Cyclopropyl Building Blocks for Organic Synthesis, Part 100.[‡] Advanced Syntheses of Cyclopropylideneacetates – Versatile Multifunctional Building Blocks for Organic Synthesis

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Dedicated to Dr. Joe P. Richmond on the occasion of his 60th birthday.

Abstract: A well reproducible and inexpensive preparation of the cyclopropylideneacetates **2**–**4** has been developed. The key intermediate 2-(1′-mesyloxycyclopropyl)acetic acid (**8**), produced either from methyl phenylacetate (**1**) or 3,3-dimethoxypropionate (**5**-Me) and 3,3-diethoxypropionate (**5**-Et) in a sequence of Kulinkovich reductive cyclopropanation, mesylation and oxidative cleavage or cleavage and oxidation, respectively, was either converted to the benzyl ester **11b**, or chlorinated (brominated) *via* the *in situ* formed acid chloride. The α-chloro- **12a** and α-bromo ester **12b** were dehydromesylated by treatment with triethylamine to furnish methyl 2-chloro-2-cyclopropylideneacetate (**3**-Me) and the 2-bromo analogue **4**-Me with an overall yield of 68% (65%, 68%) and 52% (49%, 51%) respectively, starting from **1** (**5**-Me, **5**-Et). The parent benzyl cyclopropylideneacetate **2**-Bn was obtained by dehydromesylation of **11b** with potassium *t*-butoxide in *t*-butyl methyl ether with an overall yield of 60% (57%, 9%) from **1** (**5**-Me, **5**-Et).

Keywords: building blocks; molecular diversity; small ring systems; synthetic methods; titanium

Introduction

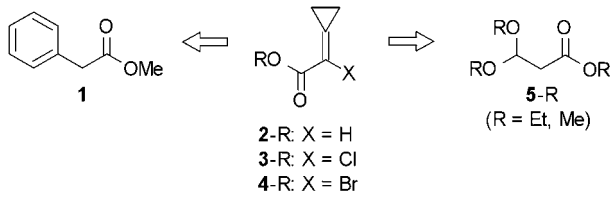
Acceptor-activated methylenecyclopropanes like alkyl cyclopropylideneacetates (**2**),[1] 2-chloro-2-cyclopropylideneacetates (**3**)[2] and 2-bromo-2-cyclopropylideneacetates (**4**)[3] are valuable building blocks for organic synthesis.[4] Due to their enhanced reactivities and their multifunctionalities, they can be applied in a broad sense towards elegant syntheses of spirocyclopropanated carbo-[5] and heterocycles,[6] various cyclopropyl group-containing amino acids[7] as well as potentially biologically active conformationally restricted peptide mimics.[8]

Unfortunately, all of these building blocks so far have not really been easily available. The known five-step preparation of the chloro derivative **3**, although reasonably productive and easily scalable, requires a halide-resistant autoclave for the third step, and the overall atom economy is rather poor. The previously developed synthesis of the bromo derivative **4** and of the parent compound **2** both start from cyclopropanone ethyl hemiacetal, the preparation of which requires the generation as well as handling of finely dispersed sodium, and the Wittig olefinations with the appropriately substituted triphenylmethylenephosphoranes of the cyclopropanone surrogate do not really provide good yields of the products **2** and **4**, respectively.

With the more recently developed conversion of carboxylic acid esters to cyclopropanols, the so-called Kulinkovich reaction[9] in hand, it appeared feasible to embark on a second-generation access to these reactive methylenecyclopropanes **2**–**4** (Scheme 1).

Results and Discussion

Having the 2-(1′-mesyloxycyclopropyl)acetic acid (**8**) in mind as a key intermediate, the two precursors **1** and **5**-R with masked carboxyl groups were considered.



Scheme 1. Retrosynthetic considerations concerning cyclopropylideneacetates **2**–**4**.

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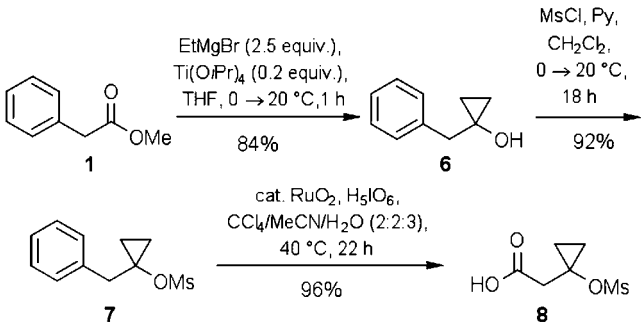
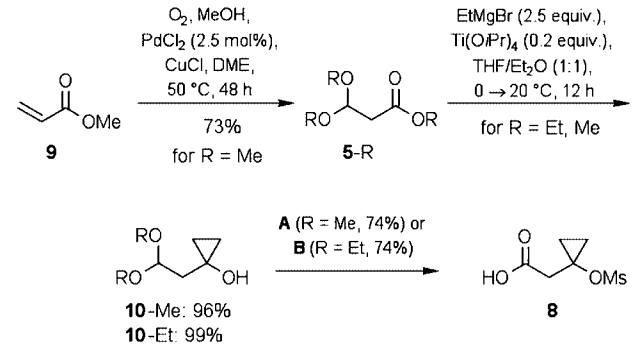


Scheme 2. Preparation of 2-(1′-mesyloxycyclopropyl)acetic acid (**8**) from methyl phenylacetate (**1**).

