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Synthetic studies towards (+)-Dihydroampullicin. Michael addition of *N*-Boc-2-(*tert*-butyldimethylsiloxy)-3-methyl-pyrrole to α-methylene lactones

Isabel Marcos, Elena Redero and Francisco Bermejo*

Departamento de Química Orgánica, Facultad de Químicas, Universidad de Salamanca, Pza de la Merced s.n. 37008 Salamanca, Spain

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Abstract

The Michael addition of *N*-(*tert*-butoxycarbonyl)-2-(*tert*-butyldimethylsiloxy)-3-methyl-pyrrole (**4**) to several α-methylene lactones catalyzed by fluoride ions yielded the corresponding homologated products (**26**–**30**) with good yields. Application of this reaction to the silyloxy bicyclic lactone (**5**) allowed us to isolate the tricyclic lactone (**26**), a highly valuable intermediate in our synthetic strategy leading to the growth regulator (+)-Dihydroampullicin (**1**).

Keywords: lactones; lactams; Michael reactions; terpenes and terpenoids; pyrrolinones.

Among the fungal metabolites isolated from a culture filtrate of *Ampulliferina*-like fungus sp. No. 27, (+)-Dihydroampullicin **1**, Ampullicin **2** and Isoampullicin **3** (Fig. 1) were found to exhibit remarkable root growth activity in lettuce seedlings.[1] At a dose of 300 mg/L, (+)-Dihydroampullicin accelerated the root growth of lettuce seedlings by 160% as compared with controls, but did not affect hypocotyl growth.[2]

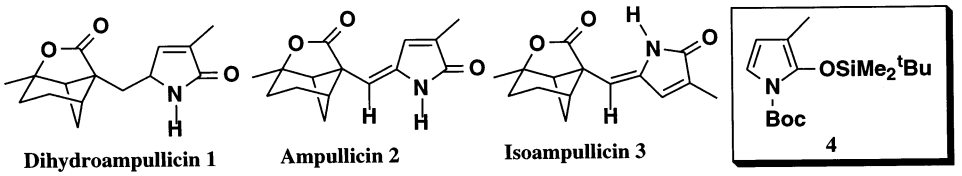

Figure 1.

* Corresponding author. Fax: 34 923 294574; e-mail: fcobmjo@gugu.usal.es

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As part of a program aimed at the synthesis of **1**, **2** and **3**, we envisaged the synthesis of **1** by intramolecular alkylation of the tosylate **6** (Fig. 2) by generation of the lactone enolate under basic conditions. We have successfully applied the same strategy to access the tricyclic lactone when we synthesized **2** and **3**.[3–5]

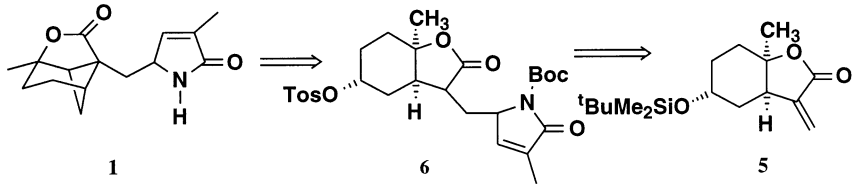
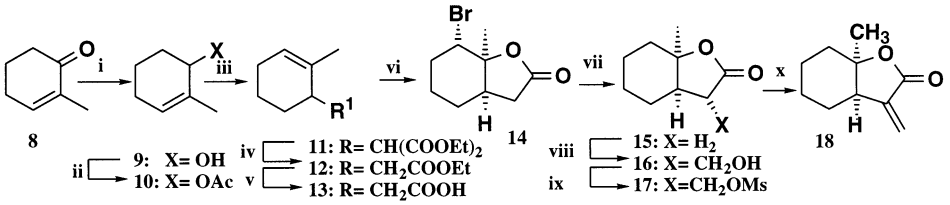


Figure 2.

