25 mL). NAD^+ (4.0 mg, 6.0 μmol), [1-^{3}H]cyclohex-2-en-1-ol (0.5 mCi), and HLADH (3.0 mg, 6.0 units) were added, and the mixture was incubated in the dark at room temperature for 6 h. The mixture was extracted with hexanes (2 × 30 mL) and the organic layers were dried ($MgSO_4$), filtered, and concentrated by rotary evaporation. After addition of carrier farnesol (1.8 mg, 8.1 μmol), flash chromatography (gradient from hexanes to 10/90 ethyl acetate/hexanes) afforded 116 μCi (46%) of (1*R*)-[1-^{3}H]farnesol.

(1*R*)-[1-^{3}H,12,13-$^{14}C_2$]Farnesyl Pyrophosphate (2k). (1*R*)-[1-^{3}H]-Farnesol (116 μCi) was converted to the pyrophosphate as for **2g**. After addition of [12,13-$^{14}C_2$]farnesyl pyrophosphate (9.6 × 10^5 dpm, 8.7 nmol), purification on a column of DEAE-Sephadex A-25 gave farnesyl pyrophosphate (**2k**): 3.5 × 10^7 dpm of ^{3}H (14%), 8.96 × 10^5 dpm of ^{14}C.

(1*R*)-[1-^{3}H,12,13-$^{14}C_2$]Farnesyl Diphenylurethane (12k). Hydrolysis of **2k** (2.4 × 10^4 dpm of ^{14}C) with acid phosphatase gave [1-^{3}H,12,13-$^{14}C_2$]farnesol (1.6 × 10^4 dpm of ^{14}C, 68% radiochemical yield, ^{3}H/^{14}C 4.72 ± 0.13), which was converted to the corresponding diphenylurethane after dilution with unlabeled farnesol. **12k**: 8680 dpm of ^{14}C, 59% radiochemical yield; ^{3}H/^{14}C 5.05 ± 0.14. The product was further purified by preparative thin-layer chromatography (three plates, 1000 μm, three elutions of 4% EtOAc/hexanes) before recrystallization from MeOH to constant melting point, ^{3}H and ^{14}C specific activities, and ^{3}H/^{14}C ratio: specific activity 62 pCi/μmol ^{3}H, 15.1 pCi/μmol ^{14}C; ^{3}H/^{14}C (average of last three crystallizations) 4.10 ± 0.02.

Cyclization of (1*R*)-[1-^{3}H,12,13-$^{14}C_2$]Farnesyl Pyrophosphate (2k) to (3*R*)-[3-^{3}H,14,15-$^{14}C_2$]Pentalenene (3k). (1*R*)-[1-^{3}H,12,13-$^{14}C_2$]Farnesyl pyrophosphate (**2k**, 1.57 × 10^5 dpm of ^{14}C) was dissolved in 200 mM Tris buffer, pH 8.4, containing 20 mM $MgCl_2$ and 5 mM β-mercaptoethanol (5 mL). Pentalenene synthase purified through the G-100 size exclusion step (50 μL, total activity 26 nmol/h)[8b] was added, and the mixture was incubated at 30 °C for 2 h. Carrier pentalenene (2.0 mg) in hexanes (5 mL) was added and the mixture extracted. After further extraction with hexanes (2 × 5 mL), the hexanes layers were passed through a flash chromatography column (hexanes). Fractions were concentrated on the rotary evaporator at room temperature to afford **3k**: 6.2 × 10^4 dpm of ^{14}C, 39% radiochemical yield; ^{3}H/^{14}C 4.09 ± 0.04.

(3*R*)-[3-^{3}H,14,15-$^{14}C_2$]-(7*S*,8*R*)- and -(7*R*,8*S*)-7,8-Dihydroxypentalenanes (13k and 14k). Labeled pentalenene (**3k**) (1.54 × 10^4 dpm of ^{14}C) was diluted with carrier (±)-pentalenene (40 mg, 196 μmol) and converted to the mixture of *cis*-diols, which was purified by flash chromatography (30/70 EtOAc/hexanes) to afford 35.7 mg (150 μmol, 55%) of product: 1.2 × 10^4 dpm of ^{14}C, 78% radiochemical yield; ^{3}H/^{14}C 4.25 ± 0.05. The individual diols were separated by fractional crystallization and recrystallized to constant melting point, ^{3}H and ^{14}C specific activity, and ^{3}H/^{14}C ratio: **13k**, 4.02 ± 0.10, and **14k**, 4.10 ± 0.14, respectively.

Incorporation of (3*R*)-[3-^{3}H,14,15-$^{14}C_2$]Pentalenene (3k) into Oxidized Metabolites by *Streptomyces* UC5319. Feeding of labeled pentalenene (**3k**) (1.0 mg, 3.11 × 10^4 dpm of ^{14}C) to 12 flasks of *Streptomyces* UC5319 in the usual manner gave the following products. Pentalenolactone methyl ester (**19k**): 5.6 mg; 1660 dpm of ^{14}C; 3.7 pCi/μmol ^{14}C; specific incorporation 1.4%; ^{3}H/^{14}C 0.065 ± 0.002. Epipentalenolactone F methyl ester (**18k**): 0.4 mg; 153 dpm of ^{14}C; 43 pCi/μmol ^{14}C; specific incorporation 1.5%; ^{3}H/^{14}C 3.73 ± 0.05. Pentalenic acid methyl ester (**15k**): <100 μg; 223 dpm of ^{14}C; ^{3}H/^{14}C 3.62 ± 0.03.

(1*S*)-[1-^{3}H]Farnesol. A solution of farnesal (80 mg, 363 μmol) in methanol (1 mL) was reduced with $NaBH_3T$ (3 mg, 24 mCi). After 3 h, excess $NaBH_4$ was added and the mixture was worked up as before to give (1*RS*)-[1-^{3}H]-*trans,trans*-farnesol (33.0 mg, 149 μmol, 41%): 8.63 mCi, 36% radiochemical yield; specific activity 58 mCi/mmol. Oxidation of 15 mg (67.6 μmol, 3.92 mCi) of the alcohol with MnO_2 gave [1-^{3}H]farnesal (5.1 μmol, 295 μCi, 7.5%), of which 1.12 mg (5.09 μmol, 295 μCi) was enzymatically reduced with HLADH to give (1*S*)-[1-^{3}H]farnesol (32 μCi, 11%), as described for the corresponding sample of (1*S*)-[1-^{2}H]farnesol.

