A Synthesis of (−)-α-Multistriatin[1]

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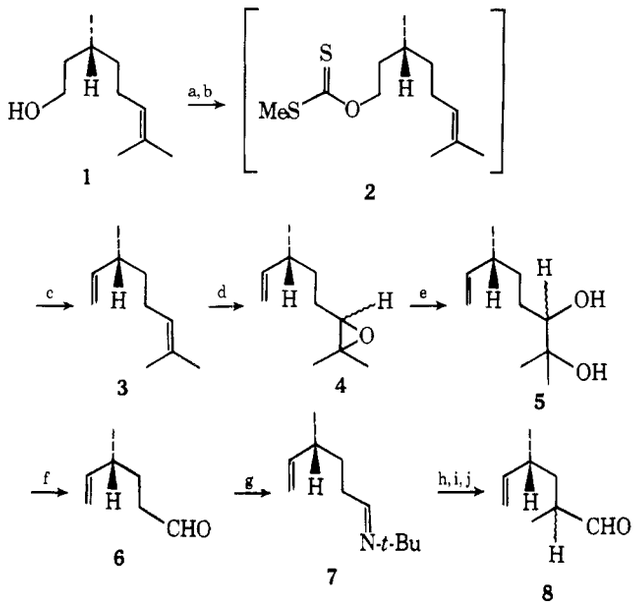
α-Multistriatin is the principal attractant of the smaller European elm bark beetle *Scolytus multistriatus* (Marsham), a vector of the Dutch elm disease pathogen *Cerocystis ulmi*. The severe devastation of elm populations in the northeastern United States has motivated the structure elucidation of the aggregation pheromone by Silverstein and co-workers[3] in the hope that mortality traps baited with the pheromone might be used for the bioassay and control of *S. multistriatus*.

The gross structure of α-multistriatin (**11α**) was deduced spectrometrically and by efficient confirmative total synthesis.[3,4] Subsequently, the relative configuration was established by a stereorational synthesis[4] and recently, the absolute configuration of (−)-**11α** was deduced by comparison of the ^{13}C NMR spectra of natural (−)-**11α** with synthetic material, prepared from chiral precursors, in the presence of a chiral shift reagent.[5,6] We report below an approach to the synthesis of natural (−)-α-multistriatin[7] from (+)-3R-citronellol (**1**).

As shown in Scheme I, (+)-(3*R*)-citronellol $[\alpha]_D$ +1.98[8] was converted to the known diene[9] **3** (46% yield from **1**) by pyrolysis of the corresponding xanthate **2**. Chemospecific epoxidation of the trisubstituted olefin of **3** afforded the epoxide **4** which was solvolyzed to the diol **5**. Subsequent $Pb(OAc)_4$ oxidation of **5** gave the aldehyde **6** in 49% overall yield from **3**. The aldehyde **6** was methylated in a three-step sequence via the Schiff base **7**[10] to give the aldehyde **8** in 53% overall yield from **6**.

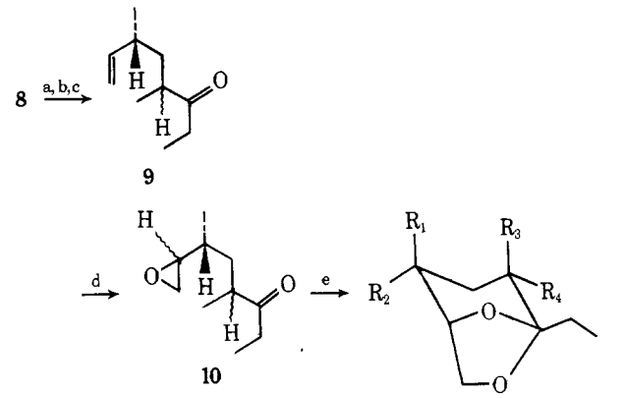
Scheme I



(a) NaH, CS_2; (b) MeI; (c) 240 °C; (d) *m*-$ClC_6H_4CO_3H$; (e) H_3O^+; (f) $Pb(OAc)_4$; (g) *t*-$BuNH_2$, Na_2CO_3; (h) (*i*-$Pr)_2NLi$; (i) MeI; (j) H_3O^+.

