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Complementary Regioselective Cyclopropyl Ring Openings of 6-Formyl-Spirobicyclo[5.2]octane Mediated by TMSCl and TBAI

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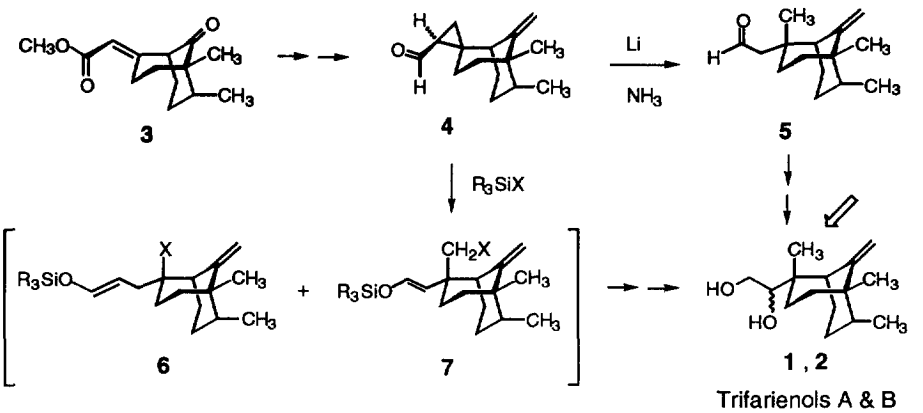
Abstract. Absolute control over the regioselectivity of trimethylsilyl halide-induced cyclopropane fragmentation of a spirofused cyclopropyl carboxaldehyde has been achieved by simply varying the reaction stoichiometry and the nature of the halide. Treatment of 6-formyl-spirobicyclo[5.2]octane with a large excess of TMSCl gave 3-(1-chlorocyclohexyl)propanal (84% yield), whereas 2-(1-iodomethylcyclohexyl)ethanal (86% yield) was obtained using 10 equivalents each TMSCl and *n*-Bu_4NI (TBAI). Use of only a moderate excess of TMSCl or TMSCl and TBAI gave the rearranged product 3-(1-cyclohexenyl)-propanal. © 1997 Elsevier Science Ltd.

Functionally activated cyclopropanes are versatile synthetic intermediates in organic chemistry because they may undergo facile and predictable ring opening reactions.[1] Factors contributing to the stereo- and regioselectivity of α-carbonyl cyclopropane opening under reductive and nucleophilic conditions have been described for a number of systems.[2-6] However, Lewis acid-promoted fragmentations of β-substituted cyclopropane carboxaldehydes have received little attention. Here, we report the results of a study that defines the mode and regioselectivity of trimethylsilyl halide-induced cyclopropane fragmentations of spiro-fused cyclopropyl carboxaldehydes.

We became interested in the controlled fragmentation of spiro-fused cyclopropanes as a potential means to install a quaternary methyl bearing center in the context of our recent total synthesis of the sesquiterpene natural products trifarienols A and B (**1** and **2**, Scheme 1).[7] After constructing the bicyclo[3.3.1]nonane trifarane core (**3**) via a tandem intramolecular carbomercuration / Pd-mediated carbonylation sequence, we encountered the problem of stereoselectively installing the final angular methyl group present in **1** and **2**. Regio- and diastereoselective cyclopropanation of the derived allylic alcohol provided the requisite angular carbon, but as the unsubstituted cyclopropane atom in a 6-hydroxymethyl-spirobicyclo[5.2]octane system. Oxidation to cyclopropyl aldehyde **4** activated the cyclopropane towards dissolving metal reduction, which gave β-methyl aldehyde **5**.[7] However, the potential use of trialkylsilyl halides[8,9] for the direct conversion of **4** into a β-(halo)methyl silyl enol ether derivative (**7**) appeared to be an attractive alternative. Hence, the previously unexplored regioselectivity of trialkylsilyl halide-induced cyclopropyl bond cleavage (i.e. **6** vs. **7**) of β-substituted cyclopropyl aldehydes emerged as a key issue.

