Preparation and Properties of 2-Methyleneoxetanes

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The methylenation of β-lactones **5** with dimethyltitanocene provides a versatile, reliable, and highly chemoselective entry to 2-methyleneoxetanes **7**. The conversion proceeds selectively in the presence of alkenes, unprotected alcohols, and a variety of other carbonyl moieties. A study of conditions for the optimization of this reaction is delineated. In addition, the first X-ray structure of a 2-methyleneoxetane, which shows its similarity to related β-lactones, is reported. Reactivity studies of 2-methyleneoxetanes are presented in which it is demonstrated that these compounds are attacked at C-4 with a nucleophile; then, subsequently, the resultant enolate reacted with an electrophile. An interesting dichotomy of reactivity was observed when methyleneoxetane **7c** was treated with electrophiles. Reaction of **7c** with acetic acid gave acetoxyoxetane **19**. When **7c** was exposed to bromine, dibromoketone **20** resulted.

Introduction

Strained, saturated heterocyclic systems have been widely employed as molecular templates in the construction of a host of organic compounds. One largely unexplored class of strained heterocycles that should provide remarkable flexibility is the 2-alkylidene oxetanes **1**.[1−4] The unique combination of functionalities—a reactive oxetane, an enol cyclic ether, and an exocyclic double bond—offers intriguing possibilities for further manipulation.

Two approaches resulting in 2-alkylidene oxetanes[5] have been previously described. The first, reported in the late 1960s by Arnold[1] and Hammond,[2] utilized the Paterno−Büchi reaction with allenes (Figure 1). A very limited range of mostly symmetrical allenes was used. Moreover, although a large excess of allene was generally employed, further photocycloaddition to give dioxaspiroheptanes **2** and **3** was common. We have reported preliminary results of our own investigation of the Paterno−Büchi reaction between aldehydes and unsymmetrical allenes.[6] The other strategy, described by Hudrlik et al.,[7] utilized intramolecular O-alkylation of enolates (e.g., **4**). The authors found the requirement for geminal

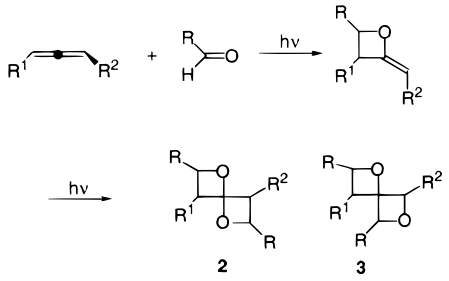
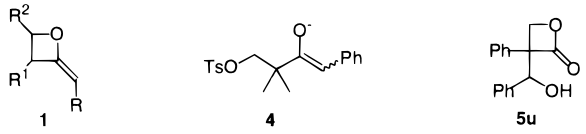


Figure 1. Paterno−Büchi reaction with allenes.

α-disubstitution to be too limiting for their purposes and did not further develop the methodology.[8]



We recently communicated a straightforward and reliable preparation of 2-methyleneoxetanes **7** by the reaction of β-lactones **5** with dimethyltitanocene **6**.[9] Further, we have demonstrated in preliminary publications that 2-methyleneoxetanes are biologically interesting[10] and that they are useful and promising synthetic intermediates.[11,12] In this paper, an investigation of the scope and optimization of the Petasis reaction with

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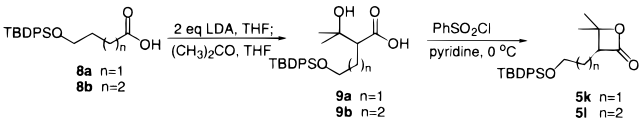
Scheme 1



β-lactones and of some of the properties of 2-methyleneoxetanes is detailed.

Results and Discussion

Preparation of 2-Methyleneoxetanes. In our previous paper,[9] we reported that β-lactones are excellent precursors for 2-methyleneoxetanes. β-Lactones themselves are readily accessible by a variety of straightforward and well-documented routes. Lactones **5b**−**e** were prepared as described in our previous paper.[9] Lactones **5f** and **5g** were prepared from (±)-tropic acid-derived lactone **5b**. Deprotonation of **5b**[13] with lithium diisopropylamide (LDA), followed by treatment with benzaldehyde, resulted in an alcohol **5u** that was either protected with *tert*-butyldimethylsilyl chloride to give **5f** or oxidized with PCC to give **5g**. Lactones **5h** and **5i** were synthesized as described by Schick,[14] lactone **5j** as described by Adam,[15] lactone **5p** as described by Romo,[16] lactone **5q** as described by Danheiser,[17] lactone **5r** as described by Vederas,[18] and lactone **5s** as described by Beaulieu.[19] Lactone **5t**, an intermediate in a published synthesis of orlistat,[20] was kindly provided by Hoffmann La Roche.

Lactones **5k** and **5l** were prepared in two steps from carboxylic acids **8a**[21] and **8b**,[22] respectively (Scheme 1). Condensation of the dianions of **8a** and **8b** with acetone resulted in β-hydroxy acids **9a** and **9b**, which were then treated with benzenesulfonyl chloride in pyridine[23] to give lactones **5k** and **5l**.

Lactones **5m**−**o** were prepared from ethyl acetoacetate (**10**) as shown in Scheme 2. Alkylation with the appropriate alkyl iodides led to substituted β-ketoesters **11a**−**c**.[24] Sodium borohydride reduction resulted in mixtures of diastereomers **12a**−**c**,[25] which were subjected to alkaline hydrolysis, followed by cyclization, providing lactones **5m**−**o**. The lactone mixtures of **5m** and **5n** were methylenated. Lactone diastereomers **5o** were separated, and the trans isomer was methylenated.

