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Preparation of large ring acetylenic lactones by iodo lactonisation

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Abstract—Reaction of ω-ene-7-yne carboxylic acids with (biscollidine)iodine(I) hexafluorophosphate led to large ring acetylenic lactones. In the case of 5- or 6-yne carboxylic acids, iodo enol lactones were preferentially obtained.

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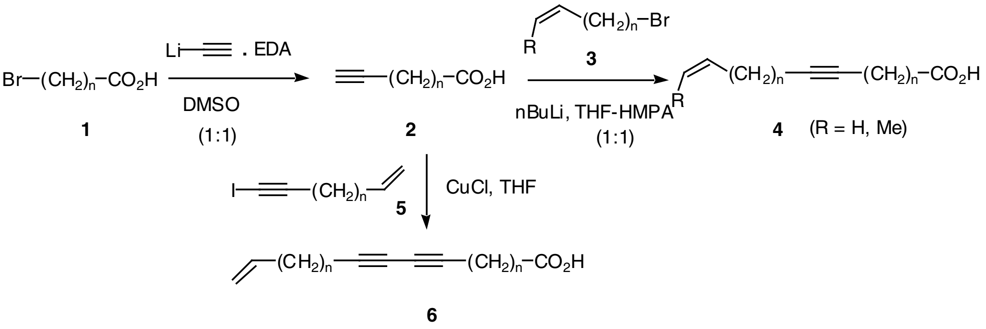
Large ring lactones are found in numerous natural products possessing antibiotic, antitumour or antifungal activities, or perfume properties.[1–3] We previously reported that macrolactones could be formed by halo lactonisation of unsaturated acids using bis(collidine)iodine and bromine hexafluorophosphates as reagents.[4] These lactones were isolated if a structural modification was introduced in the carbon–carbon chains, which lower the activation entropy of these reactions.[5]

We wish to report our results concerning the influence of a carbon–carbon triple bond within the chain on cyclisation. The reaction of acetylenic acids with halo reagents such as X_2 or NXS (X = Br, I) leading to the formation of halo enol lactones has been described. Only formation of five- and six-membered lactones was reported.[6–9]

The acetylenic acids used in this study were prepared as reported in Scheme 1. Coupling reaction of lithium acetylide with ω-bromo carboxylic acids **1** led to acetylenic acids **2** (60–86% yields). Reaction of these latter with unsaturated bromides **3**[4] led to the desired acids **4** (50–70% yields). Coupling of acetylenic acids **2** with iodoacetylenes **5**[10] led to diacetylenic acids **6** (70–80% yields). Non-7-ynoic acid **7** was prepared by alkylation of dianion of oct-7-ynoic acid (*n*-BuLi in THF) with methyl iodide (80%). The subsequent iodo lactonisations were conducted at room temperature by slow addition (6 h) of the acids in methylene chloride solution to 1.2 equiv of (biscollidine)iodine(I)



Scheme 1.

Keywords: Enol lactone; Entropy; Iodo reagent.

