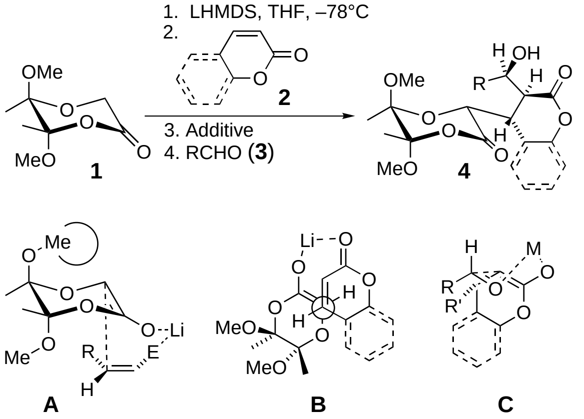
Consecutive Three- and Four-Component Coupling Reactions with Anions Generated from a Butane Diacetal Desymmetrized Glycolic Acid Derivative**

Darren J. Dixon, Steven V. Ley,* and Félix Rodríguez

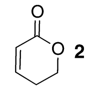
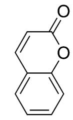
The impressive progress made in the last few years in high-throughput screening of compounds for biological testing has driven synthetic chemists to develop new procedures and technologies for the production of diverse arrays of compounds in a fast, clean, and efficient way. Among these procedures, the sequential coupling reactions (domino or consecutive) offer the opportunity of building up large libraries of complex molecules from simple substrates within a short time and with an important reduction in production costs and in the amount of waste generated.[1] For these reasons, the sequential processes extend far beyond an academic pursuit[2] by providing a rapid solution to the synthesis of new, functionally dense skeletal arrangements which may exhibit desirable biological properties. Notable sequential reactions include the four-component Ugi reaction[3] and the MIMIC chemistry introduced by Posner et al.[4] However, although these methods create desirable functional group density around a central core, more often than not these processes lack stereocontrol and lead to mixtures of diastereomers. Furthermore, such reactions are rarely enantioselective and yield racemic products. Clearly, a significant advancement in this field would be provided by sequential coupling processes in which the products are formed as single diastereomers and enantiomers.[5] To this end we have investigated the use of butane diacetal (BDA) desymmetrized glycolic acid derivative **1** (Scheme 1) for reactions of this type. This was partly a result of the abundance of biologically and pharmacologically significant α-hydroxy acids,[6] but more importantly because of the excellent levels of stereocontrol imparted by this building block in lithium enolate alkylation,[7] aldol,[8] and Michael[9] reactions to give a variety of enantiopure α-hydroxy acids. It was our view that **1** would not only be the sole source of asymmetry but would also govern the relative stereochemistry in the subsequent C–C bond-forming reactions. Herein we report new stereoselective one-pot consecutive reactions starting with anions generated from **1**. This strategy has allowed us to produce, in a single step, α-hydroxy acids with up to five new stereogenic centers in high yield and in high diastereomeric excesses.

Treatment of **1**[7] with one equivalent of lithium hexamethyldisilazide (LHMDS) in THF at $-78\,^{\circ}$C, followed by the addition of one equivalent of α,β-unsaturated lactones **2**, and after 30 min the addition of another electrophile coupling partner (e.g. aldehydes **3**) led to the three-component coupling products **4** as a mixture of only two diastereomers (Scheme 1; Table 1, entries 1, 3, and 5; only the major diastereomer is depicted). Moreover, when the reaction was carried out in the presence of one equivalent of trimethyl borate, the selectivity of the reaction was increased to give compounds **4** with d.r. values as high as 5.2:1 (Table 1, entries 2, 4, and 6).



Scheme 1. α-Hydroxy acid derivatives **4** from the one-pot consecutive Michael–aldol reaction initiated with the enolate derived from **1**. R′ = BDA moiety.

Table 1. Three-component coupling products **4** obtained according to Scheme 1.

Entry	2	R	Additive	Product	Yield [%][a]	d.r.[b]
1	 **2a**	Ph	–	**4a**	74	2.8:1
2	**2a**	Ph	$B(OMe)_3$	**4a**	72	4.0:1
3	**2a**	4-MeO-C_6H_4	–	**4b**	66	2.5:1
4	**2a**	4-MeO-C_6H_4	$B(OMe)_3$	**4b**	63	5.2:1
5	 **2b**	4-MeO-C_6H_4	–	**4c**	73	3.2:1
6	**2b**	4-MeO-C_6H_4	$B(OMe)_3$	**4c**	64	3.3:1

[a] Yield based on starting BDA desymmetrized glycolic acid derivative **1**. [b] Ratio determined by means of ^{1}H NMR spectroscopy.

