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Shorter and Easier Syntheses of Di-*tert*-butylketene and Related *gem*-Di-*tert*-butyl Compounds[‡]

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Dedicated to the memory of Professor Gert Köbrich

Keywords: Aldehydes, α-chloro / Electron transfer / Oxiranes, chloro / Ketenes / Strained molecules / Steric hindrance

The ketene tBu$_2$C=C=O is prepared from tBu$_2$C=O in three steps (performable as a two-stage operation) through elimination of HCl from the intermediate product tBu$_2$CCl–CH=O. The acid tBu$_2$CH–CO$_2$H, obtainable in two, three, or four preparative stages from tBu$_2$C=O, adds slowly to the ketene to produce the anhydride (tBu$_2$CH–CO)$_2$O. Elemental lithium together with ClSiMe$_3$ converts tBu$_2$CCl–CH=O into tBu$_2$C=CH–OSiMe$_3$, which is a durable precursor of tBu$_2$CH–CH=O, making this aldehyde easily and cheaply available from tBu$_2$C=O. By exclusion of alternative mechanistic possibilities, the reduction of tBu$_2$CCl–CH=O by tBuMgCl is shown to involve at least one single-electron transfer, leading to the enolate tBu$_2$C=CH–OMgCl, which can be converted into tBu$_2$CH–CH=O (three steps from tBu$_2$C=O) or into tBu$_2$C=CH–OSiMe$_3$. Hydride transfer from NaBH$_4$ to tBu$_2$CCl–CH=O affords tBu$_2$CCl–CH$_2$OH, the transformations of which provide an entertaining set of S$_N$1-type reactions. Several other examples of carbenium-type behavior are encountered in this *gem*-tBu$_2$ system; they are attributed to steric congestion, which also impedes bond rotations in the anhydride and in two esters. A convenient route to tBu$_2$CH–C≡N (five steps from tBu$_2$C=O) uses the conversion of tBu$_2$C=CH–OSiMe$_3$ into tBu$_2$CH–CH=NOH. The slow thermal (*Z*)/(*E*) equilibration of tBu$_2$CH–NH–CH=O reveals the ranking of ecliptic repulsions as H$_3$C < tBu < tBu$_2$CH.

Introduction

Di-*tert*-butylketene (**14**, Scheme 1) is noted for its very low reactivity:[1] unlike other ketenes,[2] it does not dimerize and adds neutral water very slowly to produce the acid **11**. The following routes (Scheme 1) to this persistent ketene, starting either from di-*tert*-butyl ketone[3] (**1**) or its imine[3] **3**, have been published.

I) The oldest and most popular route furnished a 16% yield of **14** in six steps:[4] namely **1** → **4** → **7** → **10** → **11** → **13** → **14**. However, occasional complaints about problems with the preparations of **7**,[5] **8**,[6] and **14**[7,8] led several groups[5–8] to recommend improved versions of this route.

II) A method[9] that employs the imine **3** directly provided a higher yield (<32%) of **14** in eight steps: namely **3** → **2** → **5** → **6** → **9** → **12** → **11** → **13** → **14**. However, this pathway has only rarely been used, presumably because of certain difficult techniques and unusual reagents.[10]

III) An alternative strategy[10] gave a 51% yield of the ketene **14** in four steps: namely **1** + **16** → (**17** → **18** →) **19** → **15** → **14** (three preparative stages). This approach starts with the generation of the highly unstable[11,12] carbenoid dichloromethyllithium (LiCHCl$_2$, **16**); a tetrahydrofuran (THF) solution of dichloromethane must be kept at below –100 °C during the slow addition of precooled (–100 °C) *n*-butyllithium (*n*BuLi), followed by the slow introduction of precooled (–90 °C) ketone **1**.

We show that the methods of this last route can be simplified and shortened (three steps in ≤3 stages) for an easier approach to **14** and to other *gem*-di-*tert*-butyl (tBu$_2$C) compounds.

Results and Discussion

A. Preparation and Properties of 2,2-Di-*tert*-butyl-3-chlorooxirane (18)

The easier approach to the alkoxide **17** (Scheme 2) consists of the generation of dichloromethyllithium (**16**) in THF through deprotonation of CH$_2$Cl$_2$ in the presence of di-*tert*-butyl ketone[3] (**1**), a strategy[13] that appeared to us to be an argument against the use of carbanionic bases that might add across the C=O double bond of **1**.[14a] Because the recommended[13b] base lithium dicyclohexylamide can give annoying problems with the poorly soluble dicyclohexylammonium salt during the aqueous workup, we replaced

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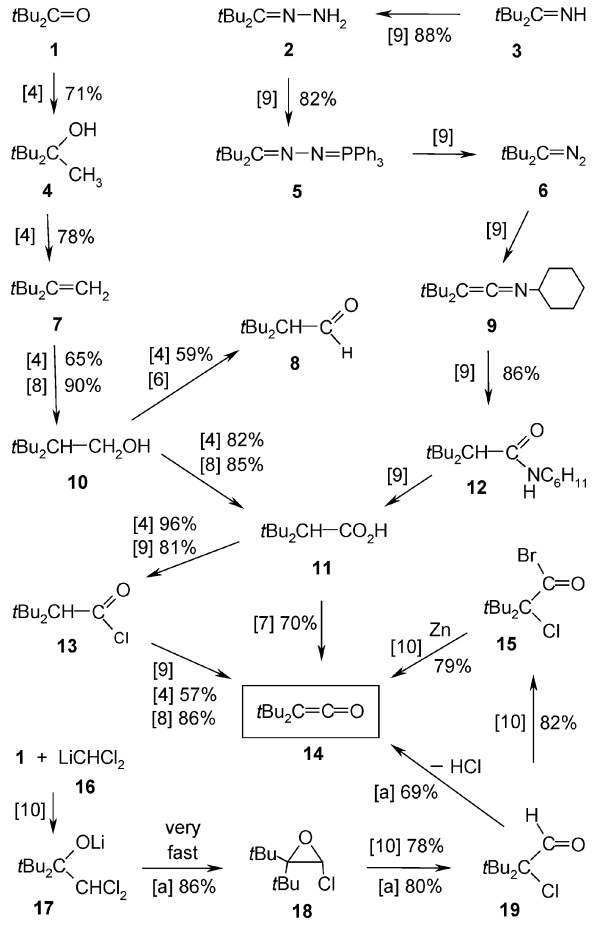
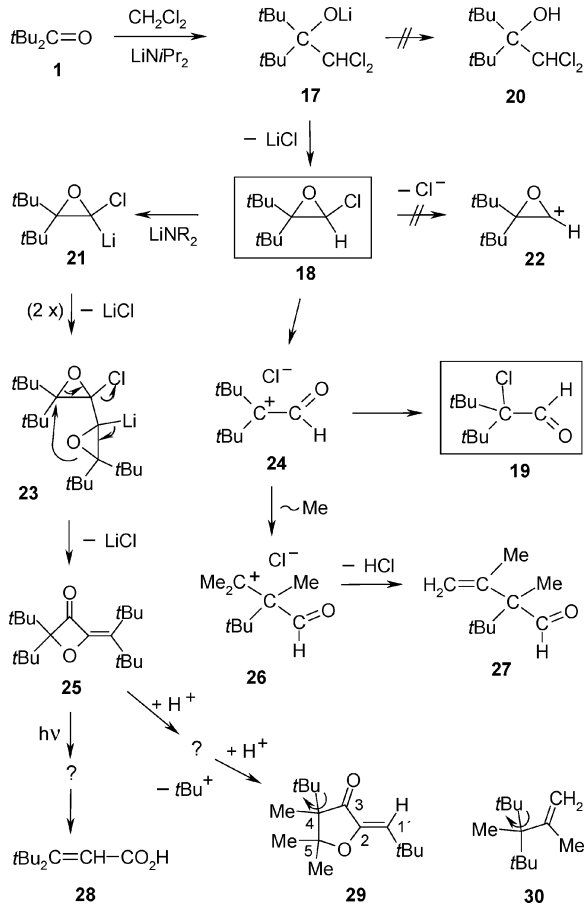


Scheme 1. Routes to di-*tert*-butylketene (**14**). [a] This work.



Scheme 2. Formation, deprotonation, and ionization of 2,2-di-*tert*-butyl-3-chlorooxirane (**18**).

it with lithium diisopropylamide[13b] (LDA), which was added dropwise to a THF solution of **1** and CH_2Cl_2 stirred at –70 °C: $LiCHCl_2$ was formed and efficiently trapped by the ketone **1**,[14b] as shown through final quenching with acids at –70 °C or 0 °C and subsequent isolation of the chlorooxirane **18** (86%) as the only product. In contrast with previous evidence with less congested systems,[13b,15,16] it was thus not possible to prevent the alkoxide **17** from cyclizing to give **18**.[17]

Dichloromethane must always be in excess in relation to LDA during the above preparation of the chlorooxirane **18**: residual LDA (and also lithium 2,2,6,6-tetramethylpiperidide, LiTMP) would lithiate **18** to give the carbenoid **21**, which forms the known[18] 3-oxetanone **25**, perhaps via the primary product **23** of a "dimerization" of **21** (an unproven possibility). Indeed, **25** was isolated as the only product (89%) from ketone **1** after treatment with 1 equiv. of CH_2Cl_2 and 4 equiv. of LDA in a one-pot synthesis at ≤0 °C. The very slow photolytic decomposition of **25** in CCl_4 solution furnished neither the ketene **14** nor an oxirane (through decarbonylation), although these two types of fissions had been observed[19,20] with other tetrasubstituted 3-oxetanones. A small amount of the unknown acid $tBu_2C{=}CH{-}CO_2H$ (**28**) could be identified and might have been formed via a photoproduct such as $tBu_2C{=}C{=}C{=}O$. In another attempt to generate **14**, we treated **25** with HCl in hot glacial acetic acid and isolated the product **29** of de-*tert*-butylation plus ring expansion. A closer examination of this tetrahydrofuran-3-one derivative **29** gave evidence of impeded rotation of the 4-*tert*-butyl substituent (but not of 1′-*t*Bu): the three methyl groups of 4-*t*Bu become nonequivalent below the coalescence temperatures of roughly –30 °C (^{13}C NMR at 100 MHz) and –50 °C (^1H NMR at 400 MHz), as documented in Table S1 in the Supporting Information, corresponding to the free enthalpy barriers of $\Delta G^{\#} \approx 10.8$ and 11.0 kcal mol^{-1} at 243 K and 223 K, respectively. The lower barrier (9.9 kcal mol^{-1}) reported[21] for *t*Bu rotation in the locally similar environment of **30** may be due to an alleviating cog-wheel rotational mode that is not possible in **29**.

The chlorooxirane **18** can be expected[22] to generate the formylcarbenium ion **24** directly (Scheme 2) rather than to ionize first to the oxiranyl cation **22**. As a tight ion pair,[22,23] **24** collapses to yield the α-chloro aldehyde[10] **19** but may also rearrange to give **26**, which produces the unsaturated aldehyde **27** as a troublesome side-product. It was somewhat difficult to avoid the formation of **27** under the reported[10] conditions, and the slow fractionating distillation of crude **19**/**27** mixtures proved to be an ugly task because of excessive foaming with generation of more aldehyde **27**.[24] Chromatographic separation (**19** elutes first!) or

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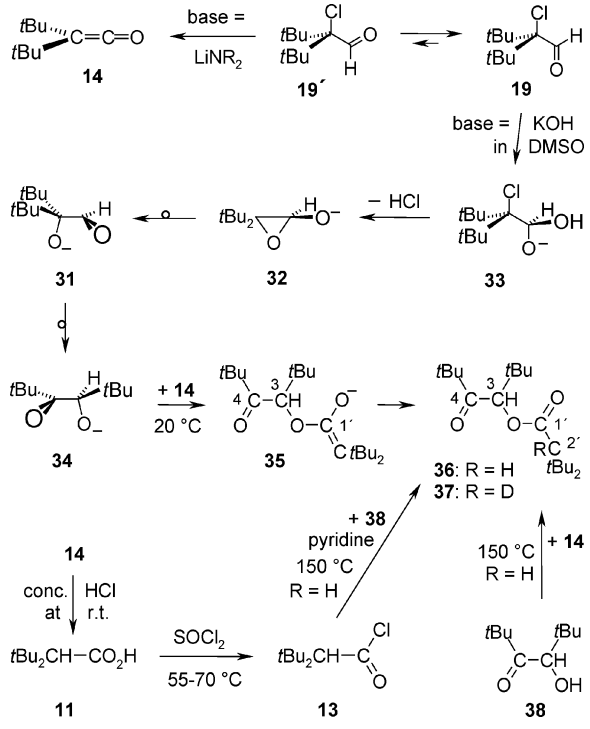
a quick trap-to-trap distillation under 20 mbar into a dry-ice cooled collector can avoid the formation of more **27** from **19**. For a more convenient preparation of **19** containing very little **27** (hence requiring no purification, yield 80%), we recommend that the rearrangement of chlorooxirane **18** be conducted with *dilute* (ca. 10%) solutions in dry toluene[10] at 110 °C, which yielded **19** together with **27** (4%) in 45 min. A more dilute sample of **18** (5% by volume) gave **19** almost free of **27** at 95 °C within 1 h, whereas a more concentrated (30%) solution yielded **19** containing **27** (13%.)

