Université des Sciences et Technologies de Lille

EA CMF 4478
Laboratoire de Chimie Organique Physique

UMR CNRS 8181

Convenient synthesis of functionalized α-methylenebutano-4-lactams or lactones.

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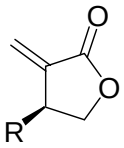
Abstract: α-Alkylidene-γ-lactams and lactones are the active constituents of many natural and synthetic compounds exhibiting pronounced biological properties. They are able to act as Michael acceptors in the reaction with thiol groups of bionucleophiles or can readily form [2 + 2] cycloadducts with DNA bases.

We have developed concise synthetic approaches towards exemplary representatives of α-methylene models that hinge upon the preliminary assembly of the lactam and lactone template. Subsequent installation of the methylidene by a metallation/alkylation/elimination sequence completed the elaboration of the racemic title compounds. The presence of a quaternary carbon center bearing the carboxylate function precluded the undesirable isomerization leading to the corresponding endocyclic unsaturated analogues.

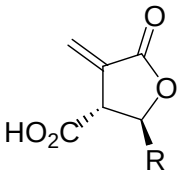
Keywords: *lactams, lactones, cyclization, transesterification, enolate, elimination*

Introduction

α-Alkylidene-γ-lactones and lactams are the active constituents of many natural and synthetic compounds exhibiting pronounced biological properties [1-3]. For example tulipaline A and B (Fig. 1) exhibit antifongic activities [4] whereas a number of functionalized models structurally related to cerulenine, e.g. methylenolactacine, protolichesterinic acid and C75 have been shown to be selective FAS inhibitors [5] (Fig. 1).



R = H Tulipaline A
R = OH Tulipaline B



R = C_5H_{11} Methylenolactocin
R = $C_{13}H_{27}$ Protolichesterinic acid
R = C_8H_{17} C75

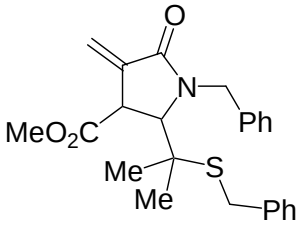


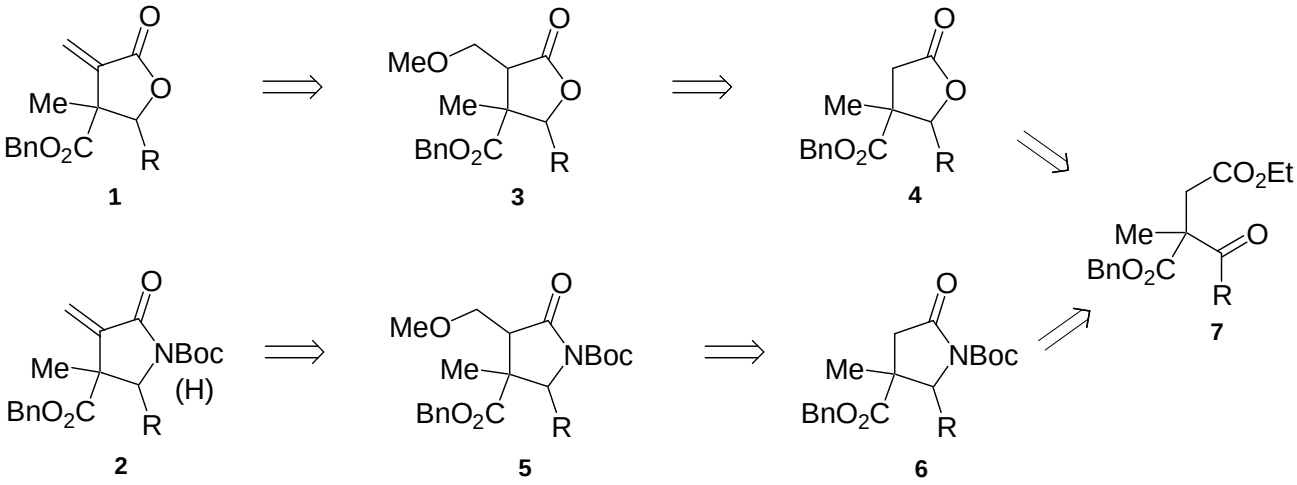
Figure 1.

