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Synthesis of (*E*)- and (*Z*)-α-Alkylidene-γ-aryl-γ-butyrolactones via Alkenylalumination of Oxiranes

P. Veeraraghavan Ramachandran,* Garrett Garner, and Debarshi Pratihar

Department of Chemistry, Purdue University, 560 Oval Drive, West Lafayette, Indiana 47907-2084

chandran@purdue.edu

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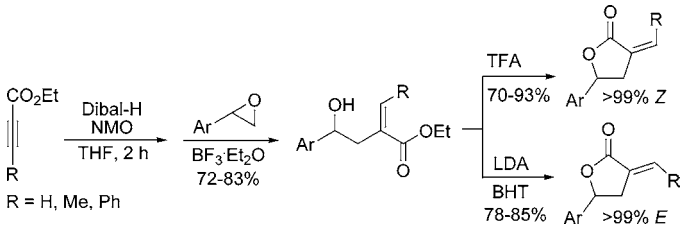
ABSTRACT



Alkenylalumination of substituted styrene oxides with [α-(ethoxycarbonyl)alkenyl]diisobutylaluminum, in the presence of BF_3·Et_2O, affords the corresponding (*Z*)-α-alkylidene-γ-aryl-γ-hydroxy esters in 81–100% *Z*-selectivity. Chromatographic separation of isomers, followed by lactonization with trifluoroacetic acid, provides isomerically pure (*Z*)-α-alkylidene-γ-aryl-γ-butyrolactones in 53–78% overall yield. Isomerization of the (*Z*)-alkylidene hydroxyl esters using LDA, followed by protonation using a bulky proton source, such as BHT, provides a simple route to the corresponding α-(*E*)-alkylidene-γ-phenyl-γ-hydroxy esters in 72–78% yield, which were cyclized to obtain the corresponding (*E*)-butyrolactones in 78–85% yield.

Interest in naturally occurring and synthetic α-alkylidene-γ-butyrolactones is surging[1] as several of them have been identified to display anti-inflammatory COX-2 inhibition, as well as phytotoxic and cytotoxic activities.[2] The binding of a series of suitably substituted γ-butyrolactones, particularly, γ-substituted-α-alkylidene-γ-butyrolactones, which are analogues of diacylglycerol (DAG) lactones, to protein kinase C (PK-C) displays an enhanced affinity due to the α-alkylidine group.[3] This family of lactones has also been tapped for their potential as versatile synthons.[4] Even though there are several protocols for their synthesis,[1,5] very few offer simple, direct routes.

We had previously reported the preparation of (*Z*)- or (*E*)-α-alkylidene-γ-alkyl-γ-butyrolactones via a crotylboration−oxonia-Cope process.[6] This method is restricted to the preparation of γ-alkyl derivatives since γ-aryl derivatives undergo a carbocation-mediated rearrangement to provide *cis*- or *trans*-β,γ-disubstituted-α-methylene-γ-butyrolactones

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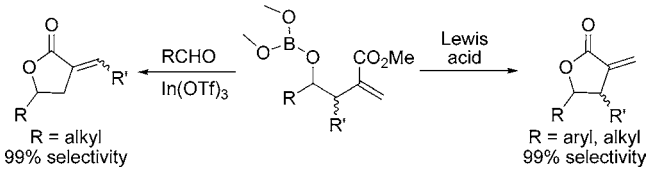
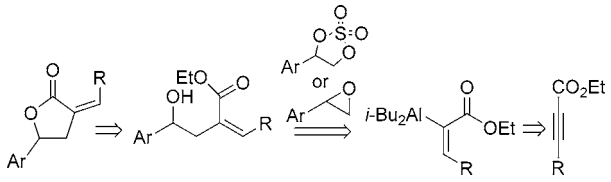
Scheme 1. Preparation of α-Alkylidene or α-Methylene-γ-butyrolactones



(Scheme 1).[7] We have designed an approach for the synthesis of the α-alkylidene-γ-aryl derivatives via the alkenylalumination[8] of oxiranes[9] or cyclic sulfates (Scheme 2) to overcome the above limitation. The results of our study follows.

