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Carbocyclic Construction by the [2,3]Sigmatropic Rearrangement of Cyclic Sulfonium Ylides. A New Entry for the Stereoselective Synthesis of Substituted Cyclohexanones

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Abstract: The rhodium(II)-catalyzed cyclization of acyclic α-diazo-β-keto esters **1c,d** provided stereoselectively the highly substituted cyclohexanones **3c,d** respectively, by the [2,3]sigmatropic rearrangement *via* stereocontrolled nine-membered allylsulfonium ylides **2c,d**. Further elaboration of **3d** toward the cyclohexanone **36** accomplished asymmetric formal syntheses of the representative elemanoids, **37** and **38**. The compound **3c** was transformed into the cyclohexanone **34a** and cyclohexene **43**, which could serve as the key intermediates for the synthesis of natural products possessing contigously *cis*-arranged trimethylcyclohexanone and its related moieties, respectively.

INTRODUCTION AND BACKGROUND

Carbocyclic construction is one of important subjects in the synthetic organic chemistry, and a variety of synthetic methodologies have been reported to date. Historically, it is well-known that synthetic studies on cyclic natural products have played an important role in the development of this subject.[1] Among these synthetic methods is intramolecular cyclization by use of the carbene insertion reaction starting with acyclic α-diazo esters. However, in practice, it seems to be applicable in the limited preparation of five membered rings.[2]

We have been studying the [2,3]sigmatropic rearrangement of cyclic allylsulfonium ylides from the viewpoint of both annulation and its reaction mechanism. At the beginning of our study, our attention was focused on the synthesis of a variety of lactones from acyclic α-diazomalonates flanking an allyl sulfide function, and many novel, but efficient synthetic routes in this area have been developed.[3] Recently, starting with α-diazo-β-keto esters in place of α-diazomalonates, the initial project was extended to the carbocycle synthesis.[4] In this report, we show that our methodology starting with acyclic α-diazo-β-keto esters possessing an allyl sulfide function at the terminal position is superior to the conventional carbene insertion reaction starting with the parent α-diazo-β-keto esters, in that not only does the former method provide effectively six-membered carbocycles as well as five-membered ones, but also could accomplish stereoselective

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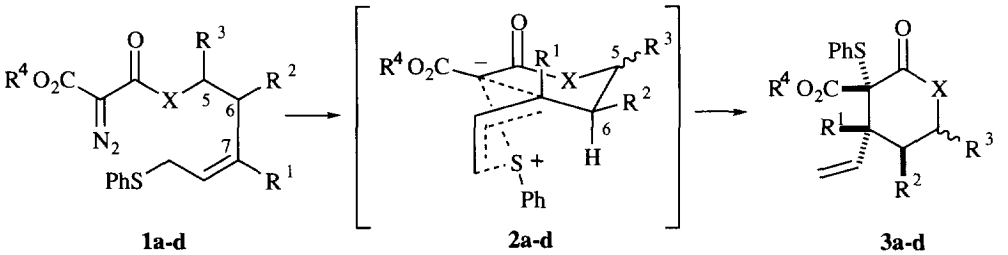
syntheses of substituted cyclohexanones *via* stereocontrolled cyclic allylsulfonium ylides, under the conditions that the starting α-diazo esters have an alkyl substituent at an appropriate position.[5]

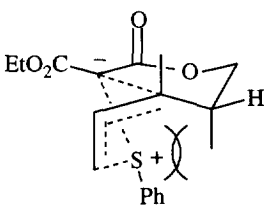
The present study was founded on the δ-lactone synthesis made earlier; when the α-diazomalonate **1a** possessing a methyl group at the C(5)-position was subjected to the rhodium(II) acetate-catalyzed [2,3]sigmatropic rearrangement,[3] it was observed that this rearrangement gave a mixture [$R^3(\alpha)/R^3(\beta)$, 4:1] of diastereomeric δ-lactones **3a**[3a] (Scheme 1). This result indicates that in our proposed nine-membered transition state **2a** consisted of two ring-components, i. e., a chair-like six-membered ring with thermodynamically stable comformation and a five-membered one, the C(5)-substituent in the former ring scarcely controls the stereochemistry of cyclization from the standpoint of a steric effect on the conformational equilibrium. On the other hand, it would be resonable to consider that the α-diazomalonate **1b** possessing a methyl group at the C(6)-position in place of the C(5) one generates predominantly, on the sulfonium-ylide formation, the cyclic transition state **2b** in which the methyl group is substituted equatorially in the six-membered ring part, rather than the other transition state **4** with a severe non-bonded interaction as depicted, consequently resulting in stereoselective formation of the δ-lactone **3b** with a *trans*-arrangement between the methyl (R^2) and newly formed vinyl groups. This synthetic design was then easily proved; rhodium(II) acetate-promoted [2,3]sigmatropic rearrangement of **1b**, prepared from diol **9** *via* regioselective displacement of the allylic hydroxyl to a phenylthio group (Ph_2S_2, Bu_3P, THF) followed by diazomalonylation with ethyl hydrogen diazomalonate (DCC, CH_2Cl_2),[6] provided the δ-lactone **3b** not only in a high yield, but also as *the sole product*.[7,8]



1a-d **2a-d** **3a-d**

a X = O, $R^1 = R^2 = H$, R^3 = Me, R^4 = Et
b X = O, $R^1 = R^2$ = Me, $R^3 = H$, R^4 = Et
c X = CH_2, $R^1 = R^2 = R^4$ = Me, $R^3 = H$
d X = CH_2, $R^1 = R^4$ = Me, R^2 = CMe=CH_2, $R^3 = H$

Scheme 1



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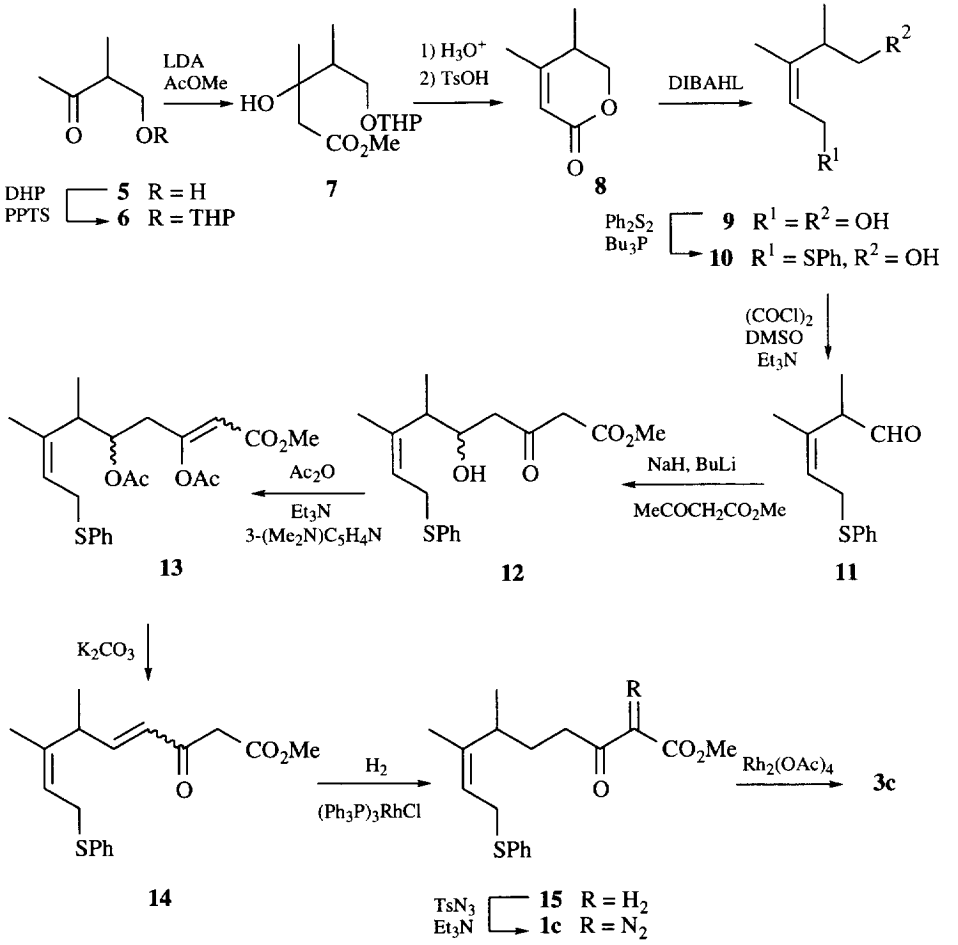
RESULTS AND DISCUSSION

Our synthetic design was then extended, starting with α-diazo-β-keto esters, to one-step stereoselective synthesis of six-membered carbocycles.

As starting materials, α-diazo esters, **1c** and **1d,** possessing two methyl groups at the C(6)- and C(7)-positions for the former, and an isopropenyl group at the C(6)- and a methyl group at the C(7)-positions for the latter, were adopted with intention of utilizing the cyclization products **3c** and **3d** as key intermediates for the synthesis of natural products (*vide post*).

