α-Substituted Cyclobutanones as Protecting Groups for Carboxylic Acids[1]

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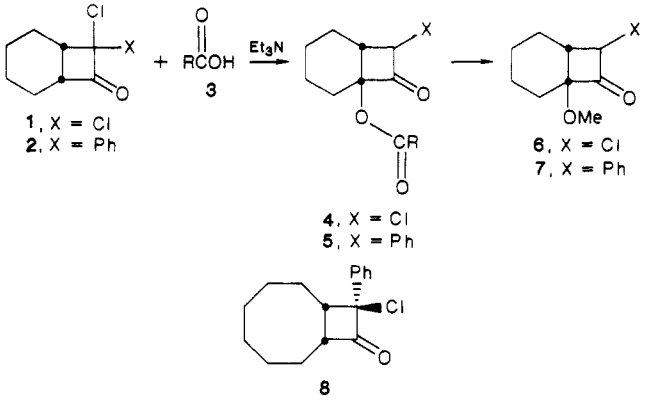
Recently we described a cine substitution reaction of fused chlorocyclobutanones **1** or **2** with carboxylic acids that proceeds rapidly and efficiently in the presence of triethylamine to produce α-acyloxy ketones **4** or **5**.[2]



These resulting ester derivatives of tertiary alcohols may be expected to be relatively stable to hydrolysis in general because of steric factors and to acid hydrolysis in particular since the presence of an α carbonyl group should destabilize an adjacent carbocation.[3] Yet our preliminary findings[2] indicated that esters **4** or **5** react with NaOMe–MeOH at room temperature to form methoxy ketone **6** or **7** with apparent release of carboxylic acid **3**. This suggested a possible application of this system to protection of carboxylic acids.[4]

We now report studies to establish to what extent esters of type **5** can be used as protecting groups that can withstand acid treatment yet be easily removed with base.

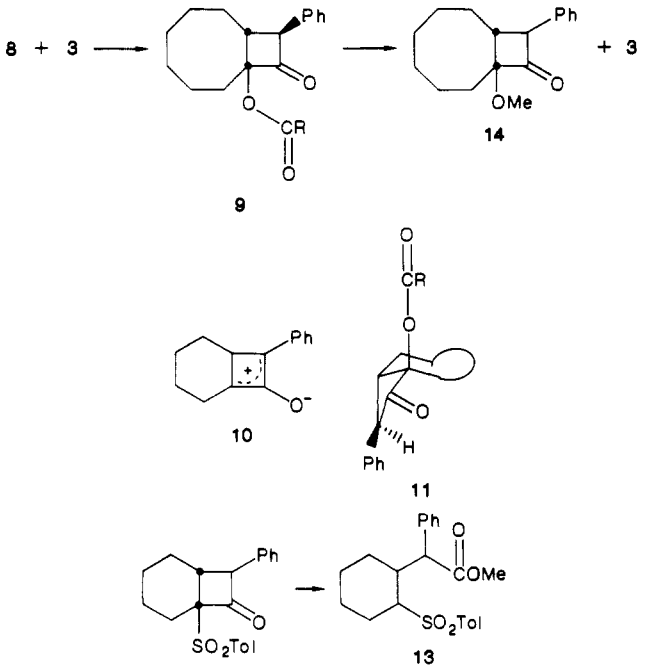
The starting chlorocyclobutanones (e.g., **1** and **2**) are readily accessible by the reaction of dichloroketene or related chloroketenes with cycloalkenes.[2,5] Among the systems that we now examined for protection of carboxylic acids, the most suitable appeared to be the 2-chloro-2-phenylbicyclo[4.2.0]octanone **2** or its bicyclodecanone analogue **8**. Because **2** decomposes more readily and is more difficult to purify, we prefer the fused cyclooctane derivative **8**. We assign the endo configuration to the phenyl substituent in **2** and **8** by analogy with related cyclopentadiene adducts.[6]

The protection step, namely, formation of the keto esters **5** or **9**, took place smoothly and in good yield at room temperature in acetone by reaction of **2** or **8** respectively with a number of carboxylic acids **3** (see Table I) in the presence of triethylamine.

Table I. Protection of Carboxylic Acids 3 by Means of 2 or 8 at 20 °C for 12 h. Formation of Acyloxycyclobutanones 5 or 9

	carboxylic acid **3**	% yield of **5**[a]	% yield of **9**[a]
a	$PhCO_2H$	80	90
b	p-$MeC_6H_4CO_2H$		95
c	o-$NO_2C_6H_4CO_2H$		50
d	$PhCH_2CO_2H$	65	86
e	$PhCH_2CH(NHBOC)CO_2H$	70	95
f	o-$AcOC_6H_4CO_2H$	95	60
g	p-$MeC_6H_4SO_2H$	50[b]	
h	$MeCO_2H$	82	80
i	mesitoic acid	82	
j	p-$NO_2C_6H_4CO_2H$		65
k	$EtO_2C(CH_2)_4CO_2H$	75	

[a] Purified by chromatography. [b] Product is sulfone **12**.



