Synthesis of 6,13-Bis(thymidinyl)-5,12-dioxocyclams and the Molecular Structure of the (*R*,*S*)-Isomer

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The three stereoisomers of the 6,13-bis(thymidinyl)dioxocyclam **6** were synthesized through photoreaction of the chromium alkoxycarbene complex **2** and 1-(benzyloxycarbonyl)-4,4-dimethyl-Δ^2-imidazoline. The molecular structure of (*R*,*S*)-**6** was elucidated by X-ray crystallography.

Introduction

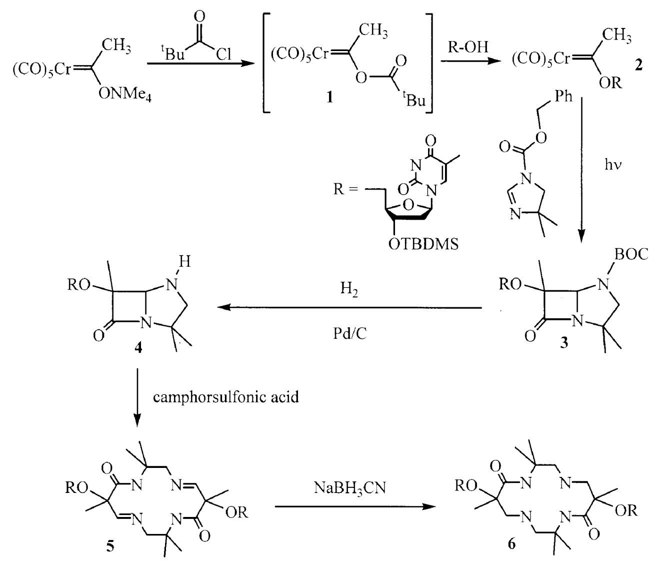
Fourteen-membered 1,4,8,11-tetraaza macrocycles (cyclams) and their 5,7-diones (dioxo cyclams) play important roles as ligands in catalysis as well as in metal complexation chemistry.[1-5] Recently, Hegedus *et al.* have found an unusual and efficient route for the synthesis of the related 1,4,8,11-tetraaza 5,12-dions, which involves the acid-catalyzed cleavage/dimerization of azapenams produced by the photochemical cycloaddition reaction between N-protected imidazolines and chromium (alkoxy)carbene complexes.[6-9] This route has the potential to afford cyclams that are not available by other synthetic methods. The utility of this method has been demonstrated in the synthesis of optically active dioxocyclams by employing optically active imidazolines.[9] However, optically active chromium carbene complexes have not been attempted in the synthesis of optically active dioxocyclams having substituents at the 6- and the 13-position.

Interesting and novel properties have been found for supramolecular complexes in which interacting components are associated by non-covalent interactions.[10] Nucleosides are good candidates for components interacting by hydrogen bonding.[11] Here we report the synthesis and photochemical reaction of the chromium carbene complex that has a thymidine moiety as the alkoxy substituent at the carbene carbon.

Results and Discussion

The dioxocyclams **6** were synthesized as a mixture of diastereomers through the route shown in Scheme 1: The chromium (pivaloyl)oxycarbene complex **1** was generated by the reaction of pivaloyl chloride and pentacarbonyl[methyl{(tetramethylammonio)oxy}carbene]chromium(0). The pivaloyloxy group was substituted by the thymidine derivative for which the secondary hydroxy group was protected with the *tert*-butyldimethylsilyl (TBDMS) group to give the alkoxycarbene complex **2**.

A dichloromethane solution of carbene complex **2** and 1-(benzyloxy)carbonyl-4,4-dimethyl-Δ^2-imidazoline in a Pyrex tube was irradiated under CO pressure (80 psi) with a medium-pressure mercury lamp. The combined yield of N-

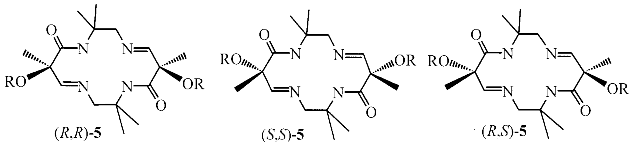


Scheme 1. The synthetic route for the cyclames **6**.

protected azapenams **3** was high (80%), but a diastereomeric mixture was obtained. The best yield resulted by using slightly less than one equivalent of the imidazoline. Excess imidazoline appeared to induce side reactions with the carbene complex. Each diastereomer was found to exist as a mixture of rotomers about the amide bond.

