(270 MHz, $CDCl_3$) δ 4.88 (1 H, t, J = 6.5 Hz), 3.70 (6 H, s), 2.78 (4 H, m), 1.95 (3 H, m), 1.61 (3 H, s), 1.50 (1 H, m), 1.33 (2 H, m), 1.10 (2 H, m), 0.84 (6 H, d, J = 7.5 Hz). Anal. Calcd for $C_{18}H_{28}O_4$: C, 70.10; H, 9.15. Found: C, 69.85; H, 9.22.

Preparation of 4,4-Bis(Methoxycarbonyl)-2-(6'-methylhept-2'-en-2'-yl)-1-methylenecyclopentane (40). FVT of 15 mg (0.049 mmol) of enyne **39** at 575 °C (0.01 mmHg) gave, after flash chromatography (15:1 hexane–ether), 12 mg (80%) of the titled compound for which VPC analysis indicated a 1.2:1 ratio of the two geometrical isomers. IR ($CDCl_3$): 1729, 1651 cm^{-1}. ^1H NMR (270 MHz, C_6D_6): δ 5.45 (0.5 H, t, J = 6 Hz), 5.37 (0.5 H, t, J = 7 Hz), 5.10 (0.5 H, s), 5.05 (0.5 H, s), 5.00 (0.5 H, s), 4.96 (0.5 H, s), 4.11 (0.5 H, t, J = 7 Hz), 3.58 (0.5 H, t, J = 7 Hz), 3.37 (1.5 H, s), 3.36 (1.5 H, s), 3.33 (1.5 H, s), 3.40–3.22 (2 H, m), 2.85 (1 H, m), 2.45 (0.5 H, t, J = 10 Hz), 2.41 (0.5 H, t, J = 13 Hz), 2.10 (2 H, m), 1.72 (1.5 H, s), 1.60 (1.5 H, s), 1.58 (1 H, m), 1.30 (2 H, m), 0.90 (3 H, d, J = 7 Hz), 0.89 (3 H, d, J = 7 Hz). MW for $C_{18}H_{28}O_4$: calcd 308.1988, found 308.1985.

Pd(2+)-Catalyzed Cyclization of Enyne 39. A solution of 10 mg (0.032 mmol) of enyne **39** and 1.2 mg (5 mol %) of catalyst **12** in 0.45 mL of benzene-d_6 heated at 66 °C for 1 h gave, after flash chromatography (20:1 hexane–ether), 7 mg (70%) of a 1:8.9:2.2 mixture of one geometrical isomer of **40**, **41**, and another geometrical isomer of **40**. IR ($CDCl_3$): 1728, 1655 cm^{-1}. ^1H NMR (270 MHz, C_6D_6): δ 5.10 (1 H, s), 5.05 (2 H, s), 4.98 (1 H, s), 3.58 (1 H, m), 3.50 (3 H, s), 3.45 (3 H, s), 3.40–3.20 (2 H, m), 2.90 (1 H, m), 2.46 (1 H, t, J = 10.5 Hz), 2.10 (2 H, m), 1.55–1.40 (3 H, m), 1.30–1.15 (2 H, m), 0.96 (6 H, d, J = 6 Hz). MW for $C_{18}H_{28}O_4$: calcd 308.1988, found 308.1979.

Annulation of Carveol to Bicycle 43. Sequential addition of 0.9 mL (6.5 mmol) of triethylamine and 274 mg (2.4 mmol) of methanesulfonyl chloride to a solution of 365 mg (2.40 mmol) of carveol in 3 mL of THF at −20 to 0 °C produced the corresponding mesylate. To this resultant solution were added a solution of 595 mg (3.50 mmol) of dimethyl propargylmalonate in 0.5 mL of THF and 3.5 mL (1 M in THF, 3.5 mmol) of lithium hexamethyldisilazide at 0 °C, and the resultant mixture was stirred for 1 h at room temperature. After addition of water, ether extraction, and drying ($MgSO_4$), flash chromatography (4:1 hexane–ether) gave 274 mg (38%) of enyne **42**. IR ($CDCl_3$): 3310, 1730, 1645 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 5.42 (1 H, bs), 4.61 (2 H, m), 3.68 (3 H, s), 3.60 (3 H, s), 3.11 (1 H, bs), 2.78 (2 H, d, J = 2.5 Hz), 2.22–2.00 (2 H, m), 1.97 (1 H, t, J = 2.5 Hz), 1.80–1.65 (3 H, m), 1.62 (6 H, s). ^{13}C NMR (15 MHz, $CDCl_3$): δ 170.5, 170.3, 148.4, 133.0, 125.6, 108.8, 79.6, 71.0, 60.4, 52.4, 52.0, 41.1, 35.9, 30.4, 30.1, 24.7, 24.2, 20.6. MW for $C_{18}H_{24}O_4$: calcd 304.1675, found 304.1664.