The formation of **5** or **9** presumably proceeds via an oxyallyl cation (see **10**) which is trapped by the carboxylate ion. Electron-withdrawing groups as in *o*-nitrobenzoic acid (**3c**) slow down the reaction, consistent with poorer nucleophilicity of the carboxylate ion. Sodium benzoate in the presence of 18-crown-6 in benzene can be substituted for the triethylammonium benzoate. Aliphatic and aromatic acids as well as *N*-BOC amino acids and hindered acids such as mesitoic acid gave good yields of the α-acyloxy ketones **5** or **9**.

The advantage of the phenyl-substituted system **5** or **9** over the chloro ketone **4** is that only one isomer (presumably with Ph cis to the acyloxy group and pseudoequatorial to the puckered cyclobutanone as shown in **11**) is formed. The stereochemical assignment is based on X-ray diffraction[2] for keto ester **5** (R = *o*-methoxyphenyl) as well as on NMR spectra. ^1H NMR spectra for the latter keto ester as well as for **5a** show a doublet for the proton α to phenyl at 4.15 ppm. All esters **5** exhibited this doublet near 4.1 + 0.1 ppm.[7] In esters **9**, the doublet α to phenyl

(1) Synthetic Methods. 31. Part 30: Hassner, A.; Rai, L. S. *Synth. Commun.*, in press.
(2) Hassner, A.; Dillon, J.; Onan, K. D. *J. Org. Chem.* **1986**, *51*, 3315.
(3) For comparison, *tert*-butyl esters are cleaved by trifluoroacetic acid at 0 °C (via a *tert*-butyl cation). See: Bryan, D. B.; Hall, R. F.; Holden, K. G.; Huffman, W. F.; Gleason, J. G. *J. Am. Chem. Soc.* **1977**, *99*, 2353. The relative stability of keto esters **5** and **9** to acids can be ascribed to reluctance to generate in acid medium a positive charge α to the keto function.
(4) For carboxylic acid protecting groups, see: Haslam, E. *Tetrahedron* **1980**, *36*, 2409. Greene, T. W. *Protective Groups in Organic Synthesis*; J. Wiley: New York, 1981.
(5) Hassner, A.; Dillon, J. L.; Krepski, L. R. *Tetrahedron Lett.* **1983**, *24*, 1135. Brady, W. T. *Tetrahedron* **1981**, *37*, 2949.
(6) Rey, M.; Roberts, S.; Dieffenbacher, A.; Dreiding, A. S. *Helv. Chim. Acta* **1970**, *53*, 417.
(7) In the chloro analogues **4**, the doublet in the trans (Cl:OCOR) isomer absorbed at 0.7 ppm lower field than in the cis isomer (ref 5).

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Table II. Reaction of Esters 5 or 9 with Et_3N in MeOH–H_2O (9:1) at 20 °C for 12–24 h. Formation of RCO_2H 3 and Ethers 7 or 14

keto ester	% yield of RCO_2H 3 + keto ether
5d	**3d** (85) + 7 (86)
5f	salicylic acid (95) + 7 (97)
9f	salicylic acid (85) + 14 (75)
5e	**3e** (70) + 7 (80)
9a	**3a** (85) + 14 (90, 45[a,b])
9b	**3b** (95) + 14 (97, 47[a,b])
9c	**3c** (90) + 14 (95, 100[a,b])
9d	**3d** (75) + 14 (88)
9e	**3e** (90) + 14 (90)
5i	**3i** (60[d]) + 7 (90)
9j	**3j** (53[a,c]) + 14 (53)
5h	**3h** (80[a])[e] + 7 (75)
9h	**3h** (90[a]) + 14 (80)
5k	**3k** (89) + 7 (95)
5a	**3a** (65) + 7 (95)

[a] 7 (or 14):RCO_2H = 1:1 determined by NMR. [b] Reaction in 3 h. [c] Reaction in 4 h. [d] 10% unreacted **5i** was present. [e] Isolated as $Et_3NH^+OAc^-$.

was found at 3.8 + 0.1 ppm. Furthermore, NOE experiments on **9b** (R = *p*-toluyl) indicated coupling between the two phenyl rings, which is only possible in the cis configuration.

Chloro ketone **2** did not react with *p*-toluenesulfonic acid but did undergo substitution with *p*-toluenesulfinic acid to produce sulfone **12**. The latter reacted with sodium methoxide or triethylamine in methanol–water with ring opening to produce sulfone ester **13**.

We investigated the stability of esters **5** or **9** and examined different reaction conditions for their deprotection to RCOOH. Benzoate **5a** was stable to trifluoroacetic acid at reflux for 24 h,[3] to 5% HCl in MeOH–water (9:1) at 20 °C overnight or in refluxing THF for 4 h, to refluxing methanol for 24 h, to trifluoroethanol–water (1:1) at 50 °C for 4 h, and to *p*-toluenesulfonic acid in MeOH at 20 °C for 24 h. Similarly, **9b** was stable to trifluoroacetic acid at room temperature for 24 h and to 5% HCl in MeOH–H_2O (9:1) at 20 °C for 18 h. Under basic conditions, the keto ester **5a** was stable to washing with 1% NaOH or to refluxing methanol in the presence of triethylamine, but hydrazine in aqueous ethanol caused slow decomposition over a 48-h period.

