Studies on the Synthesis of Tetronolide. Synthesis of a Spiro-α-acyltetronic Acid Model

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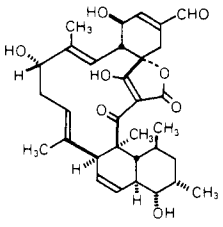
The top half models **11** and **25** of the antibiotic aglycone tetronolide (**1**) were prepared from tetrahydrophthalide and 2,4-hexadiene-1,6-diol in 8 and 12 steps, respectively. Compound **11** was coupled with the bottom half model **30a**, which was prepared via Diels–Alder reaction of methacrolein with triene **27a** or **33a** to afford α-acyltetronate **38**. The allyl chloride **39** derived from **38** was rather unstable, and attempts for macrocyclization resulted in decomposition of the key intermediate.

Tetronolide (**1**) is the aglycone of antitumor antibiotic tetrocarcins which have been isolated by chemists at Kyowa Hakko, Japan, from a culture of *Micromonospora chalcea* (KY 11091) since 1980.[1] It has a unique structural



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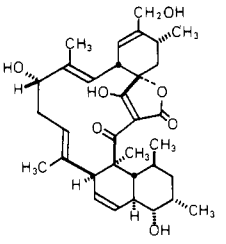

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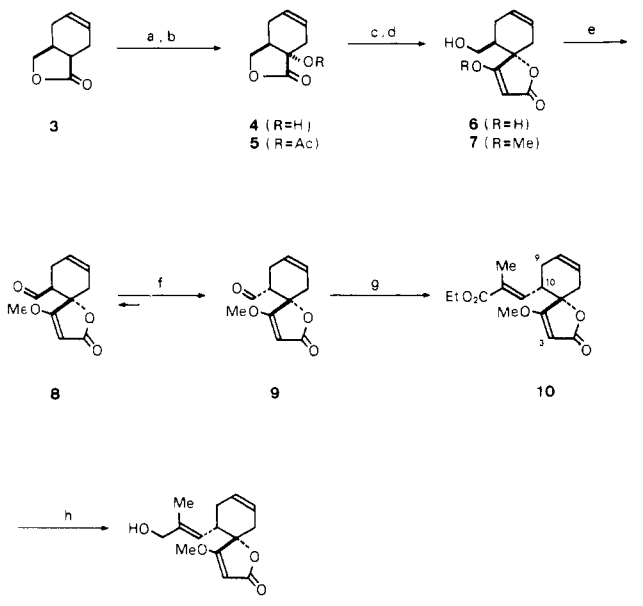
feature of a 14-memberd macrolide in which a spirotetronic acid constitutes the lactone group. The same structure, with differing functional groups and location of double bond on the cyclohexene ring, is found with kijanolide (**2**), the aglycone of kijanimicin, which was reported shortly afterward by the Schering–Plough group.[2,3]

A reasonable synthetic approach to the macrolide structure of **1** (and **2**) would involve two key steps: formation of the spiro-α-acyltetronic acid system by acylation of a "top half" spirotetronic acid with a "bottom half" octalin derivative and subsequent intramolecular coupling at the allylic termini of the intermediate. We report here our model experiments in tetronolide synthesis along this line; syntheses of top and bottom half models (**11** and **25**, and **30a**) and coupling of the two segments.

Scheme I[a]



[a] (a) LDA, THF–HMPT, then O_2, $P(OEt)_3$; (b) Ac_2O, DMAP, NEt_3; (c) 2 equiv of LDA, THF; (d) n-Bu_4NOH, then Me_2SO_4, CH_2Cl_2; (e) PCC, CH_2Cl_2; (f) DBU, CH_2Cl_2; (g) $Ph_3P{=}C(Me)COOEt$, benzene; (h) $LiB(Et)_3H$, THF.

The top half model **11** was prepared via spirotetronate carbaldehyde **9**. The corresponding carboxylic ester has already been prepared by Ireland and Thompson in their synthetic study on chlorothricolide[3a] by an intramolecular Claisen condensation of α-acetoxytetrahydrophthalic anhydride. In our hands, readily available tetrahydrophthalide **3**[5] was employed as the starting material. α-Hydroxylation of **3** was cleanly achieved by generation of the lithium enolate with lithium diisopropylamide (LDA) in tetrahydrofuran (THF) containing hexamethylphosphoric triamide (HMPT) followed by oxygenation in the presence of triethyl phosphite,[6] affording **4** in 73% yield (Scheme I). A MoO_5–HMPT-mediated oxygenation[7] resulted in poor yields (ca. 10%). O-Acetylation of **4** under standard conditions (acetic anhydride/4-(dimethyl-

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(3) Chlorothricolide, which is the aglycone of a macrolide antibiotic chlorothricin[4] having spirotetronic acid and octalin nuclei similar to those found with **1** and **2**, has been a challenging synthetic target in recent years: (a) Ireland, R. E.; Thompson, W. J. *J. Org. Chem.* **1979**, *44*, 3041. (b) Ireland, R. E.; Thompson, W. J.; Srouji, G. H.; Etter, R. *Ibid.* **1981**, *46*, 4863. (c) Roush, W. R.; Hall, S. E. *J. Am. Chem. Soc.* **1981**, *103*, 5200. (d) Hall, S. E.; Roush, W. R. *J. Org. Chem.* **1982**, *47*, 4611. (e) Takeda, K.; Shinagawa, M.; Koizumi, T.; Yoshii, E. *Chem. Pharm. Bull.* **1982**, *30*, 4000. (f) Snider, B. B.; Burbaum, B. W. *J. Org. Chem.* **1983**, *48*, 4370. (g) Schmidt, R. R.; Hirsenkorn, R. *Tetrahedron Lett.* **1984**, *25*, 4357.

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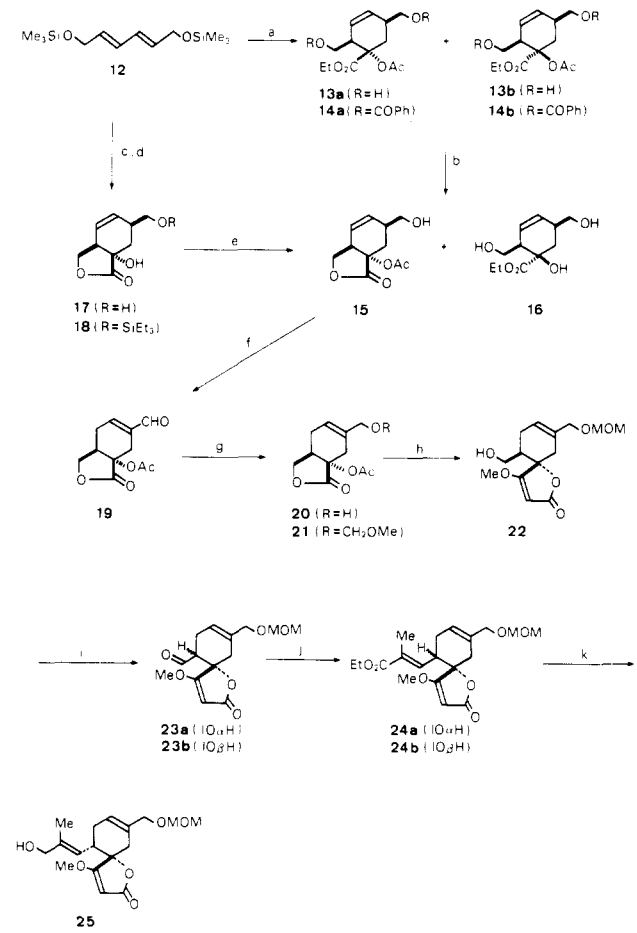
amino)pyridine/triethylamine)[8] afforded **5** in quantitative yield, which in the proton nuclear magnetic resonance (^{1}H NMR) spectrum showed signal of the angular proton at δ 3.22 (strongly deshielded by the vicinal cis acetoxyl group, cf. δ 2.77 for **4**). The α-acetoxy γ-lactone **5** was then subjected to an intramolecular Claisen condensation[3a] by use of 2 equiv of LDA in THF at −78 °C. The tetronic acid **6** obtained by this procedure was without purification transformed into the methyl ester **7** in 61% yield by reaction of its tetra-*n*-butylammonium salt with dimethyl sulfate in dichloromethane at room temperature.[9] Compound **7** was treated with pyridinium chlorochromate (PCC)[10] in dichloromethane under controlled conditions to minimize the formation of unidentified overreaction products to give rather unstable aldehyde **8**. Epimerization of the aldehyde was performed by treatment with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in dichloromethane at room temperature. The solid product isolated by silica gel chromatography in 58% yield from **7** showed that it was a 1:6 mixture of **8** and **9** as determined by the ^{1}H NMR spectrum. The desired isomer **9** could be obtained by fractional crystallization in 12% yield. Condensation of **9** with 1-[(ethoxycarbonyl)ethylidene]triphenylphosphorane[11] in hot benzene for a short period afforded stereoselectively the α,β-unsaturated ester **10** in 92% chromatographed yield. The 11% overall yield of **10** from **7** could be increased to 37% by performing the Wittig reaction with the mixture of **8** and **9** recovered from the mother liquor followed by chromatography. The *E* geometry of **10** was deduced from ^{1}H NMR spectrometry by absence of any NOE enhancement of the β-proton (δ 6.43) on irradiation of the α-methyl group (δ 1.83) (vice versa). An axial orientation of H-10 was indicated by $J_{10,9}$ = 11 and 6 Hz. Finally, reduction of the ester group of **10** was cleanly achieved with lithium triethylborohydride[3a] in THF at −15 °C, affording **11**[12] in 87% yield.

