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Studies in stereoselective [2+2]-cycloadditions with dichloroketene

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Abstract—During the investigation of the reaction of dichloroketene with cyclic enoxy-lactones and acyclic enoxy-ester substrates it was found that only the acylic variants effectively participated in the [2+2]-cycloaddition. Although a complete understanding of the reasons for this are lacking, molecular mechanics calculations do suggest that an out of plane twist of the cabonyl group in the acyclic compounds may be partially responsible. After screening a variety of chiral auxiliaries it was found that useful levels of diastereoselectivity (2.6–10.8:1) could be obtained in this cycloaddition reaction when (*R*)-2,2-diphenylcyclopentanol was used as the chiral auxiliary.

1. Introduction

(+)-Cryptosporiopsin **1**, a chlorine containing fungal metabolite was isolated in 1969 from *Sporormia affinis*, *Cryptosporiopsis* sp. and *Periconia macrospinosa*.

Bio-assay[1–3] of this natural product against a variety of wood-rotting and other filamentous fungi[2] demonstrated that (+)-cryptosporiopsin was comparable to nystatin in its antibiotic activity. These results strongly suggested that cryptosporiopsin could be used to control microorganisms associated with tree diseases and wood decay.[2]

The first total synthesis of racemic cryptosporiopsin was reported by Strunz and Court in 1973 by a formally biomimetic route.[4] Although the synthesis had the merit of being very concise, the key ring contraction step was a capricious and low yielding process. An improved synthesis was reported by Henderson and Hill a decade later, however, it was rather lengthy.[5]

As a result of the difficulties in the original syntheses, Kabanyane and co-workers[6] recently revisited this natural product, and in 2000, accomplished a new concise synthesis of related chlorine containing fungal metabolites. This synthesis consisted of a total of eight steps and involved a [2+2]-cycloaddition between dichloroketene and a silyl enol ether as one of the key steps. The new strategy provided a quick and efficient route to the carbon framework of this group of natural products, and importantly, in contrast to the original ring contraction approach, opened the way to an asymmetric synthesis. In this context, it should be noted that in a quantitative bioassay, the racemic product was only half as active as the natural material, suggesting that the dextrorotatory enantiomer alone was endowed with the bioactivity.[4]

Upon examination of the Kabanyane route, it is apparent that the crucial stereochemistry is introduced at the [2+2]-cycloaddition stage (Fig. 1). In considering methods to achieve an asymmetric [2+2]-cycloaddition, two options presented themselves; the chirality could be introduced via a substrate-based approach, that is, an optically pure chiral auxiliary covalently bonded to the ketene or the olefin, or, alternatively, the chirality could be derived from an additive such as a chiral Lewis acid. The literature contains examples of each of these strategies. [7–10] Excellent enantioselectivity was achieved in some of the methods described, however, none of the substrate types employed seemed to be directly applicable per se, to the synthesis of our target chlorine

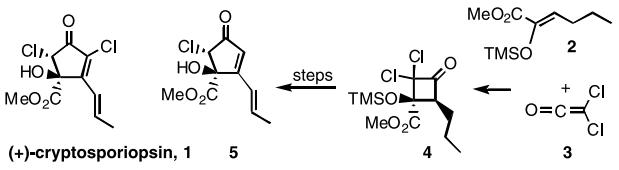

Figure 1. Attempted Kabanyane route to the synthesis of cryptosporiopsin.

Keywords: [2+2]-Cycloaddition; Diastereoselective; Chiral auxiliaries; Dioxolanones.
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containing metabolites since the substrates studied were either of limited scope or under functionalized.

To produce an optically enriched cyclobutanone like **4** (Fig. 1), it was clear that an optically pure equivalent of the enol-ether ester **2** (a tri-substituted olefin) must be employed as the precursor. To achieve this end, we realized that some type of rigid cyclic substrate such as a dioxolanone or lactone might be exploited with advantage, or drawing upon Greene[11] and Kabanyane's[6] work, presumably a suitable acyclic chiral analogue of **2** could be developed (Fig. 2). The following work describes our efforts in trying to design an appropriate substrate to achieve this goal.

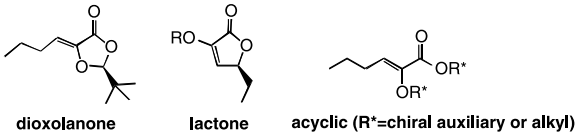
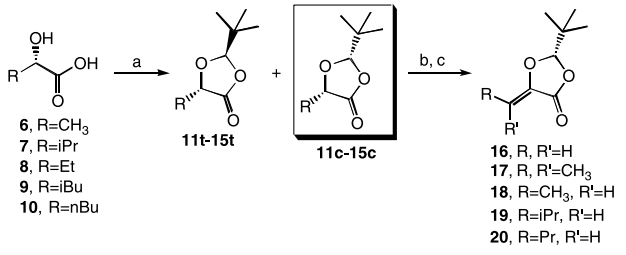


Figure 2. Potential substrates for asymmetric [2+2]-cycloaddition.

2. Results and discussion

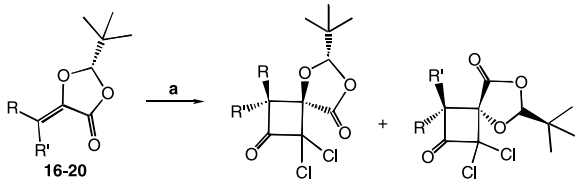
It is well established that asymmetric induction tends to be much higher when the 'chiral inducer' is held in a fixed position. With this in mind, it appeared that optimum selectivity could be obtained by using a chiral dioxolanone substrate possessing the appropriate latent functionality, such as that depicted in Figure 2. Compounds of this type are well known in the literature and have served as excellent substrates in [4+2]-cycloadditions.[12] Examples of their use in [2+2]-cycloaddition chemistry, however, are unknown so it was hoped that dichloroketene would be sufficiently reactive to add to the dioxolanone olefin with similar excellent stereoselectivity.

To initiate this study, a variety of chiral α-hydroxy acids, **6–10**, were condensed with pivaldehyde[13] under acidic catalysis to give a mixture of *cis* and *trans*-dioxolanones **11–15** (**c** and **t**) (4–8:1, 66–74% yields) with the cis-isomer always predominating (Scheme 1). The two isomers in each case were easily separated by silica gel column chromatography. The stereochemistry of the major diastereomer was assigned as the *cis*-dioxolanone by NOE difference experiments and by comparing with literature results.[13] The *cis*-dioxolanones were readily transformed[14] into the requisite olefins **16–20** by bromination with *N*-bromosuccinimide (NBS, 97–99% yields) followed by dehydrobromination with DBU (30–65% yields).



Scheme 1. (a) $(CH_3)_3CCHO$, H_2SO_4, *p*TSA, pentane, Δ; (b) NBS, CCl_4, Δ; (c) DBU, C_6H_6, rt.

With five different olefin substrates made, each was subjected to standard cycloaddition conditions (Cl_3CCOCl, Zn, Et_2O, rt)[15] (Scheme 2). The results are summarized in Table 1. The cyclobutanone obtained from cycloaddition with the dioxolanone olefin **16**, derived from lactic acid **6**, was a 2:1 diastereomeric mixture, as clearly evidenced by ^1H NMR. Thus, for example, the protons on the cyclobutanone gave rise to an AB quartet with the signals for the major diastereomer at δ 3.82 and 3.64 and those for the minor one at δ 2.95 and 2.75. Given the low stereoselectivity one comes to the disappointing conclusion that the *t*-butyl group is not providing facial discrimination to the same extent as in other cycloaddition chemistry. This was very surprising.



Scheme 2. (a) Cl_3CCOCl, Zn, Et_2O, 0 °C–rt.

