tassium carbonate were refluxed in ethanol for 24 hr. 1,3-Bis(succinimido)-2-propanol was obtained in good yield. Acid hydrolysis of the bisimide gave 1,3-diamino-2-propanol, a known compound.[6b] An authentic sample, as the hydrochloride, had the same ir as ours and gave no depression on taking a mixture melting point.
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Total Synthesis of (±)-4-Deoxydamsin. Structure Correlation of Pseudoguaianolide Sesquiterpenes

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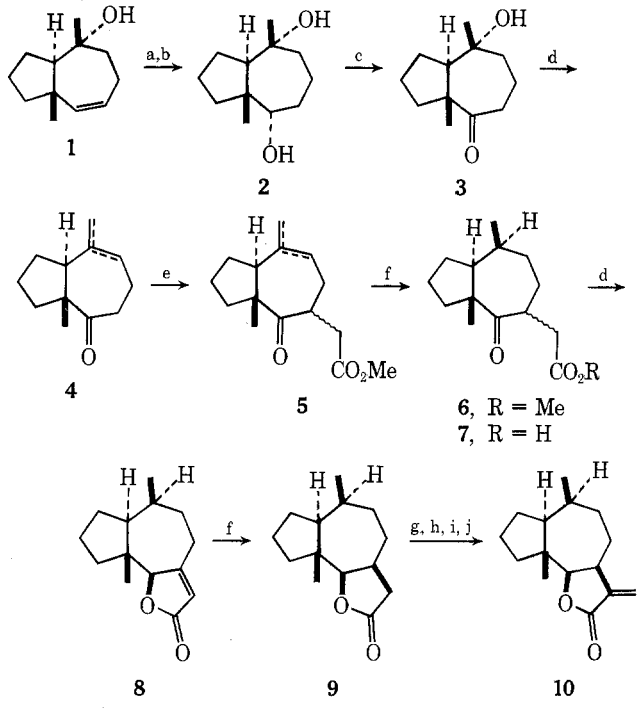
The pseudoguaianolides are a widespread class of nonisoprenoid hydroazulene lactones containing an array of functional and chiral centers which challenge present-day synthesis methodology and design.[1] Initial structure assignments based on chemical degradations erroneously classified these natural products as guaiazulene derivatives.[2] Their identity as a separate family of rearranged "pseudo" guaiazulenes was revealed by nuclear magnetic resonance (NMR), which showed the presence of a quaternary methyl grouping.[3] Stereochemical details were subsequently elucidated by NMR studies and single-crystal X-ray analysis.[1]

Despite the increasing variety of reported synthetic approaches to hydroazulenes, none of the pseudoguaianolides have yet been synthesized.[4,5] Attempts to date have failed to develop the necessary stereochemical control of the cycloheptane substituents.[5] In this report we describe a scheme for construction of the pseudoguaianolide skeleton with complete stereochemical control of the five commonly encountered chiral centers.

Our synthetic plan centered about the hydroazulenol **1**, an intermediate which we prepared via 1,6-cyclodecadienol solvolysis.[6] This intermediate with its propitious arrangement of substituents and functional groups seemed well suited for further elaboration to a pseudoguaianolide derivative for several reasons. Foremost, the rigidity imposed upon the hydroazulene system by the trans ring fusion simplifies conformational analysis, thus permitting realistic stereochemical predictions. In addition, the angular methyl grouping serves as a stereochemical directing group for the introduction of proximate chiral centers. The only real disadvantage of hydroazulenol **1** as a pseudoguaianolide precursor is its lack of functionality in the cyclopentane ring. Thus we could not expect to prepare the natural sesquiterpenes, at least initially. Nonetheless we felt that the aforementioned stereochemical problems were of sufficient intrinsic interest to justify work on the synthesis of 4-deoxypseudoguaianolides.