Next, an advanced top half model **25** was prepared by utilizing Diels–Alder reaction for installation of the requisite substitution pattern on the cyclohexene ring. Reaction of 1,6-bis[(trimethylsilyl)oxy]-2,4-hexadiene (**12**) with ethyl 2-acetoxyacrylate at 160–170 °C for 44 h followed by desilylation afforded a ca. 4:1 mixture of endo and exo adducts **13a** and **13b** in 78% yield (Scheme II). Separation of the stereoisomers in pure state by chromatography was extremely difficult since they showed similar polarity, but the major product **13a** could be obtained in 40% yield by fractional crystallization. The exo adduct **13b** was characterized as its dibenzoate **14b** which could be separated from the isomer **14a** by HPLC. The 1,2-cis stereochemistry of **13a** was supported by facile formation of the γ-lactone **15** (δ 3.72 for the angular proton), the property being applied to clean separation of the cycloadducts. Thus, treatment of the mixture of **13a** and **13b** with *p*-toluenesulfonic acid in refluxing benzene for 30 min followed by chromatography of the product afforded **15** in 62% yield from the diene **12**. During this procedure **13b** underwent deacetylation, giving triol **16**.

The Diels–Alder reaction of **12** was also carried out with trimethylsilyl 2-[(trimethylsilyl)oxy]acrylate. The adduct isolated by distillation was treated with methanol, and the

Scheme II[a]



[a] (a) CH_2=C(OAc)COOEt, xylene, 160–170 °C, then EtOH; (b) TsOH, PhH, reflux; (c) CH_2=C($OSiMe_3$)-$COOSiMe_3$, xylene, 160 °C, then MeOH followed by heating in xylene; (d) Me_2C=C(OMe)$OSiEt_3$, DMF; (e) Ac_2O, DMAP, Et_3N, then HF-MeCN; (f) oxalyl chloride, Me_2SO, CH_2Cl_2, then Et_3N; (g) $Zn(BH_4)_2$, then $ClCH_2OMe$, *i*-Pr_2NEt; (h) 2 equiv of $NaN(Me_3Si)_2$, THF, then *n*-Bu_4NOH, Me_2SO_4, CH_2Cl_2; (i) PCC, CH_2Cl_2, then DBU, CH_2Cl_2; (j) Ph_3P=C(Me)COOEt, PhH; (k) $LiB(Et)_3H$, THF.

desilylated product was heated in xylene for lactonization to afford dihydroxy γ-lactone **17** in 61% overall yield. Transformation of **17** into **15** was carried out by three steps in 80% overall yield: O-triethylsilylation of the primary alcohol,[13] O-acetylation of the tertiary hydroxyl group, and desilylation with HF in acetonitrile.[14]

Swern oxidation[15] of **15** afforded the α,β-unsaturated aldehyde **19** in 81% yield, resulting from a base-catalyzed isomerization of the initially produced β,γ-unsaturated aldehyde. The aldehyde group of **19** was then converted to the (methoxymethoxy)methyl group by two steps: reduction with zinc borohydride afforded **20**, which was O-alkylated with chloromethyl methyl ether under standard conditions to give **21**. Transformation of **21** into the spirotetronate **22** was performed, in 71% yield, according to the same procedure described for the des(methoxymethyl)methyl compound **5** except that sodium hexamethyldisilazide was used for the intramolecular Claisen condensation in place of LDA, which was less ef-

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(9) Wengel, A. S.; Reffstrup, T.; Boll, P. M. *Tetrahedron* **1979**, *35*, 2181.
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(11) House, H. O.; Rasmusson, G. H. *J. Org. Chem.* **1961**, *26*, 4278.
(12) In the NOE experiment for the *O*-tosylate of **11**, there was observed 12.5% enhancement of the γ-vinyl proton on irradiation of the α-*O*-methylene group.
(13) Yoshii, E.; Takeda, K. *Chem. Pharm. Bull.* **1983**, *31*, 4586.
(14) Newton, R. F.; Reynolds, D. P.; Finch, M. A. W.; Kelly, D. R.; Roberts, S. M. *Tetrahedron Lett.* **1979**, 3981.
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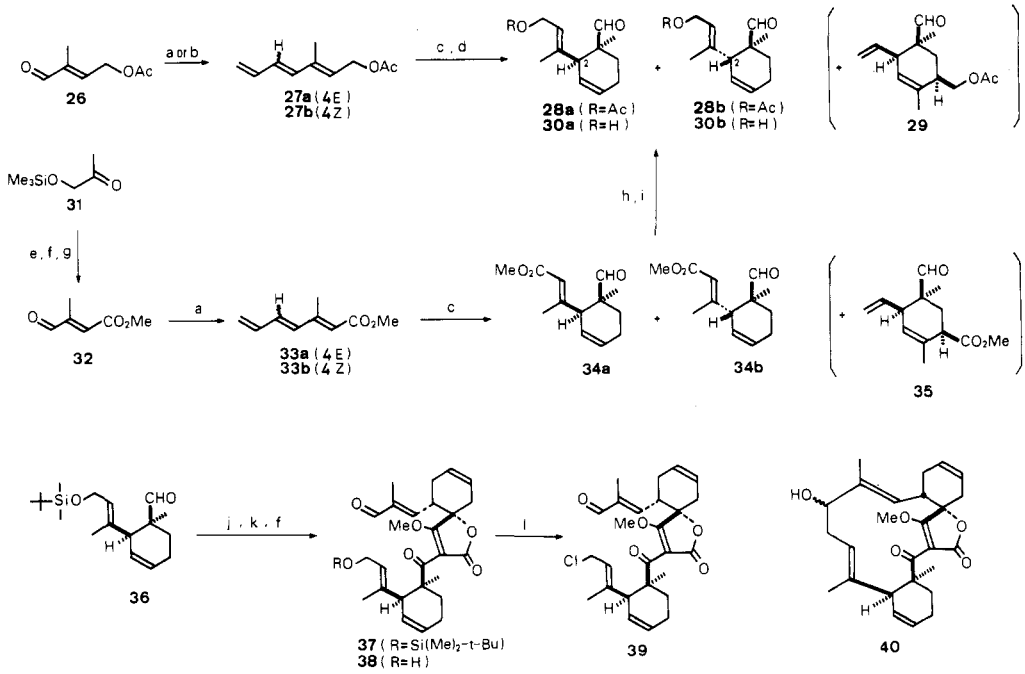
Scheme III[a]



[a] (a) $Ph_3P{=}CHCH{=}CH_2$; (b) $Ph_2(CH_2{=}CHCH_2)P{=}CHCH{=}CH_2$; (c) excess $CH_2{=}C(Me)CHO$, reflux; (d) KOH, MeOH; (e) $(EtO)_2P(O)CH_2COOMe$, NaH, THF; (f) HF, MeCN; (g) PCC, CH_2Cl_2; (h) $HOCH_2CH_2OH$, TsOH, PhH; (i) *i*-Bu_2AlH, then Me_2CO, H_2O, TsOH; (j) **11**, LDA, THF, HMPT, then **36**; (k) oxalyl chloride, Me_2SO, CH_2Cl_2, then Et_3N; (l) NCS, Me_2S, CH_2Cl_2.

fective presumably due to coordination to the oxygen functionality of the side chain.

Swern oxidation of **22** afforded the aldehyde **23a**, which without purification was subjected to a DBU-induced epimerization. The resulting mixture of **23a** and **23b** (ratio, 1:7) was treated with 1-[(ethoxycarbonyl)ethylidene]triphenylphosphorane in hot benzene to afford **24a** and **24b** in 6% and 32% chromatographed yields from **22**, respectively. The ^1H NMR data for **24b** regarding the chemical shift of β-proton of the unsaturated ester (δ 6.43) and the coupling pattern of H-10 ($J_{10,9}$ = 10 and 6 Hz) were in excellent agreement with those for **10**. Finally, the ester **24b** was reduced with lithium triethylborohydride in THF at −78 °C to afford **25** in 90% yield.

With the top half models synthesized, our attention was next directed toward joining them with an appropriate bottom half model to create α-acyltetronate structure. Thus, compound **30a**, which is a monocyclic model of the octalin moiety of tetronolide (or kijanolide), was prepared by utilizing Diels–Alder reaction of methacrolein with either triene **27a** or **33a**.

Wittig reaction of **26**[16] with allylidenetriphenylphosphorane[17] produced a 2:3 mixture of (2*E*,4*E*)- and (2*E*,4*Z*)-trienes **27a** and **27b**[18] in 56% chromatographed yield (Scheme III). Improvement of the ratio up to 4:1 (46% combined yield) could have been achieved by switching the ylide to allylallylidenediphenylphosphorane.[19] When the 4:1 mixture of **27a** and **27b** was allowed to react with a large excess of methacorlein at the reflux temperature, only the 4*E* isomer **27a** entered the cycloaddition to afford a mixture of **28a**, **28b**, and **29**[20] (ratio, 9:1:5) in 86% combined yield based on **27a**. The major product **28a** and its stereoisomer **28b** arising from addition of the dienophile at the terminal diene system of **27a** (endo and exo mode, respectively) could not be separated. Their structures were deduced from ^1H NMR spectral analysis of the mixture, the indicated stereochemistries being assigned on the basis of a diagnostic difference in the chemical shifts of H-2: δ 2.79 for **28a** and δ 3.14 for **28b**, which is deshielded by the vicinal cis aldehyde group. Saponification of the mixture of the Diels–Alder products with methanolic KOH followed by silica gel chromatography afforded a 9:1 mixture of **30a** and **30b** (25% overall yield from **26**), which was separated on a 100-mg scale by MPLC.