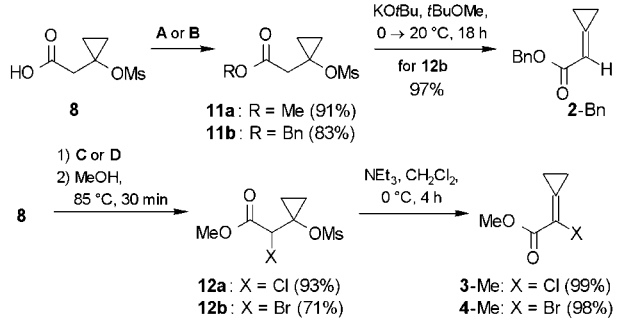


Scheme 3. Alternative preparation of 2-(1′-hydroxycyclopropyl)acetic acid (**8**) from methyl acrylate (**9**) or ethyl 3,3-diethoxypropionate (**5**-Et). **A**: 1) MsCl, Py, CH_2Cl_2, 20 °C, 15 h, 2) cat. conc. HCl, H_2O_2, THF/H_2O (2:1), 60 °C, 8 h; **B**: 1) MsCl, cat. DMAP, NEt_3, CH_2Cl_2, 20 °C, 4 h, 2) Oxone, THF/H_2O (1:2), 20 °C, 8 h.

The first one, methyl phenylacetate (**1**) was readily converted to **6**[10] in 84% yield by treatment with 2.5 equivalents of ethylmagnesium bromide in the presence of titanium tetraisopropoxide. The product **6** was pure enough for direct transformation to the more stable mesylate **7**,[11] which was obtained in 92% yield. Oxidative cleavage of the phenyl group with *in situ* generated ruthenium tetroxide under conditions developed by Sharpless et al.,[12] but with 7 equivalents of orthoperiodic acid[13] as the cooxidant, led to 2-(1′-mesyloxycyclopropyl)acetic acid (**8**) in 96% yield (74% overall from **1**), after crystallization from diethyl ether (Scheme 2).

A more atom-economical route to the same precursor **8** turned out to be that starting from methyl 3,3-dimethoxypropionate (**5**-Me), which is commercially available or easily prepared on a 200 mmol scale by Wacker oxidation of methyl acrylate (**9**).[14] Subsequent Kulinkovich reaction of **5**-Me furnished the cyclopropanol **10**-Me in 96% yield. The latter was converted under conventional conditions into the corresponding mesylate (Scheme 3).

As the mesylate of **10**-Me could not easily be purified by crystallization, but according to its ^{1}H NMR spectrum was pure enough for further transformations, it was directly treated with hydrogen chloride to cleave the acetal and subsequently with hydrogen peroxide to oxidize the aldehyde[15] to give the crystalline acid **8** in 74% yield (71% overall from **5**-Me).



Scheme 4. Transformation of **8** to cyclopropylideneacetates **2**–**4**. **A**: MeOH, cat. H_2SO_4, 20 °C, 12 h; **B**: BnOH, cat. *p*TsOH, toluene, 60 °C, 6 h; **C**: $SOCl_2$, NCS, cat. conc. HCl, 1,2-DCE, 85 °C, 15 h; **D**: $SOCl_2$, NBS, cat. conc. HBr, 1,2-DCE, 85 °C, 15 h.

The analogous ethyl 3,3-diethoxypropionate (**5**-Et) can be prepared on a large scale from ethyl vinyl ether, tetrachloromethane and ethanol without the use of a palladium catalyst.[16,17] The Kulinkovich reductive cyclopropanation of **5**-Et under the established conditions yielded the cyclopropanol **10**-Et virtually quantitatively (99%), even on a reasonably large scale (*ca.* 0.5 mol). The cyclopropanol **10**-Et was cleanly transformed under DMAP-catalysis (5 mol %) in the presence of inexpensive triethylamine as an HCl scavenger to the corresponding mesylate, which could be deprotected and *in situ* oxidized with 1.5 equivs. of oxone. With a single crystallization from diethyl ether the pure acid **8** was obtained as a colorless crystalline compound (73% over 3 steps).