Our first objective was to incorporate a properly oriented fused γ-butyrolactone at the double bond position of hydroazulenol **1** (Chart I). Toward this end the double bond

Chart I[a]



1 2 3 4 5 6, R = Me 7, R = H 8 9 10

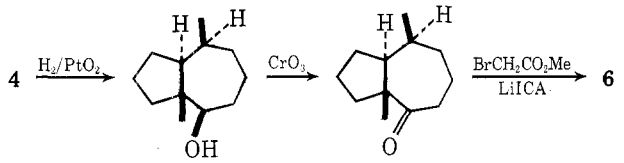
[a] a, *m*-$ClC_6H_4CO_3H$; b, $LiAlH_4$; c, H_2CrO_4, acetone; d, Ac_2O, NaOAc; e, LiICA, $BrCH_2CO_2Me$; f, H_2/PtO_2; g, NaH, HCO_2Et; h, $NaBH_4$; i, TsCl; j, C_5H_5N.

was epoxidized with *m*-chloroperoxybenzoic acid and the crude epoxide was reduced with lithium aluminum hydride to the diol **2**. Oxidation with Jones reagent[7] afforded the desired ketone intermediate **3**. However, attempted alkylation of the corresponding enolate with methyl bromoacetate proceeded poorly. Thinking that steric factors might be responsible for this result, we decided to examine the alkylation of unsaturated ketones related to ketol **3**.

Dehydration with thionyl chloride in pyridine led to a mixture of three double-bond isomers (25% exo, 60% trisubstituted, and 15% tetrasubstituted). However with acetic anhydride–sodium acetate only the trisubstituted (**4**) and exo olefins (60:40) were formed. Previous results have indicated that the dehydration of tertiary alcohols with sodium acetate–acetic anhydride proceeds via the acetate, which subsequently undergoes a pyrolytic cis elimination.[8] Accordingly, the isolation of only the trisubstituted olefin **4** and the corresponding exo isomer is unexpected. However, molecular models show that eclipsing of a tertiary acetate carbonyl grouping with the ring fusion hydrogen introduces severe steric strain in the transition state leading to the tetrasubstituted olefin. The corresponding transition states leading to olefin **4** and its exo isomer appear relatively strain free. Thus steric factors may block this elimination pathway.

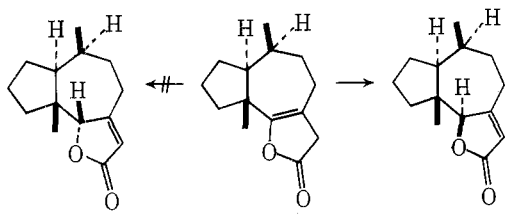
Alkylation of unsaturated ketone **4** (40% exo isomer) with methyl bromoacetate afforded the keto esters **5** as an apparent mixture of epimers and double-bond isomers in high yield. Hydrogenation of this mixture gave the saturated keto ester **6** as an epimeric mixture. Keto ester **6** could also be prepared by reordering these steps. However, this variation suffered from two drawbacks. In the first place, hydrogenation of enone **4** took place at the ketone carbonyl

as well as the double bond to give the alcohol **11**, apparently a single isomer. Secondly, the related ketone **12** obtained through Jones oxidation[7] gave an impure product in low yield upon alkylation with methyl bromoacetate. Presumably, the additional trigonal centers present in the enolate derived from unsaturated ketone **4** ameliorate the steric congestion of the seven-membered ring, thereby providing a less hindered avenue of approach for the alkylating agent.



11 **12**

The NMR spectra indicated that keto ester **6** and the corresponding acid **7** were stereochemically nonhomogeneous. Since enone **4** was found to give a single C-2 epimer upon catalytic hydrogenation, we presumed that the unsaturated keto ester **5** would behave analogously. Therefore, the epimeric center of ester **5** and acid **6** would most likely be at C-5. Our plan was to introduce unsaturation at this center and utilize the steric directing effect of the angular methyl grouping to attain the desired contrathermodynamic stereochemical orientation of the ester side chain through catalytic hydrogenation. Accordingly, the keto acid **7** was heated with sodium acetate–acetic anhydride to give the butenolide **8**, apparently a single stereoisomer according to spectral properties, as the sole reaction product. This precedented conversion[9] must proceed via the enol lactone **13**, which undergoes subsequent double-bond isomerization. The isomerization could conceivably be subject to kinetic or thermodynamic control. Kinetic protonation would expectedly lead to the observed butenolide isomer **8** on steric grounds, since the angular methyl grouping would block protonation or proton transfer leading to the alternative epimer **8a**. Molecular models indicate that butenolide **8** has fewer nonbonded interactions than the epimer **8a**. Thus an equilibrium isomerization process would likewise favor the syn isomer **8**.

