librium constant for reaction 3 is found to be well below unity. K_{eq} was determined by monitoring the relative

$$BZO^{\bullet-} + BZO\text{-}^{13}C \rightleftharpoons BZO + BZO\text{-}^{13}C^{\bullet-} \quad (3)$$

$$K_{eq} = 0.58 \pm 0.04 \text{ at } 25\ ^\circ C$$

intensities of the ESR signals for $BZO^{\bullet-}$ and $BZO\text{-}^{13}C^{\bullet-}$ using simulation techniques previously described[8] (the ^{13}C coupling constant for the free solvated ketyl in HMPA is 6.36 G) (Figure 1).

The reduction of FLU in HMPA with sodium metal also results in the formation of the free solvated anion radical ($A_{^{13}C}$ = 3.00 G). However, in strong contrast with the benzophenone system, the partial reduction of a 1:1 mixture of FLU and FLU-^{13}C results in a solution that contains much more of the isotopically heavy anion radical than of the light anion radical. Five separate experiments have shown that the equilibrium constant for the electron transfer from $FLU^{\bullet-}$ to FLU-^{13}C (reaction 4) is about five times greater than that for the transfer from $BZO^{\bullet-}$ to BZO-^{13}C.

$$FLU^{\bullet-} + FLU\text{-}^{13}C \rightleftharpoons FLU + FLU\text{-}^{13}C^{\bullet-} \quad (4)$$

$$K_{eq} = 2.74 \pm 0.34 \text{ at } 25\ ^\circ C$$

The addition of the extra electron to benzophenone results in a general bond loosening. Thus, the sum of all of the frequencies over all of the vibrational degrees of freedom ($3n - 6 = 66$) in benzophenone ($\sum \upsilon_{BZO}$) is larger than this same sum for the benzophenone ketyl ($\sum \upsilon_{BZO^{\bullet-}}$). Since the vibrational frequencies are inversely proportional to the square root of the reduced masses of the atoms involved, the difference in the two sums is greater for the ^{13}C-substituted system than it is for the ^{12}C system (eq 5). This difference is simply the difference in the solution electron affinities of BZO and BZO-^{13}C or the free energy of reaction 3.

$$\tfrac{1}{2}h([\textstyle\sum \upsilon_{BZO\text{-}^{13}C} - \sum \upsilon_{BZO\text{-}^{13}C^{\bullet-}}] - [\sum \upsilon_{BZO} - \sum \upsilon_{BZO^{\bullet-}}]) = \Delta G^\circ(\text{eq } 3) > 0 \quad (5)$$

For the case of FLU the situation is reversed. Since bonds are tightened upon electron addition, they are tightened more for ^{13}C-substituted material than for the FLU itself (eq 6). Unfortunately, present day quantum

$$\tfrac{1}{2}h([\textstyle\sum \upsilon_{FLU\text{-}^{13}C} - \sum \upsilon_{FLU\text{-}^{13}C^{\bullet-}}] - [\sum \upsilon_{FLU} - \sum \upsilon_{FLU^{\bullet-}}]) = \Delta G^\circ(\text{eq } 4) < 0 \quad (6)$$

mechanical calculations are not sufficiently advanced to allow quantitative predictions of the free energies described in eq 5 or 6. This is due, in part, to the fact that the resulting free energies reflect relatively small differences between large numbers.

What is described above is, by far, the largest thermodynamic isotope effect yet observed. Further, since the chemical properties of ketyls and ketones are very different, they can be easily separated allowing enrichment of the ^{13}C materials with an efficiency that is literally orders of magnitude greater than those of enrichment techniques used today. Enrichment of the ^{13}C carbonyl systems can be accomplished by harvesting either the neutral molecule or the anion radical as electrons are easy to put on or take off of these stable systems.[10] Indeed, we have demonstrated that enriched material can be obtained from these anion radical solutions.

The reduction of FLU containing ^{13}C in natural abundance in tetrahydrofuran (THF) with about $^1/_2$ of the stoichiometric amount of sodium metal followed by the removal of the solvent under reduced pressure leaves the solid ketone–ketyl mixture in the reaction apparatus. The ketone was selectively dissolved from the mixture in warm hexane. This recovered ketone was then sublimed, mixed with an equal number of moles of 3-pentanone, dissolved in 10 mL of $CDCl_3$, and submitted to ^{13}C NMR analysis. A control NMR sample was made with the untreated fluorenone. In each of five such experiments, it was clear that the ratio of the intensities of the FLU carbonyl carbon signal to the carbonyl carbon signal for 3-pentanone is less than the equivalent ratio based on the control sample. The two NMR spectra were obtained in exactly the same manner (same pulse delay, pulse width, number of pulses, etc.). When 50% of the FLU is reduced to the ketyl, the recovered ketone has a carbonyl ^{13}C content of 0.98 ± 0.04% as compared to 1.11% in the original ketone. The solid ketyl remaining after the removal of the ketone was then reacted with I_2 to oxidize it back to the ketone. This reconstituted ketone was sublimed and submitted to the same ^{13}C NMR analysis. It proved to be significantly enriched in carbonyl ^{13}C content (1.24 ± 0.05%). We have realized significant carbonyl ^{13}C enrichment from just a single pass of the ketone through the reduction–oxidation cycle.

