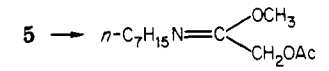

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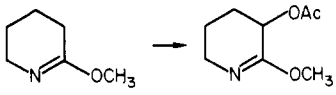

(3)

14 15

in the stereospecific synthesis of antitumor pyrrolizidine alkaloids.[12]

Experimental Section

Oxidation of 5 with Peracetic Acid. To a solution of 5 (0.27 g, 1.58 mmol) in CH_2Cl_2 (8 mL) in a 25-mL, oven-dried, round-bottomed flask was added anhydrous Na_2HPO_4 (0.45 g, 3.2 mmol). The resulting suspension was cooled to −78 °C under N_2, and then a standardized solution of peracetic acid (1.58 mmol) was added via a gas-tight syringe and Teflon needle. A white precipitate appeared upon completion of the addition; TLC of the reaction mixture at that time indicated a substantial quantity of 12 had already formed. The flask was allowed to warm to room temperature, and its contents were transferred to a separatory funnel. After being washed twice with 5% Na_2CO_3, the organic phase was dried ($MgSO_4$) and concentrated in vacuo to a pale yellow semisolid. Preparative thin-layer chromatography (Analtech silica gel plate, $CHCl_3$ eluant, two developments) gave 12 as a white solid: 49% yield; mp 53–55 °C (lit.[13] mp 57–58 °C).

Use of 2 equiv of peracid in the same experiment furnished 12 in 70% yield.

Oxidation of 5 with Lead Tetraacetate. To a suspension of poly(4-vinylpyridine) (Reilly Chemical Co., 5.3 g, 45 molar equiv) in dry hexane (20 mL) was added LTA (MC&B Corp., 98.6% pure; 1.33g, 3.0 mmol) followed 30 min later by the imino ether 5 (0.51 g, 3 mmol). The reaction mixture was stirred at room temperature for 30 min and then warmed to reflux for 75 min, whereupon a negative starch–iodide test was observed. The reaction mixture was cooled and filtered, and the precipitated solids were washed thoroughly with hexane. Concentration of the combined organic layers gave a quantitative yield of a clear, colorless oil (0.62 g) containing ca. 75% of 13 which could not be separated by distillation or chromatography from unreacted 5 (25%, the only other component of the mixture). For 13: ^1H NMR ($CDCl_3$) δ 4.60 (s, 2 H, CH_2OAc), 3.62 (s, 3 H, OCH_3), 3.27 (t, 2 H, J = 6 Hz, CH_2N), 2.1 (s, 3 H, CH_3CO); IR λ_{max} (film) 3.45 5.75, 6.0, 8.25, 9.6 μm; CIMS (isobutane) m/e (relative intensity) 230 (M + 1, base), 198 (M + 1 − CH_3OH, 54), 158 (M + 1 − H_2 − C_5H_{10}, 28); TLC R_f (EtOAc) 0.64.

Oxidation of 14 with Lead Tetraacetate. A mixture of poly(4-vinylpyridine) (75.5 g) and LTA (1.62 g) in dry THF (25 mL) was treated with imino ether 14 (0.39 g) at room temperature for 2 h and then at 50 °C for 1 h. The workup as described for 13 above afforded a pale yellow oil (0.46 g, 79%) of virtually pure 15: NMR ($CDCl_3$) δ 5.10 (t, 1 H, J = 6 Hz), 3.55 (s, 3 H), 2.11 (s, 3 H); IR λ_{max} (film) 5.85, 5.9 μM; CIMS, m/e (relative intensity) 172 (M + 1, 100), 112 (M + 1 − AcOH, 6); TLC R_f (EtOAc) 0.1.

Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, and to the National Science Foundation (Grant No. CHE 7905525) for support of this research. Support of the Cornell Nuclear Magnetic Resonance Facility by the NSF (Grants CHE 7904825, PCM 8018643) is gratefully acknowledged.

Registry No. 5, 86411-26-9; 12, 3378-34-5; 13, 86411-27-0; 14, 5693-62-9; 15, 86411-28-1; peracetic acid, 79-21-0; lead tetraacetate, 546-67-8.

