Tetraenylstannanes in the Synthesis of Retinoic Acid and Its Ring-Modified Analogues

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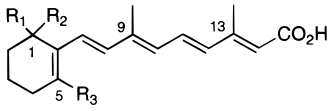
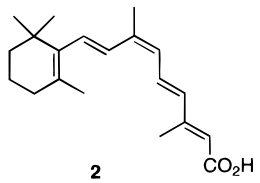
Retinoids (vitamin A and its structural and functional analogues) are currently the subject of intense biological interest stimulated by the discovery and characterization of retinoid receptors[1] and the subsequent consideration of retinoic acids as nonsteroidal small-molecule hormones. The retinoid families of nuclear proteins [RARs (retinoic acid receptors) and RXRs (retinoid X receptors)] comprising subtypes RARα,β,γ and RXRα,β,γ) act as ligand-inducible transcription factors in the proliferation and differentiation of mammalian cells. *trans*-Retinoic acid (**1a**) is the natural ligand for RAR, and its isomer 9-*cis*-retinoic acid (**2**) has high affinity for, and activates, both RAR and RXR.

The effects of retinoids on cell differentiation and proliferation have spurred the synthesis and biological evaluation of numerous retinoic acid analogues.[2] Since the subtypes within each receptor family, which are encoded by separate genes, show some differences in tissue distribution, synthetic retinoids selective for individual subtypes would be important tools for better delineation of the multiple effects of retinoids in mammalian cells.[3]



1a, $R_1 = R_2 = R_3 = Me$
1b, $R_1 = R_2 = Me, R_3 = H$
1c, $R_1 = H, R_2 = R_3 = Me$
1d, $R_1 = R_2 = H, R_3 = Me$
1e, $R_1 = H, R_2 = Me, R_3 = H$
1f, $R_1 = R_2 = R_3 = H$



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In some of the most active known retinoids, the unstable polyolefinic chain of **1a** is stabilized by the inclusion of some of its double bonds in aromatic rings. However, our structure−activity studies have recently led us to investigate a synthetically more challenging series of ring-modified retinoic acid analogues (**1b**−**f**), all of them with the unaltered side-chain of **1a**.

Traditional routes to retinoids, based on olefin elongation procedures (Wittig, Horner−Wadsworth−Emmons, and Julia reactions),[2a] are recently being replaced by more stereoselective approaches.[4−6] Use of the Suzuki reaction[5] for the synthesis of retinoic acid analogues with unmodified side chains is limited by the instability of the corresponding conjugated alkenylboronic acids. The popular Stille reaction[6] is more versatile: alkenylstannanes remain unaltered upon treatment with a variety of reagents under a diversity of reaction conditions, and recent improvements[7] using alternative catalysts, cocatalysts, and solvents can allow the use of reaction conditions that are considerably milder that those originally reported.[6]

Since we are interested in modifying only the cyclohexenyl ring of retinoic acid, we decided to use the polyenic functionalized stannane **5** (Scheme 1) as the common Stille coupling partner of vinyltriflates **8a**−**f** (which can be prepared regioselectively from the commercially available cyclohexanones **7**[8]) in a new synthesis of retinoic acid (**1a**) and the ring-modified analogues **1b**−**f**. This paper reports our results.

Tetraenylstannane **5** was prepared in good yield and with excellent stereoselectivity by Horner−Wadsworth−Emmons condensation, at −78 °C, of known stannane **3**[9] and the carbanion derived from the treatment of phosphonate **4**[10] with *n*-BuLi and 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone (DMPU) in THF at 0 °C[11] (Scheme 1). Treatment of 2,2,6-trimethylcyclohexanone (**7a**) with LDA at −78 °C, followed by *N*-phenyltriflimide,

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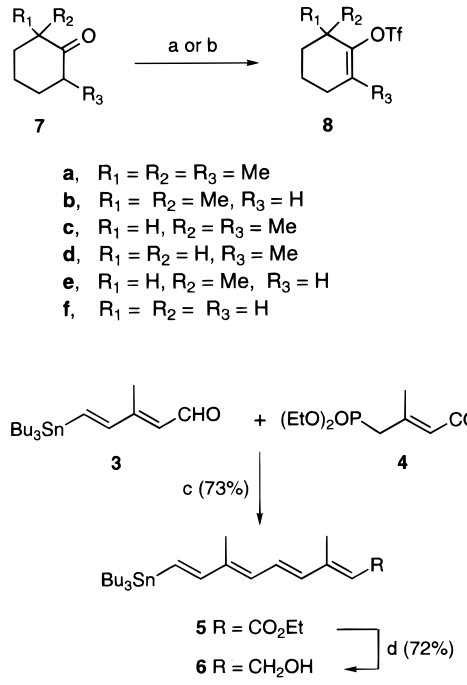
Scheme 1[a]