To complete the synthesis, the aldehyde **8** was converted by a two-step sequence to the known[5] (4*R*,*S*,6*R*)-dimethyl-7-octen-3-one (**9**). At this point our synthesis strategically intersects the procedure originally developed by Silverstein and co-workers[5] (Scheme II). The epoxide **10** reacted with $SnCl_4$ in benzene at room temperature to afford a mixture of the isomers **11α–δ** from which the desired α-isomer was isolated by preparative VPC and identified by comparison with an authentic sample kindly provided by Professor Silverstein. The observed $[\alpha]_D$ −18.7° for synthetic (−)-**11α** indicates an optical purity of 40%.[5]

Scheme II



	R_1	R_2	R_3	R_4
11α	H	Me	H	Me
11β	Me	H	Me	H
11γ	H	Me	Me	H
11δ	Me	H	H	Me

(a) EtMgBr; (b) H_3O^+; (c) H_2CrO_4; (d) *m*-$ClC_6H_4CO_3H$; (e) $SnCl_4$.

Our synthetic plan was founded upon the possibility of preparing both antipodes of **11α** from readily available, chiral precursors in order to avoid a potentially tedious resolution of racemic starting materials. Unfortunately, the advantage accrued from this approach was to some extent nullified by the insufficient enantiomeric purity of commercial (−)-(3*S*)- and (+)-(3*R*)-citronellol.[11] Although natural citronellol would have sufficed for the determination of the absolute configuration of **11α** as reported by Silverstein and co-workers,[5] further purification[12] will be essential for the bioassay of the pure **11α** antipodes prepared by the synthesis reported herein.

Experimental Section

General. Nuclear magnetic resonance spectra were recorded on a Varian HA-100 spectrometer using Me_4Si as an internal standard. Infrared spectra were obtained on a Perkin-Elmer Model 457 spectrophotometer using ca. 5% solutions in CCl_4. Mass spectra were obtained at 70 eV ionization potential using a DuPont 29-491B mass spectrometer utilizing the batch inlet. Vapor phase chromatographic (VPC) analysis was achieved with a Perkin-Elmer Model 3920 gas chromatograph equipped with a thermal conductivity detector. Unless otherwise stated, all VPC analyses were performed with a 4 ft × ¼ in. 10% SE-30/Chromosorb P (60–80 mesh) column (column A) or a 25 ft × ¼ in. 5% Carbowax 20M/Chromosorb G (60–80 mesh) column (column B). Helium served as the carrier gas. Optical rotatory dispersion curves were recorded with a JASCO ORD/CD-5 instrument. All thin layer chromatographic (TLC) analyses were performed with 2.5 × 7.5 cm Bakerflex pre-coated silica gel plates using phosphomolybdic acid for development.

The (+)-citronellol was obtained from ICN-K and K Laboratories. The $Pb(OAc)_4$ (containing 10% HOAc), obtained from Alfa Inorganics, Inc., and the *m*-chloroperbenzoic acid (unassayed, ca. 85%), obtained from Aldrich Chemical Co., were used without further purification. The *n*-BuLi was purchased from Aldrich Chemical Co.

(3*R*)-3,7-dimethylocta-1,6-diene (3). A flame-dried, 500-mL 3-neck flask fitted with a condenser, addition funnel, and magnetic stirrer was charged with 16.9 g (0.35 mol) of 50% NaH (dispersed in mineral oil) and 150 mL of dry THF. Over the course of 1 h, 50 g (0.32 mol) of (+)-(3*R*)-citronellol in 25 mL of CS_2 was added with occasional water bath moderation. After addition was complete, the mixture was refluxed for ½ h and then cooled to room temperature. After the dropwise addition of 43 g (0.40 mol) of MeI was complete, the reaction mixture was refluxed for ½ h, poured onto 300 g of ice, and the product extracted into 200 mL of ether. The organic layer was washed with

200 mL of saturated NH_4Cl, dried over $MgSO_4$, and concentrated in vacuo to a dark red oil.

