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Mild One-step Synthesis of Dibromo Compounds from Cyclic Ethers

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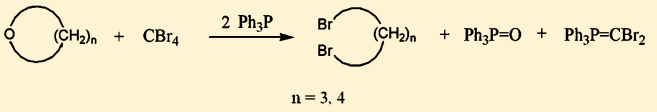
Supporting Information

ABSTRACT: A novel one-step method for mildly converting cyclic ethers into dibromo compounds is reported. Alcohols, oximes, aldehydes, and ketones are known to react under Appel or Corey–Fuchs reaction conditions, but apparently these have never been applied to oxetanes or larger cyclic ethers. Treatment of 3,3-dimethyloxetane (**1**) with tetrabromomethane and triphenylphosphine gave the corresponding dibromo compound 1,3-dibromo-2,2-dimethylpropane (**2**). The less-strained homologue oxolane (**6**) was also reacted giving 1,4-dibromobutane (**7**) in a 93% yield. Mechanistic interpretations are offered to explain the observed reaction rates of the conversions described.



INTRODUCTION

Numerous methods exist for converting oxetanes and other cyclic ethers into the corresponding dibromo compounds.[1] Even in special cases, when geminal dibromo compounds are needed as carbene precursors,[2] the corresponding ketals are transformed by reactive brominating agents, such as the Lewis acid BBr_3.[3] Amazingly, the most prominent procedures to have evolved among the plethora of choices to brominate C–O bonds involve refluxing the ethers with HBr in acetic acid or introducing PBr_3,[4,5] both of which may be formed *in situ*. These traditional halogenations afford good yields, which explains why they have become routine, but their harsh conditions, such as aggressive reagents like PBr_3, acidic conditions, and heating above $T = 25$ °C have serious drawbacks, especially for sensitive compounds. There are, however, two examples of more significance to the current endeavor that employ triphenylphosphine (Ph_3P) and Br_2 in benzonitrile (C_6H_5CN) at $T = 122$ °C.[6] This method is somewhat milder, because it proceeds through the putative 1:1 adduct dibromotriphenylphosphorane.[7,8] However, reactions in which Br_2 is present preclude their use with compounds having unmasked alkenyl functional groups and HBr is still generated. So, a different halogen source is enlisted: tetrahalomethane. In both Appel chlorination and the Corey–Fuchs reaction,[9,10] Ph_3P and the tetrahalomethane initially form halotriphenylphosphonium trihalomethanide *in situ* and no hydrohalic acid is produced. These milder conditions will be discussed further in the remainder of this report.

RESULTS AND DISCUSSION

When oxetane **1** was subjected to these reagents in solution, the reaction began to yield 1,3-dibromo-2,2-dimethylpropane (**2**) after just 2 h. However, other compounds were detected (Figures S1, S7–S9, Supporting Information). Moreover, a complication arose; the precipitation of triphenylphosphine oxide within the NMR samples halted further monitoring of the reaction. Nevertheless, the final outcome for the reaction with **1** was analyzed in more detail using GC-MS and 2-D NMR (Figures S2–S6, S10, S11, Supporting Information). Results of the preliminary experiment are shown in Scheme 1. Note that considerable C–P coupling found in the ^{13}C NMR spectrum between each phenyl ring's quaternary C atom and the neighboring P atom (i.e., $^1J_{CP} = 107$ Hz) as well as the two-bond C–P coupling between the alkoxy C atom and P atom in intermediate **4** (i.e., $^2J_{CP} = 8.3$ Hz) suggest that it is a tetravalent phosphonium salt rather than a pentavalent phosphorane (cf. Figure S9, Supporting Information).

The low yield of dibromo compound **2** from oxetane **1** was troubling. Perhaps it was just starved of reagents? So, another 2 equiv of Ph_3P were added to the reaction mixture and it was allowed to stir at room temperature for another 4 days. Then the reaction was quenched with water to hydrolyze whatever phosphorus-containing species were formed, thereby giving a single product. After an additional day of stirring and sample preparation, NMR was used to analyze the results. Indeed, feeding the reaction with more reagents followed by hydrolysis gave more insight into the reaction dynamics. From Scheme 2, one sees that increasing the amount of Ph_3P drove the reaction of **1** further to completion by converting compounds **1**, **3**, and **4** into the main product **2** (cf. Scheme 1).