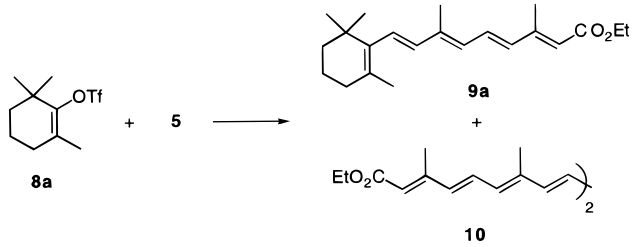


[a] Reagents and conditions: (a) LDA, THF, −78 °C, 2 h; then *N*-phenyltriflimide, THF, 0 °C, 12 h. (b) *i*-Pr_2NH, MeMgBr; then *N*-phenyltriflimide, THF, 0 °C, 12 h. (c) *n*-BuLi, DMPU, THF, 0 °C, 20 min; then aldehyde **3**, −78 °C, 3 h. (d) DIBALH, THF, −78 °C, 30 min.

gave the corresponding triflate **8a**.[12] The same procedure was employed for the synthesis of triflates **8b**, **8c**,[12b] **8e**,[12b] and **8f**[13] starting from the corresponding ketone precursors. Treatment of 2-methylcyclohexanone (**7d**) with less than 1 equiv of bromomagnesium diisopropylamide at 0 °C, followed by treatment with *N*-phenyltriflimide, afforded **8d** as the only isolable regioisomer.[14]

Table 1 shows the results of preliminary studies of the coupling reaction affording the parent ethyl retinoate **9a**.[15] Several recent modifications of the Stille protocol were examined. The catalyst system affording best conversion was Farina's "soft" palladium $Pd_2(dba)_3$ with $AsPh_3$ as ligand and *N*-methyl-2-pyrrolidinone (NMP) as solvent;[16] the optimal proportions of catalyst and ligand were found to be 2.5% $Pd_2(dba)_3$ (5% Pd) and 20% $AsPh_3$ (entries 1 and 2). As in the intramolecular reactions reported by Piers, and in contrast to other intermolecular reactions, LiCl was not necessary for coupling **5** to **8a**.[17] We tried using LiCl (3 equiv), with and without ligand (entries 3 and 4). However, since temperatures of 70 °C were required for appreciable coupling (Farina[18a] too

Table 1. Optimization of Reaction Conditions for the Palladium-Catalyzed Cross-Coupling of Tetraenylstannane 5 and Vinyl Triflate 8a



entry	**8a**:**5**	solvent	cat.[a]	additive	*T* (°C)	*t* (h)	yield **9a**[b] (%)	yield **10**[c] (%)
1	1.0:1.1	NMP	A	−	70	2	62	30[d]
2	1.1:1.0	NMP	A	−	70	2	68	29
3	1.0:1.1	NMP	B	LiCl[e]	25	2.5	77[f]	23
4	1.0:1.1	NMP	A	LiCl[e]	60	2.5	56[f]	48
5	1.0:1.1	DMF/THF	C	−	80	3	*g*	*g*
6	1.1:1.0	NMP	A	BHT[h]	70	1	61	39
7	1.1:1.0	NMP	B	−	70	5	−	78
8	1.1:1.0	NMP	A	CuI[i]	70	1	*g*	58

[a] A =2.5 mol % $Pd_2(dba)_3$, 20 mol % $AsPh_3$; B = 2.5 mol % $Pd_2(dba)_3$; C = 5 mol % $PdCl_2(CH_3CN)_2$. [b] Yield based on starting triflate **8a**. [c] Yield based on starting stannane **5**. [d] The same ratio was obtained with five freeze−thaw deoxygenation cycles and slow addition of stannane **5** (ca. 2 h, syringe pump). [e] 3 equiv. [f] Mixture of isomers. [g] Decomposition. [h] 25 mol %. [i] 5 mol %.

found **8a** to react sluggishly with arylstannanes in the presence of $AsPh_3$), omitting $AsPh_3$ allowed room-temperature coupling, but the LiCl reduced the isomeric purity of the polyene products, and omitting both $AsPh_3$ and LiCl led to the homodimer **10** alone, with no **9a** (entry 7). An alternative palladium catalyst led to extensive decomposition (entry 5).

In all coupling reactions, substantial amounts of the red homodimer **10** were obtained through a competitive process that was only slightly depressed by using excess triflate (1.1:1, entry 2). Homocoupling of vinylstannanes (and even bromides) was first described by Stille,[18b] and although Stille described it as insensitive to the presence or absence of oxygen,[18c] Farina reported it to be due to an oxidative process, caused by oxygen in the medium,[18a] that could be minimized by using both $AsPh_3$ and LiCl or by careful degassing. In this work, careful deoxygenation of reaction flasks and solvents (five freeze−thaw cycles) failed to reduce stannane homocoupling significantly, even if stannane was slowly added with a syringe pump as the reaction progressed.[19] Nor did the presence of a radical scavenger (25 mol % 2,6-di-*tert*-butyl-4-methylphenol, BHT) either reduce homocoupling or improve product yield (entry 6). Rather, it seems that factors related to substrate reactivity favor the formation of **10** (see below).

