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DIASTEREOSELECTIVE FORMATION OF CONTIGUOUS QUATERNARY CENTERS: THE MODIFIED CARROLL REARRANGEMENT

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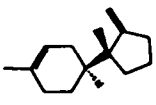
Abstract: A method is described for the diastereoselective formation of adjacent quaternary carbon atoms. The process involves a two-step transformation of an allylic β-ketoester into a single silyl keteneacetal which then undergoes a [3,3] sigmatropic rearrangement to generate the desired carbon-carbon bond in good yield and with excellent stereocontrol.

[Dedicated to Professor Michael J. S. Dewar on the occasion of his seventieth birthday]

Introduction

The presence of unsymmetrically substituted contiguous quaternary carbon centers in a target molecule can cripple a synthetic strategy. The inherent steric constraints of the severely hindered carbon-carbon bond prohibit traditional nucleophilic displacement reactions, and potential requirements of chirality forbid reactions that scramble stereochemistry. The task is especially difficult in acyclic systems. Convergent, stereoselective syntheses of a variety of natural products have eluded chemists due, in part, to the inability to produce the adjacent quaternary centers present in these molecules.[1]

Despite the lack of a general method for the construction of vicinal quaternary centers, a few diastereoselective syntheses involving formation of adjacent quaternary carbon atoms have been reported. Among these are syntheses of the sesquiterpenes trichodiene (1),[2] bazzanene (2)[3] and verrucarol (3).[4] The synthetic routes that have been devised utilize very creative manipulations to arrive at the correct carbon skeletons. Typically, the overall methodology is based on one of only a few approaches. One is the formation of the quaternary centers through a pericyclic process (Diels-Alder,[2b,c,3,4] or Nazarov cyclization,[2d]) followed by structural elaboration through a ring opening procedure. The second approach relies on the conformational bias of a ring system to impart diastereoselectivity upon an alkylation[2a] or, more recently, a radical cyclization.[5] Although these methods do produce the required functionality, each suffers from either poor yields or applicability to only specific cyclic cases. The organometallic approach of Pearson[2e] is promising since it appears immune from these problems, but its degree of stereoselectivity is, at present, varied and difficult to predict.



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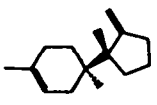

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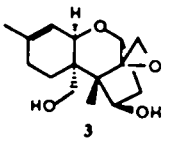
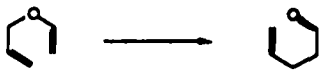


3

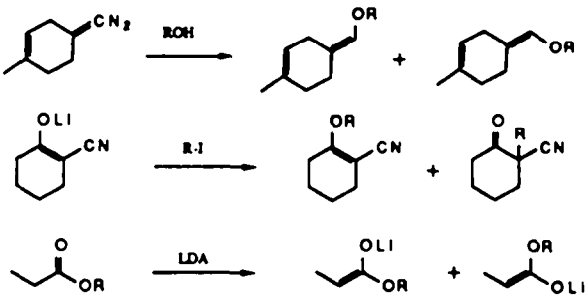
A number of investigators have recently[6] demonstrated the potential of [3,3] sigmatropic rearrangements, specifically variants of the Claisen rearrangement[7]

(equation 1), as efficient and stereoselective means of linking quaternary centers. Additionally, this type of process allows for direct stereocontrol in acyclic as well as cyclic systems. The fountainhead of this control is the well established tendency of these rearrangements to proceed through a chair-like transition state.[8]



(1)

To date, however, the full power of stereocontrol via sigmatropic processes has not been accessible due to a variety of technical problems. The stereochemical outcome of the Claisen rearrangement, for example, is dependent on the geometry of the starting allyl vinyl ether,[6a,e] so the synthetic challenge associated with the stereoselective formation of a single such ether is the predominant problem (equation 2). In some examples where the configuration of the ether can be controlled, there have been even more serious problems with regiochemical control in their formation owing to C-alkylation of a precursor enolate ion (equation 3).[6i] Similar problems exist for the enolate-ester Claisen rearrangement[9] in that known methods for the control of the geometry of simple enolates[10] are not applicable to ester enolates (equation 4). These problems decrease effective yields to less than 40% of the desired diastereomer in even the best cases.[6a,e-i]



(2)

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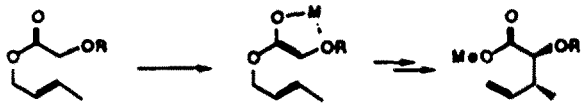
(4)

We report herein a [3,3] sigmatropic rearrangement of allylic β-ketoesters which results in the formation of contiguous quaternary centers diastereoselectively. Evidence is presented that is consistent with the proposition that the stereoselectivity originates in a deprotonation step that transforms an ester into one specific enolate ion. Silylation of this enolate cleanly generates a single (*Z*) silyl keteneacetal which then isomerizes through a chair transition state to generate the desired carbon-carbon bond in greater than 70% yield and in at least 98:2 diastereoselectivity.

Results and Discussion

It is known that diastereoselectivity can be induced in the Ireland-Claisen rearrangement[9] by controlling the direction of deprotonation by means of a chelating group α to the ester (equation 5).[11] Application of this method to the creation of contiguous quaternary centers would require the use of a β-chelating group (equation 6). Fortunately, many examples in the literature indicate that the control of ester enolate geometry by this type of chelation is indeed possible (equation 7).[12]



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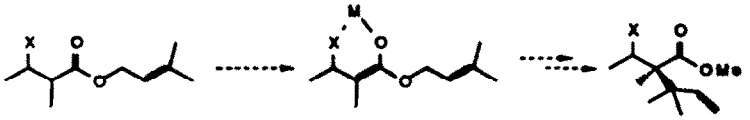

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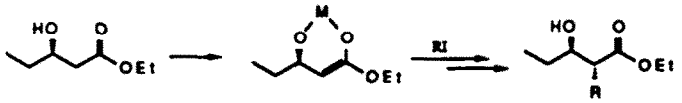
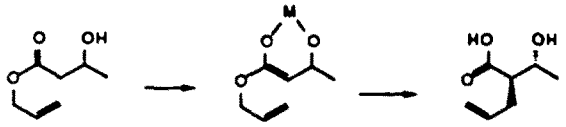


(7)

Two such approaches have been reported for the [3,3] sigmatropic rearrangement of ester-enolate anions. Kurth[13] studied the rearrangement of dianions of allylic β-hydroxyesters (equation 8) whereas Wilson[14] looked at the rearrangement of dianions of allylic β-ketoesters (equation 9). Unfortunately, neither technique turned out to be appropriate for the formation of vicinal quaternary centers.