An alternative synthesis of **30a** via Diels–Alder reaction of methyl 3-methylheptatrienoate **33a** was also carried out. Methyl 3-methyl-4-oxo-2(*E*)-butenoate (**32**),[21] the precursor of 33a, was prepared from [(trimethylsilyl)oxy]acetone (**31**) in 70% yield by a three-step sequence of reactions without purification of the intermediates: Wadsworth–Emmons reaction with methyl(diethoxyphosphinyl)acetate, desilylation, and oxidation with PCC. Reaction of **32** with allylidenetriphenylphosphorane produced a 3.5:1 mixture of (2*E*,4*E*)-trienoate **33a** and its 4*Z* isomer **33b** in 44% combined yield. Reaction of the mixture with methacrolein afforded an inseparable mixture of **34a** and **34b** (ratio, 5.4:1) in 77% yield based on **33a**. In this cycloaddition, formation of the isomer **35**[20] corresponding to **29** was less than 5%. The Diels–Alder product was then subjected to the following standard manipulation of the functional groups: ethylene ketalization of the aldehyde group, diisobutylaluminum hydride reduction of the ester group, and acid-catalyzed deketalization, affording a 5.4:1

(16) Wehrli, P. A.; Schaer, B. *Synthesis* **1977**, 649.
(17) House, H. O. Cronin, T. H. *J. Org. Chem.* **1965**, *30*, 1061. Corey, E. J.; Snider, B. B. *J. Am. Chem. Soc.* **1972**, *94*, 2549.
(18) Treatment of this mixture with iodine in dichloromethane provided a 3:1 mixture of (2*E*,3*E*)- and (2*Z*,3*E*)-trienes, but this material was not useful for us since these isomers could not be separated easily and furthermore both isomers reacted with methacrolein to give a complex mixture of cycloadducts.
(19) Vedejs, E.; Fang, H. W. *J. Org. Chem.* **1984**, *49*, 210.
(20) The stereochemistry of this regioisomer was assigned on the basis of the endo rule in Diels–Alder reaction.
(21) Sisido, K.; Kondo, K.; Nozaki, H.; Tuda, M.; Udo, Y. *J. Am. Chem. Soc.* **1960**, *82*, 2286.

mixture of **30a** and **30b** (24% overall yield from **32**). Of the two routes to **30a** described above, which provided comparable yields, the latter one starting with **31** is preferable in terms of multigram preparation.

We proceeded further to the coupling of the top and bottom halves **11** and **30a**. The dianion of **11** generated with LDA in THF was treated with the *tert*-butyldimethylsilyl ether of **30a** (compound **36**) in the presence of HMPT to give a carbinol product,[22] which on Swern oxidation afforded the acyltetronate **37** as a mixture of diastereomers in 43% chromatographed yield (for the sake of clarity only the structural formula of the desired isomer is shown in the Scheme III). The hydroxy compound **38** obtained by desilylation with HF–CH_3CN was subjected to MPLC to provide the diastereomers in a ratio of ca. 2:1 (40% combined yield). Each hydroxy aldehyde isomer was converted to the corresponding allylic chloride **39** by reaction with *N*-chslorosuccinimide and dimethyl sulfide.[23] The chlorides were rather unstable and on chromatographic purification decomposed slowly with loss of the *O*-methyl group. The instability of **39** could be attributable to a proximate arrangement of the allyl chloride system and β-methoxyvinyl ketone group on the cyclohexene ring, thus an internal S_N2' displacement of the chloride by the vinylogous ester being feasible.

Macrocyclization was first attempted with protected cyanohydrins of **39** according to the method of Takahashi and Tsuji,[24] but decomposition of the substrate occurred under standard conditions. An approach to the macrolide **40** by application of Sm(II)- and Li(0)-mediated reductive coupling methods[25,26] on **39** was also unsuccessful. Thus, some modifications of the strategy in which the acyltetronate moiety survives during the macrolide formation should be considered and will be a subject of further investigation.

Experimental Section

Infrared spectra were recorded on a Jasco IRA-1 grating spectrometer and were calibrated with the 1601-cm^{-1} absorption of polystyrene. Proton nuclear magnetic resonance spectra were taken on a JEOL PMX-60 (60 MHz), a Varian EM-390 (90 MHz), or a Varian XL-200 (200 MHz) spectrometer in deuteriochloroform unless otherwise noted. Chemical shifts are reported in parts per million relative to tetramethylsilane as an internal standard. Resonance patterns were described as s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, and br = broad. Low- and high-resolution mass spectra (EI-MS) were obtained on a JEOL JMS-D-300 spectrometer combined with a JEOL JMA-2000 data processing system. Gas–liquid partition chromatography (GLC) was performed with a Shimadzu GC-6A apparatus by FID or TCD mode using a 3 mm × 2 m column packed with 1.5% OV-17 on Chromosorb W or a 3 mm × 3 m column packed with 5% OV-17 or 5% SE-30 on Shimalite (flow rate = 32 mL/min, He, at room temperature), respectively. Liquid chromatography under medium and high pressures was carried out with a UVILOG Model ALPC-100 and a Waters Model 6000A chromatographs, respectively. For chromatography, the following adsorbents were used: E. Merck silica gel 60 (70–230 or 230–400 mesh) or Fuji-Davison BW-200 (150–325 mesh) for column chromatography; Wako precoated silica gel 70 F-254 plates for analytical thin-layer chromatography. Dry solvents and reagents were obtained by using standard procedures: THF and ether were distilled under argon atmosphere from lithium aluminum hydride shortly before use; aromatic solvents, amines, HMPT, Me_2SO, and DMF were distilled from calcium hydride under atmospheric or reduced pressure and stored over 4A molecular sieves;[27] dichloromethane was distilled from phosphorus pentoxide. Anhydrous magnesium sulfate was used for drying all organic solvent extracts in workup, and removal of the solvents were performed with a rotary evaporator. Melting points were determined by using a Yanagimoto micromelting point apparatus. All melting points and boiling points are uncorrected. Elemental combustion analysis were performed by the Microanalytical Laboratory of this university.

(3a*R,7a*S**)-7a-Hydroxy-3a,4,7,7a-tetrahydro-1(3*H*)-isobenzofuranone (4).** A solution of **3** (20.14 g, 0.146 mol) in dry HMPT (25.4 mL, 0.146 mol) and dry THF (200 mL) was added dropwise to a cold (ca. −75 °C) stirred solution of lithium diisopropylamide [prepared from diisopropylamine (24.6 mL, 0.176 mol) and *n*-butyllithium (1.56 M in hexane, 112 mL, 0.175 mol) in dry THF (400 mL) under argon atmosphere]. After 30 min, the solution was transferred with a stainless steel double-tip needle into a cold (ca. −75 °C) stirred solution of triethyl phosphite (48.45 g, 0.292 mol) in dry THF (500 mL) which had been saturated with oxygen for 25 min. The combined solutions were allowed to warm to room temperature over 1.5 h under continued introduction of dry oxygen, and then the bulk of the THF was removed under reduced pressure. The remaining solution was neutralized with 5% HCl and diluted with ether. The organic phase was washed with saturated brine, dried, and concentrated. The residue was distilled to give **4** (16.39 g, 73%) as a colorless oil, bp 112–117 °C (0.2–0.3 torr), which solidified on standing. The analytical sample was obtained by recrystallization from chloroform–hexane: mp 90–91 °C; IR (KBr) 3480, 1790 cm^{-1}; ^1H NMR (200 MHz) δ 2.00 (dm, *J* = ca. 18 Hz, 1 H, H-7), 2.26 (dm, *J* = ca. 18 Hz, 1 H, H-7), 2.38–2.60 (m, 2 H, H-4), 2.77 (qm, *J* = ca. 8 Hz, 1 H, H-3a), 2.91 (s, 1 H, OH), 3.90 (t, *J* = 8 Hz, 1 H, H-3), 4.43 (dd, *J* = 8, 6 Hz, 1 H, H-3), 5.77 (br s, 2 H, H-5 and H-6); MS, *m/e* 136 ($M^+ - H_2O$), 96, 55 (base peak). Anal. Calcd for $C_8H_{10}O_3$: C, 62.33; H, 6.54. Found: C, 62.49; H, 6.52.

(5*R,10*S**)-10-(Hydroxymethyl)-4-methoxy-1-oxaspiro[4.5]deca-3,7-dien-2-one (7).** A solution of **4** (18.5 g, 0.12 mol) in dry triethylamine (50 mL) was treated with acetic anhydride (11.4 mL, 0.12 mol) and 4-(dimethylamino)pyridine (2.93 g, 0.024 mol) at room temperature. After 10 min, triethylamine was removed under reduced pressure, and the residue was treated with 10% HCl (100 mL) and ether (200 mL). The ether layer was separated, and the water layer was extracted with ether. The combined ether extracts were washed with saturated aqueous $NaHCO_3$ and saturated brine, dried, and concentrated to afford **5** (23.6 g, ca. 100%) as a crystalline solid (essentially pure on TLC, R_f 0.49, 1:3 hexane–ether). A portion of this material was recrystallized from chloroform–hexane: mp 59–60.5 °C; IR (KBr) 1790, 1750 cm^{-1}; ^1H NMR (200 MHz) δ 2.08 (dm, *J* = ca. 16 Hz, 1 H, H-4), 2.12 (s, 3 H, OAc), 2.36 (dm, *J* = ca. 16 Hz, 1 H, H-4), 2.45 (dm, *J* = ca. 16 Hz, 1 H, H-7), 2.61 (dm, *J* = ca. 16 Hz, 1 H, H-7), 3.22 (ddd, *J* = 9, 8, 6.5, 2.5 Hz, 1 H, H-3a), 3.84 (dd, *J* = 9, 8 Hz, 1 H, H-3), 4.58 (t, *J* = 9 Hz, H-3), 5.80–6.03 (m, 2 H, H-5 and H-6). Anal. Calcd for $C_{10}H_{12}O_4$: C, 61.22; H, 6.16. Found: C, 61.26; H, 6.09.