The best conditions for release of benzoic acid from **5a** with concomitant formation of ether **7** were found to be 1 equiv of sodium methoxide in methanol for 2 h or 1.1 equiv of triethylamine in methanol–water (9:1) at 20 °C for 12–24 h. The latter conditions were adopted for most deprotection experiments, and the formation of ether **7** or **14** was used as a measure of deprotection, also verified by the NMR of the released carboxylic acid **3** and in many cases by its isolation in >95% purity.

Table II is indicative of the deprotection of esters **5** or **9** to form carboxylic acid **3** and the methoxy ketones **7** or **14**, respectively. Among the polyfunctional compounds, acetate **3f** did not withstand the hydrolysis conditions because it is a very sensitive compound that hydrolyzes even on standing. On the other hand, deprotection of the diester **5k** was accomplished, leaving the ethyl ester intact. The *N*-BOC group in **5e** also remained intact.

The deprotection step presumably proceeds first by base-catalyzed enolization followed by ester solvolysis to produce an oxyallyl cation such as **10**, which is trapped by methoxide. In this solvolysis, the opposite trend as in ester formation was observed, with *o*-nitrobenzoate being a better leaving group than benzoate and thus solvolyzing in much better yield; while the nitro ester **9c** was converted quantitatively into **14** within 3 h, **9a** or **9b** reacted only in 45% conversion during the same period (see Table II).

The ease of protection and deprotection and the stability of the keto esters to acids make this an attractive method for carboxylic acid protection.

Experimental Section

The NMR spectra were recorded on a Bruker AM 300 FT NMR instrument, ^1H NMR at 300 MHz and ^{13}C NMR at 75.5 MHz, in $CDCl_3$, with TMS as internal standard. Mass spectra were obtained on a Finnigan 4021 instrument. IR spectra were recorded on a Perkin-Elmer Model 457. Silica gel (Merck Art. No. 9385) was used for chromatography. Compound **2** was prepared according to the literature.[2] All compounds were >95% pure by ^1H and ^{13}C NMR.

9-Chloro-9-phenylbicyclo[6.2.0]decan-10-one (8). To a dry three-necked flask under argon and equipped with a reflux condenser and an addition funnel were added 70 mL of cyclooctene and 0.053 mol of 2-chloro-2-phenylacetyl chloride. To this heated mixture (70 °C) was added a solution containing 0.053 mol of triethylamine in 30 mL of cyclooctene over a period of 1 h. The mixture was heated for an additional half-hour at 80 °C, and $Et_3NH^+Cl^-$ was filtered. The filtrate was washed successively with water, 5% HCl, 10% bicarbonate, and saturated sodium chloride and dried over magnesium sulfate. Removal of the olefin in vacuo gave a yellow oil, which was crystallized with hexane and recrystallized from ethanol, giving white crystals in 60% yield: mp 87 °C; ^1H NMR ($CDCl_3$) δ 7.34 (m, 5 H), 3.78 (ddd, 1 H, J = 12, 10.5, 2.5 Hz, O=CCH), 2.97 (ddd, 1 H, J = 14.5, 10.5, 2.5 Hz, PhClCCH), 2.0 (dtd, 1 H, J = 14.5, 4.5, 2.5 Hz), 1.7–1.15 (m, 10 H), 1.02 (dtd, 1 H, J = 14.5, 12.5, 3 Hz); ^{13}C NMR ($CDCl_3$) δ 206.29 (C=O), 134.77, 128.37, 128.15, 127.40, 80.36 (s), 59.20 (d), 49.38 (d), 29.48, 28.31, 25.92, 25.66, 25.18, 21.78; MS (CI) m/e 263 (M + 1), 227 (M – Cl). Anal. Calcd for $C_{15}H_{19}ClO$: C, 73.12; H, 7.30. Found: C, 73.00; H, 7.40.

General Procedure for Reaction of 2 or 8 with Acids. To 5 mmol of the cyclobutanones **2** or **8** in 30 mL of anhydrous acetone was added with stirring 1.1 mmol of the appropriate acid followed by 1.1 equiv of triethylamine. The mixture was stirred overnight, the salt filtered, and the acetone removed in vacuo. The residue was dissolved in methylene chloride, washed successively with water, 5% hydrochloric acid, and sodium bicarbonate solution, and dried over anhydrous magnesium sulfate. Removal of the methylene chloride in vacuo gave the keto esters **5** or **9**, which were recrystallized or purified by chromatography.

***exo*-1-(Benzoyloxy)-7-phenyl-*cis*-bicyclo[4.2.0]octan-8-one (5a).** Treatment of **2** with benzoic acid gave **5a** as a pale yellow solid, colorless crystals from MeOH, 80% yield: mp 120–122 °C; ^1H NMR ($CDCl_3$) δ 8.05 (m, 2 H, Ar), 7.58 (m, 1 H, Ar), 7.45 (m, 6 H), 7.28 (m, 1 H, Ar), 4.15 (d, 1 H, J = 10 Hz, O=CCH), 3.5 (m, 1 H, OCCH), 2.27 (m, 1 H), 1.85 (m, 5 H), 1.6 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 203.0 (keto C=O), 165.0 (ester C=O), 135.0, 133.3, 129.9, 129.4, 128.7, 128.4, 128.0, 127.2, 85.1 (s), 58.1, 38.7, 28.7, 21.7, 20.5, 20.4; IR (CCl_4) 1800, 1729 cm^{-1}; MS (CI) m/e 321 (M + 1), 293, 199. Anal. Calcd for $C_{21}H_{20}O_3$: C, 78.72; H, 6.30. Found: C, 78.77; H, 6.30.

