Synthesis and Antitumor Activity of Phenyl Carbocyclic Oxetanocin and Related Compounds[1)]

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Reaction of *trans*-2,3-bis[(*tert*-butyldimethylsilyl)oxymethyl]-1-cyclobutanone (4a) with phenylmagnesium bromide or lithiated aromatic compounds gave two adducts, the (1*R,2*R**,3*R**) isomers (5a—c) and the (1*R**,2*S**,3*S**) isomers (6a—c). The major products (5a, c) were treated with tetrabutylammonium fluoride to give the (1*R**,2*R**,3*R**)-1-aryl-2,3-bis(hydroxymethyl)-1-cyclobutanols (1a, c). The 3-(oxazol-2-yl)-phenyl adduct 5b was converted to the benzamide congener 1b in 6 steps. On catalytic reduction of 1a with Raney Ni the stereochemistry at C-1′ was mostly retained, but in the case of 10% Pd–C catalyst, steric inversion occurred. Compounds 1a—c displayed no cytotoxicity towards human nasopharyngeal carcinoma KB cell line.**

Key words nucleoside analogue; cyclobutanol; addition reaction; catalytic reduction; antitumor activity

Carbocyclic oxetanocins (C.OXTs) are nucleoside analogues in which the sugar moiety is replaced with a cyclobutane ring instead of the usual pentofuranose. C.OXTs have attracted much attention because of their antiviral activities, especially against several DNA viruses.[2)] We have already reported the synthesis of C.OXTs and their analogues.[3)] In particular, the guanine congener (C.OXT-G) has been proved to be an excellent anti-herpes simplex virus (HSV) agent *in vitro*[3b,c)] and *in vivo*.[4)] The antiviral activity of 3′-fluorocarbocyclic oxetanocin A (F-C.OXT-A) against human cytomegalovirus (HCMV) is superior to that of ganciclovir.[5)] However, no analogue which shows antitumor activity has been obtained. Recently, Krohn *et al.* reported that benzamide riboside, the *C*-glycosidic analogue of nicotinamide riboside, shows potent cytotoxicity to S49.1 lymphoma cells at nanomolar concentration.[6)] That prompted us to explore the synthesis and antitumor activity of benzamide analogues which bear cyclobutanol (Fig. 1).

Addition to the Cyclobutanones By analogy with Krohn's method,[6)] addition of an organometallic reagent to the ketone moiety was employed to introduce an aryl group onto the cyclobutane. Thus, (±)-*trans*-1,2-bis-(3,3-diethoxycyclobutylen)methanol (**2**)[3a)] was subjected successively to reaction with *tert*-butyldimethylsilyl chloride, and acid treatment to afford *trans*-2,3-bis[(*tert*-butyldimethylsilyl)oxymethyl]-1-cyclobutanone (**4a**).[7)] The di-*O*-trityl derivative **4b** was also obtained in a similar way. When the cyclobutanone **4a** was treated with phenylmagnesium bromide, two adducts **5a** and **6a** were obtained in 79% and 11% yields, respectively, and the starting material was recovered in 5% yield. The major product **5a** was deprotected by treatment with tetrabutylammonium fluoride to give **1a**, which was identified as the (1*R**,2*R**,3*R**)-2,3-bis(hydroxymethyl)-1-phenyl-1-cyclobutanol based on the nuclear Overhauser effect (NOE) observed between H2 and H2′ or H4′a in the two-dimensional NOE (NOESY) spectrum (Fig. 2). Consequently, **6a** was the (1*R**,2*S**,3*S**) isomer. This preference could be explained in terms of the steric hindrance of the ketone **4a**. When a trityl group was employed as the hydroxyl-protecting group, stereoselectivity was somewhat improved to give **5d** and **6d** in 89% and 9% yields, respectively. Introduction of the benzamide was carried out in 7 steps as follows. 2-(3-Bromophenyl)-4,5-dihydro-4,4-dimethyloxazole[8)] was converted to the lithiated congener with *n*-butyllithium and reacted subsequently with the ketone **4a** to give **5b** and **6b**. Acid treatment of the major product **5b** in methanol gave the ester, which, upon hydrolysis and acetylation, gave the carboxylic acid **7**. Compound **7** was converted to the carboxamide **8** *via* the acid chloride, then the acetyl group was removed by treatment with ammonia in MeOH to give 3-[(1*R**,2*R**,3*R**)-1-hydroxy-2,3-bis(hydroxymethyl)cyclobut-1-yl]benzamide (**1b**). The ^{1}H-NMR spectrum of the product showed a doublet at 7.3—8.0 attributable to carboxamide protons. Mass spectroscopic data (M^+, *m/z* 251) also supported the structure. Addition of a 3-cyanophenyl carbanion to **4a** in the same manner as described for **5a** and subsequent

