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Radical Cyclization Followed by the Fragmentation of Carbonyl Compounds: Effect of an α-Benzoyl Group

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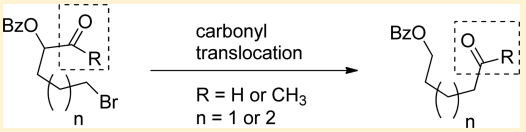
Supporting Information

ABSTRACT: To study a recently developed radical cyclization reaction followed by a fragmentation process in more detail, a series of α-benzoyl carbonyl compounds were prepared, including precursors with aldehyde and ketone moieties. Initiated by tributyltin hydride and AIBN, radical cyclization followed by fragmentation proceeded to give the desired carbonyl translocation products in 4-benzoyl-5-pentanal, 4-benzoyl-5-pentanone, 5-benzoyl-6-hexanal, and 5-benzoyl-6-hexanone radical systems. In comparison with early reports on radical cyclization reactions of α-oxy carbonyl compounds, neither a geminal dialkyl effect nor a conformationally rigid system was required to give the desired carbonyl translocation products. This effect clearly proves that a benzoyl group serves as a protecting group in these radical processes, which not only enhances cyclization efficiency but also increases the rate of the fragmentation step, eventually producing the desired carbonyl translocation products. These observations provide an alternative point of view in the field of radical cyclization reactions. Since the fragmentation step could be enhanced by appropriately positioning an α-benzoyl group, these four radical processes could be used to convert the naturally occurring D-sugars, such as D-pentoses and D-hexoses, into rare deoxy-L-sugars. Furthermore, a cascade radical process involving radical cyclization and fragmentation followed by addition to the allyltin reagent was developed and is reported herein.

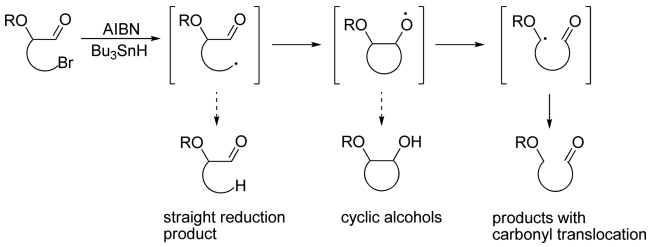


INTRODUCTION

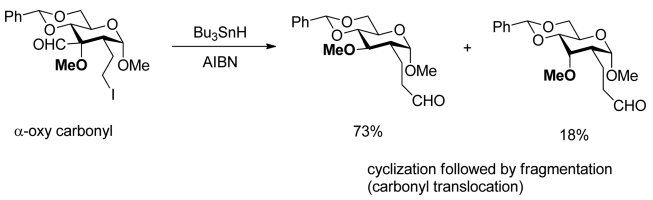
Since the discovery of the triphenylmethyl radical,[1] radicals have been widely used in organic synthesis, including radical reactions[2] and radical polymerizations.[3] A variety of useful organic reactions involving radicals remain key steps in many successful chemical transformations.[4] Among them, radical cyclization reactions of carbonyl compounds represent one of the most efficient methods for the construction of ring systems under relatively neutral conditions.[5] Regarding the formation of ring systems, several methods have been developed to produce the desired cyclic products. Cyclic ketones are afforded in the cases of radical cyclization reactions of acylgermanes[6] and thio- and selenoesters.[7] However, when acylsilanes are used, silylated cyclic alcohols are formed through an irreversible radical Brook rearrangement.[8] Positioned with an α-oxy group, the radical cyclizes onto the carbonyl group to give the resulting alkoxy radical. Depending on the reaction conditions, this alkoxy radical either abstracts a hydrogen atom to give cyclic alcohols or undergoes fragmentation to afford carbonyl translocation products, as shown in Scheme 1.

Several attempts have been made to exclusively produce either cyclic alcohols or the products with carbonyl translocation. Assisted by a conformationally rigid system and the geminal dialkyl effect, Fraser-Reid and co-workers successfully achieved carbonyl translocation in carbohydrate systems,[9] as shown in Scheme 2. Jung and co-workers also demonstrated that the efficiency of the carbonyl translocation process in cyclic carbohydrate systems could be enhanced when an additional benzyl group was present,[10] as shown in Scheme 3.

Scheme 1



Scheme 2



In comparison to results for conformationally rigid carbohydrate systems and systems with a geminal dialkyl effect, acyclic systems were less successful. Fraser-Reid reported on attempts to carry out cyclization reactions to form the cyclic alcohols when an α-benzoxy group was present. However, neither cyclic alcohols nor carbonyl translocation products were efficiently produced.[11] The reasons for this lack of success can

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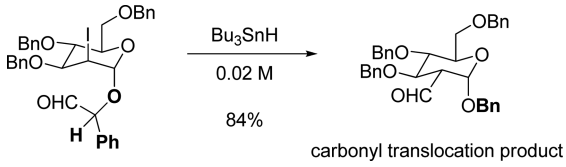
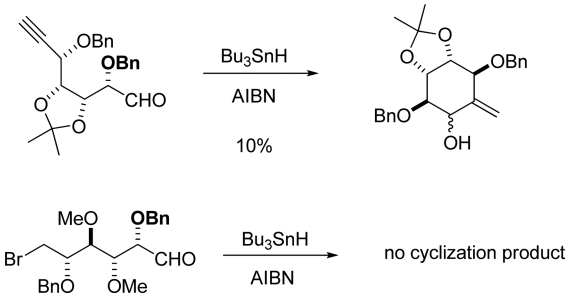
Scheme 3



be attributed to the possible abstraction of a hydrogen atom from the benzyl ether group, as shown in Scheme 4.

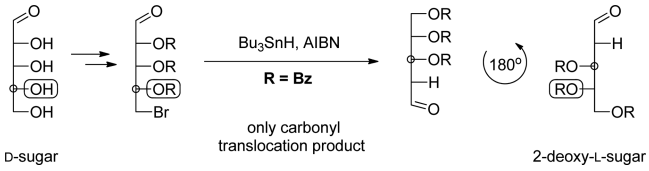
Scheme 4



When assisted by the geminal alkyl effect (two methoxy groups), different α-oxy substitutents in radical cyclization reactions of carbonyl compounds resulted in different outcomes. In a study reported by Ciufolini,[12] cyclic alcohols were obtained as the major products when a 2-methoxyisopropyl group served as the protecting group, while cyclic alcohols and carbonyl translocation products were obtained almost equally when a triethylsilyl (TES) group served as the protecting group, as shown in Scheme 5.

Among these previous reports, it was not feasible to obtain only carbonyl translocation products in acyclic systems. However, a novel and highly efficient radical process involving only carbonyl translocation was developed recently in this laboratory,[13] as shown in Scheme 6. The assistance of a geminal dialkyl effect or a conformationally rigid system was not required; when a benzoyl group was used as the protecting group, the product distribution in radical cyclization reactions of α-oxy carbonyl compounds was changed. In our studies, an acyclic precursor was transformed exclusively to the desired product with carbonyl translocation. This radical process was successfully applied to the synthesis of 2-deoxy-L-sugar

Scheme 6

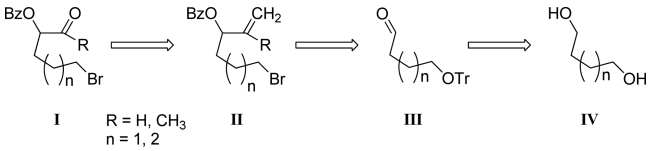


derivatives from readily available starting materials: namely, D-sugars. This radical process is so efficient that the reaction was completed in only 7 min. To further extend this novel synthetic methodology to the synthesis of other deoxy-L-sugars, the process needs to be fundamentally investigated further. To accomplish this, a model study would allow us to understand the scope and limitations of this unique radical process.