Acknowledgment. We thank the National Science Foundation (Grant CHE-841127) for support of this work.

Registry No. Benzophenone, 119-61-9; fluorenone, 486-25-9; carbon-13, 14762-74-4.

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(9) (a) Ketone anion radicals are normally free of ion association in HMPA.[9b] (b) Stevenson, G. R.; Alegria, A. E.; McB. Block, A. *J. Am. Chem. Soc.* **1975**, *97*, 4859. (c) The addition of 0.1 M sodium iodide to this free solvated anion radical solution results in the formation of the ion pair, which can be observed simultaneously with the free ion. The sodium splitting in the ion pair is 0.69 G.

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Synthetic 1-Methoxybenzo[*d*]naphtho[1,2-*b*]pyran-6-one C-Glycosides

Summary: The first synthetic benzo[*d*]naphtho[1,2-*b*]-pyran-6-one C-glycosides related to the antibiotics ravidomycin, the gilvocarcins (toromycin), and chrysomycin A and B (virenomycin) have been achieved by palladium-mediated coupling of furanoid glycals with 1-methoxy-4-(tri-*n*-butylstannyl)benzo[*d*]naphtho[1,2-*b*]pyran-6-one.

Sir: The procedure for synthesis of C-glycosides (C-nucleosides)[1] by palladium-mediated coupling of glycals with aryl or heterocyclic aglycon derivatives, which was developed in our laboratory,[2] was used to prepare the 1-methoxybenzo[*d*]naphtho[1,2-*b*]pyran-6-one furanosyl

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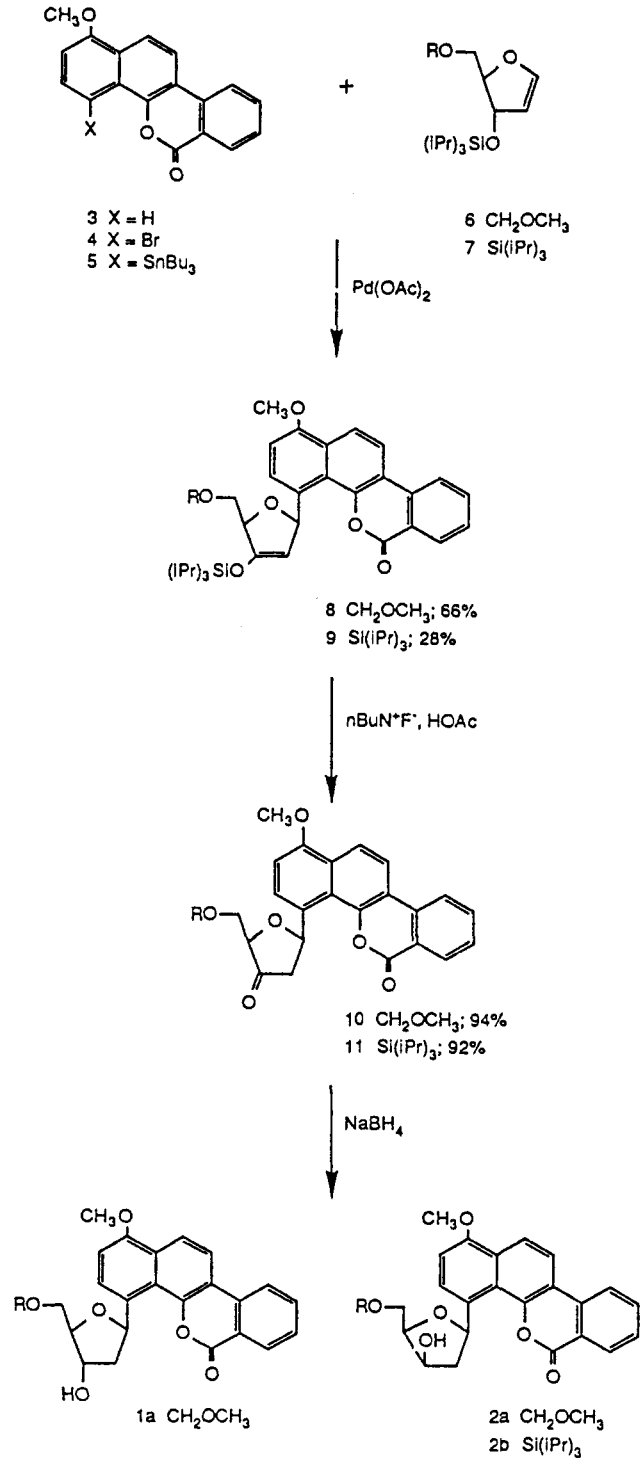
0022-3263/87/1952-5064$01.50/0

