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Synthesis of substituted cyclopropanone acetals by carbometallation and its oxidative cleavage with manganese(IV) oxide and lead(IV) oxide

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Dedicated to Prof J.F. Normant on the occasion of his 65th birthday in recognition of his outstanding contribution to organometallic chemistry

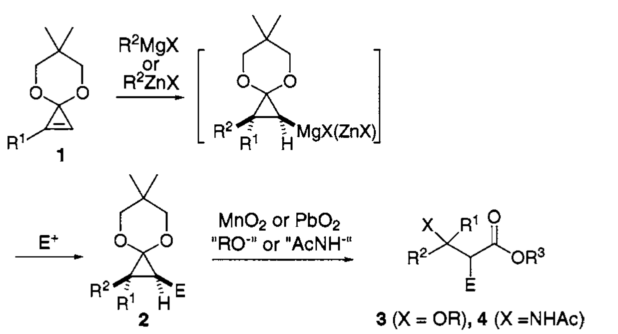
Abstract

A variety of substituted cyclopropanone acetals were prepared by the addition of an organozinc reagent or a Grignard reagent to a substituted cyclopropenone acetal. MnO_2- or PbO_2-mediated oxidative ring opening reaction of the substituted cyclopropanone acetals affords β-alkoxyesters and protected β-aminoesters with high efficiency. © 2001 Elsevier Science B.V. All rights reserved.

Keywords: Carbometallation; Cyclopropane; Oxidation; Ring opening; Manganese dioxide; Lead dioxide

1. Introduction

Synthetic transformations of cyclopropane derivatives have been the subject of numerous investigations and provided a large number of synthetically useful routes to a variety of functionalized organic molecules [1]. Among these transformations, oxidative cleavage of substituted cyclopropanes belongs to the least-developed transformations of the compounds, since it often encounters the problem of regioselectivity of the ring opening [2]. Here we report a new synthetic route to β-alkoxyesters and β-aminoesters **3** by regioselective oxidative cleavage of substituted cyclopropanone acetals **2**. The latter have been synthesized by carbometallation of readily accessible cyclopropenone acetals (CPAs) **1** [3] (Scheme 1).



(R^1 = H, Ph, 1° alkyl, alkenyl, R^2 = Ph, alkenyl, allyl, E = H, allyl, R^3 = $CH_2C(CH_3)_2CH_2OH$)

Scheme 1.

2. Results and discussion

The starting cyclopropanone acetals were prepared by allylzincation [4] or iron-catalyzed carbomagnesation [5] reaction of CPAs, which can be synthesized on a large scale from inexpensive 1,3-dichloroacetone [3,6]. Table 1 summarizes the results of carbometallation and sequential trapping of the intermediary cyclopropyl metal species. Addition of phenylmagnesium bromide to CPA **1a** (R^1 = H) proceeded smoothly at −45°C to afford 2-phenylcyclopropanone acetal **2a** in 96% yield (Table 1, entry 1). Electrophilic trapping of the cyclopropylmagnesium species with allyl bromide afforded

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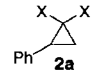
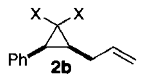
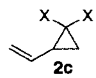
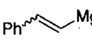
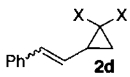
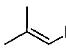
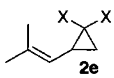
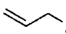
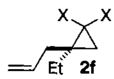
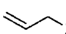
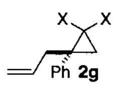
Table 1
Carbometallation and successive electrophilic trapping of cyclopropenone acetals[a,b]

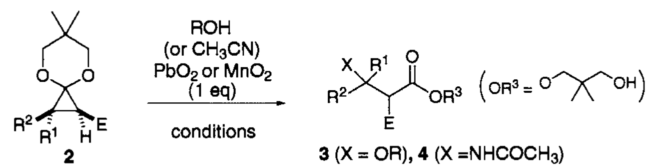
entry	cyclopropene	organometallic reagent	E^+	cyclopropane[c]	%yield
1	**1a** (R^1 = H)	PhMgBr	H_3O^+	 **2a**	96%
2	**1a** (R^1 = H)	PhMgBr	allylBr	 **2b**	85%
3	**1a** (R^1 = H)	 MgBr	H_3O^+	 **2c**	75%
4	**1a** (R^1 = H)	 Ph MgBr	H_3O^+	 **2d**	55%
5	**1a** (R^1 = H)	 MgBr	H_3O^+	 **2e**	30%
6[d]	**1b** (R^1 = Et)	 ZnBOX	H_3O^+	 **2f**	95% (>98% ee)
7[d]	**1c** (R^1 = Ph)	 ZnBOX	H_3O^+	 **2g**	98% (>98%ee)

[a]Addition of a Grignard reagent (entries 1-5) was carried out in the presence of a catalytic amount (3-5 mol%) of $FeCl_3$ at low temperature (-45°C to 25°C).
[b]Allylzincation was carried out under high pressure conditions (25°C, 1 GPa).
[c]X,X = $-OCH_2C(CH_3)_2CH_2O-$
[d]BOX = anionic bis-oxazoline ligand derived from (*S*)-(+)-2-phenylglycinol

cis-2-allyl-3-phenylcyclopropanone acetal **2b** as a single stereoisomer in 85% yield, indicating *cis*-stereochemistry of the carbomagnesation (Table 1, entry 2). The addition of a vinyl Grignard reagent took place smoothly to afford a vinylated cyclopropanone acetal in good yield, while the addition of a substituted alkenyl Grignard reagent afforded the carbometallation product in lower yield (entries 3–5). Chiral cyclopropanone acetals bearing a quaternary chiral center were prepared by enantioselective allylzincation reaction of substituted CPAs **1b** (R^1 = Et) and **1c** (R^1 = Ph) [4], in order to obtain mechanistic information on the subsequent oxidative ring opening reactions (vide infra). Addition of a chiral allylzinc reagent bearing an anionic bis-oxazoline ligand derived from (*S*)-(+)-2-phenylglycinol, thus, gave 2,2-disubstituted cyclopropanone acetal in excellent yield with high enantioselectivity (entries 6 and 7).

