Conjugate Addition of Dithianylidene Anions to α,β-Unsaturated Ketones. An Application to the Total Synthesis of (±)-Aromatin and (±)-Confertin†

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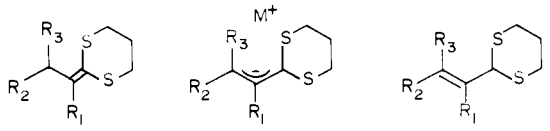
Abstract: The conjugate addition of the anions (dithianylidene) of several ketene dithioacetals and vinyldithianes to α,β-unsaturated ketones has been examined. The effect of the counterion (Li^+, Cu^+) and solvent (THF, THF–HMPA) has been investigated. The amount of conjugate 1,4 addition exceeds 1,2 addition. The ratio of γ-1,4/α-1,4 exceeds unity when lithium is the counterion and THF is the solvent. The use of the lithium cation in THF–HMPA or the cuprous ion in THF affords virtually all α-1,4 product. Mechanistic considerations of these reactions and their application to the synthesis of the pseudoguaianolides aromatin and confertin are discussed.

The use of sulfur-stabilized carbanions as umpolung-reactive reagents has been well established.[2] The kinetic control of the 1,4 addition (Michael addition) of dithiane anions,[3] trithioorthoformate anions,[4] and other localized sulfur[5,6] and selenium-stabilized[7] anions to α,β-unsaturated ketones has provided the synthetic chemist with an important, versatile synthetic method.[8] The use of the vinylogous dithiane (dithianylidene) anion has not been exploited in conjugate additions. These anions not only present the usual concern for 1,2 vs. 1,4 reactivity but also raise the added problem of α vs. γ addition.

In this paper we provide the details of our work in this area and the application of this methodology to the total synthesis of (±)-aromatin (**23b**) and (±)-confertin (**26**).[9,10]

Results and Discussion

The lithium anion **2a** is readily generated from 2-ethylidene-1,3-dithiane (**1a**) with lithium diisopropylamide (LDA) (−15 °C, 0.5 h) in THF solution. When the β position of the ketene dithioacetal is disubstituted, deprotonation can be achieved efficiently only in the presence of HMPA. Seebach[2] has observed this behavior with 2-cyclohexylidene-1,3-dithiane, as we have in the present instance with 2-isopropylidene-1,3-dithiane (**1b**). The



1 2 3

a, $R_1 = R_2 = R_3 = H$
b, $R_1 = CH_3$; $R_2 = R_3 = H$
c, $R_1 = R_2 = CH_3$; $R_3 = H$
d, $R_1 = R_3 = CH_3$; $R_2 = H$
e, $R_1 = R_3 = H$; $R_2 = CH_3$

presence of HMPA in the reaction mixture has a pronounced effect on the α/γ ratio in the conjugate addition. Consequently, HMPA can prove detrimental if particular stereocontrol is required. Dithianylidene anion **2c** or **2d** in the absence of HMPA would be inaccessible. Moreover, kinetic deprotonation of **1c** would, in comparison with ketones, be expected to occur kinetically at the methyl group. The HMPA problem notwithstanding, exchange would have to be achieved to attain **2c** or **2d**.

This problem is readily circumvented by employing the 1,3-dithiane derived from (*E*)-2-methyl-2-butenal. Under modified Fieser conditions[11] for dithiane formation, **3c** was contaminated with ~10% of the isomer **3d** because of acid-catalyzed isomerization of the unsaturated aldehyde during the reaction. Dithiane **3c** also has a distinct advantage over its ketene dithioacetal counterpart in that the dithiane can be directly deprotonated with *n*-BuLi/THF or LDA/THF, whereas 2-cyclohexylidene-1,3-dithiane is known to kinetically deprotonate adjacent to sulfur.[2] Although dithiane **3c** is contaminated with ~10% of **3d**, it is possible to generate only the *E* dithianylidene anion **2c** by employing a limited amount of *n*-BuLi to react with the kinetically more acidic isomer **3c**. The NMR spectrum of an 82/18 (**3c**/**3d**) mixture displayed the methine proton of the major component at δ 4.40 while the minor component revealed the same signal downfield at δ 4.96. The latter signal is deshielded because **3d** avoids the $A^{1,3}$ interaction between sulfur and $R_3(CH_3)$, thereby causing the methine CH bond to be in the plane of the double bond. Consequently, the overlap of the CH bond with the olefin is poorer in **3d** than it is in **3c**. When the 82/18 (0.8 equiv) mixture was treated with 0.7 equiv of *n*-BuLi (0 °C, 1 h, THF) followed by exposure to D_2O, the exclusive α deuteration of **3c** occurred with the disappearance of the δ 4.40 signal.

The mode of reaction of anions **2a–c**, as their lithium or cuprous salts, was explored in THF or THF–HMPA with cyclohexenone (**4**), cyclopentenone (**5**), and 2-methylcyclopentenone (**6**). The results are summarized in Table I. The 1,4 additions were generally conducted at −78 °C followed by warming to 0–25 °C. The reaction mixture was then cooled to −78 °C, protonated or alkylated, and warmed to ambient temperature once more. In all the examples studied, 1,4 addition predominated over 1,2 addition. Of the 1,4-addition products, γ addition predominated when the lithium counterion was employed in THF. This selectivity ranged from 3/1 (entry 6) to 35/1 (entry 11). The preference for γ-1,4 selectivity could be effectively reversed by treating the lithium anion with 3.0 equiv of HMPA or 1.5 equiv of $CuI\cdot(CH_3O)_3P$ at −78 °C prior to the addition of the enone. Under these conditions, 10/1 to 50/1 selectivity (α-1,4/γ-1,4) was routinely obtained without the appearance of 1,2 adducts.

† Dedicated to Professor George Büchi on the occasion of his 60th birthday.

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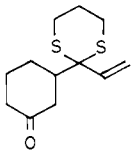

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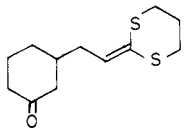

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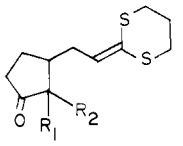
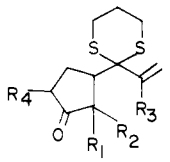


9a, $R_1 = CH_3$; $R_2 = H$
b, $R_1 = R_2 = H$



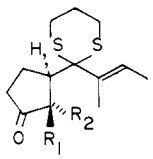
10a, $R_1 = CH_3$; $R_{2-4} = H$
b, $R_{1-4} = H$
c, $R_1 = R_2 = CH_3$; $R_3 = R_4 = H$
d, $R_1 = R_2 = R_4 = CH_3$; $R_3 = H$
e, $R_1 = R_3 = CH_3$;
e, $R_1 = R_3 = CH_3$; $R_2 = R_4 = H$
f, $R_1 = R_3 = CH_3$; $R_2 = C_3H_5$; $R_4 = H$
g, $R_1 = R_3 = CH_3$; $R_2 = R_4 = C_3H_5$
h, $R_1 = CH_3$; $R_2 = C_3H_5$; $R_3 = R_4 = H$
i, $R_1 = CH_3$; $R_2 = R_4 = C_3H_5$; $R_3 = H$

When the enolate generated in entry 2 was quenched after 15 min at −78 °C with CH_3OH without prior warming to ambient temperature, the α-1,4 adduct was isolated along with cyclohexenone, indicating the kinetic nature of the copper-assisted reaction.

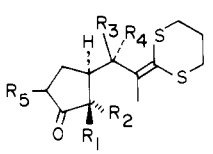
Lithium anions of dithianes are well recognized to undergo 1,2 addition in THF, whereas the presence of HMPA in the reaction medium effects kinetic 1,4 addition.[3b] Subsequent to our initial study, Haynes and co-workers[6] observed similar kinetically controlled modes of addition of the anion of phenyl allyl sulfide (Li^+–THF, Li^+–THF/HMPA, Cu^+–THF) to cyclopentenone at −78 °C.

When an aliquot of the reaction mixture of entry 11 was protonated at −78 °C after 2 h, the γ-1,4/1,2 ratio was approximately 1/1. As the reaction mixture was warmed to 25 °C (GC analysis, internal standard), the ratio approached the value of entry 11, with the amount of α-1,4-addition product remaining constant. Although the α/γ ratio of the 1,2 adducts was not ascertained, it is apparent that approximately 20% additional γ-1,4 adduct was arising from the pool of 1,2 adducts upon warming. Reversal of the 1,2 adducts followed by 1,4 addition is precluded since the α-1,4 yield remained constant. Moreover, the composition of entry 11 at 25 °C was not altered by the addition of HMPA.