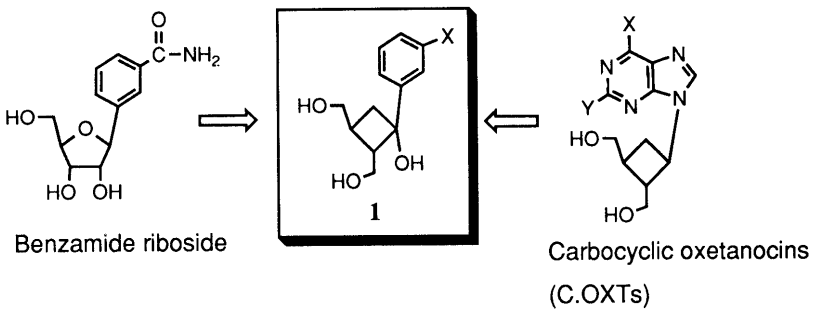

Fig. 1

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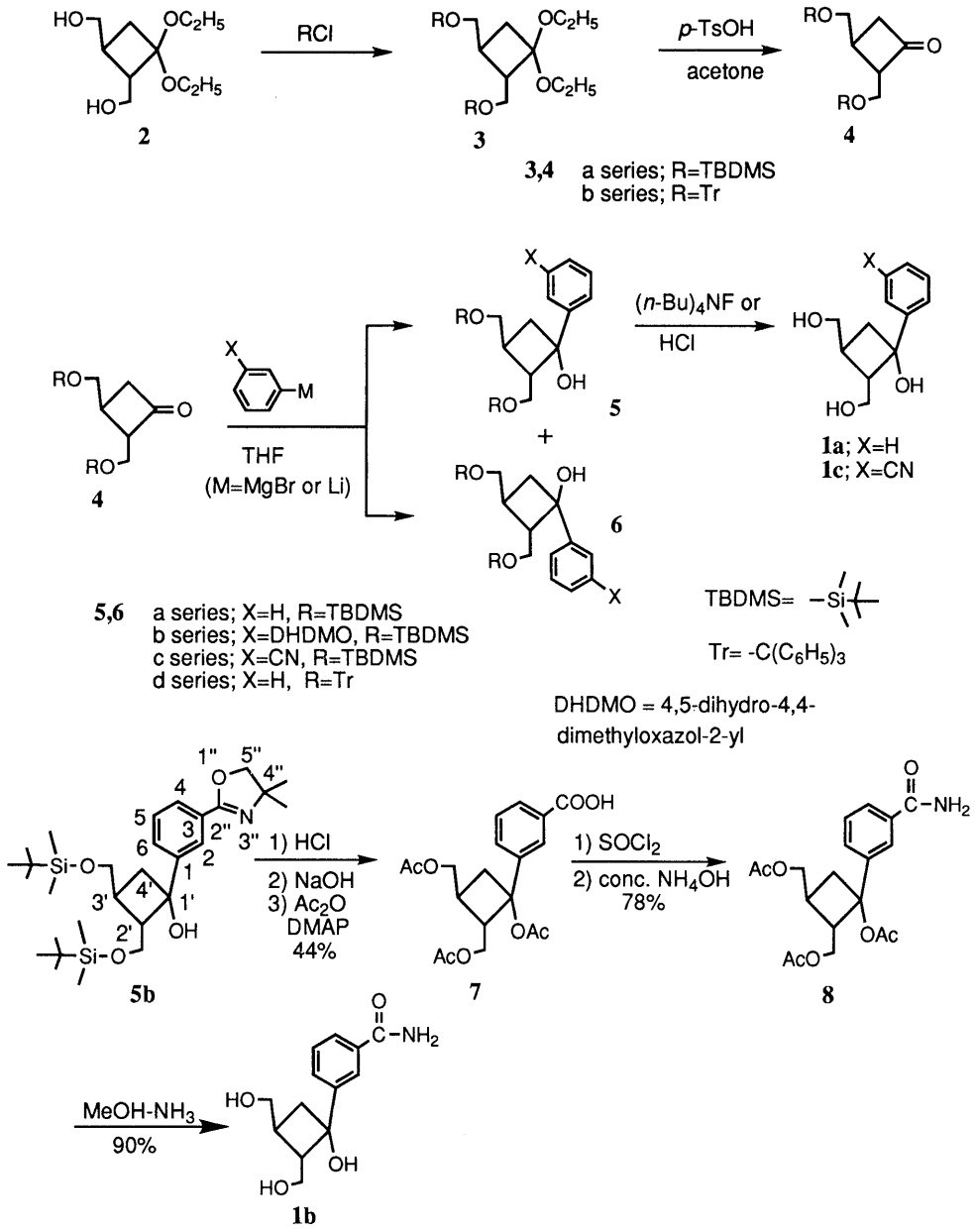

Chart 1

removal of the protecting group gave the 3-cyanophenyl congener **1c** (Chart 1).

Synthesis of Phenyl Carbocyclic Oxetanocin Ishigami *et al.*[9] have developed a method to prepare cyclobutyl *C*-nucleosides by use of the Barton radical reaction. But the C–C bond-forming position is variable depending on the individual aromatic compounds. As a result, the yields of *C*-nucleosides were not satisfactory. Also, the use of a photochemical method with a tungsten lamp is restrictive for large-scale preparation. That prompted us to explore a new method for the synthesis of cyclobutyl *C*-nucleosides from the 1-aryl-1-cyclobutanol **1**. Removal of the 1-hydroxyl group of **1a** by catalytic reduction was examined. In the case of Raney nickel in EtOH, two reduced products (**9a**, **b**) were obtained in 61% and 4% yields, respectively. In the ^{1}H-NMR spectrum of the minor product **9b**, signals of the 2′-methylene (2′-C$\underline{H}_2$OH) appeared at relatively high field compared with those of **9a**, suggesting strong diamagnetic shielding caused by the nearby benzene ring. In consequence, **9b** was assigned the (1*R**,2*R**,3*R**)-3-phenyl-1,2-biscyclobutylenmethanol structure. This was substantiated by the NOESY spectrum. The major product **9a** was assigned the (1*R**,2*S**,3*S**)-3-phenyl-1,2-biscyclobutylenmethanol structure. The two hydroxymethyl groups in **1a** and **9a** were presumed to take a quasi equatorial conformation based on the NOE between H2′ and H4′b. However, NOE between these protons was not observed in **9b**, suggesting that the hydroxymethyl groups of **9b** take quasi axial conformation (Fig. 2). To improve the selectivity and yield for **9a**, reduction using 10% Pd–C as a catalyst was examined, but thin-layer chromatography (TLC) of the reaction mixture indicated that the (1*R**,2*R**,3*R**)-isomer **9b** was the sole product.