This heterolysis of **18** occurred even at ca. 20 °C in a methanol solution containing 2 equiv. of $NaOCH_3$; it obeyed first-order kinetics with $t_{1/2}$ = 105 (±3) min (or ca. 85 min without $NaOCH_3$) but did not incorporate the methoxy group. Under these conditions, however, the intermediate **24** produced mixtures of **19** with up to 82% of **27**. Comparable mixtures of **19** and **27** were formed much more rapidly (≤70 min at room temp.) from **18** in a suspension of powdered KOH in dimethyl sulfoxide (DMSO), again without incorporation of the strong nucleophiles existing in this system. The release of repulsive $t\mathrm{Bu}_2$ interactions in **18** upon ionization to **24** appears to be important for these higher rates in comparison with the related 2-*tert*-butyl-3-chlorooxirane, which is stable[25] in aqueous methanol at room temperature for more than 24 h.[26]

B. Di-*tert*-butylketene (14) and some Derivatives

An unexpected shortcut in route III (Scheme 1) allowed the direct conversion of the α-chloro aldehyde **19** into the ketene **14** by use of the bases LiTMP or (better) LDA in THF solution. This very unusual mode[27] of HCl elimination afforded up to 70% yields of isolated, spectroscopically pure **14**, which may be used without purification. Even a one-pot preparation of **14** from the chlorooxirane **18** was possible when the solution of **19** in toluene (section A) was not worked up but treated with $LiNR_2$ in THF; the yields (45–55%) of subsequently isolated material depend strongly on consideration of the high volatility of **14**, particularly during the evaporation of toluene at reduced pressure.

Our interpretation (Scheme 3) of this surprising process as an E2-type elimination postulates an unusually increased population of the Cl,O-*cis* conformation **19′** (with dihedral angles Cl–C–C–H in the vicinity of 180°) at the expense of other conformations (**19**). A mechanistic alternative with heterolysis of **19** to generate the formylcarbenium ion **24** (Scheme 2) would be recognized through formation of the rearranged product **27**, which was not observed: **19** did not solvolyze in acid-free methanol (>6 d at room temp.) and proved stable in base-free DMSO at 148 °C for at least 8 h.[24] With the intent of employing a more convenient and cheaper base in place of LDA, we treated **19** with a suspension of solid KOH in DMSO and observed the disappearance of **19** by ^{1}H NMR (Scheme 3): the ketene **14** and the pivaloin anion **34** (molar ratio ca. 2:1) were formed at room temperature over a period of several hours, and these two compounds soon started to react with each other, yielding after workup the pivaloin ester **36** along with residual ketene **14** and pivaloin (**38**), but no acid **11**. An authentic specimen of **36** was obtained through short heating (150 °C) of pivaloin[28] (**38**) with the acyl chloride **13** and pyridine in diglyme ($MeOCH_2CH_2OCH_2CH_2OMe$), whereas the base-free acylation of **38** with ketene **14** at 150 °C in diglyme required many hours to furnish **36**. This indicates that the ketene **14** reacts exclusively with the pivaloin anion **34** (not with the pivaloin **38**) at room temperature, such that the ester enolate **35** should be an intermediate. Indeed, the formation of **35** and its protonation by the solvent (DMSO containing KOH and an equilibrium portion of H_2O) were established through a run with KOH (17 equiv.) in the solvent [D_6]DMSO, which furnished the dideuteriated pivaloin ester [3,2′-D_2]**36** with 86% D at C-2′. The label at C-3 is due to H/D isotope exchange under these strongly basic conditions, as was shown by subsequent treatment of [3,2′-D_2]**36** with KOH in unlabeled DMSO (at 95 °C for 8 h), which afforded **37** with 81% D at C-2′ (D removed from C-3). As well as showing ^{13}C NMR line broadening as an indication of conformational freezing, **36** is also remarkable for the substantial ^{1}H NMR chemical shift difference between its diastereotopic 2′-*t*Bu groups, in view of the fact that these protons are situated in a distance of six single bonds away from the center of chirality.



Scheme 3. 2-*tert*-Butyl-2-chloro-3,3-dimethylbutanal (**19**): reactions with bases.

The pathway leading to the pivaloin anion **34**, as proposed in Scheme 3, starts with the nucleophilic addition of KOH to the aldehyde function of **19** (and possibly also **19′**) to give **33**; at the same time, HCl elimination from **19′** promoted by KOH (in place of $LiNR_2$) affords the ketene **14**.

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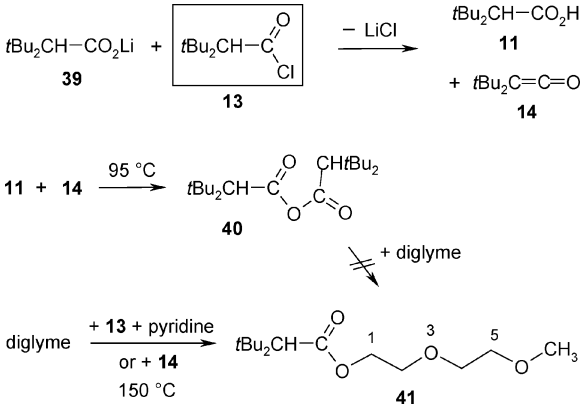
In analogy with similar additions of hydroxide[29] or methoxide[30,31] to other α-chloro aldehydes, the adduct **33** can be expected to expel its chloride anion with cyclization and subsequent deprotonation; the resulting epoxy alkoxide **32** will rearrange to the alkoxide **31** of α,α-di-*tert*-butyl-α-hydroxyacetaldehyde. The ensuing *t*Bu migration in **31** toward the aldehyde function with formation of the pivaloin anion **34** has precedent[32] in a similar aryl migration at ca. 70 °C in a sterically less congested system. The final fusion of **34** and ketene **14** occurs substantially more rapidly than the addition of **14** to KOH suspended in DMSO, as shown by the isolation of residual **14** (without acid **11**). This was confirmed in a separate run in which ketene **14** and solid KOH in DMSO at 55 °C reacted slowly (in >38 h) to yield the acid **11**.

Under more convenient conditions than those of route I in Scheme 1, the acid **11** could now be prepared through hydration of the ketene **14** with concentrated HCl at room temperature (bottom line of Scheme 3, yield up to 80%); even highly contaminated samples or THF solutions of **14** (as obtained from **18** or **19** without workup) were suitable. The acyl chloride **13** could be produced from **11** under milder conditions than reported[4] with a small excess of thionyl chloride in CCl_4 solution at 70 °C (13 h) or 55 °C (43 h); after the final evaporation of CCl_4 and residual $SOCl_2$ down to a pressure of 50 mbar at 60 °C for 3 min, the volatile liquid **13** could be used without purification.

Di-*tert*-butylacetic anhydride (**40**, Scheme 4)[33,34] was accessible through the acylation of the acid **11** with the ketene **14** when these two reagents were either employed as such or were generated in situ from the potassium or (better) lithium salt (**39**) of **11**, which is sufficiently basic to eliminate HCl from the acyl chloride **13** in anhydrous toluene. The initial formation of the ketene **14** from **13** and **39** could be observed (^{1}H NMR in situ) in THF or diglyme solutions at 55 °C. The ensuing slower formation of **40** could be monitored[35] in diglyme at 95 °C or above; however, hot diglyme is not a recommendable solvent, because it will produce the ester **41** through a slow acylation by **13** or **14** (but not by the anhydride **40**) under these conditions. With pyridine as an alternative base instead of **39**, **13** formed a transient portion (up to 26%) of ketene **14** and at 150 °C in diglyme

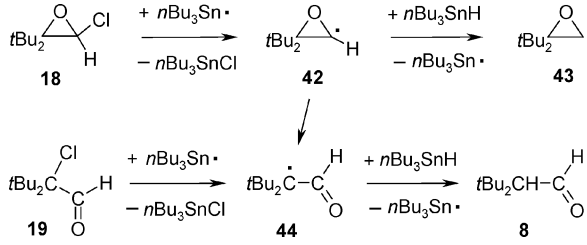


Scheme 4. Reactions of di-*tert*-butylacetyl chloride (**13**).

required more than 63 h for the acylation of both the solvent and the acid **11** to furnish the ester **41** (yield 47%) and the anhydride **40** (yield 21%). Neither **41** nor **40** were cleaved by NaOH in dioxane (2 M, at 85–95 °C, 4 d) or by solid KOH in CCl_4 (at 70 °C, 7 d).

C. Further Transformations of 18 and 19

Di-*tert*-butylacetaldehyde (**8** in Scheme 5) is difficult to purify and to handle in small batches because of its propensity toward autoxidation. Its traditional four-step synthesis[4] (21%, Scheme 1) involves certain complications,[6] and only small amounts of **8** were obtained through the isomerization[4,36] of 2,2-di-*tert*-butyloxirane (**43**), an epoxide that had been prepared in three steps from the ketone **1** with total yields of 44%[36] or 86%.[37] The one-pot preparation of **8** (54%) from the ketone **1** with the relatively expensive reagent diethyl isocyanomethanephosphonate[38] might be limited in its attraction on a larger scale.[39]



Scheme 5. Dechlorination of **18** and **19** by nBu$_3$SnH.

In a search for convenient procedures, we dechlorinated **18** and **19** by use of the following reductants. Tributylstannane (2 equiv.) reduced the chlorooxirane **18** (Scheme 5) in a benzene solution (0.52 M) under UV irradiation [with 2,2′-azobis(2-methylpropionitrile) as an initiator, 51 h] to a 1:1 mixture of the oxirane **43** (identified through its ^{1}H and ^{13}C NMR[36] data) and the aldehyde **8**. With lower concentrations of tributylstannane, the transient oxiranyl radical **42** would have been trapped less efficiently before isomerizing to the planar and "relatively persistent"[40] formyl-substituted radical **44**. In a cleaner process, the α-chloro aldehyde **19** and tributylstannane generated **44**, which furnished **8** as the only product under similar conditions (except for the much shorter reaction time of 2 h without an initiator). Nevertheless, we abandoned this approach because of the usual difficulties of removing stannyl byproducts.

The oxiranyl radical **42** should also be a first intermediate in the reduction of **18** (Scheme 6) through electron transfer from magnesium turnings (ca. 4 equiv. of Mg) in the presence of $ClSiMe_3$ (ca. 6 equiv.) in boiling THF. Upon escape of **42** from the metallic surface before a second electron transfer can occur, the isomerization of **42** to give **44** takes place in the nonreducing solution. Its considerable lifetime[40] enables **44** to approach the Mg^0 surface for a second electron transfer, producing the enolate **45**. With silylation of **45** in situ to yield the silyl enol ether **46**, a simple

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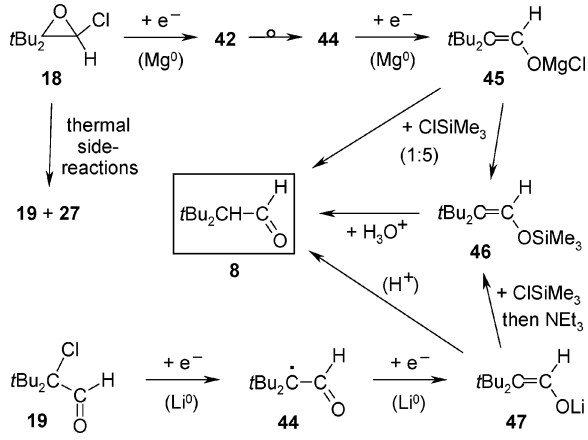
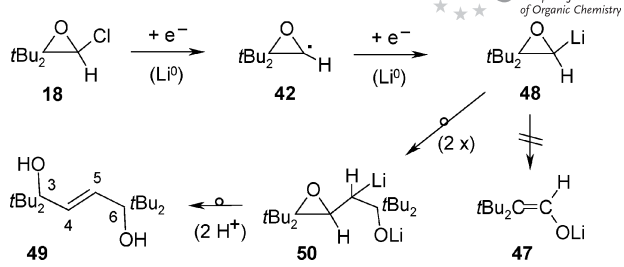
aqueous workup furnished **8** and **46** in a 1:5 ratio. Although such a conversion of **46** to **8** might be completed intentionally, this route was deemed unreliable because of difficulties in keeping the Mg^0 surface sufficiently active: in spite of the presence of $ClSiMe_3$ and the use of alternatively activated Mg^0, the repeatedly encountered delays in the reduction process allowed the decay modes of **18** to interfere, producing **19** and **27** (as depicted in Scheme 2).



Scheme 6. Metal-based reductions of **18** with Mg^0 and of **19** with Li^0 and $ClSiMe_3$; e^- = electron.