A solution of 168 mg (0.552 mmol) of the above enyne and 21 mg (5 mol %) of catalyst **12** in 1 mL of benzene heated at 60 °C for 1 h gave, after flash chromatography (6:1 hexane–ether), 101 mg (60%) of bicycle **43**. IR ($CDCl_3$): 1740, 1725, 1655 1640 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 5.52 (2 H, s), 4.84 (1 H, m), 4.76 (2 H, m), 4.63 (1 H, m), 3.68 (6 H, s), 3.25 (1 H, dt, J = 14.0, 2.2 Hz), 2.90 (1 H, dd, J = 8.3, 5.0 Hz), 2.80 (1 H, d, J = 14.0 Hz), 2.56 (1 H, bt, J = 5.0 Hz), 1.67 (3 H, bs), 1.65–1.35 (2 H, m), 1.10 (3 H, s). ^{13}C NMR (15 MHz, $CDCl_3$): δ 172.5, 170.5, 155.6, 146.8, 134.7, 127.2, 111.3, 105.6, 74.9, 61.6, 52.7, 52.3, 46.8, 45.9, 39.6, 28.1, 27.0, 21.3. MW for $C_{18}H_{24}O_4$: calcd 304.1675, found 304.1673.

Annulation of Carveol to Bicycle 45. A solution of 90 mg (0.463 mmol) of carveol acetate[33] (prepared in standard fashion from carveol,[34] acetic anhydride, and DMAP in methylene chloride), 23 mg (4.3 mol %) of tetrakis(triphenylphosphine)palladium, and 8 mg (6.5 mol %) of triphenylphosphine in 0.5 mL of THF was added to a solution of sodium dimethyl propargylmalonate at room temperature prepared by heating 120 mg (0.706 mmol) of the malonate and 15 mg (0.625 mmol) of sodium hydride in 1.5 mL of THF at 60 °C for 30 min. After the solution was heated at reflux for 1.5 days, evaporation in vacuo and flash chromatography (4:1 hexane–ether) gave 113 mg (80%) of enyne **44**. IR ($CDCl_3$): 3300, 2110, 1730, 1640 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 5.58 (1 H, bs), 4.72 (2 H, bm), 4.68 (1 H, bs), 3.80 (3 H, s), 3.78 (3 H, s), 3.30 (1 H, bm), 3.00 (1 H, d, J = 3.0 Hz), 2.92 (1 H, dd, J = 15, 3 Hz), 2.76 (1 H, dd, J = 15, 3 Hz), 2.05 (1 H, t, J = 3 Hz), 2.00–1.75 (3 H, m), 1.71 (3 H, s), 1.65 (3 H, s), 1.35 (m, 1 H). ^{13}C NMR (15 MHz, $CDCl_3$): δ 170.4, 169.5, 148.9, 133.2, 126.8, 108.8, 80.1, 70.8, 60.6, 52.3 (2C), 44.7, 41.8, 31.2, 30.9, 24.2, 23.2, 20.7. MW for $C_{18}H_{24}O_4$: calcd 306.1675, found 306.1675.

A solution of 70 mg (0.23 mmol) of enyne **44** and 10 mg (5.7 mol %) of catalyst **12** in 0.5 mL of benzene heated at 60 °C for 1 h gave, after flash chromatography (2:1 hexane–ether), 51 mg (73%) of bicycle **45**. IR ($CDCl_3$): 1735, 1675, 1665 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 5.63 (1 H, dd, J = 10.7, 2.9 Hz), 5.50 (1 H, d, J = 10.7 Hz), 4.85 (1 H, bs), 4.74 (1 H, t, J = 2.7 Hz), 4.68 (2 H, bs), 3.71 (3 H, s), 3.69 (3 H, s), 3.28 (1 H, dt, J = 18.3, 2.7 Hz), 3.02 (1 H, d, J = 18.3 Hz), 2.92 (1 H, dd, J = 14, 5 Hz), 2.70 (1 H, bd, J = 12.5 Hz) 1.60 (3 H, s), 1.35 (1 H, m), 1.15 (1 H, m), 1.04 (3 H, s). ^{13}C NMR (15 MHz, $CDCl_3$): δ 172.1, 169.9, 155.7, 148.2, 134.2, 128.3, 110.2, 106.0, 62.3, 52.9, 52.6, 49.9, 47.0, 43.1, 37.8, 30.5, 30.2, 20.2. MW for $C_{18}H_{24}O_4$: calcd 304.1675, found 304.1673.

Acknowledgment. We thank the National Science Foundation and the National Institutes of Health for their most generous continuing support of our programs. Fellowships for M.L. from the NSERC (Canada) and for T.M. from NATO are acknowledged.

Supplementary Material Available: Experimental data for **13**, **14**, **16**, **18a–d**, **24**, **27a–f**, **31a,b**, **32a**, and **33** (14 pages). Ordering information is given on any current masthead page.

(33) Fiaud, J. C.; Malleron, J. L. *Tetrahedron Lett.* **1981**, *22*, 1399.
(34) Ozawa, S.; Itoh, A.; Oshima, K.; Nozaki, H. *Tetrahedron Lett.* **1979**, 2909. Schroeter, S. H.; Eliel, E. L. *J. Org. Chem.* **1965**, *30*, 1.

