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Straightforward Enantioselective Access to γ-Butyrolactones Bearing an All-Carbon β-Quaternary Stereocenter

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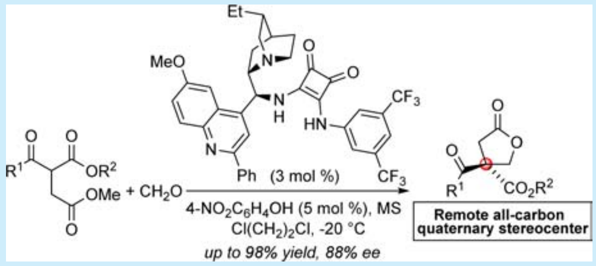
Supporting Information

ABSTRACT: An enantioselective one-pot aldol/lactonization sequence has been developed to access highly challenging γ-butyrolactones bearing an all-carbon quaternary stereocenter at the β-position by reacting acylated succinic esters with aqueous formaldehyde in the presence of 3 mol % loading of a cinchona alkaloid-derived squaramide providing direct access to paraconic acid derivatives in high yield and fairly good level of enantioselectivity (up to 88% ee).



γ-Butyrolactones bearing different stereocenters are extensively found motives in natural products, displaying a wide range of biological activities spanning from antifungal and antibiotic to anticancer.[1] Intensive efforts have been devoted to develop stereoselective approaches to these targets.[2] However, among them, only a few routes to enantioenriched γ-butyrolactones, bearing a one carbon quaternary stereocenter at the β-position, were reported, mainly through multistep preparation.[3] The synthesis of these targets is particularly challenging due to (i) the installation of an all-carbon quaternary stereocenter in an enantioselective fashion[4] and (ii) the remote position of the stereocenter, far from more easily controllable α- and γ-positions.

Recently, Cossy and Arseniyadis illustrated a palladium-catalyzed allylic alkylation of dienol carbonates to enantioenriched butenolides, which were then converted, in a two-step reduction/oxidation sequence, into β,β-disubstituted γ-butyrolactones (Figure 1, eq 1).[5] At the same time, Sun and Chen reported a chiral phosphoric acid catalyzed intramolecular desymmetrization of 1,3-diol tethered to an acetal to give five-membered acetals as the starting material useful to prepare enantioenriched β,β-disubstituted γ-butyrolactones (Figure 1, eq 2).[6] In both these elegant approaches, γ-butyrolactones were obtained from enantioenriched precursors after further derivatization with fairly good level of enantioselectivity (80–90% ee). It would be highly desirable to prepare these targets in a direct manner. In this context, the asymmetric Baeyer–Villiger reaction of 3-disubstituted cyclobutanones has been exploited to obtain β,β-disubstituted γ-butyrolactones, although with modest enantiocontrol (29–61% ee).[7]

We have been interested in the development of asymmetric methodologies for carbon-heteroatom and carbon–carbon bond formation, using easily accessible bifunctional organocatalysts.[8]

It is generally accepted that typical promoters, such as chiral amine–thioureas and amine–squaramides, activate pronucleophiles via general base catalysis and electrophiles via general acid catalysis in a variety of mechanistically different transformations.[8a,9] We envisaged a simple aldol/lactonization organocatalytic cascade sequence to access β,β-disubstituted γ-butyrolactones starting from acylated succinic esters and formaldehyde (Figure 1, eq 3). A prochiral enolate of acylated succinic esters would react in a chiral environment with formaldehyde to give an enantioenriched aldol product followed by lactonization to the desired γ-butyrolactone. Herein, we illustrate our success in developing a straightforward enantioselective route to synthetically useful β,β-disubstituted