Unlike Stille reactions with PPh_3 as palladium ligand, in which copper salts[20] seem to enhance efficiency by scavenging this ligand, reactions with low-donicity $AsPh_3$

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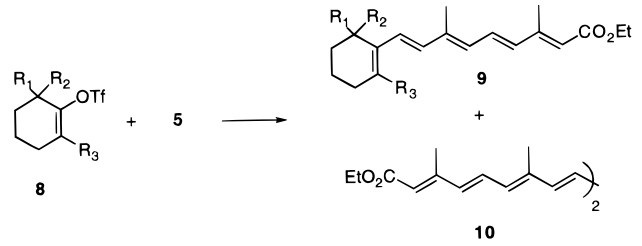
Table 2. Generalized Palladium-Catalyzed Cross-Coupling of Tetraenylstannane 5 and Vinyl Triflates 8 for the Synthesis of Ring-Modified Retinoids 9



entry[a]	R_1	R_2	R_3	T (°C)	t (h)	product	yield **9**[b] (%)	yield **10**[c] (%)
1	Me	Me	Me	70	2	**9a**	62	30
2	Me	Me	H	50	2	**9b**	82	22
3	H	Me	Me	50	2	**9c**	56[d,e]	35
4	H	H	Me	50	3	**9d**	76	18
5	H	Me	H	25	1	**9e**	70	17
6	H	H	H	25	0.5	**9f**	92	–

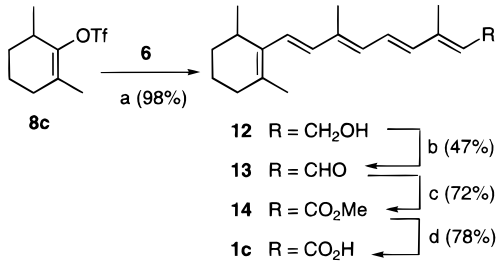
[a] Reactions were carried out with 2.5 mol % $Pd_2(dba)_3$, 20 mol % $AsPh_3$ and 1:1.1 triflate/stannane in NMP. [b] Yield based on starting triflate **8**. [c] Yield based on starting stannane **5**. [d] Mixture of isomers. [e] Lower temperatures also afforded mixtures of isomers, and longer reactions times were required.

as ligand have been reported to be enhanced by copper through the generation of an organocopper species[7] which might accelerate the rate-limiting transmetalation step of the catalytic cycle. In this work, however, addition of 5 mol % copper iodide (entry 8) or excess CuCN[4e] led to extensive decomposition.

Table 2 lists the results of applying the optimized reaction conditions (entry 1 of Table 1) to the remaining cyclohexenyl triflates, whose lesser steric hindrance of the reaction is reflected in the lower temperatures needed to achieve high conversion rates. In all but one case (entry 3) good to excellent yields of the desired ethyl retinoate analogues were obtained, and the yield of the undesired octaene **10** was reduced (to zero in the case of entry 6). Clearly the homocoupling is significant only when the reactivity of the triflate is low and requires more vigorous reaction conditions.

The coupling reaction of the 2,6-dimethyl triflate analogue **8c** was less successful. Extensive isomerization of both the starting stannane and the retinoate product was observed even after short reaction times. Reverse-phase HPLC monitoring showed very rapid catalytic turnover and deactivation within 5−10 min, even at the lowest temperature inducing coupling. Treatment of triflate **8c** under the standard reaction conditions at 40 °C with the more reactive alcoholic tetraenylstannane **6** (obtained by DIBALH reduction of ester **5**, Scheme 1) afforded 1-demethylretinol (**12**) in excellent yield, but efficiency was lost during conversion of **12** to an alkyl ester: tetrapropylammonium prerruthenate (TPAP)/*N*-methylmorpholine *N*-oxide (NMO) oxidation[21] of **12** to 1-demethylretinal (**13**),[22] followed by treatment of **13** under Corey's conditions (MnO_2/KCN/MeOH),[23] afforded the methyl ester **14** in 33% isolated yield from **8c**.

Scheme 2[a]



[a] Reagents and conditions: (a) 2.5 mol % $Pd_2(dba)_3$, 20 mol % $AsPh_3$, NMP, 40 °C, 2 h. (b) TPAP, NMO, CH_2Cl_2, 0 to 25 °C, 2 h. (c) MnO_2, KCN, MeOH, 0 °C, 2 h. (d) 1:4 2 M aqueous KOH/EtOH, reflux, 10 min.