Scheme 2

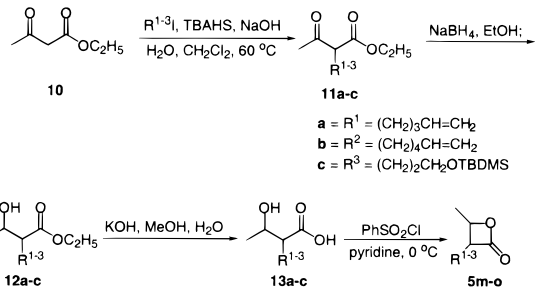
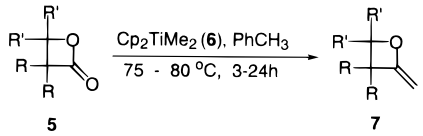
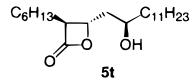


Table 1



reactant (**5**)	isolated yield (%) of **7**
a, R = H; R′ = H[a]	57[a]
b, R = Ph, H; R′ = H	76
c, R = Ph, CH_3; R′ = H	76
d, R = Ph, $CH_2CH{=}CH_2$; R′ = H	86
e, R = Ph, $CO(CH_2)_3CH{=}CH_2$; R′ = H	47
f, R = Ph, CH(OTBDMS)Ph; R′ = H	74
g, R = Ph, COPh; R′ = H	20
h, R = CH_3; R′ = $C(CH_3)_3$, H	50[b]
i, R = CH_3; R′ = $(CH_2)_5$	67[b]
j, R = CH_3, H; R′ = $(CH_2)_5$	60[b]
k, R = CH_2CH_2OTBDPS, H; R′ = CH_3	62
l, R = $(CH_2)_2CH_2$OTBDPS, H; R′ = CH_3	60
m, R = $(CH_2)_3CH{=}CH_2$, H; R′ = CH_3, H	70[b]
n, R = $(CH_2)_4CH{=}CH_2$, H; R′ = CH_3, H	80[b]
o, R = $(CH_2)_2CH_2$OTBDMS, H; R′ = CH_3, H (*trans*)	71
p, R = CH_3, H; R′ = CH_2CH_2OTBDMS, H (*trans*)	75
q, R = CH_3, H; R′ = CH_2CH_2Ph, H (*trans*)	74
r, R = NHBoc, H (*S*); R′ = H	40
s, R = N(Boc)$CH_2CH{=}CH_2$, H (*S*); R′ = H	56
t, see below	69

[a] Distilled directly from the reaction mixture; contains toluene. Yield based on ^{1}H NMR. [b] These compounds are somewhat volatile and require care when handling.



5t

The results for the methylenations of the β-lactones are shown in Table 1. There are a number of facets of this reaction that merit discussion. One noteworthy feature, as stated in our prior paper,[9] is the chemoselectivity. The preference for reaction with the lactone carbonyl over alkene (see **5d**,**e**,**m**,**n**,**s**) parallels the observation of Petasis.[26] The selectivity over other carbonyl functionalities, including ester,[10] carbamate, and particularly, ketones, is remarkable (see **5e**,**g**,**r**,**s**). The yields of these reactions vary, but it is important to note that there is no evidence for methylenation of other carbonyl functionalities present. Each of these reactions has been monitored by ^{1}H NMR. The normal observation has been that the only apparent lactone-related materials

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Table 2

	expt								
	1	2	3	4	5	6	7	8	9
T (°C)	80	50	50	50	50	110	110	110	110
time (h)	5	2	2	24	24	2	2	24	24
equiv of Cp_2TiMe_2	1.75	0.75	3.0	0.75	3.0	0.75	3.0	0.75	3.0
yield of **7b**[a] (%)	35	<5	<5	8	25	21	34	0	0
remaining **5b**[a] (%)	0	95	90	90	65	0	0	0	0

[a] Yields based on tri-*tert*-butylbenzene as internal standard.

(with no observable undissolved material) were the starting lactone and the product. The reactions were worked up once the starting material had disappeared (the issue of mass balance will be discussed separately). Also of interest is the fact that an unprotected hydroxyl group does not interfere with the outcome of the reaction (see **5t**). It should be pointed out, however, that a proximal hydroxyl is not tolerated. Thus, to date, the only *β*-lactone that we have been unable to methylenate is compound **5u**. However, when the hydroxyl was protected (see **5f**), the methylenation proceeded smoothly.

As stated above, on the basis of the ^{1}H NMR spectra of the crude reaction mixtures, these reactions appeared to be remarkably clean. For this reason, it was of some concern to us that, although the yields were generally good, they were not closer to quantitative. One potential explanation considered was the method of purification. Although reproducible yields were obtained using triethylamine-deactivated flash silica, we were concerned about loss of material, since the 2-methyleneoxetanes were sensitive under a variety of purification conditions. We ruled out purification problems when either doubling the amount of silica or recolumning the product resulted in substantially the same yield as the usual column conditions.

When the reaction of lactone **5b** with dimethyltitanocene was monitored with an internal standard (0.11 equiv of tri-*tert*-butylbenzene), we found that the isolated yield was reproducibly reflective of the calculated yield, based on the internal standard, just prior to workup. Further, earlier in the course of the reaction, when both starting material and product were present, the internal standard showed that the material balance was good. Although this would suggest that for optimum yields the reactions should be monitored to a point where product yields begins to deteriorate, based on the internal standard, rather than until the starting materials have disappeared, our own practical experience suggests that gains in yield would be negligible compared to the added difficulty of closely monitoring the reaction.

Because no lactone-related byproducts were apparent by ^{1}H NMR, even when the reactions were completely homogeneous, the task of yield optimization was rendered more difficult. We decided to systematically alter the reaction variables that we deemed most likely to affect the reaction outcome. The parameters altered were temperature, the number of equivalents of dimethyltitanocene, and reaction time. Because variables can sometimes act in a synergistic fashion, a matrix of reactions was conducted as shown in Table 2. Experiment 1 represents what we considered to be typical conditions. All of the yields were based on an internal standard. Values chosen for temperature, time, and equivalents of dimethyltitanocene were above and below the standard conditions. The most interesting trend observed was that at the lower temperature the material balances in the reactions were good. Therefore, a series of methylenation reactions with **5b** was conducted at 50, 60, and 70 °C with 3 equiv of dimethyltitanocene (data not shown). These reactions were monitored by ^{1}H NMR for disappearance of the reactant lactone. Indeed, the material balances for the these reactions were favorable over long periods of time. However, once the starting material had disappeared, there were no significant differences in yields of product in comparison to reactions run under standard conditions. We also saw no substantial increases in yields by either increasing (1.0 M) or decreasing (0.25 or 0.1 M) the concentration of dimethyltitanocene. The one exception was that in preparing 2-methyleneoxetane (**7a**), which was distilled directly from the reaction mixture, optimum yields were obtained with 1.0 M solutions of dimethyltitanocene. Reactions conducted in THF proceeded more slowly with no enhancement in yields.