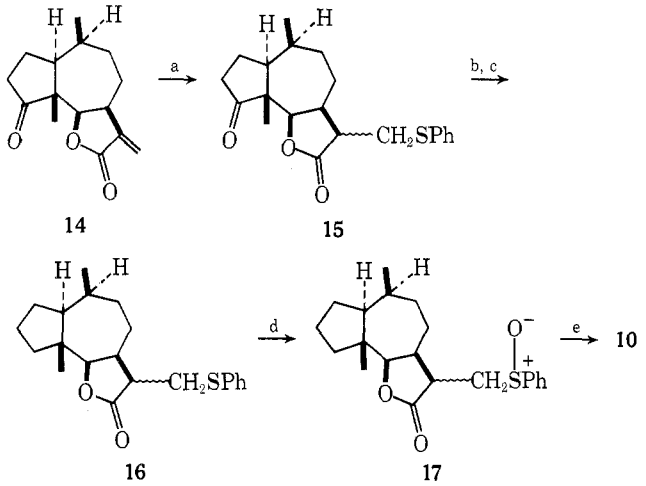


8a **13** **8**

Hydrogenation of butenolide **8** afforded, as expected, the cis lactone **9**, which displayed a sharp doublet in its NMR spectrum characteristic of cis-fused pseudoguaianolide lactone carbinyl hydrogens.[1] As previously noted, the angular methyl grouping should direct the stereochemistry of double-bond hydrogenation.

To complete the synthesis we employed the sequence of Minato and Horibe to introduce the α-methylene functionality to lactone **9**.[10] The resulting methylene lactone **10** showed NMR spectral patterns extremely similar to those of damsin (**14**), a naturally occurring pseudoguaianolide.[11] An authentic comparison sample of this lactone was obtained via the selective degradation of natural damsin according to the scheme outlined in Chart II. Addition of thiophenol[12] afforded the adduct **15**, which was condensed with *p*-toluenesulfonylhydrazine and then reduced with sodium cyanoborohydride to give the deoxy derivative **16**.[13]

Chart II[a]



14 **15** **16** **17**

[a] a, PhSH; b, $TsNHNH_2$; c, $NaBH_3CN$; d, *m*-$ClC_6H_4CO_3H$; e, heat, CH_3Ph.

Oxidation to the sulfoxide **17** and pyrolysis in toluene[14] afforded 4-deoxydamsin (**10**), identical with the synthetic material according to spectral and chromatographic criteria.

Experimental Section[15]

***t*-2,*t*-7-Dimethyl-*r*-1-*H*-bicyclo[5.3.0]decane-*c*-2,*c*-6-diol (2).** To a solution of 1.41 g (7.82 mmol) of hydroazulenol **1** in 175 ml of chloroform at 0° was added a solution of 5.90 g (34.2 mmol) of *m*-chloroperoxybenzoic acid in 200 ml of chloroform dropwise over 1 hr. Stirring was continued for 14 hr at 0°. The mixture was washed with cold 10% aqueous sodium hydroxide and saturated brine. The chloroform was removed under reduced pressure and the residue was distilled, affording 1.46 g (95%) of colorless oil: bp 110–120° (bath temperature) (0.1 mm); λ_{max} (film) 2.96 μ (OH); δ_{TMS} ($CDCl_3$) 3.34–2.79 (H-5, H-6 multiplet), 1.12 (C-2 CH_3), 1.00 ppm (C-7 CH_3).

The analytical sample was secured through preparative layer chromatography on silica gel using benzene as the eluent followed by short-path distillation.

Anal. Calcd for $C_{12}H_{20}O_2$: C, 73.43; H, 10.27. Found: C, 73.33; H, 10.27.