Scheme 2. Retrosynthetic Analysis



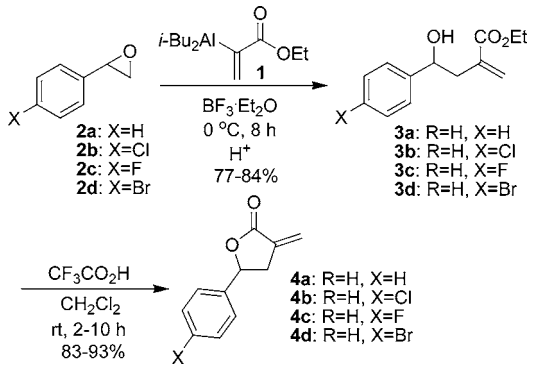
The reaction of [α-(ethoxycarbonyl)vinyl]diisobutylaluminum (**1**), prepared via the hydroalumination of ethyl propiolate with Dibal-H−NMO complex[10] and styrene oxide (**2a**) in tetrahydrofuran (THF) at room temperature (rt), failed to proceed even after 24 h. A solvent study was then conducted, involving diethyl ether, toluene, and pentane, but yielded no positive results. The lack of reactivity could be attributed to the complexation of NMO with aluminum,[8] preventing the necessary coordination of the epoxide. Indeed, our earlier studies have shown that the alkenylalumination of ketones can only be achieved with **1** in the presence of 1 equiv of BF_3-Et_2O.[8,10]

After screening different Lewis acids, such as Me_3Al, $Sc(OTf)_3$, $In(OTf)_3$, $Zn(OTf)_2$, $Ti(O^iPr)_4$, and $BF_3{\cdot}OEt_2$, it was evident that only $BF_3{\cdot}Et_2O$ was able to sufficiently activate the epoxide for the vinylalumination. A 1.3 equiv of $BF_3{\cdot}OEt_2$ was optimal, and additional equivalents did not increase the 82% yield of the homoallylic alcohol, ethyl 4-hydroxy-2-methylene-4-phenylbutanoate (**3a**).

Surprisingly, the reaction of the cyclic sulfate, prepared from styrene,[11] did not undergo vinylalumination even under the influence of Lewis acid catalysts.

Recently, reports on the lactonization of hydroxy esters of the type **3a** using trifluoroacetic acid (TFA) in dichloromethane have appeared,[12] although they are known to resist lactonization by simple acid or base hydrolysis.[13] Accordingly, the α-methylene-γ-hydroxy ester was dissolved in dichloromethane and treated with TFA for 2 h at rt to achieve γ-phenyl-α-methylene-γ-butyrolactone (**4a**) in 88% isolated yield (Scheme 3). The generality of the α-methylene-γ-aryl-

Scheme 3. Vinylalumination and Lactonization of Styrene Oxide



γ-butyrolactone synthesis was demonstrated by applying the epoxide opening−lactonization sequence to 4-chloro- (**2b**), 4-fluoro- (**2c**), and 4-bromostyrene oxides (**2d**) to provide the corresponding homoallylic alcohols in 84, 77, and 81% yields, respectively, and the resultant butyrolactones in 93, 91, and 83% yields, respectively (Table 1).

Table 1. Vinylalumination and Lactonization of Substituted Styrene Oxides[a]

	styrene oxide		homoallyl alcohol		γ-lactone	
entry	No.	X	No.	yield[b] (%)	No.	yield[b] (%)
1	**2a**	H	**3a**	82	**4a**	88
2	**2b**	Cl	**3b**	84	**4b**	93
3	**2c**	F	**3c**	77	**4c**	91
4	**2d**	Br	**3d**	81	**4d**	83

[a] Reaction conditions: styrene oxide **2** (3.0 mmol), $BF_3{\cdot}Et_2O$ (2.6 mmol) in **1** (2.0 mmol, in THF) at 0 °C for 8 h. Alcohol **3** (3.0 mmol), trifluoroacetic acid (3.3 mmol) in CH_2Cl_2 at rt for 2−10 h. [b] Isolated yields after chromatography.