Without further purification, the crude xanthate **2** was transferred to a 250-mL 3-neck flask fitted with a magnetic stirrer, thermometer, and short path distillation apparatus leading to an ice-cooled receiver. By means of a heating mantle, the internal temperature was gradually raised to 220–240 °C (Hood!) at which time the crude diene **3** was collected as a yellow oil (bp 120–160 °C). The product was extracted with 4 × 20 mL of 20% KOH, dried over $MgSO_4$, and short path distilled to give 20 g (46%) of the diene **3** as a pale yellow oil: bp 63–63.5 °C (20 mm); IR (CCl_4) 3080, 1670, 1640, 990, 910 cm^{-1}; NMR (CCl_4) δ 5.8–4.8 (m, 3H), 4.7 (m, 1H), 2.1 (m, 1H), 1.64 (s, 3H), 1.56 (s, 3H), 1.1–1.5 (m, 4H), 0.93 (d, 3H).

Minor sulfur-containing contaminants could be removed by distillation of **3** from Na. These contaminants were more effectively removed, however, in the subsequent peracid oxidation (vide infra). A neat sample of **3** gave an $[\alpha]^{25}_D$ −4.50° indicating an optical purity of 46%.

(3*R*,6*R*,*S*)-3,7-Dimethyloct-1-ene-6,7-diol (5). To a magnetically stirred solution of 22.0 g (0.159 mol) of diene **3** in 250 mL of CH_2Cl_2 was added 35.4 g (0.175 mol) of 85% *m*-chloroperbenzoic acid at a rate sufficient to maintain the temperature below 10 °C. After addition was complete, the mixture was allowed to stir at ice bath temperature for an additional 30 min whereupon the *m*-chlorobenzoic acid was removed by filtration. The filtrate was washed with 50 mL of 10% $NaHSO_3$ and 2 × 25 mL of saturated $NaHCO_3$. TLC analysis using hexane–ether (1:1) as eluent showed a single major product. A sample was purified by Kugelrohr distillation: bp 100 °C (bath) (20 mm); IR (CCl_4) 3080, 1640, 920, 900 and 880 cm^{-1}; NMR (CCl_4) δ 5.6 (m, 1H), 4.9 (m, 2H), 2.5 (m, 1H), 2.1 (m, 1H), 1.7 –1.1 (m, 4H), 1.22 (s, 3H), 1.18 (s, 3H), 0.9 (overlapping d, 3H).[13]

The crude epoxide **4** was added dropwise at 0 °C to a magnetically stirred solution of 100 mL of 0.1 M $HClO_4$ in 380 mL of THF. After 10 h at ambient temperature, TLC analysis (1:1 hexane–ether; R_f = 0.1) revealed a single major component. The mixture was concentrated in vacuo to ⅓ volume and the product extracted into 100 mL of ether. After washing with 40 mL of 2 N NaOH, followed by 10 mL of brine, the mixture was dried over $MgSO_4$, concentrated in vacuo and short path distilled to give 17.1 g (63% from **3**) of the diol **5** as a viscous, colorless oil: bp 79–80 °C (0.1 mm); IR (CCl_4) 3400, 3080, 1640, 920 cm^{-1}; NMR (CCl_4) δ 5.6 (m, 1H), 4.9 (m, 2H), 4.7 (br s, 2H, D_2O exchange), 3.2 (m, 1H), 2.1 (m, 1H), 1.1–1.8 (br m, 4H), 1.12 (s, 3H), 1.07 (s, 3H), 1.0 (d, 3H).

