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A Rapid Divergent Synthesis of Highly Substituted δ-Lactones

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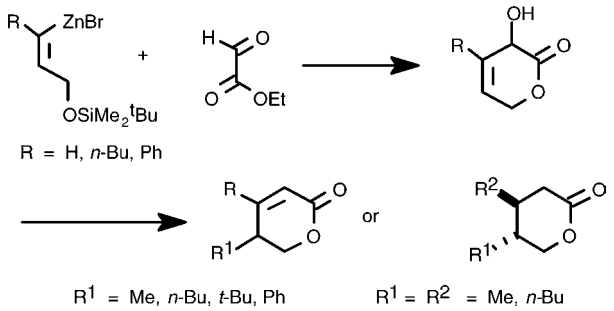
ABSTRACT



Nucleophilic 1,2-addition of (*Z*)-γ-silyloxyvinylzinc reagents to ethyl glyoxylate followed by desilylation and cyclization affords 3,6-dihydro-3-hydroxypyran-2-ones in good chemical yields. In situ formation of allylic phosphates followed by reaction with RCu(CN)Li reagents affords substituted 5,6-dihydropyran-2-ones. The parent compound, 3,6-dihydro-3-hydroxypyran-2-one, undergoes allylic phosphate formation, cuprate-mediated allylic substitution, and 1,4-conjugate addition to afford *trans*-4,5-disubstituted tetrahydropyran-2-ones in a one-pot process.

The δ-lactone moiety comprises structural subunits in a number of natural products, and substituted nonannulated δ-lactones are important both as naturally occurring compounds and in synthetic applications. Unsaturated 5,6-dihydropyran-2-one derivatives substituted at the 6-position, found largely in plants and bacteria, display antifungal, antitumor, and cytotoxic activity,[1] while the saturated analogues are aroma constituents of fruit and meat products.[2] Saturated tetrahydropyran-2-ones are also found in compactin and (+)-mevinolin (cholesterol biosynthesis inhibitors),[3] as prelactones which may serve as possible shunts in macrolide biosynthesis,[4] HMG-C-CoA reductase inhibitors,[5] the withasteroids,[6] and in the antitumor macrolide rhizoxin.[7] Rhizoxin reached Phase II clinical trials for the treatment of ovarian, colorectal, renal, breast, and melanoma cancers.[7] Tetrahydropyran-2-ones have been employed in the synthesis of amino sugars,[8] macrolides,[9] and the C16−C35 fragment of integramycin.[10] The Prelog−Djerassi lactone is an oxidative

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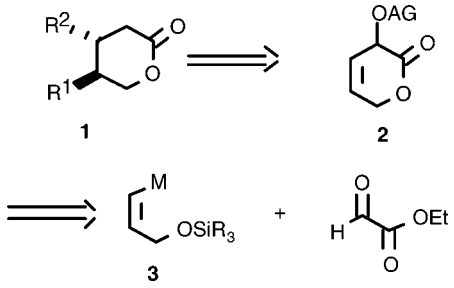
degradation product of several macrolide antibiotics and the many syntheses of this compound are illustrative of synthetic approaches to δ-lactones.[11]

Synthetic routes to 5,6-dihydropyran-2-ones include inverse-electron-demand Diels−Alder reactions,[12] Mukaiyama−aldol reactions of vinyl-substituted ketene acetals,[11] Pd(0)-catalyzed rearrangement[2] of (*Z*)-γ,δ-epoxy-α,β-enoates, Pd-promoted three-component coupling of allenoates, aldehydes, and aryl boronic acids[13] and from salts of 5-hydroxy-2-enoic acids.[14] Tetrahydropyran-2-ones have been prepared by the allylation of aldehydes,[3a,10] sequential reduction of β,δ-diketoesters,[9] desymmetrization of 1,3,5-trihydroxycyclohexane,[3b] aldol reactions involving dienolates,[5] or *N*-acyl oxazolidinones,[4f,8b] and alkylations of pyrrolidinyl hydrazones.[4d] They have also been prepared from 3,4-dihydro-δ-lactol ethers,[15] by Michael additions of allenyltitaniums to alkylidenmalonates,[16] via ring-closing reactions of 5-hydroxyalkynyl selenides,[17] by oxidation of tetrahydropyrans,[4a] via carbonyl alkylative transpositions of 5,6-dihydropyran-4-ones,[18] by conjugate addition reactions to 5,6-dihydropyran-2-ones,[19] and from diastereomerically pure 5-hydroxy esters.[20] 3,4-Dihydropyran-2-ones have been prepare by 1,4-additions of ketene acetals to enones[21] and can be converted to the tetrahydro derivatives by hydrogenation.