We now focused on expanding this protocol to include the alkenylaluminum reagents owing to the importance of α-alkylidene-γ-butyrolactones. (*Z*)-[α-(Ethoxycarbonyl)-β-methylvinyl]diisobutylaluminum (**5**), prepared via the hydroalumination of ethyl-2-butynoate with Dibal-H−NMO complex in THF,[10] also reacted with styrene oxides **2a**−**d** in the presence of $BF_3{\cdot}Et_2O$, providing homoallylic alcohols **6a**−**d** in 76−82% yield with a *Z*/*E* ratio of 3:1 (Scheme 4,

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Scheme 4. Alkenylalumination−Cyclization of Substituted Styrene Oxides

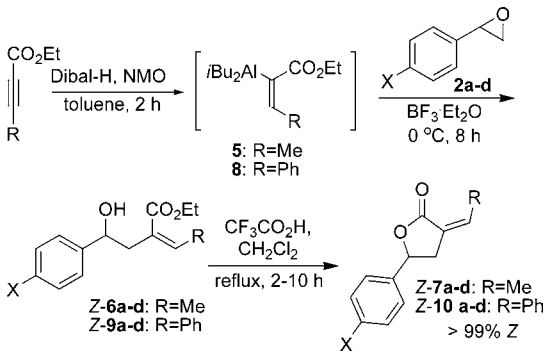


Table 2). The selectivity remained the same with Et_2O, dioxane, and pentane as solvents. A 4:1 selectivity was achieved in toluene, and this solvent was utilized for further reactions. A tentative mechanism for the predominant formation of the *Z*-isomer is given in Scheme 5.[13] Fortunately, the isomers could be readily separated by silica gel chromatography, and lactonization provided the corresponding isomerically pure α-(*Z*)-alkylidene-γ-phenyl-γ-butyrolactone (*Z*)-**7a**−**d** in 77−85% yields.

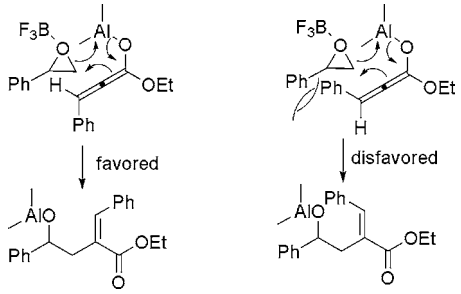
Table 2. Alkenylalumination and Lactonization of Substituted Styrene Oxides[a]

			homoallyl alcohol		lactone	
entry	reagent	styrene oxide	No.	yield[b] (%)	No.	yield[b] (%)
1	**5**	**2a**	(*Z*)-**6a**	76	(*Z*)-**7a**	82
2	**5**	**2b**	(*Z*)-**6b**	77	(*Z*)-**7b**	85
3	**5**	**2c**	(*Z*)-**6c**	81	(*Z*)-**7c**	84
4	**5**	**2d**	(*Z*)-**6d**	82	(*Z*)-**7d**	77
5	**5**[c]	**2a**	(*E*)-**6a**	72	(*E*)-**7a**	80
6	**5**[c]	**2b**	(*E*)-**6b**	73	(*E*)-**7b**	85
7	**5**[c]	**2c**	(*E*)-**6c**	77	(*E*)-**7c**	85
8	**5**[c]	**2d**	(*E*)-**6d**	78	(*E*)-**7d**	78
9	**8**	**2a**	(*Z*)-**9a**	74	(*Z*)-**10a**	79
10	**8**	**2b**	(*Z*)-**9b**	72	(*Z*)-**10b**	79
11	**8**	**2c**	(*Z*)-**9c**	76	(*Z*)-**10c**	70
12	**8**	**2d**	(*Z*)-**9d**	75	(*Z*)-**10d**	74

[a] Reaction conditions: styrene oxide **2** (3.0 mmol), BF_3•Et_2O (2.6 mmol) in **5** or **8** (2.0 mmol, in THF) at 0 °C for 8 h. Alcohol **6** or **9** (3.0 mmol), trifluoroacetic acid (3.3 mmol) in CH_2Cl_2 at reflux, for 2−10 h. [b] Isolated yields after chromatography. [c] Reaction conditions: alcohol **5** (3.0 mmol) added to LDA (12.0 mmol) in THF at −78 °C for 12 h. BHT (12 mmol) in THF added at −78 °C and warmed to rt.

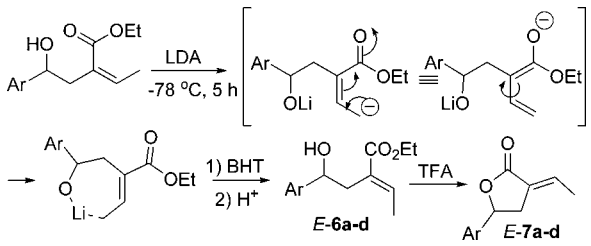
However, exclusive *Z*-selectivity was achieved during the ring opening of epoxides **2a**−**d** with [α-(ethoxycarbonyl)-β-phenylvinyl]diisobutylaluminum (**8**), generated via the hydroalumination of ethyl-3-phenylpropiolate. The α-benzylidene alcohols (*Z*)-**9a**−**d** obtained in 72−76% yields, upon lactonization, afforded the corresponding α-benzylidene-γ-butyrolactones (*Z*)-**10a**−**d** in 70−79% yields (Scheme 4, Table 2).