The synthetic route of **1c** is shown in Scheme 2, wherein *Z* geometry of the trisubstituted double bond in **1c** owes its source to that of unsaturated lactone **8**. Racemic 4-hydroxy-3-methyl-2-butanone (**5**), commercially available, was protected as the THP ether **6**, which was converted into hydroxy ester **7** by condensation with the lithium enolate of methyl acetate. Lactonization of **7** followed by dehydration provided



Scheme 2

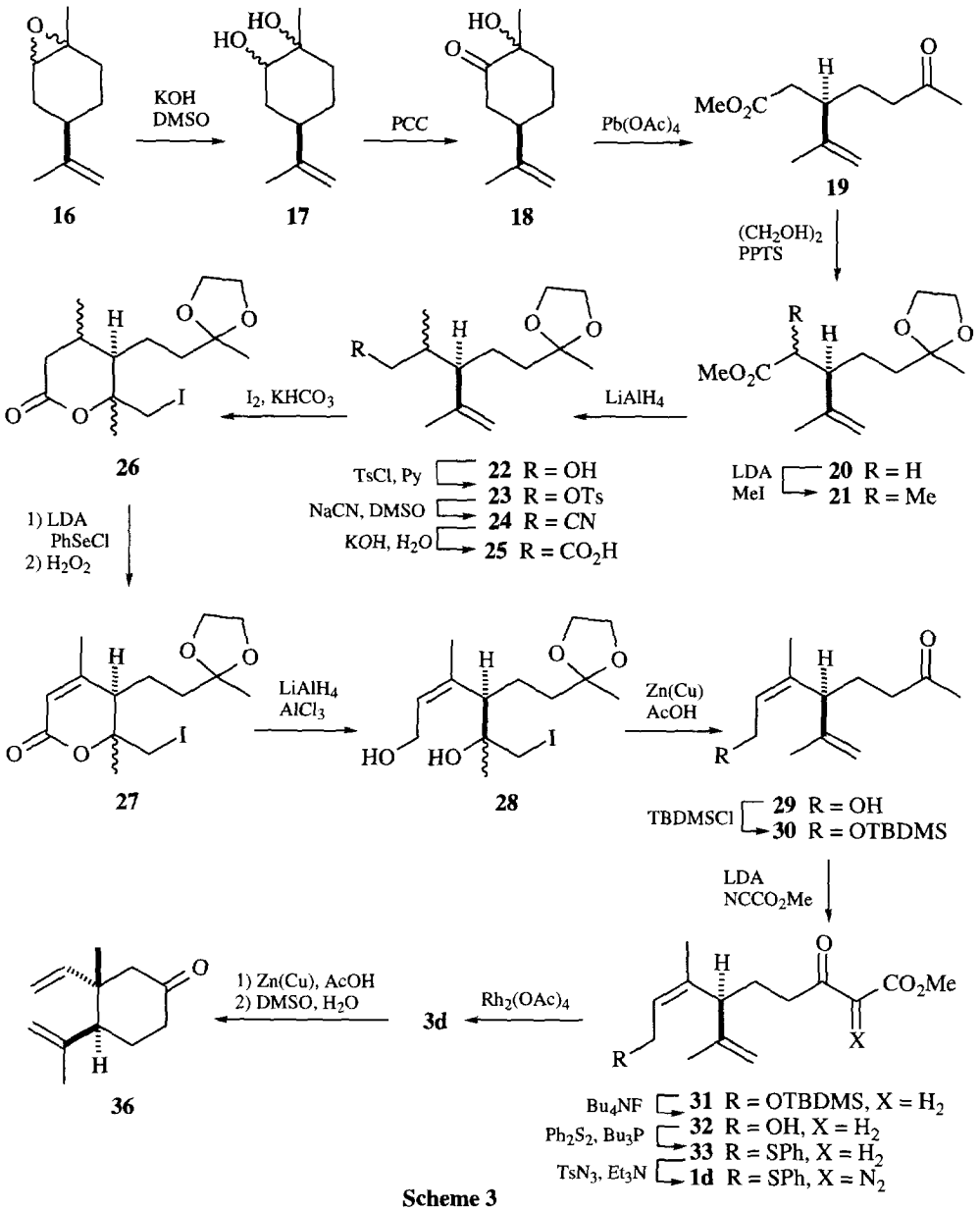
the requisite unsaturated δ-lactone **8**. Transformation of **8** into ketol **12** was carried out by a sequence of four conventional reactions; reduction of **8** with diisobutylaluminium hydride to give the diol **9**, regioselective phenylsulfenylation of **9** to give hydroxy sulfide **10**, Swern oxidation, and condensation of the resulting aldehyde **11** with the sodium-lithium dianion of methyl acetoacetate with formation of the ketol **12**. However, attempted dehydration of **12** leading the conjugated enone **14** by the conventional methods gave an intractable mixture of products, so that the compound **12** was first transformed into diacetate **13** by acetylation with acetic anhydride in the presence of 4-dimethylaminopyridine. Treatment of **13** with K_2CO_3 in methanol proceeded successfully in both removal of acetic acid as well as hydrolysis of the enol acetate function to give the desired enone **14** as a mixture of geometrical isomers. Regioselective hydrogenation of **14** under the homogeneous conditions employing tris(triphenylphosphine)rhodium(I) chloride, followed by the conventional diazo transfer reaction[9] of the resulting keto ester **15** with *p*-toluenesulfonyl azide provided the desired α-diazo ester **1c** in 59% overall yield from **5**.

Next, with intention of obtaining the cyclization product as an optically active form, preparation of α-diazo ester **1d** flanking an isopropenyl group at the C(6)-position started with a C(1)-C(2) bond cleavage of (+)-limonene oxide (**16**)[10] as the chiral source. The synthetic route is shown in Scheme 3 in which two main characteristics are included; the double bond in 2-penten-5-olide **27** is employed as the source of the *Z*-double bond in **1d**, and an isopropenyl group in **16** is introduced to **1d**, *via* a chemical transformation into an iodohydrin function, in keeping its absolute configuration.

According to the well-established carbon-carbon bond cleavage of cyclohexene oxides,[11] (+)-limonene oxide (**16**) was converted into methyl heptanoate **19** by a sequence of three reactions; epoxide ring-opening of **16** under basic conditions, PCC oxidation of the resulting diol **17** to give ketol **18**, and an oxidative cleavage of a α-ketol function in **18** with formation of **19**. The ketone group in **19** was protected as an acetal function, and methylation of the resulting acetal **20** was performed by treatment with LDA followed by addition of methyl iodide, giving ester **21**. One-carbon elongation of **21** was carried out by a sequence of conventional reactions; reduction with lithium aluminium hydride to give alcohol **22**, tosylation of **22** followed by conversion of the resulting tosylate **23** into the nitrile **24** with sodium cyanide in DMF. The nitrile **24** was then hydrolyzed to give carboxylic acid **25**.

To introduce stereoselectively an allylic alcohol moiety with an *Z*-olefinic linkage, we designed construction of 2-penten-5-olide skeleton in our substrate, followed by its reductive cleavage. Iodolactonization of the acid **25** using the isopropenyl double bond as an olefin partner provided the δ-lactone **26** in a quantitative yield. Phenylselenenylation of the latter followed by selenoxide fragmentation[12] provided the requisite unsaturated iodo lactone **27**. Reduction of **27** with lithium aluminium hydride gave the diol **28** with a *Z*-olefinic allyl alcohol function, and regeneration of an isopropenyl group was easily conducted by reductive elimination with Zn(Cu) in acetic acid, thus giving the ketol **29** in 40% overall yield from **26**. The compound **29** was protected as the TBDMS ether **30**, and construction of a β-keto ester function was carried out by condensation of the lithium enolate of **30** with methyl cyanoformate under the kinetically controlled conditions to give the β-keto ester **31**. Deprotection of **31** followed by conversion of the hydroxy group in the resulting alcohol **32** into a phenylthio function provided the sulfide **33**. Finally, the compound **33** was transformed to the requisite α-diazo ester **1d** by the diazo transfer reaction with *p*-toluenesulfonyl azide.[9]

With the desired α-diazo-β-keto esters, **1c** and **1d**, in hand, carbocyclization according to our methodology was carried out next. On treatment of the compounds, **1c** and **1d**, with a catalytic amount of



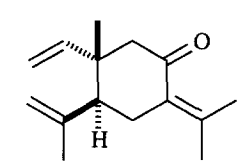
Scheme 3

rhodium(II) acetate, prepared from rhodium(III) chloride,[13] in benzene at 60 °C, the [2,3]sigmatropic rearrangement *via* the nine-membered allylsulfonium ylides, **2c** and **2d**, proceeded stereoselectively to give, as the sole product, cyclohexanones, **3c** and **3d**, in 78 and 61% yields, respectively. No isomer could be detected in each reaction in spite of a careful inspection of the reaction mixture. Stereostructure of these cyclization products deduced as depicted from the reaction mechanism[14] were proven by chemical transformations of **3c** and **3d** into the known cyclohexanones; reductive desulfurization of **3c** followed by alkaline decarboxylation of

the resulting mixture of diastereomeric esters **34a,b** (see Scheme 4) gave 3,4-dimethyl-3-vinylcyclohexanone (**35**) which has been used as the key compound for the eremophilone synthesis by Ziegler,[15] while on removal of both methoxycarbonyl and phenylthio groups in **3d** was produced the known (3*S*,4*S*)-(-)-4-isopropenyl-3-methyl-3-vinylcyclohexanone (**36**), $[\alpha]_D$ -29.8° ($CHCl_3$), [lit.$[\alpha]_D$ -29.2° ($CHCl_3$);[16] $[\alpha]_D$ -26.2° ($CHCl_3$)[17]] (Scheme 3).

