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Synthesis of C-13-Substituted Retinoic Acid Analogues

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The synthesis of nine C-13 substituted retinoic acid analogues **3a–g**, **4**, and **7** via modification and extension of Julia's retinoid sulfone method is reported.

Retinoic acid (vitamin A acid) and its analogues have received considerable attention for their importance in controlling the normal growth, development, and differentiation of epithelial cells.[1] Since natural retinoids have limited usefulness for the chemoprevention of epithelial cancers because of excessive toxicity and inadequate tissue distribution, it becomes advantageous to explore synthetic derivatives.[2] It has also been shown that 13-*cis*-retinoic acid displays a better therapeutic index than the all-trans natural substance, and clinical application has been made in the treatment of acute acne[3] and bladder cancer.[4] This communication describes a stereoselective synthesis of a series of C-13-substituted retinoic acid derivatives, six of which contain a 13-*cis*-alkene.

Traditionally a major obstacle encountered in the construction of retinoid and carotenoid skeletons has been the realization of stereoselectivity in an alkene-forming process.[5,6] One successful approach to this problem is found in the elegant work of Julia and others.[7,8] In this scheme a C-10 phenyl sulfone, **1** is alkylated with an allylic bromide followed by elimination of benzenesulfinic acid under basic conditions. Exclusive formation of an 11,12-*E* double bond results when the allylic bromide used is a 4-bromo-(*E*)-butenoate. We herein demonstrate the extension of this methodology to include 3-substituted (*E*)- as well as (*Z*)-bromobutenoates. Table I lists the retinoic acid analogues synthesized via this approach.

Scheme I illustrates this alkylation–elimination process. Deprotonation of sulfone **1**[7,8] with an alkyl lithium reagent (*n*-BuLi or MeLi) or lithium diisopropylamide (LDA) in THF at −78 °C followed by addition of bromide **2** effects alkylation. In two cases (entries 7 and 9, Table I) this intermediate was isolated and fully characterized. Elimination of benzenesulfinic acid to give retinoid **3** is most conveniently accomplished by direct treatment with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in ether. Alternatively, pyrrolidine (entry 3), potassium *tert*-butoxide (entry 9), or sodium methoxide (entry 4), have been employed in appropriate cases.

The starting materials required by this approach are all readily accessible. Sulfone **1** is prepared in high yield from β-vinylionol and sodium benzenesulfinate ($NaSO_2Ph$) in acetic acid.[7] Allylic bromides **2** are prepared by radical bromination of the parent esters (NBS, AIBN (catal Δ, hν).[9-17] The physical data for allylic bromides **2** are

(1) Boutwell, R. K. "Oncology Overview: Selected Abstracts on Vitamin A in Cancer Biology"; U. S. Department of Health, Education, and Welfare, National Cancer Institute: Washington, DC, Sept 1979.

(2) (a) Newton, D. L.; Henderson, W. R.; Sporn, M. B. *Cancer Res.* **1980**, *40*, 3413–3425. (b) Sporn, M. B.; Newton, D. L. *Fed. Proc., Fed. Am. Soc. Exp. Biol.* **1979**, *38*, 2528–2534. (c) Sporn, M. B.; Dunlop, N. M.; Newton, D. L.; Smith, J. M. Ibid. **1976**, *35*, 1332–1338. (d) Sporn, M. B.; Dunlop, N. M.; Newton, D. L.; Henderson, W. R. *Nature (London)* **1976**, *263*, 110–113.

(3) Peck, G. L.; Olsen, T. G.; Yoder, F. W.; Strauss, J. S.; Downing, D. T.; Pandya, M.; Butkis, D.; Arnaud-Battandier, J. *New England J. Med.* **1979**, *300*, 329–333.

(4) Sporn, M. B.; Squire, R. A.; Brown, C. C.; Smith, J. M. *Science* **1977**, 487–489.

(5) Mayer, H.; Isler, O. In "Carotenoids"; Isler, O., Ed.; Birkhauser: Basel, Switzerland, 1971; Chapter VI.

(6) (a) Weedon, B. C. L. *Pure Appl. Chem.* **1976**, *47*, 161–171. (b) Makin, S. M. *Ibid.* **1976**, *47*, 173–181; (c) Kienzle, F. *Ibid.* **1976**, *47*, 189–190.

(7) Julia, M.; Arnold, D. *Bull. Chim. Fr.* **1973**, 746–750.

(8) Manchand, P. S.; Rosenberger, M.; Saucy, G.; Wehrli, P. A.; Wong, H.; Chambers, L.; Ferro, M. P.; Jackson, W. *Helv. Chim. Acta* **1976**, *59*, 387–396.

