91 (100). This compound was found to be identical to a sample provided by Prof. C. W. Rees.[14]

Acknowledgment. Financial support by the DGICYT (PB87/0019) is gratefully acknowledged. Thanks are also due to Prof. J. D. Martin (U. de La Laguna) and Dr. G. Tojo (U. de Santiago de Compostela) for carrying out our HRMS.

Registry No. **1a**, 4082-25-1; **1b**, 2107-69-9; **1c**, 137542-56-4; **2a**, 137542-52-0; **2b**, 137542-55-3; **2c**, 137542-59-7; **3a**, 137542-60-0; **3b**, 137542-61-1; **3c**, 137542-62-2; **4a**, 137542-63-3; **4b**, 137542-64-4; **5a**, 137542-65-5; **5b**, 137542-66-6; **5c**, 137542-71-3; **6a**, 137542-67-7; **6b**, 137542-68-8; **6c**, 137542-72-4; **7a**, 137542-69-9; **7b**, 137542-70-2; **7c**, 137542-73-5; **8b**, 102357-91-5; PDE-I, 62497-62-5; PDE-II, 62874-94-6; 5-hydroxy-6-methoxy-1-indanone, 127399-78-4; 5-hydroxy-6-methoxy-4-nitro-1-indanone, 137542-53-1; 4-amino-5-hydroxy-6-methoxy-1-indanone, 137542-54-2; 5-hydroxy-6-methoxy-3-methyl-1-indanone, 71653-30-0; 5-hydroxy-6-methoxy-3-methyl-4-nitro-1-indanone, 137542-50-8; 4-amino-5-hydroxy-6-methoxy-3-methyl-1-indanone, 137542-51-9; 5-hydroxy-6-methoxy-2-methyl-1-indanone, 137542-56-4; 5-hydroxy-6-methoxy-2-methyl-4-nitro-1-indanone, 137542-57-5; 4-amino-5-hydroxy-6-methoxy-2-methyl-1-indanone, 137542-58-6.

Supplementary Material Available: ^{1}H NMR spectra for compounds **5c** and **6c** (2 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

Novel Carbocyclic Nucleosides Related to Oxetanocin

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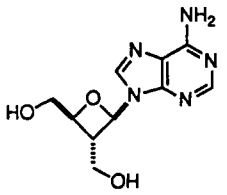
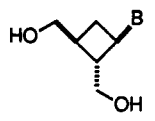
Received March 21, 1991 (Revised Manuscript Received September 20, 1991)

Carbocyclic oxetanocin analogues 9-[*trans*-2,*cis*-3-bis(hydroxymethyl)-5,9-dithiaspiro-[3.5]non-*r*-1-yl]adenine, 9-[4,4-dimethyl-*trans*-2,*cis*-3-bis(hydroxymethyl)cyclobut-*r*-1-yl]adenine, and related compounds have been prepared by a strategy utilizing nucleophilic addition of heterocyclic bases to dimethyl 4,4-disubstituted 2-cyclobutene-1,2-dicarboxylates. The latter were prepared by a process involving [2 + 2] cycloadditions of enamines and dimethyl maleate.

In 1986, Shimada and co-workers isolated oxetanocin (Oxt-A) (1) from a strain of bacteria, *Bacillus megaterium* NK84-0218;[1] oxetanocin is the first and only known example of a naturally occurring four-membered ring nucleoside.[2] Among other activities, biological testing



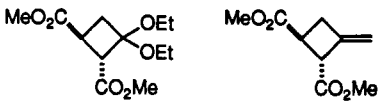
1 (Oxt-A)



2 BH = Adenine (C-Oxt-A)
3 BH = Guanine (C-Oxt-G)
4 B = NH_2

showed that oxetanocin was active against human immunodeficiency virus (HIV).[3] We began a program to synthesize carbocyclic analogues of oxetanocin. At the outset of our investigation there were no published reports of any carbocyclic analogues of oxetanocin; however, since June 1989 a number groups have published syntheses of carbocyclic oxetanocin (C-Oxt-A) (2) and related substances, e.g., 3.

Honjo and co-workers utilized cyclobutane 5[4] as starting material in their nonstereoselective synthesis of racemic C-Oxt-A (2).[5] The adenine ring was assembled from a protected 4 using the three-step sequence of Montgomery.[6]



5 6

Slusarchyk and co-workers have reported a synthesis of racemic as well as optically pure cyclobutyl nucleoside analogues from cyclobutane 5.[7] The synthesis involved an improved synthesis of 5 as well as the direct introduction of a protected guanine. Norbeck and co-workers' synthesis of racemic C-Oxt-A and C-Oxt-G[8] utilized the cyclobutane product 6 from the cyclization of allene and diethyl fumarate.[9] Katagiri and co-workers have reported the preparation of carbocyclic oxetane intermediates in the form of protected derivatives of 4 beginning with irradia-

(1) Shimada, N.; Hasegawa, S.; Harada, T.; Tomisawa, T.; Fujii, A.; Takita, T. *J. Antibiot.* **1986**, *39*, 1623. Nakamura, H.; Hasegawa, S.; Shimada, N.; Fujii, A.; Takita, T.; Iitaka, Y. *Ibid.* **1986**, *39*, 1626.

(2) For synthetic oxetanocin analogues see: Reference 1 and (a) Nishiyama, Y.; Yamamoto, N.; Yamada, Y.; Daikoku, T.; Ichikawa, Y.-I.; Takahashi, K. *J. Antibiot.* **1989**, *42*, 1854. (b) Jacobs, G. A.; Tino, J. A.; Zahler, R. *Tetrahedron Lett.* **1989**, *30*, 6955. (c) Nishiyama, S.; Ohgiya, T.; Yamamura, S.; Kato, K.; Nagai, M.; Takita, T. *Ibid.* **1990**, *31*, 705.

(3) Hoshino, H.; Shimizu, N.; Shimada, N.; Takita, T.; Takeuchi, T. *J. Antibiot.* **1987**, *40*, 1077.

(4) Brannock, K. C.; Burpitt, R. D.; Thweatt, J. G. *J. Org. Chem.* **1964**, *29*, 940.

(5) Honjo, M.; Maruyama, T.; Sato, Y.; Horii, T. *Chem. Pharm. Bull.* **1989**, *37*, 1413.

(6) Montgomery, J. A.; Temple, C., Jr. *J. Am. Chem. Soc.* **1957**, *79*, 5238.

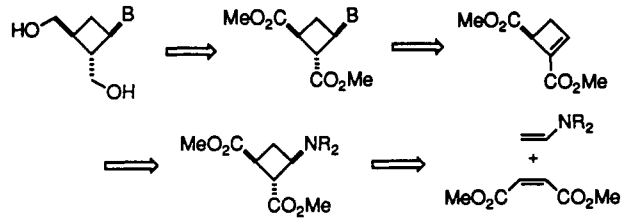
(7) (a) Slusarchyk, W. A.; Young, M. G.; Bisacchi, G. S.; Hockstein, D. R.; Zahler, R. *Tetrahedron Lett.* **1989**, *30*, 6453. (b) Bisacchi, G. S.; Braitman, A.; Cianci, C. W.; Clark, J. M.; Field, A. K.; Hagen, M. E.; Hockstein, D. R.; Malley, M. F.; Mitt, T.; Slusarchyk, W. A.; Sundeen. J. E.; Terry, B. J.; Tuomari, A. V.; Weaver, E. R.; Young, M. G.; Zahler, R. *J. Med. Chem.* **1991**, *34*, 1415.