A solution of the acetate **5** (12.0 g, 61.2 mmol) obtained above in dry THF (50 mL) was cooled to −78 °C, and to the solution was added dropwise a cold solution of lithium diisopropylamide [prepared from diisopropylamine (18.9 mL, 135 mmol) and *n*-butyllithium (1.56 M in hexane, 86.2 mL, 134 mmol) in dry THF (100 mL)]. The mixture was allowed to warm to room temperature over 1 h and then poured into a mixture of ether (200 mL) and water (200 mL). The water layer was separated, acidified with 6 N HCl (pH ca. 1), and extracted with ethyl acetate. The extract was washed with saturated brine, dried, and concentrated under reduced pressure to give crude **6**. This material was dissolved in methanol (300 mL), and the solution was neutralized with 10% methanolic tetra-*n*-butylammonium hydroxide, using phenolphthalene as a indicator, and then concentrated under reduced pressure. The residue was dissolved in dichloromethane, and after

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being dried with anhydrous magnesium sulfate, the solution (550 mL) was treated with dimethyl sulfate (7.42 mL, 78.4 mmol) at room temperature for 12 h. The mixture was concentrated under reduced pressure, and the residual crude **7** was purified by silica gel chromatography (elution with 9:1 AcOEt–hexane) to give pure **7** as a solid (7.90 g, 61%) (R_f = 0.50, AcOEt). The analytical sample was obtained by recrystallization from chloroform–hexane: mp 97–98 °C; IR (KBr) 3480, 1740, 1630 cm^{-1}; ^1H NMR (200 MHz) δ 2.20–2.62 (m, 5 H), 3.55 (dd, J = 11, 6 Hz, 1 H, C*H*HOH), 3.80 (dd, J = 11, 4.5 Hz, 1 H, C*H*HOH), 3.86 (s, 3 H, OCH_3), 5.03 (s, 1 H, H-3), 5.62 (dm, J = ca. 8 Hz, 1 H, H-7 or H-8), 5.78 (dm, J = ca. 8 Hz, 1 H, H-7 or H-8); MS, m/e 210 (M^+), 127, 69 (base peak). Anal. Calcd for $C_{11}H_{14}O_4$: C, 62.85; H, 6.71. Found: C, 63.13; H, 6.72.

(5*R,10*S**)-4-Methoxy-2-oxo-1-oxaspiro[4.5]deca-3,7-diene-10-carbaldehyde (9).** A solution of **7** (5.82 g, 27.7 mmol) in dichloromethane (90 mL) was added dropwise to a stirred suspension of pyridinium chlorochromate (9.47 g, 43.9 mmol) in the same medium (60 mL) at room temperature. After continued stirring for 1 h, the reaction mixture was diluted with ether and filtered through a column of Florisil (12 g). The filtrate was concentrated under reduced pressure to give crude **8** as an oil: ^1H NMR (60 MHz) δ 9.73 (d, J = 2 Hz, CHO). The crude aldehyde **8** was dissolved in dry dichloromethane (100 mL), and the solution was treated with DBU (0.41 mL) at room temperature for 18 h. The mixture was concentrated under reduced pressure, and the residue was subjected to chromatography (silica gel, 70 g; elution with 3:1 AcOEt–hexane) to give a 1:6 mixture of **8** and **9** (3.37 g, 58%) as a crystalline solid (R_f = 0.32, ether). The pure sample of **9** was obtained by recrystallization of the mixture from chloroform–hexane: mp 130–131 °C; IR (KBr) 1740, 1630 cm^{-1}; ^1H NMR (200 MHz) δ 2.10 (dm, J = ca. 16 Hz, 1 H, H-6), 2.30–2.45 (m, 1 H, H-9), 2.55–2.80 (m, 3 H, H-6, H-9, and H-10), 3.94 (s, 3 H, OCH_3), 5.13 (s, 1 H, H-3), 5.69 (ddd, J = ca. 10, 4, 4 Hz, 1 H, H-7 or H-8), 5.86 (ddd, J = ca. 10, 4, 4 Hz, 1 H, H-7 or H-8), 9.53 (d, J = 2 Hz, 1 H, CHO); MS, m/e 208 (M^+), 151, 69 (base peak). Anal. Calcd for $C_{11}H_{12}O_4$: C, 63.45; H, 5.81. Found: C, 63.45; H, 5.82.

Ethyl 3-[(5*R,10*R**)-4-Methoxy-2-oxo-1-oxaspiro[4.5]deca-3,7-dien-10-yl]-2-methyl-2(*E*)-propenoate (10).** A mixture of **8** and **9** obtained from **7** (11.49 g, 55.2 mmol) by PCC oxidation followed by treatment with DBU as described above was recrystallized from chloroform–hexane to afford pure **9** (1.33 g, 6.39 mmol). This material was dissolved in dry benzene (40 mL), and after addition of 1-[(ethoxycarbonyl)ethylidene]triphenylphosphorane (3.80 g, 10.5 mmol), the solution was stirred and heated to the reflux temperature over 15 min and then allowed to cool to room temperature. The reaction mixture was concentrated under reduced pressure, and the residue was extracted with ether. The ether extract was subjected to chromatography (silica gel, 30 g; elution with 1:20 ether–dichloromethane) to give **10** (1.72 g, 92% from **9**). The mixture of **8** and **9** recovered from the mother liquor was also treated with the phosphorane under the same conditions. Chromatography (silica gel, 150 g; elution with 1:30 ether–dichloromethane) of the product afforded 4.19 g of **10** (combined yield, 5.91 g; 37% from **7**). The analytical sample was obtained by recrystallization from chloroform–hexane as colorless needles: mp 108–109 °C; IR (KBr) 1750, 1700, 1635 cm^{-1}; ^1H NMR (200 MHz) δ 1.25 (t, J = 7 Hz, 3 H, CH_2CH_3), 1.83 (d, J = 1.5 Hz, 3 H, =CCH_3), 2.12 (br d, J = ca. 18 Hz, 2 H, H-6′ and H-9′), 2.22–2.42 (m, 1 H, H-9′), 2.70 (dm, J = 18 Hz, 1 H, H-6′), 2.98 (td, J = 11, 6 Hz, 1 H, H-10′), 3.82 (s, 3 H, OCH_3), 4.12 and 4.20 (dq, J = 10, 7 Hz, 2 H, CH_2CH_3), 5.01 (s, 1 H, H-3′), 5.70 (br d, J = ca. 10 Hz, 1 H, H-7′ or H-8′), 5.85 (br d, J = ca. 10 Hz, 1 H, H-7′ or H-8′), 6.43 (dq, J = 11, 1.5 Hz, 1 H, H-3); MS, m/e 292 (M^+), 246, 165 (base peak), 69. Anal. Calcd for $C_{16}H_{20}O_5$: C, 65.74; H, 6.90. Found: C, 65.81; H, 6.82.

(5*R,10*R**)-10-[3-Hydroxy-2-methyl-1(*E*)-propen-1-yl]-4-methoxy-1-oxaspiro[4.5]deca-3,7-dien-2-one (11).** A stirred solution of **10** (2.36 g, 8.08 mmol) in dry THF (20 mL) was cooled to ca. −20 °C under nitrogen atmosphere, and lithium triethylborohydride (1 M in THF, 16.2 mL) was added dropwise to the solution. After continued stirring for 15 min, the reaction mixture was quenched with 5% HCl and extracted with ether. The ether extract was washed with saturated brine, dried, and concentrated. The residue was subjected to chromatography (silica gel, 70 g; elution with 6:1 AcOEt–hexane) to afford **11** (1.76 g, 87%) as a crystalline solid. The analytical sample was obtained by recrystallization from chloroform–hexane: mp 121–123 °C; ^1H NMR (200 MHz) δ 1.37 (br t, J = ca. 5 Hz, 1 H, OH), 1.65 (br s, 3 H, 2′-CH_3), 2.00–2.35 (m, 3 H, H-6 and H-9), 2.68 (dm, J = 18 Hz, 1 H, H-6), 2.88 (dt, J = 10, 6 Hz, 1 H, H-10), 3.80 (s, 3 H, OCH_3), 3.94 (br d, J = 5 Hz, 2 H, H-3′), 4.99 (s, 1 H, H-3), 5.17 (br d, J = 10 Hz, 1 H, H-1′), 5.65 and 5.82 (dm, J = ca. 10 Hz, H-7 and H-8); MS, m/e 251 (M^+ + 1), 250 (M^+), 114 (base peak). Anal. Calcd for $C_{14}H_{18}O_4$: C, 67.18; H, 7.25. Found: C, 66.87; H, 7.32.

O-Tosylate of **11** was obtained by a standard procedure (*p*-toluenesulfonic acid anhydride/triethylamine in dichloromethane) as an oil: ^1H NMR (90 MHz) δ 1.67 (br s, 3 H, 2′-CH_3), 2.48 (s, 3 H, Ar CH_3), 3.85 (s, 3 H, OCH_3), 4.33 (br s, 2 H, H-3′), 5.03 (s, 1 H, H-3), 5.17 (br d, J = 10 Hz, 1 H, H-1′), 5.73 (m, 2 H, H-7 and H-8), 7.43 (d, J = 8.5 Hz, 2 H, Ar H), 7.82 (d, J = 8.5 Hz, 2 H, Ar H).

1,6-Bis[(trimethylsilyl)oxy]-2,4-hexadiene (12). Chlorotrimethylsilane (14.4 mL, 113 mmol) was added over ca. 5 min to a stirred suspension of 2,4-hexadiene-1,6-diol[28] (5.38 g, 47.2 mmol) in dry dichloromethane (95 mL) and *N*,*N*-diisopropylethylamine (21.8 mL, 125 mmol). After continued stirring at room temperature for 5 min, the reaction mixture was diluted with ether and washed with cold water. The organic layer was dried and concentrated under reduced pressure to give crude **12**, which was subjected to distillation: bp 86–89 °C (1 torr) (11.6 g, 95%); ^1H NMR (60 MHz) δ 0.12 (s, 18 H, Me_3Si), 4.17 (d, J = 4 Hz, 4 H, CH_2), 5.5–6.4 (m, 4 H, vinyl H).