***exo*-1-(Phenylacetoxy)-7-phenyl-*cis*-bicyclo[4.2.0]octan-8-one (5d).** The product obtained from phenylacetic acid was a pale yellow oil: ^1H NMR ($CDCl_3$) δ 7.3 (m, 10 H), 4.02 (d, 1 H, J = 10 Hz, O=CCH), 3.65 (s, 2 H, $PhCH_2$), 3.25 (m, 1 H, OCCH), 2.1–1.4 (m, 8 H); ^{13}C NMR δ 203.1 (keto CO), 170.0 (ester CO), 135.8, 133.5, 128.5, 128.0, 127.1, 85.3 (s), 57.9 (d), 40.9 (d), 37.9 (t), 28.4, 21.5, 20.1; IR (neat) 1795, 1740 cm^{-1}; MS (CI) m/e 236 (M + 2), 199 (M – RCO_2H).

***exo*-1-[(2,4,6-Trimethylbenzoyl)oxy]-7-phenyl-*cis*-bicyclo[4.2.0]octan-8-one (5i).** Treatment of **2** with mesitoic acid yielded **5i** as a yellow oil, 82%; white crystals were obtained from 95% EtOH, 60% yield: mp 106–107 °C; ^1H NMR δ 7.50–7.25 (m, 5 H, Ph), 6.86 (br s, 2 H, Ar), 4.14 (d, 1 H, J = 10 Hz, O=CCH), 3.55 (m, 1 H, OCCH), 2.35 (s, 6 H), 2.28 (s, 3 H), 2.8 (m, 1 H), 2–1.7 (m, 5 H), 1.6–1.8 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 203.0 (keto CO), 168.7 (ester CO), 139.6, 135.9, 135.3, 129.7, 128.7, 128.4, 128.1, 127.7, 85.7 (s), 58.2 (d), 38.2 (d), 28.6, 21.8, 20.4, 20.36, 19.7; MS (CI) m/e 363 (M + 1), 199 (M – RCO_2H); IR 1796, 1730 cm^{-1}.

***exo*-1-[(2-Acetoxybenzoyl)oxy]-7-phenyl-*cis*-bicyclo-[4.2.0]octan-8-one (5f).** Treatment of **2** with *O*-acetylsalicylic

acid gave a white powder, recrystallized from MeOH to give white crystals in 95% yield: mp 100–101 °C; ^{1}H NMR ($CDCl_3$) δ 8.05 (dd, 1 H, Ar), 7.62 (ddd, 1 H, Ar), 7.9 (m, 6 H), 7.67 (dd, 1 H, Ar), 4.12 (d, 1 H, J = 10 Hz, O=CCH), 3.95 (m, 1 H, OCCH), 2.68 (s, 3 H), 2.78 (d, 1 H, J = 15 Hz), 2.4 (m, 5 H), 2.1 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 202.6 (keto CO), 169.2 (ester CO), 163.0 (salicylic CO), 151.0, 136.0, 134.0, 131.8, 128.5, 127.1, 125.9, 123.8, 85.7 (s), 58.3 (d), 38.2 (d), 28.4, 21.7, 21.0, 20.3, 20.2; IR 1780, 1760, 1715 cm^{-1}; MS (CI) m/e 379 (M + 1), 215 (M – RCO). Anal. Calcd for $C_{23}H_{23}O_5$: C, 72.78; H, 5.96. Found: C, 72.60; H, 5.96.

***exo*-1-(Tolylsulfonyl)-7-phenyl-*cis*-bicyclo[4.2.0]octan-8-one (12).** Treatment of **2** with *p*-toluenesulfinic acid gave **12** as an oil. The product was purified by chromatography on silica, EtOAc–hexane, 1:4, and recrystallized from MeOH: mp 113–114 °C; ^{1}H NMR ($CDCl_3$) δ 7.9 (m, 2 H), 7.32 (m, 5 H), 7.08 (m, 2 H), 4.4 (d, 1 H, J = 10 Hz, O=CCH), 3.56 (m, 1 H, SCCH), 2.46 (s, 3 H), 2.36 (m, 1 H), 1.95–1.45 (m, 7 H); ^{13}C NMR ($CDCl_3$) δ 196.6 (keto CO), 145.2, 134.9, 133.3, 130.2, 129.7, 128.7, 127.8, 62.9 (d), 34.4 (d), 24.2, 22.2, 20.6, 19.3; MS (CI) m/e 215 (M – MePhSO), 199. Anal. Calcd for $C_{21}H_{22}SO_3$: C, 71.19; H, 6.21. Found: C, 71.06; H, 6.26.

