STEREOCONTROLLED IODOLACTONIZATION OF ERYTHRO AND THREO TERTIARY AMIDES

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Abstract - A series of α-mono and dialkyl-β-oxygenated (hydroxyl and alkyl ester) tertiary amides were subjected to iodolactonization and it was observed that with only 1 exception, (threo **11b**), all of the compounds cyclized with useful levels of stereoselection (at least 3:1). While the origin of this effect is obscure, these results suggest that in such amide substrates with at least one substituent larger than methyl α to the amide, iodolactonization is a viable strategy for the stereocontrolled preparation of highly substituted γ-butyrolactones.

INTRODUCTION:

Electrophilic cyclization of unsaturated carboxylic acids and derivatives thereof is a useful method for stereocontrolled carbon-oxygen[1] and more recently carbon-nitrogen[2] bond formation with selected diastereomers of the acyclic precursor (equations 1 and 2, respectively). We were attracted to this strategy for the efficient and stereocontrolled preparation of a series of trisubstituted γ-butyrolactones of general structures **6** and **7** to be employed as mechanistic probes for the enzyme phospholipase A_2 [(Figure 1)].[3]

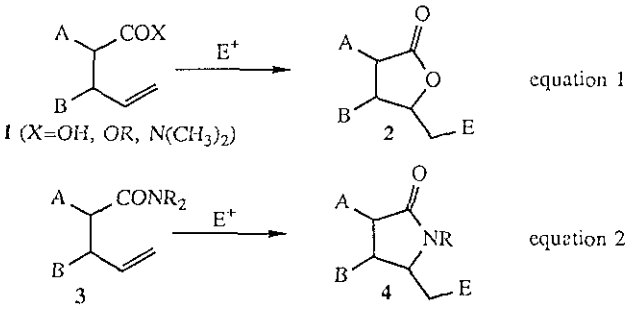
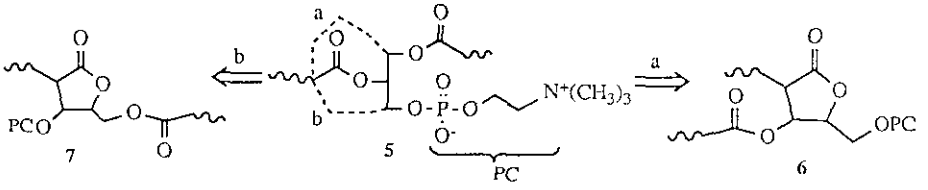


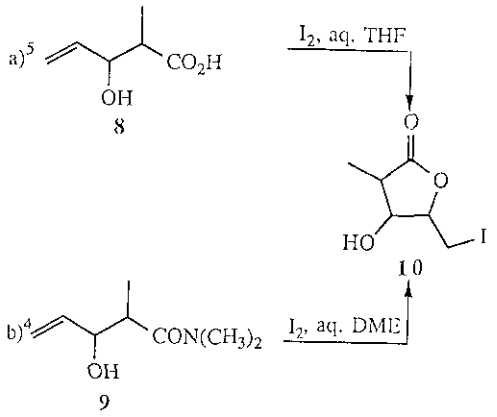
Figure 1:



In particular, we were interested in investigating the halolactonization of α-alkyl-ß-oxy-4-pentenamides because such molecules were previously reported[4] to cyclize with a higher degree of stereocontrol and/or greater yield, compared to the analogous carboxylate system[5] (Figure 2).