The benzyloxycarbonyl (BOC) group was removed readily at room temperature by Pd-catalyzed hydrogenolysis reaction in the presence of triethylamine to give free azapenams **4**. The formation of hexahydrodiazepinones has been observed under acidic conditions.[9] The virtual 1 : 1 ratio of the diastereomers was clearly determined by ^{1}H NMR, although separation was not feasible.

The 14-membered cyclic compounds **5** were formed in almost quantitative yield by treatment of the free azapenams **4** with camphorsulfonic acid. All three possible diastereomers were produced with insignificant selectivity: (*R*,*R*)-**5** : (*S*,*S*)-**5** : (*R*,*S*)-**5** = 3 : 3 : 4. Interconversion between diastereomers has been known for the methoxy analogues to give the centrosymmetric isomer in high yield by crystallization under acidic conditions.[8] Only slow decomposition to unidentified polar species was observed in a similar attempt with **5** to obtain one isomer as the predominant product. Fortunately, however, separation of (*R*,*S*)-**5** from the mixture of (*R*,*R*)-**5** and (*S*,*S*)-**5** was achieved by conventional column chromatography on silica gel.



(*R*,*R*)-**5** (*S*,*S*)-**5** (*R*,*S*)-**5**

Reduction of **5** with sodium cyanoborohydride gave the dioxocyclams **6**. In $CDCl_3$ solution (*R*,*S*)-**6** exists as two distinct conformers in about 7 : 3 ratio, as evidenced by doubling of all peaks in the ^1H and ^{13}C NMR spectra. However, only one set of resonance peaks was observed in the ^1H and ^{13}C NMR spectra for each of the (*R*,*R*)- and the (*S*,*S*)-isomer. The stereochemistry of (*R*,*S*)-**6** was confirmed by X-ray diffraction analysis: Details of the X-ray data collection and structural refinement are presented in Table 1. The molecular structure and atom-numbering schemes are given in Figure 1. Selected bond lengths and angles are given in Table 2. Notable features of the crystal structure are the unsymmetrical interactions of the two thymidine units. One is interacting in an intramolecular fashion through hydrogen bonding between N(8) and O(1) (2.942 Å) while the other is interacting with another molecule through hydrogen bonding between N(6) and O(2) (2.849 Å).

Experimental Section

General. If not otherwise stated, all NMR spectra were

Table 1. Crystallographic Data for (*R*,*S*)-**6**

molecular formula	$C_{48}H_{84}N_8O_{12}Si_2$
formula weight	1021.41
crystal system	monoclinic
space group	$P2_1$
a, Å	15.7177(2)
b, Å	11.6221(2)
c, Å	18.0412(3)
β, deg	115.3390(10)
V, Å^3	2978.57
Z	2
d_{calcd}, g cm^{-3}	1.139
crystal dimens, mm^3	0.16 × 0.45 × 0.55
temp, K	163(2)
radiation, Å	0.71073
linear abs coeff, cm^{-1}	0.119
θ range, deg	1.25 to 23.25
no. of data collcd	13912
no. of unique data	8206
no. of params refined	631
GOF	1.104
$R(F)^a$	0.0540
$R_w(F)^b$	0.1543

$^aR = \Sigma||F_o| - |F_c|| / \Sigma|F_o|$. $^bR_w = [\Sigma w(|F_o| - |F_c|)^2 / \Sigma w|F_o|^2]^{1/2}$

