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Radical cyclization–fragmentation of ω-haloalkyl cyclobutanones: a modular approach to medium-sized carbocycles

Heong-Sub Oh and Jin Kun Cha*

Department of Chemistry, University of Alabama, Tuscaloosa, AL 35487 USA and Department of Chemistry, Wayne State University, Detroit, MI 48202 USA

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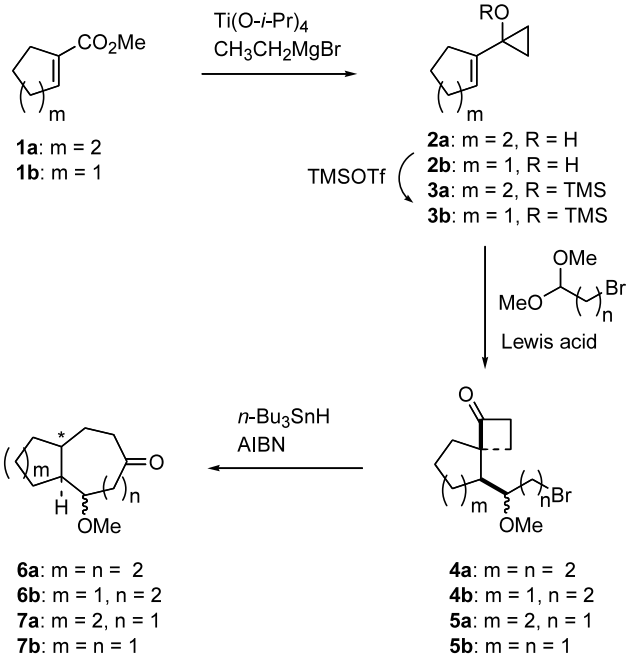
Abstract—A facile radical cyclization–fragmentation sequence of ω-haloalkyl-tethered spirocyclobutanones, which are readily available by the Kulinkovich cyclopropanation of cycloalkene carboxylates and subsequent electrophilic addition to haloalkyl acetals, provides a convenient method for appending seven- and eight-membered rings onto cycloalkene carboxylates. An enantioselective preparation of a medium-sized carbocycle is possible by the use of a non-racemic, C_2-symmetric acetal.

1. Introduction

Free radical-mediated reactions have frequently been applied in the formation of carbon–carbon bonds.[1–3] Among the unique advantages of radical chemistry are excellent reactivity, yet high levels of predictable regio- and stereoselectivity, under mild reaction conditions, and tolerance of several common functional groups. The utility of free radical cyclization reactions has been amply demonstrated in the synthesis of carbocyclic and heterocyclic natural products. Thus, useful methods for forming medium-sized rings and macrocycles, as well as five- and six-membered rings, have been developed by free radical cyclizations. A particularly useful route to medium-sized carbocycles is based on ring expansion of strained cyclobutanones via β-scission of alkoxy radicals. For example, Dowd et al. reported an elegant strategy featuring an inter- or intramolecular [2+2] photocycloaddition and an alkoxy radical fragmentation reaction of the resulting, typically fused cyclobutanone; ring expansion is facilitated by release of ring strain and does not require a radical stabilizing substituent.[4–7] We herein report an expedient method for the annulation of seven- and eight-membered rings onto cycloalkene carboxylates, affording suitably functionalized medium-sized bicyclic compounds, by means of facile radical fragmentation of spirocyclobutanones containing ω-halo tethers (Scheme 1).[8]



Scheme 1.

* Corresponding author. Tel.: (313) 577-1073; fax: (313) 577-8822; e-mail: jcha@chem.wayne.edu

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2. Results and discussion

2.1. Synthesis of spiro cyclobutanones

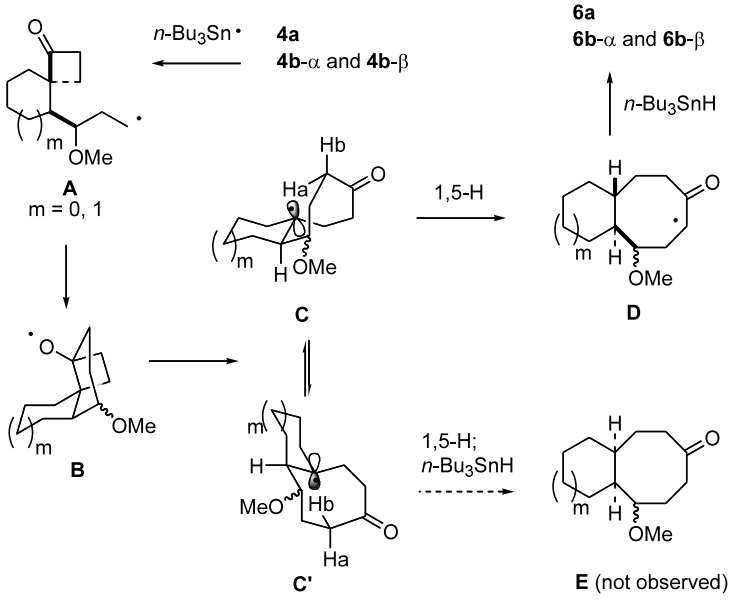
In the pioneering work by Dowd et al.,[4,5] the requisite cyclobutanone substrates were prepared by the [2+2] cycloaddition reaction of ketenes or keteniminium salts.[9] This [2+2] cycloaddition was amenable to both intermolecular and intramolecular reactions, but limited primarily to the preparation of fused cyclobutanones. It occurred to us that a vinylogous Mukaiyama[10] condensation of vinyl cyclopropanols or silyl ethers with readily available haloacetals would offer an efficient and complementary route to spiro cyclobutanones bearing ω-haloalkyl tethers. Vinyl cyclopropanols can be viewed as vinylogous enols, and their synthetic utility in electrophilic addition reactions was first demonstrated by the Wasserman and Trost groups and, more recently, in our laboratory.[11–15] Our interest in vinyl cyclopropanols as useful synthetic intermediates stemmed from their ready availability by the Kulinkovich reaction[16,17] of carboxylic esters and other derivatives; vinyl cyclopropanols **2a**,**b** had been previously prepared in our laboratory in 95 and 86% yields, respectively, by treatment of **1a** and **1b** with ethylmagnesium bromide in the presence of titanium isopropoxide.[18–20]