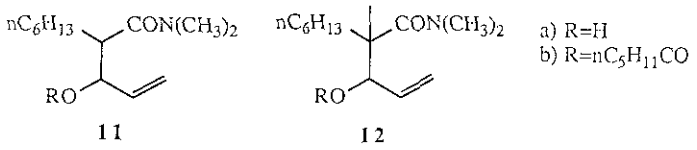
Furthermore, we sought to investigate in greater detail the effect of α and ß substituents on the iodine-mediated amide variant of this reaction in order to test and define the level of stereocontrol possible with substrates **11** and **12** (Figure 3) to expand on the series and results reported by Tamaru and coworkers.[4]

Figure 2:



	cis/trans ratio	yield %
a) *erythro*-8	77:23	74
threo-8	87:13	41
b) *erythro*-9	>99:1	84
threo-9	20:80	88

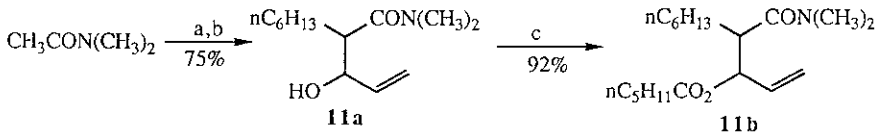
Figure 3:



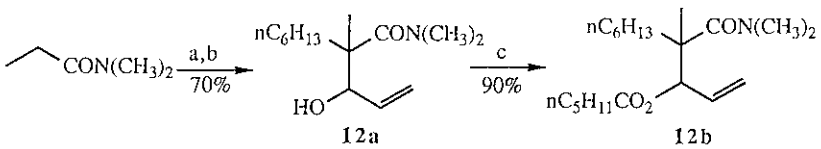
RESULTS AND DISCUSSION:

The erythro and threo pair of diastereomeric amides **11a** were prepared in excellent yield by straightforward adaptation of the method employed by Tamaru et al,[4-6] as outlined in Scheme 1. After careful separation of these isomers by flash chromatography, the hydroxyl group was converted to the hexanoyl ester (**11b**) by standard procedures.[7] This particular ester was chosen because this side chain was needed for the biological studies to be conducted with these compounds. The synthesis of **12a** and **12b** was achieved in a similar manner beginning with N,N'-dimethylpropionamide (Scheme 2) and as before, the diastereomeric acrolein adducts were purified by flash chromatography, prior to hexanoylation.

Scheme 1:



Scheme 2:



Reagents: a) i) LDA/THF,-20°C, 1 h; ii) $nC_6H_{13}Br$,-78°C to room temperature, 2 h; b) i) LDA/THF, -20°C, 1 h; ii) acrolein, -78°C to room temperature, 2 h; c) $(nC_5H_{11}CO)_2O$, DMAP, TEA, CH_2Cl_2, room temperature, 1 h.

Iodolactonization of pure diastereomers of **11** and **12** was carried out at room temperature in THF containing 20 equivalents of H_2O and 1.5 equivalents of I_2 in a flask protected from light (Scheme 3). After stirring for 16-20 hours, the reaction was generally complete and the product(s) was (were) purified by flash chromatography. The results are given in Table 1. Product ratios were determined by integration of the resonance signals for the hydrogens at C3 and C4 when the diastereoisomers were inseparable or by chromatographic separation when possible. In general, the total yield of iodolactone products was excellent and with only one exception (threo **11b**), each isomer cyclized with a useful degree (at least 4:1) of stereoselection. It is significant that in the majority of cases, **both isomers** of a given molecule cyclized with a higher level of stereocontrol than had been observed in other systematic studies with related compounds.[4,5]. The general tendency[4] for the newly created stereocenter at C4 to be cis to the oxygen substituent at C3 was followed in every instance except for **11a**. The basis for this reversal is unknown at the present time. The stereochemistry of the products was determined primarily by a combination of 300 MHz NOESY data and the vicinal coupling constants of the butryolactone ring protons. It was observed that in cases where vicinal hydrogens were cis, the J value for the interaction was at least 3 Hz; while in a trans relationship, J values ranged from ca. 1 to 2 Hz. Strong NOESY interactions were evident between cis hydrogen atoms and in the case of the geminally substituted lactones derived from **12**, both H-3 and H-4 clearly showed cross peaks with the C-2 methyl group when that substituent was cis, as in iodolactones **15** (R_1=CH_3, R_3=OH or $nC_5H_{11}CO_2$; R_4=H). In addition, molecules having a free hydroxyl group were converted[7] to their corresponding hexanoyl esters and compared to previously characterized authentic samples prepared independently by iodolactonization.

