that a steric hindrance occurs in the transition state which allows the *endo* mode cyclisation.

We have previously postulated [2] that the successful cyclisation of n-oxa-ω-alkenoic acids was mainly due to the relief of unfavourable CH···CH repulsions which are especially important for medium ring compounds. Introduction of a *gem*-dimethyl group increases these unfavourable interactions so that we explain the observed positive effect by considering a kinetic control [13] of the reaction which is mainly sensitive to steric hindrance which appears in the earlier transition state.

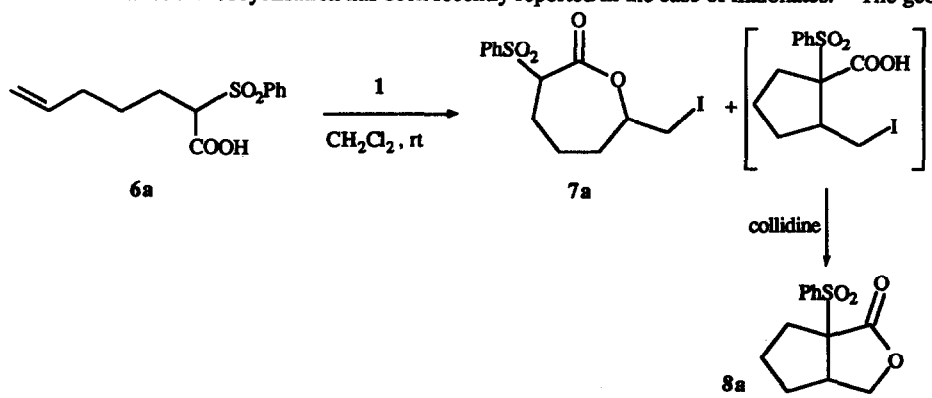


The accelerating effect of a *tert*-butyl group (anchoring effect) has been recently reported in an intramolecular Diels-Alder reaction.[3b] We wondered if such an effect could exist for the formation of medium ring lactones and, therefore we decided to test the phenylsulfonyl group which at first glance should have a larger effect than the *tert*-butyl group. The desired acids **6** were prepared in two steps (50% overall yields) by reaction of ω-alkenyl bromides with sodium benzenesulfonate,[14] followed by carboxylation of resulting sulfonates.



n=3 **6a**
n=4 **6b**

These acids were subjected to the action of reagent **1**. With acid **6a** we obtained a 1:1 mixture of iodolactones **7a** (*cis/trans*: 5/1) and bicyclic lactones **8a** (*cis/trans*: 1/1) (overall yield: 80%). The lactones **8a** resulted from a iodocarbocyclisation, followed by a subsequent lactonisation leading to the bicyclic compounds. Such a iodocarbocyclisation has been recently reported in the case of malonates.[15] The geometry



of the major isomer of lactones **7a** was found to be *cis* by ^1H NMR spectroscopy using a nOesy experiment. Base-induced epimerisation at the carbon bearing the phenylsulfonyl group resulted in the diastereomeric ratio observed.[16]

Reaction of iodine **1** with acid **6b** led only to a mixture of undefined products. The anchoring effect of the phenylsulfonyl group (if it exists) is then not sufficient to allow the formation of medium ring lactones.

Acknowledgements: We wish to thank Rhône-Poulenc Rorer for financial support to B. Simonot.

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12. Selected data; lactone **3c**: white solid mp 56°C.IR ($CHCl_3$): $\nu_{C=O}$: 1750 cm^{-1}.RMN ^1H ($CDCl_3$) δ (ppm) : 1.03 (s, 3H); 1.08 (s, 3H); 1.61 (m, 2H); 1.70 (d, J = 9.1 Hz, 1H); 1.95 (bd, J = 15.1 Hz, 1H); 2,55 (m, 1H); 2.71 (m, 1H); 3.23 (dd, J = 10.5 Hz, J = 6.5 Hz, 1H); 3.36 (dd, J = 10.3 Hz, J = 5.5 Hz, 1H) ; 4.43 (btd, J = 9.1 and 6.05 Hz, 1H).RMN ^{13}C ($CDCl_3$) δ (ppm): 8.1; 24.5; 30.3; 31.7 ; 32.3; 35.6; 46.9; 74.7; 173.8.MS *m/z* : 283 (M^+ +1, 2) ; 282 (M^+, 12); 155 (75); 141 (62); 115 (41); 109 (45); 99 (19); 97 (21); 95 (47); 83 (35); 81 (20); 70 (17); 69 (76); 67 (22); 57 (32); 56 (59); 55 (100); 43 (74); 41 (83); 39 (29). Lactone **3e**: RMN ^1H ($CDCl_3$) δ (ppm): 1.04 (s, 3H); 1.07 (s, 3H); 1.35-1.71 (m, 5H); 1.94 (m, 1H); 2.19 (bd, J = 12.1 Hz, 1H); 2.66 (bd, J = 12.1 Hz, 1H); 3.27 (bd, J = 5.5 Hz, 2H); 4.59 (m, 1H).RMN ^{13}C ($CDCl_3$) δ (ppm): 7.1; 19.4; 28.5; 30.4; 35.6; 36.7; 39.8; 4; 78.5; 172.6.MS *m/z* : 296 (M^+, 1); 170 (15); 169 (31); 127 (10); 110 (54); 109 (61); 84 (61); 83 (100); 70 (48); 69 (63); 68 (18); 67 (21); 56 (32); 55 (38); 43 (37); 41 (60); 39 (20).
13. The mechanism of these iodolactonisations and the nature of the oxygen effect will be discussed in a forthcoming paper.
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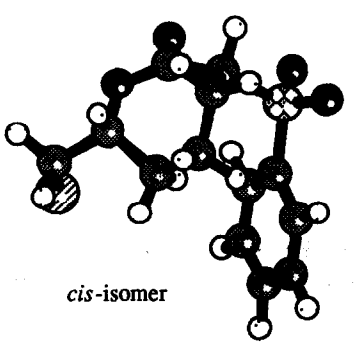
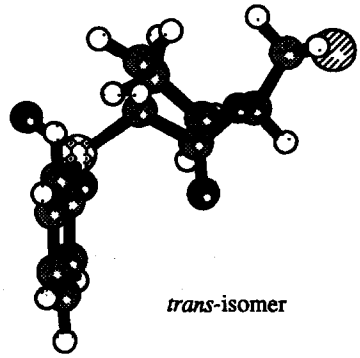
16. In the presence of *sym*-collidine *cis*-iodolactone **7a** led rapidly to a 5:1 *cis/trans* ratio. Molecular calculations (MAD version 2.0) showed that the *cis* isomer was 1.7 kcal.mole $^{-1}$ more stable than the *trans* isomer.



cis-isomer



trans-isomer

(Received in France 13 April 1993; accepted 24 May 1993)