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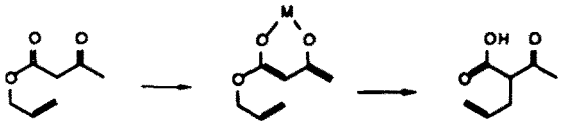
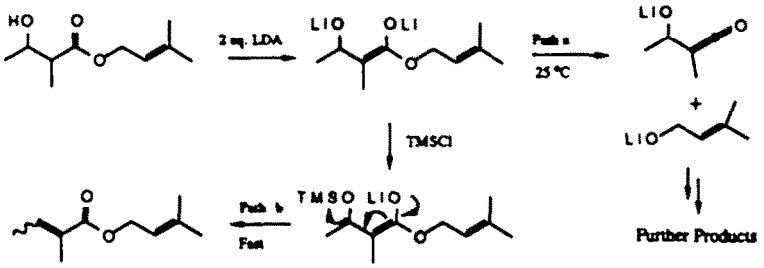


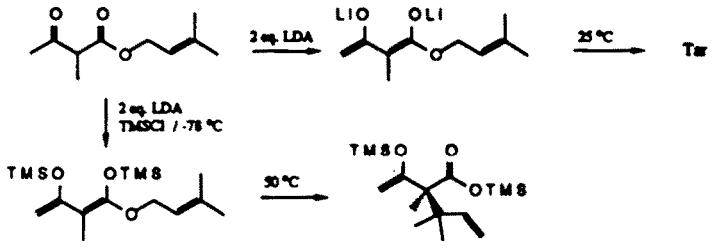
(9)

Initial efforts to extend the work of Kurth[13] failed with even slightly hindered systems (Scheme 1). Thus, treatment of the β-hydroxyester with two equivalents of lithium diisopropylamide (LDA) at -78 °C followed by warming to room temperature led only to the formation of polymeric materials. Fragmentation of the desired ester enolate to a ketene (path a) appeared to be a reasonable first step in rationalizing this result.[15] Efforts to suppress such fragmentation by silylation of the dianion led only to elimination of the chelating group (path b) and isolation of the unsaturated ester. Evidently, silylation occurred initially on the alkoxide moiety, and this was followed by an elimination that preceded silylation of the resulting ester enolate. Addition of cosolvents such as hexamethylphosphoric triamide (HMPA) did not alleviate this problem.

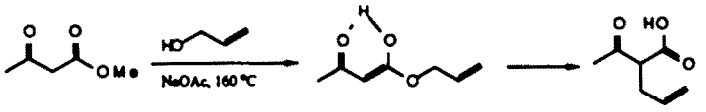


Scheme 1. Attempted Dianionic Claisen Rearrangement.

In an effort to obviate elimination, we elected to use an enolate (or its equivalent) rather than an alkoxide as the β-chelating group, a modification that was stimulated by the work of Wilson.[14] Once again, destruction of the starting material occurred with the more highly substituted systems of interest (Scheme 2). However, silylation of the intermediate dianion afforded a small amount of the bis-silylated material and the [3,3] sigmatropic rearrangement generated the desired carbon-carbon bond. From a historic standpoint, this process bears a formal resemblance to the [3,3] sigmatropic rearrangement of β-ketoesters first reported by Carroll in 1940 (equation 10).[16]



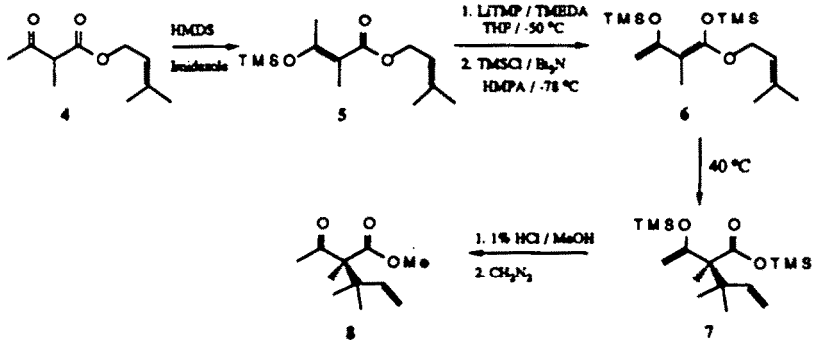
Scheme 2. Attempted Dianionic Carroll Rearrangement.



(10)

The Modified Carroll Rearrangement

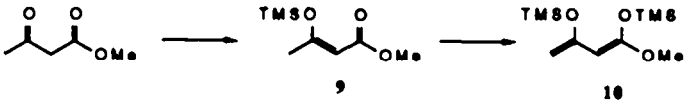
The reaction conditions for the rearrangement were first optimized on 3-methyl-2-butenyl 2-methyl-3-oxobutanoate (4, Scheme 3). This compound was prepared in 84% isolated yield as previously described.[17] Its dianion can be generated directly in THF at 0 °C using two equivalents of lithium diisopropylamide (LDA); however, reaction of this dianion with trimethylsilyl chloride (TMSCl) leads to products resulting from silylation at the terminal carbon.[18] The preferred solution to this problem is to introduce the two trimethylsilyl (TMS) groups sequentially, a technology that has resulted in the syntheses of a number of interesting dienes.[19]



Scheme 3. Conditions for the Modified Carroll Rearrangement.

Typically, the first TMS group is attached by generating the mono-enolate with a strong base and quenching it with TMSCl.[20] We found that a more efficient route was that developed by Ainsworth[21] in which the β-ketoester is heated at reflux in hexamethyldisilazane (HMDS) in the presence of a catalytic amount of imidazole. Applying this procedure to 4 gave 5 as a single isomer (by ^{1}H- and ^{13}C-NMR spectroscopy) in 84% isolated yield. Assignment of the geometry of the double bond as *E* was based on ^{1}H-NMR resonances, IR absorptions and literature precedent for these reactions.[22] Attempts to confirm the assignment by a differential NOE experiment were inconclusive.[23]

The formation of the silyl keteneacetal 6 from 5 was not so straightforward. Others have reported that simply treating the trimethylsiloxy compound 9 with LDA and TMSCl at -78 °C readily gives the silyl keteneacetal 10 in high yield (equation 11).[19] Application of similar conditions failed to convert 5 to 6. Our experience with the TMS enol ethers of 2-methyl-3-oxobutanoates (e.g. 5) indicates that their deprotonation is too slow at this temperature to be synthetically useful (days). Warming the reaction mixture to -50 °C during the deprotonation stage, in an effort to accelerate the deprotonation, generated only the starting β-ketoester 4, a result believed to be caused by nucleophilic cleavage of the TMS group by LDA.[24] Consistent with this hypothesis, it was found that cleavage could be suppressed by using a more hindered base. Thus, deprotonation was accomplished using 1.3 equivalents of a 1:1 mixture of lithium tetramethylpiperidide (LTMP)[25] and tetramethylethylenediamine (TMEDA)[26] in THF at -50 °C for four hours. The resulting enolate was silylated by cooling the mixture to -78 °C and treating it with 2.0 eq. of the supernatant from a 1:1 mixture of TMSCl and triethylamine. Addition of two equivalents of HMPA after the addition of TMSCl increases the eventual yield of 8 from 55% to 76%.