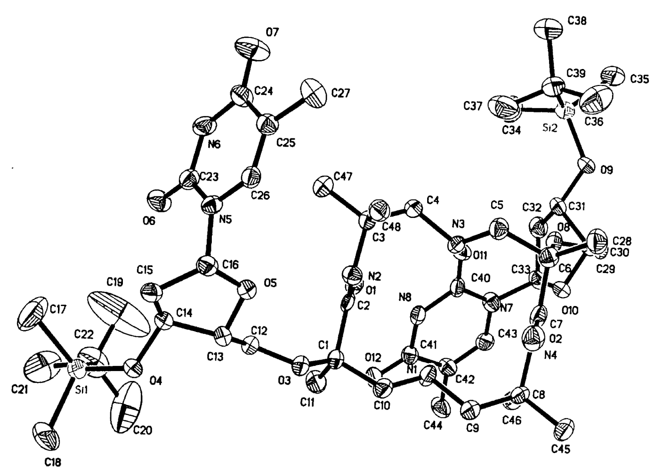


Figure 1. The molecular structure of (*R*,*S*)-**6**.

Table 2. Selected Bond Lengths (Å) and Angles (deg) for (*R*,*S*)-**6**

C(1)-O(3)	1.446(5)	C(1)-C(11)	1.501(7)
C(1)-C(2)	1.545(6)	C(1)-C(10)	1.555(6)
C(2)-O(1)	1.245(5)	C(2)-N(2)	1.329(6)
C(3)-N(2)	1.469(5)	C(3)-C(47)	1.533(6)
C(3)-C(48)	1.537(6)	C(3)-C(4)	1.541(6)
C(3)-N(3)	1.471(6)	C(5)-N(3)	1.453(6)
C(5)-C(6)	1.532(7)	C(6)-C(8)	1.428(5)
C(6)-C(28)	1.539(7)	C(6)-C(7)	1.545(7)
C(7)-O(2)	1.249(5)	C(7)-N(4)	1.341(6)
C(8)-N(4)	1.480(6)	C(8)-C(45)	1.523(7)
C(8)-C(46)	1.528(7)	C(8)-C(9)	1.540(7)
C(9)-N(1)	1.481(6)	C(10)-N(1)	1.459(6)
O(3)-C(1)-C(11)	112.9(3)	O(3)-C(1)-C(2)	108.6(3)
C(11)-C(1)-C(2)	112.2(4)	O(3)-C(1)-C(10)	101.0(3)
C(11)-C(1)-C(10)	112.6(4)	C(2)-C(1)- C(10)	108.9(4)
O(1)-C(2)-N(2)	124.5(4)	O(1)-C(2)-C(1)	121.5(4)
N(2)-C(2)-C(1)	113.9(4)	N(2)-C(3)-C(47)	109.6(4)
N(2)-C(3)-C(48)	106.0(3)	C(47)-C(3)-C(48)	109.5(4)
N(2)-C(3)-C(4)	111.7(4)	C(47)-C(3)-C(4)	108.8(4)
C(48)-C(3)-C(4)	111.2(4)	N(3)-C(4)-C(3)	115.3(4)
N(3)-C(5)-C(6)	110.5(4)	O(8)-C(6)-C(5)	103.5(3)
O(8)-C(6)-C(28)	112.8(4)	C(5)-C(6)-C(28)	110.8(4)
O(8)-C(6)-C(7)	111.1(4)	C(5)-C(6)-C(7)	107.6(4)
C(28)-C(6)-C(7)	110.7(4)	O(2)-C(7)-N(4)	124.5(4)
O(2)-C(7)-C(6)	118.2(4)	N(4)-C(7)-C(6)	117.2(4)
N(4)-C(8)-C(45)	109.8(4)	N(4)-C(8)-C(46)	106.4(4)
C(45)-C(8)-C(46)	110.6(4)	N(4)-C(8)-C(9)	110.6(4)
C(45)-C(8)-C(9)	109.0(4)	C(46)-C(8)-C(9)	110.4(4)
N(1)-C(9)-C(8)	112.2(4)	N(1)-C(10)-C(1)	113.4(4)

recorded in $CDCl_3$ at 300 MHz for ^1H and 75.5 MHz for ^{13}C. Chemical shifts are given in *δ* ppm relative to $CDCl_3$ (*δ* 77.2, ^{13}C) or $CHCl_3$ (*δ* 7.26, ^1H) which is present as an impurity in $CDCl_3$ used. IR spectra were recorded on a Perkin-Elmer 1600 series FT-IR.

