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RESEARCH ARTICLE

A NEW METHODOLOGY FOR THE SYNTHESIS OF δ-SUBSTITUTED α,β-UNSATURATED δ-LACTONES

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ABSTRACT

A new protocol for the synthesis of δ-substituted-α,β-unsaturated δ-lactones was developed. Selective reaction of 1,3-dilithiopropyne with ketones, followed by addition of ethyl chloroformate formed ethyl 5-[(ethoxycarbonyl)oxy]-5-substituted-2-ynoates, used as the basic framework for the synthesis of δ-substituted α,β-unsaturated-δ-lactones.

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INTRODUCTION

δ-Hexenolides or α,β-unsaturated lactones are structural frameworks present in a wide variety of natural products. They have been isolated from insects, [1,2] plants,[3] fruits,[4] fungi and marine organisms. Many of these naturally occurring α, β-unsaturated δ-lactones have shown important biological activity, such as antifungal, antitumoral or plant growth inhibition. [5,6] It is very common to find these lactones substituted at the C-6 position of the ring. These 6-substituted 5,6-dihydro-2-*H*-pyran-2-ones, which normally exhibit pharmacological properties, are widely distributed in plants of the Lamiaceae, Piperaceae and Annonaceae families.[7] An example of this is (+)-Boronolide, 1, (Figure 1), which was isolated from the bark and branches of *Tetradenia barberae*[8] *and Tetradenia fruticosa*, which are shrubs of the family Lamiaceae from Madagascar, where it has been used as folk medicine. Its use has also been reported in Southern Africa.[7] Lactone R-(-)-Argentilactone, 2, was first isolated in 1977, from *Aristolochia argentina*.[9] It has also been isolated from the essential oil of *Annona haematantha*[10] and from the leaves of *Chorisia crispiflora*.[11] This compound has shown cytotoxic activity.[12]

Other examples are Massoia lactone, **3**, derived from the bark of the Massoia tree (*Cryptocaria massoia*),[13] found in Papua, Indonesia. This lactone has also been identified as a defensive allomone of ants of the genus *Camponotus*.[14]

Goniothalamin, **4**, a styryl lactone, was first isolated from the bark of *Cryptocarya caloneura* (Lauraceae).[15] It has also been found within the family Annonaceae and isolated from four *Goniothalamus* species.[16] This lactone has displayed *in vitro* selective cytotoxic activity, inducing apoptosis, on different cancer cell lines.[17]

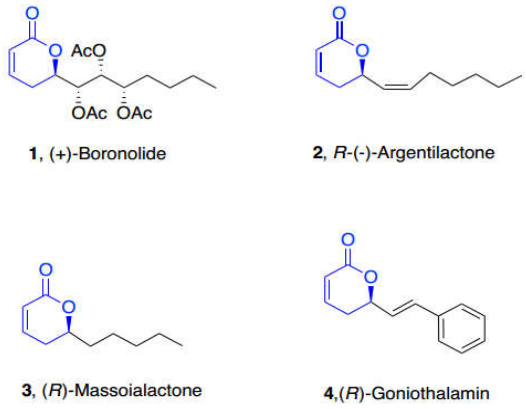

Figure 1. Examples of C-6 substituted (6R)-5,6-dihydro-2H-pyran-2-ones

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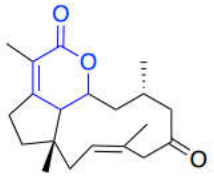
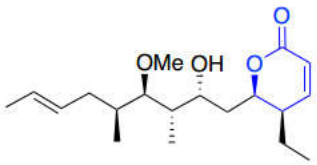
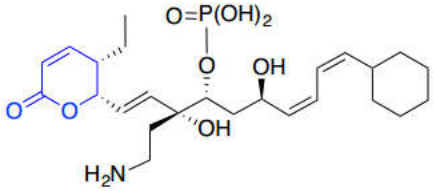
Some examples of more complex natural products containing this structural motif are Clavulactone, 5, an antitumoral lactone,[18] isolated from *Clavularia viridis* collected from Xisha Islands in the South China Sea (Figure 2).[19] (-)-Pironetin, 6, first isolated from the fermentation broth of *Streptomyces prunicolor*,[20,21] has shown anticancer activity.[22] Phoslactomycin B, 7, produced from the soil bacteria species *Streptomyces*, has antifungal and antitumor antibiotic activity.[23] (Figure 2).