Table 1. Cycloaddition results of the dioxolanone olefins

Olefin dioxolanone	R′	R″	dr	Yield (%)
16	H	H	2:1	33
17	Me	Me	—	0
18	Me	H	—	0
19	*i*Pr	H	1.4:1	13
20	*n*Pr	H	>95:1	7

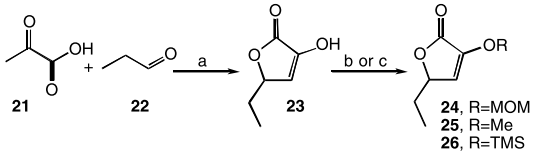
The olefin **17** derived from 2-hydroxy-3-methylbutanoic acid did not undergo cycloaddition; only starting dioxolanone olefin was recovered. This was perhaps not astonishing since **17** is a tetra-substituted alkene and therefore much less reactive towards cycloaddition. Like **17**, the tri-substituted alkene **18** also failed to react. On the other hand, tri-substituted dioxolanone olefins **19** and **20** reacted with dichloroketene to give cycloadducts in very modest yields, ranging from poor (1.4:1) to excellent (>95:5), diastereoselectivity. The reason for the differences in stereoselectivity with these tri-substituted alkenes was not obvious, however, the alkyl chain may confer a preference for a particular rotamer that gives rise to higher levels of selectivity.

Although the dioxolanone olefin cycloaddition approach was conceptually attractive, all cycloadditions were plagued with extremely low yields (0–33%). Attempts to eliminate side reactions[16] in the cycloaddition by using solvents such as dichloromethane or hexane proved fruitless. Additionally, efforts to increase the yield of the cycloadduct by using an excess of trichloroacetyl chloride and zinc, added all at once or in aliquots over a period of time, or using ultrasound and TMSCl[17] also failed.

To explain the reluctance of these cyclic olefins to participate in [2+2]-cycloadditions it was considered that geometric constraints in the rigid ring system might prevent appropriate alignment of the lone pair on the ether oxygen for activation of

the olefin. To gain insight, energy minimization of **20** was done at the MMFF94 (molecular mechanics force field 1994) level. The results indicate that the five-membered ring was essentially planar and co-planar with the olefin (a 2° deviation from co-planarity was not considered significant). Accordingly, adequate donation indeed appeared to be possible.

Although it was initially believed that sterics might not affect reactivity in a major way, it appears that in fact it does. While the unsubstituted dioxolanone **16** gave the highest yield of cycloadduct, tri-substituted olefins **19** and **20** gave diminished product whereas tetra-substituted olefin **17** did not react at all. Coupled with this steric effect was the fact that all alkene substrates studied here contained an alkyl enol-ether, rather than a trimethylsilyloxy-derivative as used by Kabanyane.[6] This change, although minor, might have contributed to the reduced reactivity of these olefins since the ether oxygen would be expected to have less electron density, and therefore be less reactive. To investigate these subtle electronic effects, an alternative cyclic substrate **24** was considered (Scheme 3). This substrate separated the two electronic factors that were potentially influencing the cycloaddition, namely the electron withdrawing nature of the carbonyl and the electron donating nature of the acyclic enol ether.



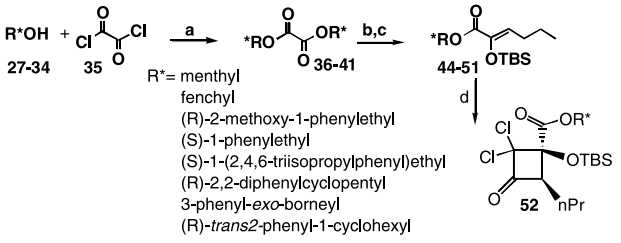
Scheme 3. (a) Concd H_2SO_4, 0 °C–rt; (b) P_2O_5, dimethoxymethane, rt; (c) AgO, CH_3I, CH_3CN, Δ.

Although several asymmetric routes to this substrate can be envisaged, including oxidation of the Mori lactone[18] or degradation of D-ribose[19] or D-mannose,[20] it was considered prudent to test the reactivity of this type of compound first using racemic models. Accordingly, pyruvic acid was condensed with propanal under acidic conditions[21] to give lactone **23** in 17% yield (Scheme 3). Attempts to protect the hydroxyl group under basic conditions resulted in the complete decomposition of starting material. Fortunately the MOM-ether, **24**, and methyl-ether, **25**, could be formed under acid conditions in 57 and 38% yields, respectively.[22,23] Unfortunately, all endeavors aimed at producing silyl ether **26** under acidic[24] or neutral[25,26] conditions failed. Subjection of lactones **24** and **25** to the standard cycloaddition conditions once again proved unsuccessful and only the starting material was recovered.

Given the reluctance of both classes of cyclic compounds investigated above to undergo cycloaddition, it appeared that the electron withdrawing ability of the carbonyl group was overriding any electron donating effect of the ether oxygen. Simple molecular mechanics (MMFF94) calculations on the Kabanyane alkene, methyl 2-trimethylsilyloxyhex-2-enoate, showed that the carbonyl carbon was twisted slightly out of plane (ca. 5°), and although this was only a minimal amount of twisting it would help render the alkene less electron deficient. This twisting effect is not possible in the dioxolanones or lactones. That said, the effect of the silyl group could not be completely dismissed. These results seemed to indicate that we could not take advantage of a rigid cyclic structure to achieve enhanced chiral induction and were thus limited to the use of chiral modifications of the acyclic Kabanyane alkene.

In view of the demonstrated efficiency of dichloroketene cycloaddition to 2-silyloxy-2-enoate esters[6] and because of potential difficulties associated with introduction of chirality into the enol ether moiety in these compounds, we were encouraged to focus on installation of chirality in the ester group. In order to furnish the appropriate compounds the respective α-keto esters had to be first generated.

There were numerous literature reports that described the synthesis of α-keto esters,[27–31] many of which we initially used to generate the various chiral compounds, **44–51**, shown in Scheme 4. However, we eventually found that these compounds could be most conveniently produced via a Grignard addition to oxalates **36–43**.[32] The oxalates themselves were generated in a straightforward manner from oxalyl chloride **35** and enantioenriched alcohols **27–34**. Once synthesized the α-keto esters were then converted to their respective silyl enol ethers following Kabanyane's protocol[6] (Scheme 4). Notably in each case only the *Z*-alkene was formed, this was important since it helped simplify analysis of the cycloaddition products.



Scheme 4. (a) Pyridine, CH_2Cl_2, rt, 24 h; (b) 1.5 equiv *n*BuMgCl, THF, 40 °C, 2 h; (c) TBSCl, DBU, C_6H_6, Δ, 2 h; (d) Cl_3CCOCl, Zn, Et_2O, 0 °C–rt.

With the chiral ester silyl enol ethers synthesized, their utility in the asymmetric [2+2]-cycloaddition reaction was probed. The TBS-enol ethers (**44–51**) were allowed to react, with dichloroketene to give cycloadducts in yields ranging from 31 to 88% (Table 2). The dramatic rise in yield realized with these substrates leant credence to our earlier observations and predictions concerning the influence of electronic effects. Examination of Table 2 shows that simple terpene based auxiliaries gave moderate levels of selectivity, 1-phenylethanol and 'synthetic' auxiliary derived

Table 2. Cycloaddition results of the enoxy-ester olefins

Entry	R*	dr	Yield (%)
1	Menthyl	1.7:1	88
2	Fenchyl	2.2:1	77
3	(*R*)-2-Methoxy-1-phenylethyl	1.3:1	35
4	(*S*)-1-Phenylethyl	1.2:1	31
5	(*S*)-1-(2,4,6-Triisopropylphenyl)ethyl	4:1	83
6	(*R*)-2,2-Diphenylcyclopentyl	7.5:1	79
7	3-Phenyl-isoborneol	2.4:1	31
8	(*R*)-*trans* 2-Phenyl-1-cyclohexyl	2.8:1	65

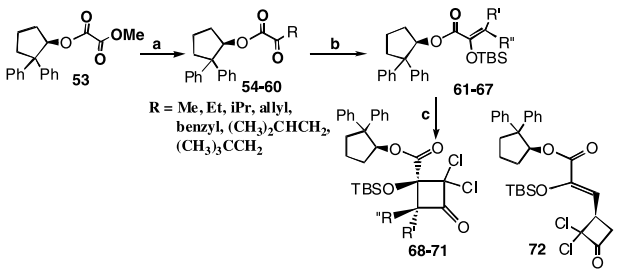
substrates ranged from poor (entries 3 and 4) to moderate (entries 7 and 8) to acceptable levels of selectivities (entries 5 and 6).

It was observed that the *trans* 2-phenyl-1-cyclohexanol derivative, entry 8, was consumed immediately after complete addition of trichloroacetyl chloride. This was not observed in any of the other cycloadditions: in fact, all other cycloadditions took 18–24 h to go to completion. Since this cycloaddition occurred at a significantly greater rate, a temperature study was done to see if the stereoselectivity could be improved. It was found that at 0 °C a 3.5:1 dr was obtained while at −30 °C no observable reaction was detected, even after 24 h.