***exo*-[[*N*-(*tert*-Butoxycarbonyl)-L-phenylalanyl]oxy]-7-phenyl-*cis*-bicyclo[4.2.0]octan-8-one (5e).** The adducts from *N*-(*tert*-butoxycarbonyl)-L-phenylalanine were obtained as a mixture of two isomers. The products were purified by chromatography on silica, EtOAc–hexane, 1:4: ^{1}H NMR ($CDCl_3$) δ 7.28 (m, 10 H), 5.05, 4.96 (br d, NH), 4.63 (m, 1 H), 4.07, 4.04 (d, 1 H, J = 10.5 Hz, O=CCH), 3.3, 3.16 (m, 1 H, OCCH), 3.11 (d, 2 H, J = 7 Hz), 2.8–1.8 (m, 8 H), 1.99, 1.96 (s, 9 H); ^{13}C NMR ($CDCl_3$) δ 202.4 (keto CO), 170.5 (ester CO), 135.6, 129.7, 129.4, 128.7, 128.5, 127.3, 127.0, 85.7 (s), 85.6 (s), 57.9 (d), 54.3 (d), 38.7 (d), 37.6 (t), 37.8 (t), 28.4, 28.3, 21.4, 20.2; MS (CI) m/e 407 (M – t-Bu).

***exo*-1-Acetoxy-7-phenyl-*cis*-bicyclo[4.2.0]octan-8-one (5h).** Treatment of **2** with acetic acid gave **5h** as a yellow powder, which was recrystallized from hexane: mp 87–87.5 °C; ^{1}H NMR ($CDCl_3$) δ 7.4 (m, 5 H, Ph), 4.06 (d, 1 H, J = 10 Hz, O=CCH), 3.31 (m, 1 H, OCCH), 2.12 (s, 3 H), 2.09 (m, 1 H), 1.85–1.4 (m, 8 H); ^{13}C NMR ($CDCl_3$) δ 203.6 (keto CO), 169.7 (ester CO), 135.9, 128.7, 127.9, 127.2, 85.5 (s), 58.0 (d), 38.1 (d), 28.5, 21.9, 20.3; IR (CCl_4) 1800, 1750 cm^{-1}; MS (CI) m/e 259 (M + 1), 199 (M – RCO_2H). Anal. Calcd for $C_{21}H_{20}O_3$: C, 78.72; H, 6.30. Found: C, 78.77; H, 6.30.

***exo*-1-Acetoxy-9-phenyl-*cis*-bicyclo[6.2.0]decan-10-one (9h).** Treatment of **8** with acetic acid yielded **9h**, recrystallized from hexane: mp 107–108 °C; ^{1}H NMR ($CDCl_3$) δ 7.40 (dt, 2 H, Ph), 7.35 (tt, 1 H, Ph), 7.25 (tt, 2 H, Ph), 3.73 (d, 1 H, J = 10 Hz, O=CCH), 2.96 (ddd, 1 H, J = 12, 10, 3 Hz, OCCH), 2.12 (s, 3 H), 2.0–1.2 (m, 12 H); ^{13}C NMR δ 206.1 (keto CO), 169.3 (ester CO), 135.6, 128.6, 127.3, 127.1, 90.1 (s), 63.3 (d), 44.3 (d), 29.2, 27.7, 27.4, 24.9, 24.2, 23.9; IR (CCl_4) 1790, 1738, cm^{-1}; MS (CI) 287 (M + 1), 227 (M – RCO_2H).

1-*exo*-[(Ethoxyadipoyl)oxy]-7-phenyl-*cis*-bicyclo[4.2.0]-octan-8-one (5k). Treatment of **2** with monoethyl adipoate gave a yellow oil, which was purified by chromatography to give a 75% yield: ^{1}H NMR ($CDCl_3$) δ 7.35 (m, 3 H), 7.25 (m, 2 H), 4.17 (q, 2 H, J = 7 Hz), 4.11 (d, 1 H, J = 10 Hz, O=CCH), 3.36 (m, 1 H, OCCH), 2.54 (m, 2 H), 2.36 (m, 2 H), 2.03 (m, 1 H), 1.9–1.4 (m, 11 H), 1.29 (t, 3 H, J = 7 Hz); ^{13}C NMR δ 203.57 (keto CO), 173.25 (ester CO), 171.90 (ester CO), 135.85, 128.70, 127.97, 127.63, 84.9 (s), 60.28 (t), 57.86 (d), 37.96 (d), 33.86, 33.56, 28.54, 24.26, 21.55, 20.27, 14.19; MS (CI) m/e 373 (M + 1), 327 (M – EtOH), 199 (M – RCO_2H); IR (neat) 1793, 1735 cm^{-1}.

***exo*-1-(Benzoyloxy)-9-phenyl-*cis*-bicyclo[6.2.0]decan-10-one (9a).** Treatment of **8** with benzoic acid gave a white powder, which was recrystallized from MeOH: mp 147 °C; ^{1}H NMR ($CDCl_3$) δ 8.07 (m, 2 H), 7.45 (m, 8 H), 3.80 (d, 1 H, J = 10 Hz, O=CCH), 3.13 (ddd, 1 H, J = 12, 10, 3 Hz, OCCH), 2.1–1.3 (m, 12 H); ^{13}C NMR ($CDCl_3$) δ 206.0 (keto CO), 164.6 (ester CO), 135.5, 133.4, 130.0, 129.5, 128.8, 128.7, 128.5, 127.8, 127.2, 90.1 (s), 63.4 (d), 44.3 (d), 29.6, 27.7, 27.5, 25.0, 24.7, 23.9; MS (CI) m/e 348 (M + 1), 321 (M – CO), 199 (M – RCO_2H).