In the initial study, cyclopropanols **2a** and **2b** were converted to the corresponding TMS ethers **3a** and **3b** by standard methods (75–88% yield), $TiCl_4$-promoted condensation of which with 3-bromopropionaldehyde dimethylacetal afforded **4a** as a 5:3 mixture of two isomers (71% yield) and a 1:1.3 mixture of **4b**-**α** and **4b**-**β** (56% yield), respectively. The ring junction stereochemistry of **4a**,**b** as shown in Scheme 1 was tentatively assigned on the basis of the stereoelectronic requirements for electrophilic addition. The relative configuration of the methoxy substituent in these products could not be ascertained at this stage, but was subsequently gleaned from X-ray analysis of the resulting ring expansion product derived from **4b**-**α** (vide infra). The cognate condensation of **3a** and **3b** with 2-bromoacetaldehyde dimethylacetal yielded **5a** and **5b** as a nearly 1:1 epimeric mixture at the methoxy stereocenter in 92 and 89% yields, respectively. A cursory survey of other Lewis acids revealed that TMSOTf, $BF_3{\cdot}Et_2O$, or Et_2AlCl were ineffective in coupling of **3a**,**b** with an acetal. More recently, however, cyclopropanols **2a**,**b** were found to undergo clean condensation with certain bromo- or iodoalkyl acetals by the action of $SnCl_4$ to afford the respective adducts in comparable or even better yields. The scope and limitations of the direct condensation reaction of free vinyl cyclopropanols with haloalkyl acetals are currently under investigation.

2.2. Radical ring expansion

In a typical example of the free radical-mediated cyclization–fragmentation sequence, *n*-tributyltin hydride was slowly added to a solution (12–14 mM) of **4a** in refluxing benzene in the presence of AIBN to afford **6a** as a single isomer in nearly quantitative yield. The parallel sequence involving **4b** was next evaluated, especially because the resulting bicyclo[6.3.0]undecane skeleton is found in increasing numbers of bioactive natural products.[21] Again, free radical-mediated cyclization–fragmentation of **4b**-**α** and **4b**-**β** proceeded smoothly to give **6b**-**α** and **6b**-**β** (84 and 93% yields), respectively, as the sole product in each case.

The operative mechanism is thought to involve addition of the initially formed primary radical **A** to the cyclobutanone carbonyl group to generate the reactive alkoxy radical **B** (Scheme 2). Ring opening, which is driven by the relief of strain present in the four-membered ring, affords the fused bicyclic radical **C**. This radical **C** is expected to suffer 1,5-hydrogen transfer leading to the



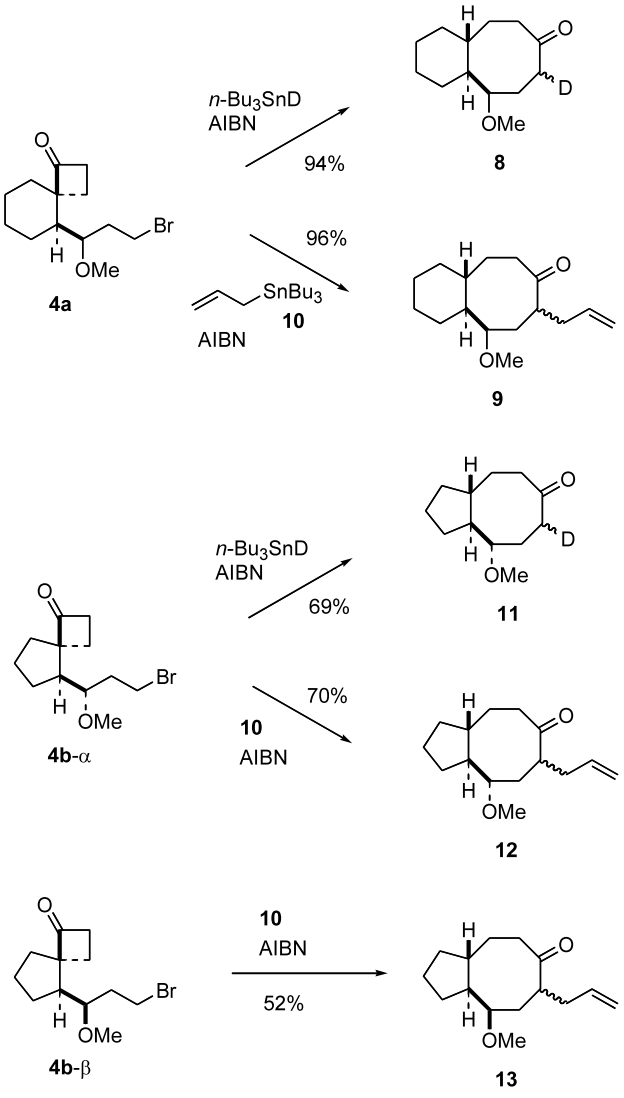
Scheme 2.

stabilized α-acyl radical **D**, which finally undergoes hydrogen abstraction from tributyltin hydride to furnish the bicyclic ketone products **6a** and **6b**. By analogy to a related system examined by Dowd,[22] the formation of the *trans* isomers would be preferred to the alternate *cis* ring junction isomers (i.e. **C** over **C′**; 1,5-hydrogen transfer of H_a versus H_b).