9 10 (11)

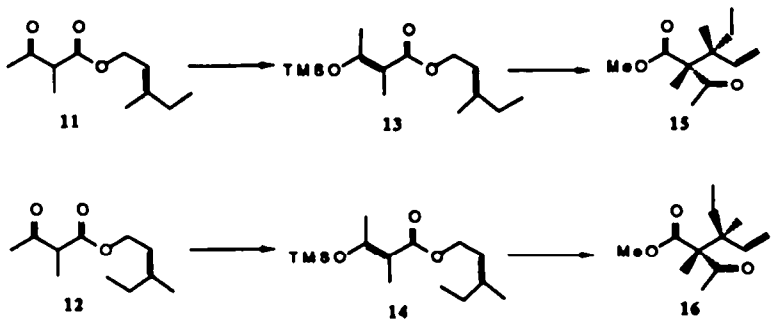
The [3,3] sigmatropic rearrangement was effected by allowing the reaction mixture to warm to room temperature gradually over three hours and then warming it to 40 °C for 12 hours. This presumably generates compound 7, which was not isolated. Rather the TMS groups were removed by hydrolysis and the resulting β-ketoacid was esterified with diazomethane.

A few words about the final work-up of the reaction mixture are in order. It is important to cleave the TMS groups at temperatures no higher than 0 °C since the intermediate β-ketoacid can readily decarboxylate. Typically we exposed intermediate 7 to 1% aqueous HCl in methanol for 15 minutes at 0 °C[27] and then treated the resulting mixture directly with an excess of diazomethane, a sequence that produces 8 in the aforementioned 76% isolated yield after flash chromatography.[28]

Diastereoselectivity

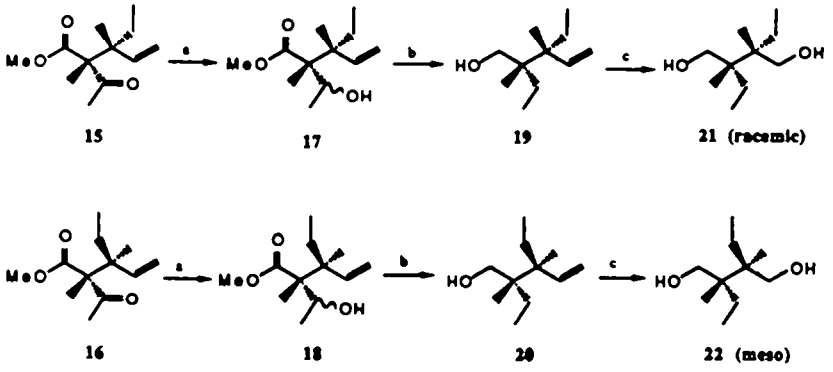
We next turned our attention to the question of the diastereoselectivity of the reaction (Scheme 4). Esters 11 and 12 were prepared from the corresponding alcohols in excellent yields. These were then converted to the (*E*)-3-trimethylsiloxy derivatives as described above. Subjection of 13 and 14 to the same reaction conditions as those given for 5 afforded the rearranged esters 15 and 16, respectively, in 73% and 77%

yields. Each compound was judged to be a single isomer (>98:2) by integration of the ^{1}H-NMR (300 MHz) peaks centered at δ 6.04 and δ 5.87 ppm for **15** and **16**, respectively.



Scheme 4. Diastereoselectivity of the Rearrangement.

Assigning the relative stereochemistry to **15** and **16** was not trivial (scheme 5). We realized that it might be possible to take advantage of hidden symmetry in the molecules and generate a *racemic* and a *meso* isomer which, theoretically, could be distinguished by NMR techniques. To achieve this end, it was necessary to make each quaternary center equivalent. Since both centers possessed a methyl group, a two carbon fragment (ethyl or acetyl) and an oxidized carbon atom (ester or alkene) the task remained to reduce the acetyl to an ethyl group and make the oxidized carbon atoms identical by oxidation-reduction techniques.



a. $NaBH_4$, EtOH. b. 1. MsCl, Et_3N, CH_2Cl_2. 2. $LiAlH_4$, HMPA. c. 1. O_3, EtOAc. 2. $LiAlH_4$, Et_2O.

Scheme 5. Proof of Relative Stereochemistry.

A number of approaches were tried to accomplish this goal, but the difficulty associated with working with neopentyl centers rendered most of them ineffective. The sequence ultimately followed was to reduce the acetyl group to an ethyl group in two steps and to convert both the ester and the alkene functionality to hydroxy methyl groups as shown in scheme 5. Thus compound **15** was reduced to isomers **17** in 62% yield by treatment with sodium borohydride ($NaBH_4$) in ethanol.[29] This material was next converted to its mesylate[30] and reduced further with lithium aluminum hydride ($LiAlH_4$). The yield of this process was low (21%) undoubtedly due to the problems inherent in hydride reduction of a neopentyl mesylate.[31] The terminal alkene **19** was then treated with ozone followed by workup with $LiAlH_4$ in refluxing ether[32] to yield

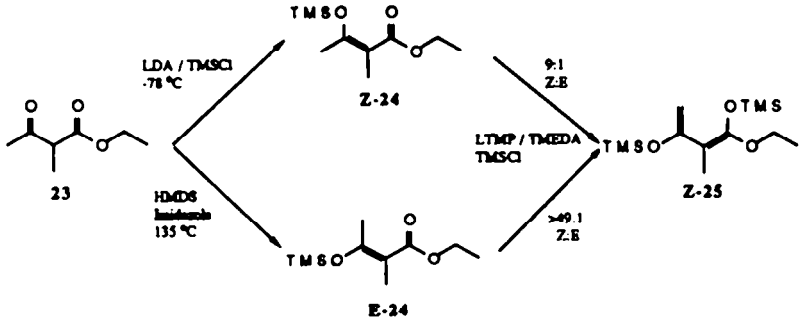
the diol **21** in 63% yield. Likewise, β-ketoester **16** was converted sequentially to **18** (65%), **20** (28%) and **22** (55%).