(1*S*)-[1-^{3}H,12,13-$^{14}C_2$]Farnesyl Pyrophosphate (2j). (1*S*)-[1-^{3}H]-Farnesol (32 μCi) was converted to the pyrophosphate, mixed with [12,13-$^{14}C_2$]FPP (6.44 × 10^5 dpm, 1.26 μmol), and purified as described for **2k** to yield 768 nmol of **2j**: 1.49 × 10^6 dpm of ^{3}H (2.1%), 3.87 × 10^5 dpm of ^{14}C; ^{3}H/^{14}C 3.56 ± 0.015.

(1*S*)-[1-^{3}H,12,13-$^{14}C_2$]Farnesyl Diphenylurethane (12j). Hydrolysis of **2j** with acid phosphatase gave farnesol, which was converted to the corresponding diphenylurethane **12j**: 1.21 × 10^4 dpm of ^{14}C, 45% radiochemical yield. Recrystallization from MeOH to constant melting point, ^{3}H and ^{14}C specific activities, and ^{3}H/^{14}C ratio gave a ^{3}H/^{14}C ratio of 2.17 ± 0.02.

Cyclization of (1*S*)-[1-^{3}H,12,13-$^{14}C_2$]Farnesyl Pyrophosphate (2j) to (3*S*)-[3-^{3}H,14,15-$^{14}C_2$]Pentalenene (3j) by Pentalenene Synthase. (1*R*)-[1-^{3}H,12,13-$^{14}C_2$]Farnesyl pyrophosphate (**2j**) (3.9 × 10^4 dpm of ^{14}C) was cyclized in the usual manner to pentalenene, which was purified after addition of carrier pentalenene (2.75 mg): 1.26 × 10^4 dpm of ^{14}C, 33% radiochemical yield; ^{3}H/^{14}C 2.50 ± 0.02.

(3*S*)-[3-^{3}H,14,15-$^{14}C_2$]-(7*S*,8*R*)- and -(7*R*,8*S*)-7,8-Dihydroxypentalenanes (13j and 14j). Labeled pentalenene (**3j**) (41 mg, 201 μmol, 1.05 × 10^4 dpm of ^{14}C) was converted to 25.5 mg of the *cis*-diol mixture: 107 μmol, 53%; 6460 dpm of ^{14}C, 62% radiochemical yield; ^{3}H/^{14}C 2.34 ± 0.03. The individual diols were separated by fractional crystallization, and each was recrystallized to constant melting point, ^{3}H and ^{14}C specific activity, and ^{3}H/^{14}C ratio: **13j**, 2.19 ± 0.04, and **14j**, 2.24 ± 0.04.

Incorporation of (3*S*)-[3-^{3}H,14,15-$^{14}C_2$]Pentalenene (3j) into Oxidized Metabolites by *Streptomyces* UC5319. Labeled pentalenene (**2j**) (1.2 × 10^4 dpm of ^{14}C, 2.75 mg) of ethanol (600 μL) was added (100 μL/flask) to six flasks of *Streptomyces* UC5319 as described above, and the resulting oxidized metabolites were isolated and purified as the corresponding methyl esters. Pentalenolactone methyl ester (19j): 3.0 mg, 468 dpm of ^{14}C; 10.2 pCi/μmol ^{14}C; specific incorporation 2.4%; ^{3}H/^{14}C 2.25 ± 0.03. Epipentalenolactone F methyl ester (**18j**): 0.9 mg; 106 dpm of ^{14}C; 15.5 pCi/μmol ^{14}C; specific incorporation 3.7%; ^{3}H/^{14}C 1.62 ± 0.03. Pentalenic acid and methyl ester (**15j**): 4 mg; 246 dpm of ^{14}C; 14 pCi/μmol ^{14}C; specific incorporation 3.3%; ^{3}H/^{14}C 2.38 ± 0.02.

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Synthesis and Chemistry of a Quinone Methide Model for Anthracycline Antitumor Antibiotics

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Abstract: In an effort to understand the chemistry of anthracycline antitumor antibiotic, a simple stable *o*-quinone methide has been constructed and fully characterized. The reaction of the quinone methide with nucleophiles, including 2′,3′-isopropylideneadenosine has been examined.

In 1977 Moore put forth a theory of "bioreductive alkylation" to rationalize the biological activity of quinonoid antitumor compounds.[1] This theory, drawing on the earlier work of Lin and Sartorelli,[2] calls for several hundred structurally similar anthracyclines to derive their antitumor activity via the same general type of process: reduction of a quinone to a hydroquinone followed by the loss of a leaving group in the benzylic position, usually a sugar, to afford a quinone methide. The quinone methide

(1) (a) Moore, H. W. *Science* **1977**, *197*, 527. (b) Moore, H. W.; Czerniak, R. *Med. Res. Rev.* **1981**, *1*, 249.

(2) Lin, A. J.; Sartorelli, A. C. *J. Med. Chem.* **1976**, *19*, 1336, and references cited therein.

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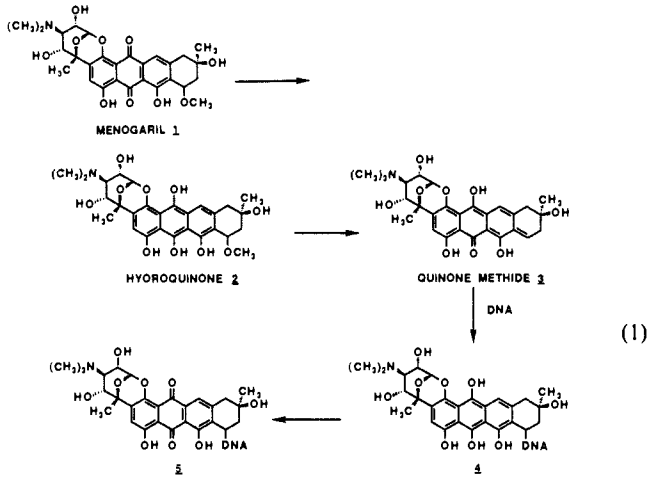
then acts as an electrophile toward some critical cellular macromolecule such as DNA to afford a new hydroquinone that then undergoes oxidation back to a quinone.[1] This process is illustrated for menogaril (**1**) in eq 1. Groups led by Lin and Sartorelli,[2] Koch,[3,4] Fisher,[5] and others[6] have provided convincing evidence for the intermediacy of quinone methides in the chemistry of some of these antitumor compounds. However, there is conflicting evidence as to whether these intermediates are responsible for the antitumor activity[5-7] or simply provide a mechanism for the observed cytotoxicity of the compounds. In either case, it is important that the chemistry of these quinone methides be well understood.

