Stereocontrolled Conversion of 1-(3-Hydroxyprop-1-enyl)uracil isomers into Polyfunctional 3,9-Propano- and 3,9(9,3)-Propeno-aza-9*H*-xanthines

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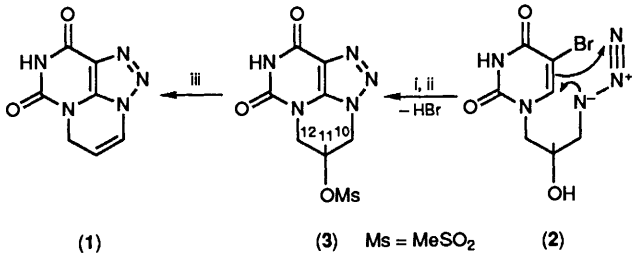
With 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), 1-(3-azido- (**6**) and 1-(3-trityloxy-2- methylsulphonyloxypropyl)-3-methyluracil (**12**) underwent elimination to give the respective *E*- and *Z*-prop-1'-enyl isomers. Treatment of (*E*)- (**15**) and (*Z*)- (**16**) 1-(3-hydroxyprop-1-enyl)-3-methyluracil with Br_2–MeOH generated asymmetric centres at C-1' and C-2', providing *threo*- (**17**) and *erythro*- (**18**) 5-bromo-1-(2-bromo-3-hydroxy-1-methoxypropyl)-3-methyluracil. Conversion of compound (**17**) and (**18**) into *erythro*- (**19**) and *threo*- (**20**) 5-bromo-1-(2,3-epoxy-1-methoxypropyl)-3-methyluracil was accomplished under mild DBU-elimination conditions. The reaction of the diastereoisomeric epoxides (**19**) and (**20**) with NaN_3–DMF produced the respective *erythro*- (**21**) and *threo*- (**22**) 1-(3-azido-2-hydroxy-1-methoxypropyl)-3-methyluracil. These isomers underwent two types of intramolecular cyclisation reaction, which gave *trans*- (**23**) and *cis*- (**24**) 2-azidomethyl-3-methoxy-6-methyl-2,3-dihydro-oxazolo[3,2-*c*]pyrimidine-5,7-dione and *cis*- (**25**) and *trans*- (**26**) 11-hydroxy-12-methoxy-1-methyl-3,9-propano-8-aza-9*H*-xanthine. The elimination reaction of 12-methoxy-1-methyl-11-methylsulphonyloxy-3,9-propano-8-aza-9*H*-xanthine (**29**) by DBU led to formation of 12-methoxy-1-methyl-9,3-propeno-8-aza-9*H*-xanthine (**30**). Its 3,9-propeno isomer (**33**) was obtained from a DBU-elimination of 11-bromo-10-methoxy-1-methyl-3,9-propano-8-aza-9*H*-xanthine (**32**). The 9,3-propeno compound (**30**) was also converted into 11-bromo-10,12-dimethoxy-1-methyl-3,9-propano-8-aza-9*H*-xanthine (**34**) on treatment with Br_2–MeOH.

Interest in the azapurines dates back to the discovery of the antibacterial and antitumour activity of 8-azaguanine.[1] In continuing our studies on the selective formation of 9,3-propeno-8-aza-9*H*-xanthine[2] (**1**) we have considered the synthesis of the corresponding 3,9-propeno isomer. Whereas the formation of the 9,3-propeno compound (**1**) was derived *via* an intramolecular C-5, C-6 cycloaddition of 1-(3-azido-2-hydroxypropyl)-5-bromouracil (**2**) and subsequent regiospecific elimination of the intermediate, 11-methylsulphonyloxy-3,9-propano-8-aza-xanthine (**3**), we thought that 1-(3-azidoprop-1-enyl)uracil with the preformed double bond and proper geometry could faciliatate formation of the hitherto unknown 3,9-propeno-8-aza-9*H*-xanthine isomer. Based on previously established chemistry of the 9,3-propeno compounds[2] of type (**1**) we also extended our studies of the Br_2–MeOH addition reactions to the prop-1'-enylic compounds. The thus obtained 3'-azido-2'-bromo-1'-methoxypropyl diastereoisomers enabled us to perform the synthesis of the stereochemically defined dihydro-oxazolo[3,2-*c*]pyrimidine-5,7(6*H*)-diones by *anti*-cyclisation reactions, and that of 3,9-propano-8-aza-9*H*-xanthine derivatives by intramolecular cycloaddition.



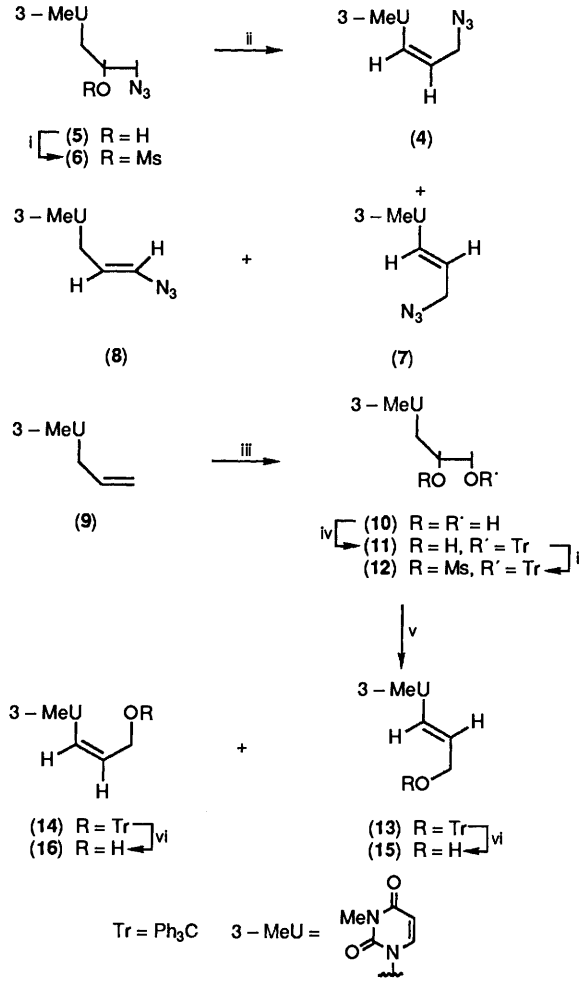
Scheme 1. *Reagents and conditions:*[2] i, DMF, 115 °C; ii, MsCl, py; iii, DBU, DMF.

Results and Discussion

Aiming to extend our synthesis of 9,3-propeno- (**1**) and 3,9-propano-(**3**) 8-aza-9*H*-xanthine compounds[2] (Scheme 1), we envisaged a route to (*Z*)-1-(3-azidoprop-1-enyl)-3-methyluracil (**4**) (Scheme 2) which, being N-3 protected,[3] called for an intramolecular C-5, C-6 cycloaddition and the formation of the hitherto unknown 3,9-propeno-8-aza-9*H*-xanthine. To evaluate this synthetic approach 1-(3-azido-2-hydroxypropyl)uracil[4] was first methylated to give 1-(3-azido-2-hydroxypropyl)-3-methyluracil (**5**) (87%), which was then mesylated to give 1-(3-azido-2-methylsulphonyloxypropyl)-3-methyluracil (**6**) (89%). The DBU-elimination[5] of the latter in dimethylformamide (DMF) generated a mixture of isomeric products, in 64% combined yield. As a consequence of C-1', C-2' elimination (*E*)-1-(3-azidoprop-1-enyl)-3-methyluracil (**7**) (29.4%), R_F 0.32; m.p. 87 °C, and the *Z*-isomer (**4**) (25.2%), R_F 0.33; m.p. 95 °C, were isolated as the major products. The structure of the *E*-isomer was established by ^{1}H NMR analysis, showing the characteristic signals for the *trans*-ethylenic C-1' and C-2' protons at δ_H 6.28 (*J* 13.4 Hz) and 5.41 (*J* 13.4, 7.3 Hz), respectively, and those of C-3' at δ_H 4.34 (*J* 7.3 Hz). The ^{1}H NMR spectrum of (*Z*)-1-(3-azidoprop-1-enyl)-3-methyluracil (**4**) exhibited the signals of the *cis*-ethylenic C-1' and C-2' protons at δ_H 6.48 (*J* 7.3 Hz) and 5.06 (*J* 7.3, 7.1 Hz), and those of C-3' at δ_H 4.38 (*J* 7.1 Hz).

The isomer with R_f 0.38, isolated from the above reaction in the lowest yield, was identified as (*E*)-1-(3-azidoprop-2-enyl)-3-methyluracil (**8**) as a consequence of C-2', C-3' elimination. This isomer exhibited signals in the ^{1}H NMR spectrum at δ_H 7.27 and 5.68 (*J* 14.4, 7.0 Hz), revealing the *trans*-oriented C-2', C-3' protons. The geminal C-1' protons appeared at δ_H 3.95 (*J* 7.0 Hz).

All our attempts to initiate the intramolecular addition of the 1,3-dipolar azido group of (*Z*)-1-(3-azidoprop-1-enyl)-3-methyluracil (**4**) by established methods[6–8] led to decomposition and very low yields of the desired 8-azaxanthine compound.



Scheme 2. *Reagents and conditions:* i, MsCl, py; ii, DBU, DMF, 100 °C; iii, 3.5% $KMnO_4$–water; iv, TrCl, py; v, DBU, benzene; vi, 80% AcOH, 100 °C.

Full details of the intramolecular reactions with compound (**4**) remain to be examined, in particular the optimization of the yields of the cycloaddition products. In order to overcome these problems, we envisaged transformation of the prop-1′-enyl moiety of compound (**4**) into a flexible and properly functionalised propyl structure. Thus $KMnO_4$ oxidation[4] of 1-allyl-3-methyluracil[9,10] (**9**) and selective tritylation of the 1-(2,3-dihydroxypropyl)-3-methyluracil[3] (**10**) thus produced gave 1-(2-hydroxy-3-trityloxypropyl)-3-methyluracil (**11**) (97%). The latter was then mesylated to give 3-methyl-1-(2-methylsulphonyloxy-3-trityloxypropyl)uracil (**12**) in 89% yield (Scheme 2).