(8) Norbeck, D. W.; Kern, E.; Hayashi, S.; Rosenbrook, W.; Sham, H.; Herrin, T.; Plattner, J. J.; Erickson, J.; Clement, J.; Swanson, R.; Shipkowitz, N.; Hardy, D.; Marsh, K.; Arnett, G.; Shannon, W.; Broder, S.; Mitsuya, H. *J. Med. Chem.* **1990**, *33*, 1281. See also: Norbeck, D.; Rosenbrook, W.; Plattner, J.; Erickson, J.; Arnett, G.; Shannon, W. Abstract of Papers. V International Conference on AIDS, Montreal, June 4-9, 1989; M.C.P. 65, p 552. Hayashi, S.; Norbeck, D. W.; Plattner, J.; Broder, S.; Mitsuya, H. *Ibid.* M.C.P 135, p 564.

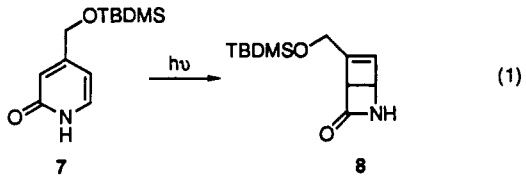
(9) Cripps, H. N.; Williams, J. K.; Sharkey, W. H. *J. Am. Chem. Soc.* **1959**, *81*, 2723.

0022-3263/92/1957-0594$03.00/0

Scheme I

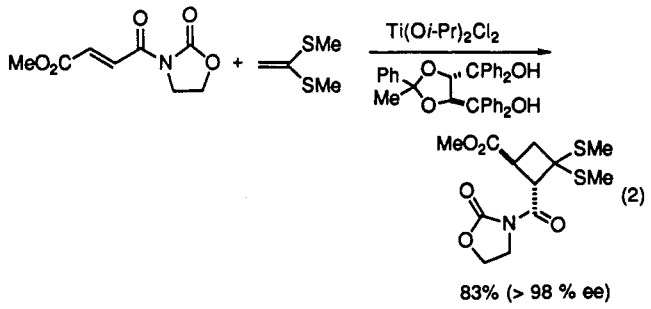


tion of 7 with a high-pressure mercury lamp which gave the bicyclohexane product 8 (eq 1).[10]



(1)

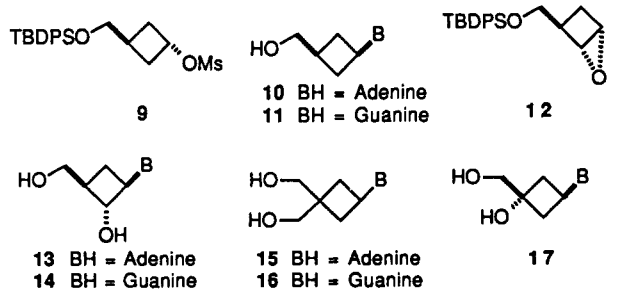
Ichikawa and co-workers[11] have reported syntheses of optically pure C-Oxt-A and C-Oxt-G. Their pivotal transformation involved an asymmetric [2 + 2] cyclization using a chiral titanium catalyst (eq 2).[12]



(2)

83% (> 98 % ee)

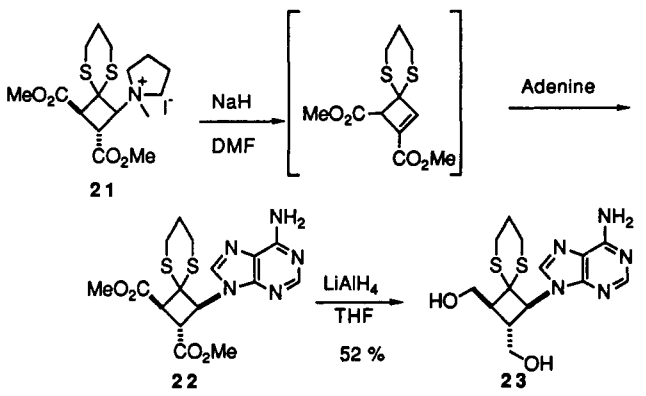
Utilizing intermediates 9 and 12, these same workers have prepared optically active derivatives (10, 11) lacking a substituent at the 2 'position as well as those (13, 14) bearing only a hydroxyl group at this position.[13] Racemic 14 has also been reported by Jacobs, Tine, and Zahler.[2b] The preparation of carbocyclic oxetanocin analogues 15 and 16 with both hydroxymethyl substituents on the 3' position have been recently reported as have A and G analogues of the structural class 17.[14]



Results and Discussion

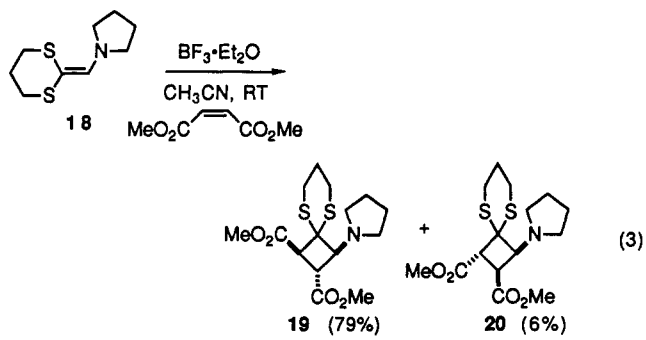
Our retrosynthetic analysis for the synthesis of carboxylic oxetanocins is outlined in Scheme I. We envisioned

Scheme II



that an enamine [2 + 2] cyclization with an appropriately substituted olefin would be an ideal reaction for establishing the required framework found in carbocyclic oxetanocin analogues. [2 + 2] Cycloaddition reactions of enamines with electrophilic alkenes are well documented, primarily by Cook,[15,16] Hall,[17] and Brannock.[18,19] In order to obtain high yields of stable cyclobutane intermediates, β,β-disubstituted enamines are required. β-Sulfur substituents appeared to be good candidates as they offer the possibility of reductive removal. Dimethyl maleate would provide the 2'- and 3'-hydroxymethyl groups after reduction.

We selected the dithiane enamine 18 for our initial studies. Formylation of 1,3-dithiane was achieved using a procedure of Meyers and Strickland,[20] and the resulting aldehyde was treated with pyrrolidine in refluxing benzene with azeotropic removal of water to provide enamine 18 in 62% overall yield. The dithio enamine 18 was treated with dimethyl maleate under the standard conditions of refluxing acetonitrile; only starting materials were recovered after 24 h. However, when 1 equiv of BF_3·Et_2O was added,[21] a mixture of product 19 and a diastereomer tentatively assigned as 20 were obtained in 79% and 6% isolated yields, respectively (eq 3). The major isomer was

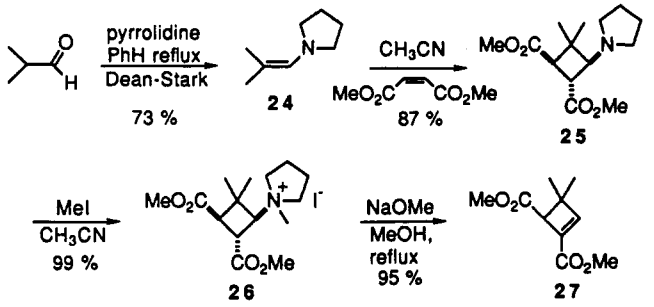


(3)

assigned the desired configuration 19 based on the findings of Lewis et al.[22] We found that methyl acrylate and enamine 18 underwent cycloaddition to afford *trans*-