SYNTHETIC STRATEGY

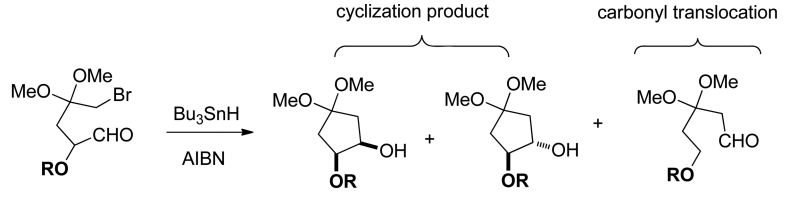
To clarify how efficient this novel radical reaction is, a series of acyclic model compounds without the assistance of the geminal dialkyl effect that were not in conformationally rigid systems were prepared. A retrosynthetic plan for the synthesis of these model compounds is shown in Scheme 7. The cyclization

Scheme 7. Retrosynthetic Plan



precursors **I** could represent two different types of carbonyl compounds, including aldehydes (R = H) and ketones (R = CH_3). These two types of carbonyl compounds could be used as model compounds for preparing aldoses and ketoses. The carbonyl moieties could be prepared from the allylic benzoates **II** through ozonolysis. The compound **II** would be envisioned to arise from addition reactions of the aldehyde compound **III** with various Grignard reagents, followed by benzoylation. The precursor **III** could then be envisioned to arise from the diols through selective protection and further oxidation. When R = H and n = 1, 2, the precursors could be used to examine 4-benzoyl-5-pentanal and 5-benzoyl-6-hexanal radical systems, respectively. The results of these two aldehyde systems could be eventually applied to convert D-aldopentoses and D-

Scheme 5



R = 2-methoxyisopropyl 	56%	6%	15%
R = triethylsilyl 	31%	-	27%

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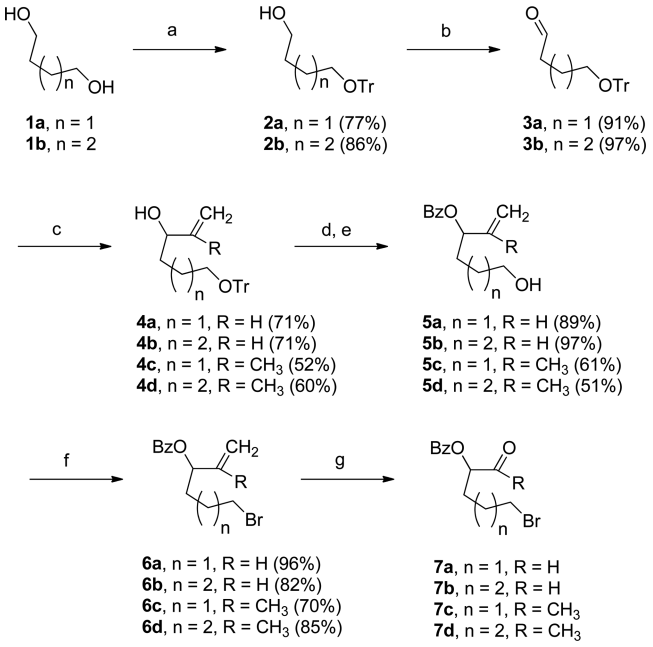
aldohexoses into deoxy-L-aldoses. When R = CH_3, and n = 1, 2, the precursors could be used to examine 4-benzoyl-5-pentanone and 5-benzoyl 6-hexanone radicals systems, respectively. The results of these two ketone systems could be eventually applied to convert D-ketopentoses and D-ketohexoses into deoxy-L-ketoses. Information regarding these four radical model systems would allow us to better understand whether these novel radical processes could be used to transform naturally occurring D-sugars into deoxy-L-sugars.

RESULTS AND DISCUSSION

Starting from 1,4-butanediol or 1,5-pentanediol (**1a** or **1b**), one of the hydroxyls was protected with a trityl group to give the monoprotected compounds **2a,b**.[14] A Swern oxidation then provided the aldehyde compounds **3a,b**.[15] To prepare precursors with an aldehyde moiety, a vinyl Grignard reagent was used to provide compounds **4a,b**. A more bulky isopropenyl Grignard reagent was used to prepare compounds **4c,d** in relatively low yields for precursors with a ketone functionality. Protection of the resulting allylic alcohols with a benzoyl group, followed by treatment with *p*-TsOH in a cosolvent system, generated the allylic benzoates **5a−d**.[13] Bromination reactions using carbon tetrabromide (CBr_4) and triphenylphosphine (PPh_3) gave the bromide compounds **6a−d**. The masked carbonyl moieties were produced by ozonolysis to give the series of cyclization precursors **7a−d**, as shown in Scheme 8. Due to the inherently unstable characteristics of these aliphatic carbonyl compounds, the resulting precursors **7a−d** were directly used for radical cyclization reactions without further purification by column chromatography.

Scheme 8[a]



[a]Reagents and conditions: (a) TrCl, NEt_3, DMAP, DCM, room temperature; (b) $(COCl)_2$, DMSO, DCM, then NEt_3, −78 °C to room temperature; (c) vinylmagnesium bromide for R = H, isopropenylmagnesium bromide for R = CH_3, −70 °C to room temperature; (d) BzCl, DMAP, NEt_3, DCM, room temperature; (e) TsOH, THF/MeOH, room temperature; (f) CBr_4, PPh_3, DCM, room temperature; (g) O_3, DCM, then Me_2S, −78 °C to room temperature.

Different radical reactions were carried out to examine the scope of the radical reactions, as shown in Scheme 9. In the case of the 4-benzoyl-5-pentanal radical (the precursor **7a**, n = 1, R = H), the radical reaction reached completion within 10 min, which is consistent with our previous report.[13] Only the carbonyl translocation product was observed in the crude spectrum.[16] Attempts were made to directly isolate the desired product **8a**, an aliphatic aldehyde. Because of the inherent instability of such aliphatic aldehydes during column chromatography, direct isolation was not feasible. Eventually, the crude product **8a** was successfully transformed into the dithiane **9a** in 50% yield (three steps from **6a**).[17] However, in the 5-benzoyl-6-hexanal radical system, the radical reaction required a longer reaction time (20 min) to reach completion. It is expected that 1,6-cyclization reactions are slower than 1,5-cyclization reactions.[18] The crude products were also treated with 1,3-propanedithiol to give the dithiane **9b** (26%, three steps from **6b**), along with the inseparable cyclization product **10b** (32%; distereometric ratio is 1.4/1). In the ketone series, as expected, the radicals did cyclize onto ketones. Since ketones are not ideal substrates for radical addition reactions, a much longer reaction time (90 min) was needed to complete the reaction. Fortunately, radical cyclization followed by a fragmentation reaction proceeded smoothly in the 4-benzoyl-5-pentanone radical system. The direct isolation of the desired ketone **8c** is feasible in this case and the yield approached 90% (over two steps from **6c**). The same conditions were also applied to the 5-benzoyl-6-hexanone radical system. The yield of the desired product **8d** was 51% (two steps from **6d**). In the studies of these four radical systems, we concluded the following. (1) A benzoyl group, positioned α to the carbonyl group, enhanced the fragmentation step to afford carbonyl translocation products. The processes in the 1,5-cyclization systems worked better than 1,6-cyclization systems. (2) Although longer reaction times were needed for the ketone systems, the yields in the ketone systems are much better than in aldehyde systems. This indicates that aliphatic ketones are inherently more stable than aliphatic aldehydes during column chromatography. (3) If the direct isolation of the carbonyl compounds is not successful, the transformation of these compounds into dithioacetals is an alternative method for isolating the product. Since this methodology could be eventually applied to carbohydrate systems, the dithiosugars would be convenient synthons for synthetic carbohydrate chemistry.[19]

A mechanism for this type of radical cyclization followed by fragmentation reactions of α-benzoyl carbonyl compounds is shown in Scheme 10. The primary carbon radical cyclizes to the carbonyl group to give a cyclic alkoxy radical. In our cases, the benzoyl group clearly enhanced the rate of the fragmentation steps, even in the absence of a geminal dialkyl effect or a conformationally rigid system. This is in contrast with previously reported results (Schemes 2−5). The reason for this effect can be attributed to the use of an electron-withdrawing benzoyl group, which increases the electrophilicity of the carbonyl groups, thus increasing the rate of the cyclization step. Meanwhile, it also pulls the electron density from the corresponding cyclic alkoxy radical, to accelerate the rate of the fragmentation step. After the fragmentation reaction, the secondary carbon radical abstracts a hydrogen atom to afford the desired carbonyl translocation product. These results clearly show that *positioning a benzoyl group α to the carbonyl group results in a more efficient production of carbonyl*

