Pergamon

Tetrahedron Letters 42 (2001) 3511–3514

TETRAHEDRON LETTERS

A concise synthesis of (±)-methylenolactocin and the formal synthesis of (±)-phaseolinic acid

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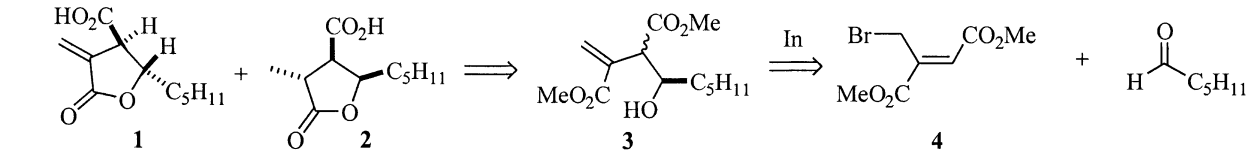
Received 2 February 2001; revised 9 March 2001; accepted 21 March 2001

Abstract—(±)-Methylenolactocin was prepared in five steps involving an indium-mediated allylation reaction as the key step.

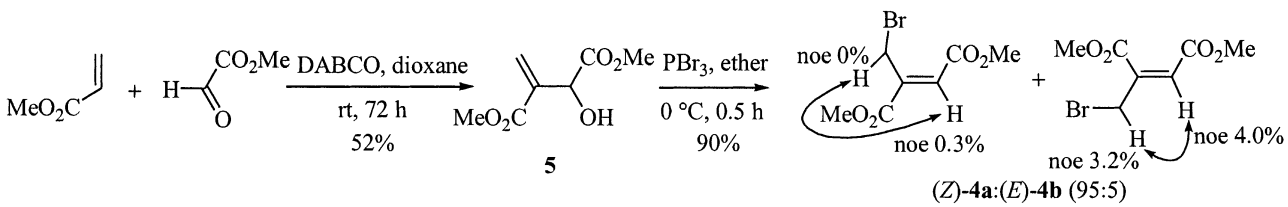
α-Methylene-β-butyrolactone is an integral building block of many bioactive natural products.[1] Among them, methylenolactocin **1** has attracted the most attention because of its interesting anti-tumour activity and its unusual structure with high functionality and stereochemistry.[2] Accordingly, many approaches to the total synthesis of this compound have been reported.[3a–c,4a–e] However, most of the reported syntheses involved long and difficult steps which rendered them impractical. Therefore, a concise approach to the synthesis of **1** is well-sought after. In this paper, we report an efficient and practical method for the synthesis of (±)-methylenolactocin **1** and (±)-phaseolinic acid **2**, a metabolite of the fungus *Macrophomina phaseolina*.[5]

We envisaged that the indium-mediated allylation[6a–d] of bromide **4** with hexanal would provide an efficient and practical route to **3**, a key intermediate for the synthesis of (±)-methylenolactocin **1** and (±)-phaseolinic acid **2** (Scheme 1).

(*Z*)-Allylic bromide **4a** was prepared in two steps from methyl acrylate. Baylis–Hillman reaction involving the coupling of methyl glyoxylate with methyl acrylate in dioxane gave alcohol **5** in 52% yield. Subsequent bromination of **5** with PBr_3 in ether proceeded smoothly to afford both (*Z*)-**4a** and (*E*)-**4b** allylic bromides in 90% overall yield. Both isomers can be easily separated through flash column chromatography and the product



Scheme 1.



Scheme 2.

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PII: S0040-4039(01)00492-0

ratio is 95:5 [(*Z*)-**4a**:(*E*)-**4b**]. The stereochemistries of both stereoisomers were determined using NOE spectroscopy (Scheme 2).

With the bromide (*Z*)-**4a** in hand, we proceeded to investigate the indium-mediated allylation with hexanal. Although organoindium chemistry, together with ring-closure olefin metathesis has been applied to achieve the synthesis of the α-methylene lactone moiety, the indium-mediated allylation reaction involving bromide (*Z*)-**4a** proved to be more difficult than we had expected.[7] Initial attempts using classical indium-mediated allylation reaction conditions in water[6] consistently afforded the undesired diester **6c** as the major product with only a trace amount of the desired product (Table 1, entry 1). Therefore, attempts were carried out to optimize the yield of **6a** and **6b** in the indium-mediated allylation reaction of allylic bromide (*Z*)-**4a** with hexanal. The results are shown in Table 1.