(9) Prepared from 3-chloro-2-butenoic acid (2:1 *E*/*Z* mixture)[10] by using K_2CO_3/CH_3I/acetone. Obtained as the *E* ester (>95%). For the stereochemical assignment see: Brouwer, H.; Strothers, J. B. *Can. J. Chem.* **1972**, *50*, 601–611.

(10) (a) Jones, D. E.; Morris, R. O.; Vernon, C. A.; White, R. F. M. *J. Chem. Soc.* **1960**, 2349. (b) Casey, C. P.; Jones, C. R.; Tukada, H. *J. Org. Chem.* **1981**, *46*, 2089–2092.

(11) Prepared from 1,1,1-trifluoroacetone and methyl (triphenylphosphoranylidene)acetate, see: (a) McBee, E. T.; Kim, Y. S.; Braendlin, H. P. *J. Am. Chem. Soc.* **1962**, *84*, 3154. (b) Dull, D. L.; Baxter, I.; Mosher, H. S. *J. Org. Chem.* **1967**, *32*, 1622–1623. (c) Camps, E.; Coll, J.; Messequer, A.; Roca, A. *Tetrahedron Lett.* **1976**, 791.

(12) Sum, F.-W.; Weiler, L. *Can. J. Chem.* **1979**, *57*, 1431–1441.

(13) Methyl 4-bromo-3-[(diethoxyphosphoryl)oxy]-2-butenoate has been prepared from trimethyl phosphite and γ-bromoacetoacetic acid and its methyl ester. No stereochemical assignment was given, see: Beriger, E. *German Offen.* 1917923, 1969; *Chem. Abstr.* **1970**, *72*, 31219.

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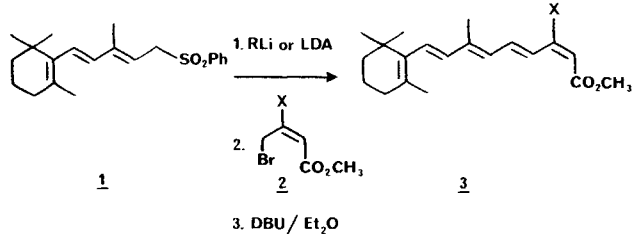
Table I

entry	retinoid (X)	formula[a] (mol wt)	mp, °C	elimination conditions	overall yield, %	IR, cm^{-1} [d]	UV, nm[e]	^1H NMR,[f,h] δ (C-11,12,14 C=CH)
1	3a (Cl)	$C_{20}H_{22}ClO_2$ (318.9)	oil	DBU/Et_2O	58	1717, 1575, 1550	374	7.34 (dd, J = 10, 15 Hz), 7.77 (d, J = 15 Hz), 5.98 (s)
2	3b (CF_3)	$C_{21}H_{27}F_3O_2$ (368.4)	oil	DBU/Et_2O	35	1725, 1617, 1581	379	6.9–7.4 (m), 7.57 (br d, K J = 15 Hz), 6.17 (br s)
3	3c ($OPO(OEt)_2$)	$C_{24}H_{37}O_6P$ (452.5)	oil	C_4H_9N/Et_2O	38	1714, 1617, 1589, 1239	369	7.0–7.5 (m, 2, C-11,12), 5.82 (d, J = 1 Hz)
4	3d (OCH_3)	$C_{21}H_{30}O_3$ (330.5)	oil	$NaOCH_3$[b]	30	1705, 1620, 1600	357	7.32 (dd, J = 12, 15 Hz), 7.58 (d, J = 15), 5.07 (s)
5	3e (CO_2Me)	$C_{22}H_{30}O_4$ (358.5)	oil	$NaOCH_3$[b]	17	1731, 1717, 1575	382	7.32 (dd, J = 12, 16 Hz), 7.60 (d, J = 12 Hz), 5.9–6.6 (m, 4, C-7,8,10,14)
6	3f (OAc)	$C_{22}H_{30}O_4$ (358.5)	73–74 (petroleum ether)	DBU/Et_2O	13, 49[c]	1775, 1720, 1620, 1585	369	6.97 (dd, J = 11, 15 Hz), 7.45 (d, J = 15 Hz), 5.53 (s)
7	3g (OAc), 13-trans)	$C_{22}H_{30}O_4$ (358.5)	90.5–91.5 (petroleum ether)	DBU/Et_2O	36	1765, 1705, 1620, 1580	366	7.02 (dd, J = 10, 16 Hz), 6.13 (d, J = 15 Hz, overlapping with m, C-7,8,10), 5.65 (s)
8	7 (OH, 13-trans)	$C_{20}H_{28}O_3$ (316.4)	65–68 (petroleum ether)	g	40[c]	1740, 1625, 1580, 1555	360	7.46 (dd, J = 9, 15 Hz), 5.87 (d, J = 15 Hz), 5.03 (s)
9	4 (lactone)	$C_{20}H_{26}O_2$ (298.4)	96.5–97.0 (hexane/Et_2O)	t-BuOK/DMF/t-BuOH	28[c]	1780, 1740, 1620, 1580	365	5.8–7.3 (m, 6, C-7,8,10–12,14)