The epoxide was reduced along the lines of Henbest and Wilson.[16] To a stirred mixture of 0.46 g (12.1 mmol) of lithium aluminum hydride in 150 ml of tetrahydrofuran (THF) at room temperature was added a solution of 1.19 g (6.07 mmol) of epoxide in 50 ml of THF. The mixture was heated at reflux for 3 hr, cooled, and carefully treated with water and 15% sodium hydroxide solution. Ether was added, the mixture was filtered, and the solvent was removed under reduced pressure to give 1.20 g (100%) of solid diol **2**: λ_{max} (melt) 3.05 μ; δ_{TMS} ($CDCl_3$) 3.68 (H-6 multiplet), 1.20 (C-2 CH_3), 0.95 ppm (C-7 CH_3).

The analytical sample, mp 152–153°, was secured by recrystallization from ether–ethyl acetate.

Anal. Calcd for $C_{12}H_{22}O_2$: C, 72.68; H, 11.18. Found: C, 72.60; H, 11.26.

***c*-2-Hydroxy-*t*-2,*t*-7-dimethyl-*r*-1-*H*-bicyclo[5.3.0]decan-6-one (3).** To a solution of 139 mg (0.70 mmol) of diol **2** in 4.0 ml of acetone at 0° was added 0.20 ml of Jones reagent[7] dropwise over 2.0 min. After stirring for 15 min at 0°, the reaction mixture was quenched by the addition of 0.10 ml of 2-propanol. The reaction mixture was poured into brine, and the product was isolated with ethyl acetate, affording 118 mg (86%) of a colorless oil which crystallized on standing (mp 80–81°). Recrystallization from ether gave analytically pure material: λ_{max} (KBr) 2.92, 5.96 μ; δ_{TMS} ($CDCl_3$) 1.25 (C-2 CH_3), 1.08 ppm (C-7 CH_3).

Anal. Calcd for $C_{12}H_{20}O_2$: C, 73.43; H, 10.27. Found: C, 73.41; H, 10.30.

***t*-7-Methyl-2-methylene-*r*-1-*H*-bicyclo[5.3.0]decan-6-one and 2,*t*-7-Dimethyl-*r*-1-*H*-bicyclo[5.3.0]dec-2-en-6-one (4).** A solution of 132 mg (0.67 mmol) of ketol **3**, 600 mg of sodium acetate, and 4.0 ml of freshly distilled acetic anhydride was heated at

reflux for 12 hr. The solution was cooled to 0° and quenched with 2.0 ml of methanol. After stirring for 1.5 hr at 0°, the solution was poured into water and the product mixture was isolated with ether. The combined ether layers were carefully washed with saturated sodium bicarbonate solution and then with saturated brine. Short-path distillation (oven temperature 90–110°, 0.05 mm) afforded 118 mg (99%) of a colorless oil: λ_{max} (film) 5.90, 6.08 μ; δ_{TMS} (CCl_4) 5.70 (t, J = 5.6 Hz, endocyclic vinyl H), 4.90 and 4.74 (exo CH_2 vinyl H's), 1.67 (vinyl CH_3), 0.97 ppm (C-7 CH_3).

Integration of the NMR spectrum indicated a 40:60 mixture of exocyclic and endocyclic olefin isomers.

Methyl (*t*-7-Methyl-2-methylene-6-oxo-*r*-1-*H*-bicyclo[5.3.0]dec-5-yl)acetate and Methyl (2,*t*-7-Dimethyl-6-oxo-*r*-1-*H*-bicyclo[5.3.0]dec-2-en-5-yl)acetate (5). The procedures developed by Rathke[17] and Schlessinger[18] were modified. To a solution of 0.29 ml (1.60 mmol) of *N*-isopropylcyclohexylamine in 4.0 ml of tetrahydrofuran at −78° was added 0.80 ml (1.60 mmol) of 2.0 *M* *n*-butyllithium–hexane solution dropwise over 2.0 min. The solution was stirred for 30 min at −78°, at which time a solution of 267 mg (1.50 mmol) of keto olefin mixture **4** in 1.0 ml of tetrahydrofuran was introduced The reaction mixture was stirred for an additional 30 min at −78°. A solution of 245 mg (1.60 mmol) of methyl bromoacetate, 0.28 ml (1.60 mmol) of hexamethylphosphoramide, and 1.0 ml of tetrahydrofuran was then introduced dropwise and the reaction temperature was allowed to reach room temperature over 1.0 hr. The reaction mixture was poured into dilute hydrochloric acid and the products were isolated with ether. Short-path distillation (oven temperature 110–130°, 0.05 mm) afforded 330 mg (88%) of a colorless oil: λ_{max} (film) 5.75, 5.88, 6.08 μ; δ_{TMS} (CCl_4) 5.27 (t, J = 5.6 Hz, endocyclic vinyl H), 4.98 and 4.85 (exo CH_2 vinyl H's), 3.56 (OCH_3), 1.05 and 0.97 ppm (C-7 CH_3).