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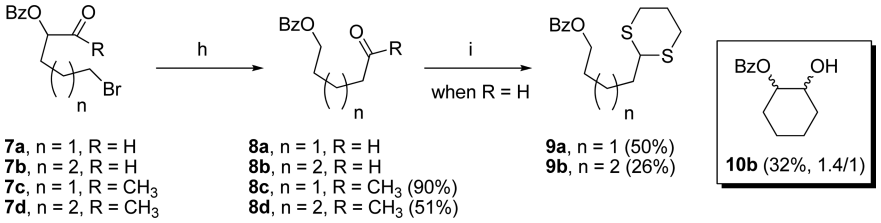
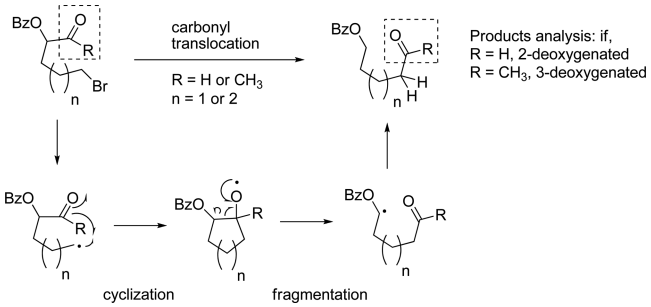
Scheme 9[a]



[a]Reagents and conditions: (h) Bu_3SnH, AIBN, PhH, reflux (R = H, 10−20 min; R = CH_3, 90 min); (i) 1,3-propanedithiol, $BF_3{\cdot}OEt_2$, DCM, −10 °C.

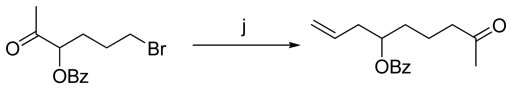
Scheme 10. Mechanism of Carbonyl Translocation



translocation product in most cases. To the best of our knowledge, this is the first report to show a radical cyclized onto a carbonyl group, which can completely fragment to give a carbonyl translocation product in an acyclic system. This provides a point of view in radical cyclization reactions of carbonyl compounds. With this new methodology in hand and appropriate structural designs, it became possible to apply these novel radical processes to the synthesis of some rare deoxy-L-sugars from readily available starting materials: namely, naturally occurring D-sugars. For example: when R = H in sugars (D-aldoses), the carbonyl translocation products are deoxy-L-aldoses. When R = CH_3 in sugars (D-ketoses), the carbonyl translocation products are deoxy-L-ketoses.

The α-oxy carbon radical, generated in the fragmentation step (Scheme 10), could further react with other alkenes to afford addition products. To further extend this methodology, a cascade radical process was investigated, as shown in Scheme 11. The process involved radical cyclization followed by fragmentation and then the addition to an allyltributyltin reagent.[20] The α-oxy alkyl radical can add to the allyltin reagent to provide non-8-en-2-one (**11**). This product could serve as the synthon for preparing 1,7-dicrbonyl compounds. Through this cascade reaction, simple α-oxy carbonyl compounds could be transformed into 1,7- or 1,8-dicarbonyl products. In comparison to previous reports on the radical cyclization of carbonyl compounds, our synthetic methodologies are unique and could also be applied to the synthesis of a wide variety of dicarbonyl compounds.

Scheme 11[a]



[a]Reagents and conditions: (j) Bu_3SnH, AIBN, allyltributyltin, PhH, reflux (47%).

CONCLUSIONS

A series of α-benzoyl carbonyl compounds were prepared for use in a study of radical cyclization reactions followed by a fragmentation process. Precursors that contained aldehyde and ketone moieties were included. Initiated by tributyltin hydride and AIBN, radical cyclization followed by fragmentation proceeded smoothly to give the desired carbonyl translocation products in the cases of 4-benzoyl-5-pentanal, 4-benzoyl-5-pentanone, 5-benzoyl-6-hexanal, and 5-benzoyl-6-hexanone radicals. In these studies, no geminal dialkyl effect was needed and a conformationally rigid system was not required for the desired carbonyl translocation products to be formed. This effect clearly proves that when *the substrate is assisted by positioning a benzoyl group α to the carbonyl group, the radical cyclization process leads to the formation of carbonyl translocation products*. To the best of our knowledge, this is the first report to show that a radical can be cyclized onto a carbonyl group, which could completely fragment to give a carbonyl translocation product in an acyclic system. This finding should provide a point of view in the use of radical cyclization reactions of carbonyl compounds. Meanwhile, a cascade radical process involving radical cyclization, fragmentation, and finally addition reaction was developed. This cascade radical process can be employed to transform simple α-oxy carbonyl compounds into special 1,7-dicarbonyl precursors. Furthermore, these four radical cyclization systems could be utilized to convert naturally occurring D-sugars, such as D-aldopentoses, D-aldohexoses, D-ketopentoses, and D-ketohexoses, into rare deoxy-L-sugars. The development of new synthetic methodology involving this novel radical process for the synthesis of natural products and rare sugars is currently underway.

EXPERIMENTAL SECTION

General Considerations. ^1H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded on a 300 MHz NMR instrument. The NMR spectra were recorded in $CDCl_3$ or CD_3OD. Chloroform (δ 7.26 ppm in ^1H NMR; δ 77.0 ppm in ^{13}C NMR) and methanol (δ 3.31 ppm in ^1H NMR; δ 49.00 ppm in ^{13}C NMR) were used as internal standards. Splitting patterns are reported as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. Coupling constants (J) are reported in Hz. IR spectra were recorded on a FT-IR spectrometer and are reported in cm^{-1}. High-resolution mass spectrometry (HRMS) was carried out on an LCMS-IT-TOF ESI, EI, or FAB mass spectrometer. The reaction products were isolated by flash chromatography performed on Merck Art. Geduran Si 60 (0.040−0.063 mm) silica gel. Yields of products refer to chromatographically purified products unless otherwise stated. THF was distilled by refluxing it over traces of sodium metal using benzophenone as an indicator under N_2. Benzene and dichloromethane were dried over

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CaH_2 and then distilled. Benzoyl chloride was distilled before use. The benzene used for radical cyclizations was deoxygenated by passing a gentle stream of argon through for 30 min before use. All reactions were performed under a blanket of N_2 or Ar.

General Procedure A. To a solution of **1a,b** (5 equiv) and 4-dimethylaminopyridine (0.1 equiv) in CH_2Cl_2 was added a solution of trityl chloride (1 equiv) in CH_2Cl_2, followed by addition of triethylamine (1 equiv). The reaction mixture was stirred at room temperature for 15 h. The resulting solution was quenched with saturated K_2CO_3(aq) and extracted with CH_2Cl_2. The organic layer was washed with water and brine, dried over $MgSO_4$, filtered, and concentrated to give a crude product, which was purified by column chromatography (EtOAc/hexanes 3/7) to give **2a,b**.

*4-Triphenylmethoxy-1-butanol (**2a**).* Compound **1a** (63.50 mmol, 6.26 g) was treated according to method A to give the white solid **2a** (3.46 g, 77%): mp 74.9−75.4 °C; IR (neat) 3343 (OH) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.46 (dd, J = 8.1, 1.2 Hz, 6H), 7.35−7.20 (m, 9H), 3.63 (t, J = 5.9 Hz, 3H), 3.13 (t, J = 5.9 Hz, 3H), 1.77−1.60 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.2 (C), 128.6 (CH), 127.7 (CH), 126.9 (CH), 86.6 (C), 63.5 (CH_2), 62.8 (CH_2), 29.9 (CH_2), 26.6 (CH_2); HRMS (ESI$^+$) m/z calcd for $C_{23}H_{24}O_2Na$ [M + Na]$^+$ 355.1669, found 355.1662.