(12) Martinez, G. R. Vedejs, E. *J. Am. Chem. Soc.* **1980**, *102*, 7993.
(13) Collin, G.; Hohn, R.; Hauthal, H. G.; Hubner, H.; Pritzkow, W.; Rolle, W.; Schaefer, H.; Wahren, M. *Justus Liebigs Ann. Chem.* **1967**, *702*, 55.

Synthesis of 2-Amino-7-(2′-deoxy-β-D-*erythro*-pentofuranosyl)-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one, a New Isostere of 2′-Deoxyguanosine

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The pyrrolo[2,3-*d*]pyrimidine nucleosides are rare constituents of nucleic acids and have been isolated in the monomeric form as nucleoside antibiotics.[1] Several transfer nucleic acids contain the rare nucleoside queuosine (**1b**,[2] Chart I) and related derivatives in the wobble position of the anticodon. Moreover, the nucleoside antibiotic cadeguomycin (**1c**)[3] has been recently obtained as a fermentation product of *Streptomyces hydroscopicus*. The parent nucleoside of queuosine and cadeguomycin is 7-deazaguanosine (**1a**).[4] The latter has been prepared in our laboratory by the technique of phase-transfer glycosylation of 4-methoxy-2-methylthio-7*H*-pyrrolo[2,3-*d*]pyrimidine with 1-bromo-2,3,5-tri-O-benzyl-D-ribofuranose followed by a multistep conversion of the condensation product.[5] By the same method *ara*-7-deazaguanosine[6] has also been obtained.

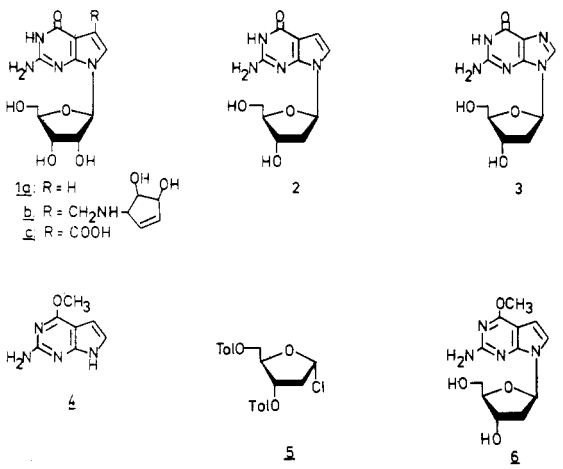
All attempts to use acetyl- or benzoyl-protected halogenoses in the synthesis of D-*ara*- or D-ribofuranosyl-nucleosides failed due to ortho amide formation.[7] Under the strongly alkaline conditions of phase-transfer glycosylation, nucleophilic displacement at the carbon of the acyloxonium intermediate is preferred, rather than a reaction at the carbon of the anomeric center. Acylated 2-deoxy sugars, however, cannot form an acyloxonium ion involving carbons 1 and 2 and should therefore be applicable to phase-transfer glycosylation reactions.

The total synthesis of sugar-modified 7-deazaguanosines has only been reported for the D-ribo- and D-arabino-furanosyl series. The 2′-deoxy series, e.g., compound **2**, is still unknown. Whereas 2′-deoxy-7-deazaadenosine can be prepared from the naturally occuring antibiotic tubercidin by nucleoside transformation[8] or by reduction of its triphosphate with ribonucleotide reductase,[9] these routes are not applicable to 2′-deoxy-7-deazaguanosine since 7-deazaguanosine has not been isolated from natural sources. We now report the total synthesis of 2′-deoxy-7-deazaguanosine (**2**), which is an isostere of the DNA constituent 2′-deoxyguanosine (**3**). Furthermore, we describe its O^4-methyl derivative **6**, which is structurally closely related to O^6-methyl-2′-deoxyguanosine[10] that causes mutations by mispairing in DNA.[11] The nucleosides **2** and