Methyl (*t*-2,*t*-7-Dimethyl-6-oxo-*r*-1-*H*-bicyclo[5.3.0]dec-5-yl)acetate (6). A suspension of 330 mg (1.32 mmol) of olefin mixture **5** and 50 mg of platinum oxide in 7.0 ml of absolute methanol was hydrogenated at room temperature and atmospheric pressure. After 2.0 hr the uptake of hydrogen ceased, the reaction mixture was filtered, and the solvent was removed by distillation at reduced pressure. Short-path distillation (oven temperature 110–130°, 0.05 mm) afforded 290 mg (88%) of a colorless oil: λ_{max} (film) 5.76, 5.90 μ; δ_{TMS} (CCl_4) 3.60 (OCH_3), 2.58 (m, C-5 methine), 2.30 (d, J = 6.0 Hz, acetate CH_2), 1.10 (C-7 CH_3), 0.97 ppm (d, J = 6.2 Hz, C-2 CH_3).

The keto ester was saponified without further purification.

(*t*-2,*t*-7-Dimethyl-6-oxo-*r*-1-*H*-bicyclo[5.3.0]dec-5-yl)acetic Acid (7). A solution of 280 mg (1.11 mmol) of keto ester **6** and 300 mg of potassium hydroxide in 6.0 ml of methanol was heated at reflux for 2.0 hr. The solution was cooled, poured into water, and washed with ether. The aqueous layer was carefully acidified with concentrated hydrochloric acid and the product was isolated with ether. The crude product crystallized on standing, affording 225 mg (85%) of white, crystalline product (mp 130–132°). Recrystallization from ether gave analytically pure material: λ_{max} (film) 3.20–3.80, 5.80, 5.92 μ; δ_{TMS} ($CDCl_3$) 9.66 (CO_2H), 3.45 (m, C-5 methine), 2.66 and 2.36 (doublets, J = 4.8 and 8.0 Hz, respectively, CH_2CO_2H), 1.08 (C-7 CH_3), 1.23 and 0.90 ppm (doublets, J = 6.5 Hz, C-2 CH_3).

Anal. Calcd for $C_{14}H_{22}O_3$: C, 70.55; H, 9.31. Found: C, 70.59; H, 9.30.

(*t*-6-Hydroxy-*t*-2,*t*-7-dimethyl-*r*-1-*H*-bicyclo[5.3.0]dec-5-ylidene)acetic Acid γ-Lactone (8). The procedure of Minato and Nagasaki[9] was employed. A mixture of 115 mg (0.484 mmol) of keto acid **7** and 200 mg of sodium acetate in 4.0 ml of acetic anhydride was heated at reflux for 2.0 hr. The mixture was cooled to 0° and 2.0 ml of methanol was added. After stirring for 1.5 hr at 0°, the solution was poured into water and the product was isolated with ether. The combined ether layers were carefully washed with saturated sodium bicarbonate solution and then with saturated brine. Distillation of the ether at reduced pressure afforded 91 mg (86%) of pale yellow oil which crystallized on standing (mp 71–73°). An analytical sample was secured by preparative thin layer chromatography using 50% ether–petroleum ether (R_f 0.20–0.45) and short-path distillation (oven temperature 120–130°, 0.10 mm): λ_{max} (film) 5.68, 6.12 μ; δ_{TMS} (CCl_4) 5.68 (vinyl H), 4.56 (C-6 methine), 2.66 (m, allylic CH_2), 0.97 (d, J = 6.4 Hz, C-2 CH_3), 0.72 ppm (C-7 CH_3).

Anal. Calcd for $C_{14}H_{20}O_2$: C, 76.32; H, 9.15. Found: C, 76.18; H, 8.98.