A deuterium labeling experiment using tributyltin deuteride and also the radical allylation reaction by allyltributyltin were undertaken next to substantiate the proposed reaction mechanism involving 1,5-hydrogen transfer (Scheme 3). Reduction of **4a** with tributyltin deuteride afforded **8** having the deuterium α to the carbonyl group as a 4:1 diastereomeric mixture (94%). Treatment of **4a** with allyltributyltin **10** resulted in the placement of an allyl group adjacent to the carbonyl group to give **9**, in 96% yield, as a ~6:1 separable mixture of two diastereomers.

In parallel, **11** was obtained as a 2:1 diastereomeric mixture in 69% yield by treatment of **4b-α** with *n*-Bu_3SnD. From individual radical allylation of **4b-α** and **4b-β** with allyltributyltin, **12** (as a 7:1 diastereomeric mixture) and **13** (as a 5:1 diastereomeric mixture) were obtained in 70 and 52% yields, respectively. The full stereochemistry of **4b-α**, **4b-β**, and **12** was unequivocally established by single-crystal X-ray analysis of carbamate **14**; the latter was prepared from the major diastereomer of **12** having the allyl group in the β-configuration by reduction with $NaBH_4$, followed by acylation of the major alcohol with *p*-bromophenylisocyanate. The X-ray structure of **14** is depicted in ORTEP presentation (Fig. 1).

Our attention was next directed at the construction of the bicyclo[5.4.0]undecane and bicyclo[5.3.0]decane rings by the analogous ring expansion sequence of **5a** and **5b** (Scheme 4). Individual treatment of **5a-α** and **5a-β** with *n*-Bu_3SnH and AIBN in refluxing benzene gave **7a-α** and **7a-β**, respectively, in excellent (96~97%) yields; the annulation products were obtained as >15:1 and 4:1 diastereomeric mixtures. In contrast to the above-mentioned eight-membered ring annulation reaction, 1,5-hydrogen transfer was anticipated to be unlikely during the corresponding formation of a seven-membered ring due to geometrical constraints. Apparently, H-abstraction (from *n*-Bu_3SnH) by the tertiary radical intermediate at the ring junction proceeded with unexpectedly high diastereoselectivity, and the *cis* stereochemistry was tentatively assigned for the ring junction of the major isomers of **7a-α** and **7a-β**. This moderate to exceptional degree of stereoselectivity is especially noteworthy, as Dowd had previously reported the loss of stereocontrol at the ring junction in related cyclobutanones **15** and **16** in the non-stereoselective preparation of **17** and **18**.[22] Elucidation of the subtle, yet important factors that are responsible for the diastereoselectivity in these systems, as well as the full stereochemical determination, must await further stud-



Scheme 3.

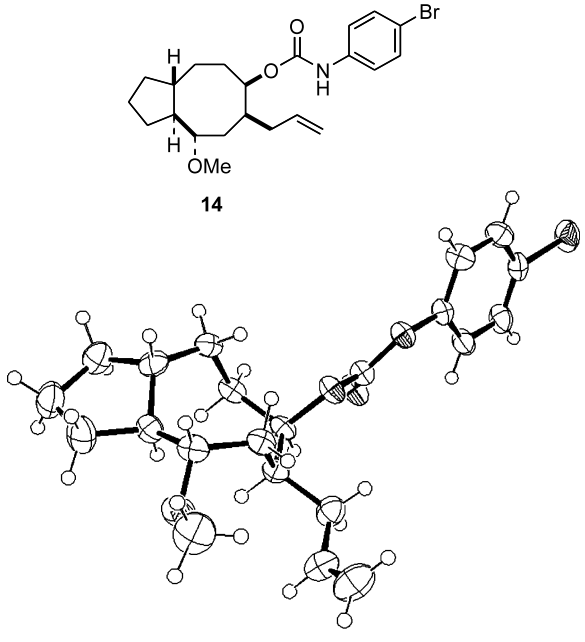


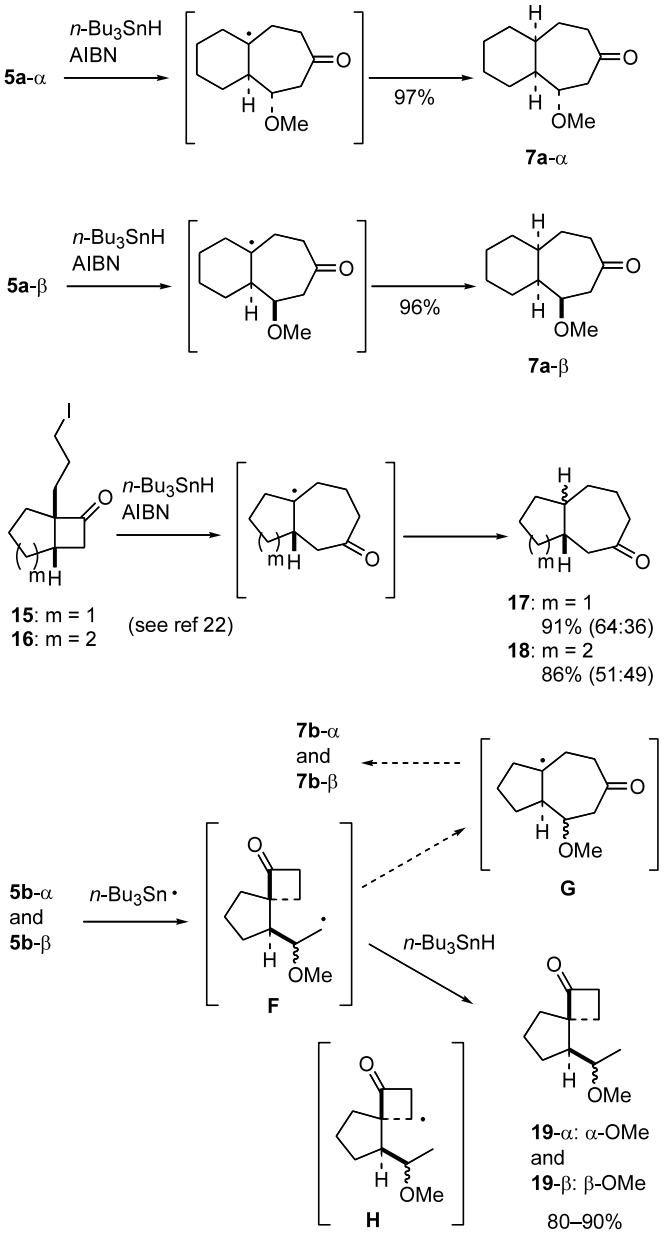
Figure 1.

