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(*Z*)-2,2-Dimethyl-5-carboxymethylene-1,3-dioxolan-4-one: a new synthon for the synthesis of α,γ-diketoacid derivatives

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ABSTRACT

The synthesis and reactivity of (*Z*)-2,2-dimethyl-5-carboxymethylene-1,3-dioxolan-4-one, a new and versatile synthon useful for the synthesis of selectively protected α,γ-diketoacid derivatives, are described. This new, protected form of hydroxyl fumaric acid along with its acid chloride was used to prepare ester, amide, and aryl derivatives. The dioxolane moiety was found to be a convenient functionality that facilitated ready unmasking by straightforward hydrolysis to reveal α,γ-diketoacid derivatives or derivatization to yield ester, amide, and 2,3-pyrrolidinedione derivatives.

HIV integrase is one of three essential enzymes in the replication cycle of the human immunodeficiency virus (HIV) and has emerged as an important target for the development of HIV therapeutics.[1] The 4-aryl-α,γ-diketoacid derivatives **1** and **2** were among the first compounds to be validated as authentic inhibitors of HIV integrase in cell culture.[2] Compounds bearing this pharmacophore were also found to demonstrate inhibitory activity toward hepatitis C virus RNA-dependent RNA polymerase, hepatitis B virus polymerase and HIV RT,[3] as well as flap endonuclease 1.[4] Given the potential broad utility of the α,γ-diketoacid acid moiety in medicinal chemistry, we were interested in developing synthetic approaches that would allow preparation and functionalization along diverse pathways.

The synthesis of α,γ-diketoacid derivatives **1** and **2** is generally accomplished through a base-promoted Claisen condensation between a methyl ketone and a dialkyl oxalate followed by alkaline or acid hydrolysis of the intermediate ester (Fig. 1, method A).[5] Alternatively, the addition of the dianion of the dimethylhydrazone of pyruvic acid to aryl esters has been reported to yield diketoacids after acidic hydrolysis of the hydrazone.[6] We proposed that a suitably functionalized hydroxyl fumaric acid derivative based on the dioxolanone **3** in Figure 1, which employs a single protecting group for both the enol and one of the carboxylic acid groups, would provide a new and versatile synthon for this class of compound that would extend existing methodology by allowing the facile preparation of esters, amides, and other derivatives.[7] Compound **3** is a protected derivative of the naturally occurring oxaloacetic acid; however, attempts to selectively protect this material were unsuccessful, thus requiring development of an alternative synthetic approach. In this Letter, we describe the initial synthetic approach developed to prepare (*Z*)-2,2-dimethyl-5-carboxymethylene-1,3-dioxolan-4-one (**10**) and its acid chloride **12**.[8]

Two approaches to highly functionalized keto-esters related to **3** are described in the literature. An approach first described by Ramage et al.[9] employed a Wittig reaction between *t*-butyl glyoxylate and a phosphorane–dioxolanone moiety to provide **4** (Fig. 2), wherein the α-enol and adjacent carboxylic acid moieties are

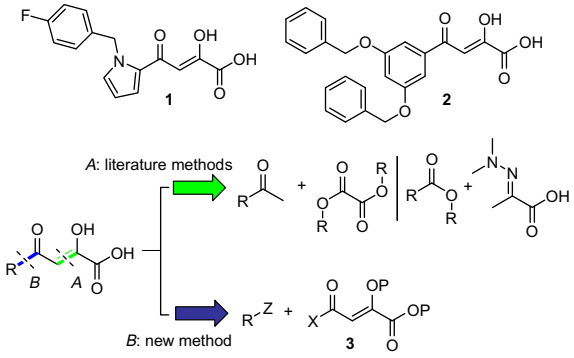

Figure 1. Comparison of method A and method B.

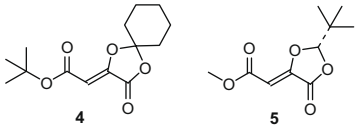

Figure 2. Compounds previously reported in the literature.