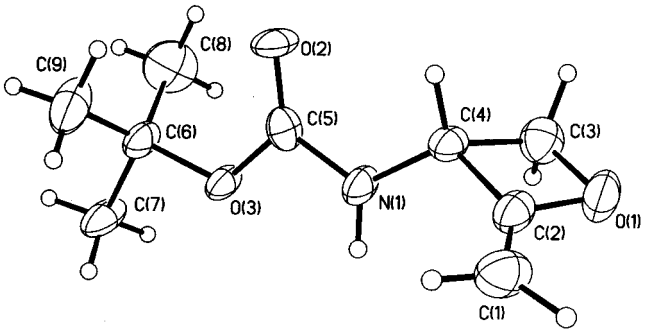

Figure 2. ORTEP drawing of **7r**.

Structure of 2-Methyleneoxetanes. 2-Methyleneoxetane **7r** was isolated as a solid, and a single X-ray study represents, to our knowledge, the first example of a crystal structure (Figure 2)[27] of a 2-methyleneoxetane. The bond lengths and angles in the oxetane ring are similar to related *β*-lactones.[28] Thus, the O(1)−C(2) bond length is 1.35 Å, and the O(1)−C(3) bond length is 1.45 Å, the latter also corresponding closely to the C−O bond lengths in oxetane.[29] The trend in bond angles in the endocylic bonds also corresponds with those observed in *β*-lactones. The observed bond angles are as follows: C(4)−C(2)−O(1), 94.7°; C(2)−O(1)−C(3), 91.3°; O(1)−C(3)−C(4), 90.0°; C(3)−C(4)−C(2), 83.3°. The observed methylene exocyclic bond angles are as follows: O(1)−

(27) For **7r**: $C_9H_{15}NO_3$, monoclinic, $P2_1$, a = 10.7776(5) Å, b = 9.3265(3) Å, c = 11.1862(5) Å, β = 115.069(2)°, V = 1018.48(7)Å^3, Z = 4, T = 198 K, D_{calc} = 1.208 g cm^{-3}, R = 7.25% for 2728 observed independent reflections (4° ≤ 2θ ≤ 50°). μ = 0.9 cm^{-1}. The asymmetric unit contains two chemically equivalent molecules. Each of these molecules is hydrogen bonded to itself and forms a one-dimensional chain. The absolute configuration has not been confirmed.

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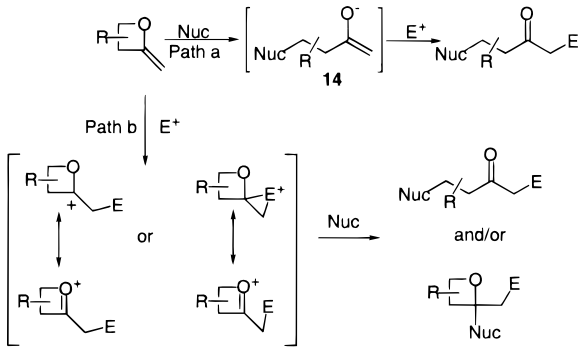


Figure 3. Potential reactivity of 2-mMethyleneoxetanes.

C(2)−C(1), 127.7°; C(4)−C(2)−C(1), 137.6°. These also correspond closely to related β-lactones, as do the ring torsional angles (alternating +6°). Taken together, these structural studies suggest that the postulation in our original paper of structural isosterism between β-lactones and 2-methyleneoxetanes is logical. Further confirmation of the potential of 2-methyleneoxetanes serving as β-lactone isosteres was the level of inhibition we reported[10] for the 2-methyleneoxetane analogue of orlistat, a potent pancreatic lipase inhibitor, currently marketed as an antiobesity drug.

Reactivity of 2-Methyleneoxetanes. In considering the structure of 2-methyleneoxetanes there were two modes of reactivity that we thought would be of particular interest. On one hand, the 2-methyleneoxetane could be viewed as a latent enolate, regiocomplementary to those generated in Michael additions (Figure 3, path a), where reaction with a nucleophile at C-4 would expose enolate **14**, which could subsequently react with an electrophile, in either an inter- or intramolecular process. A multitude of applications could be envisaged utilizing this tandem process. Alternatively, the electron-rich double bond could be exploited advantageously. Reaction of an electrophile, followed by a nucleophile (Figure 3, path b), could lead to a variety of systems, either with the oxetane ring intact or not. Reported precedent for either pathway is limited. In the preparation of the parent 2-methyleneoxetane reported by Hudrlik and coworkers,[30] structural identity was in part confirmed by the reaction of 2-methyleneoxetane with phenyllithium to give 4-phenyl-2-butanone (path a, Nuc = Ph; E = H^+). An example of path b is reported in which an ^{1}H NMR-monitored reaction between 2-methyleneoxetane and acetic acid in carbon tetrachloride provided 2-acetoxy-2-methyloxetane in over 90% yield, based on an internal standard.[31]

Although we were able to repeat the reaction between 2-methyleneoxetane and phenyllithium, we found that phenyllithium did not react with the more sterically encumbered 3-methyl-3-phenyl-2-methyleneoxetane (**7c**). However, in the presence of trimethylaluminum **7c** was converted to homopropargyl alcohol **15** in over 60% yield. Presumably, in this case deprotonation proceeds more rapidly than the corresponding ring opening. This result led to our investigation of 2-methyleneoxetanes as novel and versatile precursors of homopropargylic alcohols.[12] Interestingly, while we were investigating capture of