The structures of compounds **4** (major and minor diastereomers) were determined by means of NMR spectroscopy and confirmed by X-ray crystal structure analysis.[10] These studies indicate that the only difference between the two diastereomers is the stereochemistry of the carbon atom that bears the hydroxy group formed in the final aldol reaction. Surprisingly, the major diastereomers contain a *syn* β-hydroxycarbonyl structure, which is not the expected product from an aldol reaction between an *E* enolate and an aldehyde, according to the Zimmerman-Traxler chairlike transition-state model.[11] The stereochemical outcome of the reaction can be explained as follows: first, the Michael acceptor approaches the lithium enolate derived from glycolate **1** from

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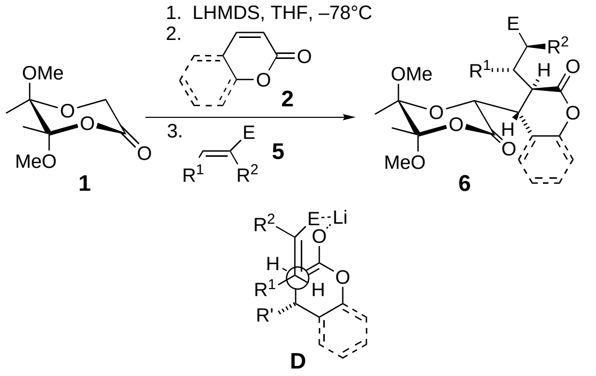
[**] We gratefully acknowledge financial support from the EPSRC (to D.J.D.), the EU (Marie Curie Fellowship to F.R.), and the Novartis Research Fellowship (to S.V.L.). We are also indebted to Dr. John E. Davis for the X-ray crystal structure determinations.

the face opposite the axial 1,3-related methoxy group (see **A** in Scheme 1). Moreover, the configurational assignment of the products is compatible with a combination of the two trigonal centers involved in this reaction according to the model shown in **B** (Scheme 1).[12] This first reaction proceeded with very high diastereoselectivity to give a new lithium enolate intermediate.[13] The reaction of this newly formed enolate with the aldehyde to give mainly the *syn* aldol product can be explained through the closed twist-boat transition state shown in **C** (Scheme 1).[14, 15]

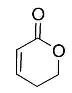
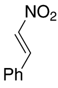
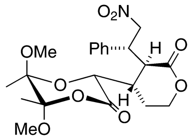
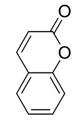
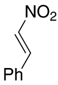
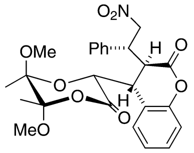
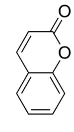
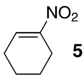
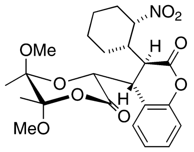
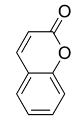
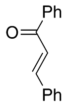
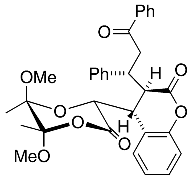
Encouraged by the results obtained in the one-pot Michael – aldol reaction described above and to extend the scope of this methodology, we decided to investigate the one-pot Michael – Michael three-component coupling reaction. Thus, treatment of the enolate derived from **1**, generated as above, with α,β-unsaturated lactones **2**, followed by reaction with a second Michael acceptor **5** gave the highly functionalized α-hydroxy acid derivatives **6** in high yields (Scheme 2). When 5,6-dihydro-2*H*-pyran-2-one **2a** was used as the first Michael acceptor, a mixture of only two diastereomers was obtained (3:1 ratio; Table 2, entry 1). Pleasingly, when the reaction was carried out with coumarin **2b** as the first Michael acceptor, selectivities higher than 20:1 were observed (Table 2, entries 2 – 4). The structures of the major and minor diastereomers of **6a**, as well as compounds **6c** and **6d**, were unequivocally determined by X-ray structure analysis.[10] The stereochemical outcome of the process can be explained, in the first steps of the reaction, as previously described for the case of the Michael – aldol reaction (see **A** and **B** in Scheme 1). The second Michael addition seems to occur through the closed (chelated) transition state model shown in **D** (Scheme 2) and previously proposed for related reactions.[12]



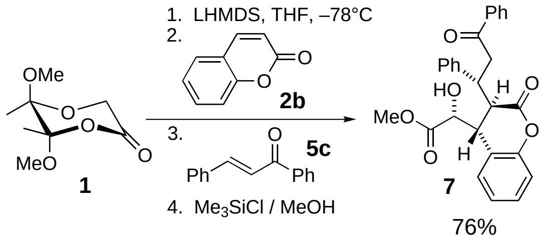
Scheme 2. α-Hydroxy acid derivatives **6** from the one-pot consecutive Michael – Michael reaction initiated with the enolate derived from **1**. R′ = BDA moiety.

We were also intrigued by the possibility of incorporating a new component into the reaction sequence with the concomitant removal of the BDA protecting group. Thus, we investigated the one-pot four-component coupling reaction described in Scheme 3. Consecutive reaction of the enolate derived from **1** with coumarin **2b** followed by reaction with *trans* chalcone **5c** and final treatment with chlorotrimethylsilane in methanol gave α-hydroxy acid derivative **7** in excellent yield (76 %) and diastereoselectivity (> 20:1) in a single step.

Table 2. Three-component coupling products **6** obtained according to Scheme 2.