In contrast to the DBU-elimination of the 3′-azido-2′-mesyloxy compound (**6**), analogous treatment of the 2′-mesyloxy-3′-trityloxy derivative (**12**) led to selective formation of crystalline (*E*)-3-methyl-1-(3-trityloxyprop-1-enyl)uracil (**13**) (61.7%), due to the acidity of the C-1′ proton generating only the C-1′, C-2′ double bond, and also due to the bulk of the trityl group blocking formation of the *Z*-isomer (**14**). A mixture of (*E*)-(**13**) and (*Z*)- (**14**) 3-methyl-1-(3-trityloxyprop-1-enyl)uracil (7.9%) was isolated from the methanolic mother liquor, as evidenced by ^1H NMR spectral data (see Experimental section). From the same mother liquor 1-(2-hydroxy-3-trityloxypropyl)-3-methyluracil (**11**) was isolated in 13% yield.

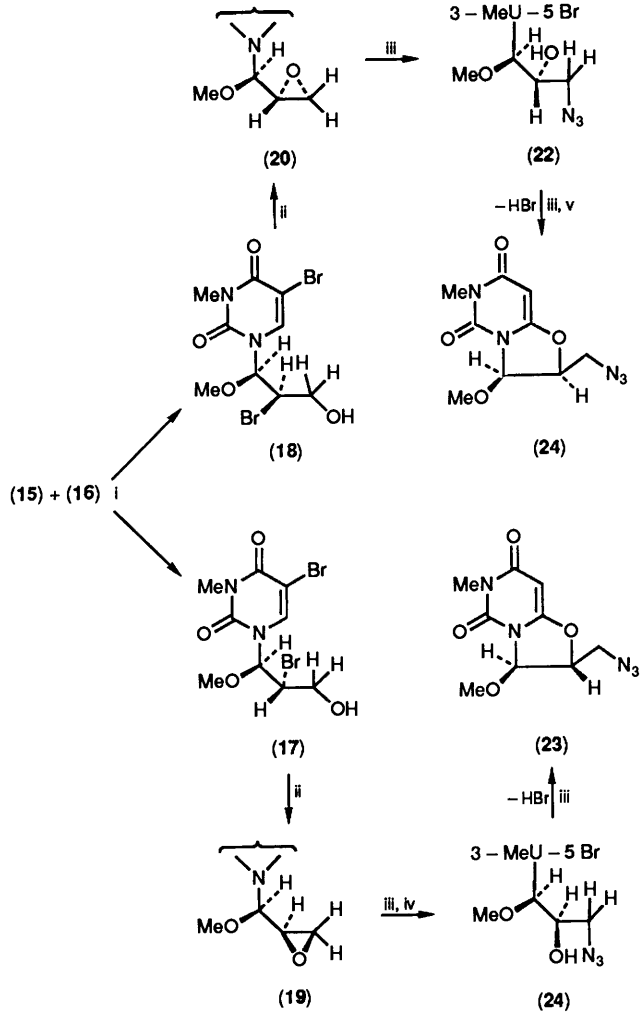
Detritylation of the *E*-3′-trityloxypropenyl isomer (**13**) with 80% acetic acid at 100 °C afforded (*E*)-1-(3-hydroxyprop-1-enyl)-3-methyluracil (**15**) in nearly quantitative yield. The structural assignment was based on comparisons of the ^1H NMR shifts of the C-1,[1] and C-2′, and C-3′ protons with those of the *E*-compound (**7**). In particular, the *trans*-relationship of the C-1′ and C-2′ protons was established (*J* 14.4 Hz).

With the hope of separating the *Z*-3′-trityloxyprop-1′-enyl isomer (**14**) from the above mentioned mixture, both isomers were first detritylated to a mixture of (*E*)- (**15**) and (*Z*)- (**16**) 1-(3-hydroxyprop-1-enyl)-3-methyluracil. The methanolic solution of the resulting mixture was then treated with bromine to give *threo*-5-bromo-1-(2-bromo-3-hydroxy-1-methoxypropyl)-3-methyluracil (**17**), R_F 0.43 (43%), and *erythro*-5-bromo-1-(2-bromo-3-hydroxy-1-methoxypropyl)-3-methyluracil (**18**), R_F 0.6 (12.3%) as the separable products (Scheme 3). The methoxide ion, as a stronger nucleophile than the bromide ion,[11,12] facilitated stereoselective formation of 1′-methoxy compounds (**17**) and (**18**), most probably *via* intermediacy of the diastereoisomeric cyclic bromium ions. It is worth noting that the *erythro*-diastereoisomer (**18**) was independently prepared from (*E*)-1-(3-hydroxyprop-1-enyl)-3-methyluracil (**15**) in good yield. The stereochemical features of the *threo*- (**17**) and *erythro*- (**18**) diastereoisomers were assigned on the basis of their ^1H spectral data, in particular by comparison with data from bicyclic and tricyclic structures (*vide infra*).

The stereoisomerism of compounds (**17**) and (**18**) rendered possible the intramolecular nucleophilic displacement of the neighbouring bromine by the hydroxy group to produce the respective 2′,3′-epoxy structures with inversion of the C-2′ configuration. Thus, the *threo*-2′-bromo-3′-hydroxypropyl diastereoisomer (**17**) in a reaction with DBU afforded *erythro*-5-bromo-1-(2,3-epoxy-1-methoxypropyl)-3-methyluracil (**19**), m.p. 95–96 °C (60%). The *erythro*-2′-bromo-3′-hydroxypropyl diastereoisomer (**18**), being analogously treated, was converted into *threo*-5-bromo-1-(2,3-epoxy-1-methoxypropyl)-3-methyluracil (**20**), m.p. 182–183 °C (86%). The ^1H NMR spectra of these epoxy compounds are summarised in the Experimental section.

Nucleophilic attack at the 2′,3′-epoxide of compounds (**19**) and (**20**) with sodium azide in DMF at room temperature produced the desired *erythro*-1-(3-azido-2-hydroxy-1-methoxypropyl)-5-bromo-3-methyluracil (**21**), R_f 0.6 (39%), and *threo*-1-(3-azido-2-hydroxy-1-methoxypropyl)-5-bromo-3-methyluracil (**22**), R_f 0.6 (50%), respectively. These azido compounds can be considered as the key intermediates in both the intramolecular *anti*-C-6–O–C-2′ cyclisation reactions to give the dihydro-oxazolo[3,2-*c*]pyrimidinediones and in the C-5, C-6 cycloaddition processes to yield 3,9-propano-8-aza-9*H*-xanthine derivatives.

A detailed examination of the transformations of epoxides (**19**) and (**20**) in reaction with sodium azide revealed the formation of the respective *trans*- (**23**) and *cis*- (**24**) 2-azidomethyl-3-methoxy-6-methyl-2,3-dihydro-oxazolo[3,2-*c*]-pyrimidine-5,7(6*H*)-dione as by-products (Scheme 3). This was borne out by an intramolecular reaction of the intermediate (ring-opened epoxide) (**21**) or (**22**). The reaction sequence for such *anti*-cyclisation, but in the presence of KCN–DMF and Bu^{t}OK–DMF, has been described previously.[3] The transformation of the 2′,3′-epoxy compound (**20**) by NaN_3–DMF at 90 °C resulted in a 58% yield of the oxazolo[3,2-*c*]pyrimidine (**24**). To our surprise, treatment of the *threo*-3′-azidopropyl derivative (**22**) under the same conditions afforded *cis* compound (**24**) in very low yield. Based on these experiments the efficiency of the intramolecular transformations of compounds (**20**) *via* the 2′,3′-oxirane ring opening, C-2′ alkoxide formation, and C- 2′–O^-,H^+ addition at the C-5, C-6 double bond was presumably



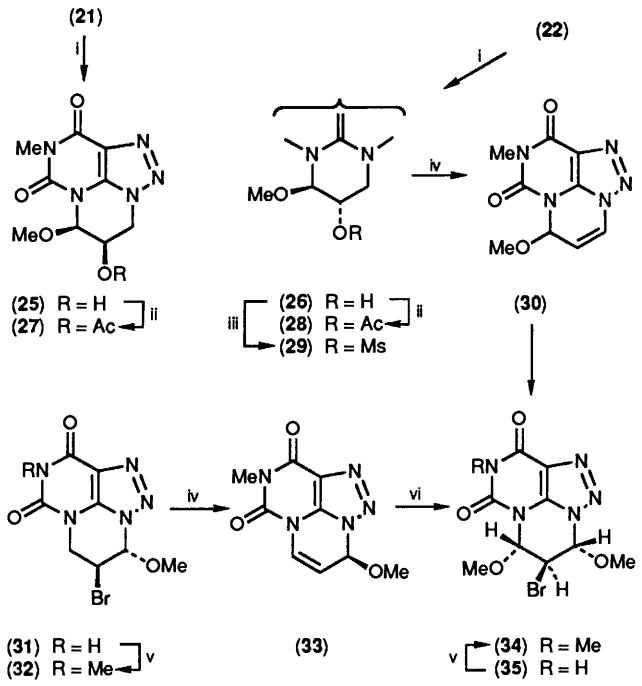
Scheme 3. *Reagents and conditions:* i, Br_2, CH_2Cl_2–MeOH; ii, DBU, CH_2Cl_2; iii, NaN_3, DMF, 40 °C; iv, NaN_3, DMF, 90 °C; v, DBU, DMF, 90 °C.

a consequence of the oxirane ring-opening step. In contrast, during a 10 min treatment with DBU at 90 °C, *anti*-cyclisation of the *threo*-3′-azidopropyl compound (**22**) proved to be very efficient, leading to *cis*-2-azidomethyl-3-methoxy-6- methyl-2,3-dihydro-oxazolo[3,2-*c*]pyrimidine-5,7(6*H*)-dione (**24**) in 72% yield.