Diels–Alder Reaction of 12 and Ethyl 2-Acetoxyacrylate. A solution of **12** (11.6 g, 44.8 mmol), ethyl 2-acetoxyacrylate[29] (7.45 g, 4.72 mmol), and 4,4′-thiobis(6-*tert*-butyl-5-methylphenol) (0.48 g) in dry *p*-xylene (25 mL) was placed in a pressure bottle and heated in an oil bath at 160–170 °C for 44 h. The solvent was removed under reduced pressure, and the residue was dissolved in ethanol (150 mL). After being stirred at room temperature overnight, the solution was concentrated under reduced pressure. The residue was subjected to chromatography (silica gel, 200 g; elution with 3:1 AcOEt–hexane) to give a mixture of **13a,b** and 2,4-hexadiene-1,6-diol as a viscous oil. The mixture was extracted with chloroform to remove the diene (0.64 g), and the extract was concentrated to afford **13a,b** as a white solid (8.26 g, 68% or 78% yield based on the diene consumed). This material was crystallized from AcOEt to give essentially pure **13a** (4.30 g, 35% or 40% yield based on the diene consumed) as colorless needles. The analytical sample was obtained by recrystallization from AcOEt–hexane: mp 126–127 °C; IR (KBr) 3525, 3370, 1740 cm^{-1}; ^1H NMR (200 MHz) δ 1.28 (t, J = 7 Hz, 3 H, CH_2CH_3), 1.76 (br s, 2 H, OH), 1.99 (dd, J = 14, 12 Hz, 1 H, H-6), 2.07 (s, 3 H, $OCOCH_3$), 2.25 (br m, 1 H, H-5), 2.52–2.70 (m, 2 H, H-2 and H-6), 3.58 (dd, J = 10.5, 5 Hz, 1 H, 2-C*H*HO), 3.59 (d, J = 5 Hz, 2 H, 5-CH_2O), 3.73 (dd, J = 10.5, 5 Hz, 1 H, 2-C*H*HO), 4.23 (qm, J = 7 Hz, 2 H, CH_2CH_3), 5.71 (ddd, J = 10, 4.5, 2.5 Hz, 1 H, H-3), 5.89 (br d, J = 10 Hz, 1 H, H-4); MS, m/e 273 (M^+ + 1), 255, 237, 213, 152 (base peak). Anal. Calcd for $C_{13}H_{20}O_6$: C, 57.34; H, 7.40. Found: C, 57.32; H, 7.47.

A ca. 2:1 mixture of **13a** and **13b** (32.5 mg, 0.12 mmol) recovered from the mother liquor of the recrystallization was dissolved in dry dichloromethane (0.2 mL), and the solution was treated with dry pyridine (48.5 μL, 0.60 mmol) and benzoyl chloride (42.0 μL, 0.36 mmol) at room temperature for 15 min. The crude product isolated by the usual manner was purified by chromatography (silica gel, 2 g; elution with 1:4 AcOEt–hexane) to give a mixture of **14a** and **14b** (40 mg), which was separated by HPLC (μ-Porasil, elution with 1:6 AcOEt–hexane, RI detection) to afford **14b** (6.3 mg) and **14a** (18.5 mg) as oils in the order of elution (relative t_R 1.18). **14a**: ^1H NMR (200 MHz) δ 1.16 (t, J = 7 Hz, 3 H, CH_2CH_3), 2.03 (dd, J = 14, 12 Hz, 1 H, H-6), 2.13 (s, 3 H, $OCOCH_3$), 2.57 (m, 1 H, H-5), 2.87 (dd, J = 14, 6 Hz, 1 H, H-6), 3.02 (m, 1 H, H-2), 4.09 (q, J = 7 Hz, 2 H, CH_2CH_3), 4.27 (dd, J = 11, 5 Hz, 1 H, 2-C*H*HO), 4.28 (d, J = 6 Hz, 2 H, 5-CH_2O), 4.38 (dd, J = 11, 5 Hz, 1 H, 2-C*H*HO), 5.83 (ddd, J = 10, 5, 2 Hz, 1 H, H-3),

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5.98 (dd, J = 10, ca. 1 Hz, 1 H, H-4), 7.44–7.54 (m, 4 H, Ar H), 7.58–7.66 (m, 2 H, Ar H), 8.03–8.12 (m, 4 H, Ar H); MS, m/e 480 (M^+), 176 (base peak), 148, 105, 77. **14b**: ^1H NMR (200 MHz) δ 1.25 (t, J = 7 Hz, 3 H, CH_2CH_3), 1.96 (s, 3 H, $OCOCH_3$), 2.07 (dd, J = 14, 12 Hz, 1 H, H-6), 2.34 (dd, J = 14, 6 Hz, 1 H, H-6), 2.71 (m, 1 H, H-5), 3.64 (m, 1 H, H-2), 4.24 (q, J = 7 Hz, 2 H, CH_2CH_3), 4.27 (d, J = 7 Hz, 2 H, 5-CH_2O), 4.30 (dd, J = 11, 5 Hz, 1 H, 2-CHHO), 4.45 (dd, J = 11, 6 Hz, 1 H, 2-CHHO), 5.83 (d, J = 10 Hz, 1 H, H-4), 5.93 (ddd, J = 10, 4, 1 Hz, 1 H, H-3), 7.42–7.52 (m, 4 H, Ar H), 7.56–7.64 (m, 2 H, Ar H), 8.03–8.07 (m, 4 H, Ar H); MS, m/e 480 (M^+), 176 (base peak), 148, 105, 77.

(3a*R,6*S**,7a*S**)-7a-Acetoxy-6-(hydroxymethyl)-3a,6,7,7a-tetrahydro-1(3*H*)-isobenzofuranone (15) and Ethyl (1*R**,2*R**,5*S**)-1-Hydroxy-2,5-bis(hydroxymethyl)cyclohex-3-ene-1-carboxylate (16).** A solution of **12** (35.0 g, 0.136 mol), ethyl 2-acetoxyacrylate (20.5 g, 0.130 mol), and 2,6-di-*tert*-butyl-4-methylphenol (1.0 g) in *p*-xylene (60 mL) was heated in a pressure bottle at 150–160 °C for 69 h. The solvent xylene was removed under reduced pressure, and the residual oil was subjected to distillation to give a mixture of cycloadducts as a colorless oil (45.83 g), bp 73–140 °C (0.6–0.05 torr). A portion of this material (23.55 g, 56.6 mmol) was subjected to desilylation as described above, and the crude product was dissolved in benzene (30 mL) and *p*-toluenesulfonic acid monohydrate (1.08 g, 5.68 mmol) was added. After being heated at the reflux temperature for 30 min, the solution was allowed to cool, diluted with AcOEt, washed with saturated aqueous $NaHCO_3$ and saturated brine, dried, and concentrated. The residual solid was crystallized from AcOEt–hexane to give essentially pure **15** (5.55 g) (R_f 0.43, 1:5 hexane–AcOEt). The solvent of the mother liquor was evaporated, and the residue was subjected to chromatography (silica gel, 200 g; elution with 3:1 AcOEt–hexane) to afford additional amount of **15** (2.10 g) (60% combined yield) and **16** (2.19 g) (R_f 0.33, AcOEt). The analytical sample of **15** was obtained by recrystallization from chloroform–hexane as colorless needles: mp 116–117 °C; IR (KBr) 3500, 1780, 1725 cm^{-1}; ^1H NMR (200 MHz) δ 1.59 (dd, J = 14, 11 Hz, 1 H, H-7), 2.12 (s, 3 H, $OCOCH_3$), 2.14 (dd, J = 14, 4 Hz, 1 H, H-7), 2.66 (br, 1 H, H-6), ca. 3.62 (m, 1 H, H-3a), 3.67 (dd, J = 11, 6 Hz, 1 H, 6-CHHO), 3.77 (dd, J = 11, 5 Hz, 1 H, 6-CHHO), 3.84 (dd, J = 10, 9 Hz, 1 H, H-3), 4.67 (t, J = 9 Hz, 1 H, H-3), 5.70 (ddd, J = 10, 4, 3 Hz, 1 H, H-5), 5.96 (d, J = 10 Hz, 1 H, H-4); MS, m/e 227 (M^+ + 1), 196, 167, 166, 136, 92, 91 (base peak), 43. Anal. Calcd for $C_{11}H_{14}O_5$: C, 58.40; H, 6.24. Found: C, 58.13; H, 6.51.

The analytical sample of **16** was obtained by recrystallization from chloroform–hexane: mp 75–76 °C; IR (KBr) 3200, 1715 cm^{-1}; ^1H NMR (200 MHz) δ 1.30 (t, J = 7 Hz, 3 H, CH_2CH_3), 1.89 (d, J = 14 Hz, 1 H, H-6), 2.37 (dd, J = 14, 9 Hz, 1 H, H-6), 2.55 (br m, 1 H, H-5), 2.83 (br m, 1 H, H-2), 3.60 (dd, J = 11, 3 Hz, 1 H, 5-CHHO), 3.75 (d, J = 6 Hz, 2 H, 2-CH_2O), 3.76 (dd, J = 11, 5 Hz, 1 H, 5-CHHO), 4.26 (q, J = 7 Hz, 2 H, CH_2CH_3), ca. 4.25 (br, 3 H, OH), 5.64 (dq, J = 10, 1.5 Hz, 1 H, H-3), 5.80 (ddd, J = 10, 3, ca. 3 Hz, 1 H, H-4); MS, m/e 231 (M^+ + 1), 195, 79 (base peak). Anal. Calcd for $C_{11}H_{18}O_5$: C, 57.38; H, 7.88. Found: C, 57.61; H, 7.91.