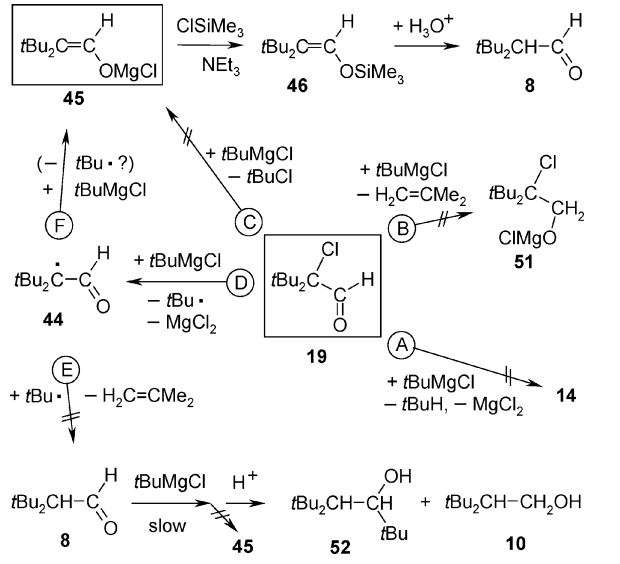
The α-chloro aldehyde **19** (Scheme 6) was readily reduced in THF at room temperature by metallic lithium (3 equiv.), the surface of which was most efficiently kept active by the presence of $ClSiMe_3$ (1.5 equiv.) in situ. This is the simplest and most productive way of preparing the silyl enol ether **46** via the radical **44** and the Li enolate **47** (δ_H = 6.82 ppm). It is essential to add NEt_3 (2 equiv.) prior to an aqueous workup, so as to avoid a premature hydrolysis of **46** through the hydrochloric acid formed from residual $ClSiMe_3$. As a less air-sensitive precursor of **8**, **46** can be stored until **8** is prepared through intentional hydrolysis of **46** with aqueous acid.

Under similar electron-transfer conditions from elemental Li^0 in THF, the chlorooxirane **18** reacted by a mechanistic modification of the Mg^0 route of Scheme 6 but furnished a different product (compound **49** in Scheme 7). The stronger reducing agent Li^0 (4 equiv.) appears to perform a faster second electron transfer before the oxiranyl radical **42** can escape from the metallic surface and isomerize to **44**: no traces of the aldehyde **8** or (with $ClSiMe_3$) of its silyl enol ether **46** could be detected. Instead, **42** was presumably reduced to the O,Li-carbenoid **48** (or a ring-opened isomer), which appears to dimerize[41] by nucleophilic attack on a second carbenoid **48** that responds by ring opening, perhaps in the sense of an intermediate **50** (an unconfirmed explanation). As usual for a 2-(1-lithioalkyl)oxirane, **50** would be expected[42] to open its oxirane ring, producing the allylic diol **49**. The (*E*) configuration of **49** was established through the NMR coupling constant $^3J_{H,H}$ = 15.7 Hz as extracted from the ^{13}C satellites of the olefinic ^1H NMR singlet.



Scheme 7. Metal-based reduction of **18** with Li^0; e^- = electron.

The clean conversion of **19** into **8** or its precursors **46** and **45** (top lines of Scheme 8) at 20 °C (^1H NMR spectroscopy in situ) by treatment with *t*BuMgCl (2.7 equiv.) in THF is also possible within 35 min. Remarkably, *t*BuMgCl did not add to the aldehyde group of **19** and acted neither as a base (pathway A) to afford the ketene **14** (not detected in situ although it would be stable for >12 d) nor as a hydride donor (pathway B) to furnish the β-chloro alkoxide **51**. As outlined below in reaction 12 in Scheme 9, **51** would be converted into the aldehyde **8**, which was not detected although it is stable under these conditions. Instead, the ^1H NMR spectra revealed the formation of the Mg enolate **45** ($\delta_H \approx$ 1.15 and 1.36 ppm) shown in Scheme 8, together with an equivalent amount of isobutene. The constitution of **45** was established through derivatization with $ClSiMe_3$ (3.2 equiv.), which afforded the silyl enol ether **46** (δ_H = 6.21 ppm in situ) as the only product. The addition of NEt_3 (2 equiv.) to neutralize the acid arising from residual $ClSiMe_3$ is essential for **46** to survive the subsequent aqueous workup. Alternatively, residual *t*BuMgCl was identified through carboxylation (solid CO_2) to give pivalic acid, showing that the excess of $ClSiMe_3$ had not reacted with *t*BuMgCl.



Scheme 8. Reductive enolization of **19** by treatment with *t*BuMgCl in THF. See the text for discussions of routes A–F.

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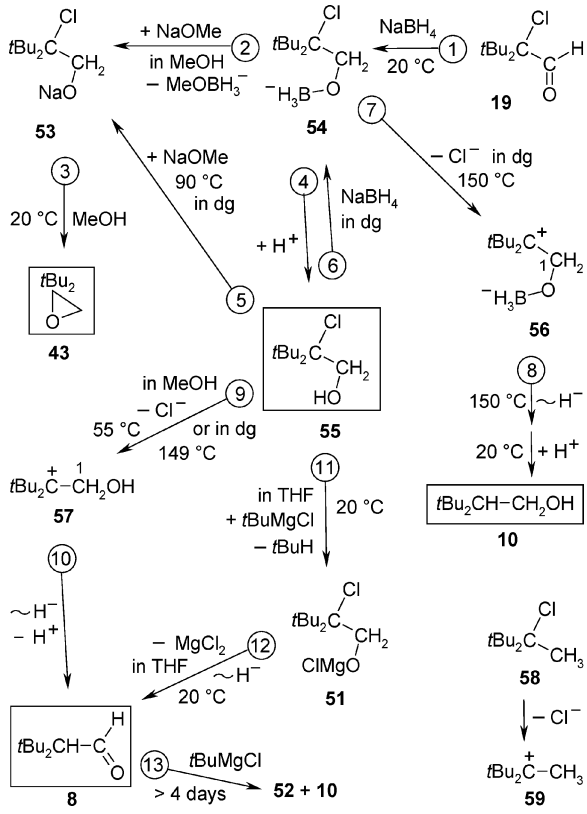
The simplest mechanistic interpretation in terms of a Cl/Mg interchange reaction (pathway C) leading directly to the Mg enolate **45** must be dismissed, because the expected byproduct *tert*-butyl chloride (*t*BuCl, δ_H = 1.59 ppm) was not detected in situ even though it would have been stable under the reaction conditions in the presence of *t*BuMgCl over a period of at least 5 d, as demonstrated in a separate run. The remaining mechanistic possibility (pathway D), a single-electron transfer (SET) from *t*BuMgCl to **19**, leads to the aforementioned "rather persistent"[40] radical **44**. The concomitant *tert*-butyl radical (*t*Bu˙) might be expected to transfer a hydrogen atom to **44** (branch E in Scheme 8) with formation of the aldehyde **8**, which would have to be deprotonated by *t*BuMgCl to explain the enolate **45**. However, **8** was not detected in situ even though it is stable against *t*BuMgCl under the reaction conditions for a much longer time: a separate experiment (bottom line of Scheme 8) showed that *t*BuMgCl did not deprotonate **8** to afford **45** but generated the *t*Bu addition product **52** and the hydride transfer product **10** very slowly over the course of 5 d. Consequently, the radical **44** appears to have been converted into the enolate **45** (rather than into **8**) with consumption of a second equivalent of *t*BuMgCl (branch F). This process may be envisioned as a second SET from *t*BuMgCl with release of another equivalent of *t*Bu˙. (Note that two *t*Bu˙ radicals can be expected to disproportionate with formation of isobutane and isobutene.) Alternatively, the first *t*Bu˙ to be generated might transfer a hydrogen atom to the oxygen atom of **44** with generation of isobutene and $tBu_2C{=}CH{-}OH$, whereupon a quick deprotonation of this enol by *t*BuMgCl would give isobutane and **45**. The simple strategy of in situ NMR spectroscopy can thus help to exclude some of the mechanistic alternatives in this system.

tert-Butyllithium (*t*BuLi) in either THF or benzene reacted more rapidly but less cleanly with **19** to furnish the Li enolate **47** (δ_H = 6.82 ppm in THF; later trapped as **46**) which could arise from a Cl/Li interchange reaction (similar to pathway C in Scheme 8) or by the D/F (but not the D/E) route shown in Scheme 8; aqueous workup afforded the aldehyde **8**. There was no unequivocal evidence for the analogues of pathways B (hydride transfer) or A (to generate ketene **14** and possibly its addition product[43] to *t*BuLi).

Steric congestion does not prevent the hydride transfer from $NaBH_4$ to the aldehyde function of **19** (step 1 in Scheme 9). This system is remarkable for its peculiar product dependence on the solvent and the temperature: the formation variously of **10** or of **43** or of **55** (and thence **8**) from **19** in Scheme 9 can be controlled as follows. The hydridoborate anion **54**, as generated in alkalized methanol (step 1), is converted at 20 °C (step 2) into the β-chloro alkoxide **53** (^{1}H NMR in situ) and then cyclized (step 3) at a somewhat slower rate to produce the oxirane **43** within 20 h. With use of a large excess (4 mol-equiv.) of $NaBH_4$ in methanol, with the goal of generating **54** within 1 h or less, the intended preparation (workup step 4) of the rather unstable chlorohydrin **55** was unsatisfactory, even though the very volatile byproduct **43** could be easily removed by evacuation.



Scheme 9. $NaBH_4$ reduction of **19** and ensuing transformations; dg = diglyme. See the text for discussions of steps 1–13.

This interfering formation of oxirane **43** can be avoided by use of dry diglyme as the solvent; it dissolves enough $NaBH_4$ and does not permit the β-chloro alkoxide **53** to be released from the conjectured hydridoborate **54**. In a saturated solution of $NaBH_4$ (2 equiv.), step 1 was sufficiently fast to allow the chlorohydrin **55** at 20 °C to be isolated after roughly 4 h (step 4) before more than traces of the side product $tBu_2CH{-}CH_2OH$ (**10**) could be detected (^{1}H NMR in situ). The non-appearance of oxirane **43** is due to the *O*-protecting BH_3 group in **54** (or a similar hydridoborate) and not to the changed solvent per se: this was established by treating the chlorohydrin **55** in diglyme with $NaOCH_3$ (step 5), which afforded only **43** (via **53**). When $NaBH_4$ was used as the base in place of $NaOCH_3$ (step 6), no traces of **43** could be detected. Instead, the *O*-protected intermediate **54** (generated by steps 6 or 1) reacted in the presence of residual $NaBH_4$ on heating to 150 °C for 3 h (step 7), possibly via the S_N1-type intermediate **56** that can be expected to shift a hydride anion to C-2 in step 8 either from the OBH_3^- group or from C-1 (with a subsequent second hydride transfer from a B–H function to C-1): the dechlorinated alcohol $tBu_2CH{-}CH_2OH$ (**10**) was obtained (19% yield) after workup. Proton abstraction from C-1 of **56** or HCl elimination from **54** in the basic milieu as an alternative to step 8 can be dismissed, because the resulting *O*-protected BH_3 enolate of aldehyde **8** would be unable to form the final product **10**.

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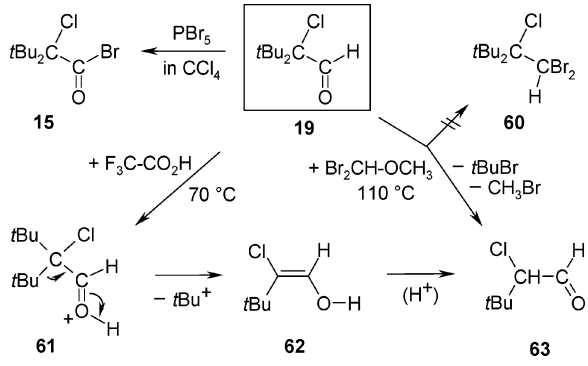
The expulsion of chloride anion from the chlorohydrin **55** (step 9) displays a characteristic solvent dependence: the first half-reaction times[44] ($t_{1/2}$) for the disappearance of **55** are ca. 3 h at 55 °C in methanol and ca. 1 h at 149 °C in diglyme solution, to be compared with the reported[45] $t_{1/2}$ = 1.1 h for the S_N1-type ionization of **58** to generate **59** at 25 °C in aqueous ethanol (20:80). The expected S_N1 intermediate **57** does not cyclize to give **43** but appears to prefer the obvious possibility of a stabilizing hydride shift from C-1 to C-2 (step 10), leading to the dechlorinated aldehyde **8** as the only product (^{1}H NMR in situ). In view of such properties, the oily key compound **55** cannot be purified by a slow fractionating distillation, because that would generate HCl and **8** by steps 9 and 10.

The Mg β-chloro alkoxide **51**, generated (step 11, Scheme 9) at 20 °C from the chlorohydrin **55** on treatment with *t*BuMgCl (2.7 equiv.) in THF in <2 min, would appear to have the options for at least four transformations: to **8**, **10** (by *t*BuMgCl), the oxirane **43**, and *t*Bu$_2$C=CH–OMgCl (**45**). Perhaps surprisingly, the ^{1}H NMR signals at δ = 1.24 (broad) and 1.22 ppm (broader) assigned to **51** (two species?) disappeared rapidly at 20 °C (step 12, first $t_{1/2} \approx$ 14 min)[44] with formation of the aldehyde **8** as the only product observable in situ over the first 97 min. As is already familiar from the bottom line of Scheme 8, residual *t*BuMgCl and **8** reacted subsequently very slowly (at 20 °C, >4 d) in step 13 to provide **52** and **10** but no trace of the oxirane **43**. The enolate *t*Bu$_2$C=CH–OMgCl (**45**) cannot have been the precursor of **8**, in view of the absence of acids in the presence of residual *t*BuMgCl. The *O*-protecting group MgCl has thus saved **51** from cyclization (to give **43**) and has facilitated step 12 (at 20 °C in THF) in preference to step 7 (at up to 150 °C) and steps 9/10 (at 149 °C in diglyme), perhaps because of intramolecular assistance to C–Cl bond heterolysis by the MgCl cation.