(10) Katagiri, N.; Sato, H.; Kaneko, C. *Chem. Pharm. Bull*, **1990**, *38*, 288.
(11) Ichikawa, Y.-I.; Narita, A.; Shiozawa, A.; Hayashi, Y.; Narasaka, K. *J. Chem. Soc. Chem. Commun.* **1989**, 1919. See also: Norbeck, D. W. 200th National Meeting of the American Chemical Society; Washington, DC, Aug 26–31, 1990; MEDI 80.
(12) Hayashi, Y.; Narasaka, D. *Chem. Lett.* **1989**, 793.
(13) Nishiyama, Y.; Yamamoto, N.; Yamada, Y.; Daikoku, T.; Ichikawa, Y.; Takahashi, K. *J. Antibiot.* **1989**, *42*, 1854.
(14) Boumchita, H.; Legraverend, M.; Huel, C.; Bisagni, E. *J. Heterocycl. Chem.* **1990**, *27*, 1815. Boumchita, H.; Legraverend, M.; Guiilhem, J.; Bisagni, E. *Heterocycles* **1991**, *32*, 867.
(15) Cook, A. G. Doctoral Dissertation, University of Illinois, 1959.
(16) Cook, A. G. In *Enamines*; Cook, A. G., Ed.; Marcel Dekker: New York, 1988; Chapter 7.
(17) Hall, H., K., Jr.; Ykman, P. *J. Am. Chem. Soc.* **1975**, *97*, 800.
(18) (a) Brannock, K. C.; Bell, A.; Burpitt, R. D.; Kelly, C. A. *J. Org. Chem.* **1961**, *26* 625; (b) *Ibid.* **1964**, *29*, 801.
(19) The process of N-alkylation and elimination followed by readdition of an amine to the resulting cyclobutenecarboxylate has been described earlier by Brannock et al (ref 18b).
(20) Meyers, A. I.; Strickland, R. C. *J. Org. Chem.* **1972**, *37*, 2579.
(21) *p*-Toluenesulfonic acid has been used to catalyze the cycloaddition of enamines to vinylpyridines: Heitmeier, D. E.; Hortenstine, J. T., Jr.; Gray, A. P. *J. Org. Chem.* **1971**, *36*, 1449.
(22) Lewis, F. D.; Ho, T.-I.; DeVoe, R. J. *J. Org. Chem.* **1980**, *45*, 5283.

Scheme III



methyl 1-(1-pyrrolinyl)-5,9-dithiaspiro[3.5]nonane-2-carboxylate.

Amine **19** (or a mixture of **19** and **20**) was treated with excess methyl iodide to provide methiodide salt **21**. Treatment of this salt with 1.2 equiv of NaH in DMF followed by 1.5 equiv of adenine resulted in a mixture of diasteromeric adenine adducts in 84% yield (Scheme II).[19] Although predominantly one isomer (59% by NMR), three of the four isomers were inseparable by flash chromatography. Recrystallization from methanol provided the pure isomer **22** in 35% yield; unfortunately, second crops were always tainted with another isomer. The relative stereochemistry of **22** was confirmed by NOE experiments. Irradiation of H-1′ gave a 11% enhancement of H-3′, while irradiation of H-2′ gave a 15% enhancement of H-8.

Reduction of the two ester groups was carried out using lithium aluminum hydride, giving diol **23**. Treatment of diol **23** with W-2 Raney nickel under a variety of conditions resulted in destruction of the starting material. Use of various tin hydrides and Caubere "complex reducing agents"[23] also failed to provide C-Oxt-A (**2**).

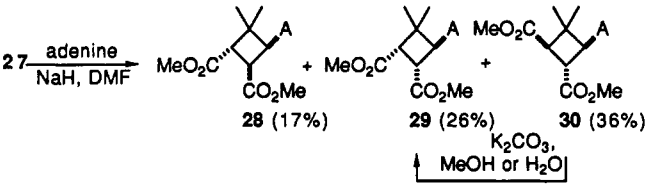
Refluxing a solution of isobutyraldehyde and pyrrolidine with azeotropic removal of water provided *N*-isobutenylpyrrolidine **24** in 73% yield after distillation. Enamine **24** was treated with dimethyl maleate to give cyclobutane **25**.[22] A quaternary salt was prepared by treatment of **25** with excess methyl iodide. Elimination of the amine salt **26** was accomplished by refluxing in methanolic sodium methoxide, affording cyclobutene **27** in 95% yield. The entire process could be carried though without isolation of intermediates in 60% overall yield from isobutyraldehyde (Scheme III).

Addition of cyclobutene **27** to a solution of sodium hydride and adenine in dimethylformamide afforded a 2.0:1.5:1.0 mixture of diastereomeric adenine products **28–30** in 79% yield after methanol recrystallization (Scheme IV). Recrystallization from water afforded pure **30** in 22% yield. The relative stereochemistry of **30** was confirmed by NOE experiments. Irradiation of the β-CH_3 group gave a 9.4% enhancement of H-2′ and a 4.1% enhancement of H-8, while irradiation of the α-CH_3 group gave a 12.9% enhancement of H-1′ and a 14.0% enhancement of H-3′.

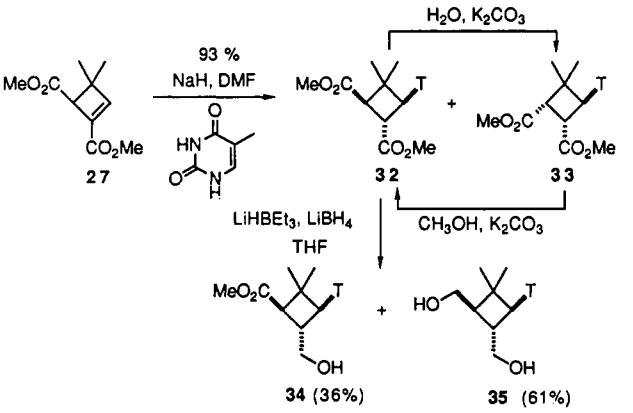
We felt from the outset of this work that we should be able to equilibrate isomers **28** and **29** into what we reasoned to be the more stable isomer **30**. Attempts at equilibration of isomeric mixtures in either methanol or water with K_2CO_3 resulted predominantly in isomer **29**; this observation may be the result of selective hydrolyses of other isomers. NOE experiments confirmed the assignment of **29**.

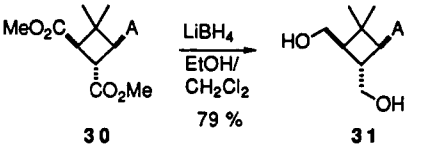
Dimethyl carbocyclic oxetanocin (**31**) was obtained by reduction of the diester **30** with lithium borohydride (eq 4). Reduction using lithium aluminum hydride or diisobutylaluminum hydride gave lower yields, due primarily to difficulty in isolating the product.

Scheme IV



Scheme V





(4)

When 1 equiv of cyclobutene **27** was combined with 0.5 equiv of sodium hydride and 1.5 equiv of thymine in dimethylformamide, a 93% yield of the two thymine adducts **32** and **33** (8.3:1.0 by NMR) was isolated (Scheme V). Partial purification was achieved by flash chromatography, giving pure **32** in 62% yield and a mixture of **32** and **33** in 31% yield. The relative stereochemistry of adduct **32** was confirmed by NOE experiments, as was the regiochemical attachment of thymine. NOE experiments also established that the addition occurred at the N-1 position exclusively. Irradiation of H-2′ gave a 6.8% enhancement of H-6, which would not be possible had the addition occurred at N-3. Pure **32** could be obtained by recrystallization from water or by equilibration in methanol with K_2CO_3. Interestingly, treatment of **32** in water with K_2CO_3 afforded predominantly the isomer **33**. This assignment was also confirmed by NOE experiments.

Reduction of the ester moieties of **32** with lithium aluminum hydride, diisobutylaluminum hydride (DIBAL), or bis(2-methoxyethoxy)aluminum hydride resulted in significant thymine ring destruction, giving only low yields of **35**. Treatment of **32** with lithium borohydride gave alcohol **34** in high yield. The outcome of prolonged reaction times was mostly compound destruction, along with low, if any, desired product. Dimethyl carbocyclic oxetanocin-T (**33**) was obtained in good yield by reduction of **32** with lithium triethylborohydride[24] combined with lithium borohydride in tetrahydrofuran.[25]

Biological Activities. Carbocyclic oxetanocin A and/or G have been reported to have activities against various viral strains including HSV-1, HSV-2, HCMV, MCMV,

(23) Caubere, P. *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 599.