(3a*R,6*S**,7a*S**)-7a-Hydroxy-6-(hydroxymethyl)-3a,6,7,7a-tetrahydro-1(3*H*)-isobenzofuranone (17) and Conversion to 15.** A solution of **12** (18.12 g, 70 mmol), trimethylsilyl 2-[(trimethylsilyl)oxy]acrylate[30] (17.26 g, 74.4 mmol), and 4,4′-thiobis(6-*tert*-butyl-5-methylphenol) (0.88 g) in dry *p*-xylene (35 mL) was heated in a sealed tube at ca. 160 °C for 46 h. Removal of the solvent under reduced pressure followed by distillation of the residue afforded an oil (22.11 g, 64%), bp 105–135 °C (0.06 torr). A solution of the cycloaddition product (23.95 g) in methanol (240 mL) was stirred at room temperature overnight and then concentrated under reduced pressure. The residue was dissolved in xylene (50 mL), and the solution was heated under reflux for 30 min and then concentrated under reduced pressure to leave a solid, which was recrystallized from AcOEt to afford **17** (8.06 g), mp 112–113 °C. An additional amount of **17** (0.44 g) (61% combined yield from **12**) was obtained by chromatography (silica gel, 50 g; elution with AcOEt) of an oil recovered from the mother liquor: ^1H NMR (200 MHz, $CDCl_3/CD_3OD$) δ 1.53 (dd, J = 14, 10 Hz, 1 H, H-7), 1.96 (dd, J = 14, 6 Hz, 1 H, H-7), 2.64 (br m, 1 H, H-6), 3.02 (br m, 1 H, H-3a), 3.61 (d, J = 6 Hz, 2 H, 6-CH_2), 3.82 (dd, J = 10, 9 Hz, 1 H, H-3), 4.55 (t, J = 10 Hz, 1 H, H-3), 5.72 (ddd, J = 10, 4, 2.5 Hz, 1 H, H-4), 5.95 (br d, J = 10 Hz, 1 H, H-5); MS, m/e 185 (M^+ + 1), 154 (base peak). Anal. Calcd for $C_9H_{12}O_4$: C, 58.77; H, 6.59. Found: C, 58.69; H, 6.57.

1-Methoxy-2-methyl-1-[(triethylsilyl)oxy]propene (27.0 g, 125 mmol) was added to a solution of **17** (7.70 g, 41.8 mmol) in dry DMF (15 mL). After being heated at 85 °C for 5.5 h, the mixture was concentrated under reduced pressure to give crude **18** as an oil, which was allowed to react with acetic anhydride (5.0 mL) and 4-(dimethylamino)pyridine (1.0 g) in triethylamine (65 mL) at room temperature for 20 min. The crude *O*-acetate of **18** obtained by usual workup was dissolved in a 1% HF solution in acetonitrile (100 mL), and the solution was stirred at room temperature for 1 h. The bulk of the solvent was evaporated, and the remaining solution was diluted with ether. The organic phase was washed with saturated aqueous $NaHCO_3$ and saturated brine, dried, and concentrated to give crude **15**. This material was crystallized from AcOEt to provide pure **15** (7.59 g, 80% from **17**), mp 116–117 °C.

(3a*R,7a*S**)-7a-Acetoxy-6-formyl-3a,4,7,7a-tetrahydro-1(3*H*)-isobenzofuranone (19).** A stirred solution of oxalyl chloride (1.90 mL, 21.8 mmol) in dry dichloromethane (35 mL) was cooled to −60 °C, and a solution of dimethyl sulfoxide (3.10 mL, 43.7 mmol) in the same medium (0.7 mL) was added dropwise. After 5 min, a solution of **15** (4.00 g, 17.7 mmol) in dichloromethane (20 mL) was introduced, and stirring of the mixture at −60 °C was continued for 25 min. The mixture was then kept at −30 °C and, after addition of triethylamine (13.9 mL, 99.7 mmol), allowed to warm to room temperature over 1 h. The reaction mixture was diluted with dichloromethane, washed with 5% HCl and saturated aqueous $NaHCO_3$, dried, and concentrated. The remaining solid was crystallized from chloroform–hexane to afford **19** (3.09 g), mp 120–121 °C. An additional amount of **19** (0.50 g) (91% combined yield) was obtained by chromatography (silica gel, 30 g; elution with 3:1 AcOEt–hexane) of an oil recovered from the mother liquor: IR ($CHCl_3$) 1790, 1740, 1685 cm^{-1}; ^1H NMR (200 MHz) δ 2.12 (s, 3 H, $OCOCH_3$), 2.40 (dm, J = ca. 17 Hz, 1 H, H-4), 2.63 (dd, J = 16, 2 Hz, 1 H, H-7), 2.75 (dm, J = 17 Hz, 1 H, H-4), 2.87 (br d, J = 16 Hz, 1 H, H-7), 3.45 (m, 1 H, H-3a), 3.84 (t, J = 9 Hz, 1 H, H-3), 4.64 (t, J = 9 Hz, 1 H, H-3), 7.00 (m, 1 H, H-5), 9.59 (s, 1 H, CHO); MS, m/e 182 (M^+ − CH_2CO), 164 (base peak), 134, 43. Anal. Calcd for $C_{11}H_{12}O_5$: C, 58.93; H, 5.39. Found: C, 58.65; H, 5.33.

(3a*R,7a*S**)-7a-Acetoxy-6-[(methoxymethoxy)methyl]-3a,4,7,7a-tetrahydro-1(3*H*)-isobenzofuranone (21).** The crude **19** obtained by Swern oxidation of **15** (6.59 g, 29.2 mmol) as described above was dissolved in a mixture of dry benzene (60 mL) and dry ether (250 mL), and to the stirred solution at room temperature was added dropwise an ethereal solution of zinc borohydride[31] (0.147 M, 202 mL, 29.7 mmol). After the addition was complete, the reaction mixture was stirred for 40 min and treated with saturated brine (300 mL) and then with a 3:8 mixture of acetic acid and brine (300 mL). The phases were separated, and the aqueous phase was extracted with AcOEt. The combined organic phases were dried and concentrated under reduced pressure to leave crude product, which was chromatographed (silica gel, 180 g; elution with 3:1 AcOEt–hexane) to afford **20** (5.58 g, 85% from **15**) as an oil: R_f 0.31 (1:3 hexane–AcOEt); IR ($CHCl_3$) 3620, 3480, 1780, 1735 cm^{-1}; MS, m/e 227 (M^+ + 1), 210, 209, 166, 43 (base peak).

Chloromethyl methyl ether (7.84 g, 97.4 mmol) was added dropwise to a stirred solution of **20** (5.58 g, 24.7 mmol) and *N*,*N*-diisopropylethylamine (25.2 g, 195 mmol) in dry dichloromethane (100 mL) at room temperature. After 1.5 h, the mixture was diluted with dichloromethane, washed with saturated brine, dried, and concentrated under reduced pressure. The residue was subjected to chromatography (silica gel, 250 g; elution with 3:1 AcOEt–hexane) to give **21** (5.55 g, 70% from **15**) as an oil: R_f 0.37 (1:1 hexane–AcOEt); IR ($CHCl_3$) 1780, 1740 cm^{-1}; ^1H NMR (200 MHz) δ 2.12 (s, 3 H, $OCOCH_3$), ca. 2.12 (m, 1 H, H-4), 2.42 (dm, J = ca. 14 Hz, 1 H, H-4), 2.49 (d, J = 17 Hz, 1 H, H-7), 2.60 (d,

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(113 mL, 0.81 mol) and dry ether (400 mL) was cooled with ice–water, and a solution of chlorotrimethylsilane (102 mL, 0.804 mol) in dry ether (50 mL) was added dropwise. After the addition was complete, the reaction mixture was stirred at room temperature for 1 h. The slurry was filtered, and the filtrate was distilled to give **31** (86.4 g, 88%) as a colorless oil: bp 65–72 °C (45 torr); ^{1}H NMR (60 MHz) δ 0.13 (s, 9 H, Me_3Si), 2.13 (s, 3 H, CH_3), 4.10 (s, 2 H, CH_2).

A stirred slurry of NaH (60% in mineral oil, 35.50 g, 0.88 mol, washed with hexane) in dry THF (770 mL) was cooled with ice–water, and a solution of methyl (diethoxyphosphinyl)acetate (124.1 g, 0.591 mol) and **31** (86.4 g, 0.591 mol) in dry THF (100 mL) was added dropwise. After the addition was complete, the reaction mixture was stirred at room temperature for 1 h. The bulk of the THF was removed under reduced pressure, and the residue was neutralized with ice-cold dilute HCl and extracted with ether. The extract was washed with saturated brine, dried, and concentrated. The residual oil (91.5 g) was dissolved in a mixture of 55% HF (5 mL) and methanol (250 mL). After 5 min, the solution was concentrated under reduced pressure, and the residue was dissolved in dichloromethane (200 mL). The dichloromethane solution was dried and added to a stirred slurry of PCC (146.4 g, 0.679 mol) and Celite (100 g) in dry dichloromethane (800 mL) over 75 min. After the addition was complete, the mixture was stirred for 30 min and then diluted with ether (100 mL). The organic phase was filtered through a column of Florisil (100 g), and the filtrate was distilled to give **32** (52.58 g, 70% from **31**): bp 80–84 °C (18 torr); ^{1}H NMR (60 MHz) δ 2.15 (d, J = 2 Hz, 3 H, 3-CH_3), 3.80 (s, 3 H, OCH_3), 6.50 (q, J = 2 Hz, 1 H, H-2), 9.53 (s, 1 H, CHO).

Methyl (2*E*,4*E*)- and (2*E*,4*Z*)-3-Methylhepta-2,4,6-trienoates (33a,b). A solution of *n*-butyllithium (1.56 M in hexane, 57.7 mL, 90.0 mmol) was added dropwise to a stirred slurry of allyltriphenylphosphonium bromide (31.60 g, 82.5 mmol) in dry THF (340 mL) under nitrogen atmosphere. After the addition was complete, a solution of **32** (9.6 g, 75 mmol) in dry THF (100 mL) was introduced at room temperature over 10 min. After 10 min, the reaction mixture was quenched with ice–water and diluted with hexane. The organic phase was washed with saturated brine, dried, and concentrated. The residual oil was subjected to chromatography (silica gel, 100 g; elution with 6:1 chloroform–hexane) to give a 3.5:1 mixture of **33a** and **33b** as a colorless oil (5.13 g, 45%), bp 63–71 °C (2.0–2.5 torr). The analytical samples of these isomers were obtained by HPLC (μ-Porasil, elution with 1:300 ether–hexane, RI detection) (relative t_R of **33a**/**33b**, 1.15).