Finally, basic hydrolysis of ethyl retinoate (**9a**) and the analogues **9b**−**f** afforded the corresponding acids **1a**−**f**.

In conclusion, tetraenylstannanes **5** and **6** were prepared and used for retinoid synthesis. Although limited in scope, this study highlights the importance of steric effects due to the electrophile, which has hitherto largely been ignored in studies of Stille reactions of vinyl systems. The occurrence of homocoupling, probably due to the low reactivity of hindered triflates, can severely limit the usefulness of highly conjugated stannanes. Despite attempts to characterize intermediates by NMR, Farina[18a] was unable to propose a detailed mechanism for the homocoupling process. We are currently examining this secondary reaction in more detail.

Experimental Section[24]

General Experimental Procedures. Proton (^{1}H NMR) and carbon (^{13}C NMR) magnetic resonance spectra were recorded in $CDCl_3$ or C_6D_6. The tin−proton and tin−carbon coupling constants (J_{Sn-H} and J_{Sn-C}) are given as an average of the ^{117}Sn and ^{119}Sn values. Infrared spectra (IR) were recorded in 0.1-mm path length sodium chloride cavity cells. High-resolution mass spectra (HRMS) data were recorded at an ionizing voltage of 70 eV.

Analytical thin-layer chromatography was performed on Merck silica gel plates with F-254 indicator. Visualization was accomplished by UV light, iodine, or a 15% ethanolic phosphomolybdic acid solution. Flash chromatography was performed using E. Merck silica gel 60 (230−400 mesh).

All reactions were performed under a dry argon atmosphere in oven- and/or flame-dried glassware. Transfer of anhydrous solvents or mixtures was accomplished with oven-dried syringes or cannula. Solvents and reagents were distilled before use: dichloromethane from calcium hydride, and tetrahydrofuran from sodium benzophenone ketyl. "Brine" refers to saturated aqueous solution of NaCl.

All reactions involving retinoids as final products or starting materials were performed under subdued red light.

6,6-Dimethyl-1-[(trifluoromethanesulfonyl)oxy]-cyclohex-1-ene (8b). A solution of diisopropylamine (0.46 mL, 3.3 mmol) in THF (3.8 mL) was cooled to 0 °C and treated with *n*-BuLi (2.94 M in hexanes, 1.12 mL, 3.3 mmol). The mixture was stirred at this temperature for 30 min and then cooled to −78 °C. A solution of 2,2-dimethylcyclohexanone (**7b**, 0.38 g, 3.0 mmol) in THF (3.8 mL) was slowly added, and the reaction mixture was stirred at −78 °C for an additional 2 h. *N*-phenyltriflimide (1.15 g, 3.21 mmol) in THF (3.8 mL) was then added, and the mixture was allowed to warm to 0 °C and was stirred at this temperature for 12 h. The solvent was then

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(24) The purity of all new compounds was judged by a combination of HPLC and ^{1}H and ^{13}C NMR analysis before mass spectra were recorded and is indicated in the Supporting Information by copies of the ^{1}H NMR/^{13}C NMR spectra of selected compounds.

removed in vacuo and the resulting residue was diluted with hexane and washed with 10% HCl. The aqueous layer was extracted with hexane, and the combined organic layers were washed with 10% HCl, 10% NaOH, and H_2O, dried ($MgSO_4$), and concentrated. The residue was distilled under vacuum (50 °C/0.1 mmHg) to obtain 0.56 g of **8b** (72%) as a colorless oil. ^{1}H NMR (400.13 MHz, C_6D_6) δ 5.66 (t, J = 4.1 Hz, 1H), 2.1−2.2 (m, 2H), 1.6−1.7 (m, 4H), 1.15 (s, 6H); ^{13}C NMR (100.61 MHz, $CDCl_3$) δ 156.3, 118.8, 116.6, 39.5, 35.4, 26.7, 25.3, 18.9.