(24) Brown, H. C.; Sim, S. C.; Krishnamurthy, S. *J. Org. Chem.* **1980**, *45*, 1.

(25) Brown, H. C.; Narasimhan, S. *J. Org. Chem.* **1982**, *47*, 1604.

VZV, HIV-1, and HIV-2.[7b,8] Compounds **23**, **31**, **34**, and **35** reported in this paper have been evaluated as inactive in in vitro anti-HIV screens (cell line CEM-IW) by the National Cancer Institute.

Experimental Section

Dimethyl *cis*-3-(1-Pyrrolidinyl)-5,9-dithiaspiro[3.5]nonane-*r*-1,*trans*-2-dicarboxylate (19). A solution of dimethyl maleate (2.05 mL, 16.39 mmol) in CH_3CN (45 mL) at 0 °C was treated with $BF_3{\cdot}Et_2O$ (2.02 mL, 16.39 mmol). After the solution was stirred for 10 min, 2-[(1-pyrrolidinyl)methylene]-1,3-dithiane (**18**)[26] (3.0 g, 14.90 mmol) in CH_3CN (15 mL) was added dropwise. The ice bath was removed and the reaction mixture stirred for 15 h. The reaction was quenched with aqueous $NaHCO_3$, concentrated partially by rotary evaporation, and then extracted with CH_2Cl_2 (3 × 50 mL). The combined extracts were dried ($MgSO_4$) and concentrated by rotary evaporation. Purification by flash chromatography (silica gel 10:1 then 5:1 petroleum ether/ethyl acetate) yielded cyclobutane **19** (4.06 g, 79%) as a white solid: mp 111–112 °C; IR (KBr) 2950, 2781, 1738, 1728, 1440, 1400, 1326, 1243, 1215, 1175, 1158, 1013, 946, 908, 880, 854 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.75 (s, 3 H), 3.67 (s, 3 H), 3.50–3.58 (m, 2 H), 3.35 (ddd, J_1 = 2.5 Hz, J_2 = 12 Hz, J_3 = 14 Hz, 1 H), 3.01 (dt, J_1 = 5.5 Hz, J_2 = 9 Hz, 1 H), 2.91 (ddd, J_1 = 3 Hz, J_2 = 12 Hz, J_3 = 14 Hz, 1 H), 2.47–2.75 (m, 6 H), 2.06–2.16 (m, 1 H), 1.80–1.97 (m, 1 H), 1.69–1.76 (m, 4 H); ^{13}C NMR ($CDCl_3$) δ 172.25, 169.44, 69.78, 54.71, 53.64, 51.91, 42.38, 27.22, 25.71, 25.22, 23.21; MS (EI) *m/z* (relative intensity) 346 ($M^{\cdot+}$ + H, 1.5), 201 (29.9), 155 (100), 140 (74.1); HRMS calcd for $C_{15}H_{23}NO_4S_2$ 345.1068 ($M^{\cdot+}$), 346.1147 ($M^{\cdot+}$ + H), found 346.1150. Anal. Calcd. for $C_{15}H_{23}NO_4S_2$: C, 52.15; H, 6.71. Found: C, 51.98; H, 6.73.

Another isomer which is believed to be the *trans*-3, *r*-1-*trans*-2-**20** (309 mg, 6%) was also isolated but not completely characterized.

Methyl *trans*-1-(1-Pyrrolidinyl)-5,9-dithiaspiro[3.5]nonane-2-carboxylate. To a solution of freshly distilled methyl acrylate (0.1 mL, 1.09 mmol) in CH_3CN (4 mL) at 0 °C was added $BF_3{\cdot}Et_2O$ (0.13 mL, 1.09 mmol) and then **18** (200 mg, 0.99 mmol) in CH_3CN (2 mL). The reaction was allowed to warm to ambient temperature and then stirred overnight. The reaction mixture was quenched with $NaHCO_3$ (0.5 g) and then H_2O (10 mL), extracted with CH_2Cl_2, dried ($MgSO_4$), and concentrated by rotary evaporation. Purification by flash chromatography (10:1 then 5:1 petroleum ether/EtOAc) gave the title compound as a colorless oil (213 mg, 75%) which solidified in the freezer: IR (KBr) 2951, 2825, 2792, 1735, 1437, 1376, 1352, 1315, 1280, 1243, 1213, 1213, 1158, 1036, 907 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.68 (s, 3 H), 3.30 (q, J = 11 Hz, 1 H), 3.16 (d, J = 11 Hz, 1 H), 2.79–3.01 (m, 3 H), 2.62–2.77 (m, 4 H), 2.47–2.55 (m, 2 H), 2.43 (dd, J_1 = 11Hz, J_2 = 9 Hz, 1 H), 2.05–2.17 (m, 1 H), 1.83–1.99 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 173.34, 71.25, 52.53, 51.89, 51.64, 40.41, 38.65, 28.02, 26.49, 26.36, 23.11; MS (EI) *m/z* (relative intensity) 287 ($M^{\cdot+}$, 0.8), 155, (93.2), 140 (100), 132 (30.8), 124 (25.9), (49.1), 58 (31.4); HRMS calcd for $C_{13}H_{21}NO_2S_2$ 287.1013 ($M^{\cdot+}$), found 287.1016.

Dimethyl *cis*-3-(1-Pyrrolidinyl)-5,9-dithiaspiro[3.5]nonane-r-1,*trans*-2-dicarboxylate *N*-Methiodide (21). To a solution of **19** (1.5 g, 4.34 mmol) in CH_3CN (15 mL) was added excess CH_3I (ca. 2 ML) and stirred 24 h. The reaction mixture was then concentrated by rotary evaporation and purified by column chromatography eluting with 30:1 and then 8:1 CH_2Cl_2/CH_3OH to yield amine salt **21** (1.95 g, 92%) as a yellow foam: ^1H NMR ($CDCl_3$) δ 4.59 (d, J = 10.5 Hz, 1 H), 3.97–4.26 (m, 5 H), 3.88 (s, 3 H), 3.84 (s, 3 H), 3.69 (d, J = 9.5 Hz, 1 H), 3.65 (s, 3 H), 3.39 (ddd, J^1 = 2.5 Hz, J_2 = 12 Hz, J_3 = 14.5 Hz, 1 H), 3.35 (ddd, J_1 = 3 Hz, J_2 = 12 Hz, J_3 = 15 Hz, 1 H), 2.82 (d, J = 4 Hz, 1 H), 2.77 (d, J = 4 Hz, 1 H), 2.26–2.55 (m, 4 H), 2.14–2.25 (m, 1 H), 1.86–2.02 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 169.17, 167.34, 72.66, 65.25, 65.15, 54.61, 54.31, 53.40, 52.91, 50.62, 40.37, 27.31, 26.84, 23.09, 22.43, 21.52. The salt was carried forward to the next reaction.

