67858-71-3; **30**, 63321-98-2; **31**, 63321-99-3; **32**, 67919-57-7; *meso*-tartaric dialdehyde, 58066-70-9; *cis*-3,4-dihydroxy-2,5-dimethyltetrahydrofuran, 67858-72-4; benzylamine hydrochloride, 3287-99-8; 1,3-acetonedicarboxylic acid, 542-05-2; allyl bromide, 106-95-6; allyl chloride, 107-05-1.

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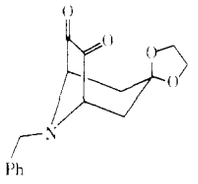

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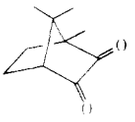

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Synthesis of Vitamin A and Related Compounds via a π-Allylpalladium Complex

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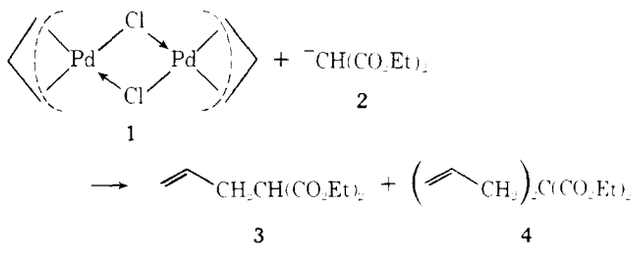
Reaction of the anion derived from 3-methyl-1-(phenylsulfonyl)-5-(2,6,6-trimethyl-1-cyclohexen-1-yl)penta-2,4-diene (**8a**), in dimethylformamide and in the presence of triphenylphosphine, with the π-allyl complex **9** prepared from prenyl acetate (**6**) and palladium(II) chloride gave 1-acetoxy-3,7-dimethyl-5-(phenylsulfonyl)-9-(2,6,6-trimethyl-1-cyclohexen-1-yl)nona-2,6,8,-triene (**10a**) in 52% yield. Treatment of **10a** with sodium ethoxide in boiling ethanol produced a stereoisomeric mixture of vitamin A (**11a**), which contained a preponderance of the all-trans isomer, in 81% yield. The reaction of **9** with some related polyisoprenoid sulfones, followed by elimination of benzenesulfinic acid, is also described. The stereostructure of **9** was established by X-ray crystallography.

Although the application of transition metal complexes in the synthesis of organic substances has burgeoned during the past decade,[1] use of these complexes in the construction of intricate natural products has emerged only recently. In this context the efforts by Corey and his collaborators using π-allylnickel complexes[2] and by Trost and his associates using π-allylpalladium complexes[3] are preeminent. Some recent, notable achievements in this area are exemplified by a facile synthesis of the alkaloid cephalotaxinone by Semmelhack[4] using a nickel complex, an elegant prostaglandin synthesis by Holton[5] using a palladium complex, and an intriguing steroid synthesis by Vollhardt[6] employing a cobalt complex. In this paper we describe a novel synthesis of vitamin A (**11a**),[7] and some related polyisoprenoids, using the crystalline π-allylpalladium complex **9**.

It is well established[8] that π-olefinpalladium and π-allylpalladium complexes are highly susceptible to attack by nucleophiles, a reaction which forms the basis of the Wacker process[9] for producing acetaldehyde from ethylene and water in the presence of palladium(II) chloride. Extension of this reaction to include carbanions was first demonstrated by Tsuji, who in 1965 reported[10] that complex **1** reacted with malonate anion in a mixture of ethanol and dimethyl sulfoxide at room temperature to give esters **3** and **4** (Scheme I).

The synthetic potential of Tsuji's reaction remained unrecognized until the recent, excellent studies by Trost and his collaborators.[3] These workers (and ourselves) have found that Tsuji's original experiment is not of general applicability in organic synthesis since it fails, or gives only very poor yields of products, when alkyl-substituted π-allylpalladium complexes that do not bear electron-withdrawing groups are used.

Scheme I



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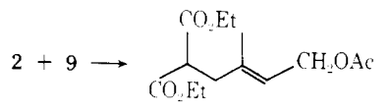
This limitation of the scope of the reaction was removed when Trost reported[3b,16] that alkylation of these inert π-allylpalladium complexes was possible if they were activated by phosphines or phosphites (vide infra). In addition, Trost and his collaborators have also shown that the reaction of carbanions with π-allylpalladium complexes is regio- and stereospecific; i.e., carbanion attack on unsymmetrical π-allylpalladium complexes occurs at the least substituted allylic carbon, and the geometry of the double bond generated in the product is related to the geometry of the complex. In general, syn complexes, which are thermodynamically more stable than anti complexes, give *E* olefins.

One of our objectives in applying the palladium-mediated alkylation reaction was to synthesize vitamin A (**11a**) by a process which did not entail extensive functionalization of intermediates and which was stereospecific. In addition, we desired a synthesis which was amenable to a $C_5 + C_{15} = C_{20}$ convergent approach.[11] Prenyl acetate (**6**) and the crystalline sulfone **8a**[12,13] were chosen as the C_5 and C_{15} units, respectively. The latter unit is readily available from the reaction between vinyl-β-ionol (**5a**) and benzenesulfinic acid, and the former, also readily available, embodies the alcohol function destined to be that group in the vitamin. The reaction sequence used in our synthesis is outlined in Scheme II.

Results and Discussion

Reaction of an acetic acid–acetic anhydride solution of prenyl acetate with palladium(II) chloride in the presence of sodium chloride, sodium acetate, and cupric chloride[14] afforded a 71% yield of crystalline complex **9**, whose structure and stereochemistry were rigorously established by spectral and X-ray crystallographic analyses. **9** is a typical π-allylpalladium complex; i.e., it is square planar (d^8), dimeric, and soluble in most organic solvents.[15] In the crystal structure of **9**, one PdCl–prenyl acetate unit is related to the other unit in the dimer by a center of symmetry. Consequently, the C-7 methyl groups are trans to each other; similarly, the acetate groups are trans to each other. A stereoscopic drawing of **9** is shown in Figure 1, and full spectral data, including photoelectron and ^{13}C NMR, are given in the Experimental Section.

