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Formation of Highly Substituted Cyclopentanes from Radical and Anionic Michael Cyclisations of α-Iodo-γ- and -δ-lactones

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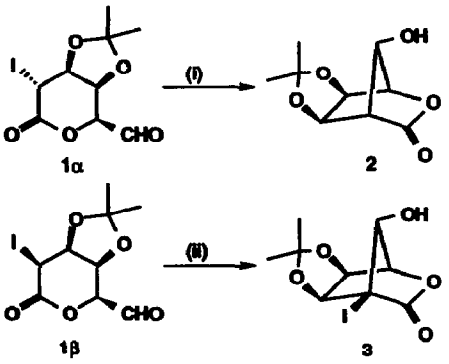
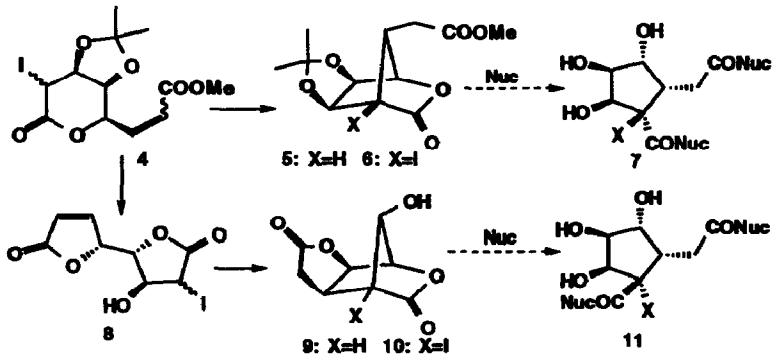
Abstract: α-Iodo-δ- and -γ-hexonolactones with α,β-unsaturated esters developed from C-6 undergo both tributyltin hydride-induced radical and base catalysed anionic Michael cyclisations to form bicyclic lactones with very highly substituted homochiral cyclopentanes. The δ-lactones give cyclopentane products in which adjacent carbon substituents on the cyclopentane ring are *cis* to each other, whereas γ-lactones give cyclopentanes in which the carbon chains are *trans*.

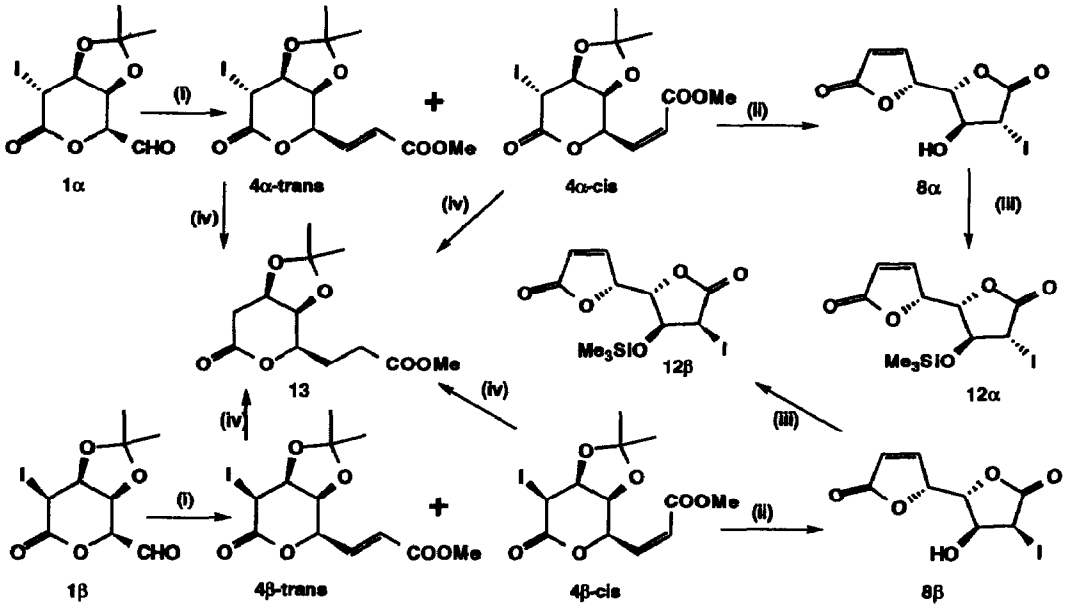
Carbohydrate lactones are almost ideal starting materials for the synthesis of a wide range of highly functionalised targets by procedures in which it is rarely necessary to use more than isopropylidene protection.[1] Recently, we have reported a number of high yielding aldol reactions[2] of 5-formyl-δ-lactones to give very highly substituted cyclopentanes. However, rather different behaviour is found in these reactions between compounds epimeric at C-2 of the lactone. Thus, the iodide **1α** reacts with lithium iodide to give **2** by an overall reductive aldol condensation in 55% yield; only very low yields of **2** are formed by treatment of the epimeric **1β** under the same conditions [Scheme 1]. The reverse was found in the efficiency of aldol condensations in the case of the two epimeric iodoaldehydes. Thus, **1β** in the presence of potassium fluoride in acetonitrile gave the bicyclic iodolactone **3** in 81% yield; in contrast, **1α** gave only trace amounts of **3**.[3] This paper extends the applications of iodoaldehydes such **1** in other cyclisation reactions; the δ-lactones **4** undergo (i) reductive radical cyclisations in good yields to give **5** and (ii) intramolecular anionic Michael closure to form **6**. The highly substituted cyclopentanes **5** and **6** have the adjacent carbon substituents on the cyclopentane *cis* to each other. Nucleophilic ring opening of **5** and **6** should give **7**. Analogous cyclisations of the γ-lactones **8** give **9** and **10** in which the adjacent carbon substituents on the cyclopentane are *trans* related. Reaction of **9** and **10** should give access to **11**, epimeric with **7**.