Scheme 1.



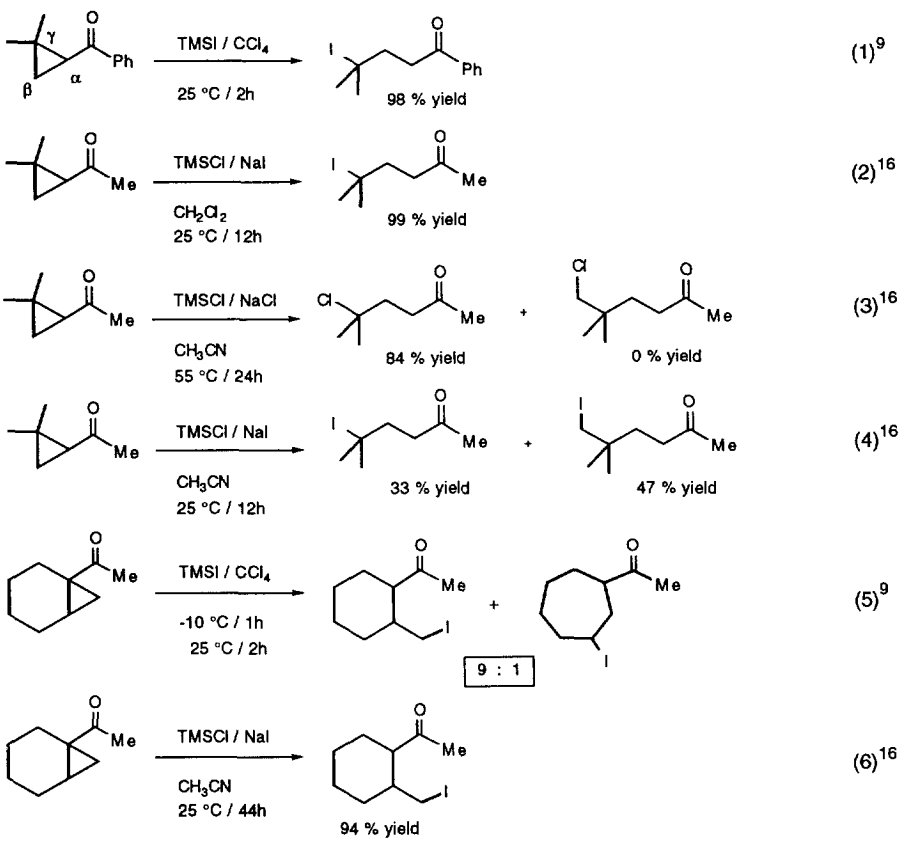
As a prelude to advancing **4** towards **1** and **2**, we examined trimethylsilyl halide-induced cyclopropane fragmentations in the parent system, 6-formyl-spirobicyclo[5.2]octane (**8**). This has provided some interesting and synthetically useful insights, including a simple and practical means to absolutely control the regioselectivity of this β,β-disubstituted cyclopropyl carboxaldehyde opening.