*5-Triphenylmethoxy-1-pentanol (**2b**).* Compound **1b** (71.75 mmol, 7.47 g) was treated according to method A to give the pale yellow oil **2b** (3.11 g, 86%): IR (neat) 3344 (OH) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.56−7.48 (m, 6H), 7.39−7.22 (m, 9H), 3.26 (t, J = 6.2 Hz, 2H), 3.13 (t, J = 6.6 Hz, 2H), 1.70 (br s, 1H, OH), 1.17 (quintet, J = 7.0 Hz, 2H), 1.63−1.41 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.3 (C), 128.6 (CH), 128.3 (CH), 127.8 (CH), 127.6 (CH), 127.3 (CH), 126.9 (CH), 126.7 (CH), 86.2 (C), 63.4 (CH_2), 62.6 (CH_2), 32.4 (CH_2), 29.7 (CH_2), 22.4 (CH_2). The spectrometric data are consistent with those in ref 14.

General Procedure B. To a solution of oxalyl chloride (2.5 equiv) in CH_2Cl_2 was added dropwise a solution of dimethyl sulfoxide (3 equiv) in CH_2Cl_2 at −78 °C over 10 min. The reaction mixture was stirred for 30 min, followed by slow addition of **2a,b** (1 equiv) in CH_2Cl_2 at the same temperature over 10 min. The resulting solution was stirred for 30 min, followed by addition of triethylamine (5 equiv) in CH_2Cl_2 over 10 min at the same temperature. The reaction solution was stirred for 30 min, and then the resulting solution was partitioned between CH_2Cl_2 and water. The organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated to give a crude product, which was purified by column chromatography (EtOAc/hexanes 1/9) to give **3a,b**.

*4-Triphenylmethoxybutanal (**3a**).* Compound **2a** (10 mmol, 3.24 g) was treated according to method B to give the pale yellow oil **3a** (3.92 g, 91%): IR (neat) 2825 (CHO), 2725 (CHO), 1723 (C═O) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.81 (s, 1H), 7.49−7.42 (m, 6H), 7.37−7.22 (m, 14H), 3.16 (t, J = 6.2 Hz, 2H), 2.57 (td, J = 7.4, 1.4 Hz, 2H), 1.96 (quintet, J = 6.7 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.4 (CH), 146.9 (C), 144.1 (C), 128.6 (CH), 127.9 (CH), 127.8 (CH), 127.2 (CH), 126.9 (CH), 86.6 (C), 62.5 (CH_2), 41.0 (CH_2), 22.8 (CH_2). The spectrometric data are consistent with those in ref 15.

*5-Triphenylmethoxypentanal (**3b**).* Compound **2b** (5.20 mmol, 1.80 g) was treated according to method B to give the pale yellow oil **3b** (1.74 g, 97%): IR (neat) 2725 (CHO), 1710 (C═O) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.74 (t, J = 1.8 Hz, 1H), 7.44 (d, J = 7.2 Hz, 6H), 7.35−7.19 (m, 9H), 3.09 (t, J = 6.2 Hz, 2H), 2.40 (t, J = 6.9 Hz, 2H), 1.81−1.60 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.6 (CH), 144.3 (C), 144.3 (C), 128.6 (CH), 127.7 (CH), 126.9 (C), 86.4 (C), 62.9 (CH_2), 43.6 (CH_2), 29.4 (CH_2), 19.0 (CH_2); HRMS (ESI$^+$) m/z calcd for $C_{24}H_{24}O_2Na$ [M + Na]$^+$ 367.1674, found 367.1669.

General Procedure C. To a solution of compound **3a,b** (1 equiv) in THF (0.1 M) was added slowly a solution of vinyl Grignard/isopropenyl Grignard reagent (1.2 equiv) at −70 °C. The reaction mixture was stirred for 2−6 h and then quenched by addition of saturated NH_4Cl and directly warmed to room temperature. The resulting solution was extracted with ether. The organic layer was washed with water and brine, filtered, and concentrated to give a crude product, which was purified by column chromatography to give **4a−d**.

*6-Triphenylmethoxy-1-hexen-3-ol (**4a**).* Compound **3a** (8.84 mmol, 2.29 g) was treated according to method C to give the pale yellow oil **4a** (2.27 g, 71%, purification by column chromatography with eluent EtOAc/hexanes 15/85): IR (neat) 3362 (OH) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.43 (d, J = 7.8 Hz, 6H), 7.33−7.17 (m, 9H), 5.85 (ddd, J = 17.0, 10.5, 6.3 Hz, 1H), 5.20 (d, J = 17.0 Hz, 1H), 5.09 (d, J = 10.5 Hz, 1H), 4.08 (d, J = 5.8 Hz, 1H), 3.10 (t, J = 5.9 Hz, 2H), 1.83−1.54 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.3 (C), 141.1 (CH), 128.7 (CH), 127.9 (CH), 127.7 (CH), 126.9 (CH), 86.6 (C), 114.7 (CH_2), 86.6 (C), 72.9 (CH), 63.5 (CH_2), 34.0 (CH_2), 25.9 (CH_2); HRMS (ESI$^+$) m/z calcd for $C_{25}H_{26}O_2Na$ [M + Na]$^+$ 381.1830, found 381.1834.

*7-Triphenylmethoxy-1-hepten-3-ol (**4b**).* Compound **3b** (0.53 mmol, 0.18 g) was treated according to method C to give the pale yellow oil **4b** (0.14 g, 71%, purification by column chromatography with eluent EtOAc/hexanes 15/85): IR (neat) 3383 (OH) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.47 (d, J = 7.8 Hz, 6H), 7.35−7.20 (m, 9H), 5.86 (ddd, J = 6.4, 10.7, 17.0 Hz, 1H), 5.22 (d, J = 17.0 Hz, 1H), 5.11 (d, J = 10.7 Hz, 1H), 4.10 (br s, 1H), 3.08 (t, J = 6.6 Hz, 2H), 1.67 (quintet, J = 7.2 Hz, 2H), 1.57−1.39 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.4 (C), 141.1 (CH), 128.7 (CH), 127.7 (CH), 126.8 (CH), 114.6 (CH_2), 86.3 (C), 76.6 (CH), 63.4 (CH_2), 36.8 (CH_2), 29.9 (CH_2), 22.0 (CH_2); HRMS (ESI$^+$) m/z calcd for $C_{26}H_{28}O_2Na$ [M + Na]$^+$ 395.1987, found 395.1982.

*2-Methyl-6-triphenylmethoxy-1-hexen-3-ol (**4c**).* Compound **3a** (1.79 mmol, 0.59 g) was treated according to method C to give the pale yellow oil **4c** (0.33 g, 52%, purification by column chromatography with eluent EtOAc/hexanes 15/85): IR (neat) 3372 (OH) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.60−7.40 (m, 6H), 7.40−7.20 (m, 9H), 4.94 (s, 1H), 4.85 (s, 1H), 4.06 (br s, 1H), 3.13 (br s, 2H), 1.80−1.60 (m, overlapped with one s at 1.73, CH_3, 7H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.4 (C), 144.3 (C), 128.6 (CH), 127.7 (CH), 126.8 (CH), 111.1 (CH_2), 86.5 (C), 75.6 (CH), 63.4 (CH_2), 31.8 (CH_2), 26.0 (CH_2), 17.6 (CH_3); HRMS (ESI$^+$) m/z calcd for $C_{26}H_{28}O_2Na$ [M + Na]$^+$ 395.1982, found 395.1976.

*2-Methyl-7-triphenylmethoxy-1-hepten-3-ol (**4d**).* Compound **3b** (4.59 mmol, 1.58 g) was treated according to method C to give the pale yellow oil **4d** (1.06 g, 60%, purification by column chromatography with eluent EtOAc/hexanes 1/9): IR (neat) 3365 (OH) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.55−7.40 (m, 6H), 7.40−7.18 (m, 9H), 4.93 (d, J = 0.6 Hz), 4.83 (d, J = 1.2 Hz), 4.04 (br d, J = 3 Hz, 1H), 3.07 (t, J = 6.6 Hz, 2H), 1.80−1.60 (m, overlapped with one s at 1.70, CH_3, 5H), 1.52−1.30 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.6 (C), 144.5 (C), 128.7 (CH), 127.7 (CH), 126.8 (CH), 111.0 (CH_2), 86.3 (C), 75.9 (CH), 63.5 (CH_2), 34.8 (CH_2), 29.9 (CH_2), 22.3 (CH), 17.5 (CH_3); HRMS (FAB$^+$) m/z calcd for $C_{27}H_{30}O_2$ [M]$^+$ 386.2246, found 386.2247. Anal. Calcd for $C_{27}H_{30}O_2$: C, 83.900; H, 7.820. Found: C, 84.188; H, 7.910.