9-[*trans*-2,*cis*-3-Bis(methoxycarbonyl)-5,9-dithiaspiro-[3.5]non-*r*-1-yl]adenine (22). To a solution of amine salt **21** (1.564 g, 3.2 mmol) in DMF (20 mL) was added NaH (153 mg, 60%, 3.85 mmol, unwashed), and the mixture was stirred for 30 min. Adenine (650 mg, 4.8 mmol) was added to the dark green solution, which was then stirred for 5 h. The reaction mixture was diluted with CH_2Cl_2 (25 mL) and then filtered through Celite, which was subsequently washed with CH_2Cl_2. The combined filtrates were concentrated in vacuo using a Kugelrohr distillation apparatus. The brown residue was flash chromatographed (50:1 then 8:1 CH_2Cl_2/CH_3OH); first to elute was residual DMF and along with a minor adenine adduct (105 mg, 8%) followed by a mixture of three adenine adducts (1.0 g, 76%). Recrystallization of the mixture from ethanol afforded pure **22** (497 mg, 38%) as a white solid: mp starts to soften at 206 °C, melts at 214–215 °C; IR (KBr) 3464, 3316, 3160, 1740, 1726, 1659, 1599, 1580, 1474, 1441, 1422, 1368, 1333, 1244, 1213, 1011, 1005, 646 cm^{-1}; ^1H NMR ($CDCl_3/CD_3OD$) δ 8.39 (s, 1 H), 8.37 (s, 1 H), 5.61 (d, J = 10.5 Hz, 1 H), 4.26 (t, J = 10 Hz, 1 H), 3.87 (s, 3 H), 3.70 (s, 3 H), 3.49 (d, J = 10 Hz, 1 H), 2.94–3.05 (m, 1 H), 2.70 (dt, J_1 = 14 Hz, J_2 = 4 Hz, 1 H), 2.37 (dt, J_1 = 14 Hz, J_2 = 4 Hz, 1 H), 1.70–1.82 (m, 2 H), 1.29–1.40 (m, 1 H); ^{13}C NMR ($CDCl_3/CD_3OD$) δ 169.81, 168.04, 155.55, 153.10, 149.70, 118.43, 61.52, 54.84, 52.60, 48.00, 41.79, 27.67, 25.97, 22.95; NOE ($CDCl_3$) irradiation of H-1′ (δ 5.61) gave 11% enhancement of H-3′ (δ 3.49), irradiation of H-2′ (δ 4.26) gave 15% enhancement of H-8 (δ 8.37); MS (EI) *m/z* (relative intensity) 409 ($M^{\cdot+}$, 0.9), 322 (10.4), 189 (100), 158 (20.6), 129 (19.5); HRMS calcd for $C_{16}H_{19}N_5O_4S_2$ 409.0878 ($M^{\cdot+}$), found 409.0882. Anal. Calcd for $C_{16}H_{19}N_5O_4S_2$: C, 46.93; H, 4.68. Found: C, 46.80; H, 4.73.

9-[*trans*-2-*cis*-3-Bis(hydroxymethyl)-5,9-dithiaspiro-[3.5]non-*r*-1-yl]adenine (23). A solution of **22** (155 mg, 0.38 mmol) in THF (5 mL) was treated with $LiAlH_4$ (57.5 mg, 1.51 mmol) for 45 min. The reaction mixture was quenched with 1 drop of H_2O, 1 drop of 15% NaOH, and then 10 drops of H_2O, filtered through Celite, and concentrated in vacuo. Purification by flash chromatography (silica gel, 8:1 then 4:1 CH_2Cl_2/MeOH) afforded diol **23** (69 mg, 52%) as a white solid: mp 237 °C dec; IR (KBr) 3409, 3324, 3179, 1651, 1615, 1572, 1480, 1420, 1314, 1248, 1055, 1028, 729, 584 cm^{-1}; ^1H NMR (DMSO-d_6) δ 8.38 (s, 1 H), 8.22 (s, 1 H), 7.32 (br, 2 H), 5.11 (d, J 10 Hz, 1 H), 4.85 (t exc, J = 5 Hz, 1 H), 4.76 (t exc, J = 5 Hz, 1 H), 3.54–3.74 (m, 2 H), 3.42–3.53 (m, 2 H), 3.00–3.12 (m, 1 H), 2.87–3.00 (m, 1 H), 2.57–2.68 (m, 1 H), 2.26–2.44 (m, 2 H), 1.46–1.68 (m, 2 H), 1.11–1.28 (m, 1 H); ^{13}C NMR (DMSO-d_6) δ 156.04, 152.60, 149.79, 140.07, 118.69, 60.13, 58.82, 59.44, 55.28, 45.80, 42.93, 27.36, 25.05, 24.22;[27] MS (CI^+) *m/z* (relative intensity) 354 ($M^{\cdot+}$ + H, 7.2), 192 (1.5), 162 (2.0), 136 (2.7); (FAB^+) 354 ($M^{\cdot+}$ + H, 24.3), 279 (10.3), 167 (33.0), 136 (29.9). In EI HRMS the molecular ion fragments by splitting the cyclobutane ring to give intense peaks corresponding to the adenine-containing fragment $C_8H_9ON_5$ + H^+ (HRMS calcd 192.08852, found 192.0880) and the dithiane-containing fragment $C_6H_{10}OS_2$ (HRMS calcd 162.0173, found 162.0170).

Dimethyl 4,4-Dimethyl-*cis*-3-(1-pyrrolidinyl)cyclobutane-*r*-1,*trans*-2-dicarboxylate (25). A solution of *N*-isobutenylpyrrolidine (**24**)[28] (2.0 g, 15.97 mmol) in CH_3CN (2 mL) was treated with dimethyl maleate (2.5 mL, 19.97 mmol). The reaction produced a mild exoterm, and the mixture turned dark yellow orange. The solution was refluxed for 3.5 h and then concentrated by rotary evaporation. Purification by Kugelrohr apparatus gave first dimethyl fumarate (sublimed) and then cyclobutane **25** (3.7 g, 87%) as a pale yellow oil (128 °C (1 mmHg) [lit.[22] 140 °C (1.5 mm Hg)]). Only a single isomer was detected by ^1H NMR: IR (neat) 2956, 2791, 1734, 1458, 1437, 1338, 1324, 1279, 1257, 1209, 1197, 1169, 1031 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.64 (s, 3 H), 3.65 (s, 3 H), 3.19 (t, J = 9.5 Hz, 1 H), 2.73 (d, J = 10 Hz, 1 H), 2.53 (d, J = 9 Hz, 1 H), 2.30–2.44 (m, 4 H), 1.65–1.73 (m, 4 H), 1.21 (s, 3 H), 0.96 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 173.80, 171.49, 69.51, 52.31, 51.84, 51.46, 46.23, 41.55, 40.96, 29.11, 23.11, 17.53; MS (EI) *m/z* (relative intensity) 270 ($M^{\cdot+}$ + H, 5.2), 238 (14.4), 156 (65.1), 155 (93.5), 140 (100), 125 (26.6). 124 (23.3), 96 (46.6); HRMS calcd for $C_{14}H_{23}NO_4$ 269.1267 ($M^{\cdot+}$), 270.1705 ($M^{\cdot+}$

(26) Seebach, D.; Gröbel, B.-Th.; Beck, A. K.; Braun, M.; Geiss, K.-H. *Angew. Chem., Int. Ed. Engl.* **1972**, *11*, 443.

(27) The chemical shifts in ^{13}C NMR of the adenyl carbons (five lines at highest field) compare quite favorably with those reported for other N-9 cyclobutyl derivatives, for example, see ref 7b.

(28) Benzing, E. *Angew Chem.* **1959**, *71*, 521. Mannich, C.; Davidsen, H. *Chem. Ber.* **1936**, *69*, 2106.

+ H), found 270.1708.

