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Carbonylative lactonization via carbonyl oxygen attack: a short and selective total synthesis of uncinine and its analogues

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Abstract—A novel cytotoxic butenolide alkaloid, uncinine, has been synthesized for the first time in 8 steps from propargyl alcohol. The sequence features a mild and efficient tandem carbonylative lactonization of a β-iodoenone precursor using an inorganic base at 1 atm CO, and an indirect attachment of the pyrrolidinone ring via nucleophilic substitution with methyl γ-aminobutyrate.

Uncinine (Fig. 1) is a novel butenolide alkaloid, isolated[1] from *Artabotrys uncinatus*, a plant used as a traditional folk medicine in Taiwan in the treatment of nasopharyngeal carcinoma. Its structural features, namely the combination of the γ-alkylidene butenolide and pyrrolidinone fragments, promise potentially interesting biological activity. Firstly, the presence of the pyrrolidin-2-one moiety is a characteristic of piracetam-derived cognitive enhancers[2] and, secondly, γ-alkylidene butenolides themselves display a wide array of biological activities. The most simple compound of this class, protoanemonin, possesses antimicrobial[3] and antifungal[4] activities, and other notable representatives include, for example, rubrolides, which exhibit a significant (2–11 μg in a standard disc assay) in vitro antibacterial effect[5] and xeruline derivatives with cholesterol biosynthesis-inhibiting properties.[6] In an in vitro assay, uncinine displayed[1] potentially promising (IC_{50} 6.1 μg/mL) cytotoxicity against the Hep G_2 cell line. However, an extensive evaluation was prevented by the minute quantity of the compound obtained from the plant material. In this letter, we report a short and flexible total synthesis, which allows an economic supply of the alkaloid as well as its analogues from trivial starting materials.

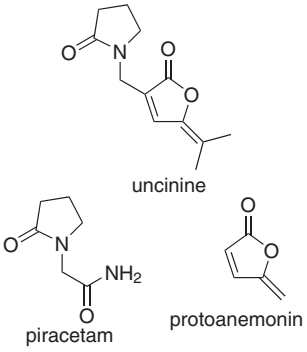

Figure 1.

Given their biological activities, a vast amount of synthetic effort has been devoted to the development of efficient synthetic strategies towards the γ-alkylidene butenolides.[7,8] This structural arrangement is available via three major routes:[7,8] (1) alkylidenation of five-membered heterocycles (2-oxyfurans,[9] γ-lactones[10] and maleic anhydrides[11]), (2) cyclization of γ-hydroxy- and γ-oxoacids[12] (or their equivalents, such as γ-oxoacylpalladium complexes[13]), and (3) lactonization reactions of alk-4-ynoic and alk-4-enoic acids.[14] The efficiency of the first two strategies depends on the accessibility of suitable precursors (especially in cases where more complex substitution on the desired butenolide is required), and a number of the methods are non-stereoselective, affording mixtures of *E*/*Z* isomers of the target γ-alkylidene butenolides. Selectivity control has been achieved,[15] for example, through the preparation of diastereopure γ-(1-heteroalkyl)-substituted butenolides,

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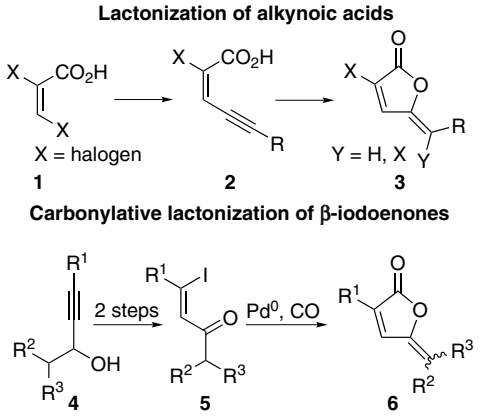
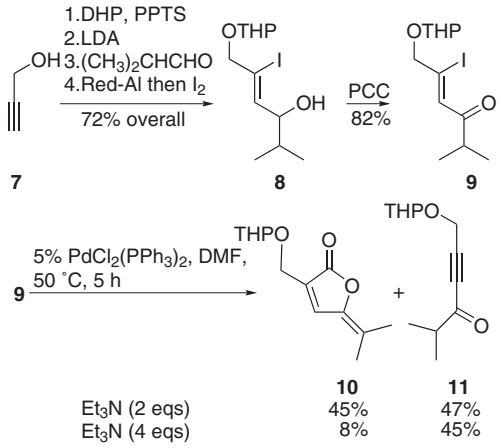


Scheme 1.