After all, the above findings not only support chemically our proposed reaction mechanism *via* the stereocontrolled nine-membered allylsulfonium transition state **2**, but also indicate that the present methodology starting with α-diazo-β-keto esters with the allyl sulfide function at the terminal position is superior to the conventional carbene insertion method which starts from the parent acyclic α-diazo esters, in that the former produces effectively six-membered carbocycles as well as five-membered one.

Both cyclohexanones, **3c** and **3d**, obtained could serve as promising key-intermediates for the synthesis of natural products. First, cyclohexanones, **3d** and **36**, are versatile compounds for enantioselective synthesis of elemanoid sesquiterpenes. Utility of **36** in this area has been discussed using its racemic form by Bohlmann.[18] In fact, we have succeeded in the asymmetric synthesis of (+)-β-elemenone (**37**)[16,19] and (+)-eleman-8β,12-olide (**38**) from (-)-β-pinene *via* (-)-**36**,[16] so that the present synthesis of (-)-**36** is the enantioselective synthesis of these natural products from (+)-limonene.



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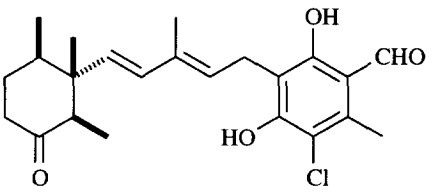

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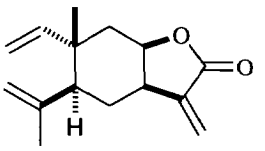

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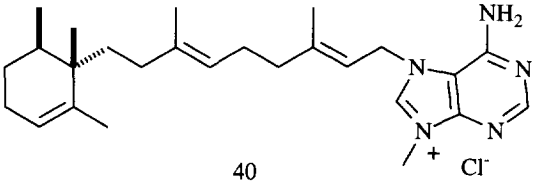
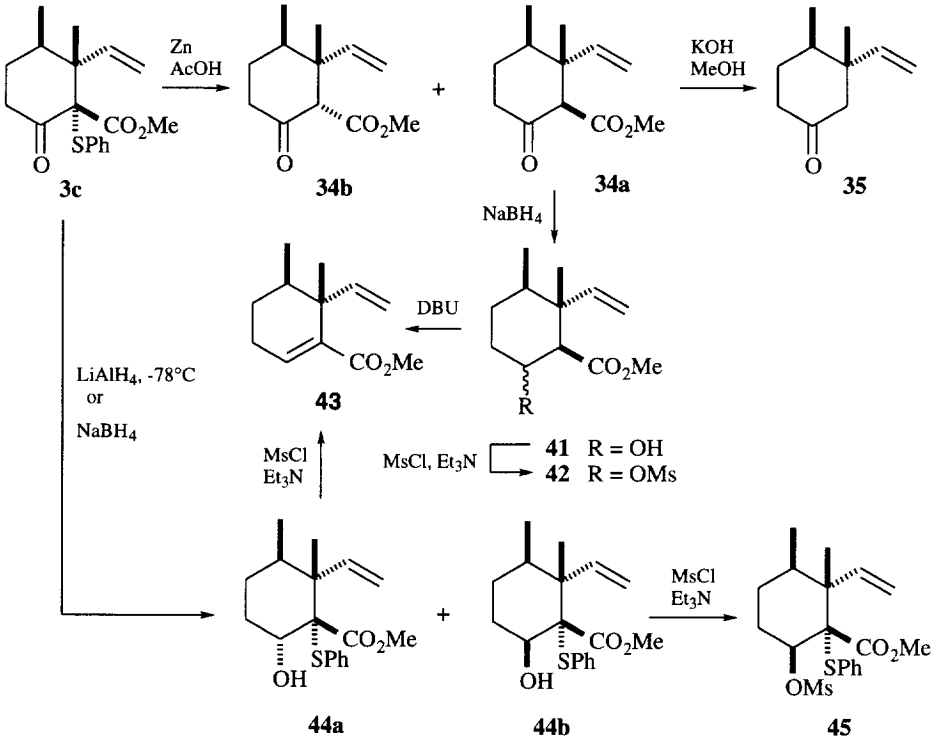


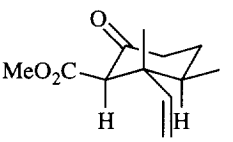
40

Second, the compound **3c** may be useful for the synthesis of some natural products possessing contigously *cis*-arranged trimethylcyclohexanone and its related moieties, i. e., judging from the fact that an ester group is synthetically equivalent to a methyl one, and that a vinyl group serves as a convenient clue necessary for carbon-chain elongation, the cyclohexanone **34a** convertible from **3c** is synthetically equivalent to a contiguously *cis*-arranged 3-substituted 2,3,4-trimethylcyclohexanone part of ascochlorin (**39**),[20] while the unsaturated ester **43** could serve as a cyclohexene part on the synthesis of ageline-A (**40**)[21] (see Scheme 4). A few manipulations of **3c** were then carried out.

Reductive elimination of the phenylthio group in **3c** with zinc in acetic acid provided a mixture (a 3:1 ratio) of separable diastereomeric esters, **34a** and **34b**, in 81% yield. Treatment of the minor **34b** with base resulted in complete isomerization to **34a**, suggesting that the compound **34a** possesses thermodynamically stable stereostructure as depicted in **46**. Sodium borohydride reduction of **34a** provided a mixture of epimeric



Scheme 4



46

alcohols **41**, whose mesylation with methanesulfonyl chloride followed by elimination of the resulting mesylate **42** with DBU provided the unsaturated ester **43** in 65% overall yield from **3c**. As an alternative synthesis of **43**, the compound **3c** was reduced with sodium borohydride or an equimoler amount of lithium aluminium hydride at -78 °C to give a mixture (a ca. 1:1 ratio) of separable epimeric alcohols, **44a** and **44b**, in a quantitative yield. Configuration of the newly formed hydroxy group was easily deduced from the coupling pattern of the proton adjacent to the hydroxyl in the ^{1}H NMR spectrum; α, equatorial for **44a** and β, axial for **44b** (see Experimental Section). Direct preparation of **43** from **44a** was accomplished in a high yield on treatment with mesyl chloride in Et3N in the presence of 4-dimethylaminopyridine, whereas the reaction of **44b** under the same reaction conditions as above gave the corresponding mesylate **45**, formation of which forced the reaction to completion.

Conclusions

It was demonstrated that α-diazo-β-keto esters **1c,d** with the allyl sulfide function at the terminal position proceeded, on treatment with rhodium(II) acetate, in the [2,3]sigmatropic rearrangement of nine-membered allylsulfonium ylides to give effectively six-membered carbocycles, and that an alkyl group at the C(6) position in the starting material controls the stereochemistry of cyclization *via* the cyclic allylsulfonium ylide-transition state **2** wherein the alkyl group is substituted equatorially in a six-membered part, producing stereoselectively cyclohexanones **3c,d** with a *trans*-disposition between the alkyl and newly formed vinyl groups. In addition, trisubstituted cyclohexanones, **3d** and **36** are key-intermediates for the enantioselective synthesis of elemanoids, while the compounds **34a** and **43** derived from **3c** could act as precursors for the synthesis of natural products possessing contiguously *cis*-arranged trimethylcyclohexanone and its related moieties, such as **39** and **40**, respectively.

EXPERIMENTAL SECTION

General Methods. Melting points are uncorrected. ^{1}H NMR spectra were recorded at 90 MHz. All reactions were carried out under dry N_2 or Ar atmosphere with use of standard procedures for the exclusion of moisture, except those in aqueous solution. Dry tetrahydrofuran (THF) was obtained by distillation over sodium benzophenone ketyl. Other organic solvents were purified and dried by using standard procedure. Extracts obtained on aqueous workup of the reaction mixtures were washed successively with water and brine, and dried over $MgSO_4$, unless otherwise stated. Column and flash column chromatography were performed on 70 - 230- and 230 - 400-mesh silica gel (Merck), respectively, and kieselgel GF_{254} was employed for preparative thin-layer chromatography (TLC). Solvents for elution are shown in parentheses.

3,4-Dimethyl-2-penten-5-olide (8). A solution of 4-hydroxy-3-methyl-2-butanone (**5**) (2.48 g, 24.3 mmol), 3,4-dihydro-2*H*-pyrane (DHP) (6.7 mL, 73.4 mmol) and PPTS (610 mg, 2.43 mmol) in CH_2Cl_2 (30 mL) was stirred at rt for 2 h, and washed successively with aqueous $NaHCO_3$ and brine, and dried. Evaporation of the solvent followed by filtration of the residue through a short silica-gel column (hexane-AcOEt, 5:1) gave the ether **6** (4.12 g, 91%) as an oil; IR (film) 1710 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.08 and 1.10 (d, J = 7.0 Hz each, 3 H in total), 1.4 - 2.0 (m, 6 H), 2.20 (s, 3 H), 2.5 - 3.0 (m, 1 H), 3.25 - 4.05 (m, 4 H), 4.60 (br s, 1 H).