The experiment was repeated using just 1 equiv of CBr_4 and an excess of Ph_3P (2 equiv). Furthemore, the problematic precipitation of triphenylphosphine oxide was prevented by changing the reaction solvent from CD_2Cl_2 to $CDCl_3$, which was doped with toluene as an internal standard. Thus, the reaction with **1** could be monitored by NMR in 2–3 h intervals at first and then twice daily. The amounts of each compound analyzed using NMR were plotted against reaction time to yield kinetic information (Figure 1). The curves for **1** and **4** flatten after ca. 1000 min. Most notably, the reaction of **1** stops after ca. 75% consumption and the presumed reaction intermediate **4** resists yielding more **2** for the most part (<10%). The experiment was performed in triplicate to ensure reliability.

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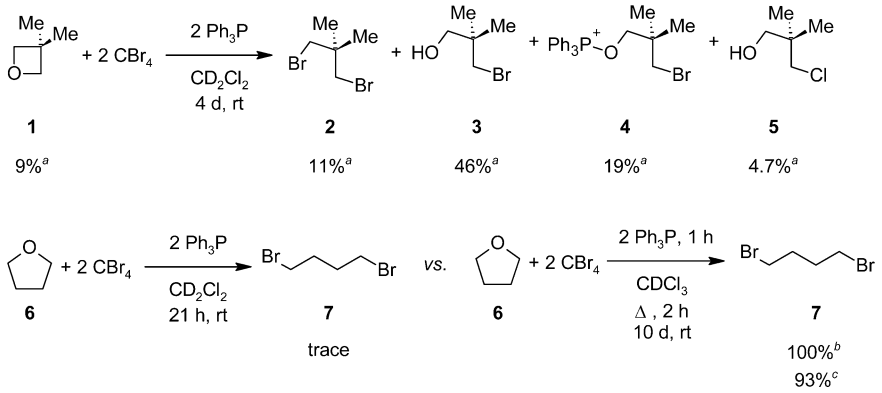
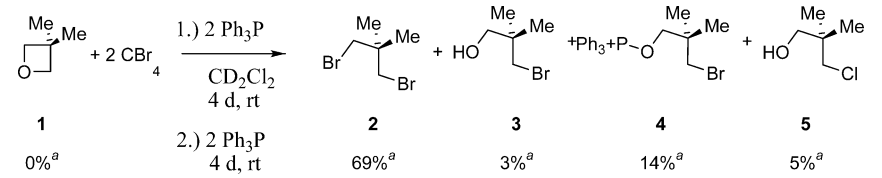
Scheme 1. Reactions of Cyclic Ethers 1 and 6 (Byproducts from the Reaction of Ph_3P and CBr_4 are Omitted)



[a]Yields were determined from NMR solutions doped with toluene as an internal standard. Uncertainties in yields are ±7 rel% and were calculated using Gaussian's propagation of uncertainty.[11] Formulas are given in the Supporting Information. [b] Due to longer reaction times, mesitylene was used as an internal standard. [c] Isolated yield.

Scheme 2. Reaction of Cyclic Ether 1 Four Days after Two Additional Equivalents of Ph_3P



[a]Yields were determined from NMR solutions doped with toluene as an internal standard. Uncertainties in yields are ±7 rel% and were calculated using Gaussian's propagation of uncertainty.[11] Formulas are given in the Supporting Information.