5, Clavulactone



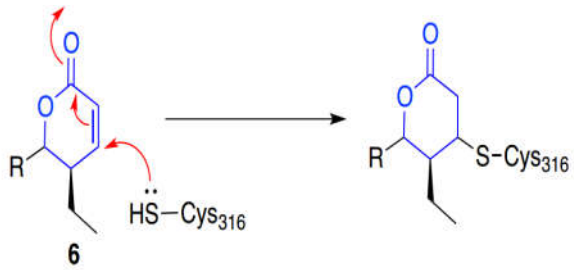
6, Pironetin



7, Phoslactomycin B

Figure 2. Natural products containing α, β-unsaturated δ-lactones

It is believed that the biological activity displayed by these lactones, is due to the presence of a Michael acceptor moiety (conjugated double bond) in their structures. Thus, it has been reported that Pironetin, 6, covalently binds to Cys316 of α-tubulin[24] (Scheme 1).

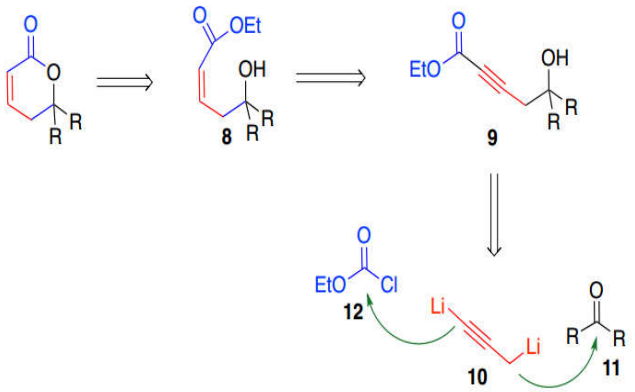


Scheme 1. Michael addition of Cys316 of α-tubulin to Pironetin, **6**.

Many methods for the asymmetric synthesis of C-6 substituted-δ-lactones have reported. We would like to report herein the preliminary results of a short and efficient protocol for the synthesis of C-6 disubstituted δ-lactones.

RESULTS AND DISCUSSION

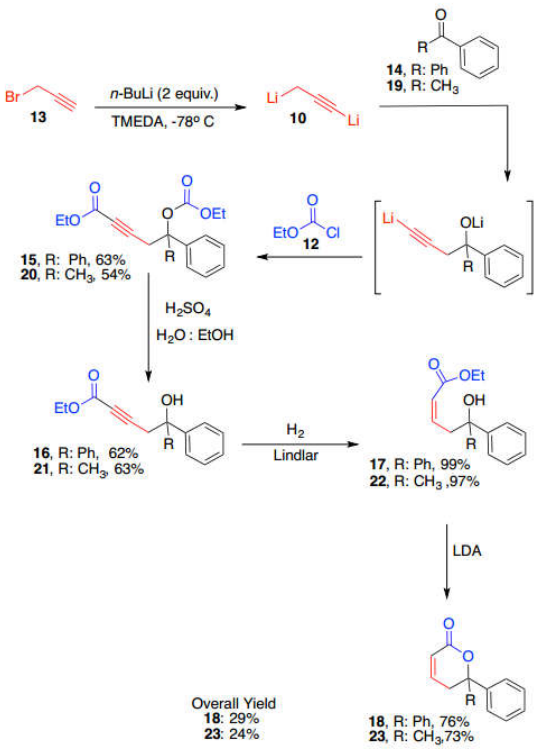
We envisioned that these C-6-disubstituted δ-lactones could be synthesized by the transesterification of hydroxy ester, 8, which in turn can be obtained from catalytic hydrogenation of homopropargyl alcohol, 9 (Scheme 2).