Antitumor Activity Krohn *et al.* reported that the benzamide riboside shows potent cytotoxicity to S49.1 lymphoma cells at nanomolar concentration. Therefore, the antitumor activity of the cyclobutanols **1a**—**c** was

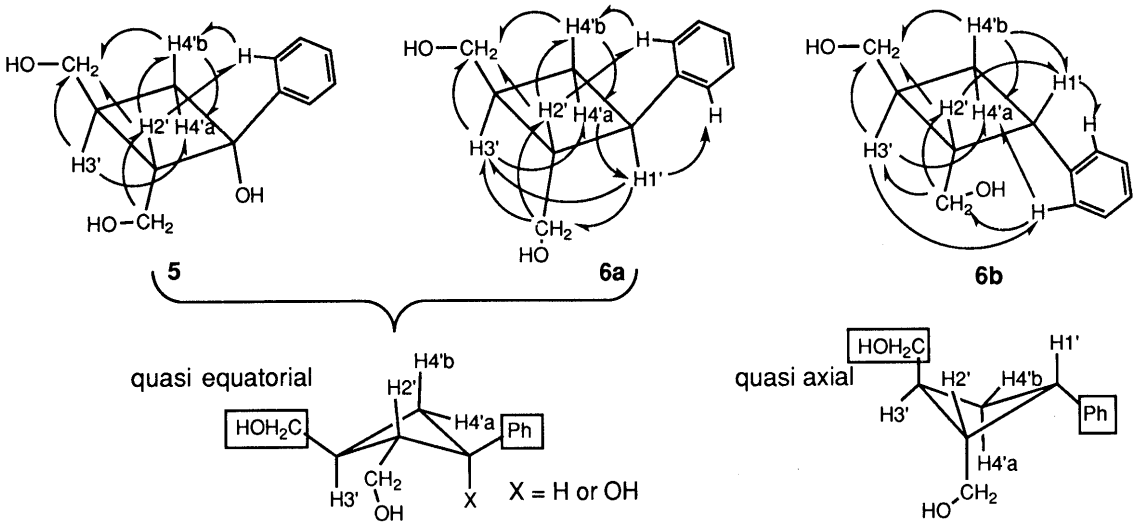

Fig. 2. NOESY Spectra of Compound **5** and **6a, b**

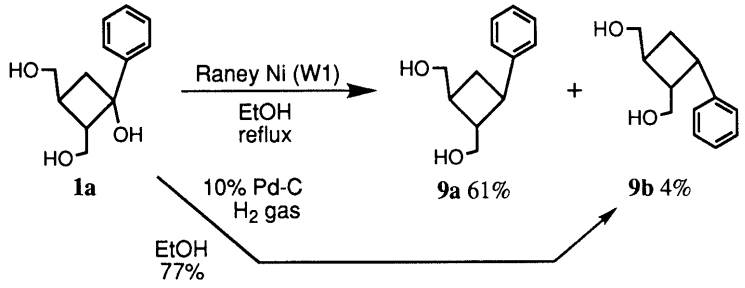

Chart 2

evaluated using human nasopharyngeal carcinoma KB cell line as described in the experimental section. These compounds, including the benzamide congener **1b**, displayed no activity against KB cells. This result indicates that the replacement of ribofuranose with 2,3-bis(hydroxymethyl)-1-cyclobutanol diminishes the antitumor activity of benzamide riboside. Reduced affinity for cellular nucleoside kinase or weaker activity against a target enzyme in tumor cells might explain these results.

Experimental

Melting points (mp) were determined using a Yanagimoto micro-melting point apparatus (hot stage type) without correction. UV spectra were recorded with a Shimadzu UV-190 digital spectrometer. Low-resolution mass spectra were obtained on a JEOL JMS-AX500 mass spectrometer in the direct-inlet mode. ^{1}H-NMR spectra were recorded on a Varian UNITY 200 (200 MHz) or UNITY 600 (600 MHz) in $CDCl_3$ (or dimethyl sulfoxide (DMSO)-d_6) with tetramethylsilane as an internal standard. Merck Art 5554 plates precoated with Silica gel 60 containing the fluorescent indicator F_{254} were used for TLC and Silica gel 60 (Merck 7734, 60—200 mesh) was employed for column chromatography.

