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Synthesis of Bicyclic γ-Ylidenetetronates

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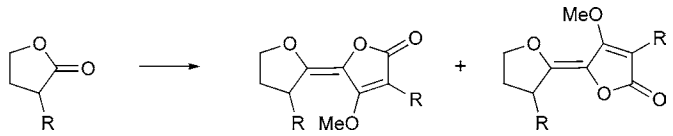
ABSTRACT



The bicyclic γ-ylidenetetronate motif found in several *Stemona* alkaloids was prepared in a stereoselective manner by addition of lithium methyl tetronate to an alkoxy oxonium ion formed from a lactone. The corresponding mixed alkyl ketal obtained was subjected to a Lewis acid–base-promoted dealkoxylation reaction to deliver the desired products.

Several naturally occurring alkaloids containing a γ-ylidenetetronate connected to a furan ring by a conjugated exocyclic double-bond moiety (bicyclic γ-ylidenetetronate) have been shown to possess insecticidal, antifeedant, and anticoughing activities, i.e., structures **1**−**4** in Figure 1.[1] Asparagamine-A

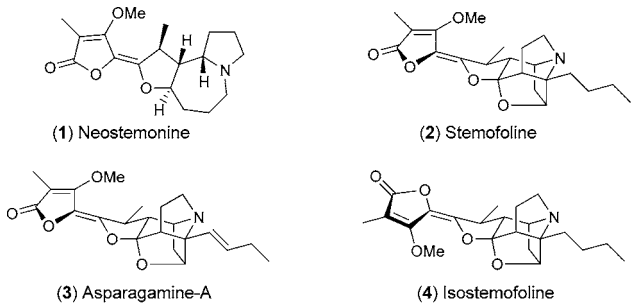


Figure 1.

(**3**), isolated from *Asparagus racemosus*, was reported to show potent inhibition of oxytocin.[2] More recently, asparagamine-A together with its geometrical isomer was also isolated from *Stemona collinsae*.[3] Several sesquiterpenes possess a more simple γ-ylidenetetronate moiety, and a variety of methodologies for their preparation have been developed.[4] However, methodology for the synthesis of the more challenging bicyclic γ-ylidenetetronate is lacking and hampering the efficient syntheses of the alkaloids. Aside from the total synthesis of isostemofoline by Kende and coworkers,[5] none of the alkaloids containing a bicyclic γ-ylidenetetronate motif have been synthesized. Hence, an efficient methodology for the construction of the challenging bicyclic γ-ylidenetetronate will allow the total synthesis of the *Stemona* alkaloids containing this unique structural motif.

The construction of bicyclic γ-ylidenetetronates was attempted by Thomas group.[6] Thomas' strategy involved the addition of a lithiated α-benzenesulfonyl tetrahydropyran to a hydroxybutenolide followed by elimination of the benzenesulfonyl group. However, a mixture of spiro alcohols was obtained instead of the desired bicyclic γ-ylidenetetronate. In Kende's synthesis of isostemofoline, the natural product skeleton was elegantly assembled by means of a triple-tandem cyclization process.[5] A stereocontrolled dehy-

(1) For a review on the isolation and synthesis of Stemona alkaloids, see: Pilli, R. A.; Ferreira de Oliveira, M. C. *Nat. Prod. Rep.* **2000**, *17*, 117−127.

(2) Sekine, T.; Ikegami, F.; Fukusawa, N.; Kashiwagi, Y.; Aizawa, T.; Fujii, Y.; Ruangrungsi, N.; Murakoshi, I. *J. Chem. Soc., Perkin Trans. 1* **1995**, 391−393.

(3) Jiwajinda, S.; Hirai, N.; Watanabe, K.; Santisopasri, V.; Chuengsamarnyart, N.; Koshimidzu, K.; Ohigashi, H. *Phytochem.* **2001**, *56*, 693−695.

(4) For reviews on the synthesis of butenolides and tetronates, see: (a) Pattenden, G. *Fortschr. Chem. Org. Naturst.* **1978**, *35*, 133−198. (b) Negishi, E.; Kotora, M. *Tetrahedron* **1997**, *53*, 6707−6738. (c) Brückner, R. *Curr. Org. Chem.* **2001**, *5*, 679−718.

(5) Kende, A. S.; Smalley, T. L.; Huang, H. *J. Am. Chem. Soc.* **1999**, *121*, 7431−7432.