It was gratifying to find that Denmark's diphenylcyclopentanol auxiliary,[33] present in entry 6, gave acceptable levels of asymmetric induction. Since the cycloadduct was crystalline, simple recrystallization from hexane increased the diasteromeric ratio to 11.5:1. Although not pursued, presumably further recrystallizations would produce a diastereomerically pure cycloadduct.

Since it was not evident how important a role the silyloxy function played in determining the course of the cycloaddition, either in rate or stereoselectivity, a quick investigation into the use of other silyl groups was pursued. Upon changing to the less robust trimethylsilyl ether (TMS) no change in reaction rate or stereoselectivity was observed. However, when the *t*-butyldiphenylsilyl ether (TBDPS) was used only starting silyl enol ether was recovered. This was surprising but presumably meant that both faces of the alkene were now effectively blocked from reaction.

Given the success of the diphenylcyclopentyl auxiliary it remained to be seen how limited the scope of this cycloaddition was. To probe this a variety of substrates were generated that explored both the electronic and steric limitations of this reaction (Scheme 5). When compounds **61**–**67** were subjected to the standard cycloaddition several trends became abundantly clear (Table 3). First, successful cycloaddition is only possible if the olefin is not overly hindered. For example, when the olefin is tetrasubstituted or R is very bulky (*t*Bu) then either no reaction is observed or the rate is greatly diminished. Second, if alternative alkenes are present in the molecule then they react in preference to the enoxy-alkene. Third, additional conjugation of the enoate with a phenyl group completely inactivates the reaction. Finally, diastereomeric ratios improve as R



Scheme 5. (a) 1.5 equiv RMgCl, THF, 40 °C, 2 h; (b) TBSCl, DBU, C_6H_6, Δ, 2 h; (d) Cl_3CCOCl, Zn, Et_2O, 0 °C–rt.

Table 3. Cycloaddition results of different alkyl substituted dioxolanone olefins

Olefin dioxolanone	R′	R″	dr	Yield (%) (product)
61	H	H	3.5:1	80 (**68**)
62	H	Me	3.8:1	68 (**69**)
63	Me	Me	—	No reaction
64	H	Vinyl	2.6:1	44 (**72**)
65	H	Ph	—	No reaction
66	H	*i*Bu	10.8:1	94 (**70**)
67	H	*t*Bu	8.2:1	32 (**71**)

increases in size, at least to a point. This suggests that the observed good levels of diasteroselectivities in this reaction are the result of a balancing of nonbonding steric interactions between the chiral auxiliary, the silyl ether and the alkyl group attached to the alkene.

Molecular modeling of the (*R*)-2,2-diphenylcyclopentyl chiral enol ether† using the MMFF94 force field was performed in order to ascertain some type of transition state model. These calculations allowed prediction that *Si*-face addition of dichloroketene should be more favorable than the *Re*-face addition when using (*R*)-2,2-diphenylcyclopentanol as the chiral auxiliary (Fig. 3). Although there were many low energy conformations (approximately 20 within 2.5 kcal/mol) 15 of them adopted the *s*-trans conformation with all having the *Si*-face more accessible for cycloaddition. Of the remaining five low energy conformations they all had the *s*-cis arrangement, again with the *Si*-face most accessible.

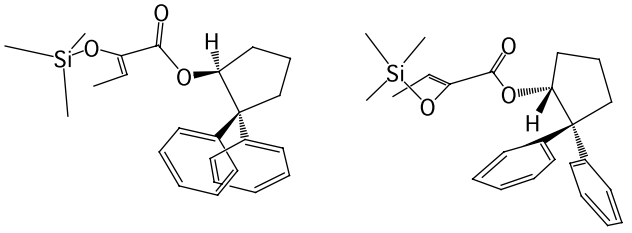


Figure 3. Molecular mechanics (MMFF94) calculated structures of *S*-diphenylcyclopentyl TMS-enol ester.

Of particular interest in these calculations was that a dihedral angle of 139° between the carbonyl and the carbon–carbon double bond (O═C–C═C) was observed. This twist, reducing the electron-attracting effect of the ester carbonyl, once again helps to explain the enhanced reactivity of this alkene towards [2+2]-cycloaddition. Although these calculations were not performed on the other enoxy-ester models we believe that the same subtleties exist, but to varying degrees, and thus account for the reactivities and stereoselectivities that were observed.

Lastly, the absolute stereochemistry was shown to coincide with our transition state model by conversion[34]

† A modified version of enoxy-ester **62** was used in order to simplify the calculations; the TBS-group was replaced with a TMS-group.

of cycloadduct **52** into (−)-cryptosporiopsin, a known natural product.[35] Since the (−)-enantiomer was generated this indeed meant that dichloroketene added to the *Si*-face of **49**, consistent with the molecular mechanics calculations.

3. Conclusion

During the investigation of the reaction of dichloroketene with cyclic enoxy-lactones and acyclic enoxy-ester substrates it was found that only the acylic variants effectively participated in the [2+2]-cycloaddition. Although complete understanding of this discrepancy is lacking at this time, molecular mechanics calculations do suggest that an out of plane twist of the cabonyl group (up to 41° see Fig. 3) in the acyclic compounds may be partially responsible. An additional factor may be the nucleophilicty of the enoxy oxygen since only the silyloxy derivatives gave efficient reaction. Acyclic silyl enol ether substrates bearing a chiral auxiliary on the ester proved to be viable candidates for the production of optically enriched cycloadducts with diastereomeric ratios ranging from 1.5–10.8:1. Effort to further improve the diastereoselection is currently in progress.

4. Experimental

4.1. General experimental procedures

All reactions except those stated otherwise were performed under inert atmospheres of either argon or nitrogen in flame dried glassware (Pyrex). All solvents were dried according to established procedures prior to use.[36] Standard techniques were used in handling air sensitive reagents. All commercially available reagents and solvents were used without further purification. All oxalates required for the preparation of 2-enoxy-esters **44**–**51** and **61**–**67** were synthesized according to literature,[32] Silicycle Ultra Pure Silica Gel was used for all flash chromatography. All ^{1}H and ^{13}C NMR spectra were performed on a Varian UNITY 400 MHz or Varian (INOVA 300 MHz) spectrometer. Optical rotation measurements were taken on a Perkin-Elmer 241 Polarimeter using the Na lamp. All IR spectra were recorded on a Bruker IFS 25 instrument and all mass spectra were run on a Kratos MS50 instrument and were done under electron impact conditions at 80 eV unless stated otherwise.

4.2. General preparation of olefin dioxolanone, 16–20

A mixture of α-hydroxy acid (10 mmol), pivaldehyde (2.2 mL, 20 mmol), *p*TSA (50 mg), and concd H_2SO_4 (2 drops) in pentane (70 mL) was heated to reflux with azeotropic removal of the water using a Dean Stark apparatus. After complete reaction, the mixture was diluted with ether and washed with H_2O (1×), brine (1×), dried over $MgSO_4$ and the solvent evaporated. Purification by SiO_2 chromatography using hexane/ethyl acetate as eluant furnished the *cis*-dioxolanones as colorless oils.

N-Bromosuccinimide (1.33 g, 7.4 mmol) in carbon tetrachloride (20 mL) was combined with *cis*-dioxolanone (5 mmol) in carbon tetrachloride (5 mL). The reaction mixture was heated at reflux for 3 h, cooled and then filtered. The solvent was removed in vacuo to provide the bromo-dioxolanones as pale green oils of sufficient purity to be used directly in the next step.

To a solution of brominated dioxolanone (5 mmol) in benzene (20 mL) was added DBU (0.85 mL, 5.75 mmol) dropwise over 5 min at rt. After complete addition, the mixture was stirred for 20 min then filtered and the solvent was removed. The crude product was purified by SiO_2 chromatography using 20:1 hexane/ethyl acetate to furnish the olefins as pale yellow oils.

