Synthetic Methods

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Regioselective Oxidative Cleavage of Benzylidene Acetals: Synthesis of α- and β-Benzoyloxy Carboxylic Acids**

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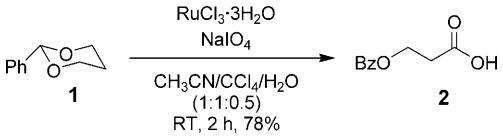
Dedicated to Professor Srinivasan Chandrasekaran

In nature, α- and β-hydroxy carboxylic acids occur in a wide variety of microorganisms and are recurrent intermediates in the α- and β-oxidation pathways of fatty-acid degradation.[1] Moreover, α-hydroxy acids have found extensive application in synthetic organic chemistry as chiral intermediates,[2] chiral ligands,[3] and resolving agents for alcohols and amines;[4] they have also found application as antiaging factors in the cosmetics industry.[5] As a consequence of the wide-ranging biological and synthetic applications of this class of molecules, the development of new methods for their synthesis has attracted considerable interest.[6]

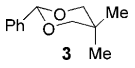
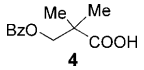
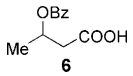
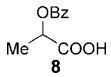
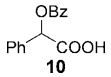
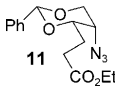
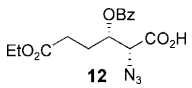
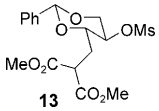
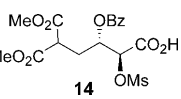
Benzylidene acetals are widely used for the protection of 1,2- and 1,3-diols;[7] deprotection occurs readily under catalytic hydrogenation conditions or by hydrolysis.[8] Furthermore, benzylidene acetals can be cleaved regioselectively under reductive conditions to give the corresponding synthetically useful monoprotected diols.[9] Moreover, the oxidative cleavage of benzylidene acetals to the corresponding hydroxy benzoates has been achieved with several reagent systems with varying degrees of regioselectivity.[10] Herein we report a novel method for the direct conversion of benzylidene acetals into the corresponding synthetically useful α- and β-benzoyloxy carboxylic acids.

Intriguingly, the benzylidene acetal **1** underwent smooth oxidative cleavage on treatment with $RuCl_3$–$NaIO_4$[11] to give the corresponding benzoate-protected β-hydroxy carboxylic acid **2** in good yield (Scheme 1). Encouraged by the facile reaction of **1** with the $RuCl_3$–$NaIO_4$ reagent system, we tested the generality of this methodology further with both five- and six-membered benzylidene acetals, including substrates containing sensitive functional groups (Table 1). Remarkably, unsymmetrical benzylidene acetals underwent smooth oxidative cleavage in a highly regioselective manner to give the corresponding α- and β-benzoyloxy carboxylic acids in good yields (Table 1, entries 2–6).[12] The structure of oxidation product **8** was confirmed unambiguously by single-crystal X-ray analysis (Figure 1).[13]



Scheme 1. Direct oxidation of the benzylidene acetal **1** to the β-benzoyloxy carboxylic acid **2**. Bz = benzoyl.

Table 1: Direct oxidation of benzylidene acetals to α- and β-benzoyloxy carboxylic acids.

Entry	Substrate	Product	*t* [h]	Yield[a] [%]
1	 **3**	 **4**	1.5	78
2	 **5**	 **6**	2	68
3	 **7**	 **8**	2	68
4	 **9**	 **10**	2	66
5	 **11**	 **12**	2.5	65
6	 **13**	 **14**	2.5	61

[a] Yield of the pure isolated product. Ms = methanesulfonyl.

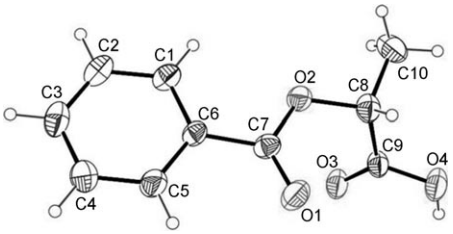


Figure 1. ORTEP diagram of compound **8**.

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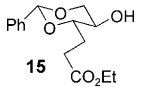
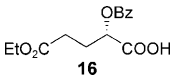
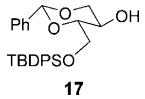
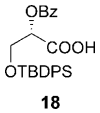
Reactive functional groups, such as *tert*-butyldiphenylsilyl (TBDPS) ether, azide, ester, and *N*-Ts groups, were found to be stable under the reaction conditions. Notably, optically active benzylidene acetals underwent smooth oxidation to the corresponding benzoyloxy carboxylic acids without any epimerization (Table 1, entries 5 and 6).

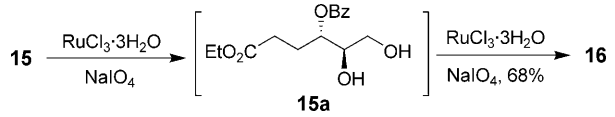
Interestingly, benzylidene acetals with a free hydroxy group underwent facile cleavage to give the corresponding α-benzoyloxy carboxylic acids with the loss of one carbon atom (Table 2). The reaction sequence involved in the direct

Table 2: Direct oxidation of hydroxy benzylidene acetals to α-benzoyloxy carboxylic acids.