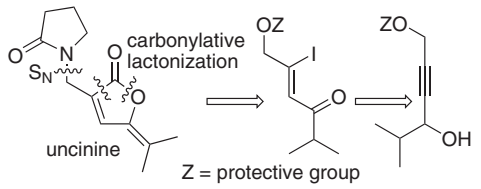


Scheme 3.

and subsequent stereospecific anti-elimination of a leaving group located at C(1) of the alkyl moiety. On the other hand, the third strategy (Scheme 1) has become increasingly popular in recent years[16] due to its stereoselectivity as well as the possibility of an easy assembly of the starting acids **2**. This approach does not, however, allow a single-step construction of γ-alkylidene butenolides, disubstituted at the exocyclic terminus of the double bond. Also, the choice of substituents to be attached to Cα of the butenolide at a later stage is dictated by the necessity to use metal-catalyzed reactions for further elaboration of this position.

With the stereoselective introduction of the exocyclic double bond not being an issue in the case of uncinine, the disconnection (Scheme 2) based on Pd-catalyzed carbonylative lactonization (i.e., the above-mentioned cyclization of γ-oxoacylpalladium complexes) (Scheme 1) appeared a particularly attractive solution. The precursors for this reaction, stereodefined β-iodoenones **5**, can be easily accessed via hydroalumination/iodination of simple propargylic alcohols[17] **4** followed by oxidation. Their carbonylative lactonization results in the formation of the sensitive γ-alkylidene butenolide arrangement in a single operation that can be carried out under relatively mild conditions. This strategy has remained synthetically less developed, despite being extremely suitable for the synthesis of various Cα-substituted γ-alkylidene butenolides, including those with a tetrasubstituted exocyclic double bond.

Thus, iodoalcohol **8** was prepared in three steps from propargyl alcohol,[18] and oxidized to iodoenone **9** with pyridinium chlorochromate (PCC) (Scheme 3). With



Scheme 2.

compound **9** in hand, the crucial cyclization process could be attempted and its conditions optimized with respect to the limited stability[19] of this enone (and, probably, β-iodoenones in general) as well as to the relatively sensitive functionality present in the target γ-alkylidene butenolides. Thus, we intended to find conditions that were as mild as possible. Negishi and co-workers[13] cyclized similar β-iodoenones in DMF with 2 equiv of Et_3N and 5% $PdCl_2(PPh_3)_2$ at 100 °C and 20–40 atm CO; when we applied milder and operationally more simple conditions avoiding the use of an autoclave (1 atm CO, 50 °C), the starting material was consumed completely within 5 h, but, apart from the desired furanone **10**, a substantial amount of propargylic ketone **11** was formed. Hence, the desired carbonylative lactonization did not require a high CO pressure, but, at the pressure of 1 atm, this process was competing with an elimination reaction.

Notably, using 4 equiv of the base gave nearly the same yield of the elimination product **11** but the yield of butenolide **10** dropped to 8%. Further experiments showed that triethylamine itself is capable of effecting the elimination, since treatment of iodoenone **9** under non-carbonylative conditions with Et_3N in both the absence and presence of 5% of the Pd catalyst in DMF at 50 °C for 5 h resulted in a complete conversion into the propargylic ketone **11**. Thus, we concluded that the dramatic decrease in the yield of **10** upon using 4 equiv of base must have been a reflection of the base sensitive nature of the γ-alkylidene butenolide core, and that the undesirable side process depended more on the nature than the amount of the base.

While the rate of CO insertion and hence carbonylative lactonization can be accelerated[13] by using a high pressure of CO, we decided to screen various bases, with a view to identifying one that might allow us to work at the more convenient 1 atm. Having employed several different examples (Table 1), we were eventually pleased to find that using 2 equiv of $NaHCO_3$ at 50 °C did not effect elimination, and the cyclization product was formed in a respectable, 77% isolated yield. Obviously, while Et_3N is capable of abstracting the double bond

Table 1.