In a preliminary experiment, complex **9** was reacted with malonate anion in Me_2SO at room temperature to give the desired ester **13** in 25% yield. Despite this low yield, we proceeded to examine the reaction between **9** and the anion generated from sulfone **8a** with sodium hydride in Me_2SO. To our surprise a complex mixture was produced which contained none of the required product **10a**. A similar result was obtained with DMF as solvent. When, however, the reaction was carried out in DMF and in the presence of a large excess of triphenylphosphine (ca. 4 equiv per Pd),[16] a rapid reaction ensued with the precipitation of a pale yellow solid, presumably $Pd(PPh_3)_4$.[17] Workup of the reaction mixture furnished a 52% yield of all-*E* **10a**, identical (melting point, mixture melting point, TLC, and UV, IR, NMR, and mass spectra) with a sample prepared by an alternative route.[12]



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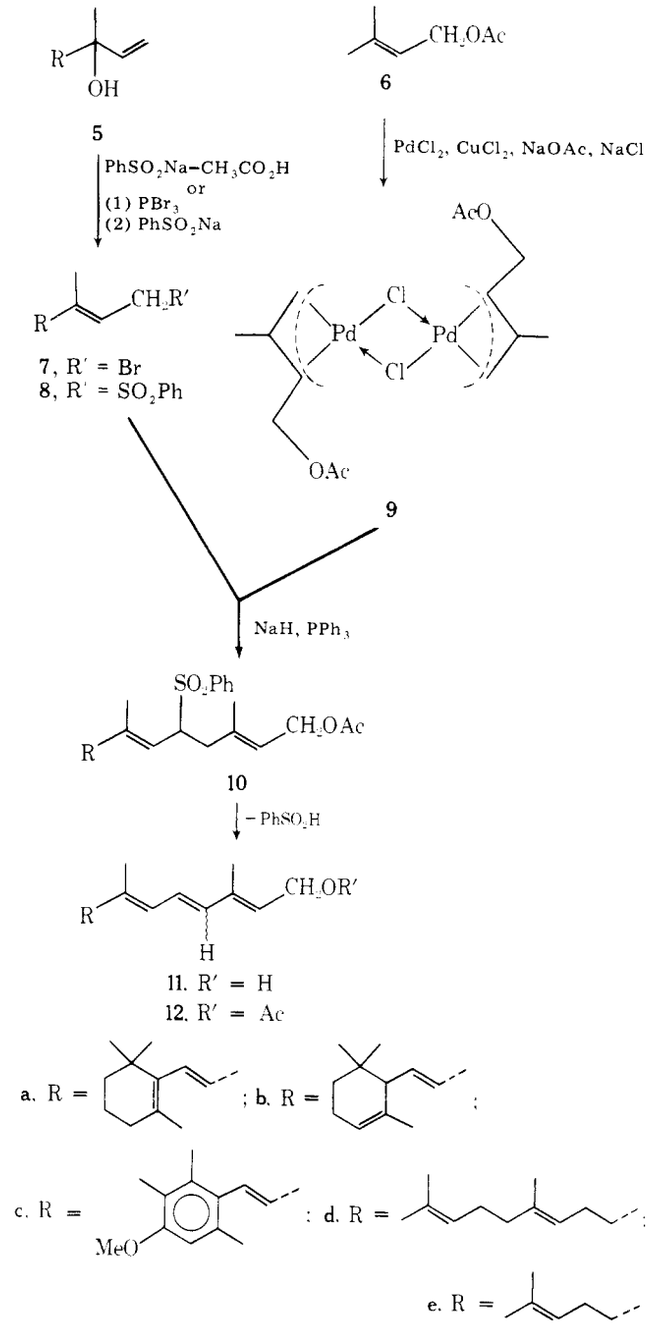
The synthesis of vitamin A was completed by elimination of benzenesulfinic acid from **10a** using sodium ethoxide in boiling ethanol.[12] Crude vitamin A thus produced (81% yield) was acetylated (acetic anhydride–pyridine), and the crude acetate was analyzed by high-pressure liquid chromatography using naphthalene as an internal standard. The analysis revealed the following distribution of stereoisomers: all-trans, 67%; 9/9,13-dicis, 9%; 13-cis, 1%; and 11-cis, 1%; no separation between the 9 and 9,13-dicis isomers was achieved. Crystallization of the crude acetate afforded vitamin A acetate (**12a**) which contained 95% of the all-trans isomer.

Scheme II



The reaction of **9** with a few other isoprenoid sulfones, **8b, 8c, 8d,** and **8e,** proceeded as anticipated to give the required products **10b, 10c, 10d,** and **10e,** respectively, in unoptimized yields of 20–65%; ^1H NMR spectroscopy indicated that these sulfones were most likely the all-trans isomers. However, unlike the situation with **10a,** we encountered considerable difficulties in effecting the elimination of benzenesulfinic acid from these C_{20} sulfones. For example, treatment of **10b** with sodium ethoxide in boiling ethanol failed to give any α-vitamin A (**11b**);[18] an estimated (UV) yield of ~10% was subsequently obtained using KOH in hot aqueous 1-butanol. However, the aromatic vitamin A analogue **11c,** the corresponding acid of which is of some interest in the treatment of certain experimentally induced tumors,[19] was obtained in 64% yield from **10c** with sodium ethoxide in boiling ethanol. The use of

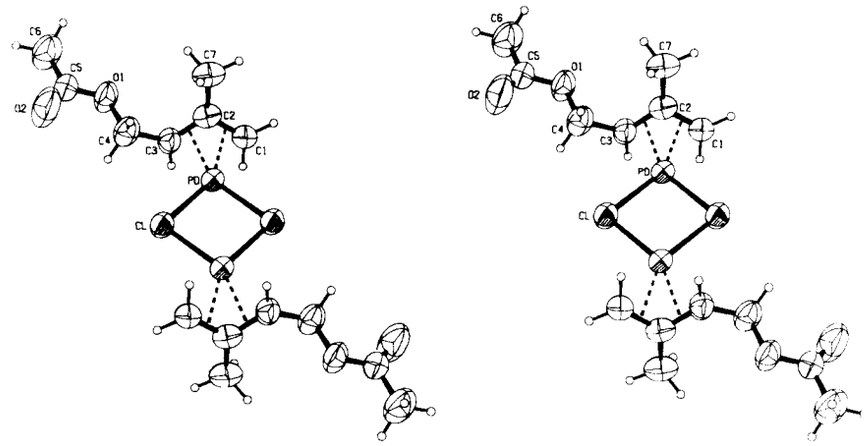
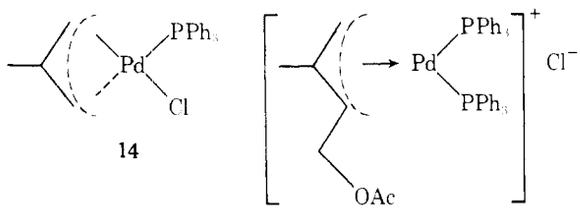


Figure 1. A stereoscopic drawing of complex 9.

solid-phase systems[20] in these eliminations was not investigated.