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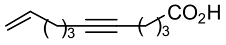
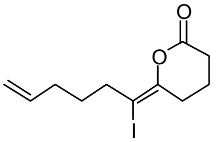
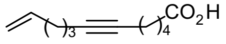
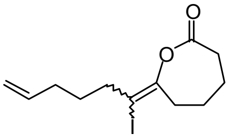
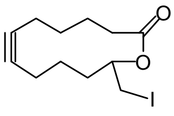
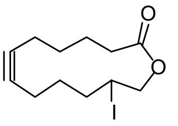
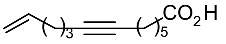
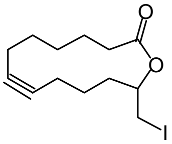
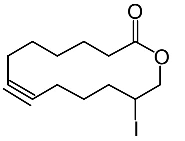
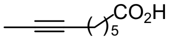
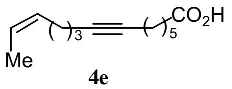
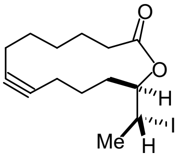
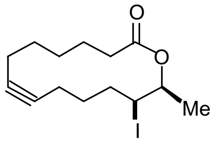
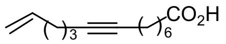
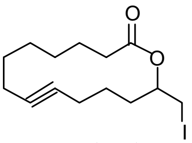
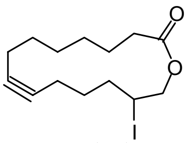
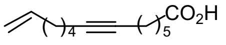
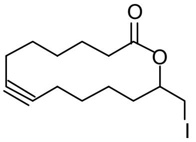
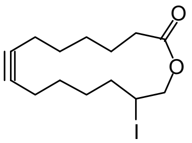
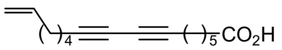
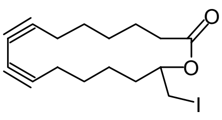
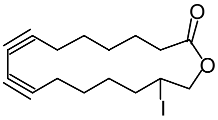
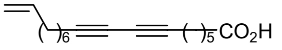
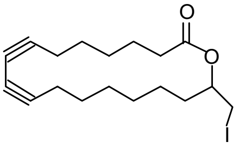
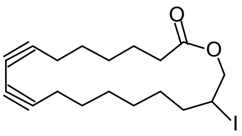
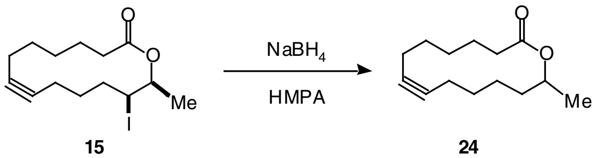
Table 1. Reaction of acetylenic acids with biscollidine iodine(I) hexafluorophosphate

Entry	Acid	Lactone(s) (yield, %)
a	 **4a**	 **8** (78%) (*E*)
b	 **4b**	 **9** (33%) (*E*–*Z*: 14–86)  **10** (3.5%)  **11** (1.5%)
c	 **4c**	 **12** (21%)  **13** (21%)
d	 **7**	N. R.
e	 **4e**	 **14** (8%)  **15** (45%)
f	 **4f**	 **16** (14%)  **17** (7%)
g	 **4g**	 **18** (45%)  **19** (15%)
h	 **6h**	 **20** (7%)  **21** (4%)
i	 **6i**	 **22** (15%)  **23** (10%)

hexafluorophosphate[11] in methylene chloride solution. After completion of the addition, the reaction mixture was concentrated under vacuum, and the residue purified by liquid chromatography over silica gel. The products were identified from their NMR, IR and mass spectra.[12] Our results are reported in Table 1.

With acid **4a**, the iodo enol lactone formed by attack of the acid function on the intermediate iodonium obtained from the acetylenic bond was observed. Only the (*E*)-isomer was obtained.[6,8] Reaction of acid **4b** in the same conditions led to a mixture of the three lactones **9**–**11**. However the iodo enol lactone **9** was the major product. The enol lactone **9** was indeed a (*E*)–(*Z*) mixture (14:86 from the ^{13}C NMR spectra) of the two isomers. This cyclisation should lead only to the (*E*)-isomer.[6,8] The formation of the major (*Z*)-isomer seems due to isomerisation during the silica gel chromatography.



Scheme 2.