C-glycosides **1** and **2**. The new C-glycosides (**1** and **2**) are the first synthetic members of a class of anthracycline C-glycosides[1] which includes the antibiotics ravidomycin,[3] the gilvocarcins[4] (toromycin[5]), and chrysomycin A and B[6] (virenomycin[7]). The key reaction in the syntheses was the regio- and stereospecific formation of the glycosidic carbon–carbon bond between a furanoid glycal (**6**[2a] or **7**[8]) and the tri-*n*-butylstannyl derivative of the aglycon (**5**) in the presence of stoichiometric palladium(II) acetate. Prior syntheses of C-glycosides (C-nucleosides) by palladium-mediated coupling of glycals have utilized aglycon–mercuric acetates.[2,9] Mercuric derivatives of benzo[*d*]-naphtho[1,2-*b*]pyran-6-ones exhibited very low solubility; the corresponding tri-n-butylstannyl derivative[10] **5** is soluble in acetonitrile, the preferred reaction solvent,[11] and is an effective precursor to the organopalladium reagent[2] which reacts with a glycal (**6** or **7**). This modification of the palladium-mediated coupling of carbohydrate and aglycon derivatives[2] extends the utility of this direct and facile route to synthesis of C-glycosides of complex anthracycline systems.[1a,12]

1-Methoxybenzo[*d*]naphtho[1,2-*b*]pyran-6-one[13,14] (**3**) was brominated (*N*-bromosuccinimide in dimethylformamide, room temperature, 30 min, 81%)[15] para to methoxy and the bromo substituent of the resulting product, **4**, was replaced by tri-*n*-butylstannyl by reaction[16] of **4** with hexa-*n*-butylditin in the presence of 2.0 mol % of tetrakis(triphenylphosphine)palladium(0)[17] in toluene (N_2, 115 °C, 12 h) to yield stannane **5**[18] (65%). Coupling of **5** with furanoid glycal **6**[2a] (1.3 equiv) in the presence of stoichiometric palladium(II) acetate (CH_3CN, room temperature, 24 h) produced C-glycoside **8**[18] in 66% yield. Similar coupling of **5** with glycal **7**,[8] which is significantly more sterically hindered toward β-face attack,[2b] formed the corresponding C-glycoside **9**[18] in a yield of 28%.



In each reaction a single C-glycosidic product was formed (**8** and **9**, respectively). The 1-methoxybenzo[*d*]-naphtho[1,2-*b*]pyran-6-one C-glycosides **8** and **9** obtained in this way were assigned to the β-C-glycoside series by ^1H nuclear magnetic resonance spectrometry. In the ^1H NMR spectra of **8** and **9** the coupling constants, $^4J_{1',4'}$, were 3.75

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and 3.74 Hz, respectively; for 2,3-unsaturated furans of known structure, $^4J_{1',4'} > 5$ Hz for 1,4-trans H's and <4 Hz for 1,4-cis H's[2a,19] permitting assignment of the C-glycosidic linkages of **8** and **9** as β in accord with previous results using this glycal.[2]

Removal of the triisopropylsilyl group from the 3'-enol moieties of **8** and **9** (2 equiv of $(n\text{-Bu})_4N^+F^-$, 1 equiv of acetic acid, tetrahydrofuran, room temperature, 2 h) yielded the corresponding 3'-keto C-glycosides **10**[18] and **11**[18] (94% and 92% respectively); reduction of the ketones ($NaBH_4$, H_2O, tetrahydrofuran) afforded the corresponding 2'-deoxy C-glycosides **1** and **2**. From **8**, a 7:5 mixture (93%) of **1a**[18,20] and **2a**[18,21] was obtained and separated by preparative thin-layer chromatography (silica gel GF; $CHCl_3$/ether, 3:2); borohydride reduction of keto C-glycoside **9** yielded a single 2'-deoxy C-glycoside (**2b**).[18]