The history and mechanistic interpretation of reductive and nucleophilic openings of electrophilic cyclopropanes are well documented in the literature, dating back over 100 years.[10] Salient features include a strong bias for regio- and stereoselectivity arising from that conformation and particular bond cleavage which maintains maximal overlap of the cleaving σ bond and the developing π-system of the enolate.[2-6] Rapid and irreversible protonation of a γ-carbanion resulting from reductive opening may kinetically define its regiochemistry. Depending upon the substrate and reaction conditions, Lewis and protic acid assisted nucleophilic opening of cyclopropyl ketones can occur by a concerted S_N2 process,[11-15] or may involve stabilized carbocationic intermediates. Miller and McKean introduced the use of TMSI for cyclopropyl ring cleavage,[8] and observed that the regioselectivity may be rationalized on the basis of some of the same steric and electronic considerations put forth for reductive cleavage.[9] Treatment of cyclopropyl ketones with TMSI,[9,16] or other strong Lewis acid-nucleophile pairs[15] predictably yields γ-functionalized ketones, arising from Lewis acid coordination of the carbonyl oxygen, and nucleophilic attack upon an activated β- (or γ) carbon. However, for unsymmetrically β–substituted cyclopropyl ketones, attack at either β-carbon may lead to regioisomeric products. Trialkylsilyl-induced olefin formation via rearrangement of cyclopropyl cations has also been observed.[17] In contrast to reductive openings, Lewis and protic acid assisted cyclopropyl openings may involve considerable carbocationic character at the γ-carbon, and reversibility may lead to product distributions that reflect both kinetic and thermodynamic control. Hence, a subtle interplay of factors may converge to define the regioselectivity and mode of α-carbonyl cyclopropane cleavage.

Some specific consequences of cyclopropane β-substitution and conformational rigidity, nucleophilicity, and solvent polarity on the regioselectivity of cyclopropyl ketone fragmentation are known. In TMS halide-

induced cleavage of conformationally unbiased systems, cationic charge stabilization via σ–π overlap and β–alkyl substitution may act in concert in solvents of lower polarity (eqns. 1 and 2, Scheme 2) or with a weak nucleophile (eqn. 3).[9,16] When used in a polar solvent, the highly reactive TMSI is much less regioselectively discriminate, even in unconstrained systems (eqn. 4).[16] In conformationally constrained systems, reduced opportunities for σ–π overlap may completely override the carbocationic stabilizing effect of enhanced β–alkyl substitution, regardless of solvent polarity (eqns. 5 and 6).[9,16] Although the more highly substituted γ-halo ketone products may be obtained regioselectively from conformationally unbiased cyclopropyl ketones (eqns. 1-3), conditions that provide exclusively the less substituted γ-halo ketone from unconstrained α-carbonyl cyclopropanes have not been defined prior to this work.

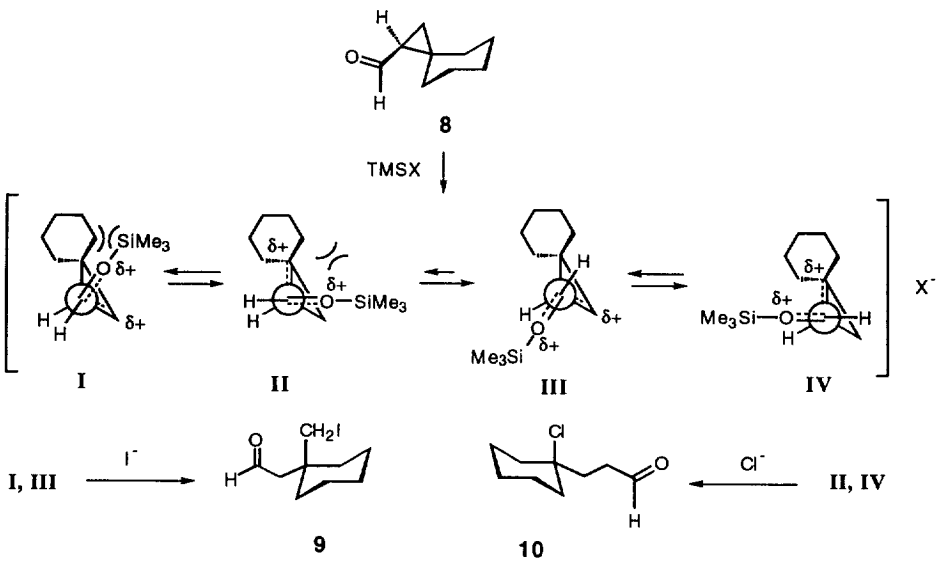
Scheme 2.