In DMF solution, thermally (at 110–120 °C), cycloaddition[13] of the *erythro*- (**21**) and *threo*- (**22**) 3′-azido-2′-hydroxy-1′-methoxypropyl compound was induced, affording the respective *cis*- (**25**) and *trans*- (**26**) 11-hydroxy-12-methoxy-1-methyl-3,9-propano-8-aza-9*H*-xanthine. Acetylation gave the corresponding *cis*- (**27**) and *trans*- (**28**) 11-acetoxy-12-methoxy-1-methyl-3,9-propano-8-aza-9*H*-xanthine (Scheme 4). In the ^1H NMR spectra of compounds (**27**) and (**28**) the signals of the C-11 proton were shifted downfield to δ_H 5.23 (*J* 11, 5.6, 2.4 Hz) and δ_H 5.61 (*J* 2.9, 2.7, 2.0 Hz), respectively.

Mesylation of *trans*-alcohol (**26**) gave *trans*-12-methoxy-1-methyl-11-methylsulphonyloxy-3,9-propano-8-aza-9*H*-xanthine (**29**) in 81% yield. The DBU–DMF elimination of the latter at 80 °C afforded 12-methoxy-1-methyl-9,3-propeno-8-aza-9*H*-xanthine (**30**), the ^1H NMR spectrum of which exhibited signals for the C-10 proton at δ_H 7.69 (*J* 8.1, 0.5 Hz), for the C-11 proton at δ_H 5.78 (*J* 8.1, 4.2 Hz), and for the C-12 proton at δ_H 6.22 (*J* 4.2, 0.5 Hz).

In order to prepare the positional isomer of the 9,3-propeno compound (**30**) containing a C-11, C-12 double bond, 11-



Scheme 4. *Reagents and conditions:* i, DMF, heat; ii, Ac_2O, py; iii, MsCl, py; iv, DBU, DMF, 80 °C; v, CH_2N_2, Et_2O; vi, Br_2, MeOH.

bromo-10-methoxy-3,9-propano-8-aza-9*H*-xanthine[2] (**31**) was methylated to give the corresponding 1-methyl derivative (**32**), which was then dehydrobrominated by base (DBU).[14] The ^1H NMR spectrum of the 10-methoxy-1-methyl-3,9-propeno-8-aza-9*H*-xanthine (**33**) obtained showed signals for the C-10 proton at δ_H 6.47 (*J* 3.4, 0.6 Hz), the C-11 proton at δ_H 5.63 (*J* 8.3, 3.4 Hz), and the C-12 proton at δ_H 7.48 (*J* 8.3, 0.6 Hz).

The 1-methyl-9,3-propeno isomer (**30**) was also functionalized by a *trans*-addition reaction with bromine[2,11,12] in MeOH to yield 11-bromo-10,12-dimethoxy-1-methyl-3,9-propano-8-aza-9*H*-xanthine (**34**) (71%). This structural assignment was confirmed by alternative preparation from the previously described 11-bromo-10,12-dimethoxy-3,9-propano-8-aza-9*H*-xanthine[2] (**35**) by methylation in high yield.

Experimental

The same techniques and apparatus were used as described previously.[2]

1-(3-Azido-2-hydroxypropyl)-3-methyluracil (**5**).—1-(3-Azido-2-hydroxypropyl)uracil[4] (220 mg, 1.04 mmol) was treated with diazomethane [prepared from *N*-methyl-*N*-nitroso-toluene-4-sulphonamide (2.14 g, 10 mmol) in diethyl ether (30 mg)] at 0 °C and the mixture was kept at room temperature for 6 h. The solvent was removed under reduced pressure and the residue, being dissolved in CH_2Cl_2, was subjected to preparative TLC (PLC) to give the *oily product* (**5**) (205 mg, 87%), R_f 0.55, reprecipitated from CH_2Cl_2–Et_2O–hexane (Found: C, 42.65; H, 5.05; N, 30.95. $C_8H_{11}N_5O_3$ requires C, 42.65; H, 4.9; N, 30.95%); λ_{max} 263 nm (log ε 3.96); ν_{max} 3 401br, 2 972, 2 095, 1 701, 1 656, 1 535, 1 451, 1 406, 1 373, 1 311, 1 271, 1 229, 1 101, 800, and 759 cm^{-1}; δ_H 7.57 (1 H, d, *J* 8.1 Hz, 6-H), 5.67 (1 H, d, *J* 8.1 Hz, 5-H), 5.57 (1 H, d, *J* 5.1 Hz, 2′-OH), 4.01–3.31 (1 H, m, 2′-H), 3.86 (1 H, dd, *J* 13.9, 2.9 Hz, 3′-H_a), 3.6 (1 H, dd, *J* 13.9, 8.8 Hz, 3′-H_b), 3.35–3.20 (2 H, m, 1′-H_2), and 3.16 (3 H, s, Me); δ_C 162.8 (s, C-4), 151.5 (s, C-2), 145.0 (d, C-6), 99.5 (d, C-5), 67.6 (d, C-2′), 53.7 (t, C-3′), 52.4 (t, C-1′), and 27.3 (q, Me).

1-(3-*Azido*-2-*methylsulphonyloxypropyl*)-3-*methyluracil* (**6**).—Methanesulphonyl chloride (0.05 ml, 0.69 mmol) was added to a solution of 1-(3-azido-2-hydroxypropyl)-3-methyluracil (**5**) (92 mg, 0.14 mmol) in pyridine (2 ml) at 0 °C and the mixture was stirred at room temperature for 16 h. The solvent was removed under reduced pressure and the residue was subjected to PLC to give the *oily product* (**6**) (110 mg, 88.7%), R_f 0.76 (Found: C, 35.7; H, 4.45; N, 23.2. $C_9H_{13}N_5O_5S$ requires C, 35.65; H, 4.3; N, 23.1%); λ_{max} 259 nm (4.06); ν_{max} 3 008, 2 926, 2 102, 1 704, 1 660br, 1 627, 1 458, 1 408, 1 353, 1 276, 1 236, 1 171, 1 118, 918, 799, and 760 cm^{-1}; $\delta_H(CDCl_3)$ 7.21 (1 H, d, *J* 7.9 Hz, 6-H), 5.77 (1 H, d, *J* 7.9 Hz, 5-H), 5.05 (1 H, dddd, *J* 7.05, 5.9, 4.1, and 3.6 Hz, 2′-H), 4.16 (1 H, dd, *J* 14.7, 4.1 Hz, 3′-H_a), 3.87 (1 H, dd, *J* 14.7, 7.05 Hz, 3′-H_b), 3.79 (1 H, dd, *J* 13.8, 3.6 Hz, 1′-H_a), 3.51 (1 H, dd, *J* 13.8, 5.9 Hz, 1′-H_b), 3.32 (3 H, s, NMe), and 3.09 (3 H, s, SMe); δ_C 162.64 (C-4), 151.53 (C-2), 144.3 (C-6), 100.34 (C-5), 77.1 (C-2′), 51.3 (C-3′), 49.8 (C-1′), 38.04 (SMe), and 27.26 (NMe).

Elimination Products of 1-(3-*Azido*-2-*methylsulphonyloxypropyl*)-3-*methyluracil* (**6**) *in Reaction with DBU*.—DBU (0.25 ml, 1.72 mmol) was added dropwise to a solution of the mesyloxy compound (**6**) (135.5 mg, 0.447 mmol) in DMF (4 ml) and the mixture was stirred at 100 °C for 1 h. The solvent was removed under reduced pressure and the residue was subjected to PLC (CH_2Cl_2–Et_2O–hexane (3:3:4) and then CH_2Cl_2–MeOH (20:1)] to give three components (R_f 0.32, 0.33, and 0.38) and the starting material (25 mg recovery), R_f 0.76.

The fraction with R_f 0.32 was identified as (E)-1-(3-*azidoprop*-1-*enyl*)-3-*methyluracil* (**7**) [22.2 mg, 29.4%, based on consumed substrate (**6**)], m.p. 85–87 °C (from CH_2Cl_2–Et_2O–hexane) (Found: C, 46.15; H, 4.5; N, 34.0. $C_8H_9N_5O_2$ requires C, 46.35; H, 4.4; N, 33.8%); λ_{inf} 245 nm (4.07); λ_{max} 259 nm (4.12); ν_{max} 3 435, 3 095, 2 115, 1 710, 1 667, 1 465, 1 414, 1 382, 1 355, 1 316, 1 278, 1 218, 1 208, 937, 825, and 755 cm^{-1}; $\delta_H(CDCl_3)$ 7.13 (1 H, d, *J* 7.8 Hz, 6-H), 6.28 (1 H, dt, *J* 13.4, 1.0 Hz, 1′-H), 5.76 (1 H, d, *J* 7.8 Hz, 5-H), 5.41 (1 H, dt, *J* 13.4, 7.3 Hz, 2′-H), 4.34 (2 H, dd, *J* 7.3, 1.0 Hz, 3′-H_2), and 3.34 (3 H, s, Me).

The fraction with R_f 0.33 was identified as (Z)-1-(3-*azidoprop*-1-*enyl*)-3-*methyluracil* (**4**) [19 mg, 25.2%, based on consumed (**6**)], m.p. 93–95 °C (from CH_2Cl_2–Et_2O–hexane) (Found: C, 46.2; H, 4.65; N, 33.5%); λ_{inf} 246 nm (3.99); λ_{max} 260 nm (4.03); ν_{max} 3 430, 2 925, 2 105, 1 699, 1 663, 1 463, 1 408, 1 380, 1 360, 1 335, 1 291, 1 225, 802, and 764 cm^{-1}; $\delta_H(CDCl_3)$ 7.2 (1 H, d, *J* 7.8 Hz, 6-H), 6.48 (1 H, dt, *J* 7.3, 1.2 Hz, 1′-H), 5.74 (1 H, d, *J* 7.8 Hz, 5-H), 5.06 (1 H, dt, *J* 7.3, 7.1 Hz, 2′-H), 4.38 (2 H, dd, *J* 7.1, 1.2 Hz, 3′-H_2), and 3.33 (3 H, s, Me).