The following chemicals were prepared according to literature procedures: pentacarbonyl[methyl{(tetramethylammonio)oxy}carbene]chromium(0).[12] 1-(benzyloxycarbonyl)-4,4-dimethyl-Δ^2-imidazoline,[13] and the TBDMS-protected thymidine.[14]

Chromium Carbene Complex 2. Pentacarbonyl[methyl{(tetramethylammonio)oxy}carbene]chromium(0) (583 mg, 1.89 mmol) was dissolved in dry CH_2Cl_2 (15 mL) under an argon atmosphere, and the solution was cooled to −65 °C. Pivaloyl chloride (0.23 mL, 1.9 mmol) was added dropwise, and the resulting suspension was stirred at −65 °C~−25 °C over 3 h. The suspension was cooled again to −65 °C and a solution of the TBDMS-protected thymidine (565 mg, 1.72 mmol) in dry CH_2Cl_2 (5 mL) was added through a cannula, and the resulting suspension was stirred at −65 °C~25 °C over 15 h. The suspension was diluted with CH_2Cl_2 (60 mL), washed with H_2O (40 mL × 2) and brine (40 mL), dried over $MgSO_4$, and the solvent was evaporated to yield a gum which was chromatographed on silca gel (1/1 ethyl acetate/hexane, R_f = 0.69) to give 562 mg (0.978 mmol, 57%) of complex **2** as yellow-orange solid. ^{1}H NMR δ 9.08 (br s, 1 H, NH), 7.11 (s, 1H), 6.27 (dd, J_1 = 6.6 Hz, J_2 = 6.3 Hz, 1 H), 5.02 (br m, 2H), 4.56 (br s, 1H), 4.30 (br, s, 1H), 3.02 (s, 3 H), 2.32 (m, 2H), 1.90 (s, 3H), 0.91 (s, 9H), 0.109 (s, 3H), 0.105 (s, 3H). ^{13}C NMR δ 361.1, 223.0, 216.4, 163.8, 150.4, 135.5, 111.7, 85.6, 84.2, 71.6, 40.6, 25.9, 18.1, 12.7, −4.46, −4.76. IR (NaCl) ν 2064 (C=O), 1932 (C=O), 1693 (C=O) cm^{-1}.

BOC-Protected Azapenam 3. The chromium carbene complex **2** (340 mg, 0.592 mmol) and 1-(benzyloxycarbonyl)-4,4-dimethyl-Δ^2-imidazoline (137 mg, 0.589 mmol) were dissolved in dry and degassed CH_2Cl_2 (30 mL), and the resulting yellow-orange solution was irradiated at 35 °C in a Pyrex tube under CO (80 psi). After 16 h the resulting light brown solution was concentrated and chromatographed on silica gel (1/1 ethyl acetate/hexane, R_f = 0.45) to give 306 mg (0.476 mmol, 80.3%) of a mixture of 4 rotomers of 1 : 1 diastereomeric mixture as a white solid. ^{1}H NMR δ 8.83/8.77/8.74/8.73 (br s, 1H, NH), 7.56/7.49/7.41/7.33 (s, 1H), 7.37-7.32 (m, 5H), 6.40-6.23 (m, 1H), 5.32-5.00 (m, 3H), 4.49-4.25 (m, 1H), 4.05-3.67 (m, 3H), 3.53-3.14 (m, H), 2.30-2.00 (m, 2H), 1.96/1.93/1.88/1.86 (s, 3H), 1.63/1.62/1.61 (s, 3H), 1.34/1.26/1.22/1.20/1.19/1.17 (s, 6H), 0.87 (s, 9H), 0.077/0.074/0.059/0.052/0.043/0.033 (s, 6H) IR (NaCl) ν 3201 (NH), 1778 (C=O), 1696 (C=O). Anal. Calcd for $C_{32}H_{46}N_4O_8Si$: C, 59.79; H, 7.21; N, 8.72. Found: C, 59.72; H, 7.08; N, 8.54.