Base (2 equiv)	Isolated yield		T (°C)[c]/time (h)[d]
	10	**11**	
K_2CO_3	29	63	55/3
CH_3COONa	35	63	40/1
Pyridine (4 equiv)	16	—[a]	60/8
LiCl (4 equiv)	5	—[a]	60/8
$NaHCO_3$	**77**	**—[a]**	**50/7**
NaF	5	—[b]	60/5

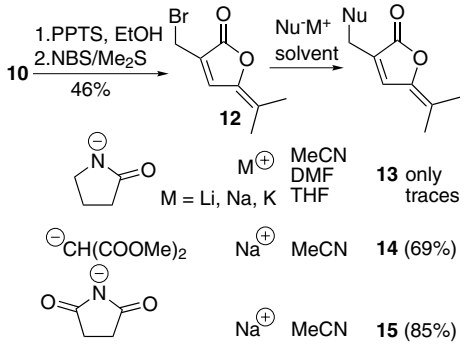
[a] The remainder was an intractable mixture.
[b] 40% of the starting material was recovered.
[c] The reaction did not proceed at lower temperatures.
[d] Time necessary for the starting material to be consumed.

hydrogen under the reaction conditions and the rate of this process is, at 1 atm, comparable to that of CO insertion, the role of $NaHCO_3$ is limited to buffering the proton from the enolizable position of enone **3** and regenerating the Pd^0 species.

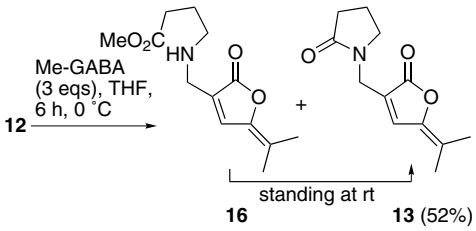
Having established an easy, short and efficient access to butenolide **10**, the completion of the synthesis appeared a simple task. Compound **10** was therefore deprotected[20] with PPTS in 96% EtOH, and the hydroxy group converted into the bromo function with NBS/Me_2S[21] (Scheme 4).

To our surprise, attempted nucleophilic substitution of bromo derivative **12** with the anion of pyrrolidin-2-one failed to deliver the target uncinine **13**, regardless of the cation (Li^+, Na^+, and K^+) or solvent (THF, MeCN, and DMF). The reason must have been the relatively high basicity of the pyrrolidinone anion, since treatment of **12** with sodium dimethyl malonate and sodium succinimidate in MeCN smoothly afforded diester **14** and uncinine analogue **15**, respectively, in high yields.

Thus, methyl γ-aminobutyrate (Me-GABA) became a logical choice as a pyrrolidin-2-one equivalent of lower basicity, which would enable us to attach the heterocyclic moiety via nucleophilic substitution at the bromomethyl group of furanone **12**, followed by intramolecular cyclization[22] to form the pyrrolidinone ring. Hence, Me-GABA was prepared[23] by passing a stream of NH_3 through a $CHCl_3$ solution of its hydrochloride, and used immediately for the nucleophilic substitution reaction.



Scheme 4.



Scheme 5.

Since preliminary experiments showed that secondary amine **16** (Scheme 5) is quite prone to further alkylation, the reaction was carried out with 3 equiv of Me-GABA under high dilution conditions in THF at 0 °C. In the event, a mixture of secondary amine **16** and uncinine **13**, which was difficult to separate by column chromatography, was obtained (Scheme 5). The cyclization of **16** to the natural product proceeded to completion upon allowing the mixture of **16** and **13** to stand for a few days. Finally, another round of purification furnished uncinine in 52% yield; the spectral characteristics of the synthetic substance were in excellent agreement with those, published by Wu and co-workers for the natural product.[1]

In conclusion, we have demonstrated the synthetic potential of carbonylative lactonization through trapping the intermediate acylpalladium species with carbonyl oxygen as the internal nucleophile, and prepared uncinine for the first time from a trivial starting material in eight steps with 11% overall yield. Employing $NaHCO_3$ as the base suppressed an undesirable elimination process, while enabling us to carry out the key step at atmospheric CO pressure. The base-sensitive nature of the alkylidene butenolide was circumvented by using Me-GABA as a precursor of the pyrrolidinone cycle. Uncinine as well as its analogues can thus be easily supplied in quantities, necessary for extensive biological evaluation. Finally, an exploration of the factors that govern the stereoselectivity of this type of carbonylative lactonization is in progress, and the results will be reported in due course.

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Supplementary data

Supplementary data (experimental procedures, copies of ^1H and ^{13}C NMR spectra for all new compounds) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2005.09.128.

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