The fraction with R_f 0.38 was identified as (*E*)-1-(3-azidoprop-2-enyl)-3-methyluracil (**8**) [7 mg, 9.2%, based on the consumed (**6**)], m.p. 119–120 °C (from CH_2Cl_2–Et_2O–hexane); λ_{max} 224 and 276 nm (3.94 and 3.95); λ_{min} 244 nm (3.51); ν_{max} 3 432br, 2 924, 2 113, 1 712, 1 662, 1 632, 1 459, 1 412, 1 377, 1 342, 1 292, 1 277, 1 232, 812, and 752 cm^{-1}; $\delta_H(CDCl_3)$ 7.44 (1 H, d, *J* 8.2 Hz, 6-H), 7.27 (1 H, dt, *J* 14.35 Hz, 3′-H), 5.89 (1 H, d, *J* 8.2 Hz, 5-H), 5.68 (1 H, dt, *J* 14.35, 7.0 Hz, 2′-H), 3.95 (2 H, dt, *J* 7.0 Hz, 1′-H_2), and 3.66 (3 H, s, Me).

1-*Allyl*-3-*methyluracil* (**9**).—1-Allyluracil[10] (1.0 g, 6.6 mmol) was treated with diazomethane [prepared from *N*-methyl-*N*-nitrosotoluene-4-sulphonamide (4.3 g, 20 mmol) in diethyl ether (60 ml)] at 0 °C and the mixture was kept at room temperature for 6 h. The solvent was removed under reduced pressure and the residue was dissolved in CH_2Cl_2 and then chromatographed on a silica gel (16 g) column. The CH_2Cl_2 eluate afforded the product (**9**) (992 mg, 91%), R_f 0.56; m.p. 56–57 °C (from Me_2CO–Et_2O–hexane) (Found: C, 57.9; H, 6.1; N, 16.65. Calc. for $C_9H_{10}N_2O_2$: C, 57.8; H, 6.05; N, 16.85%); λ_{max} 262 nm (3.995); ν_{max} 3 327br, 3 076, 1 707, 1 656br, 1 530, 1 459, 1 433, 1 403, 1 382, 1 356, 1 287, 1 273, 1 230, 1 214, 1 162, 992, 830, 762, and 693 cm^{-1}; $\delta_H(CDCl_3)$ 7.15 (1 H, d, *J* 8.3 Hz, 6-H), 5.90 (1 H, ddt, *J* 17.8, 9.3, 5.6 Hz, 2′-H), 5.77 (1 H, d, *J* 8.3 Hz, 5-H), 5.30 (1 H, ddt, *J* 9.3, 2.95, 1.2 Hz, 3′-H_b), 5.26 (1 H, ddt, *J* 17.8, 2.95, 1.2 Hz, 3′-H_a), 4.38 (2 H, ddd, *J* 5.6, 1.2, and 1.2 Hz, 1′-H_2), and 3.35 (3 H, s, Me); $\delta_C(CDCl_3)$ 163.1 (s, C-4), 151.5 (s, C-2), 142.1 (d, C-6), 131.95 (d, C-2′), 118.9 (t, C-3′), 101.4 (d, C-5), 51.0 (t, C-1′), and 27.7 (q, Me).

1-(2,3-*Dihydroxypropyl*)-3-*methyluracil* (**10**).—To a solution of 1-allyl-3-methyluracil (**9**) (1.12 g, 6.74 mmol) in acetone (36 ml), cooled at 10–15 °C, was added dropwise 3.5% $KMnO_4$ in water (42 ml) for 5 min, and the mixture was then stirred vigorously for an additional 5 min. A precipitate was then filtered off and the filtrate was neutralized by Amerlite IRC-50(H^+). The resin was removed by suction to be washed with 70% ethanol (3 × 100 ml). The combined filtrate and washings were evaporated to dryness under reduced pressure. PLC [CH_2Cl_2–MeOH (8:2); recovery with Me_2CO] yielded the product (**10**) (778 mg, 57.7%), m.p. 84–86 °C, identical (mixed m.p., IR, and ^1H NMR spectra) with that obtained by methylation of 1-(2,3-dihydroxypropyl)uracil.[3]

1-(2-*Hydroxy*-3-*trityloxypropyl*)-3-*methyluracil* (**11**).—(*a*) 1-(2-Hydroxy-3-trityloxypropyl)uracil[3] (4.69 mg, 1.1 mmol) was treated with diazomethane [prepared from *N*-methyl-*N*-nitrosotoluene-4-sulphonamide (2.14 g, 10 mmol) in diethyl ether (30 ml)] at 0 °C and the mixture was kept at room temperature for 6 h. The solvent was removed under reduced pressure and the residue was dissolved in CH_2Cl_2 (5 ml) and chromatographed on a silica gel (20 g) column [eluant CH_2Cl_2–MeOH (98:2)] to afford the *title product* (**11**) (470 mg, 97%), R_f 0.40 [CH_2Cl_2–Et_2O (8:2)], which was rechromatographed [PLC; CH_2Cl_2–Et_2O, (98:2)] and obtained as a foam (Found: C, 73.05; H, 5.7; N, 6.15. $C_{27}H_{26}N_2O_4$ requires C, 73.3; H, 5.9; N, 6.35%); λ_{max} 262 nm (4.01); ν_{max} 3 436br, 2 945, 1 706, 1 656, 1 462, 1 446, 1 407, 1 376, 1 350, 1 225, 1 070, 800, 758, and 703 cm^{-1}; $\delta_H(CDCl_3)$ 7.49–7.23 (15 H, m, ArH), 7.1 (1 H, d, *J* 8.1 Hz, 6-H), 5.6 (1 H, d, 8.1 Hz, 5-H), 4.2–4.0 (1 H, m, 2′-H), 4.1 (1 H, dd, *J* 14.5, 3.2 Hz, 3′-H_a), 3.65 (1 H, dd, *J* 14.5, 7.6 Hz, 3′-H_b), 3.27 (3 H, s, Me), 3.21–3.15 (2 H, m, 1′-H_2), and 3.15–3.0 (1 H, m, 2′-OH); $\delta_C(CDCl_3)$ 163.3 (s, C-4), 152.3 (s, C-2), 143.6 (d, C-6), 143.5 (s, C-Ar), 128.6, 127.9, 127.3 (3 d, C-Ar), 100.7 (d, C-5), 87.0 (s, *C*Ph_3), 69.2 (d, C-2′), 64.7 (t, C-3′), 52.6 (t, C-1′), and 27.8 (q, Me).

(*b*) Chlorotriphenylmethane (1.27 g, 4.56 mmol) was added to a solution of 1-(2,3-dihydroxypropyl)-3-methyluracil (**10**) (720 mg, 3.6 mmol) in freshly distilled pyridine (17 ml). The mixture was stirred and heated at 100 °C for 3 h, and was then concentrated and coevaporated with toluene under reduced pressure. The resultant oily residue was dissolved in CH_2Cl_2 and purified on a silica gel column as described under method (*a*). It gave the title compound (**11**) (1.43 g, 89.8%), identical (IR and ^1H NMR spectra) with that compound obtained under method (*a*).

3-*Methyl*-1-(2-*methylsulphonyloxy*-3-*trityloxypropyl*)*uracil* (**12**).—Methanesulphonyl chloride (0.04 ml, 0.5 mmol) was added to a solution of 1-(2-hydroxy-3-trityloxypropyl)-3-methyluracil (**11**) (150 mg, 0.4 mmol) in dry pyridine (1.5 ml) at 0 °C and the mixture was stirred at 3–5 °C for 16 h. The solvent was removed under reduced pressure and the residue was subjected to PLC [CH_2Cl_2–Et_2O (8:2)] to give the *title product* (**12**) (164 mg, 88.8%), R_f 0.63 [CH_2Cl_2–Et_2O, (8:2)]; m.p. 128–130 °C (from CH_2Cl_2–Et_2O–hexane) (Found: C, 64.8; H, 5.45; N, 5.2. $C_{28}H_{28}H_2O_6S$ requires C, 64.6; H, 5.4; N, 5.4%); λ_{max} 259 nm (3.7); ν_{max} 3 445br, 3 215, 2 938, 1 709, 1 670br, 1 492, 1 464, 1 451, 1 411, 1 358, 1 180, 1 001, 944, 800, 750, and 710 cm^{-1};

$\delta_H(CDCl_3)$ 7.5–7.2 (15 H, m, ArH), 7.06 (1 H, d, *J* 7.9 Hz, 6-H), 5.66 (1 H, d, *J* 7.9 Hz, 5-H), 5.1–4.9 (1 H, m, 2′-H), 4.18 (1 H, dd, *J* 14.4 Hz, 1′-H_a), 3.81 (1 H, dd, *J* 14.4, 7.6 Hz, 1′-H_b), 3.54 (1 H, dd, *J* 11.1, 3.5 Hz, 3′-H_a), 3.27 (3 H, s, NMe), 3.25 (1 H, dd, *J* 11.1, 5.0 Hz, 3′-H_b), and 2.95 (3 H, s, SMe); $\delta_C(CDCl_3)$ 162.9 (s, C-4), 151.7 (s, C-2), 142.9 (s, C-Ar), 142.6 (d, C-6), 128.5, 128.1, 127.5 (3 d, C-Ar), 101.7 (d, C-5), 87.5 (s, *C*Ph_3), 77.99 (d, C-2′), 62.98 (t, C-3′), 50.6 (t, C-1′), 38.4 (q, SMe), and 27.2 (q, NMe).