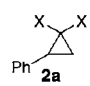
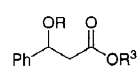
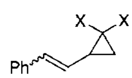
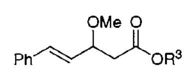
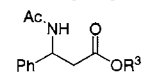
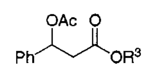
We first examined the oxidative ring cleavage reaction of 2-phenycyclopropanone acetal **2a** (R^1 = H, R^2 = Ph, E = H) under a variety of oxidative conditions. The oxidative ring opening reaction [7] with cerium(IV) ammonium nitrate (CAN) or thallium(III) nitrate under various conditions gave a mixture of products, and the reaction with lead tetraacetate gave none of the desired ring opening product. We finally found that manganese(IV) dioxide (MnO_2) in the presence of an acid is an effective oxidant for the selective ring opening reaction.

The oxidative ring opening reaction was conducted by the addition of a slight excess amount of MnO_2 to the solution of **2a** in methanol in the presence of



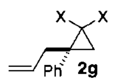
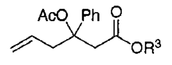
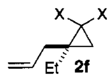
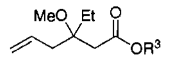
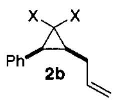
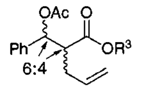
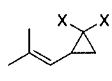
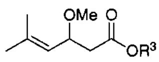
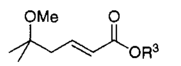
Scheme 2.

Table 2
Oxidative ring opening reaction of **2** with MnO_2 and PbO_2[a]

entry	cyclopropane[c] 2	oxidant /additive[d]	nucleophile /solvent	time	major product[e] [% yield]
1[f]	 **2a**	MnO_2 /CF_3SO_3H	MeOH /MeOH	1 h	 **3a** (R = Me) [71%]
2[f]	 **2d**	MnO_2 /CF_3SO_3H	MeOH /MeOH	2 h	 **3d** [63%]
3[f]	**2a**	MnO_2 /CF_3SO_3H	CH_3CN /CH_3CN	1 h	 **4a** [78%]
4	**2a**	PbO_2 /CF_3SO_3H	MeOH /MeOH	1 h	**3a** (R = Me) [80%]
5	**2a**				**3a** (R = Et) [83%]
6	**2a**	PbO_2 /CF_3SO_3H	ROH /ROH	1.5 - 4.5 h	**3a** (R = *i*-Pr) [81%]
7	**2a**				**3a** (R = OCH_2Ph) [78%]
8	**2a**	PbO_2 /none	AcOH /AcOH	6 h	 **3a** (R = Ac) [84%]
9	**2a**	PbO_2 /CF_3SO_3H	CH_3CN /CH_3CN	2 h	**4a** [77%]

[a]All reactions were carried out at 25°C under nitrogen.
[b]One equivalent of oxidant was used unless otherwise noted.
[c]X, X = $-OCH_2C(CH_3)_2CH_2O-$
[d]Two equivalents of acid were used.
[e]Isolated yield. *Ca.* 5 -15 % of α,β-unsaturated esters (elimination products) formed as byproduct.
[f]Slight excess of trifluoromethane sulfonic acid and MnO_2 were used.

Table 3
Oxidative ring opening reaction of substituted cyclopropanone acetal **2** under various conditions[a]

entry	cyclopropane[c]	oxidant[b]	product [% yield]
1[d]		PbO_2	 **3g** [67%] (racemic)
2[d]		PbO_2	 **3f** [18%] (racemic)
3[e]		PbO_2	 **3b** [54%]
4	 **2e**	MnO_2	 **3e** [39%] +  **3e'** [51%]

[a]All reactions were carried out under N_2 at 25°C for 2-8 h.
[b]PbO_2 (1.0 eq) in acetic acid; MnO_2 (1.3 eq) in the presence of TfOH (2.5 eq) in MeOH.
[c]X, X = -$OCH_2C(CH_3)_2CH_2O$-
[d]Enantiomeric excess of the starting material was >98% ee determined by chiral GC analysis
[e]Geometry of the starting cyclopropanone was determined as >98% cis by ^{1}H NMR.

trifluoromethanesulfonic acid (TfOH) at 25°C. The reaction was complete in 1 h at 25°C to afford β-methoxypropionate ester **3a** in 71% yield (Scheme 2 and Table 2, entry 1). As shown in entry 2, 2-styrylcyclopropanone acetal was also converted to the corresponding β-methoxyester **3d** in good yield under the same conditions. The geometry of the alkenic moiety in the product was exclusively *trans* in spite of the fact that the starting olefin was a mixture of geometrical isomers (*trans*/*cis* = 76:24), indicating the involvement of a sequential one-electron oxidation mechanism (vide infra). An amination reaction could also be achieved when the ring opening reaction of **2a** was carried out in acetonitrile (entry 3). Consecutive regioselective ring opening and trapping of the resulting cationic intermediate with acetonitrile (Ritter-type reaction) accounts for the formation of the β-aminopropionate derivative **4a**.

Lead dioxide (PbO_2) was also found to promote selective ring opening reaction of the cyclopropanone acetals **2**. A stoichiometric amount of PbO_2 in methanol converts **2a** to **3a** in 80% yield in the presence of two equivalents of TfOH (entry 4). This reaction was found to be applicable also to ethanol and isopropanol, and afforded 3-ethoxy and 3-isopropoxy substituted ester, respectively (entries 5 and 6). As shown in entry 7, 3-benzyloxy-3-phenylpropionate derivative **3a** (R = OBn) was also synthesized in 78% yield by using benzyl alcohol as a solvent. When the ring opening reaction of **2a** was carried out in acetic acid, β-acetoxypropionate **3a** (R = OAc) was obtained in 84% yield (entry 8). The ring opening reaction with PbO_2 in CH_3CN afforded the β-aminophenylpropionate derivative **4a** in 77% yield as observed in the reaction with MnO_2 (entry 9).