Scheme 2. Retrosynthetic analysis for the synthesis of C-6 disubstituted δ-hexenolides

We developed a procedure for the facile preparation of dianion 1,3-dilithiopropyne, 10, and its use in the efficient synthesis of homopropargyl alcohols.[25] When this dianion, 10, is reacted with aromatic aldehydes or ketones the corresponding homopropargyl alcohols are obtained in very high yields. In these cases, the reaction of 1,3-dilithiopropyne, 10, is very selective and only attack through its sp^3-carbon is observed. We demonstrated the selectivity of this species (10), by reaction with two different electrophiles, first at the "soft" propargyl position (sp^3-carbon) with an aromatic aldehyde or ketone, 11, and later at the "hard" acetylide anion with a second electrophile.

Thus, this protocol could be used for the "one-pot" formation of substrate 9, by reation of dianion, 10, with a ketone, 11, and later with ethyl chloroformate, 12 (Scheme 2). We decided to use the latter strategy to prepare homopropargyl alcohol, 9. Thus, we prepared 1,3-diltiopropyne, 10, by treatment of propargyl bromide, 13, with 2 equivalents of *n*-BuLi, in the presence of tetramethylethylendiamine (TMEDA) at -78°C (Scheme 3). The species obtained (10), was treated with benzophenone, 14, and the reaction mixture was allowed to reach room temperature in 2 hours. After this time, the reaction mixture was cooled to -78° C and treated with an ethereal solution of ethyl chloroformate, 12, and the mixture was allowed to warm to room temperature overnight. After treatment with NH_4Cl (aq), extraction (Et_2O), and purification by column chromatography, carbonate 15, was isolated in 63% yield (Scheme 3). This carbonate was treated with H_2SO_4 in a mixture H_2O: EtOH, under reflux for 5 hours and the corresponding alcohol, 16, was obtained in 62% yield. The hydroxy ester, 16, was reduced with hydrogen using Lindlar's catalyst to obtain the corresponding alkene, 17, in 99% yield. Finally, treatment of hydroxy ester, 17, with lithium diisopropylamide (LDA) afforded δ-lactone, 18, in 76% isolated yield, and with an overall yield of 29% from benzophenone, 14 (Scheme 3). To show the applicability of this new protocol, we repeated the synthetic procedure, using acetophenone, 19, as starting material. In this case, the corresponding lactone, 23, was obtained with an overall yield of 24%.



Scheme 3. Synthesis of 6,6-disubstituted δ-lactones **18** and **23**.

Experimental section

General Information: All glassware and syringes were dried in an oven ovemight at 140° C and flushed with nitrogen immediately prior to use. Transfers of reagents were performed with syringes equipped with stainless-steel needles. All reactions were carried out under a positive pressure of nitrogen. Nitrogen was passed through a Drierite gas-drying unit. Diethyl ether and tetrahydrofuran were refluxed and freshly distilled from sodium and potassium /benzophenone ketyl respectively, under nitrogen atmosphere. ^{1}H-NMR and ^{13}C-NMR spectra were recorded on a 400 MHz Bruker spectrometer. IR spectra were measured in a FT-IR Spectrum 1000 Perkin Elmer spectrometer. *n*-BuLi was titrated according to Watson and Easthman.[26]

General Procedure for the Preparation of Carbonates 15, 20: In a dry flask, under nitrogen, a solution of dry diethyl ether (12.4 mL), dry hexane (7.0 mL) and *n*-BuLi in hexanes (5.4 mL, 16.4 mmol) was cooled to -78° C and TMEDA added (0.62 mL, 4.1 mmol), followed by dropwise addition of propargyl bromide, **13**, (0.78 mL, 8.2 mmol) and the resulting mixture stirred for 20 minutes at this temperature. After this time a white precipitate formed. A solution of the ketone (3.90 mmol) in diethyl ether (5 mL) was added over 5 minutes and the reaction mixture was allowed to warm to room temperature over 2 h. After this time the mixture was cooled to -78° C and an ether solution (10 mL) of ethyl chloroformate, **12**, (1.90 mL, 19.9 mmol) added dropwise. After stirring for 16 h a saturated NH_4Cl solution was added and extracted with ether. The product was isolated by column chromatography.