(E)-3-*Methyl*-1-(3-*trityloxyprop*-1-*enyl*)*uracil* (**13**).—DBU (0.6 ml, 4.14 mmol) was added dropwise to a solution of 3-methyl-1-(2-methylsulphonyloxy-3-trityloxypropyl)uracil (**12**) (1.016 g, 1.95 mmol) in anhydrous benzene (5 ml), and the solution was flushed with nitrogen (dried over KOH) for 10 min, then was heated at 110–115 °C to remove the solvent and for an additional 1 h. The residue was triturated with MeOH (3 × 10 ml) to give the *crystalline product* (**13**) (508 mg, 61.7%), R_f 0.84 [CH_2Cl_2–MeOH (8:2)]; m.p. 190–192 °C (from CH_2Cl_2–Et_2O–hexane) (Found: C, 76.6; H, 5.75; N, 6.35. $C_{27}H_{24}N_2O_3$ requires C, 76.4; H, 5.7, N, 6.6%); λ_{inf} 219 nm (4.39); λ_{max} 276 nm (4.12); λ_{min} 246 nm (3.79); ν_{max} 3 040br, 2 975, 2 938, 1 713, 1 673, 1 633, 1 450, 1 413, 1 370, 1 344, 1 292, 1 041, 751, and 713 cm^{-1}; $\delta_H(CDCl_3)$ 7.52–7.12 (15 and 1 H, m, ArH and 6-H), 7.2 (1 H, dt, *J* 14.4, 1.5 Hz, 1′-H), 5.81 (1 H, d, *J* 7.8 Hz, 5-H), 5.63 (1 H, dt, *J* 14.4, 5.9 Hz, 2′-H), 3.78 (2 H, dd, *J* 5.9, 1.5 Hz, 3′-H_2), and 3.35 (3 H, s, Me); $\delta_C(CDCl_3)$ 162.0 (s, C-4), 149.7 (s, C-2), 143.4 (s, C-Ar), 137.3 (d, C-6), 128.2, 127.6, 126.9 (3 d, C-Ar), 126.15 (d, C-1′), 115.9 (d, C-2′), 102.4 (d, C-5), 87.05 (s, *C*Ph_3), 62.2 (t, C-3′), and 27.8 (q, Me).

The combined mother liquors from the above triturations with MeOH were evaporated to dryness under reduced pressure and the residue was subjected to PLC [CH_2Cl_2–Et_2O (98:2)] to give three components (R_f 0.4, 0.84, and 0.84).

The foamy fraction with R_f 0.4 was identified as 1-(2-hydroxy-3-trityloxypropyl)-3-methyluracil (**11**) (112 mg, 13%), identical (IR and ^1H NMR spectra) with an authentic sample.

The oily fraction with R_f 0.84 was identified as a mixture of *E*- (**13**) and *Z*- (**14**) 3-methyl-1-(3-trityloxyprop-1-enyl)uracil (57 mg, 7.0%); $\delta_H(CDCl_3)$ 7.59–7.23 (m, ArH; *E*- and *Z*-), 7.14 (d, *J* 8.1 Hz, 6-H; *E*-), 7.09 (d, *J* 8.1 Hz, 6-H; *Z*-), (1′-H; *E*-, obscured by those of ArH), 6.66 (d, *J* 8.6 Hz, 1′-H; *Z*-), 5.88–5.44 (m, 2′-H; *E*- and *Z*-), 5.58 (d, *J* 8.1 Hz, 5-H; *E*-), 5.49 (d, *J* 8.1 Hz, 5-H; *Z*-), 4.44–4.22 (m, 3′-H_2; *Z*-), 3.9–3.6 (m, 3′-H_2; *E*-), 3.29 (s, NMe; *Z*-), and 3.27 (s, NMe; *E*-).

(E)-1-(3-*Hydroxyprop*-1-*enyl*)-3-*methyluracil* (**15**).—A solution of (*E*)-3-methyl-1-(3-trityloxyprop-1-enyl)uracil (**13**) (508 mg, 1.2 mmol) in 80% acetic acid (15 ml) was heated at 100 °C for 10 min. The solvent was removed under reduced pressure and the residue was subjected to PLC [two developments in CH_2Cl_2–MeOH (95:5)] to give the *title product* (**15**) (208 mg, 95.4%), R_f 0.18 [CH_2Cl_2–MeOH (95:5)]; m.p. 117–118 °C (from CH_2Cl_2–Et_2O) (Found: C, 52.85; H, 5.45; N, 15.5. $C_8H_{10}N_2O_3$ requires C, 52.75; H, 5.55; N, 15.4%); λ_{max} 223 and 276 nm (4.07 and 4.05); λ_{min} 244 nm (3.59); ν_{max} 3 440, 3 098, 2 866, 1 703, 1 655, 1 622, 1 468, 1 620, 1 578, 1 348, 1 319, 1 228, 1 096, 948, 821, and 750 cm^{-1}; $\delta_H([^2H_6]DMSO)$ 7.96 (1 H, d, *J* 8.1 Hz, 6-H), 7.03 (1 H, dt, *J* 14.4, 1.6 Hz, 1′-H), 5.98 (1 H, dt, *J* 14.4, 5.1 Hz, 2′-H), 5.81 (1 H, d, *J* 8.1 Hz, 5-H), 4.98 (1 H, br s, 3′-OH, exchangeable in D_2O, 4.08 (2 H, dd, *J* 5.1, 1.6 Hz, 3′-H_2), and 3.18 (3 H, s, Me); $\delta_C([^2H_6]DMSO)$ 161.5 (s, C-4), 149.4 (s, C-2), 138.8 (d, C-6), 123.9 (d, C-1′), 118.9 (d, C-2′), 101.2 (d, C-5), 59.0 (t, C-3′), and 27.3 (q, Me).

threo- (**17**) *and* erythro- (**18**) -5-*Bromo*-1-(2-*bromo*-3-*hydroxy*-1-*methoxypropyl*)-3-*methyluracil*.—A solution of a mixture of (*E*)- (**13**) and (*Z*)- (**14**) -3-methyl-1-(3-trityloxyprop-1-enyl)uracil (57 mg, 0.135 mmol) in 80% acetic acid (2 ml) was heated at 100 °C for 10 min and worked up as described for compound (**15**) to afford the corresponding mixture of (*E*)- (**15**) and (*Z*)- (**16**) 1-(3-hydroxyprop-1-enyl)-3-methyluracil (23 mg, 94%), R_f 0.18 (CH_2Cl_2–MeOH (95:5)]. This mixture was dissolved in MeOH (6 ml) and treated with a solution of bromine (0.025 ml) in CH_2Cl_2 (6 ml) during 30 min and was then stirred at room temperature for 3 h [until disappearance of the starting material (TLC)]. The solvent was removed under reduced pressure and the residue was subjected to PLC [CH_2Cl_2–MeOH (95:5)] to give two components (R_f 0.43 and 0.6).

The fraction with R_f 0.43 was identified as the threo-*isomer* (**17**) (21 mg, 42.9%), m.p. 172–174 °C (from CH_2Cl_2–Et_2O–hexane) (Found: C, 29.25; H, 3.3; N, 7.55. $C_9H_{12}Br_2N_2O_4$ requires C, 29.05; H, 3.25; N, 7.55%); λ_{max} 274 nm (3.9); ν_{max} 3 440, 3 080, 2 968, 1 708, 1 660, 1 630, 1 613, 1 461, 1 333, 1 298, 1 194, 1 134, 1 041, 845, and 759 cm^{-1}; $\delta_H(CDCl_3)$ 7.8 (1 H, s, 6-H), 5.78 (1 H, d, *J* 3.5 Hz, 1′-H), 4.3–4.1 (1 H, m, 2′-H), 4.0–3.9 (2 H, m, 3′-H_2), 3.5 (3 H, s, OMe), 3.4 (3 H, s, NMe), and 2.5 (1 H, t, *J* 6.5 Hz, 3′-OH); $\delta_C([^2H_6]DMSO)$ 158.5 (C-4), 150.0 (C-2), 137.9 (C-6), 94.8 (C-5), 85.9 (C-1′), 62.26 (C-3′), 57.1 (OMe), 55.3 (C-2′), and 28.6 (NMe).

The fraction with R_f 0.6 was identified as the *erythro*-isomer (**18**) (6 mg, 12.3%) (*vide infra*).

erythro-5-*Bromo*-1-(2-*bromo*-3-*hydroxy*-1-*methoxypropyl*)-3-*methyluracil* (**18**).—A solution of crude (*E*)-1-(3-hydroxyprop-1-enyl)-3-methyluracil (**16**) (208 mg, 1.14 mmol) in MeOH (56 ml) was treated with bromine (0.246 ml) dissolved in CH_2Cl_2 (56 ml) for 30 min, and was then worked up as for the mixture of isomers (**17**) and (**18**) to afford the title compound (**18**) as an oily product (282 mg, 66.4%), R_f 0.6, and a minor component identified as the *threo*-isomer (**17**) (32 mg, 7.5%), R_f 0.43; m.p. 170–174 °C; identical (mixed m.p., IR, and ^1H NMR spectra) with an authentic sample. The erythro-*isomer* (**18**) was purified by PLC to give an analytical sample (Found: C, 28.8; H, 3.0; N, 7.8%); λ_{max} 274 nm (3.85); ν_{max} 3 420br, 3 065, 2 920, 1 707, 1 660, 1 628, 1 470, 1 450, 1 230, 1 061, 800, and 760 cm^{-1}; $\delta_H(CDCl_3)$ 7.79 (1 H, s, 6-H), 5.89 (1 H, d, *J* 4.6 Hz, 1′-H), 4.4–4.2 (1 H, m, 2′-H), 3.9–3.69 (2 H, m, 3′-H_2), 3.47 (3 H, s, OMe), 3.44 (3 H, s, NMe) and 2.43 (1 H, br, 3′-OH; $\delta_C([^2H_6]DMSO)$ 158.3 (s, C-4), 150.7 (s, C-2), 138.1 (d, C-6), 95.9 (s, C-5), 86.1 (d, C-1′), 61.7 (t, C-3′), 57.1 (q, OMe), 55.1 (d, C-2′), and 28.8 (q, NMe).