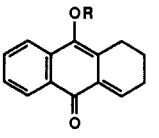


(1)

Reports from the Koch[3,4] and Fisher[5] groups have described the spectroscopic observation of quinone methides derived from menogaril[3] (**1**) and daunomycin.[4,5] Thus far, studies on the chemistry and mode of action of the compounds have provided indirect evidence for the alkylation of DNA;[7] however, to our knowledge, no anthracycline–DNA adduct has been isolated. After the completion of this work, Koch and Egholm reported the successful reductive coupling of menogaril at the 7-position to 2′-deoxyguanosine at the 2-amino position.[3b] They found treatment of menogaril under reductive conditions in the presence of a 100-fold excess of 2′-deoxyguanosine for 6 days afforded a 17% isolated yield of adduct. The reaction is proposed to occur via nucleophilic addition of the guanosine to menogaril quinone methide **3**.[3b]

We report herein the study of a stable quinone methide, which serves as a simple model for a complex antitumor compound such as menogaril. In spite of its simplicity, the study is important because of the total lack of knowledge about the chemistry of *o*-quinone methides of this type. Use of a stable, fully characterized, quinone methide allows our results to be used to make definitive conclusions about the reactivity and stability of *o*-quinone methides and the adducts derived from them. Our results show the model *o*-quinone methide undergoes facile reaction with nucleophiles, even with a protected adenosine derivative, to afford stable adducts that can be isolated and characterized.

Quinone methide **6a**, an ideal model to study, is anticipated to be extremely unstable due to the dienol functionality that imparts nucleophilic character to the quinone methide and thus facilitates dimerization.[7] To minimize complications in this initial

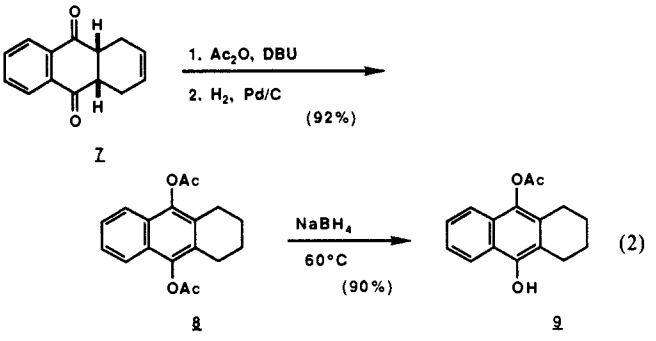


6a R = H
6b R = CH_3
6c R = Ac

study, we deemed it wise to mask this reactive functionality. Initial studies with methyl ether **6b** afforded adducts that were extremely oxygen sensitive.[8] We thus chose to work with acetate **6c**, which is undoubtedly electronically different from **6b**; however, it does allow us to examine several critical questions prior to studying quinone methides **6a** and **6b**.

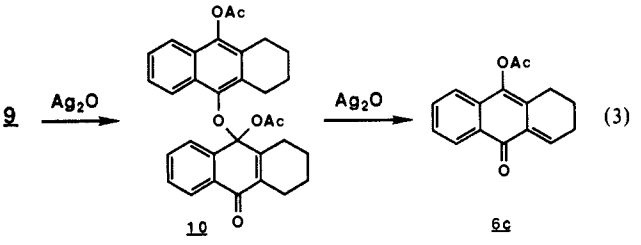
Results and Discussion

The precursor to quinone methide **6c** was synthesized via a straightforward three-step sequence (eq 2). Bisacetylation of commercially available tetrahydroanthraquinone **7** followed by hydrogenation of the isolated alkene afforded diacetate **8** in 92% overall yield. The selective cleavage of a single acetate was unsuccessful under standard hydrolysis conditions (e.g., aqueous NaOH/THF or CH_3OH). However, by use of a modification of a procedure by Quick and Crelling[9] for the deprotection of *O*-(acetyloxy)phenols with $NaBH_4$, a 90% yield of monoacetate **9** was obtained.



(2)

Oxidation of **9** with Ag_2O (2 equiv, 25 °C, 30 min) initially afforded an unsymmetrical dimer, believed to have the structure **10**, (eq 3), which upon further reaction at room temperature for 18 h, or at 80 °C for 15 min, afforded quinone methide **6c** along with 3–5% of a second dimer, **11**.[10] The high-temperature oxidation of **9** proved to be the most reliable method for the preparation of 10–60-mg quantities of >90% pure (^1H NMR analysis) quinone methide **6c**. If solutions of **6c** were allowed to sit for several hours, the amount of dimer **11** increased steadily. For example, after 16 h at room temperature ($CDCl_3$ solution) a 24% yield of **11** was obtained.



(3)

The structure proposed for dimer **10** is supported by the ^{13}C NMR spectrum, which shows a resonance at δ 183.8, assigned to the cyclohexadienone carbonyl carbon, and a resonance at δ 100.1, assigned to the new benzylic ketal. In addition, the ^1H NMR spectrum shows two different acetyloxy methyl resonances, one at δ 2.45, consistent with an acetylated phenol, and a second

(3) (a) Boldt, M.; Guadiano, G.; Haddadin, M. J.; Koch, T. H. *J. Am. Chem. Soc.* **1989**, *111*, 2283; **1988**, *110*, 3330, and references cited therein. (b) Egholm, M.; Koch, T. H. *Ibid.* **1989**, *111*, 8291.
(4) (a) Kleyer, D. L.; Gaudiano, G.; Koch, T. H. *J. Am. Chem. Soc.* **1984**, *106*, 1105. (b) Kleyer, D. L.; Koch, T. H. *Ibid.* **1984**, *106*, 2380. (c) Olson, J. B.; Koch, T. H. *Ibid.* **1986**, *108*, 756, and references cited therein.
(5) (a) Ramakrishnan, K.; Fisher, J. F. *J. Med. Chem.* **1986**, *29*, 1215. (b) Fisher, J. F.; Abdella, B. R. J.; McLane, K. E. *Biochemistry* **1985**, *24*, 3562. (c) Fisher, J. F.; Aristoff, P. A. *Prog. Drug Res.* **1988**, *32*, 411.
(6) (a) Anne, A.; Moiroux, J. *Nouv. J. Chim.* **1985**, *9*, 83. (b) Land, E. J.; Mukherjee, T.; Swallow, A. J.; Bruce, J. M. *Arch. Biochem. Biophys.* **1983**, *225*, 116. (c) Land, E. J.; Mukherjee, T.; Swallow, A. J.; Bruce, J. M. *Br. J. Cancer* **1985**, *51*, 515.
(7) (a) Abdella, B. R. J.; Fisher, J. *EHP, Environ. Health Perspect.* **1985**, *64*, 3. (b) Powis, G. *Pharmacol. Ther.* **1987**, *35*, 57.