(1) Suhadolnik, R. J. "Nucleosides as Biological Probes"; Wiley: New York, 1979.
(2) Kasai, H.; Ohashi, Z.; Harada, F.; Nishimura, S.; Oppenheimer, N. J.; Crain, P. F.; Liehr, J. G.; von Minden, D. L.; McCloskey, J. A. *Biochemistry* **1975**, *14*, 4198.
(3) (a) Tanaka, N.; Wu, R. T.; Okabe, T.; Yamashita, H.; Shimazu, A.; Nishimura, T. *J. Antibio.* **1982**, *35*, 272. (b) Wu, R. T.; Okabe, T.; Namikoshi, M.; Okuda, S.; Nishimura, T.; Tanaka, N. *Ibid.* **1982**, *35*, 279.
(4) Townsend, L. B.; Tolman, R. L.; Robins, R. K.; Milne, G. H. *J. Heterocycl. Chem.* **1976**, *13*, 1363.
(5) Seela, F.; Hasselmann, D. *Chem. Ber.* **1981**, *114*, 3395.
(6) Seela, F.; Winkeler, H.-D. *J. Org. Chem.* **1982**, *47*, 226.
(7) Seela, F.; Lüpke, U.; Hasselmann, D. *Chem. Ber.* **1980**, *113*, 2808.
(8) Robins, M. J.; Muhs, W. H. *J. Chem. Soc., Chem. Commun.* **1976**, 269.
(9) (a) Suhadolnik, R. J.; Finkel, S. I.; Chassy, B. M. *J. Biol. Chem.* **1968**, *243*, 3532. (b) Chassy, B. M.; Suhadolnik, R. J. *Ibid.* **1968**, *243*, 3538.
(10) Gaffney, B. L.; Jones, R. A. *Tetrahedron Lett.* **1982**, *23*, 2253.

0022-3263/83/1948-3119$01.50/0

Chart I



6 should be useful biological probes analogous to 7-deazaguanosine.[12]

The most appropriate chromophore for the synthesis of compound **2** is 2-amino-4-methoxy-7*H*-pyrrolo[2,3-*d*]pyrimidine (**4**).[13] Its lactam moiety is methyl protected to prevent glycosylation at the N-1, N-3, or O-4 position. The methyl-protecting group can be easily removed, yielding the final aglycon.[13] As the sugar component we employed 1-chloro-2-deoxy-3,5-di-*O*-p-toluoyl-D-*erythro*-pentofuranose (**5**),[14] which has been sucessfully used in the synthesis of other 2′-deoxynucleosides.

Reaction of the chromophore **4** with the halogenose **5** in a biphasic mixture of benzene/50% aqueous NaOH in the presence of Aliquat 336 under the conditions of phase-transfer catalysis resulted in a complex mixture. After treatment of the content of the organic phase with concentrated aqueous ammonia the number of reaction products was reduced to one main product. A similar composition of products was found in the aqueous phase. After both phases were pooled, the reaction products were chromatographed on silica gel to give the chromophore **4** in 37% yield and a glycosylation product in 48% yield. Analytical data showed that the glycosylation resulted in the formation of a pure anomer.

Attempts to optimize the reaction by increasing the amount of phase-transfer catalyst/chromophore from 0.1 mol % to about 0.5 mol % increased the decomposition of the halogenose **5**, thereby reducing the yield of the glycosylation product. Even 0.1 mol % of catalyst/chromophore led to partial saponification of the halogenose.

We propose that an 1′–3′ or 1′–5′ ortho amide structure[15] can be formed as an intermediate. As we have shown, ortho amides are quite stable in the case of pyrrolo[2,3-*d*]pyrimidines[7] and do not rearrange to the final glycosylation product. However, such ortho amides are cleaved by aqueous ammonia to give the chromophore and the hydrolyzed sugar.[7] Ortho amide formation and decomposition of the halogenose **5** limit the yield of nucleosides.

The UV spectrum of the glycosylation product was similar to that of the chromophore **4**, and N-7 substitution was therefore assumed. This was confirmed by an independent assignment for the final nucleoside and was found to be N-7.

Table I. Fine Splitting Pattern[a] and ^1H–^{13}C Coupling Constants of Nucleoside **2** in Me_2SO-d_6

	C-6	C-5	C-4a
splitting	ddd	dd	dd
coupling const, Hz	$^1J_{H\text{-}6}$ = 188.6 $^2J_{H\text{-}5}$ = 7.9 $^3J_{H\text{-}1'}$ = 4.6 Hz	$^1J_{H\text{-}5}$ = 174.7 $^2J_{H\text{-}6}$ = 7.1	$^2J_{H\text{-}5}$ = 7.6 $^3J_{H\text{-}6}$ = 4.1

[a] dd = doublet of doublets, ddd = doublet of doublets of doublets; C-2 and C-4 are singlets, and C-7a shows a complex multiplet.