Ethyl 5-[(ethoxycarbonyl)oxy]-5,5-diphenylpent-2-ynoate (15): ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.26 (t, 3H, *J* = 7.1 Hz), 1.27 (t, 3H, *J* = 7.1Hz), 3.86 (s, 2H), 4.14 (q, 2H, *J* = 7.1 Hz), 4.18 (q, 2H, *J* = 7.1 Hz), 7.26-7.37 (m, 10H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 14.0, 14.2, 29.9, 61.8, 64.0, 76.6, 83.3, 84.9, 126.4, 128.0, 128.2, 142.8, 152.8, 153.4; IR (KBr, cm^{-1}) 2985, 2361, 2342, 2242, 1751, 1705, 1495, 1448, 1369, 1284, 1237, 1077, 1010, 779, 760, 700.

Ethyl 5-[(ethoxycarbonyl)oxy]-5-phenylhex-2-ynoate (20). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.27 (t, 3H, *J* = 7.2 Hz), 1.29 (t, 3H, *J* = 7.2 Hz), 1.98 (s, 3H), 3.06 (d, 1H, *J* = 17.3 Hz), 3.22 (d, 1H, *J* = 17.3 Hz), 4.10 (q, 2H, *J* = 7.2 Hz), 4.20 (q, 2H, *J* = 7.2 Hz), 7.25-7.42 (m, 5 H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 14.5, 14.6, 25.5, 33.1, 62.3, 64.1, 82.8, 83.9, 124.8, 128.2, 128.7, 142.5, 152.9, 153.5; IR (film, cm^{-1}) 2985, 2240, 1750, 1712, 1497, 1449, 1370, 1253, 1168, 1073, 1008, 789, 765.

General Procedure for the obtention of Hydroxy Esters 16, 21: The corresponding carbonate (3.28 mmol of **15** or **20**) was dissolved in a mixture of water (25 mL) and ethanol (5mL). To this mixture was added H_2SO_4 (1 mL) and it was refluxed for 5 h. After this time, it was neutralized with $NaHCO_3$ (10%) and extracted with ether. The product was isolated by column chromatography.

Ethyl 5-hydroxy-5,5-diphenylpent-2-ynoate (16): ^{1}H-NMR (400 MHz, $CDCl_3$) d 1.28 (t, 3H, *J* = 7.0 Hz), 2.98 (s, 1H), 3.30 (s, 2H), 4.18 (q, 2H, *J* = 7.0 Hz), 7.25-7.45 (m, 10 H);IR (film, cm^{-1}) 3477, 3060, 2980, 2238, 1708, 1597, 1494, 1448, 1369, 1256, 1177, 1101, 757, 701.

Ethyl 5-hydroxy-5-phenylhex-2-ynoate (21): ^{1}H-NMR (400 MHz, $CDCl_3$) δ1.29 (t, 3H, *J* = 7.2 Hz), 1.69 (s, 3H), 2.40 (s, 1H), 2.81 (d, 1H, *J* = 17.3 Hz), 2.88 (d, 1H, *J* = 17.3 Hz), 4.19 (q, 2H, *J* = 7.2 Hz), 7.25-7.50 (m, 5H);^{13}C-NMR (100 MHz, $CDCl_3$) δ 14.4, 29.6, 35.3, 62.3, 73.7, 85.0, 124.8, 127.6, 128.6, 146.0, 153.8; IR (film, cm^{-1}) 3443, 3061, 2982, 2935, 2237, 1713, 1603, 1495, 1464, 1447, 1368, 1258, 1095, 1074, 1029, 1013, 949, 856, 765, 753, 700.

General procedure for the hydrogenation of hydroxy carbonates. Synthesis of ethyl acrylates 17 and 22: To a round-bottom flask with a septum, punctured with a needle bearing a balloon, was added the corresponding alkyne (1.29 mmol of 16 or 21), Lindlar's catalyst (75 mg), THF (37 mL) and a drop of quinoline. The flask was charged with hydrogen and the system was stirred for 16 hours at room temperature. The final product was purified by column chromatography.

