parison of the sulfur a and c coordinates calculated from Kraitchman's equations.[17]

The fits show the sensitivity to the model assumptions. These and other calculations indicate that d(NS) is between 2.25 and 2.30 Å while α is 19° ± 5° and β is 91° ± 2°. The inertial data cannot distinguish whether the TMA staggers or eclipses the S–O bonds. It appears worthwhile to examine this question and to ascertain the extent of any structural changes in TMA and SO_2 by obtaining additional isotopic data. This work is in progress as well as a reevaluation of the structure of crystalline TMA·SO_2.

Acknowledgment. This work was supported by Grant CHE-8614340 from the National Science Foundation, Washington, D.C.

Supplementary Material Available: Tables S1–S3 listing hyperfine fitting of transition frequencies and centrifugal distortion fitting of the unsplit frequencies (6 pages). Ordering information is given on any current masthead page.

(17) Kraitchman, J. *Am. J. Phys.* **1953**, *21*, 17.

Novel Approaches to Functionalized Nucleosides via Palladium-Catalyzed Cross Coupling with Organostannanes

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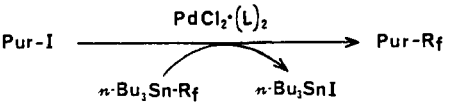
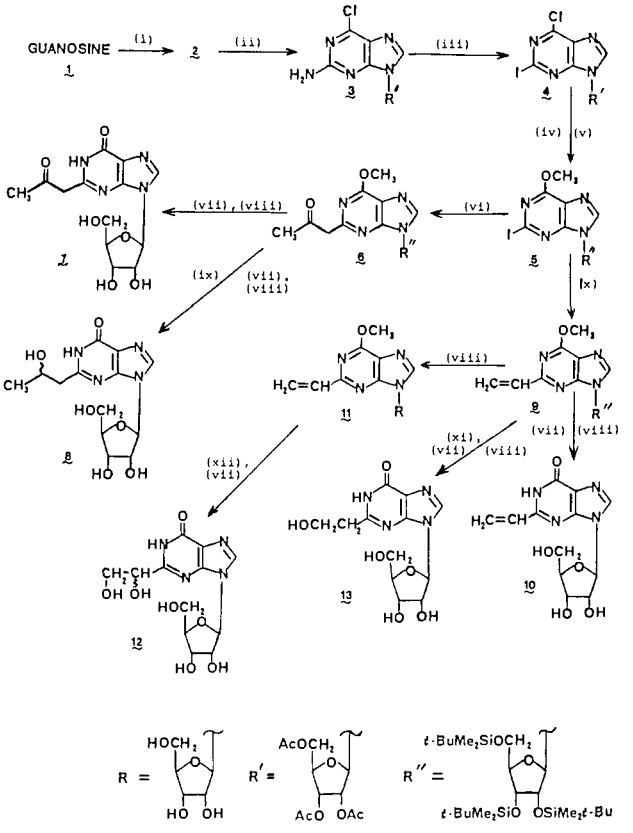
Purine nucleosides and related systems are currently receiving a considerable amount of renewed interest because of the remarkable biological activity of some of these compounds as antiviral agents.[1-4] Although a wide variety of C-6 substituted purine nucleosides bearing functionalized alkyl groups are known, the same cannot be said for the C-2 position.[5] While a number of simple C-2 alkylated compounds have been synthesized,[6-9] very few functionalized alkyl derivatives have been reported.[10] The single general method known for obtaining 2-alkylated purine nucleosides involves ring closure from the appropriately substituted ribofuranosyl imidazole.[6-8] A few other methods are known but are of limited scope.[11,12] Functionalized C-2 alkylated inosine analogues are not only of considerable potential interest as antiviral agents[4] but also there is enzymological interest in these novel compounds as potential inhibitors of a key purine metabolizing enzyme, inosine monophosphate dehydrogenase.[13] This communication reports on the development and application of a general methodology (Scheme I) for the introduction of functionalized