Preparation of the tosylate **6** requires the development of a procedure mainly consisting of the Michael addition of *N*-(*tert*-butoxycarbonyl)-2-(*tert*-butyldimethylsiloxy)-3-methyl-pyrrole (**4**) to the α-methylene lactone **5**. In this paper, we wish to describe the results obtained for this particular transformation and assess the synthetic viability of the strategy envisaged. Some examples in the literature illustrate the successful addition of 2-(trialkylsiloxy)furans to α,β-unsaturated systems;[6] however, to the best of our knowledge, there are none describing the Michael addition of 2-(trialkylsiloxy)pyrroles to α-methylene lactones.[7–12]

The α-methylene lactones **5**, **18** and **25** were successfully synthesized from the corresponding bicyclic lactones[3,5] following standard procedures.[13,14]

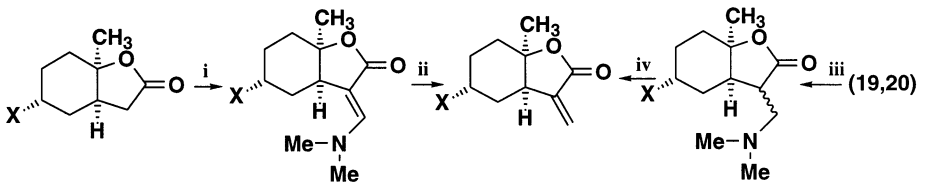
The bicyclic methylene lactone **18** was prepared from 2-methyl-2-cyclohexenone **8** by application of a 10-step sequence, with 15% overall yield (Scheme 1).[15,16]



Scheme 1. Reagents: **i**: $NaBH_4$, CH_3OH, 0°C, 95%; **ii**: Ac_2O, pyr, rt, 8 h; 95%; **iii**: (a) $Pd(PPh_3)_4$, PPh_3, THF, reflux, 0.5 h; (b) $NaCH(COOEt)_2$, THF, reflux, 15 h, 85%; **iv**: NaCl, H_2O, DMSO, 160°C, 15 h, 70%; **v**: KOH, H_2O, MeOH, 85%; **vi**: NBS, acetone, 0°C, 85%; **vii**: $n Bu_3SnH$, AIBN, THF, 55°C, 1 h, 75%; **viii**: LDA, THF, −78°C, $(HCHO)_x$, 65%; **ix**: MsCl, CH_2Cl_2, pyr, DMAP, 85%; **x**: DBU, THF, rt, 1 h, 95%

The methylene lactones **5** and **25** were prepared from the bicyclic lactones **19** and **20**, readily available from *R*-(−)-carvone.[5]

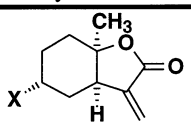
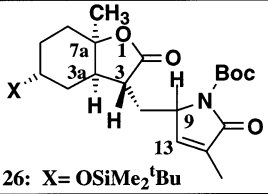
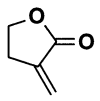
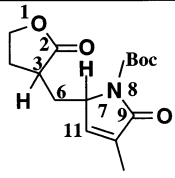
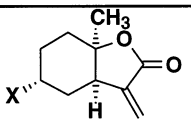
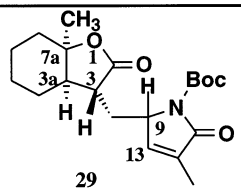
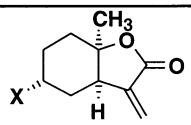
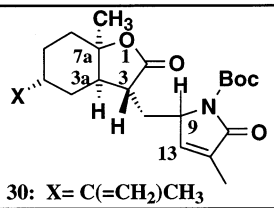
Treatment of **19** and **20** with excess of *tert*-butoxybis (dimethylamino)methane (Bredereck's reagent) followed by dibah reduction of the resulting enamines afforded **5** and **25** with 60 and 65% yields, respectively (Scheme 2). However, addition of the Eschenmoser salt to the kinetic enolates resulting from the LDA deprotonation of lactones **19** and **20**, followed by quaternization of the resulting amines and further elimination, afforded **5** and **25** in higher yields (72 and 78%, respectively).[17,18]