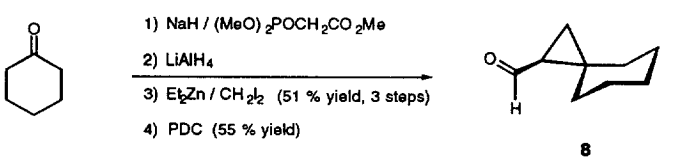
Results and Discussion

The effects of trimethylsilyl halide stoichiometry and nucleophilicity on the regioselectivity of cyclopropyl cleavage were probed using spiro-fused cyclopropyl carboxaldehyde **8**. Free rotation about the cyclopropyl carboxaldehyde bond of **8** should allow alignment of the carbonyl π-system with either α,β-cyclopropyl σ bond to conjugativly stabilize cationic charge development at either β-carbon upon trimethylsilyl halide activation (Scheme 3). If an approximate conformational equivalence existed between rotamers **III** and **IV**, then the additional alkyl substitution at the spiro carbon might be expected to preferentially generate **10** via halide capture of a tertiary carbocationic-like intermediate derived from **IV**. To generate isomer **9**, conformer **I** or **III** would have to be intercepted in preference to **II** and **IV**.

Scheme 3.



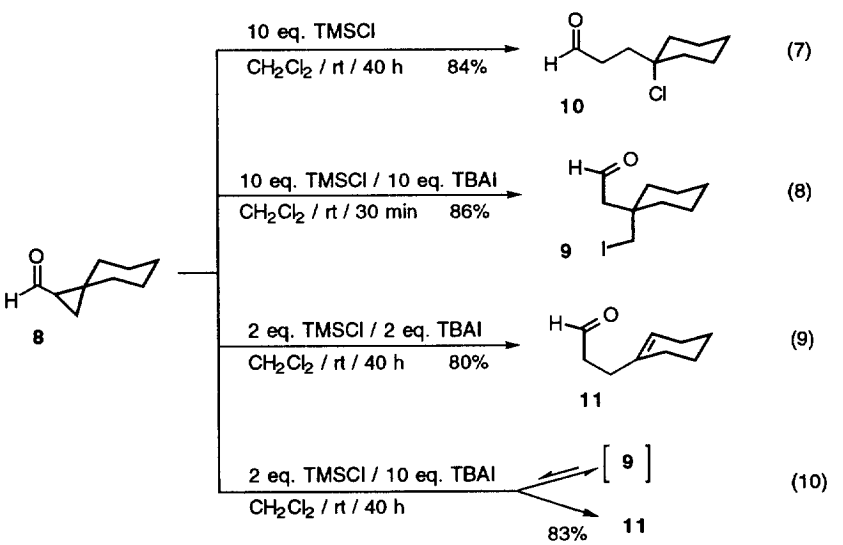
6-Formyl-spirobicyclo[5.2]octane (**8**) was prepared conveniently from cyclohexanone. Treatment of cyclohexanone with trimethyl phosphonoacetate and NaH in THF gave the corresponding acrylate, which was reduced to the allylic alcohol with $LiAlH_4$. Cyclopropanation using Et_2Zn-CH_2I_2 in the presence of oxygen,[18] followed by PDC oxidation gave **8**.



Upon treatment of **8** with 10 equivalents of TMSCl in CH_2Cl_2 at room temperature, little reaction occurred within 1 h. However, after 40 h, **8** had been converted cleanly into tertiary chloride **10** in 84% yield (eqn. 7, Scheme 4). None of the regioisomeric cyclopropane opening product was detected. As expected, only the product resulting from a potential additive combination of σ–π overlap and maximal β–alkyl substitution was obtained in the presence of the weakly nucleophilic chloride anion under these prolonged reaction conditions.