A series of substituted cyclopropanes **2** were next subjected to the oxidative ring opening reaction conditions (Table 3) in order to study selectivity issues. When an optically active cyclopropanone acetal **2g** was subjected to the PbO_2-promoted ring opening reaction, *racemic* 3-acetoxy-3-phenyl-5-hexenoate ester **3g** was obtained in 67% yield as a sole regioisomer (Table 3, entry 1). An optically active cyclopropanone acetal bearing an ethyl group (**2f**) also gave a racemic product (Table 3, entry 2). When a *cis*-disubstituted cyclopropanone acetal **2b** was treated with PbO_2 in MeOH, 2-allyl-3-methoxy-3-phenylpropionate **3b** was obtained as a sole regioisomer in 54% yield (Table 3, entry 3). The product, however, was a 6:4 mixture of diastereomers, and therefore, it was found that the stereochemistry of starting material was lost completely. The rate of the oxidative ring opening reaction of a cyclopropane substrate without a stabilizing group (e.g. **2f**) was found to be much slower than those of **2a** and **2g** bearing a phenyl group (Table 3, entry 2).

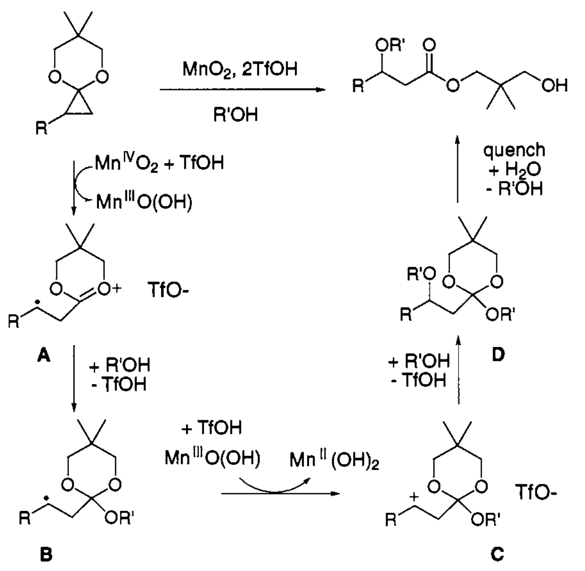
The reaction of 2-styrylcyclopropanone acetal **2d** with MnO_2 in methanol afforded only one product owing to the regioselective ring opening and the regioselective addition of methanol (Table 2, entry 2). However, the oxidative ring opening reaction of *iso*-butenyl cyclopropanone acetal (**2e**) under the same conditions gave a mixture of isomers concerning to the position of double bond in the product (Table 3, entry 4). It should be noted that the regioselectivity of the cyclopropane cleavage is highly selective in all cases as shown in Table 3.

These experimental observations suggest that the reaction proceeds via a stepwise ring opening mechanism. Scheme 3 depicts a plausible reaction mechanism. Thus, one-electron oxidation of the acetal by the metal oxide and addition of solvent take place sequentially to generate a radical cation and a neutral radical intermediates **A** and **B**, respectively. The second one-electron oxidation generates the cation **C**, which is trapped by solvent to give **D**. The regioselectivity of the ring opening depends on the stability of the radical cation intermediate **A**; namely, an sp^2 carbon substituent, such as phenyl or alkenyl group, stabilizes the radical in **A**.

3. Experimental

3.1. General considerations

All reactions were carried out under inert atmosphere (Ar or N_2) in a pre-dried glassware. Anhydrous tetrahydrofuran and diethylether were purchased from Kanto



Scheme 3.

Chemical Co. These ethereal solvents were dried over molecular sieves in a storage flask. The water content of the solvent was determined with a Karl–Fischer Moisture Titrator (MKC-210, Kyoto Electronics Company) to be less than 10 ppm. Unless otherwise noted, materials purchased from Tokyo Kasei Co, Aldrich Inc., and other commercial suppliers, were distilled or recrystallized before use. Alkyllithium reagents were purchased from Aldrich Inc. and Kanto Chemical Co, and titrated prior to use. $FeCl_3$ was purchased from Kanto Chemical Co. Inc. and thoroughly dehydrated by $SOCl_2$ and dried over P_2O_5 under reduced pressure. All ^{1}H-NMR spectra were taken at 400 MHz and ^{13}C-NMR spectra at 100 MHz using a JEOL EXcaliber-400 instrument, are reported in ppm (δ). IR spectra recorded on a JASCO IR-800 are reported in cm^{-1}. GC analysis was performed on a Shimadzu GC 14A and 14B equipped with a capillary column, HR-1 (0.25 mm ID × 25 m) or CP-Chirasil-DEX CB (0.25 mm ID × 25 m). Elemental analyses were performed on a Perkin–Elmer 2400CHN elemental analyzer. Mass spectra were obtained by the atmospheric chemical ionization (APCI) method with a Shimadzu LCMS-QP8000.

*3.2. Representative procedure for carbometallation and successive electrophilic trapping reaction of cyclopropenone acetal; preparation of 2-allyl-3-phenylcyclopropanone 2,2-dimethyl-1,3-propanediyl acetal (**2b**)*

To a solution of phenylmagnesium bromide (12 mmol) and cyclopropenone acetal **1** (1.40 g, 10 mmol) in dry THF (36 ml) was added a 0.1 M THF solution of $FeCl_3$ (3 ml, 0.3 mmol) at −45°C. The colorless reaction mixture turned dark brown and the resulting solution was stirred for about 4 h at that temperature. Allyl bromide (3.63 g, 30 mmol) was added at −45°C dropwise, and then the reaction mixture was warmed to 25°C. The reaction mixture was diluted with ethyl acetate and 1.5 N aqueous HCl. Aqueous layer was extracted with ethyl acetate twice and combined organics were washed with brine, and then dried over $MgSO_4$. Evaporation of solvent afforded a pale yellow oil (2.77 g). Purification by silica gel chromatography (silica gel; 60 g, eluent hexane–ethyl acetate; 100:0–95:5) afforded 2.21 g of disubstituted cyclopropanone acetal **2b** ($R^1 = H$, $R^2 = Ph$, $E = CH_2CH{=}CH_2$) (85% yield).