With water as the solvent, most of the allyllic bromide (*Z*)-**4a** was converted to the undesired diester **6c** (entry 1). In an aqueous medium (H_2O/THF), the desired product was obtained but in poor yield (entry 2). Even when the reaction was carried out in pH 7 buffer solution, the undesired **6c** was still obtained in significant amounts (entry 3). Attempts using dry THF showed a similar result (entry 4). Fortunately, when the reaction was performed neat, the desired product was obtained as a mixture of two isomers (**6a**:**6b** 40:45) in a combined yield of 85% (entry 5).

Interestingly, the *anti* isomer cyclized under the reaction conditions to afford **6a**. The stereochemistries for both **6a** and **6b** were determined through NOESY spectroscopy, where the ring cyclized product **6a** was determined as a *trans*-substituted lactone and thus the cyclized product from the *anti* isomer. The homoallylic alcohol **6b** was determined to be the *syn* isomer based on the NOESY studies of lactone **11** obtained from **6b** after treatment with TFA (Fig. 1).

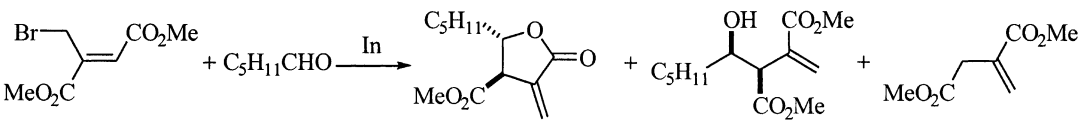
With these optimized conditions, the reactions of allylic bromide (*Z*)-**4a** with four other different aldehydes were investigated. The results are shown in Table 2.

All reactions proceeded smoothly to afford the desired products in moderate to excellent yields. Except for the reaction with 3-methoxybenzaldehyde (entry 4), all other reactions gave low stereoselectivities.

With the product **6** obtained from hexanal, we embarked on the total synthesis of (±)-methylenolactocin **1** (Scheme 3).

Both the isomers, **6a** and **6b**, can be easily separated through flash column chromatography and converted to (±)-methylenolactocin **1**. In the presence of TFA, **6b** was cyclized to the *cis*-β,γ-substituted **11** in 79% yield. Acid hydrolysis of **6a** and **11** with 6N HCl afforded **1** in 70% yield, whereas **11** underwent epimerization.[8] The relative stereochemistry of both lactones **6a** and **11** was confirmed by NOESY spectroscopy and the reported ^1H and ^{13}C NMR data.[8,9] In addition, the target molecule **1** obtained is identical to the natural product by ^1H and ^{13}C NMR.[10] On the other hand, **11** can lead to a formal synthesis of (±)-phaseolinic acid via a stereoselective hydrogenation using thiophenol, followed by the removal of the sulfide group with Na–Hg.[11]

Table 1. Optimization of allylation reaction of allylbromide (*Z*)-**4a** with hexanal



4a **6a** **6b** **6c**

Entry	Conditions[a]	% Yield (**6a** + **6b**)[b] (**6a**:**6b**:**6c**)[c]
1	H_2O	Mainly **6c**
2	THF:H_2O (1:1)	8 (20:20:60)
3	THF:H_2O:buffer pH 7.0 (1:1:2)	60 (36:36:28)
4	Dry THF	60 (40:40:20)
5	Neat	85 (40:45:15)

[a] All reactions were performed at room temperature for 3 days.
[b] Overall purified yield for **6a** and **6b**.
[c] Product ratios (**6a**:**6b**:**6c**) were determined based on ^1H NMR analysis.

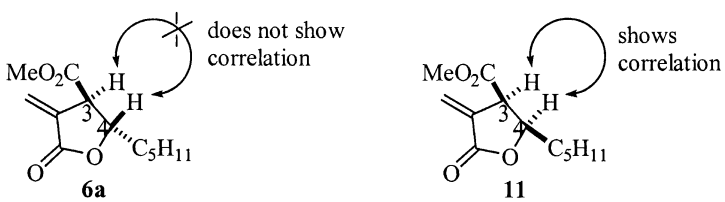
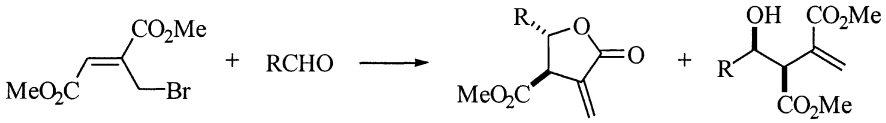


Figure 1.