erythro-5-*Bromo*-1-(2,3-*epoxy*-1-*methoxypropyl*)-3-*methyluracil* (**19**).—DBU (0.1 ml, 0.69 mmol) was added dropwise to a solution of *threo*-5-bromo-1-(2-bromo-3-hydroxy-1-methoxypropyl)-3-methyluracil (**17**) (98 mg, 0.26 mmol) in CH_2Cl_2 (24 ml) and the mixture was stirred at room temperature for 30 h. It was then concentrated to small volume (5 ml) and subjected to PLC [CH_2Cl_2–MeOH (95:5) to give the starting material (25 mg recovery) and the *title product* (**19**) [34 mg, 59.7%, based on consumed substrate (**17**)], R_f 0.7; m.p. 95–96 °C (from CH_2Cl_2–Et_2O) (Found: C, 36.9; H, 3.7; N, 9.65. $C_9H_{11}BrN_2O_4$ requires C, 37.15; H, 3.8; N, 9.6%); λ_{max} 274 nm (3.89); ν_{max} 3 431br, 3 091, 3 006, 1 711, 1 662, 1 626, 1 441, 1 400, 1 357, 1 341, 1 284, 1 194, 1 161, 1 080, 887, 863, 748, and 760 cm^{-1}; $\delta_D(CDCl_3)$ 7.66 (1 H, s, 6-H), 5.87 (1 H, d, *J* 2.4 Hz, 1′-H), 3.41 (2 × 3 H, s, OMe and NMe), 3.31 (1 H, ddd, *J* 4.2, 2.7, and 2.4 Hz, 2′-H), 2.88 (1 H, dd, *J* 4.6, 4.2 Hz, 3′-H_a), and 2.57 (1 H, dd, *J* 4.6, 2.7 Hg, 3′-H_b); $\delta_C([^2H_6]DMSO)$ 158.7 (C-4), 150.8 (C-2), 138.5 (C-6), 95.9 (C-5), 85.7 (C-1′), 56.7 (OMe), 50.7 (C-2′), 44.3 (C-3′), and 28.9 (NMe).

threo-5-*Bromo*-1-(2,3-*epoxy*-1-*methoxypropyl*)-3-*methyluracil* (**20**).—DBU (0.065 ml, 0.448 mmol) was added to a solution of *erythro*-5-bromo-1-(2-bromo-3-hydroxy-1-methoxypropyl)-3-methyluracil (**18**) (107 mg, 0.29 mmol) in

CH_2Cl_2 (23 ml) and the mixture was stirred at room temperature for 10 h. It was worked up as described for compound (**19**). Besides the starting material (18 mg recovery) the title compound (**20**) (60 mg) was isolated in 86% yield [based on consumed substrate (**18**)], R_f 0.7; m.p. 182–183 °C (from MeOH) (Found: C, 37.2; H, 3.85; N, 9.6%); λ_{max} 274 nm (3.97); ν_{max} 3 435br, 3 060, 2 950, 1 695, 1 675, 1 655, 1 625, 1 443, 1 285, 1 230, 1 213, 1 165, 1 090, 1 010, 955, 907, 865, 848, 755, and 715 cm^{-1}; $\delta_H(CDCl_3)$ 7.8 (1 H, s, 6-H), 5.7 (1 H, d, *J* 3.7 Hz, 1′-H), 3.43 (3 H, s, OMe), 3.4 (3 H, s, NMe), 3.2 (1 H, ddd, *J* 3.7, 3.7, and 2.7 Hz, 2′-H), 2.9 (1 H, dd, *J* 5.2, 2.7 Hz, 3′-H_a), and 2.8 (1 H, dd, *J* 5.2, 3.7 Hz, 3′-H_b); $\delta_C(CDCl_3)$ 158.86 (s, C-4), 150.96 (s, C-2), 137.14 (d, C-6), 97.5 (s, C-5), 85.5 (d, C-1′), 57.3 (q, OMe), 52.1 (d, C-2′), 44.1 (t, C-3′), and 29.2 (q, NMe).

Reaction of erythro-5-*Bromo*-1-(2,3-*epoxy*-1-*methoxypropyl*)-3-*methyluracil* (**19**) *with* NaN_3.—Sodium azide (49 mg, 0.76 mmol) was added to a solution of *erythro*-2′,3′-epoxy compound (**19**) (43 mg, 0.15 mmol) in DMF (10 ml) and the suspension was stirred at room temperature for 40 h. The solvent was removed under reduced pressure and the oily residue was subjected to PLC [CH_2Cl_2–MeOH (95:5)] to give two components (R_F 0.6 and 0.75).

The fraction with R_F 0.6 was identified as erythro-1-(3-*azido*-2-*hydroxy*-1-*methoxypropyl*)-5-*bromo*-3-*methyluracil* (**21**) (19 mg, 38.5%), m.p. 124–126 °C (from CH_2Cl_2–Et_2O) (Found: C, 32.15; H, 3.7; N, 21.05. $C_9H_{12}BrN_5O_4$ requires C, 32.35; H, 3.65; N, 20.95%); λ_{max} 276 nm (4.01); ν_{max} 3 432, 3 376, 3 046, 2 930, 2 097, 1 710, 1 665, 1 618, 1 456, 1 286, 1 191, 1 112, 1 086, and 749 cm^{-1}; $\delta_H(CDCl_3)$ 7.68 (1 H, s, 6-H), 5.66 (1 H, d, *J* 6.6 Hz, 1′-H), 3.9–3.85 (1 H, m, 2′-H), 3.57–3.5 (2 H, m, 3′-H_2), 3.41 (2 × 3 H, s, OMe and NMe), and 3.1 (1 H, d, *J* 5.4 Hz, 2′-OH); δ_C([$^2H_6$]DMSO) 158.8 (C-4), 151.2 (C-2), 139.0 (C-6), 95.7 (C-5), 87.6 (C-1′), 70.0 (C-2′), 56.4 (OMe), 52.8 (C-3′), and 28.8 (NMe).

The fraction with R_f 0.75 was identified as oily trans-2-*azidomethyl*-3-*methoxy*-6-*methyl*-2,3-*dihydro-oxazolo*[3,2-c]-*pyrimidine*-5,7(6H)-*dione* (**23**) (5 mg, 13.4%); *m/z* 253 (M^+). $C_9H_{11}N_5O_4$ requires *M*, 253.21; λ_{max} 249 nm (4.17); λ_{inf} 278 nm (3.51); ν_{max} 3 436br, 2 916, 2 100, 1 718, 1 658br, 1 466, 1 372, 1 276, 1 230, 1 190, 1 100, and 752 cm^{-1}; $\delta_H(CDCl_3)$ 5.57 (1 H, d, *J* 1.95 Hz, 3-H), 5.23 (1 H, s, 8-H), 4.75 (1 H, ddd, *J* 4.4, 3.9, and 1.95 Hz, 2-H), 3.72 (1 H, d, *J* 4.4 Hz, CH_aN_3), 3.68 (3 H, s, OMe), 3.67 (1 H, d, *J* 3.9 Hz, CH_bN_3), and 3.3 (3 H, s, NMe); δ_C([$^2H_6$]DMSO) 163.5 (C-7), 160.3 (C-5), 148.1 (C-8a), 87.1 (C-8), 85.4 (C-3), 75.4 (C-2), 57.3 (OMe), 50.7 (2-CH_2), and 27.2 (NMe).

Reaction of threo-5-*Bromo*-1-(2,3-*epoxy*-1-*methoxypropyl*)-3-*methyluracil* (**20**) *with* NaN_3.—(*a*) Sodium azide (48 mg, 0.74 mmol) was added to a solution of *threo*-2′,3′-epoxy compound (**20**) (42 mg, 0.144 mmol) in DMF (10 ml) and the suspension was stirred at room temperature for 20 h. The solvent was removed under reduced pressure and the residue was subjected to PLC [CH_2Cl_2–MeOH (95:5)] to give two components (R_f 0.6 and 0.75).

The fraction with R_f 0.6 was identified as threo-1-(3-*azido*-2-*hydroxy*-1-*methoxypropyl*)-5-*bromo*-3-*methyluracil* (**22**) (24 mg, 50%), m.p. 174 °C (decomp.) (from CH_2Cl_2–Et_2O) (Found: C, 32.4; H, 3.8; N, 21.05. $C_9H_{12}BrN_5O_4$ requires C, 32.35; H, 3.65; N, 20.95%); λ_{max} 276 nm (3.92); ν_{max} 3 412, 3 092, 2 952, 2 110, 1 713, 1 646, 1 619, 1 458, 1 327, 1 292, 1 184, 1 133, 1 087, 1 023, 955, 936, 884, 860, 852, and 752 cm^{-1}; δ_H([$^2H_6$]DMSO) 7.84 (1 H, s, 6-H), 5.75 (1 H, d, *J* 6.1 Hz, 2′-OH, exchangeable in D_2O), 5.45 (1 H, d, *J* 3.7 Hz, 1′-H), 3.81–3.7 (1 H, m, 2′-H), 3.31 (3 H, s, OMe), and 3.23 (3 H, s, NMe); $\delta_H(CDCl_3)$ 7.8 (1 H, s, 6-H), 5.62 (1 H, d, *J* 3.5 Hz, 1′-H), 4.06–3.7 (1 H, m, 2′-H), 3.49–3.40 (2 H, m, 3′-H_2), 3.45 (3 H, s, OMe), 3.4 (3 H, s, NMe), and 2.77 (1 H, d, *J* 5.8 Hz, 2′-OH); δ_C([$^2H_6$]DMSO) 158.9 (C-4), 150.5 (C-2), 138.8 (C-6), 94.9 (C-5), 87.75 (C-1′), 70.1 (C-2′), 57.1 (OMe), 52.0 (C-3′), and 28.7 (NMe).