***exo*-1-[(*p*-Methylbenzoyl)oxy]-9-phenyl-*cis*-bicyclo-[6.2.0]decan-10-one (9b).** Treatment of **8** with toluic acid yielded **9b**, which was crystallized from MeOH: mp 128 °C; ^{1}H NMR ($CDCl_3$) δ 7.87 (d, 2 H), 7.3 (7 H), 3.71 (d, 1 H, J = 10 Hz, O=CCH), 3.05 (ddd, 1 H, J = 11, 10, 4 Hz, OCCH), 2.34 (s, 3 H), 2.1–1.2 (m, 12 H); ^{13}C NMR ($CDCl_3$) δ 206.1 (keto CO), 164.6 (ester CO), 144.1, 135.6, 130.0, 129.2, 128.6, 127.8, 127.1, 89.9 (s), 63.4 (d), 44.3 (d), 29.6, 27.7, 27.5, 25.0, 24.7, 23.9; IR 1780, 1740 cm^{-1}; MS (CI) m/e 362 (M + 1), 227 (M – RCO_2H).

***exo*-1-(*o*-Nitrobenzoyl)-9-phenyl-*cis*-bicyclo[6.2.0]decan-10-one (9c).** The adduct obtained with *o*-nitrobenzoic acid was recrystallized from MeOH, to give colorless crystals: mp 94–95 °C; ^{1}H NMR ($CDCl_3$) δ 8.01 (d, 1 H, Ar), 7.66 (m, 3 H, Ar), 7.34 (m, 5 H), 3.83 (d, 1 H, J = 9 Hz, O=CCH), 2.16 (ddd, 1 H, J = 11, 9, 3 Hz, OCCH), 2.2–1.2 (m, 12 H); ^{13}C NMR ($CDCl_3$) δ 205.1 (keto CO), 164.1 (ester CO), 147.1, 135.2, 133.3, 131.6, 129.7, 128.61, 127.6, 127.4, 127.2, 124.0, 92.0 (s), 63.7 (d), 43.6 (d), 29.2, 27.7, 27.4, 24.7, 24.4, 23.8; MS (CI) m/e 394 (M + 1), 272 (M – o-nitrophenyl), 227 (M – RCO_2H).

***exo*-1-(Phenylacetoxy)-9-phenyl-*cis*-bicyclo[6.2.0]decan-10-one (9d).** The adduct obtained from phenylacetic acid was purified by chromatography on silica gel, EtOAc–hexane, 1:4, and recrystallized from MeOH: mp 82–83 °C; ^{1}H NMR ($CDCl_3$) δ 7.3 (m, 10 H), 3.7 (d, 1 H, J = 10 Hz, O=CCH), 3.67 (s, 2 H, $PhCH_2$), 2.88 (ddd, 1 H, J = 12, 10, 3.5 Hz, OCCH), 1.9–1.0 (m, 12 H); ^{13}C NMR ($CDCl_3$) δ 205.9 (keto CO), 167.5 (ester CO), 135.4, 133.3, 129.2, 128.5, 127.1, 90.1 (s), 63.2 (d), 44.1 (d), 41.2 (t), 29.2, 27.3, 27.5, 23.3, 24.7, 24.0; MS (CI) m/e 363 (M + 1), 227 (M – RCO_2H).

***exo*-1-[(2-Acetoxybenzoyl)oxy]-9-phenyl-*cis*-bicyclo-[6.2.0]decan-10-one (9f).** Treatment of **5** with *O*-acetylsalicylic acid yielded **9f**, which was recrystallized from MeOH: mp 117–118 °C; ^{1}H NMR ($CDCl_3$) δ 8.02 (dd, 1 H, Ar), 7.58 (dt, 1 H, Ar), 7.46 (dd, 1 H, Ar), 7.3 (m, 5 H, Ph), 7.10 (dd, 1 H, Ar), 3.78 (d, 1 H, J = 10 Hz, O=CCH), 3.03 (ddd, 1 H, J = 10, 10, 3 Hz, OCCH), 2.19 (s, 3 H), 2.15–1.2 (m, 12 H); ^{13}C NMR δ 205.5 (keto CO), 169.6 (ester CO), 162.3, 151.3, 134.2, 131.3, 128.4, 127.6, 127.0, 125.9, 123.9, 122.1, 90.5 (s), 63.4 (d), 44.3 (d), 29.2, 27.7, 27.6, 25.0, 24.6, 24.0, 20.8; IR 1780, 1715 cm^{-1}; MS (CI) m/e 407 (M + 1), 227 (M – RCO_2H); high-resolution MS calcd 406.17801, found 406.195.