Scheme 3:

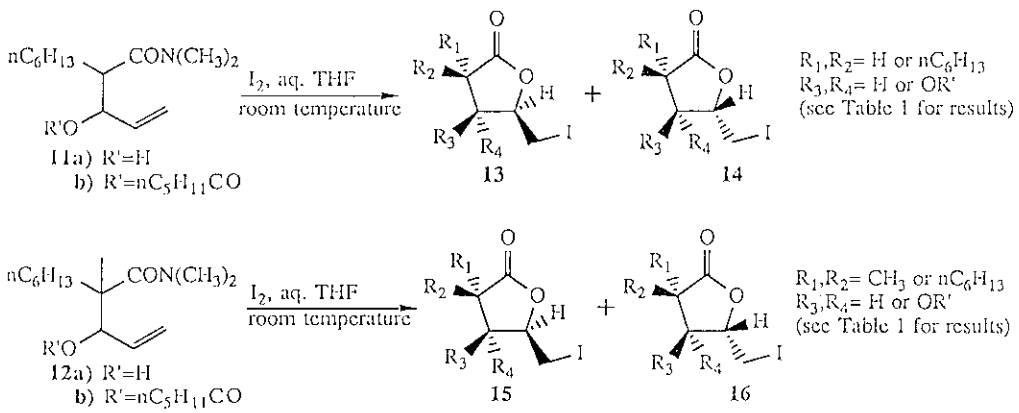


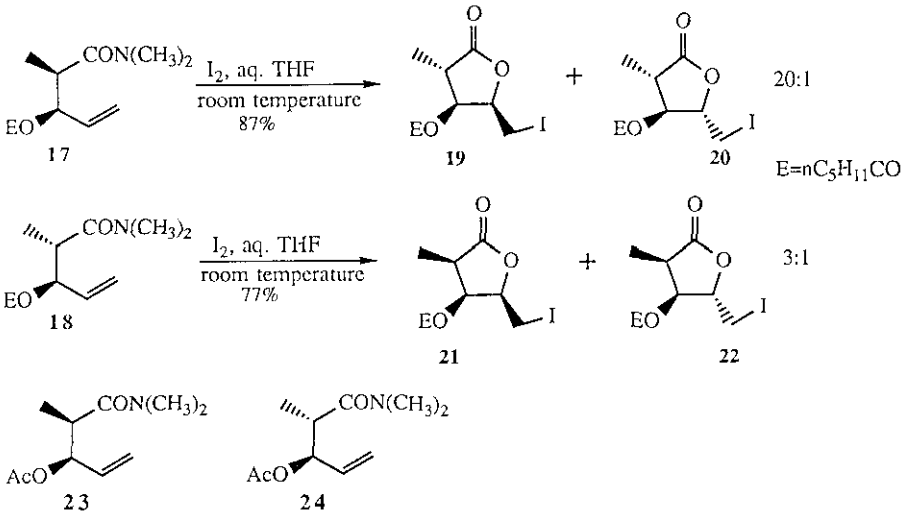
Table 1: Iodolactonization Results (see Scheme 3)

	Olefin	Product(s)[d]		Ratio[a]	Yield %
		major (**13** or **15**)	minor (**14** or **16**)		
a)	erythro **11**a	R_1=alkyl; R_2=H R_3=OH; R_4=H	R_1=alkyl; R_2=H R_3=OH; R_4=H	7:1 (ii)	60
b)	threo **11**a	R_1=alkyl; R_2=H R_3=H; R_4=OH[b]	R_1=alkyl; R_2=H R_3=OH; R_4=H[b]	6:1 (ii)	74
c)	erythro **11**b	R_1=alkyl; R_2=H R_3=ester; R_4=H	none isolated	>95:5 (i,ii)	86
d)	threo **11**b	R_1=alkyl; R_2=H R_3=H; R_4=ester	R_1=H; R_2=alkyl R_3=H; R_4=ester	2:1 (i)	89
e)	erythro **12**a	R_1=CH_3; R_2=alkyl R_3=OH; R_4=H	none isolated	>95:5 (ii)	98[c]
f)	threo **12**a	R_1=CH_3; R_2=alkyl R_3=OH; R_4=H	R_1=CH_3; R_2=alkyl R_3=OH; R_4=H	10:1 (i)	95
g)	erythro **12**b	R_1=alkyl; R_2=CH_3 R_3=ester; R_4=H	none isolated	>95:5 (i)	81
h)	threo **12**b	R_1=CH_3; R_2=alkyl R_3=ester; R_4=H	R_1=CH_3; R_2=alkyl R_3=ester; R_4=H	4:1 (i)	86