(8) Yang, W. Unpublished results from this laboratory.
(9) Quick, J.; Crelling, J. K. *J. Org. Chem.* **1978**, *43*, 155.
(10) The oxidation conditions are a modification of those reported by: Dyall, L. K.; Winstein, S. *J. Am. Chem. Soc.* **1972**, *94*, 2196. The conditions appear to be quite general for the formation of quinone methides, cf.: Angle, S. R.; Turnbull, K. D. *J. Am. Chem. Soc.* **1989**, *111*, 1136.

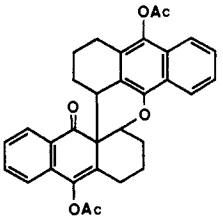
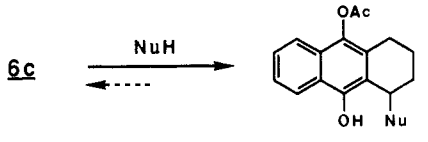


Figure 1.

at δ 2.04, consistent with a monoacetyloxy ketal structure. The UV spectrum of **10** shows a strong absorption at 234 nm characteristic of the substituted naphthalene chromophore.

The HRMS of dimer **11** shows a parent ion at m/z 508, with the expected exact mass for a dimer of **6c**. The ^{13}C NMR spectrum shows a resonance at δ 197.3, indicative of a ketone. DEPT ^{13}C NMR experiments show a methine carbon at δ 76.8 and a quaternary carbon at δ 52.3. We propose the tentative structure shown in Figure 1 for dimer **11**. This structure is consistent with all the spectral data. A dimer with this structure might arise from a [4 + 2] cycloaddition, where one quinone methide serves as a heterodiene and the second as a dienophile. This type of cycloaddition is precedented in the trimerization of simple *o*-quinone methides.[11] Confirmation of the structure assignment by single-crystal X-ray analysis has thus far been hampered by the lack of suitable crystals.

Quinone methide **6c** underwent a facile reaction with aniline (1.1 equiv; $CDCl_3$, 0.1 M; 2 min, 95% conversion by ^1H NMR analysis) to afford adduct **13a** (eq 4). Chromatography and



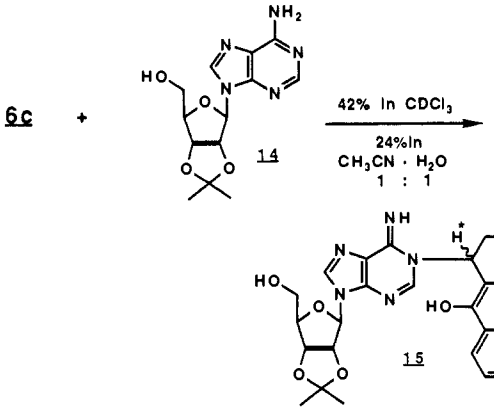
(4)

13a Nu = -NH(C_6H_5)
13b Nu = -OCH$_2$CH$_3$

recrystallization afforded a 52% yield of analytically pure **13a** (mp 142–145 °C). If **13a** was allowed to sit in solution ($CDCl_3$) for 20 min, 5–8% of quinone methide **6c** and free aniline were formed (^1H NMR analysis). Treatment of a $CDCl_3$ solution of **6c** with ethanol (excess, 25 °C) resulted in slow conversion to **13b** (15 min; 90% crude yield; 42% after flash chromatography). If **13b** was allowed to sit in solution ($CDCl_3$) for several hours, 3–5% of quinone methide **6c** and ethanol were formed (^1H NMR analysis).

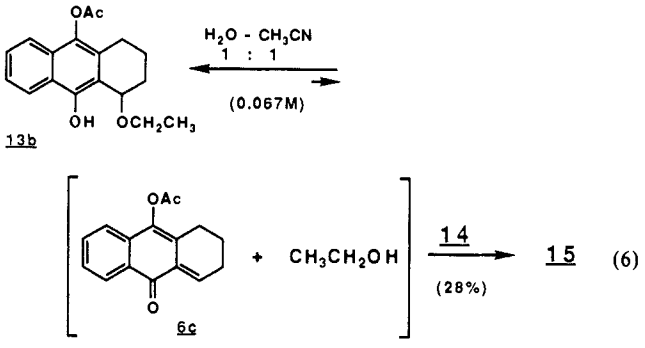
Treatment of quinone methide **6c** with 2′,3′-isopropylideneadenosine (**14**; 1.2 equiv, $CDCl_3$, 25 °C) afforded imine **15** in 42% yield as a 1:1 mixture of diastereomers (eq 5). HPLC separation afforded the faster eluting diastereomer essentially pure. The structure of **15** is supported by a strong band in the IR spectrum at 1621 cm^{-1} assigned to the imine, and the well-precedented N(1) alkylation of adenosine.[12] In addition, the ^1H NMR spectrum shows a broad multiplet at δ 5.85 assigned to the new benzylic hydrogen (H*). These results show an *o*-quinone methide can undergo a facile reaction with a protected nucleoside under carefully controlled conditions. However, we desired to probe the reaction under conditions more relevant to the biological activity of the anthracycline antitumor antibiotics.

Our results with ethanol adduct **13b** showed it to be in equilibrium with the quinone methide in $CDCl_3$ and it was hoped that this compound would provide a source of low concentrations of quinone methide **6c** in a water/organic solvent mixture. Accordingly, **13b** was treated with nucleoside **14** (1.2 equiv) in 1:1



(5)

H_2O/CH_3CN (0.067 M, homogeneous solution) for 48 h at room temperature and a 28% yield of adduct **15** was obtained (eq 6). Thus, even in the presence of water, a good yield of adenosine alkylation was observed. Treatment of quinone methide **6c** under these same conditions (1:1 H_2O/CH_3CN, 0.10 M, homogeneous solution) afforded a 24% yield of **15**.



