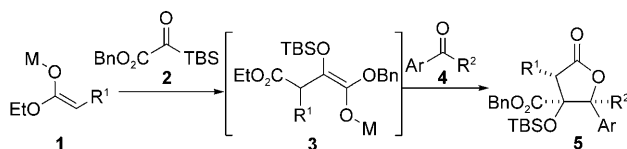


Diastereoselective Synthesis of Pentasubstituted γ -Butyrolactones from Silyl Glyoxylates and Ketones through a Double Reformatsky Reaction**

Stephen N. Greszler and Jeffrey S. Johnson*

The prevalence of γ -butyrolactone substructures in natural products continues to stimulate interest in the development of concise and selective methods for their preparation. The assembly of γ -butyrolactones that contain multiple stereocenters typically requires the synthesis of complex precursors through specialized routes.^[1] Modular assembly strategies that circumvent this limitation would be welcome additions to the synthetic toolbox. Herein, we report diastereoselective reactions of Reformatsky reagents, silyl glyoxylates, and ketones that provide densely functionalized pentasubstituted γ -butyrolactones containing three contiguous stereocenters. The reactions collectively constitute a rare example of the diastereoselective generation of vicinal stereogenic tertiary alcohols through aldolization.^[2]

Silyl glyoxylates are conjunctive reagents that participate in coupling reactions initiated by hydrides and nonstabilized carbon nucleophiles.^[2c,3] We examined the use of enolates and their equivalents in an effort to expand the range of nucleophilic promoters in transformations based on silyl glyoxylates. The projected transformation, outlined in Scheme 1, involves aldol addition to the silyl glyoxylate **2** to

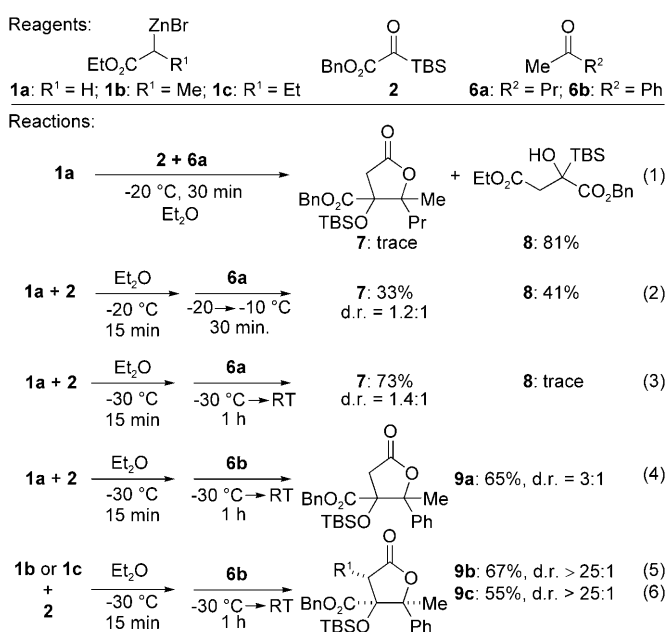


Scheme 1. Three-component lactone synthesis. Bn = benzyl, TBS = *tert*-butyldimethylsilyl.

expose, after a [1,2]-Brook rearrangement,^[4,5] a new enolate **3** capable of a second aldol reaction with an aldehyde or ketone electrophile. Lactonization would then provide γ -butyrolactone **5**.

Initial experiments with magnesium and lithium enolates provided complex product mixtures; the desired lactones or

their acyclic precursors were formed in low yield. We speculated that moderation of the enolate reactivity might be necessary and screened Reformatsky reagents under standard conditions.^[6–8] The use of zinc enolates in combination with the appropriate reaction temperature facilitated the development of a workable experimental protocol (Scheme 2). The hydroxysilane **8** was isolated as the predom-



Scheme 2. Optimization of the double Reformatsky reaction. General conditions for all reactions: enolate (1.5 equiv), ketone (2.0 equiv), **2** (1.0 equiv), $[\text{2}]_0 = 0.05\text{ M}$ in Et_2O . See the Supporting Information for further details.