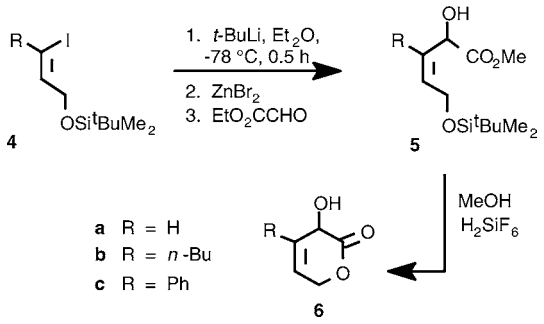
While several of the methodologies noted above are quite efficient, they all required modifications of the starting components in order to prepare a diverse array of δ-lactones (e.g., **1**). The ability to introduce a variety of substituents onto the 2-pyranone ring in a single pot operation would provide a combinatorial approach to the synthesis of substituted dihydro- and tetrahydropyran-2-ones. We envisioned utilization of a core dihydropyrone framework (e.g., **2**, AG = activating group) upon which a wide range of substituents could be introduced in a sequential fashion and perhaps in a single pot (Scheme 1). The strategy required sequential copper-mediated allylic substitution of **2** followed by conjugate addition. Conceptually, the unknown 3,6-dihydro-3-hydroxypyran-2-one (**2**) is available by addition of a γ-silyloxyvinyl organometallic reagent to ethyl glyoxylate. Additionally, *cis*-4,5-dialkyl-substituted tetrahydropyran-2-ones are potentially available from 4-substituted derivatives of **2**.

Scheme 1. Retrosynthetic Analysis for δ-Lactones



The requisite vinyl iodides **4a**−**c** were readily prepared from 2-alkynoates via (*Z*)-3-iodo-2-alkenyl esters[22a] by established procedures.[22] Metalation of **4b** with *t*-BuLi in THF resulted in the formation of (*E*) 3-trimethylsily-2-en-1-ol (91%) via rearrangement of the silyl group from oxygen to carbon. This retro-Brook rearrangement[23] could be prevented by carrying out the halogen−metal exchange reaction in Et_2O. Conversion of the vinyllithium reagents to vinylzinc species by addition of $ZnBr_2$ afforded organometallic reagents that underwent clean 1,2-addition to commercially available ethyl glyoxylate in good to excellent yields (Scheme 2, Table 1, entries 1, 3, and 4). These α-hydroxy esters **5a**−**c**

Scheme 2. Synthesis of 3,6-Dihydropyran-2-ones



were stable both at room temperature and when stored in the refrigerator.

Initial efforts to effect silyl ether deprotection and subsequent cyclization in a two phase CH_2Cl_2/fluosilicic acid (25% aqueous solution) gave only recovered starting material. Utilization of a homogeneous methanol solution afforded the previously unknown δ-lactones **6a**−**c** in very good to excellent yields (Table 1). Although these lactones were relatively stable, $CDCl_3$ NMR samples of **6b** underwent chemical changes upon standing.

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Table 1. 1,2-Additions of Vinyl Zinc Reagents to Ethyl Glyoxylate and Cyclization to δ-Lactones (Scheme 2)

entry	vinyl iodide	rxn cond[a]	alcohol	% yield[b]	lactone	% yield[b]
1	**4a**	A	**5a**	78−91	**6a**	80−90
2	**4b**	B	**5b**	34	**6b**	95
3	**4b**	A	**5b**	71−91	**6b**	72−91
4	**4c**	A	**5c**	88−86	**6c**	76−90

[a] A = Et_2O. B = THF/Et_2O (1:1). [b] Yields are based upon isolated products purified by column chromatography.

Application of cuprate substitution chemistry required conversion of the hydroxy substituent into a good leaving group. Attempted conversion to mesylates proved unsuccessful and initial efforts to prepare [$(PhO)_2P(O)Cl$, pyridine, 0 °C, 6 h] and isolate the allylic phosphates proved unsatisfactory. Product isolation generally gave a mixture of phosphate and starting alcohol and complex mixtures were obtained when the mixtures of allylic phosphates and starting alcohols were resubmitted to the phosphorylation reaction. In situ generation of the allylic phosphates [(i) *i*-Pr_2NLi, THF, −78 °C; (ii) $(PhO)_2P(O)Cl$, −78 to −20 or 0 °C.] followed by treatment of the reaction mixture with alkyl(cyano)cuprate reagents [i.e., $R^1Cu(CN)Li$] failed to give allylic substitution products. However, utilization of lithium hexamethyldisilazide (LiHMDS) in place of LDA afforded δ-lactone **8a** (57%) from **6b** and MeCu(CN)Li in modest yield. This protocol was successful with lactones **6b**,**c** which were deprotonated at −78 °C, quenched with $(PhO)_2P(O)Cl$ at −78 °C, and warmed to −20 to 0 °C before cannulation of the cuprate reagent into the reaction mixture. Deprotonation of lactone **6a** gave a precipitate and the solution was warmed to −20 °C to effect dissolution of the solid (2−6 h) before being cooled to −78 °C for addition of the chlorophosphate.

