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Ethyl Alkynyl Ethers: A Convenient Ketene Source for Lactone Formation

Li Liang, Mahesh Ramaseshan, and David I. MaGee*

Department of Chemistry, University of New Brunswick
Fredericton, New Brunswick, Canada E3B 6E2

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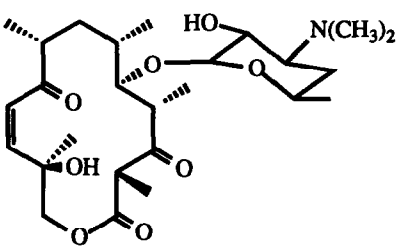
Abstract: A convenient and general method for the preparation of lactones of varying size via the intramolecular trapping of a ketene has been developed Simple thermolysis of various ethoxy acetylene derivatives at 150°C for 2 hours produced the desired compounds in yields ranging from 30%-75% The addition of tri-n-butylamine was required to achieve reasonable yields for medium and large rings

INTRODUCTION

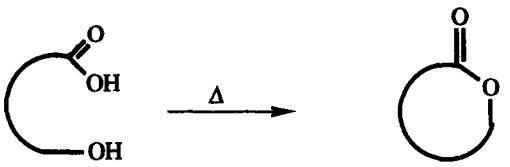
Lactones constitute a common class of compounds which are widely found in nature Interest in these natural products experienced a resurgence in the 1950's after Brockman an d'Henkel isolated the first macrolide antibiotic picromycin **1** from an *Actinomycess* culture[1] Since then, many lactonic products have been isolated from natural sources, and have attracted considerable attention due to their novel and potentially useful biological properties For instance they show antibiotic[2], antitumor and cytostatic action[3], anabolic and uterotrophic activity[4], and pheromone activity[5]



Picromycin **1**

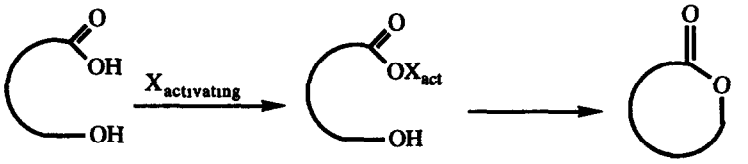
Due primarily to these biological properties, the synthetic chemist has devised several methods to construct these compounds The earliest, and perhaps most direct route, was first reported by Stoll and Rouvé[6] in which simple heating of a hydroxy acid furnished the corresponding lactone, albeit sometimes in low yield, (equation 1) Subsequent methods utilized an activated carboxyl group to substantially improve yields[7-14],

(equation 2). Other methods which do not involve carboxyl group activation have also been developed[14-19], but most of these strategies suffer from certain limitations. functional group non-compatibility, harsh reaction



(1)

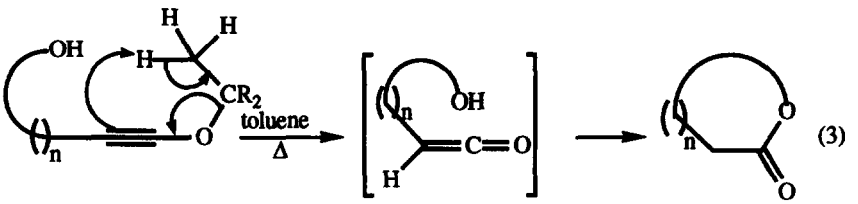
conditions or substrate specificity. A common theme in most of these methods, however, involves generation of activated complexes such that the carbonyl carbon becomes more electrophilic It occurred to us that an alternative strategy would be to produce a reactive intermediate from a neutral precursor, by photolytic or thermolytic means, which would subsequently cyclize in an intramolecular sense The ketene functionality appeared ideally suited for this approach.



(2)

There is literature precedence for this type of strategy, however, the evidence for a general reaction is rather conflicting at best[20-23]. Sato's results, when using thermally generated β-acyl ketenes, suggest that γ-lactones are formed efficiently, but the method fails for δ-lactone formation[20] Boeckman, on the other hand, has reported efficient formation of macrocyclic lactones when using the same β-acyl ketene precursors[21, 22] Wakefield demonstrated that both γ- and δ-lactones can be formed from photochemically generated ketenes[23], but no other examples were shown