ies. The analogous sequence involving **5b-α** and **5b-β** was next examined under identical conditions: in each case, only **19-β** and **19-β** were obtained in 80–90% yields. The desired ring expansion pathway (**F→G**) was thwarted by direct reduction by *n*-Bu_3SnH or, possibly, 1,5-hydrogen transfer (**F→H**); further experiments with *n*-Bu_3SnD are necessary to determine whether 1,5-hydrogen transfer is operative. The *n*-Bu_3SnH experiments with **5a** and **5b** illustrate a delicate balance between the two competing reaction manifolds available to the initial primary radical.

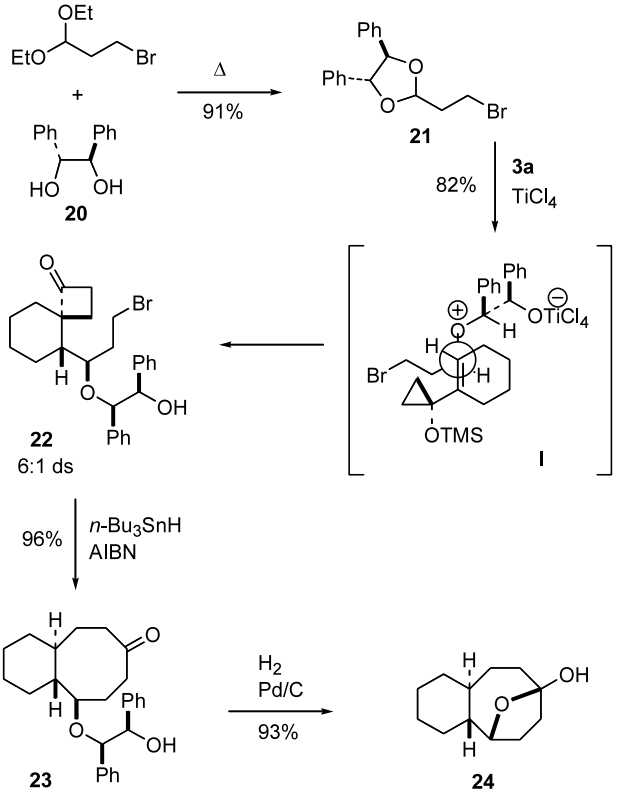
2.3. Enantioselective annulation

Particularly noteworthy is the concise and convergent nature of the present annulation procedure: this method for assembling seven- or eight-membered rings requires two straightforward transformations involving condensation of readily available vinyl cyclopropanols or TMS ethers with known ω-haloalkyl acetals and subsequent radical ring expansion of the resulting ω-haloalkyl-tethered cyclobutanones. In the first step, a simple, yet versatile coupling of the two modules generates three contiguous stereocenters, one of which becomes a tertiary radical following the ring construction. Enantio- and diastereoselective construction of these stereocenters would greatly enhance the synthetic utility of this new annulation procedure. Following the seminal contributions by W. S. Johnson,[23] C_2-symmetric chiral acetals have emerged as useful tools in asymmetric induction.[24–26]

Toward this end, we chose (*R*,*R*)-(+)-hydrobenzoin **20** as a chiral auxiliary because of its commercial availability, ease of removal and subsequent preparation of enantiopure **21** in good yield (Scheme 5). Titanium chloride-promoted condensation of **21** with **3a** afforded a 6:1 mixture of two isomeric cyclobutanones (82%); the major product was tentatively assigned to have the stereochemistry as shown in **22** on the basis of mechanistic considerations in terms of an open-chain transition state.[10] A working model **I** is shown, but is a matter of speculation at this juncture. The provisional stereochemical assignment needs to be confirmed by X-ray analysis. The use of a bulkier alkyl acetal **21**, vis-à-vis a dimethyl acetal (e.g. 3-bromopropionaldehyde dimethylacetal), could reinforce the preference for an extended, open-chain transition state, which could account for enhanced diastereoselectivity. The ring



Scheme 4.



Scheme 5.

expansion reaction of **22** was then achieved by slow addition of Bu_3SnH to give **23** in 96% yield. Finally, the chiral auxiliary was removed cleanly by hydrogenolysis (H_2, Pd/C) to afford **24**, $[\alpha]_D = -8.3$ (*c* 0.004, $CHCl_3$), in 93% yield. Thus, the feasibility of an enantioselective formation of an eight-membered ring under the aegis of a chiral acetal was demonstrated in this preliminary investigation. Other readily available chiral acetals will be evaluated in due course for further refinement of the cyclobutanone-based enantio- and diastereoselective annulation strategy.