General Procedure D. To a solution of compound **4a−d** (1 equiv) and 4-dimethylaminopyridine (0.1 equiv) in CH_2Cl_2 (0.1 M) were added triethylamine (3 equiv) and benzoyl chloride (2.5 equiv). The reaction mixture was stirred at room temperature for 15−19 h. The resulting solution was diluted with CH_2Cl_2 and then washed with saturated $NaHCO_3$, water, and brine, filtered, and concentrated to give the crude product, which was used for the next step without purification.

To a solution of this crude product (1 equiv) in a cosolvent system (THF/MeOH 1/1, 0.1 M) was added *p*-toluenesulfonic acid (0.5 equiv). The reaction mixture was stirred at room temperature for 15−21 h and then quenched by addition of solid $NaHCO_3$. The reaction mixture was filtered and concentrated to give a crude product, which was purified by column chromatography (EtOAc/hexanes 3/7) to give **5a−d**.

*4-(1-Hydroxylhex-5-enyl) Benzoate (**5a**).* Compound **4a** (2.79 mmol, 1.00 g) was treated according to method D to give the colorless oil **5a** (0.55 g, 89%, over two steps): IR (neat) 3387 (OH), 1715 (C═O) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.06 (d, J = 7.8 Hz, 2H), 7.56 (t, J = 7.1 Hz, 1H), 7.44 (t, J = 7.5 Hz, 2H), 5.91 (ddd, J = 17.4,

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10.7, 6.3 Hz, 1H), 5.54 (q, J = 6.3 Hz, 1H), 5.34 (d, J = 17.4 Hz, 1H), 5.22 (d, J = 10.7 Hz, 1H), 3.70 (t, J = 6.5 Hz, 2H), 1.92−1.81 (m, 2H), 1.75−1.63 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.0 (C), 136.3 (CH), 133.0 (CH), 130.5 (C), 129.7 (CH), 128.4 (CH), 117.0 (CH_2), 75.0 (CH), 62.5 (CH_2), 30.7 (CH_2), 28.3 (CH_2); HRMS (ESI$^+$): m/z calcd for $C_{13}H_{17}O_3$ $[M + H]^+$: 221.1178, found 221.1172.

*5-(1-Hydroxylhept-6-enyl) Benzoate (**5b**).* Compound **4b** (3.28 mmol, 1.22 g) was treated according to method D to give the pale yellow oil **5b** (0.24 g, 97%, over two steps): IR (neat) 3382 (OH), 1715 (C═O) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.06 (d, J = 7.8 Hz, 2H), 7.56 (t, J = 7.4 Hz, 1H), 7.46 (t, J = 7.7 Hz, 2H), 5.90 (ddd, J = 17.3, 10.5, 6.3 Hz, 1H), 5.51 (q, J = 6.3 Hz, 1H), 5.33 (d, J = 17.3 Hz, 1H), 5.21 (d, J = 10.5 Hz, 1H), 3.66 (t, J = 6.6 Hz, 2H), 1.92−1.69 (m, 2H), 1.62 (q, J = 6.7 Hz, 2H), 1.56−1.42 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.9 (C), 136.3 (CH), 132.9 (CH), 130.4 (C), 129.5 (CH), 128.3 (CH), 116.7 (CH_2), 75.1 (CH), 62.5 (CH_2), 34.0 (CH_2), 32.3 (CH_2), 21.3 (CH_2); HRMS (ESI$^+$) m/z calcd for $C_{14}H_{18}O_3Na$ $[M + Na]^+$ 257.1148, found 257.1145.

*4-(1-hydroxyl-5-methylhex-5-enyl) Benzoate (**5c**).* Compound **4c** (0.88 mmol, 0.31 g) was treated according to method D to give the colorless oil **5c** (0.12 g, 61%): IR (neat) 3401 (OH), 1713 (C═O) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.06 (d, J = 7.8 Hz, 2H), 7.57 (t, J = 7.1 Hz, 1H), 7.44 (t, J = 7.5 Hz, 2H), 5.46 (t, J = 6.5 Hz, 1H), 5.05 (s, 1H), 4.94 (s, 1H), 3.70 (t, J = 6.3 Hz, 2H), 1.94−1.83 (m, 2H), 1.81 (s, 3H), 1.72−1.59 (m, 2H), 1.45 (br s, 1H, OH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.8 (C), 142.9 (C), 132.9 (CH), 130.5 (C), 129.6 (CH), 128.4 (CH), 112.9 (CH_2), 77.6 (CH), 62.5 (CH_2), 29.1 (CH_2), 28.5 (CH_2), 18.2 (CH_3); HRMS (ESI$^+$) m/z calcd for $C_{14}H_{18}O_3Na$ $[M + Na]^+$ 257.1154, found 257.1147.

*5-(1-Hydroxyl-6-methylhept-6-enyl) Benzoate (**5d**).* Compound **4d** (2.20 mmol, 0.85 g) was treated according to method D to give the colorless oil **5d** (0.28 g, 51%): IR (neat) 3379 (OH), 1716 (C═O) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.06 (d, J = 6.6 Hz, 2H), 7.55 (tt, J = 7.2, 1.5 Hz, 1H), 7.44 (t, J = 7.4 Hz, 2H), 5,43 (t, J = 6.6 Hz, 1H), 5.04 (s, 1H) 4.93 (s, 1H), 3.64 (t, J = 6.6 Hz, 2H), 1.92−1.69 (m, overlapped with one s at 1.80, 5H), 1.68−1.55 (m, 2H), 1.53−1.35 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.8 (C), 143.0 (C), 132.9 (CH), 130.5 (C), 129.5 (CH), 128.3 (CH), 112.9 (CH_2), 77.7 (CH), 62.6 (CH_2), 32.5 (CH_2), 32.4 (CH_2), 21.6 (CH_2), 18.2 (CH_3); HRMS (ESI$^+$) m/z calcd for $C_{15}H_{20}O_3Na$ $[M + Na]^+$ 271.1305, found 271.1301.

General Procedure E. To the solution of compound **5a−d** (1 equiv) and triphenylphosphine (1.75 equiv) in CH_2Cl_2 was added slowly a solution of tetrabromomethane (1.5 equiv) in CH_2Cl_2. The reaction mixture was stirred at room temperature for 5 h. The reaction solution was directly concentrated to give a crude product, which was purified by column chromatography to give **6a−d**.

*3-(6-Bromohex-1-enyl) Benzoate (**6a**).* Compound **5a** (1.29 mmol, 0.30 g) was treated according to method E to give the colorless oil **6a** (0.35 g, 96%, purification by column chromatography with eluent EtOAc/hexanes 5/95): IR (neat) 1716 (C═O) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.06 (d, J = 7.2 Hz, 2H), 7.57 (t, J = 7.5 Hz, 1H), 7.45 (t, J = 7.5 Hz, 2H), 5.90 (ddd, J = 17.1, 10.7, 6.3 Hz, 1H), 5.54 (m, 1H), 5.35 (d, J = 17.1 Hz, 1H), 5.24 (d, J = 10.7 Hz, 1H), 3.54 (t, J = 5.9 Hz, 2H), 2.09−1.87 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.8 (C), 136.1 (CH), 133.1 (CH), 130.4 (C), 129.7 (CH), 128.5 (CH), 117.2 (CH_2), 74.3 (CH), 33.3 (CH_2), 33.0 (CH_2), 28.5 (CH_2); HRMS (FAB$^+$) m/z calcd for $C_{13}H_{15}O_2{}^{79}Br$ $[M]^+$ 282.0255, found 282.0259; $C_{13}H_{15}O_2{}^{81}Br$ $[M]^+$ 284.0235, found 284.0234. Anal. Calcd for $C_{13}H_{15}O_2Br$: C, 55.140; H, 5.340. Found: C, 55.662; H, 5.427.