It is postulated that the increased amount of γ-1,4 adduct formed upon warming arises from an alkoxy–Cope rearrangement[12] via a chairlike transition state of the α-1,2 adduct. Such a rearrangement would be in accord with the stereochemistry of the γ-1,4 adduct **12a**. An independent study of the reaction of



11a, R_1; R_2 = CH
b, $R_1 = CH_3$; R



12a, R_1, $R_2 = R_3$, $R_4 = CH_3$, H; $R_5 = H$
b, $R_1 = R_3 = CH_3$; $R_2 = C_3H_5$; $R_4 = R_5 = H$
c, $R_1 = R_4 = CH_3$; $R_2 = C_3H_5$; $R_3 = R_5 = H$
d, $R_1 = C_3H_5$; $R_2 = R_3 = CH_3$; $R_4 = R_5 = H$
e, R_1, $R_2 = CH_3$, C_3H_5; R_3, $R_4 = CH_3$, H; $R_5 = C_3H_5$

anion **1e** and cyclopentenone has conclusively confirmed the presence of alkoxy–Cope rearrangements in these systems.[13]

Table I

entry	anion	enone	reaction conditions	products (%)[a]	yield, %
1	2a	4	LDA, THF	8 (71) 7 (20) 1,2 (9)[c]	68[b]
2	2a	4	LDA, THF CuI·$(CH_3O)_3P$	7 (98) 8 (2)	67[b]
3	2a	6	LDA, THF	9a (60) 10a (16) 1, 2 (24)	82[b]
4	2a	6	LDA, THF CuI·$(CH_3O)_3P$	10a (98) 9a (2)	54[b]
5	2a	6	LDA, THF-HMPA[d]	10a (100)	66[b]
6	2a	5	LDA, THF	9b (70) 10b (26) 1, 2 (4)	44[b]
7	2a	6	1. LDA, THF-HMPA 2. CH_3I	10c (89) 10d (6) 10a (5)	70[b]
8	2b	6	LDA, THF-HMPA	10e (100)	71[b]
9	2b	6	1. LDA, THF-HMPA 2. CH_2=$CHCH_2Br$	10f (90) 10g (10)	68[b]
10	2a	6	1. LDA, THF-HMPA 2. CH_2=$CHCH_2Br$	10h (90) 10i (6) 10a (4)	67[b]
11	2c	6	LDA, THF	12a (71) 11a (2) 1, 2 (27)	
12	2c	6	1. LDA, THF 2. CH_2=$CHCH_2Br$[e]	12b (78)[f] 12c (4.5) 12d (4.5) 12a (9) 12e (4)	43[g]
13	2c	6	1. LDA, THF-HMPA 2. CH_2=$CHCH_2Br$	11b (69) 12b-d (19)[h] 1,2 (12)	49[i]

[a] Relative yields. [b] Isolated yield of products. [c] 1,2 products could not be analyzed as to α vs. γ substitution. [d] ~3 equiv of HMPA. [e] The Cu(I) enolate was used. [f] These products are derived from allylation of the intermediate enolate in entry 11 that gives 12a; 11b was not detected. [g] Combined isolated yield of 12b-d. [h] No stereochemical assignment made. [i] Isolated yield of 11b.

The enolate generated from the Li^+–THF/HMPA additions could be readily methylated (entry 7) with a minor amount (6%) of methylation product derived from enolate exchange along with unmethylated material. The allylation of the enolates derived from the Li^+–THF/HMPA additions gave minor amounts (entries 9 and 10) of over-alkylated products. The monoallylation products were found to be stereochemically homogeneous and were presumed to have the allyl group trans to the bulky dithiane unit. This assignment, as shall be demonstrated, is reasonable on the basis of the rigorous stereochemical proof applied to **12b–d** (entry 12).

The relative kinetic selectivity of 1,2 vs. 1,4 addition of nucleophiles in the presence of a cation and a solvated cation has been explained in frontier molecular orbital terms. The protonation[14] or cation coordination[15] of the carbonyl oxygen increases the carbonyl carbon orbital coefficient in the HOMO relative to the uncoordinated system (Li^+–THF/HMPA), thereby giving a higher kinetic percentage of the 1,2 adduct in the former instance.[16] No definitive treatment of the regioselectivity of electrophile reactions of sulfur-stabilized allylic anions has been presented. It would be anticipated that more charge localization would occur at the α position in the solvated case, thereby permitting stabilization of the charge by the adjacent polarizable sulfur atoms.[17]

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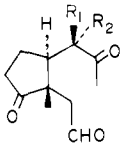
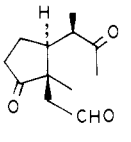
The addition of anion **2c** to 2-methylcyclopentenone (entry 11) provided a 1,4/1,2 ratio of ~3/1. Of the 1,4-addition products, virtually all of the material was γ-1,4 adduct. This mode of addition raises the question of the stereochemistry of the side chain relative to the ring junctures. Rather than protonate the enolate of entry 11, it was alkylated with allyl bromide as its Cu^+ enolate to minimize exchange alkylation. Under these conditions, a 90/5/5 mixture of three diastereomeric adducts **12b–d** was obtained in 43% isolated yield.

Ozonolysis of the mixture of **12b–d** provided a 67% yield of three diketoaldehydes in a 90/5/5 ratio. The major and one minor component, **13a** and **14**, respectively, were found to be identical



13a, $R_1 = CH_3$; $R_2 = H$
b, $R_1 = H$; $R_2 = CH_3$



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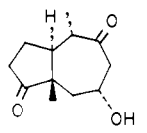
with substances obtained from the Cope–Claisen rearrangement, whose structures have been rigorously demonstrated.[18] The stereochemistry of the other minor component was shown to be isomer **13b** by relating it to material of known structure.[19] Since the trans/cis selectivity is 18/1 (**13a**/**14**) for one side-chain stereochemistry, it can be inferred that the observable alkylation product from the other side-chain stereoisomer should be of the trans arrangement, the side-chain stereochemistry having little influence on the trans/cis ratio.

Paquer[20] has reported that 1,1-bis(methylthio)-1-propene in the presence of pyridine undergoes abnormal ozonolysis to provide 1,1-bis(methylthio)-2-propanone. In the present instance, no evidence of abnormal products could be detected; straightforward olefin cleavage occurred. The byproduct of the reaction was identified as 2-oxo-1,3-dithiane.

The mixture of tricarbonyl compounds served as a useful starting material for the synthesis of (±)-aromatin and (±)-confertin. Accordingly, exposure of the trio to 2% aqueous methanolic KOH at 25 °C gave a single aldol product **15** in 83% yield. Of the several aldol products that, in principle, can arise from this reaction, those leading to trans-fused bicyclo[3.3.0]octane ring systems can be considered strained and are not formed under reversible conditions. The same argument can be offered for bridged aldol products. Tricarbonyl **14**, because of the cis relationship of the reactive functionality, forms some of these alternative structural types and is subsequently lost during the isolation. The alkaline reaction conditions serve to epimerize the side-chain methyl group after aldolization, thereby coalescing **13a** and **13b** into a single aldol product.[21] Exposure of the aldol **15** to $NaO\text{-}CH_3\text{–}HOCH_3$ failed to effect elimination, as was the case with the aldolization conditions. However, methoxide was readily exchanged for hydroxide, requiring the transient presence of the enone **16**. The lack of facile dehydration under alkaline conditions was construed as a reluctance on the part of the trans-fused bicyclo[5.3.0]decanedione system to entertain the presence of two additional sp^2-hybridized carbon atoms in the seven-membered ring.

The mesylate of **15** readily underwent elimination at 25 °C in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in THF providing a 65/35 mixture of α,β-isomer **16** and β,γ-isomer **17**, respectively. This mixture was demonstrated to be thermodynamically controlled, since at early conversion, the α,β isomer predominated. Exposure of the β,γ isomer to *t*-BuOK/*t*-BuOH at 25 °C provided the 65/35 ratio. This equilibrium value is close to that obtained for cycloheptenone[22] itself (73/27) and cycloheptenone **18** (70/30).[23]



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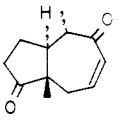

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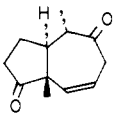

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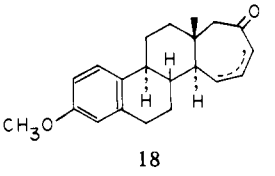

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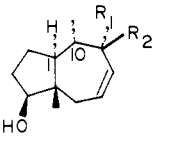
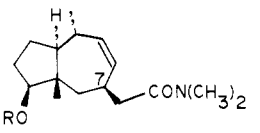


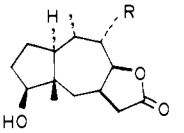
19a, $R_1 = H$; $R_2 = OH$
b, $R_1 = OH$; $R_2 = H$

Dehydration of **15** with $CH_3SO_3H\text{-}P_2O_5$ at 25 °C provided a 91/9 mixture of **16**/**17**, respectively.[24] Although pure enone **15** provided an 85/15 mixture of diols **19a** and **19b**, respectively, upon reduction with $LiAlH_4$, it was found to be expedient to reduce directly the mixture of dehydration products. The stereochemistry of the reduction of the cyclopentanone ring bears ample precedent in the chemistry of pseudoguaianolides.[25] The stereochemistry at C_{10} in diol **19a** was revealed by an NMR decoupling experiment. Irradiation of the C_{10} Me group (δ 0.97, J = 6.6 Hz) transformed the multiplet for the C_{10} H (δ 1.64) into a triplet (J = 10.0 Hz) requiring large dihedral angles between the C_{10} H and the C_1 H and C_9 H. Moreover, irradiation of the vinylic protons (δ 5.67) caused the C_9 H (δ 3.85) to appear as a doublet (J = 10.0 Hz) coupled to the C_{10} H.

The crystalline diol **19a** possesses the correct relative stereochemistry at C_1, C_5, and C_{10} of aromatin. The β-hydroxyl group at C_9 served to introduce the C_7 acetic acid chain. This transformation was accomplished with facility by the Eschenmoser variant of the Claisen rearrangement,[26] providing amide alcohol **20a** and amide acetate **20b**. The acetate group of **20b** was readily



20a, R = H
b, R = $COCH_3$



21a, R = I
b, R = H

removed by mild saponification (K_2CO_3, aqueous CH_3OH) to provide **20a** in 72% overall yield. A small amount of byproducts from the rearrangement was identified by mass spectroscopy as dienic alcohols (M^+ 178) arising from elimination of the elements of water from diol **19a**. The refunctionalization of C_9 and the

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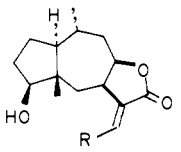
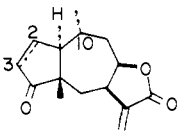
formation of the *cis*-lactone **21** was readily achieved by iodolactonization of amide **20a** in the presence of 3 equiv of I_2 in aqueous THF at 25 °C.[27] The C_9 H appeared in the NMR spectrum of **21a** at δ 4.67 (dd, J = 8.1 and 3.1 Hz), the larger coupling constant being associated with the trans C_8 H at δ 4.92 (dd, J = 8.1 and 6.7 Hz). The smaller coupling constant supported the cis relationship of the C_9 H and C_{10} H. Iodo lactone **21a** served as a common point of departure for the synthesis of aromatin and confertin.