4.2.1. (*S*)-2-*tert*-Butyl-5-methylene-[1,3]dioxolan-4-one, 16. 39% overall yield from (*S*)-lactic acid. ^{1}H NMR ($CDCl_3$): δ 1.00 (s, 9H), 4.86 (d, J=2.6 Hz, 1H), 5.13 (d, J=2.6 Hz, 1H), 5.44 (s, 1H). ^{13}C NMR ($CDCl_3$): δ 22.8, 35.9, 90.8, 144.2, 162.5. IR (NaCl plates, cm^{-1}): 3020, 2972, 2940, 2883, 1796, 1670, 1475, 1311, 1133, 992. MS: m^{+}/z=156.0787 (calculated 156.0787). $[\alpha]_D^{22}$ −1.9 (*c* 1.1, CH_2Cl_2).

4.2.2. (*Z*)-(*S*)-2-*tert*-Butyl-5-ethylidene-[1,3]dioxolan-4-one, 17. 22% yield from (*S*)-2-hydroxybutanoic acid. ^{1}H NMR ($CDCl_3$): δ 0.97 (s, 9H), 1.77 (d, J=7.8 Hz, 3H), 5.42 (s, 1H), 5.60 (q, J=7.6 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ 10.7, 22.8, 35.8, 105.0, 109.5, 139.2, 163.0. IR (NaCl plates, cm^{-1}): 2970, 2924, 2876, 1798, 1702, 1478, 1342, 1240, 1134, 1086, 968. MS: m^{+}/z=170.0941 (calculated=170.0943). $[\alpha]_D^{22}$ +33.7 (*c* 1.55, CH_2Cl_2).

4.2.3. (*Z*)-(*S*)-2-*tert*-Butyl-5-(2-methylpropylidene)-1,3-dioxolan-4-one 18. 44% yield from (*S*)-2-hydroxy-4-methylpentanoic acid. ^{1}H NMR ($CDCl_3$): δ 0.92 (s, 9H) 1.79 (s, 3H), 2.04 (s, 3H), 5.29 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 16.7, 19.2, 23.0, 35.8, 108.3, 121.5, 133.4, 162.9. IR (NaCl plates, cm^{-1}): 2958, 2912, 2876, 1774, 1678, 1490, 1276, 1216, 1158, 1074, 980, 730. MS: m^{+}/z=184.1094 (calculated 184.1099). $[\alpha]_D^{25}$ −16.6 (*c* 2.7, CH_2Cl_2).

4.2.4. (*Z*)-(*S*)-2-*tert*-Butyl-5-(3-methylbutylidene)-1,3-dioxolan-4-one, 19. 21% yield from (*S*)-2-hydroxy-5-methylhexanoic acid. ^{1}H NMR ($CDCl_3$): δ 0.99 (s, 9H) 1.10 (d, J=6.1 Hz, 6H), 2.72 (d of heptet, J=4.4, 6.2 Hz, 1H), 5.42 (s, 1H), 5.49 (d, J=4.5 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ 22.1, 23.0, 25.8, 36.2, 109.7, 116.9, 137.0, 163.7. IR (NaCl plates, cm^{-1}): 2958, 2918, 2854, 1794, 1690, 1478, 1362, 1302, 1216, 1150, 1076, 988, 732. MS: m^{+}/z= 198.1254 (calculated=198.1256). $[\alpha]_D^{25}$ −34.0 (*c* 1.72, CH_2Cl_2).

4.2.5. (*Z*)-(*S*)-2-*tert*-Butyl-5-butylidene-[1,3]dioxolan-4-one 20. 31% yield from (*S*)-2-hydroxyhexanoic acid. ^{1}H NMR ($CDCl_3$): δ 0.95 (t, J=7.3 Hz, 3H), 0.98 (s, 9H), 1.49 (heptet, J=7.4 Hz, 2H), 2.19 (q, J=7.1 Hz, 2H), 5.42 (s, 1H) 5.59 (t, J=7.7 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ 13.9, 22.0, 23.0, 27.5, 36.1, 109.7, 110.2, 138.7, 163.4. IR (NaCl plates, cm^{-1}): 2978, 2918, 2854, 1794, 1690, 1478, 1406, 1368, 1310, 1208, 1090, 974, 740. MS: m^{+}/z=198.1260 (calculated=198.1256). $[\alpha]_D^{25}$ −28.4 (*c* 1.02, CH_2Cl_2).

4.2.6. Preparation of 5-ethyl-3-methoxymethoxy-5*H*-furan-2 one, 24. In a flask cooled in an ice bath was put

concd H_2SO_4 (30 mL) followed by a mixture of pyruvic acid (7.85 mL, 0.114 mol) and propanal (8.19 mL, 0.11 mol) dropwise over 30 min. The temperature of the reaction mixture was maintained below 5 °C. After complete addition the dark colored mixture was poured into cold H_2O (60 mL) and extracted with ether (3×). The combined organic extracts were washed with H_2O, 5% HCl, brine, dried over $MgSO_4$ and solvent evaporated. The residue was purified by SiO_2 chromatography (3:1 hexane/ethyl acetate) to give lactone **23** (2.54 g, 17%) as a brown oil.

To a solution of enol lactone **23** (500 mg) and CH_2Cl_2 (20 mL) was added dimethoxymethane (23 mL, 264 mmol) and P_2O_5 (1.95 g, 17.0 mmol). The reaction mixture was stirred overnight, diluted with ether and then poured into a cold Na_2CO_3 solution. The organic layer was then washed with brine, dried over Na_2SO_4 and the solvent evaporated. The oily residue was purified by SiO_2 chromatography (3:1 hexane/ethyl acetate) to give MOM-lactone **24** (510 mg, 76%) as a tan colored oil. ^{1}H NMR ($CDCl_3$): δ 1.00 (t, J=7.5 Hz, 3H), 1.76 (dq, J=7.2, 11.0 Hz, 2H), 3.50 (s, 3H), 4.90 (dt, J=1.9, 6.3 Hz, 1H), 5.11 (s, 2H) 6.38 (d, J=1.9 Hz, 1H). ^{13}C NMR ($CDC1_3$): δ 8.8, 27.2, 56.6, 80.0, 96.0, 121.0, 143.7, 168.2. IR (NaCl plates, cm^{-1}): 2958, 2901, 2832, 1772, 1654, 1456, 1236, 1156, 1128, 1084, 958. MS: m^+/z=172.0739 (calculated=172.0736).

4.3. General preparation of TBS-enoxy esters 44–51 and 60–67

A mixture of α-keto ester[32] (1.9 g, 5.5 mmol) and TBS-Cl (1.0 g, 6.6 mmol) in THF (35 mL) was added dropwise to a solution of DBU (1.24 mL, 8.3 mmol) in THF (5 mL). The reaction mixture was stirred at rt for 12 h then diluted with ether and filtered through Celite®. The filtrate was washed with cold HCl (5%, 2×), H_2O (1×), brine (1×), dried over $MgSO_4$ and the solvent removed in vacuo. Purification by SiO_2 chromatography provided silyl enol ethers **44–51** and **61–67**.

4.3.1. (*Z*)-(1*R*,2*S*,5*R*)-2-Isopropyl-5-methylcyclohexy 2-*tert*-butyldimethylsilyloxyhex-2-enoate, 44. Colorless oil, 65% yield. ^{1}H NMR ($CDCl_3$): δ 0.15 (s, 3H), 0.17 (s, 3H), 0.75 (d, J=6.8 Hz, 3H), 0.89 (t, J=6.3 Hz, 3H), 0.92 (d, J=7.5 Hz, 3H), 0.94 (d, J=7.4 Hz, 3H), 0.96 (s, 9H), 1.02 (m, 2H), 1.43 (q, J=2.7 Hz, 1H), 1.68 (m, 2H), 1.88 (m, 1H), 2.00 (m, 1H), 2.17 (m, 2H), 4.73 (t of d, J=4.4, 10.9 Hz, 1H), 5.98 (t, J=7.4 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ −4.3, −4.2, 14.0, 16.4, 18.6, 20.6, 22.0, 22.1, 23.3, 25.9, 26.3, 27.8, 31.4, 34.3, 40.8, 47.1, 74.8, 122.5, 140.9, 164.5. IR (NaCl plates, cm^{-1}): 2936, 2854, 1712, 1648, 1464, 1150, 834. MS: [$m^+/z-C_6H_{15}Si$]=267.1960 (calculated=267.1964). $[\alpha]_D^{25}$ −36.5 (*c* 2.6, EtOH).