(4*R*)-Methylhex-5-enal (6). To a magnetically stirred solution of 15.0 g (87 mmol) of diol **5** in 125 mL of ether was added portionwise 48.1 g (96 mmol) of $Pb(OAc)_4$ (containing 10% HOAc) at a rate sufficient to maintain the temperature <20 °C (ice bath). After addition was complete the mixture was stirred at ambient temperature for 45 min whereupon the lead salts were removed by suction filtration. After adding 200 mL of saturated $NaHCO_3$, the mixture was continuously extracted for 20 h with ether. The product was isolated from the ether solution by drying over $MgSO_4$, concentration at ambient pressure, and short path distillation of the residue into an ice-cooled receiver. The aldehyde **6** (7.49 g, 77%) was isolated as a colorless, pungent oil: bp 39–40 °C (20 mm); IR (CCl_4) 3080, 2820, 2720, 1720, 1630, 990, 910 cm^{-1}; NMR (CCl_4) δ 9.6 (t, 1H), 5.8–5.2 (m, 1H), 5.0–4.5 (m, 2H), 2.4–1.8 (m, 3H), 1.6–1.2 (m, 2H), 0.9 (d, 3H); MS *m/e* 112 (M^{+}·, 10), 68 (100); VPC (column A, 100 °C) retention time 3.5 min (>95% pure).

***N*-((4*R*)-Methylhex-5-en-1-ylidene)-*tert*-butylamine (7).** A mixture of 5.03 g (69 mmol) of *t*-$BuNH_2$, 7.00 g (63 mmol) of aldehyde **6** and 11.7 g of anhydrous Na_2CO_3 in 30 mL of ether was magnetically stirred under N_2 at ambient temperature for 12 h. The mixture was filtered, concentrated in vacuo, and short path distilled to give 9.02 g (86%) of Schiff base **7** as a colorless oil: bp 69–70 °C (20 mm); IR (CCl_4) 1670, 1640, 990, 930 cm^{-1}; NMR (CCl_4) δ 7.5 (t, 1H, J = 4 Hz), 5.8–5.4 (m, 1H), 5.0–4.8 (m, 2H), 2.2 (m, 3H), 1.5 (m, 2H), 1.10 (s, 9H), 1.02 (d, 3H).

(2*R*,*S*,4*R*)-2,4-Dimethylhex-5-enal (8). A flame-dried 250-mL 3-neck flask fitted with a condenser, magnetic stirrer, addition funnel, and nitrogen inlet was charged with 37 mL (56 mmol) of 1.5 M *n*-BuLi in hexane and 40 mL of ether. After cooling to 0 °C under nitrogen, 5.67 g (56 mmol) of (*i*-Pr)$_2$NH (freshly distilled from CaH_2) in 10 mL of ether was added, followed after 15 min by dropwise addition of 8.5 g (51 mmol) of Schiff base **7**[14] in 15 mL of ether. Stirring was continued at 0 °C for 1 h whereupon 14.4 g (102 mmol) of MeI was added dropwise. The mixture was then refluxed for 30 min, stirred at ambient temperature for 63 h, and finally treated, with rapid magnetic stirring, with 112 mL of 1.0 M oxalic acid. The ether layer was washed with 5 mL of saturated $NaHCO_3$. The aqueous layer was neutralized with solid $NaHCO_3$ (until CO_2 evolution ceased) and continuously extracted with ether for 20 h. The combined ether extracts were dried over $MgSO_4$ and concentrated at ambient pressure. The residue was short path distilled to give 4.04 g (62%) of the aldehyde **8** as a colorless oil: bp 47–48 °C (20 mm); IR (CCl_4) 3080, 2817, 2710, 1720, 1630, 988, 810 cm^{-1}; NMR (CCl_4) δ 9.5 (t, 1H, J = 2 Hz), 5.8–5.3 (m, 1H), 5.1–4.8 (m, 2H), 2.3 (br m, 1H), 1.7 (m, 1H), 1.3 (m, 2H), 1.2–1.0 (set of 3 overlapping doublets, 6H); VPC (column A, 110 °C) one major component (>95%) retention time 3.8 min.