The anomeric configuration of the isolated nucleoside was assigned by ^1H NMR spectroscopy. The pattern of the H-1′ signals exhibits a doublet of doublets with coupling constants of $J_{1'2'a}$ = 8.4 Hz and $J_{1'2'b}$ = 5.9 Hz. These data confirm the β configuration and are in close agreement with values published for 2′-deoxytubercidin[8] as well as for other 2′-deoxyribonucleosides.

Efforts to isolate the α anomer failed. This result was unexpected and in contrast to other glycosylation procedures. Since the deoxyhalogenose **5** prepared according to the method of Hoffer[14] has the α configuration,[16] formation of the β-nucleoside **6** would be the result of a direct S_N2 displacement. This is presumably the preferred mechanism in the absence of a 2′-acyl group which can participate in the glycosylation reaction.

The short reaction time of the phase-transfer glycosylation would also favor specific formation of the β anomer as opposed to reactions which require longer times,[14,17] allowing the halogenose **5** to equilibrate.[18]

Cleavage of the 4-methoxy group in nucleoside **6** with 1 N aqueous HCl at 60 °C under nitrogen leads to complete hydrolysis of the N-glycosylic bond. This is in agreement with the rates of N-glycosylic hydrolysis of 2′-deoxyribofuranosyl vs. ribofuranosyl nucleosides.[19]

Sodium *p*-thiocresolate[20] was chosen for cleavage and was used in hexamethylphosphoric triamide/toluene under nitrogen to cleave the ether linkage of **6**, which was split within 3 h by heating under reflux. The nucleoside **2** was isolated after crystallization from water in 91% yield. The structure of **2** was in agreement with its NMR data.

Previous investigations have demonstrated that the use of ^1H–^{13}C NMR long-range coupling appears to be a useful tool in determining the site of alkylation or glycosylation in nucleo bases.[21] The coupling appears to extend up to three bond lengths, and its effects are quite uniform for a variety of nucleosides.

The fine coupling splittings of the nucleoside **2** are shown in Figure 1 and the data are summarized in Table I. From the ring system of pyrrolo[2,3-*d*]pyrimidine nucleosides it is obvious that the coupling pattern of the pyrrole moiety is more complex than in the imidazole ring of purine nucleosides. A positive indicator for the substitution at N-7 by the sugar ring should be carbon 6. On comparison of the pattern of C-5 and C-6 only C-6 exhibits three different coupling constants with H-6, H-5, and H-1′. The small coupling of 4.6 Hz definitely demonstrates N-7

(11) Loveless, A. *Nature (London)* **1969**, *223*, 206.
(12) (a) Seela, F.; Tran-Thi, Q.-H.; Franzen, D. *Biochemistry* **1982**, *21*, 4338. (b) Tran-Thi, Q.-H.; Franzen, D.; Seela, F. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 367.
(13) Seela, F.; Kehne, A.; Winkeler, H.-D. *Liebigs Ann. Chem.* **1983**, 137.
(14) Hoffer, M. *Chem. Ber.* **1960**, *93*, 2777.
(15) Wierenga, W.; Skulnick, H. I. *Carbohydr. Res.* **1981**, *90*, 41.
(16) Bhattacharya, A. K.; Ness, R. K.; Fletcher, H. G., Jr. *J. Org. Chem.* **1963**, *28*, 428.
(17) Seela, F.; Winkeler, H.-D. *Liebigs Ann. Chem.* **1982**, 1634.
(18) Kotick, M. P.; Szantay, C.; Bardos, T. J. *J. Org. Chem.* **1969**, *34*, 3806.
(19) Kochetkov, N. K.; Budovskii, E. I. "Organic Chemistry of Nucleic Acids"; Plenum Press: London and New York, 1972.
(20) Hansson, C.; Wickberg, B. *Synthesis* **1976**, 191.
(21) Cline, B. L.; Fagerness, P. E.; Panzica, R. P.; Townsend, L. B. *J. Chem. Soc., Perkin Trans. 2* **1980**, 1586.