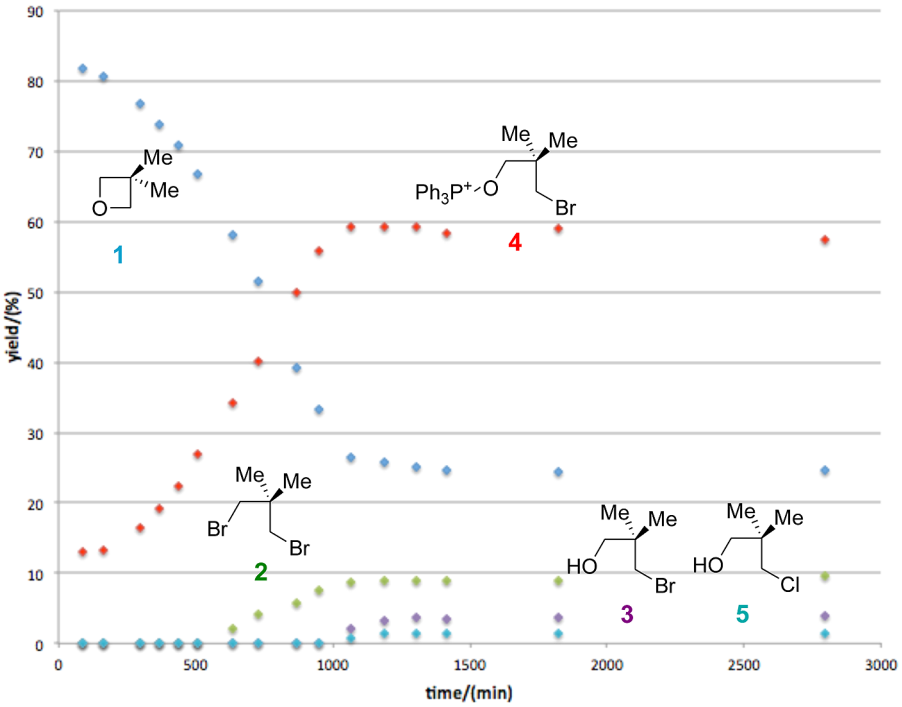


Figure 1. Conversion of oxetane **1** to dibromo compound **2** proceeds via reaction intermediates. This explains the formation of side products.

Traces of an acid–base catalyst might explain the acceleration of **4** → **2**. The sigmoidal shapes of the curves in Figure 1 may indicate autocatalysis, but they could also result from a rapid pre-equilibrium followed by a slow irreversible reaction. This is illustrated in Scheme 3.

The mechanistic scenario depicted in Scheme 3 is consistent with phosphorus chemistry,[12] the spectroscopically observed formation of the dibromo compounds, and the kinetic measurements. But it is abridged for clarity. Other conceivable elementary steps and equilibria may be operable. Nonetheless, at least three phosphorus species are initially formed from the

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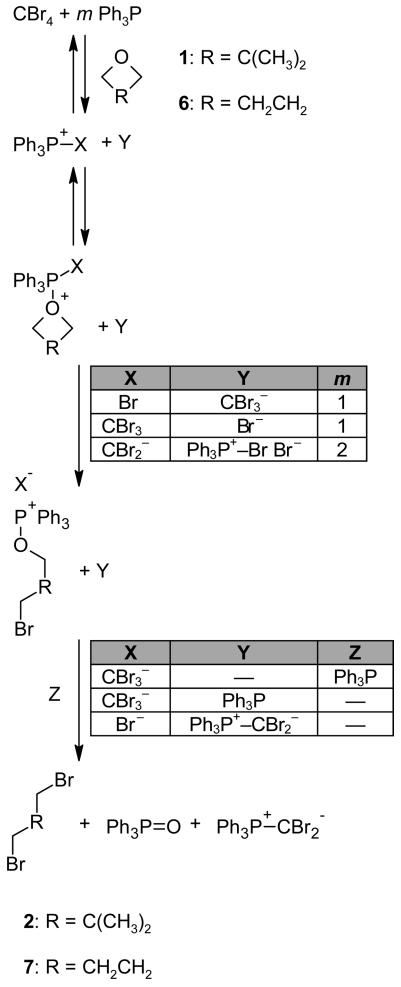
Scheme 3. Proposed Mechanism for Cyclic Ethers under Appel/Corey–Fuchs Reaction Conditions



reaction of Ph_3P and CBr_4 (cf. X/Y pairings in Scheme 3). These and subsequent ion-exchange reactions can be envisioned as bimolecular nucleophilic substitution (S_N2) reactions. All of these anionic displacements are reversible and likely in equilibria with each other as well as with the reactants. The first stages of the mechanism therefore parallel those in Appel chlorination and the Corey–Fuchs reaction.[9,10] In addition, association–dissociation equilibria of each reactant (i.e., cyclic ether **1** or **6**) with the assorted phosphorus species are plausible. The various intermediates may interact with each other depending on the substrate and its lifetime (τ). However, once a Br^- nucleophile engages with an ether–phosphorus complex it impinges upon the unstable oxonium ion intermediate and an (ω-bromoalkoxy)triphenylphosphonium salt is irreversibly formed (cf. Scheme 3). To illustrate with Y = Br^-, the first equilibrium reaction will be shifted to the right, according to the Le Châtelier Principle, as Y reacts with the cyclic ether to give intermediate **4**. This causes an increase in the concentration of Ph_3P^+–X and consequently raises that of its ether complex, which hastens the formation of **4**. As the reaction progresses to completion, the rate of formation of **4** slows down because the concentrations of Br^- and the ether complex decrease due to consumption. In all, the proposed mechanism is consistent with the kinetic measurements (Figure 1). The longevities of (ω-bromoalkoxy)triphenylphosphonium intermediates, such as **4**, depend on reaction conditions (e.g., the amount of Br^-, H_2O, etc., vide infra).