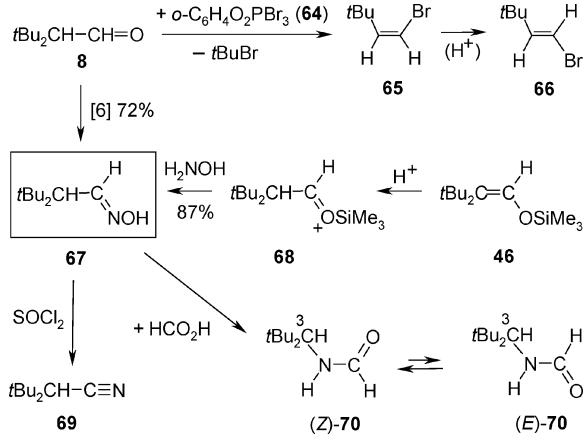
The aldehyde function of **19** is not prone to autoxidation, yet is readily brominated. The product *t*Bu$_2$CCl–CO–Br (**15**, shown in Scheme 1)[10] was obtained here (Scheme 10) on treatment with PBr_5 in boiling CCl_4 (yield 21% in 14 h); it was identified through comparison with the published[10] ^{13}C NMR chemical shifts. In a second futile attempt directed towards 1,1,2-trihalogeno derivatives **60**, we heated **19** with dibromomethoxymethane[46] and obtained only 2-chloro-3,3-dimethylbutanal (**63**), as identified through its ^{1}H NMR spectrum,[47] along with *t*BuBr (δ = 1.78 ppm) and CH_3Br (δ = 2.58 ppm). Neither PCl_5 nor PPh_3 in hot CCl_4 reacted with **19**, but $F_3C–CO_2H$ in $CDCl_3$ solution at 70 °C converted **19** slowly into **63**, presumably by de-*tert*-butylation (**61** → **62**).



Scheme 10. 2-*tert*-Butyl-2-chloro-3,3-dimethylbutanal (**19**) in reactions with electrophiles.

D. Descendants of Di-*tert*-butylacetaldehyde (8)

The aldehyde **8** is almost instantaneously deoxygenated by the catechyl phosphorus tribromide **64** (Scheme 11), which is approved[48] for the preparation of 1,1-dibromides such as the desired *t*Bu$_2$CH–CHBr$_2$. However, the repulsive strain inherent in the *gem*-*t*Bu$_2$ fragment appears to lead **8** away from the intended course, producing instead the de-*tert*-butylated alkenyl bromide **65** as the pure (*Z*) isomer,[49] which was slowly converted into the (*E*) isomer **66** under the reaction conditions.



Scheme 11. Some transformations of 2-*tert*-butyl-3,3-dimethylbutanal (**8**).

The propensity of the aldehyde **8** to autoxidize is an inconvenient property that interferes with the preparation of the oxime **67** (Scheme 11). Although we were able to confirm the reported[6] yield of **67** (72% in 18 h), we preferred to employ the silyl enol ether **46** under milder conditions that furnished almost pure, undistilled **67** (87% in only 2 h). This significant acceleration suggests that a proton transfer reaction from HO–$NH_3^+AcO^-$ to **46** generated **68** as an activated form of aldehyde **8**. The usual hydrolysis of **68** in aqueous ethanol to give **8** was overcome here by the faster addition of HO–NH_2. The previously unreported dehydration of oxime **67** by the usual simple treatment with $SOCl_2$ (1.1 equiv.) in warm benzene afforded the nitrile **69** (yield 74% after distillation). With a total of five steps (or <5 preparative stages), this preparation of **69** from ketone **1** is shorter and more convenient than the traditional synthesis.[4] Our attempts to prepare nitrile **69** through some of the recommended one-pot procedures, variously from the acid **11** with chlorosulfonyl isocyanate and then DMF[50] (decomposition), or from aldehyde **8** with hydroxylamine-*O*-sulfonic acid[51] (no conversion), or with $HONH_3^+Cl^-$ in DMF at reflux[52] (basic side products), were all unsatisfac-

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tory. The shortcut treatment of **8** with $HONH_3^+Cl^-$ in hot formic acid[53] furnished some strongly contaminated nitrile **69**, accompanied by *N*-(di-*tert*-butylmethyl)formamide (**70**) in a (*Z*)/(*E*) ratio of ca. 74:26 after distillation. Such a Beckmann rearrangement competing with the dehydration of an aldoxime is only rarely observed.[54] The spontaneously crystallizing[9] (*Z*) isomer was recognized through its small $^3J_{H,H}$ NMR coupling constant of 2.0 Hz [for the *cis* *H*–(O=)C–N–*H* fragment] and its upfield ^{13}C NMR signal of *C*H-3 (δ = 62.0 ppm), in relation to $^3J_{H,H}$ = 11.6 Hz (*trans*) and δ = 68.9 ppm for *C*H-3 of the previously[9] not reported (*E*) isomer. The slow formation of (*E*)-**70** in $CDCl_3$ solution is consistent with observations on other sterically congested amides.[55] The (*Z*)/(*E*) equilibrium mixture of 59:41, obtained after 6 h at 20 °C, might be due to a stronger ecliptic repulsion of the oxygen atom by the tBu$_2$CH group in relation to other *N*-substituents, such as *t*Bu [78–82% (*Z*)][56,57] and H_3C [92% (*Z*)][57] in other formamides.

Conclusions

The *gem*-di-*tert*-butyl compounds studied in this work are remarkable for some unusual properties and reactivity patterns. The surprisingly volatile key substance tBu$_2$CCl–CH=O (**19**) appears to arise (Scheme 2) through a heterolytic C–O bond fission that is accelerated by steric overcrowding to such an extent that the nonpolar toluene can be recommended as a most suitable solvent.

The unusual elimination of HCl from tBu$_2$CCl–CH=O (**19**) by LDA (Scheme 2) or (much more slowly) by KOH in DMSO (Scheme 3) to produce the ketene tBu$_2$C=C=O (**14**) is interpreted as an E2-type elimination, because we were unable to ionize **19** by an uncatalyzed heterolysis reaction (types E1 or S_N1) of the C–Cl bond in hot DMSO (148 °C) or in methanol. As soon as the aldehyde group of **19** was disabled through the addition of the small nucleophiles OH^- (Scheme 3) or H^- (Scheme 9) or through an electron transfer (ET, Schemes 6 and 8), the expulsion of Cl^- from the tBu$_2$CCl group became possible and exhibited a solvent dependence (Scheme 9, step 9) that points to a certain carbenium character before product formation. However, a bulkier nucleophile such as *t*BuMgCl at room temp. required 5 d (bottom lines of Schemes 8 and 9) for its addition (**52**) and hydride transfer (**10**) to the aldehyde function of tBu$_2$CH–CH=O (**8**). A comparably strong retardation is to be expected with tBu$_2$CCl–CH=O (**19**) and provided an opportunity to study the rarely observed ET reaction from *t*BuMgCl (Scheme 8): the enolate tBu$_2$C=CH–OMgCl (**45**) was produced at room temp. via the radical **44** within 35 min, while alternative mechanistic possibilities were excluded through ^1H NMR spectroscopy in situ. The replacement of X = H by non-hydrogen atoms X in tBu$_2$CH–CO–X can impede carbonyl addition reactions still further: the esters **36** and **41** and the anhydride (tBu$_2$CH–CO)$_2$O (**40**) were shown to resist alkaline hydrolysis partially (**36**) or completely at 95 °C, and tBu$_2$CH–CO–Cl (**13**, Scheme 4) reacted with tBu$_2$CH–CO$_2$Li (**39**) via tBu$_2$C=C=O (**14**) plus tBu$_2$CH–CO$_2$H (**11**) rather than by addition/elimination at 95 °C.

The ketene **14** did not react with LDA or with *t*BuMgCl (at room temp., >12 d), yet it can acylate the following nucleophiles with synthetically acceptable rates at widely differing temperatures: the alkoxide *t*Bu–CH(OK)–CO–*t*Bu (**34**) of pivaloin in DMSO at room temp. slowly (Scheme 3), a suspension of KOH in DMSO at 55 °C much more slowly, pivaloin (**38**) in diglyme at 150 °C within 21 h (Scheme 3), tBu$_2$CH–CO$_2$H (**11**) in toluene at 95 °C in 3 h (Scheme 4), or H_2O in the presence of concd. HCl at room temp. within 2 h. Because the uncatalyzed addition of **14** to adventitious traces of H_2O in hot DMSO or hot diglyme can be a disturbing side-reaction in small-scale runs, it is advisable to employ less polar aprotic solvents (such as toluene) which are kept dry more easily. Electrophiles tend to de-*tert*-butylate *gem*-di-*tert*-butyl compounds (Schemes 2, 10, and 11). A very simple ET reduction of tBu$_2$CCl–CH=O (**19**) employs lithium metal (Scheme 6) to produce tBu$_2$C=CH–OSiMe$_3$ (**46**), which is a useful precursor of the activated form **68** of aldehyde **8**, as shown by its fast and clean condensation reaction with $HO–NH_3^+$ AcO^- in aqueous ethanol (Scheme 11) to provide the oxime **67** and from this the nitrile **69**.

Experimental Section

NMR Spectroscopy in situ: The progress of many of the reactions described above was observed in situ by ^1H NMR spectroscopy at 200 MHz and 20–23 °C, with use of NMR tubes (outer diameter 5 mm) that were either tightly stoppered and sealed with stretchable plastic foil or were closed with a glass stopper in a gas-tight ground-glass joint. Occasional final in situ analyses by ^1H (400 MHz) and ^{13}C NMR (100.6 MHz) spectroscopy served to confirm the NMR signal assignments of the primary products before workup. Most of these runs were carried out in nondeuterated solvent (0.5–1.5 mL) containing [D_{12}]cyclohexane (as the "lock substance", at least 0.03 mL), a trace of TMS (δ = 0 ppm), and the reagents (≥0.1 mmol). Thanks to the strong 18-proton singlets of the starting and final compounds, the *gem*-tBu$_2$ system proved well suited for studies in the solvents diglyme, THF, methanol, DMSO, toluene, and also benzene or CCl_4. However, the δ_H values of the tBu$_2$CH groups depend slightly on the solvent, so detailed δ_H collection was essential for the differential in situ analyses and is reproduced in part below (excluding those solutions that are used for characterization in the pertinent paragraphs).

δ_H Values (ppm): *t*BuMgCl/tBu$_2$Mg 0.90 and 0.88 in THF, consistent with ref.[58] tBu$_2$CH–CO$_2$H (**11**) 1.10/2.11 in diglyme, 1.13/2.18 in diglyme containing pyridine, 1.07/2.06 in DMSO, 1.06/2.15 in toluene, 1.14/2.15/11.3 in CCl_4; tBu$_2$CH–CO–Cl (**13**) 1.17/2.90 in diglyme, 1.18/2.84 in CCl_4, 0.99/2.70 in toluene; tBu$_2$C=C=O (**14**) 1.21 in diglyme or THF, 1.22 in CCl_4; tBu$_2$C(Cl)–CH=O (**19**) 1.20/9.87 in [D_6]DMSO, 1.23/9.82 in diglyme, 1.24/9.77 in toluene or CCl_4 (consistent with ref.[10]); *t*BuCH(OK)–CO–*t*Bu (**34**) 0.89/1.16/4.23–4.37 in THF; *t*BuCH(OLi)–CO–*t*Bu 0.87/1.15/4.28–4.36 (br) in THF; *t*BuCH(OH)–CO–*t*Bu (**38**) 0.94/1.15/4.02 in THF or CCl_4, 0.98/1.19/4.21 in $CDCl_3$; tBu$_2$CH–CO$_2$Li (**39**) 1.17/hidden in toluene; tBu$_2$CH–CO$_2$Na 1.08/1.99 in diglyme; tBu$_2$CH–CO$_2$K 1.04/2.05 in DMSO; (tBu$_2$CH–CO)$_2$O (**40**) 1.13/2.14 in diglyme without

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or with DMSO, 1.10/hidden in toluene, 1.13/2.07 in CCl_4. The experiments with volatile compounds (but without the evolution of significant amounts of gases) were performed in tightly closed vessels at temperatures well below the b.p. of the solvent.

2-*tert*-Butyl-3,3-dimethylbutanal (8) from 46: A solution of 2-*tert*-butyl-3,3-dimethyl-1-(trimethylsiloxy)but-1-ene (**46**, 229 mg, 1.00 mmol) in methanol (0.4 mL) was stirred with aqueous HCl (2 M, 0.1 mL) under argon for 40 min and was then poured into distilled water (5 mL) and extracted with Et_2O (3× 8 mL). The combined ethereal layers were washed with water until neutral, dried with Na_2SO_4 under argon, filtered, and concentrated under reduced pressure. The complete removal of Et_2O caused some loss of the slightly yellow liquid, which consisted entirely of the aldehyde **8** (crude yield 119 mg, 76%). ^{1}H NMR (CCl_4): δ = 1.08 (s, 18 H), 1.70 and 9.67 (AB system with ^3J = 6.0 Hz) ppm. ^{1}H NMR ($CDCl_3$): δ = 1.10 (s, 18 H), 1.75 and 9.77 (AB system with ^3J = 6.3 Hz) ppm, consistent with ref.[59] ^{13}C NMR ($CDCl_3$): δ = 30.57 (qoct, ^1J = 125.4 Hz, 2× C*Me*$_3$), 34.14 (apparent sept, J = 3.8 Hz, 2× *C*Me$_3$), 68.78 (ddm, ^1J = 125.5, ^2J = 22.5, ^3J = 3.5 Hz, C-2), 206.61 (dd, ^1J = 167.1, ^2J = 8.0 Hz, C=O) ppm. IR (film): $\tilde{\nu}$ = 2959, 2724 (w, OC–H), 1721 (C=O), 1478, 1370 cm^{-1}.