3. Conclusion

A concise method for appending medium-sized rings to cycloalkene carboxylates has been developed by employing a tandem radical cyclization–fragmentation sequence of bromoalkyl-tethered spirocyclobutanones. The requisite substrates for ring expansion were readily prepared by a modular approach involving the Kulinkovich cyclopropanation of cycloalkene carboxylates and subsequent electrophilic addition of the resulting alkenyl cyclopropanols or TMS ethers to bromoalkyl acetals. Also included is an enantioselective preparation of a medium-sized bicyclic compound by employing a nonracemic, C_2-symmetric acetal.

4. Experimental

Representative procedure for the Kulinkovich cyclopropanation: To a solution of methyl 1-cyclohexene-1-carboxylate **1a** (0.71 mL, 5.1 mmol) in THF (23 mL) was added titanium tetraisopropoxide (1.5 mL, 4.9 mmol). A 1 M THF solution (an excess; ~4 equiv.) of freshly prepared ethylmagnesium bromide was then added at 5–10°C over a period of 1 h (via syringe pump). TLC (using 4:1 hex–EtOAc as eluent) indicated no starting ester, and water (1.7 mL) was then added slowly to quench the reaction. After the resulting mixture had been stirred for 30 min, Celite was added and the resulting mixture was stirred for an additional 3–4 h at rt. The mixture was dried over $MgSO_4$ for 30 min and filtered through a pad of Celite. The filtrate was concentrated under reduced pressure. Purification by column chromatography (using 7:1 to 4:1 hex–EtOAc) afforded 655 mg (93%) of **2a** as a colorless oil.

Representative procedure for silylation of vinylcyclopropanols: To a mixture of **2a** (0.39 g, 2.82 mmol) and 2,6-lutidine (3.5 g, 280 mmol) in CH_2Cl_2 (15 mL) at 0°C was added TMSOTf (1.7 mL, 8.5 mmol). After the reaction mixture had been stirred for 1 h at the same temperature, saturated aqueous $NaHCO_3$ solution (10 mL) was added. The aqueous layer was extracted with Et_2O. The combined organic extracts were washed with water and brine, then dried ($MgSO_4$), and concentrated under reduced pressure. Purification by silica gel column chromatography (10:1 hex–EtOAc containing 1% Et_3N) afforded **3a** (523 mg, 88%) as a colorless liquid: ^{1}H NMR (360 MHz, $CDCl_3$) δ 0.12 (s, 9H), 0.69 (m, 2H), 0.77 (m, 2H), 1.55 (m, 2H), 1.62 (m, 2H), 1.98–2.05 (m, 4H), 5.66 (m, 1H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 1.3, 13.0, 22.7, 23.0, 25.3, 25.6, 60.3, 122.0, 138.3.

3b. ^{1}H NMR (360 MHz, $CDCl_3$) δ 0.11 (s, 9H), 0.79 (m, 2H), 0.89 (m, 2H), 1.87 (m, 2H), 2.55 (m, 2H), 2.33 (m, 2H), 5.52 (m, 1H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 1.30, 14.0, 23.9, 32.5, 32.7, 56.5, 123.8, 146.8.

Representative procedure for a vinylogous Mukaiyama-type condensation: To a solution of **3a** (0.50 g, 2.38 mmol) in CH_2Cl_2 (4 mL) at –40°C were added sequentially 3-bromopropionadehyde dimethylacetal (0.63 g, 3.1 mmol) and $TiCl_4$ (0.59 g, 3.1 mmol). The reaction mixture was stirred at the same temperature for 2 h. The reaction was then quenched by addition of wet ether (20 mL) and allowed to warm to rt. The mixture was washed with brine (10 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo to give the crude product. Purification by column chromatography on silica gel (using 10:1 hex–EtOAc as eluent) afforded **4a** as a mixture of two isomers, 0.30 g (44%) and 0.19 g (27%).

Spectra data for the more polar isomer (on TLC) of **4a**: IR (film) 1774 cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) δ 0.97 (m, 1H), 1.26 (m, 2H), 1.47 (m, 1H), 1.59–1.73 (m, 5H), 1.85–1.99 (m, 2H), 2.07 (m, 1H), 2.26 (m, 1H), 2.87–3.01 (m, 2H), 3.18 (dt, J = 9.0, 4.7 Hz, 1H), 3.28 (s, 3H), 3.44 (dd, J = 8.1, 7.3, 2H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 18.6, 22.0, 25.4, 26.3, 28.8, 34.2, 34.3, 41.5, 44.3, 56.5, 67.1, 81.3, 215.0.

Spectral data for the less polar isomer: IR (film) 1766 cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) δ 1.22 (m, 1H), 1.48–1.68 (m, 9H), 1.74–1.82 (m, 2 H), 2.25 (dt, J = 11.0, 8.4 Hz, 1H), 2.91 (t, J = 8.4 Hz, 2H), 3.33 (s, 3H), 3.44–3.57 (m, 3H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 23.1, 23.3, 25.7, 25.9, 31.1, 35.8, 36.1, 41.6, 46.3, 58.2, 67.1, 80.2, 215.2.

4b-α. IR (film) 1774 cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) δ 1.58 (m, 2H), 1.68–1.95 (m, 5H), 2.07 (m, 2H), 2.29 (m, 2H), 2.82 (ddd, J = 17.6, 9.7, 5.0 Hz, 1H), 3.13 (ddd, J = 17.6, 10.2, 7.8 Hz, 1H), 3.37 (s, 3H), 3.42–3.52 (m, 3H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 21.2, 24.1, 27.3, 30.5, 35.9, 38.7, 43.0, 44.9, 57.6, 72.5, 79.9, 215.5.