Compound **33a**: IR (neat) 1715, 1615 cm^{-1}; ^{1}H NMR (200 MHz) δ 2.32 (d, J = 1.5 Hz, 3 H, 3-CH_3), 3.73 (s, 3 H, OCH_3), 5.53 (dd, J = 21, 1.5 Hz, 1 H, H-7), 5.39 (d, J = 27 Hz, 1 H, H-7), 5.81 (br s, 1 H, H-2), 6.29 (d, J = 15 Hz, 1 H, H-4), 6.45 (ddd, J = 27, 21, 10 Hz, 1 H, H-6), 6.64 (dd, J = 15, 10 Hz, 1 H, H-5); MS, m/e 152 (M^+), 125, 93 (base peak); exact mass calcd for $C_9H_{12}O_2$ 152.0838, found 152.0854.

Compound **33b**: IR (neat) 1715, 1612 cm^{-1}; ^{1}H NMR (200 MHz) δ 2.32 (br s, 3 H, 3-CH_3), 3.74 (s, 3 H, OCH_3), 5.28 (d, J = 10 Hz, 1 H, H-7), 5.38 (d, J = 17 Hz, 1 H, H-7), 5.83 (br s, 1 H, H-2), 5.91 (d, J = 11 Hz, 1 H, H-4), 6.19 (t, J = 11 Hz, 1 H, H-5), 6.86 (ddd, J = 17, 11, 10 Hz, 1 H, H-6); MS, m/e 153 ($M^+ + 1$), 125, 95 (base peak); exact mass calcd for $C_9H_{12}O_2$ 152.0838, found 152.0873.

(1*R,2*R**)- and (1*R**,2*S**)-1-Methyl-2-[1-hydroxy-2(*E*)-buten-3-yl]-3-cyclohexene-1-carbaldehydes (30a,b).** (a) A solution of a 4:1 mixture of **27a** and **27b** (1.15 g, 6.9 mmol) obtained above and 4,4′-thiobis(2-*tert*-butyl-5-methylphenol) (ca. 5 mg) in methacrolein (5 mL) was heated under reflux for 18 h. Excess methacrolein was evaporated, and the residual oil was distilled with a Kugelrohr apparatus to collect the product (1.20 g), bp 100–140 °C (0.2 torr), which was found to contain **28a,b** (62%), **29** (31%), and low-boiling impurities by a programmed GLC (1.5% OV-17). A portion of the sample was subjected to preparative GLC to obtain a mixture **28a,b** and **29** (relative t_R of **28a,b**/**29**, 1.73; 10% OV-17, 5 mm × 1 m, 145 °C). These isomers were characterized by ^{1}H NMR (200 MHz): [**28a**] δ 1.12 (s, CCH_3), 1.62 (br s, $=CCH_3$), 2.07 (s, $OCOCH_3$), 2.79 (br s, H-2), 9.58 (s, CHO), [**28b**] 0.92 (s, CCH_3), 1.68 (br s, $=CCH_3$), 2.07 (s, $OCOCH_3$), 3.14 (br s, H-2), 9.50 (s, CHO), [**29**] 1.11 (s, 3 H, CCH_3), 1.74 (br s, 3 H, $=CCH_3$), 2.06 (s, 3 H, $OCOCH_3$), 2.36 (br m, 1 H, C*H*CH_2OCOCH_3), 2.79 (br t, J = ca. 6.5 Hz, 1 H, $=CCHC=$), 4.12 (dd, J = 11, 6 Hz, 1 H, C*H*$HOCOCH_3$), 4.23 (dd, J = 11, 3.5 Hz, 1 H, C*H*$HOCOCH_3$), 5.06 and 5.13 (m, 2 H, $=CH_2$), 5.38 (dm, J = ca. 5 Hz, 1 H, ring vinyl H), 5.62 (ddd, J = 17, 9, 8 Hz, 1 H, C*H*$=CH_2$), 9.50 (s, 1 H, CHO).

A sample of the Diels–Alder product (500 mg) obtained above was dissolved in 3% methanol KOH, and the solution was stirred at room temperature for 20 min. The product isolated by ether extraction was purified by chromatography (silica gel, 60 g; elution with 1:2 ether–hexane) to give a 9:1 mixture of **30a** and **30b** (244 mg, 19% from **26**), bp 107–113 °C (0.03 torr), which showed a single peak in GLC (OV-17). Anal. Calcd for $C_{12}H_{18}O_2$: C, 74.19; H, 9.34. Found: C, 73.95; H, 9.10. These isomers were separated by MPLC (10-μm silica gel, elution with 1:50 AcOEt–chloroform) and characterized by the following spectral data.

Compound **30a** (a colorless oil): IR (neat) 3370, 1705 cm^{-1}; ^{1}H NMR (200 MHz) δ 1.10 (s, 3 H, 1-CH_3), 1.43 (dt, J = 13, 5 Hz, 1 H, H-6), 1.56 (d, J = 1 Hz, 3 H, 3′-CH_3), 1.87 (ddd, J = 13, 8.5, 6 Hz, 1 H, H-6), 2.03–2.20 (m, 2 H, H-5), 2.34 (br s, 1 H, OH), 2.76 (br s, 1 H, H-2), 4.12 (d, J = 6 Hz, 2 H, H-1′), 5.47 (dm, J = ca. 10 Hz, 1 H, H-3 or H-4), 5.54 (tm, J = 6 Hz, 1 H, H-2′), 5.84 (dm, J = ca. 10 Hz, 1 H, H-3 or H-4), 9.56 (s, 1 H, CHO); MS, m/e 194 (M^+), 28 (base peak); exact mass calcd for $C_{12}H_{18}O_2$ 194.1306, found 194.1318.

Compound **30b** (a colorless oil): IR (neat) 3400, 1710 cm^{-1}; ^{1}H NMR (200 MHz) δ 0.92 (s, 3 H, 1-CH_3), 1.42 (br s, 1 H, OH), 1.47–1.88 (m, 2 H, H-6), 1.65 (br s, 3 H, 3′-CH_3), 2.08 (m, 2 H, H-5), 3.13 (br s, 1 H, H-2), 4.21 (d, J = 6.5 Hz, 2 H, H-1′), 5.48 (br t, J = 6.5 Hz, 1 H, H-2′), 5.58 (dm, J = ca. 10 Hz, 1 H, H-3 or H-4), 5.81 (dm, J = ca. 10 Hz, 1 H, H-3 or H-4), 9.45 (s, 1 H, CHO); MS, m/e 194 (M^+), 41 (base peak); exact mass calcd for $C_{12}H_{18}O_2$ 194.1306, found 194.1298.

(b) A solution of a 3.5:1 mixture of **33a** and **33b** (4.23 g, 27.8 mmol) in methacrolein (8.5 mL) was heated under reflux for 18 h. The crude product obtained by removal of excess methacrolein under reduced pressure was subjected to Kugelrohr distillation to give a colorless oil (3.69 g, 60%), bp 70–110 °C (0.12 torr), which in GLC showed two peaks with a peak area ratio of 1:20 (t_R 4.8 and 8.9 min; 5% SE-30 at 180 °C). The ^{1}H NMR analyses of the products isolated by preparative GLC indicative that the major one was a mixture of **34a** and **34b** (5.4:1) and the minor one was **35**. **34a**: ^{1}H NMR δ 1.15 (s, CCH_3), 2.86 (br s, $=CCHC=$), 5.80 (br s, $=CHCOOCH_3$), 9.61 (s, CHO). **34b**: ^{1}H NMR δ 0.94 (s, CCH_3), 3.26 (br s, $=CCHC=$), 5.74 (br s, $=CHCOOCH_3$), 9.50 (s, CHO). **35** ^{1}H NMR δ 1.10 (s, 3 H, CCH_3), 1.72 (br s, 3 H, $=CCH_3$), 1.79 (dd, J = 14, 7 Hz, 1 H, C*H*H), 2.08 (dd, J = 14, 9 Hz, 1 H, C*H*H), 2.81 (m, 1 H, $=CCHC=$), 3.07 (m, 1 H, C*H*$COOCH_3$), 3.72 (s, 3 H, OCH_3), 5.14 (d, J = 10 Hz, 1 H, $=CHH$), 5.16 (d, J = 18 Hz, 1 H, $=CHH$), 5.45 (br d, J = ca. 5 Hz, 1 H, ring vinyl H), 5.68 (ddd, J = 18, 10, 8 Hz, 1 H, C*H*$=CH_2$), 9.53 (s, 1 H, CHO).

A solution of a 5.4:1 mixture of **34a** and **34b** (7.24 g, 32.6 mmol), ethylene glycol (18.2 mL, 326 mmol), and *p*-toluenesulfonic acid monohydrate (620 mg, 3.26 mmol) in benzene (330 mL) was heated at reflux for 14 h in a Dean–Stark apparatus. The solution was allowed to cool to ambient temperature, washed with saturated aqueous $NaHCO_3$ and brine, dried, and concentrated under reduced pressure. The residual crude ethylene ketal (8.80 g) was dissolved in dry ether (130 mL), and to the solution, which was cooled with ice–water under stirring, was added dropwise a solution of diisobutylaluminum hydride (25% w/v in hexane, 55.6 mL, 99.7 mmol). After the addition was complete, the reaction mixture was stirred at room temperature for 25 min and then quenched with methanol. The precipitate was removed by filtration, and the filtrate was concentrated under reduced pressure. The residue (7.45 g, ethylene ketal of **30a,b**) was dissolved in acetone (200 mL) and water (90 mL), and after addition of *p*-toluenesulfonic acid monohydrate (590 mg, 3.1 mmol), the solution was heated at reflux for 11 h. The bulk of the solvent was removed under reduced pressure, and the residue was extracted with ether. The extract was washed with saturated aqueous $NaHCO_3$ and saturated brine, dried, and concentrated. The residual oil was subjected to chromatography (silica gel, 100 g; elution with 1:2 AcOEt–hexane) to give a 5.4:1 mixture of **30a** and **30b** (4.43 g, 70%).