Lactones **6a**−**c** could be converted into α,β-unsaturated-δ-lactones **7**−**9** by utilization of LiHMDS for in situ phosphate formation followed by treatment of the allylic phosphate with specific cuprate reagents (Table 2). Although the lithium dialkycuprate (i.e., R_2CuLi) reagents failed to give the desired products in all instances, lithium alkyl(cyano)cuprate reagents gave good yields of di-substituted lactones **8** and **9** from allylic alcohols **6b**,**c**. The lactones **8a**−**d** and **9a**−**d** proved difficult to purify by column chromatography, since a phosphorus byproduct [i.e., *n*-$BuOP(O)(OPh)_2$] had nearly identical R_f values as the lactone.[24] Utilization of diethyl chlorophosphate [$(EtO)_2P(O)Cl$] resolved the purification problem. The optimized protocol readily generated lactones **8a**−**d** and **9a**−**d** in modest to good chemical yields from alcohols **6b**,**c** in a one-pot operation.

In situ formation of the allylic phosphate (i.e., **10**, vide infra) from lactone **6a** and subsequent reaction with lithium alkyl(cyano)cuprates gave low yields of lactones **7a**,**b** (Table 2, entries 1 and 3). Sequential treatment of the alkyllithium

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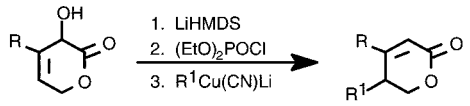
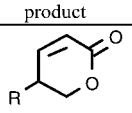
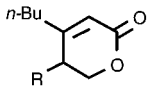
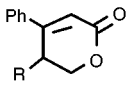
Table 2. Cuprate Mediated S_N2'-Substitutions on α-Phosphonoyl-β,γ-unsaturated-δ-lactones **6a**−**c**



6 **a** R = H; **b** R = *n*-Bu; **c** R = Ph

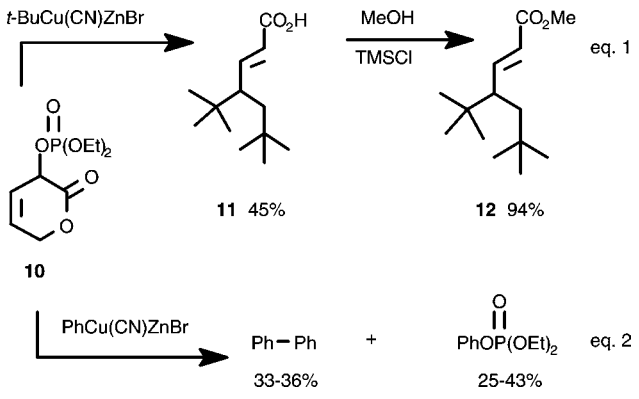
a R^1 = Me; **b** R^1 = *n*-Bu; **c** R^1 = *t*-Bu; **d** R^1 = Ph

7 R = H; **8** R = *n*-Bu; **9** R = Ph

entry	allylic alcohol	$(R^1)^a$	product	cmpd no.	% yield[b]
1	**6a**	Me		**7a**	30-40
2		Me[c]		**7a**	59-69
3		*n*-Bu		**7b**	31
4		*n*-Bu[c]		**7b**	49-70
5	**6b**	Me		**8a**	57-71
6		*n*-Bu		**8b**	50-72
7		*t*-Bu		**8c**	60
8		Ph		**8d**	61-66
9	**6c**	Me		**9a**	43-75
10		*n*-Bu		**9b**	68
11		*t*-Bu		**9c**	55-62
12		Ph		**9d**	77

[a] Ligand delivered from $R^1Cu(CN)Li$ unless otherwise noted. [b] Yields based upon isolated products purified by column chromatography and are given for the range of yields obtained for several reactions over the course of development. [c] Ligand delivered from $R^1Cu(CN)ZnBr$

reagents with $ZnBr_2$ and CuCN generated zinc alkyl(cyano)-cuprates [i.e., $RCu(CN)ZnBr$] that gave good chemical yields of 4-substituted-δ-lactones **7a**,**b** upon reaction with allylic phosphate **10** (Table 2, entries 2 and 4). The dialkylzinc cuprate, *n*-$Bu_2CuZnBr$, gave none of the desired product **7b**. Zinc cuprates prepared from *t*-BuLi or PhLi, however, gave a number of side reactions (eqs 1 and 2). Reaction of allylic phosphate **10** with *t*-BuCu(CN)ZnBr gave α,β-enoic acid **11** which was converted to ester **12**. The vicinal vinylic coupling constants for **11** (J = 15.6 Hz) and **12** (J = 15.6 Hz) are consistent with the (*E*)-isomer.[25] Thus, enoic acid **11** plausibly arises via intial cuprate mediated lactone cleavage followed by allylic substitution.