2-*tert*-Butyl-3,3-dimethylbutan-1-ol (10): The α-chloro aldehyde **19** (314 mg, 1.65 mmol) and $NaBH_4$ (190 mg, 5.02 mmol) in dry diglyme (3.0 mL) were heated at 150 °C for 3.5 h (copious precipitate). After 2 d at room temperature (room temp.), the mixture was dissolved in Et_2O/H_2O (slow evolution of H_2 for 1 h). The Et_2O layer was washed first with water and then with HCl (2 M), shaken with water (5× for complete removal of diglyme), dried with Na_2SO_4, and concentrated under 60 mbar at room temp. for 10 s to furnish the highly contaminated alcohol **10**. The only distillable components of this material were **10** (49 mg, 19%) and a trace of the aldehyde **8**; b.p. of **10**: 127–132 °C (bath temp.)/4 mbar. ^{1}H NMR ($CDCl_3$): δ = 1.06 (s, 18 H), ca. 1.08 (hidden, 2-H), 3.73 (d, ^3J = 3.5 Hz, CH_2O) ppm. ^{1}H NMR (400 MHz, [D$_6$]benzene): δ = 1.01 (t, ^3J = 3.5 Hz, 2-H), 1.03 (s, 18 H), 3.54 (d, ^3J = 3.5 Hz, CH_2O) ppm. ^{13}C NMR ($CDCl_3$): δ = 30.97 (2× C*Me*$_3$), 35.57 (2× *C*Me$_3$), 60.51 (C-2), 63.68 (CH_2O) ppm, in reasonable accord with ref.[60] ^{13}C NMR (100.6 MHz, [D$_6$]benzene): δ = 31.27, 35.62, 59.94, 63.14 ppm.

2-*tert*-Butyl-3,3-dimethylbutanoic Acid (11): A solution of the chlorooxirane **18** (1.91 g, 10.0 mmol) in dry toluene (18 mL) was heated at 110 °C for 45 min and was then cooled and added dropwise at –70 °C to LDA (20.3 mmol) in dry THF (10 mL) and hexane (ca. 10 mL). After 20 min at –70 °C, the mixture (containing the crude ketene **14**) was stirred with concentrated HCl (15 mL) at room temp. for 2 h and then diluted with distilled water and Et_2O. The aqueous layer was shaken with more Et_2O (2× 10 mL) and discarded. The combined Et_2O phases were extracted with NaOH (2 M, 3× 10 mL) and then discarded. These alkaline aqueous phases were combined, acidified with conc. HCl, extracted with Et_2O (3× 15 mL), and discarded. The final three Et_2O extracts were combined, washed with distilled water until neutral, and dried with Na_2SO_4, and the solvents were evaporated to dryness, yielding crude **11** (1.14 g, 66%) with m.p. 69–72 °C (ref.[4] 72–74 °C or 80.5–81.5 °C). ^{1}H NMR ($CDCl_3$): δ = 1.13 (s, 18 H), 2.20 (s, 2-H), 11.5 (br, OH) ppm. [35] ^{13}C NMR ($CDCl_3$): δ = 30.7 (qoct, ^1J = 125.5, ^3J = 4.6 Hz, 2× C*Me*$_3$), 34.5 (m, ^2J = 4.0 Hz, 2× *C*Me$_3$), 64.5 (dm, ^1J = 128 Hz, C-2), 180.5 (d, ^2J = 8.3 Hz, C=O) ppm. IR (KBr): $\tilde{\nu}$ = 3600–2500 (br, O–H), 2959, 1704 (C=O), 1476 (w), 1371, 1245, 1177, 939 (w), 712 (w) cm^{-1}. An analogous preparation starting with the addition of a THF solution of the α-chloro aldehyde **19** (in place of **18**) to LDA yielded **11** (80%) with m.p. 71.5–73 °C.

2-*tert*-Butyl-3,3-dimethylbutanoyl Chloride (13): The acid **11** (276 mg, 1.60 mmol) in dry CCl_4 (2.0 mL) was heated with $SOCl_2$ (0.180 mL, 2.48 mmol) under a dry double-walled reflux condenser (fitted with an N_2 bubbler) at 55 °C for up to 43 h. Residual $SOCl_2$ and CCl_4 were removed in a rotary evaporator under ca. 50 mbar and 60 °C (ref.[4] b.p. 83–86 °C/12 Torr) for 3 min, leaving pure **13** (310 mg, 101%). ^{1}H NMR ($CDCl_3$): δ = 1.18 (s, 18 H), 2.90 (s, 2-H) ppm.[35] ^{13}C NMR (CCl_4): δ = 30.52 (2× C*Me*$_3$), 36.35 (2× *C*Me$_3$), 77.67 (C-2), 173.83 (C=O) ppm.

2-*tert*-Butyl-3,3-dimethylbut-1-en-1-one (14)

(a) From 19: A solution of LDA (16.5 mmol) in THF (10 mL) and hexane (6.6 mL) was prepared in a Schlenk flask (50 mL) with magnetic stirring at 3 °C under argon and then cooled to –70 °C. The α-chloro aldehyde **19** (3.00 g, 15.7 mmol) in dry THF (5 mL) was added dropwise over 20 min. After another 15 min, the mixture was warmed up in an ice bath and acidified with HCl (2 M, 10 mL) containing a little ice, then diluted with distilled water and extracted with Et_2O (3× 25 mL). The combined Et_2O phases were washed until neutral, dried with K_2CO_3 or Na_2SO_4, and carefully concentrated to leave an orange-colored liquid (2.15 g). This almost pure ketene (**14**) was distilled at room temp. und 0.03 mbar into a trap cooled to –70 °C to give pure **14** (1.67 g, 69%) as a yellow liquid. ^{1}H NMR ($CDCl_3$): δ = 1.21 ppm.[35] ^{13}C NMR ($CDCl_3$): δ = 31.3 (2× *C*Me$_3$), 32.3 (2× C*Me*$_3$), 52.2 (C-2), 203.9 (C=O) ppm, consistent with ref.[10]. IR (film): $\tilde{\nu}$ = 2086, 1469, 1368, 1227 cm^{-1}.

(b) From 18: The chlorooxirane **18** (2.45 g, 12.8 mmol) in dry toluene (20 mL) was heated at 110 °C for 45 min and then cooled but not worked up. Instead, the resulting mixture (containing **19**) was pipetted into a cooled solution (–70 °C) of LDA (25.7 mmol) in THF (10 mL) and hexane (20 mL). After another 15 min, this yellow mixture was warmed up in an ice bath, acidified with ice-cold HCl (2 M, 45 mL), and extracted with Et_2O (3× 15 mL). The combined Et_2O layers were washed neutral, dried with K_2CO_3, and concentrated under 25 mbar to provide an orange-colored liquid (925 mg) containing **14** (886 mg, 45%) and toluene only. This material was used without purification; analogous specimens were distilled at 76–81 °C/80 mbar or at 30–35 °C/40 Torr (ref.[4] b.p. 74–76 °C/47 Torr). It was difficult to distill the last portions of **14** out of the residue.

2-*tert*-Butyl-2-chloro-3,3-dimethylbutanoyl Bromide (15): An NMR tube charged with the α-chloro aldehyde **19** (50 mg, 0.26 mmol) and PBr_5 (1.31 mmol) in CCl_4 (0.5 mL) was heated at 70 °C for 14 h for total consumption of **19**. The mixture was dissolved in Et_2O and extracted with NaOH (2 M). The Et_2O layer was washed until neutral, dried with Na_2SO_4, and concentrated in vacuo. ^{1}H NMR ($CDCl_3$): δ = 1.31 (s) ppm (ref.[10] δ = 1.05 ppm in CCl_4). ^{13}C NMR ($CDCl_3$): δ = 30.12 (qsept, ^1J = 127.0, ^3J = 4.7 Hz, 2× C*Me*$_3$), 45.15 (m, ^2J = 3.7 Hz, 2× *C*Me$_3$), 99.12 (m, C-2), 174.75 (s, C=O) ppm, in rough accord with ref.[10] IR (film): $\tilde{\nu}$ = 1780 cm^{-1} (C=O; ref.[10] 1765 cm^{-1} in CCl_4).

2,2-Di-*tert*-butyl-3-chlorooxirane (18): A two-necked flask (500 mL) was fitted with an internal thermometer, a magnetic stirring bar, and a large pressure-equalizing addition funnel with an argon bubbler. The flask was loaded with dry THF (70 mL), di-*tert*-butyl ketone (**1**, 17.06 g, 120.0 mmol),[3] and dry dichloromethane (23.16 mL, 30.69 g, 361.4 mmol) and was then cooled with stirring at –70 °C. A solution of LDA (241 mmol), prepared by addition of *n*BuLi (103 mL in hexanes, 240 mmol) to diisopropylamine (241 mmol) in dry THF (70 mL) at 3 °C, was added (not vice versa!) dropwise with stirring from the addition funnel at such a rate that the internal temperature remained below –50 °C (60 min). After another 15 min, the cooling bath may be replaced by an ice

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bath, whereupon the orange reaction mixture will turn into a black suspension. The mixture was quenched by pouring it into a separating funnel (1 L) containing ice-cold aqueous HCl (2 M, 300 mL). After extraction with Et_2O (4× 100 mL), the combined Et_2O extracts were washed until neutral and dried with Na_2SO_4. The Et_2O was removed in a rotary evaporator at room temp. under 40 mbar to leave pure **18** (22.59 g, 99%) as a brown liquid. This rather volatile material should not be distilled but should be stored at –18 °C in order to avoid its conversion into **19** and **27**. Purification is unnecessary for the subsequent transformations but may be performed by a trap-to-trap distillation at 30 °C (bath temp.)/0.02 mbar into a receiving trap cooled to –70 °C, providing **18** as a viscous, colorless liquid. ^{1}H NMR (CCl_4 or $CDCl_3$): δ = 1.08 and 1.28 (2× s, 2×C*Me*$_3$), 5.22 (s, 3-H) ppm. ^{13}C NMR (CCl_4/[D_{12}]-cyclohexane, 10:1): δ = 28.4 and 30.2 (2× qsept, ^1J = 126, ^3J = 4.9 Hz, 2×C*Me*$_3$), 36.7 (m, ^2J = 3.8 Hz, *C*Me$_3$ *cis* to Cl?), 37.4 (br m, ^2J = 3.7 Hz, *C*Me$_3$ *trans* to Cl?), 70.1 (m, apparent $J \approx 4$ Hz, C-2), 72.7 (d, ^1J = 215.2 Hz, C-3) ppm. IR (film): $\tilde{\nu}$ = 2971, 2930, 1490 (s), 1394 (s), 1370 (s), 1343, 982, 951, 841, 789, 767 cm^{-1}. $C_{10}H_{19}ClO$ (190.7): calcd. C 62.98, H 10.04; found C 63.52, H 10.02.

2-*tert*-Butyl-2-chloro-3,3-dimethylbutanal (19): The chlorooxirane **18** (9.536 g, 50.00 mmol) in dry toluene (75 mL) was heated under a double-walled reflux condenser with drying tube at 110 °C for 45 min. Concentration in a rotary evaporator down to a final pressure of 8 mbar at 60 °C afforded partially solidifying, brownish **19** (8.90 g, 93%) containing a trace of toluene. A sample distilling at 88–92 °C/15 Torr (ref.[10] b.p. 85 °C/12 Torr) with vigorous foaming furnished waxy, block-shaped crystals with m.p. 81–84 °C (ref.[10] 83–85 °C). Because of its volatility, **19** should not be stored in an evacuated desiccator. ^{1}H NMR ($CDCl_3$): δ = 1.25 (s, 18 H), 9.83 (s, CHO) ppm.[35] ^{13}C NMR ($CDCl_3$): δ = 29.67 (2×C*Me*$_3$), 42.32 (2×*C*Me$_3$), 93.20 (*C*-Cl), 200.71 (*C*H=O) ppm, in rough accord with ref.[10] IR (film): $\tilde{\nu}$ = 1732 cm^{-1}. A sample of **19** in [D_6]DMSO solution remained unchanged over at least 8 h at 148 °C. A less pure sample (obtained from 47.2 mmol of **18**) was adsorbed on a column of silica gel (90 g, 60 Å, ICN 63–200) and eluted with low-boiling petroleum ether (PE) containing Et_2O (2%). After a forerun of 150 mL, the next 250 mL of eluent furnished pure **19** (6.01 g, 67%), followed by the elimination product **27**.