4.3.2. (*Z*)-(1*R*)-1,3,3-Trimethylbicyclo[2.2.1]heptan-2-yI 2-*tert*-butyldimethylsilyloxyhex-2-enoate, 45. Colorless oil, 42% yield. ^{1}H NMR ($CDCl_3$): δ 0.17 (s, 3H), 0.17 (s, 3H), 0.78 (s, 3H), 0.94 (t, J=7.4 Hz, 3H), 0.97 (s, 9H), 1.05 (s, 2H), 1.11 (s, 2H), 1.21 (m, 2H), 1.4 (m, 3H), 1.59 (d of d, J=1.7, 10.3 Hz, 1H), 1.74 (m, 3H), 2.19 (q, J=7.4 Hz, 2H), 4.44 (d, J=1.9 Hz, 1H), 6.00 (t, J=7.4 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ −4.3, 13.9, 18.6, 19.4, 20.4, 22.1, 25.5, 25.9, 26.8, 27.7, 29.8, 39.8, 41.4, 48.3, 48.5, 76.3, 86.4, 122.2, 140.7, 165.1. IR (NaCl plates, cm^{-1}): 2958, 2874, 1720, 1640, 1464, 1252, 1150, 842. MS: [$m^+/z-C_6H_{15}Si$]=265.1804 (calculated=265.1804). $[\alpha]_D^{25}$ +14.9 (*c* 2.37, EtOH).

4.3.3. (*Z*)-(*R*)-2-Methoxy-1-phenylethyl 2-*tert*-butyldimethylsilyloxyhex-2-enoate, 46. Colorless oil, 67% yield. ^{1}H NMR ($CDCl_3$): δ 0.09 (s, 3H), 0.14 (s, 3H), 0.93 (t, J=3.6 Hz, 3H), 0.94 (s, 9H), 1.43 (q, J=7.5 Hz, 2H), 2.17 (q, J=7.3 Hz, 2H), 3.36 (s, 3H), 3.59 (d of d, J=4.1, 10.9 Hz, 1H), 3.75 (d of d, J=7.9, 10.8 Hz, 1H), 6.01 (d of d, J=3.9, 7.9 Hz, 1H), 6.11 (t, J=7.5 Hz, 1H), 7.30 (m, 5H). ^{13}C NMR ($CDCl_3$): δ −4.4, 14.0, 18.5, 22.0, 25.8, 27.9, 59.0, 74.7, 75.3, 123.5, 126.7, 128.2, 137.5, 140.6, 164.1. IR (NaCl plates, cm^{-1}): 2936, 1728, 1648, 1456, 1150, 834, 702. MS: [$m^+/z-C_6H_{15}Si$]=378.2226 (calculated=378.2226). $[\alpha]_D^{25}$ −28.4 (*c* 1.05, EtOH).

4.3.4. (*Z*)-(*R*)-1-Phenylethyl2-*tert*-butylydimethylsilyloxyhex-2-enoate, 47. Colorless oil, 77% yield. ^{1}H NMR ($CDCl_3$): δ 0.09 (s, 3H), 0.13 (s, 3H), 0.95 (t, J=7.5 Hz, 3H), 0.95 (s, 9H), 1.43 (sextet, J=7.5 Hz, 2H), 1.58 (d, J=5.0 Hz, 3H), 2.17 (d of q, J=0.9, 7.2 Hz, 2H), 5.94 (q, J=6.3 Hz, 1H), 6.08 (t, J=7.5 Hz, 1H), 7.25–7.4 (m, 5H). ^{13}C NMR ($CDCl_3$): δ −3.98, −3.93, 14.3, 18.9, 22.4, 22.5, 26.2, 28.2, 73.2, 123.5, 126.5, 128.2, 128.8, 141.2, 141.9, 164.6. IR (NaCl plates, cm^{-1}): 2946, 2855, 1720, 1640, 1456, 1368, 1258, 1142, 834. MS: [$m^+/z-C_{12}H_{18}$]=186.0717 (calculated=186.0712), $[C_8H_9]^+$=105.0705 (calculated=105.0704). $[\alpha]_D^{25}$ +2.2 (*c* 1.08, CH_2Cl_2).

4.3.5. (*Z*)-(*R*)-1-(2,4,6-Triisopropylphenyl)ethyl 2-*tert*-butyldimethylsilyloxyhex-2-enoate, 48. Colorless waxy solid, 72% yield. ^{1}H NMR (DMSO, 80 °C): δ 0.06 (s, 3H) 0.12 (s, 3H), 0.88 (t, J=7.3 Hz, 3H), 0.92 (s, 9H), 1.19 (d, J=7.0 Hz, 12H) 1.24 (d, J=6.8 Hz, 6H), 1.37 (h, J=7.5 Hz, 2H), 1.59 (d, J=7.0 Hz, 3H), 2.13 (q, J=7.5 Hz, 2H), 2.84 (heptet, J=6.8 Hz, 1H), 3.52 (broad heptet, J=6.7 Hz, 2H) 5.96 (t, J=7.5 Hz, 1H), 6.47 (q, J=6.8 Hz, 1H), 7.00 (s, 2H). ^{13}C NMR (DMSO, 80 °C): δ −4.8, −4.7, 13.1, 17.7, 21.0, 21.4, 23.21, 23.24, 23.7, 24.1, 25.3, 26.8, 28.3, 32.9, 35.9, 68.2, 121.2, 121.4, 131.4, 140.3, 147.3, 163.1. IR (NaCl plates, cm^{-1}): 2948, 2855, 1722, 1644, 1452, 1367, 1268, 1060, 834. MS: (30 eV): [m^+/z]=473.3451 (calculated=473.3451). $[\alpha]_D^{25}$ +3.2 (*c* 1.45, CH_2Cl_2).

4.3.6. (*Z*)-(*R*)-2,2-Diphenylcyclopentyl 2-*tert*-butyldimethylsilyloxyhex-2-enoate, 49. Colorless oil, 70% yield. ^{1}H NMR ($CDCl_3$): δ 0.108 (s, 3H), 0.11 (s, 3H), 0.79 (t, J=7.4 Hz, 3H), 0.92 (s, 9H), 1.24 (m, 2H) 1.57 (m, 1H), 1.75 (m, 1H), 1.95 (m, 1H), 2.23 (m, 1H) 2.47 (m, 1H), 2.63 (m, 1H), 5.33 (t, J=7.9 Hz, 3H), 6.01 (m, 1H), 7.17 (m, 10H). ^{13}C NMR ($CDCl_3$): δ −4.4,−4.3, 13.8, 14.1, 18.5, 20.4, 21.8, 22.7, 25.8, 27.5, 30.6, 31.6, 35.5, 59.1, 80.3, 123.0, 125.8, 126.1, 127.88, 127.9, 128.4, 140.4, 145.0, 145.6, 164.4. IR (NaCl plates, cm^{-1}) 2936, 1720, 1648, 1376, 1252, 1150, 834. MS: [$m^+/z-C_6H_{15}Si$]=349.1791 (calculated=349.1804). $[\alpha]_D^{25}$ −37.0 (*c* 3.0, CH_2Cl_2).

4.3.7. (*Z*)-(1*R*,2*R*,3*S*,4*S*)-4,7,7-Trimethyl-3-phenylbicyclo[2.2.1]heptan-2-yl 2-*tert*-butyldimethylsilyloxyhex-2-enoate, 50. Colorless of 77% yield. ^{1}H NMR ($CDCl_3$):

δ −0.05 (s, 3H), 0.04 (s, 3H), 0.61 (t, J=7.4 Hz, 3H), 0.82 (s, 9H), 0.88 (m, 2H), 1.01 (s, 3H), 1.30 (s, 3H), 1.32 (s, 3H), 1.55 (m, 2H), 1.71 (m, 3H), 1.94 (m, 1H), 2.03 (d, J= 5.1 Hz, IH), 4.09 (d, J=8.7 Hz, 1H), 4.25 (t, J=7.0 Hz, 1H), 5.39 (d, J=8.7 Hz, 1H), 7.41 (m, 3H), 7.66 (m, 2H), 7.76 (d of d, J=1.4, 8.0 Hz, 1H), 8.00 (d, J=8.4 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ −4.8, −4.5, 13.7, 14.8, 18.4, 21.6, 21.7, 23.9, 23.93, 25.8, 26.1, 27.2, 42.6, 48.2, 49.3, 51.1, 55.4, 76.3, 80.3, 122.4, 123.3, 124.3, 125.0, 126.1, 126.6, 126.8, 128.8, 133.4, 133.5, 135.9, 139.9, 163.7. IR (NaCl plates, cm^{-1}): 2948, 1726, 1632, 1466, 1252, 1146, 836, 778. MS: [$m^+/z-C_6H_{15}Si$]=391.2274 (calculated= 391.2273). $[\alpha]_D^{25}$ −53.5 (c 1.05, EtOH).