Scheme I



R_f = functionalized alkyl group

Scheme II



[a] (i) Ac_2O, $(C_2H_5)_3N$, *N,N*-(dimethylamino)pyridine; (ii) $POCl_3$, *N,N*-diethylaniline, Δ; (iii) n-$C_5H_{11}ONO$, CH_2I_2, CH_3CN; (iv) NaO-CH_3, MeOH; (v) t-Bu$(CH_3)_2SiCl$, imidazole, DMF; (vi) $Pd(OAc)_2$, $(o$-Tolyl$)_3P$, n-Bu_3SnOMe, $CH_2{=}C(CH_3)OAc$, toluene, Δ; (vii) $(CH_3)_3SiI$, CH_3CN; (viii) Et_4NF, CH_3CN; (ix) $NaBH_4$, THF; (x) n-$Bu_3SnCH{=}CH_2$, $PdCl_2(CH_3CN)_2$, toluene, Δ; (xi) 9-BBN, THF, Δ; (xii) OsO_4, pyridine.

carbon–carbon bonding at the 2-position of the hypoxanthine ring.

A logical approach to the synthesis of these rare nucleosides would be through the corresponding 2-halogenated precursor. Thus, protected 2-iodo-6-methoxypurine **5** was the key precursor for all of the target molecules described in this communication. This precursor can be prepared from the 6-chloro-2-aminopurine **3**[14,15] in three steps. The first step (i.e., **3** → **4**) involved a radical deamination–halogenation procedure developed and previously reported by us.[16,17] Nucleophilic displacement of the 6-chloro group in **4** with methoxide was accompanied by the desired deprotection of the acetate groups (96% yield). Subsequent protection of the carbohydrate moiety with *tert*-butyldimethylsilyl chloride and imidazole in DMF[18] gave **5** in 96% yield. The key step in the synthesis of the target molecule **7** was the conversion of **5** to **6** in 70% yield by a palladium-catalyzed cross-coupling reaction (Schemes I and II). This conversion presumably involves

(1) De Clercq, E. *J. Med. Chem.* **1986**, *29*, 1561.
(2) Robins, R. K. *Chem. Eng. News* **1986** (Jan. 27, 28).
(3) Mitsuya, H.; Broder, S. *Proc. Natl. Acad. Sci. U.S.A.* **1986**, *83*, 1911.
(4) *Targets for the Design of Antiviral Agents*, De Clercq, E., Walker, R. T., Eds.; Plenum Press: New York, 1984.
(5) (a) Nair, V.; Chamberlain, S. D. *J. Am. Chem. Soc.* **1985**, *107*, 2183. (b) Nair, V.; Chamberlain, S. D. *J. Org. Chem.* **1985**, *50*, 5069.
(6) Yamazaki, A.; Kumashiro, I.; Takenishi, T. *J. Org. Chem.* **1967**, *32*, 3258.
(7) Imai, K.; Marumoto, R.; Kobayashi, K.; Yoshioka, Y.; Toda, J. *Chem. Pharm. Bull.* **1971**, *19*, 576.
(8) Marumoto, R.; Yoshioka, Y.; Miyashita, O.; Shima, S.; Imai, K.; Kawazoe, K.; Honjo, M. *Chem. Pharm. Bull.* **1975**, *23*, 759.
(9) *Chem. Abstr.* **1983**, *99*, P120680n.
(10) Matsuda, A.; Nomato, Y.; Ueda, T. *Chem. Pharm. Bull.* **1979**, *27*, 183.
(11) Matsuda, A.; Satoh, K.; Miyasaka, T.; Ueda, T. *Chem. Pharm. Bull.* **1984**, *32*, 2048.
(12) Matsuda, A.; Shinozaki, M.; Miyasaka, T.; Machida, H.; Abiru, T. *Chem. Pharm. Bull.* **1985**, *33*, 1766.
(13) Wong, C. G.; Meyer, R. B., Jr. *J. Med. Chem.* **1984**, *27*, 429.
(14) Gerster, J. F.; Jones, J. W.; Robins, R. K. *J. Org. Chem.* **1963**, *28*, 945.
(15) Nair, V.; Young, D. A.; DeSilvia, R., Jr. *J. Org. Chem.* **1987**, *52*, 1344.
(16) Nair, V.; Richardson, S. G. *J. Org. Chem.* **1980**, *45*, 3969.
(17) Nair, V.; Richardson, S. G. *Synthesis* **1982**, 670.
(18) Ogilvie, K. K.; Beaucage, S. L.; Shifman, A. L.; Theriault, N. Y.; Sadana, K. L. *Can. J. Chem.* **1978**, *56*, 2768.