Scheme 1 (i) LiI, THF (ii) KF, 18-crown-6, MeCN



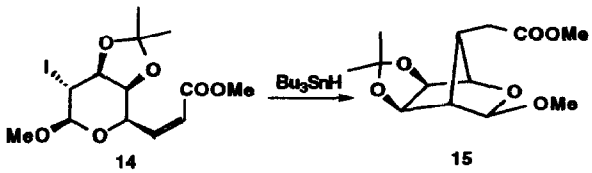
The precursors for the cyclisation reactions are readily available from the aldehydes **1α** and **1β**.[2] Thus, reaction of **1α** with the stabilised Wittig reagent Ph_3P=CHCOOMe gave a mixture of **4α-trans**, m.p. 125-127°C, $[\alpha]_D^{20}$ -22.4 (*c*, 1.04 in $CHCl_3$) in 12% yield and **4α-cis**, m.p. 107-108°C, $[\alpha]_D^{20}$ -8.6 (*c*, 0.99 in $CHCl_3$) in 59% yield [Scheme 2]. Treatment of **4α-cis** with trifluoroacetic acid in aqueous dioxan caused removal of the isopropylidene protecting group, isomerisation of the δ-lactone to the more stable γ-lactone and closure of the C-5 hydroxyl group onto the ester carbonyl to give the dilactone **8α**, an oil, $[\alpha]_D^{20}$ -47.0 (*c*, 1.64 in CH_3CN) in 63% yield. The remaining free hydroxyl group in **8α**, with trimethylsilyl chloride in tetrahydrofuran in the presence of pyridine, was converted into the silyl ether **12α**, m.p. 97-99°C, $[\alpha]_D^{20}$ -53.3 (*c*, 0.75 in $CHCl_3$), in 76% yield.



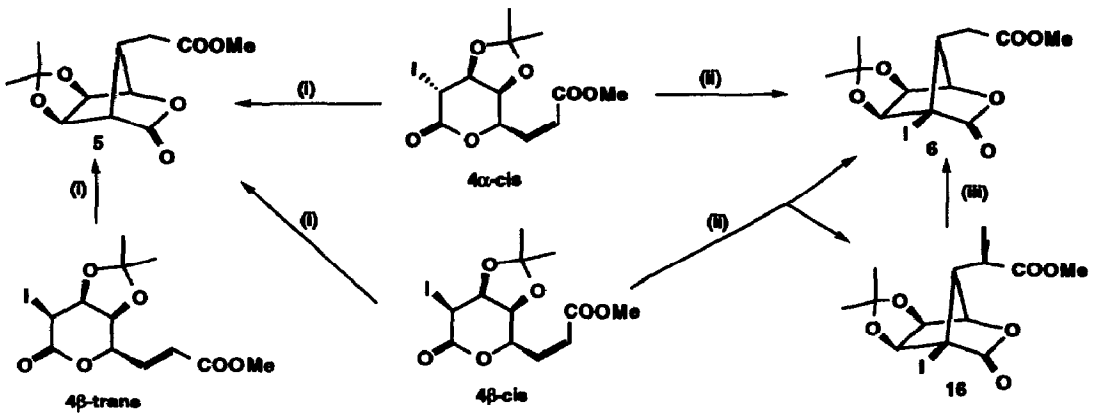
Scheme 2 (i) $Ph_3PCHCOOMe$, toluene (ii) CF_3COOH, H_2O, dioxan (iii) Me_3SiCl, pyridine, THF (iv) H_2, Pd, NaOAc, MeOH