It was anticipated that a stronger nucleophile would substantially increase the rate of reaction and perhaps alter the regioselectivity. Accordingly, treatment of **8** with 10 equivalents each of tetra-*n*-butylammonium iodide (TBAI) and TMSCl in CH_2Cl_2 at room temperature completely consumed the starting material within 30 min. Work up and chromatography gave **9** as the only product (86% yield, eqn. 8, Scheme 4). In contrast to the openings of 2,2-dimethylcyclopropyl ketone using moderate amounts of added TMSI or TMSI generated in situ from TMSCl and NaI (eqns. 1 and 2, Scheme 2), the use of a large excess of the highly dissociative TBAI in conjunction with TMSCl led to nucleophilic attack exclusively upon the less substituted β-carbon of **8**. This is consistent with rapid S_N2 attack upon reactive conformers **I** or **III** (Scheme 3). Upon reaction with Et_3N (5 equivalents) in either CH_3CN, or CH_2Cl_2 at room temperature, cyclopropane **8** was regenerated from **9** in quantitative yield. Similar treatment of **10** gave no reaction.

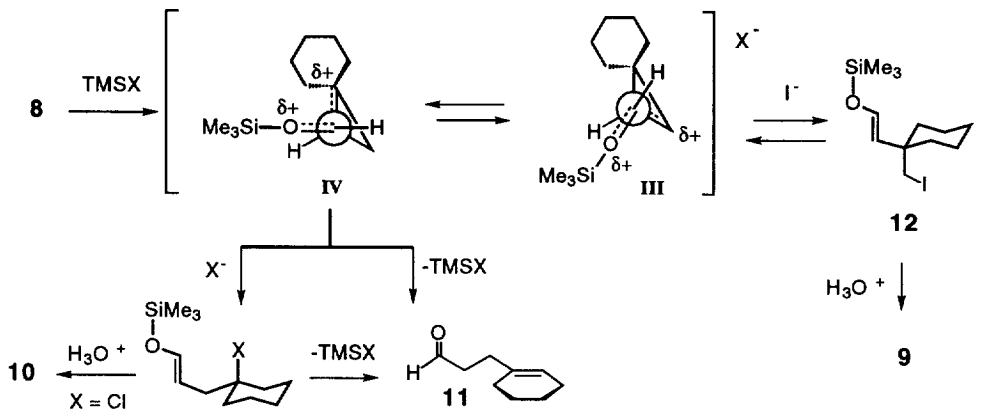
Scheme 4.



Reducing the TMSCl and TBAI to 2 equivalents each greatly retarded the reaction rate, and gave a different major product. After 40 h at room temperature, **8** yielded a mixture of **9** and **10** in less than 10% combined yield, whereas the rearrangement product 3-(1-cyclohexenyl)propanal (**11**)[19-21] was obtained in 80% yield under these conditions (eqn. 9, Scheme 4). Increasing the amount of TBAI to 10 equivalents, while maintaining TMSCl at 2 equivalents initially generated small amounts of **9**, as detected by TLC and gc analysis.

But after 40 h, **11** was again formed and isolated as the major product (83% yield, eqn. 10). Although the formation of silyl enol ether **12** may be kinetically favored, equilibration via cyclopropane reclosure and alternative opening with concomitant or subsequent elimination to give **11** appears to occur under these conditions (Scheme 5).

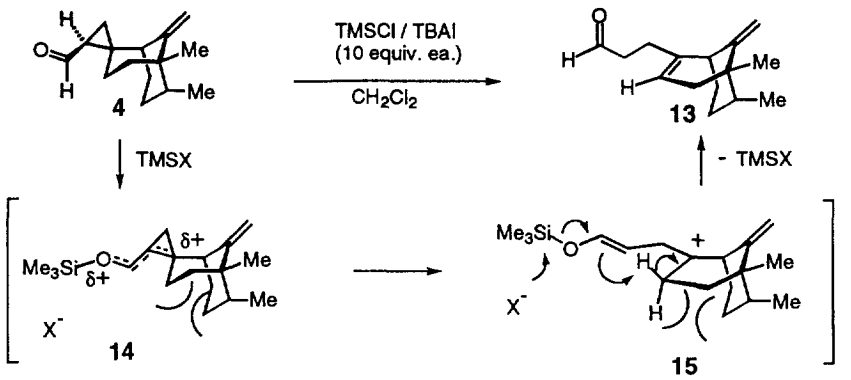
Scheme 5.