Assignment of configuration at C-3' for 2'-deoxy C-glycosides **1** and **2** was accomplished by detailed comparison of ^1H NMR data with those from previous published NMR studies of 2'-deoxypentofuranosyl glycosides.[22-26] These studies show that the 2'-H trans to the aglycon is deshielded with respect to the cis 2'-H. Thus, for **1a** multiplets in the ^1H NMR spectrum at δ 2.00 and 3.37 are assigned to 2'-H_β and 2'-H_α, respectively; resonances in the spectrum of **2a** at δ 1.96 and 2.97 are similarly assigned. With these assignments of the hydrogens at 2'-C and the knowledge[22] that $J_{2'\text{-H},3'\text{-H}}(\text{trans}) < J_{2'\text{-H},3'\text{-H}}(\text{cis})$, definite assignment of structure to **1** and **2** was straightforward.[27]

Acknowledgment. Appreciation is expressed to the American Cancer Society for financial support.

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(20) ^{13}C NMR ($CDCl_3$) δ 160.59 (C-6), 154.04 (C-1), 147.75 (C-5a), 135.45 (C-10a), 134.86 (C-9), 132.58 (C-7), 130.09 (C-8), 128.63 (C-10), 127.38 (C-12a), 124.08 (C-3), 122.29 (C-11), 121.86 (C-7a), 120.39 (C-4a), 119.31 (C-4), 118.17 (C-12), 114.38 (C-11a), 105.82 (C-2), 97.04 (OCH_2O), 81.50 (C-4'), 78.30 (c-1'), 73.59 (C-3'), 66.60 (C-5'), 55.66, 55.49 (OCH_3s), 44.93 (C-2').

(21) ^{13}C NMR ($CDCl_3$) δ 160.90 (C-6), 154.13 (C-1), 147.75 (C-5a), 135.54 (C-10a), 135.00 (C-9), 130.89 (C-7), 128.72 (C-10), 127.20 (C-12a), 124.55 (C-3), 122.38 (C-11), 121.95 (C-7a), 120.32 (C-4a), 119.40 (C-4), 118.21 (C-12), 114.47 (C-11a), 105.86 (C-2), 96.86 (OCH_2O), 85.11 (C-4'), 78.44 (C-1'), 74.49 (C-3'), 68.80 (C-5'), 55.69, 55.37 (OCH_3s), 44.86 (C-2').

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(27) For **1a**: $J_{2'\alpha,3'} = 5.7$ H, $J_{2'\beta,3'} = 1.5$ Hz. For **2a**: $J_{2'\alpha,3'} = 3.0$ Hz, $J_{2'\beta,3'} = 5.7$ Hz.

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Additions and Corrections

Vol. 51, 1986

Rui Tamura,* Masahiro Sao, and Daihei Oda. Facile Synthesis of Allylic Nitro Compounds by *N,N*-Dimethylethylenediamine-Catalyzed Condensation of Aliphatic and Alicyclic Ketones with Primary Nitroalkanes.

Page 4369, column 1, line 4–8. "For example, conversion of allylic halides to allylic nitro compounds by displacement with nitrite ion is not practical because of the ambident character (N vs. O attack) of the nitrite anion[5]" should be deleted and replaced by "Thus, only two examples of the conversion of allylic halides to the nitro compounds by the use of silver nitrite have been reported.[5]"

Page 4372, Table III, entry 11. The yield "72" should read "72[f]".

S. H. Nahm* and H. N. Cheng*. Transition-State Geometry and Stereochemistry of the Ene Reaction between Olefins and Maleic Anhydride.

Page 5099, column 1, line 5 from bottom. "of Z, R, and R' (as long as Z, R, and R' = H)." should read "of Z, R, and R' (as long as Z, R, and R' are not equal to H)."

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Henry A. Kurtz,* Roger V. Lloyd,* and Richard V. Williams*. The Bridgehead Decalin Radicals: An MM2 and MNDO Study.

Page 302. In Table I, the value of ΔH calculated by MM2 for *cis*-decalin should be −41.02, not −35.84 as reported. The calculated cis and trans energy difference is then 2.7, not 7.9.

Francis X. Webster and Robert M. Silverstein*. Synthesis of Diacids and Keto Acids by Ruthenium Tetraoxide Catalyzed Oxidation of Cyclic Allylic Alcohols and α,β-Unsaturated Ketones.

Page 689. Francis X. Webster and Robert M. Silverstein are the authors of this paper. The name of Jose Rivas-Enterrios was inserted by misrepresentation.

Seshadri Veeraraghavan,* Scott Jostmeyer, J'né Myers, and James C. Wiley, Jr. A Convenient Synthesis of Cyclopenta[*cd*]pyrene.

Page 1356, column 2, lines 27 and 40 of the Experimental Section. "C*H*CH_3" should read "C*H*SCH_3".