The methyl ester **11a** was obtained in 91% yield by treatment of a solution of **8** in methanol with a catalytic amount of concentrated sulfuric acid, and was used without further purification. The corresponding benzyl ester **11b** was prepared in 83% yield by refluxing **8** in benzyl alcohol/toluene under Dean–Stark conditions in the presence of a catalytic amount of *p*-toluenesulfonic acid. Dehydromesylation of **11b** could be achieved by stirring it with potassium *tert*-butoxide in *tert*-butyl methyl ether at 0 °C for 18 h to furnish benzyl cyclopropylideneacetate (**2**-Bn) as a viscous liquid in 97% yield (59% overall from **5**-Me) after Kugelrohr distillation (Scheme 4).

An attempted α-chlorination of **11a** with sulfuryl chloride in the presence of a catalytic amount of AIBN at 70 °C failed. Instead, a significant amount of the elimination product, the methyl cyclopropylideneacetate corresponding to **2**-Bn, was formed. Attempted bromination of the *in situ* generated acid chloride of **8**

with a catalytic amount of chlorosulfonic acid and molecular bromine at 85 °C also failed just like the first attempts to halogenate **8** with NCS according to Wohl and Ziegler, probably because of the poor solubility of **8** and the acid chloride of **8** in tetrachloromethane. However, 1,2-dichloroethane (DCE) turned out to be a better solvent for the starting material and thus upon chlorination with NCS in DCE and subsequent treatment with methanol the α-chloro ester **12a** was obtained in 93% yield. Under the same conditions, the acid chloride of **8** could be transformed to the α-bromo ester **12b** with NBS and a catalytic amount of concentrated hydrobromic acid in 71% yield. Although **12a** and **12b** could be purified by silica gel chromatography, they appeared not to be very stable under these conditions. Therefore the crude halogenated esters **12a** and **12b** were directly subjected to dehydrohalogenation by treatment with triethylamine in dichloromethane at 0 °C. The resulting 2-chloro- (**3**-Me) and 2-bromocyclopropylideneacetates **4**-Me could be purified by crystallization and chromatography, respectively (Scheme 4).

Conclusion

This new approach which furnishes methyl 2-chloro-2-cyclopropylideneacetate (**3**-Me) and the 2-bromo analogue **4**-Me each in 6 simple steps (4 distinct operations) with an overall yield of 68 and 51% respectively, starting from ethyl 3,3-diethoxypropionate (compared to 5 steps with 18% overall yield and 3 steps with 13% overall yield in the past[18]), makes these valuable multifunctional building blocks much more conveniently available than previously. The parent benzyl cyclopropylideneacetate **2**-Bn was accessible in 5 simple steps (4 distinct operations) with an overall yield of 59% compared to 31% in 4 steps (including the generation and handling of freshly prepared, finely dispersed sodium) according to the best previously published protocol.

Experimental Section

General Remarks

All reagents were used as purchased from commercial suppliers without further purification. All reactions in non-aqueous solvents were carried out using standard Schlenk techniques under an atmosphere of dry nitrogen. Solvents were purified and dried according to conventional methods prior to use; diethyl ether (Et_2O), 1,2-dimethoxyethane (DME) and tetrahydrofuran (THF) were freshly distilled from sodium/benzophenone. Solvents are abbreviated as follows: DCM = dichloromethane, DCE = 1,2-dichloroethane, MeCN = acetonitrile, Py = pyridine, MTBE = *tert*-butyl methyl ether, EtOAc = ethyl acetate, MeOH = methanol, BnOH = benzyl alcohol, Pent = pentane. ^{1}H and ^{13}C NMR spectra were recorded at ambient temperature on a Bruker AM 250 instrument. Chemical shifts δ are given in ppm relative to resonances of solvent (^{1}H: 7.26 ppm for chloroform; ^{13}C: 77.0 ppm for chloroform-d), coupling constants *J* are given in Hertz. Characterization of the multiplicity of signals: s = singlet, br s = broad singlet, d = doublet, t = triplet, m = multiplet. The multiplicities of signals were determined by the DEPT technique: DEPT: + = primary or tertiary (positive DEPT-signal), − = secondary (negative DEPT-signal), C_{quat} = quaternary C-atoms. IR: Bruker IFS 66. MS: Finnigan MAT. Chromatography: Separations were carried out on Merck Silica 60 (0.063–0.200 mm, 70–230 mesh ASTM). The dimensions of the columns are given as "diameter × height of the silica column". TLC: Machery-Nagel, TLC plates Alugram® Sil G/UV_{254}. Detection under UV light at 254 nm, development with MOPS reagent (10% molybdophosphoric acid, solution in ethanol). Melting points: apparatus according to Dr. Tottoli (Büchi); mps are uncorrected. Elemental analyses: Mikroanalytisches Laboratorium des Instituts für Organische Chemie der Universität Göttingen.