[a] All new compounds have acceptable combustion analyses (±0.4%) or high-resolution mass spectral MS data. [b] Added directly to the alkylation reaction mixture. [c] Overall yield, includes purification of intermediate; see Experimental Section. [d] Solution spectra ($CHCl_3$); CCl_4 for 3a–c,e. [e] Taken in 95% EtOH, log ε = 4.4 for 3b and 3e; log ε = 4.6–4.7 for all others. [f] 60 MHz, $Me_4Si/CDCl_3$. [g] Prepared from 3f + 3g by treatment with pyrrolidine in Et_2O followed by H_2O. [h] All analogues also displayed resonances typical of the β-ionylidine unit.

Scheme I



Scheme II

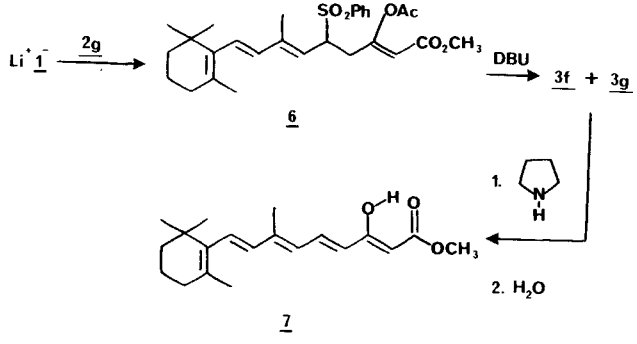
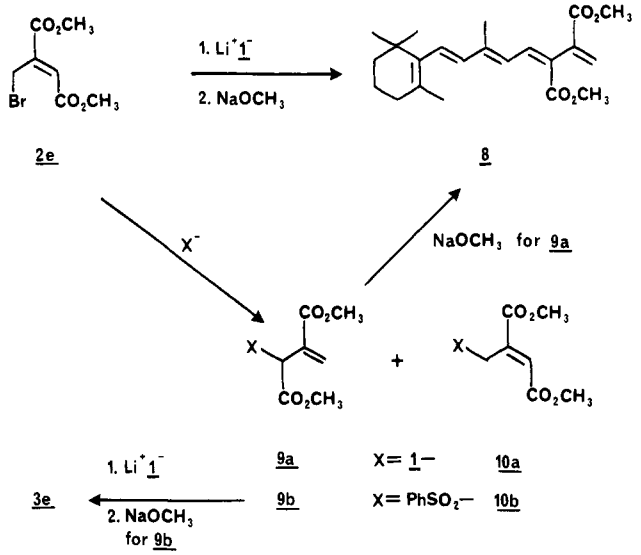


Table II

bromide	X	formula[a] (mol wt)	starting matl ref	bp, °C (torr)[b]	method of purif (% yield)[b]	IR, cm^{-1} [c]	^{1}H NMR,[d] δ
2a	Cl	$C_5H_6BrClO_2$ (212.5)	9, 10	140 (150)	A, B (50)	1725, 1631	3.75 (s, 3), 4.70 (s, 2), 6.10 (s, 1)
2b	CF_3	$C_6H_6BrF_3O_2$ (209.0)	11	100 (150)	A, B (84)	1733, 1672	3.81 (s, 3), 4.53 (s, 2), 6.40 (m, 1)
2c	$OPO(OEt)_2$	$C_9H_{16}BrO_6P$ (331.1)	12, 13	120 (0.5)	A, B (50)	1722, 1647, 1266	1.42 (t, 6, J = 6 Hz), 3.75 (s, 3), 4.20 (q, 4, J = 6 Hz), 4.58 (s, 2), 5.92 (d, 4, J = 1 Hz)
2d	OCH_3	$C_6H_9BrO_3$ (209.0)	14	80 (1.0) [lit.[14b] 70 (0.5)]	A (90)	1715, 1630	3.70 (s, 3), 3.76 (s, 3), 4.50 (s, 2), 5.07 (s, 1)
2e	CO_2CH_3	$C_7H_9BrO_4$ (237.1)	15	85 (2.5)	A (93)	1720, 1640	3.82 (s, 3), 3.88 (s, 3), 4.70 (s, 2), 6.78 (s, 1)
2f	OAc (cis)	$C_7H_9BrO_4$ (237.1)	16	130 (1.0)	A, B (31)	1775, 1720, 1660	2.25 (s, 3), 3.75 (s, 3), 4.75 (s, 2), 5.85 (s, 1)
2g	OAc (trans)	$C_7H_9BrO_4$ (237.1)	16	150 (1.0)	A, B (30)	1775, 1725, 1660	2.28 (s, 3), 3.68 (s, 3), 3.98 (s, 2), 5.92 (s, 1)
5		$C_5H_5BrO_2$ (177.0)	17	100 (0.2) [lit.[17g] 120 (0.1)]	A (47)	1780, 1750	4.92 (s, 2), 4.98 (br s, 2), 6.13 (br s, 1)