The α-methylenebutanolactams exhibit cytotoxicity but less cytotoxicity than the corresponding lactones [2g] rendering them promising compounds as potential anticancer [2a] and anti-inflammatory agents [2]. Several structurally sophisticated models (Fig. 1) have been notably designed and developed for the treatment of immunopathy [6].
All these compounds are able to act as Michael acceptors in the reaction with thiol groups of bionucleophiles or can readily form [2 + 2] cycloadducts with DNA bases [7].
Consequently the development of general synthetic methodologies providing molecular complexity and tolerating appended functional groups is an area of current interest.

Results and Discussion

1. Retrosynthetic analysis

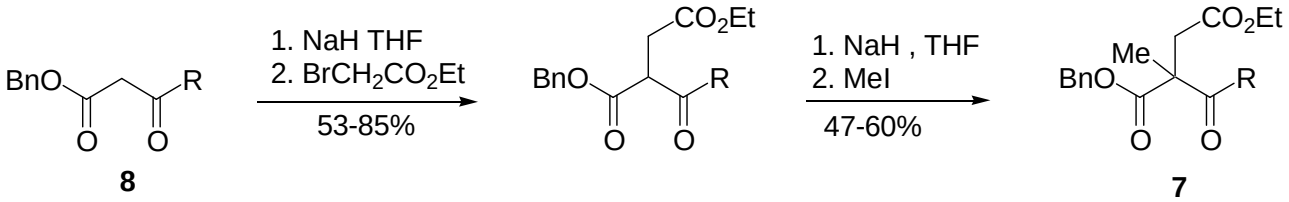
In this context we aimed to develop synthetic approaches to exemplary oxo and aza models **1** and **2** respectively, equipped with a carboxylate function which may serve as a handle or key branching point for alternative functionalization (Retrosynthetic Scheme 1)



Scheme 1. Retrosynthetic analysis.

2. Synthesis of the key precursors 7

The highly functionalized precursors **7** were obtained through a double deprotonation/alkylation sequence applied to a β-ketoesters **8** (Scheme 2, Table 1).

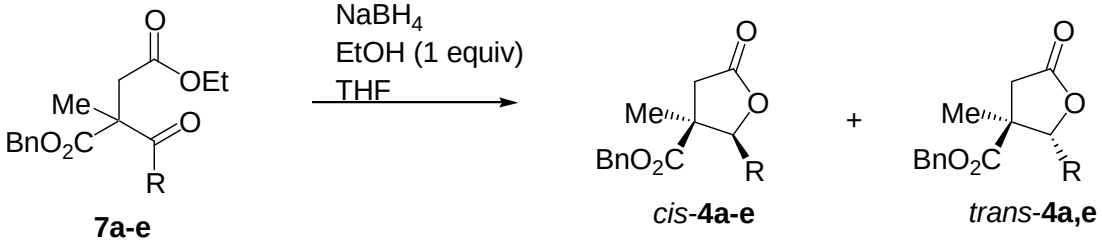


R = Me, Pr, CH_2=$CHCH_2CH_2$, nC_5H_{11}, nC_8H_{17}

Scheme 2

3. Preliminary assembly of the lactone template. Synthesis of the suitably functionalized lactones 4.

Reduction of the ketodiesters **7** was accompanied with a concomitant annulation process thus providing straightforward access to the targeted lactones **4** which were exclusively obtained in the *cis* configuration for reduction carried out in EtOH. Interestingly reactions carried out in THF delivered diastereoisomeric mixture of cyclized compounds as exemplified by the formation of *cis*-**4a,e** and *trans*-**4a,e** (Table 1).



Scheme 3.

Table 1.