To a stirred solution of diisopropylamine (3.80 mL, 27.1 mmol) in THF (50 mL) was added dropwise at -78 °C a 1.64 M solution of BuLi in hexane (16.5 mL, 27.1 mmol), and stirring was continued at 0 °C for 30 min, and then recooled to -78 °C. To the reaction mixture, a solution of methyl acetate (2.6 mL, 26.6 mmol) in HMPA (4.6 mL, 26.4 mmol) was added dropwise, and after being stirred for 1 h, a solution of **6** (2.50 g, 13.4 mmol) in THF (10 mL) was added dropwise. The reaction mixture was stirred for 1 h and quenched with aqueous NH_4Cl. The product was extracted with ether, and removal of the solvent followed by purification of the residue by filtration through a short silica-gel column (hexane-AcOEt, 1:1) gave a colorless oil. The oil was dissolved in 20% aqueous MeOH (80 mL) containing 37% HCl (1.5 mL). The reaction mixture was stirred at rt for 6 h, saturated with NaCl (s), and extracted with CH_2Cl_2. Removal of the solvent followed by filtration of the residue through a short silica-gel column (hexane-AcOEt, 1:1) gave a colorless oil which was dissolved in

benzene containing *p*-toluenesulfonic acid (1.5 g). The reaction mixture was refluxed azeotropically for 7 h, and after cooling to rt, washed with brine. Evaporation of the solvent followed by purification of the residue with flash-column chromatography on silica gel (hexane-AcOEt, 5:1) gave **8** (1.29 g, 76%) as an oil; IR (film) 1723 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.21 (d, *J* = 6.1 Hz, 3 H), 1.97 (s, 3 H), 2.40 (m, 1 H), 4.08 (dd, *J* = 10.8, 3.6 Hz, 1 H), 4.40 (dd, *J* = 10.8, 4.3 Hz, 1 H), 5.75 (br s, 1 H). Anal. Calcd for $C_7H_{10}O_2$: C, 66.64; H, 7.99. Found: C, 66.78; H, 7.68.

(*Z*)-3,4-Dimethyl-2-pentene-1,5-diol (9). To a stirred solution of **8** (454 mg, 3.60 mmol) in THF (10 mL) was added dropwise at -20 °C a 0.95 M solution of diisobutylaluminium hydride in hexane (11.4 mL), and stirring was continued for 3 h. Ether (10 mL) and aqueous NH_4Cl were added successively, and the solid was filtered off through a small bed of Celite 545, and the filtrate was dried. Removal of the solvent followed by chromatography of the residue on silica gel (hexane-AcOEt, 5:1) gave **9** (432 mg, 92%) as an oil; IR (film) 3674 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.97 (d, *J* = 7.0 Hz, 3 H), 1.66 (br s, 3 H), 2.06 (br s, 2 H), 3.02 (m, 1 H), 3.3 - 3.7 (m, 2 H), 3.95 (dd, *J* = 11.5, 7.2 Hz, 1 H), 4.23 (dd, *J* = 11.5, 7.2 Hz, 1 H), 4.76 (t, *J* = 7.2 Hz, 1 H). Anal. Calcd for $C_7H_{14}O_2$: C, 64.58; H, 10.84. Found: C, 64.61; H, 10.70.

(*Z*)-2,3-Dimethyl-5-phenylthio-3-pentenol (10). A solution of **9** (734 mg, 5.64 mmol), tributylphosphine (1.62 g, 8.03 mmol), and phenyl disulfide (1.60 g, 7.33 mmol) in THF (5 mL) was stirred at rt for 12 h, and quenched with water. Extraction with CH_2Cl_2 followed by concentration of the combined extracts left an oil, which was chromatographed on silica gel (hexane-AcOEt, 4:1) to give **10** (432 mg, 92%) as an oil; IR (film) 3379 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.90 (d, *J* = 6.8 Hz, 3 H), 1.64 (br s, 3 H), 2.86 (sixtet, *J* = 6.8 Hz, 1 H), 3.3 - 3.7 (m, 4 H), 5.51 (t with fine sprittings, *J* = 6.5 Hz, 1 H), 7.2 - 7.5 (m, 5 H). Anal. Calcd for $C_{13}H_{18}OS$: C, 70.22; H, 8.61; S, 14.42. Found: C, 70.29; H, 8.39; S, 14.53.

(*Z*)-2,3-Dimethyl-5-phenylthio-3-pentenal (11). To a stirred solution of oxalyl dichloride (36 mg, 0.29 mmol) in CH_2Cl_2 (0.5 mL) was added at -78 °C a solution of DMSO (44 mg, 0.56 mmol) in CH_2Cl_2 (0.2 mL). After being stirred briefly, a solution of **10** (50 mg, 0.23 mmol) in CH_2Cl_2 (0.3 mL) was added dropwise, and the mixture was stirred at -78 °C for 20 min. Et_3N (0.12 mg, 1.15 mmol) was added, and stirring was continued for 20 min, and then at 0 °C for 20 min. Water was added and the product was extracted with CH_2Cl_2. Removal of the solvent followed by purification of the residue by preparative TLC (hexane-AcOEt, 10:1) gave **11** (45 mg, 90%) as an oil; IR (film) 1722 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.08 (d, *J* = 7.2 Hz, 3 H), 1.62 (br s, 3 H), 3.43 (q, *J* = 7.0 Hz, 1 H), 3.59 (d, *J* = 7.6 Hz, 2 H), 5.67 (t with fine splittings, *J* = 7.6 Hz, 1 H), 7.2 - 7.5 (m, 5 H), 9.32 (br s, 1 H). Anal. Calcd for $C_{13}H_{16}OS$: C, 70.87; H, 7.32; S, 14.55. Found: C, 71.14; H, 7.48; S, 14.43.

Methyl (*Z*)-5-Hydroxy-6,7-dimethyl-3-oxo-9-phenylthio-7-nonenoate (12). To a stirred mixture of sodium hydride (642 mg, 26.8 mmol) in THF (70 mL) was added dropwise at 0 °C a solution of methyl acetoacetate (3.12 g, 26.9 mmol) in THF (20 mL), and stirring was continued for 1 h. To the reaction mixture was added dropwise at -78 °C over 10 min a 1.68 M solution of BuLi in hexane (16.0 mL, 26.9 mmol), and stirring was continued for an additional 1 h. To the reaction mixture, a solution of **11** (4.92 g, 22.3 mmol) in THF (60 mL) was added and stirring was continued for an additional 3 h. The reaction was quenched by

addition of aqueous NH_4Cl, followed by addition of 5% HCl, and the product was extracted with CH_2Cl_2. Removal of the solvent followed by chromatography of the oily residue on silica gel (hexane-AcOEt, 5:1) gave **12** (6.21 g, 83%) as an oil; IR (film) 3578, 1740, 1714 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.05 (d, *J* = 7.0 Hz, 3 H), 1.58 (br s, 3 H), 2.5 - 3.0 (m, 3 H), 3.46 (s, 2 H), 3.5 - 4.1 (m, 3 H), 3.72 (s, 3 H), 5.40 (t, *J* = 7.1 Hz, 1 H), 7.2 - 7.5 (m, 5 H). Anal. Calcd for $C_{18}H_{24}O_4S$: C, 64.27; H, 7.19; S, 9.52. Found: C, 64.38; H, 7.25; S, 9.38.

Methyl (7*Z*)-3,5-Diacetoxy-6,7-dimethyl-9-phenylthio-2,7-nonadienoate (13). To a stirred solution of **12** (1.82 g, 5.41 mmol) and Et_3N (0.60 g, 5.95 mmol) in CH_2Cl_2 (10 ml) was added dropwise at -40 °C a solution of 4-dimethylaminopyridine (165 mg, 1.35 mmol) and acetic anhydride (1.23 mL, 13.0 mmol) in CH_2Cl_2 (15 ml), and stirring was continued for an additional 30 min. Water was added, and the product was extracted with CH_2Cl_2. Evaporation of the solvent followed by flash-column chromatography of the residue on silica gel (hexane-AcOEt, 15:1) provided **13** (2.13 g, 90%) as an oil; IR (film) 1766, 1740, 1723 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.86 (d, *J* = 7.0 Hz, 3 H), 1.66 (br s, 3 H), 1.98 (s, 3 H), 2.13 (s, 3 H), 2.7 - 3.9 (m, 6 H), 3.68 (s, 3 H), 5.40 (t, *J* = 7.1 Hz, 1 H), 5.80 (s, 1 H), 7.2 - 7.4 (m, 5 H). Anal. Calcd for $C_{22}H_{28}O_6S$: C, 62.84; H, 6.71; S, 7.62. Found: C, 62.59; H, 6.50; S, 7.80.