(6)

Conclusion

Our results point out that quinone methides should be excellent electrophiles toward nucleotides and DNA itself. Thus, even though our model quinone methide is electronically different (due to the electron-withdrawing acetyloxy group) from those derived from actual antitumor compounds, this is the first study to show the facile reaction of a fully characterized quinone methide with a nucleoside to afford stable covalent adducts in good yield. In addition, it sets the stage for future studies with quinone methides **6a** and **6b** and other models that are better mimics of the anthracycline antitumor antibiotics.

Experimental Section

General Information. NMR spectra were recorded on a General Electric QE-300 NMR; shifts reported are relative to internal tetramethylsilane; coupling constants, J, are reported in hertz and refer to apparent peak multiplicities and not true coupling constants; abbreviations used are as follows: s = singlet, br s = broad singlet, d = doublet, t = triplet, q = quartet, p = pentuplet. Mass spectra were recorded at the UCR-MS facility on a VG-7070EHF or a VG-ZAB1FHF and are reported as percent relative intensity to the parent peak. IR spectra were recorded on a Nicolet-5DX FT-IR. UV spectra were recorded on a Hewlett-Packard 8451A diode array spectrophotometer. Microanalyses were performed by Desert Analytics, Tucson, AZ. Flash chromatography was done on E. Merck silica gel 60, 230–400 mesh, and analytical TLC was preformed on E. Merck glass-backed silica gel 60 plates, 250 μm thickness, with a 254-nm fluorescent indicator. HPLC was carried out on a Rainin HPLC system with HPX pumps and a Knauer Model 198 RI detector. Capillary GC was carried out on a Hewlett-Packard 5890 equipped with a HP-3393A computing integerator. DBU (used without purification) and 1,4,4a,9a-tetrahydroanthraquinone [purified by flash chromatography (silica gel, 9:1 hexane/ethyl acetate)] were purchased from Aldrich Chemical Co., Milwaukee, WI. 2′,3′-Isopropylideneadenosine was purchased from Sigma Chemical Co., St. Louis, MO, and used without purification. DME and THF were distilled from sodium benzophenone. Acetic anhydride was distilled under argon. Solvents for chromatography and recrystallization were distilled prior to use. "Concentration" refers to isolation of product(s) from a solvent/product mixture by removal of the solvent under reduced pressure (water

(11) Cf.: Mcintosh, C. L.; Chapman, O. L. *J. Chem. Soc., Chem. Commun.* **1971**, 771.

(12) In contrast to N(3) alkylation of adenosine, which is observed in duplexed DNA, as a free nucleoside adenosine affords products of alkylation at N(1), cf.: Srivastava, P. C.; Robins, R. K.; Meyer, P. B., Jr. In *Chemistry of Nucleosides and Nucleotides*; Townsend, L. B., Ed.; Plenum Press: New York, 1988; Vol. 1, pp 113–282.

aspirator) with a Büchi Rotavapor. Unless stated otherwise, all reactions were run under an atmosphere of nitrogen or argon in oven-dried glassware.

9,10-Bis(acetyloxy)-1,4-dihydroanthracene. 1,8-Diazabicyclo[5.4.0]-undec-7-ene (DBU; 8.8 mL, 60 mmol) was added to a stirred solution of 1,4,4a,9a-tetrahydroanthraquinone (**7**; 4.24 g, 20 mmol) and THF (30 mL) at room temperature. Acetic anhydride (9.2 mL, 100 mmol) was added to the resulting orange-yellow solution and the reaction mixture became colorless. After stirring 1.5 h, ether (20 mL) was added and a white precipitate formed. The precipitate was filtered and washed with ether (50 mL) to give 5.79 g (98%) of the title compound analytically pure as a white powder: mp 256–258 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.48 (s, 6 H), 3.37 (br s, 4 H), 5.92 (s, 2 H), 7.47 (dd, J = 6.4, 3.2 Hz, 2 H), 7.72 (dd, J = 6.4, 3.2 Hz, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.6, 24.5, 121.0, 122.9, 124.8, 126.0, 126.3, 141.7, 168.9; IR (KBr) 3041, 2877, 1747, 1601, 1430, 1374, 1213, 1179, 1051, 1009, 759 cm^{-1}; UV (CH_3CN) λ_{max}, nm (log ϵ) 230 (4.68), 290 (3.71); MS (EI, 20 eV) m/z 296 (M^+, 5), 254 (21), 212 (100), 208 (74), 194 (61), 180 (54), 165 (39), 152 (50); HRMS calcd for $C_{18}H_{16}O_4$ 296.1049, found 296.1037. Anal. Calcd for $C_{18}H_{16}O_4$: C, 72.96; H, 5.44. Found: C, 72.74; H, 5.39.

9,10-Bis(acetyloxy)-1,2,3,4-tetrahydroanthracene (8). Pd/C (5%, 180 mg) was added to a solution of 9,10-bis(acetyloxy)-1,4-dihydroanthracene (501 mg, 1.69 mmol) in acetone (25 mL). The resulting suspension was stirred under 1 atm hydrogen at room temperature for 17 h. The solution was filtered through Celite (3 g) and the filtrate was rinsed with ethyl acetate (50 mL). Concentration afforded crude **8** as a white solid. Recrystallization (ethyl acetate/hexane) afforded 475 mg (94%) of **8** as white needles: mp 214–215 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.83 (br s, 4 H), 2.47 (s, 6 H), 2.76 (br s, 4 H), 7.45 (dd, J = 6.4, 3.2 Hz, 2 H), 7.70 (dd, J = 6.3, 3.2 Hz, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.5, 21.9, 24.0, 120.9, 125.7, 126.0, 127.5, 141.9, 168.8; IR (KBr) 3068, 2938, 1749, 1599, 1500, 1438, 1366, 1210, 1177, 1050, 1006, 761 cm^{-1}; UV (CH_3CN) λ_{max}, nm (log ϵ) 230 (4.74), 292 (3.71); MS (EI, 70 eV) m/z 298 (M^+, 29), 256 (19), 214 (100), 197 (5), 128 (6); HRMS calcd for $C_{18}H_{18}O_4$ 298.1205, found 298.1199. Anal. Calcd for $C_{18}H_{18}O_4$: C, 72.47; H, 6.08. Found: C, 72.37; H, 5.92.