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oxidative insertion of palladium into the carbon–iodine bond of the iodopurine followed by coupling of the derived Pd(II) complex with the tin enolate of acetone (formed in situ from isopropenyl acetate and tri-*n*-butyltin methoxide), trans–cis isomerization, and reductive elimination to give the product with concomitant regeneration of the Pd(0) catalyst.[19] It is the first example of the use of an organotin reagent in a palladium-catalyzed cross-coupling reaction involving nucleosides. Other methods attempted, such as the photoinduced $S_{RN}1$ reaction,[5,20] the Eschenmoser sulfide contraction,[21] and Meerwein-type reactions[22] were all unsuccessful.

The aforementioned protected acetonylated nucleoside **6** was converted to the target molecule **7** in two steps by reaction first with trimethylsilyl iodide (64%) and subsequently with tetraethylammonium fluoride (93%). The overall yield of **7** starting from guanosine was 18%. Masking of the amide carbonyl oxygen at the 6-position as a methoxy group is an effective way of protecting the inosine system as this group is relatively stable and can be easily removed at the conclusion of a reaction sequence. Compound **7** (a solid, mp 114–116 °C) was purified by reversed-phase HPLC on Amberlite XAD-4 resin and was characterized by UV, FTIR, and high field NMR spectroscopy. Only the keto tautomer of the compound was present, this form being stabilized by intramolecular hydrogen bonding. The 2-acetonyl compound **6** could be reduced readily by sodium borohydride to give, after deprotection, the diastereoisomeric alcohols **8**.

The scope of this palladium-catalyzed cross-coupling reaction can be extended to include other activated organostannanes. For example, reaction of **5** with tri-*n*-butyl(cyanomethyl)stannane[23] under palladium catalysis resulted in the formation of the 2-cyanomethylinosine in 55% yield. 2-Vinylinosine **10** (or **9**), potentially a key precursor for the synthesis of a variety of functionalized alkylated purine nucleosides, is also readily available with use of the aforementioned methodology. Thus, the thermal reaction of **5** with tri-*n*-butyl(vinyl)stannane in the presence of palladium chloride afforded **9** in excellent yields (>90%). Compound **11** (the partially deprotected form of **9**), can be hydroxylated with osmium tetroxide (65%) and then deprotected to give the highly hydroxylated compound **12**. Additionally, reaction of the vinyl compound **9** with 9-BBN followed by oxidative workup resulted in the regiospecific formation (52% yield, 65% conversion) of the terminal alcohol which was deprotected to afford **13**. Hydroboration reactions have rarely been used previously to elaborate structures in purine nucleoside chemistry.

In summary, palladium-catalyzed cross-coupling reaction of 2-iodinated purines with organostannanes is a highly efficient approach to the synthesis of new and rare functionalized purine nucleosides. This approach may find wide application in purine and related heterocyclic chemistry. Biological studies assessing the antiviral activities of the target molecules against RNA viruses are currently under investigation.[24]

Acknowledgment. We thank the U.S. Army Medical Research and Development Command for support of this research. The high field NMR spectrometer and the FTIR instrument used in this work were purchased in part from funds provided by the National Science Foundation.

Supplementary Material Available: NMR (^1H and ^{13}C), UV, FTIR, and FAB (HRMS) spectral data for target molecules (5 pages). Ordering information is given on any current masthead page.