1-Benzylcyclopropanol (6)

To a solution of 15.0 g (99.9 mmol) of methyl phenylacetate in 100 mL of THF at 0 °C were added 5.70 mL (20.0 mmol) of titanium(IV) isopropoxide and slowly within 20 min 125 mL (250 mmol) of ethylmagnesium bromide (2 M solution in diethyl ether). The black solution was stirred for 40 min, the reaction quenched by addition of 200 mL of 1 M sulfuric acid at 0 °C, the aqueous phase was extracted with Et_2O (3 × 200 mL), and the combined organic phases were dried over $MgSO_4$. Removal of volatiles under vacuum (water bath temperature < 30 °C!) afforded **6** as a slightly yellow liquid, which was used in the next step without further purification; yield: 12.4 g (84%). ^{1}H NMR ($CDCl_3$, 250 MHz): δ = 0.75 (m, 2H, Cpr-CH_2), 1.02 (m, 2H, Cpr-CH_2), 3.24 (s, 2H, CH_2Ph), 3.62 (br s, 1H, OH), 7.26–7.36 (m, 5H, aryl-H); ^{13}C NMR ($CDCl_3$, 62.9 MHz): δ = 13.2 (−, 2C, Cpr-C), 44.1 (−, CH_2Ph), 56.1 (C_{quat}, Cpr-C), 126.6 (C_{quat}, aryl-C), 128.5 (+, 2C, aryl-C), 129.5 (+, 2C, aryl-C), 138.6 (C_{quat}, C_{ipso}). The additional experimental data are identical to those reported in the literature.[10]

1-Benzylcyclopropyl Mesylate (7)

To a solution of 14.8 g (99.9 mmol) of **6** in 300 mL of DCM at 0 °C were added 17.4 g (220 mmol) of pyridine and slowly within 30 min 9.3 mL (120 mmol) of mesyl chloride. The solution was stirred under rewarming to room temperature for 18 h, extracted with 1 N hydrochloric acid (2 × 50 mL), water (1 × 50 mL) and brine (1 × 50 mL). Drying of the organic phase over $MgSO_4$, removal of the solvent under vacuum and crystallization from Pent/Et_2O (2:1, R_f = 0.5, MOPS) afforded **7** as a colorless solid; yield: 20.7 g (92%); mp 79–81 °C; IR (film): $\tilde{\nu}$ = 3089, 3063, 3035, 3022, 2943, 2926, 1602, 1498, 1453, 1436, 1423, 1333, 1245, 1173, 974, 942, 921 cm^{-1}; ^{1}H NMR ($CDCl_3$, 250 MHz): δ = 0.83 (m, 2H, Cpr-CH_2), 1.33 (m, 2H, Cpr-CH_2), 2.88 (s, 3H, CH_3), 3.26 (s, 2H, CH_2Ph), 7.26–7.34 (m, 5H, aryl-H); ^{13}C NMR ($CDCl_3$, 62.9 MHz): δ = 11.2 (−, 2C, Cpr-C), 39.7 (+, CH_3), 41.2 (−, CH_2Ph), 66.2 (C_{quat}, Cpr-C), 126.8 (C_{quat}, aryl-C), 128.4 (+, 2C, aryl-C), 129.4 (+, 2C, aryl-C), 136.7 (C_{quat}, C_{ipso}); MS (EI, 70 eV): *m*/z (%) = 226 (1)

[M^+], 130 (48), 91 (100), 65 (10); anal. calcd. for $C_{11}H_{14}O_3S$ (226.3): C 58.38, H 6.24; found: C 58.09, H 5.97.

Methyl 3,3-Dimethoxypropionate (5-Me)

To a suspension of 837 mg (4.72 mmol) of palladium(II) chloride in 50 mL of DME were added 19.8 g (200 mmol) of copper(I) chloride. At 20 °C a solution of 17.2 g (200 mmol) of acrylic acid methyl ester in 64.1 g (2.00 mol) of MeOH was added, the flask was flooded with oxygen and the mixture was heated at 50 °C for 48 h under an atmosphere of oxygen (balloon). After cooling to room temperature, 50 mL of Et_2O were added, the precipitate was filtered off, washed with Et_2O, and the volatiles were removed under vacuum (40 °C water bath). Distillation of the residue under reduced pressure (10 mbar, bp 57–60 °C) afforded **5**-Me as a colorless liquid; yield: 21.7 g (73%); ^{1}H NMR ($CDCl_3$, 250 MHz): δ = 2.62 (d, ^3J = 7.1 Hz, 2H, CH_2), 3.22 (s, 6H, 2OCH_3), 3,64 (s, 3H, OCH_3), 4.68 (t, ^3J = 7.1 Hz, 1H, CH); ^{13}C NMR ($CDCl_3$, 62.9 MHz): δ = 38.6 (−, CH_2), 51.7 (+, OCH_3), 53.4 (+, 2C, OCH_3), 101.2 (+, CH), 170.2 (C_{quat}, C=O). The additional experimental data are identical to those reported in literature.[15]

1-(2,2-Dimethoxyethyl)cyclopropanol (10-Me)