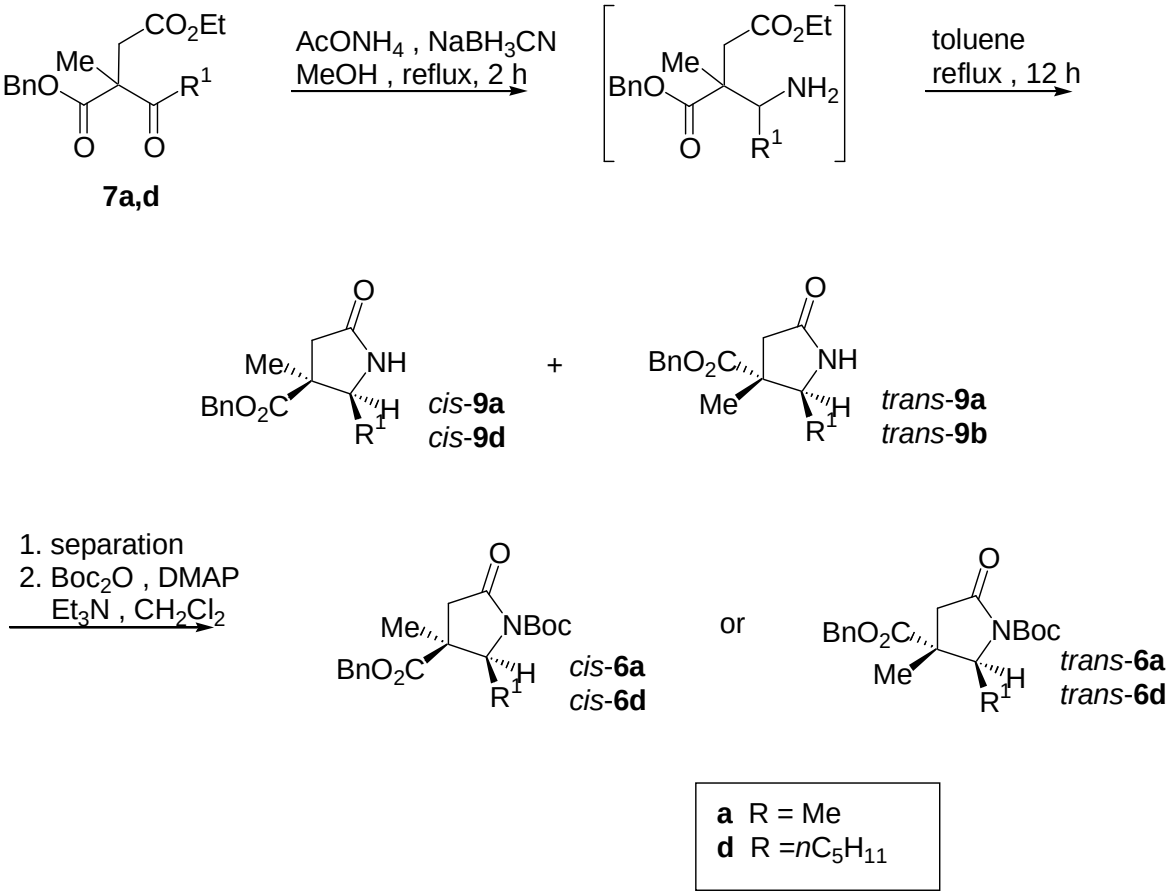
	R	Ketodiester **7**	Lactone **4**	
			(EtOH)	(THF)
		Yield (%)	Yield (%) , *cis*[a]	Yield (%) , *cis:trans*[a]
a	Me	40	55	70 , 90:10
b	Pr	48	44	-
c	CH_2=$CHCH_2CH_2$	44	40	-
d	nC_5H_{11}	41	60	-
e	nC_8H_{17}	28	50	57 , 80:20

[a] *Cis: (2S*,3S*), trans: (2S*,3R*).*

4. Preliminary assembly of the lactam template. Synthesis of the suitably functionalized lactams **6.**

Reductive amination was followed by spontaneous intramolecular regioselective aminolysis leading to the lactam unit.