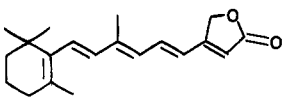
[a] All new compounds have acceptable combustion analyses (±0.4%) or high-resolution mass spectral data (2a). [b] A, Kugelrohr distillation (bath temperature in parentheses); B, column chromatography (SiO_2): for 2a,b,g,f, 5%, 7.5%, and 16% Et_2O/petroleum ether; for 2c, 45% EtOAc/petroleum ether). [c] Taken as a film, except for 2a,b (CCl_4). [d] 60 MHz, Me_4Si/CCl_4, except for 2e-g and 5 ($CDCl_3$).

Scheme III

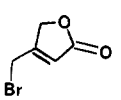


summarized in Table II. Although the overall transformation proceeds in only moderate yields, the stereochemical integrity of the polyene products and the operational simplicity serve to recommend this methodology.

In addition to the 13-cis retinoids **3a–d**, two 13-trans derivatives that contain functionality at the 13-position were also constructed. Lactone **4** and enol acetate **3g** were



4



5

prepared. Again, no 11,12-cis isomers could be detected. The synthesis of **4** begins with bromo lactone **5**.[17] A convenient one-step synthesis of **5** is achieved by dibromination of 3,3-dimethylacrylic acid with 2 equiv of NBS followed by lactonization (aqueous $NaHCO_3$). Bromide **2g** required for the synthesis of **3g** could be obtained by bromination of (*E*)- and (*Z*)-methyl 3-acetoxybutenoate (30:70, respectively). Bromination under standard conditions with added K_2CO_3 to minimize isomerization produced **2f** (30%) and **2g** (31%).[16] Alkylation of **1** with **2f** (Scheme II) produced **6** in 53% isolated yield. DBU-induced elimination, however, caused some isomerization of the 13,14-double bond, thus giving rise to a mixture of **3f** (25%) and **3g** (67%), easily separated by chromatography on silica gel (in general, 13-*cis*/*trans*-retinoates differ significantly in chromatographic behavior). Treatment of **3e** and **3f** with pyrrolidine affords the 13-hydroxy retinoid **7** after the workup. The all-trans enolic nature of **7** is clearly evidenced by the proton NMR data listed in Table I. The relative downfield position of the C-12 proton doublet for the 13-*cis*-retinoates distinguishes the cis from the trans structures.[18]

The alkylation of **2e**, however, proved to be exceptional. The sole polyene product (50% from **1**) was **8** (Scheme III). Apparently **2e** reacts under these conditions exclusively by an S_N2' mechanism to give **9a**. Methoxide treatment

(14) (a) Smissman, E. E.; Voldeng, A. N. *J. Org. Chem.* **1964**, *29*, 3161. (b) Weinreb, S. M.; Auerbach, J. *J. Am. Chem. Soc.* **1975**, *97*, 2503.
(15) (a) Schaltegger, H. U. S. Patent 2 790 757; *Chem. Abstr.* **1958**, *52*, 1250a. (b) Kluender, H.; Bradley, C. H.; Sih, C. J.; Fawcett, P.; Abraham, E. P. *J. Am. Chem. Soc.* **1973**, *95*, 6149–6150.
(16) (a) Casey, C. P.; Martin, D. F. *Tetrahedron Lett.* **1974**, 925–928. (b) Casey, C. P.; Martin, D. F.; Boggs, R. A. *Ibid.* **1973**, 2071–2074.
(17) (a) Martin, R.; Chapleo, C. B.; Svanholt, K. L.; Dreiding, A. S. *Helv. Chim. Acta* **1976**, *59*, 2724–2727. (b) Boeckman, R. K., Jr.; Ko, S. S. *J. Am. Chem. Soc.* **1980**, *102*, 7146–7149.
(18) Vetter, W.; Englert, G.; Nigassi, N.; Schwieter, U. In "Carotenoids"; Isler, O., Ed.; Birkhauser: Basel, Switzerland, 1971; Chapter IV.