The ^{1}H-NMR spectra of **21** and **22** both displayed a methyl singlet and a methyl triplet, as expected. When their spectra were recorded in the presence of 60 mol% of the chiral shift reagent, tris[3-(heptafluoropropylhydroxymethylene)-(+)-camphorato] europium(III) [Eu(hfc)],[33] all of these resonances were shifted downfield. Furthermore, the methyl resonances of **21** were split into two sets of peaks. The new singlets were centered at δ 2.93 ppm and δ 2.95 ppm and the triplets at δ 2.09 ppm and δ 2.13 ppm. Compound **22** only showed one set of peaks in the presence of the shift reagent, and these appeared at δ 2.18 ppm and δ 1.97 ppm for the singlet and triplet, respectively. Interestingly the ^{13}C-NMR spectra allowed no distinction between the two isomers in the presence of Eu(hfc).

These data are unambiguously in accord with the assignment of **21** as the *racemic* isomer and **22** as the *meso*. Based on these structural assignments, relative stereochemistries could be assigned for all of the compounds of scheme 5 including those of the initial rearrangement products, **15** and **16**.

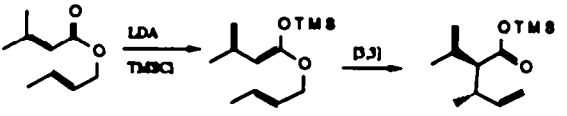
The stereochemical course of the reactions that transform **11** and **12** into **15** and **16**, respectively (Scheme 4), is defined in three stages. The first stage involves the geometry about the new double bond in **13** and **14**. The second is the preferential formation of one ester enolate over the other, and the third is the chair-boat selectivity of the sigmatropic process.

We decided to examine the first two of these variables by looking at the model system in scheme 6. Treatment of ethyl 2-methyl-3-oxobutanoate (**23**) with LDA in the presence of TMSCl at -78 °C gave exclusively *Z*-**24**. The same compound afforded *E*-**24** when treated with HMDS and imidazole at 135 °C. As alluded to earlier, the geometries of the two compounds could be assigned by the ^{1}H-NMR resonances for the terminal methyl group and IR absorptions for the ester carbonyl (δ 2.27 ppm and 1720 cm^{-1} respectively for *E*-**24** and δ 1.89 ppm and 1740 cm^{-1} respectively for *Z*-**24**). These two compounds were then treated with LTMP-TMEDA in the presence of TMSCl to yield the intermediate dienes. Curiously, both *E*-**24** and *Z*-**24** gave the same diene as the major product. However, while this diene was the only product from the *E*-isomer, it was contaminated by 10% of a minor diene in the reaction of the *Z*-isomer. The major diene had ^{1}H-NMR resonances for its terminal methylene at δ 4.28 ppm and δ 4.42 ppm while the minor diene's resonances appeared at δ 4.27 ppm and δ 4.39 ppm. The major diene was assigned the *Z* geometry by the method of Cameron[19] in which thermolysis of this compound initiates a [1,5] sigmatropic shift of silicon from oxygen to carbon. The minor isomer does not rearrange or isomerize under these conditions.



Scheme 6. Stereoselectivity of Diene Formation.

With these data we can now attempt to rationalize the stereochemical course of the method. The transformation of *E*-24 into the *Z*-diene is reminiscent of work done on the Ireland-Claisen rearrangement of crotyl senecioates[34] (equation 12). The conversion of *Z*-24 into the *Z*-diene (equation 13) raises the possibility of a chelated intermediate, a suggestion which superficially opposes some recent literature reports.[35] There are, however, other possible explanation for this result, among which are steric arguments.



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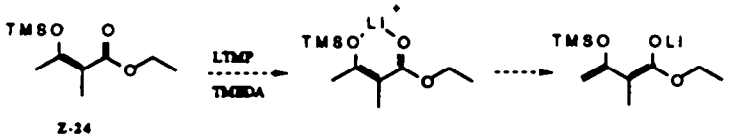
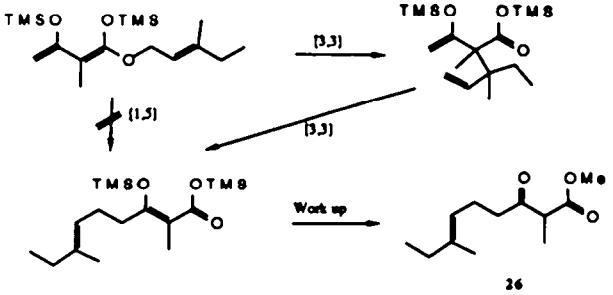


(13)

Z-24

The formation of only the *Z*-silyl keteneacetal and knowledge of the stereochemistry of the products allows us to infer that the [3,3] sigmatropic rearrangement occurs solely by way of the chair transition state. This final piece of the puzzle should allow for predictability of the stereochemical course in further applications of this method.

It should be noted that an interesting side reaction was observed when the rearrangement of **13** was performed at 65 °C for 36 hours. It appears that the initial product undergoes a second [3,3] sigmatropic rearrangement to generate compound **26** after workup (Scheme 7). NMR evidence indicates that **26** is generated in two steps as opposed to a single [1,5] sigmatropic shift. Tandem Claisen-Cope rearrangements have been observed before[36] but they usually require higher temperatures. Apparent driving forces for the second rearrangement are relief of the steric strain associated with the contiguous quaternary centers, formation of a more substituted alkene, and restoration of conjugation in the resulting unsaturated ester. Additionally, the presence of an ester moiety at C-3 of a 1,5-diene is known to have a large accelerating effect upon the Cope rearrangement.[37] Fortunately, the second rearrangement has an activation energy that is higher than that of the first, thereby allowing its suppression by use of shorter reaction times and lower reaction temperatures.



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Scheme 7. Tandem Carroll-Cope Rearrangements.

Conclusions

A highly convergent and diastereoselective route to vicinal quaternary centers in acyclic systems has been developed. The key step is the [3,3] sigmatropic rearrangement of a silyl ketenoacetal through a chair transition state to generate the requisite quaternary centers in high yields and excellent stereoselectivity. The acetal itself is produced from trapping of a *Z* ester enolate that can be formed with high diastereoselectivity. In addition to containing the core quaternary centers, the product should allow for further selective elaboration through judicious exploitation of the residual ketone, ester and alkene functionalities.

This approach is presently being used in an attempt to synthesize the trichothecene skeleton (e.g. 3).

Acknowledgement

We are grateful to the Robert A. Welch Foundation for financial support of this work. We also thank Mr. Steven Sorey and Dr. Ben Shoulders for assistance in performing the high field NOE and chiral shift reagent experiments.