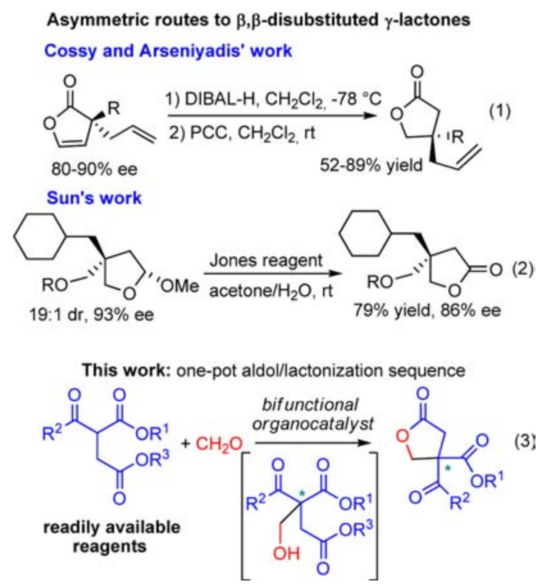


Figure 1. Asymmetric approaches to β,β-disubstituted γ-butyrolactones.

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γ-butyrolactones[10] starting from easily available reagents catalyzed by cinchona alkaloid-derived squaramides.

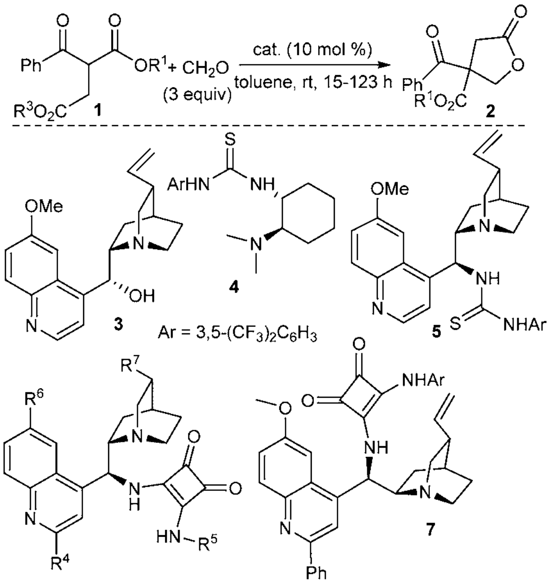
The asymmetric hydroxymethylation reaction of 2-substituted 1,3-dicarbonyl compounds has been scarcely investigated, and limited success has been attained, likely to be due to the highly reactive nature of formaldehyde as a C1 unit in the aldol reaction. Surprisingly, only transition-metal-based systems, based on Pd–BINAP[11] and chiral Ni_2–Schiff base[12] complexes, have been reported to catalyze this reaction achieving moderate to high enantioselectivity (60–94% ee).[13] We commenced our study by investigating the reactivity of diethyl 2-benzoylsuccinate **1a** and paraformaldehyde in toluene at room temperature with 10 mol % of quinine **3** (Table 1). To our delight, γ-butyrolactone **2a** was formed, although in low yield and as a racemate (entry 1). The activity markedly improved when using Takemoto thiourea **4** (entry 2) and *epi*-quinine derived thiourea **5** (entry 3), which is in agreement with a better H-bonding donor ability of this class of organocatalysts. We reasoned that differentiating the steric features of the two ester groups in compound **1** would have positively affected the enantiocontrol of the aldol reaction. Indeed, when reacting compound **1b**, with amine–thioureas **4** and **5** good conversion to product **2b** with significant improvement of the enantioselectivity were observed (entries 4 and 5). *epi*-Quinine-derived squaramide **6a** afforded the product with 50% ee (entry 6), showing amine squaramides to be suitable organocatalysts to check in the process. The reaction of compounds **1c–f**, bearing sterically demanding ester groups, catalyzed by **6a** (entries 7–10) enabled selection of reagent **1f** (entry 10) as the most promising for further catalyst screening. Pleasingly, squaramide **6b**, bearing a phenyl group at 2′-position of the quinoline residue, afforded product **2f** in good yield and 65% ee (entry 11). A solvent screening using organocatalyst **6b**[14] enabled us to improve the enantiomeric excess of product **2f** up to 74% when working in 1,2-dichloroethane (entry 12). Differently 2′-substituted *epi*-quinine- or *epi*-cinchonidine-derived squaramides catalyzed the process in a slightly less efficient way (entries 13–16). Catalyst **7**, the pseudoenantiomer of catalyst **6b**, gave the opposite enantiomer of product **2f** with comparable performance (entry 17). Finally, *epi*-hydroquinine-derived squaramide **6g** performed at best as product **2f** was isolated in 79% yield and 78% ee (entry 18).