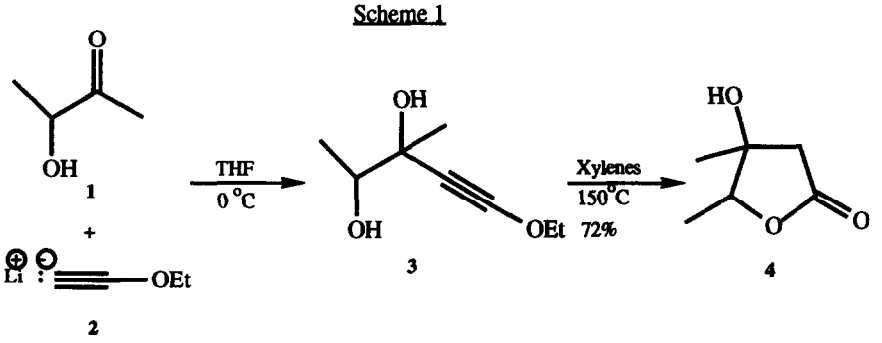
Arens[26, 27], however, demonstrated that various ethoxy alkynyl ether compounds, when thermolized, suffer a reto-ene reaction to generate a ketene and ethylene, which could be subsequently trapped by an alcohol in an intramolecular reaction to produce γ-butyrolactone in good yield[27], (equation 3 , n= 2, R=H) In a later report, Funk utilized the same technique to generate a macrocyclic lactone[24], (equation 3, n=12, R=CH_3) These are the only two reports, to our knowledge to use this technique for the construction of lactones Clearly this method shows promise, but to date no rigorous investigation as to its generality has been undertaken Herein we present our results on the scope of this potentially useful reaction



RESULTS AND DISCUSSION

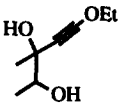
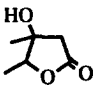
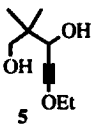
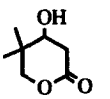
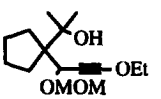
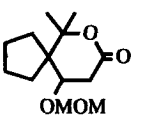
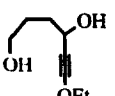
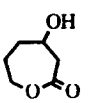
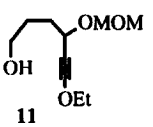
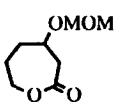
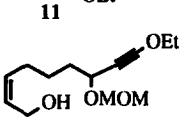
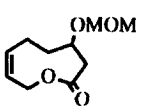
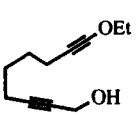
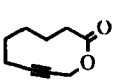
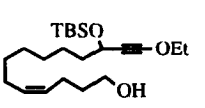
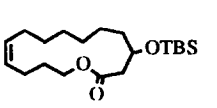
To test the potential of this approach we synthesized a simple precursor and initiated our studies (scheme 1)[28] Thermolysis of diol **3** in refluxing toluene for 6 hours produced γ-lactone **4** in moderate yield, but with only 50% conversion Clearly longer reaction times were needed with this solvent. However, simply changing the solvent to xylenes (150 °C compared to 120 °C) and shortening reaction times to 2 hours produced the same lactone **4** in 72% yield with no traces of starting material. Extreme care had to be exercised to remove all traces of water and ethanol from the solvent, or significant decomposition was observed. Encouraged by this result, we proceeded with our investigation, the results of which are presented in Table 1[29]

Scheme 1



Several points are worth noting about Table 1 First, *primary, secondary and tertiary alcohols cyclize efficiently* (compare entries 1, 2 and 3). In each of these three examples, no β-lactone products were formed, and if addition was done carefully, *no dimeric or oligomeric materials were observed* and ring sizes of 5, 6 and 7 form with equal ease and in good yields. Ether protecting groups on the β-hydroxyl group tolerate the reaction conditions, but acetate or benzoate groups undergo unwanted rearrangement reactions It is

Table 1

Entry	Substrate	Product [1]	Yield [2]
1	 3	 4	72%
2	 5	 6	76%
3	 7	 8	74%
4	 9	 10	62%
5	 11	 12	65%
6	 13	 14	30% [3]
7	 15	 16	50% [3]
8	 17	 18	49% [3]

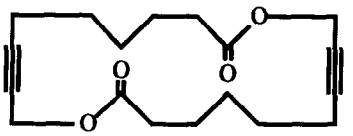
[1] All new compounds gave satisfactory ^{1}H, ^{13}C spectra, IR and HRMS analysis

[2] All yields are isolated, and unoptimized

[3] 10 equivalents of tri-n-butylamine was added to facilitate cyclization

interesting and surprising to note that the β-hydroxyl, or ether functionality appears to offer no advantages or disadvantages in helping to effect cyclization (compare entries 2 vs. 3 and 4 vs. 5).