Entry	Substrate	Product	*t* [h]	Yield[a] [%]
1	 **15**	 **16**	2.5	68
2	 **17**	 **18**	1.5	71

[a] Yield of the pure isolated product.

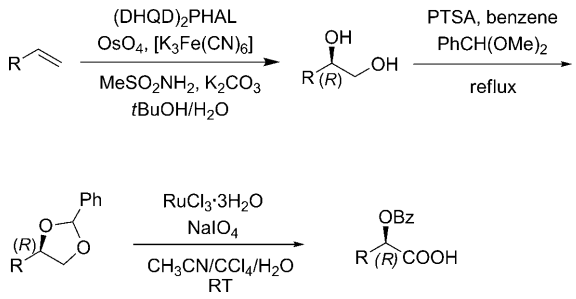
conversion of the hydroxy benzylidene acetal **15** into the corresponding α-benzoyloxy carboxylic acid **16** is shown in Scheme 2. The oxidation of **15** with $RuCl_3$–$NaIO_4$ results in the vicinal-diol intermediate **15a**, which undergoes further oxidative cleavage to give compound **16**.



Scheme 2. Regioselective oxidative cleavage of the hydroxy benzylidene acetal **15** to the α-benzoyloxy carboxylic acid **16**.

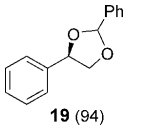
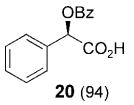
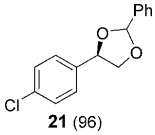
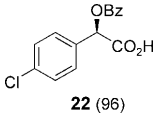
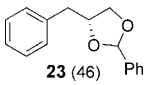
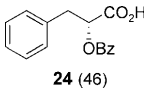
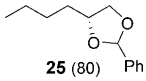
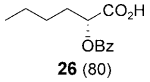
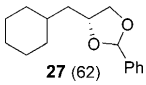
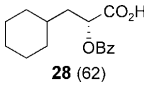
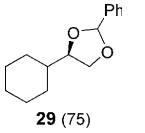
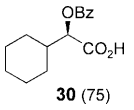
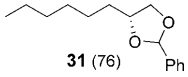
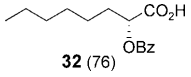
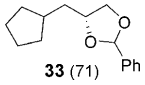
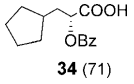
Since the stereochemical integrity of the benzoyloxy carboxylic acid product is maintained under the reaction conditions, a reliable three-step protocol was developed for the synthesis of optically active α-benzoyloxy carboxylic acids from terminal olefins. Optically active benzylidene acetals were prepared readily from terminal olefins through Sharpless asymmetric dihydroxylation (SAD) of a 1-alkene, followed by treatment with benzaldehyde dimethyl acetal under acidic conditions (Scheme 3). The exposure of the resulting chiral benzylidene acetal to the $RuCl_3$–$NaIO_4$ reagent system led to smooth regioselective oxidative cleavage to the corresponding optically active (*R*)-α-benzoyloxy carboxylic acid in good yield without any racemization (Table 3).[12] Similarly, (*S*)-α-benzoyloxy carboxylic acids can be synthesized from terminal olefins by using hydroquinine 1,4-phthalazinediyl diether ($(DHQ)_2PHAL$) as a catalyst in the SAD step. The optical purity of the synthesized compounds was determined by HPLC analysis on chiral columns (see the Supporting Information).

The synthetic potential of this methodology was further tested in the stereoselective synthesis of the protected



Scheme 3. Synthesis of chiral α-benzoyloxy carboxylic acids from terminal olefins. $(DHQD)_2PHAL$ = hydroquinidine 1,4-phthalazinediyl diether; PTSA = *p*-toluenesulfonic acid.

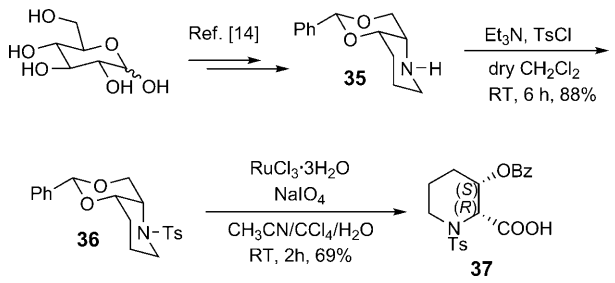
Table 3: Synthesis of optically active α-benzoyloxy carboxylic acids.