To a solution of 10.4 g (70.5 mmol) of **5**-Me in 200 mL of Et_2O were added 4.00 mL (13.6 mmol) of titanium(IV) isopropoxide at 0 °C and slowly 88 mL (176 mmol) of EtMgBr (2 M solution in Et_2O). The deep black solution was stirred at 25 °C for 18 h, the reaction quenched by slow addition of 15 mL of water at 0 °C, and the mixture stirred until the precipitate was complete. Filtration of the precipitate over $MgSO_4$ and removal of the solvent under vacuum afforded **10**-Me as a slightly yellow liquid; yield: 9.88 g (96%); IR (film): $\tilde{\nu}$ = 3420, 2938, 2835, 1717, 1700, 1457, 1387, 1192, 1122, 1053 cm^{-1}; ^{1}H NMR ($CDCl_3$, 250 MHz): δ = 0.46 (m, 2H, Cpr-CH_2), 0.75 (m, 2H, Cpr-CH_2), 1.84 (d, ^3J = 7.2 Hz, 2H, CH_2), 3.39 (s, 6H, 2 CH_3), 3.45 (br s, 1H, OH), 4.63 (t, ^3J = 7.2 Hz, 1H, CH); ^{13}C NMR ($CDCl_3$, 62.9 MHz): δ = 12.5 (−, 2C, Cpr-C), 39.8 (−, CH_2), 52.9 (C_{quat}, Cpr-C), 53.1 (+, 2C, OCH_3), 104.6 (+, CH); MS (DCI, 70 eV): *m/z* (%) = 146 (20) [M^+], 75 (100), 58 (60), 43 (41); anal. calcd. for $C_7H_{14}O_3$ (146.2): C 57.51, H 9.65; found: C 57.42, H 9.62.

1-(2,2-Diethoxyethyl)cyclopropanol (10-Et)

To a solution of 95.0 g (499 mmol) of **5**-Et in 1.00 L of THF/Et_2O (1:1) was added 28.4 mL (99 mmol) of titanium(IV) isopropoxide at 0 °C and 520 mL (1.25 mol) of EtMgBr (2.4 M solution in Et_2O) over 60 min. The deep black solution was stirred at 20 °C for 18 h, the reaction quenched by slow addition of 100 mL of water at 0 °C and 500 mL of Et_2O, and the mixture stirred until the precipitate was complete. Filtration of the precipitate over $MgSO_4$ and then over Celite and removal of the solvent under vacuum afforded **10**-Et as a slightly yellow liquid; yield: 85.9 g (99%); IR (film): $\tilde{\nu}$ = 3420, 2938, 2835, 1717, 1700, 1457, 1387, 1192, 1122, 1053 cm^{-1}; ^{1}H NMR ($CDCl_3$, 250 MHz): δ = 0.42 (m, 2H, Cpr-CH_2), 0.73 (m, 2H, Cpr-CH_2), 1.21 (t, ^3J = 7.3 Hz, 6H, 2 CH_3), 1.85 (d, ^3J = 7.2 Hz, 2H, CH_2), 3.42–3.78 (m, 5H, 2 CH_2 + OH), 4.77 (t, ^3J = 7.2 Hz, 1H, CH); ^{13}C NMR ($CDCl_3$, 62.9 MHz): δ = 9.7 (+, 2C, CH_3), 12.3 (−, 2C, Cpr-C), 40.8 (−, CH_2), 53.1 (C_{quat}, Cpr-C), 61.7 (−, 2C, OCH_2), 102.9 (+, CH); MS (EI, 70 eV): *m/z* (%) = 129 (6), 128 (10), 103 (49), 83 (92), 75 (48), 55 (63), 47 (100); anal. calcd. for $C_9H_{18}O_3$ (174.2): C 62.04, H 10.41; found: C 61.79, H 10.38.

2-(1′-Mesyloxycyclopropyl)acetic Acid (8)