(4*R*,*S*,6*R*)-4,6-Dimethyloct-7-en-3-one (9). To the Grignard reagent prepared from 2.00 g (82 mg-atom) of Mg and 5.97 g (55 mmol) of EtBr in 45 mL of ether was added dropwise at ambient temperature 3.48 g (27.4 mmol) of aldehyde **8** in 10 mL of ether. After stirring for 1 h the mixture was cooled to 0 °C and quenched with 50 mL of saturated NH_4Cl. The ether layer was washed with 25 mL of water, dried over $MgSO_4$, and concentrated in vacuo to a colorless oil which was used in the next step without further purification.

To a magnetically stirred solution of the crude carbinol (vide supra) in 40 mL of acetone cooled to 0 °C was added dropwise 10.1 mL of 2.67 M H_2CrO_4. After addition was complete the mixture was stirred an additional minute, concentrated in vacuo to ~5 mL, diluted with 30 mL of H_2O and extracted with 4 × 10 mL of ether. The combined ether layers were washed with 2 × 15 mL of 0.15 M NaOH followed by one wash with 10 mL of H_2O. After drying over $MgSO_4$, the solvent was removed in vacuo and the residue short path distilled to give 3.31 g (79% from **8**) of enone **9** identical by NMR, IR, and MS with an authentic sample kindly provided by Professor Silverstein. VPC analysis (column A, 120 °C) showed a single major component (>95%), retention time 5.4 (>95%), retention time 5.4 min.

(4*R*,*S*,6*R*,7*R*,*S*)-4,6-Dimethyl-7,8-epoxyoctan-3-one (10). The epoxyketone **10** was prepared in 77% yield as described by Silverstein and co-workers.[5]

(−)-α-Multistriatin (11α). The epoxyketone **10** rearranged in benzene solution in the presence of $SnCl_4$[15] to give an 80% isolated yield of the four isomers **11α–δ** as previously described.[5] Using column B (170 °C) the four isomers eluted from the gas chromatograph in the following order (% composition, retention time in min): **11δ** (53, 23.4), **11α** (35, 23.9), **11γ** (8, 25.6), and **11β** (4, 27.9). The retention times and ratios of isomers were virtually identical with a sample provided by Professor Silverstein.

A pure sample of **11α** was collected by preparative VPC (column B, 170 °C) and was identical by IR and NMR with the data reported[5] for **11α**. An $[\alpha]_D$ −18.7° was observed for an 0.074 M solution **11α** in hexane.

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Registry No.—**1**, 1117-61-9; **2**, 63215-84-9; **3**, 10281-56-8; **4**, 15103-27-2; **5**, 57714-93-9; **6**, 63215-85-0; **7**, 63215-86-1; **8**, 63215-87-2; 8 (carbinol deriv.), 63466-90-0; **9**, 63323-26-2; **10**, 63324-22-1; 59014-03-8;,**11α**, 59014-03-8; **11β**, 59014-05-0; **11γ**, 59014-07-2; **11δ**, 59014-09-4; EtBr, 74-96-4.

References and Notes

(1) Part 6 of a series on pheromone synthesis. For part 5, see P. J. Kocienski and J. M. Ansell, *J. Org. Chem.*, in press.
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(7) (−)-α-Multistriatin is the trivial name for (1*S*,2*R*,4*S*, 5*R*)-2,4-dimethyl-5-ethyl-6,8-dioxabicyclo[3.2.1]octane.
(8) Based on an estimated maximum rotation of +5.60°, the $[\alpha]_D$ +1.98° for the (+)-3*R*-citronellol used in this investigation indicates an optical purity of 35% (cf. ref 11).
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(13) A claim for the preparation of 4 was not substantiated by spectral data: E. Eschinazi, Isr. J. Chem., 6, 713 (1968).
(14) The Schiff base 7 deteriorates on standing and should be used immediately after preparation for maximum yields in the alkylation step.
(15) Rearrangement of 10 in 0.1 M $HClO_4$ (heterogeneous) for 2.5 h at 25 °C gave a 90% yield of isomers 11α–δ in the ratio 37(δ):11(α):26(γ):26(β). Subsequent equilibration (see ref 5) with $SnCl_4$ gave the same ratios reported in the Experimental Section.