Nitrogen-15-Labeled Deoxynucleosides. 4. Synthesis of [1-^{15}N]- and [2-^{15}N]-Labeled 2'-Deoxyguanosines

Bhaswati Goswami and Roger A. Jones*

Contribution from the Department of Chemistry, Rutgers, The State University of New Jersey, Piscataway, New Jersey 08855. *Received June 18, 1990*

Abstract: The syntheses of [1-^{15}N]- and [2-^{15}N]-2'-deoxyguanosines are reported via transformation of 2'-deoxyadenosine. The ^{15}N source for the [1-^{15}N] label is [6-^{15}N]-2'-deoxyadenosine, while for the [2-^{15}N] label it is [^{15}N]KCN. The synthetic route is particularly straightforward in that there are no protection and deprotection steps and only one chromatographic purification. Furthermore, it is directly applicable to preparation of the labeled ribonucleosides. These [1-^{15}N]- and [2-^{15}N]-labeled guanine nucleosides are now available by routes that give material in sufficient yields that they can be prepared for incorporation into nucleic acid fragments.

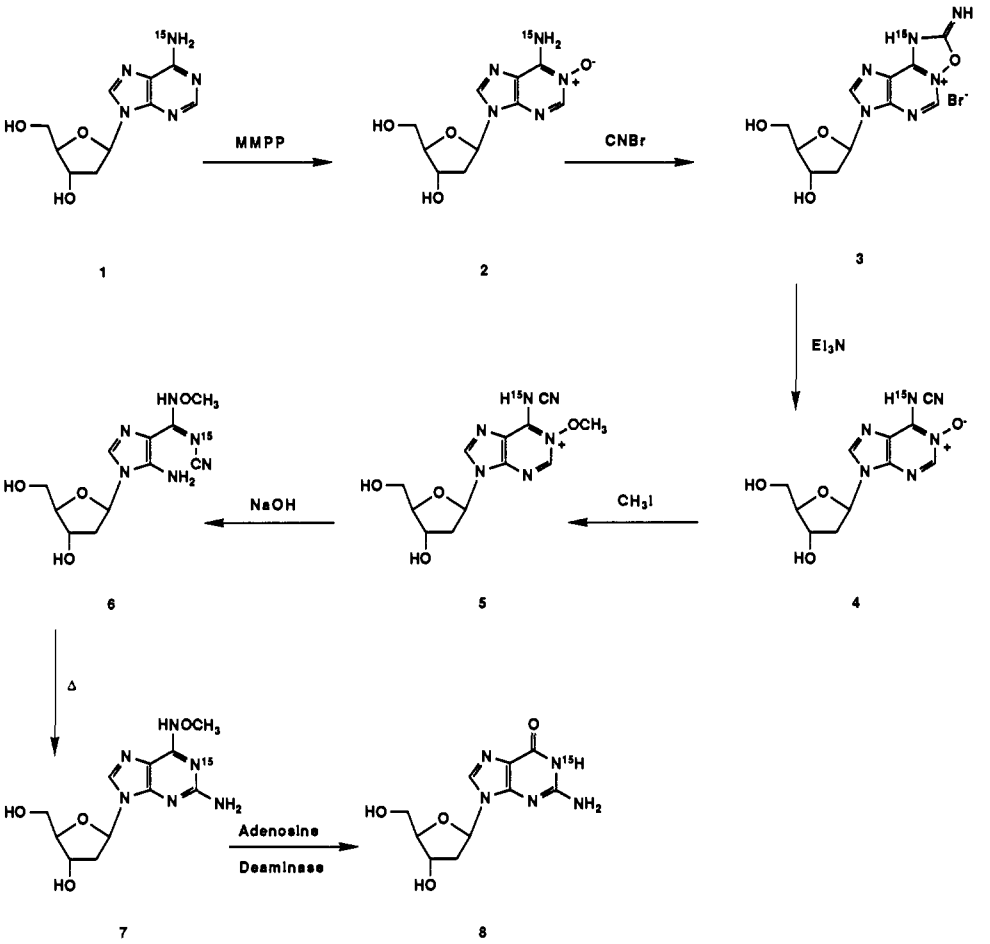
The potential utility of ^{15}N-labeled oligonucleotides to probe uniquely nucleic acid structure, drug-binding, and nucleic acid–protein interactions[1-3] has led to considerable interest in the development of routes to the requisite ^{15}N-labeled monomers. Our report of synthetic routes to [1-^{15}N]- and [6-^{15}N]-labeled deoxyadenosines[4] was quickly followed by an alternate route to the

* To whom correspondence should be addressed.

(1) Kamamori, K.; Roberts, J. D. *Acc. Chem. Res.* **1983**, *16*, 35–41.
(2) Gao, X.; Jones, R. A. *J. Am. Chem. Soc.* **1987**, *109*, 3169–3171.
(3) Buchanan, G. W. *Tetrahedron* **1989**, *45*, 581–604.