Deiodination of **21a** was realized with *n*-Bu_3SnH, providing lactone **21b** in 94% yield. Introduction of the methylene group on the lactone ring was achieved by a new method.[28] Exposure of lactone **21b** to bis(dimethylamino)methoxymethane (Bredereck's reagent)[29] gave rise to a mixture of the hydroxy vinylogous carbamate **22a** and its formate.[30] Brief exposure to alkali con-



22a, R = $N(CH_3)_2$
b, R = H

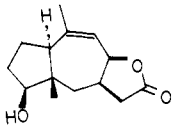


23a, 2,3-dihydro
b, 2,3-dehydro

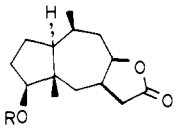
verted the formate to **22a**. Reduction of the carbamate was effected with DIBAL (2.4 equiv) followed by treatment with saturated aqueous NH_4Cl, providing the α-methylene-γ-butyrolactone **22b** in excellent yield.

Oxidation of alcohol **22b** with pyridinium chlorochromate proceeded without incident, affording dihydroaromatin **23a** whose 270-MHz NMR spectrum, IR spectrum, and TLC behavior were identical with an authentic sample of (±)-dihydroaromatin, which had been transformed into and compared with an authentic sample of (−)-aromatin by Lansbury.[31] Selenylation and selenoxide elimination of **23a** gave rise to **23b**, whose spectral properties (NMR, IR) were in accord with data reported for (−)-aromatin[32] and whose melting point agreed with that reported for the racemate.[31]

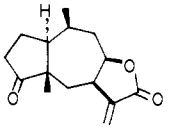
Confertin (**26**)[33] could be realized from the iodide **21a**. Dehydrohalogenation required a large excess (30 equiv) of 1,5-diazabicyclo[4.3.0]non-5-ene (DBN) in THF at 53 °C for a period of 10 h to effect efficient elimination of the elements of HI at an appreciable rate to provide olefin **24**. Molecular models indicate



24



25a, R = H
b, R = $COCH_3$



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that some distortion of the seven-membered ring is required to attain the required antiperiplanar arrangement of the C_{10} H and the C_9 I necessary for E2 elimination.

After investigation of several catalyst systems, PtO_2 in ethanol was demonstrated to give the C_{10}-β-CH_3 isomer **25a** without the appearance of the α-isomer **21b**.[34] Acetylation of **25a** afforded the acetoxylactone **25b**, which was identical (NMR, IR, TLC, GC/MS, melting point) with an authentic sample that had been previously converted to confertin.[33d]

The utility of dithianylidene anions as masked enolate equivalents has been amply demonstrated in the synthesis of two naturally occurring pseudoguaianolides. The method, by virtue of one's ability to control to a reasonable degree the modes of 1,4 and 1,2 addition, holds promise as a viable method in synthetic organic chemistry.

Experimental Section

Gas chromatography (GC) was performed on a Perkin-Elmer Series 1400 thermal or 3920 flame ionization chromatograph using the following columns: (A) 1.5% OV-101 on Chromosorb GHP 100/120, 5 ft × $^1/_8$ in.; (B) 3% OV-101, Chromosorb WHP 80/100, 7 ft × $^1/_8$ in.; (C) 5% OV-1 on Chromosorb WHP 80/100, 5 ft × $^1/_8$ in. Entries 1–6 (Table 1) employed column B for analysis, entries 7–13, column A.

Analytical thin-layer chromatography (TLC) was performed on Baker-flex silica gel 1B-F plates; preparative TLC employed Analtech 20 cm × 20 cm (2000) plates. Column chromatography was conducted with Grace silica gel (100/200 mesh) or Florisil. Flash chromatography was performed as described by Still.[35] High-pressure liquid chromatography was carried out on a Waters LC 500 with silica gel cartridges.

Reactions requiring anhydrous conditions were performed in flame-dried glassware under an inert atmosphere. Dry $CHCl_3$, CH_2Cl_2, pyridine, diisopropylamine, and HMPA were distilled from CaH_2 under N_2 and stored over molecular sieves (4×). Ether and THF were distilled from sodium benzophenone ketyl under N_2. Commercial *n*-BuLi (Alfa-Ventron) was standardized by the method of Kofron.[36] Methyl iodide and allyl bromide were distilled before use.

Materials characterized only by GC/MS were assigned their structures on the basis of reasonable over-methylated or allylated products and are accordingly tentative assignments.

2-((*E*)-1-Propenyl)-1,3-dithiane (3c). A mixture of 1,3-propanedithiol (5.0 mL, 50 mmol), freshly distilled boron trifluoride etherate (6.1 mL, 50 mmol), glacial acetic acid (12.0 mL, 210 mmol), and anhydrous chloroform (80 mL) was vigorously stirred at −20 °C. A solution of (*E*)-2-methyl-2-butenal (4.2 g, 50.0 mmol) in anhydrous chloroform (18 mL) was added dropwise over a period of 15 min, while the temperature was maintained below −10 °C. The mixture was warmed to 0 °C over a period of 25 min and siphoned by positive nitrogen pressure into ice-cold 10% aqueous KOH (180 mL). After the mixture was vigorously stirred for 15 min, the organic phase was separated and successively washed twice with 10% aqueous KOH and three times with water. The organic phase was dried over anhydrous K_2CO_3, filtered, concentrated, and distilled (Kugelrohr, 72 °C, 0.02 mmHg) to afford the dithiane (7.83 g, 45.0 mmol) in 90% yield. GC and NMR analyses revealed that the product mixture contained 13% of *Z*-isomer **3d**.

3c: GC (Column A, 120 °C); ^{1}H NMR (90 MHz, CCl_4) δ 5.60 (1 H, q, J = 7.0 Hz), 4.40 (1 H, s, $RCHS_2$), 2.76 (4 H, m), 1.98 (2 H, m), 1.74 (3 H, s), 1.64 (3 H, s); GC/MS (70 eV), m/e (rel intensity) 174 (100, M^+), 100 (36), 99 (76), 85 (99).

3d: GC (Column A, 120 °C); ^{1}H NMR (90 MHz, CCl_4, partial) δ 5.27 (1 H, q, J = 7.0 Hz), 4.96 (1 H, s, $RCHS_2$); GC/MS (70 eV), m/e (rel intensity) 174 (97, M^+), 100 (37), 99 (82), 85 (100).

General Procedure for Addition–Alkylation Reactions. The anions from ketene dithioacetals **1a,,b** (1.0 equiv) were prepared at −78 °C (N_2, THF) on a 1–3-mmol scale as previously described.[37] HMPA (3.0 equiv) or CuI $(CH_3O)_3P$[38] (1.5 equiv) was added to the anions in the appropriate cases at −78 °C. The enones (1.0 equiv) in a minimal volume of THF were added to the solution via syringe–serum cap technique at −78 °C. The solutions were allowed to warm slowly (4–5 h) to 25 °C followed by 3–14 h at 25 °C. The enolates were quenched with HOAc (1.5 equiv) in THF at 25 °C. Alkylations were conducted by cooling the enolate solutions to −78 °C, followed by introduction of the alkyl halide (2.0 equiv) and warming to 25 °C over 3–15 h. Reaction mixtures were worked up by pouring them into water, extracting with ether, backwashing with aqueous $NaHCO_3$ solution (protonations) or aqueous $NaCN(Cu^+)$, and washing with saturated brine. The organic phases were dried over anhydrous $MgSO_4$, filtered, and concentrated. Spectral

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and combustion data samples were obtained by GC collection.

Cyclohexanone 7: bp 150–200 °C (0.02 mm, Kugelrohr); ^{1}H NMR (CCl_4, 270 MHz) δ 1.54 (2 H, m), 1.81–2.31 (6 H, m), 2.60 (3 H, m), 2.84 (4 H, m), 5.45 (1 H, dd, J_c = 9.3 Hz, J_g = 1.6 Hz), 5.46 (1 H, dd, J_t = 17.6 Hz, J_g = 1.6 Hz), 5.74 (1 H, dd, J_t = 17.1 Hz, J_c = 10.1 Hz); IR (CCl_4) 1715, 1620 cm^{-1}; MS (70 eV), *m/e* (rel intensity) 242 (8, M^+), 147 (8), 146 (8), 145 (100), 106 (4), 97 (4), 71 (8).

Anal. Calcd for $C_{12}H_{18}OS_2$: C, 59.46; H, 7.48. Found: C, 59.77; H, 7.31.

Cyclohexanone 8: bp < 200 °C (0.02 mm, Kugelrohr); ^{1}H NMR (CCl_4, 270 MHz) δ 1.61–2.37 (13 H, m), 2.83 (4 H, t, J = 6.0 Hz), 5.80 (1 H, t, J = 7.7 Hz); IR (CCl_4) 1715, 1650 cm^{-1}; MS (70 eV), *m/e* (rel intensity) 242 (9, M^+), 147 (8), 146 (8), 145 (100), 97 (2), 73 (1), 71 (13).

Anal. Calcd for $C_{12}H_{18}OS_2$: C, 59.46; H, 7.48. Found: C, 59.61; H, 7.60.