Ethyl (Z)-5-hydroxy-5,5-diphenylpent-2-enoate (17): ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.29 (t, 3H, *J* = 7.4 Hz), 3.58 (s, 1H), 3.64 (dd, 2H, *J* = 7.4, 1.4 Hz), 4.19 (q, 2H, *J* = 7.4 Hz) 5.92 (dt, 1H, *J* = 11.7, 1.4 Hz), 6.19 (dt, 1H, *J* = 11.7, 7.4 Hz), 7.20-7.50 (m, 10H); IR (film, cm^{-1}) 3470, 3059, 2957, 2929, 1715, 1642, 1493, 1448, 1387, 1232, 1194, 1032, 752, 700.

Ethyl (Z)-5-hydroxy-5-phenylhex-2-enoate (22): ^{1}H-NMR (400 MHz, $CDCl_3$) δ1.39 (t, 3H, *J* = 7.4 Hz), 1.60 (s, 3H), 3.06 (ddd, 1H, *J* = 14.8, 7.6, 1.3 Hz), 3.23 (ddd, 1H, *J* = 14.8, 8.2, 1.3 Hz), 4.18 (q, 2H, *J* = 7.4), 5.90 (dt, 1H, *J* = 11.5, 1.3 Hz), 6.17 (ddd, 1H, *J* = 11.5, 8.2, 7.6 Hz), 7.25-7.50 (m, 5H).

General procedure for the lactonization of hydroxy esters. Synthesis of δ-lactones 18, 23. In a dry round-bottom flask, a cooled (-20° C) THF solution (4 mL) of diisopropylamine (0.1 mL, 0.5 mmol) was treated with *n*-BuLi (0.2 mmol, 0.5 mmol), and the mixture was stirred for 30 min. After this time, the hydroxy ester (**17** or **22**), dissolved in THF (3 mL) was added dropwise and allowed to react for 3 h. The crude reaction was

treated with NH_4Cl (aq) and extracted with ether. The product was purified by column chromatography.

6,6-Diphenyl-5,6-dihydro-2*H*-pyran-2-one (18): ^{1}H-NMR (400 MHz, $CDCl_3$) δ 3.25 (dd, 2H, *J* = 4.3, 1.8 Hz) 6.02 (dt, 1H, *J* = 9.7, 1.8 Hz), 6.9 (dt, 1H, *J* = 9.7, 4.3 Hz), 7.20-7.50 (m, 10H); ^{13}C-NMR ($CDCl_3$) δ 35.0, 86.0, 122.8, 125.9, 127.8, 128.5, 143.1, 143.8.

6-Methyl-6-phenyl-5,6-dihydro-2*H*-pyran-2-one (23): ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.74 (s, 3H), 2.80 (ddd, 1H, *J* = 18.5, 3.4, 2.4 Hz), 2.97 (ddd, 1H, *J* = 18.5, 5.0, 1.4 Hz), 6.01 (ddd, 1H, *J* = 9.8, 2.4, 1.4 Hz), 6.75 (ddd, 1H, *J* = 9.8, 5.0, 3.4 Hz), 7.25-7.40 (m, 5H);^{13}C-NMR (100 MHz, $CDCl_3$) δ 30.2, 35.4, 83.1, 121.7, 124.3, 127.4, 128.4, 143.3, 143.7, 164.0.

Conclusions

In summary, we have developed a new protocol of synthesis to convert ketones into the corresponding 6, 6-disubstituted α, β-unsaturated δ-lactones efficiently. The reaction of dianion 1,3-dilithiopropyne, 10, with ketones, followed by addition of ethyl chloroform ate, 12, afforded highly functionalized precursors (15, 20, Scheme 3) in "one-pot" synthesis. These precursors were used to obtain δ-lactones in good yields. This procedure involves only four synthetic steps from the corresponding ketone, to the final products.

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Conflicts of interest

The authors declare that there is no conflict of interest.

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