Methyl (7*Z*)-5,6-Dimethyl-3-oxo-9-phenylthio-4,7-nonadienoate (14). A mixture of **13** (1.14 g, 2.61 mmol) and K_2CO_3 (360 mg, 2.60 mmol) in methanol (30 mL) was stirred at rt for 3 h. After the solvent was mostly taken off under the reduced pressure, water was added, and the product was extracted with CH_2Cl_2. Concentration followed by purification of the oily residue by flash-column chromatography on silica gel (hexane-AcOEt, 30:1) gave **14** (654 mg, 80%) as an oil; IR (film) 1743, 1670 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.07 (d, *J* = 7.2 Hz, 3 H), 1.59 (br s, 3 H), 3.4 - 3.7 (m, 2 H), 3.56 (s, 2 H), 3.71 (s, 3 H), 5.35 (br t, *J* = 7 Hz, 2 H), 5.6 - 6.9 (m, 2 H), 7.2 - 7.4 (m, 5 H). Anal. Calcd for $C_{18}H_{22}O_3S$: C, 67.89; H, 6.96; S, 10.07. Found: C, 68.09; H, 7.01; S, 9.95.

Methyl (*Z*)-6,7-Dimethyl-3-oxo-9-phenylthio-7-nonenoate (15). A solution of tris(triphenylphosphine)rhodium(I) chloride (922 mg, 1.0 mmol), **14** (3.17 g, 9.96 mmol) and degassed benzene (90 mL) was hydrogenated at atmospheric pressure for 3 d. The solvent was removed at reduced pressure, and oily residue was filtered through a short silica-gel column to give an oil, whose purification by flash-column chromatography on silica gel (hexane-AcOEt, 15:1) provided **15** (3.13 g, 98%) as an oil; IR (film) 1744, 1717 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.90 (d, *J* = 7 Hz, 3 H), 1.60 (br s, 3 H), 1.5 - 1.8 (m, 2 H), 2.44 (d, *J* = 7.4 Hz, 2 H), 2.4 - 2.8 (m, 1 H), 3.48 (s, 2 H), 3.76 (s, 3 H), 4.58 (d, *J* = 7.4 Hz, 2 H), 5.43 (t, *J* = 7.4 Hz, 1 H), 7.2 - 7.4 (m, 5 H). Anal. Calcd for $C_{18}H_{24}O_3S$: C, 67.47; H, 7.55; S, 10.01. Found: C, 67.58; H, 7.59; S, 9.80.

Methyl (*Z*)-2-Diazo-3-oxo-6,7-dimethyl-9-phenylthio-7-nonenoate (1c). A solution of **15** (3.10 g, 9.67 mmol), *p*-toluenesulfonyl azide (2.04 g, 10.6 mmol), Et_3N (2.45 g, 24.2 mmol) and acetonitrile (100 mL) was stirred at 45 °C for 2 d, and after cooling to rt, poured into water. The product was extracted with ether, and the combined extracts were washed successively with aqueous 10% K_2CO_3, water and brine, and dried. Evaporation of the solvent followed by flash-column chromatography of the residue on silica gel

(hexane-AcOEt, 25:1) gave **1c** (3.31 g, 99%) as an oil; IR (film) 2141, 1719, 1652 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.01 (d, J = 7.0 Hz, 3 H), 1.67 (br s, 3 H), 1.5 - 1.8 (m, 2 H), 2.7 - 2.9 (m, 3 H), 3.64 (dd, J = 4.3, 4.9 Hz, 2 H), 3.90 (s, 3 H), 4.43 (t, J = 7.2 Hz, 1 H), 7.1 - 7.5 (m, 5 H). Anal. Calcd for $C_{18}H_{22}O_3N_2S$; C, 62.40; H, 6.40; N, 8.09: S, 9.26. Found. C, 62.10; H, 6.37; N, 8.36; S; 9.38.

Methyl (3*R*)-3-Isopropenyl-6-oxoheptanoate (19). A mixture of (+)-limonene oxide (**16**)[10] (50.0 g, 0.33 mol), KOH (109 g, 1,65 mol), DMSO (165 mL) and water (150 mL) was heated at 110 °C for 3 d. Extractive workup followed by purification of the oily residue by flash-column chromatography on silica gel (hexane-AcOEt, 3:1) gave the diol **17** (42.9 g, 76%) as an oil; IR ($CHCl_3$) 3600, 3400, 3080, 1640, 1145, 900 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.25 (s, 3 H), 1.72 (s, 3 H), 1.4 - 2.8 (m, 9 H), 3.62 (br s, 1 H), 4.74 (s, 2 H).

To a stirred suspension of PCC (94.8 g, 0.44 mol) and Celite 545 (47 g) in CH_2Cl_2 (350 mL) was added dropwise at rt a solution of **17** (15.0 g, 0.088 mol) in CH_2Cl_2 (100 mL), and stirring was continued for an additional 2 h. The reaction mixture was filtered through a short silica-gel column with CH_2Cl_2, and the filtrate was concentrated. Purification of the residue by flash-column chromatography on silica gel (hexane-AcOEt, 20:1) gave the hydroxy ketone **18** (11.7 g, 79%) as an oil; IR (film) 4350, 1710 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.37 (s, 3 H), 1.75 (s, 3 H), 1.6 - 2.9 (m, 7 H), 3.62 (s, 1 H, OH), 4.70 and 4.86 (s, 1 H each).

To a stirred solution of **18** (2.05 g, 12.2 mmol) in methanol (40 mL), lead tetraacetate (6.07 g, 13.0 mmol) was added portion by portion at -5 °C over 30 min. The reaction mixture was stirred at 0 °C for an additional 1 h and filtered through a bed of alumina with CH_2Cl_2. Water was added and the product was extracted with CH_2Cl_2. The combined extracts were washed successively with aqueous K_2CO_3 and brine, and dried. Removal of the solvent follwed by chromatography of the residue (hexane-AcOEt, 9:1) gave **19** (2.40 g, 99%) as an oil; IR (film) 3080, 1725, 1710, 1640, 900 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.66 (s, 3 H), 2.15 (s, 3 H), 1.8 - 2.7 (m, 7 H), 3.65 (s, 3 H), 4.75 (br s, 2 H). Anal. Calcd for $C_{11}H_{18}O_3$: C, 66.64; H, 9.15. Found: C, 66.78; H, 9.34.

Methyl (3*R*)-3-Isopropenyl-2-methyl-6-oxoheptanoate Ethylene Acetal (21). A solution of **19** (2.40 g, 12.0 mmol), ethylene glycol (7.4 g, 12.0 mmol) and PPTS (96 mg) in benzene (50 mL) was refluxed azeotropically for 12 h. Extractive workup in the usual manner, followed by chromatography of the residue on silica gel (hexane-AcOEt, 9:1) gave the acetal **20** (2.28 g, 79%) as an oil; IR ($CHCl_3$) 3080, 1715, 1640, 1070, 900 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.30 (s, 3 H), 1.4 - 1.8 (m, 4 H), 1.67 (s, 3 H), 2.3 - 2.7 (m, 3 H), 3.63 (s, 3 H), 3.92 (s, 4 H), 4.74 (br s, 2 H). Anal. Calcd. for $C_{13}H_{22}O_4$: C, 64.44: H, 9.15. Found: C, 64.70; H, 9.35.

To a stirred LDA-THF solution, prepared from diisopropylamine (2.61 g, 25.8 mmol), a 1.59 M solution of BuLi in hexane (16.2 mL, 25.8 mmol), and THF (25 mL), was added at -78 °C a solution of **20** (5.20 g, 21.5 mmol) in THF (5 mL). After being stirred for 30 min, a solution of methyl iodide (1.6 mL, 25.8 mmol) in THF (5 mL), followed by HMPA (4.5 mL, 25.8 mmol) was added, and the reaction mixture was stirred for 3 h, during which the reaction temperature was gradually rose to -30 °C. The reaction mixture was quenched with aqueous NH_4Cl, and the product was extracted with ether. Removal of the solvent followed by chromatography of the residue (hexane-ether, 5:1) gave **21** (5.30 g, 96%) as an oil; IR ($CHCl_3$) 3080, 1730, 1640, 1060, 900 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.05 and 1.12 (d, J = 7.0 Hz each, 3 H in total,), 1.25 (s, 3 H),

1.2 - 2.6 (m, 6 H), 1.59 (s, 3 H), 3.60 and 3.68 (s each, 3 H in total), 3.90 (s, 4 H), 4.6 - 4.95 (m, 2 H). Anal. Calcd for $C_{14}H_{24}O_4$: C, 65.60; H, 9.44. Found: C, 65.45; H, 9.45.

(4*R*)-4-Isopropenyl-3-methyl-7-oxooctanenitrile Ethylene Acetal (24). To a stirred mixture of lithium aluminium hydride (288 mg, 7.6 mmol) in ether (15 mL) was added at 0 °C a solution of **21** (1.94 g, 7.6 mmol) in ether (5 mL), and stirring was continued for an additional 2 h. Workup in the usual manner followed by purification of the residual oil by chromatography on silica gel (hexane-AcOEt, 1:1) gave the alcohol **22** (1.60 g, 93%) as an oil; IR (film) 3400, 3080, 1640, 1050, 900 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.90 (d, J = 7.0 Hz, 3 H), 1.30 (s, 3 H), 1.2 - 2.0 (m, 6 H), 1.60 (s, 3 H), 3.3 - 3.7 (m, 2 H), 3.93 (s, 4 H), 4.63 - 4.75 (m, 2 H). Anal. Calcd for $C_{13}H_{24}O_3$: C, 68.38; H, 10.59. Found: C, 68.55; H, 10.49.