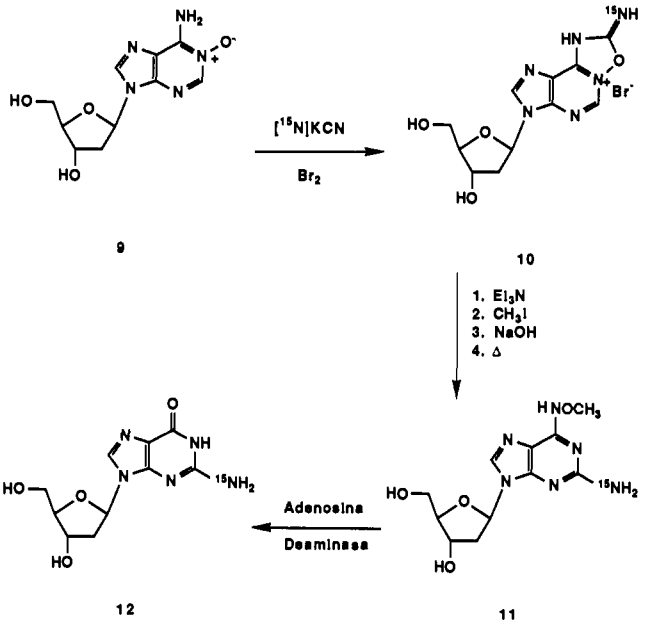
0002-7863/91/1513-644$02.50/0

Scheme I



[6-^{15}N]-labeled compound.[5] More recently, routes to [3-^{15}N]- and [7-^{15}N]-labeled purine nucleosides of the adenine and guanine families have been reported.[6-8] The guanine N1 and N2 positions are also of interest for ^{15}N labeling since they are involved both in normal Watson–Crick H-bonding and in the Hoogsteen H-bonding that may be present in triplex and tetraplex structures.[9-17] Although a synthesis of [2-^{15}N]-labeled deoxyguanosine has been reported, there is to date no report of a synthetic route to [1-^{15}N]-2′-deoxyguanosine.[18] We now report efficient synthetic routes to both [1-^{15}N]-2′-deoxyguanosine (**8**) and [2-^{15}N]-2′-deoxyguanosine (**12**).

Scheme II



The route we employed is based on Ueda's syntheses of 6-thioguanine and 2,6-diaminopurine nucleosides.[19] In this approach, adenine nucleosides are transformed into 2-aminopurine nucleosides via reaction of the N^1-oxide with cyanogen bromide followed by a Dimroth rearrangement (Schemes I and II). The

(4) Gao, X.; Jones, R. A. *J. Am. Chem. Soc.* **1987**, *109*, 1275–1278.
(5) Kupferschmitt, G.; Schmidt, J.; Schmidt, T.; Fera, B.; Buck, F.; Rüterjans, H. *Nucleic Acids Res.* **1987**, *15*, 6225–6241.
(6) Massefski, W., Jr.; Redfield, A.; Sarma, U. D.; Bannerji, A.; Roy, S. *J. Am. Chem. Soc.* **1990**, *112*, 5350–5351.
(7) Gaffney, B. L.; Kung, P.-P.; Jones, R. A. *J. Am. Chem. Soc.* **1990**, *112*, 6748, 6749.
(8) Rhee, Y. S.; Jones, R. A. *J. Am. Chem. Soc.* **1990**, *112*, 8174, 8175.
(9) Mirkin, S. M.; Lyamichev, V. I.; Drushlyak, K. N.; Dobrynin, V. N.; Filippov, S. A.; Frank-Kamenetskii, M. D. *Nature (London)* **1987**, *330*, 495–497.
(10) Johnston, B. H. *Science* **1988**, *241*, 1800–1804.
(11) Sen, D.; Gilbert, W. *Nature (London)* **1988**, *334*, 364–366.
(12) Htun, H.; Dahlberg, J. E. *Science* **1989**, *243*, 1571–1576.
(13) Rajagopal, P.; Feigon, J. *Nature (London)* **1989**, *339*, 637–640.
(14) Williamson, J. R.; Raghuraman, M. K.; Cech, T. R. *Cell* **1989**, *59*, 871–880.
(15) Sundquist, W. I.; Klug, A. *Nature* **1989**, *342*, 825–829.
(16) Santos, C. D. L.; Rosen, M.; Patel, D. *Biochemistry* **1989**, *28*, 7282–7289.
(17) Panyutin, I. G.; Kovalsky, O. I.; Budowsky, E. I.; Dickerson, R. E.; Rikhirev, M. E. *Proc. Natl. Acad. Sci. U.S.A.* **1990**, *87*, 867–870.
(18) Kieper, I.; Schmidt, T.; Fera, B.; Rüterjans, H. *Nucleosides Nucleotides* **1988**, *7*, 821–825.
(19) Ueda, T.; Miura, K.; Kasai, T. *Chem. Pharm. Bull.* **1978**, *26*, 2122–2127.

2-amino group in the product is derived from the cyanogen bromide, while the N1 is from the adenine 6-amino group. The initial products of the reaction sequence are the N^6-methoxy derivatives. In this case, we have used enzymatic deamination by adenosine deaminase to generate the corresponding guanine derivatives. The set of reactions that we used for both syntheses is then identical, with the only difference being in the ^{15}N source (Schemes I and II). Significantly, these transformations are carried out without the use of protecting groups and with minimal isolation of intermediates. Thus, the [1-^{15}N]-labeled deoxyguanosine was obtained by transformation of [6-^{15}N]-labeled deoxyadenosine (**1**, Scheme I), prepared as reported previously.[4] Conversely, the [2-^{15}N]-labeled deoxyguanosine was obtained by reaction of ^{15}N-labeled cyanogen bromide (Scheme II) with 2'-deoxyadenosine N^1-oxide. The [^{15}N]CNBr is prepared conveniently in situ by reaction of bromine with [^{15}N]KCN.

The N^1-oxides **2/9** were prepared with magnesium monoperoxyphthalate (MMPP) rather than the more common procedure with *m*-chloroperbenzoic acid[20] because of the present unavailability of the latter reagent. The oxidation using MMPP is carried out in aqueous dioxane for 48 h and gives **2/9** in yields of 70% (one crop) upon crystallization from water/methanol mixtures.