***trans*-2,3-Bis[(*tert*-butyldimethylsilyl)oxymethyl]-1,1-diethoxycyclobutane (3a)** To an ice-cooled solution of *trans*-1,2-bis-(3,3-diethoxycyclobutylen)methanol (**2**, 3.5 g, 17.2 mmol) and imidazole (5.86 g, 86 mmol) in dry dimethylformamide (DMF) (300 ml) was added *tert*-butyldimethylsilyl chloride (6.48 g, 43 mmol) and the solution was stirred at 0 °C for 1 h, then diluted with benzene (300 ml). The organic layer was washed with water twice (600 ml), dried over $MgSO_4$ and concentrated to a small volume. This solution was chromatographed over a column of Silica gel G (3.2 × 28 cm) with 10% AcOEt in hexane (1.6 l) to give a syrup (7.08 g, 95%). ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 3.81 (1H, dd, J=8.4, 10.1 Hz, one of 2-CH_2O), 3.47—3.63 (3H, m, one of 2-CH_2O, 3-CH_2O), 3.41 (2H, q, J=7.1 Hz, $OC\underline{H}_2CH_3$), 3.43 (2H, q, J=7.0 Hz, $OC\underline{H}_2CH_3$), 2.17—2.31 (2H, m, H-2, H-4a), 1.71—1.81 (2H, m, H-3, H-4b), 1.16 (3H, t, J=7.0 Hz, $OCH_2C\underline{H}_3$), 1.15 (3H, t, J=7.1 Hz, $OCH_2C\underline{H}_3$), 0.08 (18H, $C(CH_3)_3 \times 2$), 0.04 (12H, $Si(CH_3)_2 \times 2$). MS m/z: 431 $(M-1)^+$, 417 $(M-CH_3)^+$, 375 $(M-C(CH_3)_3)^+$.

***trans*-2,3-Bis[(*tert*-butyldimethylsilyl)oxymethyl]-1-cyclobutanone (4a)** To an ice-cooled solution of **3a** (5.51 g, 12.8 mmol) in acetone (260 ml) was added *p*-toluenesulfonic acid (200 mg). The solution was stirred at 0 °C for 1 h and poured into the mixture of benzene (100 ml) and hexane (50 ml). The organic layer was washed with water three times (300 ml), dried over $MgSO_4$ and evaporated to a small volume. This solution was chromatographed over a column of Silica gel G (3.0 × 28 cm) with 10% AcOEt in hexane (2.0 l) to give a syrup (4.27 g, 93%). ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 3.90 (1H, dd, J=4.4, 10.6 Hz, one of 2-CH_2O), 3.79 (2H, dd, J=2.1, 4.9 Hz, 3-CH_2O), 3.69 (1H, ddd, J=0.7, 3.9, 10.5 Hz, one of 2-CH_2O), 3.22 (1H, m, H-2), 2.85 (2H, m, H-4), 2.65 (1H, m, H-3), 0.88 (*ca.* 18H, $C(CH_3)_3 \times 2$), 0.03—0.06 (*ca.* 12H, $Si(CH_3)_3 \times 2$). MS m/z: 359 $(M+1)^+$, 343 $(M-CH_3)^+$, 301 $(M-C(CH_3)_3)^+$.

1,1-Diethoxy-*trans*-2,3-bis(trityloxymethyl)cyclobutane (3b) Compound **2** (1.36 g, 6.7 mmol) and trityl chloride (7.45 g, 26.7 mmol) were dissolved in pyridine (80 ml) and the solution was stirred at room temperature for 1 d. After addition of water (10 ml), the solution was evaporated and the residue was partitioned between $CHCl_3$ (100 ml) and water (100 ml). The organic layer was washed with water twice (200 ml), dried over $MgSO_4$ and evaporated. The residue was evaporated azeotropically with toluene three times (120 ml) and chromatographed over a column of Silica gel G (5.0 × 40 cm) with benzene (2 l) to afford a white solid (3.5 g, 76%). mp 165.5—166 °C. ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 7.17—7.45 (*ca.* 30H, m, $C(C_6H_5)_3 \times 2$), 3.37—3.73 (5H, m, $OC\underline{H}_2CH_3 \times 2$, one of 2-$CH_2O$), 3.02—3.19 (3H, m, one of 2-CH_2O,3-CH_2O), 2.45 (1H, m, H-2), 2.28 (1H, dd, J=8.0, 10.2 Hz, H-4a), 1.87 (1H, m, H-3), 1.72 (1H, m, H-4b), 1.21 (3H, t, J=7.1 Hz, $OCH_2C\underline{H}_3$), 1.17 (3H, t, J=7.1 Hz, $OCH_2C\underline{H}_3$). MS m/z: 688 (M^+). *Anal.* Calcd for $C_{48}H_{48}O_4$: C, 83.69; H, 7.02. Found: C, 83.58; H, 7.24.

***trans*-2,3-Bis(trityloxymethyl)-1-cyclobutanone (4b)** In a manner similar to that described for **4a**, **3b** (770 mg, 1.12 mmol) was treated with *p*-toluenesulfonic acid (100 mg) in acetone (120 ml) to afford a white solid (590 mg, 86%). mp 90—92 °C. ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 7.15—7.58 (*ca.* 30H, m, $C(C_6H_5)_3 \times 2$), 3.45 (1H, m, one of 2-CH_2O), 3.36 (1H, dd, J=5.3, 9.3 Hz, one of 3-CH_2O), 3.16—3.29 (3H, m, one of 2-CH_2O, one of 3-CH_2O, H-2), 3.07 (1H, m, H-4a), 2.86 (1H, m, H-4b), 2.78 (1H, m, H-3). MS m/z: 371 $(M-Tr)^+$.