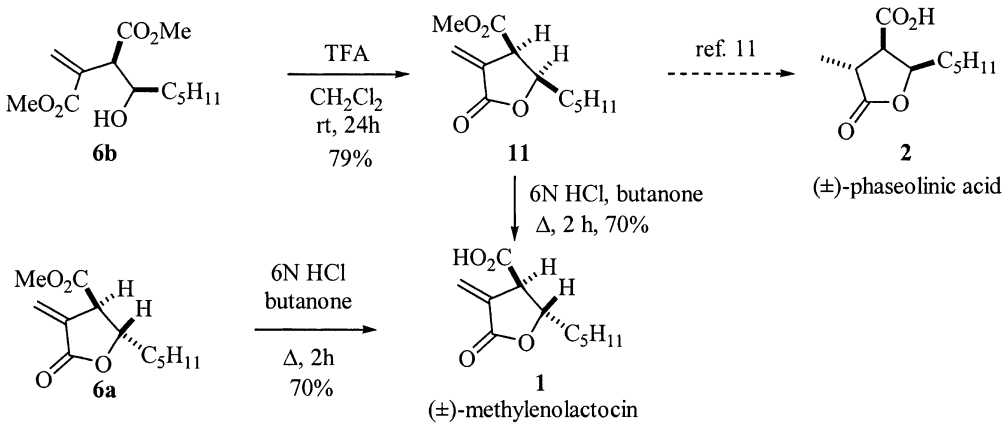
Table 2. Allylation reaction with four different aldehydes



4a **7a-10a** **7b-10b**

Entry	Aldehyde[a]	Ratio **a**:**b**[b]	Total yield (**a**+**b**%)[c]
1	Nonyl aldehyde	(**7a**:**7b**) (53:47)	34[d]
2	Cyclohexanecarboxaldehyde	(**8a**:**8b**) (64:36)	95
3	Benzaldehyde	(**9a**:**9b**) (35:65)	77
4	3-Methoxybenzaldehyde	(**10a**:**10b**) (15:85)	60

[a] All reactions were performed under neat conditions at room temperature for 3 days.
[b] Product ratios (**a**:**b**) were determined based on isolated yields.
[c] Overall purified yield for **a** and **b**.
[d] Reaction not optimized.



Scheme 3. The ^{1}H and ^{13}C NMR data for compounds **6a**, **11** and **1** are given in Ref. 12.

In conclusion, we have developed a short and efficient route for the synthesis of (±)-methylenolactocin **1**. Especially noteworthy is that both the diastereomers obtained from indium-mediated allylation of allylic (*Z*)-**4a** with hexanal can be converted to (±)-**1** in just five steps.

Furthermore, this method allows easy access to a wide variety of analogues. The synthesis and biological evaluation of various analogues are currently in progress.

Acknowledgements

This research was assisted financially by grants from the National University of Singapore.

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12. ^{1}H and ^{13}C NMR data for compound **6a**: **^{1}H NMR (300 MHz)**: δ 0.85–0.89 (m, 3H), 1.30–1.33 (m, 6H), 1.68–1.76 (m, 2H), 3.58 (m, 1H), 3.80 (s, 3H), 4.79 (q, $J=6.4$ Hz, 1H), 5.91 (d, $J=2.4$ Hz, 1H), 6.40 (d, $J=2.4$ Hz, 1H); **^{13}C NMR (75.4 MHz)**: δ 13.8, 22.3, 24.3, 29.6, 35.6, 49.7, 52.8, 78.9, 125.0, 133.0, 168.2, 169.6. Compound **11**: ^{1}H **NMR (300 MHz)**: δ 0.88–0.90 (m, 3H), 1.29–1.31 (m, 6H), 1.55–1.64 (m, 2H), 3.75 (s, 3H), 4.00 (d, $J=7.6$ Hz, 1H), 4.58–4.65 (m, 1H), 5.82 (d, $J=2.4$ Hz, 1H), 6.40 (d, $J=2.4$ Hz, 1H); **^{13}C NMR (75.4 MHz)**: δ 13.8, 22.3, 25.1, 31.2, 31.4, 49.0, 52.2, 78.1, 124.9, 133.6, 168.8, 169.3. Compound **1**: **^{1}H NMR (300 MHz)**: δ 0.88–0.91 (m, 3H), 1.25–1.33 (m, 6H), 1.70–1.74 (m, 2H), 3.61 (m, 1H), 4.78–4.82 (m, 1H), 6.00 (d, $J=2.8$ Hz, 1H), 6.44 (d, $J=2.8$ Hz, 1H); **^{13}C NMR (75.4 MHz)**: δ 13.9, 22.3, 24.3, 31.2, 35.6, 49.6, 79.0, 125.4, 132.7, 168.2, 172.8.