These results provide a simple and reliable approach for opening formyl substituted spiro-fused cyclopropane **8** into 3 different γ-halogenated or γ-alkenyl aldehyde products in high yields and with absolute regiochemical control, as summarized in Scheme 4. Analogous to previous results,[16] the weakly nucleophilic Cl^- generated from TMSCl alone does not participate appreciably in S_N2 attack. Instead, positive charge localization at the spiro carbon activates the trisubstituted cyclopropyl bond towards cleavage. Either elimination, or halogenation at the tertiary center then occurs, depending upon the concentration of the nucleophile. Where these results differ most significantly is in the exclusive generation of a kinetic opening product from a conformationally mobile α-carbonyl cyclopropane, which was achieved by treatment of **8** with a large excess of TMSCl and TBAI in CH_2Cl_2 (eqn. 8, Scheme 4).

Encouraged by these findings, we returned to the issue of regioselectively opening the cyclopropane ring of the trifarienol synthetic intermediate **4** (Scheme 1). Given that treatment of **8** with a large excess of TMSCl and TBAI in CH_2Cl_2 at room temperature gave an 86% yield of β-iodomethyl aldehyde **9**, cyclopropane **4** was expected to give the corresponding kinetic opening product **7** under similar conditions. However, the γ-alkenyl aldehyde **13** was obtained as the major product, even after short reaction times (Scheme 6). This seemingly anomalous result may be ascribed to the overriding steric compression built into the 6-formyl-spirobicyclo[5.2]octane system of **4**. Trimethylsilyl activation may lead to a rapid cyclopropane opening of **14** driven by both the relief of cyclopropane and transannular ring strain. Rehybridization of the spiro carbon to form carbocation **15**, and either inter- or intramolecular[17] proton abstraction to planarize the adjacent carbon would relieve transannular steric interactions and provide **13**.

Scheme 6.



Although a unique solution to the problem of regioselectively opening cyclopropane **4** to give β-(halo)methyl silyl enol ether **7** was not found, this study has defined an array of reaction conditions that should prove to be applicable for the selective formation of each of 3 different products (Scheme 4) from simpler β-substituted cyclopropyl carboxaldehydes. This features the use of TBAI and TMSCl for the in situ generation of TMSI in CH_2Cl_2, which when used in large excess provides exclusively the kinetic S_N2 ring opening products.

Experimental Section

6-Formyl-spirobicyclo[5.2]octane (8). To a stirred rt suspension of NaH (1.60 g, 64.0 mmol) in THF (20 mL) was slowly added a solution of cyclohexanone (5.89 g, 60.0 mmol) and trimethyl phosphonoacetate (11.3 g, 62.0 mmol) in THF (150 mL) under Ar. After 2 h, the mixture was cooled to 0 °C, excess $LiAlH_4$ was added, and the mixture was allowed to warm to rt and stir over 2 h. The mixture was re-cooled to 0 °C before aqueous 3 N HCl (50 mL) was added. The resulting mixture was extracted with diethyl ether, and the combined extract was washed with brine, dried over Na_2SO_4, filtered, and concentrated. The residue was dissolved in hexanes (150 mL), and Et_2Zn (1 M solution in hexanes, 144 mL, 144 mmol) was added slowly at 0 °C under Ar. After 5 min, CH_2I_2 (11.6 mL, 144 mmol) was added and dry air (5 mL) was injected into the solution. The mixture was warmed to rt and stirred over 14 h, then filtered through celite and concentrated. Silica gel column chromatography of the residue gave 6-hydroxymethyl-spirobicyclo[5.2]octane (**16**, 4.25 g, 30.6 mmol, 51% over 3 steps) as a clear oil. To a stirred rt solution of solution of **16** (1.40 g, 10.0 mmol) in CH_2Cl_2 (50 mL) was added pyridinium dichromate (7.52 g, 20.0 mmol) and 4Å molecular sieves. After stirring at rt for 14 h, the mixture was filtered through a pad of silica gel, and the filtrate was chromatographed to give **8** (764 mg, 5.50 mmol, 55%) as a clear oil: IR (neat) 2853, 2724, 1701 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.06-0.85 (m, 2H),1.66-1.32 (m, 11H), 9.35 (d, J = 5.4, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.9, 25.6, 25.8, 25.9, 30.0, 34.5, 35.8, 37.2, 201.4; HRMS (CI) calcd for $C_9H_{14}O$ 138.1045, found 138.1039; calcd for $C_9H_{15}O$ $(M+H)^+$ 139.1130, found 139.1124.