Table II. Chromatographic and Electrophoretic Mobilities of Pyrrolo[2,3-*d*]pyrimidine and Guanine Derivatives

compd	R_f (silica gel, solvent C)	R_e[a] silica gel (solvent D)	R_e[a] silica gel (solvent E)
2′-deoxy-7-deazaguanosine (2)	0.35	1.5 (−)	1.9 (−)
7-deazaguanosine (1a)	0.28	0.6 (−)	0
7-deazaguanine	0.39	1.0 (−)	1.0 (−)
2′-deoxyguanosine (3)	0.20	1.3 (−)	1.5 (−)

[a] (−) toward cathode, (+) toward anode.

glycosylation. Moreover, C-2 remains a singlet, which should show fine couplings in the case of N-1 or N-3 glycosylation.

The pyrrolo[2,3-*d*]pyrimidine nucleoside **2** exhibits a UV spectrum with a maximum at 257 nm (methanol), which is 5 nm bathochromically shifted relative to that of 2′-deoxyguanosine (**3**; 252 nm, methanol). On TLC (Table II) compound **2** migrates somewhat faster than 7-deazaguanosine. It can be easily distinguished from the latter by thin-layer electrophoresis in sodium tetraborate.

Investigation in regard to incorporation of **2** in oligo- and polynucleotides are in progress. Such polymers should give useful information on base pairing and enzyme recognition.

Experimental Section

Melting points were determined on a Berl apparatus (Wagner & Munz, Munich, FRG) and were not corrected. Elemental analyses were performed by Mikroanalytisches Labor Beller (Göttingen, FRG). ^{1}H NMR and ^{13}C NMR spectra were recorded on Varian EM-390 or Bruker WM-250 spectrometers, and δ values are in parts per million relative to tetramethylsilane as an internal standard. UV spectra were measured on an Uvicon 810 spectrophotometer (Kontron, Switzerland). Thin-layer chromatography (TLC) was carried out on silica gel Sil-G-25-UV$_{254}$ plates (Macherey & Nagel, Düren, FRG). Column chromatography was performed on silica gel 60 (230–400 mesh ASTM, Merck, Darmstadt, FRG). Solvent systems: A, $CHCl_3$–MeOH (95:5); B, $CHCl_3$–MeOH (9:1); C, $CHCl_3$–MeOH (8:2); D, 0.1 M sodium citrate (pH 6.5); E, 0.1 M sodium tetraborate (pH 9.0).

2-Amino-7-(2′-deoxy-β-D-*erythro*-pentofuranosyl)-4-methoxy-7*H*-pyrrolo[2,3-*d*]pyrimidine (6). A suspension of **4**[13] (0.5 g, 3.05 mmol) and Aliquat 336 (methyltrioctylammonium chloride, 133 mg, 0.3 mmol) in benzene/dimethoxyethane (4:1), 20 mL) and an equal volume of 50% aqueous sodium hydroxide was stirred with a vibromixer for 30 min. During this time the halogenose **5**[14] (1.66 g, 4.26 mmol) dissolved in hot benzene (30 mL) was added in small portions. After this the suspension was diluted with water (100 mL) and dichloromethane (100 mL). The organic phase was separated and evaporated in vacuo. The resulting syrup was dissolved in methanol (20 mL), treated with concentrated ammonia, and stirred for 24 h at room temperature. The solvent was removed in vacuo to give a light brown syrup (520 mg). The aqueous phase was acidified with concentrated hydrochloric acid to pH 4. Precipitated *p*-toluic acid was filtered off. The filtrate was evaporated to dryness. The residue was suspended in methanol (100 mL) and heated under reflux for 10 min. Inorganic salt was filtered off, and the solvent was removed in vacuo to leave a brown amorphous residue (650 mg). The contents of both phases were combined and dissolved in methanol (30 mL), adsorbed on silica gel (5 g), and evaporated in vacuo. The residue was suspended in dichloromethane and applied to a silica gel column (2.5 × 20 cm). A prerun with dichloromethane gave only nonnitrogeneous material, which was discarded. Further elution with solvent system A gave two zones. From the more rapidly migrating zone was isolated unreacted chromophore **4** (198 mg, 39.6%) after evaporation of the solvent. From the slower migrating zone was isolated nucleoside **6**, and it was obtained from water as colorless crystals: 411 mg, 48%, methanol; mp 152–154 °C; TLC (silica gel, solvent B) R_f 0.7; $[\alpha]^{20}_D$ −91.1° (*c* 1.35, H_2O); UV (methanol) λ_{max} 225, 259, 285 nm (ϵ 24 900, 9600, 7600); ^{1}H NMR (Me_2SO-d_6) δ 2.05 (1 H, m, H-2′b), 2.40 (1 H, m, H-2′a), 3.50 (2 H, m, H-5′), 3.77 (1 H, m, H-4′), 3.91 (3 H, s, OCH_3), 4.30 (1 H, m, H-3′), 4.93 (1 H, t, OH-5′, J = 5 Hz), 5.21 (1 H, d, OH-3′, J = 3.5 Hz), 6.20 (2 H, s br, NH_2), 6.27 (1 H, d, H-5, J = 3.7 Hz), 6.42 (1 H, d of d, H-1′, $J_{1',2'a}$ = 8.4 Hz, $J_{1',2'b}$ = 5.9 Hz), 7.10 (1 H, d, H-6, J = 3.7 Hz); 52.49 (OCH_3), 61.95 (C-5′), 70.89 (C-3′), 82.37 (C-1′), 86.88 (C-4′), 97.28 (C-4a), 98.85 (C-5), 119.45 (C-6), 154.24 (C-7a), 159.40 (C-2), 163.00 (C-4). Anal. Calcd for $C_{12}H_{16}N_4O_4$: C, 51.42; H, 5.75; N, 19.99. Found: C, 51.55; H, 5.74; N, 19.99.