(1*R,2*R**)-1-Methyl-2-[1-(*tert*-butyldimethylsiloxy)-2-(*E*)-buten-3-yl]-3-cyclohexene-1-carbaldehyde (36).** A solution of **30a** (320 mg, 1.65 mmol) in dry DMF (1 mL) was treated with *tert*-butyldimethylsilyl chloride (273 mg, 1.81 mmol) and imidazole (283 mg, 4.16 mmol) at room temperature. After 5 min, the solution was diluted with ether (10 mL), washed with aqueous ammonium chloride and brine, dried, and concentrated. The residue was subjected to chromatography (silica gel, 2 g; elution with 1:20 AcOEt–hexane) to afford **36** as an oil (466 mg, 92%): ^{1}H NMR (200 MHz) δ 0.07 (s, 6 H, $SiCH_3$), 0.90 (s, 9 H, t-C_4H_9), 1.12 (s, 3 H, 1-CH_3), 1.45 (dt, J = 13, 5 Hz, 1 H, H-6), 1.55 (br s, 3 H, 3′-CH_3), 1.87 (ddd, J = 13, 8.5, 6 Hz, 1 H, H-6), 2.15 (m, 2 H, H-5), 2.79 (br s, 1 H, H-2), 4.20 (d, J = 6 Hz, 2 H, H-1′), 5.52 (m, 2 H, H-2′ and H-3 or H-4), 5.97 (dm, J = ca. 10 Hz, 1 H, H-3 or H-4), 9.62 (s, 1 H, CHO).

3-[(5*R,10*R**)-3-[(3*R**,4*R**)- and 3-[(5*R**,10*R**)-3-[(3*S**,4*S**)-3-[1-Hydroxy-2(*E*)-buten-3-yl]-4-methylcyclohexen-4-yl)carbonyl]-4-methoxy-2-oxo-1-oxaspiro[4.5]deca-3,7-dien-10-yl]-2-methyl-2(*E*)-propenal (38).** A solution of **11** (197 mg, 0.787 mmol) in dry THF (0.6 mL) was syringed into a cold (−78 °C) stirred solution of lithium diisopropylamide [prepared from n-butyllithium (1.56 M in hexane, 1.26 mL, 1.97 mmol) and diisopropylamine (276 μL, 1.97 mmol) in dry THF (1.2 mL) under nitrogen atmosphere]. After 30 min, to the mixture were added a solution of **36** (291 mg, 0.943 mmol) in dry THF (0.6 mL) and dry HMPT (0.6 mL) over 10 min. The reaction mixture was allowed to warm to room temperature over 2 h and then poured onto a mixture of ether (10 mL) and ice–water (10 mL) containing 12 N HCl (0.83 mL). The phases were separated, and the aqueous phase was extracted with ether. The combined ether phases were washed with saturated brine, dried, and concentrated under reduced pressure. The residual oil (736 mg) was dissolved in dry dichloromethane (0.9 mL), and the solution was added dropwise to a cold stirred solution of chlorodimethylsulfonium chloride, which was prepared by addition of Me_2SO (279 μL, 3.93 mmol) in dichloromethane (0.3 mL) to a solution of oxalyl chloride (127 μL, 1.97 mmol) in the same solvent (1.5 mL) at ca. −70 °C.[15] After being allowed to warm to −35 °C over 30 min, the mixture was treated with triethylamine (1.24 mL, 8.90 mmol) and then brought to room temperature over 25 min. The reaction mixture was diluted with dichloromethane (15 mL), washed with 1% HCl (15 mL) and brine (5 mL), dried, and concentrated under reduced pressure. The residue was subjected to chromatography (silica gel, 26 g; elution with 1:3 AcOEt–hexane) to afford **37** as an oil (186 mg, 43%), R_f 0.56 (1:3 AcOEt–hexane).

A solution of **37** (490 mg, 0.883 mmol, combined with that obtained in a separate run) in 0.2% HF in acetonitrile (14.4 mL) was stirred at room temperature for 30 min. The solution was diluted with ether (20 mL), washed with saturated aqueous $NaHCO_3$ and brine, dried, and concentrated. The residue (442 mg) was subjected to chromatography (silica gel, 8 g; elution with 1:2 AcOEt–chloroform) to give a mixture of **38** and its diastereomer as an oil (270 mg, 69%), R_f 0.53 (1:2 AcOEt–chloroform). These diastereomers were separated by MPLC (10-μm silica gel, elution with 1:3 hexane–ether) to afford less polar isomer (113 mg) and more polar isomer (57 mg), which was crystallized from ether–hexane.

Less polar **38** (major product): mp 154–155 °C; IR (KBr) 3475, 1750, 1665, 1615 cm^{-1}; ^{1}H NMR (200 MHz) δ 1.32 (s, 3 H), 1.62 (br s, 3 H), 1.76 (d, J = 1.5 Hz, 3 H), 2.75 (br d, J = ca. 18 Hz, 1 H), 3.19 (td, J = 11, 6 Hz, 1 H), 3.27 (br s, 1 H), 3.78 (s, 3 H), 4.05 (dd, J = 11, 7 Hz, 1 H), 4.16 (dd, J = 11, 7 Hz, 1 H), 5.49 (m, 1 H), 5.59 (br t, J = 7 Hz, 1 H), 5.68–5.94 (m, 3 H), 6.18 (dq, J = 11, 1.5 Hz, 1 H), 9.36 (s, 1 H); MS, m/e 440 (M^+), 147 (base peak). Anal. Calcd for $C_{26}H_{32}O_6$: C, 70.89; H, 7.32. Found: C, 70.70; H, 7.45.

More polar **38** (minor product): mp 137–138 °C; IR (KBr) 3530, 1750, 1680, 1615 cm^{-1}; ^{1}H NMR (200 MHz) δ 1.31 (s, 3 H), 1.60 (br s, 3 H), 1.76 (d, J = 1.5 Hz, 3 H), 2.72 (br d, J = ca. 18 Hz, 1 H), 3.21 (td, J = 11, 6 Hz, 1 H), 3.45 (br d, J = ca. 5 Hz, 1 H), 3.69 (s, 3 H), 4.06 (dd, J = 11, 7 Hz, 1 H), 4.15 (dd, J = 11, 7 Hz, 1 H), 5.49 (m, 1 H), 5.62 (br t, J = 7 Hz, 1 H), 5.68–5.94 (m, 3 H), 6.22 (dq, J = 11, 1.5 Hz, 1 H), 9.35 (s, 1 H); MS, m/e 440 (M^+), 147 (base peak). Anal. Calcd for $C_{26}H_{32}O_6$: C, 70.89; H, 7.32. Found: C, 70.84; H, 7.51.

3-[(5*R,10*R**)-3-[(3*R**,4*R**)- and 3-[(5*R**,10*R**)-3-[(3*S**,4*S**)-3-[1-Chloro-2(*E*)-buten-3-yl]-4-methylcyclohexen-4-yl)carbonyl]-4-methoxy-2-oxo-1-oxaspiro[4.5]deca-3,7-dien-10-yl]-2-methyl-2(*E*)-propenal (39).** Dimethyl sulfide (23 μL, 0.313 mmol) was syringed into a cold (0 °C) stirred solution of N-chlorosuccinimide (38 mg, 0.285 mmol) in dichloromethane (1.3 mL) under nitrogen atmosphere. After 3 min, the solution was cooled to −25 °C, and a solution of the major isomer of **38** (113 mg, 0.257 mmol) in dichloromethane (0.2 mL) was introduced. The mixture was then stirred at the ice–water temperature for 25 min. The reaction mixture was diluted with ether, washed with cold saturated brine, dried, and concentrated under reduced pressure. The residue was subjected to chromatography (silica gel, 10 g; elution with 1:3 AcOEt–hexane) to afford a chloride (27 mg, 23%) as an amorphous solid, which decomposed on attempted crystallization: IR (film) 1765, 1695, 1615 cm^{-1}; ^{1}H NMR (200 MHz) δ 1.26 (s, 3 H), 1.76 (d, J = 1.5 Hz, 3 H), 1.81 (s, 3 H), 2.75 (br d, J = ca. 18 Hz, 1 H), 3.21 (td, J = 10, 6 Hz, 1 H), 3.53 (br s, 1 H), 3.78 (s, 3 H), 4.12 (d, J = 8 Hz, 2 H), 5.46–5.64 (m, 2 H), 5.64–5.93 (m, 3 H), 6.20 (dq, J = 10, 1.5 Hz, 1 H), 9.39 (s, 1 H); MS, m/e 423.2198 (M^+ − Cl, calcd 423.2172), 422.2069 (M^+ − HCl, calcd 422.2091), 147 (base peak).

The minor diastereomer of **38** (57 mg) was also chlorinated by the same procedure to give the corresponding chloride (14 mg, 24%) as a solid: IR (film) 1765, 1695, 1625 cm^{-1}; ^{1}H NMR (200 MHz) δ 1.31 (s, 3 H), 1.65 (s, 3 H), 1.78 (d, J = 1.5 Hz, 3 H), 2.72 (br d, J = ca. 18 Hz, 1 H), 3.21 (td, J = 10, 6 Hz, 1 H), 3.55 (br d, J = ca. 5 Hz, 1 H), 3.70 (s, 3 H), 4.04 (dd, J = 8, 2 Hz, 2 H), 5.42–5.54 (m, 1 H), 5.60–5.93 (m, 4 H), 6.23 (dd, J = 10, 1.5 Hz, 1 H), 9.37 (s, 1 H); MS, m/e 423.2129 (M^+ − Cl, calcd 423.2169), 147, 91 (base peak).

Oxocyclopentenol Syntheses

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Metal-assisted decompositions of α-diazo carbonyl compounds in 1,2-dialkoxy-1-alkenes are shown to yield β,β′-dialkoxycyclopropyl carbonyl systems, whose acid hydrolysis produces α-alkoxy-γ-dicarbonyl substances. Intramolecular condensations of the latter lead to oxocyclopentenols. Application of this reaction scheme to the syntheses of a prostaglandin intermediate and of tetrahydropyrethrolone is described.

The three-step reaction scheme of copper-catalyzed reaction between enol derivatives and α-diazo ketones, hydrolysis of the resultant β-oxycyclopropyl ketones, and base-induced aldolization and dehydration of the thus-produced γ-dicarbonyl compounds has constituted for some time the basis of a short, general method of cyclo-

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