Long-Chain Stereomeric 2-Alkyl-4-methoxycarbonyl-1,3-dioxolanes in Glycerol Acetal Synthesis[1]

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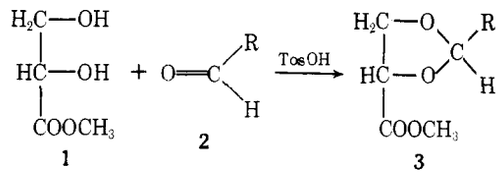
The prostaglandin-like, smooth muscle contracting effect of lipophilic glycerol acetal phosphates, the physiologically active principle of "Darmstoff" described by Vogt[2] and others,[3] has stimulated interest in an efficient synthesis of isomeric long-chain cyclic glycerol acetals. Current procedures of glycerol acetal synthesis are based on the condensation of glycerol and aldehyde[4,5] and favor formation of the isomeric 1,3-dioxanes;[5] the lesser amounts of *cis*- and *trans*-1,3-dioxolanes formed are separable, as acetates only, by tedious multiple gas chromatographic (GC) fractionation.[5]

In the present note we describe a convenient preparative method for the specific synthesis of pure *cis*- and pure *trans*-2-alkyl-4-hydroxymethyl-1,3-dioxolanes. 1,3-Dioxane formation is avoided through use of methyl glycerate as the three-carbon backbone. More important, the stereomeric glycerate acetals are separable by adsorption chromatography due to their significantly different polarities dependent upon the orientation of the methoxycarbonyl function relative to the long-chain substituted ring system. Subsequent conversion of the individual glycerate acetals to glycerol acetals by $LiAlH_4$ hydrogenolysis is quantitative.

Results and Discussion

Acid-catalyzed condensation of methyl glycerate (**1**) with hexadecanal (**2a**),[6] or *cis*-9-octadecenal (**2b**),[6] afforded a mixture of geometrical isomers of methyl glycerate cyclic acetals **3** (Scheme I) which were readily separated by thin-layer

Scheme I



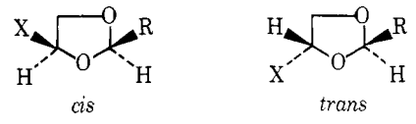
1 2 3

a, R = pentadecyl ($C_{15}H_{31}$)
b, R = *cis*-8-heptadecenyl ($C_{17}H_{33}$)

chromatography (TLC)[7] (developing solvent, hexane–diethyl ether, 75:25, v/v). Both the smaller (~40%), more polar (R_f 0.54) fraction, and the larger (~60%), less polar (R_f 0.64) fraction of **3a** (or **3b**) showed mass spectral fragmentation profiles consistent with the long-chain acetal structure **3** with characteristic ions M^+, $[M - H]^+$, $[M - alkyl]^+$, and $[M - alkyl\ CO]^+$ (ref 8). Their infrared spectra showed characteristic carbonyl splittings ($\Delta\nu$ ~22 cm^{-1}) probably due to coupling between the carbonyl stretching mode and ring vibrations.[9]