(*t*-6-Hydroxy-*t*-2,*t*-7-dimethyl-*r*-1-*H*-bicyclo[5.3.0]dec-*t*-5-yl)acetic Acid γ-Lactone (9). A suspension of 873 mg (3.97 mmol) of butenolide **8** and 100 mg of platinum oxide in 20 ml of absolute ethanol was hydrogenated at room temperature and atmospheric pressure. After 6.5 hr the uptake of hydrogen ceased, the reaction mixture was filtered, and the solvent was removed by distillation at reduced pressure. Short-path distillation (oven temperature 120–130°, 0.05 mm) afforded 782 mg (89%) of colorless oil. An analytical sample was secured by preparative thin layer chromatography using 50% ether–petroleum ether and short-path distillation (as above): λ_{max} (film) 5.63 μ; δ_{TMS} (CCl_4) 4.18 (d, J = 8.5 Hz, C-6 methine), 2.37 and 2.20 (doublets, J = 9.0 and 6.0 Hz, respectively, acetate CH_2), 1.00 (d, J = 6.2 Hz, C-2 CH_3), 0.97 ppm (C-7 CH_3).

Anal. Calcd for $C_{14}H_{22}O_2$: C, 75.63, H, 9.98. Found: C, 75.43; H, 10.15.

(±)-4-Deoxydamsin (10). The procedure of Minato and Horibe[10] was employed. To a suspension of 42 mg (1.75 mmol) of sodium hydride in 4.0 ml of ether at 0° was added at solution of 319 mg (1.44 mmol) of lactone **9** and 0.17 ml (2.00 mmol) of ethyl formate in 4.0 ml of ether dropwise over 2.0 min. The solution was stirred for 1.0 hr at 0°. The cooling bath was removed and the solution was stirred for an additional 12 hr at room temperature. The solution was poured into dilute hydrochloric acid and the product was isolated with ether, affording 342 mg (95%) of a yellow gum. No further purification of this product was attempted.

To a solution of 50 mg (1.31 mmol) of sodium borohydride in 3.0 ml of absolute methanol was added a solution of 342 mg (1.37 mmol) of the above α-formyl-γ-butyrolactone in 2.0 ml of absolute methanol. The solution was stirred for 1.0 hr at room temperature and poured into dilute hydrochloric acid, and the product was isolated with ether, affording 342 mg (99%) of a viscous yellow oil. No further purification of this product was attempted.

A solution of 342 mg (1.35 mmol) of the above β′-hydroxy-γ-butyrolactone and 315 mg (1.65 mmol) of *p*-toluenesulfonyl chloride in 4.0 ml of freshly distilled pyridine was stirred for 20 hr at 0°. The solution was poured into water and extracted with four portions of ether. The combined ether extracts were washed with dilute hydrochloric acid until the washes were acidic to litmus paper. The crude product, 372 mg (68%), was a brown, viscous oil: λ_{max} [film ($CDCl_3$)] 5.66, 6.24 μ; δ_{TMS} ($CDCl_3$) 7.48 (AB, J_{AB} = 7 Hz, $\Delta\nu_{AB}$ = 27 Hz, aromatic H's), 4.40–3.60 (m, C-6 methine and C-13 methylene), 2.40 ($ArCH_3$), 1.00 (d, J = 6.2 Hz, C-10 CH_3), 0.97 ppm (C-5 CH_3).

A solution of 372 mg (0.92 mmol) of the above tosylate in 5.0 ml of pyridine was heated at reflux for 5.0 hr. The solution was cooled and poured into water and the product was isolated with ether, affording 215 mg (100%) of a yellow oil. Short-path distillation (oven temperature 120–140°, 0.10 mm) and preparative thin layer chromatography on silica gel using 30% ether–benzene (R_f 0.55) afforded a white, crystalline product which was recrystallized from petroleum ether to give analytically pure material (mp 87–88°): λ_{max} (KBr) 3.38, 3.48, 5.70, 6.02, 7.85, 8.76, 10.04, 10.24, 10.60, 12.16 μ; δ_{TMS} ($CDCl_3$) 6.15 and 5.40 (doublets, J = 3.0 Hz, vinyl H's), 4.30 (d, J = 8.2 Hz, C-6 methine), 0.97 (d, J = 6.4 Hz, C-10 CH_3), 0.82 ppm (C-5 CH_3); MS *m/e* 234 (M^+), 219, 206, 177, 163.