Method A: To a solution of 14.8 g (101 mmol) of **10**-Me in 200 mL of DCM were added 19.2 mL (243 mmol) of pyridine and slowly within 30 min 13.9 mL (180 mmol) of mesyl chloride. The solution was stirred for 18 h at 20 °C, extracted with 1 N HCl (2 × 50 mL), water (1 × 50 mL) and saturated aqueous $NaHCO_3$ solution (1 × 50 mL). Drying over $MgSO_4$ and evaporation of the solvent yielded the raw mesylate as a dark oil, which was dissolved in 30 mL of THF/H_2O (2:1). To this solution were added at 0 °C 5 mL of concentrated aqueous HCl, and it was stirred at this temperature for 30 min. At 20 °C were added 23.5 g (206 mmol) of 30% aqueous H_2O_2, and the light yellow solution was heated at 60 °C for 8 h. Extraction of the mixture with DCM (3 × 100 mL), drying of the combined organic phases over $MgSO_4$, evaporation of the solvent and recrystallization of the residue from Et_2O/Pent afforded **8** as colorless crystals; yield: 14.6 g (74%); mp 96–98 °C; IR (film): $\tilde{\nu}$ = 3032, 1710, 1424, 1408, 1331, 1265, 1230, 1184, 1155, 942, 907 cm^{-1}; ^{1}H NMR ($CDCl_3$, 250 MHz): δ = 0.93 (m, 2H, Cpr-CH_2), 1.42 (m, 2H, Cpr-CH_2), 2.91 (s, 2H, CH_2), 3.05 (s, 3H, CH_3), 10.85–11.23 (br s, 1H, CO_2H); ^{13}C NMR ($CDCl_3$, 62.9 MHz): δ = 12.0 (−, 2C, Cpr-C), 39.7 (+, CH_3), 40.9 (−, CH_2), 61.6 (C_{quat}, Cpr-C), 175.9 (C_{quat}, C=O); MS (DCI, 70 eV): *m/z* (%) = 406 (3) [$2M^+ + NH_4^+$], 212 (100) [$M^+ + NH_4^+$]; anal. calcd. for $C_6H_{10}O_5S$ (194.2): C 37.11, H 5.19; found: C 37.39, H 4.96.

Method B: To a solution of 68.7 g (394 mmol) of **10**-Et in 700 mL of DCM were added 65.5 mL (474 mmol) of triethylamine, 2.40 g (19.8 mmol) of DMAP and slowly within 30 min 49.6 g (435 mmol) of mesyl chloride. The solution was stirred for 4 h at 20 °C, extracted with 1 N HCl (1 × 200 mL) and water (1 × 200 mL). Drying over Na_2SO_4 and evaporation of the solvent yielded the raw mesylate as a brown oil, which was dissolved in 1.00 L of THF/H_2O (1:2). To this solution were added 350 g (570 mmol) of oxone at 0 °C and the suspension was stirred at 20 °C for 8 h. Water (500 ml) was added and the aqueous phase was extracted with EtOAc (3 × 500 mL). Drying over $MgSO_4$, evaporation of the solvent and recrystallization of the residue from Et_2O afforded **8** as colorless crystals; yield: 57.0 g (74%).

Method C: To a solution of 10.0 g (44.2 mmol) of **7** in a ternary system of 50 mL of tetrachloromethane, 50 mL of acetonitrile and 75 mL of water were added 90.0 g (314 mmol) of orthoperiodic acid and 274 mg of $RuO_2 \cdot H_2O$. The originally colorless mixture, which immediately turned yellow upon addition of the catalyst, was vigorously stirred at 40 °C for 22 h. At 0 °C, 10 mL of Et_2O were added, the aqueous solution was stirred for 10 min and extracted with EE (3 × 100 mL). Extraction of the combined organic phases with saturated brine (1 × 50 mL), drying over $MgSO_4$, evaporation of the solvent and recrystallization from Et_2O afforded **8** as a colorless solid; yield: 8.18 g (96%).

Methyl 2-(1′-Mesyloxycyclopropyl)acetate (11a)

To a solution of 2.20 g (11.3 mmol) of **8** in 100 mL of methanol were added ten drops of concentrated sulfuric acid, and the solution was stirred at 20 °C for 18 h. The solvent was removed under vacuum, the residue dissolved in 50 mL of EtOAc, and the solution neutralized with 20 mL of saturated $NaHCO_3$ solution. The aqueous phase was extracted with EtOAc (3 × 50 mL), drying of the combined organic phases over Na_2SO_4 and removal of the solvent under vacuum afforded **11a** as a slightly yellow oil; yield: 2.15 g (91%); (Et_2O, $R_f = 0.66$, MOPS). IR (film): $\tilde{\nu} = 3023$, 2956, 1739, 1439, 1352, 1175, 1031, 942, 908, 824 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz): $\delta =$ 0.86 (m, 2H, Cpr-CH_2), 1.35 (m, 2H, Cpr-CH_2), 2.83 (s, 2H, CH_2), 3.00 (s, 3H, CH_3), 3.70 (s, 3H, OCH_3); ^{13}C NMR ($CDCl_3$, 62.9 MHz): $\delta = 12.0$ (−, 2C, Cpr-C), 39.6 (+, CH_3), 40.8 (−, CH_2), 51.9 (+, OCH_3), 62.0 (C_{quat}, Cpr-C), 170.2 (C_{quat}, C=O); MS (DCI, 70 eV): *m/z* (%) = 209 (8) [$M^+ + H$], 129 (100), 101 (55), 97 (82), 81 (34), 79 (30), 59 (92), 55 (60), 42 (32); anal. calcd. for $C_7H_{12}O_5S$ (208.2): C 40.38, H 5.81; found: C 40.46, H 5.61.