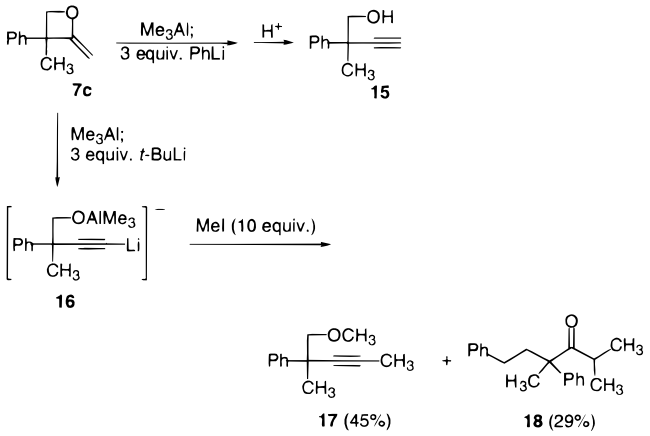
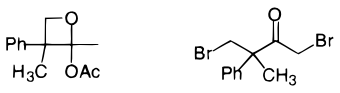


Figure 4.

homopargylic alcohol dianion **16** to give **17** under the conditions shown in Figure 4, a byproduct, subsequently identified as **18**, was also isolated in 29% yield. Once we recognized that the trimethylaluminum was used as a solution in toluene, we realized that, under the reaction conditions, benzyllithium was being generated. The benzyllithium acted as a nucleophile, rather than a base, leading to an enolate that reacted with the large excess of iodomethane. Further, in the presence of excess *tert*-butyllithium, deprotonation of the resultant ketone led to incorporation of an additional methyl group. Thus, it is apparent that tandem reactions of nucleophiles, followed by electrophiles, are possible, and we are exploring this currently.

With 3-methyl-3-phenyl-2-methyleneoxetane (**7c**) we have also confirmed that in the presence of acetic acid addition to the enol ether gave oxetane **19**, a 4:1 mixture of diastereomers, as the sole product by ^{1}H NMR. However, when **7c** was treated with bromine, dibromoketone **20** was isolated in 87% yield. The divergence in outcome is noteworthy and might be explained by greater steric hindrance in the bromonium ion or bromooxonium ion, leading to preferential attack at C-4 to give **20**. The synthetic implications are interesting, especially if alternative electrophiles (e.g., Hg(II)) or nucleophiles could be utilized.



19 **20**

Conclusions

We have demonstrated that the methylenation of β-lactones with dimethyltitanocene provides a versatile, reliable and highly chemoselective entry to 2-methyleneoxetanes. It is also apparent that the 2-methyleneoxetanes display a useful range of reactivity. It is possible to exploit both the ring strain and the exocylic enol ether, sometimes in a one-pot process. Further, in this and other publications we have seen some unexpected reactivities that suggest that there is much fertile ground for the exploration of this, now, readily available, but little investigated, class of strained heterocycles.

Experimental Section

General Experimental Procedures. Tetrahydrofuran was distilled from dark blue solutions of sodium/benzophenone. Toluene was distilled from sodium. Methylene chloride was

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distilled from CaH_2. Pyridine was dried over KOH and distilled. Acetone was dried over calcium sulfate and distilled. Petroleum ether was purchased from Baker and distilled. Carbon tetrachloride was washed with aqueous KOH and water, distilled, and then stored over molecular sieves (4 Å) for 3 days. The concentrations of solutions of methyllithium and *n*-butyllithium were determined by titrations with *sec*-butyl alcohol using 1,10-phenanthroline as the indicator. With the exceptions noted, all starting reagents were purchased from Aldrich and used without further purification. 5-Hexenal was obtained by PCC mediated oxidation of 5-hexenol. Cyclohexanone was purchased from Aldrich and distilled. *β*-Propiolactone (**5a)** was purchased from Acros. Lactone **5t** was kindly provided by Hoffmann La Roche.

Literature procedures were followed for the preparation of 4-*tert*-butyl-3,3-dimethyloxetan-2-one (**5h**),[14] 3,3-dimethyloxetan-2-on-4-spirocyclohexane (**5i**),[1] 3-methyl-4-spirocyclohexyloxetan-2-one (**5j**),[15] *trans*-4-(2-*tert*-butyldimethylsilyloxyethyl)-3-methyloxetan-2-one (**5p**),[16] *trans*-3-methyl-4-phenylethyloxetan-2-one (**5q**),[17] (*S*)-*N*-(*t*-butoxycarbonyl)-3-amino-2-oxetanone (**5r**),[18] and (*S*)-*N*-allyl-*N*-(*t*-butoxycarbonyl)-3-amino-2-oxetanone (**5s**).[19] 3-Phenyloxetan-2-one (**5b**), 3-methyl-3-phenyloxetan-2-one (**5c**), 3-allyl-3-phenyloxetan-2-one (**5d**), and 3-(1-oxo-5-hexenyl)-3-phenyloxetan-2-one (**5e**) were prepared as described in our previous paper,[9] and experimental procedures can be found in the Supporting Information.

3-[*tert*-Butyldimethylsilyloxy(phenyl)methyl]-3-phenyloxetan-2-one (5f). Compound **5u** (0.21 g, 0.83 mmol) was dissolved in dry CH_2Cl_2 (5 mL) and treated with 2,6-lutidine (0.18 g, 1.66 mmol). The solution was cooled to −10 °C, and *tert*-butyldimethylsilyltriflate (0.33 g, 1.25 mmol) was added. After 45 min, water (5 mL) and EtOAc (10 mL) were added. The aqueous layer was removed and was further extracted with EtOAc (2 × 10 mL). The combined organic extracts were washed with H_2O (10 mL) and brine (10 mL) and dried ($MgSO_4$). The solvent was removed in vacuo, and the crude product was purified by flash chromatography on silica gel (petroleum ether/EtOAc 85:15) to give a white solid (0.25 g, 82%): mp 96−98 °C; IR (KBr) 3028, 2954, 2856, 1813, 1128, 1093, 1070 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.25 (m, 6H), 7.17 (m, 4H), 4.92 (s, 1H), 4.76 (d, J = 4.7 Hz, 1H), 4.51 (d, J = 4.7 Hz, 1H), 0.87 (s, 9H), −0.15 (s, 3H), −0.35 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.9, 138.6, 135.4, 128.3, 128.2, 127.9, 127.8, 127.6, 127.5, 77.8, 72.0, 67.9, 25.7, 18.1, −4.9, −5.7; MS (EI) m/z 353 ($M^+ - CH_3$), 311, 221, 91, 73 (100). Anal. Calcd for $C_{22}H_{28}O_3Si$: C, 71.74; H, 7.60. Found: C, 71.60: H, 7.83.