Dimethyl 4,4-Dimethyl-2-cyclobutene-1,2-dicarboxylate (27). A solution of cyclobutane **25** (30 g, 237 mmol) in CH_3CN (30 mL) was treated with CH_3I (35 mL) in the dark for 2 h. The reaction was concentrated to yield the crude amine salt **26** (97 g, 99%) as a yellow foam/gum. The salt could be purified by flash chromatography (30:1 then 8:1 CH_2Cl_2/CH_3OH), but was generally used crude: ^1H NMR ($CDCl_3$) δ 4.28 (d, J = 10.5 Hz, 1 H), 3.47–3.72 (m including 2 CH_3's, 11 H), 3.08 (s, 3 H), 2.71 (d, J = 9.5 Hz, 1 H), 1.98–22.4 (m, 4 H), 1.40 (s, 3 H), 1.14 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 169.86, 168.97, 71.76, 64.13, 62.23, 52.71, 52.12, 48.10, 44.98, 44.53, 39.17, 29.25, 21.36, 20.37, 18.75. The amine salt **26** (24 g, 58.4 mmol) was taken up in CH_3OH (200 mL) and treated with $NaOCH_3$ (9.5 g, 175.1 mmol) at reflux for 10 h. The cooled reaction mixture was poured into saturated NH_4Cl solution, diluted with H_2O, and extracted with diethyl ether (2 × 200 mL). The ethereal extracts were dried over $MgSO_4$ and concentrated by rotary evaporation to yield a yellow oil. Kugelrohr distillation (90–95 °C (0.05 mmHg)) afforded cyclobutene **27** (11 g, 95%) as a colorless oil: IR (neat) 2957, 1728, 1437, 1342, 1311, 1289, 1264, 1214, 1163, 1114, 1033, 775 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.86 (s, 1 H), 3.67 (s, 3 H), 3.63 (s, 3 H), 3.39 (s, 1 H), 1.28 (s, 3 H), 1.08 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 171.04, 162.16, 155.35, 132.70, 54.54, 51.43, 51.35, 45.24, 26.03, 21.07; MS (EI) m/z (relative intensity) 198 ($M^{\bullet+}$, 2.7), 167 (25.6), 166 (21.9), 139 (23.2), 138 (100) 110 (29.8), 79, (57.2), 59 (26.2); HRMS calcd for $C_{10}H_{14}O_4$ 198.0892 ($M^{\bullet+}$), found 198.0890.

9-[4,4-Dimethyl-*trans*-2,*cis*-3-bis(methoxycarbonyl)cyclobut-*r*-1-yl]adenine (30). NaH (182 mg, 60% in oil, 4.5 mmol) was added to an Ar purged round-bottomed flask and washed with pentane (2 × 1 mL) under Ar. DMF (20 mL) and adenine (3.068 g, 22.7 mmol) were added. After 10 min cyclobutene **27** (3 g, 15.1 mmol) in DMF (4 mL) was added and the reaction mixture was stirred at room temperature for 9 h. The reaction was quenched with solid NH_4Cl (0.5 g), diluted with CH_2Cl_2 (30 mL), and filtered through Celite. The filtrate was concentrated to a yellow gum in vacuo. The residue was flash chromatographed (50:1 then 8:1 CH_2Cl_2/CH_3OH) to remove the remaining DMF and polar products and then recrystallized from CH_3OH to yield the adenine adduct (4 g, 79%) as a mixture of isomers (2:1.5:1/**30**:**29**:**28**). Recrystallization from H_2O afforded pure **30** (1.1 g, 22%) as a white solid: mp milky gum at 145–147 °C then completely melts at 190–191 °C; IR (KBr) 3443, 3324, 3177, 3122, 2957, 1739, 1726, 1653, 1599, 1475, 1438, 1331, 1282, 1259, 1216, 729 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.33 (s, 1 H), 7.94 (s, 1 H), 5.95 (br, 2 H), 4.83 (d, J = 10 Hz, 1 H), 4.26 (t, J = 10 Hz, 1 H), 3.74 (s, 3 H), 3.68 (s, 3 H), 3.08 (d, J = 9.5 Hz, 1 H), 1.53 (s, 3 H), 0.76 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 170.72, 171.28, 155.83, 152.95, 150.28, 138.68, 119.61, 57.39, 52.35, 51.98, 45.66, 43.71, 39.39, 28.48, 17.20; NOE ($CDCl_3$) irradiation of β-CH_3 (δ 0.76) gave 9.4% enhancement of H-2′ (δ 4.26) and 4.1% enhancement of H-8 (δ 7.94), irradiation of α-CH_3 (δ 1.53) gave 12.9% enhancement of H-1′ (δ 4.83) and 14.0% enhancement of H-3′ (δ 3.08); MS (EI) m/z (relative intensity) 333 ($M^{\bullet+}$, 55.2), 302 (44.6), 274 (61.6), 219 (97.1), 204 (100), 188 (52.8), 161 (61.3), 135 (78.6); HRMS calcd for $C_{15}H_{19}N_5O_4$ 333.1437 ($M^{\bullet+}$), found 333.1438. Anal. Calcd for $C_{15}H_{19}N_5O_4$: C, 54.05; H, 5.74; N, 21.01. Found: C, 54.14; H, 5.62; N, 20.98.

Attempts at equilibration of isomeric mixtures in either MeOH or H_2O with K_2CO_3 resulted in the formation of isomer **29** predominately: ^1H NMR ($CDCl_3$) δ 8.22 (s, 1 H), 7.79 (s, 1 H), 6.98 (br, 2 H), 5.16 (d, J = 10 Hz, 1 H), 4.71 (t, J = 10 Hz, 1 H), 3.67 (s, 3 H), 3.59 (s, 3 H), 3.18 (d, J = 10 Hz, 1 H), 1.19 (s, 3 H), 0.98 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 171.72, 171.20, 155.92, 152.57, 150.51, 139.34, 119.79, 58.38, 53.24, 51.83, 51.70, 48.36, 42.28, 38.82, 23.68, 23.01; NOE ($CDCl_3$) irradiation of β-CH_3 (δ 0.98) gave a 3.2% enhancement of H-3′ (δ 3.18) and a 3.1% enhancement of H-2′ (δ 4.71), irradiation of CH_3 (δ 1.19) gave a 4.3% enhancement of H-1′ (δ 5.16). The other remaining isomer present in the crude reaction mixture was the isomer **28**: ^1H NMR ($CDCl_3$) δ 8.29 (s, 1 H), 7.76 (s, 1 H), 5.22 (d, J = 10.5 Hz, 1 H), 4.36 (t, J = 10 Hz, 1 H), 3.13 (d, J = 9.5 Hz, 1 H), 1.65 (s, 3 H), 0.74 (s, 3 H).

9-[4,4-Dimethyl-*trans*-2,*cis*-3-bis(hydroxymethyl)cyclobut-*r*-1-yl]adenine (31). A solution of cyclobutane **30** (500 mg, 1.5 mmol) in $EtOH/CH_2Cl_2$ (15 mL, 2:1) at 0 °C was treated with $LiBH_4$ (490 mg, 22.5 mmol). After 2.5 h the reaction was quenched with acetone and then 2 N HCl (15 mL) to give a homogeneous solution. The pH was adjusted to 7 with 6 N NaOH, combined with silica gel (~1 g) and concentrated in vacuo. The resultant white powder was applied to the top of a silica gel column packed with 8:1 CH_2Cl_2/CH_3OH as eluant. Flash chromatography yielded **31** contaminated with LiCl. The mixture was taken up in H_2O and purified via a Sephadex (DEAE A-25) column using water as eluent. The fractions containing product were pooled and lyophilized to afford **31** (308 mg, 74%) as a hygroscopic white foam: IR (KBr) 3326, 3198, 2955, 2929, 2866, 1646, 1600, 1572, 1476, 1413, 1371, 1331, 1309, 1253, 1218, 1059, 1015, 799, 724 cm^{-1}; ^1H NMR (CD_3OD) δ 8.26 (s, 1 H), 8.18 (s, 1 H), 4.49 (d, J = 9.5 Hz, 1 H), 3.62–3.76 (m, 4 H), 2.95–3.07 (m, 1 H), 1.99 (dt, J = 8 Hz, 1 H), 1.36 (s, 3 H), 0.78 (s, 3 H); ^{13}C NMR (CD_3OD δ 157.15, 153.65, 151.30, 141.56, 120.21, 63.56, 62.29, 58.97, 44.87, 42.45, 42.25, 29.90, 16.91;[27] MS (EI) m/z (relative intensity) 277 ($M^{\bullet+}$, 14.1), 246 (19.0), 191 (84.2), 190 (50.1), 162 (49.9), 135 (56.3), 135 (100), 69 (42.0), 44 (63.6); MS (FAB^+) m/z (relative intensity) 278 ($M^{\bullet+}$ + H, 93.7), 136 (93.5); HRMS calcd for $C_{13}H_{19}N_5O_2$ 277.1539 ($M^{\bullet+}$), found 277.1536.