Transformation of **2/9** to the methoxyamino derivatives **7/11**, respectively, is then carried out as a one-flask reaction. By use of a methanolic solution of **2/9** and 1.1 equiv of cyanogen bromide (for **2**) or a mixture of bromine and [^{15}N]KCN in methanol (for **9**), the corresponding oxadiazoline (**3/10**) is formed within 2–3 h at room temperature. After evaporation of the mixture to dryness and dissolution of the residue in dimethylformamide, treatment with triethylamine opens the oxadiazoline to give the corresponding N^6-cyano derivative (e.g., **4**). Methylation using methyl iodide then gives the N^1-alkoxy derivative (e.g., **5**). Such N^1-alkoxy derivatives readily undergo Dimroth rearrangement to the corresponding N^6-alkoxy derivative. Thus, after evaporation but without purification, treatment of the reaction mixture with 0.25 N NaOH effects ring opening (e.g., **6**), and subsequent Dimroth rearrangement gives **7/11**. These methoxyamino derivatives are then isolated and purified by reversed-phase chromatography using a gradient of 2–5% acetonitrile/0.1 M ammonium bicarbonate in yields in the range of 50–64% overall from **2/9**.

The methoxyamino compounds (**7/11**), like the 6-(methylamino)-, (hydroxylamino)-, and methoxyadenosines,[21] are substrates for deamination using adenosine deaminase, although the reaction is significantly slower than is the case for deamination of either deoxyadenosine or 2,6-diamino-9-(2-deoxy-β-D-*erythro*-pentofuranosyl)purine.[7] Nevertheless, by use of ~500 units of adenosine deaminase per mmol of **7/11**, the deamination to **8/12** is quantitative after two days at room temperature.

This is the first report of synthesis of [1-^{15}N]-2'-deoxyguanosine (**8**). The [2-^{15}N] derivative (**12**) has been reported via ammonolysis of a 2-fluoro derivative.[18] However, a direct comparison to this route cannot be made as the report did not include yields.[18] The present route is particularly straightforward in that there are no protection and deprotection steps and only one chromatographic purification. Furthermore, it is directly applicable to preparation of the labeled ribonucleosides. In the ribo series, a mixture of the [1-^{15}N]- and [2-^{15}N]-labeled guanosines has been prepared by a route that is not applicable to the deoxy series.[22] Finally, it should be noted that although the reactions reported above for **8** and **12** are identical, in practice it is clearly much easier to get to the [2-^{15}N] derivative **12** than to the [1-^{15}N] derivative **8**, since the ^{15}N source of the former is [^{15}N]KCN while for the latter it is [6-^{15}N]-2'-deoxyadenosine (**1**). Nevertheless, the synthesis of **1** is not difficult.[4] Thus, [1-^{15}N]- and [2-^{15}N]-labeled guanine nucleosides are now available by routes that give material in sufficient yields that they can be prepared for incorporation into nucleic acid fragments.

Experimental Section

General Methods. Melting points were determined on a Thomas-Hoover apparatus and are uncorrected. Ultraviolet spectra were recorded on a Cary 118C or an Aviv 14. The ^1H and ^{15}N NMR spectra were recorded on a Varian XL-200 or XL-400. The mass spectra were obtained in the Mass Spectrometry Department of the Center for Advanced Food Technology, Cook College, Rutgers University. Preparative reversed-phase HPLC was performed on a system consisting of a Waters 590 EEF pump and Model 660 gradient controller with an Autochrom OPG to allow a single-pump gradient and a Beckman 153B detector.

The [^{15}N]KCN was obtained from Cambridge Isotope Laboratories. Adenosine deaminase (A-5773) was obtained from Sigma Chemical Co. Magnesium monoperoxyphthalate and other general reagents were obtained from Aldrich Chemical Co.

[6-^{15}N]-2'-Deoxyadenosine N^1-Oxide (2). To 1.43 g (5.65 mmol) of **1** dissolved in 142 mL of 30% aqueous dioxane was added 3.16 g (6.39 mmol) of MMPP. The mixture was allowed to stir in the dark at room temperature for 48 h. The mixture was then evaporated to dryness, the residue was dissolved in a minimum amount of water, and methanol was added until cloudiness persisted. The mixture was cooled at 0 °C until crystallization appeared to be complete. Filtration gave 1.06 g (3.95 mmol, 70%) of **2**: mp 215 °C dec; UV (H_2O) λ_{max} 235, 263 nm; UV λ_{min} 255 nm; ^1H NMR (DMSO-d_6) δ 8.61 (s, 1, H_2), 8.49 (s, 1, H_8), 8.30 (br, 2, NH_2), 6.3 ("t", 1, J_{app} = 6.7 Hz, $H_{1'}$), 5.35 (d, 1, J = 4.3 Hz, 3'-OH), 4.98 (t, 1, J = 5.8 Hz, 5'-OH), 4.38 (m, 1, $H_{3'}$), 3.85 (m, 1, $H_{4'}$), 3.53 (m, 2 $H_{5'}$, $H_{5''}$), 2.68 and 2.31 (m and m, 1 and 1, $H_{2'}$ and $H_{2''}$); FAB MS *m/z* 269 (M^+ + 1). Anal. ($C_{10}H_{13}N_4{}^{15}NO_4{}^{\cdot 1}/_2H_2O$) C, H, N: calcd, 25.61; found, 25.05.