The crystalline C_{15} sulfones **8a** and **8c** were prepared by treating the corresponding allylic alcohols **5a** and **5c**, respectively, with the sodium salt of benzenesulfinic acid in acetic acid at room temperature. Sulfones **8b, 8d,** and **8e** were obtained from the reaction between the corresponding crude allylic bromides **7b, 7d,** and **7e,** respectively; these in turn were acquired severally by the low-temperature bromination of allylic alcohols **5b, 5d,** and **5e** with PBr_3 in ether.[21] In all cases the C_{15} sulfones were purified by chromatography and, where applicable, crystallization, and they were judged to be chemically and stereochemically pure by TLC and ^1H NMR spectroscopy. No attempt was made to optimize their yields.

We have already mentioned that prior "activation" of complex **9** (with PPh_3 in this study) was apparently necessary for it to react with the sulfone anions used, but not for malonate anion in Me_2SO. Powell and Shaw have reported[22] that the products obtained from the reaction between π-allylpalladium complexes and triphenylphosphine depend to some extent on the nature of the solvent used and on the quantity of phosphine employed. With 1 mol of triphenylphosphine (per Pd) in nonpolar solvents σ-allyl complexes (e.g., **14**) are produced, whereas 4 mol of phosphine (per Pd) in polar solvents gave cationic complexes, exemplified by **15** (for **9**). Intermediate molar quantities of phosphine gave mixtures which were described as "dynamic σ-allyl systems".



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The cationic complex **15,** an ambient electrophile, is presumably one of the species that undergoes nucleophilic substitution at carbon with the sulfone anions used in this study; the involvement of cationic complexes in this reaction was first suggested by Trost.[3b,16] Although cationic complexes related to **15** have been implicated[23] also in the reaction between π-allylpalladium complexes and Me_2SO, and thus account for the formation of **13** from **2** and **9** in Me_2SO without the need for added PPh_3, the low yield of **13** is in accord with Trost's observation that Me_2SO, a poor π acceptor, does not make palladium as electropositive as do phosphine ligands. Other factors that are expected to influence this reaction are electronic and steric effects associated with the anion, and also the equilibrium between π-allyl, σ-allyl, and cationic complexes of palladium.

Experimental Section

All reactions involving polyenes were carried out in amber-colored flasks and in an inert atmosphere (argon or nitrogen). Melting points were determined on a Thomas-Hoover capillary apparatus and are uncorrected. Unless otherwise indicated, infrared (IR) and ultraviolet (UV) spectra were determined in chloroform and ethanol, respectively. ^1H NMR spectra were determined at 100 MHz (Varian XL-100 or HA-100 spectrometer) in $CDCl_3$ with Me_4Si as an internal standard. Chemical shifts are expressed in δ values (ppm) and coupling constants (J) in hertz (Hz) (s = singlet, d = doublet, t = triplet, m = multiplet, and br = broad). Mass spectra were recorded on a Varian CH-5 or CEC-110 instrument operating at 70 eV; m/e values are given with relative intensities in parentheses. Thin-layer chromatography (TLC) was carried out on silica gel (Pf_{254}, Merck, Darmstadt) plates, and, where necessary, spots were made visible by spraying with 10% ethanolic phosphomolybdic acid followed by heating to ~120 °C. Preparative-scale TLC was carried out on 1 mm thick silica gel plates. Identification of the isomers of vitamin A acetate was achieved by high-pressure liquid chromatography (LC) using conditions reported elsewhere.[12]

Preparation of 1-Acetoxy-3-methylbut-2-enyl-π-allylpalladium Chloride Dimer (9). To a three-neck, 1-L, round-bottom flask equipped with a mechanical stirrer, addition funnel, condenser, thermometer, and an argon inlet tube was added 24.0 g (0.293 mol) of anhydrous sodium acetate, 17.0 g (0.293 mol) of NaCl, 23.4 g (0.175 mol) of $CuCl_2$, 4.0 g (0.022 mol) of palladium(II) chloride, 250 mL of acetic acid, and 5.0 mL of acetic anhydride. The mixture was stirred at 95 °C for 2 h, cooled to 60 °C, and then treated with 6.65 g (0.05 mol) of prenyl acetate (**6**)[24] in 15 mL of acetic acid. The mixture was stirred at 85 °C for 2 h, cooled to room temperature, and filtered through a pad of Celite (~20 g). The Celite was washed with 20 mL of $CHCl_3$, and the combined washing and filtrate were evaporated in vacuo to give an orange-colored gum. Chromatography of the latter on 100 g of silica gel (Type 60) with chloroform as eluent, collection of the pale yellow band, and evaporation of the solvent gave 9.6 g (71%) of **9** as pale yellow crystals, mp 155–159 °C. Recrystallization from CH_2Cl_2–hexane afforded 5.3 g of pure **9** (a further 3.2 g was obtained from the mother liquor): mp 157–159 °C; UV 330 nm (ϵ 2030); IR 1740, 1230 cm^{-1}; ^1H NMR δ 2.02 (3 H, s), 2.12 (3 H, s), 2.88 (1 H, s), 3.57 (1 H, t, J = 7 Hz), 3.88 (1 H, s), 4.38 (2 H, d, J = 7 Hz); ^{13}C NMR (at 25.4 MHz, $CDCl_3$) 18.3 (q, C-6), 20.6 (q, C-7), 61.0 (t, C-1), 62.3 (t, C-4), 72.1 (d, C-3), 125.6 (s, C-2), 170.0 (s, C-5) ppm. The X-ray photoelectron spectrum (ESCA)[25] gave the following binding energies (assignments and relative amounts are given in parentheses): 200 (Cl_{2p}, 0.304), 270 (Cl_{2s}, 0.079), 285 (C_{1s}, 1.00), 335 and 340 (Pd_{3d}, 0.149 and 0.130, respectively), 535 (Pd_{3p} and O_{1s}, unresolved) eV. Anal. Calcd for $C_{14}H_{22}O_4Cl_2Pd_2$: C, 31.25; H, 4.12; Cl, 13.18; Pd, 39.55. Found: C, 31.03; H, 3.97; Cl, 13.28; Pd, 39.40.