10-(Acetyloxy)-9-hydroxy-1,2,3,4-tetrahydroanthracene (9). $NaBH_4$ (567 mg, 15 mmol) was added to a stirred solution of 9,10-bis(acetyloxy)-1,2,3,4-tetrahydroanthracene (**8**; 447 mg, 1.5 mmol) and DME (40 mL). The resulting suspension was stirred at 60 ± 5 °C and monitored by GC (25-m methyl silicone column, 0.25 mm i.d. × 0.25 μm film thickness; injector, 200 °C; detector, 280 °C; program, 40–280 °C at 18 °C/min, final time, 5 min; retention time of **9**, 14.7 min). After 30 h, the mixture was cooled to room temperature and quenched with NH_4Cl (saturated aqueous, 25 mL). Ethyl acetate (25 mL) was added and stirring was continued for 5 min. The aqueous layer was extracted with ethyl acetate (25 mL) and the combined organic extracts were washed with brine (2 × 20 mL), dried (Na_2SO_4), concentrated and recrystallized (ether/hexane) to yield 347 mg (90%) of **9** as a white powder: mp 167–169 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.76 (br s, 4 H), 2.48 (s, 3 H), 2.57 (br s, 2 H), 2.69 (br s, 2 H), 5.33 (br s, 1 H), 7.33–7.42 (m, 2 H), 7.62 (d, J = 8.1 Hz, 1 H), 8.01 (d, J = 8.1 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.6, 21.9, 22.1, 23.1, 24.1, 117.4, 120.3, 121.4, 122.9, 124.7, 125.4, 126.0, 127.3, 137.1, 146.4, 169.9; IR (KBr) 3459, 2933, 2870, 1742, 1597, 1572, 1546, 1369, 1227, 1181, 1046, 761 cm^{-1}; UV (CH_3CN) λ_{max}, nm (log ϵ) 214 (4.44), 238 (4.65), 306 (3.60); MS (EI, 70 eV) m/z 256 (M^+, 19), 214 (100), 197 (7), 165 (4), 157 (4), 105 (5); HRMS calcd for $C_{16}H_{16}O_3$ 256.1099, found 256.1085.

10-(Acetyloxy)-9-oxo-2,3,4-trihydroanthracene (6c). General Procedure. Silver(I) oxide (92.8 mg, 0.4 mmol) was added to a solution of phenol 9 (51.2 mg, 0.2 mmol) and $CDCl_3$ (1.1 mL) in a dry 5-mm NMR tube. The resulting suspension was heated in a water bath at 80 °C until the oxidation was complete (15 min, ^{1}H NMR monitoring). The suspension was filtered through glass wool and the residue was rinsed with $CDCl_3$ to give a solution of quinone methide **6c**. Concentration of a portion of this solution afforded a sample of **6c** for analysis: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.79–1.83 (m, 2 H), 2.40 (s, 3 H), 2.50–2.55 (m, 4 H), 7.27 (d, J = 7.1 Hz, 1 H), 7.35 (t, J = 7.6 Hz, 1 H), 7.56 (t, J = 7.5 Hz, 1 H), 7.69 (t, J = 4.7 Hz, 1 H), 8.20 (d, J = 7.8 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.4, 21.0, 23.2, 26.8, 121.6, 124.2, 127.4, 128.0, 130.9, 132.1, 133.8, 134.3, 136.8, 147.4, 168.4, 183.0; IR (CCl_4) 3073, 2944, 1764, 1666, 1632, 1597, 1581, 1453, 1367, 1204, 1175, 1064, 932, 909, 891 cm^{-1}; MS (EI, 20 eV) m/z 254 (M^+, 33), 228 (5), 212 (100), 197 (9); HRMS calcd for $C_{16}H_{14}O_3$ 254.0943, found 254.0934.

Dimer 10. Silver(I) oxide (56.1 mg, 0.24 mmol) was added to a solution of phenol 9 (30.5 mg, 0.12 mmol) and $CDCl_3$ (0.6 mL) in a dry 5-mm NMR tube at room temperature. The reaction was followed by ^{1}H NMR. When the phenol was consumed (approximately 10 min at room temperature) the suspension was filtered through glass wool to remove solids and concentrated to afford essentially pure dimer **10** as a yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.35–1.54 (br m, 2 H), 1.63–1.87 (m, 6 H), 2.04 (s, 3 H), 2.30–2.44 (m, 2 H), 2.45 (s, 3 H), 2.50–2.90 (m, 6 H), 6.48 (d, J = 7.8 Hz, 1 H), 7.01 (t, J = 7.5 Hz, 1 H), 7.26–7.39 (m, 4 H), 7.60 (d, J = 8.2 Hz, 1 H), 8.05 (d, J = 7.7 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.6, 21.4, 21.5, 21.6, 21.8, 22.6, 23.6, 24.2, 24.3, 25.4, 100.8, 120.0, 120.1, 123.8, 124.7, 125.4, 125.6, 125.7, 126.5, 127.2, 129.2, 130.7, 131.1, 131.4, 134.1, 137.2, 141.3, 144.7, 150.0, 167.6, 168.9, 183.8; IR (CCl_4) 2941, 2864, 1762, 1662, 1600, 1457, 1359, 1204, 1175, 1048, 947, 908 cm^{-1}; UV (CH_3CN) λ_{max}, nm (log ϵ) 212 (4.64), 234 (4.81), 260 (4.25), 267 (4.16), 289 (4.06); MS (EI, 20 eV) m/z 256 (22), 254 (22), 214 (97), 212 (100), 180 (18).

Dimer 11. A solution of quinone methide **6c** (prepared from 45.3 mg, 0.18 mmol of phenol 9) and $CDCl_3$ (1.0 mL) was allowed to stand at room temperature in a 5-mm NMR tube for 16 h. Concentration and chromatography (silica gel, 4:1 hexane/ethyl acetate) afforded 22.3 mg (49%) of pure dimer **11** as a yellow solid: mp 182–185 °C; ^{1}H NMR (300 MHz, CD_2Cl_2) δ 0.98 (ddd, J = 12.1, 11.6, 11.0 Hz, 1 H), 1.47–1.77 (m, 2 H), 1.85–2.06 (m, 3 H), 2.11–2.35 (m, 3 H), 2.42 (s, 3 H), 2.43 (s, 3 H), 2.45–2.77 (br m, 3 H), 3.51 (dd, J = 12.4, 3.2 Hz, 1 H), 4.58 (dd, J = 11.4, 5.0 Hz, 1 H), 7.29 (d, J = 7.8 Hz, 1 H), 7.39 (dd, J = 7.5, 7.5 Hz, 1 H), 7.43–7.52 (m, 2 H), 7.61 (m, 2 H), 7.87 (d, J = 7.5 Hz, 1 H), 8.26 (dd, J = 6.8, 2.7 Hz, 1 H); ^{13}C NMR (75 MHz, CD_2Cl_2) δ 20.7, 20.8, 22.9, 22.9, 23.0, 24.2, 30.5, 38.1, 52.3, 76.8, 112.0, 120.6, 122.0, 122.6, 123.7, 125.1, 126.4, 126.5, 126.7, 127.2, 128.9, 130.0, 131.6, 134.2, 134.5, 137.4, 140.3, 145.3, 168.9, 169.8, 197.3; IR (CCl_4) 3072, 2943, 2866, 1765, 1683, 1656, 1598, 1577, 1452, 1407, 1365, 1336, 1205, 1139, 1068, 909 cm^{-1}; UV (CH_3CN) λ_{max}, nm (log ϵ) 214 (4.46), 246 (4.78), 280 (3.71), 290 (3.67), 320 (3.70); MS (FAB, positive ion, nitrobenzyl alcohol matrix) m/z 508 (M^+, 25), 255 (98), 254 (38), 212 (100); HRMS calcd for $C_{32}H_{28}O_6$ 508.1886, found 508.1913.