Cyclopentanone 9a: bp < 180 °C (0.02 mm, Kugelrohr); ^{1}H NMR (CCl_4, 270 MHz) δ 1.06 (3 H, d, J = 6.2 Hz), 1.92–2.32 (8 H, m), 2.47–2.57 (2 H, m), 2.84 (4 H, m), 5.87 (1 H, t, J = 7.7 Hz); IR (CCl_4) 1745, 1685 cm^{-1}; MS (70 eV), *m/e* (rel intensity) 242 (15, M^+), 168 (6), 147 (9), 146 (10), 145 (100), and 71 (16).

Anal. Calcd for $C_{12}H_{18}OS_2$: C, 59.46; H, 7.48. Found: C, 59.47; H, 7.47.

Cyclopentanone 9b: bp < 160 °C (0.04 mm, Kugelrohr); ^{1}H NMR (CCl_4, 270 MHz) δ 2.04–2.35 (11 H, m), 2.84 (4 H, m), 5.82 (1 H, t, J = 7.3 Hz); IR (CCl_4) 1745 cm^{-1}; MS (70 eV), *m/e* (rel intensity) 228 (14, M^+), 147 (8), 146 (8), 145 (100), 97 (3), 71 (15).

Anal. Calcd for $C_{11}H_{16}OS_2$: C, 57.85; H, 7.06. Found: C, 58.08; H, 7.20.

Cyclopentanone 10a: bp 150–200 °C (0.03 mm, Kugelrohr); ^{1}H NMR (CCl_4, 270 MHz) δ 1.19 (3 H, d, J = 6.7 Hz), 1.79–2.31 (6 H, m), 2.53–2.64 (2 H, m), 2.80–2.93 (4 H, m), 5.44 (1 H, dd, J_c = 10.1 Hz, J_g = 1.6 Hz), 5.52 (1 H, dd, J_t = 17.0 Hz, J_g = 1.6 Hz), 5.80 (1 H, dd, J_t = 17.0 Hz, J_c = 10.1 Hz); IR ($CDCl_3$) 1735 cm^{-1}; MS (70 eV), *m/e* (rel intensity) 242 (23, M^+), 147 (9), 146 (8), 145 (100), 135 (5), 112 (4), 111 (5), 106 (13), 97 (6), 91 (5), 79 (7), 74 (4), 71 (11).

Anal. Calcd for $C_{12}H_{18}OS_2$; C, 59.46; H, 7.48. Found: C, 59.50; H, 7.54.

Cyclopentanone 10b: bp <160 °C (0.04 mm, Kugelrohr); ^{1}H NMR (CCl_4, 270 MHz) δ 1.83–2.64 (9 H, m), 2.86 (4 H, m), 5.45 (1 H, d, J_c = 10.3 Hz), 5.52 (1 H, d, J_t = 16.9 Hz), 5.80 (1 H, dd, J_t = 16.9 Hz, J_c = 10.3 Hz); IR (CCl_4) 1750 cm^{-1}; MS (70 eV), *m/e* (rel intensity) 228 (27, M^+), 147 (8), 146 (8), 145 (100), 112 (9), 111 (4), 106 (7), 97 (7), 79 (6), 74 (6), 73 (4), 71 (12).

Anal. Calcd for $C_{11}H_{16}OS_2$: C, 57.85; H, 7.06. Found: C, 58.03; H, 7.18.

Cyclopentanone 10c: bp 110 °C (0.02 mm, Kugelrohr); ^{1}H NMR (CCl_4, 270 MHz) δ 1.00 (3 H, s), 1.21 (3 H, s), 1.72–2.37 (6 H, m), 2.50–2.63 (1 H, m), 2.79–2.84 (4 H, m), 5.42 (1 H, dd, J_c = 10.2 Hz, J_g = 1.5 Hz), 5.50 (1 H, dd, J_t = 17.2 Hz, J_g = 1.5 Hz), 5.88 (1 H, dd, J_t = 17.2 Hz, J_c = 10.2 Hz); IR (CCl_4) 1745 and 1625 cm^{-1}; MS (70 eV), *m/e* (rel intensity) 256 (54, M^+), 147 (9), 146 (8), 145 (100), 139 (10), 135 (7), 126 (8), 111 (14), 107 (11), 106 (33), 97 (8), 93 (11), 91 (12), 79 (14), 77 (16), 73 (7), 71 (37), 69 (11), 67 (7), 65 (7), 55 (8).

Anal. Calcd for $C_{13}H_{20}OS_2$: C, 60.89; H, 7.86. Found: C, 60.97; H, 7.78.

Dialkylated cyclopentanone 10d: MS (70 eV), *m/e* (rel intensity) 270 (15, M^+), 256 (23), 147 (9), 146 (8), 145 (100), 126 (13), 125 (8), 111 (13), 107 (10), 106 (34), 97 (8), 93 (12), 91 (11), 79 (10), 77 (12), 71 (22), 69 (8).

Cyclopentanone 10e: bp 160–180 °C (0.5 mm, Kugelrohr); ^{1}H NMR (CCl_4, 270 MHz) δ 1.15 (3 H, d, J = 7.3 Hz), 1.72–2.47 (6 H, m), 1.92 (3 H, s), 2.51–2.65 (2 H, m), 2.78–2.89 (4 H, m), 5.33 (1 H, m), 5.74 (1 H, m); IR ($CDCl_3$) 1730 and 1630 cm^{-1}; MS (70 eV), *m/e* (rel intensity) 256 (25, M^+), 161 (9), 160 (10), 159 (100), 126 (6), 111 (6), 107 (9), 106 (21), 97 (6), 93 (7), 91 (7), 85 (19), and 77 (7).

Anal. Calcd for $C_{13}H_{20}OS_2$: C, 60.89; H, 7.86. Found: C, 61.07; H, 7.94.

Cyclopentanone 10f: bp 120 °C (0.02 mm, Kugelrohr); ^{1}H NMR (CCl_4, 270 MHz) δ 1.24 (3 H, s), 1.95 (3 H, s), 1.72–2.18 (2 H, m), 2.26–2.59 (7 H, m), 2.73–2.95 (4 H, m), 5.03 (1 H, d, J = 10.3 Hz), 5.04 (1 H, d, J = 18.0 Hz), 5.36 (1 H, br s), 5.42–5.55 (1 H, m), 5.58 (1 H, m); IR (CCl_4) 1745, 1640, 1625 cm^{-1}; MS (70 eV), *m/e* (rel intensity) 296 (44, M^+), 221 (13), 179 (14), 161 (15), 160 (11), 159 (100), 149 (74), 105 (19), 97 (17), 95 (24), 93 (17), 91 (27), 85 (41), 79 (27), 77 (21), 67 (14).

Anal. Calcd for $C_{16}H_{24}OS_2$: C, 64.82; H, 8.16. Found: C, 65.01; H, 8.24.

Diallylated cyclopentanone 10g: MS (70 eV), *m/e* (rel intensity) 336 (58, M^+), 261 (12), 161 (12), 160 (11), 159 (100), 125 (10), 119 (13), 111 (12), 107 (17), 106 (45), 105 (22), 95 (16), 93 (12), 91 (25), 85 (29), 79 (16), 77 (12), 67 (15).

Cyclopentanone 10h: bp 120 °C (0.02 mm, Kugelrohr); ^{1}H NMR (CCl_4, 270 MHz) δ 1.05 (3 H, s), 1.80–2.07 (4 H, m), 2.14–2.36 (2 H, m), 2.41–2.63 (3 H, m), 2.84–2.98 (4 H, m), 5.01 (1 H, d, J_c = 6.2 Hz), 5.03 (1 H, d, J_t = 17.2 Hz), 5.43 (1 H, dd, J_c = 10.1 Hz, J_g = 1.6 Hz), 5.49 (1 H, m), 5.50 (1 H, dd, J_t = 17.0 Hz, J_g = 1.6 Hz), 5.90 (1 H, dd, J_t = 17.2 Hz, J_c = 10.2 Hz); IR (CCl_4) 1735, 1640, 1625 cm^{-1}; MS (70 eV), *m/e* (rel intensity) 282 (30, M^+), 207 (20), 197 (6), 175 (6), 165 (8), 151 (9), 147 (14), 146 (9), 145 (100), 111 (68), 107 (10), 106 (68), 105 (15), 97 (16), 95 (77), 93 (13), 91 (24), 79 (26), 78 (8), 77 (26), 73 (12), 71 (53), 67 (21), 65 (16), 55 (16), and 53 (13). The combustion analysis was consistently high in carbon.

Dialkylated cyclopentanone 10i: MS (70 eV), *m/e* (rel intensity) 322 (26, M^+), 281 (2), 247 (10), 147 (11), 146 (9), 145 (100), 107 (10), 106 (50), 95 (15), 91 (15), 79 (9), 77 (10), 71 (16), 67 (10).

Cyclopentanone 11b: IR ($CHCl_3$): 2975, 2900, 1730, 990, 905 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 6.23 (1 H, q, J = 6.6 Hz, MeCH=CR_2), 5.83–4.92 (3 H, CH_2=CHR), 2.88–1.86 (13 H), 1.82 (3 H, s), 1.77 (3 H, d, J = 6.6 Hz), 1.24 (3 H, s). MS (70 eV), *m/e* (rel intensity) 310 (44, M^+), 193 (29), 173 (100), 106 (40), 91 (30). Unstable to combustion analysis.

Cyclopentanone 11a: MS (70 eV), *m/e* (rel intensity) 270 (23, M^+), 175 (9), 174 (11), 173 (100), 163 (9), 125 (20), 107 (8), 106 (21), 99 (10).