The *cis*-olefin **4β-cis**,[4] m.p. 171-173°C, $[\alpha]_D^{20}$ +20.6 (*c*, 1.06 in $CHCl_3$), was also the major product [46% yield] from the Wittig reaction of **1β** with $Ph_3PCHCOOMe$; the *trans*-isomer **4β-trans**, m.p. 192-194°C, $[\alpha]_D^{20}$ +63.1 (*c*, 1.0 in $CHCl_3$). was isolated in 24% yield. Treatment of **4β-cis**, with acid gave the dilactone **8β**, oil, $[\alpha]_D^{20}$ -9.9 (*c*, 1.3 in CH_3CN) in 80% yield, which was converted into the corresponding silyl ether **12β**, m.p. 146-148°C, $[\alpha]_D^{20}$ -66.7 (*c*, 1.0 in $CHCl_3$) in 76% yield. All four diastereomeric olefins **4** with hydrogen in methanol in the presence of palladium black gave the same saturated ester **13**, m.p. 73-74°C, $[\alpha]_D^{20}$ +107.4 (*c*, 1.02 in $CHCl_3$).

Cyclisations of iodo-δ-lactones 4. Fraser-Reid and co-workers[5] have developed the use of intramolecular radical cyclisations to form very highly substituted cyclopentanes. For example, the iodoester **14** with tributyltin hydride undergoes a reductive cyclisation to give the bicyclic acetal **15** in 97% yield;[6] this procedure efficiently produces a cyclopentane ring in which the two carbon substituents are *cis*-related.

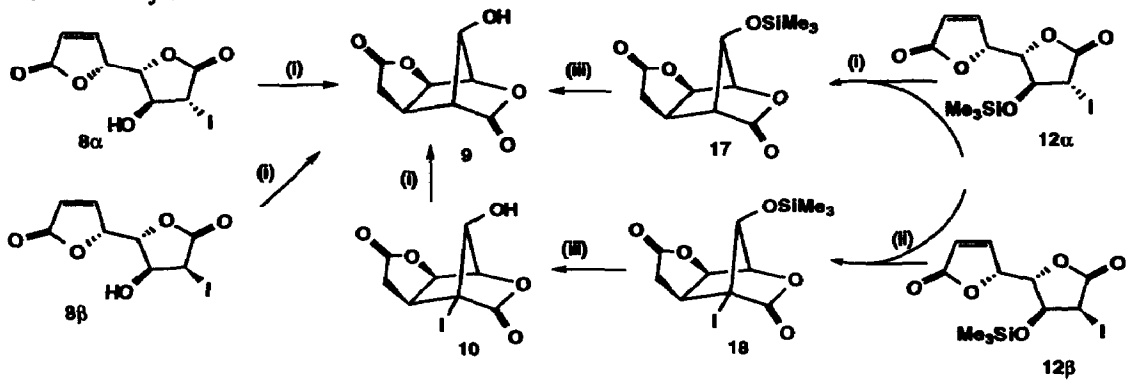


The cyclisations of the iodo-δ-lactones **4** induced by tributyltin hydride provide a complementary procedure to that of methyl pyranosides such as **14**; thus, **4α-cis**, **4β-cis**, **and 4β-trans** on treatment with tributyltin hydride in toluene at 80°C in the presence of AIBN cyclise gave the bicyclic lactone **5**, m.p. 60-61°C, $[\alpha]_D^{20}$ -45.7 (*c*, 1.02 in $CHCl_3$) in yields of 79, 77 and 83% respectively [Scheme 3].