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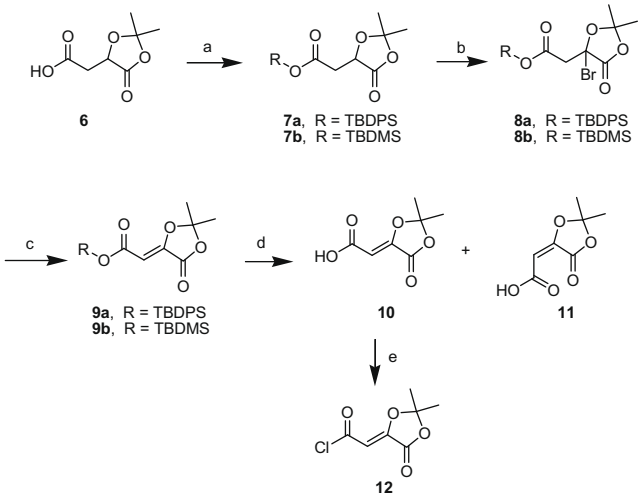
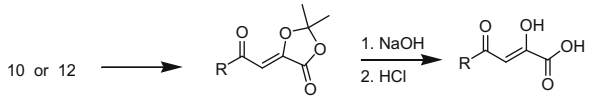


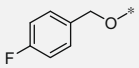
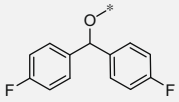
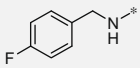
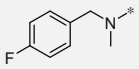
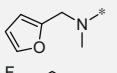
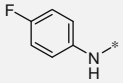
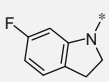
Scheme 1. Synthesis of compounds **10** and **12**. Reagents and conditions: (a) TBDPSCl, imidazole, DMF, 99% for **7a**; TBDMSCl, imidazole, DMF, 96% for **7b**; (b) NBS, AIBN, CCl_4, reflux; (c) DBU, THF; (d) TBAF, AcOH or AcOH, 1 N HCl, 82%; (e) oxalyl chloride, CH_2Cl_2, quantitative.

included in a cyclohexanone ketal. This ketal is quite stable to aqueous acid but the carbonyl group of the five-membered ring in **4** was found to be quite sensitive to nucleophilic attack. An alternative synthetic method was subsequently described by both Kneer et al.[10] and Schwenker and Stiefvater[11] in which unsaturated dioxolanone esters **5** (Fig. 2) were obtained from saturated dioxolanone esters similar to **7** (R = Et and Me), in turn derived from malic acid, by using a synthetic sequence similar to that depicted in Scheme 1. This approach appeared to be suitable for the purpose at hand; however, since it was deemed unlikely that the desired acid **3** could be obtained by saponification of the terminal ester in **5** in the presence of the highly reactive lactone carbonyl, a modification of this route was required in order to provide easy access to the carboxylic acid. A silyl ester was anticipated to be a suitable protecting group for this purpose since it can readily be removed under acidic conditions or by exposure to fluoride.

Toward this end, both the *tert*-butyldiphenylsilyl and the *tert*-butyldimethylsilyl esters were explored, as summarized in Scheme 1. Reaction of (S)-(+)-2,2-dimethyl-5-oxo-dioxolane-4-acetic acid (**6**) with *tert*-butlyldiphenylsilyl chloride gave **7a** in quantitative yield after chromatography on silica gel, while *tert*-butyldimethylsilyl chloride provided **7b** in 96% yield after distillation. The reaction of **7a** and **7b** with *N*-bromosuccinimide[12] in CCl_4 in the presence of 2,2-azobisisobutyronitrile at reflux resulted in a mild exothermic reaction and clean formation of the bromides **8a** and **8b**. These bromides were immediately treated with 1,8-diazabicyclo[5,4,0]undec-7-ene to give the unsaturated esters **9a** and **9b**, respectively. Attempts to purify **9a** by chromatography on silica gel gave variable yields, probably due to partial hydrolysis of the silyl group during the purification process. In contrast, crude **9a** could be treated with tetrabutylammonium fluoride and acetic acid to give crystalline **10** in 70% overall yield from **7a**. The crude silyl ester **9b** is also easily hydrolyzed with acetic acid and dilute HCl to provide the acid **10** in 82% yield by what is, essentially, a one-pot reaction from the silyl ester **7b**. ^{1}H NMR analysis ($CDCl_3$) of the acid obtained using this method indicated that in addition to the expected (*Z*)-isomer **10**, in which the vinyl proton resonates at $\delta = 5.89$, a trace amount (<5%) of the (*E*)-isomer **11** was also formed, detected by the presence of the vinyl proton resonating at $\delta = 6.03$. The identity of the products was confirmed by analysis of the proton gate-decoupled ^{13}C NMR spectrum, an experiment performed in DMSO-d_6. The ring carbonyl carbon of **10** resonates as a doublet, $J = 3.8$ Hz, at δ 95.63, consistent with a *cis* relationship between the exocyclic proton (δ 5.55) and the ring carbon.[13] In