Anal. Calcd for $C_{15}H_{22}O_2$: C, 76.88; H, 9.46. Found: C, 76.74; H, 9.49.

4-Deoxydamsin (10) from Degradation of Damsin (14). The procedure of Romo and coworkers[12] was modified. A solution of 566 mg (2.28 mmol) of damsin, 0.54 ml (5.36 mmol) of thiophenol, and 0.30 ml of triethylamine in 15 ml of benzene was stirred at room temperature for 10 hr. The solution was diluted with ether and washed with two portions of 10% sodium hydroxide followed by two portions of saturated brine. Filtration of the crude product mixture through a 15-ml column of silica gel using benzene afforded 199 mg of nonpolar aromatic impurities. Elution with ether afforded 519 mg (64%) of the desired adduct **15:** δ_{TMS} ($CDCl_3$) 7.20 (m, aromatic H's), 4.30 (d, J = 8.2 Hz, C-6 methine), 3.50–3.10 (m, C-13 methylene), 1.10 (d, J = 6.4 Hz, C-10 CH_3), 1.00 ppm (C-5 CH_3). No further purification of this compound was attempted.

A solution of 519 mg (1.45 mmol) of the above thioether **15** and 372 mg (2.00 mmol) of *p*-toluenesulfonylhydrazide in 20 ml of absolute methanol was heated at reflux for 5.5 hr. The reaction mixture was poured into water and the product was isolated with ether, affording 708 mg (93%) of a white foam.

This material was reduced according to the procedure of Hutchins, Maryanoff, and Milewski.[13]

To a solution of 708 mg (1.35 mmol) of the tosylhydrazone in 3.5 ml of dimethylformamide and 3.5 ml of freshly distilled sulfolane was added 20 mg of *p*-toluenesulfonic acid and 340 mg (5.40 mmol) of sodium cyanoborohydride. The solution was heated at 100° for 6 hr, cooled, and diluted with water. The product was isolated with

ether, affording 504 mg of crude material containing some unreacted starting material. The desired thioether **16** was isolated by column chromatography on silica gel using 30% ether–benzene.

To a solution of 367 mg (1.07 mmol) of chromatographed thioether **16** in 5 ml of methylene chloride at 0° was added a solution of 190 mg (1.10 mmoles) of *m*-chloroperoxybenzoic acid in 5 ml of methylene chloride dropwise over 2.0 min. The solution was stirred for 2.0 hr at 0° and the solvent was removed by distillation at reduced pressure. The residue was taken up in ether and washed with two portions of saturated sodium bicarbonate solution to give the crude sulfoxide **17** as a white foam (276 mg).

This material was directly converted to the methylene lactone **10** according to the procedure of Trost and Salzmann.[14] A solution of 276 mg (0.77 mmol) of crude sulfoxide **17** in 8.0 ml of toluene was heated at reflux for 4.0 hr. The solution was cooled, diluted with ether, and washed with two portions of saturated sodium bicarbonate solution to afford 175 mg (98%) of crude product. Preparative thin layer chromatography on silica gel using 5% ether–benzene gave 4-deoxydamsin (R_f 0.39) as a white, crystalline solid: mp 108–110°; λ_{max} (melt) 3.38, 3.48, 5.70, 6.02, 7.85, 8.76, 10.04, 10.24, 10.60, 12.16 μ; δ_{TMS} ($CDCl_3$) 6.15 and 5.40 (doublets, J = 3.0 Hz, vinyl H's), 4.30 (d, J = 8.2 Hz, C-6 methine), 0.97 (d, J = 6.4 Hz, C-10 CH_3), 0.82 ppm (C-5 CH_3).

Anal. Calcd for $C_{15}H_{22}O_2$: C, 76.88; H, 9.46. Found: C, 76.65; H, 9.61.