We next turned our attention to carrying out a one-pot tandem phosphorylation, cuprate-mediated allylic substitu-

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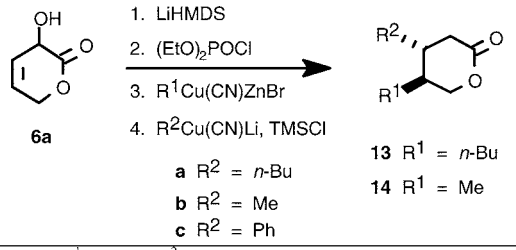
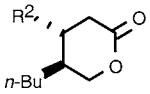
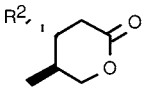
tion, and susbsequent cuprate-mediated 1,4-conjugate addition with allylic alcohol **6a**. In situ generation of **10** followed by subsequent treatment with two equivalents of *n*-BuCu(CN)ZnBr gave a mixture of **7b** (23%) and **13a** (40%). To deliver two different ligands to the 2-pyrone core, the second cuprate reagent must either be prepared separately and added to the reaction mixture or generated in situ in the presence of the dihyro-2-pyranone intermediate. After **10** was allowed to react with *n*-BuCu(CN)ZnBr (−78 to +25 °C), the reaction mixture was cooled to −78 °C and chlorotrimethylsilane was added followed by *n*-BuCu(CN)Li to afford **13a** (61%, Table 3, entry 1) in good yield after workup. Utilizing this protocol, two different alkyl substituents could be introduced onto the 2-pyrone framework in a one-pot operation (entries 2−4). Higher yields were not achieved when Me_3SiCl was added immediately after the addition of the RCu(CN)Li reagent. Attempted introduction of a phenyl substituent in the conjugate addition reaction gave none of the desired product (entry 5), and only small amounts of **7a** (20%) were isolated.

Table 3. Tandem Phosphorylation, Allylic Substitution, and Conjugate Addition from **6a**



entry	R^1	R^2	product	% yield
1	*n*-Bu	*n*-Bu		61
2	*n*-Bu	Me		59
			13a R^2 = *n*-Bu **b** R^2 = Me	
3	Me	*n*-Bu		65
4	Me	Me		55
5	Me	Ph		0
			14a R^2 = *n*-Bu **b** R^2 = Me **c** R^2 = Ph	

Tetrahydropyran-2-one **13a** was formed as a single diastereomer, while **14b** was formed as a 92:8 trans/cis mixture of diastereomers as evidenced by comparison with reported ^1H and ^{13}C NMR data for these known diastereomers.[26]

In summary, both 4-substituted and 4-unsubstituted 3,6-dihydro-3-hydroxypyran-2-ones **6a**−**c** are readily available by the 1,2-addition of 3-silyloxyvinylzinc reagents to ethyl glyoxylate. Activation of the hydroxyl substituent as the diethyl phosphate derivative permits cuprate mediated allylic substitution. The resulting 5-substituted or 4,5-disubstituted 5,6-dihydropyran-2-ones can be isolated and the 5-substituted derivatives used in subsequent conjugate addition reactions. The latter process can be carried out in a one-pot operation permitting the rapid construction of a wide range of 4,5-dialkyl-substituted tetrahydropyran-2-ones. Ongoing studies are aimed at the preparation of 4,5,6-trisubstituted tetrahydropyrones and extension of the methodology to asymmetric variations for the preparation of enantiomerically enriched δ-lactones.

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Supporting Information Available: General experimental information, general procedures A−E, experimental procedures for **4b**, **5a**,**b**, **6a**−**c**, and **12**, data reduction for **7a**,**b**, **8a**−**d**, **9a**−**d**, **13a**,**b**, **14a**,**b**, references, and ^1H and ^{13}C NMR spectra for **4b**, **5a**,**b**, **6a**−**c**, **7a**,**b**, **8a**−**d**, **9a**−**d**, **12**, **13a**,**b**, **14a**,**b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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