Cyclopentanone 12a, major isomer: IR (CCl_4) 1740 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 3.26 (1 H, m, C_{10} H), 2.96–2.77 (4 H, m), 2.39–1.70 (8 H, m), 1.83 (3 H, s), 1.20 (3 H, d, J = 7.3 Hz, C_5 CH_3), 1.07 (3 H, d, J = 6.6 Hz, C_{10} CH_3). MS (70 eV), *m/e* (rel intensity) 270 (7, M^+), 173 (100).

Anal. Calcd for $C_{14}H_{22}OS_2$: C, 62.17; H, 8.20. Found: C, 61.95; H, 8.12.

Cyclopentanone 12b. A solution of *n*-BuLi (15.12 mL, 37.8 mmol, 2.5 M solution in hexane) was added dropwise to a solution of dithiane **3c,d** (7.59 g, containing 37.8 mmol of **3c** and 5.65 mmol of **3d**) in anhydrous THF (115 mL) at 0 °C. After 1 h, the resulting yellow solution was cooled to −78 °C, and a solution of 2-methyl-2-cyclopentenone[39] (3.63 g, 37.8 mmol) in THF (20 mL) was added dropwise over a period of 15 min. The reaction mixture was allowed to warm slowly to 25 °C over a period of 3 h and was stirred for an additional 1 h at 25 °C. GC analysis of the reaction aliquot revealed that the product mixture contained 1,2, α-1,4, and γ-1,4 adducts in a ratio of 27:2:71 (entry 11, Table I). The mixture was recooled to −78 °C, and a solution of cuprous iodide–trimethyl phosphite complex (11.89 g, 37.8 mmol) in THF (40 mL) was added. The solution changes color from pale yellow to brown. After 5 min, allyl bromide (6.58 mL, 76 mmol) was added. The reaction mixture was stirred for 2.5 h and quenched with a solution of acetic acid (6.84 mL, 114 mmol) in THF (10 mL) at −78 °C. The mixture was warmed to 25 °C and concentrated in vacuo; the residual oil was taken up in ether (200 mL), and saturated NH_4Cl (30 mL) was added. After stirring for 10 min, the precipitates were filtered off through a bed of Celite 545 and rinsed with ether. The aqueous phase was separated from the filtrate and extracted twice with ether. The combined organic phases were successively washed with 10% aqueous sodium cyanide (4×) and saturated ammonium chloride (2×), dried ($MgSO_4$), and concentrated in vacuo. The residual oil (10.7 g) was chromatographed (Waters LC-500, CH_2Cl_2) to give 5.0 g (16.1 mmol) of compounds **12b**, **12c**, and **12d** (90:5:5) in 43% yield. Data for **12b** are reported: ^{1}H NMR (270 MHz, $CDCl_3$) δ 5.64–4.91 (3 H, CH_2=CHR), 3.42 (1 H, m, C_{10} H), 2.96–2.76 (4 H, RCH_2S), 2.67–1.35 (9 H), 1.82 (3 H, s), 1.08 (3 H, d, J = 6.6 Hz, C_{10} CH_3), 1.01 (3 H, s, C_5 CH_3); ^{13}C NMR (67.5 MHz, $CDCl_3$, ppm) 222.5, 141.6, 134.3, 119.7, 51.5, 43.6, 41.7, 38.5, 37.4, 30.0, 29.5, 24.7, 24.0, 17.9, 17.1, 14.6; MS (70 eV), *m/e* (rel intensity) 310 (3, M^+), 173 (100); IR (neat, FT) 2965, 2933, 2908, 1735, 1276, 912 cm^{-1}.

Anal. Calcd for $C_{17}H_{26}OS_2$: C, 65.76; H, 8.44; S, 20.65. Found: C, 65.81; H, 8.26; S, 20.39.

Diallylated cyclopentanone 12e: MS (70 eV), *m/e* (rel intensity) 350 (4, M^+), 173 (100).

Keto Aldehyde 13a (13b, 14). Ozone was passed via a fritted bubbler through a stirred solution of ketenedithioacetal **12b** (4.34 g, 12.6 mmol) in anhydrous dichloromethane (85 mL) and absolute methanol (85 mL) at −75 °C. After 1.5 h, the uptake of ozone was complete and the blue color of ozone persisted in the solution. The solution was purged with nitrogen for 10 min and quenched with dimethyl sulfide (2.8 mL, 39 mmol). The mixture was allowed to warm to 25 °C under a nitrogen atmosphere. After 16 h at 25 °C, the volatiles were removed and the

(39) Gaddis, A. M.; Butz, L. W. *J. Am. Chem. Soc.* **1947**, *69*, 1203.

residual mixture, containing Me_2SO, 2-oxo-1,3-dithiane, diketo aldehyde **13a**, and partial acetal (or hemiacetal) derivatives, was dissolved in glacial acetic acid (5 mL) and water (1.5 mL) and stirred at 25 °C for 4 h. The mixture was cooled in an ice bath, and saturated sodium carbonate was added carefully until the solution became slightly alkaline (pH 8). The aqueous phase was separated and extracted three times with ethyl acetate. The combined organic phases were washed with brine, dried ($MgSO_4$), and concentrated in vacuo to afford a crude oil (4.39 g), which was chromatographed (Waters LC-500, 1:1 ethyl acetate–hexane) to give 1.78 g (8.48 mmol) of the desired diketo aldehyde **13a** in 67% yield. The NMR spectrum revealed the presence of diastereomers in a ratio of 90:5:5; GC (Column A, 135 °C).

13a: ^{1}H NMR (270 MHz, $CDCl_3$) δ 9.61 (1 H, br s, $w_{1/2}$ = 3 Hz, CHO), 3.02–1.22 (8 H), 2.17 (3 H, s, $COCH_3$), 1.16 (3 H, d, J = 6.6 Hz, C_{10} CH_3), 0.96 (3 H, s, C_5 CH_3); MS (70 eV), m/e (rel intensity) 210 (1, M^+), 168 (57), 139 (20), 138 (9), 125 (13), 111 (21), 110 (95), 97 (100); ^{13}C NMR (67.5 MHz, $CDCl_3$) 220.4, 210.7, 199.4, 51.6, 48.8, 47.9, 44.0, 35.7, 28.2, 24.2, 16.8, 15.8.

13b: ^{1}H NMR (270 MHz, $CDCl_3$) δ 9.56 (1 H, br s, $w_{1/2}$ = 3 Hz, CHO), 3.03–1.93 (8 H), 2.20 (3 H, s, $COCH_3$), 1.17 (3 H, d, J = 6.6 Hz, C_{10} CH_3), 0.86 (3 H, s, C_5 CH_3); MS (70 eV), m/e (rel intensity) 210 (3, M^+), 168 (61), 139 (16), 138 (25), 125 (22), 111 (21), 110 (53), 97 (100).

14: ^{1}H NMR (270 MHz, $CDCl_3$, partial) δ 9.72 (1 H, t, J = 2.3 Hz, CHO), 2.18 (s, $COCH_3$), 1.30 (3 H, s, C_5 CH_3), 1.22 (3 H, d, J = 7.0 Hz, C_{10} CH_3).

Anal. (Mixture of diastereomers) Calcd for $C_{12}H_{18}O_3$: C, 68.55; H, 8.63. Found: C, 68.27; H, 8.46.

Aldol 15. A solution of 1.12 g (5.33 mmol) of diketo aldehyde **13a** (**13b** and **14**) dissolved in 70 mL of CH_3OH at 0 °C (N_2) was treated with 14 mL of 10% aqueous KOH. After 4 h at 25 °C, the resulting brown solution was cooled in an ice bath and acidified to pH 2 with concentrated HCl (2.7 mL). The mixture was concentrated in vacuo; the residue was extracted with ethyl acetate (3×). The combined extracts were washed with saturated NaCl, dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo to give crude aldol **15**. Purification on a short silica gel column (ethyl acetate) provided 926 mg (4.40 mmol) of **15** in 83% yield as a colorless oil: ^{1}H NMR (270 MHz, $CDCl_3$) δ 4.46 (1 H, br s, OH), 4.00 (1 H, tdd, J = 11.2, 4.4, 2.6 Hz, C_7 H), 3.01 (1 H, dd, J = 11.2, 10.0 Hz, C_8 H), 2.61 (1 H, dt, J = 10.0, 2.6 Hz, C_8 H), 2.59–1.32 (8 H), 1.22 (3 H, d, J = 7.0 Hz, C_{10} CH_3), 0.78 (3 H, s, C_5 CH_3); IR (neat) 3460 (OH), 1739, 1700 cm^{-1}; GC/MS (70 eV, partial), m/e (rel intensity) 210 (79, M^+), 192 (14), 97 (100).

Anal. Calcd for $C_{12}H_{18}O_3$: C, 68.54; H, 8.63. Found: C, 68.74; H, 8.72.

Enones 16 and 17 (Mesylate Route). Aldol **15** (473 mg, 2.25 mmol) was dissolved in anhydrous CH_2Cl_2 (18 mL) and cooled to 0 °C. Anhydrous triethylamine (0.47 mL, 3.38 mmol) was added, followed by the dropwise addition of distilled methanesulfonyl chloride (0.23 mL, 2.93 mmol) over a period of 3 min. After being stirred at 0 °C for 45 min, the mixture was quenched with 1.5 mL of ice water. The organic phase was separated and washed successively with 10% aqueous NaH_2PO_4, saturated $NaHCO_3$, and water. The solution was dried over anhydrous $MgSO_4$, filtered, and concentrated to give 574 mg of crude mesylate compound; ^{1}H NMR ($CDCl_3$) δ (3.01, s, OSO_2CH_3).