inant product when the reaction was conducted at -20°C . This result reflects an inability of the initial zinc aldolate to undergo Brook rearrangement at this temperature [Scheme 2, Eq. (1)].^[9] We took advantage of this finding by forming the initial adduct between the Reformatsky reagent and the silyl glyoxylate at -20°C prior to the introduction of the ketone electrophile. Once the initial reaction between the silyl glyoxylate and the zinc enolate was complete, the addition of the ketone, followed by warming to -10°C for 30 min, gave the desired product **7** in 33% yield; however, **8** was still the major product [Scheme 2, Eq. (2)]. Optimal conditions involved this stepwise addition of the reagents, with an initial reaction temperature of -30°C ; the reaction mixture was then warmed to room temperature and stirred at this temperature for 1 h to afford the desired product in 73% yield along

[*] S. N. Greszler, J. S. Johnson
 Department of Chemistry
 The University of North Carolina at Chapel Hill
 Chapel Hill, NC 27599 (USA)
 Fax: (+1) 919-962-2388
 E-mail: jsj@unc.edu

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with only trace quantities of **8** [Scheme 2, Eq. (3)]. The impact of the counteranion on the facility of the Brook rearrangement remains a point of interest and development.^[9] The present example appears to involve an equilibrating mixture of C–Si and O–Si isomers: The warming of a solution of the unrearranged zinc aldolate to room temperature in the absence of a ketone electrophile resulted in a complex mixture that contained both the hydroxysilane **8** and the product derived from protonation of the enolate **3** in similar amounts.

Subsequent experiments were directed at improving the diastereoselectivity of the reaction. The use of the acetate-derived Reformatsky reagent **1a** in conjunction with acetophenone led to modest diastereoselectivity [d.r. 3:1; Scheme 2, Eq. (4)]; however, when the propionate reagent **1b** was used to initiate the reaction, the desired lactone product was obtained in 67% yield with d.r. > 25:1 [**9b**/all other diastereomers; Scheme 2, Eq. (5)]. Similar results were obtained with the Reformatsky reagent derived from ethyl 2-bromobutyrate [Scheme 2, Eq. (6)], but the use of the analogous isovalerate led to a low yield and complex diastereomer mixtures.^[10] The results with **1b** and **1c** were somewhat unexpected, as diastereoselectivities in Reformatsky reactions with simple ketones are generally modest.^[11] The use of other alkyl esters or other silyl groups in the silyl glyoxylate reagent generally led to lower yields and/or diastereoselectivities.^[12]

An examination of a variety of alkyl aryl ketones revealed favorable results within this subset of electrophile (Table 1). The yields of the isolated products ranged from 40 to 73% with diastereomer ratios from 7.5:1 to > 25:1. Surprisingly high selectivity was also observed in the formation of **10f** with benzoylthiophene. In contrast, the equivalent reaction with benzaldehyde provided the product **10m** with only 3:1 diastereoselectivity.

In cases in which modest yields were observed, the quenched glycolate enolate **3** comprised the majority of the mass balance; intermolecular proton transfer is a likely pathway with certain ketone electrophiles.^[10] The highly substituted γ -butyrolactones were purified conveniently in most cases through selective crystallization from pentane after column chromatography to afford the products as single diastereomers.^[12]

The high diastereoselectivity observed in the formation of isobenzofuranone **10q** (terminating electrophile: methyl 2-acetylbenzoate), which must result from lactonization via a different transition state, suggests that selective lactonization by one of a mixture of equilibrating stereoisomeric aldolates is probably not responsible for the remarkable diastereoselectivity. The alkyl group R^1 ($R^1 = \text{Me}$ in Scheme 3) in the substituted Reformatsky reagents is thus a likely determinant of the facial selectivity in the second Reformatsky reaction. In the present case, the ethyl ester could conceivably enforce the illustrated boat/twist-boat transition state^[11a] through chelation. This type of organized structure, **11**, provides a plausible rationalization for the high enolate facial selectivity insofar as an approach of the ketone *syn* to the hydrogen atom α to the ester group should be preferred.^[13] The model shown in Scheme 3 further supposes

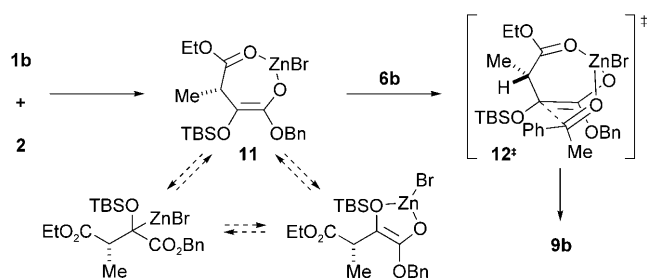
Table 1: Scope of the reaction in terms of the Reformatsky reagent and terminal electrophile.^[a,b]