*3-(7-Bromohept-1-enyl) Benzoate (**6b**).* Compound **5b** (2.67 mmol, 0.63 g) was treated according to method E to give the colorless oil **6b** (0.65 g, 82%, purification by column chromatography with eluent EtOAc/hexanes 5/95): IR (neat) 1715 (C═O) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.06 (d, J = 7.8 Hz, 2H), 7.57 (t, J = 6.9 Hz, 1H), 7.45 (t, J = 7.1 Hz, 2H), 5.90 (ddd, J = 17.0, 10.6, 6.3 Hz, 1H), 5.50 (q, J = 6.3 Hz, 1H), 5.34 (d, J = 17.0 Hz, 1H), 5.23 (d, J = 10.6 Hz, 1H), 3.41 (t, J = 6.6 Hz, 2H), 1.92 (quintet, J = 7.2 Hz, 2H), 1.86−1.69 (m, 2H), 1.66−1.50 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.9 (C), 136.3 (CH), 133.0 (CH), 130.5 (C), 129.7 (CH), 128.5 (CH), 117.1 (CH_2), 75.0 (CH), 33.5 (CH_2 × 2), 32.5 (CH_2), 23.8 (CH_2); HRMS (EI$^+$) m/z calcd for $C_{14}H_{17}{}^{81}BrO_2$ $[M]^+$ 298.0391, found 298.0391; $C_{14}H_{17}{}^{79}BrO_2$ $[M]^+$ 296.0412, found 296.0411.

*3-(6-Bromo-2-methylhex-1-enyl) Benzoate (**6c**).* Compound **5c** (0.51 mmol, 0.12 g) was treated according to method E to give the colorless oil **6c** (0.11 g, 70%, purification by column chromatography with eluent EtOAc/hexanes 4/96): IR (neat) 1716 (C═O) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.06 (d, J = 8.4 Hz, 2H), 7.57 (t, J = 7.1 Hz, 1H), 7.45 (t, J = 7.7 Hz, 2H), 5.46 (br s, 1H), 5.06 (s, 1H), 4.95 (s, 1H), 3.45 (t, J = 3.0 Hz, 2H), 2.10−1.90 (m, 4H), 1.82 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.8 (C), 142.6 (C), 133.0 (CH), 129.6 (CH), 128.4 (CH), 113.1 (CH_2), 76.6 (CH), 33.3 (CH_2), 31.2 (CH_2), 28.5 (CH_2), 18.2 (CH_3); HRMS (EI$^+$) m/z calcd for $C_{14}H_{17}{}^{81}BrO_2$ $[M]^+$ 298.0391, found 298.0391; $C_{14}H_{17}{}^{79}BrO_2$ $[M]^+$ 296.0412, found 296.0406.

*3-(7-Bromo-2-methylhept-1-enyl) Benzoate (**6d**).* Compound **5d** (2.09 mmol, 0.52 g) was treated according to method E to give the colorless oil **6d** (0.55 g, 85%, purification by column chromatography with eluent EtOAc/hexanes 3/97): IR (neat) 1716 (C═O) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.06 (d, J = 7.8 Hz, 2H), 7.57 (t, J = 7.4 Hz, 1H), 7.45 (t, J = 7.5 Hz, 2H), 5.43 (t, J = 6.5 Hz, 1H, C*H*OBz), 5.05 (s, 1H), 4.95 (s, 1H), 3.41 (t, J = 6.8 Hz, 2H), 1.92 (quintet, J = 7.3 Hz, 2H), 1.85−1.70 (m, overlapped with one s at 1.80, CH_3, 5H), 1.59−1.43 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.8 (C), 142.8 (C), 132.9 (CH), 130.4 (C), 129.6 (CH), 128.4 (CH), 113.1 (CH_2), 77.4 (CH), 33.4 (CH_2), 32.4 (CH_2), 31.7 (CH_2), 23.9 (CH_2), 18.2 (CH_3); HRMS (EI$^+$) m/z calcd for $C_{15}H_{19}{}^{81}BrO_2$ $[M]^+$ 312.0548, found 312.0544; $C_{15}H_{19}{}^{79}BrO_2$ $[M]^+$ 310.0568, found 310.0573.

6-Benzoyloxy-2-hexanone (8c). A solution of **6c** (0.36 mmol, 0.11 g) in CH_2Cl_2 (5 mL) was cooled to −78 °C, and then a stream of ozone was bubbled into the reaction solution. Once the solution turned blue, ozone was bubbled for around 10 min, and then the ozone generator was turned off. Oxygen was continuously bubbled into the solution for another 5 min in order to disperse ozone remaining in the solution. While the solution turned from blue to colorless, excess dimethyl sulfoxide (0.9 mL) was added at the same temperature. The reaction mixture was warmed to room temperature and stirred for 5 h and then diluted with CH_2Cl_2 (60 mL). The organic layer was washed with water (20 mL) and brine (20 mL), filtered, and concentrated to give **7c**, which was used for the next step without purification.

To a refluxing solution of the radical precursor **7c** (0.22 mmol, 0.07 g) in benzene (3.7 mL) at 88 °C was added dropwise a solution of AIBN (0.040 mmol, 0.007 g) and tributyltin hydride (0.33 mmol, 0.09 mL) in benzene (3.6 mL) over 1 h. The resulting solution was stirred at same temperature for 30 min. The solution was cooled and directly concentrated to give a crude product. To a solution of this crude product in THF (2.2 mL) was added triethylamine (0.06 mL). The reaction mixture was stirred for 3 h and then concentrated to give a crude product, which was purified by column chromatography (silica gel/KF 9/1; EtOAc/hexanes 2/8) to give the colorless oil **8c** (44 mg, 90%, over two steps): IR (neat) 1713 (C═O) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.03 (d, J = 7.8 Hz, 2H), 7.56 (t, J = 7.1 Hz, 1H), 7.34 (t, J = 8.1 Hz, 2H), 4.32 (t, J = 6.0 Hz, 2H), 2.52 (t, J = 6.8 Hz, 2H), 2.15 (s, 3H), 1.83−1.72 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 208.4 (C), 166.6 (C), 132.9 (CH), 130.3 (C), 129.5 (CH), 128.3 (CH), 64.5 (CH_2), 43.0 (CH_2), 29.9 (CH_3), 28.1 (CH_2), 20.2 (CH_2); HRMS (ESI$^+$) m/z calcd for $C_{13}H_{16}O_3K$ $[M + K]^+$ 259.0737, found 259.0739.

7-Benzoyloxy-2-heptanone (8d). A solution of **6d** (1.77 mmol, 0.55 g) in CH_2Cl_2 (18 mL) was cooled to −78 °C, and then a stream of ozone was bubbled into the reaction solution. Once the solution turned blue, ozone was bubbled for around 10 min, and then the ozone generator was turned off. Oxygen was continuously bubbled into the solution for another 5 min in order to disperse ozone remaining in the solution. While the solution turned from blue to colorless, excess dimethyl sulfoxide (4.5 mL) was added at the same temperature. The reaction mixture was warmed to room temperature and stirred for 5 h and then diluted with CH_2Cl_2 (120 mL). The organic layer was washed with water (40 mL) and brine (40 mL),

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filtered, and concentrated to give **7d**, which was used for the next step without purification.