A mixture of **22** (8.37 g, 37.0 mmol), *p*-toluenesulfonyl chloride (8.48 g, 44.5 mmol) and pyridine (50 mL) was stirred at rt for 12 h. Extractive workup in the usual manner followed by filtration of the oily residue through a short silica-gel column (hexane-ether, 1:1) gave the tosylate **23** (14.1 g, quantitative) as an oil; IR (film) 3080, 1640, 1600, 1180, 960 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.85 and 0.95 (d, J = 7.0 Hz each, 3 H in total), 1.13 (s, 3 H), 1.2 - 2.0 (m, 6 H), 1.57 (s, 3 H), 2.43 (s, 3 H), 3.6 - 4.2 (m, 2 H), 3.90 (s, 4 H), 4.5 - 4.8 (m, 2 H), 7.31 and 7.78 (d, J = 9.6 Hz each, 2 H). Anal. Calcd for $C_{20}H_{30}SO_5$: C, 62.80; H, 7.91; S, 8.38. Found: C, 62.73; H, 7.58; S, 8.00.

A mixture of **23** (14.0 g, 36.6 mmol), sodium cyanide (3.58 g, 73.2 mmol) and DMSO (50 mL) was stirred at 95 °C for 1.5 h, and after cooling to rt, diluted with water. Extraction of the product with CH_2Cl_2 followed by evaporation of the solvent left the oily residue whose chromatography on silica gel (hexane-AcOEt, 4:1) gave **24** (7.89 g, 91%) as an oil; IR (film) 3080, 2250, 1640, 900 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.05 (d, J = 7.0 Hz, 3 H), 1.2 - 2.6 (m, 8 H), 1.30 (s, 3 H), 1.60 (s, 3 H), 3.92 (s, 4 H), 4.7 - 4.9 (m, 2 H). Anal Calcd for $C_{14}H_{23}NO_2$: C, 70.85: H, 9.77; N, 5.90. Found: C, 71.01; H, 9.98; N, 5.73.

(4*R*)-4-Isopropenyl-3-methyl-7-oxooctanoic Acid Ethylene Acetal (25). A mixture of **24** (660 mg, 2.78 mmol), 20% aqueous KOH (5 mL) and ethanol (5 mL) was stirred at 110 °C for 2 d. After cooling to rt, the reaction mixture was diluted with water, and washed with ether. The aqueous layer was acidified with 1 M HCl, extracted with ether, and combined extracts were concentrated to leave an oil, whose filtration through a short silica-gel column (hexane-AcOEt, 1:1) gave **25** (683 mg, 96%) as an oil; IR (film) 2950 (br), 1705, 1640, 900 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.92 (d, J = 7.0 Hz, 3 H,), 1.30 (s, 3 H), 1.2 - 2.7 (m, 8 H), 1.62 (s, 3 H), 3.95 (s, 4 H), 4.70 and 4.85 (br s, 1 H each), 8.5 (br, 1 H). Anal. Calcd for $C_{14}H_{24}O_4$: C, 65.59; H, 9.44. Found: C, 65.48; H, 9.44.

(4*R*)-5-Iodomethyl-3,5-dimethyl-4-(3,3-ethylenedioxybutyl)-2-penten-5-olide (27). The acid **25** (8.53 g, 33.3 mmol) was dissolved into saturated aqueous $KHCO_3$ (100 mL), followed by addition of ether (50 mL). To the stirred reaction mixture was added portion by portion a mixture of I_2 (8.89 g, 35 mmol) and KI (16.59 g, 100 mmol), and the reaction mixture was stirred at rt for 40 h. The ether layer was separated and the aqueous layer was extracted with ether. The combined ether extracts were washed successively with aqueous sodium thiosulfate, water, and brine, and dried. Removal of the solvent followed by chromatography of the residue on silica gel (hexane-AcOEt, 4:1) gave iodo lactone **26** (12.46 g, 98%) as an oil; IR (film) 1730 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.05 (br d, J = 7.0 Hz, 3 H), 1.30 (s, 3 H), 1.55 and 1.60 (s each, 3 H in total), 1.2

- 2.8 (m, 8 H), 3.44 and 3.50 (s each, 2 H in total), 3.96 (s, 4 H). Anal. Calcd for $C_{24}H_{23}O_4I$: C, 43.99; H, 6.17; I, 33.20. Found: C, 44.16; H, 6.09; I, 32.84.

To a stirred LDA-THF solution, prepared from diisopropylamine (4.8 mL, 34.2 mmol), a 1.49 M solution of BuLi in hexane (22.9 mL, 34.2 mmol) and THF (40 mL), was added at -78 °C a solution of **26** (11.87 g, 31.0 mmol) in THF (10 mL), and stirring was continued for an additional 1.5 h. To the reaction mixture was added a solution of phenylselenenyl chloride (6.55 g, 34.2 mmol) in THF (10 mL) followed by HMPA (6.0 mL, 34.2 mmol), and the reaction mixture was stirred for 30 min, quenched with aqueous NH_4Cl, and extracted with ether, and dried. Removal of the solvent followed by filtration of the residue through a short silica-gel column (hexane-ether, 1:1) gave oily selenide (16.5 g) which was dissolved in a mixture of THF (50 mL) and pyridine (10 mL). The reaction mixture was stirred at 0 °C, as 30% H_2O_2 (10.5 mL) was added dropwise. Stirring was continued at 0 °C for 15 min, and then at rt for 15 min. Extractive workup in the usual manner followed by chromatography of the residue on silica gel (hexane-AcOEt, 4:1) gave **27** (8.25 g, 70%) and the unreacted **26** (590 mg).

27; IR (film) 1710 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.25 (s, 3 H), 1.60 (s, 3 H), 1.5 - 2.8 (m, 5 H), 2.0 (s with fine splittings, 3 H), 3.39 (m, 2 H), 3.97 (s, 4 H), 5.84 (s with fine splittings, 1 H). Anal. Calcd for $C_{14}H_{21}O_4I$: C, 44.22; H, 5.57; I, 33.38. Found: C, 44.53; H, 5.77; I, 32.96.

(5*S*)-(*Z*)-8-Hydroxy-4-isopropenyl-6-methyl-6-octen-2-one (29). To a stirred mixture of lithium aluminium hydride (418 mg, 11.0 mmol) and aluminium chloride (1.47 g, 11.0 mmol) in THF (20 mL) was added dropwise at -70 °C a solution of **27** (1.90 g, 5.0 mmol) in THF (5 mL), and stirring was continued for 20 min over a range of -30 to -20 °C. To the reaction mixture, wet ether followed by water was added, and the resulting solid was filtered off through a bed of Celite 545. The filtrate was concentrated, and chromatography of the residue on silica gel (Hexane-AcOEt, 5:1) gave the diol **28** (1.29 g, 67%) as an oil; IR (film) 3400 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.30 and 1.45 (s each, 6 H in total), 1.75 (s, 3 H), 1.4 - 3.0 (m, 7 H), 3.41 (m, 2 H), 3.94 (s, 4 H), 4.1 (m, 2 H), 5.77 (m, 1 H). Anal. Calcd for $C_{14}H_{25}O_4I$: C, 43.76; H, 6.56; I, 33.03. Found: C, 43.70; H, 6.29; I, 32.62.

To a stirred solution of **28** (829 mg, 2.15 mmol) in acetic acid (5 mL), Zn-Cu couple (706 mg, 10.9 mmol) was added portion by portion at rt, and stirring was continued for 2 h, and then at 50 °C for 15 min. After cooling to rt, the mixture was diluted with ether and filtered through a bed of Celite 545. The filtrate was washed successively with aqueous $NaHCO_3$, water and brine,and dried. Removal of the solvent followed by chromatography of the residue on silica gel (hexane-ether, 4:1) gave **29** (294 mg, 70%) as an oil; IR ($CHCl_3$) 3450, 3080, 1710, 1640, 1000, 900 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.52 (d, J = 7.0, 1.1 Hz, 3 H), 1.64 (s, 3 H), 1.6 - 2.0 (m, 2 H), 2.13 (s, 3 H), 2.41 (t, J = 7.4 Hz, 2 H), 3.05 (m, 1 H), 4.15 (m, 2 H), 4.74 and 4.90 (s with fine splittings, 1 H each), 5.62 (td, J = 7.0, 1.1 Hz, 1 H). Anal. Calcd for $C_{12}H_{20}O_2$: C, 73.43; H, 10.27. Found: C, 73.71; H, 10.19.