a) as determined by nmr (i) and or isolated yield (ii)
b) major product=**14**, minor product=**13**
c) corrected for recovered olefin (44%) after 16 h
d) alkyl=nC_6H_{13}; ester=$nC_5H_{11}COO$

A comparison of these results with those obtained earlier[4] with α-CH_3 and ß-OH or OAc substituted olefins reveals that of the two acyclic diastereomers, the erythro isomer cyclizes with greater selectivity. However in the present study, the threo olefins **11a** and **12a** display greater stereocontrol than the methylated analogues in the earlier work. This observation prompted us to test the effect of the hydroxyl substituent on the degree of stereoselection using hexanoylated derivatives **17** and **18** of erythro and threo α-methyl-ß-hydroxy-4-pentenamide, compared to the acetylated species employed previously[4] (Scheme 4). In the present case, the erythro amide afforded at least a 20:1 ratio (by nmr) of products in 87% yield where the ester and iodomethyl moieties are cis and anti to the methyl substituent. This compares well with both the stereochemistry and ratio of products produced by acetate **23**. The threo diastereomer **18** afforded a 77% yield of a 3:1 ratio (by nmr) of iodolactones epimeric at C4, with the major isomer **21** having all three nonhydrogen substituents cis. In contrast, the iodolactonization of acetate **24** was reported to be nearly stereorandom (55:45) with the major component also having all cis stereochemistry.

Scheme 4:



The results obtained with **12a** and **12b** extend the structure-stereochemistry relationship reported by Tamaru et al.[4] to include α-geminally substituted substrates. The data suggests that moderate (4:1) to high levels (at least 10:1) of stereocontrol are possible in both esterified and unprotected hydroxyl systems. In each instance studied except threo **11a** the new stereocenter created at C4 has the iodomethyl group cis to the oxygen substituent, a trend that was noted by others.[4,5]

At this point, the basis for the increased stereoselectivity of the threo derivatives of the hexanoylated amides is unclear. It does not appear to be a function of either the amount of water present or the ethereal solvent employed, because analogous results were obtained when

ether was substituted for THF, or when the amount of water was increased to 40 equivalents or decreased to 5 equivalents in THF. It is possible that there are subtle changes induced by the lipophilic substituents at C2 and/or C3 that sufficiently influence the conformational bias (and hence lower the E_{act}) in favor of one of the rotamers, leading to the observed results. This selectivity is even more pronounced in a similar series of olefins having a C_{18} alkyl group α to the carbonyl. Based on the data in Table 1, it is difficult to pinpoint the sources (cf. **11a**, **11b**, and **18**) for this effect. However, our observations suggest that hexanoylation reduces stereoselectivity in the threo isomers of **11** and **12**, in particular **11b**. This is the only instance where we observed such a significant erosion of the diastereomeric outcome and cannot explain this result at the present time. We do know that all of the product iodolactones are configurationally stable upon resubmission to the reaction conditions, ruling out epimerization of the alkyl group. The demonstration of improved stereocontrol by systems such as **18** compared to **24** as well as the excellent selectivity of geminally disubstituted substrates **12a** examined makes this variant of amide iodolactonization strategy a more general and useful approach for the construction of densely substituted oxygenated heterocycles.

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