Scheme 2. Reagents: **i**: (a) $^{t}BuOCH_2(NMe_2)_2$, 90°C; (b) K_2CO_3, MeOH, reflux, 45 min.; **ii**: dibah (20 equiv.), −78°C, 3 h; **iii**: LDA, THF, −78°C, $CH_2{=}N(Me)_2$ I^-; **iv**: ICH_3, CH_3OH, $KHCO_3$

The results obtained for the Michael addition of *N*-(*tert*-butoxycarbonyl)-2-(*tert*-butyldimethylsiloxy)-3-methyl-pyrrole **4** to several α-methylene lactones are summarized in Table 1.

Table 1
Michael addition of **4** to α-methylene lactones catalyzed by fluoride ions[a]

Entry	methylene lactone	product	^{1}H NMR (δ, ppm)	Yield %
1	 **5: X= OSiMe$_2$^{t}Bu**	 **26: X= OSiMe$_2$^{t}Bu**	H-3: 2.67 H-9: 4.63 H-13: 6.99	70
2	 **7**	 **27: (*R,R*)** **28: (*R,S*)**	**27:** H-3: 2.44 H-7: 4.72 H-11: 6.77 **28:** H-3: 2.47 H-7: 4.55 H-11: 6.80	65 (**26**: **27**= 1:1)
3	 **18: X= H**	 **29**	H-3: 2.65 H-9: 4.61 H-13: 6.90	75
4	 **25: X= C(=CH$_2$)CH$_3$**	 **30: X= C(=CH$_2$)CH$_3$**	H-3: 2.80 H-9: 4.68 H-13: 6.92	78

[a] All reactions were run in THF by dropwise addition of the ethereal solution of **4** (1.2 equiv.) to the α-methylene lactone (1 equiv.) at −78°C followed by addition of a THF solution of Bu_4NFxH_2O (1.3 equiv.). The reaction mixture was stirred for 15 h at that temperature and quenched by addition of sat. NH_4Cl aqueous solution.[20] No condensation product at the α position of the pyrrolinone moiety was found in any case.

The addition of **4** to the commercially available α-methylene-γ-butyrolactone **7** catalyzed by fluoride ions (entry 1, Table 1) afforded a mixture of diastereomers **27**:**28** in a 1:1 ratio, with moderate yields. The two diastereomers were successfully separated by flash chromatography. The structural elucidation of both isomers was accomplished by a complete ^{1}H and ^{13}C NMR analysis.[19]

However, the reaction of **4** with methylene lactones **5**, **18** and **25** under identical conditions took place stereoselectively from the *exo* face. Only one diastereomer was present in the reaction mixture in all cases. We assume that the configuration at C-3 is that shown above by comparison with the chemical shifts described for other derivatives obtained in previous synthetic work.[3–5] Indetermination of the configuration at C-9 in the pyrrolinone moiety does not affect the homogeneity of the product since according to the complete spectroscopic analysis all the isolated products, **26**, **29** and **30**, were chromatographically pure.

The reaction of **4** with the α-methylene lactone **5** yielded the lactone **26**, whose trivial transformation into the tosylate **6** opens access to the natural product **1** and demonstrates the viability of our synthetic strategy leading to **1**. The key cyclization step of our synthesis was successfully achieved when we synthesized **2** and **3** to gain access to the tricyclic lactone core present in this interesting series of sesquiterpenic amides.[3–5]

In conclusion, we have developed a homologation method of α-methylene lactones by Michael addition with *N*-(*tert*-butoxycarbonyl)-2-(*tert*-butyldimethylsiloxy)-3-methyl-pyrrole **4** catalyzed by fluoride ions. This reaction proved to be a clean transformation; it takes place under very soft conditions and the yields are acceptable in all cases (65–78%).

Acknowledgements

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