[1-^{15}N]-2-Amino-6-(methoxyamino)-9-(2-deoxy-β-D-*erythro*-pentofuranosyl)purine (7). To 0.88 g (3.3 mmol) of **2** were added 82 mL of anhydrous methanol and 0.4 g (3.8 mmol) of cyanogen bromide. The mixture was allowed to stir for 2 h and evaporated to dryness. The residue was dissolved in a mixture of anhydrous DMF (5.6 mL) and triethylamine (1.1 mL, 7.9 mmol) under N_2. The mixture was allowed to stir at room temperature for 40 min, after which 0.67 mL of CH_3I (10.8 mmol) was added. Stirring was continued for a further 3.5 h, whereupon the reaction was evaporated to dryness and the residue dissolved in 55 mL of 0.25 N NaOH. After 30 min, the pH was adjusted to 7.4 with use of 1 N HCl. Ethanol (65 mL) was then added, and the mixture was heated at 60 °C for 4 h. The mixture was then evaporated to dryness and the residue purified on a Dynamax reversed-phase column (21.4 mm × 25 cm) with a gradient of 2–5% acetonitrile/0.1 M ammonium bicarbonate. Evaporation of appropriate fractions gave pure **7** (0.62 g, 2.1 mmol, 64%): mp 118 °C; UV (H_2O) λ_{max} 280 nm; UV λ_{min} 241 nm; ^1H NMR (DMSO-d_6) δ 9.85 (bs, 1, NHO), 7.7 (s, 1, H_8), 6.55 (bs, 2, NH_2), 6.05 ("t", 1, $H_{1'}$, J_{app} = 7.4 Hz), 5.27 (d, 1, 3'-OH, J = 3 Hz), 5.01 (t, 1, 5'-OH, J = 5.4 Hz), 4.3 (m, 1, $H_{3'}$), 3.79 (m, 1, $H_{4'}$), 3.75 (s, 3, OCH_3), 3.5 (m, 1, $H_{5'}$), 2.5 and 2.2 (m and m, 1 and 1, $H_{2'}$ and $H_{2''}$); EI MS *m/z* 297 (M^+), 267, 208, 181, 151, 136, 109.

[1-^{15}N]-2'-Deoxyguanosine (8). To 0.59 g of **7** (2 mmol) dissolved in 40 mL of 0.1 M TEAA buffer (pH 6.8) was added adenosine deaminase (917 units). The mixture was allowed to stir at room temperature for 2 days, during which time the product crystallized. The mixture was then cooled to 4 °C and filtered to give a first crop of 0.40 g (1.5 mmol, 75%) of **8**: mp >250 °C; UV (H_2O) λ_{max} 254, sh 274 nm; ^1H NMR (DMSO-d_6) δ 10.62 (d, 1, H_1, J = 89 Hz), 7.93 (s, 1, H_8), 6.47 (s, 2, NH_2), 6.11 ("t", 1, J_{app} = 6.4 Hz, $H_{1'}$), 5.28 (d, 1, J = 3.8 Hz, 3'-OH), 4.97 (t, 1, J = 5.3 Hz, 5'-OH), 4.33 (m, 1, $H_{3'}$), 3.81 (m, 1, $H_{4'}$), 3.49 (m, 2, $H_{5'}$), 2.48 and 2.20 (m and m, 1 and 1, $H_{2'}$ and $H_{2''}$); ^{13}C NMR (^1H decoupled, DMSO-d_6) δ 156.98 (d, C_6, J = 11 Hz), 153.898 (d, C_2, J = 13 Hz), 151.015 (s, C_4), 135.417 (s, C_8), 116.842 (d, C_5, J = 8 Hz), 87.69 (s, $C_{4'}$), 82.67 (s, $C_{1'}$), 70.85 (s, $C_{3'}$), 70.85 (s, $C_{3'}$), 61.83 (s, $C_{5'}$); ^{15}N NMR (10 mM sodium phosphate, 0.1 M NaCl, 0.1 mM EDTA, pH 6.5, H_2O/D_2O = 80/20) δ 125.88 (s), ref $^{15}NH_4Cl$ in 10% HCl; FAB MS *m/z* 269 (M^+ + 1). Anal. ($C_{10}H_{13}N_4{}^{15}NO_4{}^{\cdot 1}/_2H_2O$) C, H, N.