9-[4,4-Dimethyl-*trans*-2,*cis*-3-bis(methoxycarbonyl)cyclobut-*r*-1-yl]thymine (32). A slurry of thymine (954 mg, 7.57 mmol) in DMF (10 mL) was treated with NaH (40 mg, 60% in oil, 1.01 mmol). After the cessation of bubbling, cyclobutene **27** (1.0 g, 5.04 mmol) in DMF (5 mL) was added to the reaction mixture, stirred 5 h, and then quenched with $NH_4Cl_{(s)}$ (100 mg, 1.9 mmol). The now homogeneous solution was concentrated by Kugelrohr distillation and purified by flash chromatography (3:1 then 1:1 petroleum ether/EtOAc) affording pure **32** (1.02 g, 62%) as a white solid: mp softens at 176 °C, melts at 184–185 °C; IR (KBr) 3429, 3178, 3051, 2956, 1744, 1721, 1697, 1689, 1466, 1438, 1373, 1298, 1275, 1230, 1206, 1090, 791, 759 cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.44 (br, 1 H), 7.23 (s, 1 H), 4.64 (d, J = 10.5 Hz, 1 H), 3.83 (t, J = 10 Hz, 1 H), 3.76 (s, 3 H), 3.74 (s, 3 H), 2.97 (d, J = 9.5 Hz, 1 H), 1.97 (s, 3 H), 1.46 (s, 3 H), 0.84 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 171.02, 170.98, 163.83, 151.27, 136.51, 110.21, 59.82, 52.56, 52.16, 45.10, 44.03, 38.50, 28.94, 17.00, 12.63; NOE ($CDCl_3$) irradiation of β-CH_3 (δ 1.5) gave 4.5% enhancement of H-3′ (δ 2.97) and 4.0% enhancement of H-1′ (δ 4.64), irradiation of α-CH_3 (δ 1.97) gave 1.3% enhancement of H-2′ (δ 3.83), irradiation of H-2′ (δ 3.83) gave 6.8% enhancement of H-6 (δ 7.23), confirming that addition occurs with N-1 rather than N-3; MS (EI) m/z (relative intensity) 324 ($M^{\bullet+}$, 6.8), 293 (11.7), 210 (100), 180 (6.7), 151 (68.1), 59 (21.3); HRMS calcd for $C_{15}H_{20}N_2O_6$ 324.1321 ($M^{\bullet+}$), found 324.1322. Anal. Calcd. for $C_{15}H_{20}N_2O_6$: C, 55.55; H, 6.22; N, 8.64. Found: C, 55.59; H, 6.15; N, 8.64.

A mixture of **32** and the isomer **33** (500 mg, 2:1 ratio **32**:**33**) was also isolated giving an overall yield of 93% for the thymine addition. Pure **32** could be obtained by recrystallization from H_2O or by equilibration. A solution of **32** and **33** (500 mg) in CH_3OH was treated with K_2CO_3, refluxed for 24 h, and concentrated by rotary acetone and then 2 N HCl (15 mL) to give a homogeneous solution. The pH was adjusted to 7 with 6 N NaOH, combined with silica gel (~1 g) and concentrated in vacuo. The resultant white powder was applied to the top of a silica gel column packed with 8:1 CH_2Cl_2/CH_3OH as eluant. Flash chromatography yielded **31** contaminated with LiCl. The mixture was taken up in H_2O and purified via a Sephadex (DEAE A-25) column using water as eluent. The fractions containing product were pooled and lyophilized to afford **31** (308 mg, 74%) as a hygroscopic white foam: IR (KBr) 3326, 3198, 2955, 2929, 2866, 1646, 1600, 1572, 1476, 1413, 1371, 1331, 1309, 1253, 1218, 1059, 1015, 1015, 799, 724 cm^{-1}; ^1H NMR (CD_3OD) δ 8.26 (s, 1 H), 8.18 (s, 1 H), 4.49 (d, J = 9.5 Hz, 1 H), 3.62–3.76 (m, 4 H), 2.95–3.07 (m, 1 H), 1.99 (dt, J = 8 Hz, 1 H), 1.36 (s, 3 H), 0.78 (s, 3 H); ^{13}C NMR (CD_3OD) δ 157.15, 153.65, 151.30, 141.56, 120.21, 63.56, 62.29, 58.97, 44.87, 42.45, 29.90, 16.91;[27] MS (EI) m/z (relative intensity) 277 ($M^{\bullet+}$, 14.1), 246 (19.0), 191 (84.2); 190 (50.1), 162 (49.9), 135 (56.3), 135 (100), 69 (42.0), 44 (63.6); MS (FAB^+) m/z (relative intensity) 278 ($M^{\bullet+}$ + H, 93.7), 136 (93.5); HRMS calcd for $C_{13}H_{19}N_5O_2$ 277.1539 ($M^{\bullet+}$), found 277.1536.

9-[4,4-Dimethyl-*trans*-2,*cis*-3-bis(methoxycarbonyl)cyclobut-*r*-1-yl]thymine (32). A slurry of thymine (954 mg, 7.57 mmol) in DMF (10 mL) was treated with NaH (40 mg, 60% in oil, 1.01 mmol). After the cessation of bubbling, cyclobutene **27** (1.0 g, 5.04 mmol) in DMF (5 mL) was added to the reaction

mixture, stirred 5 h, and then quenched with $NH_4Cl_{(s)}$ (100 mg, 1.9 mmol). The now homogeneous solution was concentrated by Kugelrohr distillation and purified by flash chromatography (3:1 then 1:1 petroleum ether/EtOAc) affording pure **32** (1.02 g, 62%) as a white solid: mp softens at 176 °C, at 184–185 °C; IR (KBr) 3429, 3178, 3051, 2956, 1744, 1721, 1697, 1689, 1466, 1438, 1373, 1298, 1275, 1230, 1206, 1090, 791, 759 cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.44 (br, 1 H), 7.23 (s, 1 H), 4.64 (d, J = 10.5 Hz, 1 H), 3.83 (t, J = 10 Hz, 1 H), 3.76 (s, 3 H), 3.74 (s, 3 H), 2.97 (d, J = 9.5 Hz, 1 H), 1.97 (s, 3 H), 1.46 (s, 3 H), 0.84 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 171.02, 170.98, 163.83, 151.27, 136.51, 110.21, 59.82, 52.56, 52.16, 45.10, 44.03, 38.50, 28.94, 17.00, 12.63; NOE ($CDCl_3$) irradiation of β-CH_3 (δ 1.5) gave 4.5% enhancement of H-3′ (δ 2.97) and 4.0% enhancement of H-1′ (δ 4.64), irradiation of α-CH_3 (δ 1.97) gave 1.3% enhancement of H-2′ (δ 3.83), irradiation of H-2′ (δ 3.83) gave 6.8% enhancement of H-6 (δ 7.23), confirming that addition occurs with N-1 rather than N-3; MS (EI) m/z (relative intensity) 324 ($M^{\bullet+}$, 6.8), 293 (11.7), 210 (100), 180 (6.7), 151 (68.1), 59 (21.3); HRMS calcd for $C_{15}H_{20}N_2O_6$ 324.1321 ($M^{\bullet+}$), found 324.1322. Anal. Calcd for $C_{15}H_{20}N_2O_6$: C, 55.55; H, 6.22; N, 8.64. Found: C, 55.59; H, 6.15; N, 8.64.