Methyl (6*S*)-(*Z*)-9-Hydroxy-6-isopropenyl-7-methyl-3-oxo-7-nonenoate (32). A mixture of **29** (121 mg, 0.62 mmol), *tert*-butyldimethylsilyl chloride (112 mg, 0.74 mmol), imidazole (63 mg, 0.93 mmol) and DMF (2 mL) was stirred at rt for 12 h. Workup in the usual manner followed by purification of the oily residue by chromatography on silica gel (hexane-AcOEt, 10:1) gave the silyl ether **30** (176 mg, 92%) as an oil; ^1H NMR ($CDCl_3$) δ 0.05 (s, 6 H), 0.88 (s, 9 H), 1.50 (s with fine splittings, 3 H), 1.62 (s with fine splittings,

3 H), 1.2 - 3.0 (m 5 H), 4.15 and 4.22 (s with fine splittings, 1 H each), 4.80 (m, 2 H), 5.47 (t with fine splittings, J = 7.1 Hz, 1 H). Anal. Calcd for $C_{18}H_{34}O_2Si$: C, 69.62; H, 11.04. Found. C, 69.33; H, 11.36.

To a stirred LDA-THF solution, prepared from diisopropylamine (0.28 mL, 1.98 mmol), a 1.49 M solution of BuLi in hexane (1.33 mL, 1,98 mmol), and THF (3 mL), was added at -78 °C a solution of **30** (511 mg, 1.65 mmol) in THF (2 mL). After being stirred for 1 h, HMPA (0.35 mL, 1.98 mmol) was added, followed by addition of a solution of methyl cyanoformate (0.16 mL, 1.98 mmol) in THF (2 mL). The reaction mixture was stirred for 30 min, and quenched with aqueous NH_4Cl. The extractive workup followed by chromatography of the residue on silica gel (hexane-AcOEt, 10:1) gave the β-keto ester **31** (490 mg, 81%) as an oil; IR ($CHCl_3$) 3080, 1750, 1720, 1640, 850 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.05 (s, 6 H), 0.90 (s, 9 H), 1.50 (s with fine splittings, 3 H), 1.61 (s, 3 H), 1.6 - 2.0 (m, 2 H), 2.47 (t, J = 7.2 Hz, 2 H), 2.90 (m, 1 H), 3.43 (s, 2 H), 3.71 (s, 3 H), 4.15 and 4.22 (br s, 1 H each), 4.80 (m, 2 H), 5.49 (t, J = 7.2 Hz, 1 H). Anal. Calcd for $C_{20}H_{36}O_4Si$: C, 65.17; H, 9.85. Found: C, 65.09; H, 9.48.

A mixture of **31** (470 mg, 1.28 mmol) and a 1 M solution of tetrabutylammonium fluoride in THF (1.55 mL, 1.55 mmol) and THF (3 mL) was stirred at rt for 12 h, and quenched with aqueous NH_4Cl. Workup in the usual manner followed by purification of the residue by chromatography on silica gel (hexane-AcOEt, 4:1) gave the alcohol **32** (308 mg, 95%) as an oil; IR ($CHCl_3$) 3400, 3080, 1740, 1705, 1000, 900 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.55 and 1.62 (s, 3 H each), 1.6 - 2 2 (m, 3 H), 2.53 (t, J = 7.2 Hz, 2 H), 3.10 (m, 1 H), 3.48 (s, 2 H), 3.73 (s, 3 H), 4.15 (m, 2 H), 4.75 and 4.85 (s, 1 H each), 5.60 (t, J = 7.0 Hz, 1 H). Anal. Calcd for $C_{14}H_{22}O_4$: C, 66.11; H, 8.72. Found: C, 66.09; H, 9.08.

Methyl (6*S*)-(*Z*)-6-Isopropenyl-7-methyl-3-oxo-9-phenylthio-7-nonenoate (33). A solution of **32** (180 mg, 0.68 mmol), diphenyl disulfide (304 mg, 1.36 mmol) and tributylphosphine (0.35 mL) in pyridine (2 mL) was stirred at rt for 16 h. Extractive workup followed by chromatography of the residue on silica gel (hexane-ether, 3:1) gave **33** (210 mg, 89%) as an oil; IR ($CHCl_3$) 1740, 1710, 1640, 1590, 900 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.55 and 1.63 (s, 3 H each), 1.6 - 2.2 (m, 2 H), 2.45 (t, J = 7.2 Hz, 2 H), 3.05 (m, 1 H), 3.45 (s, 2 H), 3.60 (m, 2 H), 3.73 (s, 3 H), 4.75 and 4.88 (br s, 1 H each), 5.50 (t, J = 7.3 Hz, 1 H), 7.3 (m, 5 H). Anal. Calcd for $C_{20}H_{26}O_3S$: C, 69.33; H, 7.56; S, 9.25. Found: C, 69.11, H, 7.76; S, 9.43.

Methyl (6*S*)-(*Z*)-2-Diazo-6-isopropenyl-7-methyl-3-oxo-9-phenylthio-7-nonenoate (1d). A solution of **33** (142 mg, 0.41 mmol), *p*-toluenesulfonyl azide (97 mg, 0.49 mmol), and Et_3N (0.27 mL, 1.96 mmol) in acetonitrile (2 mL) was stirred at 45 °C for 40 h. Workup according to the procedure for preparation of **1c** gave **1d** (150 mg, 98%) as an oil; IR ($CHCl_3$) 3080, 2150, 1730, 1650, 1590, 900 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.55 and 1.61 (s, 3 H each), 1.6 - 2.2 (m, 2 H), 2.78 (t, J = 7.2 Hz), 2 H), 3.15 (m, 1 H), 3.62 (d, J = 7.4 Hz, 2 H), 3.80 (s, 3 H), 4.75 and 4.88 (br s, 1 H each), 5.50 (t, J = 7.2 Hz, 1 H), 7.3 (m, 5 H). Anal Calcd for $C_{20}H_{24}N_2O_3S$: C, 64.49; H, 6.49; N; 7.52; S, 8.61. Found: C, 64.37; H, 6.70; N, 7.88; S, 8.50.

Reaction of α-Diazo Esters with Rhodium(II) Acetate. General Procedure. A solution of α-diazo esters **1c,d** (1.0 mmol) and rhodium(II) acetate (0.005 mmol) in dry benzene (10 mL) was stirred at rt for 10 min, then gently refluxed for an additional 30 min. Removal of the solvent followed by chromatography of the residue on silica gel (hexane-AcOEt, 15:1 - 15: 3) gave the cyclization products **3c,d.**

Methyl (1*S,5*R**,6*S**)-5,6-Dimethyl-2-oxo-1-phenylthio-6-vinylcyclohexanecarboxylate (3c):** Crystals; 78% yield; mp 76 - 78° C; IR (film) 1741, 1702, 1637, 921 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.91 (d, *J* = 7.2 Hz, 3 H), 1.16 (s, 3 H), 1.3 - 3.3 (m, 5 H), 3.63 (s, 3 H), 5.04 (d, *J* = 16.8 Hz, 1 H), 5.48 (d, *J* = 10.2 Hz, 1 H), 6.11 (dd, *J* = 16.8, 10.2 Hz, 1 H), 7.2 - 7.5 (m, 5 H). Anal Calcd for $C_{18}H_{22}O_3S$: C, 67.89; H, 6.96; S, 10.07. Found: C, 67.63; H, 6.79: S, 10.25.

Methyl (1*S*,5*S*,6*S*)-5-Isopropenyl-6-methyl-2-oxo-1-phenylthio-6-vinylcyclohexanecarboxylate (3d): Oil; 61% yield; IR ($CHCl_3$) 3080, 1740, 1705, 1640, 900 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.21 (s, 3 H), 1.3 - 2.5 (m, 5 H), 1.80 (s, 3 H), 3.60 (s, 3 H), 4.72 and 4.96 (br s, 1 H each), 4.93 (d, *J* = 17.3 Hz, 1 H), 5.13 (d, *J* = 10.8 Hz, 1 H), 6.40 (dd, *J* = 17.3, 10.8 Hz, 1 H), 7.3 (m, 5 H). Anal. Calcd for $C_{20}H_{24}O_3S$, C, 69.73; H, 7.02; S, 9.31. Found: C, 69.52; H, 6.98; S, 9.37.

Methyl (1*R,5*R**,6*S**)-5,6-Dimethyl-2-oxo-6-vinylcyclohexanecarboxylate (34a) and Methyl (1*S**,5*R**,6*S**)-5,6-Dimethyl-2-oxo-6-vinylcyclohexanecarboxylate (34b).** A suspension of **3c** (100 mg, 0.31 mmol) and zinc powder (205 mg, 3.14 mmol atom) in acetic acid (3 mL) was heated at 60 °C with stirring for 30 min. After cooling to rt, the reaction mixture was diluted with ether, and washed successively with 10% aqueous K_2CO_3, water, and brine, and dried. Removal of the solvent followed by purification of the residue by HPLC (hexane-AcOEt, 4:1) gave **34a** (40.0 mg, 61%) as crystals and **34b** (13.0 mg, 20%) as an oil.

34a: mp 56 - 57 °C; IR (film) 1756, 1717, 1369,920 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.88 (d, *J* = 6.5 Hz, 3 H), 1.15 (s, 3 H), 1.6 - 2.1 (m. 3 H), 2.3 - 2.6 (m, 2 H), 3.94 (s, 1 H), 3.65 (s, 3 H), 5.04 (dd, *J* = 17.3, 1.8 Hz, 1 H), 5.13 (dd, *J* = 10.8, 1.8 Hz, 1 H), 5.74 (dd, *J* = 17.3, 10.8 Hz, 1 H). Anal. Calcd for $C_{12}H_{18}O_3$: C, 68.54; H, 8.63. Found: C, 68.42; H, 8.55.