(6) Beddoes, R. L.; Davies, M. P. H.; Thomas, E. J. *J. Chem. Soc., Chem. Commun.* **1992**, 538−540.

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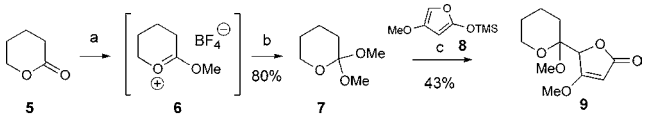
dration of the hemiketal intermediate obtained in the cyclization process was required to form the desired bicyclic (*Z*)-γ-ylidenetetronate motif and thus complete the total synthesis of stemofoline. However, the dehydration reaction proved to be extremely difficult and occurred in very low yield (12%), delivering instead the geometrical isomer isostemofoline (**4**).

We envisioned that a general and valuable synthetic disconnection for the bicyclic γ-ylidenetetronate system would be the bridge double bond that connects the tetronate motif to the tetrahydrofuran ring. In the synthetic direction, addition of a nucleophilic species derived from methyltetronate to the electrophilic center of a lactone, or lactone derivative, would deliver a hemiketal intermediate that, upon dehydration, would give the desired bicyclic γ-ylidenetetronate system. Herein, we describe the development of an efficient methodology for the synthesis of bicyclic γ-ylidenetetronates using methyltetronates and lactone derivatives as coupling partners.

Our initial strategy involved the addition of nucleophilic species derived from methyltetronates to lactone systems. Although there is precedent for the addition of lithium enolates derived from tetronic acids and methyltetronates to aldehydes and ketones,[4] lactones proved to be totally unreactive to the lithium enolate derived from methyltetronate. We also investigated the Lewis acid-promoted addition of 2-trimethylsilyloxy-4-methoxyfuran to lactones without success. Due to the lack of reactivity of lactones toward nucleophiles derived from methyl tetronate, more reactive lactone-derivatives were investigated. The known orthomethylester **7** was synthesized from δ-valerolactone (**5**) using the protocol described by Deslongchamps.[7] Ortho ester **7** was subjected to Lewis acid-promoted addition of 2-trimethylsilyloxy-4-methoxyfuran (**8**) to yield the desired mixed methyl ketal products **9**, Scheme 1. We observed that

Scheme 1[a]

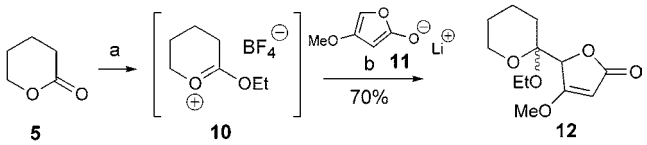


[a] Reagents and conditions: (a) $Me_3O^+BF_4^-$, room temp, overnight, CH_2Cl_2; (b) NaOMe, MeOH, from −78 °C to room temp; (c) $ZnCl_2$, from −10 °C to room temp, 48 h.

addition occurred when using zinc chloride as catalyst albeit in low yield (<45%). Other Lewis acids such as $TiCl_4$ and $BF_3{\cdot}OEt_2$ were investigated without success.

We envisioned that a direct addition of a nucleophile to the oxonium ion obtained by treatment of lactones with trialkyloxonium tetrafluoroborate could be more beneficial. After extensive experimentation, we found that mixed ethyl ketal **12** could be obtained in 70% yield by treatment of δ-valerolactone (**5**) with excess triethyloxonium tetrafluoroborate followed by direct addition of the lithium enolate **11** derived from methyltetronate at low temperature, Scheme 2.[8] Thus, employing this methodology, we synthesized mixed

Scheme 2[a]

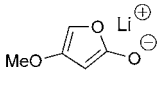
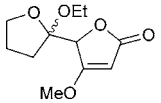
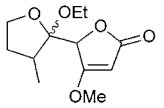
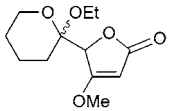
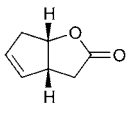
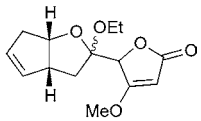
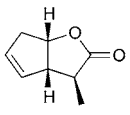
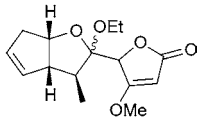
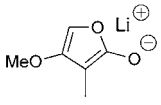
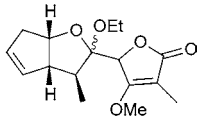


[a] Reagents and conditions: (a) $Et_3O^+BF_4^-$ (6 equiv), room temp, overnight, CH_2Cl_2; (b) lithium enolate (1.3 equiv) in THF, −78 °C, 1 h.

ethyl ketals in good to very good yields (65−90%). The results are summarized in Table 1. The mixed ethyl ketals proved to be excellent substrates for the synthesis of bicyclic γ-ylidenetetronates.