(19) (a) Stille, J. K. *Agnew Chem., Int. Ed. Engl.* **1986**, *25*, 508. (b) Heck, R. F. *Palladium Reagents in Organic Synthesis*; Academic Press: Orlando, FL, 1985.
(20) Bunnett, J. F. *Acc. Chem. Res.* **1978**, *11*, 413.
(21) Vorbruggen, H.; Krolikiewicz, K. *Angew. Chem., Int. Ed. Engl.* **1976**, *15*, 689.
(22) Doyle, M. P.; Siegfried, B.; Elliot, R. C.; Dellaria, J. F., Jr. *J. Org. Chem.* **1977**, *42*, 2431.
(23) Tri-*n*-butyl(cyanomethyl)stannane was prepared from tributyltin methoxide and trimethylsilylacetonitrile (cf. Pereyre, M.; Bellegarde, B.; Valada, J. *C. R. Acad. Sci.* **1967**, *265*, 939).
(24) One of the target molecules, 2-acetonylinosine, shows very high activity against some RNA viruses.

Albomitomycin A and Isomitomycin A: Products of Novel Intramolecular Rearrangement of Mitomycin A

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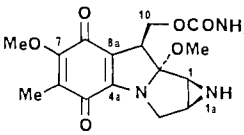
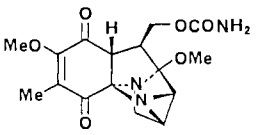
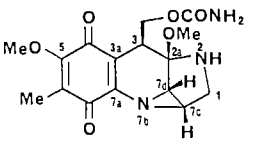
Mitomycins are potent antitumor antibiotics,[1] and considerable research efforts have been made to rationalize the mechanism of action of mitomycins.[2] As part of our approach, we have been screening the minor constituents from the fermentation broth of mitomycins[3] since 1977. Fortuitously, we found two novel isomers of mitomycin A (**1**), designated as albomitomycin A (**2**) and isomitomycin A (**3**), from *streptomyces caespitosus*, and their tripartite interconversion (**1** and **3** via **2**), refered to as mitomycin rearrangement. We herein report the structure elucidation of **2** and **3** and their unique intramolecular reactions in Michael and retro-Michael modes.



1



2



3

Albomitomycin A (**2**), isolated as colorless plates from $CHCl_3$[4] ($[\alpha]^{23}_D$ – 2.7° (*c* 0.50, $CHCl_3$)), decomposed at a temperature over 130 °C, converting, in part, to **1** and **3**. Its molecular formula, $C_{16}H_{19}N_3O_6$, was determined on the basis of elemental analysis and high resolution EI–MS.[5] The mass fragments[6] were completely the same as those of **1**, suggesting that **2** was changed to **1** in the ionization process. Furthermore, **2** was changed, in part, to **1** on TLC silica gel accompanied by a change in hue to **1**'s characteristic reddish purple color in several hours. In the electronic spectrum[7] of **2**, an important characteristic was its colorless state; it did not show any R absorption band of a quinone

(1) *Mitomycin C; Current Status and New Developments*; Carter, S. K., Crooke, S. T., Eds.; Academic Press: New York, 1979.
(2) Tomasz, M.; Lipman, R.; Chowdary, D.; Pawlak, J.; Verdine, G. L.; Nakanishi, K. *Science (Washington D.C.)* **1987**, *235*, 1204 and references therein.
(3) (a) Shirahata, K.; Kono, M.; Matsubara, I.; Kasai, M. The 23th Symposium on the Chemistry of Natural Products, Nagoya, Japan, 1980; Abstracts pp 608–615. (b) Shirahata, K.; Morimoto, M.; Ashizawa, T.; Mineura, K.; Kono, M.; Saithoh, Y.; Kasai, M. The 21st Interscience Conference on Antimicrobial Agents and Chemotherapy, Chicago, Nov. 1981; Abstracts p 421.
(4) The procedures of chromatographic separations for **2** and **3** are given in the Supplementary Material.
(5) Anal. Calcd for $C_{16}H_{19}N_3O_6$: C, 55.01; H, 5.48; N, 12.03. Found: C, 54.93; H, 5.43; N, 12.01. HRMS calcd for $C_{16}H_{19}N_3O_6$ *m/z* 349.1274, found *m/z* 349.1276.
(6) Mass fragments of **1** and **2**: *m/z* 349 (M^+), 317, 302, 288, 273, and 257.
(7) The electronic spectrum of **2**: λ_{max}^{EtOH} 288 nm, ϵ 10000, 215 nm, ϵ 6300.

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