4,4-Di-*tert*-butyl-2-(1-*tert*-butyl-2,2-dimethyl-1-propylidene)oxetan-3-one (25): Di-*tert*-butyl ketone (**1**, 2.00 g, 14.1 mmol) and CH_2Cl_2 (0.920 mL, 14.4 mmol) were dissolved in dry THF (8 mL) and cooled to –70 °C with stirring. A solution of LDA (56.2 mmol) in dry THF (16 mL) and hexanes (ca. 15 mL) was added dropwise over 15 min. After further stirring without cooling until the internal temperature reached 0 °C (<4 h), the mixture had become orange-colored and was poured into aqueous HCl (2 M, 80 mL) and then extracted with Et_2O (3× 25 mL). The combined extracts were washed with distilled water until neutral, dried with Na_2SO_4, and concentrated in vacuo, providing **25** as an almost pure yellow solid (2.32 g) that was recrystallized from pentane at –20 °C to afford colorless crystals of pure **25** (yield 89%) with m.p. 45.5–47 °C (ref.[18] 46–47 °C). ^{1}H NMR ($CDCl_3$): δ = 1.14 (s, 2×4-C*Me*$_3$), 1.30 and 1.40 (2× s, 2×1′-C*Me*$_3$) ppm. ^{13}C NMR ($CDCl_3$): δ = 28.3 (qsept, ^1J = 125.9, ^3J = 4.9 Hz, 2×4-C*Me*$_3$), 31.0 and 32.5 (2× qsept, ^1J = 126.2, ^3J = 4.9 Hz, 2×1′-C*Me*$_3$), 37.22 and 38.44 (2× m, ^2J = 3.7 Hz, 2×1′-*C*Me$_3$), 38.37 (m, ^2J = 3.8 Hz, 2×4-*C*Me$_3$), 109.1 (m, $^3J \approx$ 3.7 Hz, C-4), 136.5 (m, $^3J \approx$ 3.6 Hz, olefinic C-1′), 161.2 (s, C-2), 193.2 (s, C-3) ppm. IR (KBr): $\tilde{\nu}$ = 1780 (C=O), 1562 (w), 1481, 1390, 1363, 1224, 1028, 963, 934 cm^{-1}. This ketene "dimer" **25** may also be obtained from the chlorooxirane **18** with LiTMP under similar conditions (yield 93% after recrystallization).

2-*tert*-Butyl-2,3-dimethylbut-3-enal (27): This compound was obtained along with **19**, b.p. 77–108 °C (bath temp.)/4 mbar (ref.[10] 60–65 °C/12 Torr). ^{1}H NMR ($CDCl_3$): δ = 1.03 (s, 2-C*Me*$_3$), 1.16 (s, 2-CH$_3$), 1.84 (dd, $|^4J|$ = 1.43 and 0.68 Hz, 3-CH$_3$), 4.74 (dq, $^2J \approx 0.8$, $|^4J|$ = 0.68 Hz, 4-H *trans* to 3-CH$_3$), 5.16 (dq, $^2J \approx 0.8$, $|^4J|$ = 1.43 Hz, 4-H *cis* to 3-CH$_3$), 9.80 (s, CH=O) ppm, assigned through comparison with ^4J(*trans*) = –0.6 Hz and ^4J(*cis*) = –1.5 Hz of 2,3,3-trimethylbut-1-ene.[61] ^{13}C NMR ($CDCl_3$): δ = 15.3 (2-CH$_3$), 23.4 (3-CH$_3$), 26.8 (2-C*Me*$_3$), 35.8 (2-*C*Me$_3$), 58.3 (C-2), 116.4 (CH$_2$-4), 144.4 (C-3), 204.6 (C-1) ppm, assigned through HSQC of the proton-bearing ^{13}C nuclei and comparisons of *C*Me$_3$ and C-2 with those[21] of **30**. FT-IR (film on diamond, ATR): $\tilde{\nu}$ = 2959, 1722, 1368 cm^{-1}.

3-*tert*-Butyl-4,4-dimethylpent-2-enoic Acid (28): The acid fraction of the photolysis products of the oxetanone **25** was filtered through silica gel (60 Å, 171 mg) with light PE and then crystallized from pentane at –18 °C to give colorless blocklets (21 mg, ~1%) with m.p. 98–99 °C. ^{1}H NMR ($CDCl_3$): δ = 1.25 and 1.38 (2× s, 2×C*Me*$_3$), 5.84 (s, 2-H), 10.8 (br, CO_2H) ppm. ^{13}C NMR ($CDCl_3$): δ = 31.63 and 32.34 (2×C*Me*$_3$), 38.60 (br, 1×*C*Me$_3$), 39.45 (1×*C*Me$_3$), 115.57 (C-2), 166.76 (C-3), 174.78 (br, CO_2H) ppm. FT-IR (diamond, ATR): $\tilde{\nu}$ = 3200–2400 (br, O–H), 1688 (s), 1615, 1254 (s) cm^{-1}. $C_{11}H_{20}O_2$ (184.28): calcd. C 71.70, H 10.94; found C 71.44, H 11.06.

4-*tert*-Butyl-2-[(*Z*)-2′,2′-dimethyl-1′-propylidene]-4,5,5-trimethyltetrahydrofuran-3-one (29): The oxetanone **25** (700 mg, 2.27 mmol) was heated overnight at 80 °C in a mixture of glacial acetic acid (14 mL) and concentrated HCl (1.4 mL). The resulting mixture was poured into distilled water (50 mL) and extracted with Et_2O (4× 15 mL). The combined extracts were shaken with NaOH (2 M, 3×), washed with water until neutral, dried with Na_2SO_4, and concentrated to yield **29** as a brownish liquid (469 mg, 82%) that solidified slowly (m.p. 31–37 °C). Colorless platelets of analytically pure **29** were obtained from a pentane solution at –70 °C. M.p. 47–48 °C, b.p. 150–170 °C (bath temp.)/12 mbar. ^{1}H NMR ($CDCl_3$): δ = 1.055 (s, 4-CH$_3$), 1.060 (s, 4-C*Me*$_3$), 1.143 (s, 1′-C*Me*$_3$), 1.250 (s, 5-CH$_3$ *trans* to 4-CMe$_3$), 1.512 (s, 5-CH$_3$ *cis* to 4-CMe$_3$), 5.442 (s, 1′-H) ppm, assigned through the NOESY correlations 1′-H ↔ 1′-C*Me*$_3$ and 4-C*Me*$_3$ ↔ *cis*-5-CH$_3$ ↔ *trans*-5-CH$_3$ ↔ 4-CH$_3$. ^{13}C NMR ($CDCl_3$): δ = 16.1 (sharp q, ^1J = 128.6 Hz, 4-CH$_3$), 25.7 (qq, ^1J = 127.0, ^3J = 4.2 Hz, 5-CH$_3$ *cis* to 4-C*Me*$_3$), 27.1 (qq, ^1J = 126.7, ^3J = 4.2 Hz, 5-CH$_3$ *trans* to 4-C*Me*$_3$), 27.6 (br qm, ^1J = 126, $^3J \approx$ 4.8 Hz, 4-C*Me*$_3$), 29.5 (sharp qdm, ^1J = 126.3, ^3J = 3.4, ^3J = 4.8 Hz, 1′-C*Me*$_3$), 31.21 (dm, ^2J = 1.6, ^2J = 4.0 Hz, 1′-*C*Me$_3$), 35.3 (m, apparent J = 3.7 Hz, 4-*C*Me$_3$), 57.2 (septm, ^3J = 2.4 Hz to both 5-CH$_3$ groups, C-4), 86.9 (m, apparent J = 4.1 Hz, C-5), 116.7 (dm, ^1J = 156.6, ^3J = 4.5 Hz, C-1′), 146.2 (sharp d, ^2J = 4.4 Hz, C-2), 205.7 (dq, ^3J = 3.3, ^3J = 3.8 Hz, C-3) ppm, assigned in the following manner. The olefinic carbon nuclei C-1′ and C-2 were recognized through their coupling patterns as given above. The only CH$_3$ group showing a sharp ^1J quartet (no ^3J coupling) must be 4-CH$_3$. The other methyl groups were unambiguously assigned through selective {^{1}H} decoupling experiments, which also provided the above ^2J and ^3J values as follows: {1′-H} → 1′-C(*C*H$_3$)$_3$ simplified to a quartet (^1J) of septets with $^3J \approx$ 4.8 Hz, 1′-*C*Me$_3$ as a sharpened m with ^2J = 4.0 Hz, C-2 as a sharp s, and C-3 as a sharp q with ^3J = 3.8 Hz; {*cis*-5-CH$_3$} → C-5 simplified, *trans*-5-*C*H$_3$ as a sharp ^1J q (^3J removed); {*trans*-5-CH$_3$} → C-5 simplified, *cis*-5-*C*H$_3$ as a phase-distorted yet sharp ^1J q (^3J removed); {1′-C(C*H*$_3$)$_3$} → C-1′ simplified to a sharp ^1J d, 1′-*C*Me$_3$ to a d with ^2J = 1.6 Hz, and 1′-C(*C*H$_3$)$_3$ to a d with ^3J = 3.4 Hz; {4-C(C*H*$_3$)$_3$} → 4-*C*(CH$_3$)$_3$ as a sharp s, C-3 as a sharp d with ^3J = 3.3 Hz (hence *cis* to 1′-H), C-4 as a clear septet with ^3J = 2.4 Hz, and C-5 simplified. IR (KBr): $\tilde{\nu}$

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= 2959 (s), 1732 (s), 1655, 1478, 1376, 1340, 1271 (s), 1096, 862 cm^{-1}. $C_{16}H_{28}O_2$ (252.40): calcd. C 76.14, H 11.18; found C 76.35, H 11.49. The unequivocal assignments shown above allow a straightforward interpretation of the NMR spectroscopic data (Table S1 in the Supporting Information) at low temperatures in terms of an impeded rotation of 4-*t*Bu. The decoalesced signals (^1H, ^{13}C) of 4-*t*Bu remained sharp down to –97 °C, whereas the ^{13}C signals (100.6 MHz) of 4-CH_3, *cis*-5-CH_3, and *trans*-5-CH_3 started broadening (Table S1 in the Supporting Information), possibly because of a decelerating ring inversion.

2,2,5,5-Tetramethyl-4-oxo-3-hexyl 2′-*tert*-Butyl-3′,3′-dimethylbutanoate (36)

(a) From 19: The α-chloro aldehyde **19** (381 mg, 2.00 mmol) was dissolved in dry DMSO (2.0 mL) and stirred magnetically with pulverized KOH (303 mg, 5.41 mmol) at room temp. in a tightly closed round-bottomed flask (10 mL). After 6 h, **19** had been transformed into a mixture (ca. 2:1) of ketene **14** and pivaloin (**38**). When **38** had disappeared after another 4 d at 20 °C (or after <4 d at 60 °C), the contents were dissolved in Et_2O/H_2O. The Et_2O layer was washed until neutral, dried with Na_2SO_4 for ca. 1 h, and concentrated under moderately reduced pressure to furnish the ester **36** along with residual ketene **14** (IR: $\tilde{\nu}$ = 2086 cm^{-1}). The Et_2O extract of the acidified aqueous layer provided mainly the acid **11** (30 mg). The pure ester **36** (171 mg, 26%) distilled at 137–145 °C (bath temp.)/4 mbar, and a second distillation afforded the analytical sample (133 mg). ^1H NMR (CD_2Cl_2): δ = 1.01 (s, 3 CH_3-1), 1.04 (br s, first 3 CH_3-4′), 1.08 (sharp s, second 3 CH_3-4′), 1.24 (sharp s, 3 CH_3-6), 2.22 (s, 2′-H), 5.11 (s, 3-H) ppm, assigned through HMBC correlations (see below) consistent with the δ_H values of pivaloin (**38**). ^1H NMR ($CDCl_3$): δ = 1.02, 1.06, 1.09, 1.26, 2.22, 5.12 ppm. ^1H NMR (400 MHz, Cl_2CD–$CDCl_2$ at +80 °C): δ = 1.01, 1.05, 1.08, 1.23, 2.21, 5.13 ppm. ^{13}C NMR (CD_2Cl_2): δ = 26.86 (3 CH_3-1), 28.05 (3 CH_3-6), 30.93 (all 6 CH_3-4′), 34.22 (C-2), 35.29 (sharp, first C-3′), 35.63 (br, second C-3′), 44.44 (C-5), 64.3 (very br, C-2′), 78.03 (br, C-3), 174.53 (C-1′), 215.40 (C-4) ppm, assigned through HSQC ($^1J_{C,H}$) cross peaks in combination with the following HMBC correlations: for $^3J_{C,H}$, 3-H → *C*H_3-1 → C*H*$_3$-1 → C-3, 2′-H → all 6 *C*H_3-4′ → all 6 C*H*$_3$-4′ → C-2′, and C*H*$_3$-6 → *C*H_3-6; for $^2J_{C,H}$, C*H*$_3$-1 → C-2, C*H*$_3$-6 → C-5, 2′-H → the sharper C-3′ → the sharper C*H*$_3$-4′, and the broader C*H*$_3$-4′ → the broader C-3′. ^{13}C NMR ($CDCl_3$): δ = 26.73, 27.89, 30.76 + 30.78 (3 + 3 *C*H_3-4′), 33.96, 35.00, ca. 35.31 (very br), 44.20, ca. 64.0 (very br), ca. 77.6 (very br, hidden), 174.27, 215.32 ppm. The three conspicuously broadened resonances of C-3, C-2′, and one of the two C-3′ indicate the freezing of some conformational motions (as also observed with **41**); accordingly, these lines became narrowed to normal linewidths at +80 °C. ^{13}C NMR (100.6 MHz, Cl_2CD–$CDCl_2$ at +80 °C): δ = 26.78, 27.86, 30.80 (all 6 CH_3-4′), 33.91, 34.88, 35.15 (sharp), 44.14, 64.34 (sharp), 77.50 (sharp), 173.89, 214.81 ppm. FT-IR (film on diamond, ATR): $\tilde{\nu}$ = 2959 (s), 2909, 2874, 1724 (s), 1705 (stronger), 1481, 1368, 1229, 1135 (s), 988 cm^{-1}. $C_{20}H_{38}O_3$ (326.52): calcd. C 73.57, H 11.73; found C 73.10, H 11.84.

