Enantioselective Halolactonisation of Bis-γ,δ-unsaturated Carboxylic Acid Derivatives: Use of a Sultam and Oxazolidine-2-ones as Chiral Auxiliary

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Iodolactonisation of heptadienoic acid derivatives **2** and **3** having oxazolidin-2-ones or a sultam as chiral auxiliary gave the chiral iodolactones **4** and **5** in moderate to excellent enantioselectivity.

Discrimination of diastereotopic alkene groups with concomitant face differentiation in halolactonisation of symmetrical diene-carboxylic acids has recently proved to be a useful strategy for efficient construction of chiral synthons with diastereoisomeric purity.[1] Enantioselective halolactonisation of bis-γ,δ-unsaturated amides **1**, derived from chiral amines, was also pursued in order to obtain asymmetric synthons with high optical purity.[2,3] However, the enantioselectivities are generally low, owing, in part, to the existence of C(O)–N rotamers arising from restricted rotation about the amide bond, when unsymmetrical chiral amines were used as chiral auxiliary.[2] Fuji used C_2 symmetric pyrrolidines as chiral auxiliary to avoid the need for C(O)–N rotamer control and succeeded in obtaining high enantioselectivity.[2] If an oxazolidin-2-one or a sultam[4] were used as chiral auxiliary, restricted rotation about the amide bond would be minimized by the effects of the electron-deficient carbonyl or sulfone functions, and control of the population of the C(O)–N rotamers would be feasible. We now describe enantioselective iodolactonisation of the imides **2** and **3**, derived from easily available oxazolidine-2-ones and a sultam,[4] which provided a high degree of diastereo- and enantio-selectivity (Scheme 1).

First we explored the enantioselective iodolactonisation of heptadienoic acid derivatives **2**. The substituent on the oxazolidin-2-one ring was varied in order to examine the effects of its bulk on enantioselectivity. Iodine and *N*-iodosuccinimide (NIS) were used as iodolactonisation promoter. Iodine was totally ineffective for the iodolactonisation.

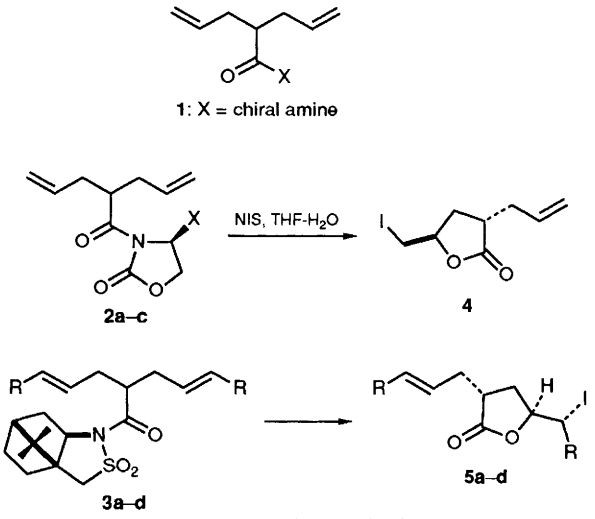
Table 1 Iodolactonisation of **2** with *N*-iodosuccinimide in THF–H_2O

		4	
2	X	Yield (%)	E.e. (%)
2a	$PhCH_2$	30	20
2b	Pr^i	35	54
2c	Bu^t	16	56

Table 2 Enantioselective iodolactonisation of **3a–d**

Entry	3	Reagent (temp./°C)	Product[d]	Yield (%)	E.e. (%)[e]	$[\alpha]_D$ (*c*)[f]
1	**3a**(R = H)	I(collidine)$_2$ClO$_4$ (−40)[a]	**5a**	87	>98	−22.9 (1.4)
2	**3a**	I(collidine)$_2$ClO$_4$ (25)[b]	**5a**	38	58	
3	**3a**	KI–I$_2$ (0→25)[c]	**5a**	39	>98	
4	**3b** (R = CH_2Ph)	I(collidine)$_2$ClO$_4$ (−40)[a]	**5b**	54	86	−4.4 (1.8)
5	**3c** (R = Pr^i)	I(collidine)$_2$ClO$_4$ (−40)[a]	**5c**[g]	77	56	−21.0 (0.8)
6	**3d** (R = Me)	I(collidine)$_2$ClO$_4$ (−40)[a]	**5d**[h]	70	57	−29.2 (1.6)

[a] Carried out in CH_2Cl_2–MeOH containing 1.2 equiv. of H_2O for 48 h. [b] Carried out in MeOH–H_2O for 0.5 h. [c] Carried out in CH_2Cl_2 in the presence of aq. $NaHCO_3$ for 48 h. [d] 3,5-*cis*-isomers were not detected by NMR, unless stated otherwise. [e] Determined by ^1H NMR (300 MHz) with Eu(hfc)$_3$. [f] Measured in $CHCl_3$ at 20 °C. [g] 3,5-*trans*/*cis* = 10. [h] 3,5-*trans*/*cis* = 13.