To improve the reaction outcome, additives, nature of formaldehyde, and reaction temperature were investigated (Table 2). Formalin gave a result (entry 1) similar to that obtained when using paraformaldehyde (entry 18, Table 1). A slight improvement of the enantioselectivity and activity was observed when Na_2SO_4 was added as drying agent (entry 2). Decreasing the reaction temperature and addition of molecular sieves were beneficial in terms of conversion and enantiocontrol (entries 3–5). However, carrying out the reaction at −30 °C was detrimental in both respects (entry 6). The effect of acidic additives was also investigated.[15]

The addition of benzoic acid or less acidic 4-nitrophenol improved the conversion when working at 0 or −20 °C, and the enantioselectivity of **2f** increased up to 86% ee (entries 7–9).[16]

Catalyst loading could be conveniently decreased (entries 10 and 11) to 3 mol %, leading to the product in 95% yield and 87% ee (entry11).

Table 1. Screening of Catalysts and Substrates[a]



6a R^4 = H, R^5 = 3,5-$(CF_3)_2C_6H_3$, R^6 = OMe, R^7 = vinyl
6b R^4 = Ph, R^5 = 3,5-$(CF_3)_2C_6H_3$, R^6 = OMe, R^7 = vinyl
6c R^4 = *n*Bu, R^5 = 3,5-$(CF_3)_2C_6H_3$, R^6 = OMe, R^7 = vinyl
6d R^4 = *t*Bu, R^5 = 3,5-$(CF_3)_2C_6H_3$, R^6 = OMe, R^7 = vinyl
6e R^4 = 1-naphthyl, R^5 = 3,5-$(CF_3)_2C_6H_3$, R^6 = H, R^7 = vinyl
6f R^4 = Ph, R^5 = 3,5-$(CF_3)_2C_6H_3CH_2$, R^6 = OMe, R^7 = vinyl
6g R^4 = Ph, R^5 = 3,5-$(CF_3)_2C_6H_3$, R^6 = OMe, R^7 = ethyl

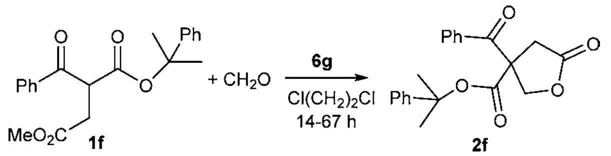
entry	R^1	R^3	cat.	yield[b] (%)	ee[c] (%)	2
1	Et	Et	**3**	28	2	**2a**
2	Et	Et	**4**	80	−7	**2a**
3	Et	Et	**5**	88	7	**2a**
4	*t*-Bu	Me	**4**	68	47	**2b**
5	*t*-Bu	Me	**5**	64	−35	**2b**
6[d,e,f]	*t*-Bu	Me	**6a**	31	−50	**2b**
7[d,e,f]	C_6H_{11}	Me	**6a**	83	−42	**2c**
8[d,e,f]	2-adamanthyl	Me	**6a**	74	40	**2d**
9[d,e,f]	1-carbonaphthyl	Me	**6a**	95	−36	**2e**
10[d,e,f]	cumyl	Me	**6a**	47	−59	**2f**
11[d,e,f]	cumyl	Me	**6b**	74	−65	**2f**
12[e,g]	cumyl	Me	**6b**	72	−74	**2f**
13[e,g]	cumyl	Me	**6c**	65	−69	**2f**
14[e,g]	cumyl	Me	**6d**	75	−69	**2f**
15[e,g]	cumyl	Me	**6e**	71	−68	**2f**
16[e,g]	cumyl	Me	**6f**	48	−70	**2f**
17[e,g]	cumyl	Me	**7**	64	68	**2f**
18[e,g]	cumyl	Me	**6g**	79	−78	**2f**

[a]Reactions were carried out on a 0.1 mmol scale of **1** (C 0.05 M). [b]Isolated yield. [c]Determined by chiral HPLC analysis. [d]In $CHCl_3$ as solvent. [e]5 mol % of catalyst was used. [f]Reaction carried out at C 0.1 M of **1**. [g]In $Cl(CH_2)_2Cl$ as solvent.