Contrary to the above observations, when medium and large ring analogues were subjected to our normal protocol only di- and oligomeric products were observed. Although not totally unexpected, it was surprising to see no prduct formation Clearly we were faced with the problem of the rate of cyclization being much slower than the rate of side reactions Protection of the β-hydroxyl group led to no improvement. Pracejus has demonstrated that the addition of alcohols to ketenes can be catalyzed by the addition of tertiary amines[30], so we decided to investigate this possibility Indeed it was found that addition of *10 equivalents of tri-n-butylamine led to the production of the desired medium and macrocyclic lactones in moderate to good yields* (entries 6-8) These yields are comparable, and in some cases superior, to other literature methods[11, 12] (our synthesis of the ε-lactone, entry 5, gave 65% unoptimized yield of the monomeric lactone product, while the Corey procedure[11] gives 71% yield along with 7% of the dimeric lactone) It is worth noting that for entry 7, if extreme care was not taken in slow addition of the alcohol, then up to 10% of dimer **21** could be isolated. This was the only example where we observed this anomaly, which parallels the results of Deslongchamps in cyclization studies on related systems[31]



21

CONCLUSIONS

We have demonstrated the feasability of utilizing a ketene cyclization strategy for the construction of small, medium and large ring lactones. The method appears equally general and effective for the cyclization of 1°, 2° or 3° alcohols. To obtain acceptable yields for medium and large rings, 10 equivalents of tri-n-butylamine were required. Results for this method are comparable to existing ones, but mildness of formation and neutral reaction conditions should offer it as an attractive alternative. Further studies to extend this methodology are in progress

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EXPERIMENTAL

Unless indicated otherwise all reactions were conducted in flame dried or oven-dried (120°C) glassware under a nitrogen atmosphere Temperatures reported refer to external bath temperatures. All commercial reagents were purchased from Aldrich Chemicals (Milwaukee) and used without further purification Xylene (mixture of isomers) was dried according to established procedures[32]. Infrared spectra were recorded using NaCl cells, and are reported in wave numbers (cm^{-1}) High Resolution mass spectra are reported as follows m/z (parent ion or fragment, relative intensity). All ^1H and ^{13}C nuclear magnetic resonance (NMR) spectra have chemical shifts reported in ppm (δ) ^1H NMR data are reported as follows· chemical shift (multiplicity, number of protons, coupling constant in Hz) ^{13}C NMR data are reported as follows chemical shift (number of carbons) Analytical thin layer chromatography (TLC) was performed using Merck silica gel 60 F_{254} precoated glass plates (0.25 mm thickness). Column chromatography or "SiO_2 chromatography" was performed on Merck silica gel (230-400 mesh) according to the procedure of Still[33] Reagent grade solvents were used as eluant for all separations.

General procedure for small rings:: Preparation of γ-lactone **4**

In a base-washed 50 ml RBF, equipped with a reflux condenser, was put xylenes (15 ml) The flask was immersed in an oil bath and heated to 150°C, at which time diol **3** (100 mg, 0 64 mmol) in xylenes (2 ml) was added dropwise over 1/2 hour Following complete addition, the solution was refluxed for an additional 2 hours After cooling to room temperature, the solvent was removed *in vacuo* and the residue was purified by silica gel chromatography (2·1 hexane/ethyl acetate) to produce lactone **4** as a colorless oil (60 mg, 72%) ^1H NMR ($CDCl_3$) δ 4 48 (q, 1H, J=6 7), 2 61 (s, 2H), 1 37 (s, 3H), 1 30 (d, 3H, J=6 7); ^{13}C NMR ($CDCl_3$) δ 174 5 (1C), 85 4 (1C), 61 0 (1C), 43 1 (1C), 22 2 (1C), 16 0 (1C), IR (neat). 3440 (br), 2981 (m), 1766 (s), 1384 (s), 1200 (s), 1090 (s), 1059 (s), HRMS $C_6H_{11}O_3^+$ calc 131 0708, $C_6H_{11}O_3^+$ obs 131 0708 (m^+ + 1, 29 2)

