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Synthesis of 2-oxa-4-azabicyclo[3.2.1]-octane and -octene systems *via* X-ray-analyzed *trans*-3-dibenzamido-cyclopentene-1-oxide*

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ABSTRACT

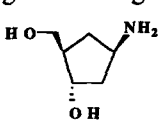
3,4-*trans*-Epoxidation of (cyclopent-3-en-1-yl)dibenzamide gave, in 82% yield, the 1,5-epoxide, the structure of which was confirmed by X-ray crystallographic analysis. Epoxide ring opening by trimethylsilyl cyanide, under the catalysis of diethylaluminum chloride, did not lead to the expected *trans*-β-trimethylsilyl-oxynitrile as a potential precursor of carbocyclic 2-deoxy-D-*erythro*-pentofuranosylamine, but to 4-benzamido-3-cyano-3-phenyl-7-trimethylsilyloxy-2-oxa-4-azabicyclo[3.2.1]octane, which resulted from the participation of the benzoyl group in the epoxide ring cleavage.

INTRODUCTION

The cyclopentane analog **1** of 2-deoxy-D-*erythro*-pentofuranosylamine is a key precursor of 2′-deoxycarbocyclic nucleoside analogs. It has been prepared mainly from *exo*-[1,2] or *endo*-5-norbornen-2-yl acetate[3,4] (**2**), but cyclopentanes **3** (ref. 5) or **4** (ref. 6) also led to 2′-deoxycarbocyclic nucleoside analogs.We examined another route to **1** from known[7] 1-amino-cyclopent-3-ene (**5**). Our goal was to synthesize the nitrile **7** from the *trans*-epoxide **9** by assuming that nitrile **7** could lead to **1** after hydrolysis to give the ester, followed by a further reduction to the alcohol. We report herein an attempt of epoxide group opening with trimethylsilyl cyanide that led to 2-oxa-4-azabicyclo[3.2.1]octane (**11**), which was characterized by ^{1}H- and ^{13}C-n.m.r. spectroscopy.

RESULTS AND DISCUSSION

Dibenzoylation was chosen to protect the amino group in order to prevent hydrogen bonding between peracid and monoamide, and also because bulky groups are



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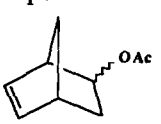

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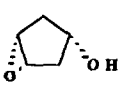

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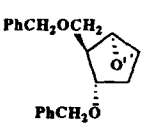

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* Dedicated to Professor Serge David on the occasion of his 70th birthday.

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TABLE I

Atomic coordinates (× 10^4) and equivalent isotropic thermal factor (× 10^3) for **9** as measured by X-ray analysis[a]

Atom	*x*	*y*	*z*	*U*
C-4	2395 (2)	967 (3)	9749 (2)	42 (2)
C-3	1236 (2)	1533 (3)	9612 (3)	51 (3)
C-2	936 (3)	1202 (3)	10682 (3)	60 (3)
C-1	1670 (3)	239 (3)	11256 (3)	62 (3)
C-5	2468 (3)	−108 (3)	10569 (3)	54 (3)
O-1	1818 (2)	1465 (2)	11698 (2)	70 (2)
N	2651 (2)	661 (2)	8661 (2)	45 (2)
C-6	3594 (2)	1210 (3)	8422 (3)	50 (3)
O-2	3915 (2)	2202 (2)	8814 (3)	85 (3)
C-7	4239 (2)	489 (3)	7766 (2)	42 (2)
C-8	4793 (2)	1099 (3)	7073 (3)	51 (3)
C-9	5440 (3)	463 (3)	6507 (3)	60 (3)
C-10	5575 (3)	−785 (3)	6652 (3)	66 (3)
C-11	5049 (3)	−1402 (3)	7352 (3)	62 (3)
C-12	4364 (3)	−776 (3)	7904 (3)	53 (3)
C-6′	1909 (3)	−62 (3)	7861 (2)	49 (3)
O-2′	1281 (2)	−776 (2)	8147 (2)	71 (2)
C-7′	1821 (2)	173 (3)	6634 (3)	52 (3)
C-8′	1768 (3)	1356 (3)	6216 (3)	62 (3)
C-9′	1581 (4)	1574 (4)	5067 (3)	82 (4)
C-10′	1457 (4)	628 (5)	4328 (4)	90 (5)
C-11′	1506 (4)	−560 (5)	4722 (4)	97 (5)
C-12′	1677 (3)	−802 (4)	5883 (3)	75 (4)

[a] Estimated standard deviations (on the last digit quoted) given in parentheses.

