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C. R. Chimie 8 (2005) 841–844
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Preliminary communication / Communication

Towards a novel synthesis of eleuthesides

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Received 2 November 2004; accepted after revision 14 December 2004

Available online 13 March 2005

Abstract

Preliminary results concerning the functionalization of suitably 4,4-disubstituted butyrolactones are presented as part of a study for the total synthesis of eleuthesides. ***To cite this article: S. Samaritani et al., C. R. Chimie 8 (2005)***.

Résumé

Nous présentons ici les résultats préliminaires concernant la fonctionnalisation de butyrolactones 4,4-disubstituées. Ce travail s'inscrit dans un projet de synthèse totale des éleuthésides. ***Pour citer cet article : S. Samaritani et al., C. R. Chimie 8 (2005)***.

Keywords: Eleuthesides; Eleutherobin; Sarcodyctyins; Weinreb amides; Enolate additions

Mots clés : Éleuthésides ; Éleuthérobine ; Sarcodictyines ; Amide de Weinreb ; Additions d'énolate

1. Introduction

Eleutherobin [1] and sarcodyctyins [2,3] (**1** and **2**, Fig. 1) are natural diterpenic compounds extracted from corals and sponges. Eleutherobin (**1**) exhibits antitumor properties and its mechanism of action was found similar to that of paclitaxel (Taxol®) [4].

Only a few total syntheses of eleutherobin [5,6], sarcodyctyins [7] and analogs [8–10] have been described up to now. We have recently got involved into a project of convergent synthesis of the title compounds: our retrosynthetic approach, which involves the functionalization of suitably substituted 5-methylfuran-2(5*H*)-ones, followed by an intramolecular Diels–Alder cyclization as the key step, is outlined in Scheme 1.

We have recently shown [11] that acylation of 5-methyl-4-(pyrrolydin-1′-yl)-furan-2(5*H*)-one, followed by the reduction of the intermediate, afforded the corresponding *syn* products in good diastereoselectivity and yield, thus making the introduction of the necessary diene moiety possible [12]. We hereby report on the main results of a preliminary investigation aimed at introducing the dienophile residue by addition reactions of suitable enolates to the required lactone. This study was carried out on the racemic model systems **3a** and **3b** (cf. Schemes 2 and 3).

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doi:10.1016/j.crci.2005.02.016

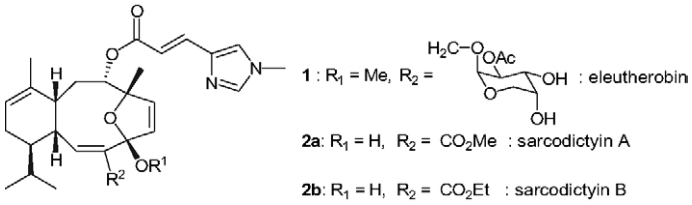
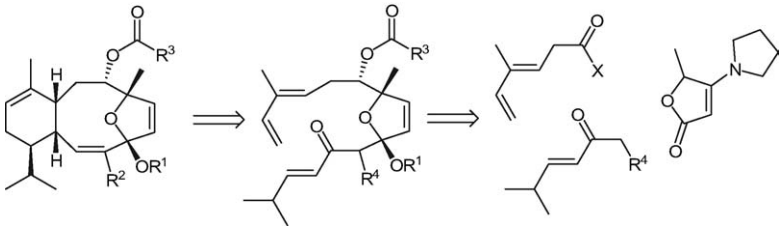
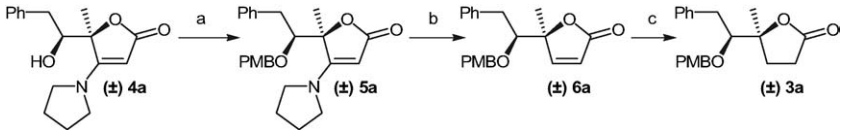


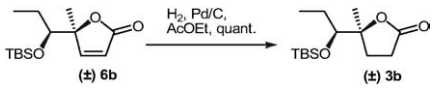
Fig. 1.



Scheme 1.