Support for the different phosphorus species depicted in Scheme 3 comes from the ^{31}P NMR spectrum of the reaction with **1**. Four major peaks as well as some minor ones were present (Figure S8, Supporting Information). Their exact structures were not immediately determinable for three reasons: it was impossible to glean proton signals in the ^1H NMR spectra due to extensive overlap; the carbon signals in the ^{13}C NMR spectra exhibited unusual upfield, or highfield, shifts due to shielding; and the absence of proton and carbon signals due to specific structural characteristics. Therefore, spectral libraries for compounds with similar chemical shifts and C–P and H–P coupling constants were consulted.[13] The experimental values were compared with known values for congruous structural elements.[12a,d] In addition, chemical shifts for the hypothesized compounds were computed using the increment method.[14] In this way, the compositions of the simple phosphorus species proposed in the first step of the reaction mechanism were established (Scheme 3). Further evidence was collected from GC-MS analysis. The nature of these P species was corroborated by the detection of $CHBr_3$, $CDBr_3$, and CBr_2Cl_2 within the reaction mixture. They can form from traces of adventitious water. Reproduction of this chemical menagerie was achieved by repeating the experiment without the cyclic ether. Once the signals from the simple phosphorus compounds were assigned, attention to the remaining P species could be paid. They were attributed to more complex phosphorus-containing structures that arose by reaction of the aforementioned P species with the cyclic ether, as delineated in Scheme 3.

Reaction with the parent oxolane **6** was also conducted but it was stymied under the original conditions. NMR signals from 1,4-dibromobutane (**7**) were not observed and only trace amounts of it were detected by sensitive GC-MS even after 21 h (Figure S14, Supporting Information). So, the reaction solvent was again changed from CD_2Cl_2 to $CDCl_3$ and the reaction was repeated under reflux. An aliquot taken after 2 h still showed only traces of **7**. But when stirring was continued for 10 days at room temperature (Scheme 1), dibromo compound **7** was detected and identified by ^1H and ^{13}C NMR.[14] No reaction byproducts were observed in either the GC-MS chromatograms (Figure S15, Supporting Information) or the NMR spectra (Figures S19, S21, Supporting Information).

Although dibrominations of cyclic ethers **1** and **6** were accomplished under the same reaction conditions, reaction intermediates and byproducts were detected for **1** but not **6** (Scheme 1). This can reasonably be attributed to structural differences (Scheme 4). In the transition state for **4** → **2**, an incoming Br^- must correctly navigate through twin methyl groups that neighbor the reaction site. The somewhat cluttered intermediate **4** will be less susceptible to nucleophilic substitution and consequently have an appreciable lifetime. In contrast, no such steric hindrance exists for the analogous (ω-bromoalkoxy)triphenylphosphonium intermediate between reactant **6** and product **7**. Thus, its lifetime is expected to be shorter than that of **4**. Hence, there is less opportunity for it to be sabotaged. This is not the case with **4**, which is hydrolyzed by water impurities to 3-bromo-2,2-dimethylpropanol (**3**). There is, however, another structural feature that cannot be ignored: ring strain. The cyclic ethers must first be ruptured according to Scheme 3. Therefore, if that is indeed the rate

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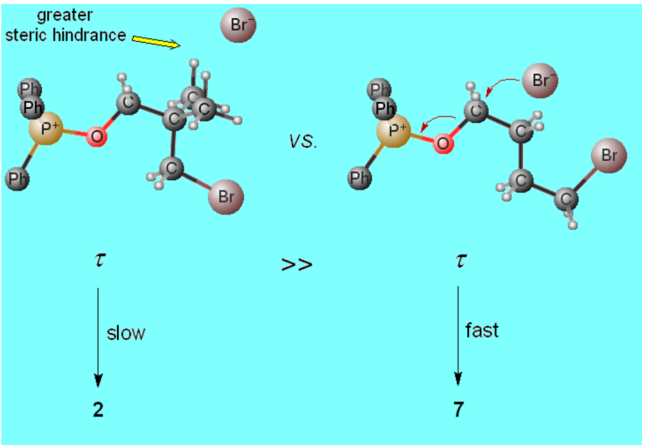
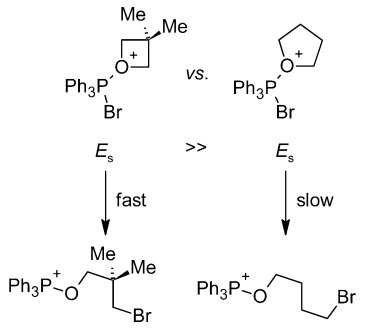
Scheme 4. Transition States for the Conversion of Monobrominated Reaction Intermediates of Cyclic Ethers 1 and 6 to their Respective Dibromo Compounds 2 and 7