X-ray Crystallographic Analysis of 9. Crystals of **9** belong to space group $I2/a$, with a = 29.987 (12) Å, b = 4.690 (2) Å, c = 13.363 (5) Å, β = 92.73 (3)°, Z = 4, d_{calcd} = 1.902 g cm^{-3}, and μ(Cu Kα) = 187.0 cm^{-1}. Of a total of 1909 accessible reflections, which were collected on a Hilger-Watts diffractometer (θ–2θ scans, Ni-filtered Cu Kα radiation, pulse height discrimination), 1251 were considered to be observed [$I > 2.5\sigma(I)$] and were used in the structure analysis.

Application of Patterson and Fourier techniques with full-matrix least-squares refinement led to the final discrepancy indices of R = 0.053 and wR = 0.046. In the final refinement, hydrogen atoms had isotropic parameters and other atoms had anisotropic thermal parameters, respectively.

The angle between the plane of the five carbon atoms of the prenyl moiety and the plane of the two palladium and two chlorine atoms is 105°. C-2 is 0.66 Å from the Pd_2Cl_2 plane, and C-1 and C-3 are 0.05 and 0.03 Å, respectively, from the Pd_2Cl_2 plane on the opposite side from C-2. The two Pd–Cl distances are 2.410 (3) and 2.406 (3) Å, and the Cl–Pd–Cl angle is 88.1 (1)°. The Pd–C distances are 2.115 (10), 2.138 (9), and 2.091 (10) Å from C-1, C-2, and C-3, respectively. The C-1–C-2 and C-2–C-3 distances are 1.394 (12) and 1.419 (12) Å, respectively.

1-Acetoxy-3,7-dimethyl-5-(phenylsulfonyl)-9-(2,6,6-trimethylcyclohexen-1-yl)nona-2,6,8-triene (10a). To a cooled (−10 °C), stirred mixture of 170 mg (4.0 mmol, 57%) of NaH in 25 mL of anhydrous DMF was added, under argon, 1.38 g (4.0 mmol) of sulfone **8a**[12] in 10 mL of anhydrous DMF. Stirring was continued for a further 15 min, and the resulting deep red solution was treated with 4.20 g (16 mmol) of triphenylphosphine followed by 1.076 g (2 mmol) of π-allylpalladium complex **9**. After ~15 min, a pale yellow solid precipitated from the reaction mixture. The mixture was stirred at −5 °C for 1 h and then at 10 °C for 2 h, it was filtered through a plug of Celite, and the filtrate was diluted with 100 mL of saturated brine. The mixture was extracted with ether (2 × 10 mL), and the extract was washed, dried ($MgSO_4$), and evaporated to give a red gum. TLC analysis (1:1 ether–hexane) showed two main spots: product (R_f 0.34) and triphenylphosphine (R_f 0.48); the starting material had R_f 0.40. Preparative-scale TLC (1:1 ether–hexane, silica gel) followed by extraction into CH_2Cl_2, filtration, and evaporation gave 980 mg (52%) of **10a** which was crystallized from methanol at −20 °C to give 680 mg of pure **10a:** mp 85–86 °C; UV (*i*-PrOH) 215 (ε 20 470), 248 sh (12 880), 267 sh (14 620), 273 (15 020) nm; IR 1737, 1145, 970, 600 cm^{-1}; ^1H NMR δ 0.94 (3 H, s), 0.96 (3 H, s), 1.24 (3 H, s), 1.63 (6 H, s), 1.96 (3 H, s), 2.40 (1 H, dd, J = 14 and 11 Hz), 3.00 (1 H, dd, J = 14 and 3 Hz), 4.01 (1 H, dt, J = 11 and 3 Hz), 4.50 (2 H, d, J = 7 Hz), 5.08 (1 H, d, J = 11 Hz), 5.37 (1 H, t, J = 7 Hz), 5.96 (2 H, s), 7.54 (3 H, m), 7.81 (2 H, dd, J = 7 and 2 Hz); MS m/e 470 (M^+, 0.01), 410 ($M - CH_3CO_2H$, 0.1), 329 ($M - CH_3CO_2H - C_6H_5SO_2$, 100). Anal. Calcd for $C_{28}H_{38}O_4S$: C, 71.45; H, 8.14; S, 6.81. Found: C, 71.61; H, 8.22; S, 6.90.

The product obtained above was identical (melting point, mixture melting point, TLC, and UV, IR, NMR, and mass spectra) with a sample prepared by an alternative route.[12]

Conversion of 10a into Vitamin A Acetate (12a). To a stirred solution of sodium ethoxide in ethanol (from 1.23 g of Na and 27.0 mL of EtOH) was added 2.53 g (5.4 mmol) of **10a** in 10.0 mL of ethanol (warming necessary) under argon. The resulting deep red solution was boiled under reflux for 17 h, cooled to room temperature, and poured into a separatory funnel containing 50.0 mL of Et_2O and 50.0 mL of saturated brine. The organic phase was separated and the aqueous phase reextracted with Et_2O. The combined extracts were washed with saturated brine, dried ($MgSO_4$), and evaporated to give 1.86 g of crude vitamin A. This material was dissolved in 30.0 mL of hexane and treated with 10 mg of butylated hydroxytoluene followed by 3.3 mL of pyridine and 4.5 mL of acetic anhydride. The mixture was stirred at room temperature for 3.5 h, cooled to 10 °C, treated dropwise with 10.0 mL of methanol, and then stirred for a further 1 h. The mixture was poured into ice-cold water, and the organic phase was separated, washed with 50.0 mL of ice-cold 0.1 N H_2SO_4 followed by saturated brine, dried ($MgSO_4$), and evaporated to give 1.8 g of vitamin A acetate (**12a**) as an orange-colored gum: UV (*i*-PrOH) 325 nm (ε 41 450). LC gave the following analysis: all-trans, 67%; 9/9,13-dicis, 9%; 13-cis, 1%; 11-cis, 1%. Crystallization from 4.0 mL of hexane at −20 °C (seeding necessary) gave 850 mg of crystalline vitamin A acetate: mp 51–58 °C; UV 325 nm (ε 48 500); ^1H NMR δ 1.00 (6 H, s), 1.66 (3 H, s), 1.86 (3 H, s), 1.93 (3 H, s), 2.00 (3 H, s), 4.70 (2 H, d, J = 7 Hz), 5.56 (1 H, t, J = 7 Hz), 6.00 (1 H, d, J = 7 Hz), 6.08 (2 H, s), 6.22 (1 H, d, J = 12 Hz), 6.60 (1 H, dd, J = 12 and 7 Hz); MS m/e 328. LC gave the following analysis: all-trans, 95%; 9/9,13-dicis, 1%; 13-cis, 3%.