$\text{EtO}-\text{C}(=\text{O})-\text{CH}(\text{R}^1)-\text{ZnBr} + \mathbf{2} \xrightarrow[2. \text{R}^2-\text{C}(=\text{O})-\text{R}^3, -30^\circ\text{C} \rightarrow \text{RT}]{1. \text{Et}_2\text{O}, -30^\circ\text{C}}$					
Product	Yield [%]	d.r.	Product	Yield [%]	d.r.
	52	11:1		40	12:1
	67	> 25:1		57	30:1
	46	> 25:1		53	> 25:1
	73	7.5:1		40	> 25:1
	70	18:1		68	3:1
	41	9.5:1		63	1.6:1
	48	> 25:1		71	–
	44	> 25:1		68	1.2:1
				51	20:1

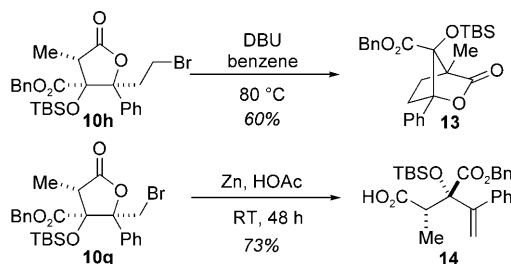
[a] Reagents: enolate (1.5 equiv), ketone (3.0 equiv), **2** (1.0 equiv), [**2**]₀ = 0.05 M in Et₂O. [b] See the Supporting Information for detailed procedures. Stereostructures were determined through NOESY experiments.

a pseudoequatorial orientation of the aryl group and an *E* enolate geometry (as in **12**⁺); however, it would be premature to discount alternative models (including those involving other structures of the organometallic intermediate) in the absence of more-complete experimental data.

The transformations shown in Scheme 4 further highlight the synthetic utility of this methodology. Alkylation occurred faster than dehydrohalogenation when **10h** was heated with DBU and resulted in the formation of the bicyclic lactone **13**, which contains three contiguous fully substituted stereogenic centers. A zinc-insertion/elimination reaction of bromolactone **10g** provided the γ,δ -unsaturated acid **14**, which can be



Scheme 3. Transition-state model.



Scheme 4. Secondary transformations of lactone products. DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene.

viewed formally as a product of glycolate enolate alkenylation.

In summary, we have developed a highly diastereoselective route to pentasubstituted γ -butyrolactones in the form of a double Reformatsky reaction of propionate enolates with silyl glyoxylates and aryl ketones. The moderate yields observed in certain cases are offset by the high level of structural complexity engendered: The reaction generates three contiguous stereocenters and two carbon–carbon bonds with unusually high diastereoselectivity. Second-stage transformations of the product lactones further enhance their synthetic utility.

Experimental Section

9b: A freshly prepared solution of the Reformatsky reagent **1b** (1.5 mL, 0.6 mmol, 1.5 equiv) was diluted with diethyl ether (4 mL), and the resulting solution was cooled to -30°C in an acetone/dry-ice bath. (The bath temperature was monitored with a thermocouple probe). The silyl glyoxylate **2** (112 mg, 0.4 mmol, 1.0 equiv) was placed in an oven-dried vial. The vial was then purged with N_2 , and diethyl ether (1 mL) was added. The resulting solution of **2** was added dropwise to the solution of the Reformatsky reagent over 2 min with a syringe. Additional diethyl ether (0.5 mL) was used to rinse the vial. When the consumption of the silyl glyoxylate was complete (generally 10–15 min at -30°C , as determined by TLC), acetophenone (**6b**; 0.140 mL, 1.2 mmol, 3.0 equiv) was added, and the reaction mixture was allowed to warm to 0°C in the acetone bath over 45 min. The reaction mixture was then stirred at room temperature for 30 min, diluted with diethyl ether (5 mL), and quenched with saturated ammonium chloride (1 mL). The resulting mixture was stirred until a clear solution was obtained. The organic layer was removed, and the aqueous layer was extracted with diethyl ether (3×5 mL). The combined organic extracts were washed with brine (5 mL), dried with magnesium sulfate, and concentrated in vacuo. The residue was purified by flash chromatography (hexanes/ethyl acetate 9:1), and the product was crystallized from pentane to give **9b** (121 mg, 69%) as

transparent colorless crystals. Additional details and full characterization data are presented in the Supporting Information.

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