3-Benzoyl-3-phenyloxetan-2-one (5g). Sodium acetate (0.047 g, 0.67 mmol) and PCC (1.07 g, 4.95 mmol) were added to compound **5u** (0.21 g, 0.83 mmol) in dry CH_2Cl_2 (20 mL) at rt. The reaction mixture was stirred for 5 h. Et_2O (40 mL) was then added, and stirring was continued for 30 min. The reaction mixture was filtered through silica gel/Florisil (1:1), and the filtrate was concentrated to 50 mL, washed with 2 M NaOH (10 mL) and brine (10 mL), and dried ($MgSO_4$). Purification by flash chromatography on silica gel (dry loaded, CH_2Cl_2) (petroleum ether/EtOAc 95:5) afforded lactone **5g** (0.17 g, 81%) as a white solid: mp 72−74 °C; IR (CH_2Cl_2) 1820, 1690, 1285 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.08 (d, J = 8.5 Hz, 2H), 7.49 (t, J = 8.5 Hz, 1H), 7.3 (m, 7H), 5.34 (d, J = 5.0 Hz, 1H), 4.32 (d, J = 5.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.3, 166.5, 134.7, 133.9, 133.6, 130.7, 129.8, 128.8, 128.5, 125.9, 77.7, 70.3; MS (EI) m/z 224 ($M^+ - CH_2O$), 196, 165, 115, 105 (100), 77. Anal. Calcd for $C_{16}H_{12}O_3$: C, 76.17; H, 4.80. Found: C, 76.06; H, 4.84.

General Procedure for the Preparation of Lactones 5k−o. 3-(2-*tert*-Butyldiphenylsilyloxy)ethyl-4,4-dimethyloxetan-2-one (5k). A solution of **9a** (1.05 g, 3.37 mmol) in anhydrous pyridine (35 mL) was cooled to 0−5 °C, and benzenesulfonyl chloride (1.49 g, 8.43 mmol) was added dropwise with stirring. After being stirred overnight at 0−5 °C, the reaction mixture was poured onto crushed ice (150 mL), stirred, and extracted with of Et_2O (5 × 60 mL). The combined organic extracts were washed with saturated aqueous sodium bicarbonate (3 × 60 mL) and water (200 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Flash chromatography of the crude product on silica gel (petroleum ether/EtOAc/triethylamine 92:7:1) gave 5**k** (0.76 g, 76%) as a colorless oil: IR (film) 3073, 2931, 1816, 1113, 1072 cm^{-1}; ^1HNMR (400 MHz, $CDCl_3$) δ 7.65 (m, 4H), 7.41 (m, 6H), 3.65−3.80 (m, 2H), 3.50 (dd, J = 8.5, 6.9 Hz, 1H), 2.00 (m, 1H), 1.89 (m, 1H), 1.58 (s, 3H), 1.45 (s, 3H), 1.06 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.3, 135.5, 133.3, 129.8, 127.8, 80.1, 61.2, 55.0, 27.8, 27.8, 26.8, 22.2, 19.2; MS (FAB) m/z 338 ($M^+ - CO_2$), 281 (338 − *t*-Bu), 199 (100), 135, 105, 83, 55; Anal. Calcd for $C_{23}H_{30}O_3Si$: C, 72.21; H, 7.90. Found: C, 72.35; H, 8.30.

3-[Hydroxy(phenyl)methyl]-3-phenyloxetan-2-one (5u). *n*-Butyllithium (1.6 M in hexane, 16.8 mL, 26.8 mmol) was added dropwise to a stirred solution of diisopropylamine (2.98 g, 29.5 mmol) in dry THF (55 mL) at 0 °C under N_2, stirred for 15 min, then cooled to −78 °C. A solution of 3-phenyloxetan-2-one (**5b**) (3.96 g, 26.8 mmol) in THF (55 mL) was added dropwise, and the solution was stirred for 15 min. Benzaldehyde (8.50 g, 80.4 mmol) in dry THF (27 mL) was then added dropwise. After 1.5 h at −78 °C, the reaction mixture was poured into saturated aqueous NH_4Cl (100 mL). The organic layer was removed, and the aqueous layer was further extracted with Et_2O (4 × 250 mL). The combined organic extracts were dried ($MgSO_4$), and the solvents were removed in vacuo. The residue was first purified by flash chromatography on silica gel (petroleum ether/EtOAc 85:15) to remove the benzaldehyde. This gave the product (4.66 g, 70%), a mixture of two diastereomers, as a white solid. The diastereomers could be separated by careful chromatography (petroleum ether/EtOAc 92.5:7.5) in a 15:85 ratio: **5u** (less polar, minor diastereomer) ^1H NMR ($CDCl_3$) δ 7.27 (m, 6H), 7.05 (d, J = 6.9 Hz, 2H), 6.91 (d, J = 6.9 Hz, 2H), 5.16 (s, 1H), 5.04 (d, J = 5.2 Hz, 1H), 4.48 (d, J = 5.2 Hz, 1H), 2.51 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 171.3, 138.0, 134.4, 128.5, 128.4, 128.2, 128.1, 127.4, 126.7, 75.9, 71.6, 66.3. **5u** (more polar, major diastereomer): mp 104−106 °C; IR (KBr) 3537, 3060, 1826, 1111 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.29 (m, 6H), 7.20 (m, 4H), 5.07 (s, 1H), 4.86 (d, J = 4.8 Hz, 1H), 4.85 (d, J = 4.8 Hz, 1H), 2.40 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 170.1, 137.9, 134.8, 128.6, 128.5, 128.2, 128.1, 127.3, 127.2, 76.7, 71.0, 68.1; MS (EI) m/z 224 ($M^+ - CH_2O$), 148 (100), 103, 77, 51. Anal. Calcd for $C_{16}H_{14}O_3$: C, 75.57; H, 5.55. Found: C, 75.39; H, 5.43.