Experimental Section

Infrared spectra were recorded with a Beckman IR-5A spectrophotometer as liquid samples between salt plates. Absorptions are reported in cm^{-1}. ^1H- and ^{13}C- nuclear magnetic resonance spectra were measured at 300 MHz on a GE QE-300 spectrometer. Deuteriochloroform was used as an internal standard and deuterium lock. Chemical shifts are reported in ppm (from TMS). Coupling constants are reported in Hz. Low resolution electron impact (EI) mass spectra were obtained with a du Pont (CEC) 21-471 double focusing mass spectrometer operating at 70 eV; only peaks greater than 30% of the base peak are reported. Exact mass measurements were obtained on a du Pont (CEC) 21-110 instrument for compounds which had a LRMS M+ peak >1% of the base peak. High pressure liquid chromatography was performed on a Waters 6000A instrument with two linked 2' x 1/4" columns packed with LC Porasil (type A) silica gel.

Skelly B was stirred over sulfuric acid for 24 h, over sodium carbonate for 12 h, and was then filtered and distilled. Diazomethane was generated from *N*-methyl-*N*-nitroso-*p*-toluenesulfonamide (Aldrich-Diazald) as an ethereal solution and used immediately. All other reagents and solvents were obtained from commercial sources and purified by standard methods.

(*E*)-3-Methyl-2-penten-1-ol.[38] A stirred suspension of 3.0 g (80.0 mmol) of $LiAlH_4$ in 150 mL of dry diethyl ether was cooled in an ice-water bath, and a solution of 2.6 mL (80.0 mmol) of methanol in 25 mL of ether was added over 30 min. Ethyl (*E*)-3-methyl-2-pentenoate[38] in 25 mL of ether was then added dropwise, and the resulting solution was stirred at 4 °C for 12 h. Cautious, sequential treatment of the reaction mixture with 3 mL of H_2O, 3 mL of 4*N* NaOH and 9 mL of H_2O afforded an ethereal solution, which was filtered, dried ($MgSO_4$) and concentrated by rotary evaporation. Distillation (84-85 °C, 40 mm Hg) yielded 6.8 g (96.3%) of the spectroscopically pure (^1H-NMR) alcohol.

(*Z*)-3-Methyl-2-penten-1-ol.[38] This alcohol was made in 91% yield by reduction of ethyl (*Z*)-3-methyl-2-pentenoate[39] as described above for the *E*-isomer.

General Procedure for the Formation of β-Ketoesters 11 and 12.[17] A mixture of 5.0 g (35 mmol) of ethyl 2-methyl-3-oxobutanoate, 3.4 g (34 mmol) of 3-methyl-2-penten-1-ol and 4.2 g (35 mmol) of 4-*N*,*N*-dimethylaminopyridine was dissolved in 200 mL of toluene which contained 25 g of oven-dried molecular sieves (4-A). The mixture was then heated under reflux until no starting material was detectable by ^1H-NMR spectroscopy (approximately 24 h). After being cooled to room temperature, the solution was washed with saturated ammonium chloride (2 x 25 mL) and dried ($MgSO_4$). The toluene was removed by rotary evaporation and the products were purified by distillation.

(*E*)-3-Methyl-2-pentenyl 2-methyl-3-oxobutanoate (11). Bp: 134-136 °C, 40 mm Hg; ^1H-NMR: δ 0.98 (t, *J* = 9.5 Hz, 3 H), 1.28 (d, *J* = 7.6 Hz, 3 H), 1.67 (s, 3 H), 2.01 (q, *J* = 7.6 Hz, 2 H), 2.19 (s, 3 H), 3.47 (q, *J* = 7.6 Hz, 1 H), 4.62 (d, *J* = 6.6 Hz, 2 H), 5.30 (t, *J* = 6.6 Hz, 1 H); ^{13}C-NMR: δ 12.1, 12.6, 16.2, 28.1, 32.1, 53.6, 62.1, 116.5, 144.7, 170.4, 203.2; IR: 2995 (m),

2960 (m), 1760 (s), 1740 (s), 1665 (w); LRMS: 198 (M+, <0.01), 99 (0.61), 83 (0.32), 82 (0.47), 67 (0.38), 55 (0.68), 43 (1.00), 41 (0.35).

(*Z*)-3-Methyl-2-pentenyl 2-methyl-3-oxobutanoate (12). Bp: 76-77 °C, 0.3 mm Hg; ^{1}H-NMR: δ 0.98 (t, *J* = 7.9 Hz, 3 H), 1.32 (d, *J* = 7.8 Hz, 3 H), 1.74 (s, 3 H), 2.10 (q, *J* = 7.9 Hz, 2 H), 2.21 (s, 3 H), 3.48 (q, *J* = 7.8 Hz, 1 H), 4.62 (d, *J* = 7.1 Hz, 1 H), 5.29 (t, *J* = 7.1 Hz, 1 H); ^{13}C-NMR: δ 12.4, 12.7, 22.7, 24.9, 28.1, 53.4, 61.5, 117.3, 145.1, 170.2, 203.2; IR: 2995 (m), 2960 (m), 1760 (s), 1740 (s), 1665 (w); LRMS: 198 (M+, <0.01), 99 (0.79), 83 (0.35), 82 (0.71), 67 (0.41), 55 (0.67), 43 (1.00), 41 (0.32).

General Method for the Formation of Silyl Enol Ethers. These were made by the procedure of Ainsworth.[21] Typically, 3.00 g of the allylic β-ketoester was dissolved in 20 mL of hexamethyldisilazane (HMDS) in the presence of 0.1 g of imidazole. This mixture was then heated under reflux for 4 h after which the apparatus was modified to allow distillation of the HMDS. The silyl enol ether was then purified via distillation at reduced pressure.

3-Methyl-2-butenyl (*E*)-2-methyl-3-trimethylsiloxy-2-butenoate (5). ^{1}H-NMR: δ 0.21 (s, 9 H), 1.68 (s, 3 H), 1.79 (s, 3 H), 1.74 (s, 3 H), 2.24 (s, 3 H), 4.58 (d, *J* = 6.6 Hz, 2 H), 5.35 (t, *J* = 6.6 Hz, 1 H); ^{13}C-NMR: δ 0.7, 12.4, 17.9, 21.5, 25.6, 60.7, 109.1, 119.5, 137.5, 161.0, 169.6; IR: 2700 (s), 1720 (s), 1650 (s); LRMS: 256 (M+, 0.01), 188 (0.35), 173 (0.60), 147 (0.80), 98 (0.46), 75 (0.64), 70 (0.32), 69 (1.00), 43 (0.64), 41 (0.62); HRMS: $C_{13}H_{24}O_3Si$, calc.: 256.14947, found: 256.15027.