Azapenam 4. The BOC-protected azapenam **3** (685 mg, 1.07 mmol) was dissolved in degassed MeOH (30 mL). 10% Pd in carbon powder (303 mg) and triethylamine (0.5 mL) were added, and the resulting suspension was stirred at 25 °C under H_2 (55 psi). After 2 h the suspension was filtered through Celite, and the solvents were evaporated to give 573 mg of crude products, which was chromatographed on silica gel (ethyl acetate, R_f = 0.45) to give 410 mg (0.806 mmol, 75.4%) of a colorless gum. The gum was crystallized at 25 °C from hexane and a small amount of CH_2Cl_2 to give 336 mg (0.661 mmol, 61.7%) of a 1 : 1 diastereomeric mixture as white solid. ^{1}H NMR δ 9.19 (br s, 1H), 7.53/7.51 (s, 1H), 6.34/6.29 (dd, J_1 = 8.1 Hz, J_2 = 6.0 Hz/ J_1 = 7.5 Hz, J_2 = 6.6 Hz, 1H), 4.76/4.71 (s, 1H), 4.47-4.36 (m, 1H), 4.02-3.65 (m, 3H), 3.08/2.62 (d, J = 11.4 Hz, 2H), 2.36 (br s, 1H), 2.28-1.97 (m, 2H), 1.93 (s, 3H), 1.56/1.09 (s, 6H), 1.33 (s, 3H), 0.87 (s, 9H), 0.06 (s, 6H); ^{13}C NMR δ 175.0, 174.9, 164.2, 164.1, 150.6, 135.9, 135.8, 111.1, 111.0, 90.1, 89.9, 86.4, 86.3, 85.4, 85.1, 77.7, 72.5, 65.4, 65.3, 62.1, 61.4, 41.5, 41.4, 25.8, 25.0, 21.9, 18.1, 15.3, 14.5, 12.8, 12.6, −4.46, −4.53, −4.64; IR (NaCl) ν 3350 (NH), 1755 (C=O), 1696 (C=O), 1684 (C=O). Anal. Calcd for $C_{24}H_{40}N_4O_6Si$: C, 56.67; H, 7.94; N, 11.01. Found: C, 56.47; H, 7.88; N, 10.86.