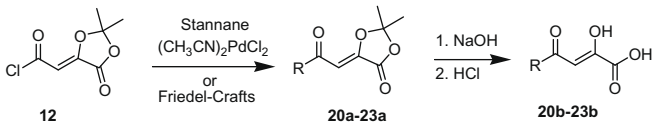
Table 1
Ester and amides derived from **10** and **12**



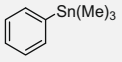
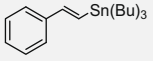
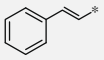
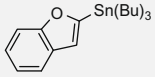
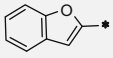
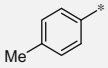
Entry	R	Method[a]	Compd	% Yield[b]	Compd	% Yield
1		A	**13a**	78	**13b**	55
2		A	**14a**	73	**14b**	90
3		A	**15a**	88	**15b**	91
4		B	**16a**	81	**16b**	100
5		B	**17a**	90	**17b**	95
6		A	**18a**	95	**18b**	85
7		A	**19a**	93	**19b**	89

[a] Method A: Acid chloride **12**/alcohol or amine/pyridine/CH_2Cl_2. Method B: Acid **10**/amine/BOP/Et_3N/CH_3CN.
[b] Yields are for recrystallized material except for **16b** which was obtained as a syrup.

Table 2
Diketoacid derivatives



12 **20a-23a** **20b-23b**

Entry	Reactant	R	Compd	% Yield	Compd	% Yield
1			**20a**	71	**20b**	48
2			**21a**	75	**21b**	65
3			**22a**	69	**22b**	95
4			**23a**	61	**23b**	88

contrast, the carbonyl carbon of the minor isomer **11** resonates as a doublet centered at δ 102.45 that couples to the vinyl proton resonating at δ 5.99 with J = 10.0 Hz. A simple recrystallization of the crude acid from ethyl acetate gave the pure (*Z*)-isomer **10** with high recovery.

As an illustration of the acid stability of the unsaturated dioxolanone moiety, the acid chloride **12** was easily prepared using oxalyl chloride and obtained as a stable, crystalline solid. Acid chloride **12** reacted smoothly and selectively with 4-fluorobenzyl alcohol and 4,4′-difluorobenzhydrol to afford the corresponding esters **13a** and **14a** in 78% and 73% yield, respectively. The acid chloride **12**, or the acid **10** combined with standard peptide coupling reagents like BOP, reacts with a variety of amines to provide amides in high yield, as summarized in Table 1. Both the ester and amide derivatives were found to be stable compounds readily purified by chromatography on silica gel.

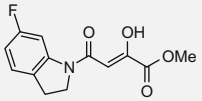
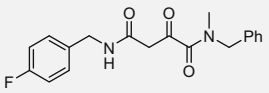
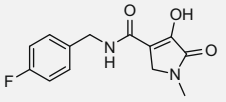
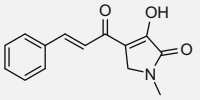
The final step to release the α,γ-diketoacid required the hydrolysis of the dioxolanone moiety to give the ester and amide ketoacid derivatives. In the case of the esters **13a** and **14a**, the dioxolanone ring could be selectively cleaved at low temperature (ice bath) with 1 N NaOH followed by acidification to give the acids **13b** and **14b** in good yield (Table 1, entries 1 and 2). The amides **15a**–**19a** were also rapidly hydrolyzed at 25 °C to provide the diketoacids **15b–19b** in excellent yield using 2 equiv of 1 N NaOH solution (Table 1, entries 3–7).

To complement the formation of ester and amide derivatives, the preparation of C-linked, α,γ-diketoacid derivatives was also explored with the palladium-catalyzed coupling of the acid chloride **12** with unsymmetrical organotin reagents[14] examined first. Reaction of **12** with trimethyl(phenyl)tin and (*E*)-β-styryltributyltin[15] catalyzed by bis(acetonitrile)dichloropalladium (II) produced dioxolanones **20a** and **21a** in 71% and 75% yield, respectively (Table 2, entries 1 and 2). Also, 2-(Tri-*n*-butylstannyl)benzofuran[16] gave the dioxolanone **22a** in 69% yield.

We were also pleased to find that the acid chloride **12** was sufficiently stable to react with nucleophiles under Friedel–Crafts conditions. For example, the reaction of **12** with toluene in the presence of $AlCl_3$ gave the dioxolanone **23a** in 61% yield (Table 2, entry 4). This is another good example that demonstrates the stability of this ketal under acidic conditions. Similar to the case of the amides described above, these aryl dioxolanones were easily hydrolyzed to the known α,γ-diketoacid derivatives **20b**,[17] **21b**,[18] and **23b**[19] and the new α,γ-diketoacid **22b**.