Scheme 2. Reagents and conditions: (**a**) KOH, PMBBr, CH_2Cl_2, TBAI, 90%; (**b**) (*i*) $NaBH_3CN$, AcOH; (*ii*) *m*CPBA, CH_2Cl_2, aq. $NaHCO_3$, 98% (two steps); (**c**) $NaBH_4$, $CoCl_2{\cdot}6\,H_2O$, EtOH quant.



Scheme 3.

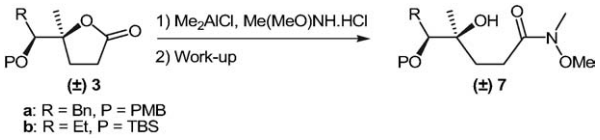
2. Results and discussion

The starting materials **3a** and **3b** used in the present study were prepared in four steps from *syn* disubsituted furanones **4** [11]. Protection of the hydroxyl group of **4a** as a *p*-methoxybenzyl ether gave **5a**, which was transformed into furanone **6a** upon a known reduction-elimination procedure. Reduction of **6a** afforded **3a** in quantitative yield.

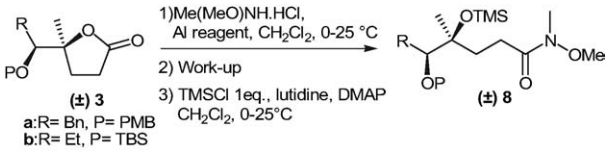
Similarly, **3b** was obtained by hydrogenation of known **6b** [11] (Scheme 3).

Attempts to react **3a** and **3b** with lithium enolate of (*E*)-5-methylhex-3-en-2-one failed, probably because of the acidity of protons at the α position to the lactone carbonyl group [13]. Consequently we considered activating **3a** and **3b** towards nucleophilic addition through the conversion of the lactones into the corresponding Weinreb amides **7** (Scheme 4).

Despite the followed procedure (Me(MeO)NH·HCl in the presence of Me_2AlCl) was described as particularly useful for the preparation of Weinreb amides of 4,4-disubstituted lactones [14], all attempts to purify **7** afforded the desired products in low yield together with the starting materials **3**. The latter appeared to be formed by recyclization of **7** since TLC analysis of the reaction mixtures prior to work-up always showed the complete disappearance of the precursors **3**. Further efforts were thus made in order to convert **7** into the corresponding trimethylsilyl derivatives **8** (Scheme 5). The main collected data regarding the preparation of compounds **8** are summarized in Table 1.



Scheme 4.



Scheme 5.

Table 1
Preparation and protection of Weinreb amides of lactones **3**

Entry	Lactone	Al reagent	Work-up procedure	**8/3** ratio[a]	**8**% yield[b,c]
1	**3b**	Me_2AlCl	*A*	50/50	36 (**b**)
2[d]	**3b**	Me_2AlCl	*A*	30/70	25 (**b**)
3	**3b**	Me_2AlCl	*B*	70/30	40 (**b**)
4	**3b**	Me_2AlCl	*C*	99/1	64 (**b**)
5[e]	**3a**	Me_3Al	*C*	60/40	50 (**a**)
6[f]	**3a**	Me_3Al	*C*	80/20	58 (**a**)

Work-up procedures *A*: (1) pH 8 hydrolysis (phosphate buffer solution); (2) filtration on celite pad; (3) extraction. *B*: (1) pH 8 hydrolysis (phosphate buffer solution, reversed addition); (2) extraction. *C*: filtration on silica gel pad.

[a] **8/3** molar ratio was evaluated by integration of selected ^1H NMR resonance signals of crude material.

[b] isolated yield, starting from 100 mg of **3**, after purification of crude material by flash chromatography.

[c] MS, ^1H and ^{13}C NMR analyses were in agreement with the structures.

[d] two equivalents of TMSCl were used.

[e] THF was used as solvent.

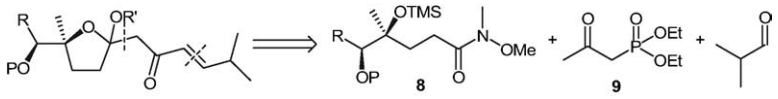
[f] a CH_2Cl_2 solution of Me_3Al was used.