4b-β. IR (film) 1774 cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) δ 1.29 (m, 1H), 1.60–1.87 (m, 5H), 1.94–2.09 (m, 2H), 2.14–2.24 (m, 2H), 2.39 (m, 1H), 2.88–3.05 (m, 2H), 3.29 (s, 3H), 3.37 (m, 1H), 3.45 (m, 2H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 21.2, 23.4, 27.9, 28.9, 34.9, 37.9, 43.1, 48.3, 55.8, 72.3, 80.3, 215.8.

Representative procedure for free radical-mediated cyclization-fragmentation: A solution of *n*-Bu_3SnH (62 mg, 0.2 mmol) and AIBN (2 mg, 0.01 mmol) in benzene (5 mL) was added slowly over a period of 8 h (syringe pump) to a solution of **4a** (the more polar isomer; 20 mg, 0.07 mmol) in benzene (5 mL) at reflux. The reaction mixture was cooled to rt and concentrated under reduced pressure. The resulting crude product

was dissolved in CH_2Cl_2 (20 mL) and washed with 10% potassium fluoride solution (10 mL), dried ($MgSO_4$), filtered, and concentrated. Purification by column chromatography on silica gel (15:1 hex–EtOAc) gave **6a** (14.3 mg, 99%): IR (film) 1699 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 1.02–1.47 (m, 6H), 1.51–1.90 (m, 6H), 2.09 (ddd, $J=12.3$, 6.6, 3.7 Hz, 1H), 2.18 (m, 1H), 2.29 (ddd, $J=15.6$, 6.5, 3.6 Hz, 1H), 2.44 (dt, $J=2.7$, 12.3 Hz, 1H), 2.59 (m, 1H), 2.92 (dt, $J=3.1$, 11.7 Hz, 1H), 3.20 (m, 1H), 3.34 (s, 3H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 23.7, 26.6, 26.7, 30.1, 31.7, 32.9, 35.2, 38.9, 41.7, 44.8, 58.1, 85.4, 218.3; MS m/z 210 (M^+).

6b-α. IR (film) 1698 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 1.16 (m, 1H), 1.26–1.73 (m, 6H), 1.82 (m, 2H), 1.96 (m, 1H), 2.11–2.31 (m, 4H), 2.60 (m, 1H), 2.79 (dt, $J=11.5$, 3.5 Hz, 1H), 2.99 (dt, $J=2.7$, 10.3 Hz, 1H), 3.30 (s, 3H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 23.4, 25.7, 29.9, 33.2, 36.4, 39.0, 40.0, 41.9, 47.5, 57.0, 84.7, 218.4.

6b-β. IR (film) 1701 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 1.15 (m, 1H), 1.25–1.68 (m, 6H), 1.78–1.88 (m, 1H), 1.91–1.98 (m, 1H), 2.02–2.30 (m, 5H), 2.44 (m, 1H), 2.78 (dt, $J=3.6$, 11.7 Hz, 1H), 3.17 (m, 1H), 3.39 (s, 3H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 26.5, 26.6, 28.5, 32.2, 36.4, 38.1, 39.9, 41.1, 47.0, 58.0, 82.7, 217.7.

7a-α. IR (film) 1702 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.30–1.40 (m, 2H), 1.42–1.54 (m, 4H), 1.58–1.66 (m, 2H), 1.76 (m, 1H), 1.96–2.15 (m, 3H), 2.44–2.47 (m, 2H), 2.74–2.75 (m, 2H), 3.32 (m, 1H), 3.34 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.2, 24.4, 25.5, 26.5, 34.1, 35.6, 43.0, 43.3, 43.8, 56.8, 80.3, 212.9; HRMS calcd for $C_{12}H_{20}O_2Na$ (M^+) 219.1355, found 219.1354.

7a-β. IR (film) 1702 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.24–1.42 (m, 3H), 1.46–1.50 (m, 1H), 1.52 (m, 1H), 1.59–1.62 (m, 3H), 1.80 (m, 1H), 1.90 (m, 1H), 1.99 (m, 1H), 2.13 (m, 1H), 2.41 (dd, $J=14.7$, 3.0 Hz, 1H), 2.44 (m, 1H), 2.63 (dd, $J=16.5$, 5.1 Hz, 1H), 2.67 (dd, $J=16.5$, 10.1 Hz, 1H), 3.33 (s, 3H), 3.55 (ddd, $J=10.1$, 5.1, 2.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.4, 21.7, 25.2, 26.6, 34.5, 38.7, 43.5, 44.2, 45.2, 56.9, 80.4, 211.7; HRMS calcd for $C_{12}H_{20}O_2Na$ (M^+) 219.1355, found 219.1358.

8. IR (film) 1702 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 1.03–1.35 (m, 5H), 1.45 (m, 1H), 1.53–1.70 (m, 5H), 1.72–1.81 (m, 1H), 2.08 (m, 1H), 2.19 (dt, $J=5.7$, 14.7 Hz, 1H), 2.31 (ddd, $J=15.7$, 6.6, 3.6 Hz, 1H), 2.45 (m, 1H), 2.61 (m, 1H), 3.21 (m, 1H), 3.36 (s, 3H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 26.6, 26.7, 30.1, 31.6, 32.9, 34.1, 34.8 (t), 38.9, 41.7, 44.8, 58.0, 85.5, 218.3; HRMS calcd for $C_{13}H_{21}DO_2$ (M^+) 211.1683, found 211.1657.