The crude mesylate was dissolved in anhydrous THF (9 mL), and 1.03 g (6.75 mmol) of DBU was added. The mixture was stirred at 25 °C for 7 h, concentrated in vacuo, and taken up in CH_2Cl_2 (20 mL). The solution was washed successively with dilute HCl, saturated $NaHCO_3$, and water. The organic anhydrous $MgSO_4$ solution was dried, filtered, and concentrated. The residue was composed of enones **16** and **17** in a ratio of 65:35, respectively; GC (column C, 125 °C). Two components were separated by flash chromatography (1% ethyl acetate in CH_2Cl_2) to afford 107 mg of crude **17** and 200 mg of crude **16** in 71% total yield.

α,β-Unsaturated ketone 16: ^{1}H NMR (270 MHz, $CDCl_3$) δ 6.26 (1 H, ddd, J = 13.0, 5.6, 3.3 Hz, C_7 H), 6.01 (1 H, dd, J = 13.0, 2.7 Hz, C_8 H), 2.68–2.07 (8 H), 1.26 (3 H, d, J = 7.1 Hz, C_{10} CH_3), 0.99 (3 H, s, C_5 CH_3); IR (CCl_4, FT) 1745, 1665, 1662 cm^{-1}; GC/MS (70 eV, partial), m/e (rel intensity) 192 (15, M^+), 96 (100), 95 (22). The ketone was subjected to reduction without further purification.

β,γ-Unsaturated ketone 17: ^{1}H NMR (270 MHz, $CDCl_3$) δ 5.93 (1 H, dd, J = 11.0, 3.3 Hz, C_6 H), 5.56 (1 H, ddd, J = 11.0, 8.4, 2.2 Hz, C_7 H), 3.60 (1 H, ddd, J = 14.7, 3.3, 2.2 Hz, C_8 H), 2.81 (1 H, dd, J = 14.7, 8.4 Hz, C_8 H), 2.68–2.07 (6 H), 1.26 (3 H, d, J = 7.1 Hz, C_{10} CH_3), 0.93 (3 H, s, C_5 CH_3); IR (CCl_4, FT) 1740, 1709, 1650 cm^{-1}; GC/MS (70 eV, partial), m/e (rel intensity) 192 (56, M^+), 96 (100), 95 (82), 93 (99).

Diols 19a and 19b. Enone **16** (300 mg, 1.56 mmol) dissolved in anhydrous diethyl ether (10 mL) was added dropwise to a suspension of $LiAlH_4$ (420 mg, 11 mmol) in diethyl ether (50 mL) at 25 °C. After being stirred for 3 h at 25 °C, the reaction mixture was quenched with 0.5 mL of saturated sodium sulfate. The solids were filtered, dissolved in 3 N hydrochloric acid (20 mL), and extracted with ethyl acetate. The filtrate and extracts were combined, washed with brine, and dried over $MgSO_4$. The volatiles were removed to afford 290 mg (95%) of material that contained two components in 85:15 ratio by GC analysis (column C, 135 °C).

The major component was crystallized ($CHCl_3$) from the product mixture to afford a white solid, which was identified as diol **19a**: mp 163–165 °C; IR ($CHCl_3$, FT) 3605, 3464, 2971, 1658, 1464, 1376 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 5.77–5.57 (2 H), 3.85 (1 H, ddd, J = 9.7, 3.0, 2.8 Hz, C_9 H), 3.61 (1 H, t, J = 8.6 Hz, C_4 H), 2.28 (1 H, dd, J = 14.7, 8.8 Hz, C_6 H), 2.00 (1 H, C_3 H), 1.85–1.70 (2 H, C_3 H, C_6 H), 1.70–1.51 (1 H, m, C_{10} H), 1.50–1.15 (3 H), 0.97 (3 H, d, J = 6.6 Hz, C_{10} CH_3), 0.72 (3 H, s, C_5 CH_3); GC/MS (70 eV), m/e (rel intensity) 196 (23, M^+), 178 (3), 163 (10), 145 (11), 137 (33), 109 (86), 97 (100).

Anal. Calcd for $C_{12}H_{20}O_2$: C, 73.43; H, 10.27. Found: C, 73.31; H, 10.29.

The minor component was isolated as a white solid from the mother liquors by flash chromatography (2:3 ethyl acetate–hexane) and assigned structure **19b**: mp 143–145 °C; ^{1}H NMR (270 MHz, $CDCl_3$) δ 6.02 (1 H, m, C_8 H), 5.80 (1 H, m, C_7 H), 4.02 (1 H, dt, J = 7.3, 1.1 Hz, C_9 H), 3.69 (1 H, t, J = 8.8 Hz, C_4 H), 2.24 (1 H, dd, J = 14.7, 8.6 Hz, C_6 H), 2.13–2.10 (1 H, C_6 H), 2.10–1.93 (1 H), 1.80–1.60 (2 H), 1.52–1.31 (3 H), 0.99 (3 H, d, J = 6.6 Hz, C_{10} CH_3), 0.73 (3 H, s, C_5 CH_3), MS (70 eV), m/e (rel intensity) 196 (18, M^+), 178 (10), 163 (12), 145 (17), 137 (18), 109 (92), 97 (100).

Diols 19a and 19b (P_2O_5–CH_3SO_3H Route). To a 1:10 solution (w/w) of P_2O_5 in CH_3SO_3H (27 mL) was added aldol **15** (1.65 g, 7.86 mmol). The dark red mixture was stirred at 25 °C (N_2) for 1 h. The reaction mixture was slowly added to water (150 mL). The yellow solution was extracted several times with CH_2Cl_2 and backwashed with water. The solution was dried over anhydrous $MgSO_4$, filtered, and concentrated to give 1.58 g of a crude mixture containing unsaturated ketones **16** and **17** (91:9).

Without further purification, the mixture was dissolved in anhydrous THF (25 mL) and added dropwise over a 20-min period to a suspension of $LiAlH_4$ (1.75 g, 46 mmol) in ether (150 mL) at 25 °C. After being stirred for 2 h, the reaction mixture was carefully decomposed with 2.5 mL of saturated Na_2SO_4. The resulting mixture was filtered and rinsed with ethyl acetate. The residual solid was dissolved in 3 N HCl (80 mL) and extracted with ethyl acetate. The filtrate and extracts were combined and washed with water and brine. Workup gave 1.48 g of a crude oil. Flash chromatography (2:3 ethyl acetate–hexane) gave 534 mg of the major isomer **16**, 96 mg of the minor isomer **17**, and 126 mg of an intermediate fraction of the major and the minor isomers in a 3:1 ratio.

Amide 20a. A mixture of diol **19a** (540 mg, 2.76 mmol), *N*,*N*-dimethylacetamide dimethyl acetal (3.72 g, 30 mmol), and anhydrous xylene (25 mL, distilled from calcium hydride) was refluxed by using a Soxhlet trap (4-Å molecular sieve) and a condenser for a period of 8 h. The solution was concentrated, and the residual orange oil was dissolved in 5 mL of methanol; 5 mL of 20% aqueous K_2CO_3 was added to the methanolic solution, and the mixture was refluxed for 2 h. The resulting mixture was cooled to 0 °C, acidified to pH 5–6 with concentrated HCl, and extracted with ethyl acetate (4×). The combined extracts were washed with brine, dried ($MgSO_4$), filtered, and concentrated to give 868 mg of an orange oil. The oil displayed two spots (R_f 0.73 and 0.30) on TLC (silica gel, 7% methanol in ether). The two components were separated by flash chromatography. The component with higher R_f value (130 mg) was found to be composed of two isomeric dienes in the ratio of 1:7 (GC, column C, 100–200 °C). Minor isomer: GC/MS (70 eV), m/e (rel intensity) 178 (16, M^+), 163 (7), 160 (8), 145 (52), 131 (33), 119 (43), 106 (43), 105 (79), 93 (31), 91 (100). Major isomer: GC/MS (70 eV), m/e (rel intensity) 178 (39, M^+), 163 (4), 160 (23), 145 (31), 131 (56), 119 (45), 107 (82), 105 (79), 104 (58), 93 (31), 91 (100). The component with R_f 0.30 was isolated to give the desired unsaturated amide **20a** as a yellow viscous oil (523 mg, 72% yield): IR ($CHCl_3$, FT) 3406, 3003, 1632 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 5.27 (2 H), 3.84 (1 H, t, J = 8.4 Hz, C_4 H), 3.10 (1 H, OH), 3.00 (3 H, s, $N(CH_3)_2$), 2.95 (3 H, s, $N(CH_3)_2$), 2.41–1.17 (11 H), 0.95 (3 H, d, J = 6.6 Hz, C_{10} H), 0.85 (3 H, s, C_5 CH_3)); GC/MS (70 eV, partial), m/e (rel intensity) 265 (21, M^+), 145 (19), 87 (100), 72 (84). The material was subjected to subsequent reactions without further purification.

Iodo Lactone 21a. A mixture of amide **20a** (857 mg, 3.23 mmol), THF (10 mL), water (10 mL), and iodine (2.55 g, 10 mmol) was stirred at 25 °C under a nitrogen atmosphere for 10 h. The excess of iodine was discharged by the addition of $Na_2S_2O_3$ (3 g). The resulting yellow solution was extracted with CH_2Cl_2 (3×). The combined organic phases were washed with aqueous $Na_2S_2O_3$ and water, dried over anhydrous

$MgSO_4$, filtered, and concentrated to afford 1.04 g of iodo lactone **21a** as a pale yellow solid (89% yield). Trituration with benzene afforded white crystals: mp 150–152 °C dec; IR ($CHCl_3$, FT) 3607, 1787 (Fermi resonance?), 1771 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 4.92 (1 H, dd, J = 8.1, 6.7 Hz, C_8 H), 4.67 (1 H, dd, J = 8.1, 3.1 Hz, C_9 H), 3.68–3.59 (1 H, C_4 H), 3.04–2.91 (2 H, C_7 H, C_{11} H), 2.47–2.36 (1 H, C_{11} H), 2.13–2.04 (1 H, C_3 H), 1.92 (1 H, dd, J = 15.0, 4.8 Hz, C_6 H), 1.71 (1 H, dd, J = 15.0, 6.6 Hz, C_6 H), 1.64–1.35 (5 H), 1.07 (3 H, d, J = 6.3 Hz, C_{10} H), 0.86 (3 H, s, C_5 H); GC/MS (70 eV), m/e (rel intensity) 364 (3, M^+), 237 (58), 219 (100), 177 (63), 173 (46), 159 (86), 133 (74), 121 (47), 119 (56), 107 (42), 105 (70).