TABLE II

Selected torsional angles (degrees) for **9**[a]

Bond angles		
C-1–C-2–C-3–C-4	−15.4	(0.3)
C-2–C-3–C-4–C-5	25.6	(0.3)
C-3–C-4–C-5–C-1	−25.9	(0.3)
C-4–C-5–C-1–C-2	16.8	(0.3)
C-5–C-1–C-2–C-3	−0.9	(0.3)
C-3–C-4–N–C-6	121.2	(0.3)
C-3–C-4–N–C-6′	−53.0	(0.3)
C-4–N–C-6–O-2	−28.5	(0.3)
C-4–N–C-6′–O-2′	−25.3	(0.3)
N–C-6–C-7–C-8	149.9	(0.3)
N–C-6′–C-7′–C-8′	−43.6	(0.3)

[a]Estimated standard deviations in parentheses.

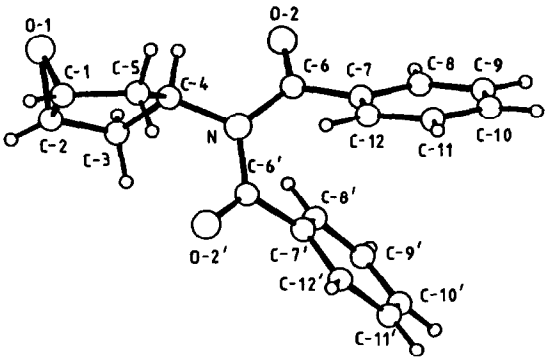


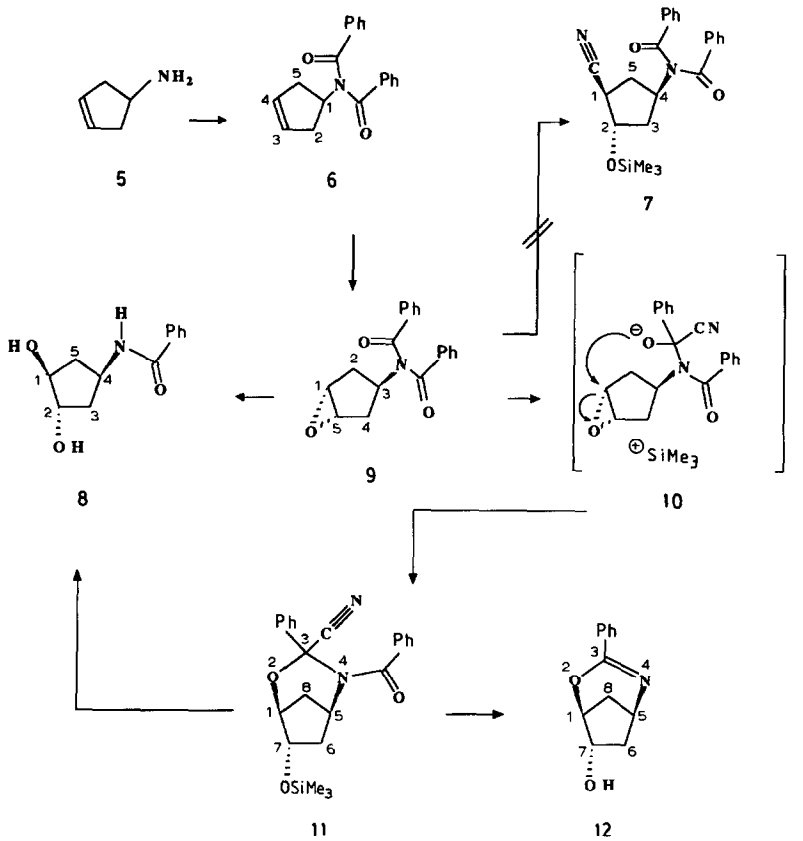
Fig. 1. ORTEP[13] drawing for **9**.