Scheme 1 Iodolactonisations

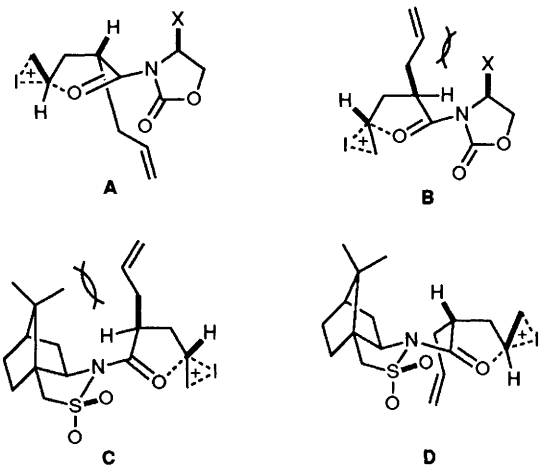


Fig. 1 Transition state structures

However, upon treatment of **2a** with NIS (1.5 equiv.) in tetrahydrofuran (THF)–H_2O (1:1) at 0 to 25 °C for 36 h, the *trans*-iodolactone **4** was obtained in 30% yield. The enantiomeric excess (e.e.) of **4** was determined to be 20% by ^1H NMR (300 MHz) analysis with tris[(heptafluoropropylhydroxymethylene)-(+)-comphorato]europium(III) [Eu(hfc)$_3$]. When isopropyloxazolidin-2-one **2b** and *tert*-butyloxazolidin-2-one **2c** were used as substates, the e.e. of **4** increased to 54 and 56%, respectively, but in the case of **2c**, the chemical yield was quite low (Table 1). The absolute configuration of **4**† was assigned as 3*S*,5*R* by comparison of the sign of its specific rotation with that reported in the literature.[2,3] The cyclisation probably proceeds *via* transition state **A** which is favoured over transition state **B** because of steric repulsion between the allyl substituent α to carbonyl and the alkyl substituent on the oxazolidin-2-one (Fig. 1). This route for cyclisation is consistent with the assigned stereochemistry of **4**.

In an effort to achieve higher enantioselectivity, we next employed a sultam,[4] derived from D-camphorsulfonic acid, as chiral auxiliary (Table 2). Treatment of **3a** with iodonium di-*sym*-collidine perchlorate[5] (2.3 equiv.) in CH_2Cl_2–MeOH containing 1.2 equiv. of H_2O at −40 °C for 48 h gave **5a**, $[\alpha]_D^{20}$ −22.9 (*c* 1.4, $CHCl_3$), enantiomeric to **4**, in excellent enantioselectivity (>98% e.e.) and good yield (87%) (entry 1, Table 2). In this reaction the sultam was recovered in 90% yield without loss of optical purity. Under similar conditions, iodolactonisation of heptadienoic acid derivatives **3b–d**‡ having alkyl substituents at the δ- and δ′-positions afforded the corresponding lactones **5b–d** diastereo- and enantio-selectively. The optical purity of the product decreased slightly (86% e.e.) in the case of **3b**, and significantly decreased to around 56% e.e. for **3c** and **3d** (entries 4–6, Table 2).

The reaction temperature strongly affected the enantioselectivity and yield. Upon treatment of **3a** with iodonium di-*sym*-collidine perchlorate at 25 °C, **5a** was obtained in low yield and modest enantioselectivity (entry 2, Table 2). Reaction of **3a** with KI–I_2 in the present of aqueous $NaHCO_3$ in CH_2Cl_2 also gave **5a** with high enantioselectivity but in low chemical yield (entry 3, Table 2). Of two transition states **C** and **D** leading to 3,5-*trans*-lactones, we assume that transition state **D** providing the 3*R*,5*S* enantiomer is favoured over **C**, because of steric repulsion between the allyl substituent and the camphor moiety (Fig. 1). The observed enantioselection in halolactonisation of **3** can be also rationalized by this cyclisation process.

In conclusion our studies have shown that a sultam is a good chiral auxiliary to differentiate diastereotopic alkene groups of symmetrical diene-carboxylic acids in halolactonisation with a high degree of diastereo- and enantio-selectivity. Chiral synthons obtained in these studies should be useful for the synthesis of biologically important compounds.

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† Specific rotation (in $CHCl_3$) of **4** obtained by this method ranged from +7.6 to +17.2.

‡ The heptadienoic acids corresponding to **3b–d** were prepared stereoselectively from (*E*)-5-alkylpent-4-enoic acids and 1-alkylpent-2-enols *via* an Ireland–Claisen rearrangement[6] using lithium bis(trimethylsilyl)amide and *tert*-butyldimethylchlorosilane as base and silylating agent, respectively.

References

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