Compound **2b**. IR (neat, cm^{-1}) 3060(s), 2956(m), 2866(s), 1732(m), 1498(s), 1471(m), 1394(s), 1263(m), 1105(m), 1022(m), 910(s), 766(s), 702(s); ^{1}H-NMR (400 MHz, $CDCl_3$) (δ) 0.94 (s, 3H), 1.08 (s, 3H), 1.62 (ddd, $J = 7.1$, 7.3, 11.0 Hz, 1H), 2.08–2.16 (m, 1H), 2.18–2.25 (m, 1H), 2.38 (d, $J = 11.0$ Hz, 1H), 3.46 (d, $J = 10.5$ Hz, 1H), 3.57 (d, $J = 10.5$ Hz, 1H), 3.58 (br s, 2H), 4.93 (ddd, $J = 10.3$, 4.2, 1.5 Hz, 1H), 5.02 (ddd, $J = 17.1$, 3.4, 1.6 Hz, 1H), 5.70–5.82 (m, 1H), 7.10–7.35 (m, 5H); ^{13}C-NMR (100 MHz, $CDCl_3$) (δ) 22.3, 22.6, 26.2, 29.1, 30.9, 31.5, 75.5, 76.2, 91.5, 114.9, 125.6, 127.8 (2C), 129.0 (2C), 136.1, 137.0; Anal. Found: C, 79.30; H, 8.60. Calc. for $C_{17}H_{22}O_2$: C, 79.03; H, 8.58%.

2-Phenylcyclopropanone 2,2-dimethyl-1,3-propanediyl acetal (**2a**). IR (CCl_4, cm^{-1}) 2958(s), 2856(m), 1471(m), 1173(s), 1074(s), 1043(m), 908(s), 696(s); ^{1}H-NMR (400 MHz, $CDCl_3$) (δ) 0.80 (s, 3H), 1.13 (s, 3H), 1.36 (dd, $J = 6.4$, 7.2 Hz, 1H), 1.52 (dd, $J = 6.4$, 10.4 Hz, 1H), 2.37 (dd, $J = 7.2$, 10.4 Hz, 1H), 3.12 (d, $J = 10.8$ Hz, 1H), 3.32 (d, $J = 10.8$ Hz, 1H), 3.59 (distorted d, $J = 12.4$ Hz, 1H), 3.61 (distorted d, $J = 12.4$ Hz, 1H), 7.1–7.3 (m, 5H); ^{13}C-NMR (100 MHz, $CDCl_3$) (δ) 19.6, 22.1, 22.5, 30.0, 30.5, 75.7, 76.2, 90.5, 125.4, 126.9 (2C), 127.8 (2C), 137.2; Anal. Found: C, 77.00; H, 8.30. Calc. for $C_{14}H_{18}O_2$: C, 77.03; H, 8.31%.

*3.3. Preparation of (2S)-2-allyl-2-phenylcyclopropanone 2,2-dimethyl-1,3-propanediyl acetal (**2g**)*

To a solution of bis-oxazoline (170 mg, 0.56 mmol) and 2,2′-bipyridyl (ca. 1 mg) in dry THF (0.56 ml) was added a 1.60 M solution of BuLi in hexane at 0°C until the clear solution turned into a red-brown suspension. After the addition of BuLi, the reaction mixture was stirred for 20 min at room temperature (r.t.) and then cooled to 0°C at which time a 0.88 M solution of allylzinc bromide in THF (0.55 ml, 0.48 mmol) was added to the solution. The clear red solution was allowed to warm to r.t. for 20 min and then cooled back to 0°C. A solution of CPA **1c** (95.1 mg, 0.44 mmol) in dry THF (1.07 ml) was then added dropwise to the reaction mixture. The reaction mixture (1.73 ml) was transferred into an oven-dried Teflon® vessel with a screw cap under an inert atmosphere. The reaction vessel was maintained under high pressure (1 GPa) for 13 h at 25°C. The reaction mixture was quenched with saturated NH_4Cl (20 μl), filtered through a pad of Florisil®, and concentrated in vacuo. Purification of the residual oil on silica gel afforded the allylation product as a colorless oil (77 mg, 98% yield). Enantiomeric excess of **2g** was determined as > 98% ee by capillary GLC analysis (CP-Chirasil-DEX-CB, 0.25-mm ID × 25 m, 120°C, retention times; 59.24 and 59.92 min, respectively).

Compound **2g**. IR (neat, cm^{-1}) 3073, 2956, 2856, 1639, 1602, 1498, 1471, 1446, 1351, 1292, 1157, 1132, 1070, 1043, 910, 700; ^{1}H-NMR (400 MHz, $CDCl_3$) (δ) 0.93 (s, 3H), 1.07 (d, $J = 5.9$ Hz, 1H), 1.07 (s, 3H), 1.37 (dd, $J = 1.5$, 5.9 Hz, 1H), 2.34 (dd with shoulders, $J = 7.3$, 14.7 Hz, 1H), 2.76 (ddd, $J = 1.5$, 6.4, 14.7 Hz, 1H), 3.30 (d, $J = 11.0$ Hz, 1H), 3.35 (dd, $J = 0.97$, 11.0 Hz, 1H), 3.60 (distorted dd, $J = 0.97$, 10.7 Hz, 1H), 3.62 (distorted d, $J = 10.7$ Hz, 1H), 4.86–4.94 (m, 2H), 5.61–5.73 (m, 1H) 7.15–7.22 (m, 1H) 7.27–7.31 (m, 4H); ^{13}C-NMR (100 MHz, $CDCl_3$) (δ) 22.0, 22.1, 22.7, 30.6, 37.4, 38.6, 75.5, 76.4, 92.0, 116.3, 126.2, 127.9 (2C), 129.2 (2C), 135.4, 139.4; $[\alpha]_D^{20} = 1.02$ ($c = 3.9$, benzene); Anal. Found: C, 79.07; H, 8.83. Calc. for $C_{17}H_{22}O_2$: C, 79.03; H, 8.59%.