The fraction with R_f 0.75 was identified as oily cis-2-*azidomethyl*-3-*methoxy*-6-*methyl*-2,3-*dihydro-oxazolo*[3,2-c]-*pyrimidine*-5,7(6H)-*dione* (**24**) (4 mg, 10.7%) (Found: C, 42.55; H, 4.7; N, 27.8. $C_9H_{11}N_5O_4$ requires C, 42.7; H, 4.4; N, 27.65%); λ_{max} 249 nm (4.2); λ_{inf} 280 nm (2.75); ν_{max} 3 420br, 2 936, 2 096, 1 716, 1 660br, 1 462, 1 279, 1 234, 1 204, 1 098, 1 040, 906, and 753 cm^{-1}; δ_H([$^2H_6$]DMSO) 5.79 (1 H, d, *J* 5.4 Hz, 3-H), 5.24 (1 H, s, 8-H), 4.98 (1 H, ddd, *J* 7.1, 5.4, and 5.1 Hz, 2-H), 3.79 (1 H, d, *J* 7.1 Hz, CH_aN_3), 3.78 (1 H, d, *J* 5.1 Hz, CH_bN_3), 3.6 (3 H, s, OMe), and 3.13 (3 H, s, NMe); δ_C([$^2H_6$]DMSO) 163.1 (s, C-7), 159.35 (s, C-5), 148.1 (s, C-8a), 85.8 (d, C-8), 83.2 (d, C-3), 75.4 (d, C-2), 59.8 (q, OMe), 48.1 (t, CH_2N_3), and 27.05 (q, NMe).

(*b*) Sodium azide (50 mg, 0.77 mmol) was added to a solution of the *threo*-2′,3′epoxy compound (**20**) (30 mg, 0.1 mmol) in DMF (8 ml) and the suspension was stirred at 90 °C for 10 min, then was worked up as described under method (*a*) to afford the fraction with R_f 0.6, identified as the *threo*-3′-azidopropyl compound (**22**) (3 mg, 8.7%), m.p. 174 °C; identical (mixed m.p., IR, and ^1H NMR spectra) with that compound described under method (*a*). The main fraction, with R_f 0.75, was identified as the bicyclic compound (**24**) (13 mg, 57.5%), identical (IR and ^1H NMR spectra) with that described under method (*a*).

cis-2-*Azidomethyl*-3-*methoxy*-6-*methyl*-2,3-*dihydro-oxazolo*-[3,2-c]*pyrimidine*-5,7(6H)-*dione* (**24**).—DBU (0.029 ml, 0.2 mmol) was added to a solution of *threo*-1-(3-azido-2-hydroxy-1-methoxypropyl)-5-bromo-3-methyluracil (**22**) (30 mg, 0.09 mmol) in DMF (2 ml) and the mixture was stirred and heated at 90 °C for 10 min. The solvent was removed under reduced pressure and the residue was subjected to PLC [CH_2Cl_2–MeOH (95:5)] to give the title compound (**24**) (16 mg, 72%), identical (IR and ^1H NMR spectra) with an authentic sample.

trans-11-*Acetoxy*-12-*methoxy*-1-*methyl*-3,9-*propano*-8-*aza*-9H-*xanthine** (**27**).—A solution of *erythro*-1-(3-azido-2-hydroxy-1-methoxypropyl))-5-bromo-3-methyluracil (**21**) (32 mg, 0.096 mmol) in DMF (4 ml) was heated at 110–120 °C for 9 h. The solvent was then removed under reduced pressure and the residue was subjected to PLC to give a product (9 mg), R_f 0.31 [CH_2Cl_2–MeOH (95:5)], which was dissolved in anhydrous pyridine (2 ml) and treated with acetic anhydride (0.07 ml, 0.075 mmol). This mixture was stirred at room temperature for 16 h and evaporated to dryness under reduced pressure. The oily residue was subjected to PLC [CH_2Cl_2–MeOH (95:5)] to give the *title product* (**27**) [9 mg, 32.1%, based on consumed substrate (**21**)], R_f 0.83 (Found: C, 44.8; H, 4.6; N, 23.85. $C_{11}H_{13}N_5O_5$ requires C, 44.75; H, 4.45, N, 23.7%); λ_{max} 250 nm (3.97); ν_{max} 3 426br, 2 946, 2 846, 1 736, 1 692, 1 659, 1 591, 1 430, 1 366, 1 306, 1 216, 1 184, 1 137, 1 074, 984, 908, 816, 766, and 745 cm^{-1}; δ_H([$^2H_6$]DMSO) 5.77 (1 H, d, *J* 2.6 Hz, 12-H), 5.37 (1 H, ddd, *J* 11.1, 5.9, and 2.6 Hz, 11-H), 4.88 (1 H, dd, *J* 12.0, 5.9 Hz, 10-H_a), 4.35 (1 H, dd, *J* 12.0, 11.1 Hz, 10-H_b), 3.50 (3 H, s, OMe), 3.24 (3 H, s, NMe), and 2.15 (3 H, s, Ac); δ_C([$^2H_6$]DMSO) 169.5 (*C*OMe), 155.2 (C-6), 149.6 (C-2), 138.4 (C-4), 122.7 (C-5), 78.8 (C-12), 65.7 (C-11), 58.0 (OMe), 42.2 (C-10), 28.2 (NMe), and 20.7 (CO*Me*).

trans-11-*Acetoxy*-12-*methoxy*-1-*methyl*-3,9-*propano*-8-*aza*-9H-*xanthine*† (**28**).—A solution of *threo*-1-(3-azido-2-hydroxy-1-methoxypropyl)-5-bromo-3-methyluracil (**22**) (99 mg, 0.3 mmol) in DMF (8 ml) was heated at 110–120 °C for 3 h. The

* *Systematic name: trans*-4-acetoxy-5-methoxy-7-methyl-4,5-dihydro-1,2,2a,5a,7-penta-aza-acenaphthylene-6,8(3*H*, 7*H*)-dione.

† *Systematic name: cis*-4-acetoxy-5-methoxy-7-methyl-4,5-dihydro-1,2,2a,5a,7-penta-aza-acenaphthylene-6,8(3*H*,7*H*)-dione.

solvent was removed under reduced pressure and the residue was triturated with MeOH–CH_2Cl_2 (9:1; 2 × 1 ml) to afford a crude product (57 mg), which was dissolved in anhydrous pyridine (2 ml) and treated with acetic anhydride (0.08 ml, 0.086 mmol). The mixture was then stirred at room temperature for 10 h. The solvent was removed under reduced pressure and the residue was subjected to PLC [CH_2Cl_2–MeOH (95:5)] to give the *title compound* (**28**) (56 mg, 64%), R_f 0.88, m.p. 201–203 °C (from 70% EtOH) (Found: C, 44.65; H, 4.5; N, 23.8%); λ_{max} 250 nm (3.87); ν_{max} 3 412br, 2 964, 1 734, 1 692br, 1 656, 1 587, 1 432, 1 368, 1 298, 1 228, 1 182, 1 092, 989, 880, 826, 763, and 743 cm^{-1}; δ_H([$^2H_6$]DMSO) 5.70 (1 H, d, *J* 2.9 Hz, 12-H), 5.57 (1 H, ddd, *J* 2.95, 2.7 and 1.5 Hz, 11-H), 4.9 (1 H, dd, *J* 14.7, 1.5 Hz, 10-H_a), 4.6 (1 H, dd, *J* 14.7, 2.7 Hz, 10-H_b), 3.5 (3 H, s, OMe), 3.3 (3 H, s, NMe), and 1.95 (3 H, s, COMe); δ_C([$^2H_6$]DMSO) 168.7 (*C*OMe), 154.7 (C-6), 149.5 (C-2), 137.1 (C-4), 122.2 (C-5), 79.2 (C-12), 63.9 (C-11), 57.5 (OMe), 44.7 (C-10), 28.0 (NMe), and 20.4 (CO*Me*).

trans-12-*Methoxy*-1-*methyl*-11-*methylsulphonyloxy*-3,9-*propano*-8-*aza*-9H-*xanthine** (**29**).—Methanesulphonyl chloride (0.03 ml, 0.41 mmol) was added dropwise to a solution of *trans*-11-hydroxy-12-methoxy-1-methyl-3,9-propano-8-aza-9*H*-xanthine (**26**) (56 mg, 0.22 mmol) in pyridine (2 ml), cooled to 0 °C. The mixture was then stirred at 3–5 °C for 16 h. The solvent was removed under reduced pressure and the residue was subjected to PLC [CH_2Cl_2–MeOH (95:5)] to give the *title product* (**29**) (59 mg, 80.8%), R_f 0.52; m.p. 230–232 °C (from MeOH–Et_2O) (Found: C, 36.35; H, 4.15; N, 21.0. $C_{10}H_{13}N_5O_6S$ requires C, 36.25; H, 3.95; N, 21.15%); λ_{max} 245 nm (3.49); ν_{max} 3 435br, 3 035, 2 955, 1 732, 1 694, 1 660, 1 586, 1 428, 1 370, 1 340, 1 300, 1 255, 1 175, 1 117, 1 095, 1 043, 995, 975, 926, 868, 794, 767, and 744 cm^{-1}; δ_H($CDCl_3$) 5.86 (1 H, d, *J* 2.9 Hz, 12-H), 5.48–5.4 (1 H, ddd, *J* 2.9, 2.6, and 2.6 Hz, 11-H), 4.99 (1 H, dd, *J* 14.7, 2.6 Hz, 10-H_a), 4.62 (1 H, dd, *J* 14.7, 2.6 Hz, 10-H_b), 3.64 (3 H, s, OMe), 3.46 (3 H, s, NMe), and 3.07 (3 H, s, SMe); δ_C([$^2H_6$]DMSO) 154.9 (C-6), 149.7 (C-2), 137.3 (C-4), 122.5 (C-5), 79.8 (C-12), 69.5 (C-11), 57.7 (OMe), 45.5 (C-10), 28.2 (NMe), and 38.0 (SMe, obscured by those of [$^2H_6$]DMSO).