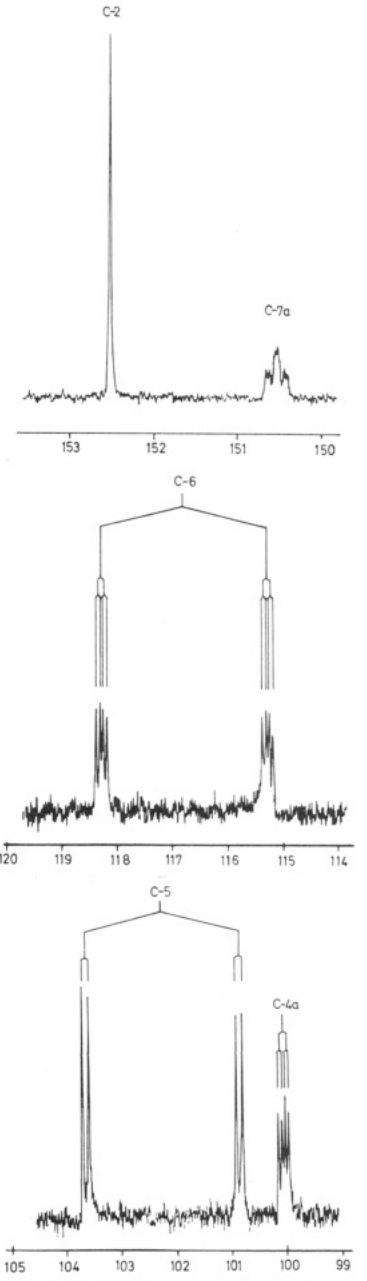


Figure 1. ^{13}C/^{1}H NMR fine coupling pattern of 2-amino-7-(2′-deoxy-β-D-*erythro*-pentofuranosyl)-3,7-dihydro-4*H*-pyrrolo-[2,3-*d*]pyrimidin-4-one (**2**) in Me_2SO-d_6.

2-Amino-7-(2′-deoxy-β-D-*erythro*-pentofuranosyl)-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one (2). Compound **6** (0.5 g, 1.78 mmol) in dry toluene (15 mL) was treated with sodium *p*-thiochresolate (391 mg, 2.68 mmol) and hexamethylphosphoric triamide (479 mg, 2.68 mmol, stored over 4-Å molecular sieves). The reaction mixture was refluxed under nitrogen. After 3 h the resulting suspension was treated with 50 mL of water and washed twice with chloroform (50 mL). Then the aqueous solution was acidified with 2 N hydrochloric acid to pH 2 and extracted twice