Scheme 3 (i) Bu_3SnH, AIBN, toluene, 80°C (ii) *tert*-BuOK, THF (iii) LiI.H_2O, THF

Intramolecular anionic Michael cyclisations are widely used in synthesis, although such closures to form highly functionalised bicyclic systems are rare.[7] Both **4α-cis** and **4β-cis** react with potassium *tert*-butoxide in tetrahydrofuran to give the bridgehead bicyclic iodolactone **6**,[8] m.p. 113-114°C, $[\alpha]_D^{20}$ +43.1 (*c*, 1.01 in $CHCl_3$) in yields of approximately 25%. The diiodo compound **16**,[9] m.p. 180-181°C, $[\alpha]_D^{20}$ +83.9 (*c*, 0.81 in $CHCl_3$) could also be isolated in yields of around 10%. The formation of a small amount of **16** indicates that the initially formed bicyclic anion may abstract a positive iodine from the starting material in preference to a proton. Unlike the marked difference in the yields of aldol products from the iodoaldehydes **1α** and **1β**, the behaviour of the two Z-enoates **4α-cis** and **4β-cis** in the intramolecular anionic Michael addition is almost identical; in contrast, **4β-trans** did not give any of the bicyclic lactone products. Work is in progress to optimise the yields of these ionic cyclisations. The structure of **16** was determined by X-ray crystallographic analysis; **16** could be converted to the monoiodo lactone **6** by treatment with lithium iodide hydrate in tetrahydrofuran[10] in 80% yield while further reduction of **6** with tributyltin hydride gave **5**. Thus the structures of all the bicyclic lactones with the carbon chains *cis* to each other are firmly established.



Scheme 4 (i) Bu_3SnH, AIBN, toluene or benzene, 80°C (ii) *tert*-BuOK, THF (iii) CF_3COOH, H_2O, dioxan

Cyclisations of iodo-γ-lactones 8 and 12. Both **8α** and **8β** reacted with tributyltin hydride, added over six hours, in benzene to give the bicyclic lactone **9**,[11] m.p. 189-191°C, $[\alpha]_D^{20}$ -60.6 (*c*, 0.99 in CH_3CN), in yields of 50 and 49% respectively [Scheme 4]. Reduction of the trimethylsilyl ethers **12α** and **12β** with tributyltin hydride, added over six hours in toluene, gave the bicyclic lactone **17**,[12] m.p. 168-170°C, $[\alpha]_D^{20}$ -35.0 (*c*, 0.65 in CH_3CN), in yields of 66 and 64% respectively. Treatment of **17** with trifluoroacetic acid in aqueous dioxan resulted in loss of the trimethylsilyl ether protecting group to give **9** in

quantitative yield. In all cases, competition with capture of the uncyclised radical by the tin hydride was more problematic than in the cyclisation of the radicals derived from the δ-lactones. In contrast to the *cis* relationship of the carbon side chains on the cyclopentane rings formed by cyclisation reactions of the δ-lactones, the adjacent carbon chains on the cyclopentane ring formed in **9** are *trans* to each other.

All attempts to induce **8α** and **8β** to undergo intramolecular base-catalysed Michael reactions failed. However, reaction of potassium *tert*-butoxide with **12α** and **12β**, in which the free hydroxyl group was protected as the trimethylsilyl ether, afforded the bridgehead iodolactone **18**,[13] m.p. decomposes at 202°C, $[\alpha]_D^{20}$ +46.8 (*c*, 1.02 in $CHCl_3$), in yields of 35%, regardless of which epimer was used as the starting material. Removal of the trimethylsilyl ether in **18** by trifluoroacetic acid in aqueous dioxan gave **10**,[14] m.p. decomposes at 225°C, $[\alpha]_D^{20}$ +10.6 (*c*, 0.71 in CH_3CN) in 81% yield; the structure of **10** was established by X-ray crystallographic analysis. Reaction of **10** with tributyltin hydride in benzene gave **9** in 67% yield. In all the γ-lactone cyclisations, the new chiral centre formed in the reactions is controlled by the chirality of the carbon bearing the oxygen in the unsaturated lactone ring.