(b) Independent Synthesis of 36 from Pivaloin (38): An NMR tube (5 mm) was charged with pivaloin[62] (64 mg, 0.37 mmol), pyridine (0.050 mL, 0.62 mmol), [D_{12}]cyclohexane (0.030 mL), and a solution of the acyl chloride **13** (83 mg, 0.44 mmol) in dry diglyme (0.65 mL). The ^1H NMR spectra displayed the formation of ketene **14** (δ = 1.20 ppm, up to 0.12 equiv.) over 60 min at room temp. Within 40 min at 150 °C, **13** and **38** disappeared almost completely (and **14** completely), while the esters **36** and **41** were formed in a 87:13 ratio (further 2 h at 150 °C) that did not change upon isolation (97 mg) and distillation (140–150 °C bath temp./4 mbar) of the non-acidic product fraction. A corresponding run with the ketene **14** (employed in place of **13** and pyridine) at 150 °C required 21 h for the complete consumption of **14** and partial (60%) conversion of pivaloin (**38**) to the product ester **36**, whereas traces of the ester **41** (from diglyme) appeared only after much longer periods of time.

2,2,5,5-Tetramethyl-4-oxo-3-hexyl 2′-*tert*-Butyl-2′-deuterio-3′,3′-dimethylbutanoate (37): Pulverized KOH (225 mg, 4.02 mmol) was added to an NMR tube containing the α-chloro aldehyde **19** (94 mg, 0.49 mmol) in [D_6]DMSO (0.80 mL). As described above for **36**, the black suspension produced the ketene **14** and a transient amount of pivaloin (**38**) at 20 °C during 57 h. After 87 h at 60 °C, the mixture was worked up as above to yield the acid [α-D]**11** (14 mg, 16%) and the dideuteriated ester [3,2′-D_2]**36** (36 mg, 22%). Isotope-modified NMR spectroscopic data[63] for [3,2′-D_2]**36** in CD_2Cl_2: δ_H = 2.22 (11% of 2′-H), 5.10 (14% of 3-H) ppm; δ_C = 34.12 (C-2, 82% D with $^2\Delta$ = –0.091 ppm), 35.19 (first C-3′, 86% D with $^2\Delta$ = –0.089 ppm), 35.53 ppm (the broader second C-3′ with $^2\Delta \approx$ –0.089 ppm). Isotope-modified NMR spectroscopic data[63] for [α-D]**11** in $CDCl_3$: δ_H = 2.20 (ca. 12% of 2-H) ppm; δ_C = 63.97 ppm (C-2, ca. 87% D with $^1\Delta$ = –0.493 ppm and $^1J_{C,D}$ = 19.3 Hz). This sample of ester [3,2′-D_2]**36** (0.11 mmol) was heated in an NMR tube with KOH (106 mg, 1.89 mmol) in unlabeled DMSO (0.7 mL) and [D_{12}]cyclohexane (0.03 mL) at 95 °C for 8 h. The workup procedure described above for **36** provided the monodeuteriated ester **37** (24 mg, 67%) and the acid [α-D]**11** (5 mg, 26%, formed through hydrolytic cleavage of **37**). Isotope-modified NMR spectroscopic data[63] for **37** in CD_2Cl_2: δ_H = 2.22 (16% of 2′-H), 5.12 (96% of 3-H) ppm; δ_C = 35.20 (C-3′, 81% D with $^2\Delta$ = –0.090 ppm). Isotope-modified NMR spectroscopic data[63] for [α-D]**11** in $CDCl_3$: δ_H = 2.21 (ca. 14% of 2-H) ppm.

Lithium 2-*tert*-Butyl-3,3-dimethylbutanoate (39): Elemental lithium (5.90 mg, 0.85 mmol) was dissolved in methanol (1.0 mL) in a small round-bottomed flask (10 mL). The acid **11** (148 mg, 0.85 mmol) was added, and the mixture was slowly concentrated in a rotary evaporator to avoid splashing of the suddenly crystallizing product. After 4 d under 4 mbar close to KOH and P_4O_{10}, the sample weighed 155 mg ("102%"). ^1H NMR (diglyme): δ = 1.10 (s, 6 × CH_3), 2.06 (s, 2-H) ppm.[35]

2-*tert*-Butyl-3,3-dimethylbutanoic Anhydride (40): A solution of the acyl chloride **13** (0.80 mmol), prepared as above from **11** (138 mg) and dissolved in dry toluene (0.90 mL), was added to a round-bottomed flask (10 mL) containing the dried lithium salt **39** (0.85 mmol, obtained above). The flask was stoppered tightly and heated at 95 °C until the last traces of **13** had been consumed (2–3.5 h). The mixture was dissolved in Et_2O and distilled water and was then extracted with NaOH (2 M, 2 ×). The combined two NaOH extracts were shaken with Et_2O, which was combined with the first Et_2O layer, washed until neutral, dried with Na_2SO_4, concentrated to dryness, and dried further in vacuo to afford the almost pure anhydride **40** (176 mg, 67%). The acid **11** (36 mg, 13%) was isolated as a byproduct from the acidified NaOH layer. Analytically pure anhydride **40** distilled at 146–153 °C (bath temp.)/4 mbar, yielding colorless, bunchy fibers (109 mg, 42%) with m.p. 69–70.5 °C (ref.[33] 72–74 °C), mixed m.p. with the acid **11** 43–69 °C. ^1H NMR ($CDCl_3$ at 27 °C): δ = 1.15 (s, 36 H), 2.16 (s, 2 × 2-H) ppm.[35] ^{13}C NMR ($CDCl_3$ at 27 °C): δ = 30.66 (4 × C*Me*$_3$), 35.75 (br, 4 × *C*Me$_3$), 65.26 (very br, 2 × C-2), 169.72 (2 × C-1) ppm; the two broadened resonances indicate the beginning of some conformational freezing (compare **41**). FT-IR (powder on diamond, ATR): $\tilde{\nu}$ = 3006, 2955 (s), 2912, 1797 (s), 1728 (w), 1366, 1003 (s), 941 cm^{-1}. FT-IR (film on diamond, ATR): $\tilde{\nu}$ = 1805, 1733

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(weaker), 1371, 1002, 915 cm^{-1}. $C_{20}H_{38}O_3$ (326.52): calcd. C 73.57, H 11.73; found C 73.28, H 11.93. The anhydride **40** was formed much more slowly from ketene **14** with the acid **11** in hot diglyme (2 h at 150 °C) in the absence of bases.

3,6-Dioxaheptyl 2′-*tert*-Butyl-3′,3′-dimethylbutanoate (41): The acyl chloride **13** (305 mg, 1.60 mmol), dry diglyme (1.0 mL), and pyridine (0.160 mL, 2.00 mmol) were heated to 150 °C in a tightly stoppered flask. The first trace of the product **41** was observed after 5 h, along with residual **13** and substantial portions of the ketene **14** and the anhydride **40** (δ_H = 1.08, 1.16, 1.20, and 1.14 ppm, respectively). After 86 h at 150 °C, the cooled mixture was diluted with Et_2O and HCl (2 M) and filtered to remove insoluble resins. The Et_2O layer was extracted with NaOH [2 M, for separation from the pure acid **11** (23 mg, 8%)] and was then washed with distilled water until neutral, dried with Na_2SO_4, and concentrated to give a mixture of **41** (206 mg, 47%) with the anhydride **40** (54 mg, 21%). A small sample of this mixture did not react with NaOH (2 M, 10 equiv.) in [D_8]dioxan at 85 °C (3 d) and 95 °C (6 h), so **40** could not be separated from **41** through differential hydrolysis. The mixture was distilled at 132–151 °C (bath temp.)/6 mbar and then adsorbed on silica gel (4 g) and eluted with PE/Et_2O (98:2) to yield pure **40**, followed by contaminants. Further elution with PE/Et_2O (9:1, 80 mL) provided pure **41** as a colorless oil (101 mg, 23%). ^1H NMR ($CDCl_3$): δ = 1.09 (s, 6 × CH_3), 2.23 (s, 2′-H), 3.38 (s, OCH_3), 3.54 (m, CH_2-5), 3.63 (m, CH_2-4), 3.70 (m, CH_2-2), 4.21 (m, CH_2-1) ppm, assigned through the NOESY correlations C(CH_3)$_3$ ↔ 2′-H, and OCH_3 ↔ CH_2-5 ↔ CH_2-4 ↔ CH_2-2 ↔ CH_2-1. ^{13}C NMR ($CDCl_3$): δ = 30.72 (2 × CMe_3), 34.86 (2 × *C*Me$_3$), 59.05 (OCH_3), 62.19 (CH_2-1), 64.44 (br, CH-2′), 69.24 (CH_2-2), 70.34 (CH_2-4), 71.94 (CH_2-5), 174.54 (OCO) ppm, assigned through $^1H/^{13}C$ cross peaks in an HSQC ($^1J_{C,H}$) spectrum and in an HMBC spectrum that displayed the $^3J_{C,H}$ interactions C(CH_3)$_3$ ↔ *C*H-2′, C(*C*H$_3$)$_3$ ↔ 2′-H, OCH_3 ↔ *C*H$_2$-5, O*C*H$_3$ ↔ CH_2-5, CH_2-4 ↔ *C*H$_2$-2, *C*H$_2$-4 ↔ CH_2-2, and CH_2-1 ↔ O*C*O, in addition to the $^2J_{C,H}$ correlations 2′-H ↔ *C*Me$_3$, CH_2-5 ↔ *C*H$_2$-4, *C*H$_2$-5 ↔ CH_2-4, CH_2-2 ↔ *C*H$_2$-1, and *C*H$_2$-2 ↔ CH_2-1. The broad *C*H-2′ resonance indicates the freezing of a conformational process that was confirmed through low-temperature ^{13}C NMR spectroscopy. The first decoalescence at –15 °C gave rise to a signal pair with $\Delta\delta_C$ = 3.63 ppm in an intensity ratio of 13:87 that was also shown by all other pairs of carbon nuclei below –45 °C (but *C*H$_2$-2 and the O*C*H$_3$ group did not split). ^{13}C NMR ($CDCl_3$, 100.6 MHz, –55 °C) for the 13/87 signal pairs: δ = 30.75/30.45 (C*Me*$_3$), 34.07/34.87 (*C*Me$_3$), 62.54/61.83 (CH_2-1), 66.70/63.07 (CH-2′), 69.99/70.12 (CH_2-4), 71.61/71.48 (CH_2-5), 174.92/174.70 (OCO). There were therefore only two significantly populated conformers, but their detailed structures remained unknown. FT-IR of **41** (film on diamond, ATR): $\tilde{\nu}$ = 2957, 2908, 2874, 1727 (s), 1370, 1123 (s), 1054 cm^{-1}. $C_{15}H_{30}O_4$ (274.40): calcd. C 65.66, H 11.02; found C 65.70, H 10.73.

2-*tert*-Butyl-3,3-dimethyl-1-(trimethylsilyloxy)but-1-ene (46): A mixture of the α-chloro aldehyde **19** (2.86 g, 15.0 mmol) and dry THF (2.0 mL) was added slowly with magnetic stirring to cold THF (25 mL) that contained $ClSiMe_3$ (2.85 mL, 22.5 mmol) and elemental lithium (312 mg, 45 mmol). Without further cooling, the internal temperature rose to 33 °C within 60 min, whereupon LiCl precipitated. After further stirring for 2.5 h, triethylamine (4.15 mL, 30.0 mmol) was added at once. The suspension was filtered from residual lithium through a glasswool plug that was rinsed with Et_2O (100 mL). This THF/Et_2O solution was washed with distilled water (not more than 3 × 25 mL), dried with Na_2SO_4, and concentrated in a rotary evaporator down to 70 mbar, yielding the intact enol ether **46** (4.00 g, no aldehyde **8**) along with residual NEt_3 and THF. Almost pure **46** (2.18 g, 64%) was obtained through fractional distillation at 91–113 °C/48 mbar. The analytical sample was prepared through chromatography on a cold column (diameter 15 mm, 25 g of silica gel, with pure low-boiling PE) with 95% recovery and a second distillation at 120–125 °C (bath temp.)/58 mbar. ^1H NMR ($CDCl_3$): δ = 0.18 (s, $OSiMe_3$), 1.15 (s, CMe_3 *anti* to $OSiMe_3$), 1.28 (s, *syn*-CMe_3), 6.16 (s, 1-H) ppm. ^1H NMR ([D_6]benzene): δ = 0.10, 1.21, 1.51, 6.33, assigned through the $^3J_{C,H}$ values for 1-H (see below) ppm. ^{13}C NMR ([D_6]benzene): δ = 0.00 (qsept, ^1J = 118.6, ^3J = 1.5 Hz, $SiMe_3$), 32.54 (qm, ^1J = 125.5, ^3J = 5.1 Hz, *syn*-CMe_3), 32.74 (qm, ^1J = 125.5, ^3J = 5.0 Hz, *anti*-CMe_3), 36.55 (dm, ^3J = 3.4, ^2J = 3.7 Hz, *anti*-*C*Me$_3$), 36.83 (dm, ^3J = 6.5, ^2J = 3.9 Hz, *syn*-*C*Me$_3$), 134.94 (dm, $^2J \approx$ 8.2 Hz, C-2), 135.70 (sharp d, ^1J = 175.4 Hz, C-1) ppm, assigned through selective {^1H} decoupling experiments as follows: {*anti*-C(CH_3)$_3$} → *anti*-C(*C*H$_3$)$_3$ decoupled and *anti*-*C*Me$_3$ as a d with ^3J = 3.4 Hz to 1-H; {*syn*-C(CH_3)$_3$} → *syn*-C(*C*H$_3$)$_3$ decoupled and *syn*-*C*Me$_3$ as a d with ^3J = 6.5 Hz to 1-H; {*anti*- and *syn*-C(CH_3)$_3$} → C-2 as a d with $^2J \approx$ 8.2 Hz. IR (film): $\tilde{\nu}$ = 2956, 2915, 1618, 1254, 1135 (s), 879 (s), 844 cm^{-1}. $C_{13}H_{28}OSi$ (228.46): calcd. C 68.35, H 12.35; found C 68.34, H 12.28.