Addition of Phenylmagnesium Bromide to the Ketone 4a To an ice-cooled solution of **4a** (716 mg, 2 mmol) in dry tetrahydrofuran (THF) (10 ml) was added 3 M solution of phenylmagnesium bromide in THF (1.33 ml, 4 mmol). The mixture was stirred for 45 min, then 20% NH_4Cl solution (50 ml) was added. After addition of benzene (50 ml) to the solution, the organic layer was washed with water twice (60 ml), dried over $MgSO_4$ and evaporated to a small volume. This solution was chromatographed over a column of Silica gel G (2.2 × 52 cm) with 0—7% AcOEt in hexane. The starting material was recovered from the first fraction in 5% yield. Evaporation of the second fraction gave (1*R**,2*R**,3*R**)-2,3-bis[(*tert*-butyldimethylsilyl)oxymethyl]-1-phenyl-1-cyclobutanol (**5a**) as a caramel (687 mg, 79%). ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 7.2—7.6 (5H, m, C_6H_5), 4.05 (1H, s, 1′-OH), 3.96 (1H, dd, J=3.5, 10.7 Hz, one of 2′-CH_2O), 3.90 (1H, dd, J=5.9, 10.7 Hz, one of 2′-CH_2O), 3.69 (1H, dd, J=4.6, 10.2 Hz, one of 3′-CH_2O), 3.61 (1H, dd, J=6.0, 10.1 Hz, one of 3′-CH_2O), 2.65 (2H, m, H-2′, H-3′), 2.27 (2H, d, J=1.8, 8.4 Hz, H-4′), 0.90 (9H, s, $C(CH_3)_3$), 0.89 (9H, s, $C(CH_3)_3$), 0.09 (3H, s, $SiCH_3$), 0.06 (3H, s, $SiCH_3$), 0.05 (3H, s, $SiCH_3$), 0.01 (3H, s, $SiCH_3$). MS *m/z*: 419 $(M-OH)^+$, 379 $(M-C(CH_3)_3)^+$, 305 $(M-OSiC(CH_3)_3(CH_3)_2)^+$, 287 $(M-OSiC(CH_3)_3(CH_3)_2-H_2O)^+$. The third fraction was evaporated to give (1*R**,2*S**,3*S**)-2,3-bis[(*tert*-butyldimethylsilyl)oxymethyl]-1-phenyl-1-cyclobutanol (**6a**) as a caramel (85 mg, 10%). ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 7.25—7.55 (5H, m, C_6H_5), 3.77 (2H, dd, J=0.9, 3.6 Hz, 3′-CH_2O), 3.38 (1H, s, 1′-OH), 3.24 (2H, dd, J=1.2, 7.3 Hz, 2′-CH_2O), 2.90 (1H, m, H-4′a), 2.58 (1H, dq, J=1.8, 6.7 Hz, H-2′), 1.18 (2H, m, H-3′, H-4′b), 0.96 (9H, s, $C(CH_3)_3$), 0.80 (9H, s, $C(CH_3)_3$), 0.14 (3H, s, $SiCH_3$), 0.02 (3H, s, $SiCH_3$), −0.12 (3H, s, $SiCH_3$), −0.17 (3H, s, $SiCH_3$). MS *m/z*: 379 $(M-C(CH_3)_3)^+$, 287 $(M-OSiC(CH_3)_3(CH_3)_2-H_2O)^+$.

Addition of Phenylmagnesium Bromide to the Ketone 4b In a manner similar to that described for **5a**, **4b** (300 mg, 0.49 mmol) was reacted with phenylmagnesium bromide (1.0 mmol), and the mixture was separated by silica gel column chromatography. Evaporation of the first fraction gave (1*R**,2*R**,3*R**)-2,3-bis(trityloxymethyl)-1-phenyl-1-cyclobutanol (**5d**) as a caramel (300 mg, 89%). ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 7.2—7.6 (*ca.* 35H, m, $C(C_6H_5)_3 \times 2$, C_6H_5), 3.55 (1H, dd, J=3.8, 7.6 Hz, one of 2′-CH_2O), 3.36 (1H, t, J=7.6 Hz, one of 2′-CH_2O), 3.12 (2H, m, 3′-CH_2O), 2.98 (1H, m, H-2′), 2.63 (1H, s, 1′-OH), 2.53 (1H, m, H-3′), 2.10 (2H, m, H-4′). The second fraction was evaporated to give (1*R**,2*S**,3*S**)-2,3-bis(trityloxymethyl)-1-phenyl-1-cyclobutanol (**6d**) as a caramel (32 mg, 9%). ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 7.2—7.6 (*ca.* 35H, m, $C(C_6H_5)_3 \times 2$, C_6H_5), 3.24 (2H, t, J=5.9 Hz, 3′-CH_2O), 2.95 (1H, dd, J=5.5, 8.6 Hz, one of 2′-CH_2O), 2.65—2.9 (2H, m, H-2, one of 2′-CH_2O), 2.58 (1H, t, J= 9.2 Hz, H-4′a). 2.38 (1H, s, 1′-OH), 2.07 (1H, dd, J=9.2, 2.6 Hz, H-4′b), 1.90 (1H, m, H-3′).

(1*R,2*R**,3*R**)-2,3-Bis(hydroxymethyl)-1-phenyl-1-cyclobutanol (1a) Method A** To a solution of **5a** (658 mg, 1.51 mmol) in THF (10 ml) and AcOH (0.24 ml) was added tetrabutylammonium fluoride (1 M solution in THF, 4 ml, 4 mmol) and the solution was stirred at room temperature overnight, then concentrated to a small volume. The residue was chromatographed over a column of Silica gel G (2.0 × 20 cm) with 8% EtOH in $CHCl_3$ (500 ml) to give a syrup, which was passed through a column of Amberlite IR 120B (H^+, 30 ml) to give a gum (318 mg, quantitative). ^{1}H-NMR (200 MHz, DMSO-d_6) δ: 7.17—7.45 (5H, m, C_6H_5), 5.12 (1H, s, 1′-OH), 4.49 (1H, br s, 3′-OH), 4.31 (1H, br s, 2′-OH), 3.69 (1H, dd, J=10.7, 7.3 Hz, one of 2′-CH_2O), 3.52 (1H, dd, J=10.7, 6.4 Hz, one of 2′-CH_2O), 3.44 (2H, m, 3′-CH_2O), 2.38 (1H, m, H-2′), 2.28 (1H, m, H-3′), 2.08 (1H, dd, J=11.7, 8.3 Hz, H-4′a), 2.04 (1H, dd, 11.7, 9.0 Hz, H-4′b). MS *m/z*: 190 $(M-H_2O)^+$.