In summary, this work describes the opportunities for stereochemical control in the synthesis of highly functionalised cyclopentanes in which the *cis*- or *trans* relationship of adjacent carbon substituents can be guaranteed by use of a γ- or δ- lactone starting material. Radical cyclisations proceed in good yield in all cases but at present only moderate yields have been obtained in intramolecular anionic Michael cyclisations. The analogous iodoaldehydes for a number of sugars are available as both γ- and δ-lactones[15] and the generality of this strategy for the use of carbohydrates in the synthesis of carbocycles[16] is currently under investigation.[17]

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[3]Elliott, R. P., Fleet, G. W. J., Pearce, L., Smith, C., Watkin, D. J., *Tetrahedron Lett.*, **1991**, **32**, 6227.

[4]All new compounds in this paper have spectroscopic data consistent with the structures proposed; correct microanalyses have been obtained for **4α-cis**, **4α-trans**, **4β-cis**, **4β-trans**, **5**, **6**, **8β**, **9**, **12α**, **12β**, **13**, **17** and **18**.

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[8]Selected data for iodolactone **6**: ν_{max} (KBr disc): 1799 (lactone C=O), 1737 cm^{-1} (ester C=O); δ_C ($CDCl_3$): 171.4 (s, C=O), 170.8 (s, C=O), 115.0 (s, $\underline{C}Me_2$), 81.0, 80.6, 78.5 (3 x d, C-3, C-4, C-5), 52.2 (q, OMe), 47.6 (d, C-6), 41.3 (s, C-2), 29.9 (t, C-7), 25.3, 24.5 (2 x q, $C\underline{Me}_2$).

[9]Selected data for diiodo lactone **16**: ν_{max} (KBr disc): 1789 (lactone C=O), 1737 cm^{-1} (ester C=O); δ_C ($CDCl_3$): 170.1 (s, C=O), 169.4 (s, C=O), 115.2 (s, $\underline{C}Me_2$), 85.3, 83.5, 77.6 (3 x d, C-3, C-4, C-5), 53.9 (d, C-6), 53.4 (q, OMe), 37.6 (s, C-2), 25.5, 24.7 (2 x q, $C\underline{Me}_2$), 14.2 (d, C-7).

[10]Elliott, R. P., Fleet, G. W. J., Gyoung, Y. S., Ramsden, N. G., Smith, C., *Tetrahedron Lett.*, 1990, **31**, 3785.

[11]Selected data for bicyclic lactone **9**: ν_{max} (KBr disc): 3437 (OH), 1799 (lactone C=O), 1767 cm^{-1} (ester C=O); δ_C (CD_3CN): 177.0 (s, C=O), 175.4 (s, C=O), 82.1, 78.5, 73.9 (3 x d, C-4, C-5, C-6), 50.2 (d, C-3), 34.0 (t, C-7), 31.2 (d, C-2).

[12]Selected data for trimethylsilyl lactone **17**: ν_{max} (KBr disc): 1795 (C=O), 1781 cm^{-1} (C=O); δ_C ($CDCl_3$): 175.8 (s, C=O), 174.2 (s, C=O), 81.8, 78.2, 74.4 (3 x d, C-4, C-5, C-6), 51.2 (d, C-3), 33.5 (d, C-2), 31.8 (t, C-7), -0.4 (q, $SiMe_3$).

[13]Selected data for trimethylsilyl iodolactone **18**: ν_{max} (KBr disc): 1797 (C=O), 1783 cm^{-1} (C=O); δ_C (CD_3CN): 175.0 (s, C=O), 172.4 (s, C=O), 80.2, 78.7, 77.4 (3 x d, C-4, C-5, C-6), 45.8 (s, C-2), 41.5 (d, C-3), 33.4 (t, C-7), -1.1 (q, $SiMe_3$).

[14]Selected data for iodolactone **10**: ν_{max} (KBr disc): 1794 (C=O), 1751 cm^{-1} (C=O); δ_C (CD_3CN): 175.7 (s, C=O), 173.1 (s, C=O), 81.1, 78.5, 78.4 (3 x d, C-4, C-5, C-10), 46.2 (s, C-1), 43.0 (d, C-9), 34.5 (t, C-8).

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