Preparation of δ-lactone **6**

The corresponding diol **5** (100 mg, 0 58 mmol) was treated as described in the general procedure above Chromatography on SiO_2 (2:1 to 1.1 hexane/ethyl acetate) gave lactone **6** as a colorless oil (63 mg, 76%) ^1H NMR ($CDCl_3$) δ. 4.24 (d, 1H, J=11 2), 3 86 (d, 1H, J=11 3), 3 76 (t, 1H, J=5 7), 2.86 (dd, 1H, J=5 8, 12 9), 2.53 (dd, 1H, J=5.8, 12.9), 1 05 (s, 3H), 1.01 (s, 3H), ^{13}C NMR ($CDCl_3$) δ: 170 6 (1C), 75 2 (1C), 70 8 (1C), 36 6 (1C), 34.2 (1C), 22.4 (1C), 18 5 (1C), IR (neat) 3435 (br), 2966 (s), 2879 (m), 1738 (s), 1068 (m), 1050 (m); HRMS· $C_7H_{11}O_2$ calc 127 0759, $C_7H_{11}O_2$ obs. 127 0757 (m^+ - OH, 32 7).

Preparation of δ-lactone **8**

The corresponding tertiary alcohol **7** (168 mg, 0 62 mmol) was treated as described in the general procedure above Silica gel chromatography (3·1 hexane/ethyl acetate) gave lactone **8** as a colorless oil (112 mg, 74%). ^1H NMR ($CDCl_3$) δ· 4.70 (d, 1H, J=7 0), 4 65 (d, 1H, J=7 1), 4.03 (dd, 1H, J=8 5, 7.2), 3 39 (s, 3H), 3 02 (dd, 1H, J=8 6, 18 7), 2.55 (dd, 1H, J=8.6, 18 7), 1.70 (m, 8H), 1 37 (s, 6H), ^{13}C NMR ($CDCl_3$) δ 170 7 (1C), 96 4 (1C), 85 6 (1C), 75 8 (1C), 56 0 (1C), 51 3 (1C), 35 9 (1C), 34.3 (1C), 28.0 (1C), 27 5 (1C), 27.4 (1C), 25 9 (1C), 24 5 (1C), IR (neat) 2954 (s), 2895 (m), 2872 (m), 1733 (s), 1393 (m), 1277 (s), 1137 (s), 1037 (s), 982 (m), 963 (m), HRMS $C_{12}H_{19}O_4$ calc 227.1284, $C_{12}H_{19}O_4$ obs 227.1275 (m^+ - CH_3, 4 3)

Preparation of ε-lactone **10**

The corresponding diol **9** (250 mg, 1 58 mmol) was treated according to the general procedure described above Purification on SiO_2 chromatography (2 1 hexane/ethyl acetate) produced lactone **10** as a colorless oil (125 mg, 61%) ^1H NMR ($CDCl_3$) δ· 4 20 (m, 3H), 2 94 (m, 2H), 1 91 (m, 4H), ^{13}C NMR ($CDCl_3$) δ 173 0 (1C), 69 1 (1C), 64 8 (1C), 42 7 (1C), 36 5 (1C), 24.4 (1C), IR (neat) 3420 (s), 2938 (s), 1732 (s), 1433 (s), 1396 (s), 1291 (s), 1022(s); HRMS $C_6H_{10}O_3$ calc 130 1630, $C_6H_{10}O_3$ obs 130 0634 (m^+, 6 4)

Preparation of ε-lactone **12**

The corresponding diol **11** (90 mg, 0 45 mmol) was treated according to the general procedure described above Purification on silica gel chromatography (1 1 hexane/ethyl acetate) produced lactone **12** as a colorless oil (51 mg, 65%) ^1H NMR ($CDCl_3$) δ 4 70 (d, 1H, J=7 0), 4 62 (d, 1H, 7 0), 4 22 (m, 2H), 3 99 (m, 1H), 3 36 (s, 3H), 2 99 (dd, 1H, J=8.1, 13.7), 2 82 (dd, 1H, J=0 8, 13 7), 2 40-1.55 (m, 4H);

^{13}C NMR ($CDCl_3$) δ: 171.7 (1C), 94.1 (1C), 68.3 (1C), 68.2 (1C), 55.1 (1C), 39.5 (1C), 33.9 (1C), 23.9 (1C); IR (neat): 2975 (s), 2928 (s), 2896 (s), 2830 (m), 1732 (s), 1470 (m), 1390 (m), 1158 (s), 1033 (s), 911 (m); HRMS: $C_7H_{11}O_3$ calc 143.0708, $C_7H_{11}O_3$ obs. 143 0706 (m^+-OCH_3, 13.4)