determining step then it is sensible that oxolane **6** reacted more slowly than oxetane **1** because it is considerably less strained.[15,16] This is depicted in Scheme 5.

Scheme 5. Influence of Strain Energy (E_s) on the Rate of the Ring-Opening Step: Four- versus Five-membered Ring



Inspection of Schemes 3 and 6 reveals that the formation of the intermediary monobrominated (ω-bromoalkoxy)-triphenylphosphonium salt is relatively more likely than that of the dibrominated product, which requires two equivalents of Br^-. The addition of 2 equiv of Ph_3P was therefore necessary to drive the reaction further toward completion, as shown in Scheme 2. An excess of Ph_3P is expected to shift the initial equilibria to the right thereby making the species required in the first irreversible step more available.

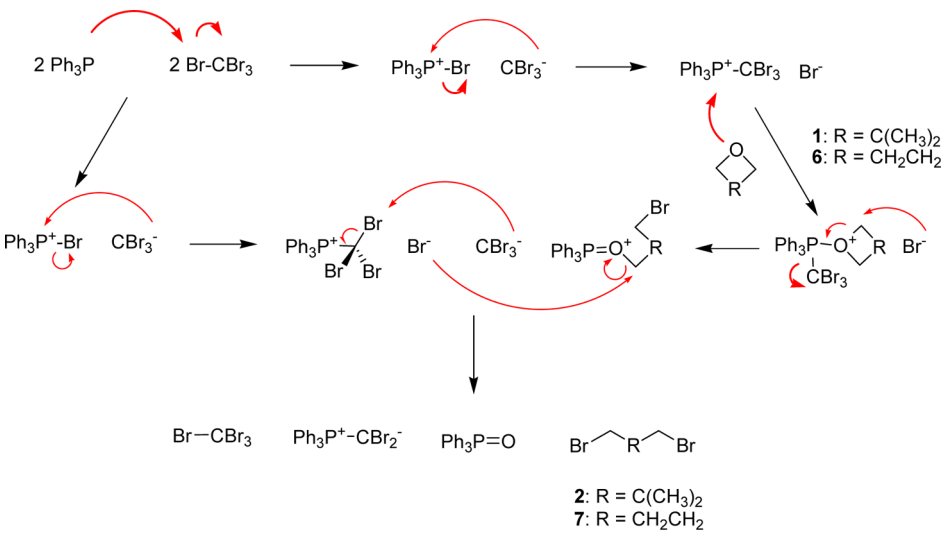
CONCLUSION

In conclusion, a new method that converts cyclic ethers into dibromo compounds in one step under conditions that are neutral and Br_2-free was implemented on **1** and **6**. They were converted into their respective dibromo compounds **2** and **7** in moderate to excellent yields. Experimental evidence indicates the participation of phosphorus-containing intermediates in the reaction mechanism. The loss of four-membered ring strain within oxetane **1** certainly helps to drive its reaction but side products were formed. In contrast, the less-strained oxolane **6** was cleanly converted into dibromide **7** almost quantitatively. One may therefore conjecture that other oxolanes, oxanes, oxepanes, etc. and perhaps even acyclic ethers might undergo dibromination by this method as well. Thus, the new application of Appel/Corey–Fuchs reaction conditions introduced herein may be of wide use in syntheses that require the conversion of sensitive (a)cyclic ethers into dibromo compounds.