*3.4. Oxidative ring opening reaction of **2a** with MnO_2 in MeOH; preparation of 3-hydroxy-2,2-dimethylpropyl 3-methoxy-3-phenylpropanoate (**3a**) (R = Me)*

To a solution of 2-phenylcycropropanone acetal **2a** (64.9 mg, 0.30 mmol) in 1.5 ml of MeOH was added 25.9 mg of MnO_2 (0.30 mmol). To this reaction mixture was added CF_3SO_3H (52.2 μl, 0.40 mmol) at 25°C. After stirring for 2 h, the solution was quenched by the addition of water (1.5 ml). The suspension was filtered and organic layer was separated and aqueous layer was extracted with 1.5 ml of ether (three times). Combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated in vacuo to afford a crude product (73.9 mg). The crude product was purified by flash column chromatography (silica gel 2.3 g, elution with 12.5% and then 20% EtOAc–hexane) to afford **3a** (56.7 mg, 71%) and the elimination compound (3.5 mg, 5%).

Compound **3a**. IR (neat, cm^{-1}) 3481(br s), 2960(s), 2875(w), 1734(s), 1456(m), 1375(m), 1271(m), 1161(s), 1105(s), 1055(s), 762(m), 702(s), 447(s); ^{1}H-NMR (400 MHz, $CDCl_3$) (δ) 0.89 (s, 3H), 0.90 (s, 3H), 2.62 (dd, $J = 4.8$, 14.8 Hz, 1H), 2.83 (dd, $J = 9.2$, 15.2 Hz, 1H), 3.21 (s, 3H), 3.25 (dd, $J = 11.2$, 15.2 Hz, 2H), 3.96 (dd, $J = 11.2$, 16.0 Hz, 2H), 4.62 (dd, $J = 4.8$, 9.2 Hz, 1H), 7.29–7.39 (m, 5H); ^{13}C-NMR (100 MHz, $CDCl_3$) (δ) 21.5 (2C), 36.4, 43.6, 55.7, 68.1, 69.6, 80.1, 126.5 (2C), 128.0, 128.5 (2C), 140.1, 171.5; Anal. Found: C, 67.37; H, 8.27. Calc. for $C_{15}H_{22}O_4$: C, 67.65; H, 8.33%.

3-Hydroxy-2,2-dimethylpropyl 3-methoxy-5-phenyl-4-(*E*)-pentenoate (**3d**). IR (neat, cm^{-1}) 3481(br s), 2962(s), 2866(m), 1732(s), 1473(m), 1375(m), 1161(s), 1101(s), 1055(s), 970(m), 910(m), 733(s), 694(m); ^{1}H-NMR (400 MHz, $CDCl_3$) (δ) 0.91 (s, 3H), 0.92 (s, 3H), 2.59 (dd, $J = 4.8$, 14.8 Hz, 1H), 2.72 (dd, $J = 8.4$, 14.8 Hz, 2H), 3.30 (s, 2H), 3.32 (s, 3H), 3.97 (s, 2H), 4.18–4.24 (m, 1H), 6.07 (dd, $J = 8.0$, 16.0 Hz, 1H), 6.63 (d, $J = 16.0$ Hz, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$) (δ) 21.7 (2C), 36.4, 41.4, 56.4, 68.1, 69.7, 78.8, 126.4 (2C), 127.7, 127.9, 128.4 (2C), 133.3, 135.9, 171.3; Anal. Found: C, 69.61; H, 8.08. Calc. for $C_{17}H_{24}O_4$: C, 69.84; H, 8.27%.

*3.5. Oxidative ring opening reaction of **2a** with MnO_2 in CH_3CN; preparation of 3-hydroxy-2,2-dimethylpropyl 3-(acetylamino)-3-phenylpropanoate (**4a**)*

To a solution of phenylcyclopropanone acetal **2a** (43.2 mg, 0.20 mmol) in 1.0 ml of CH_3CN was added 21.3 mg of MnO_2 (0.24 mmol). To this reaction mixture was added CF_3SO_3H (48.7 μl, 0.55 mmol) at 25°C. After stirring for 1 h, the reaction was quenched with H_2O (1.0 ml). The suspension was filtered and organic layer was separated and aqueous layer was extracted with 1.0 ml of ether (three times). Combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated in vacuo to afford a crude product (61.0 mg). The crude product was purified by flash column chromatography (silica gel 2.7 g, elution with 25% and then 70% EtOAc–hexane) to afford **4a** (45 mg, 78%) and the elimination compound (8.9 mg, 11%).