Ethyl (2*E*,4*E*,6*E*,8*E*)-3,7-Dimethyl-9-(tri-*n*-butylstannyl)-nona-2,4,6,8-tetraenoate (5). A solution of diethyl 3-(ethoxycarbonyl)-2-methylprop-2-enylphosphonate **4** (1.07 g, 4.05 mmol) in THF (4 mL) was cooled to 0 °C and treated with DMPU (1 mL, 8.32 mmol) and *n*-BuLi (1.66 M in hexanes, 2.3 mL, 3.82 mmol). The mixture was stirred at this temperature for 20 min and then cooled to −78 °C. A solution of aldehyde **3**[9] (0.87 g, 2.25 mmol) in THF (4 mL) was slowly added, and the reaction mixture was stirred at −78 °C for 3 h. The mixture was allowed to warm to 0 °C to complete the reaction. Saturated aqueous NH_4Cl was added, and the reaction mixture was extracted with Et_2O. The combined organic layers were washed with H_2O and brine, dried ($MgSO_4$), and concentrated. The residue was purified by chromatography on silica gel (93:5:2 hexane/ethyl acetate/Et_3N) to afford 0.82 g of **5** (73%) as a yellow oil. IR (NaCl, cm^{-1}) ν 1713 (m); ^{1}H NMR (400.13 MHz, C_6D_6) δ 6.93 (dd, J = 19.2 Hz, $^3J_{Sn-H}$ = 62.7 Hz, 1H), 6.89 (dd, J = 15.1, 11.4 Hz, 1H), 6.61 (dd, J = 19.2 Hz, $^2J_{Sn-H}$ = 97.7 Hz, 1H), 6.18 (d, J = 15.1 Hz, 1H), 6.13 (d, J = 11.4 Hz, 1H), 5.98 (s, 1H), 4.11 (q, J = 7.1 Hz, 2H), 2.46 (s, 3H), 1.82 (s, 3H), 1.6−1.7 (m, 6H), 1.4−1.5 (m, 6H, 3 × CH_2), 1.0−1.1 (m, 9H), 0.99 (t, J = 7.3 Hz, 9H); ^{1}H NMR (400.13 MHz, $CDCl_3$) δ 6.98 (dd, J = 15.0, 11.4 Hz, 1H), 6.63 (d, J = 19.2 Hz, $^3J_{Sn-H}$ = 61.4 Hz, 1H), 6.43 (d, J = 19.2 Hz, $^2J_{Sn-H}$ = 63.6 Hz, 1H), 6.32 (d, J = 15.0 Hz, 1H), 6.17 (d, J = 11.4 Hz, 1H), 5.78 (s, 1H), 4.17 (q, J = 7.1 Hz, 2H), 2.36 (s, 3H), 1.95 (s, 3H), 1.5−1.6 (m, 6H), 1.2−1.4 (m, 9H), 0.8−1.0 (m, 15H); ^{13}C NMR (100.61 MHz, $CDCl_3$) δ 167.1, 152.5, 150.1 ($^5J_{Sn-C}$ = 10.4 Hz), 140.0, 136.0, 131.2 ($^1J_{Sn-C}$ = 213.9 Hz), 131.0, 130.4, 118.9, 59.7, 29.1 ($^3J_{Sn-C}$ = 20.4 Hz), 27.3 ($^2J_{Sn-C}$ = 54.0 Hz), 14.7, 13.8, 13.7, 12.4, 9.53 ($^1J_{Sn-C}$ = 336.5 Hz). HRMS *m*/*z* (M^+) calcd for $C_{21}H_{35}O_2{}^{118}Sn$ 437.1653, found 437.1666.

Ethyl Retinoate (9a). General Procedure for Stille Reactions. A solution of $Pd_2(dba)_3$ (3.4 mg, 0.004 mmol) in NMP (1.4 mL) was treated with $AsPh_3$ (9 mg, 0.029 mmol) and, after 5 min, with a solution of triflate **8a** (40 mg, 0.147 mmol) in NMP (0.2 mL). After stirring for 10 min, a solution of stannane **5** (80 mg, 0.161 mmol) in NMP (0.2 mL) was added. The resulting solution was stirred at 70 °C for 2 h. After cooling, saturated aqueous KF solution (2 mL) was added, and the mixture was stirred for 30 min and extracted with Et_2O. The combined organic extracts were washed with H_2O and saturated aqueous KF solution, dried over $MgSO_4$, and concentrated to dryness. The residue was purified by chromatography (SiO_2, 98:2 hexane/ethyl acetate) to afford 30 mg (62%) of **9a**[15] as a yellow oil and 10 mg (30%) of diethyl (2*E*,4*E*,6*E*,8*E*,10*E*,12*E*,14*E*,16*E*)-3,7,12,16-tetramethyloctadeca-2,4,6,8,10,12,14,16-octaene-1,18-dioate (**10**) as a red solid (mp: 150−158 °C). Data for **9a**: ^{1}H NMR (400.13 MHz, $CDCl_3$) δ 7.00 (dd, J = 15.0, 11.2 Hz, 1H), 6.29 (d, J = 15.0 Hz, 1H), 6.28 (d, J = 16.1 Hz, 1H), 6.15 (d, J = 11.2 Hz, 1H), 6.14 (d, J = 16.1 Hz, 1H), 5.78 (s, 1H), 4.17 (q, J = 7.1 Hz, 2H), 2.36 (d, J = 1.0 Hz, 3H), 2.0−2.1 (m, 2H), 2.00 (s, 3H), 1.72 (s, 3H), 1.4−1.6 (m, 4H), 1.29 (t, J = 7.1 Hz, 3H), 1.03 (s, 6H); ^{13}C NMR (100.61 MHz, $CDCl_3$) δ 167.2, 152.8, 139.5, 137.6, 137.2, 135.1, 130.9, 130.0, 129.4, 128.5, 118.5, 59.7, 39.4, 34.2, 33.0, 28.9, 21.8, 19.1, 14.3, 13.7, 12.9. Data for **10**: IR (NaCl, cm^{-1}) ν 1698 (s), 1574 (m), 1150 (s); ^{1}H NMR (400.13 MHz, $CDCl_3$) δ 6.98 (dd, J = 15.0, 11.5 Hz, 2H), 6.4−6.5 (m, 4H), 6.33 (d, J = 15.1 Hz, 2H), 6.24 (d, J = 11.5 Hz, 2H), 5.80 (s, 2H), 4.18 (q, J = 7.1 Hz, 4H), 2.36 (s, 6H), 2.00 (s, 6H), 1.30 (t, J = 7.1 Hz, 6H); ^{13}C NMR (100.61 MHz, $CDCl_3$) δ 167.6, 152.9, 139.6, 138.2, 136.6, 132.2, 131.1, 130.9, 119.6, 60.2, 14.8, 14.2, 13.4; HRMS *m*/*z* (M^+) calcd for $C_{26}H_{34}O_4$ 410.2457, found 410.2463.