EXPERIMENTAL SECTION

General Information. FT-NMR spectra were recorded at T = 300 K while applying the following radio frequencies: $\nu(^1H)$ = 400.13 MHz, $\nu(^{13}C)$ = 100.58 MHz, and $\nu(^{31}P)$ = 162.02 MHz. Hydrogen-1 and carbon-13 chemical shift (δ) values are reported relative to tetramethylsilane (TMS), although the deuterated solvents used were not doped with that internal standard. Instead, the solvents' residual peaks were used to calibrate the ^1H and ^{13}C NMR spectra: $\delta_H(CDCl_3)$ = 7.26 ppm, $\delta_C(CDCl_3)$ = 77.16 ppm, $\delta_H(CD_2Cl_2)$ = 5.30 ppm, and $\delta_C(CD_2Cl_2)$ = 53.52 ppm. Coupling constants (J) are reported in Hz. Structural assignments were made based on the following 2-D NMR experiments: COSY, NOESY, HMQC, and HMBC. Mass spectra were recorded using an electron impact (EI) beam of 70 eV. Tandem GC-MS analyses were conducted by passing He carrier gas through an HP-5 column (Model No. HP 19091J-433) and a mass-selective detector (70 eV).

Scheme 6. Electron Flow during the Conversion of Cyclic Ethers 1 and 6 to their Respective Dibromo Compounds 2 and 7



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General Procedures. The cyclic ether of interest was dissolved to give a 0.6 M solution in either $CDCl_3$ or CD_2Cl_2, whichever was found to be more suitable. Next, 2 equiv CBr_4 were added with an internal standard (toluene). Using the appropriate amount of Ph_3P given in Schemes 1 and 2, a 0.6 M solution of Ph_3P dissolved in the same solvent was added dropwise to the stirred mixture for ca. 60 min. The solution became slightly yellow and then colorless over time. Sometimes a white precipitate was observed between 10−60 min after the addition of Ph_3P. In some cases it dissolved after ca. 2−4 h but in others it remained. Aliquots from the reactions of **1** and **6** were periodically withdrawn and analyzed by NMR and GC-MS. After the durations listed in Scheme 1 and Scheme 2, the reaction mixtures were quenched and worked up in the standard manner.

*1,3-Dibromo-2,2-dimethylpropane (**2**):* t_R 6.49 min; *m/z* (EI) 230 ([M]$^+$, 20), 151 (65), 149 (65), 137 (80), 135 (95), 109 (18), 107 (18), 95 (18), 93 (18), 55 (100).

*3-Bromo-2,2-dimethylpropanol (**3**):* t_R 5.14 min; *m/z* (EI) 137 ([M − HCHO]$^+$, 12), 135 (12), 109 (3), 107 (3), 86 (14), 69 (5), 56 (100).

*(3-Bromo-2,2-dimethylpropoxy)triphenylphosphonium cation (**4**):* δ_H/ppm (400.1 MHz, CD_2Cl_2) 1.17 (6 H, s), 3.50 (2 H, s), 4.15 (2 H, d, $^3J_{PH}$ 3.9), see the Supporting Information for aromatic protons; δ_C/ppm (100.6 MHz, CD_2Cl_2) 22.9, 30.0 (d $^1J_{CP}$ 47.2), 37.1, 41.2, 76.6 (d $^2J_{CP}$ 8.3), 116.4 (d $^1J_{CP}$ 107), 130.5 (d J_{CP} 13.0), 135.3 (d J_{CP} 10.0), 135.9 (d J_{CP} 13.0); δ_P/ppm (162.02 MHz, CD_2Cl_2) 63.2 (see Figures S7−S11).

*3-Chloro-2,2-dimethylpropanol (**5**):* t_R 3.87 min; *m/z* (EI) 91 ([M − HCHO]$^+$, 9), 90 (9), 73 (37), 63 (9), 56 (100).

*1,4-Dibromobutane (**7**):* 670 μL (596 mg; 8.27 mmol) of oxolane (**6**) was dissolved in 15 mL of $CHCl_3$ and 6.12 g (18.45 mmol) of CBr_4 were added. Then 8.29 g (31.61 mmol) of Ph_3P dissolved in 5 mL of $CHCl_3$ were added dropwise to the stirred mixture over 60 min. After stirring for 10 d at room temperature the reaction mixture was quenched with water, transferred into a separatory funnel and the organic layer was washed once with water. After drying over $MgSO_4$, filtration, and rotary-evaporating of the solvent, the crude product was Kugelrohr-distilled (9 Torr, oven temperature ca. 90 °C) to afford **7** in a yield of 1.66 g (93%); t_R 6.97 min; *m/z* (EI) 216 (M^+, 1), 137 (95), 135 (98), 111 (13), 109 (12), 93 (6), 81 (4), 55 (100).

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

NMR and GC-MS spectra of all new compounds and of known compounds to use for comparison. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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