Preparation of Dimethyltitanocene (6). Dimethyltitanocene was prepared with some modification of a previously described procedure.[32] Methyllithium (1.4 M in Et_2O, 132 mL, 185 mmol) was added dropwise under N_2 to a stirred slurry of titanocene dichloride (20.0 g, 80.3 mmol) in dry toluene (160 mL) at −5 °C. The mixture was stirred at −5 °C for 1 h and then allowed to warm to rt over 1 h. The mixture was cooled to 0 °C and then quenched carefully with ice-cold 6% aqueous NH_4Cl (50 mL). After separation, the organic layer was washed with water (50 mL) and brine (50 mL), dried ($MgSO_4$), and filtered to provide a red solution. The solution was concentrated to one-third the volume. ^1H NMR assay indicated 15.2 g (91%) of dimethyltitanocene: ^1H NMR (400 MHz, $CDCl_3$) δ 6.09 (s, 5H), 6.08 (s, 5H), −0.11 (s, 3H), −0.12 (s, 3H). The dimethyltitanocene was generally stored in the freezer as a 0.5 M solution in toluene.

General Procedure for Methylenation. 3-Allyl-2-methylene-3-phenyloxetane (7d). Dimethyltitanocene (0.5 M in toluene, 10.8 mL, 5.4 mmol) and 3-allyl-3-phenyloxetan-2-one (0.50 g, 2.7 mmol) were stirred at 80 °C under N_2 in the dark. The reaction was monitored by TLC and/or ^1H NMR, and after the disappearance of the starting material (2−15 h) the solution was allowed to cool. An equal volume of petroleum ether was then added, at which point a yellow precipitate formed. The mixture was stirred for 30 min and then passed through Celite with petroleum ether until the filtrate was colorless. After concentration, if large amounts of solid were still present, the mixture was diluted with petroleum ether and filtered through Celite a second time. The residue was then purified by flash chromatography on silica gel (petroleum

(32) Claus, K.; Bestian, H. *Justus Liebigs Ann. Chem.* **1962**, *654*, 8.

ether/EtOAc/triethylamine 98.5:0.5:1), which afforded methyleneoxetane **7d** (0.33 g, 76%) as a pale yellow oil: IR (film) 3150, 3000, 2900, 1650, 1500, 1490, 1190, 980 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.35 (m, 5H), 5.76 (m, 1 H), 5.15 (m, 1 H), 5.12 (m, 1H), 4.76 (d, J = 5.0 Hz, 1H), 4.72 (d, J = 5.0 Hz, 1H), 4.32 (d, J = 4.0 Hz, 1 H), 4.03 (d, J = 4.0 Hz, 1 H), 2.74 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.3, 141.9, 133.2, 128.5, 126.9, 126.2, 118.8, 80.4, 79.1, 54.0, 44.0; MS (EI) m/z 186 (M^+), 158, 115, 103 (100), 77; HRMS (EI) calcd for $C_{13}H_{14}O$ (M^+) 186.1045, found 186.1044.

General Procedure for the Preparation of Acids 9a and 9b. 2-(2-*tert*-Butyldiphenylsilyloxy)ethyl-3-hydroxy-3-methylbutanoic Acid (9a). *n*-Butyllithium (2.6 mmol, 1.6 M in hexane) was added dropwise to a stirred solution of diisopropylamine (0.27 g, 2.6 mmol) in dry THF (1.3 mL) at 0 °C under N_2. The solution was maintained at 0 °C for 10 min and then warmed to rt. 4-(*tert*-Butyldiphenylsilyloxy)butanoic acid[21] (0.45 g, 1.30 mmol) in dry THF (1.3 mL) was then added to the resulting solution, and the reaction was maintained at rt for 1.5 h. Anhydrous acetone (0.080 g, 1.3 mmol) in THF (0.52 mL) was added, and the mixture was stirred for 16 h. The mixture was cooled to 0 °C and acidified to pH 2 with 2 N HCl. The resulting mixture was extracted with Et_2O (5 × 20 mL), and the combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo. Purification by flash chromatography on silica gel (petroleum ether/EtOAc 9:1; then petroleum ether/EtOAc/acetic acid 75:25:0.3) gave **9a** (0.43 g, 81%) as a white solid: mp 94−94.5 °C; IR (diffuse reflectance FTIR) 3425, 3073, 2966, 1710, 1590 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.68 (m, 4H) 7.38 (m, 6H), 3.75 (m, 1H), 3.69 (m, 1H), 2.68 (dd, J = 9.7, 3.3 Hz, 1H), 2.00 (m, 1H), 1.93 (m, 1H) 1.32 (s, 3H), 1.27 (s, 3H), 1.05 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 179.9, 135.5, 133.3, 129.7, 127.7, 71.4, 62.4, 52.8, 30.7, 28.7, 26.8, 26.6, 19.1; MS (FAB) m/z 384 (M^+ + H − OH), 366, 282, 201, 135 (100), 105, 83. Anal. Calcd for $C_{23}H_{32}O_4Si$: C, 68.96; H, 8.05. Found: C, 68.87; H, 8.12.