3-(1-Chlorocyclohexyl)propanal (9). To a stirred rt solution of **8** (138 mg, 1.00 mmol) in CH_2Cl_2 (5 mL) was added TMSCl (634 mL, 5.00 mmol) under Ar. The mixture was stirred at rt for 40 h, then worked up and chromatographed to give **9** (147 mg, 840 μmol, 84%) as a clear oil: IR (neat) 2862, 2723, 1725 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.53 (m, 4H), 1.69 (m, 3H), 1.20 (m, 1H), 1.93 (m, 2H), 2.07 (t, J = 7.5 Hz, 2H), 2.72 (dt, J = 1.0, 7.5 Hz, 2H), 9.83 (t, J = 1.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 22.2, 25.3, 39.1, 36.9, 39.7, 74.6, 201.7; HRMS (CI) calcd for $C_9H_{15}OCl$ $(M+H)^+$ 175.0889, found 175.0892.

2-[1-(Iodomethyl)cyclohexyl]ethanal (10). To a stirred rt solution of **8** (138 mg, 1.00 mmol) and TBAI (3.69 g, 10.0 mmol) in CH_2Cl_2 (5 mL) was added TMSCl (1.27 mL, 10.0 mmol) under Ar. The mixture was stirred at rt for 30 min, then worked up and chromatographed to give **10** (229 mg, 860 μmol, 86%) as a clear, pale yellow oil: IR (neat) 2852, 2724, 1718 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.43 (m, 8H), 1.60 (m, 2H), 2.51 (d, J = 2.4, 2H), 3.43 (s, 2H), 9.80 (t, J = 2.4 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.5, 21.6, 25.6, 35.3, 36.4, 50.9, 201.7; HRMS (CI) calcd for $C_9H_{15}OI$ $(M+H)^+$ 267.0246, found 267.0247.

3-(1-Cyclohexenyl)propanal (11).[19-21] To a stirred rt solution of **8** (138 mg, 1.00 mmol) and tetrabutylammonium iodide (738 mg, 2.00 mmol) in CH_2Cl_2 (5 mL) was added TMSCl (253 mL, 2.00 mmol) under Ar. The mixture was stirred at rt for 40 h, then worked up and chromatographed to give **11** (110 mg, 800 μmol, 80%) as a clear, pale yellow oil: IR (neat) 2856, 2836, 2719, 1725, 1684 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.57 (m, 4H), 1.90 (m, 2H), 1.96 (m, 2H), 2.26 (t, J =7.2 Hz, 2H), 2.51 (dt, J =1.8, 7.2 Hz, 2H), 5.40 (m, 1H), 9.75 (t, J = 1.8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.3, 22.8, 25.1, 28.4, 30.1, 41.8, 121.8, 135.6, 202.8; HRMS (EI) calcd for $C_9H_{14}O$ 138.1405, found 138.1042.

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