3-Methyl-1-(phenylsulfonyl)-5-(2,6,6-trimethylcyclohex-2-en-1-yl)penta-2,4-diene (8b). A stirred mixture of 16.5 g (0.075 mol) of vinyl-α-ionol (**5b**)[26] in 150 mL of anhydrous Et_2O and 15 mL of pyridine was cooled to −15 °C and treated dropwise with 31.5 g (0.116 mol) of PBr_3 in 50 mL of Et_2O during 30 min at such a rate that the temperature of the mixture was kept at ~−10 °C. The mixture was stirred at 0 °C for 3 h, cooled to −20 °C, and treated dropwise with 100 mL of water. The organic phase was separated, washed with saturated brine, dried ($MgSO_4$), and evaporated to give 18.05 g of crude bromide **7b** as a pale yellow oil. The latter was dissolved in 100 mL of dimethylformamide and treated with 24.0 g (0.09 mol) of benzenesulfinic acid (sodium salt, 98%). The mixture was stirred at 25 °C overnight, diluted with 400 mL of water, and extracted with Et_2O (2 × 200 mL). The extract was washed with saturated brine (3 × 300 mL), dried ($MgSO_4$), and evaporated to give 16.8 g of an oil, which was shown by TLC (25% ethyl acetate in hexane) to be a mixture of four compounds having R_f values of 0.98, 0.70, 0.60, and 0.56 (product). Chromatography on neutral alumina (1 kg, Woelm Grade II) with 5% ethyl acetate in hexane followed by 10% ethyl acetate in hexane gave a gum which was crystallized twice from 20 mL of methanol at −15 °C overnight to give 9.6 g (37% from **5b**) of **8b** as colorless crystals: mp 69–70 °C; UV 217 (ε 19 820), 243 (28 200) nm; IR 3000, 1470, 1300, 1145, 1020, 965 cm^{-1}; ^1H NMR δ 0.78 (3 H, s), 0.88 (3 H, s), 1.34 (3 H, s), 1.53 (3 H, d, J = 1 Hz), 2.00 (2 H, m), 2.16 (1 H, br s), 3.88 (2 H, d, J = 9 Hz), 5.33 (1 H, d, J = 16 Hz), 5.41 (2 H, m), 6.00 (1 H, d, J = 16 Hz), 7.50 (3 H, m), 7.80 (2 H, m); MS m/e 344 (M^+, 1). Anal. Calcd for $C_{21}H_{28}O_2S$: C, 73.21; H, 8.19; S, 9.31. Found: C, 73.33; H, 7.98; S, 9.10.

1-Acetoxy-3,7-dimethyl-5-(phenylsulfonyl)-9-(2,6,6-trimethylcyclohex-2-en-1-yl)nona-2,6,8-triene (10b). A stirred solution of 344 mg (1.0 mmol) of **8b** in 20 mL of anhydrous dimethylformamide was cooled to −10 °C and treated, under argon, with 47.8 mg of NaH (obtained by washing 84 mg of 57% material with hexane). The mixture was stirred at −10 °C for 15 min, and the resulting deep red solution was treated with 1.04 g (4.0 mmol) of triphenylphosphine followed by 269 mg (0.5 mmol) of **9** in 10 mL of dimethylformamide. The mixture was stirred at 0 °C for 45 min and then worked up as described for **10a.** TLC (25% ethyl acetate in hexane) indicated the presence of three compounds: PPh_3, R_f 0.70; product, R_f 0.32; and hydrolyzed product, R_f 0.13. The starting material had R_f 0.40. The product was isolated by preparative-scale TLC (25% ethyl acetate in hexane, silica gel) and dried in vacuo overnight to give 230 mg (48%) of **10b** as a gum: UV 218 (ε 23 030), 247 (30 260) nm; IR 3000, 1730, 1300, 1230, 1140, 970, 660 cm^{-1}; ^1H NMR δ 0.75 (3 H, d, J = 1 Hz), 0.85 (3 H, d, J = 1 Hz), 1.16 (3 H, s), 1.53 (3 H, d, J = 1 Hz), 1.62 (3 H, s), 1.96 (3 H, s), 2.37 (1 H, dd, J = 14 and 11 Hz), 2.98 (1 H, dd, J = 14 and 3 Hz), 3.97 (1 H, dt, J = 11 and 3 Hz), 4.48 (2 H, d, J = 7 Hz), 5.07 (1 H, d, J = 12 Hz), 5.30 (3 H, m), 5.93 (1 H, d, J = 16 Hz), 7.50 (3 H, m), 7.75 (2 H, m); MS m/e 470 (M^+, 0.1).

Treatment of 10b with KOH. A solution of 70 mg (0.15 mmol) of **10b** in 5 mL of 1-butanol was treated with 480 mg of KOH (85%, pulverized) under nitrogen. The mixture was boiled under reflux for 17 h, cooled to room temperature, diluted with 50 mL of water, and extracted with 50 mL of Et_2O. The extract was washed, dried ($MgSO_4$), and evaporated to give 62 mg of a gum: UV 298 (ε 3170), 310 (5424), 323 (4160) nm. Pure α-vitamin A[18] has UV 298 (ε 32 890), 310 (45 474), and 325 (37 738) nm.