Benzyl 2-(1′-Mesyloxycyclopropyl)acetate (11b)

To a solution of 4.45 g (22.91 mmol) of **8** in 150 mL of toluene were added 2.00 g (10.5 mmol) of *p*-toluenesulfonic acid hydrate and 10.0 g (92.5 mmol) of benzyl alcohol. The solution was heated under reflux in a Dean–Stark apparatus for 6 h, diluted with 100 mL of DCM, extracted with saturated aqueous $NaHCO_3$ solution (2 × 50 mL) and dried over $MgSO_4$. Removal of the volatiles under vacuum and chromatographic purification of the residue on 150 g of silica gel (column, 3 × 25 cm, Pent/Et_2O = 1:1; $R_f = 0.36$, MOPS) afforded **11b** as a colorless liquid; yield: 5.41 g (83%); IR (film): $\tilde{\nu} = 3033$, 2941, 1739, 1456, 1353, 1175, 940, 907 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz): $\delta =$ 0.96 (m, 2H, Cpr-CH_2), 1.44 (m, 2H, Cpr-CH_2), 2.45 (s, 2H, CH_2), 2.94 (s, 3H, CH_3), 5.18 (s, 2H, CH_2Ph), 7.28–7.39 (m, 5H, aryl-H); ^{13}C NMR ($CDCl_3$, 62.9 MHz): $\delta = 12.1$ (−, 2C, Cpr-C), 39.6 (+, CH_3), 41.1 (−, CH_2), 62.0 (C_{quat}, Cpr-C), 66.7 (−, CH_2Ph), 128.27 (+, 2C, aryl-C), 128.33 (+, aryl-C), 128.5 (+, 2 C, aryl-C), 135.6 (C_{quat}, C_{ipso}), 169.9 (C_{quat}, C=O); MS (EI, 70 eV): *m/z* (%) = 284 (2) [M^+], 205 (4), 97 (10), 91 (100); anal. calcd. for $C_{13}H_{16}O_5S$ (284.3):C 54.92, H 5.67; found: C 54.83, H 5.66.

Benzyl Cyclopropylideneacetate (2-Bn)

To a solution of 4.30 g (15.1 mmol) of **11b** in 100 mL of MTBE were added at 0 °C in small portions 2.04 g (18.1 mmol) of *t*-BuOK, the solution was stirred at this temperature for 18 h and then diluted with 100 mL of Et_2O. The organic phase was extracted with 50 mL of water, dried over $MgSO_4$, and the solvents were evaporated. Column chromatography on 150 g of silica gel (column, 3 × 25 cm, Et_2O/PE = 1:9, $R_f = 0.45$; MOPS) afforded **2**-Bn as a colorless oil; yield: 2.76 g (97%); ^1H NMR ($CDCl_3$, 250 MHz): $\delta = 1.24$ (m, 2H, Cpr-CH_2), 1.46 (m, 2H, Cpr-CH_2), 5.20 (s, 2H, CH_2Ph), 6.32 (m, 1H, CH), 7.28–7.42 (m, 5H, aryl-H); ^{13}C NMR ($CDCl_3$, 62.9 MHz): $\delta =$ 2.0 (−, Cpr-C), 4.6 (−, Cpr-C), 65.7 (−, CH_2Ph), 110.9 (CH), 127.8 (+, 2C, aryl-C), 128.3 (+, aryl-C), 128.6 (+, 2C, aryl-C), 136.4 (C_{quat}, C_{ipso}), 145.2 (C_{quat}, Cpr-C), 165.5 (C_{quat}, C=O). The additional experimental data are identical to those reported in literature.[1]

Methyl 2-Bromo-(1-methanesulfonyloxy-cyclopropyl)acetate (12b)

To a solution of 4.00 g (20.6 mmol) of **8** in 50 mL of DCE were added 1.82 mL (25.0 mmol) of thionyl chloride, and the solution was heated under reflux for 30 min. At ambient temperature were added 4.44 g (25.0 mmol) of NBS and 4 drops of concentrated aqueous HBr, and the solution was heated under reflux at 90 °C for 8 h. MeOH (50 mL) was added at 20 °C, and the solution was stirred for an additional 1 h. The solvents were removed under vacuum, the residue suspended in tetrachloromethane, and the mixture filtered. Removal of the solvent and chromatographic purification of the residue on 40 g of silica gel (column, 3 × 20 cm, Pent/Et_2O = 3:1; $R_f = 0.19$) afforded **12b** as a slightly yellow liquid; yield: 4.24 g (71%); IR (film): $\tilde{\nu} =$ 3031, 2944, 1423, 1366, 1168 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz): $\delta = 0.82$ (m, 2H, Cpr-CH_2), 1.21 (m, 2H, Cpr-CH_2), 3.08 (s, 3H, CH_3), 3.82 (s, 3H, OCH_3), 4.85 (s, 1H, Br-CH); ^{13}C NMR ($CDCl_3$, 62.9 MHz): $\delta = 11.2$ (−, 2C, Cpr-C), 40.4 (+, CH_3), 52.5 (+, OCH_3), 62.3 (C_{quat}, Cpr-C), 63.2 (+, Br-CH), 171.2 (C_{quat}, C=O); MS (EI, 70 eV): *m/z* (%) = 288/286 (3/4) [M^+], 209 (63) [$M^+ - Br$], 207 (19), 129 (100), 79 (28), 56 (75); anal. calcd. for $C_7H_{11}BrO_5S$ (287.1): C 29.28, H 3.86; found: C 29.17, H 3.83.