Method B A solution of **5d** (106 mg, 0.15 mmol) in MeOH (3 ml) was treated with 1 N HCl (1 ml). The solution was stirred at 65 °C for 1 h, then Amberlite IR400 (OAc^-, 5 ml) was added. After removal of the resin by filtration, the filtrate was evaporated and the residue was chromatographed over a column of Silica gel G (2.3 × 30 cm) with 0—9% EtOH in $CHCl_3$ (1.0 l) to give a syrup (25 mg, 78%). The sample thus obtained was identical with that described above.

Addition of Lithiated Oxazolylbenzene to the Ketone 4a A solution of 2-(3-bromophenyl)-4,5-dihydro-4,4-dimethyloxazole (2.67 g, 10.5 mmol) in dry THF was cooled at −78 °C under an N_2 atmosphere and *n*-butyllithium (1.6 M solution in THF, 6.6 ml, 10.5 mmol) was added dropwise. The mixture was stirred for 30 min. A solution of **4a** (2.5 g, 7.0 mmol) in dry THF (20 ml) was added dropwise to the solution and the reaction was continued for a further 2 h, then the solution was warmed to room temperature. Water (100 ml) was added and the organic layer was taken and evaporated to dryness. The residue was dissolved in benzene (100 ml) and the solution was washed with water twice (200 ml), dried over $MgSO_4$ and evaporated to a small volume. This solution was chromatographed over a column of silica gel G (3.0 × 32 cm) with 25% AcOEt in benzene (2.0 l). Evaporation of the first fraction gave (1*R**,2*R**,3*R**)-2,3-bis[(*tert*-butyldimethylsilyl)oxymethyl]-1-[3-(4,5-dihydro-4,4-dimethyloxazol-2-yl)phenyl]-1-cyclobutanol (**5b**) as a syrup (2.42 g, 65%). ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 7.32—8.04 (4H, phenyl), 4.10 (1H, s, 1′-OH), 4.09 (2H, s, 5″-CH_2), 3.93 (2H, m, 3′-CH_2O), 3.65 (2H, m, 2′-CH_2O), 2.68 (2H, m, H-2′, H-3′), 2.27 (2H, m, H-4′), 1.38 (6H, s, 4″-$CH_3 \times 2$), 0.88 (*ca.* 18H, $C(CH_3)_3 \times 2$), 0.04—0.09 (*ca.* 12H, $Si(CH_3)_2 \times 2$). MS *m/z*: 534 $(M+1)^+$, 476 $(M-C(CH_3)_3)^+$. The second fraction was evaporated to give (1*R**,2*S**,3*S**)-2,3-bis[(*tert*-butyldimethylsilyl)oxymethyl]-1-[3-(4,5-dihydro-4,4-dimethyloxazol-2-yl)phenyl]-1-cyclobutanol (**6b**) as a syrup (0.26 g, 7%). ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 7.34—8.00 (4H, phenyl), 4.10 (2H, s, 5″-CH_2), 3.75 (4H, 2′-CH_2O, 3′-CH_2O), 3.59 (1H, s, 1′-OH), 2.93 (1H, m, H-4′a), 2.58 (1H, m, H-2′), 2.12 (2H, m, H-3′, H-4′b), 1.38 (6H, s, 4″-$CH_3 \times 2$), 0.95 (9H, $C(CH_3)_3$), 0.78 (9H, $C(CH_3)_3$), 0.12 (6H, $Si(CH_3)_2$), −0.17 (3H, s, $SiCH_3$), −0.20 (3H, s, $SiCH_3$).

3-[(1*R,2*R**,3*R**)-1-Acetyloxy-2,3-bis(acetyloxymethyl)cyclobut-1-yl]benzoic Acid (7)** A solution of **5b** (1.0 g, 1.88 mmol) in MeOH (40 ml) and 1 N HCl (4 ml) was refluxed for 3 h and the solution was evaporated to dryness. The residue was dissolved in a mixture of 2 N NaOH (4 ml) and MeOH (6 ml) and the solution was refluxed for 4 h, neutralized with 1 N HCl and evaporated to dryness. To the residue were successively added triethylamine (2 ml), acetic anhydride (1.3 ml) and 4-dimethylaminopyridine (10 mg) and the solution was stirred at room temperature for 4 h. After evaporation of the solution, the residue was dissolved in CH_2Cl_2 (30 ml) and the organic layer was washed with water twice (60 ml), dried over $MgSO_4$ and concentrated to a small volume. This solution was chromatographed over a column of Silica gel G (2.6 × 33 cm) with 0—10% MeOH in CH_2Cl_2 (1.6 l) to give a caramel (310 mg, 44%). ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 7.43—8.20 (4H, phenyl), 4.56 (1H, dd, J=7.8, 11.4 Hz, one of 2′-CH_2O), 4.34 (1H, dd, J=5.7, 11.4 Hz, one of 2′-CH_2O), 4.12 (2H, m, 3′-CH_2O), 2.76 (2H, m, H-4′), 2.66 (2H, m, H-2′, H-3′), 2.05—2.10 (9H, OAc × 3). MS *m/z*: 361 $(M-OH)^+$, 335 $(M-Ac)^+$.