3-Methyl-1-(phenylsulfonyl)-5-(2,3,6-trimethyl-4-methoxyphenyl-1-yl)penta-2,4-diene (8c). A solution of 5.05 g (25 mmol) of 1-methyl-3-(2,3,6-trimethyl-4-methoxyphenyl-1-yl)prop-2-enone[27] in 150 mL of anhydrous THF was cooled to −60 °C and treated dropwise with a solution of vinylmagnesium chloride (10.25 mL of a 2.93 M solution in THF, diluted to 50 mL). The mixture was stirred at −50 °C for 3 h, quenched with 100 mL of saturated NH_4Cl, and extracted with Et_2O (2 × 100 mL). The extract was washed, dried ($MgSO_4$), and evaporated to give 6.0 g of **5c.** A 4.72-g portion of this material was dissolved in 30 mL of acetic acid (a transient green was observed) and treated with 7.0 g of benzenesulfinic acid (Na salt, 98%). The mixture was stirred at 25 °C for 6 h, diluted with 100 mL of water, and extracted with Et_2O (2 × 200 mL). The extract was washed with saturated brine, dried ($MgSO_4$), and evaporated to give 6.1 g of a gum which was crystallized twice from methanol (−15 °C) to give 4.8 g (65%) of **8c:** mp 117–118 °C; UV (*i*-PrOH) 217 (ε 24 486), 232 (22 210), 290 (16 950) nm; IR 1580, 1300, 1125, 975 cm^{-1}; ^1H NMR δ 1.56 (3 H, s), 2.10 (3 H, s), 2.16 (3 H, s), 2.22 (3 H, s), 3.79 (3 H, s), 3.96 (2 H, d, J = 7 Hz), 5.43 (1 H, t, J = 7 Hz), 6.11 (1 H, d, J = 16 Hz), 6.52 (1, H, d, J = 16 Hz), 6.60 (1 H, s), 7.52 (3 H, m), 7.85 (2, H, m); MS m/e 370 (M^+, 5). Anal. Calcd for $C_{22}H_{26}O_3S$: C, 71.32; H, 7.07; S, 8.65. Found: C, 71.09; H, 7.07; S, 8.38.

1-Acetoxy-3,7-dimethyl-5-(phenylsulfonyl)-9-(2,3,6-trimethyl-4-methoxyphenyl-1-yl)nona-2,4,6-triene (10c). A stirred, cooled (−10 °C) solution of 130 mg (0.35 mmol) of **8c** in anhydrous DMF was treated with 26 mg of NaH (57%) under argon. The cooling source was removed, and the resulting deep red solution was stirred at ~0 °C for 5 min and then treated with 370 mg (1.4 mmol) of PPh_3 followed by 95 mg (0.176 mmol) of **9.** The mixture was stirred at room temperature for 1 h and worked up as described for **10a.** Preparative-scale TLC (25% ethyl acetate in hexane; the product had R_f 0.70 and **8c** had R_f 0.75) gave 68 mg (39%) of **10c** as a gum: UV 217 (ε 26 080), 238 (18 440), 292 (14 900) nm; IR 1735 cm^{-1}; ^1H NMR δ 1.44 (3 H, s), 1.68 (3 H, s), 1.99 (3, H, s), 2.14 (3 H, s), 2.18 (3 H, s), 2.24 (3 H, s), 2.41 (1 H, dd, J

= 14 and 11 Hz), 3.01 (1 H, dd, J = 14 and 3 Hz), 3.80 (3 H, s), 4.08 (1 H, dt, J = 11 and 3 Hz), 4.51 (2 H, d, J = 7 Hz), 5.15 (1 H, d, J = 11 Hz), 5.38 (1 H, t, J = 7 Hz), 6.06 (1 H, d, J = 16 Hz), 6.43 (1 H, d, J = 16 Hz), 6.59 (1 H, s), 7.55 (3 H, m), 7.82 (2 H, m); MS m/e 355 (M^+ − $PhSO_2$, 44; the molecular ion was not observed). Anal. Calcd for $C_{29}H_{36}O_5S$: C, 70.13; H, 7.31; S, 6.45. Found: C, 69.92; H, 7.56; S, 6.35.

Treatment of 10c with NaOEt. A solution of 100 mg (0.2 mmol) of **10c** in 3 mL of ethanol was added to a solution of sodium ethoxide (from 100 mg of Na and 5 mL of EtOH). The stirred mixture was boiled under reflux for 12 h, cooled to room temperature, diluted with 50 mL of water, and extracted with ether (2 × 50 mL). The extract was washed, dried ($MgSO_4$), and evaporated to give a red oil, which was subjected to preparative-scale TLC (1:1 ethyl acetate–hexane). Collection of the band at R_f 0.60 (the starting material had R_f 0.80) gave 40 mg of **11c** as an amorphous solid: mp 114–121 °C; UV (*i*-PrOH) 220 (ε 13 930), 326 (47 300) nm; IR 3620, 980 cm^{-1}; ^1H NMR δ 1.87 (3 H, s), 2.05 (3 H, s), 2.14 (3 H, s), 2.22 (3 H, s), 2.28 (3 H, s), 3.79 (3 H, s), 4.30 (2 H, d, J = 7 Hz), 5.69 (1 H, t, J = 7 Hz), 6.14 (1 H, d, J = 11 Hz), 6.19 (1 H, d, J = 16 Hz), 6.29 (1 H, d, J = 15 Hz), 6.58 (1 H, d, J = 16 Hz), 6.59 (1 H, s), 6.64 (1 H, d, J = 15 Hz); MS m/e 312 (M^+, 75).

Farnesyl Phenyl Sulfone (8d). A solution of 11.40 g (40 mmol) of farnesyl bromide (**7d**)[28] in 110 mL of anhydrous DMF was treated with 12 g (73 mmol) of benzenesulfinic acid (Na salt, 98%), and the mixture was stirred under argon for 20 h. It was then diluted with 300 mL of water and extracted with Et_2O (2 × 150 mL). The extract was washed with saturated brine, dried ($MgSO_4$), and evaporated to give 11.7 g of crude **8d** as a pale yellow oil. TLC (20% ethyl acetate in hexane) showed spots at R_f 0.83 (byproduct), 0.60 (byproduct), and 0.46 (product). Chromatography of the mixture on 300 g of neutral alumina (Woelm Grade II, dry pack) with 20% ethyl acetate in hexane as eluent (15-mL fractions) gave 8.5 g (61%) of **8d** as an oil: IR 1450, 1305, 1160, 980 cm^{-1}; ^1H NMR δ 1.33 (3 H, s), 1.60 (3 H, s), 1.69 (6 H, s), 2.0 (8 H, br s), 3.80 (2 H, d, J = 7 Hz), 5.10 (2 H, m), 5.20 (2 H, t, J = 7 Hz), 7.50 (3 H, m), 7.85 (2 H, m); MS m/e 346 (M^+, 1). Anal. Calcd for $C_{21}H_{30}O_2S$: C, 72.79; H, 8.73; S, 9.29. Found: C, 72.71; H, 8.81; S, 9.11.