4.3.8. (*Z*)-(1*R*,2*S*)-2-Phenylcyclohexyl 2-*tert*-butyldimethylsilyloxyhex-2-enoate, 51. Colorless oil 75% yield. ^{1}H NMR ($CDCl_3$): δ −0.04 (s, 3H), 0.02 (s, 3H), 0.86 (t, J=9.8 Hz, 3H), 0.91 (s, 9H), 1.23–1.65 (m, 4H), 1.31 (q, J=9.8 Hz, 2H), 1.78–2.21 (m, 4H), 2.02 (dq, J=1.1, 10.1 Hz, 2H), 2.72 (ddd, J=5.0, 17.2, 16.4 Hz, 1H) 4.96 (dt, J=6.1, 14.0 Hz, 1H), 5.66 (t, J=9.9 Hz, 1H), 7.18 (m, 5H). ^{13}C NMR ($CDCl_3$): δ −4.4, −4.2, 10.7, 14.0, 18.7, 22.1, 24.9, 26.0, 27.7, 32.5, 34.1, 50.0, 122.7, 126.5, 127.1, 128.4, 140.7, 143.3, 164.4. IR (NaCl plates, cm^{-1}): 2946, 1730, 1630, 1456, 1250, 1146, 832, 778. MS: (30 eV): [$m^+/z-C_4H_9$]=345.1886 (calculated=345.1886). $[\alpha]_D^{25}$ −11.6 (c 3.1, CH_2Cl_2).

4.3.9. (*R*)-2,2-Diphenylcyclopentyl 2-(*tert*-butyldimethylsilyloxy)acrylate, 61. Colorless oil, 71%. ^{1}H NMR ($CDCl_3$): δ 0.00 (s, 3H), 0.04 (s, 3H), 0.84 (s, 9H), 1.54 (m, 1H), 1.67–1.89 (m, 2H), 2.14 (m, 1H), 2.45–2.62 (m, 2H), 4.60 (d, J=1.0 Hz, 1H), 4.95 (d, J=1.0 Hz, 1H), 6.04 (dd, J=2.6, 0.9 Hz, 1H), 7.01–7.26 (m, 10H). ^{13}C NMR ($CDCl_3$): δ −5.1, −5.0, 18.2, 20.4, 25.5, 30.5, 35.1, 59.2, 80.7, 103.6, 125.8, 126.1, 126.5, 127.8, 127.9, 128.4, 144.8, 145.4, 147.3, 163.8. IR (NaCl plates, cm^{-1}): 3059, 3032, 2955, 2884, 2857, 1730, 1624, 1599, 1485, 1463, 1447, 1377, 1322, 1253, 1169, 1031, 1005. MS: [$m^+/z-C_6H_{15}Si$]=307.1330 (calculated=307.1334). $[\alpha]_D^{25}$ −76 (c 0.48, EtOH).

4.3.10. (*Z*)-(*R*)-2,2-Diphenylcyclopentyl 2-(*tert*-butyldimethylsilyloxy)but-2-enoate, 62. Colorless oil, 69%. ^{1}H NMR ($CDCl_3$): δ 0.11 (s, 3H), 0.13 (s, 3H), 0.94 (s, 9H), 1.56 (d, J=7.1 Hz, 3H), 1.61–1.79 (m, 2H), 1.91 (m, 1H), 2.20 (m, 1H), 2.48–2.67 (m, 2H), 5.49 (q, J=7.1 Hz, 1H), 6.04 (dd, J=5.3, 2.6 Hz, 1H), 7.07–7.31 (m, 10H). ^{13}C NMR ($CDCl_3$): δ −4.37, −4.28, 11.3, 18.5, 20.4, 25.8, 30.5, 35.3, 59.1, 80.3, 117.6, 125.8, 126.1, 126.6, 127.9, 128.4, 141.5, 144.9, 145.6, 164.1. IR (NaCl plates, cm^{-1}): 3087, 3059, 3024, 2956, 2884, 2857, 1717, 1648, 1598, 1494, 1472, 1447, 1389, 1343, 1264, 1145, 1090. MS: [$m^+/z-C_6H_{15}Si$]=321.1503 (calculated=321.1491). $[\alpha]_D^{25}$ −73 (c 0.95, EtOH).

4.3.11. (*R*)-2,2-Diphenylcyclopentyl 2-(*tert*-butyldimethylsilyloxy)-3-methylbut-2-enoate, 63. White solid, 44%. Mp: 56–58 °C. ^{1}H NMR ($CDCl_3$): δ 0.07 (s, 3H), 0.09 (s, 3H), 0.93 (s, 9H), 1.43 (s, 3H), 1.59 (m, 1H), 1.68 (s, 3H), 1.75–1.99 (m, 2H), 2.18 (m, 1H), 2.53–2.69 (m, 2H), 6.27 (d, J=4.9 Hz, 1H), 7.05–7.27 (m, 8H), 7.36 (d, J=8.2 Hz, 2H). ^{13}C NMR ($CDCl_3$): δ −4.3, −4.2, 18.4, 19.2, 20.3, 20.7, 25.9, 30.8, 35.0, 59.2, 80.9, 125.7, 126.1, 126.4, 128.8, 127.9, 128.0, 128.4, 136.2, 145.10, 145.13, 165.3. IR (NaCl plates, cm^{-1}): 3059, 3023, 2955, 2929, 2857, 1704, 1634, 1472, 1463, 1371, 1300, 1250, 1192, 1090. MS: [$m^+/z-C_6H_{15}Si$]=335.1645 (calculated=335.1647). $[\alpha]_D^{25}$ −63 (c 0.40, EtOH).

4.3.12. (*Z*)-(*R*)-2,2-Diphenylcyclopentyl 2-(*tert*-butyldimethylsilyloxy)penta-2,4-dienoate, 64. Colorless oil, 16%: ^{1}H NMR ($CDCl_3$): δ 0.14 (s, 3H), 0.143 (s, 3H), 0.94 (s, 9H), 1.56–1.82 (m, 2H), 1.92 (m, 1H), 2.26 (m, 1H), 2.48 (m, 1H), 2.67 (dt, J=12.9, 9.3 Hz, 1H), 5.13 (m, 2H), 5.83 (d, J=11.0 Hz, 1H), 6.03 (dd, J=5.7, 3.1 Hz, 1H), 6.60 (ddd, J=17.0, 11.0, 10.0 Hz, 1H), 7.09–7.34 (m, 10H). ^{13}C NMR ($CDCl_3$): δ −4.3, −4.1, 18.6, 20.4, 25.8, 30.7, 35.5, 59.1, 80.6, 120.2, 120.6, 125.9, 126.2, 126.6, 127.9, 128.0, 128.4, 130.4, 140.3, 144.9, 145.6, 164.4. IR (NaCl plates, cm^{-1}): 3060, 3024, 2956, 2929, 2857, 1726, 1645, 1599, 1495, 1471, 1390, 1362, 1255, 1151. MS: [$m^+/z-C_6H_{15}Si$]=333.1489 (calculated=333.1491). $[\alpha]_D^{25}$ −40 (c 0.70, EtOH).

4.3.13. (*Z*)-(*R*)-2,2-Diphenylcyclopentyl 2-(*tert*-butyldimethylsilyloxy)-3-phenylacrylate, 65. Colorless oil, 44%. ^{1}H NMR ($CDCl_3$): δ 0.12 (s, 3H), 0.13 (s, 3H), 0.91 (s, 9H), 1.66 (m, 1H), 1.77–1.98 (m, 2H), 2.30 (m, 1H), 2.51 (m, 1H), 2.72 (dt, J=12.3, 9.1 Hz, IH), 6.05 (t, J=2.9 Hz, 1H), 6.07 (s, 1H), 7.13–7.33 (m, 13H), 7.49 (d, J=7.0 Hz, 2H). ^{13}C NMR ($CDCl_3$): δ −3.9, −3.8, 18.6, 20.4, 25.8, 30.6, 35.6, 59.1, 80.7, 118.5, 125.9, 126.1, 126.6, 127.8, 127.9, 128.0, 128.4, 129.7, 129.8, 134.1, 140.3, 144.9, 145.6, 164.9. IR (NaCl plates, cm^{-1}): 3058, 3024, 2956, 2929, 2883, 2857, 1717, 1634, 1598, 1494, 1463, 1386, 1321, 1254, 1130, 1071, 1006. MS: [$m^+/z-C_6H_{15}Si$]=383.1643 (calculated=383.1647). $[\alpha]_D^{25}$ −81 (c 0.99, EtOH).