***exo*-1-[(*p*-Nitrobenzoyl)oxy]-9-phenyl-*cis*-bicyclo[6.2.0]-decan-10-one (9j).** Treatment of **8** with *p*-nitrobenzoic acid yielded **9j** as a white powder, which was crystallized from MeOH: mp 181 °C; ^{1}H NMR ($CDCl_3$) δ 8.31 (dt, 2 H, Ar), 8.21 (dt, 2 H, Ar), 7.48 (d, 2 H, Ph), 7.39 (tt, 2 H, Ph), 7.30 (tt, 1 H, Ph), 3.85 (d, 1 H, J = 10 Hz, O=CCH), 3.14 (ddd, 1 H, J = 12, 10, 3.5 Hz, OCCH), 2.1–1.2 (m, 12 H); ^{13}C NMR ($CDCl_3$) δ 205.1 (keto CO), 162.7 (ester CO), 150.7, 135.2, 134.8, 130.0, 128.7, 127.6, 127.3, 123.6, 91.0 (s), 63.5 (d), 44.3 (d), 29.4, 27.52, 27.45, 24.9, 24.7, 24.0; IR 1770, 1710 cm^{-1}; MS (CI) m/e 394 (M + 1), 364 (M – NO), 366 (M – CO), 277 (M – RCO_2H). Anal. Calcd for $C_{23}H_{23}NO_5$: C, 70.21; H, 5.89. Found: C, 68.31; H, 5.90.

***exo*-1-[[*N*-(*tert*-Butoxycarbonyl)-L-phenylalanyl]oxy]-9-phenyl-*cis*-bicyclo[6.2.0]decan-10-one (9e).** The product from (*tert*-butoxycarbonyl)-L-phenylalanine was obtained as a mixture of two isomers, which were purified by chromatography on silica, EtOAc–hexane, 1:4: ^{1}H NMR ($CDCl_3$) δ 7.3 (m, 10 H), 5.04, 4.92 (d, 1 H, J = 8 Hz, NH), 4.65 (m, 1 H, CHNH), 3.70 (d, 1 H, J = 10 Hz, O=CCH), 3.72 (d, 1 H, J = 9 Hz, O=CCH), 3.2–2.85 (m, 3 H, $PhCH_2$, OCCH), 2–1.2 (m, 14 H), 1.43, 1.39 (s, 9 H); ^{13}C NMR δ 204.9 (keto CO), 170.1 (ester CO), 154.7 (BOC CO), 90.7, 90.8 (s), 63.4, 63.3 (d), 54.2, 53.9 (d), 44.0 (d), 38.3, 38.25 (t); MS (CI) m/e 437, 227.

General Procedure for Reaction of Acyloxycyclobutanones 5 or 9 with Et_3N in MeOH–H_2O. To 2 mL of the ester in 20 mL of MeOH–H_2O, 9:1, was added 2.1 mmol of Et_3N. The mixture was stirred overnight, MeOH was removed in vacuo, and CH_2Cl_2 was added to the residue. The solution was washed successively with water, 5% $NaHCO_3$, and saturated NaCl and dried ($MgSO_4$). Removal of the solvent left the ether product as an oil. The aqueous layer was acidified and extracted a few times with CH_2Cl_2 to obtain the acids **3**, which were identified by comparison with spectra of authentic samples.

General Procedure for Reaction of Acyloxycyclobutanones 5 or 9 with NaOMe. To 0.4 mmol of the ester in 10 mL of anhydrous MeOH was added a solution containing 0.4 mmol of NaOMe in 1 mL of MeOH. The mixture was stirred for 2 h at 25 °C, and the MeOH was removed in vacuo. The resulting oil was dissolved in 25 mL of CH_2Cl_2, washed successively with water, 10% $NaHCO_3$, and saturated NaCl, and dried ($MgSO_4$). Removal of the CH_2Cl_2 left **7** or **14**. The bicarbonate layer was

acidified and extracted with three 25-mL portions of CH_2Cl_2. Removal of the solvent left the carboxylic acid **3**.

***exo*-1-Methoxy-7-phenyl-*cis*-bicyclo[4.2.0]octan-8-one (7)**: ^1H NMR ($CDCl_3$) δ 7.26 (m, 5 H), 4.13 (d, 1 H, J = 11 Hz, O=CCH), 3.41 (s, 3 H, CH_3), 2.88 (dd, 1 H, J = 11, 5 Hz), 2.05 (br d, 1 H, J = 15 Hz), 2-1.4 (m, 7 H); ^{13}C NMR ($CDCl_3$) δ 206.9 (keto CO), 135.5, 128.5, 127.5, 127.1, 88.5 (s), 57.0 (d), 52.9 (q), 35.5 (d), 28.1, 21.8, 20.4, 20.3; IR (neat) 1765 cm^{-1}; MS (CI) m/e 231 (M + 1), 199 (M - MeOH). Anal. (7 semicarbazone). Calcd for $C_{16}H_{21}N_3O_2$: C, 66.87; H, 7.38. Found: C, 66.94; H, 7.39.

***exo*-1-Methoxy-9-phenyl-*cis*-bicyclo[6.2.0]decan-10-one (14)**: ^1H NMR ($CDCl_3$) δ 7.3 (m, 5 H), 3.70 (d, 1 H, J = 10 Hz, O=CCH), 3.46 (s, 3 H), 2.51 (ddd, 1 H, J = 12, 10, 3 Hz, OCCH), 2.1-1.2 (m, 12 H); ^{13}C NMR δ 211.2 (keto CO), 135.7, 128.7, 127.4, 127.1, 92.9 (s), 63.6 (d), 52.4 (q), 43.9 (d), 28.2, 27.9, 27.3, 25.1, 23.8, 23.7; IR (neat) 1770 cm^{-1}; MS (CI) m/e 258 (M + 1), 277 (M - MeOH).