Having on hand several mixed ethyl ketal precursors, we proceeded to investigate their dealkoxylation reaction to form the conjugated system present in the bicyclic γ-ylidenetetr-

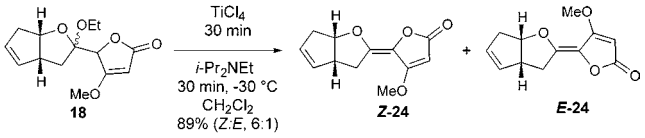
Table 1. Synthesis of Mixed Ethyl Ketals

entry	lactone	Li enolate	mixed ketal (% yield)
1	 **13**	 **11**	 **14** (65%)
2	 **15**	**11**	 **16** (88%)
3	 **5**	**11**	 **12** (70%)
4	 **17**	**11**	 **18** (76%)
5	 **19**	**11**	 **20** (84%)
6	**19**	 **22**	 **23** (65%)

(7) Deslongchamps, P.; Lessard, J.; Nadeau, Y. *Can. J. Chem.* **1985**, *63*, 2485−2492.

onates. Initially, we tested some of the previously reported methodologies developed for the synthesis of acyclic γ-ylidenetetronates.[9,10] Attempts for the dealkoxylation of mixed ethyl ketals by treatment with DBU at room temperature as reported by Takei[10] or with *t*-BuLi at low temperature as described by Pelter[9] failed to provide the desired conjugated system of γ-ylidenetetronates. We also found that the dealkoxylation reaction under protic acid conditions was not successful. We envisioned that the reaction conditions used for the soft enolization of *N*-acyloxazolidinethiones and thiazolidienthiones would promote the dealkoxylation of the mixed ethyl ketal precursors.[11] Thus, we were delighted to see that treatment of mixed ethyl ketal **18** with 1 equiv of $TiCl_4$ at low temperature, followed by addition of 1 equiv of diisopropylethylamine resulted in the smooth conversion to the desired γ-ylidenetetronates (*Z*)-**24** and (*E*)-**24** in 89% yield (ratio of *Z*:*E* = 6:1),[12] Scheme 3. The geometrical

Scheme 3



isomers were easily separated by column chromatography, and the stereochemistry of the newly created double bond was confirmed by NOE experiments.

We applied this methodology for the dealkoxylation of several mixed ethyl ketal precursors to obtain different bicyclic γ-ylidenetetronates in excellent yields (Table 2). Interestingly, we observed that the dealkoxylation of mixed ethyl ketal substrates containing a methyl group in the α-position with respect to the "anomeric carbon" delivered a mixture of γ-ylidenetetronates in which the (*E*)-stereoisomer was the major product (entries 2 and 6). It appears that steric interactions of the methyl group with the methoxy group in the methyltetronate motif are sufficiently severe to reverse the stereochemical outcome of the reaction. To attempt to overcome this problem, we investigated the use of other Lewis acids such as $ZnCl_2$ and $BF_3{\cdot}OEt_2$ to promote the dealkoxylation. However, Lewis acids other than $TiCl_4$ proved to be ineffective in promoting the elimination reaction. We also investigated other amine bases such as 2,2,6,6-tetramethylpiperidine and obtained results similar to those obtained when using diisopropylethylamine. Interestingly, we observed that the number of equivalents of amine base employed in the reaction, as well as the reaction time, had an impact in the stereochemical outcome of the reaction. We found that the dealkoxylation of mixed ethyl ketal **20** using 1 equiv of $TiCl_4$ and 2 equiv of diisopropylethylamine delivered a mixture of stereoisomers in which the (*Z*)-stereoisomer was the major product (entry 3). However, using 3 equiv of amine base and a longer reaction time leads to the formation of the (*E*)-stereoisomer as the major product (entry 4). Finally, typical dealkoxylation reactions using 1 equiv of $TiCl_4$ and 2 equiv of amine base resulted in the formation of the corresponding (*Z*)-stereoisomers as the major products in excellent yields (entry 5, 7 and 8). It is important to mention that mixed ethyl ketals **12** and **14** were obtained as a 1:1 mixture of erythro and threo products, and their dealkoxylation reaction yielded a 4:1 mixture of (*Z*)- and (*E*)-γ-ylidenetetronates in both cases. From this observation, we can assume that the anomeric ratio of the mixed ethyl ketal substrates has little or no impact on the stereochemical outcome of the dealkoxylation reaction.