Methyl 2-Bromo-2-cyclopropylideneacetate (4-Me)

To a solution of 4.48 g (15.6 mmol) of **12b** in 50 mL of DCM kept at 0 °C were added 1.72 mL (12.4 mmol) of triethylamine, and the solution was stirred at this temperature for 4 h. DCM (100 mL) and 1 N aqueous HCl (10 mL) were added. Separation of the phases, drying of the organic phase over $MgSO_4$ and removal of the solvent under vacuum afforded **4**-Me as a slightly yellow liquid; yield: 2.92 g (98%); ^1H NMR ($CDCl_3$, 250 MHz): $\delta = 1.39$ (m, 2H, Cpr-CH_2), 1.76 (m, 2H, Cpr-CH_2), 3.82 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 62.9 MHz): $\delta =$ 7.0 (−, Cpr-C), 12.1 (−, Cpr-C), 53.2 (+, CH_3), 103.7 (C_{quat}, Cpr-C), 143.6 (C_{quat}, Br-C), 162.6 (C_{quat}, C=O). The additional experimental data are identical to those reported in literature.[3]

Methyl 2-Chloro-(1-methanesulfonyloxy-cyclopropyl)acetate (12a)

To a solution of 14.0 g (72.1 mmol) of **8** in 450 mL of DCE were added 6.52 mL (89.9 mmol) of thionyl chloride, and the solution was heated under reflux for 60 min. At room temperature were added 14.4 g (108 mmol) of NCS and 15 drops of concentrated aqueous HCl, and the solution was heated under reflux at 90 °C for 12 h. At 20 °C, MeOH (50 mL) was added, and the solution stirred at this temperature for an additional 1 h. The solvent was removed under vacuum, the residue suspended in cold (0 °C) tetrachloromethane, and the mixture was filtered. Removal of the solvent afforded **12a** as a yellow oil, which was used in the next step without further purification; yield: 16.3 g (93%). An analytical sample was purified on

100 g of silica gel (column, 4 × 20 cm, Pent/Et_2O = 3:1; R_f = 0.16). IR (film): $\tilde{\nu}$ = 3045, 2830, 1717, 1456, 1424, 1408, 1329, 1175, 987, 935, 882 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz): δ = 0.84 (m, 2H, Cpr-CH_2), 1.33 (m, 2H, Cpr-CH_2), 3.01 (s, 3H, CH_3), 3.77 (s, 3H, OCH_3), 4.58 (s, 1H, Cl-CH); ^{13}C NMR ($CDCl_3$, 62.9 MHz): δ = 10.0 (−, 2C, Cpr-C), 39.3 (+, CH_3), 52.0 (+, OCH_3), 62.0 (C_{quat}, Cpr-C), 63.2 (+, Cl-CH), 170.8 (C_{quat}, C=O); MS (DCI, 70 eV): *m/z* (%) = 244/242 (2/7) [M^+], 207 (63) [$M^+ - Cl$], 129 (100), 99 (35), 97 (28); anal. calcd. for $C_7H_{11}ClO_5S$ (242.7): C 34.65, H 4.57; found: C 34.60, H 4.56.

Methyl 2-Chloro-2-cyclopropylideneacetate (3-Me)

To a solution of 8.96 g (36.9 mmol) of **12a** in 150 mL of DCM kept at 0 °C were added 7.68 mL (55.2 mmol) of triethylamine, and the solution was stirred at this temperature for 8 h. DCM (100 mL) and aqueous 1 N HCl (3 × 10 mL) were added and the phases were separated. Drying of the organic phase over $MgSO_4$ and removal of the solvent under vacuum afforded **3**-Me as colorless crystals; yield: 5.35 g (99%); ^1H NMR ($CDCl_3$, 250 MHz): δ = 1.41–1.50 (m, 2H, Cpr-CH_2), 1.66–1.75 (m, 2H, Cpr-CH_2), 3.83 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 62.9 MHz): δ = 5.5 (−, Cpr-C), 9.7 (−, Cpr-C), 52.9 (+, CH_3), 114.7 (C_{quat}, Cpr-C), 139.1 (C_{quat}, Cl-C), 162.7 (C_{quat}, C=O). The additional experimental data are identical to those reported in literature.[18]

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