To a refluxing solution of the radical precursor **7d** (0.16 mmol, 0.05 g) in benzene (2.7 mL) at 88 °C was added dropwise a solution of AIBN (0.032 mmol, 0.005 g) and tributyltin hydride (0.26 mmol, 0.07 mL) in benzene (2.6 mL) over 1 h. The resulting solution was stirred at same temperature for 30 min. The solution was cooled and directly concentrated to give a crude product. To a solution of this crude product in THF (1.6 mL) was added triethylamine (0.04 mL). The reaction mixture was stirred for 3 h and then concentrated to give a crude product, which was purified by column chromatography (silica gel/KF 9/1; EtOAc/hexanes 15/85) to give the colorless oil **8d** (19 mg, 51%, over two steps): IR (neat) 1713 (C═O) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.03 (d, J = 7.8 Hz, 2H), 7.55 (t, J = 6.8 Hz, 1H), 7.43 (t, J = 7.5 Hz, 2H), 4.31 (t, J = 6.6 Hz, 2H), 2.46 (t, J = 7.2 Hz, 2H), 2.14 (s, 3H), 1.80 (quintet, J = 7.2 Hz, 2H), 1.65 (quintet, J = 7.5 Hz, 2H), 1.52−1.38 (m, 2H) ; ^{13}C NMR (75 MHz, $CDCl_3$) δ 208.8 (C), 166.6 (C), 132.8 (CH), 130.4 (C), 129.5 (CH), 128.3 (CH), 64.7 (CH_2), 43.5 (CH_2), 29.9 (CH_3), 28.6 (CH_2), 25.6 (CH_2), 23.4 (CH_2); HRMS (ESI$^+$) m/z calcd for $C_{14}H_{19}O_3$ $[M + H]^+$ 235.1329, found 235.1326.

1,3-Dithianebutyl Benzoate (9a). A solution of **6a** (1.43 mmol, 0.41 g) in CH_2Cl_2 (14 mL) was cooled to −78 °C, and then a stream of ozone was bubbled into the reaction solution. Once the solution turned blue, ozone was bubbled for around 10 min, and then the ozone generator was turned off. Oxygen was continuously bubbled into the solution for another 5 min in order to disperse ozone remaining in the solution. While the solution turned from blue to colorless, excess dimethyl sulfoxide (4 mL) was added at the same temperature. The reaction mixture was warmed to room temperature and stirred for 5 h and then diluted with CH_2Cl_2 (120 mL). The organic layer was washed with water (40 mL) and brine (40 mL), filtered, and concentrated to give **7a**, which was used for the next step without purification.

To a refluxing solution of the radical precursor **7a** (0.21 mmol, 0.06 g) in benzene (3.5 mL) at 88 °C was added a solution of AIBN (0.040 mmol, 0.007 g) and tributyltin hydride (0.26 mmol, 0.07 mL) in benzene (3.5 mL) in one portion. The resulting solution was stirred at same temperature for 10 min. The solution was cooled and directly concentrated to give **8a**, which was used for the next step without purification.

To a solution of **8a** (0.21 mmol, 0.04 g) in CH_2Cl_2 (0.42 mL) were added 1,3-propanedithiol (0.42 mmol, 0.04 mL) and $BF_3{\cdot}OEt_2$ (1.70 mmol, 0.20 mL) at −10 °C. The reaction mixture was stirred at same temperature for 30 min and then worked up by addition of saturated $NaHCO_3$. The resulting solution was warmed to room temperature and then neutralized with saturated $NaHCO_3$ until the pH value was 7. The solution was diluted with CH_2Cl_2 (60 mL), and then the organic layer was washed with water (20 mL), and brine (20 mL), filtered, and concentrated to give a crude product, which was purified by column chromatography (EtOAc/hexanes 1/9) to give the colorless oil **9a** (31 mg, 50%, over three steps): IR (neat) 1705 (C═O) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.07−8.02 (m, 2H), 7.56 (tt, J = 7.5, 1.8 Hz, 1H), 7.47−7.40 (m, 2H), 4.32 (t, J = 6.3 Hz, 2H, CH_2OBz), 4.07 (t, J = 6.6 Hz, 1H, −SCHS−), 2.94−2.77 (m, 4H), 2.20−2.07 (m, 1H) 1.93−1.74 (m, 5H), 1.74−1.64 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.6 (C), 132.8 (CH), 130.3 (C), 129.5 (CH), 128.3 (CH), 64.6 (CH_2), 47.3 (CH), 35.0 (CH_2), 30.4 (CH_2 × 2), 28.3 (CH_2), 26.0 (CH_2), 23.2 (CH_2); HRMS (EI$^+$) m/z calcd for $C_{15}H_{20}O_2S_2$ $[M]^+$ 296.0905, found 296.0904.

1,3-Dithianehexyl Benzoate (9b) and 2-Hydroxylcyclohexyl Benzoate (10b). A solution of **6b** (2.30 mmol, 0.65 g) in CH_2Cl_2 (23 mL) was cooled to −78 °C, and then a stream of ozone was bubbled into the reaction solution. Once the solution turned blue, ozone was bubbled for around 10 min, and then the ozone generator was turned off. Oxygen was continuously bubbled into the solution for another 5 min in order to disperse ozone remaining in the solution. While the solution turned from blue to colorless, excess dimethyl sulfoxide (6 mL) was added at the same temperature. The reaction mixture was warmed to room temperature and stirred for 5 h and then diluted with CH_2Cl_2 (150 mL). The organic layer was washed with water (50 mL) and brine (50 mL), filtered, and concentrated to give **7b**, which was used for the next step without purification.

To a refluxing solution of the radical precursor **7b** (0.24 mmol, 0.07 g) in benzene (4 mL) at 88 °C was added a solution of AIBN (0.050 mmol, 0.008 g) and tributyltin hydride (0.36 mmol, 0.10 mL) in benzene (4 mL) in one portion. The resulting solution was stirred at the same temperature for 10 min. The solution was cooled and directly concentrated to give **8b**, which was used for the next step without purification.

To a solution of **8b** (0.24 mmol, 0.05 g) in CH_2Cl_2 (0.5 mL) were added 1,3-propanedithiol (0.48 mmol, 0.05 mL) and BF_3 OEt_2 (1.92 mmol, 0.24 mL) at −10 °C. The reaction mixture was stirred at the same temperature for 30 min and then worked up by addition of saturated $NaHCO_3$(aq). The resulting solution was warmed to room temperature and then neutralized with saturated $NaHCO_3$(aq) until the pH value was 7. The solution was diluted with CH_2Cl_2 (30 mL), and then the organic layer was washed with water (10 mL) and brine (10 mL), filtered, and concentrated to give a crude product, which was purified by column chromatography (EtOAc/hexanes 1/9) to give the colorless oil **9b** (13 mg, 26%, over three steps) and **10b** (17 mg, 32%, over three steps, diastereomeric ratio 1.4:1). Data for compound **9b**: IR (neat) 1715 (C═O) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.07−8.02 (m, 2H), 7.56 (tt, J = 7.5, 1.8 Hz, 1H), 7.47−7.40 (m, 2H), 4.31 (t, J = 6.6 Hz, 2H), 4.05 (t, J = 6.9 Hz, 1H), 2.93−2.77 (m, 4H), 2.16−2.06 (m, 1H), 1.93−1.72 (m, 5H), 1.64−1.52 (m, 2H), 1.52−1.40 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.7 (C), 132.9 (CH), 130.4 (C), 129.6 (CH), 128.4 (CH), 64.9 (CH_2), 47.5 (CH), 35.3 (CH_2), 30.5 (CH_2 × 2), 28.5 (CH_2), 26.3 (CH_2), 26.0 (CH_2), 25.7 (CH_2); HRMS (FAB$^+$) m/z calcd for $C_{16}H_{22}O_2S_2$ $[M]^+$ 310.1061, found 310.1065. Data for compound **10b** (diastereomeric ratio 1.4:1): IR (neat) 3435 (OH), 1707 (C═O) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.08−8.04 (m, 4H), 7.61−7.54 (m, 2H), 7.49−7.41 (m, 4H), 5.25−5.20 (m, 1H, H_{minor}), 4.90−4.80 (m, 1H, H_{major}), 3.90−4.00 (m, 1H, H_{minor}), 3.80−3.60 (m, 1H, H_{major}), 2.23 (d, J = 3.6 Hz, 1H), 2.22−2.04 (m, 4H), 2.04−1.80 (m, 2H), 1.82−1.50 (m, 7H), 1.55−1.20 (m, 8H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.7 (C, major), 166.2 (C, minor), 133.0 (CH), 130.4 (C), 130.3 (CH), 129.6 (CH), 128.3 (CH), 78.7 (CH, major), 74.6 (CH, minor), 72.8 (CH, major), 69.6 (CH, minor), 33.0 (CH_2, major), 30.4 (CH_2, minor), 30.0 (CH_2, major), 27.4 (CH_2, minor), 23.9 (CH_2, major), 23.8 (CH_2, major), 21.8 (CH_2, minor), 21.5 (CH_2, minor); HRMS (FAB$^+$) m/z calcd for $C_{13}H_{16}O_3$ $[M]^+$ 220.1099, found 220.1102.