[2-^{15}N]-2-Amino-6-(methoxyamino)-9-(2-deoxy-β-D-*erythro*-pentofuranosyl)purine (11). To 0.22 g (3.3 mmol) of [^{15}N]KCN dissolved in 75 mL of anhydrous methanol and cooled to 0–10 °C was added bromine (0.17 mL, 3.3 mmol). After being stirred for 3 h, **9** (0.80 g, 3.0 mmol) was added. After an additional 2–3 h, the reaction mixture was evaporated to dryness. The residue was dissolved in a mixture of anhydrous DMF (10.6 mL) and triethylamine (1.12 mL, 8.05 mmol) under N_2. The mixture was allowed to stir at room temperature for 40 min, after which 0.67 mL of CH_3I (10.8 mmol) was added. Stirring was continued for a further 3.5 h, whereupon the reaction mixture was evaporated to dryness and the residue dissolved in 75 mL of 0.25 N NaOH. After 30 min, the pH was adjusted to 7.4 with use of 1 N HCl. Ethanol (80 mL) was

(20) MacCoss, M.; Ryu, E. K.; White, R. S.; Last, R. L. *J. Org. Chem.* **1980**, *45*, 788–794.
(21) Bär, H.-P.; Drummond, G. I. *Biochem. Biophys. Res. Commun.* **1966**, *24*, 584–587.
(22) Golding, B. T.; Slaich, P. K.; Watson, W. P. *J. Chem. Soc., Chem. Commun.* **1986**, 901, 902.

then added, and the mixture was heated at 60 °C for 4 h. The mixture was then evaporated to dryness and the residue purified on a Dynamax reversed-phase column (21.4 mm × 25 cm) with a gradient of 2-5% acetonitrile/0.1 M ammonium bicarbonate. Evaporation of appropriate fractions gave pure **11** (0.444 g, 1.49 mmol, 50%): mp 118 °C; UV (H_2O) λ_{max} 280 nm; UV λ_{min} 241 nm; ^1H NMR (DMSO-d_6) δ 9.8 (br, 1, NHO), 7.74 (s, 1, H_8), 6.53 (d, 2, J = 89 Hz, NH_2), 6.05 ("t", 1, J_{app} = 7.4 Hz, $H_{1'}$), 5.25 (d, 1, J = 3.0 Hz, 3'-OH), 5.01 (t, 1, J = 5.4 Hz, 5'-OH), 4.31 (m, 1, $H_{3'}$), 3.8 (m, 1, $H_{4'}$), 3.75 (s, 3, OCH_3), 3.51 (m, 1, $H_{5'}$), 2.45 and 2.20 (m and m, 1 and 1, $H_{2'}$ and $H_{2''}$); EI MS m/z 297 (M^+), 267, 208, 181, 151, 136, 109.

[2-^{15}N]-2'-Deoxyguanosine (12). To 0.424 g (1.43 mmol) of **11** dissolved in 28.6 mL of 0.1 M TEAA buffer (pH 6.8) was added adenosine deaminase (660 units). The mixture was allowed to stir at room temperature for 2 days, during which time the product crystallized. The mixture was then cooled to 4 °C and filtered to give a first crop of 0.31 g (1.07 mmol, 75%) of **12**: mp >250 °C; ^1H NMR (DMSO-d_6) δ 10.58 (s, 1, H_1), 7.92 (s, 1, H_8), 6.47 (d, 2, J = 90 Hz, NH_2), 6.12 ("t", 1, J_{app} = 6.3 Hz, $H_{1'}$), 5.26 (d, 1, J = 4.0 Hz, 3'-OH), 4.94 (t, 1, J = 5.4 Hz, 5'-OH), 4.3 (m, 1, $H_{3'}$), 3.79 (m, 1, $H_{4'}$), 3.51 (m, 2, $H_{5'}$), 2.50 and 2.21 (m and m, 1 and 1, $H_{2'}$ and $H_{2''}$); ^{13}C NMR (^1H decoupled, DMSO-d_6) δ 157.093 (s, C_6), 154.189 (d, C_2, J = 23 Hz), 151.2 (d, C_4, J = 4 Hz), 135.613 (s, C_8), 116.963 (s, C_5), 87.88 (s, $C_{4'}$), 82.87 (s, $C_{1'}$), 71.05 (s, $C_{3'}$), 62.025 (s, $C_{5'}$); ^{15}N NMR (10 mM sodium phosphate, 0.1 M NaCl, 0.1 mM EDTA, pH 6.5, H_2O/D_2O = 80/20) δ 50.786 (t, J = 90 Hz), ref $^{15}NH_4Cl$ in 10% HCl. Anal. ($C_{10}H_{13}N_4{}^{15}NO_4{}^{\cdot 1}/_2H_2O$) C, H, N: calcd, 25.61; found, 25.19.

Acknowledgment. This work was supported by grants from the National Institutes of Health (GM31483) and the Busch Memorial Fund and an American Cancer Society Faculty Research Award to R.A.J.

Registry No. **1**, 106568-85-8; **2**, 130434-93-4; **7**, 130434-94-5; **8**, 130434-96-7; **9**, 3506-01-2; **11**, 130434-95-6; **12**, 121409-37-8; CNBr, 506-68-3; adenosine deaminase, 9026-93-1.