The conversion of **3b** into **8b** was strongly affected by the work-up procedure prior to the treatment with the silylating agent. Basic hydrolysis (work-up procedures *A* and *B*) of the reaction mixtures (Table 1, entries 1–3) afforded **8b** in low isolated yields (25–40%) and, in each case, the formation of slightly variable amounts of starting material **3b** was observed. Further efforts to carry out the hydrolysis under weak acidic conditions afforded similar results. Nevertheless when the crude reaction mixture was treated with silica gel, filtered and engaged into the following protection step (work-up procedure *C*) the cyclization of the intermediate amide **7b** into **3b** was minimized and a satisfactory 64% yield of **8b** was obtained (Table 1, entry 4).

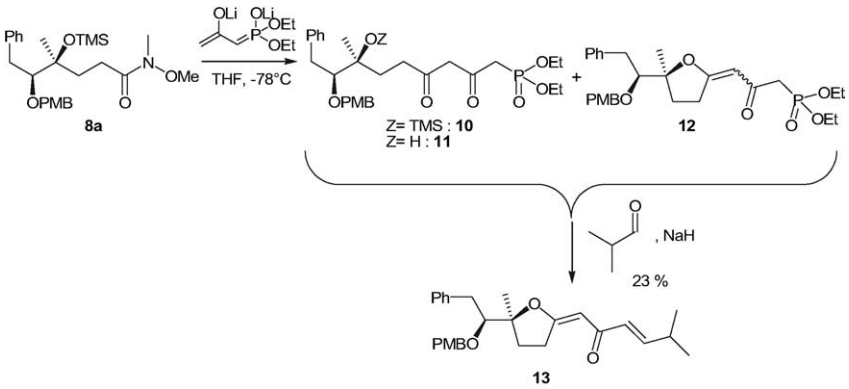
It has to be underlined that the separation of **8b** and **3b** was always possible, thus allowing the recovery of the starting material. For the synthesis of **8a**, Me_2AlCl caused the elimination of the *p*-methoxybenzyl group of **3a** and had to be replaced by Me_3Al. The more sluggish reaction, followed by the same treatment successfully used for the preparation of **8b**, finally afforded **8a** in acceptable yield (Table 1, entry 6).

The protected Weinreb amides were then tested for their reactivity towards various nucleophiles. Reaction between **8** and lithium enolate of (*E*)-5-methylhex-3-en-2-one failed, even when three molar equivalents of the nucleophile were used. Another synthetic sequence, involving an addition reaction of the ketophosphonate **9** followed by a Horner–Emmons condensation with *iso*-butyraldehyde was attempted, according to the retrosynthesis described in Scheme 6.

The reaction between **8a** and the lithium dienolate of diethyl 2-oxopropylphosphonate (Scheme 7) caused the rapid disappearance (TLC) of the starting material. After usual work-up, a mixture of inseparable products **10**–**12** was obtained, whose structures (Scheme 7) were assigned on the basis of mass spectrometry analyses. It seems reasonable to ascribe the formation of **11** to the



Scheme 6.



Scheme 7.

instability of TMS protecting group under the strongly basic conditions necessary for the dienolate formation and the formation of **12** to the cyclization of **11**, followed by water elimination.

Anyway, the treatment of the mixture of **10–12** with *iso*-butyraldehyde, under Horner–Emmons reaction conditions, afforded (1*E*,3*E*)-1-{5-[1-(4-methoxybenzyloxy)-2-phenylethyl]-5-methyldihydrofuran-2-ylidene}-5-methyl-hex-3-en-2-one **13** (Scheme 7) as a unique isolated product in 23% yield over the two steps.

The formation of intermediates **11** and **12**, along with product **13**, clearly enlightened the necessity of replacing TMS in **8** by a more stable and selectively removable protecting group. Studies are in progress to identify new suitable reaction conditions for the preparation of such a compound and to functionalize the enol ether group of **13**.

Acknowledgements

We are grateful to the CNRS for financing SS with a post-doctoral fellowship.

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