Compound **4a**. IR (neat, cm^{-1}) 3298(br s), 3065(w), 2963(s), 1732(s), 1652(s), 1548(s), 1375(s), 1259(s), 1168(s), 1034(s), 1004(m), 762(m), 701(s), 639(m); ^{1}H-NMR (400 MHz, $CDCl_3$) (δ) 0.83 (s, 3H), 0.83 (s, 3H), 2.01 (s, 3H), 2.86 (dd, $J = 6.0$, 15.2 Hz, 1H), 2.92 (dd, $J = 7.2$, 15.2 Hz, 1H), 3.10 (d, $J = 11.2$ Hz, 1H), 3.27 (d, $J = 11.2$ Hz, 1H), 3.84 (dd, $J = 11.2$, 16.4 Hz, 2H), 5.48 (dd, $J = 6.4$, 14.4 Hz, 1H), 6.48 (br d, $J = 6.0$ Hz, 1H), 7.24–7.37 (m, 5H); ^{13}C-NMR (100 MHz, $CDCl_3$) (δ) 21.6 (2C), 23.5, 36.1, 40.6, 49.9, 67.8, 69.8, 126.2 (2C), 127.8, 128.7 (2C), 140.1, 169.3, 171.5; Anal. Found: C, 64.92; H, 7.92; N, 4.59. Calc. for $C_{16}H_{23}NO_4$: C, 65.51; H, 7.90; N, 4.77%.

*3.6. Oxidative ring opening reaction of **2a** by PbO_2 in MeOH; preparation of 3-hydroxy-2,2-dimethylpropyl 3-methoxy-3-phenylpropanoate (**3a**) (R = Me)*

To a solution of 2-phenyl cyclopropenone acetal **2a** (43.1 mg, 0.20 mmol) in 0.5 ml of MeOH was added 47.8 mg of PbO_2 (0.20 mmol). To this reaction mixture was added CF_3SO_3H (34.7 μl, 0.40 mmol) at 25°C.

After stirring for 1 h, the reaction was quenched with H_2O (0.5 ml). The suspension was filtered and organic layer was separated. The aqueous layer was extracted with 0.5 ml of ether (three times). Combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated in vacuo to afford a crude product (51.5 mg). The crude product was purified by flash column chromatography (silica gel 2.0 g, elution with 12.5% and then 20% EtOAc–hexane) to afford **3a** (42.2 mg, 80%) and the elimination compound (4.9 mg, 11%).

3-Hydroxy-2,2-dimethylpropyl 3-ethoxy-3-phenylpropanoate **3a** (R = Et). IR (neat, cm^{-1}) 3468(br s), 2972(s), 2876(s), 1735(s), 1474(m), 1455(m), 1376(s), 1345(m), 1309(m), 1270(s), 1171(s), 1096(s), 1056(s), 1003(m), 914(m), 761(m), 734(s), 703(s); ^{1}H-NMR (400 MHz, $CDCl_3$) (δ) 0.90 (s, 3H), 0.93 (s, 3H), 1.15 (t, $J = 7.2$ Hz, 3H), 2.62 (dd, $J = 4.8$, 14.8 Hz, 1H), 2.83 (dd, $J = 9.6$, 14.8 Hz, 1H), 3.26 (dd, $J = 9.6$, 22.0 Hz, 2H), 3.49 (q, 6.0 Hz, 2H), 3.95 (dd, $J = 6.8$, 17.6 Hz, 2H), 4.74 (dd, $J = 4.8$, 17.6 Hz, 1H), 7.26–7.38 (m, 5H); ^{13}C-NMR (100 MHz, $CDCl_3$) (δ) 15.1, 21.4 (2C), 36.4, 43.8, 64.3, 68.0, 69.5, 78.3, 126.5 (2C), 128.0, 128.5 (2C), 141.0, 171.8; APCI–MS m/z (%) = 281 (13) [$M^+ - H$], 277 (100) [$M^+ - 3H$], 263 (99) [$M^+ - OH$], 235 (17) [$M^+ - OMe$], 217 (21) [$M^+ - OMe - H_2O$].

3-Hydroxy-2,2-dimethylpropyl 3-isopropoxy-3-phenylpropanoate **3a** (R = *i*-Pr). IR (neat, cm^{-1}) 3462(br s), 2970(s), 2885(w), 1732(s), 1456(m), 1377(m), 1269(m), 1167(s), 1051(s), 912(m), 733(m), 702(m); ^{1}H-NMR (400 MHz, $CDCl_3$) (δ) 0.89 (s, 3H), 0.90 (s, 3H), 1.05 (d, $J = 6.0$ Hz, 3H), 1.11 (d, $J = 5.6$ Hz, 3H), 2.58 (dd, $J = 4.4$, 14.8 Hz, 1H), 2.79 (dd, $J = 9.6$, 14.8 Hz, 1H), 3.20 (d, $J = 11.6$ Hz, 1H), 3.29 (d, $J = 11.6$ Hz, 1H), 3.49 (sep, $J = 6.0$ Hz, 1H), 3.84 (d, $J = 11.2$ Hz, 1H), 4.04 (d, $J = 10.8$, Hz, 1H), 4.86 (dd, $J = 4.4$, 9.6 Hz, 1H), 7.26–7.40 (m, 5H); ^{13}C-NMR (100 MHz, $CDCl_3$) (δ) 21.1, 21.6, 23.4, 36.5, 44.2, 68.1, 69.3, 69.6, 75.5, 126.4 (2C), 127.7, 128.4 (2C), 141.7, 171.7; Anal. Found: C, 69.07; H, 8.62. Calc. for $C_{17}H_{26}O_4$: C, 69.36; H, 8.90%.