1-Acetoxy-3,7,11,15-tetramethyl-5-(phenylsulfonyl)hexadeca-2,6,10,14-tetraene (10d). A cooled (0 °C), stirred solution of 346 mg (1 mmol) of **8d** in 10 mL of anhydrous DMF was treated with 84 mg of NaH (57% dispersion in mineral oil) under argon. The mixture was then stirred at this temperature for 10 min and treated with 1.04 g (4.0 mmol) of PPh_3 followed by 280 mg (0.5 mmol) of **9** in 10 mL of DMF. After the solution was stirred at 0 °C for 30 min and at 25 °C for 45 min, the resulting heterogeneous mixture was worked up as described for **10a.** Preparative-scale TLC (60% Et_2O in hexane) removed PPh_3 (R_f 0.83) and a byproduct (R_f 0.77) and furnished 93 mg (20%) of **10d** (R_f 0.51) as a gum: UV 220 (ε 15 820), 258 (860), 265 (1070), 272 (910) nm; IR 1735, 1450, 980 cm^{-1}; ^1H NMR δ 1.19 (3 H, s), 1.60 (3 H, s), 1.64 (3 H, s), 1.68 (6 H, s), 2.00 (3 H, s), 2.35 (1 H, dd, J = 11 and 14 Hz), 2.95 (1 H, dd, J = 14 and 3 Hz), 3.89 (1 H, dt, J = 11 and 3 Hz), 4.50 (2 H, d, J = 7 Hz), 5.05 (3 H, m), 5.35 (1 H, t, J = 7 Hz), 7.55 (3 H, m), 7.75 (2 H, m); MS m/e 472 (M^+, 0.1). Anal. Calcd for $C_{28}H_{40}O_4S$: C, 71.15; H, 8.53; S, 6.78. Found: C, 71.00; H, 8.50; S, 6.67.

Treatment of 10d with KOH in 1-Butanol. A solution of 944 mg (2 mmol) of **10d** in 20 mL of 1-butanol was treated with 1.12 g (20 mmol) of pulverized KOH, and the mixture was boiled under reflux for 2.5 h. The mixture was cooled to room temperature, poured into 100 mL of water, and extracted with 100 mL of Et_2O. The extract was washed with saturated brine until neutral, dried ($MgSO_4$), and evaporated. The residue was dissolved in 20 mL of hexane, cooled to 0 °C, and treated with 4 mL of triethylamine followed by 4 mL of acetic anhydride. The mixture was stirred at room temperature for 3 h, cooled to 0 °C, treated dropwise with 10 mL of methanol, and stirred for a further 30 min. Evaporation of the mixture in vacuo at 35 °C gave an oil which was subjected to preparative-scale TLC (1:1 Et_2O–hexane) in order to remove two small impurities at R_f 0.86 and 0.60; the product had R_f 0.74. Collection of the product in the usual manner using CH_2Cl_2 gave, after evaporation, 580 mg (87%) of **12d** as a gum: UV 280 nm (ε 34 900); IR 1730, 980 cm^{-1}; ^1H NMR δ 1.60 (3 H, s), 1.68 (3 H, s), 1.80 (3 H, s), 1.86 (3 H, s), 2.01 (3 H, s), 2.06 (3 H, s), 4.71 (2 H, d, J = 7 Hz), 5.10 (2 H, br s), 5.55 (1 H, t, J = Hz), 5.90 (1 H, d, J = 11 Hz), 6.10 (1 H, d, J = 16 Hz), 6.45 (1 H, d, J = 16 Hz); MS m/e 330 (M^+, 10). Anal. Calcd for $C_{22}H_{34}O_2$: C, 79.95; H, 10.37. Found: C, 79.58; H, 10.41.

1-Acetoxy-3,7,11-trimethyl-5-(phenylsulfonyl)-2,6,10-dodecatriene (10e). To a stirred, cooled (0 °C) solution of 278 mg (1 mmol) of geranyl phenyl sulfone (**8e**)[29] in 20 mL of anhydrous DMF was added, under argon, 84 mg of NaH (57% dispersion). The deep red solution was stirred for a further 5 min and treated with 1.04 g (4 mmol) of PPh_3 followed by 270 mg (0.5 mmol) of **9** in 15 mL of anhydrous DMF. The mixture was stirred at room temperature for 2 h and then worked up as described for **10a.** The product was isolated by preparative-scale TLC (60% Et_2O in hexane) to give 125 mg (31%) of **10e** as a gum: UV 217 (ε 17 590), 264 (1090), 272 (940) nm; IR 1730, 1307, 1235, 1145 cm^{-1}; ^1H NMR δ 1.19 (3 H, d, J = 1 Hz), 1.59 (3 H, s), 1.64 (3 H, d, J = 1 Hz), 1.66 (3 H, s), 2.01 (2 H, s), 2.31 (1 H, dd, J = 11 and 14 Hz), 2.95 (1 H, dd, J = 11 and 3 Hz), 3.90 (1 H, dd, J = 11 and 3 Hz), 4.50 (2 H, d, J = 7 Hz), 5.00 (2 H, m), 5.36 (1 H, t, J = 7 Hz), 7.55 (3 H, m), 7.85 (2 H, m); MS m/e 263 (M^+ − SO_2Ph, 2).

Conversion of 10e into 12e. A stirred solution of 202 mg (0.5 mmol) of **10e** in 15 mL of 1-butanol was boiled under reflux with 1.5 g (26 mmol) of KOH (85%) for 30 min. The mixture was cooled to room temperature, diluted with 50 mL of water, and extracted with Et_2O (2 × 50 mL). The extract was washed with saturated brine until neutral, dried ($MgSO_4$), and evaporated to give a gum which was acetylated according to the procedure described for the preparation of **12d.** Preparative-scale TLC (30% ethyl acetate in hexane) gave 108 mg (82%) of **12e** as an oil: UV 281 nm (ε 46 355); IR 1730, 1627, 1240, 960 cm^{-1}; ^1H NMR δ 1.72 (3 H, s), 1.79 (3 H, s), 1.81 (3 H, s), 1.87 (3 H, s), 2.06 (3 H, s), 4.71 (2 H, d, J = 7 Hz), 5.10 (1 H, t, J = 7 Hz), 5.58 (1 H, t, J = 7 Hz), 5.91 (1 H, d, J = 11 Hz), 6.15 (1 H, d, J = 16 Hz), 6.52 (1 H, dd, J = 16 and 11 Hz); MS m/e 262 (16). Anal. Calcd for $C_{17}H_{26}O_2$: C, 77.81; H, 9.99. Found: C, 77.86; H, 9.95.