then produces 8. Literature precedent for this mode of reactivity is found in the reaction of **2e** with dimethylsulfide/$NaHCO_3$.[19] Further evidence of kinetics S_N2' reactivity is obtained from the reaction of **2e** with sodium benzenesulfinate. Treatment of **2e** in DMF at −15 °C with 0.5 equiv of $NaSO_2Ph$ affords a 3:1 mixture of **9b** (45% isolated yield; MPLC, silica gel) and **10b** (15%). In contrast, at room temperature with 1.1 equiv $NaSO_2Ph$ only **10b** is observed. The rationale behind the synthesis of **9b** was that it is appropriately funtionalized for a Michael addition of $Li^+ 1^-$ to give the desired alkylation product, **10a**. Elimination then should give **3e**. In practice, treatment of Li^+1^- with **9b** followed by in situ elimination with sodium methoxide did indeed produce **3e** (17%) together with substantial amounts of recovered **1**. Apparently proton transfer competes with the Michael addition process.

Experimental Section

Materials and Techniques. Melting points were determined on a Büchi melting point apparatus and are uncorrected. Analyses were performed by Spang Microanalytical Laboratory. Silica gel 60, F-254 (E. Merck No. 5765) and silica gel 60 (E. Merck No. 7734, 70–230 mesh) which were available from Brinkmann Instruments were used for thin-layer and column chromatography, respectively. Medium-pressure liquid chromatography (MPLC) consisting of a Fluid Lab Model RPSYX pump, and a Brinkmann prepared column B, having a column volume of 152 mL and being packed with silica gel 60 (E. Merck. No. 9385, 230-400 mesh, available from Brinkmann Instruments), was also used.[20] Ultraviolet (UV) spectra were recorded on a Cary-14 spectrometer in 95% ethanol. Infrared (IR) spectra were recorded on a Perkin-Elmer 237B spectrometer in spectroquality solvents as 10% solutions by using 0.10-mm sodium chloride cells, as thin films between sodium chloride cells, or as thin films between sodium chloride crystals. Nuclear magnetic resonance (NMR) spectra were measured on a Varian Associates Model T-60 spectrometer. High-resolution mass spectra (HRMS) were recorded on a Du Pont Flash CEC 21-110B spectrometer at 70 eV. For all reactions performed under an atmosphere of dry nitrogen the equipment was dried in an oven at 120 °C for several hours and then allowed to cool in an atmosphere of dry nitrogen. All liquid transfers were made with nitrogen-filled syringes. The term "petroleum ether" refers to the Baker "Analyzed Reagent", bp 30–60 °C. The term "dry tetrahydrofuran" (THF) refers to commercial tetrahydrofuran purified by distillation from lithium aluminum hydride. "Dry *N,N*-dimethylformamide" (DMF) was obtained by vacuum distillation of commercial material from calcium hydride (−40 mesh) on to activated Type 4A molecular sieves. The nomenclature utilized is compatible with that used by Chemical Abstracts.[21]

Preparation of Allylic Bromides 2a–q and 5. General Procedure. To a solution of 3-substituted crotonate (see Table II for references) in CCl_4 (1.5 mL/mmol of substrate) were added freshly purified NBS (1.0 equiv) and a catalytic amount of azobis(isobutyronitrile) (AIBN, 5 mg). This mixture was heated at reflux with a 200-W incandescent lamp until complete consumption of NBS was noted (2–10 h). The reaction mixture was cooled to room temperature, diluted with petroleum ether, and filtered. The filtrate was washed with saturated $NaHCO_3$, dried ($MgSO_4$), and concentrated in vacuo to afford the crude allylic bromides. Specific methods of purification and physical data are given in Table II. Bromo lactone **5** was prepared in an analogous manner by using 2.0 equiv of NBS, and the $NaHCO_3$ extraction step was conducted (shaken occasionally) over 1 h.

Retinoid Synthesis, Typical Procedure. Methyl (*all-E*)-7-Methyl-3-chloro-9-(2,6,6-trimethyl-1-cyclohexen-1-yl)-2,4,6,8-nonatetraenoate (3a). To a solution of sulfone **1** (0.900 g, 2.62 mmol)[7,8] in dry THF (15 mL) at −78 °C (dry ice/acetone) was added *n*-butyllithium (2.10 mL, 2.62 mmol, 1.25 M in hexane, Aldrich No. 18,617-1). The reaction mixture was allowed to warm to 0 °C over 30 min, was cooled −78 °C, and was treated with **2a** (0.669 g, 3.14 mmol) in THF (7.0 mL, precooled to −78 °C, rapid addition). After 5 min the reaction mixture was diluted with H_2O (150 mL), washed with saturated $NaHCO_3$ (2 × 25 mL), dried ($MgSO_4$), and concentrated in vacuo. The residue was dissolved in Et_2O (50 mL) and treated with DBU (0.597 g, 3.93 mmol) in Et_2O (5.0 mL). After 1.5 h, additional Et_2O (50 mL) was added, and the resultant solution was washed with saturated $NaHCO_3$ (25 mL), dried ($MgSO_4$), and concentrated in vacuo. Column chromatography on silica gel (70–230 mesh, E. Merck) with 2% Et_2O/98% petroleum ether (v/v) as an eluant affords 0.512 g (58%) of **3a** as a yellow oil.