Anal. Calcd for $C_{14}H_{21}O_3I$: C, 46.17; H, 5.81. Found: C, 46.12; H, 5.83.

Lactone 21b. To a suspension of iodo lactone **21a** (109 mg, 0.3 mmol) in 3 mL of anhydrous benzene at 50 °C was added n-Bu_3SnH (180 mg, 0.165 mL, 0.6 mmol) and 1.4 mg of azobis(isobutyronitrile). After being stirred for 1 h at 50 °C, the solution was cooled and concentrated to an oil, which was purified by preparative TLC (ethyl acetate) to afford 67 mg of lactone **21b** as a pale yellow viscous oil in 94% yield. Crystallization from ethyl acetate–pentane gave white crystals: mp 148–149.5 °C dec; IR ($CHCl_3$, FT) 3607–3487, 3020–2875, 1765 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 4.77 (1 H, ddd, J = 11.8, 8.0, 3.0 Hz, C_8 H), 3.67 (1 H, t, J = 8.4 Hz, C_4 H), 2.89 (1 H, dd, J = 18.3, 10.3 Hz, C_{11} H), 2.73–2.55 (1 H, C_7 H), 2.16 (1 H, dd, J = 18.3, 3.0 Hz, C_{11} H), 2.12–1.13 (10 H), 0.98 (3 H, d, J = 7.3 Hz, C_{10} CH_3), 0.84 (3 H, s, C_5 CH_3); GC/MS (70 eV), m/e (rel intensity) 238 (4, M^+), 220 (7), 178 (59), 152 (92), 121 (100), 108 (93), 93 (100).

2,3-Dihydroaromatin (23a). A mixture of lactone **21b** (96 mg, 0.40 mmol) and 0.5 mL (3.3 mmol) of Bredereck's reagent, bis(dimethylmino)methoxymethane,[29] was heated in an oil bath from 25 °C to 83 °C over a 1.5-h period and maintained at 83 °C for 8 h. The excess reagent and volatiles were removed in vacuo. The residual oil was dissolved in methanol (0.9 mL); 0.5 mL of 20% aqueous potassium carbonate was added to the methanolic solution, and the mixture was refluxed for 0.5 h. The resulting mixture was cooled in an ice bath, neutralized with 2.5 mL of 50% NaH_2PO_4, and extracted with CH_2Cl_2 (3×). The combined organic phases were dried and volatiles removed to give 118 mg of **22a** as a yellow semisolid (100% yield). Trituration of a sample with ethyl acetate gave a pale yellow solid (77 mg): mp 178–180 °C dec; IR (CH_2Cl_2, FT) 3606, 3417, 3052, 2961, 1714, 1624, 1347, 1202, 1058 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 7.09 (1 H, s, vinyl proton), 4.58 (1 H, ddd, J = 11.8, 8.0, 2.9 Hz, C_8 H), 3.67 (1 H, t, J = 8.8 Hz, C_4 H), 3.32 (1 H, m, C_7 H), 3.03 (6 H, s, $N(CH_3)_2$), 2.15–1.21 (11 H, 0.98 (3 H, d, J = 7.4 Hz, C_{10} CH_3), 0.82 (3 H, s, C_5 CH_3); GC/MS (70 eV), m/e (rel intensity) 293 (17, M^+), 153 (11), 152 (100).

A solution of the crude carbamate **22a** (29.3 mg, 0.1 mmol) in anhydrous THF (2 mL) was cooled to −78 °C. A solution of diisobutylaluminum hydride (0.24 mL, 1 M solution in hexane) was added dropwise over a 5-min period. After being stirred for 15 min, the reaction mixture was warmed slowly and allowed to stir at 25 °C for 2 h. The mixture was quenched with 0.3 mL of saturated ammonium chloride and stirred at 25 °C for 8 h. A small amount of anhydrous $MgSO_4$ was added; the mixture was filtered, rinsed with ethyl acetate, and concentrated to give 24 mg of α-methylene-γ-butyrolactone **22b** as a clear viscous oil, 97% yield: IR (CH_2Cl_2, FT) 3604, 3386, 3051, 2959, 1758, 1275 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 6.26 (1 H, d, J = 2.6 Hz, olefinic proton), 5.59 (1 H, d, J = 2.6 Hz, olefinic proton), 4.74 (1 H, ddd, J = 11.8, 8.0, 2.9 Hz, C_8 H), 3.83–3.71 (1 H, br, C_4 H), 3.19–3.07 (1 H, br, C_7 H), 2.14–2.02 (2 H, m, C_3 H, C_9 H), 1.91 (1 H, dd, J = 14.9, 4.2 Hz, C_6 H), 1.83–1.70 (2 H, m, C_3 H, C_9 H), 1.61–1.09 (5 H), 0.99 (3 H, d, J = 7.0 Hz, C_{10} CH_3), 0.82 (3 H, s, C_5 CH_3); GC/MS (70 eV), m/e (rel intensity) 250 (2, M^+), 232 (7), 121 (41), 108 (100), 107 (34), 93 (43), 91 (36).

To a solution of α-methylen-γ-butyrolactone **22b** (35 mg, 0.14 mmol) dissolved in anhydrous CH_2Cl_2 (3 mL) were added pyridinium chlorochromate (45 mg, 0.21 mmol) and sodium acetate (17 mg, 0.21 mmol). The mixture was stirred at 25 °C for 2 h and then filtered through a column of Florisil with ethyl acetate. The filtrate was concentrated to give 35 mg of dihydroaromatin as a semisolid, 100% yield. The material was crystallized from ethyl acetate–pentane to give white crystals: mp 118.5–120.5 °C (lit.[31] mp 113–114 °C); IR ($CHCl_3$, FT) 1756 (C=O, α,β-unsaturated lactone), 1740 (C=O, cyclopentanone), 1602 (C=C) cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 6.29 (1 H, d, J = 2.2 Hz, olefinic proton), 5.67 (1 H, d, J = 2.2 Hz, olefinic proton), 4.76 (1 H, ddd, J = 11.8, 8.0, 2.9 Hz, C_8 H), 3.05 (1 H, br, $w_{1/2}$ = 40 Hz, C_7 H), 2.54 (1 H, dd, J = 17.6, 8.4 Hz, C_3 H), 2.42 (1 H, dd, J = 15.4, 4.4 Hz, C_6 H), 2.25–1.58 (8 H), 1.12 (3 H, d, J = 6.6 Hz, C_{10} CH_3), 0.93 (3 H, s, C_5 CH_3); GC/MS (70 eV), m/e (rel intensity) 249 (16), 248 (100, M^+), 204 (35), 189 (25), 159 (26), 150 (39), 137 (73).

(±)-Aromatin (23b). A mixture of dihydroaromatin (**23a**) (25 mg, 0.10 mmol), phenylselenenyl chloride (23 mg, 0.12 mmol), and trifluoroacetic acid (11 mg) (0.10 mmol) in ethyl acetate (1 mL) was stirred at 25 °C for 22 h. The resulting yellow solution was diluted with ethyl acetate and washed with saturated $NaHCO_3$ and brine. After being dried over anhydrous $MgSO_4$, the mixture was filtered and concentrated to afford 45 mg of a crude oil. The oil was dissolved in THF (3 mL) and water (0.5 mL), and sodium periodate (64 mg, 0.30 mmol) was added. The mixture was stirred for 7 h at 25 °C. The suspension was diluted with ethyl acetate (5 mL) and washed successively with brine, saturated $NaHCO_3$, and brine. After drying, the mixture was filtered and concentrated to give 28 mg of a yellow oil, which was purified by flash chromatography (1:1 ethyl acetate–hexane) to afford 13 mg of aromatin (52% yield): mp 123–124 °C (lit.[31] 125–126 °C); IR ($CHCl_3$, FT) 1759 (C=O, α,β-unsaturated lactone), 1710 (C=O, α,β-unsaturated cyclopentanone), 1642, 1599 (C=C) cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ 7.53 (1 H, dd, J = 6.2, 1.8 Hz, C_2 H), 6.30 (1 H, d, J = 2.6 Hz, $R_2C{=}CH_2$), 6.12 (1 H, dd, J = 6.2, 2.6 Hz, C_3 H), 5.69 (1 H, d, J = 2.6 Hz, $R_2C{=}CH_2$), 4.82 (1 H, ddd, J = 11.8, 8.0, 2.9 Hz, C_8 H), 3.23 (1 H, m, C_7 H), 2.47 (1 H, dd, J = 15.0, 5.9 Hz, C_6 H) 2.40 (1 H, ddd, J = 10.0, 2.6, 1.8 Hz, C_1 H), 2.17–1.85 (3 H), 1.70 (1 H, dd, J = 15.0, 11.8 Hz, C_6 H), 1.26 (3 H, d, J = 7.0 Hz, C_{10}, CH_3), 1.16 (3 H, s, C_5 CH_3); GC/MS (70 eV), m/e (rel intensity) 246 (32, M^+), 231 (48), 218 (38), 173 (37), 161 (40), 159 (58), 147 (43), 146 (47), 145 (64), 133 (47), 131 (100).