Ethyl 5-Demethylretinoate (9b). In accordance with the general procedure described above, a mixture of $Pd_2(dba)_3$ (5 mg, 0.005 mmol), $AsPh_3$ (13.5 mg, 0.044 mmol), triflate **8b** (57 mg, 0.22 mmol), and stannane **5** (120 mg, 0.24 mmol) in NMP (3.3 mL) was stirred at 50 °C for 2 h. The residue was purified by chromatography (SiO_2, 98:2 hexane/ethyl acetate) to afford 57 mg (82%) of **9b**[25] as a yellow oil and 11 mg (22%) of **10**.

Ethyl 1,1-Didemethylretinoate (9d). In accordance with the general procedure described above, a mixture of $Pd_2(dba)_3$ (6.9 mg, 0.0075 mmol), $AsPh_3$ (18.4 mg, 0.06 mmol), triflate **8d** (67 mg, 0.3 mmol), and stannane **5** (163 mg, 0.33 mmol) in NMP (4.4 mL) was stirred at 50 °C for 3 h. The residue was purified by chromatography (SiO_2, 98:2 hexane/ethyl acetate) to afford 68 mg (76%) of **9d**[25] as a yellow oil and 12 mg (18%) of **10**.

Ethyl 1,5-Didemethylretinoate (9e). In accordance with the general procedure described above, a mixture of $Pd_2(dba)_3$ (5.7 mg, 0.006 mmol), $AsPh_3$ (15.3 mg, 0.05 mmol), triflate **8e** (61 mg, 0.25 mmol), and stannane **5** (136 mg, 0.275 mmol) in NMP (3.3 mL) was stirred at room temperature for 1 h. The residue was purified by chromatography (SiO_2, 98:2 hexane/ethyl acetate) to afford 52 mg (70%) of **9e**[25] as a yellow oil and 10 mg (17%) of **10**.

Ethyl 1,1,5-Tridemethylretinoate (9f). In accordance with the general procedure described above, a mixture of $Pd_2(dba)_3$ (3.6 mg, 0.004 mmol), $AsPh_3$ (9.6 mg, 0.031 mmol), triflate **8f** (36 mg, 0.156 mmol), and stannane **5** (85 mg, 0.172 mmol) in NMP (2.3 mL) was stirred at room temperature for 30 min. The residue was purified by chromatography (SiO_2, 98:2 hexane/ethyl acetate) to afford 41 mg (92%) of **9f**[25] as a yellow oil.

Retinoic Acid (1a). General Procedure for Ester Hydrolysis. A solution of ethyl retinoate (**9a**; 20 mg, 0.061 mmol) in 1.9 mL of a 1:4 mixture of 2 M aqueous KOH and ethanol was refluxed for 10 min. The solution was cooled to room temperature and diluted with Et_2O (5 mL) and brine (5 mL). The organic layer was washed with H_2O, and the combined aqueous layers were acidified with 5% HCl to give a solution which was extracted with Et_2O. The combined organic extracts were washed with H_2O and brine and then dried ($MgSO_4$) and concentrated. The residue was purified on silica gel (95:5 CH_2Cl_2/MeOH) to afford 13 mg of **1a** (71%) as a yellow solid (mp 178−180 °C, EtOH). Physical and spectroscopic data matched those of commercially available retinoic acid.