Methyl (*all-E*)-7-Methyl-3-(trifluoromethyl)-9-(2,6,6-trimethyl-1-cyclohexen-1-yl)-2,4,6,8-nonatetraenoate (3b). From 2.62 mmol of **1**[7,8] was obtained 0.336 g (35%) of **3b** after column chromatography (2% Et_2O/98% petroleum ether) and MPLC (Merck LiChroprep Si-60, size B column, petroleum ether) as a yellow oil.

Methyl (*all-E*)-7-Methyl-3-[(diethoxyphosphoryl)oxy]-9-(2,6,6-trimethyl-1-cyclohexen-1-yl)-2,4,6,8-nonatetraenoate (3c). From 1.0 g (2.91 mmol) of **1**[7,8] there was obtained 1.72 g (72%) of the alkylated sulfone after column chromatography (80% Et_2O/20% petroleum ether). To 0.459 g (0.757 mmol) of this material in Et_2O (15 mL) was added 0.5 mL of pyrrolidine. After 2 h, Et_2O (50 mL) was added, and the resultant solution was washed with saturated $NaHCO_3$ (2 × 25 mL), dried ($MgSO_4$), and concentrated in vacuo. Column chromatography (75% Et_2O/25% petroleum ether) afforded 0.187 g (53%, 38% overall) of **3c** as a yellow oil.

Methyl (*all-E*)-7-Methyl-3-methoxy-9-(2,6,6-trimethyl-1-cyclohexen-1-yl)-2,4,6,8-nonatetraenoate (3d). From 0.180 g (0.524 mmol) of **1**[7,8] and 0.131 g (0.628 mmol) of **2d** there was obtained 0.052 g (30%) of **3d** as a yellow oil. The benzenesulfinate elimination was performed by adding sodium methoxide (0.20 g, 3.8 mmol) directly to the alkylation reaction mixture (after allowing it to warm to room temperature rt over 2 h). After 3 h at room temperature a workup as before afforded **3d**.

Methyl 7-Methyl-3-acetoxy-9-(2,6,6-trimethyl-1-cyclohexen-1-yl)-(2*Z*,4*E*,6*E*,8*E*)-2,4,6,8-nonatetraenoate (3f) and Methyl (*all-E*)-7-Methyl-3-acetoxy-9-(2,6,6-trimethyl-1-cyclohexen-1-yl)-2,4,6,8-nonatetraenoate (3g). To a solution of **1** (0.658 g, 2.0 mmol) in THF (10 mL) and diisopropylamine (0.30 mL, 2.2 mmol) maintained at −78 °C was added methyllithium (1.66 mL, 1.99 mmol, 1.2 M in Et_2O, Aldrich No. 19, 734-3). After warming to 0 °C for 10 min, the reaction mixture was cooled to −78 °C, and a precooled (−78 °C) solution of **2g** (0.522 g, 2.2 mmol) in THF (5 mL) was rapidly added. After 20 min the reaction mixture was partitioned between Et_2O (150 mL) and saturated $NaHCO_3$ (100 mL). The organic portion was dried ($MgSO_4$) and concentrated in vacuo. Column chromatography (50% Et_2O/50% petroleum ether) gave 0.532 g (53%) of **6**: mp 94–95 °C; IR ($CHCl_3$) 1767, 1719 cm^{-1}; NMR ($CDCl_3$) δ 1.00 (br s, 6, 2 C-1 CH_3's), 1.27 (s, 3, C-9 CH_3), 1.4–1.6 (m, 4, 3 C-2 CH_2's), 1.8–2.2 (m, 2, C-4 CH_2), 2.16 (s, 3, CH_3CO), 3.59 (s, 3, OCH_3), 4.14 (dt, 1, J = 3, 10 Hz, $CHSO_2C_6H_5$), 5.12 (d, 1, J = 10 Hz, C-10 C=CH), 5.62 (s, 1, C-14 C=CH), 5.95 (s, 2, 8 C-7 C=CH's) 7.2–7.9 (m, 5, C_6H_5). Anal. Calcd for $C_{28}H_{36}O_5S$: C, 67.17; H, 7.25. Found: C, 67.29; H, 7.12.