General Procedure for the Preparation of Esters 11a−c. Ethyl 2-Acetyl-6-heptenoate (11a). A solution of ethyl acetoacetate (4.69 g, 36.1 mmol) and 5-iodopent-1-ene (5.90 g, 30.1 mmol) in CH_2Cl_2 (100 mL) was added to a vigorously stirred solution of tetra-*n*-butylammonium hydrogen sulfate (10.2 g, 30.1 mmol) and sodium hydroxide (2.41 g, 60.1 mmol) in H_2O (100 mL). The mixture was heated at reflux for 2.5 h. The mixture was then cooled to rt, and the layers were separated. The aqueous layer was further extracted with CH_2Cl_2 (3 × 30 mL). The combined organic extracts were concentrated in vacuo, and the residue was taken up in Et_2O (50 mL). The insoluble material was removed by filtration and washed with Et_2O. The filtrate was washed with H_2O (15 mL) and brine (15 mL) and dried (Na_2SO_4), and the solvent was removed in vacuo. The residue was purified by flash chromatography on silica gel (petroleum ether/EtOAc 93:7), and **11a** was isolated as a colorless oil (3.1 g, 52%): IR (film) 3050, 2990, 1750, 1720, 1630, 1490, 1480 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.74 (m, 1H), 4.99 (m, 1H), 4.94 (m, 1H), 4.18 (q, J = 7.1 Hz, 2H), 3.38 (dd, J = 7.4, 7.4 Hz, 1H), 2.20 (s, 3H), 2.04 (m, 2H), 1.83 (m, 2H), 1.35 (m, 2H), 1.25 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.1, 169.8, 137.9, 115.0, 61.3, 59.7, 33.3, 28.7, 27.5, 26.6, 14.1; MS (EI) m/z 199 (M^+ + H), 156, 143, 130, 109, 101, 73, 68, 55 (100). Anal. Calcd for $C_{11}H_{18}O_3$: C, 66.44; H, 9.15. Found: C, 66.07; H, 9.38.

General Procedure for the Preparation of β-Hydroxyesters 12a−c. Ethyl 2-(1-Hydroxyethyl)-6-heptenoate (12a). A solution of ethyl 2-acetyl-6-heptenoate (**11a**) (3.16 g, 16.0 mmol) in 95% ethanol (20 mL) was added dropwise over 0.5 h to a stirred suspension of $NaBH_4$ (0.60 g, 16.0 mmol) in 95% ethanol (35 mL) at 0 °C. The mixture was stirred for 2.5 h at 0 °C and then acidified (pH 3−4) by dropwise addition of 2 N HCl. The ethanol was evaporated under reduced pressure. The resulting slurry was dissolved in H_2O (35 mL) and extracted with Et_2O (3 × 20 mL). The combined organic extracts were dried ($MgSO_4$), and the solvent was removed under reduced pressure. Purification by flash chromatography on silica gel (petroleum ether/EtOAc 88:12) afforded a 3:2 mixture of diastereomers (2.6 g, 81%) as a colorless oil: IR (film) 3500 (br), 3050, 2950, 1710, 1620, 1490, 1400 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.76 (m, 1H), 5.01 (m, 1H), 4.97 (m, 1H), 4.20 (q, J = 9.5 Hz, 0.6H), 4.19 (q, J = 9.5 Hz, 0.4H), 4.00 (m, 0.4H), 3.90 (ddq, J = 8.5, 8.5, 8.5 Hz, 0.6H), 2.50 (m, 2H), 2.12 (m, 2H), 1.81−1.32 (m, 4H), 1.29 (t, J = 9.5 Hz, 3H), 1.23 (d, J = 8.5 Hz, 1.6H), 1.20 (d, J = 8.5 Hz, 1.4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.4, 175.2, 138.3, 138.2, 114.9, 114.8, 68.4, 68.2, 60.5, 52.5, 52.1, 35.8, 33.6, 33.5, 28.9, 26.9, 26.7, 21.6, 20.3, 14.3; MS (EI) m/z 201 (M^+ + H), 185, 156, 132, 109, 101, 73 (100), 67, 55. Anal. Calcd for $C_{11}H_{20}O_3$: C, 65.97; H, 10.07. Found: C, 65.60; H, 9.94.

General Procedure for the Preparation of Acids 13a−c. 2-(1-Hydroxyethyl)-6-heptenoic Acid (13a). A solution of 2 N KOH (30.3 mL, 60.6 mmol) and ethyl 2-(1-hydroxyethyl)-6-heptenoate (**12a**) (2.16 g, 10.8 mmol) in MeOH (70 mL) was stirred at rt for 20 h. The reaction mixture was acidified (pH 2−3) by dropwise addition of phosphoric acid. The MeOH was evaporated under reduced pressure, and the resulting slurry was dissolved in H_2O (60 mL) and extracted with Et_2O (3 × 30 mL). The combined organic extracts were dried ($MgSO_4$), and the solvent was removed in vacuo. Purification by flash chromatography on silica gel (petroleum ether/EtOAc/acetic acid 90:10:0.3) afforded a 1:1 mixture of diastereomers as a viscous, colorless oil (1.6 g, 86%): IR (film) 3500−3100 (br), 2950, 1720, 1640, 1490, 1420 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.77 (m, 1H), 5.00 (m, 1H), 4.97 (m, 1H), 4.05 (dq, J = 6.4, 6.4 Hz, 0.5H), 3.95 (dq, J = 6.4, 6.4 Hz, 0.5H), 2.47 (m, 0.5H), 2.40 (m, 0.5H), 2.07 (m, 2H), 1.69 (m, 1H), 1.59 (m, 1H), 1.43 (m, 2H), 1.26 (d, J = 6.4 Hz, 1.5H), 1.23 (d, J = 6.4 Hz, 1.5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 180.1 170.9, 138.2, 138.0, 115.0, 114.9, 68.3, 68.2, 52.6, 51.7, 33.6, 33.5, 28.6, 26.9, 26.5, 26.4, 21.5, 20.1; MS (EI) m/z 154 (M^+ − H_2O), 132, 124, 96, 81, 73, 67, 55(100); HRMS (EI) calcd for $C_9H_{14}O_2$ (M^+ − H_2O) 154.0994, found 154.0991.