with chloroform (30 mL). The aqueous phase was separated, neutralized, and evaporated in vacuo. The resulting crude residue was recrystallized from water (10 mL) to give **2**: 430 mg (91%); colorless needles; mp 262–265 °C dec; TLC (silica gel, B) R_f 0.23; $[\alpha]^{20}_D$ −77.0° (*c* 1.06, H_2O); UV (methanol) λ_{max} 217, 257, 281 (sh) nm (ϵ 19 500, 12 900, 7300); ^1H NMR (Me_2SO-d_6) δ 2.05 (1 H, m, H-2′b), 2.40 (1 H, m, H-2′a), 3.48 (2 H, m, H-5′), 3.75 (1 H, m, H-4′), 4.28 (1 H, m, H-3′), 4.89 (1 H, t, OH-5′, *J* = 5.5 Hz), 5.20 (1 H, d, OH-3′, *J* = 3.8 Hz), 6.23 (2 H, br s, NH_2), 6.26 (1 H, d, H-5, *J* = 3.6 Hz), 6.30 (1 H, d of d, H-1′, $J_{1',2'a}$ = 8.4 Hz, $J_{1',2'b}$ = 6.0 Hz), 6.92 (1 H, d, H-6, *J* = 3.6 Hz), 10.35 (1 H, br s, NH), ^{13}C NMR (Me_2SO-d_6) δ 39.50 (C-2′), 61.92 (C-5′), 70.84 (C-3′), 82.23 (C-1′), 86.85 (C-4′), 100.08 (C-4a), 102.09 (C-5), 116.67 (C-6), 150.50 (C-7a), 152.50 (C-2), 158.51 (C-4). Anal. Calcd for $C_{11}H_{14}N_4O_4$: C, 49.61; H, 5.30; N, 21.04. Found: C, 49.66; H, 5.31; N, 21.18.

Acknowledgment. We thank Dr. V. Armstrong for critical reading. Financial support by the Deutsche Krebshilfe is gratefully acknowledged.

Registry No. **2**, 86392-75-8; **4**, 84955-32-8; **5**, 4330-21-6; **6**, 86392-74-7.

Chemistry of Organosilicon Compounds. 171. Isoprenylation of Carbonyl Compounds with 2-[(Trimethylsilyl)methyl]-1,3-butadiene Initiated by a Catalytic Amount of Tetra-*n*-butylammonium Fluoride. The Most Convenient Route to Ipsenol and Ipsdienol

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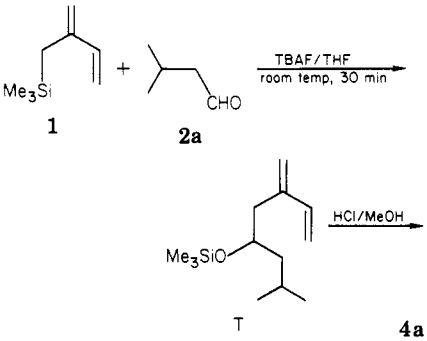
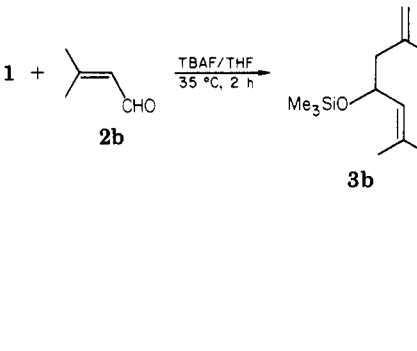
Many efforts have been directed to the synthesis of isoprenylated naturally occurring materials,[1] especially to the synthesis of ipsenol and ipsdienol, principal components of the aggregation pheromones of *Ips paraconfusus*, a bark beetle of California Ponderosa Pine.[2] During the course of studies on the application of allylsilanes to organic synthesis,[3] we have found that 2-[(trimethylsilyl)methyl]-1,3-butadiene (**1**)[1p] provides one of the most convenient and simple route to these compounds.

Isoprenylsilane (**1**) reacted with isovaleraldehyde (**2a**) or 3-methyl-2-butenal (**2b**) very smoothly in the presence of a catalytic amount of tetra-*n*-butylammonium fluoride (TBAF)[4] in tetrahydrofuran to give ipsenol (**4a**) and ipsdienol (**4b**) in 74% and 70% yields, respectively, after careful acid-catalyzed hydrolysis by use of a "one pot" operation (eq 1 and 2). The formation of the silyl ethers



(1)

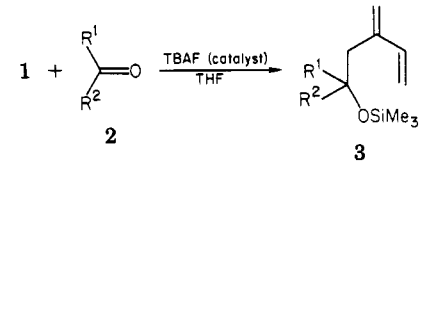


(2)

(**3**) was confirmed by GC/MS spectroscopic analysis of the reaction mixture before hydrolysis.