11. IR (film) 1698 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 1.16 (m, 1H), 1.35–1.73 (m, 6H), 1.80 (m, 2H), 1.95 (m, 1H), 2.13–2.19 (m, 1H), 2.21–2.30 (m, 2H), 2.56 (m, 1H), 2.80 (m, 1H), 2.99 (dt, $J=10.1$, 2.9 Hz, 1H), 3.30 (s, 3H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 23.3, 25.7, 33.3, 36.4, 38.7 (t; another small triplet at 38.6), 38.9, 40.0, 41.9, 47.5, 57.0, 84.7, 217.2; HRMS calcd for $C_{12}H_{19}DO_2$ (M^+) 197.1526; found 197.1557.

Representative procedure for radical allylation: A solution of allyltributyltin (102 mg, 0.3 mmol) and AIBN (6 mg, 0.04 mmol) in benzene (1 mL) was added, over a period of 6 h (syringe pump), to a solution of **4a** (the more polar isomer; 30 mg, 0.1 mmol) in benzene (1 mL) at reflux. The reaction mixture was cooled to rt and concentrated under reduced pressure. The residue was then dissolved in CH_2Cl_2 (30 mL) and washed with 10% potassium fluoride solution (10 mL), dried over $MgSO_4$, filtered, and concentrated to give the crude product. Purification by column chromatography on silica gel (15:1 hex–EtOAc) afforded **9** (24 mg, 96%) as a 5:1 diastereomeric mixture: IR (film) 1704 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 1.09–1.44 (m, 6H), 1.52–1.75 (m, 5H), 1.78 (dd, $J=5.3$, 3.2 Hz, 1H), 1.81–1.91 (m, 2H), 2.10 (m, 1H), 2.41 (dt, $J=14.1$, 6.8 Hz, 1H), 2.45–2.57 (m, 2H), 2.78 (m, 1H), 3.25 (s, 3H), 3.41 (m, 1H), 5.01 (dd, $J=9.9$, 1.5 Hz, 1H), 5.03 (dd, $J=17.2$, 1.5 Hz, 1H), 5.72 (m, 1H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 26.3, 26.6 (2 C's), 32.5, 34.6, 35.8, 36.7, 38.9, 42.0 (2 C's), 46.1, 56.9, 83.5, 116.9, 136.1, 216.4; MS m/z 250 (M^+).

12. IR (film) 1711 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 0.90 (m, 1H), 1.16 (m, 1H), 1.35–1.55 (m, 3H), 1.58–1.68 (m, 2H), 1.78 (m, 2H), 1.92–2.25 (m, 6H), 2.62 (m, 1H), 2.77 (m, 1H), 2.96 (dt, $J=10.0$, 2.8 Hz, 1H), 3.28 (s, 3H), 5.04 (dd, $J=17.9$, 1.2 Hz, 1H), 5.05 (dd, $J=10.1$, 1.2 Hz, 1H), 5.71 (m, 1H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 25.7, 29.4, 33.4, 36.3, 36.4, 37.9, 38.0, 41.9, 47.6, 48.1, 56.9, 84.3, 117.4, 135.3, 218.9.

13. IR (film) 1698 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 0.90 (m, 1H), 1.15 (m, 1H), 1.42–1.68 (m, 5H), 1.77–1.98 (m, 4H), 2.00–2.30 (m, 5H), 2.76 (m, 1H), 3.14 (ddd, $J=10.7$, 5.1, 3.0 Hz, 1H), 3.36 (s, 3H), 5.04 (dd, $J=17.2$, 1.4 Hz, 1H), 5.05 (dd, $J=10.1$, 1.4 Hz, 1H), 5.71 (m, 1H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 26.5, 31.8, 32.9, 36.2, 36.4, 38.0, 38.2, 38.4, 46.9, 51.2, 58.1, 82.1, 117.6, 135.0, 219.2.

(4*R*, 5*R*)-2-Bromoethyl-4,5-diphenyl-1,3-dioxolane 21: A mixture of (*R*,*R*)-(+) hydrobenzoin (950 mg, 4.43 mmol) and 3-bromopropionaldehyde diethylacetal (900 mg, 4.27 mmol) was heated at 135–145°C for 2 h and then cooled. The product was recrystallized from isopropanol to give **21** (1.3 g, 91%) as a white solid: ^1H NMR (400 MHz, C_6D_6) δ 2.21 (dt, $J=7.3$, 4.9 Hz, 2H), 3.30 (t, $J=7.3$ Hz, 2H), 4.56 (d, $J=8.1$ Hz, 1H), 4.60 (d, $J=8.1$ Hz, 1H), 5.44 (t, $J=4.9$ Hz, 1H), 7.00–7.20 (m, 10H); ^{13}C NMR (100 MHz, C_6D_6) δ 27.2, 38.1, 85.2, 87.1, 103.7, 126.6, 127.0, 128.5, 128.6; GC-MS m/z 333 (M^+).

22 (the major isomer; the less polar fraction): IR (film) 1765 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.86 (m, 1H), 1.14–1.35 (m, 2H), 1.44–1.52 (m, 2H), 1.66–1.74 (m, 3H), 1.78 (m, 1H), 1.96–2.08 (m, 3H), 2.28 (m, 1H), 3.15–3.29 (m, 3H), 3.44 (dt, $J=6.1$, 10.6 Hz, 1H), 3.49 (dt, $J=5.0$, 10.6 Hz, 1H), 4.31 (d, $J=8.1$ Hz, 1H), 4.75 (d, $J=8.1$ Hz, 1H), 7.01 (m, 2H), 7.07 (m, 2H), 7.14 (m, 3H), 7.25 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 18.3, 22.0, 25.3, 26.2, 26.6, 32.4, 34.1, 42.2, 43.1, 67.0,

75.6, 78.2, 84.0, 127.2, 127.8, 128.1, 128.3, 128.6, 128.7, 136.4, 139.2, 218.4.