5-Demethylretinoic Acid (1b). Application of the general procedure for ester hydrolysis to ethyl 5-demethylretinoate (**9b**) afforded, after chromatography on silica gel (95:5 CH_2Cl_2/MeOH), an 83% yield of 5-demethylretinoic acid (**1b**) as a yellow solid (mp 83−85 °C, EtOH).[25]

1,1-Didemethylretinoic Acid (1d). Application of the general procedure for ester hydrolysis to ethyl 1,1-didemethylretinoate (**9d**) afforded, after chromatography on silica gel (95:5 CH_2Cl_2/MeOH), a 92% yield of 1,1-didemethylretinoic acid (**1d**) as a yellow solid (mp 211−213 °C, EtOH).[25]

1,5-Didemethylretinoic Acid (1e). Application of the general procedure for ester hydrolysis to ethyl 1,5-didemethylretinoate (**9e**) afforded, after chromatography on silica gel (95:5 CH_2Cl_2/MeOH), a 66% yield of 1,5-didemethylretinoic acid (**1e**) as a yellow solid (mp 170−172 °C, EtOH).[25]

1,1,5-Tridemethylretinoic Acid (1f). Application of the general procedure for ester hydrolysis to ethyl 1,1,5-tridemethylretinoate (**9f**) afforded, after chromatography on silica gel (95:5 CH_2Cl_2/MeOH), a 75% yield of 1,1,5-tridemethylretinoic acid (**1f**) (mp 173−175 °C, EtOH).[25]

(2*E*,4*E*,6*E*,8*E*)-3,7-Dimethyl-9-(tri-*n*-butylstannyl)nona-2,4,6,8-tetraen-1-ol (6). A cooled (−78 °C) solution of tetraenylstannane **5** (0.25 g, 0.5 mmol) in THF (1.7 mL) was treated with DIBALH (1 M, 1 mL, 1 mmol) and stirred at −78 °C for 1 h. The reaction was quenched with a 2:3 MeOH/Et_2O mixture (2 mL) and allowed to reach room temperature. H_2O was added, and the mixture was extracted with Et_2O. The

(25) Spectroscopic data are provided in the Supporting Information.

combined organic extracts were washed with 10% NH_4Cl and brine, dried ($MgSO_4$), and concentrated to yield 0.16 g of **6** (72%) as a yellow oil which was used in the next step without further purification. IR (NaCl, cm^{-1}) ν 3500−3100 (br); ^1H NMR (400.13 MHz, C_6D_6) δ 6.95 (dd, J = 19.2 Hz, $^3J_{Sn-H}$ = 64.1 Hz, 1H), 6.62 (dd, J = 15.1, 11.3 Hz, 1H), 6.50 (dd, J = 19.2 Hz, $^2J_{Sn-H}$ = 69.0 Hz, 1H), 6.2−6.3 (m, 2H), 5.59 (t, J = 6.6 Hz, 1H), 4.01 (br, 2H), 1.89 (s, 3H), 1.65 (quintet, J = 7.3 Hz, 6H), 1.59 (s, 3H), 1.40 (sextet, J = 7.3 Hz, 6H), 1.05 (t, J = 7.3 Hz, 6H), 0.94 (t, J = 7.3 Hz, 9H); ^{13}C NMR (100.61 MHz, C_6D_6) δ 151.7 ($^4J_{Sn-C}$ = 10.2 Hz), 138.5, 136.8 ($^3J_{Sn-C}$ = 66.1 Hz), 135.9, 132.6, 132.5, 127.8, 125.1, 59.5, 29.7 ($^3J_{Sn-C}$ = 20.4 Hz), 27.9 ($^2J_{Sn-C}$ = 54.0 Hz), 14.1, 12.6, 12.4, 10.0 ($^1J_{Sn-C}$ = 334.2 Hz).

1-Demethylretinol (12). The general procedure for Stille reactions coupled triflate **8c** (35 mg, 0.15 mmol) and stannane **6** (82 mg, 0.165 mmol) after the reaction mixture was stirred at 40 °C for 2 h. The residue was purified by chromatography (silica, 80:18:2 hexane/ethyl acetate/Et_3N) to afford 42 mg (98%) of **12** as a yellow oil, which was immediately used in the next reaction (samples stored after their preparation underwent extensive decomposition).