3-[(1*R,2*R**,3*R**)-1-Acetyloxy-2,3-bis(acetyloxymethyl)cyclobut-1-yl]benzamide (8)** To a solution of **7** (236 mg, 0.62 mmol) in $SOCl_2$ (1.7 ml) was added one drop of DMF and the solution was refluxed for 30 min, then ice-cooled. The solution was added dropwise to 4% NH_4OH (35 ml) with stirring and the solution was extracted with CH_2Cl_2 twice (40 ml). The organic layer was washed with water, dried over $MgSO_4$ and concentrated to a small volume. This solution was chromatographed over a column of Silica gel G (2.4 × 24 cm) with 0—10% MeOH in CH_2Cl_2 (800 ml) to give a caramel. Crystallization from ether (2 ml) gave a white crystalline product (183 mg, 78%). mp 134—135 °C. ^{1}H-NMR ($CDCl_3$) δ: 7.38—7.98 (4H, phenyl), 5.90—6.52 (2H, m, $CONH_2$), 4.58 (1H, m, one of 2′-CH_2O), 4.31 (1H, m, one of 2′-CH_2O), 4.10 (2H, m, 3′-CH_2O), 2.71—2.78 (2H, m, H-4′), 2.04—2.09 (2H, m, H-2′, H-3′), 2.03—2.07 (9H, OAc × 3). MS *m/z*: 377 (M^+). *Anal.* Calcd for $C_{19}H_{23}NO_7$: C, 60.47; H, 6.14; N, 3.71. Found: C, 60.66; H, 6.28; N, 3.74.

3-[(1*R,2*R**,3*R**)-1-Hydroxy-2,3-bis(hydroxymethyl)cyclobut-1-yl]-benzamide (1b)** A solution of **8** (302 mg, 0.8 mmol) in MeOH saturated with ammonia at 0 °C was heated in a steel bomb at 50 °C for 1 d, then ice-cooled. The solution was concentrated to a small volume and chromatographed over a column of Silica gel G (2.0 × 30 cm) with 0—25% MeOH in CH_2Cl_2 (800 ml) to give a caramel. Crystallization from AcOEt (2 ml) gave a white crystalline product (181 mg, 90%). mp 140—142 °C. ^{1}H-NMR (200 MHz, DMSO-d_6) δ: 7.31—7.99 (6H, m, phenyl, $CONH_2$), 5.24 (1H, s, 1′-OH), 4.52 (1H, t, J=5.1 Hz, 3′-$CH_2O\underline{H}$), 4.33 (1H, t, J=5.1 Hz, 2′-$CH_2O\underline{H}$), 3.71 (1H, m, one of 2′-CH_2O), 3.57 (1H, m, one of 2′-CH_2O), 3.44 (2H, m, 3′-CH_2O), 2.43 (1H, m, H-2′), 2.40 (1H, m, H-3′), 2.11 (2H, m, H-4′). MS *m/z*: 251 (M^+). *Anal.* Calcd for $C_{13}H_{17}NO_4 \cdot 1/4H_2O$: C, 61.04; H, 6.90; N, 5.48. Found: C, 60.70; H, 6.82; N, 5.66.

Addition of Lithiated Benzonitrile to the Ketone 4a In a manner similar to that described for **5b**, 3-bromobenzonitrile (437 mg, 2.4 mmol) was converted to the 3-lithiated congener with *n*-butyllithium (1.6 M solution in THF, 1.5 ml, 2.4 mmol), followed by reaction with the ketone **4a** (716 mg, 2.0 mmol). The products were separated by silica gel column chromatography. Evaporation of the first fraction gave (1*R**,2*R**,3*R**)-

2,3-bis[*tert*-butyldimethylsilyl)oxymethyl]-1-(3-cyano)phenyl-1-cyclobutanol (**5c**, 621 mg, 67%) as a syrup. ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 7.36—7.87 (4H, phenyl), 4.42 (1H, s, 1′-OH), 3.90 (2H, m, 3′-CH_2O), 3.70 (1H, dd, J=3.8, 10.4 Hz, one of 2′-CH_2O), 3.61 (1H, dd, J=4.1, 10.4 Hz, one of 2′-CH_2O), 2.65—2.76 (2H, m, H-2′, H-3′), 2.29 (2H, m, H-4′), 0.90 (*ca.* 18H, $C(CH_3)_3 \times 2$), 0.06 (*ca.* 12H, $Si(CH_3)_2 \times 2$). MS *m/z*: 462 $(M+1)^+$, 404 $(M-C(CH_3)_3)^+$. The second fraction was evaporated to give (1*R**,2*S**,3*S**)-2,3-bis[(*tert*-butyldimethylsilyl)oxymethyl]-1-(3-cyano)phenyl-1-cyclobutanol (**6c**) (86 mg, 9%) as a syrup. ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 7.37—7.89 (4H, phenyl), 4.01 (2H, s, 1′-OH), 3.76 (1H, d, J=3.2 Hz, 3′-CH_2O), 3.27 (2H, m, 2′-CH_2O), 2.90 (1H, m, H-4′a), 2.58 (1H, m, H-2′), 2.14 (2H, m, H-3′, H-4′), 0.96 (9H, s, $C(CH_3)_3$), 0.78 (9H, s, $C(CH_3)_3$), 0.14 (6H, $Si(CH_3)_2$), −0.17 (3H, s, $SiCH_3$), −0.21 (3H, s, $SiCH_3$).