10-(Acetyloxy)-9-hydroxy-1-(phenylamino)-1,2,3,4-tetrahydroanthracene (13a). Aniline (19.0 mg, 0.204 mmol) was added to a solution of quinone methide **6c** (from 51.5 mg, 0.201 mmol, of phenol 9) and $CDCl_3$ (2.0 mL) in a dry reaction vial. The reaction was complete within 2 min. The reaction mixture was concentrated to afford 68.3 mg of crude **13a** as a yellow oil. Chromatography (silica gel, 85:15 hexane/ethyl acetate) followed by recrystallization (ethyl acetate/hexane) afforded 36.6 mg (52%) of **13a** as a white solid: mp 142–145 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.73 (m, 2 H), 1.86 (m, 1 H), 2.24 (br m, 1 H), 2.46 (s, 3 H), 2.68 (m, 2 H), 3.77 (d, J = 9.9 Hz, 1 H, NH), 4.97 (br m, 1 H), 6.96 (m, 3 H), 7.29 (m, 2 H), 7.40–7.51 (m, 2 H), 7.64 (d, J = 8.2 Hz, 1 H), 8.27 (d, J = 8.0 Hz, 1 H), 10.25 (br s, 1 H, OH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.2, 20.6, 24.5, 29.2, 53.4, 115.2, 117.8, 120.1, 121.5, 122.6, 124.2, 124.8, 126.7, 127.1, 127.3, 129.5, 136.2, 144.9, 151.5, 169.6; IR (CCl_4) 3302, 3276, 3053, 2942, 1762, 1751, 1600, 1497, 1373, 1231, 1208, 1181, 1061 cm^{-1}; MS (FAB, positive ion, nitrobenzyl alcohol matrix) m/z 347 (M^+, 18), 286 (7), 255 (100), 212 (68), 197 (8), 133 (46); HRMS calcd for $C_{22}H_{21}NO_3$ 347.1521, found 347.1538. Anal. Calcd for $C_{22}H_{21}NO_3$: C, 76.06; H, 6.09; N, 4.03. Found: C, 76.08; H, 6.01; N, 3.83.

10-(Acetyloxy)-1-ethoxy-9-hydroxy-1,2,3,4-tetrahydroanthracene (13b). A solution of quinone methide **6c** (from 51.4 mg, 0.201 mmol, of phenol **9**) and $CDCl_3$ (2.0 mL) was added to ethanol (0.5 mL) in a dry reaction vial. This solution was stirred at room temperature until the reaction was complete (15 min, TLC monitoring). Concentration afforded 58.5 mg of crude **13b**, >90% pure by ^{1}H NMR analysis. Chromatography (silica gel, 85:15 hexane/ethyl acetate) afforded 26.5 mg (42%) of **13b** as a yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.35 (t, J = 7.0 Hz, 3 H), 1.70 (br m, 1 H), 1.83–2.05 (br m, 2 H), 2.32 (br m, 1 H), 2.44 (s, 3 H), 2.66 (br m, 2 H), 3.66 (m, 1 H), 3.83 (m, 1 H), 5.06 (dd, J = 6.1, 8.9 Hz, 1 H), 7.44 (m, 2 H), 7.60 (d, J = 8.0 Hz, 1 H), 8.25 (d, J = 8.0 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 15.5, 20.0, 20.6, 24.3, 27.7, 62.2, 77.2, 115.1, 120.1, 122.5, 123.9, 124.7, 126.8, 127.0, 127.1, 136.2, 150.9, 169.4; IR (neat) 3238, 2973, 2941, 1760, 1637, 1596, 1575, 1507, 1391, 1369, 1209, 1199, 1069, 947, 763 cm^{-1}; MS (FAB, positive ion, nitrobenzyl alcohol matrix) m/z 300 (M^+, 16), 255 (54), 212 (100), 195 (5), 154 (6), 136 (6); HRMS calcd for $C_{18}H_{20}O_4$ 300.1362, found 300.1346.

1-[10″-(Acetyloxy)-9″-hydroxy-1″-,2″,3″,4″-tetrahydroanthracenyl]-2′,3′-isopropylideneadenosine (15). (a) Preparation in $CDCl_3$. A solution of quinone methide **6c** (from 51.8 mg, 0.202 mmol, of phenol **9**) and $CDCl_3$ (1.1 mL) was added to 2′,3′-isopropylideneadenosine (**14**) in a dry reaction vial. This solution was stirred at room temperature until all of the quinone methide was consumed (10 h, ^{1}H NMR monitoring). The reaction mixture was concentrated and chromatographed (silica gel, 4:1 hexane/2-propanol) to afford 47.1 mg (42%) of **15** as a white solid (mp 135–137 °C and 1:1 mixture of diastereomers by HPLC analysis).

(b) Preparation in CH_3CN/H_2O from Ethanol Adduct 13b. A solution of 2′,3′-isopropylideneadenosine (24.8 mg, 0.081 mmol, 1.20 equiv) and

H_2O/CH_3CN (1:1, v/v; 1.0 mL) as added to ethanol adduct **13b** (20.2 mg, 0.067 mmol) in a 5-mL reaction flask. The resulting homogeneous solution was stirred at room temperature for 48 h. The mixture was then diluted with water (2 mL) and extracted with $CHCl_3$ (3 × 5 mL). The combined organic extracts were dried (Na_2SO_4), concentrated, and chromatographed (silica gel, 4:1 hexane/2-propanol) to afford 10.6 mg (28%) of **15** as a white solid (1:1 mixture of diastereomers by ^1H NMR analysis).