3-Hydroxy-2,2-dimethylpropyl 3-benzyloxy-3-phenylpropanoate **3a** (R = CH_2Ph). IR (neat, cm^{-1}) 3467(br s), 3063(m), 3031(m), 2961(s), 2875(w), 1735(s), 1495(m), 1472(m), 1455(m), 1377(m), 1308(m), 1271(m), 1200(m), 1168(s), 1057(s), 1004(m), 912(w), 759(m), 739(m), 701(s); ^{1}H-NMR (400 MHz, $CDCl_3$) (δ) 0.85 (s, 6H), 2.67 (dd, $J = 4.8$, 15.2 Hz, 1H), 2.91 (dd, $J = 9.2$, 15.2 Hz, 1H), 3.17 (dd, $J = 11.2$, 28.0 Hz, 2H), 3.88 (d, $J = 10.8$ Hz, 1H), 3.97 (d, $J = 10.8$, Hz, 1H), 4.30 (d, $J = 11.6$ Hz, 1H), 4.43 (d, $J = 11.6$, Hz, 1H), 4.86 (dd, $J = 4.8$, 9.2 Hz, 1H), 7.18–7.43 (m, 10H); ^{13}C-NMR (100 MHz, $CDCl_3$) (δ) 21.4 (2C), 36.4, 43.6, 68.0, 69.5, 70.7, 78.0, 126.7 (2C), 127.6, 127.8 (2C), 128.2, 128.3 (2C), 128.7 (2C), 137.9, 140.5, 171.6; Anal. Found: C, 73.84; H, 7.63. Calc. for $C_{21}H_{26}O_4$: C, 73.66; H, 7.65%.

3-Hydroxy-2,2-dimethylpropyl 3-acetoxy-3-phenylpropanoate **3a** (R = Ac). IR (neat, cm^{-1}) 3843(br s), 2964(s), 2875(m), 1739(s), 1456(m), 1373(s), 1232(s), 1171(s), 1026(s), 733(m); ^{1}H-NMR (400 MHz, $CDCl_3$) (δ) 0.88 (s, 3H), 0.88 (s, 3H), 2.06 (s, 3H), 2.81 (dd, $J = 5.2$, 15.6 Hz, 1H), 3.00 (dd, $J = 9.2$, 15.6 Hz, 1H), 3.24 (dd, $J = 11.6$, 15.6 Hz, 2H), 3.93 (dd, $J = 10.8$, 22.4 Hz, 2H), 6.17 (dd, $J = 4.8$, 9.2 Hz, 1H), 7.27–7.39 (m, 5H); ^{13}C-NMR (100 MHz, $CDCl_3$) (δ) 21.12, 21.46 (2C), 36.27, 41.54, 67.88, 69.67, 72.19, 126.34 (2C), 128.34, 128.52 (2C), 138.80, 169.70, 170.13; APCI–MS m/z (%) = 295 (8) [$M^+ + H$], 277 (100) [$M^+ - OH$], 235 (18) [$M^+ - OAc$], 217 (40) [$M^+ - OAc - H_2O$].

*3.7. Oxidative ring opening reaction of **2g** with PbO_2 in AcOH; preparation of 3-hydroxy-2,2-dimethylpropyl 3-acetoxy-3-phenyl-5-hexenoate (**3g**)*

To a solution of 2-allyl-2-phenylcyclopropanone acetal (**2g**) (49.2 mg, 0.19 mmol) in 0.5 ml of dry acetic acid was added 49.5 mg of PbO_2 (0.21 mmol) at 25°C. The reaction mixture was stirred for 4 h and, then, quenched with H_2O (0.5 ml). The suspension was filtered and organic layer was separated and aqueous layer was extracted with 0.5 ml of ether (three times). Combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated in vacuo. The crude product (66.1 mg) was purified by flash column chromatography (silica gel 2.0 g, elution with 12.5% and then 20% EtOAc–hexane) to afford **3g** (48.7 mg, 67%) and the elimination compound (8.9 mg, 14%).

Compound **3g**. IR (neat, cm^{-1}) 3566(br s), 2960(s), 2866(w), 1732(s), 1448(m), 1373(s), 1236(s), 1018(m), 920(m), 700(m); ^{1}H-NMR (400 MHz, $CDCl_3$) (δ) 0.75 (s, 3H), 0.78 (s, 3H), 2.11 (s, 3H), 2.96 (dd, $J = 6.8$, 14.0 Hz, 1H), 3.03 (s, 2H), 3.19 (dd, $J = 8.0$, 18.4 Hz, 1H), 3.29 (d, $J = 14.0$ Hz, 1H), 3.51 (d, $J = 18.4$ Hz, 1H), 3.77 (dd, $J = 10.8$, 13.2 Hz, 2H), 5.06 (d, $J = 9.6$ Hz, 1H), 5.08 (d, $J = 9.2$ Hz, 1H), 5.41–5.51 (m, 1H), 7.25–7.29 (m, 1H), 7.33–7.38 (m, 4H); ^{13}C-NMR (100 MHz, $CDCl_3$) (δ) 21.4, 21.5, 22.2, 36.1, 41.9, 43.1, 67.8, 69.5, 82.8, 119.4, 124.8 (2C), 127.4, 128.2 (2C), 131.5, 141.7, 170.0; Anal. Found: C, 67.94; H, 7.81. Calc. for $C_{19}H_{26}O_5$: C, 68.24; H, 7.84%.

3-Hydroxy-2,2-dimethylpropyl 3-methoxy-3-ethyl-5-hexenoate (**3f**). IR (neat, cm^{-1}) 3446(br s), 2968(s), 2885(w), 1732(s), 1458(m), 1373(m), 1186(m), 1065(m), 918(m); ^{1}H-NMR (400 MHz, $CDCl_3$) (δ) 0.89 (t, $J = 7.2$ Hz, 3H), 0.93 (s, 6H), 1.62 (dq, $J = 2.0$, 7.6 Hz, 2H), 3.39 (d, $J = 6.4$ Hz, 2H), 2.54 (dd, $J = 14.0$, 17.2 Hz, 2H), 3.24 (s, 3H), 3.33 (s, 2H), 3.94 (s, 2H), 5.13 (d, $J = 9.2$ Hz, 1H), 5.14 (d, $J = 17.6$ Hz, 1H), 5.76–5.86 (m, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$) (δ) 7.5, 21.7, 21.7, 27.3, 36.4, 39.0, 39.7, 49.0, 68.5, 69.9, 78.0, 118.4, 122.2, 171.3; APCI–MS m/z (%) = 259 (30) [$M^+ + H$], 241 (13) [$M^+ - OH$], 227 (100) [$M^+ - OMe$], 209 (11) [$M^+ - OMe - H_2O$].