(*E*)-3-Methyl-2-pentenyl (*E*)-2-methyl-3-trimethylsiloxy-2-butenoate (13). ^{1}H-NMR: δ 0.22 (s, 9 H), 1.01 (t, *J* = 7.2 Hz, 3 H), 1.70 (s, 3 H), 1.78 (s, 3 H), 2.05 (q, *J* = 7.2 Hz, 2 H), 2.29 (s, 3 H), 4.62 (d, *J* = 7.2 Hz, 2 H), 5.36 (t, *J* = 7.2 Hz, 1 H); ^{13}C-NMR: δ 0.7, 12.2, 12.5, 16.2, 21.5, 32.2, 60.8, 109.2, 118.0, 142.8, 160.8, 169.6; IR: 2700 (s), 1720 (s), 1640 (s); LRMS: 270 (M+, <0.01), 147 (1.00), 99 (0.32), 55 (0.48), 43 (0.65).

(*Z*)-3-Methyl-2-pentenyl (*E*)-2-methyl-3-trimethylsiloxy-2-butenoate (14). ^{1}H-NMR: δ 0.22 (s, 9 H), 0.99 (t, *J* = 7.5 Hz, 3 H), 1.73 (s, 3 H), 1.78 (s, 3 H), 2.11 (q, *J* = 7.5 Hz, 2 H), 2.28 (s, 3 H), 4.59 (d, *J* = 7.5 Hz, 2 H), 5.34 (t, *J* = 7.5 Hz, 1 H); ^{13}C-NMR: δ 0.8, 12.4, 12.9, 21.5, 22.8, 25.0, 60.3, 109.0, 118.9, 143.5, 161.1, 169.7; IR: 2700 (s), 1720 (s), 1640 (s); LRMS: 270 (M+,<0.01), 147 (1.00), 99 (0.33), 55 (0.39), 43 (0.75).

Methyl 2-(1-oxoethyl)-2,3,3-trimethyl-4-pentenoate (8). This general procedure for the modified Carroll rearrangement MUST be carried out with rigorous exclusion of moisture. To a stirred solution of 0.22 mL (1.3 mmol) of tetramethylpiperidine in 5 mL of anhydrous THF under a positive pressure of nitrogen at -78 °C was added 0.49 mL (1.3 mmol) of a 2.68 *M* solution of butyllithium in hexanes. Tetramethylethylenediamine (0.20 mL, 1.3 mmol) was then added and the reaction mixture was stirred for 10 min. Next a solution of 0.26 g (1.0 mmol) of 5 in 2 mL of THF was added dropwise over 3 min. After an additional 15 min. at -78 °C, the flask was transferred to a cold temperature bath measuring -50 °C (temperature control was maintained using a Neslab Cryocool CC-100 II with a stirred acetone bath). The reaction mixture was held at this temperature for 4 h after which the flask containing it was cooled to -78 °C in a Dry Ice-isopropyl alcohol bath. Next, the mixture was treated with 0.80 mL (3.0 mmol TMSCl) of the supernatant of a 1:1 mixture of TMSCl and Et_3N and this was followed by the addition of 0.45 mL (2.6 mmol) of HMPA. The solution was then allowed to warm to room temperature over 3 h. The flask was next carefully fitted with a reflux condenser and warmed to 40 °C for a period of 12 h. After the mixture had been cooled in an ice-water bath, a 20-mL portion of a 1% solution of aqueous HCl in MeOH was added slowly, and the mixture was stirred for 15 min, after which it was treated with an excess of ethereal diazomethane. The extra diazomethane was quenched after 5 min by the careful addition of 1 mL of glacial acetic acid, and the entire solution was transferred into a separatory funnel and washed with 5 100-mL portions of saturated sodium bicarbonate (*n.b.* the aqueous base layer contains the HMPA at this point and should be treated and disposed of accordingly). The ethereal solution was then dried ($MgSO_4$), concentrated (rotary evaporation) and purified by flash chromatography using a 5% EtOAc: 95% Skelly B solvent system. Occasionally, when incomplete reaction led to the presence of starting β-ketoester, further purification by HPLC (3% EtOAc: 97% Skelly B) was needed to separate these components. Yield 154 mg (78%). ^{1}H-NMR: d 1.11 (s, 3 H), 1.16 (s, 3 H), 1.31 (s, 3 H), 2.08 (s, 3 H), 3.68 (s, 3 H), 4.94 (dd, *J* = 1.4, 17.3 Hz, 1 H), 4.97 (dd, *J* = 1.4, 10.8 Hz, 1 H), 6.13 (dd, *J* = 10.8, 17.3 Hz, 1 H); ^{13}C-NMR: δ 17.8, 23.2, 23.9, 29.2, 41.5, 51.6, 64.9, 112.5, 144.7, 172.9, 205.1; IR: 3100 (w), 2850 (s), 1750 (s), 1715 (s), 1645 (m); LRMS: 198 (0.02, M+), 141 (0.90), 130 (0.70), 109 (0.31), 99 (0.30), 98 (0.34), 69 (1.00), 43 (0.84), 41 (0.71); HRMS: $C_{11}H_{18}O_3$, calc.: 198.12559, found: 198.12614.

Methyl (2*R,3*R**)-2,3-dimethyl-3-ethyl-2-(1-oxoethyl)-4-pentenoate (15).** Compound 15 was prepared from 13 by the modified Carroll rearrangement described above. Yield: 155 mg (73%). ^{1}H-NMR: δ 0.72 (t, *J* = 7.7 Hz, 3 H), 1.02 (s, 3 H), 1.34 (s, 3 H), 1.69 (q, *J* = 7.6 Hz, 2 H), 2.10 (s, 3 H), 3.71 (s, 3 H), 4.96 (dd, *J* = 1.2, 16.5 Hz, 1H), 5.14 (dd, *J* = 1.2, 11.7 Hz, 1 H), 6.04 (dd, *J* = 11.7, 16.5 Hz, 1 H); ^{13}C-NMR: δ 8.6, 16.6, 18.0, 27.4, 29.7, 45.4, 51.8, 65.9, 115.0, 142.1, 173.2, 205.6; IR: 3100 (w), 2850 (s), 1750 (s), 1720 (s), 1640 (w); LRMS: 212 (M+, 0.01), 141 (0.55), 130 (0.34), 83 (0.55), 55 (0.69), 43 (1.00), 41 (0.40); HRMS: $C_{12}H_{20}O_3$, calc.: 212.14134, found: 212.14206.