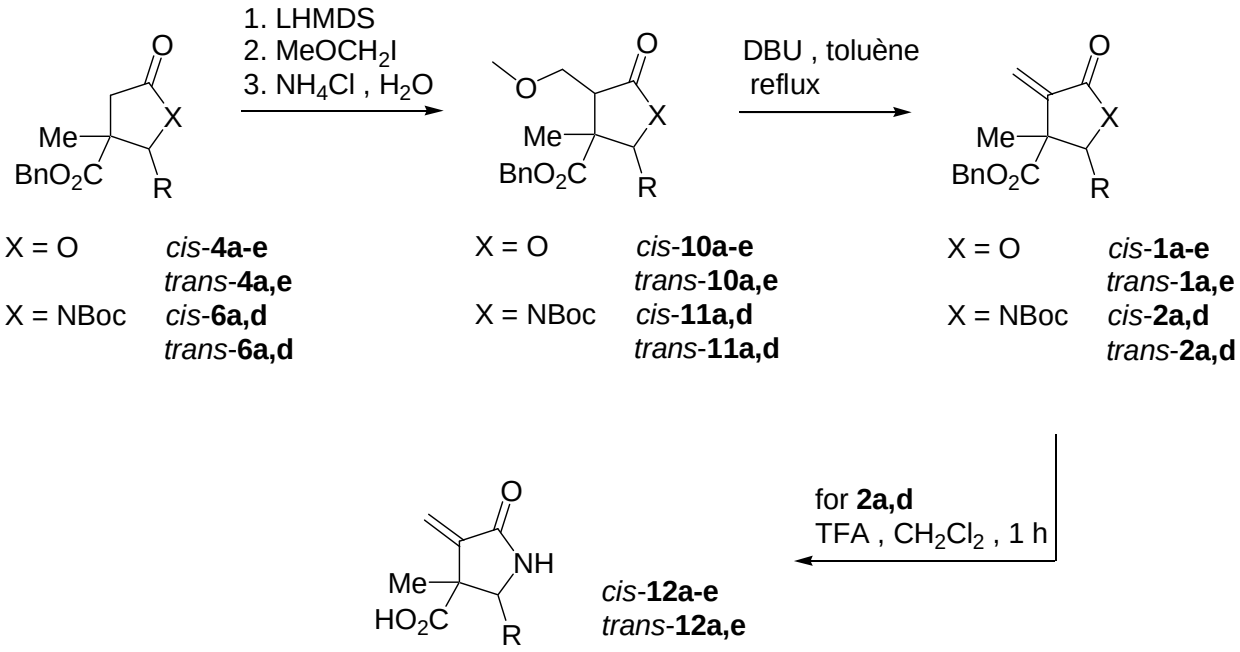
The resulting lactams were obtained as almost equimolecular mixtures of easily separable diastereoisomers *cis* and *trans* **9a,d** which were subsequently *N*-Boc protected to afford the requisite targeted compounds *cis* and *trans* **6a,d** (Scheme 4).



Scheme 4.

5. Ultimate installation of the exocyclic methylene unit.

For the creation of the methylidene unit, a metallation/electrophilic attack/elimination sequence precluding the use of paraformaldehyde was preferred (Scheme 5, Table 2).



Scheme 5.

Table 2.

			Yield (%)						
	R		X	**10a-e**	**1a-e**	X	**2a,d**	X	**12a,d**
a	Me	*cis*[a]	O	75	78	NBoc	74	NH	95
		trans[a]		84	70	NBoc	57	NH	97
b	Pr	*cis*[a]	O	68	80	-	-		-
c	CH_2=$CHCH_2CH_2$	*cis*[a]	O	50	66	-	-		-
d	*n*C_5H_{11}	*cis*[a]	O	80	79	- NBoc	70	NH	93
		trans[a]		-	-	NBoc	65	NH	98
e	*n*C_8H_{17}	*cis*[a]	O	90	73		-		-
		trans[a]		55	57		-		-

[a] *Cis: (2S*,3S*), trans: (2S*,3R*).*

Conclusion

In conclusion we have devised a concise and efficient method to synthesize functionalized *α*-methylene-*γ*-butyrolactams and lactones. The notable advantages of this method are operational simplicity, mild reaction conditions and ease of isolation of racemic *cis* and *trans* products. This simple protocol developed in this study paves the way for further biological studies and we believe that this work provides a strong incentive for the elaboration of structurally modified models.

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