4.3.14. (*Z*)-(*R*)-2,2-Diphenylcyclopentyl 2-(*tert*-butyldimethylsilyloxy)-4-methylpent-2-enoate, 66. Colorless oil, 61%. ^{1}H NMR ($CDCl_3$): δ 0.12 (s, 3H), 0.13 (s, 3H), 0.77 (d, J=6.7 Hz, 3H), 0.86 (d, J=6.7 Hz, 3H), 0.93 (s, 9H), 1.59 (m, 1H), 1.78 (m, 1H), 1.90 (m, 1H), 2.27 (m, 1H), 2.45 (ddd, J=12.3, 7.9, 1.7 Hz, 1H), 2.59–2.72 (m, 2H), 5.08 (d, J=9.7 Hz, 1H), 6.00 (dd, J=5.7, 2.7 Hz, 1H), 7.08–7.34 (m, 10H). ^{13}C NMR ($CDCl_3$): δ −4.4, −4.3, 18.6, 20.5, 22.0, 22.1, 24.8, 25.8, 30.7, 35.6, 59.3, 80.3, 125.8, 126.1, 126.6, 127.9, 128.0, 128.3, 129.8, 138.5, 145.0, 145.6, 164.6. IR (NaCI, plates, cm^{-1}): 3088, 3060, 3025, 2957, 2857, 1716, 1643, 1599, 1494, 1471, 1447, 1387, 1362, 1303, 1257, 1157, 1113, 1032, 1007. MS: [$m^+/z-C_6H_{15}Si$]=349.1802 (calculated=349.1804). $[\alpha]_D^{25}$ −66 (c 0.92, EtOH).

4.3.15. (*Z*)-(*R*)-2,2-Diphenylcyclopentyl 2-(*tert*-butyldimethylsilyloxy)-4,4-dimethylpent-2-enoate, 67. White Solid, 21%. Mp: 94–96 °C. ^{1}H NMR (C_6D_6): δ 0.16 (s, 3H), 0.18 (s, 3H), 0.92 (s, 9H), 0.96 (s, 9H), 1.68–1.98 (m, 2H), 2.27 (m, 1H), 2.44 (m, 1H), 2.64 (m, 1H), 4.99 (s, 1H), 5.95 (dd, J=2.3, 5.5 Hz, 1H), 7.08–7.28 (m, 10H). ^{13}C NMR (C_6D_6): δ 165.4, 146.1, 145.5, 139.9, 129.3, 128.7, 126.4, 126.1, 80.8, 59.6, 36.0, 31.7, 31.1, 30.0, 29.9, 26.7, 20.7, 19.4, −2.6, −2.7. IR (NaCl, plates, cm^{-1}): 3088, 3050, 3022, 2950, 2863, 1716, 1645, 1601, 1495, 1471, 1447, 1377, 1361, 1303, 1027, 1005. MS: [$m^+/z-$

$C_6H_{15}OSi]=347.2011$ (calculated=347.2024). $[\alpha]_D^{25}$ −123 (*c* 2.2, CH_2Cl_2).

4.4. General cycloaddition reaction

4.4.1. Preparation of 1-*tert*-butyldimethylsilyloxy-2,2-dichloro-3-oxo-4-*n*-propyl-cyclobutanecarboxylic acid (*S*)-(2,2-diphenyl)cyclopentyl ester, 52. Zn dust was activated by vigorously stirring with HCl (10%) for 1–2 min, filtered, then washed with H_2O (3×) followed by acetone (3×). The activated Zn was stored in an oven heated at approximately 140–150 °C. To a flask of activated Zn dust (1.12 g, 17.1 mmol) and ether (10 mL) was added a mixture of trichloroacetyl chloride (1.53 mL, 13.7 mmol) and alkene **49** (3.20 g, 6.9 mmol) dropwise over 4–5 h. The heterogeneous solution was stirred for 16 h at rt, diluted with diethyl ether and filtered through Celite®. The filtrate was concentrated to 1–5 mL by rotary evaporation, diluted with pentane (15 mL) then vigorously stirred for 5 min to induce precipitation of Zn salts. After allowing the precipitate to settle, the pentane solution was decanted from the Zn salts. This decanting/washing protocol was repeated twice more. The combined pentane extracts were washed with cold saturated $NaHCO_3$ (5%, 2×), H_2O (1×), brine (1×), dried over Na_2SO_4, and the solvent evaporated. The crude residue was purified by filtration through SiO_2 (20:1 hexane/ethyl acetate) followed by recrystallization from hexanes to furnish cycloadduct **52** (3.07 g, 79% yield) as a colorless solid. Mp: 76–78 °C. ^{1}H NMR ($CDCl_3$). δ 0.22 (s, 3H), 0.36 (s, 3H), 0.73 (t, J=7.3 Hz, 3H), 0.92 (s, 9H), 1.29 (m, 2H), 1.51 (m, 3H), 1.87 (m, 1H), 2.04 (m, 1H), 2.31 (m, 1H), 2.47 (m, 1H), 2.65 (m, 1H), 2.95 (t, J=7.7 Hz, lH), 6.24 (d, J=4.8 Hz, 1H), 7.23 (m, 10H). ^{13}C NMR ($CDCl_3$): δ −2.8, 14.1, 19.9, 20.7, 21.2, 26.3, 26.7, 28.8, 30.3, 35.2, 59.9, 64.3, 83.9, 126.3, 126.5, 126.7, 126.8, 127.6, 128.4, 128.5, 128.7, 128.8, 144.5, 145.1, 168.2, 194.8. IR (NaCl plates, cm^{-1}): 3030, 2878, 1818, 1735, 1518, 1460, 1225, 920. $[\alpha]_D^{25}$ −65.2 (*c* 2.5, CH_2Cl_2).

4.4.2. Preparation of 1-*tert*-butyldimethylsilyloxy-2,2-dichloro-3-oxocyclobutanecarboxylic acid (*S*)-(2,2-diphenyl)cyclopentyl ester, 68. Starting with alkene **61** a clear yellow oil was produced in 80% as a 3.5:1 ratio of diastereoisomers. ^{1}H NMR ($CDCl_3$): δ 7.12–7.37 (m, 10H), 6.29 (d, J=4.6 Hz, 0.78H), 6.16 (dd, J=5.2, 2.8 Hz, 0.22H), 3.49 (d, J=17.6 Hz, 0.22H), 3.20 (d, J=17.7 Hz, 0.2H), 3.03 (d, J=17.1 Hz, 0.78H), 2.57–2.65 (m, 1H), 2.16–2.48 (m, 2H), 2.06 (d, J=17.5 Hz, 0.78H), 1.82–2.07 (m, 2H), 1.44–1.62 (m, 1H), 0.95 (s, 7.02H), 0.93 (s, 1.98H), 0.26 (s, 2.34H), 0.16 (s, 0.66H), 0.06 (s, 0.66H), −0.01 (s, 2.34H). ^{13}C NMR ($CDCl_3$): Major diastereomer δ 188.8, 167.9, 145.1, 144.1, 128.54, 128.52, 127.3, 126.4, 126.2, 126.0, 91.8, 83.6, 78.1, 59.8, 53.8, 34.9, 29.9, 25.7, 20.5, 18.5, −3.6, −4.0. Minor diastereomer (visible peaks) δ 189.1, 168.0, 145.2, 143.8, 128.5, 128.2, 128.0, 126.5, 126.3, 91.2, 83.3, 78.6, 58.6, 53.7, 30.6, 25.8, 25.6, 19.8, 18.4, −3.7. IR (NaCl plates, cm^{-1}): 3088, 3059, 3024, 2955, 2931, 2885, 2858, 1813, 1756, 1598, 1472, 1463, 1388, 1300, 1252, 1220, 1181, 1132, 1103, 1032. MS: $[m^+/z-C_6H_{15}Si]=417.0670$ (calculated=417.0660). $[\alpha]_D^{25}$ −36 (*c* 0.99 EtOH).