6-Benzoylvinyloxy-2-hexanone (11). A solution of **6c** (0.34 mmol, 0.10 g) in CH_2Cl_2 (10 mL) was cooled to −78 °C, and then a stream of ozone was bubbled into the reaction solution. Once the solution turned blue, ozone was bubbled for around 10 min, and then the ozone generator was turned off. Oxygen was continuously bubbled into the solution for another 5 min in order to disperse ozone remaining in the solution. While the solution turned from blue to colorless, excess dimethyl sulfoxide (0.8 mL) was added at the same temperature. The reaction mixture was warmed to room temperature and stirred for 5 h and then diluted with CH_2Cl_2 (60 mL). The organic layer was washed with water (20 mL) and brine (20 mL), filtered, and concentrated to give **7c**, which was used for the next step without purification.

To a refluxing solution of the radical precursor **7c** (0.18 mmol, 0.05 g) and allyltributyltin (1.80 mmol, 0.55 mL) in benzene (3 mL) at 88 °C was added dropwise a solution of AIBN (0.040 mmol, 0.007 g) and tributyltin hydride (0.004 mmol, 0.004 mL) in benzene (3 mL) over 1 h. The resulting solution was stirred at same temperature for 30 min. The solution was cooled and directly concentrated to give the crude product. To a solution of this crude product in THF (1.8 mL) was added triethylamine (0.05 mL). The reaction mixture was stirred for 3 h and then concentrated to give a crude product which was purified by column chromatography (silica gel/KF 9/1; EtOAc/hexanes 15/85) to give the colorless oil **11** (22 mg, 47%, over two steps): IR (neat) 1711 (C═O) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.03 (d, J = 8.1 Hz, 2H), 7.55 (t, J = 7.4 Hz, 1H), 7.43 (t, J = 6.9 Hz, 2H), 5.81 (ddt, J = 16.8, 10.7, 7.2 Hz, 1H), 5.20−5.00 (m, CH_2═CH, 2H overlapped

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with CHOBz, 1H), 2.50−2.42 (m, 4H), 2.11 (s, 3H), 1.75−1.65 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 208.4 (C), 166.2 (C), 133.4 (CH), 132.8 (CH), 130.4 (C), 129.5 (CH), 128.3 (CH), 118.0 (CH_2), 73.4 (CH_2), 43.1 (CH_2), 38.5 (CH_2), 32.9 (CH_2), 29.9 (CH_3), 19.4 (CH_2); HRMS (EI$^+$) m/z calcd for $C_{16}H_{20}O_3$ $[M]^+$ 260.1412, found 260.1413.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b01754.

^{1}H and ^{13}C/DEPT NMR spectra of **2a,b**, **3a,b**, **4a−d**, **5a−d**, **6a−d**, **8c,d**, **9a,b**, **10b**, and **11** (PDF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) National Historic Landmark commemorating the isolation and discovery of the first "free radical" by Moses Gomberg.

(2) Renaud, P.; Sibi, M. *Radical in Organic Synthesis*; Wiley-VCH: Weinheim, Germany, 2001.

(3) Matyjaszewski, K.; Davis, T. P. *Handbook of Radical Polymerization*; Wiley-Interscience: New York, 2002.

(4) (a) Müller, D. S.; Untiedt, N. L.; Dieskau, A. P.; Lackner, G. L.; Overman, L. E. *J. Am. Chem. Soc.* **2015**, *137*, 660−663. (b) Renata, H.; Zhou, Q.; Dünstl, G.; Felding, J.; Merchant, R. R.; Yeh, C.-H.; Baran, P. S. *J. Am. Chem. Soc.* **2015**, *137*, 1330−1340. (c) Diethelm, S.; Carreira, E. M. *J. Am. Chem. Soc.* **2015**, *137*, 6084−6096. (d) Xu, Z.; Wang, Q.; Zhu, J. *J. Am. Chem. Soc.* **2015**, *137*, 6712−6724. (e) Quiclet-Sire, B.; Zard, S. Z. *J. Am. Chem. Soc.* **2015**, *137*, 6762−6765. (f) Zhu, R.; Buchwald, S. L. *J. Am. Chem. Soc.* **2015**, *137*, 8069−8077. (g) Jeffrey, J. L.; Petronijević, F. R.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2015**, *137*, 8404−8407.

(5) (a) Tsang, R.; Fraser-Reid, B. *J. Am. Chem. Soc.* **1986**, *108*, 2116−2117. (b) Dickson, J. K.; Tsang, R.; Llera, J. M.; Fraser-Reid, B. *J. Org. Chem.* **1989**, *54*, 5350−5356. (c) Walton, R.; Fraser-Reid, B. *J. Am. Chem. Soc.* **1991**, *113*, 5791−5799. (d) Beckwith, A. L. J.; Raner, K. D. *J. Org. Chem.* **1992**, *57*, 4954−4962.

(6) (a) Curran, D. P.; Diederichsen, U.; Palovich, M. *J. Am. Chem. Soc.* **1997**, *119*, 4797−4804. (b) Iserloh, U.; Curran, D. P. *J. Org. Chem.* **1998**, *63*, 4711−4716.

(7) Kim, S.; Jon, S. Y. *Chem. Commun.* **1996**, 1335−1336.

(8) (a) Tsai, Y.-M.; Cherng, C. D. *Tetrahedron Lett.* **1991**, *32*, 3515−3518. (b) Tsai, Y.-M.; Nieh, H.-C.; Pan, J.-S.; Hsiao, D.-D. *Chem. Commun.* **1996**, 2469−2470. (c) Huang, C.-H.; Chang, S.-Y.; Wang, N.-S.; Tsai, Y.-M. *J. Org. Chem.* **2001**, *66*, 8983−8991.

(9) Tsang, R.; Fraser-Reid, B. *J. Am. Chem. Soc.* **1986**, *108*, 8102−8104.

(10) Jung, M. E.; Choe, S. W. T. *Tetrahedron Lett.* **1993**, *34*, 6247−6250.

(11) Yeung, B.-W. A.; Alonso, R.; Vite, G. D.; Fraser-Reid, B. *J. Carbohydr. Chem.* **1989**, *8*, 413−427.

(12) Ciufolini, M. A.; Zhu, S. *J. Org. Chem.* **1998**, *63*, 1668−1675.

(13) Hsu, N.-Y.; Chang, C.-C. *Eur. J. Org. Chem.* **2013**, *2013*, 658−661.

(14) Hernández, A.-I.; Familiar, O.; Negri, A.; Rodriguez-Barrios, F.; Gago, F.; Karlsson, A.; Camarasa, M.-J.; Balzarini, J.; Pérez-Pérez, M.-J. *J. Med. Chem.* **2006**, *49*, 7766−7773.

(15) Chen, C.; Ahlberg, L. A.; Randall, A.; Miller, R. B.; Jones, A. D.; Kurth, M. J. *J. Am. Chem. Soc.* **1994**, *116*, 2661−2662.

(16) Only the product with carbonyl translocation was observed in the crude spectrum.

(17) Marshall, J. A.; Belletire, J. L. *Tetrahedron Lett.* **1971**, *12*, 871−874.

(18) Beckwith, A. L. J.; Schiesser, C. H. *Tetrahedron* **1985**, *41*, 3925−3941.

(19) Horton, D.; Norris, P. In *Preparative Carbohydrate Chemistry*; Hanessian, S., Ed.; Marcel Dekker: New York, 1997; pp 35−52.

(20) (a) Rosenstein, I. J. In *Radical in Organic Synthesis*; Renaud, P., Sibi, M., Eds.; Wiley-VCH: Weinheim, Germany, 2001; pp 50−71. (b) Jarosz, S.; Kozlowska, E. *Pol. J. Chem.* **1998**, *72*, 815−831. (c) Roe, B. A.; Boojamra, C. G.; Griggs, J. L.; Bertozzi, C. R. *J. Org. Chem.* **1996**, *61*, 6442−6445.

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