23. IR (film) 1693 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.90–0.13 (m, 6H), 1.44–1.75 (m, 6H), 2.08 (ddd, $J=$ 15.4, 6.5, 2.4 Hz, 1H), 2.20 (m, 1H), 2.32 (ddd, $J=15.4$, 6.5, 3.3 Hz, 1H), 2.44 (m, 1H), 2.60 (m, 1H), 2.84 (m, 1H), 3.28 (m, 1H), 3.31 (d, $J=2.4$ Hz, 1H, O*H*) 4.34 (d, $J=7.3$ Hz, 1H), 4.78 (dd, $J=7.3$, 2.4 Hz, 1H), 7.01–7.30 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.4, 26.5, 30.5, 31.0, 32.7, 33.9, 35.0, 39.0, 41.6, 44.6, 78.6, 80.5, 85.0, 127.1, 127.3, 127.9, 128.1, 128.3, 128.5, 138.0, 139.9, 218.0.

24. To a solution of **23** (8 mg, 0.02 mmol) in EtOH (3 mL) at rt was added 10% palladium on activated carbon (5 mg). The reaction mixture was hydrogenated in a Parr hydrogenator under 60 psi for 4 h, filtered through a pad of Celite and $MgSO_4$, and then concentrated in vacuo to give the crude product. Purification by column chromatography on silica gel (using 7:1 hex–EtOAc as eluent) afforded **24** (3.5 mg, 93%) as a colorless oil: $[\alpha]_D=-8.3$ (*c* 0.004, $CHCl_3$); IR (film) 3398, 1729 (w) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.90 (m, 1H), 1.10–1.23 (m, 3H), 1.24–1.48 (m, 5H), 1.61–1.84 (m, 6H), 1.96 (dt, $J=12.2$, 3.0 Hz, 1H), 2.09–2.15 (m, 1H), 2.39 (m, 1H), 2.55 (s, br, 1H), 4.02 (br d, $J=8.6$ Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 26.6, 26.9, 32.3, 34.0, 34.5, 34.9, 36.1, 40.3, 41.0, 54.4, 83.3, 108.7; GC-MS m/z 196 (M^+).

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References

1. Giese, B. *Radicals in Organic Synthesis*: *Formation of Carbon–Carbon Bonds*; Pergamon Press: Oxford, 1986.
2. Motherwell, W. B.; Crich, D. *Free Radical Chain Reactions in Organic Synthesis*; Academic Press: San Diego, 1992.
3. *Radicals in Organic Synthesis*; Renaud, P., Sibi, M. P., Eds.; Wiley-VCH: Weinheim, Germany, 2001.
4. Dowd, P.; Zhang, W. *J. Am. Chem. Soc.* **1991**, *113*, 9875–9876.
5. Dowd, P.; Zhang, W. *Chem. Rev.* **1993**, *93*, 2091–2115.
6. Yet, L. *Tetrahedron* **1999**, *55*, 9349–9403.
7. Zhang, W. *Curr. Org. Chem.* **2002**, *6*, 1015–1029.
8. Oh, H.-S.; Lee, H. I.; Cha, J. K. *Org. Lett.* **2002**, *4*, 3707–3709.
9. Tidwell, T. T. *Ketenes*; Wiley: New York, 1995.
10. Murata, S.; Suzuki, M.; Noyori, R. *J. Am. Chem. Soc.* **1980**, *102*, 3248–3249.
11. Wasserman, H. H.; Cochoy, R. E.; Baird, M. S. *J. Am. Chem. Soc.* **1969**, *91*, 2375–2376.
12. Trost, B. M.; Brandi, A. *J. Am. Chem. Soc.* **1984**, *106*, 5041–5043.
13. Trost, B. M.; Lee, D. C. *J. Am. Chem. Soc.* **1988**, *110*, 6556–6558.
14. Trost, B. M. *Top. Curr. Chem.* **1986**, *133*, 3–82.
15. Youn, J.-H.; Lee, J.; Cha, J. K. *Org. Lett.* **2001**, *3*, 2935–2938.
16. Kulinkovich, O. G.; de Meijere, A. *Chem. Rev.* **2000**, *100*, 2789–2834.
17. Sato, F.; Urabe, H.; Okamoto, S. *Chem. Rev.* **2000**, *100*, 2835–2886.
18. Lee, J.; Kim, H.; Cha, J. K. *J. Am. Chem. Soc.* **1995**, *117*, 9919–9920.
19. Lee, J.; Kim, H.; Cha, J. K. *J. Am. Chem. Soc.* **1996**, *118*, 4198–4199.
20. For a previous synthesis of **2a** and **2b**, see: Salaun, J.; Garnier, B.; Conia, J. M. *Tetrahedron* **1974**, *30*, 1413–1421.
21. Mehta, G.; Vishwakarma, S. *Chem. Rev.* **1999**, *99*, 881–930.
22. Zhang, W.; Collins, M. R.; Mahmood, K.; Dowd, P. *Tetrahedron Lett.* **1995**, *36*, 2729–2732.
23. Johnson, W. S.; Harbert, C. A.; Stipanovic, R. D. *J. Am. Chem. Soc.* **1968**, *90*, 5279–5280.
24. Alexakis, A.; Mangeney, P. *Tetrahedron: Asymmetry* **1990**, *1*, 477–511.
25. Denmark, S. E.; Almstead, N. G. *J. Am. Chem. Soc.* **1991**, *113*, 8089–8110.
26. Sammakia, T.; Smith, R. S. *J. Am. Chem. Soc.* **1992**, *114*, 10998–10999.