12-*Methoxy*-1-*methyl*-9,3-*propeno*-8-*aza*-9H-*xanthine*† (**30**).—DBU (0.01 ml, 0.07 mmol) was added to a solution of *cis*-12-methoxy-1-methyl-11-methylsulphonyloxy-3,9-propano-8-aza-9*H*-xanthine (**29**) (16 mg, 0.06 mmol) in DMF (1.2 ml) and the mixture was heated at 80 °C for 5 min. The solvent was removed under reduced pressure and the residue was subjected to PLC [CH_2Cl_2–Et_2O–MeOH (8:2:1)] to give the *title product* (**30**) (6 mg, 54%), R_f 0.55 [CH_2Cl_2–MeOH (95:5)], m.p. 168–170 °C (from CH_2Cl_2–Et_2O) (Found: C, 45.95; H, 4.15; N, 29.9. $C_9H_9N_5O_3$ requires C, 45.95; H, 3.85; N, 29.8%); λ_{inf} 230 nm (3.95); λ_{max} 245 nm (3.86); ν_{max} 3 427br, 3 077, 2 499, 1 737, 1 697, 1 580, 1 436, 1 403, 1 347, 1 296, 1 243, 1 190, 1 067, 980, 942, 897, and 742 cm^{-1}; δ_H($CDCl_3$) 7.69 (1 H, dd, *J* 8.1, 0.5 Hz, 10-H), 6.22 (1 H, dd, *J* 4.2, 0.5 Hz, 12-H), 5.78 (1 H, dd, *J* 8.1, 4.2 Hz, 11-H), 3.58 (3 H, s, OMe), and 3.46 (3 H, s, NMe).

trans-11-*Bromo*-10-*methoxy*-1-*methyl*-3,9-*propano*-8-*aza*-9H-*xanthine*‡ (**32**).—*trans*-11-Bromo-10-methoxy-3,9-propano-8-aza-9*H*-xanthine[2] (**31**) (98 mg, 0.32 mmol) was treated with diazomethane [prepared from *N*-methyl-*N*-nitrosotoluene-4-sulphonamide (1.07 g, 5 mmol) in diethyl ether (15 ml)] at 0 °C. The suspension was then kept at room temperature for 6 h. The solvent was removed under reduced pressure and the residue was subjected to PLC [CH_2Cl_2–MeOH (95:5)] to give the *title product* (**32**) (86 mg, 83.8%), R_f 0.7; m.p. 189–190 °C (from MeOH–Et_2O) (Found: C, 34.15; H, 3.26; N, 22.1. $C_9H_{10}BrN_5O_3$ requires C, 34.2; H, 3.2; N, 22.15%); λ_{max} 253 nm (3.59); ν_{max} 3 436, 3 005, 1 738, 1 696, 1 668, 1 576, 1 427, 1 372, 1 316, 1 188, 1 118, 1 084, 1 032, 984, 858, and 742 cm^{-1}; δ_H([$^2H_6$]DMSO) 6.28 (1 H, d, *J* 2.2 Hz, 10-H), 5.23 (1 H, ddd, *J* 2.2, 2.2, and 2.2 Hz, 11-H), 4.44 (1 H, dd, *J* 14.7, 2.2 Hz, 12-H_a), 4.08 (1 H, dd, *J* 14.7, 2.2 Hz, 12-H_b), 3.59 (3 H, s, OMe), and 3.25 (3 H, s, NMe).

10-*Methoxy*-1-*methyl*-3,9-*propeno*-8-*aza*-9H-*xanthine*¶ (**33**).—DBU (0.022 ml, 0.15 mmol) was added to a solution of 11-bromo-10-methoxy-1-methyl-3,9-propano-8-aza-9*H*-xanthine (**32**) (29 mg, 0.092 mmol) in DMF (2.2 ml) and the mixture was heated at 80 °C for 5 min, and the mixture was then worked up following the previously described procedure.[2] An *analytical sample* had R_f 0.65, m.p. 197–198 °C (from MeOH–Et_2O) (Found: C, 46.15; H, 4.0; N, 29.55. $C_9H_9N_5O_3$ requires C, 45.95; H, 3.85; N, 29.8%); λ_{max} 223 and 264 nm (3.94 and 4.05); λ_{min} 238 nm (3.78); ν_{max} 3 430br, 3 070, 1 744, 1 693, 1 638, 1 577, 1 430, 1 366, 1 300, 1 238, 1 205, 1 101, 1 074, 1 043, 990, 955, 893, and 736 cm^{-1}; δ_H 7.5 (1 H, dd, *J* 8.3, 1.0 Hz, 12-H), 6.74 (1 H, dd, *J* 3.4, 1.0 Hz, 10-H), 5.69 (1 H, dd, *J* 8.3, 3.4 Hz, 11-H), 3.45 (3 H, s, OMe), and 3.26 (3 H, s, NMe); δ_C($CDCl_3$) 154.6 (s, C-6), 146.7 (s, C-2), 136.5 (s, C-4), 122.4 (s, C-5), 120.8 (d, C-12), 105.7 (d, C-11), 82.1 (d, C-10), 57.95 (q, OMe), and 28.7 (q, NMe).

11-*Bromo*-10,12-*dimethoxy*-1-*methyl*-3,9-*propano*-8-*aza*-9H-*xanthine*‖ (**34**).—(*a*) A solution of 11-bromo-10,12-dimethoxy-3,9-propano-8-aza-9*H*-xanthine[2] (**35**) (50 mg, 0.15 mmol) was treated with diazomethane [prepared from *N*-methyl-*N*-nitrosotoluene-4-sulphonamide (1.07 g, 5 mmol) in diethyl ether (15 ml)] and worked up as already described. PLC afforded the *title product* (**34**) (45 mg, 86%), R_f 0.72 (CH_2Cl_2–MeOH (95:5)]; m.p. 180–182 °C (from CH_2Cl_2–Et_2O–hexane) (Found: C, 34.85; H, 3.6; N, 20.05. $C_{10}H_{12}BrN_5O_4$ requires C, 34.7; H, 3.5; N, 20.25%); λ_{max} 248 nm (3.91); ν_{max} 3 434br, 2 944, 1 740, 1 702, 1 654, 1 574, 1 425, 1 306, 1 195, 975, 883, 765, and 750 cm^{-1}; δ_H($CDCl_3$) 5.92 (1 H, dd, *J* 1.5, 0.5 Hz, 10-H), 5.85 (1 H, dd, *J* 2.2, 0.5 Hz, 12-H), 4.75 (1 H, dd, *J* 2.2, 1.5 Hz, 11-H), 3.76 and 3.67 (2 × 3 H, 2 s, 2 × OMe), and 3.47 (3 H, s, NMe).

(*b*) A solution of bromine (0.014 ml, 0.26 mmol) in MeOH** (7.5 ml) was added to a solution of 10-methoxy-1-methyl-3,9-propeno-8-aza-9*H*-xanthine (**33**) (45 mg, 0.18 mmol) in MeOH (7.5 ml) and the mixture was stirred at room temperature for 20 min. The solvent was removed under reduced pressure and the residue was subjected to PLC [CH_2Cl_2–MeOH (95:5)] to give the title product (**34**) (47 mg, 71.2%), R_f 0.72; m.p. 180–182 °C; identical (mixed m.p., IR and ^1H NMR spectra) with a sample prepared under method (*a*).

* *Systematic name: trans*-5-methoxy-7-methyl-4-methylsulphonyloxy-4,5-dihydro-1,2,2a,5a,7-penta-aza-acenaphthylene-6,8(3*H*,7*H*)-dione.

† *Systematic name:* 5-methoxy-7-methyl-1,2,2a,5a,7-penta-aza-acenaphthylene-6,8(5*H*,7*H*)-dione.

‡ *Systematic name: trans*-4-bromo-3-methoxy-7-methyl-4,5-dihydro-1,2,2a,5a,7-penta-aza-acenaphthylene-6,8(3*H*,7*H*)-dione.

¶ *Systematic name:* 3-methoxy-7-methyl-1,2,2a,5a,7-penta-aza-acenaphthylene-6,8(3*H*,7*H*)-dione.

‖ *Systematic name:* 4-bromo-3,5-dimethoxy-7-methyl-4,5-dihydro-1,2,2a,5a,7-penta-aza-acenaphthylene-6,8(3*H*,7*H*)-dione.

** **CAUTION**: There are warnings in the literature that this mixture could cause an explosion.

References

1 J. A. Montgomery, R. D. Elliott, and H. J. Thomas, *Ann. N. Y. Acad. Sci.*, 1975, **255**, 292.

2 M. Jokić and V. Škarić, *J. Chem. Soc., Perkin Trans. 1*, 1989, 757.

3 V. Škarić and B. Kašnar, *Croat. Chem. Acta*, 1985, **58**, 583.
4 V. Škarić and M. Jokić, *Croat. Chem. Acta*, 1983, **56**, 125.
5 J. Zimmermann and D. Seebach, *Helv. Chim. Acta*, 1987, **70**, 1104.
6 J. March, 'Advanced Organic Chemistry,' McGraw-Hill Kogakusha, Tokyo, 1977, p. 758.
7 A. Padwa, *Angew. Chem.*, 1976, **88**, 131.
8 T. Sasaki, K. Minamoto, T. Suzuki, and S. Yamashita, *Tetrahedron*, 1980, **36**, 865.
9 A. Holý and G. S. Ivanova, *Nucleic Acid Res.*, 1974, **1**, 19.
10 V. Škarić, D. Erben, Z. Raza, and D. Škarić, *Croat. Chem. Acta*, 1979, **52**, 281.
11 P. D. Barlett, and D. S. Tarbell, *J. Am. Chem. Soc.*, 1963, **85**, 466.
12 J. P. H. Verheyden, I. D. Jenkins, G. R. Owen, S. D. Dimitrijevich, C. M. Richards, P. C. Srivastava, N. Le-Hong, and J. E. Moffat, *Ann. N. Y. Acad. Sci.*, 1975, **255**, 151 and references cited therein.
13 T. Sasaki, K. Minamoto, T. Suzuki, and T. Sugiura, *J. Am. Chem. Soc.*, 1978, **100**, 2248.
14 R. G. Carlson and R. Ardon, *J. Org. Chem.*, 1971, **36**, 216.

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