When the glycerate acetal fractions of **3a** were reduced with $LiAlH_4$,[10] the more polar isomer (R_f 0.54) gave *cis*-2-pentadecyl-4-hydroxymethyl-1,3-dioxolane (*cis*-**4a**), the less polar isomer (R_f 0.64) yielded *trans*-2-pentadecyl-4-hydroxymethyl-1,3-dioxolane (*trans*-**4a**). *cis*- and *trans*-**4a** were identified, after acetylation with Ac_2O/pyridine,[5] by comparison with authentic 2-pentadecyl-4-acetoxymethyl-1,3-dioxolanes *cis*- and *trans*-**5a** of known configuration prepared via an alternate route (Scheme II)[5]

Scheme II



cis *trans*

3, X = MeO–CO–
4, X = HO–CH_2–
5, X = MeCO–O–CH_2–

Configurational assignments for the isomers of glycerate acetal **3** were substantiated by ^1H NMR on the basis of the chemical shifts observed for the H-2 signals in the spectra of **3a–5a** (Table I).[11] The H-2 triplet at δ 4.98 ppm for the *cis*-methoxycarbonyl-1,3-dioxolane **3a** was shifted to 5.08 ppm for the trans-isomer **3a**. Such deshielding by 0.1 ppm was also observed for the *trans*-hydroxymethyl and *trans*-acetoxymethyl isomers **4a** and **5a**.[5,12] These NMR data also demonstrated that configurations were maintained in the process of converting **3a** to **5a**.

The ^1H NMR spectra of the 4-hydroxymethyl and 4-acetoxymethyl-1,3-dioxolanes (**4** and **5**) showed poorly resolved signals near 3.5–4.3 ppm due to H-4,5 and the 4-substituent protons. In contrast, the methoxycarbonyl isomers **3a** (or **3b**) gave characteristic and better resolved H-4,5 signals. The pairs of doublets centered at 4.55 ppm ($J_{4,5}$ = 7.5 Hz, *cis*-**3a**) and 4.58 ppm ($J_{4,5}$ = 7.1 Hz, *trans*-**3a**) were readily assigned to the proton (1 H) at carbon-4 with J values as expected for such 1,3-dioxolane systems.[13] The spectrum of the trans isomer also exhibited well-resolved signals at 4.28 ppm (pair of doublets, 1 H) and 3.86 ppm (pair of doublets, 1 H) for the H-5 protons in positions syn and anti, respectively, relative to the vicinal methoxycarbonyl function. Interference between 2-alkyl and 4-methoxycarbonyl substituents in the cis isomer of **3a** resulted in a less methoxycarbonyl-deshielded syn H-5 and in overlapping multiplets in the 4.29–3.92 ppm region for syn and anti H-5 in *cis*-**3a**.

Proton-decoupled ^{13}C NMR spectra of the glycerate and glycerol cyclic acetals **3–5** revealed distinct spectral differences between cis/trans isomeric pairs, and as a result of different substituents in position 4 (Table II). Assignments of ring and 4-substituent carbons were based on off-resonance proton decoupling and on specific deuteration in position 2 and in the methylene group in position 4 (**4b, 5b**).

Comparison of the carbon chemical shifts in 2-pentadecyl-1,3-dioxolane with those of the unsubstituted 1,3-dioxolane (C-2, 94.3; C-4, 63.8)[15] made it possible to estimate the deshielding increments due to the 2-alkyl group. 2-Alkyl substitution produced a downfield shift of 10.6 ppm for C-2, while the effect of the 4-substituents on C-2 in **3b–5b** was in the order of 0.1–1.9 ppm downfield, with cis substitution leading to larger deshielding than trans. In contrast, introduction of a 2-alkyl substituent into 1,3-dioxolane affected C-4,5 by a small (1.0 ppm) downfield shift only, but methoxycarbonyl (**3**) or acetoxymethyl (**5**) substitution at the 4 position produced a deshielding effect of ~8.9 ppm on C-4, and hydroxymethyl substitution (**4**) an even larger effect of ~11.6 ppm. The C-4 chemical shifts were minimally affected by the dioxolane configuration.

More surprising was the overall effect of the C-4 substitu-