However, exposure of this mixture to silica gel for a longer time did not modify the ratio. The presence of the two macrolactones **10**, **11**, in these ring sizes, results from the *endo–exo* cyclisation competition.[4] Reaction of acid **4c** with the iodo reagent led only to the two macrolactones **12**, **13**, without any trace of the eight-membered ring enol lactone. The difficulty of formation of eight-membered enol lactones was confirmed by the fact that acid **7** remained unchanged after 1 day in the presence of the iodo reagent. Results obtained for the cyclisation of acid **4e** show that introduction of a methyl group on the carbon–carbon double bond favour the formation of the *endo* lactone. Only one diastereomer for the lactones **14**, **15** was obtained, corresponding to the antiattack on the iodonium intermediate of the acid function.[5] Entries f and g show that larger ring lactones can be obtained. Introduction of 1,3-diynes on the carbon chain of the acid also allowed the formation of the macrolactones, even if the yields are low. Such a result was not observed with (*Z*)-trideca-7,12-dienoic acid since a mixture of iodolactones and nonidentified products (probably oligomers) was obtained. We explain these results by the fact that introduction of an acetylenic bond, decreased the entropy of the chain to cyclise. This interpretation was confirmed by the fact that only traces of iodo lactone could be obtained by reaction of pentadec-14-enoic acid with (biscollidine)iodine(I) hexafluorophosphate (see also Ref. 13). Treatment of lactone **15** with NaBH$_4$ in HMPA[14] led cleanly to the lactone **24** (80% yield) (Scheme 2).

In conclusion we report that introduction of a triple bond in the carbon-chain of ω-unsaturated acids allows the formation of macrolactones. However, the triple bond must be separated of at least five carbon of the acid function, to avoid formation of enol lactones of lower ring sizes.