This is the most efficient and concise procedure of the synthesis of ipsenol (**4a**) and ipsdienol (**4b**) in the highest yield from the readily available starting materials among various methods known hitherto.

The wide utility and general superiority of the present isoprenylating system to **4a** and **4b** have been further demonstrated by the isoprenylation of a variety of carbonyl compounds (**2**) such as aldehydes and ketones. Thus, when a mixture of **1**, **2**, and a catalytic amount of TBAF was stirred in THF at room temperature or at slightly higher temperature (around 30–50 °C) for 1.5–4 h, the corresponding isoprenylated derivatives were obtained in high yield (eq 3). The results are summarized in Table I.



(3)

The alcohols **4** and their silyl ethers **3** involving an isoprenyl moiety should be treated carefully during the hydrolysis under acid conditions in order to avoid lowering the yields, presumably due to polymerization and other side reactions. In the case of enolizable aldehydes and

(1) (a) Silverstein, R. M.; Rodin, J. O.; Wood, D. L.; Browne, L. E. *Tetrahedron* **1966**, *22*, 1929. (b) Reece, C. A.; Rodin, J. O.; Brownlee, R. G.; Duncan, W. G.; Silverstein, R. M. *Ibid.* **1968**, *24*, 4249. (c) Vig, O. P.; Anad, R. C.; Kad, G. L.; Sehgal, J. M. *J. Indian Chem. Soc.* **1970**, *47*, 999. (d) Katzenellenbogen, J. A.; Lenox, R. S. *J. Org. Chem.* **1973**, *38*, 326. (e) Riley, R. G.; Silverstein, R. M.; Katzenellenbogen, J. A.; Lenox, R. S. *Ibid.* **1974**, *39*, 1957. (f) Wilson, S. R.; Phillips, L. R. *Tetrahedron Lett.* **1975**, 3047. (g) Garbers, J. F.; Scott, F. *Ibid.* **1976**, 1625. (h) Karlsen, S.; Frøyen, P.; Skattebøl, L. *Acta Chem. Scand., Ser. B* **1976**, *B30*, 644. (i) Ohloff, G.; Giersch, W. *Helv. Chim. Acta* **1977**, *60*, 1496. (j) Mori, K. *Tetrahedron Lett.* **1975**, 2187. (k) *Ibid.* **1976**, 1609. (l) *Tetrahedron* **1976**, *32*, 1101. (m) Bertland, M.; Viala, J. *Tetrahedron Lett.* **1978**, 2575. (n) Kondo, K.; Dobashi, S.; Matsumoto, M. *Chem. Lett.* **1976**, 1077. (o) Cazes, B.; Guitlet, E.; Julia, S.; Ruel, O. *J. Organometal. Chem.* **1979**, *177*, 67. (p) Hosomi, A.; Saito, M.; Sakurai, H. *Tetrahedron Lett.* **1979**, 429. (q) Wilson, S. R.; Phillips, L. R.; Natalie, K. J., Jr. *J. Am. Chem. Soc.* **1979**, *101*, 3340.

(2) (a) Silverstein, R. M.; Rodin, J. O.; Wood, D. L. *Science (Washington, D.C.)* **1966**, *154*, 509. (b) *J. Econ. Entmol.* **1967**, *60*, 944.

(3) (a) Sakurai, H. *Pure Appl. Chem.* **1982**, *54*, 1. (b) Hosomi, A.; Iguchi, H.; Hayashi, J.; Sakurai, H. *Tetrahedron Lett.* **1982**, *23*, 551. (c) Hosomi, A.; Saito, M.; Sakurai, H. *Ibid.* **1980**, *21*, 355. (d) Hosomi, A.; Hashimoto, H.; Sakurai, H. *Ibid.* **1980**, *21*, 951. (e) Hosomi, A.; Kobayashi, H.; Sakurai, H. *Ibid.* **1980**, *21*, 955 and references cited therein.

(4) Hosomi, A.; Shirahata, A.; Sakurai, H. *Tetrahedron Lett.* **1978**, 3043.

0022-3263/83/1948-3122$01.50/0