Single-crystal X-ray analysis of (*Z*)-γ-ylidenetetronate **25** confirmed the correct assignment of the stereochemistry of the bridge double bond of the γ-ylidenetetronate system, Figure 2.

In summary, bicyclic γ-ylidenetetronates were successfully synthesized for the first time in a very efficient manner.

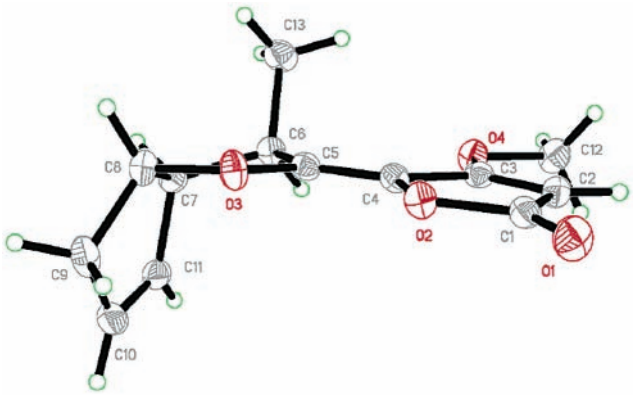


Figure 2. X-ray crystal structure of γ-ylidinetetronate (*Z*)-**25**.

(8) A typical procedure is as follows. Lactone (neat, 1 mmol) was added to a stirred solution of triethyloxonium tetrafluoroborate (6 mmol, 6 mL of a 1 M solution in CH_2Cl_2) in CH_2Cl_2 under an N_2 atmosphere. The reaction was stirred for 15−20 h and then cooled to −78 °C where a solution of lithium tetronate (1.3 mmol) was added via cannula. The lithium tetronate solution was prepared by addition of LHMDS (1.3 mmol, 1.3 mL of a 1 M solution in THF) to a cooled (−78 °C) solution of methyltetronate (1.3 mmol, 148.3 mg) in dry THF (10 mL) and stirred for 30 min, the resulting solution was transferred via cannula. After 1 h, the reaction mixture was diluted with 20 mL of CH_2Cl_2 and poured into 20 mL of a saturated solution of sodium bicarbonate. Layers were separated, and the aqueous one was back extracted with CH_2Cl_2 (3 × 20 mL). Combined organic layers were washed with 20 mL of a saturated solution of sodium bicarbonate and dried over $MgSO_4$. Solvent was removed under reduced pressure, and the product was purified by column chromatography.

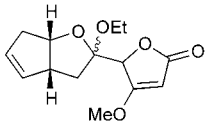
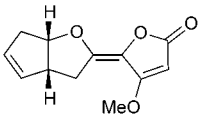
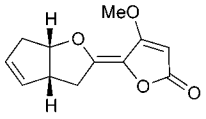
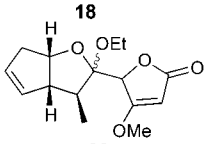
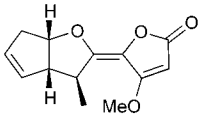
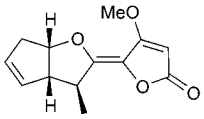
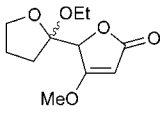
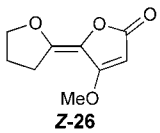
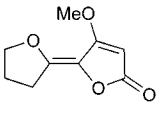
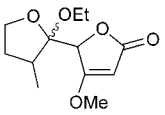
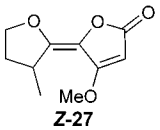
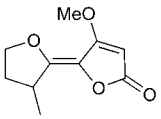
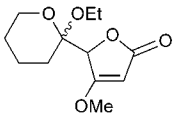
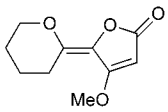
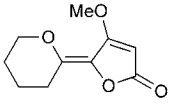
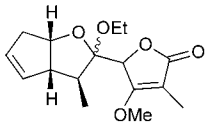
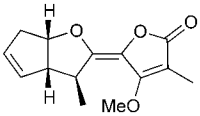
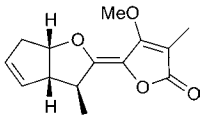
(9) (a) Pelter, A.; Al-Bayati, R.; Lewis, W. *Tetrahedron Lett.* **1982**, *23*, 353−356. (b) Pelter, A.; Al-Bayati, R. I. H.; Ayoub, M. T.; Lewis, W.; Pardasani, P. *J. Chem. Soc., Perkin Trans. 1* **1987**, 717−742.