2,4-Dimethyl-4,6-diphenylhexan-3-one (18). Trimethylaluminum (2.0 M in toluene, 0.31 mL, 0.62 mmol) was added dropwise to a solution of 3-methyl-3-phenyl-2-methyleneoxetane (**7c**) (0.10 g, 0.62 mmol) in THF (2 mL) at 0 °C under N_2, and the solution was maintained at 0 °C for 10 min. *tert*-Butyllithium (1.6 M in heptane, 2.36 mL, 3.6 mmol) was then added dropwise, and the resulting yellow solution was maintained at 0 °C for 5 min. Iodomethane (0.88 g, 6.2 mmol) was then added. The solution was slowly warmed to rt and maintained overnight. NaF (0.11 g, 2.5 mmol) and H_2O (1 drop, ca. 25 mg) were added. The mixture was stirred for 20 min, and the resulting yellow solid was filtered and washed with Et_2O (10 mL). The filtrate was washed with H_2O (10 mL). The aqueous layer was then further extracted with Et_2O (3 × 5 mL), and the combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo. Purification by flash chromatography on silica gel (petroleum ether/EtOAc 98:2) afforded (1-methoxymethyl-1-methylbut-2-ynyl)benzene (**17**)[12] (0.052 g, 45%) as a colorless oil: IR (film) 3150, 3100, 3000, 2950, 2850, 1650, 1540, 1510, 1480, 1180, 1100 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.57 (m, 2H), 7.31 (m, 2H), 7.25 (m, 1H), 3.55 (d, J = 9.0 Hz, 1H), 3.48 (d, J = 9.0 Hz, 1H), 3.35 (s, 3H), 1.92 (s, 3H), 1.59 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.8, 128.1, 126.6, 126.5, 83.0, 81.8, 78.8, 59.6, 41.2, 26.0, 3.8; MS (EI) m/z 173 (M^+ − CH_3) 158, 143 (100), 120, 115, 65; HRMS (EI) calcd for $C_{12}H_{13}O$ (M^+ − CH_3) 173.0966, found 173.0969. (1-Methoxymethyl-1-methylprop-2-ynyl)benzene was also isolated as a colorless oil (0.014 g, 14%): ^1H NMR (400 MHz, $CDCl_3$) δ 7.57 (m, 2H), 7.31 (m, 2H), 7.25 (m, 1H), 3.59 (d, J = 9.0 Hz, 1H), 3.52 (d, J = 9.0 Hz, 1H), 3.37 (s, 3H), 2.43 (s, 1H), 1.64 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.5, 128.2, 126.9, 126.4, 88.1, 81.3, 71.3, 59.6, 41.2, 25.7; MS (EI) m/z 159 (M^+ − CH_3), 144, 129 (100), 115, 77, 51; HRMS (EI) calcd for $C_{11}H_{11}O$ (M^+ − CH_3) 159.0810, found 159.0814. 1,3-Dimethyl-3,6-diphenylhexane-2-one (**18**) (0.052 g, 29%) was isolated as a pale yellow oil: ^1H NMR (400 MHz, $CDCl_3$) δ 7.35 (m, 3H), 7.28 (m, 5H), 7.14 (m, 2H), 2.68 (m, 1H), 2.43 (m, 1H), 2.28 (m, 1H), 2.21 (m, 2H), 1.63 (s, 3H), 0.93 (d, J = 6.7 Hz, 3H), 0.83 (d, J = 6.7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 216.9, 142.5, 141.6, 128.6, 128.3, 128.2, 127.0, 126.9, 125.7, 56.2, 39.4,

35.7, 30.8, 21.1, 20.2, 20.3; MS (EI) *m*/*z* 237 ($M^+ - 43$) 209, 170, 131, 105, 91 (100).

2-Acetoxy-2,3-dimethyl-3-phenyloxetane (19). Acetic acid (11 μL, 0.18 mmol) was added to 3-methyl-2-methylene-3-phenyloxetane (**7c**) (25 mg, 0.16 mmol) in CCl_4 (2 mL) in an NMR tube at room temerature. The reaction was monitored by ^{1}H NMR, and after 23 days the reaction reached equilibrium. Integration indicated that 2-acetoxy-2,3-dimethyl-3-phenyloxetane (**19**) was formed in 84% yield, as a mixture (6:1) of diastereomers (16% remaining **7c**): ^{1}H NMR (400 MHz, CCl_4) (major diastereomer) δ 7.20−7.49 (m, 5H), 4.76 (d, J = 5.3 Hz, 1H), 4.18 (d, J = 5.3 Hz, 1H), 2.00 (s, 3H), 1.60 (s, 3H), 1.51 (s, 3H).

1,4-Dibromo-2-methyl-2-phenyl-3-butanone (20). Bromine (77 μL, 0.63 mmol) in CCl_4 (2 mL) was added dropwise, via syringe, to a stirred solution of 3-methyl-3-phenyl-2-methyleneoxetane (**7c**) (0.10 g, 0.63 mmol) in CCl_4 (2 mL) at 0 °C. The rate of addition was such as to maintain the reaction temperature at 0 °C. After 20 min, the reaction mixture was washed with $NaHSO_3$ (5 mL), NaOH 10% (5 mL), and brine (5 mL) and dried ($MgSO_4$). The solvent was removed in vacuo, and the crude product was purified by flash chromatography on silica gel (dry loaded, CH_2Cl_2) (petroleum ether/EtOAc 99:1) to give **20** as a colorless oil (0.16 g, 81%): IR (CH_2Cl_2) 1710 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (m, 3H), 7.24 (m, 2H), 3.98 (d, J = 14 Hz, 1H), 3.97 (d, J = 11 Hz, 1H), 3.84 (d, J = 14 Hz, 1H), 3.72 (d, J = 11 Hz, 1H), 1.80 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.3, 138.7, 129.7, 128.8, 126.7, 56.5, 40.8, 32.4, 21.3; MS (EI) 199, 197, 118 (100), 91, 77; HRMS (EI) calcd for $C_{11}H_{12}Br_2O$ (M^+) 317.9255, found 317.9244.

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Supporting Information Available: Experimental procedures and characterization data for compounds **5b**−**e**. Characterization data for compounds **5l**−**o**, **7a**−**c**,**e**−**t**, **9b**, **11b**,**c**, **12b**,**c**, and **13b**,**c**. Copies of high-resolution ^{1}H NMR spectra of those new compounds for which elemental analyses are not reported. Tables giving crystallograpic details for crystal data and structure refinement, atomic coordinates, bond lengths and angles, anisotropic displacement coefficients, and H-atom coordinates. This material is available free of charge via the Internet at http://pubs.acs.org.

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