Acetoxy Lactone 25b. A mixture of iodo lactone **21a** (221 mg, 0.61 mmol), 1,5-diazabicyclo[4.3.0]non-5-ene (2.26 mL, 18 mmol), and THF (9 mL) was heated at 53 °C for 10 h. The reaction mixture was concentrated, diluted with water (4 mL), acidified with concentrated HCl (1.5 mL), and extracted with ethyl acetate (4×). The combined extracts were washed with brine, dried ($MgSO_4$), and concentrated to give crude **24** (168 mg). Flash chromatography (ethyl acetate) provided 135 mg of pure olefin **24**, obtained as colorless oil, 96% yield. Crystallization of a sample of the oil (ethyl acetate–pentane) gave colorless solids material: mp 120.5–121.5 °C; IR ($CHCl_3$, FT) 3670, 3600–3300, 3020, 2966, 2877, 1765, 1665 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 5.41 (1 H, br s, $w_{1/2}$ = 6 Hz, C_9 H), 5.32 (1 H, br s, $w_{1/2}$ = 13 Hz, C_8 H), 3.89 (1 H, t, J = 8.2 Hz, C_4 H), 2.85 (1 H, dd, J = 17.6, 9.1 Hz, C_{11} H), 2.72–2.50 (2 H, C_1 H, C_7 H), 2.19 (1 H, d, J = 17.6 Hz, C_{11} H), 2.20–1.41 (6 H), 1.74 (3 H, br s, C_{10} CH_3), 0.76 (3 H, s, C_5 CH_3). GC/MS (70 eV), m/e (rel intensity) 236 (68, M^+), 221 (27), 203 (36), 133 (42), 124 (58), 123 (30), 108 (31), 107 (33), 105 (39), 95 (35), 93 (100).

A mixture of olefin **24** (68 mg, 0.29 mmol), platinum oxide (3.4 mg), and absolute ethanol (12 mL) was subjected to hydrogenation at 26 °C and atmospheric pressure. After 1.5 h, the mixture was filtered through a column of Kieselguhr, followed by a methanol wash. The filtrate was concentrated to afford a crude oil (62 mg), which contained 80% of the desired lactone **25a** as determined by GC (column C, 190 °C) and NMR (vide infra); no olefin **24** or lactone **21b** was detected. Lactone **25a** (50 mg, 73% yield) was isolated from the crude oil by flash chromatography (3:1 ethyl acetate–hexane): IR ($CHCl_3$, FT) 3608, 3485, 3019, 2965, 1765, 1214, 998 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 4.72 (1 H, ddd, J = 11.8, 7.8, 3.4 Hz, C_8 H), 3.65 (1 H, t, J = 8.7 Hz, C_4 H), 2.89 (1 H, dd, J = 18.3, 10.4 Hz, C_{11} H), 2.75–2.58 (1 H, m, C_7 H), 2.17 (1 H, dd, J = 18.3, 2.6 Hz, C_{11} H), 2.19–1.05 (10 H), 1.02 (3 H, d, J = 7.0 Hz, C_{10} CH_3), 0.91 (3 H, s, C_5 CH_3); GC/MS (70 eV), m/e (rel intensity) 238 (3, M^+), 220 (9), 195 (21), 194 (7), 178 (21), 161 (22), 152 (72), 135 (50), 134 (39), 133 (39), 122 (52), 121 (80), 119 (55), 108 (47), 107 (75), 105 (48), 97 (47), 95 (68), 93 (100).

Lactone **25a** (50 mg) was stirred with acetic anhydride (0.54 mL) and dry pyridine (0.58 mL) at 25 °C under a nitrogen atmosphere. After 2 h, the mixture was quenched with ice water (1.5 mL) and taken up in ethyl acetate. The organic phase was washed several times with brine, dried over $MgSO_4$, and concentrated to give a quantitative yield of crude acetoxy lactone **25b**, which was crystallized from ether–pentane: mp 108.5–109.5 °C; IR ($CHCl_3$, FT) 3027, 2971, 2883, 1765, 1727, 1254, 1048, 1007 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 4.72 (1 H, ddd, J = 11.8, 8.0, 3.6 Hz, C_8 H), 4.63 (1 H, dd, J = 9.2, 8.1 Hz, C_4 H), 2.89 (1 H, dd, J = 18.3, 10.3 Hz, C_{11} H), 2.78–2.62 (1 H, m, C_7 H), 2.24–1.40 (11 H), 2.07 (3 H, s), 1.02 (3 H, d, J = 7.3 Hz, C_{10} CH_3), 1.00 (3 H, s, C_5 CH_3); GC/MS (70 eV), m/e (rel intensity) 280 (1, M^+), 220 (69, $M^+ - CH_3CO_2H$), 205 (30), 178 (51), 161 (69), 160 (77), 159 (28), 147 (35), 145 (41), 135 (38), 134 (90), 133 (49), 125 (44), 122 (34), 121 (100), 119 (67). Acetoxy lactone **25b** was identical with a sample prepared by Schlessinger.[33d]

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Registry No. 2a (M = Li), 81850-59-1; **2a** (M = Cu), 83573-02-8; **2b** (M = Li), 83562-41-8; **2c** (M = Li), 83562-42-9; **3c**, 74149-62-5; **3d**, 76156-81-5; **4**, 930-68-7; **5**, 930-30-3; **6**, 1120-73-6; (±)-**7**, 83562-43-0; (±)-**8**, 83562-44-1; **9a**, 73798-21-7; (±)-**9b**, 83562-45-2; **10a**, 73798-22-8; (±)-**10b**, 83562-46-3; (±)-**10c**, 83562-47-4; **10d**, 73798-26-2; **10e**, 73798-27-3; **10f**, 73798-28-4; **10g**, 73798-29-5; **10h**, 73798-30-8; **10i**, 73798-31-9; **11a**, 83562-48-5; (±)-**11b**, 83562-49-6; **12a**, 83602-29-3; (±)-**12b**, 83602-32-8; (±)-**12c**, 83562-50-9; (±)-**12d**, 83602-30-6; **12e**, 83562-51-0; (±)-**13a**, 76156-83-7; (±)-**13b**, 81939-03-9; (±)-**14**, 83602-31-7; (±)-**15**, 81875-17-4; (±)-**16**, 76156-87-1; (±)-**17**, 83562-52-1; (±)-**19a**, 76156-88-2; (±)-**19b**, 83562-53-2; (±)-**20a**, 76156-89-3; (±)-**21a**, 76156-90-6; (±)-**21b**, 76156-91-7; (±)-**22a**, 76156-92-8; (±)-**22b**, 76189-79-2; (±)-**23a**, 74645-42-4; (±)-**23b**, 74645-43-5; (±)-**24**, 76156-93-9; (±)-**25a**, 72341-86-7; (±)-**25b**, 72341-85-6; (±)-**26**, 60426-81-5; 1,3-propanedithiol, 109-80-8; (*E*)-2-methyl-2-butenal, 497-03-0; allyl bromide, 106-95-6.

Tandem Cope–Claisen Rearrangement: Scope and Stereochemistry†

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Abstract: The complete details of the seminal study on the tandem Cope–Claisen rearrangement are presented. The reaction uses an initial Cope rearrangement to trigger an irreversible Claisen rearrangement. In several cases, the Claisen step drives an unfavorable Cope equilibrium. Typically, vinyl ether **1c** provides aldehyde **3**, which, under certain conditions, can be transformed into the Conia products **4** and **5**. The stereochemical course of the rearrangement of the four 2-vinyl-3-isopropenylcyclohexyl vinyl ethers **8c**, **8d**, **9c**, and **9d** leading to aldehyde **18** is discussed. The Cope–Claisen rearrangement of **26b** and related isomers is studied in detail. The stereochemical consequences of the reaction are applied to the construction of an intermediate employed in the synthesis of the pseudoguaianolides aromatin and confertin.

The Cope rearrangement of unadorned 1,5-hexadienes suffers as a useful synthetic reaction for a number of reasons.[2] Foremost among them are the reversibility of the reaction and the preference for the formation of highly substituted olefins in the equilibrium mixture. Imaginative solutions to these difficulties have been realized by rendering the reaction irreversible through the formation of stable carbonyls (oxy–Cope),[3] enolates (alkoxy–Cope),[4] or other subsequent irreversible transformations.[5] In the latter context, we entertained the idea that the irreversible Claisen rearrangement could serve to trap, in the contrathermodynamic sense, unfavorable Cope equilibria. The union and utility of these reactions in the tandem mode has been realized in the elegant studies of Thomas[6] and Cookson[7] wherein the Claisen rearrangement precedes the Cope rearrangement (i.e., Claisen–Cope rearrangement). In such formulations, it is necessary for the Cope product to be judiciously chosen as the more highly substituted 1,5-hexadiene if the reaction is to have a favorable equilibrium. Intermediate Claisen products could be isolated in Cookson's studies since the lower activation energy process constituted the initial rearrangement. Accordingly, the lack of intermediates in most Cope–Claisen rearrangements was anticipated and confirmed.

This paper contains a complete account of our communicated studies on the tandem Cope–Claisen rearrangement.[8]

Results and Discussion

Our initial study focused upon an acyclic model. Alkylation of ethyl crotonate with 1-bromo-3-methyl-2-butene provided ester **1a**.[9] Thermolysis of ester **1a** at 266° C provided an 80/20 equilibrium mixture of **1a** and **2a** (K_{eq} **2a**/**1a** = 0.25). If ester

1 2

a, R = $CO_2C_2H_5$; b, R = CH_2OH; c, R = $CH_2OCH{=}CH_2$

2a were the desired product of such a rearrangement for the purpose of converting it into vinyl ether **2c** (via alcohol **2b**) for subsequent Claisen rearrangement, the sequence would have been rendered impractical, since the desired component is the minor constituent of the equilibrium mixture. Ester **1a** was successively

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