(10) Asaoka, M.; Yanagida, N.; Ishibashi, K.; Takei, H. *Tetrahedron Lett.* **1981**, *22*, 4269−4270.

(11) For a review on thiazolidinethiones, see: Velázquez, F.; Olivo, H. F. *Curr. Org. Chem.* **2002**, *6*, 303−340.

(12) A typical procedure for the dealkoxidation reaction is as follows. $TiCl_4$ (1.05 mmol, 1.05 mL of a 1 M solution in CH_2Cl_2) was added dropwise to a cooled (−30 °C) solution of mixed ethyl ketal (1 mmol) in dry CH_2Cl_2. The resulting orange solution was stirred for 30 min followed by addition of *i*-Pr_2NEt (in 2 mL of CH_2Cl_2). After addition of the amine, the reaction mixture became dark and was stirred for an additional 30 min. The reaction was quenched by addition of 20 mL of a saturated solution of sodium bicarbonate. The product was taken into CH_2Cl_2 (3 × 20 mL). The combined organic layers were washed with 20 mL of a saturated solution of sodium bicarbonate and dried over $MgSO_4$. Solvent was removed under reduced pressure, and the residue was chromatographed on a silica gel column to deliver the (*Z*)- and (*E*)-γ-ylidenetetronates.

Table 2. Dealkoxylation Reaction of Mixed Ethyl Ketals[a]

entry	mixed ethyl ketal	temp. eq. base time, yield *Z:E* ratio	γ-ylidenetetronates
1	 **18**	-30 °C 1 eq. base 30 min, 89% 6:1	 +  ***Z*-24** ***E*-24**
2	 **20**	-50 °C 1 eq. base 20 min, 84% 1:2	 +  ***Z*-25** ***E*-25**
3	**20**	-20 °C 2 eq. base 30 min, 84% 2:1	***Z*-25** + ***E*-25**
4	**20**	-20 °C 3 eq. base 60 min, 98% 1:2	***Z*-25** + ***E*-25**
5	 **14**	-20 °C 2 eq. base 30 min, 92% 4:1	 +  ***Z*-26** ***E*-26**
6	 **16**	-20 °C 2 eq. base 30 min, 83% 1:2	 +  ***Z*-27** ***E*-27**
7	 **12**	-20 °C 2 eq. base 30 min, 64% 4:1	 +  ***Z*-28** ***E*-28**
8	 **23**	-20 °C 2 eq. base 30 min, 72% 2:1	 +  ***Z*-29** ***E*-29**

[a] In all entries, 1.05 equiv of $TiCl_4$ was added to the mixed ethyl ketals and the reaction mixture was stirred for 30 min before adding DIPEA; see ref 12 for a general procedure.

Unactivated lactones proved to be completely unreactive toward different nucleophiles derived from methyltetronate. Activation of lactones using trialkyloxonium tetrafluoroborate salts allowed the nucleophilic attack of lithium enolates derived from methyltetronates. Finally, a new methodology for the dealkoxylation reaction of mixed ethyl ketal intermediates was successfully developed. This methodology delivered bicyclic γ-ylidenetetronates in excellent yields and in some cases with good stereocontrol. Experiments are underway in our laboratories to elucidate the mechanism of the reaction and to improve its stereoselectivity. This methodology should be valuable for the synthesis of *Stemona* alkaloids containing a bicyclic γ-ylidenetetronate motif.

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Supporting Information Available: Spectroscopic data and copies of ^1H and ^{13}C NMR spectra for all γ-ylidenetetronates (*Z*)- and (*E*)-**24**−**29**. This material is available free of charge via the Internet at http://pubs.acs.org.

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