Methyl (2*R,3*S**)-2,3-dimethyl-3-ethyl-2-(1-oxoethyl)-4-pentenoate (16).** This compound was made from 14 by the modified Carroll rearrangement described above. Yield: 163 mg (77%). ^{1}H-NMR: δ 0.71 (t, *J* = 7.8 Hz, 3 H), 1.11 (s, 3 H), 1.38 (s, 3 H), 1.72 (m, 2 H), 2.13 (s, 3 H), 3.70 (s, 3 H), 4.96 (dd, *J* = 1.5, 16.5 Hz, 1 H), 5.16 (dd, *J* = 1.5, 12.0 Hz, 1 H), 5.87 (dd, *J* = 12.0, 16.5 Hz, 1 H); ^{13}C-NMR: δ 8.8, 16.7, 18.0, 27.4, 29.7, 45.4, 51.8, 65.7, 115.1, 142.0, 173.0, 205.5; IR: 3150 (w), 2900 (m), 1745 (s), 1710 (s), 1645 (w); LRMS: 212 (M+, <0.01), 141 (0.37), 130 (0.42), 83 (0.60), 55 (0.87), 43 (1.00), 41 (0.42).

General Procedure for the $NaBH_4$ Reduction of 15 and 16. A solution of 117 mg (0.55 mmol) of the β-ketoester in 0.5 mL of absolute ethanol was cooled to 0 °C. $NaBH_4$ (11 mg, 0.3 mmol) was added and the mixture was allowed to stir for 2 h. At the end of 2 h, another 11 mg portion of $NaBH_4$ was added. This was repeated as necessary (3 to 4 total portions of $NaBH_4$) until all of the starting material had disappeared by TLC. The mixture was then poured into saturated sodium bicarbonate, extracted into ether ($MgSO_4$) and concentrated by rotary evaporation. Flash chromatography yielded two diastereomers from 15 (9:1, denoted 17a and 17b, respectively) whose stereochemistry was assigned by comparing the ^{13}C chemical shifts of the methyl groups at the new chiral center.[40] Compound 16 gave only one apparent diastereomer (18), whose stereochemistry was assigned based on comparison to 17a and 17b.

Methyl (2*R,3*R**)-2,3-dimethyl-3-ethyl-2-(1-(*S**)-hydroxyethyl)-4-pentenoate (17a).** Yield: 66 mg, 56%; Rf = 0.34 (1:2 EtOAc: Skelly B); ^{1}H-NMR: δ 0.69 (t, *J* = 7.7 Hz, 3 H), 1.00 (d, *J* = 6.3 Hz, 3 H), 1.04 (s, 3 H), 1.08 (s, 3 H), 1.54 (d, *J* = 6.0 Hz, 1 H), 1.70 (m, 2 H), 3.62 (s, 3 H), 4.46 (m, 1 H), 5.01 (dd, *J* = 1.4, 17.3 Hz, 1 H), 5.14 (dd, *J* = 1.4, 11.0 Hz, 1 H), 6.14 (dd, *J* = 11.0, 17.3 Hz, 1 H); ^{13}C-NMR: δ 8.5, 11.3, 17.2, 19.9, 28.3, 45.5, 51.2, 57.0, 69.8, 113.6, 144.2, 175.7; IR: 3500 (b), 3050 (w), 1710 (s), 1630 (w); LRMS: 214 (M+, <0.01), 141 (0.48), 114 (0.44), 109 (0.35), 83 (0.73), 69 (0.33), 55 (1.00), 43 (0.40), 41 (0.55).

Methyl (2*R,3*R**)-2,3-dimethyl-3-ethyl-2-(1-(*R**)-hydroxyethyl)-4-pentenoate (17b).** Yield: 7 mg, 6%; Rf = 0.29 (1:2 EtOAc: Skelly B); ^{1}H-NMR: δ 0.70 (t, *J* = 7.1 Hz, 3 H), 1.01 (s, 3 H), 1.09 (s, 3 H), 1.18 (d, *J* = 6.3 Hz, 3 H), 1.50 (m, 2 H), 2.33 (d, 1 H), 3.68 (s, 3 H), 4.18 (m, 1 H), 4.94 (dd, *J* = 1.6, 17.3 Hz, 1 H), 5.13 (dd, *J* = 1.6, 11.0 Hz, 1 H), 5.95 (dd, *J* = 11.0, 17.3 Hz, 1 H); ^{13}C-NMR: δ 8.6, 13.9, 17.1, 20.1, 28.6, 44.6, 51.3, 57.9, 70.7, 114.3, 142.9, 176.4.

Methyl (2*R,3*S**)-2,3-dimethyl-3-ethyl-2-(1-(*S**)-hydroxyethyl)-4-pentenoate (18).** Yield: 75 mg, 65%; Rf = 0.34 (1:2 EtOAc: Skelly B); ^{1}H-NMR: δ 0.67 (t, *J* = 7.9 Hz, 3 H), 0.99 (d, *J* = 6.3 Hz, 3 H), 1.20 (s, 3 H), 1.25 (s, 3 H), 1.74 (m, 2 H), 2.07 (s, 1 H), 3.65 (s, 3 H), 4.52 (m, 1 H), 5.13 (dd, *J* = 1.4, 17.3 Hz, 1 H), 5.23 (dd, *J* = 1.4, 11.0 Hz, 1 H), 5.94 (dd, *J* = 11.0, 17.3 Hz, 1 H); ^{13}C-NMR: δ 8.4, 11.0, 15.8, 19.2, 28.4, 45.1, 51.3, 57.8, 69.6, 115.3, 144.9, 176.2; IR: 3500 (b), 3045 (w), 1710 (s), 1620 (w); LRMS: 214 (M+, <0.01), 69 (0.61), 55 (0.54), 44 (1.00), 43 (0.33).

Procedure for the Mesylation and Reduction of 17 and 18. A solution of 17 (200 mg, 0.9 mmol) and 0.25 mL of triethylamine in 5 mL of methylene chloride was cooled to 0 °C. Methanesulfonylchloride (0.1 mL, 1.3 mmol) was added dropwise and the reaction mixture was stirred at that temperature for 6 h. The mixture was then poured into 2 mL of ice-water, washed with successive 5-mL portions of 10% HCl and saturated NaCl, dried ($MgSO_4$) and concentrated by rotary evaporation (the temperature of the bath should not exceed 25 °C). The residue was then dissolved in 0.5 mL of HMPA and added to a suspension of 0.1 g $LiAlH_4$ in 1 mL of HMPA. The mixture was heated at 60 °C for 6 h and then allowed to cool to room temperature. Quenching of the excess reducing agent was effected by the cautious addition of 0.1 mL of water, 0.1 mL of 4*N* NaOH and 0.3 mL of water. Dilution of the mixture with 5 mL of ether, followed by filtration, washing with saturated sodium bicarbonate, drying (Na_2SO_4) and rotary evaporation, yielded compound 19 (33 mg, 21%) after flash chromatography (1:5:44 triethylamine:EtOAc:Skelly B). In the same manner, 18 gave 20 (28%).