3,6-Di-*tert*-butyl-2,2,7,7-tetramethyloct-4-ene-3,6-diol (49): A round-bottomed Schlenk flask (100 mL), fitted with a reflux condenser with drying tube, was charged with granulated elemental lithium (278 mg, 40.0 mmol), dry THF (20 mL), and a magnetic stirring bar. An ice bath was employed to mitigate the moderately exothermic reaction caused by the slow addition of chlorooxirane **18** (1.907 g, 10.0 mmol) to the stirred mixture. After 2 d of continued stirring without cooling, the solution was poured into ice-cold water (100 mL) through a plug of glass wool, which retained residual lithium metal (ca. 50%), and was rinsed with Et_2O. The aqueous layer was extracted with more Et_2O (3 × 50 mL) and then discarded. The combined THF/Et_2O layers were washed until neutral, dried with Na_2SO_4, and concentrated to furnish only the crude diol **49** (1.55 g, <99%). The colorless needles of pure **49** had a m.p. of 151.5–152 °C (from pentane at –30 °C). ^1H NMR ($CDCl_3$): δ = 1.07 (s, 12 × CH_3, ^{13}C satellites forming a d with $^1J_{C,H}$ = 125.2 Hz), 1.42 (s, 2 × OH), 5.89 (s, olefinic 4- and 5-H, ^{13}C satellites appearing as the dd of the A part of an ABX system with $^1J_{AX} = {}^1J_{H,C}$ = 152.0 and $^3J_{AB} = {}^3J_{H,H}$ = 15.7 Hz) ppm. ^{13}C NMR ($CDCl_3$): δ = 29.08 (qsept, ^1J = 125.2, ^3J = 5.0 Hz, 12 × CH_3), 41.00 (m, ^2J = 3.4 Hz, 4 × *C*Me$_3$), 82.10 (unresolved, C-3/-6), 130.39 (ddd, ^1J = 152, apparent $^2J \approx$ 4.4, $^3J \approx$ 2 Hz, C-4/-5) ppm, assigned through selective {^1H} decoupling experiments as follows: {C(CH_3)$_3$ and OH} → *C*Me$_3$ as a s, C-3/-6 as a t with apparent J = 5.3 Hz, and C-4/-5 as an apparent dd (X-part of ABX) with $|^1J + {}^2J|$ = 155.9 Hz. IR (KBr): $\tilde{\nu}$ = 3604 (sharp O–H), 2961, 2920, 1483, 1393, 1367, 923 cm^{-1}. $C_{20}H_{40}O_2$ (312.54): calcd. C 76.86, H 12.90; found C 77.02, H 12.82.

2-*tert*-Butyl-2-chloro-3,3-dimethylbutan-1-ol (55): An NMR tube (5 mm) was charged with the α-chloro aldehyde **19** (133 mg, 0.70 mmol), dry diglyme (0.7 mL), [D_{12}]cyclohexane (0.030 mL), TMS, and $NaBH_4$ (49 mg, 1.30 mmol). ^1H NMR spectra showed the presence of dissolved $NaBH_4$ (δ_H = –0.49 ppm) and revealed the conversion of **19** (δ_H = 1.23 and 9.82) into the hydridoborate **54** (δ_H = 1.29 ppm) to be complete after 4.5 h at 20 °C, at which point a trace of aldehyde **8** was already detectable. Without delay, the contents were poured into a separating funnel that contained ice and enough HCl (2 M) to destroy the residual hydrides (moderate foaming by H_2 formation!). The mixture was extracted with Et_2O (2 × 10 mL), and the combined extracts were washed with HCl (2 M, 2 ×), NaOH (2 M, 1 ×), and distilled water until neutral. After drying with Na_2SO_4 for not more than 1 h, the filtered Et_2O

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solution was concentrated in a rotary evaporator at ≤50 °C and kept in a desiccator at 3 mbar for 30 min to furnish crude **55** (105 mg, <97%), which was stored at –18 °C. Most of the contaminants were removed by two successive filtrations through silica gel (60 Å, 200 mg and then 435 mg) with low-boiling PE as the eluent (50 mL in each filtration). The eluted material was dried at 3 mbar for 20 min, furnishing **55** as a waxy, not completely pure product (79 mg, 58%). ^{1}H NMR ($CDCl_3$): δ = 1.25 (s, 6 × CH_3), 2.01 (br s, OH), 3.93 (s, CH_2O) ppm. ^{13}C NMR ($CDCl_3$): δ = 30.3 (qsept, ^1J = 126.6, ^3J = 4.9 Hz, 6 CH_3), 42.8 (oct, apparent J = 3.4 Hz, 2 × C-3), 65.3 (sharp t, ^1J = 145.2 Hz, CH_2OH), 91.4 (m, C-2) ppm. FT-IR (film on diamond, ATR): $\tilde{\nu}$ = 3439 (br O–H), 2964 (s), 1395, 1369 cm^{-1}. Because of its ready transformation into **8**, this chlorohydrin (**55**) could neither be recrystallized nor distilled for characterization by elemental analyses or mass spectrometry.

2-Chloro-3,3-dimethylbutanal (63): Distilled at 50–60 °C (bath temp.)/100 Torr (ref.[46] 38 °C/12 Torr). ^{1}H NMR ($CDCl_3$): δ = 1.09 (s, 3 × CH_3), 3.78 and 9.39 (AB system with ^3J = 4.5 Hz) ppm.

1-Bromo-3,3-dimethylbut-1-ene (65 and 66): The reaction between the aldehyde **8** (50 mg, 0.32 mmol) and 2,2,2-tribromo-2,2-dihydrobenzo-1,3,2-dioxaphosphole (**64**, 1.60 mmol)[48] in 1,2-dichloroethane (0.5 mL) was complete within <5 min at room temp., as shown by in situ ^{1}H NMR spectroscopy, which also revealed the formation of *t*BuBr (δ_H = 1.78 ppm) and exclusively the (*Z*) isomer **65**. ^{1}H NMR ($ClCH_2CH_2Cl$): δ = 1.24 (s, 3 × CH_3), 6.02 and 6.16 (AB system with ^3J = 8 Hz, 1-/2-H) ppm.[49] After 23 d at room temp., **65** had been transformed entirely into the (*E*) isomer **66**. ^{1}H NMR ($ClCH_2CH_2Cl$): δ = 1.03 (s, 3 × CH_3), 6.00 and 6.25 (AB system with ^3J = 14 Hz, 1-/2-H) ppm.[49]

2-*tert*-Butyl-3,3-dimethylbutanal Oxime (67)

(a) From 46: A solution of hydroxylammonium chloride (417 mg, 6.00 mmol) and sodium acetate (492 mg, 6.00 mmol) in ethanol (4.83 mL) and distilled water (1.57 mL) was degassed by ultrasonification under argon gas for 15 min. After addition of the Si enol ether **46** (457 mg, 2.00 mmol), the mixture was heated at 60 °C under argon for 2 h and was then diluted with water (10 mL) and shaken with Et_2O (3 × 10 mL). The combined Et_2O layers were washed with a little water, dried with Na_2SO_4, and concentrated to afford the almost pure oxime **67** (297 mg, 87%) as a colorless liquid (ref.[6] m.p. 30 °C). ^{1}H NMR (CCl_4): δ = 1.05 (s, 6 × CH_3), 1.84 and 7.33 (AB system with ^3J = 10.1 Hz, 2- and 1-H, respectively), 8.15 (br, OH) ppm. ^{1}H NMR ($CDCl_3$): δ = 1.03, 1.88 and 7.46 (^3J = 10.3 Hz) ppm. ^{13}C NMR ($CDCl_3$): δ = 30.75 (qoct, ^1J = 125.1, ^3J = 4.5 Hz, 6 × CH_3), 34.99 (m, ^2J = 3.8 Hz, 2 × CMe_3), 57.45 (dm, ^1J = 127 Hz, ^3J = 3.8 Hz, C-2), 154.11 [dd, ^1J = 161 as expected for the (*E*) conformation, ^2J = 8.0 Hz, C-1] ppm.

(b) From 8: The protocol of Grundmann and Datta,[6] improved by working under argon in an EtOH/H_2O (1:1) mixture, furnished **67** (yield 68%) in a quality that required no distillation.

2-*tert*-Butyl-3,3-dimethylbutanenitrile (69): The addition of $SOCl_2$ (0.64 mL, 8.82 mmol) to the undistilled oxime **67** (1.37 g, 8.00 mmol) in dry benzene (5 mL) at room temp. caused an immediate evolution of gases, which ceased after warming to 60 °C for 10–30 min. The cooled solution was diluted with distilled water (5 mL) and extracted with Et_2O (3 × 10 mL). The combined Et_2O extracts were washed with distilled water (3 × 5 mL), dried with Na_2SO_4, and concentrated in vacuo to leave a yellow liquid (1.06 g) from which the nitrile **69** distilled at 80–85 °C/15 Torr (ref.[4] 76–78 °C/10 Torr) as a colorless liquid (911 mg, 74%). ^{1}H NMR ($CDCl_3$): δ = 1.19 (s, 6 × CH_3), 2.30 (s, 2-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 30.4 (qoct, ^1J = 125.9, ^3J = 4.5 Hz, 6 × CH_3), 35.4 (dm, ^2J = 5.4, ^2J = 3.8 Hz, 2 × CMe_3), 54.6 (dm, ^1J = 130.1, ^3J = 4.2 Hz, C-2), 121.4 (d, ^2J = 12, linewidth = 7 Hz, CN) ppm. IR (film): $\tilde{\nu}$ = 2231 (w) cm^{-1}.

***N*-(2,2,4,4-Tetramethyl-3-pentyl)formamide (70):** The aldehyde **8** (569 mg, 3.64 mmol) and hydroxylammonium chloride (330 mg, 4.75 mmol) in HCO_2H/H_2O (95:5, 3.20 mL)[53] were heated at reflux at 120 °C overnight ($t_{1/2}$ ≈ 2 h).[44] The cooled solution was diluted with iced water (45 mL) and extracted with Et_2O (3 × 20 mL). The combined Et_2O extracts were shaken with NaOH (2 M, 20 mL) and then with distilled water until neutral, dried with $MgSO_4$, and concentrated in vacuo. Distillation of the remaining brown liquid (667 mg) at 14 Torr provided a forerun of heavily contaminated nitrile **69** (up to 140 °C bath temp., 185 mg), followed by almost pure (*Z*)- and (*E*)-**70** (74:26, 115 mg, 18%) at 140–180 °C (bath temp.) as a slightly yellow, solidifying mixture (ref.[9] m.p. 89–91 °C). Isomer (*Z*)-**70**: ^{1}H NMR ($CDCl_3$): δ = 1.04 (s, 6 × CH_3), 3.77 (d, ^3J = 11.1 Hz, 3-H), 5.86 (unresolved, ^3J ≤ 11.1 Hz, NH), 8.28 (d, ^3J = 2.0 Hz, CHO) ppm. ^{13}C NMR ($CDCl_3$): δ = 29.39 (6 × CH_3), 36.68 (2 × CMe_3), 62.02 (C-3), 160.86 (CHO) ppm. Isomer (*E*)-**70**: ^{1}H NMR ($CDCl_3$): δ = 1.05 (s, 6 × CH_3), 2.76 (d, ^3J = 10.9 Hz, 3-H), 6.50 (hardly resolved, quasi-dd, ^3J ≈ 11.6 and 10.9 Hz, NH), 7.90 (d, ^3J = 11.6 Hz, CHO) ppm. ^{13}C NMR ($CDCl_3$): δ = 29.60 (6 × CH_3), 36.89 (2 × CMe_3), 68.90 (C-3), 165.37 (CHO) ppm.

Supporting Information (see footnote on the first page of this article): Low-temperature NMR (^{1}H, ^{13}C) chemical shifts δ and shift non-equivalences of the 3-furanone derivative **29** (Table S1).

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