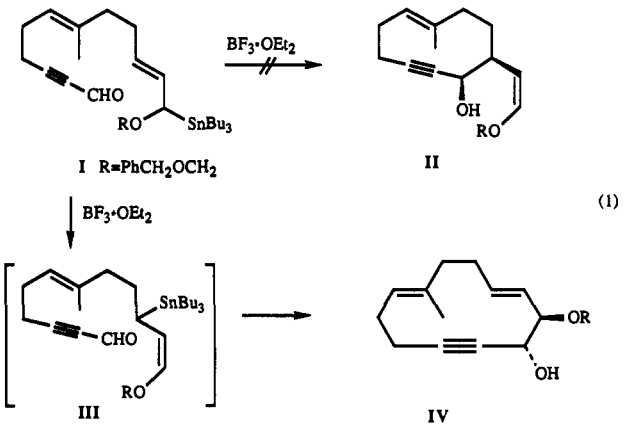
On the 1,3-Isomerization of Nonracemic α-(Alkoxy)allyl Stannanes

James A. Marshall,* Gregory S. Welmaker, and Benjamin W. Gung

Contribution from the Department of Chemistry, The University of South Carolina, Columbia, South Carolina 29208. *Received June 27, 1990*

Abstract: A set of optically active (*E*)-α-(alkoxy)allyl stannanes **10-13** and *ent*-**10-13** was prepared by reduction of the acyl stannanes **4-6** with (*R*)-(+)-BINAL-H or $LiAlH_4$-Chirald and protection of the resulting hydroxy stannanes with MOMCl or BOMCl. On treatment with $BF_3{\cdot}OEt_2$ these stannanes rearranged stereospecifically to the (*Z*)-γ-(alkoxy)allyl stannanes **21-24** by 1,3-migration of Bu_3Sn. The rearrangement was shown to take place by an intermolecular anti pathway. Addition of the γ-alkoxy stannanes **21-24** to representative aldehydes afforded optically active *syn*-1,2-diol monoethers **25-28** as the major diastereomers with high anti S_E' stereoselectivity.

α-Alkoxy stannanes[1] and allylic stannanes[2] have played a useful role as nucleophilic reagents in carbon-carbon bond forming reactions with electrophiles.[3] We recently described a highly efficient macrocyclization involving α-(alkoxy)allyl stannanes and acetylenic aldehydes.[4] Our initial application yielded 14-membered cyclic intermediates related to cembranolides. In a further extension of the methodology we examined a possible application to 10-membered carbocycles (eq 1).[5] However, the precursor stannane I afforded none of the desired enol ether II upon treatment with $BF_3{\cdot}OEt_2$ under the usual cyclization conditions. The sole isolable product was the 12-membered 1,2-diol derivative IV. Evidently, alkoxy stannane I is not favorably disposed to undergo direct intramolecular S_E' addition. Consequently, isomerization to stannane III precedes cyclization, which then affords the 12-membered product IV.



(1)

Interestingly, when nonracemic alkoxy stannane I was employed, the cyclododecynol IV was formed as a single nonracemic diastereoisomer with an ee equal to that of starting I. Thus, the presumed rearrangement of I to III must occur stereospecifically. This intriguing observation prompted our further study of the 1,3-isomerization process.[6]

The nonracemic α-(hydroxy)allyl stannanes **7-9** were prepared from the appropriate enals **1-3**. Accordingly, addition of Bu_3SnLi and direct oxidation of the intermediate alkoxides, as previously described, afforded the stannyl enones **4-6**.[7] These isolable, air-sensitive, yellow ketones were readily purified by careful column chromatography. Reduction with (*R*)-(+)-BINAL-H afforded the *S* alcohols (e.g., **7**) of >95% ee.[8] The *R* alcohols

(1) Still, W. C. *J. Am. Chem. Soc.* **1978**, *100*, 1481. Still, W. C.; Sreekumar, C. *J. Am. Chem. Soc.* **1980**, *102*, 1201. Sawyer, J. S.; Kucerovy, A.; Macdonald, T. L.; McGarvey, G. J. *J. Am. Chem. Soc.* **1988**, *110*, 842.
(2) Yamamoto, Y. *Acc. Chem. Res.* **1987**, *20*, 243. Yamamoto, Y. *Aldrichimica Acta* **1987**, *20*, 45. Keck, G. E.; Abbott, D. E. *Tetrahedron Lett.* **1984**, *25*, 1883. Keck, G. E.; Boden, E. P. *Tetrahedron Lett.* **1984**, *25*, 1879. Shimagaki, M.; Takubo, H.; Oishi, T. *Tetrahedron Lett.* **1985**, *26*, 6235. Andrianome, M.; Häberle, K.; Delmond, B. *Tetrahedron* **1989**, *45*, 1079. Koreeda, M.; Tanaka, Y. *Chem. Lett.* **1982**, 1299.
(3) Pereyre, M.; Quintard, J-P.; Rahm, A. *Tin in Organic Synthesis*; Butterworths: London, 1987; pp 211-231.
(4) Marshall, J. A.; Crooks, S. L.; DeHoff, B. S. *J. Org. Chem.* **1988**, *53*, 1616. Marshall, J. A.; Gung, W. Y. *Tetrahedron Lett.* **1988**, *29*, 1657. Marshall, J. A.; Markwalder, J. A. *Tetrahedron Lett.* **1988**, *29*, 4811.
(5) Marshall, J. A.; Gung, W. Y. *Tetrahedron Lett.* **1989**, *30*, 2183.
(6) For recent observations on 1,3-isomerizations of racemic α-(alkoxy)-allylic stannanes see: Quintard, J-P.; Dumartin, G.; Elissondo, B.; Rahm, A.; Pereyre, M. *Tetrahedron* **1989**, *45*, 1017. Quintard, J-P.; Elissondo, B.; Pereyre, M. *J. Org. Chem.* **1983**, *48*, 1559.
(7) Marshall, J. A.; Gung, W. Y. *Tetrahedron* **1989**, *45*, 1043.

0002-7863/91/1513-647$02.50/0