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11. Homsi, F.; Robin, S.; Rousseau, G. *Org. Synth.* **2000**, *77*, 206–211.
12. *Selected data. Iodolactone* **8**: ^{1}H NMR (250 MHz, CDCl$_3$) δ 5.95–5.70 (m, 1H); 5.10–4.90 (m, 2H); 2.75 (t, $J = 13$ Hz, 2H); 2.65–2.50 (m, 4H); 2.15–1.95 (m, 2H); 1.95–1.80 (m, 2H); 1.70–1.45 (m, 2H). ^{13}C NMR (CDCl$_3$) δ 167.7; 146.7; 138.0; 114.7; 88.8; 37.5; 35.1; 32.3; 28.2; 18.3. *Iodolactone* **9**: ^{1}H NMR (250 MHz, CDCl$_3$) (*E* and *Z* isomers) δ 5.86–5.18 (m, 1H); 5.10–4.92 (m, 2H); 2.72–2.65 (m, 2H); 2.60–2.45 (m, 2H); 2.20–2.12 (m, 2H); 1.95–1.72 (m, 4H); 1.53 (m, 2H). ^{13}C NMR (CDCl$_3$) (*E* isomer) δ 171.7; 150.7; 137.5; 115.3; 90.5; 37.3; 36.3; 33.0; 31.2; 25.2; 24.8; 23.5. ^{13}C NMR (CDCl$_3$) (*Z* isomer) δ 171.7; 149.0; 137.7; 115.0; 96.0; 36.5; 35.5; 33.5; 32.4; 28.1; 26.1; 23.1. *Iodolactone* **10**: ^{1}H NMR (250 MHz, CDCl$_3$) δ 4.95 (m, 1H); 3.30 (d, $J = 6$ Hz, 2H); 2.65–1.40 (m, 16H). ^{13}C NMR (CDCl$_3$) δ 173.2; 81.5; 81.5; 72.3; 33.8; 31.4; 27.5; 23.5; 22.3; 18.4; 17.9; 6.3. *Iodolactone* **11**: ^{1}H NMR (250 MHz, CDCl$_3$) δ 4.65 (m, 1H); 4.15 (m, 2H); 2.65–1.40 (m, 16H). ^{13}C NMR (CDCl$_3$) δ 172.1; 82.2; 79.2; 67.6; 34.5; 33.2; 28.2; 26.3; 24.2; 23.6; 16.7. *Iodolactone* **12**: ^{1}H NMR (250 MHz, CDCl$_3$) δ 5.15 (m, 1H); 3.22 (m, 2H); 2.60–1.30 (m, 16H). ^{13}C NMR (CDCl$_3$) δ 172.7; 81.4; 80.3; 72.4; 34.3; 33.7; 27.0; 25.9; 24.3; 23.2; 18.3; 17.9; 5.3. *Iodolactone* **13**: ^{1}H NMR (250 MHz, CDCl$_3$) δ 4.60 (dd, $J = 10$ and 1.5 Hz, 1H); 4.28 (t, $J = 10$ Hz, 1H); 4.17 (m, 1H); 2.50–2.10 (m, 8H); 1.90–1.40 (m, 8H). ^{13}C NMR (CDCl$_3$) δ 172.6; 81.1; 80.2; 68.3; 34.3; 33.7; 29.6; 28.0; 27.7; 27.1; 24.6; 18.1; 16.9. *Iodolactone* **15**: ^{1}H NMR (250 MHz, CDCl$_3$) δ 4.95 (dq, $J = 7$ and 2 Hz, 1H); 4.25 (dt, $J = 10$ and 5 Hz, 1H); 2.60–1.38 (m, 16H); 1.43 (d, $J = 5$ Hz, 3H). ^{13}C NMR (CDCl$_3$) δ 172.7; 81.3; 80.2; 72.2; 37.6; 34.7; 32.1; 28.9; 27.9; 27.1; 24.8; 18.2; 17.7; 17.2. *Iodolactone* **16**: ^{1}H NMR (250 MHz, CDCl$_3$) δ 5.20 (m, 1H); 3.25 (dd, $J = 2$ and 6 Hz, 2H); 2.50–1.10 (m, 18H). ^{13}C NMR (CDCl$_3$) δ 172.9; 80.8; 80.4; 72.2; 33.4; 31.2; 27.7; 27.5; 27.3; 24.5; 21.5; 18.1; 17.9; 48. *Iodolactone* **17**: ^{1}H NMR (250 MHz, CDCl$_3$) δ 4.55 (dd, $J = 3$ and 10 Hz, 1H); 4.35 (t, $J = 10$ Hz, 1H); 4.25 (m, 1H); 2.60–1.20 (m, 18H). ^{13}C NMR (CDCl$_3$) δ 172.6; 80.9; 79.4; 68.5; 34.2; 33.2; 30.4; 28.4; 27.9; 27.7; 27.3; 24.4; 17.9; 17.4. *Iodolactone* **18**: ^{1}H NMR (250 MHz, CDCl$_3$) δ 4.92 (m, 1H); 3.27 (d, $J = 6$ Hz, 2H); 2.60–1.20 (m, 18H). ^{13}C NMR (CDCl$_3$) δ 173.0; 81.1; 80.5; 71.7; 34.5; 33.5; 27.9; 27.6; 27.1; 24.7; 23.4; 18.2; 18.2; 8.00. *Iodolactone* **19**: ^{1}H NMR (250 MHz, CDCl$_3$) δ 4.00 (d, $J = 7$ Hz, 1H); 4.32–4.16 (m, 2H); 2.60–1.20 (m, 18H). ^{13}C NMR (CDCl$_3$) δ 172.4; 81.0; 80.1; 68.3; 34.8; 34.4; 29.0; 28.3; 27.0; 26.5; 24.8; 24.2; 18.3; 17.9. *Iodolactone* **20**: ^{1}H NMR (250 MHz, CDCl$_3$) δ 4.85 (m, 1H); 3.30 (m, 2H); 2.60–1.20 (m, 18H). *Iodolactone* **21**: ^{1}H NMR (250 MHz, CDCl$_3$) δ 4.45 (m, 1H); 4.25 (m, 2H); 2.60–1.20 (m, 18H). *Lactone* **24**: ^{1}H NMR (250 MHz, CDCl$_3$) δ 5.05 (m, 1H); 2.50–2.00 (m, 6H); 1.70–1.20 (m, 12H); 1.20 (d, $J = 7$ Hz, 3H). ^{13}C NMR (CDCl$_3$) δ 173.5; 81.0; 80.7; 69.8; 35.3; 34.9; 28.1; 27.7; 27.2; 24.9; 23.6; 20.6; 18.3; 18.3.
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