General procedure for medium and macrocyclic compounds: Preparation of lactone **14**

In a 50 ml base-washed RBF, fitted with a condenser, was put xylenes (30 ml) and tri-n-butylamine (1.14 ml, 4.8 mmol). The flask and contents were immersed in an oil bath and heated to 150°C at which time alcohol **13** (115 mg, 0.48 mmol), in xylenes (2 ml) was added dropwise over 2 hours After complete addition, the solution was refluxed for an additional 2 hours, cooled, and washed with 10% HCl (2 x 25 ml), aqueous $NaHCO_3$ (1 x 25 ml), and brine (1 x 25 ml). Following drying ($MgSO_4$), evaporation of solvent *in vacuo*, and purification by silica gel chromatography (1.1 hexane/ethyl acetate), lactone **14** was obtained as a colorless oil (30 mg, 30%). ^1H NMR ($CDCl_3$) δ: 5 75 (m, 2H), 4.87 (dd, 1H, J=2.8, 13.0), 4 65 (s, 2H), 4 60 (dd, 1H, J=3.7, 10.2), 4.05 (m, 1H), 3 37 (s, 3H), 2.85 (dd, 1H, J=4 6, 13.2), 2.40 (dd, 1H, J=9.5, 13.2), 2.25 (m, 2H), 2.05 (m, 2H), ^{13}C NMR ($CDCl_3$) δ 172.3 (1C), 134 5 (1C), 126.7 (1C), 95 1 (1C), 75 0 (1C), 61.5 (1C), 55.5 (1C), 41 3 (1C), 34 0 (1C), 24 7 (1C), IR (neat). 2992 (m), 2889 (m), 1741 (s), 1640 (w), 1226 (s), 1150 (s), 1101 (s), 1046 (s); HRMS $C_9H_{13}O_3^+$ calc. 169.0865, $C_9H_{13}O_3^+$ obs 169.0869 (m^+ - OCH_3, 4 6)

Preparation of lactone **16**

The corresponding alcohol **15** (100 mg, 0.56 mmol) was treated according to the general procedure for medium ring formation Purification by silica gel chromatography (5·1 hexane/ethyl acetate) produced lactone **16** as a pale yellow oil (42 mg, 50%) ^1H NMR ($CDCl_3$) δ 4.65 (t, 2H, J=2.1), 2.39 (t, 2H, J=6 4), 2.26 (m, 2H), 1.69 (p, 2H, J=6.7), 1 53 (m, 4H), ^{13}C NMR ($CDCl_3$) δ· 173.0 (1C), 86. 9 (1C), 76 1 (1C), 52.5 (1C), 34.0 (1C), 27 4 (1C), 27 2 (1C), 24 2 (1C), 18.4 (1C); IR (neat) 2934 (s), 2236 (w), 1738 (s), 1430 (m), 1350 (s), 1125 (s), HRMS $C_9H_{12}O_2$ calc 152 0837, $C_9H_{12}O_2$ obs. 152 0840 (m^+, 19.9)

Preparation of lactone **18**

The corresponding alcohol **17** (100 mg, 0 26 mmol) was treated according to the general procedure for macrocyclic ring formation. Purification on SiO_2 chromatography (10.1 hexane/ethyl acetate) gave lactone **18** as a colorless oil (45 mg, 49%) ^1H NMR ($CDCl_3$) δ 5 48 (m, 1H), 5.29 (m, 1H), 4 15 (m, 2H), 4 05 (m, 1H), 2.52 (m, 2H), 2 37-1 19 (m, 16H), 0 89 (s, 9H), 0 08 (s, 6H), ^{13}C NMR ($CDCl_3$) δ 171.5 (1C),

131 4 (1C), 128 6 (1C), 68 9 (1C), 63 3 (1C), 43 5 (1C), 36 9 (1C), 29.7 (1C), 28 6 (1C), 27 7 (1C), 26 8 (1C), 26 1 (1C), 25 8 (3C), 23 5 (1C), 22.7 (1C), 18 0 (1C), 4 7 (2C); IR (neat)· 2927 (s), 2856 (s), 1735 (s), 1462 (m), 1256 (m), 836 (s), 775 (s), HRMS $C_{16}H_{29}O_3Si^+$ calc 297 1887, $C_{16}H_{29}O_3Si^+$ obs 297 1891 ($m^+ - C_4H_9$, 55 1)

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