4.4.3. Preparation of 1-*tert*-butyldimethylsilyloxy-2,2-dichloro-4-methyl-3-oxo-cyclobutanecarboxylic acid (*S*)-(2,2-diphenyl)cyclopentyl ester, 69. Starting with alkene **62** a colorless oil was produced in 68% as a 3.8:1 ratio of inseparable diastereoisomers. ^{1}H NMR ($CDCl_3$): δ 7.10–7.33 (m, 10H), 6.19 (d, J=5.3 Hz, 0.79H), 6.06 (m, 0.21H), 3.50 (q, J=7.2 Hz, 0.21H), 3.07 (q, J=7.6 Hz, 0.79H), 2.44–2.60 (m, 2H), 2.22–2.34 (m, 1H), 1.97–2.07 (m, 1H), 1.80–1.92 (m, 1H), 1.47–1.66 (m, 1H), 1.02 (d, J=7.2 Hz, 0.63H), 0.89 (s, 7.11H), 0.87 (s, 1.89H), 0.81 (d, J=7.5 Hz, 2.37H), 0.34 (s, 3H), 0.15 (s, 2.37H), 0.08 (s, 0.63H). ^{13}C NMR ($CDCl_3$): Major diastereomer δ 195.0, 167.4, 144.8, 144.3, 128.5, 128.4, 127.5, 126.4, 126.3, 126.1, 90.7, 83.4, 80.4, 59.7, 58.6, 35.3, 30.4, 26.4, 20.6, 19.6, 9.5, −2.8, −3.0. Minor diastereomer (visible peaks) δ 194.2, 162.0, 145.0, 144.2, 128.5, 128.2, 127.9, 126.5, 89.8, 82.7, 80.9, 58.9, 57.2, 35.5, 30.7, 26.0, 20.1, 19.1, 7.6, −3.0, −3.6. IR (NaCl plates, cm^{-1}): 3059, 2958, 2932, 2884, 2858, 1817, 1744, 1494, 1472, 1463, 1448, 1258, 1252, 1207, 1156, 1111, 1054, 1031. MS: $[m^+/z-C_6H_{15}Si]=325.0431$ (calculated=325.0430). $[\alpha]_D^{25}$ −45 (*c* 1.10, EtOH).

4.4.4. Preparation of 1-*tert*-butyldimethylsilyloxy-2,2-dichloro-3-oxo-4-isopropyl-cyclobutanecarboxylic acid (*S*)-(2,2-diphenyl)cyclopentyl ester, 70. Starting with alkene **66** a colorless oil was produced in 94% as a 10.8:1 ratio of inseparable diastereoisomers. ^{1}H NMR ($CDCl_3$) δ 7.22 (m, 1H), 6.21 (d, J=5.0 Hz, 0.92H), 6.03 (dd, J=5.9, 3.4 Hz, 0.08H), 3.32 (d, J=10.6 Hz, 0.08H), 2.44–2.63 (m, 2H), 2.40 (d, J=10.6 Hz, 0.92H), 1.98–2.26 (m, 3H), 1.80–1.91 (m, 1H), 1.49–1.64 (m, 1H), 0.98 (s, 0.72H), 0.91 (s, 8.28H), 0.82 (d, J=6.8 Hz, 2.76H), 0.71 (d, J=6.3 Hz, 0.24H), 0.62 (d, J=6.3 Hz, 0.24H), 0.41 (d, J=6.4 Hz, 2.76H), 0.33 (s, 2.76H), 0.27 (s, 2.76H), 0.18 (s, 0.24H), 0.04 (s, 0.24H). ^{13}C NMR ($CDCl_3$): Major diastereomer δ 193.5, 168.3, 144.8, 144.3, 128.57, 128.55, 127.4, 126.4, 126.2, 83.7, 80.7, 70.8, 59.6, 35.0, 30.0, 28.0, 26.6, 26.0, 21.8, 20.4, 20.3, 19.7, −2.6, −2.8. Minor diastereomer (visible peaks) δ 193.8, 167.0, 144.7, 144.1, 128.8, 128.4, 128.3, 128.2, 128.1, 126.6, 91.1, 82.4, 68.1, −3.4, −3.7. IR (NaCl plates, cm^{-1}): 2960, 2927, 2847, 1808, 1754, 1722, 1643, 1568, 1494, 1470, 1388, 1362, 1254, 1200, 1110, 1031. MS: $[m^+/z-C_6H_{15}Si]=459.1130$ (calculated=459.1130). $[\alpha]_D^{25}$ −31 (*c* 0.60, EtOH).

4.4.5. Preparation of 1-*tert*-butyldimethylsilyloxy-2,2-dichloro-4,4-dimethyl-3-oxo-cyclobutanecarboxylic acid (*S*)-(2,2-diphenyl)cyclopentyl ester 71. Starting with 220 mg (0.46 mmol) of alkene **67**, a 4:1 inseparable mixture of starting material and cycloadduct was produced. Based on consumed starting material (determined by ^{1}H NMR) **71** was produced as a colorless oil in 32% yield in a 8.2:1 ratio of inseparable diastereosiomers. ^{1}H NMR (C_6D_6): Major diastereosiomer δ 6.87–7.21 (m, 10H), 6.16 (d, J=3.6 Hz, 1H), 3.45 (s, 1H), 1.23–2.61 (m, 6H), 1.08 (s, 9H), 0.92 (s, 9H), 0.55 (s, 3H), 0.53 (s, 3H). ^{13}C NMR (C_6D_6): Major diastereomer δ 194.6, 169.0, 145.3, 144.7, 129.0, 128.9, 127.9, 127.6, 126.54, 126.5, 84.5, 83.9, 73.4, 35.1, 34.6, 32.4, 30.2, 30.1, 29.9, 28.7, 28.5, 27.2, 23.2, 20.3, 14.4, −1.8. IR (NaCl plates, cm^{-1}); most distinguishable peak for cycloadduct **71**: 1814.

4.4.6. Preparation of (*Z*)-(*R*)-diphenylcyclopentyl 2-(*tert*-butyldimethylsilyloxy)-3-(3,3-dichloro-2-oxocyclobutyl)acrylate, 72. Starting with alkene **64**, a colorless oil was produced in 44% as a 2.6:1 ratio of inseparable diastereoisomers. ^{1}H NMR ($CDCl_3$): δ 7.05–7.27 (m, 10H), 6.01–6.06 (m, 1H), 5.33 (d, J=9.2 Hz, 0.28H) 5.08 (d, J=9.5 Hz, 0.72H), 3.80 (d, J=4.8 Hz, 0.28H), 3.46 (m, 0.72H), 3.38 (dd, J=17.8, 10.1 Hz, 0.72H), 3.00 (dd, J=17.9, 8.6 Hz, 0.28H), 2.86 (dd, J=18.0, 4.9 Hz, 0.28H), 2.78 (dd, J=17.8, 8.6 Hz, 0.72H), 2.59–2.71 (m, 1H), 2.45–2.56 (m, 1H), 2.23–2.41 (m, 1H), 2.07 (m, 0.28H), 1.77–1.96 (m, 1.72H), 1.36–1.47 (m, 1H), 1.01 (s, 2.52H), 0.94 (s, 6.48H), 0.38 (s, 0.84H), 0.30 (s, 0.84H), 0.19 (s, 2.16H), 0.18 (s, 2.16H). ^{13}C NMR ($CDCl_3$): Major diastereomer δ 192.2, 163.4, 145.1, 144.3, 143.7, 130.9, 128.8, 128.4, 128.2, 127.8, 126.5, 126.3, 81.5, 68.1, 59.6, 48.7, 41.8, 35.7, 30.4, 25.8, 20.7, 18.6, −4.2. Minor diastereomer (visible peaks) δ 132.5, 128.7, 128.1, 127.3, 126.2, 125.8, 81.1, 66.4, 59.5, 45.9, 44.1, 35.7, 30.2, 25.8, 20.5, −2.2, −2.5. IR (NaCl plates, cm^{-1}): 3060, 3024, 2957, 2930, 2858, 1815, 1760, 1725, 1645, 1599, 1495, 1447, 1386, 1291, 1254, 1212, 1162, 1124, 1071. MS: $[m^{+}/z-C_6H_{15}Si]$=337.0417 (calculated=337.0430). $[\alpha]_D^{25}$ −69 (*c* 0.26, EtOH).

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