3-Hydroxy-2,2-dimethylpropyl 2-[acetoxy(phenyl)-methyl]-4-pentenoate (**3b**) major diastereomer. IR (neat, cm^{-1}) 3525(br s), 2962(s), 2875(w), 1734(s), 1373(m), 1232(s), 1182(m), 1024(m), 916(m), 733(m), 702(m); ^1H-NMR (400 MHz, $CDCl_3$) (δ) 0.93 (s, 3H), 0.94 (s, 3H), 2.01 (s, 3H), 1.95–2.01 (m, 1H), 2.15–2.23 (m, 1H), 3.01–3.07 (m, 1H), 3.33 (dd, $J = 11.6$, 31.6 Hz, 1H), 3.94 (dd, $J = 10.8$, 12.8 Hz, 2H), 4.97 (dd, $J = 1.2$, 8.0 Hz, 1H), 5.00 (d, $J = 10.0$ Hz, 1H), 5.58–5.68 (m, 1H), 5.86 (d, $J = 10.4$ Hz, 1H); 7.30–7.37 (m, 5H); ^{13}C-NMR (100 MHz, $CDCl_3$) (δ) 21.1, 21.6 (2C), 33.3, 35.3, 51.7, 68.0, 69.8, 76.5, 117.6, 127.3 (2C), 128.5 (2C), 128.6, 133.6, 137.4, 169.5, 172.8. Minor diastereomer. IR (neat, cm^{-1}) 3523(br s), 2962(s), 2885(w), 1732(s), 1456(m), 1373(s), 1234(s), 1026(s), 916(s), 734(s), 700(s); ^1H-NMR (400 MHz, $CDCl_3$) (δ) 0.76 (s, 3H), 0.78 (s, 3H), 2.08 (s, 3H), 2.42–2.54 (m, 2H), 3.01 (dd, $J = 11.6$, 20.0 Hz, 1H), 3.03–3.08 (m, 1H), 3.65 (d, $J = 10.8$ Hz, 1H), 3.78 (d, $J = 11.2$ Hz, 1H), 5.04 (dd, $J = 1.6$, 8.4 Hz, 1H), 5.08 (ddd, $J = 1.2$, 2.4, 16.8 Hz, 1H), 5.70–5.81 (m, 1H), 5.96 (d, $J = 8.8$ Hz, 1H); 7.26–7.47 (m, 5H); ^{13}C-NMR (100 MHz, $CDCl_3$) (δ) 21.2, 21.5, 33.0, 36.1, 51.8, 67.7, 69.6, 75.5, 117.2, 127.0 (2C), 128.4 (3C), 134.4, 137.9, 169.7, 172.3; APCI–MS m/z (%) = 335 (35) $[M^+ + H]$, 317 (43) $[M^+ - OH]$, 275 (100) $[M^+ - OAc]$, 257 (33) $[M^+ - OAc - H_2O]$.

3-Hydroxy-2,2-dimethylpropyl 2-methoxy-5-methyl-4-hexenoate (**3e**). IR (neat, cm^{-1}) 3459(br s), 2969(s), 2821(w), 1737(s), 1452(m), 1377(m), 1278(m), 1212(m), 1151(m), 1099(m), 1057(m), 1004(m), 838(m); ^1H-NMR (400 MHz, $CDCl_3$) (δ) 0.92 (s, 6H), 1.73 (s, 3H), 1.76 (s, 3H), 2.42 (dd, $J = 5.6$, 14.8 Hz, 2H), 2.60 (dd, $J = 8.4$, 14.8 Hz, 2H), 3.23 (s, 3H), 3.29 (s, 2H), 3.96 (dd, $J = 10.8$, 22.0 Hz, 2H), 4.34 (m, 1H), 5.03 (d, $J = 8.4$ Hz, 1H), ^{13}C-NMR (100 MHz, $CDCl_3$) (δ) 18.4, 21.6, 21.6, 25.9, 36.5, 41.3, 55.7, 68.2, 69.6, 74.0, 123.9, 137.7, 171.6; Anal. Found: C, 63.76; H, 9.65. Calc. for $C_{13}H_{24}O_4$: C, 63.91; H, 9.90%.

3-Hydroxy-2,2-dimethylpropyl 5-methoxy-5-methyl-2-hexenoate (**3e′**). IR (neat, cm^{-1}) 3450(br s), 2977(s), 2826(w), 1737(s), 1473(m), 1376(m), 1254(m), 1170(s), 1062(s), 1006(m), 978(m), 853(w), 754(w); ^1H-NMR (400 MHz, $CDCl_3$) (δ) 0.92 (s, 6H), 1.27 (s, 6H), 3.13 (d, $J = 6.8$ Hz, 2H), 3.15 (s, 3H), 3.31 (s, 2H), 3.96 (s, 2H), 5.58 (d, $J = 16.4$ Hz, 1H), 5.69 (dt, $J = 6.8$, 15.6 Hz, 1H), ^{13}C-NMR (100 MHz, $CDCl_3$) (δ) 21.5, 25.7, 36.5, 37.9, 50.4, 68.3, 69.6, 74.7, 121.5, 139.5, 172.1; Anal. Found: C, 63.68; H, 9.62. Calc. for $C_{13}H_{24}O_4$: C, 63.91; H, 9.90%.

4. Conclusions

In summary, we have demonstrated that carbometallation of a cyclopropenone acetal provides useful synthetic routes to a variety of substituted esters. The two-step reaction sequence afforded β-alkoxy and β-aminoesters of some structural varieties. It has been shown for the first time that metal oxide such as MnO_2 and PbO_2 can be used for selective ring opening reaction of substituted cyclopropanes and the reaction affords a variety of synthetically valuable protected β-hydroxy and β-aminopropionate esters.

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