To **6** (0.250 g, 0.50 mmol) in benzene (6 mL) was added DBU (0.15 mL, 1.0 mmol) at room temperature. After 10 min, Et_2O (100 mL) was added, and the resultant solution was washed with saturated $NaHCO_3$ (2 × 30 mL), dried ($MgSO_4$), and concentrated in vacuo. Column chromatography (16% Et_2O/84% petroleum ether) gave 0.045 g (25%) of **3f** and 0.119 g (67%) of **3g** as crystalline solids.

Methyl 7-Methyl-3-hydroxy-9-(2,6,6-trimethyl-1-cyclohexen-1-yl)-(2*Z*,4*E*,6*E*,8*E*)-2,4,6,8-nonatetraenoate (7). To the unpurified mixture of **3f** and **3g** (from the preceding experiment, 0.40-mmol-scale reaction) in Et_2O (15 mL) was added pyrrolidine (1.0 mL). After 1 h at room temperature the reaction

(19) Garbers, C. F.; Labuschagne, J. H.; Meyer, C. J.; Schneider, D. F. *Chem. Soc., Perkin Trans. 1* **1973**, 2016–2019. Likewise C-alkylation–Michael reaction of dimethyl γ-bromomesaconate (**2e**) also occurs with the pyrrolidine enamine of cyclopentanone. See: Nelson, R. P.; McEuen, J. M.; Lawton, R. G. *J. Org. Chem.* **1969**, *34*, 1225–1229.

(20) Meyers, A. I.; Slade, J.; Smith, R. K.; Mihelich, E. D.; Hershenson, F. M.; Liang, C. D. *J. Org. Chem.* **1979**, *44*, 2247–2249.

(21) Loening, K. L., Nomenclature Director, Chemical Abstracts Service, Columbus, OH 43210.

mixture was worked up in the usual way to afford after column chromatography (10% Et_2O/90% petroleum ether) 0.095 g (76%) of **7** as a crystalline solid.

(*E*,*E*,*E*)-4-[4-Methyl-6-(2,6,6-trimethyl-1-cyclohexen-1-yl)-1,3,5-hexatrienyl]-2(5*H*)-furanone (4). By use of the procedure cited for a **2a**, with 5.0 mmol of **1**[7,8] there was obtained 0.929 g (42%) of the alkylated sulfone upon trituration of the crude product with Et_2O: mp 125.5–127.0 °C (Et_2O); IR ($CHCl_3$) 1780, 1750 cm^{-1}; NMR ($CDCl_3$) δ 1.00 (s, 6), 1.23 (s, 3), 1.4–1.7 (m, 4), 1.67 (s, 3), 2.0–2.3 (m, 2), 2.55–3.65 (m, 2), 3.90–4.39 (m, 1), 4.75 (d, 2, J = 1 Hz), 5.15 (d, 1, J = 10 Hz), 5.85 (t, 1, J = 1 Hz), 5.98 (s, 2), 7.3–8.0 (m, 5). Anal. Calcd for $C_{26}H_{32}O_4S$: C, 71.66; H, 7.13. Found: C, 71.58; H, 7.06. To this sulfone (0.450 g, 1.02 mmol) in dry DMF (15 mL) maintained at −78 °C was added a solution of *t*-BuOK in 1:4 DMF/*tert*-butyl alcohol [1.2 mmol, 2.04 mL; 0.5 M solution prepared from potassium (195 mmol), dry *tert*-butyl alcohol (8 mL), and DMF (2 mL)]. When the addition was completed (approximately 3 min), the mixture was allowed to warm to 10 °C (3 h) and quenched with AcOH (3.0 mL). This mixture was partitioned between saturated $NaHCO_3$ (50 mL) and Et_2O (200 mL). The organic solution was extracted with saturated $NaHCO_3$ (2 × 50 mL), dried ($MgSO_4$), and concentrated in vacuo. Column chromatography (50% CH_2Cl_2/50% pentane) afforded 0.195 g (67%) of **4** as a crystalline solid.