Scheme 5. Tentative Mechanism for the Predominant Formation of (*Z*)-Alkylidene Products via the Alkenylalumination of Styrene Oxides



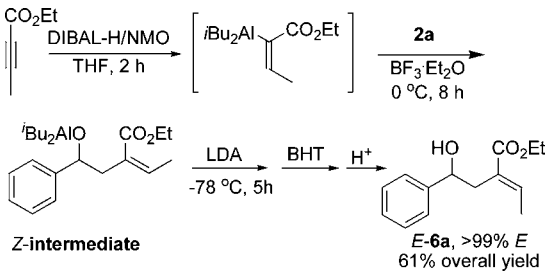
We then desired to prepare the corresponding the α-(*E*)-alkylidene-γ-aryl-γ-butyrolactones. Isomerization of crotonates using LDA is known,[14] and a bulky proton source, such as 2,6-di-*tert*-butyl-4-methylphenol (BHT), has been employed to preferentially protonate the less hindered position. Accordingly, the reaction of (*Z*)-**6a** with LDA, followed by treatment with BHT, provided the isomerized product (*E*)-**6a** in 95% yield. The isomerization process, aided by the chelation of the lithium to the oxygen anion, is illustrated in Scheme 6. Lactonization using trifluoroacetic acid, as in the case of (*Z*)-**6a**, provided (*E*)-**7a** in 82% yield.

Scheme 6. Isomerization−Cyclization of Substituted Styrene Oxides



A direct isomerization of the intermediate from alkenylalumination, without the need for the isolation of the homoallyl alcohol, provided 61% overall yield of (*E*)-**6a** (Scheme 7). We preferred the isomerization of the isolated

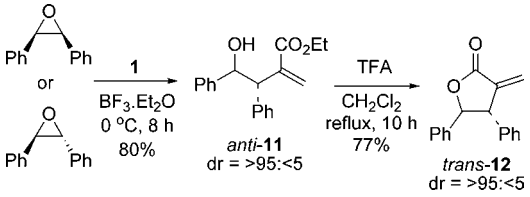
Scheme 7. One-Pot Alkenylalumination−Isomerization of Styrene Oxide



homoallyl alcohols to the one-pot synthesis since we achieved consistently higher overall yields. All of the (*Z*)-alcohols (*Z*)-**6b**−**d** were converted to (*E*)-**6b**−**d** and lactonized to (*E*)-**7b**−**d** in 78−85% yields.

Finally, we examined the alkenylalumination of 2,3-disubstituted oxiranes (e.g., stilbene oxide) with **1** for the preparation of β,γ-disubstituted-α-methylene-γ-butyrolactones. Interestingly, both (*E*)- and (*Z*)-stilbene oxides provided the *trans*-lactone, **12**, in 62% overall yield and >95% diastereoselectivity (Scheme 8). The formation of *trans*-**12** from both oxiranes can be rationalized via the formation of the benzylic carbocation in the presence of $BF_3{\cdot}Et_2O$ during alkenylalumination, followed by the formation of the thermodynamic hydroxy ester, *anti*-**11**.

Scheme 8. Alkenylalumination of 2,3-Disubstituted Oxiranes



In conclusion, we have achieved a convenient and general synthesis of α-(*Z*)-4-hydroxy-2-alkylidene-4-arylbutanoates via alkenylalumination of the corresponding 2-aryloxiranes using [α-(ethoxycarbonyl)alkenyl]diisobutylaluminum in the presence of BF_3-Et_2O. The corresponding α-(*E*)-4-hydroxy-2-alkylidene-4-arylbutanoates were achieved via the isomerization of the alkenylalumination intermediate or the homoallylic alcohol with LDA, followed by quenching with BHT. These hydroxy esters were lactonized using trifluoroacetic acid to provide the corresponding α-(*E*)- or α-(*Z*)-alkylidene-γ-phenyl-γ-butyrolactones in high yields. This reaction is amenable to scale-up and should find applications in natural product syntheses.

Supporting Information Available: Experimental procedures, characterization data, and copies of spectra for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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