(c) **Preparation in CH_3CN/H_2O from Quinone Methide 6c.** A solution of 2',3'-isopropylideneadenosine (36.9 mg, 0.121 mmol, 1.20 equiv) and H_2O/CH_3CN (1:1, v/v; 1.0 mL) was added to quinone methide **6c** (prepared from 25.8 mg, 0.101 mmol, of phenol 9) in a reaction flask. The resulting homogeneous solution was stirred at room temperature for 48 h. The mixture was then diluted with water (2 mL) and extracted with $CHCl_3$ (3 × 5 mL). The combined organic extracts were dried (Na_2SO_4), concentrated, and chromatographed (silica gel, 4:1 hexane/2-propanol) to afford 13.2 mg (24%) of **15** as a white solid (1:1 mixture of diastereomers by ^1H NMR analysis).

15 (mixture of diastereomers): ^1H NMR (300 MHz, $CDCl_3$) δ 1.35 (s, 3 H), 1.38 (s, 3 H), 1.60 (s, 3 H), 1.64 (s, 3 H), 2.09 (br s, 6 H), 2.26 (br m, 2 H), 2.46 (s, 6 H), 2.60–2.85 (br m, 2 H), 2.85–3.10 (br m, 2 H), 3.93 (d, J = 12.1 Hz, 1 H), 3.98 (d, J = 12.5 Hz, 1 H), 4.51 (s, 2 H), 5.10 (m, 3 H), 5.19 (t, J = 5.29 Hz, 1 H), 5.72 (br d, J = 7.21 Hz, 2 H), 5.76–5.82 (m, 2 H), 6.18 (t, J = 11.5 Hz, 2 H), 6.50 (d, J = 8.2 Hz, 1 H), 6.63 (br s, 1 H), 7.34–7.48 (m, 4 H), 7.58 (d, J = 8.1 Hz, 2 H), 7.72 (s, 1 H), 7.77 (s, 1 H), 8.31 (d, J = 8.0 Hz, 2 H), 8.45 (s, 1 H), 8.46 (s, 1 H), 11.48 (br s, 2 H); IR (CCl_4) 3422, 3255, 2938, 1763, 1624, 1583, 1477, 1383, 1374, 1332, 1210, 1114, 1082, 1054, 852 cm^{-1}; MS (FAB, positive ion, nitrobenzyl alcohol matrix) m/z 561 (M^+, 50), 518 (6), 398 (7), 346 (14), 308 (33), 212 (100); HRMS calcd for $C_{29}H_{31}N_5O_7$ 561.2223, found 561.2238. Anal. Cald for $C_{29}H_{31}N_5O_7$: C, 62.02; H, 5.56; N, 12.47. Found: C, 61.34; H, 5.45; N, 12.50.

The two diastereomers were subjected to HPLC (8-μm Rainin Dynamax silica gel column, 4.6 × 250 mm, 5:1 hexane/2-propanol; flow rate, 0.8 mL·min^{-1}; retention time, 15.62 and 16.76 min) to afford the high R_f diastereomer analytically pure. High-R_f diastereomer: ^1H NMR (300 MHz, $CDCl_3$) δ 1.38 (s, 3 H), 1.6 (s, 3 H), 2.10 (br s, 3 H), 2.26–2.32 (m, 1 H), 2.46 (s, 3 H), 2.60–2.80 (br m, 1 H), 2.80–3.20 (br m, 1 H), 3.76 (t, J = 11.8 Hz, 1 H), 3.94 (d, J = 12.7 Hz, 1 H), 4.51 (s, 1 H), 5.10 (d, J = 5.8 Hz, 1 H), 5.19 (t, J = 5.3 Hz, 1 H), 5.72 (br d, J = 7.1 Hz, 1 H), 5.81 (d, J = 4.8 Hz, 1 H), 6.14 (d, J = 11.2 Hz, 1 H), 6.50 (d, J = 8.2 Hz, 1 H), 7.37–7.48 (m, 2 H), 7.58 (d, J = 8.2 Hz, 1 H), 7.77 (s, 1 H), 8.31 (d, J = 8.0 Hz, 1 H), 8.46 (s, 1 H), 11.48 (br s, 1 H).

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Efficient Synthetic Routes to Fluorinated Isosteres of Inositol and Their Effects on Cellular Growth

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Abstract: Efficient synthetic routes to several fluorinated isosteres of inositol have been developed that are based upon the unexpected selectivity observed in the (diethylamido)sulfur trifluoride reaction of polyhydroxylated cyclohexane derivatives. The conversion of D-pinitol to 1D-1,5-dideoxy-1,5-difluoro-*neo*-inositol and to 1D-1-deoxy-1-fluoro-*myo*-inositol is reported along with a mechanistic rationale for their formation. Furthermore, the cell growth inhibitory properties of three fluorinated inositol analogues on NIH 3T3 (normal fibroblasts) and v-*sis*-transformed NIH 3T3 cells are described. These inositol isosteres hold promise as tools for furthering our understanding of the phosphatidylinositol cascade and may also offer a new strategy in the treatment of neoplastic diseases.

One of the major advances in cell biology in recent years has been the discovery of a series of intracellular signaling pathways that couple the messages derived from the binding of biologically active molecules with receptors in the cell surface to effector mechanisms within the cell. These signaling pathways have been found in all cell types and modulate the actions of hormones, neurotransmitters, growth factors, and oncogenes.[1] One of the most extensively studied signaling pathways is the phospholipase C dependent hydrolysis of membrane phosphoinositide to form inositol polyphosphates and diacylglycerol.[2] As part of the larger effort to understand the mechanism of inositol-based intracellular signaling in relation to cell growth control, we have been interested in the synthesis of fluorinated isosteres of *myo*-inositol which may act as antimetabolites for the inositol pathway.[3] Such isosteres could act either by blocking the formation of certain inositol phosphates or by forming fraudulent analogues.

In this article we detail an expedient route to 1D-1-deoxy-1-fluoro-*myo*-inositol (**1**) as well as 1D-1,5-dideoxy-1,5-difluoro-*neo*-inositol (**2**). The synthesis of the latter compound rests upon the surprising regioselectivity observed in the fluorination reaction of an inositol derivative with DAST ((diethylamido)sulfur trifluoride). While we have already reported a 10-step route to the

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