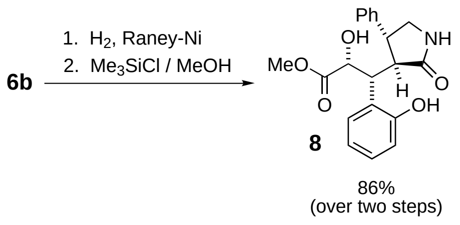
Entry	2		5		Product		Yield [%][a]	d.r.[b]
1		**2a**		**5a**		**6a**	80	3:1
2		**2b**		**5a**		**6b**	81	> 20:1
3		**2b**		**5b**		**6c**	90	> 20:1
4		**2b**		**5c**		**6d**	95	> 20:1

[a] Yield based on **1**. [b] Ratio determined by means of ^{1}H NMR spectroscopy.



Scheme 3. α-Hydroxy ester **7** from the one-pot consecutive Michael – Michael – Michael reaction initiated with the enolate derived from **1**.

The synthetic utility of some of these multicomponent coupling products is illustrated by the transformation of compound **6b** into γ-lactam **8** through the sequential nitro reduction/cyclization process shown in Scheme 4. The highly functional compound **8** is readily prepared and combines α-hydroxy acid, γ-lactam, phenol functionalities, and four stereogenic centers in its structure.[6, 16] Furthermore, these functional groups could be modified to lead to even larger arrays of compounds.



Scheme 4. Highly functionalized γ-lactam **8** from compound **6b**.

In summary, BDA desymmetrized glycolic acid has proved to be an interesting reagent in one-pot, consecutive, three- and four-component coupling reactions. Highly functionalized α-hydroxy acid derivatives are obtained in good yields and with high diastereoselectivities from simple and readily available starting materials. The simplicity of the method should allow the synthesis of large libraries of compounds with potential biological activity in an easy, fast, clean, and efficient way. Investigations along these lines as well as on the mechanisms of the reactions and the applications of this methodology in the synthesis of natural products are underway in our laboratories.

Experimental Section

Representative procedure for the preparation of **7**: A solution of lithium hexamethyldisilazide in THF (1M, 0.20 mL, 0.20 mmol) was added dropwise to a solution of **1** (0.038 g; 0.20 mmol) in THF (0.5 mL) at −78 °C. The resulting pale yellow solution was stirred for 10 min at the same temperature, and then a solution of coumarin **2b** (0.032 g; 0.22 mmol) in THF (0.5 mL) was added dropwise at −78 °C. After 30 min, a solution of *trans* chalcone **5c** (0.045 g, 0.22 mmol) was added dropwise. The reaction mixture was stirred for a further 30 min at the same temperature, and then a solution of trimethylsilyl chloride (0.31 mL) in methanol (5 mL) was added at −78 °C. The reaction mixture was warmed to room temperature overnight. The solvents were removed in vacuo to give the crude product, which was purified by column chromatography (1:1 petroleum ether/ethyl acetate) to afford pure **7** (0.063 g, 76 %): $[\alpha]_D^{25} = +30.5$; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.75-6.69$ (m, 14H; ArH), 4.15 (dd, $J = 5.9$, 3.1 Hz, 1H; C*H*OH), 3.61 (s, 3H; OCH_3) 3.48 (d, $J = 6.6$ Hz, 2H; CH_2CO), 3.29 (dt, $J = 11.6$, 6.6 Hz, 1H; CHPh), 3.14 (dd, $J = 11.6$, 1.0 Hz, 1H; $CHCO_2$), 2.88 (d, $J = 3.1$ Hz, 1H; OH), 2.81 (d, $J = 5.9$ Hz, 1H; C*H*CHOH; unresolved coupling to $CHCO_2$); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 197.2$, 172.2, 169.2, 152.2, 140.6, 136.7, 133.0, 129.0, 128.4, 127.9, 127.8, 124.6, 117.7, 74.7, 52.6, 49.1, 43.5, 42.9, 39.8; HRMS (EI): calcd for $C_{27}H_{24}O_6NNa$ $[M+Na]^+$: 467.1471, found: 467.1481.

Received: September 5, 2001 [Z17855]

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Total Synthesis of Nominal Diazonamides—Part 1: Convergent Preparation of the Structure Proposed for (−)-Diazonamide A**

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In 1991 Fenical, Clardy and co-workers reported the composition and skeletal stereochemistry of two unique toxins extracted from tissues of the marine invertebrate *Diazona angulata*.[1] The structure of the major isolate, termed diazonamide B (**1b**, Scheme 1), was given from X-ray diffraction measurements on a crystal of derived *p*-bromobenzamide **2**. The acylation of **1b** purportedly caused dehydration of its C11 hemiacetal, which leaves the configuration at this position the one noted ambiguity in an analysis that included designation of absolute stereochemistry. The core of the minor metabolite was subsequently assigned by analogy and a complete proposal (**1a**) made more consistent with available

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[**] Funding provided by the NIH (RO1-GM60591), the NSF (CAREER 9984282), the Howard Hughes Medical Institute (junior faculty support), the Robert A. Welch Foundation, and the Advanced Research Program of the Texas Higher Education Coordinating Board.