Taking advantage of the reactivity of the dioxolane ring toward nucleophiles, the protected carboxylic acid moiety was also found to be a convenient functionality for direct derivatization. When

Table 3
Reactions at the dioxolane moiety

Entry	Dioxolane	Method	Compd	Structure	% Yield*
1	**19a**	A	**24**		88
2	**15a**	B	**25**		69
3	**15a**	C	**26**		33
4	**21a**	C	**27**		40

Method A: 0.03 equiv of NaOMe/22 °C/4 h/THF, MeOH. Method B: 2.0 equiv of *N*-benzyl-*N*-methylamine/50 °C/4 h/THF. Method C: 2.0 equiv of paraformaldehyde and methylamine/50 °C/1 h/MeOH.

* Yields are for recrystallized material except for **25** which was obtained as an oil.

treated with an alcohol and a trace of base, the dioxolanone ring was readily cleaved to provide the corresponding ketoester derivative. For example, reaction of the dioxolanone **19a** with MeOH and a catalytic amount of NaOMe gave the ketoester **24** in high yield (Table 3, entry 1). The dioxolane ring in **15a** could also be opened by a secondary amine, exemplified by the reaction with *N*-benzyl-*N*-methylamine which gave **25** in 69% yield (Table 3, entry 2). Interestingly, while the α,γ-diketoacids and their ester derivatives exist mainly in the enol form, the amide derivative **25** exists predominantly in the keto form in solution in $CHCl_3$.

2,3-Pyrrolidinediones are highly functionalized heterocycles which, like the α-ketoacids, have been found to possess HIV integrase inhibitory activity.[20] It has been demonstrated that 2,3-pyrrolidinediones can be obtained via the Mannich reaction of α,γ-diketoester derivatives with an imine generated in situ from an aldehyde and a primary amine.[21] The dioxolanone scaffold is a useful substrate for the synthesis of 2,3-pyrrolidinediones. Thus, reaction of the dioxolanones **15a** and **21a** with paraformaldehyde and methylamine in MeOH gave the pyrrolidinenones **26** and **27** in 33% and 40% yield, respectively, after crystallization. Methanol was found to be essential for the reaction to proceed, which probably implies the formation of an intermediate α,γ-diketo methyl ester prior to pyrrolidinedione formation.

In conclusion, we have demonstrated a convenient method for the synthesis of a selectively protected derivative of oxalacetic acid that is a useful synthetic precursor to a wide range of products.[22] It can readily be appreciated by the examples described that the chemistry used to derivatize this starting material is readily amenable to high throughput synthetic methods, an aspect that will be described in due course. One additional feature of this chemistry that is worthy of note is that we have found that the dioxolane protecting group confers stability to the diketoacid moiety, often an unstable functional group. For example, when incorporated into the dioxolane ring, diketoacids such as those described are much more resistant to decomposition upon storage when compared to the corresponding free keto-acids.

Acknowledgment

The authors wish to acknowledge Stella Huang for carrying out the ^{13}C NMR experiments on compound **10**.