Ester 13. To a stirred solution of 32.0 mg of diethyl malonate in 3 mL of Me_2SO was added, under N_2, 2.0 mg of NaH (57%). The mixture was stirred at room temperature for 15 min, treated with 53.8 mg of **9,** and stirred for a further 4 h (palladium precipitated after ~30 min). It was diluted with 20 mL of CH_2Cl_2 and filtered over 10 g of Celite, and the filtrate was diluted with 25 mL of water. The organic phase was separated, washed with saturated brine, dried ($MgSO_4$), and evaporated to give 40 mg of a gum. Purification of the latter by preparative-scale TLC (30% ethyl acetate in hexane; for the purpose of visualization, a small strip of the adsorbent was sprayed with 10% ceric sulfate in 10% H_2SO_4 followed by heating to 120 °C) gave 15 mg (25%) of **13** as a gum: IR 1740–1715 cm^{-1}; ^1H NMR δ 1.26 (6 H, t, J = 7 Hz), 1.66 (3 H, s), 2.05 (3 H, s), 2.70 (2 H, d, J = 7 Hz), 3.56 (1 H, t, J = 7 Hz), 4.20 (4 H, q, J = 7 Hz), 4.56 (2 H, d, J = 7 Hz), 5.43 (1 H, t, J = 7 Hz); MS m/e 226 (M^+ − CH_3CO_2H, 30; the molecular ion was not observed).

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Registry No.—5b, 5208-92-4; **5c,** 67689-03-6; **6,** 1191-16-8; **7b,** 67689-04-7; **7d,** 28290-41-7; **8a,** 38987-91-6; **8b,** 67689-05-8; **8c,** 67689-06-9; **8d,** 56881-53-9; **8e,** 56691-80-6; **9,** 12245-52-2; **10a,** 67689-07-0; **10b,** 63860-01-5; **10c,** 67689-08-1; **10d,** 67689-09-2; **10e,** 67689-10-5; **11a,** 68-26-8; **11b,** 67772-69-4; **11c,** 61630-49-7; **11d,** 67689-11-6; **11e,** 67689-12-7; **12a,** 127-47-9; **12d,** 67689-13-8; **12e,** 67689-14-9; **13,** 66855-36-5; palladium(II) chloride, 7647-10-1; phosphorus tribromide, 7789-60-8; sodium benzenesulfinate, 873-55-2; 1-methyl-3-(2,3,6-trimethyl-4-methoxyphenyl-1-yl)prop-2-enone, 62924-31-6; vinyl chloride, 75-01-4; diethyl malonate, 105-53-3.

Supplementary Material Available: Final atomic and anisotropic thermal parameters for **9** (2 pages). Ordering information is given on any current masthead page.

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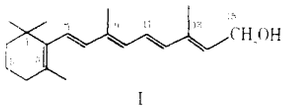

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5-Aza-7-deazapurine Nucleosides. 1. Synthesis of Some 1-(β-D-Ribofuranosyl)imidazo[1,2-*a*]-1,3,5-triazines

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Stannic chloride catalyzed condensation of 2-aminoimidazole with 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose somewhat surprisingly gives 2-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosylamino)imidazole (**10**) rather than the expected glycosylation of a ring nitrogen. Reaction of **10** with a number of different aryloxycarbonyl isocyanates and their sulfur analogues afforded 1-(β-D-ribofuranosyl)imidazo[1,2-*a*]-1,3,5-triazines bearing oxo and thiono substituents at the 2 and 4 positions. Certain amino-substituted compounds were also prepared via aminolysis of the thiones or their *S*-methyl derivatives. The orientation of substituents was generally deduced through the use of ^{13}C NMR spectroscopy with particular reference to the existence of small three-bond couplings involving the anomeric proton.

During the past few decades, innumerable analogues of purine nucleosides modified in either the heterocyclic base or the sugar moiety have been described.[1] In spite of this plethora of base analogues, relatively few compounds have been prepared in which a nitrogen atom is located at one of the ring junctions. The most noticeable exception to this generality has been a quite detailed study on the synthesis of nucleosides derived from *s*-triazolo[2,3-*a*]pyrimidin-7-one (e.g., **1**)[2] and imidazo[1,2-*c*]pyrimidines (e.g., **2**).[3] In addition, a few *C*-glycosyl nucleosides derived from heterocycles containing bridgehead nitrogens have been described.[4] Our present concern has been the synthesis of nucleosides derived from suitably substituted derivatives of the imidazo[1,2-*a*]-1,3,5-triazine ring system (**3**), compounds which, unlike **1** and **2**, bear nitrogen atoms positionally equivalent to N^1 and N^3 of purine nucleosides. These substances can, accordingly, be looked upon as 5-aza-7-deazapurine nucleosides and are hence structurally related to other biologically interesting 7-deazapurine nucleosides such as tubercidin.[5] In this and a forthcoming paper[6] we describe our work on the synthesis of such nucleosides, part of which has previously been disclosed.[7]

The parent imidazo[1,2-*a*]-1,3,5-triazine ring system is not at all well studied. The patent literature gives reference to a number of variously substituted, and frequently reduced, derivatives.[8] A paper by Kobe et al.,[9] however, provides the only well-documented approach for the synthesis of simple 2,4-disubstituted compounds via reaction of 2-amino-1,3,5-triazines with bromoacetaldehyde. In this way several compounds substituted with alkylthio and dialkylamino groups were prepared. In view of the general paucity of simple *N*-alkylated and otherwise functionalized derivatives to serve as reference compounds for spectral analysis, we felt that direct ribosidation of derivatives of the parent ring system would be fraught with difficulties in structural assignments.[10] Since our primary objective was the synthesis of 8-ribofuranosyl