3-[(1*R,2*R**,3*R**)-1-Hydroxy-2,3-bis(hydroxymethyl)cyclobut-1-yl]-benzonitrile (1c)** To a solution of **5c** (369 mg, 0.80 mmol) in dry THF (5 ml) was added tetrabutylammonium fluoride (1 M solution in THF, 3.2 ml, 3.2 mmol) and the solution was stirred at room temperature for 2 h. After concentration to a small volume, the solution was chromatographed over a column of Silica gel G (2.0 × 23 cm) with 0—20% EtOH in $CHCl_3$ (800 ml) to give a syrup, which was passed through a column of Amberlite IRB 120 (H^+, 30 ml) to afford a gum (144 mg, 77%). ^{1}H-NMR (200 MHz, DMSO-d_6) δ: 7.50—7.88 (4H, phenyl), 5.41 (1H, s, 1′-OH), 4.54 (1H, t, J=4.4 Hz, OH), 4.36 (1H, t, J=4.4 Hz, OH), 3.71 (1H, m, one of 2′-CH_2O), 3.52 (1H, m, one of 2′-CH_2O), 3.44 (2H, m, 3′-CH_2O), 2.42 (1H, m, H-2′), 2.25 (1H, m, H-3′), 2.10 (2H, m, H-4′). MS *m/z*: 215 $(M-H_2O)^+$.

Reduction of 1a with Raney Ni To a solution of **1a** (254 mg, 1.22 mmol) in EtOH (3 ml) was added Raney Ni (W1, 2 ml) and the solution was refluxed for 5 h, then cooled. The catalyst was filtered off and the filtrate was evaporated to give a residue, which was dissolved in a small amount of EtOH and chromatographed over a column of Silica gel G (2.6 × 33 cm) with 0—9% EtOH in $CHCl_3$ (1.5 l). Evaporation of the first fraction gave (1*R**,2*S**,3*S**)-3-phenyl-1,2-biscyclobutylenmethanol (**9a**) (phenyl carbocyclic oxetanocin) as a gum (143 mg, 61%). ^{1}H-NMR (600 MHz, $CDCl_3$) δ: 7.17—7.35 (5H, m, C_6H_5), 3.87 (1H, dd, J=3.5, 9.7 Hz, one of 2′-CH_2O), 3.79 (1H, dd, J=3.6, 9.7 Hz, one of 3′-CH_2O), 3.53 (1H, t, J=9.7 Hz, one of 2′-CH_2O), 3.45 (1H, t, J=9.7 Hz, one of 3′-CH_2O), 3.10 (1H, q, J=10.2 Hz, H-1′), 2.80 (2H, br s, OH × 2), 2.39 (1H, dq, J=10.2, 2.0 Hz, H-4′a), 2.35 (1H, m, H-2′), 2.26 (1H, m, H-3′), 1.74 (1H, q, J=10.2 Hz, H-4′b). MS *m/z*: 192 (M^+). The second fraction was evaporated to afford (1*R**,2*R**,3*R**)-3-phenyl-1,2-biscyclobutylenmethanol (**9b**) as a gum (9 mg, 4%). MS *m/z*: 192 (M^+). ^{1}H-NMR (600 MHz, $CDCl_3$) δ: 7.16—7.35 (5H, m, C_6H_5), 3.76 (1H, dd, J=4.9, 10.2 Hz, one of 3′-CH_2O), 3.64 (1H, dt, J=4.2, 9.0 Hz, H-1′), 3.54 (1H, t, J=10.2 Hz, one of 3′-CH_2O), 3.34 (1H, dd, J=5.2, 10.4 Hz, one of 2′-CH_2O), 3.23 (1H, br s, 3′-OH), 3.02 (1H, t, J=10.4 Hz, one of 2′-CH_2O), 2.71 (1H, br s, 2′-OH), 2.58 (1H, m, H-2′), 2.50 (1H, m, H-3′), 2.37 (1H, m, H-4′a), 2.10 (1H, dt, J=9.0, 12.2 Hz, H-4′b).

(1*R,2*R**,3*R**)-3-Phenyl-1,2-biscyclobutylenmethanol (9b)** A solution of **1a** (73 mg, 0.35 mmol) and 10% Pd–C (30 mg) in EtOH (8 ml) was stirred vigorously at 45 °C for 4.5 h, then cooled. The catalyst was removed by filtration and the filtrate was concentrated to a small volume. This solution was chromatographed over a column of Silica gel G (2.0 × 33 cm) with 0—9% EtOH in $CHCl_3$ (1.5 l) to give a gum (52 mg, 77%). The sample thus obtained was identical with that described in the above section.

Antitumor Activity[10] KB cells (2×10^3 cells/well) were seeded into 96-well plates and incubated overnight for reattachment. Samples were dissolved in water, diluted with medium and applied at appropriate concentrations. Three days after sample exposure, the plates were pulsed with MTT [3-(4,5-dimethyl-2-thiazoyl)-2,5-diphenyl-2*H*-tetrazolium bromide] and incubated for 4 h. Subsequently, DMSO was added to each well and the optical density at 570 nm was read on a biokinetic reader (Bio-Tec Instruments, Winooski, VT).

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