Unsaturated Dioxocyclam 5. The free azapenam **4** (225 mg, 0.442 mmol) and racemic camphorsulfonic acid (27 mg, 0.12 mmol) were dissolved in dry CH_2Cl_2 (10 mL), and the resulting solution was stirred at 25 °C for 24 h. The solution was diluted with CH_2Cl_2 (50 mL), washed with aqueous 5% $NaHCO_3$ (20 mL) and brine (20 mL), and dried over $MgSO_4$. The solvent was evaporated to give 216 mg (0.212 mmol, 96%) of a mixture which appeared as two spots (ethyl acetate: R_f = 0.66 and 0.52) on TLC. (*R,S*)-**5**: ^{1}H NMR (two conformers, a/b ~ 7/3) δ 9.33(b)/9.32(a) (br s, 2 H), 9.08(b)/8.50(a) (s, 2H), 7.89(a)/7.72(b) (s, 2H), 7.66(a)/7.62(b) (s, 2H), 6.40(b)/6.27(a) (dd, J_1 = 7.5/6.6 Hz, J_2 = 6.4/6.6 Hz, 2H), 4.79(b)/4.42(a) (br s, 2H), 4.10(a)/3.95(b) (br s, 2H), 3.90-3.70 (m, 4H), 3.60-3.20 (m, 4H), 2.30-2.05 (m, 4 H), 1.92(a)/1.90(b) (s, 6H), 1.54/1.51/1.47 (s, 12H), 1.22 (s, 6H), 0.87 (s, 18H), 0.088(b)/0.072(a)/0.063(a)/0.054(a) (s, 12H). ^{13}C NMR δ 169.0(a)/168.5(b), 167.9, 164.3, 150.6(b)/150.5(a), 135.6(a)/136.0(b), 110.9(b)/110.8(a), 86.9(b)/86.4(a), 85.9(a)/85.2(b), 80.2(a)/80.1(b), 73.1(b)/72.7(a), 70.6(b)/69.7(a), 65.9(b)/65.6(a), 53.8(a)/53.7(b), 41.3(b)/41.2(a), 25.9(b)/25.8(a), 25.2(b)/25.0(a), 24.8(a)/24.7(b), 24.4, 18.1(a)/18.0(b), 12.8(b)/12.2(a), −4.52(a)/-4.59(b)/−4.69(a)/−4.72(b). IR (NaCl) ν 3198 (NH), 1688 (C=O), 1678 (C=O) cm^{-1}. (*R,R*)-**5** + (*S,S*)-**5**: ^{1}H NMR δ 9.12/9.01 (br s, 2H), 7.91/7.77 (s, 2H), 7.73/7.65 (s, 2H), 7.59/7.50 (s, 2H), 6.37/6.29 (dd, J_1 = 6.6/6.6 Hz, J_2 = 6.9/6.9 Hz, 2H), 4.62/4.42 (br m, 2H), 4.02/3.97 (br d, J =2.7/2.1 Hz, 2H), 3.80-3.35 (m, 8 H), 2.30-2.05 (m, 4H), 1.91 (s, 6H), 1.52/1.51 (s, 6H), 1.39/1.37/1.35/1.34 (s, 12H), 0.88 (s, 18H), 0.082/0.076 (s, 12H). ^{13}C NMR δ 168.8, 167.7/167.0, 164.1/163.8, 150.5/150.4, 136.5/135.7, 111.2/110.9, 86.4/86.3, 85.8/85.0, 81.1/80.7, 73.0/72.6, 68.2/67.9, 65.3/64.7, 54.3/54.2, 41.2/41.1, 25.9, 26.1/25.6, 25.5/25.2, 23.1/21.8, 18.1, 12.9/12.3, −4.45/−4.54/−4.59/−4.65. IR (NaCl) ν 3191 (NH), 1688 (C=O) cm^{-1}.

Dioxocyclam 6. The unsaturated dioxocyclam **5** (176 mg, 0.172 mmol), $NaBH_3CN$ (23 mg, 0.37 mmol), and a small amount of bromocresol green were dissolved in 1 : 1 $MeOH/CH_2Cl_2$ (4 mL). HCl/MeOH (0.9 N) was added dropwise to the cooled (0 °C) blue solution until the yellow-green color remained, and the resulting solution was stirred at 0 °C~25 °C for 24 h. HCl/MeOH (0.9 N) was added, and the resulting yellow solution was stirred for 30 min to destroy $NaBH_3CN$ unreacted. Aqueous 5% NaOH was added until the solution turned to blue. The solvents were evaporated, and the resulting residue was dissolved in CH_2Cl_2 (30 mL).