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Registry No.—**1**, 54798-48-0; **1** epoxide, 54798-49-1; **2**, 54798-50-4; **3**, 54798-51-5; *exo*-**4**, 54798-52-6; *endo*-**4**, 54798-53-7; *exo*-**5** epimer A, 54798-54-8; *exo*-**5** epimer B, 54798-55-9; *endo*-**5** epimer A, 54798-56-0; *endo*-**5** epimer B, 54798-65-1; **6** epimer A, 54910-30-4; **6** epimer B, 54809-86-8; **7** epimer A, 54798-63-9; **7** epimer B, 54798-64-0; **8**, 54798-58-2; **9**, 54798-60-6; **9** α-tosylate, 54798-61-7; (±)-**10**, 54798-59-3; (*S*)-**10**, 54831-46-8; **14**, 1216-42-8; **15**, 54798-57-1; **16**, 54798-62-8; *m*-chloroperoxybenzoic acid, 937-14-4; methyl bromoacetate, 96-32-2; *p*-toluenesulfonyl chloride, 98-59-9; thiophenol, 108-98-5.

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Use of the Azido Group in the Synthesis of 5′ Terminal Aminodeoxythymidine Oligonucleotides[1]

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Phosphoramidate analogs of oligonucleotides possess unique features which have interesting implications in nucleic acid chemistry.[2,3] In extending the synthetic methodology for this class of compounds we have explored the utility of the azido group as a synthon for a terminal amino group in an oligonucleotide. The formation of aminonucleosides by catalytic reduction of azidonucleosides is well known; representative examples include the preparation of 5′-amino-5′-deoxythymidine,[4] 2′-amino-2′-deoxyuridine,[5] and 5′-amino-2′,5′-dideoxyadenosine.[6] In addition, 5′-amino-5′-deoxythymidine 3′-phosphate and 3′-amino-3′-deoxythymidine 5′-phosphate have been obtained by catalytic hydrogenation of the corresponding azidonucleotides.[7]

As target compounds for study we selected di- and tetranucleotide analogs **2** and **4**. The synthetic scheme, outlined in Chart I, utilized the condensation procedure employed previously for preparation of some thymidylyl phosphoramidate analogs.[2]

5′-Azido-5′-deoxythymidine (**1a**) reacted smoothly with phenyl phosphorodichloridate in pyridine to give an active phosphorylated intermediate, which on treatment with 5′-amino-5′-deoxythymidine afforded the desired azidodinucleoside phosphate analog, **2**, in good yield. In contrast to the facile catalytic hydrogenation of **1a**, however, the reduction of **2** with hydrogen over a platinum catalyst was sluggish. Under conditions where **1a** was converted to the aminodeoxythymidine in high yield (90% isolated), little reduction of **2** was achieved. When the time of reaction was increased fivefold (to 2.5 hr), **2** was partially reduced, and the desired amino derivative (**3**) was isolated in 54% yield.

Repetition of the synthetic sequence with **2** in place of **1a** and **3** in place of 5′-amino-5′-deoxythymidine gave compound **4**. This tetranucleotide derivative, however, proved to be resistant to hydrogenation with palladium and platinum catalysts under all conditions that were explored. The decrease in susceptibility to catalytic reduction for the series **1a**, **2**, **4** correlates with increasing steric bulk at the 3′-O position.

Of the other methods available for converting azides to amines, the most promising for application in the nucleotide field appeared to be that utilizing triphenylphosphine, first described by Staudinger and Hauser.[8] Thus, methyl and ethyl azide are converted by triphenylphosphine to phosphinimines, which are reported to hydrolyze on exposure to moisture to triphenylphosphine oxide and the corresponding amines. Other workers have used alkali (refluxing 2% alcoholic potassium hydroxide)[9] and strong acid (hot 40% hydrogen bromide in acetic acid)[10] to liberate substituted alkylamines from phosphinimines. The conversion of an azido sugar, tetraacetyl-β-D-glucosyl azide, to a triphenylphosphinimine has also been reported.[11]

Experiments with model nucleosides, 5′-azido-5′-deoxythymidine (**1a**), 3′-*O*-mono-*p*-methoxytrityl-5′-azido-5′-deoxythymidine (**1b**), and 3′-*O*-α-naphthylcarbamoyl-5′-azido-5′-deoxythymidine (**1c**), indeed showed that the triphenylphosphine hydrolytic sequence constitutes a convenient preparative technique for this class of compounds. The aminonucleoside (**5a–c**) was isolated in high yield