Under optimized reaction conditions, a variety of acylated succinic esters **1** were screened to study the scope of the one-pot sequence to prepare γ-butyrolactones **2** (Figure 2).

Electron-donating and electron-withdrawing groups on the phenyl ring of the aroyl residue or heteroaromatic moieties were well-tolerated (**2f–n**), with the exception of the *ortho*-substitution (**2i**), achieving the products with high yield and fairly good ee values (up to 88%). Interestingly, the sequence was applicable to compounds **1o–q**, bearing either linear or sterically demanding alkyl groups. The products (**2o–q**) were recovered in good yield and only slightly decreased ee values. Interestingly, 1-cumyl-5-methyl-2-benzoylpentanedioate **1r**,

Table 2. Optimization of the Aldol/Lactonization Sequence[a]



entry	6g (mol %)	additive	temp (°C)	yield[b] (%)	ee[c] (%)
1	5		rt	77	73
2	5	Na_2SO_4	rt	83	75
3[d]	5		0	94	80
4[d]	5		−20	70	84
5[d,e]	5	3 Å MS	−20	80	83
6[d,e]	5	3 Å MS	−30	58	79
7[d,e,f]	5	$PhCO_2H$	0	52	83
8[d,e,f]	5	$4\text{-}NO_2C_6H_4OH$	0	98	84
9[d,e,f]	5	$4\text{-}NO_2C_6H_4OH$	−20	90	86
10[d,e,f]	2	$4\text{-}NO_2C_6H_4OH$	−20	81	84
11[d,e,f]	3	$4\text{-}NO_2C_6H_4OH$	−20	95	87

[a]Reactions were carried out at 0.1 mmol scale of **1** (C 0.05 M) using formalin (2 equiv). [b]Isolated yield. [c]Determined by chiral HPLC analysis. [d]Reaction carried out at C 0.1 M of **1**. [e]3 Å molecular sieves were added. [f]5 mol % of additive was used.

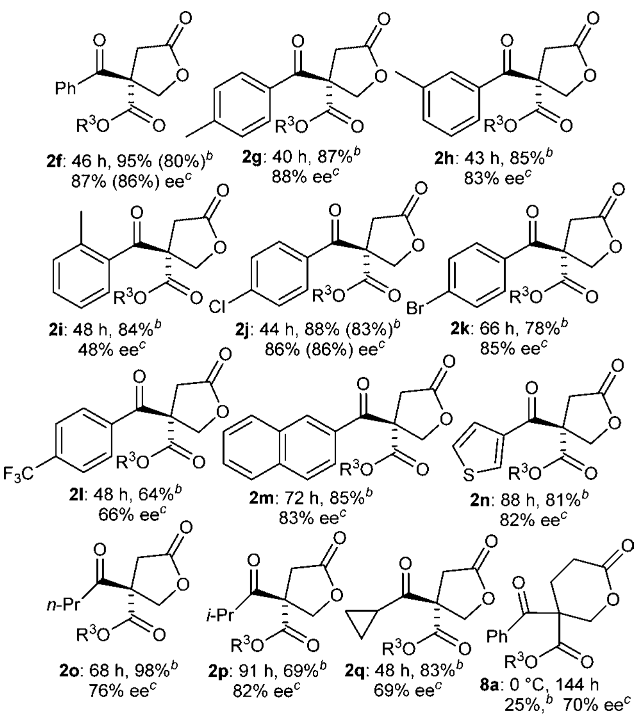
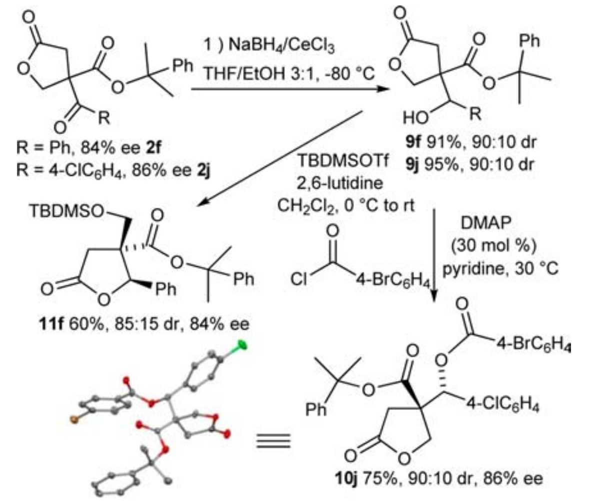