A mixture of **32** and the isomer **33** (500 mg, 2:1 ratio **32:33**) was also isolated giving an overall yield of 93% for the thymine addition. Pure **32** could be obtained by recrystallization from H_2O or by equilibration. A solution of **32** and **33** (500 mg) in CH_3OH was treated with K_2CO_3, refluxed for 24 h, and concentrated by rotary evaporation. The residue was taken up in H_2O and extracted with CH_2Cl_2, dried ($MgSO_4$), and concentrated by rotary evaporation to afford **32** (251 mg, 50%) as a white solid. Equilibration in H_2O/K_2CO_3, however, gave the isomer **33**. A mixture of **32** and **33** (1.02 g, 3.14 mmol) in H_2O (50 mL) and K_2CO_3 (~300 mg) was refluxed for 36 h. Upon cooling, fine, white crystals precipitated and were filtered off giving pure **33** (382 mg, 37%): ^1H NMR ($CDCl_3$) δ 9.01 (br, 1 H), 6.97 (s, 1 H), 4.98 (d, J = 10 Hz, 1 H), 3.83 (t, J = 10 Hz, 1 H), 3.11 (d, J = 10 Hz, 1 H), 1.93 (s, 3 H), 1.24 (s, 3 H), 1.14 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 171.62, 171.02, 163.73, 151.12, 137.03, 110.14, 60.68, 52.26, 51.98, 48.14, 42.40, 38.91, 24.36, 22.85, 12.61; NOE ($CDCl_3$) irradiation of β-CH_3 (δ 1.14) gave 3.5% enhancement of H-3′ (δ 3.11) and 1.8% enhancement of H-2′ (δ 3.38), irradiation of α-CH_3 gave 2.8% enhancement of H-1′ (δ 4.98).

9-[4,4-Dimethyl-*trans*-2,*cis*-3-bis(hydroxymethyl)cyclobut-*r*-1-yl]thymine (Dimethyl-C-Oxt-T) (35). To a solution of $LiBEt_3H_{24}$ (0.18 mmol) in THF (5 mL) was added $LiBH_4$ (101 mg, 4.62 mmol) and then diester **32** (300 mg, 0.92 mmol).[25] After stirring 24 h 0.3 mmol more $LiBEt_3H$ was added, and the reaction mixture stirred 24 h longer. The reaction was quenched with acetone and then 1 M H_2SO_4 (2 mL). The pH of the solution was adjusted to 7 with 6 N NaOH, combined with silica gel (1 g) and concentrated in vacuo. The white solid was applied to a silica gel column packed with 30:1 CH_2Cl_2/CH_3OH, and eluted with 30:1 then 15:1 then 8:1 CH_2Cl_2/CH_3OH to yield **35** (163 mg, 61%) as a white solid: mp 224–225 °C; IR (KBr) 3356, 3093, 3033, 2958, 2926, 2869, 1688, 1654, 1474, 1390, 1296, 1286, 1065, 1022 cm^{-1}; ^1H NMR (CD_3OD) δ 7.55 (s, 1 H), 4.20 (d, J = 10 Hz, 1 H), 3.55–3.69 (m, 4 H), 2.58–2.73 (m, 1 H), 1.88 (s, 3 H), 1.79 (dt, J_1 = 9 Hz, J_2 = 7.5 Hz, 1 H), 1.27 (s, 3 H), 0.86 (s, 3 H); ^{13}C NMR (CD_3OD) δ 153.45, 140.22, 109.84, 63.97, 62.24, 61.84, 44.46, 42.67, 41.29, 16.66, 12.39; MS (FAB$^+$) m/z (relative intensity) 269 ($M^{\bullet+}$ + 61.7), 126 (26.8). Anal. Calcd for $C_{13}H_{20}N_2O_4$: C, 58.19; H, 7.51; N, 10.44. Found: C, 58.37; H, 7.71; N, 10.37.

Also isolated was monoester **34** (105 mg, 36%): mp 189–190 °C; IR (KBr) 3490, 3397, 3159, 3032, 2959, 1732, 1715, 1693, 1652, 1479, 1464, 1438, 1369, 1298, 1272, 1243, 1220, 1152, 1003, 907, 874, 762 cm^{-1}; ^1H NMR (CD_3OD) δ 7.59 (s, 1 H), 4.34 (d, J = 10 Hz, 1 H), 3.69 (s, 3 H), 3.65/3.56 (AB of ABX, J_{AB} = 12 Hz, J_{AX} = 4 Hz, J_{BX} = 5.5 Hz, 2 H), 3.20–3.30 (m, J = 5 Hz, 1 H), 2.59 (d, J = 10 Hz, 1 H), 1.89 (s, 3 H), 1.36 (s, 3 H), 0.81 (s, 3 H); ^{13}C NMR (CD_3OD) δ 173.68, 139.93, 110.24, 62.14, 60.45, 52.11, 45.09, 44.84, 39.21, 29.47, 17.63, 12.34; MS (EI) m/z (relative intensity) 296 ($M^{\bullet+}$, 2.0), 265 (3.6), 182 (26.7), 153 (7.8), 127 (17.0), 126 (100); HRMS calcd for $C_{14}H_{23}N_2O_5$ 296.1372, found 296.1368.

Acknowledgment. This work was supported by a grant from the National Cancer Institute (CA37806).

Photoinduced Molecular Transformations. 128.[1] Regioselective [2 + 2] Photocycloaddition of 3-Acetoxyquinolin-2(1*H*)-one with Alkenes and Formation of Furo[2,3-*c*]quinolin-4(5*H*)-ones, 1-Benzazocine-2,3-diones, and Cyclopropa[*d*]benz[1]azepine-2,3-diones via a β-Scission of Cyclobutanoxyl Radicals Generated from the Resulting [2 + 2] Photoadducts

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Received August 7, 1991

We have found that [2 + 2]π photoadducts can be obtained by the photoaddition of 3-acetoxyquinolin-2(1*H*)-one with acyclic and cyclic alkenes. The photoaddition of 3-acetoxy-2-quinolin-2(1*H*)-one with 2-methylpropene, 2,3-dimethyl-2-butene, and 2-methoxypropene thus afforded regioselective head-to-tail adducts in 59–97% yields. The photoaddition of 3-acetoxy-2-quinolin-2(1*H*)-one with cyclopentene and cyclohexene resulted in the formation of sterically disfavored cis-cisoid-cis photoadducts as the major products, with the accompanying formation of cis-transoid-cis photoadducts as the minor products in combined yields of 87 and 66%, respectively. The photolysis of the hypoiodites generated in situ from cyclobutanols derived from all of the photoadducts induced β-scissions at the outer bonds of the corresponding cyclobutanoxyl radicals to give furo[2,3-*c*]quinolin-4(5*H*)-ones in 15–50% yields with an accompanying formation of 7- and 8-membered lactams arising from β-scissions at the catacondensed bonds of the cyclobutanoxyl radicals in 2–62% yields. The molecular structure of one of the novel 7-membered lactams that successively fused with cyclopropane and cyclopentane rings was established to be *trans*-5,8,9,10,10a,10b-hexahydro-5-methylcyclopenta[3,4]cyclopropa[1,2-*d*]benzazepine-6,7-dione by X-ray crystallographic analysis. The pathways leading to the formation of all of these products arising from β-scissions are discussed.

In previous papers,[2,3] we reported that the [2 + 2] photoaddition of an alkene to an enolyzed 1,3-dicarbonyl compound or its acetate to form β-ketocyclobutanol or its acetate, followed by a regioselective β-scission of the cy-

0022-3263/92/1957-0599$03.00/0