Dimethyl (*all-E*)-2-[4-Methyl-6-(2,6,6-trimethyl-1-cyclohexen-1-yl)-1,3,5-hexatrienyl]-2-butenedioate (3e). To bromide **2e** (2.84 g, 12.0 mmol) in DMF (25 mL) maintained at −15 °C (ice–methanol bath) was added a solution of $NaSO_2Na$ (0.984 g, 6.0 mmol) in DMF (30 mL) over 5 min. The reaction mixture was stirred at −15 °C for 45 min and then poured into Et_2O (200 mL) and extracted with saturated $NaHCO_3$ (3 × 100 mL). The organic phase was dried ($MgSO_4$) and concentrated in vacuo. NMR analysis of this crude product indicated a 62:29:9 ratio of **2e**/**9b**/**10b**. MPLC with 40% Et_2O/60% petroleum ether as the eluant gave 0.805 g (45% yield based on $NaSO_2Ph$) of sulfone **9b** as a colorless oil: IR (film) 1750 (CO_2Me), 1722 (CO_2Me), 1625 (C=C) cm^{-1}; NMR ($CDCl_3$) δ 3.67 (s, 6, $2CO_2CH_3$), 5.53 (s, 1, $SCHCO_2CH_3$), 6.52 (s, 1, C=CH), 6.72 (s, 1, C=CH), 7.5–8.0 (m, 5, Ar H). Without further manipulation, characterization, or attempts to maximize the conversion of **2e** to **9b**, sulfone **9b** was utilized directly in the next reaction. To a solution of sulfone **1** (0.619 g, 1.80 mmol) in THF (15 mL) cooled to −78 °C (dry ice bath) was added *n*-butyllithium (1.3 mL, 1.8 mmol, 1.4 M in hexane). The reaction mixture was warmed to 0 °C for 30 min and then recooled to −78 °C. Then a solution of sulfone **9b** (0.805 g, 2.70 mmol, precooled to −78 °C) in THF (6 mL) was added rapidly. After 10 min the reaction mixture was poured into Et_2O (200 mL) and extracted with saturated $NaHcO_3$ (2 × 30 mL). The organic phase was dried ($MgSO_4$) and concentrated in vacuo. This crude product was dissolved in Et_2O (100 mL) and treated with DBU (0.410 g, 2.70 mmol). After 1 h at room temperature, Et_2O (100 mL) was added, and the mixture was washed with saturated $NaHCO_3$ (2 × 50 mL), dried ($MgSO_4$), and concentrated in vacuo. Column chromatography (10% Et_2O/90% petroleum ether) afforded 0.110 g (17%) of **3e** as a yellow oil.

(*all-E*)-2,3-Bis(carbomethoxy)-6-methyl-8-(2,6,6-trimethyl-1-cyclohexen-1-yl)-1,3,5,7-octatetraene (8). The procedure described for the synthesis of **3d** was used by starting with 2.54 mmol of **1** and 5.0 mmol of **2d**. Column chromatography (20% Et_2O/80% petroleum ether) afforded 0.457 g (50%) of **8** as a yellow oil: UV max (95% C_2H_5OH) 334 nm; IR (film) 1715 (CO_2CH_3) 1585 (C=C) cm^{-1}; NMR ($CDCl_3$) 1.00 (s, 6, 2 C-1 CH_3's), 1.68 (s, 3, C-5 CH_3), 2.06 (s, 3, C-9 CH_3), 3.72 (s, 6, $2CO_2CH_3$), 5.55–5.60 (m, 5, C=CH), 7.75 (d, 1, J = 12 Hz, C-12 C=CH); low-resolution mass spectrum (relative intensity) 358 (m^+, 32), 326 (16), 311 (19), 105 (63), 69 (100), 59 (52), 55 (98), 41 (84); calcd for $C_{22}H_{30}O_4$ m/z 358.2144, found m/z 358.2130 (3.9 ppm error by high-resolution mass spectroscopy.

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Reactions of Propargyl Alcohols with Amide Acetals[1]

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The reaction of a propargyl alcohol with an amide acetal affords enamine products, an allenic amide (a sigmatropic rearrangement product), or a product resulting from enamine formation followed by sigmatropic rearrangement. Subsequent procedures afforded α,β-unsaturated aldehydes, α-hydroxy ketones, β-keto amides, and spiro lactones.

A number of reactions of the amide acetal reagents have been reported.[2] We have found that mixed amide acetals derived from propargyl alcohols react to give one or more products resulting from intramolecular amine addition to the carbon–carbon triple bond and/or rearrangement. The pathway which such mixed amide acetals follow is dependent in a predictable way on the nature of substituents

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(1) Portions of this work have been reported in communication form: (a) K. A. Parker and J. J. Petraitis, *Tetrahedron Lett.*, 4561 (1977); (b) K. A. Parker, R. W. Kosley, Jr., S. L. Buchwald, and J. J. Petraitis, *J. Am. Chem. Soc.*, **98**, 7104 (1976); (c) K. A. Parker and R. W. Kosley, Jr., *Tetrahedron Lett.*, 341 (1976); (d) K. A. Parker and R. W. Kosley, Jr., *ibid.*, 3039 (1975).

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