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22. Procedures for key compounds:
(S)-(+)-2,2-Dimethyl-5-oxo-1,3-dioxolane-4-acetic acid, tert-butyldimethylsilyl ester (**7b**): A solution of (*S*)-(+)-2,2-dimethyl-5-oxo-1,3-dioxolane-4-acetic acid (**6**) (13.20 g, 75.8 mmol) in DMF (25 mL) was treated at 22 °C with imidazole (10.56 g, 0.155 mmol) followed by *tert*-butyldimethylsilyl chloride (12.0 g, 79.6 mmol) and the resulting mixture was stirred for 18 h. The mixture was diluted with toluene (500 mL), washed with H_2O, saturated $NaHCO_3$, brine, and dried ($MgSO_4$). The solvent was evaporated under reduced pressure and the residual oil was distilled under vacuum to give 20.9 g (96% yield) of **7b** as a clear oil, bp 80–90 °C/0.1 torr (bulb–bulb distillation). ^1H NMR (C_6D_6) δ 0.33 (s, 3H), 0.36 (s, 3H), 1.0 (s, 9H), 1.11 (s, 3H), 1.37 (s, 3H), 2.72 (AB part of ABX system, $J_{(AX)}$ = 6.1 Hz, $J_{(BX)}$ = 4.1 Hz, $J_{(AB)}$ = 17.0 Hz, $\Delta\nu$ = 41.5 Hz, 2H), 4.35 (dd, $J_{(AX)}$ = 6.1 Hz, $J_{(BX)}$ = 4.1 Hz, 1H).
4-Bromo-2,2-dimethyl-5-oxo-1,3–dioxolane-4-acetic acid, tert-butyldimethylsilyl ester (**8b**): A solution of (*S*)-(+)-2,2-dimethyl-5-oxo-1,3-dioxolane-4-acetic acid, *tert*-butyldimethylsilyl ester **7b** (20.9 g, 72.4 mmol) in CCl_4 (200 mL) was treated with freshly recrystallized *N*-bromosuccinimide (14.18 g, 79.6 mmol) and 2,2′-azobisisobutyronitrile (0.30 g) and the resulting mixture was heated under reflux while irradiating with a 500 W lamp. After 5 min, a mild exothermic reaction was observed and the mixture was heated for an additional 5 min (at this point most of the succinimide was floating on the solvent). The mixture was cooled in an ice bath and the succinimide was filtered and washed with a small amount of CCl_4. The filtrate was used immediately without further purification for the next step. ^1H NMR (CCl_4–$CDCl_3$) δ 0.27 and 0.28 (2s, 2 × 3H), 0.94 (s, 9H), 1.66 (s, 3H), 1.84 (s, 3H), 3.62 (AB system, $J_{(AB)}$ = 21.2 Hz, $\Delta\nu$ = 11.8 Hz, 2H).
(Z)-2,2-Dimethyl-5-(tert-butyldimethylsilyloxycarbonylmethylene)-1,3-dioxolan-4-one (**9b**): Under vigorous mechanical stirring, the solution of crude ester **8b** (72.4 mmol) in CCl_4 (~220 mL) was cooled to 0–5 °C and treated, dropwise over 10 min, with a solution of 1,8-diazabicyclo [5,4,0] undec-7-ene (12.1 g, 79.6 mmol) in dry THF (125 mL). A heavy precipitate formed that was difficult to stir but which gradually became a granular solid. After 1 h, the solid was filtered and washed with a small amount of THF. The filtrate was concentrated under reduced pressure to give the crude silyl ester **9b** as a light orange oil which was used as such for the next step. ^1H NMR ($CDCl_3$) δ 0.33 (s, 6H), 0.97 (s, 9H), 1.75 (s, 6H), 5.85 (s, 1H).
(Z)-2,2-Dimethyl-5-carboxymethylene-1,3-dioxolan-4-one (**10**) from **9b**: Crude dioxolan-4-one **9b** (72.4 mmol) in THF (50 mL) was treated at 22 °C with CH_3CO_2H (10 mL, 0.17 mmol) followed by H_2O (50 mL) and 1 N HCl solution (20 mL). The mixture was stirred vigorously for 1 h during which time partial precipitation of the title acid usually occurred. After the addition of EtOAc (700 mL), the clear solution was washed with H_2O, brine, and dried over anhydrous $MgSO_4$. Evaporation of the solvent under reduced pressure and trituration of the residual solid with toluene (50 mL) gave 13.58 g of the acid **10** as a white solid (82% yield for three steps from **7b**). By ^1H NMR this material contained less than 5% of the (*E*)-isomer **11**. The acid was recrystallized from EtOAc (80% recovery) to give the pure (*Z*)-isomer **10** as colorless needles; mp 203–204 °C (dec.). IR (KBr) ν_{max} (1805, 1707 and 1662 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.78 (s, 6H), 5.89 (s, 1H). Anal. Calcd for $C_7H_8O_5$: C, 48.84; H, 4.68. Found: C, 48.84; H, 4.65.
(E)-2,2-Dimethyl-5-carboxymethylene-1,3-dioxolan-4-one (**11**): ^1H NMR ($CDCl_3$) δ 1.80 (s, 6H), 6.03 (s, 1H).
(Z)-2,2-Dimethyl-5-chlorocarbonylmethylene-1,3-dioxolan-4-one (**12**): A mixture of (*Z*)-2,2-dimethyl-5-carboxymethylene-1,3-dioxolan-4-one (0.50 g, 2.9 mmol) in dry CH_2Cl_2 (10 mL) was treated at 22 °C with oxalyl chloride (0.5 mL, 5.8 mmol) followed by a trace (capillary) of DMF. After 1 h at 22 °C, the clear solution was concentrated in vacuo to give 0.55 g (quantitative yield) of the title acid chloride **12** as a white crystalline solid. ^1H NMR (CDCl3) δ 1.80 (s, 6H), 6.19 (s, 1H).