Entry	Substrate (*ee* [%])	Product (*ee* [%])	*t* [h]	Yield[a] [%]
1	 **19** (94)	 **20** (94)	2	61
2	 **21** (96)	 **22** (96)	2	62
3	 **23** (46)	 **24** (46)	2.5	66
4	 **25** (80)	 **26** (80)	2	64
5	 **27** (62)	 **28** (62)	2.5	63
6	 **29** (75)	 **30** (75)	2.5	66
7	 **31** (76)	 **32** (76)	2	63
8	 **33** (71)	 **34** (71)	2.5	64

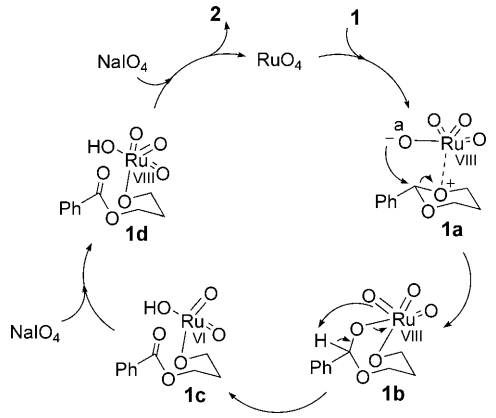
[a] Yield of the pure isolated product.

cis-(2*R*,3*S*)-3-hydroxypipecolic acid **37** from D-glucose. The piperidine–benzylidene acetal derivative **35**, prepared from D-glucose by a previously reported procedure,[14] was transformed into the corresponding *N*-Ts-protected piperidine derivative **36** in 88% yield upon treatment with tosyl chloride. Direct oxidation of the benzylidene acetal derivative **36** with the $RuCl_3$–$NaIO_4$ reagent system furnished the corresponding *cis*-(2*R*,3*S*)-3-hydroxypipecolic acid derivative **37** as the only product in 69% yield (Scheme 4).

A plausible mechanism for the direct oxidation of benzylidene acetals to α- and β-benzoyloxy carboxylic acids is shown in Scheme 5. It is likely that coordination of RuO_4 to



Scheme 4. Stereoselective synthesis of protected *cis*-(2*R*,3*S*)-3-hydroxypipecolic acid **37**. Ts = *p*-toluenesulfonyl.



Scheme 5. Plausible mechanism for the direct oxidation of benzylidene acetals to benzoyloxy carboxylic acids.

a less hindered oxygen atom of the benzylidene acetal is followed by nucleophilic attack of oxygen atom "a" of the ruthenium reagent at the benzylic carbon atom. Subsequent carbon–oxygen bond cleavage would lead to intermediate **1b**. Reductive elimination of intermediate **1b** would then lead to the formation of intermediate **1c**, the further oxidation of which via **1d** would furnish the corresponding β-benzoyloxy carboxylic acid **2**.

In conclusion, novel and facile methodology has been developed for the direct oxidation of benzylidene acetals to the corresponding α- and β-benzoyloxy carboxylic acids with the reagent system $RuCl_3$–$NaIO_4$. Salient features of this methodology are 1) its high stereo- and regioselectivity, 2) the mild reaction conditions, and 3) the stability of reactive functional groups, such as TBDPS ether, azide, ester, and *N*-Ts groups, under the reaction conditions. This methodology provides ready access to synthetically useful chiral α-benzoyloxy carboxylic acids from terminal olefins. The synthetic potential of this methodology was further exemplified by the stereoselective synthesis of protected biologically active *cis*-(2*R*,3*S*)-3-hydroxypipecolic acid from D-glucose. We strongly believe that this reaction will find broad application in synthetic organic chemistry.

Experimental Section

Typical procedure: $NaIO_4$ (652 mg, 3.05 mmol) and $RuCl_3{\cdot}3H_2O$ (12.6 mg, 0.061 mmol) were added successively to a stirred solution of **1** (100 mg, 0.61 mmol) in the solvent system $CH_3CN/CCl_4/H_2O$ (1:1:0.5; 6 mL), and the resulting mixture was stirred at room temperature for 2 h. 2-Propanol (1 mL) was then added to the reaction mixture, and the mixture was filtered through a pad of Celite. The solid mass collected was washed with EtOAc. The filtrate was then washed with an aqueous $NaHCO_3$ solution (0.5 M; 10 mL), and the aqueous layer was acidified with 1N HCl (pH 2) and then extracted with EtOAc (2 × 20 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Purification of the crude compound by column chromatography on silica gel (gradient elution with 25–30% EtOAc in hexane) yielded pure **2** (92 mg, 78%) as a foamy solid. IR (neat): $\nu = 2931$, 2857, 1724, 1452, 1272, 1111, 710 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.96$–7.94 (m, 2H), 7.48–7.47 (m, 1H), 7.37–7.34 (m, 2H), 4.53 (t, $J = 6.2$ Hz, 2H), 2.78 ppm (t, $J = 6.2$ Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 176.2$, 166.3, 133.2, 129.8, 129.7, 128.4, 59.9, 33.7 ppm; HRMS (ESI): *m/z* calcd for $C_{10}H_{10}O_4Na$: 217.0473 $[M+Na]^+$; found: 217.0477.

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Keywords: benzylidene acetals · hydroxy carboxylic acids · oxidation · regioselectivity · terminal alkenes

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[13] CCDC 751483 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif..

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