Figure 2. Substrate scope of the asymmetric aldol/lactonization sequence. (a) Reactions were carried out on a 0.1 mmol scale of **1** (C 0.1 M) using formalin (2 equiv), 3 mol % of **6g**, 5 mol % of $4\text{-}NO_2C_6H_4OH$, and 3 Å MS in $Cl(CH_2)_2Cl$ at −20 °C (R^3 = cumyl). (b) Isolated yield, in parentheses yield at 1 mmol scale. (c) Determined by chiral HPLC analysis, in parentheses ee at 1 mmol scale.

when reacted under usual conditions at 0 °C, afforded the corresponding *δ*-valeroactone **8a** with an encouraging 70% ee.

γ-Butyrolactones **2** can be stereoselectively transformed into differently decorated *β*-(hydroxyalkyl)-*γ*-butyrolactones **9** and **11** bearing contiguous quaternary and tertiary stereocenters (Scheme 1).

Scheme 1. Elaboration to *β*-(Hydroxyalkyl)-*γ*-butyrolactones



Derivatives **9** and **11** are a subset of more general class of hydroxy-*γ*-butyrolactones, important motives in natural products and synthetically useful building blocks.[17] Hydroxy-*γ*-butyrolactones are difficult to access, and only a few stereoselective methodologies, yielding *β*-(hydroxyalkyl)-*γ*-butyrolactones bearing two contiguous tertiary stereocenters, have been developed.[18] Reduction of enantioenriched compounds **2f,j** afforded *β*-(hydroxyalkyl)-*γ*-butyrolactones **9f,j** in high yield and 90:10 dr. Benzoylation of alcohol **9j** gave product **10j** in 75% yield. Single-crystal X-ray analysis on the major diastereoisomer of compound **10j** enabled us to assign the relative and absolute configuration of the stereocenters as (*R*,*R*).[19] By analogy, *γ*-butyrolactones were assigned as (*R*)-**2**. The diastereoisomeric mixture of enantioenriched compound **9f** (90:10 dr) was rearranged to *O*-protected-*β*,*γ*-substituted *γ*-butyrolactone **11f** using TBDMSOTf and 2,6-lutidine.[18b,20] No erosion of the enantioselectivity was observed as confirmed by chiral HPLC analysis on major diastereoisomer (*R*,*R*)-**11f**.

In conclusion, a one-pot aldol/lactonization process of acylated succinic esters with formalin catalyzed by a cinchona alkaloid-derived squaramide has been developed. Highly challenging *γ*-butyrolactones, bearing an all-carbon quaternary stereocenter at the remote *β*-position, have been isolated in high yield and with an enantioselectivity level comparable to indirect methods. The salient features of this methodology are readily available reagents, with low catalyst loading and mild reaction conditions. It has to be noted that this work illustrates the first example of an enantioselective organocatalyzed reaction of 2-substituted 1,3-dicarbonyl compounds with a highly reactive and challenging formaldehyde unit. Finally, the *β*,*β*-disubstituted *γ*-butyrolactones can be elaborated to stereoselectively prepare *β*-(hydroxyalkyl)-*γ*-butyrolactones bearing contiguous tertiary and quaternary stereocenters hitherto not accessible by alternative methods.

■ ASSOCIATED CONTENT

Supporting Information

Experimental details, analytical data, crystal data for **10j** (CIF), ^1H, ^{13}C NMR spectra, and HPLC traces. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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