(3*R,4*S**)-3,4-dimethyl-2-ethyl-4-(hydroxymethyl)-1-hexene (19).** Yield: 21%; ^{1}H-NMR: δ 0.69 (t, *J* = 7.9 Hz, 3 H), 0.71 (s, 3 H), 0.87 (t, *J* = 7.9 Hz, 3 H), 0.97 (s, 3 H), 1.30 - 1.70 (m, 5 H), 3.35 (dd, *J* = 7.9, 12.6 Hz, 1 H), 3.62 (dd, *J* = 3.2, 12.6 Hz, 1 H), 5.03 (dd, *J* =

1.6, 17.4 Hz, 1 H), 5.15 (dd, J = 1.6, 11.0 Hz, 1 H), 6.02 (dd, J = 11.0, 17.4 Hz, 1 H); ^{13}C-NMR: δ 8.5, 9.0, 15.9, 16.7, 24.2, 26.8, 43.4, 45.2, 66.4, 113.9, 146.1; IR: 3500 (b), 2950 (s); LRMS: 170 (M+, <0.01), 84 (0.92), 83 (0.55), 69 (1.00), 55 (0.98), 45 (0.53), 43 (0.46), 41 (0.72); HRMS: $C_{11}H_{21}O$ (M-1), calc: 169.15924, found: 169.15931.

(3*R,4*R**)-3,4-dimethyl-2-ethyl-4-(hydroxymethyl)-1-hexene (20).** Yield: 28%; ^{1}H-NMR: δ 0.71 (t, J = 7.9 Hz, 3 H), 0.79 (s, 3 H), 0.85 (t, J = 7.9 Hz, 3 H), 0.95 (s, 3 H), 1.30 - 1.60 (m, 5 H), 3.49 (d, J = 1.6 Hz, 1 H), 3.51 (s, 1 H), 4.98 (dd, J = 1.6, 17.3 Hz, 1 H), 5.12 (dd, J = 1.6, 11.0 Hz, 1 H), 5.95 (dd, J = 11.0, 17.3 Hz, 1 H); ^{13}C-NMR: δ 8.6, 8.9, 16.1, 16.3, 24.9, 26.8, 42.8, 45.3, 66.6, 113.5, 145.6; IR: 3500 (b), 2950 (s), 1620 (w); LRMS: 170 (M+, <0.01), 86 (0.32), 84 (0.74), 83 (0.39), 69 (1.00), 55 (0.92), 45 (0.48), 43 (0.41), 41 (0.62); HRMS: $C_{11}H_{21}O$ (M-1), calc: 169.15924, found: 169.15965.

Ozonolysis and Reduction of 19 and 20. Compound **19** (30 mg, 0.18 mmol) was dissolved in 20 mL of EtOAc. This solution was then cooled to -78 °C and ozone gas was passed through it until a light blue color persisted. The flask was purged sequentially with oxygen and nitrogen and the mixture was warmed to room temperature. The EtOAc was removed by rotary evaporation and the ozonide was dissolved in 0.5 mL of dry ether. This solution was slowly added to a suspension of $LiAlH_4$ (100 mmol, 2.5 mmol) in 5 mL of dry ether and the new suspension was warmed to 35 °C for 4 h. After cooling the reaction mixture to room temperature, the excess $LiAlH_4$ was quenched by the careful addition of 0.1 mL of water, 0.1 mL of 4*N* NaOH and 0.3 mL of water. The mixture was then filtered, dried ($MgSO_4$) and concentrated to give the product **21** (19.3 mg, 63%) after flash chromatography (1:1 EtOAc: Skelly B). Likewise, compound **20** gave product **22** (55%).

(3*S,4*S**)-3,4-dihydroxymethyl-3,4-dimethylhexane (21).** Yield: 63%; ^{1}H-NMR: δ 0.77 (s, 3 H), 0.84 (t, J = 7.5 Hz, 3 H), 1.26 - 1.33 (m, 1 H), 1.47 -1.54 (m, 1 H), 3.48 (s, 2 H), 3.91 (s, 1 H); ^{13}C-NMR: δ 8.8, 16.6, 24.3, 42.5, 65.1; IR: 3500 (b), 2980 (s); LRMS: 174 (M+, <0.01), 126 (0.32), 97 (0.85), 86 (0.49), 85 (0.85), 83 (0.54), 71 (1.00), 70 (0.84), 69 (0.81), 57 (0.61), 57 (0.62), 56 (0.62), 55 (0.80), 43 (0.94).

***meso*)-3,4-dihydroxymethyl-3,4-dimethylhexane (22).** Yield: 55%; ^{1}H-NMR: δ 0.67 (s, 3 H), 0.86 (t, J = 7.4 Hz, 3 H), 1.27 - 1.34 (m, 1 H), 1.65 -1.70 (m, 1 H), 3.43 (ABq, J_{AB} = 11.8 Hz, ν = 70 Hz, 2 H), 4.37 (s, 1 H); ^{13}C-NMR: δ 8.3, 17.3, 23.3, 42.7, 63.9; IR: 3500 (b), 2960 (s); LRMS: 174 (M+, <0.01), 97 (0.68), 85 (0.68), 83 (0.31), 71 (1.00), 70 (1.00), 69 (0.82), 57 (0.41), 55 (0.98), 45 (0.47), 43 (0.80), 41 (0.63).

Methyl (*E*)-2,7-dimethyl-5-oxo-6-nonenate (26). This compound was prepared by an alteration of the modified Carroll rearrangement of **11**. Instead of being warmed to 40 °C for 12 h, the mixture was heated at 65 °C for 36 h to effect the second [3,3] sigmatropic rearrangement. The rest of the procedure is identical to that reported above. Yield: 117 mg (55%). ^{1}H-NMR: δ 0.95 (t, J = 7.9 Hz, 3 H), 1.34, (d, J = 6.9 Hz, 3 H), 1.60 (s, 3 H), 1.95 (q, J = 7.9 Hz, 2 H), 2.28 (q, J = 7.9 Hz, 2 H), 2.55 (m, 2 H), 3.54 (q, J = 6.9 Hz, 1 H), 3.72 (s, 3 H), 5.05 (t, J = 7.1 Hz, 1 H); ^{13}C-NMR: δ 12.6, 12.7, 15.8, 22.1, 32.2, 41.4, 52.2, 52.7, 120.8, 138.4, 170.9, 205.4; IR: 3600 (m), 3000 (s), 1740 (s), 1710 (s), 1670 (m); LRMS: 212 (M+, 0.03), 125 (0.34), 83 (0.69), 82 (0.41), 55 (1.00), 43 (0.60), 41 (0.45); HRMS: $C_{12}H_{20}O_3$, calc.:212.14124, found: 212.14096.

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