34b: IR (film) 1733, 1716, 1367, 920 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.86 (d, *J* = 6.8 Hz, 3 H), 0.96 (s, 3 H), 1.4 - 3.1 (m, 5 H), 3.14 (d, *J* = 2.5 Hz, 1 H), 3.66 (s, 3 H), 5.07 (dd, *J* = 18.0, 1.8 Hz, 1 H), 5.13 (dd, *J* = 11.5, 1.8 Hz, 1 H), 5.85 (dd, *J* = 18.0, 11.5 Hz, 1 H). Anal. Calcd for $C_{12}H_{18}O_3$: C, 68.54; H, 8.63. Found: C, 68.75; H, 8.61.

(3*S,4*R**)-3,4-Dimethyl-3-vinylcyclohexanone (35).** To a solution of the diastereomeric mixture **34a,b** (30 mg, 0.095 mmol) in ethanol (0.5 mL) was added a 2 M aqueous solution of KOH (0.1 mL), and the reaction mixture was stirred at rt for 13 h, and then acidified with 3 M aqueous HCl. The reaction mixture was saturated by addition of NaCl(s), and the product was extracted with CH_2Cl_2. Removal of the solvent followed by purification of the residue by HPLC (hexane-AcOEt, 4:1) gave cyclohexanone **35** (13 mg, 92%), IR (film) 1717 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.91 (s, 3 H), 0.93 (d, *J* = 6.1 Hz, 3 H), 1.0 - 2.5 (m, 7 H), 4.96 (d, *J* = 16.9 Hz, 1 H), 5.05 (d, *J* = 10.1 Hz, 1 H), 5.85 (dd, *J* = 16.9, 10.1 Hz, 1 H), whose spectral data are identical with those of the authentic sample.[14]

Methyl (1*S,2*R**,5*R**,6*S**)-2-Hydroxy-5,6-dimethyl-1-phenylthio-6-vinylcyclohexanecarboxylate (44a) and Methyl (1S*,2*S**,5*R**,6*S**)-2-Hydroxy-5,6-dimethyl-1-phenylthio-6-vinylcyclohexanecarboxylate (44b).** (1) To a mixture of sodium borohydride (4.8 mg, 0.13 mmol) and isopropanol (0.6 mL) was added dropwise at 0 °C a solution of **3c** (20 mg, 0.06 mmol) in THF (0.2 mL), and

the reaction mixture was stirred at rt for 13 h, and recooled at 0 °C. Water was added, followed by addition of 3 M aqueous HCl, and the product was extracted with CH_2Cl_2. Removal of the solvent followed by purification of the residue by preparative TLC (CH_2Cl_2-hexane, 10:1) gave **44a** (7.9 mg, 39%) as crystals and **44b** (5.6 mg, 28%) as an oil.

44a: mp 60 - 62 °C; IR (film) 3551, 1702, 1633, 908 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.77 (d, *J* = 6.7 Hz, 3 H), 0.99 (s, 3 H), 1.2 - 2.3 (m, 5 H), 3.19 (s, 3 H), 4.50 (dd, *J* = 9.8, 4.8 Hz, 1 H), 4.85 (dd, *J* = 18.6, 1.2 Hz, 1 H), 5.16 (dd, *J* = 11.0, 1.2 Hz, 1 H), 6.65 (dd, *J* = 18.6, 11.0 Hz, 1 H), 7.2 - 7.5 (m, 5 H). Anal. Calcd for $C_{18}H_{24}O_3S$: C, 67.48; H, 7.55; S, 9.98. Found: C, 67.70; H, 7.23; S, 9.70.

44b: IR (film) 3542, 1741, 1635, 911 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.88 (d, *J* = 6.5 Hz, 3 H), 1.28 (s, 3 H), 1.2 - 2.5 (m, 5 H), 3.70 (s, 3 H), 4,13 (t, *J* = 3.2 Hz, 1 H), 5.06 (dd, *J* = 17.3, 1.2 Hz, 1 H), 5.30 (dd, *J* = 11.9, 1.2 Hz, 1 H), 6.34 (dd, *J* = 17.3, 11.9 Hz, 1 H), 7.2 - 7.5 (m, 5 H). Anal. Calcd for $C_{18}H_{24}O_3S$: C, 67.48; H, 7.55; S, 9.98. Found: C, 67.40; H, 7.32; S, 9.80.

(2) To a stirred solution of lithium aluminium hydride (35.8 mg, 0.94 mmol) in THF (6 mL) was added dropwise at -78 °C a solution of **3c** (300 mg, 0.94 mmol) in THF (3 mL), and stirring was continued for an additional 30 min. To the reaction mixture, wet ether followed by water was added, and resulting solid was filtered off through a bed of Celite 545. The filtrate was dried, and concentrated to leave an oily residue,which was purified by HPLC (hexane-AcOEt, 4:1) to give **44a** (131 mg, 44%) and **44b** (162 mg, 54%).

Methyl (5*R,6*S**)-5,6-Dimethyl-6-vinyl-1-cyclohexenecarboxylate (43).** (1) To a mixture of sodium borohydride (45.0 mg, 1.19 mmol) in methanol (1 mL) was added dropwise at 0° C a solution of **34a** (50.0 mg, 0.24 mmol) in methanol (0.5 mL). The reaction mixture was stirred for 2 h, quenched with water, and the product was extracted with CH_2Cl_2. Removal of the solvent followed by filtration of the residue through a short silica-gel column (hexane-ether, 1:1) gave the oily hydroxy ester **41** (50.4 mg, 100%); IR (film) 3450, 1720 cm^{-1}, which was dissolved in CH_2Cl_2 (1 mL). To this solution was added successively 4-dimethylaminpyridine (5.8 mg, 0.05 mmol), Et_3N (100 mg, 0.95 mmol), and methanesulfonyl chloride (0.11 mg, 0.95 mmol). The reaction mixture was stirred at rt for 12 h, water was added, and the product was extracted with ether. Evaporation of the solvent followed by filtration of the residue through a short silica-gel colume (hexane-ether, 1:1) gave the oily mesylate **42** (72.0 mg, 100%); IR (film) 1720 cm^{-1}. A solution of the above oil **42** and DBU (72.5 mg, 0.48 mmol) in benzene (1.5 mL) was gently refluxed for 12 h, and cooled to rt. Water was added and the product was extracted with benzene. Removal of the solvent left an oil which was purified by preparative TLC (hexane-AcOEt, 5:1) to give **43** (23.2 mg, 53% from **3c**) as an oil; IR (film) 1722, 1635, 905 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.87 (d, *J* = 6.4 Hz, 3 H), 1.24 (s, 3 H) 1.2 - 1.7 (m, 3 H), 2.1 - 2.3 (m, 3 H), 3.66 (s, 3 H), 4.96 (dd, *J* = 17.0, 1.5 Hz, 1 H), 5.07 (dd, *J* = 10.7, 1.5 Hz, 1 H), 5.77 (dd, *J* = 17.0, 10.7 Hz, 1 H), 6.90 (t, *J* = 4.6 Hz, 1 H). Anal. Calcd for $C_{12}H_{18}O_2$: C, 74.19; H, 9.34. Found: C, 74.34; H, 9.44.

(2) To a stirred solution of **44a** (135 mg, 0.42 mmol), 4-dimethylaminopyridine (10.3 mg, 0.08 mmol) and Et_3N (213 mg, 2.10 mmol) in CH_2Cl_2 (2 mL) was added dropwise at 0 °C a solution of methanesulfonyl chloride in CH_2Cl_2 (1 mL), and stirring was continued for an additional 12 h. Water was added, and the product was extracted with CH_2Cl_2. Combined extracts were washed successively with 3 M aqueous HCl, water, and brine and dried. Evaporation of the solvent followed by purification of the residue by preparative TLC (hexane-AcOEt, 3:1) gave **43** (66.3 mg, 91%).

(3*R*,4*S*)-4-Isopropenyl-3-methyl-3-vinylcyclohexanone (36). To a stirred solution of **3d** (20 mg, 0.05 mmol) in acetic acid (0.5 mL) was added zinc powder (19 mg, 0.29 mmol), and the reaction mixture was stirred at 60 °C for 2 h, and after cooling to rt, diluted with ether. Solid was filtered off through a bed of Celite 545 with ether, and the filtrate was washed successively with aqueous $NaHCO_3$, water, and brine and dried. Removal of the solvent left an oily residue, which was dissolved in DMSO containing one drop of brine. The resulting mixture was heated at 150 °C for 1 h, and after cooling to rt, diluted with water. Extractive workup followed by chromatography of the residue on silica gel (hexane-ether, 4:1) gave **36** (12 mg, 54%), $[\alpha]_D$ -29.8° (*c* 0.86, $CHCl_3$), whose spectral data (IR and ^1H NMR) are identical with those of the authentic sample.[16]

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