The solution was washed with H_2O (20 mL) and brine (20 mL), and dried over K_2CO_3. The solvent was evaporated to give 101 mg (0.0989 mmol, 57%) of a white solid, which was recrystallized from hexane and a small amount of CH_2Cl_2 to give 77 mg (0.075 mmol, 44%) of white micro crystals. (*R,S*)-**6**: ^{1}H NMR (two conformers, a/b ~ 7/3) δ 9.85 (br s, 2 H), 7.20(a)/7.15(b) (s, 2H), 7.11(a)/6.85(b) (s, 2H), 6.11(a)/6.03(b) (dd, J_1 = 6.3/6.6 Hz, J_2 = 6.6/6.6 Hz, 2 H), 4.30 (m, 2H), 3.91 (m, 2H), 3.73-3.45 (m, 4H), 3.45-3.25/2.80-2.60 (m, 8H), 2.20-2.10 (m, 4H), 1.88(a)/1.86(b) (s, 6H), 1.31(b)/1.10(b) (s, 6H), 1.30 (s, 12H), 0.85 (s, 18H), 0.045 (s, 12H). ^{13}C NMR δ 171.6(b)/171.5(a), 164.2(a)/164.1(b), 150.5(b)/150.4(a), 136.4(a)/136.3(b), 111.1(b)/110.0(a), 86.6(b)/86.1(a), 85.7, 80.8(b)/80.3(a), 72.1(a)/72.0(b), 63.8, 57.1/57.0, 53.2(b)/53.0(a), 40.4, 26.9(b)/26.4(a), 25.8, 25.3, 19.7(a)/19.5(b), 18.0, 12.8, −4.45/−4.63. IR (NaCl) ν 3190 (NH), 3049 (NH), 1684 (C=O) cm^{-1}. (*R,R*)-**6** + (*S,S*)-**6**: ^{1}H NMR δ 9.35 (br s, 2 H), 7.59/7.42 (s, 2H), 7.33/7.11 (s, 2H), 6.26/5.89 (dd, J_1 = 6.3/6.0 Hz, J_2 = 6.9/6.6 Hz, 2H), 4.65/4.32 (br m, 2H), 3.97/3.85 (m, 2H), 3.75-3.35 (m, 4H), 3.30/3.13 (d, J = 12.0/11.1 Hz, 2H), 2.90-2.60 (m, 4H), 2.40-1.95 (m, 8H), 1.91/1.90 (s, 6H), 1.40/1.33/1.32/1.30/1.26/1.16 (s, 18H), 0.88/0.87 (s, 18H), 0.067 (s, 12H). ^{13}C NMR δ 171.6/171.5, 163.9, 150.3/150.1, 137.3/135.7, 111.0/110.9, 87.9, 86.2/85.5, 80.3/79.7, 73.0/70.8, 63.9/62.7, 59.5/58.9/58.7, 53.9/53.6, 40.9/40.2, 27.2/26.4/24.5/24.2, 25.9, 19.4/19.3, 18.12/18.07, 12.8/12.6, −4.47/−4.53/−4.65. IR (NaCl) ν 3193 (NH), 1692 (C=O) cm^{-1}. Anal. Calcd for $C_{48}H_{84}N_8O_{12}Si_2$: C, 56.44; H, 8.29; N, 10.97. Found: C, 56.49; H, 8.24; N, 11.01.

X-ray Structure Analysis of (*R,S*)-6. Crystals of (*R,S*)-**6** were grown from a CH_2Cl_2-MeOH-hexane solution at room temperature. Diffraction data were collected by employing graphite-monochromated Mo K_α radiation (λ = 0.71073 Å) at 163 K. A total of 13912 reflections were measured over the following ranges: $2.50 \leq 2\theta \leq 46.50°$, $-16 \leq h \leq 17$, $-12 \leq k \leq 12$, $-19 \leq l \leq 20$. The crystallographic data and additional details of data collection are summarized in Table 1. The structure was refined by full-matrix least-squares methods. All the non-hydrogen atoms were refined anisotropically. The final cycle of refinement led to the R indices listed in Table 1.

Conclusion

A novel chromium carbene complex **2**, which has a thymidine moiety as the alkoxy substituent at the carbene carbon, was synthesized. Its photochemical cycloaddition reaction with an achiral imidazoline produced the corresponding azapenams **3** in good yield. The unsaturated dioxocyclams **5** were formed by dimerization of the free azapenam **4**. Insignificant stereoselectivity was observed in the photochemical cycloaddition as well as in the dimerization. However, the unsaturated dioxocyclam (*R,S*)-**5** was separated from the other isomers. The molecular structure of the dioxocyclam (*R,S*)-**6** was determined by X-ray crystallography.

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Supplementary Material Available. Tables of crystal data, atom coordinates, bond lengths and angles, and anisotropic displacement parameters for (*R,S*)-**6** (7 pages). Ordering information is given on any current masthead page.

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