Methyl *cis*-2-[2-(*p*-tolylsulfonyl)cyclohexyl]-2-phenylacetate (13): ^1H NMR δ 7.78 (2 H, Ar), 7.38 (2 H, Ar), 7.3 (5 H, Ph), 4.31 (d, 1 H, J = 9 Hz, PhCH), 3.55 (s, 3 H), 2.94 (q, 1 H, J = 5.5 Hz, $CHSO_2$), 2.84 (dq, 1 H, J = 9, 5 Hz, $CHCHSO_2$), 2.64 (s, 3 H), 2.05-1.7 (m, 5 H), 1.4-1.2 (m, 3 H), 0.98 (m, 1 H); ^{13}C NMR δ 173.9 (ester CO), 144.4, 136.0, 135.5, 129.7, 129.6, 128.7, 128.5, 127.5, 62.4 (d), 52.0 (d), 43.35 (d), 23.8, 23.2, 22.1, 21.1, 20.1; MS (CI) m/e 355 (M - MeOH), 327, 231.

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Synthesis of Acyclic Sugar Aldehydes by Ozonolysis of Oximes

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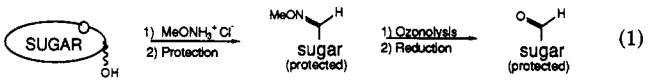
This note reports on an efficient method for the synthesis of acyclic sugar aldehydes based on the ozonolysis of methyloxime-protected aldoses. Readily accessible protected sugar oximes are converted into the corresponding aldehydo sugars in good yield and high purity on a multigram scale. This methodology eliminates problems associated with decomposition of these aldehydes by β-elimination and the formation of side products that contaminate the aldehyde after deprotection. The availability of these aldehydes should further facilitate their use in organic synthesis.[1-3]



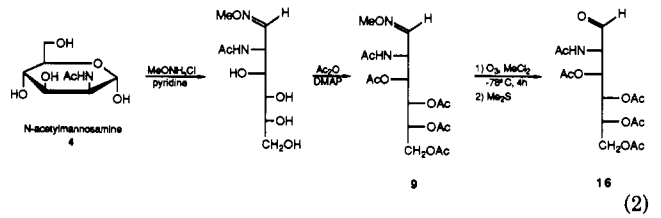
(1)

The mechanism of the cleavage of a carbon-nitrogen double bond by ozonolysis was thoroughly investigated in 1969 by Erikson and co-workers.[4] More recently, Enders has used this reaction to regenerate ketones (and aldehydes) from hydrazones after asymmetric alkylation reactions.[5] We reasoned that acyclic sugar oximes, which are readily accessible from carbohydrates by treatment with methoxyamine hydrochloride, can be protected and the oxime ozonized to generate acyclic aldehydo sugars. Deprotection of aldehydo sugars by ozonolysis produces volatile and water-soluble byproducts that can easily be removed from the reaction mixture. The mild reaction conditions also allow for the synthesis of acyclic α-acylamino sugar aldehydes without problems associated with decomposition by β-elimination[6] or participation of the acylamino group during deprotection.[7] The reaction can be performed on a multigram scale to give aldehydo sugars in greater than 95% purity and in good overall yields (approximately 90%). Oximes have been previously converted to aldehydes by using $TiCl_3$/AcOH,[8] aqueous NaH_2SO_3,[9] $(PhSeO)_2O$,[10] and $Pb(OAc)_4$.[11] These methods generally use acidic or basic reaction conditions that lead to decomposition of acyclic sugar aldehydes by β-elimination and limit the use of acid- or base-sensitive protecting groups. Other methods used to generate aldehydo sugars such as the cleavage of dithianes using mercury salts,[12] electrochemical oxidation,[13] *N*-bromosuccinimide,[6] or methyl iodide and cadmium carbonate[14] also result in β-elimination and loss of labile protecting groups. Corey has reported the synthesis of ketones from ketoxime acetates under mild conditions using chromous acetate.[15] Acetylation of aldose hydroxyoximes, however, yield the corresponding peracetylated sugar nitriles.[16]

Table I

sugar	protecting group	oxime	aldehyde
glucose (1)	acetates	85% 6	87% 13
arabinose (2)	acetates	82% 7	90% 14
mannose (3)	acetates	87% 8	92% 15
N-acetylmannosamine (4)	acetates	92% 9	93% 16
	benzoates	42% 10	99% 17
N-acetylglucosamine (5)	acetates	86% 11	85% 18
	isopropylidenes	62% 12	90% 19

Sugars **1-5** (see Table I) were treated with methoxyamine hydrochloride in pyridine (12 h) and then acetylated or benzoylated in situ by the addition of acetic anhydride or benzoylchloride (an outline of this sequence is shown in eq 2 for *N*-acetylmannosamine). To investigate the use



(2)

of the acid labile isopropylidene protecting group, the *N*-acetylglucosamine methyloxime derivative **12** was syn-

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