1-Demethylretinal (13). To a solution of the alcohol **12** (88 mg, 0.323 mmol) in CH_2Cl_2 (4 mL) were added 4 Å molecular sieves and NMO (76 mg, 0.647 mmol). After stirring for 10 min and cooling to 0 °C, TPAP (5.7 mg, 0.016 mmol) was added and the mixture was stirred for 1 h at 0 °C, allowed to reach room temperature, stirred for an additional 1 h, diluted with CH_2Cl_2, filtered, and washed with saturated aqueous Na_2SO_3, brine, and saturated aqueous $CuSO_4$. The organic layer was dried over $MgSO_4$, filtered, and concentrated. The residue was purified by chromatography (silica, 93:5:2 hexane/ethyl acetate/Et_3N) to afford 41 mg (47%) of **13** as a yellow oil.[22] IR (NaCl, cm^{-1}) ν 1657 (s); ^1H NMR (400.13 MHz, C_6D_6) δ 10.02 (d, J = 7.9 Hz, 1H), 6.86 (dd, J = 15.0, 11.4 Hz, 1H), 6.81 (d, J = 15.0 Hz, 1H), 6.41 (d, J = 15.0 Hz, 1H), 6.08 (d, J = 11.4 Hz, 1H), 6.07 (d, J = 15.0 Hz, 1H), 6.00 (d, J = 7.9 Hz, 1H), 2.70 (br, 1H), 1.8−2.0 (m, 2H), 1.82 (s, 3H), 1.73 (s, 3H), 1.68 (s, 3H), 1.4−1.7 (m, 4H), 1.17 (d, J = 7.0 Hz, 3H); ^{13}C NMR (100.61 MHz, C_6D_6) δ 188.9, 153.7, 141.6, 135.5, 135.0, 134.5, 132.2, 131.0, 130.0, 128.8, 128.7, 34.0, 30.6, 28.6, 20.9, 20.1, 18.4, 13.4, 12.9; HRMS m/z (M^+) calcd for $C_{19}H_{26}O$ 270.1984, found 270.1986.

Methyl 1-Demethylretinoate (14). To a cooled (0 °C) solution of aldehyde **13** (40 mg, 0.148 mmol) in MeOH (1 mL) was added a mixture of KCN (48 mg, 0.741 mmol) and MnO_2 (257 mg, 2.96 mmol). After being stirred at 0 °C for 2 h, the mixture was filtered, diluted with Et_2O, and washed with brine. The residue was purified on silica gel (98:2 hexane/ethyl acetate) to afford 32 mg (72%) of **14** as a yellow oil. IR (NaCl, cm^{-1}) ν 1713 (m); ^1H NMR (400.13 MHz, $CDCl_3$) δ 7.02 (dd, J = 15.0, 11.4 Hz, 1H), 6.73 (d, J = 15.9 Hz, 1H), 6.30 (d, J = 15.9 Hz, 1H), 6.29 (d, J = 15.0 Hz, 1H), 6.22 (d, J = 11.4 Hz, 1H), 5.78 (s, 1H), 3.72 (s, 3H), 2.67 (br, 1H), 2.37 (s, 3H), 2.0−2.3 (m, 2H), 2.02 (s, 3H), 1.82 (s, 3H), 1.6−1.8 (m, 4H), 1.08 (d, J = 7.0 Hz, 3H); ^{13}C NMR (100.61 MHz, $CDCl_3$) δ 167.6, 153.1, 140.3, 135.0, 134.7, 133.5, 131.2, 130.1, 129.8, 127.5, 117.8, 50.9, 33.4, 29.9, 27.7, 20.2, 19.7, 17.6, 13.8, 13.0; HRMS m/z (M^+) calcd for $C_{20}H_{28}O_2$ 300.2089, found 300.2085.

1-Demethylretinoic Acid (1c). Application of the general procedure for ester hydrolysis to methyl 1-demethylretinoate (**14**) afforded, after chromatography on silica gel (95:5 CH_2Cl_2/MeOH), a 78% yield of 1-demethylretinoic acid (**1c**) as a yellow solid (mp 187−190 °C, EtOH). IR (NaCl, cm^{-1}) ν 3600−3200 (br), 1679 (s); ^1H NMR (400.13 MHz, $CDCl_3$) δ 7.06 (dd, J = 15.0, 11.5 Hz, 1H), 6.75 (d, J = 16.0 Hz, 1H), 6.32 (d, J = 15.0 Hz, 1H), 6.31 (d, J = 16.0 Hz, 1H), 6.22 (d, J = 11.5 Hz, 1H), 5.80 (s, 1H), 2.68 (br, 1H), 2.38 (s, 3H), 2.0−2.2 (m, 2H), 2.04 (s, 3H), 1.83 (s, 3H), 1.5−1.8 (m, 4H), 1.08 (d, 3H, J = 7.0 Hz); ^{13}C NMR (100.61 MHz, $CDCl_3$) δ 172.3, 155.8, 141.4, 135.7, 135.0, 133.9, 132.4, 130.5, 130.2, 128.2, 117.8, 33.9, 30.3, 28.2, 20.6, 20.2, 18.0, 14.4, 13.5; HRMS m/z (M^+) calcd for $C_{19}H_{26}O_2$ 286.1933, found 286.1932.

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Supporting Information Available: Characterization data for compounds **9b**, **9d**−**f**, and **1d**−**f**, and copies of ^1H/^{13}C NMR spectra of selected compounds described in the text (38 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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