known to favor the formation of *trans*-epoxides[8,9]. Thus, the *trans*-epoxide **9** was obtained with 3-chloroperoxybenzoic acid in good yield, as shown by ^{1}H-n.m.r. spectroscopy and X-ray crystal analysis (Tables I and II, and Fig. 1). Only traces of a second compound were detected by thin-layer chromatography; it corresponded to the *cis* isomer according to the ^{1}H-n.m.r. spectrum of the mixture of isomers. Epoxide group opening with trimethylsilyl cyanide and diethylaluminum chloride as a catalyst usually leads to the *trans*-β-trimethylsiloxynitrile[10,11]. However in the present case, epoxide **9** did not lead to **7** but rather to its bicyclic isomer **11**, resulting from the addition of a cyanide group to one of the carbonyl groups, thus leading to the transient intermediate **10** and to subsequent opening of the epoxide ring.

Structure **11** was ascertained by the ^{13}C- and ^{1}H-n.m.r. spectra which were not compatible with structure **7**. Thus, both structures **7** and **11**have five quaternary carbon atoms, which may easily be assigned in the ^{13}C-n.m.r. spectrum. The five quaternary carbon atoms of **7** are expected to give three signals if both benzoyl groups were identical, or five signals if not, but in this last hypothesis two different carbonyl carbon atoms would be observed. In contrast, the presence of five quaternary carbon atoms having different chemical shifts was observed, with only one carbonyl carbon atom signal at δ 170.6, which is clearly in favor of structure **11**. The signal corresponding to a quaternary carbon atom at δ 81.3 can be assigned to C-3 of **11**, and this signal is incompatible with any carbon atom of **7**. The presence of two sets of phenyl carbon atoms confirmed that two phenyl groups, which are not magnetically equivalent, are present in the molecule. Furthermore, the ^{1}H-n.m.r. spectrum at 400 MHz corroborated the nonequivalence of the two phenyl groups. The absence of a signal around δ 3, assignable to H-1 in the ^{1}H-n.m.r. spectrum of **7**, is also indicative of structure **11**.

Acid hydrolysis of **11** in ethanol–water led to the diol **8** which was also obtained by direct acid hydrolysis of the epoxide **9**. Acid hydrolysis of **11** under anhydrous conditions in 1,4-dioxane led to the bicyclic compound **12**, which was identified by ^{1}H-n.m.r. spectroscopy and chemical-ionization mass spectrometry.

The present work shows that epoxide ring opening by trimethylsilyl cyanide cannot take place in the usual way where benzoyl groups are present in 1,3-position with



respect to the epoxide ring, since benzamides are better electrophiles than epoxides, and it provides a unique route to 2-oxa-4-azabicyclo[3.2.1]-octane or -octene systems (**11** and **12**, respectively), although oxazolines have previously been synthesized from epoxides[12].

EXPERIMENTAL

General methods. — Melting points are uncorrected. I.r. spectra were recorded with a MXS Nicolet instrument; ^{1}H-n.m.r. spectra with a Bruker AM 400 WB spectrometer operating at 400 MHz and a Varian XL 100 spectrometer operating at 100 MHz; and ^{13}C-n.m.r. spectra with a Bruker spectrometer operating at 100 MHz. Chemical shifts (δ) are reported downfield from the signal of tetramethylsilane. Elemental analyses were performed by the "Service Central de Microanalyse", ICSN, CNRS, 91190 Gif-sur-Yvette, France.

Crystal structure of **9**. — A crystal of about 0.7 × 0.6 × 0.4 mm^3 was mounted on a 4-circle PW 1100 diffractometer (λ 1.5418 Å). The cell is monoclinic, $P2_1/a$, $Z = 4$, with $a = 12.368$ (6), $b = 10.926$ (5), $c = 12.150$ (6) Å, and $\beta = 104.84$ (6)°. Lorentz and

polarization corrections were applied, but none for absorption. The structure was solved by direct methods, and refined by the full-matrix, least-squares method (SHELX 76 program). From 2552 measured reflections, 1648 above the $3\sigma(I)$ level were used in the calculations. Hydrogen atoms were located in Fourier-difference syntheses and refined in theoretical position with the isotropic thermal parameter of C. C, N, and O atoms were anisotropically refined. The final *R* factor is 4.75% Atomic coordinates, bond lengths and angles, anisotropic thermal parameters, and a list of observed and calculated structure factors have been deposited*.

(Cyclopent-3-en-1-yl)dibenzamide (**6**). — An excess of benzoyl chloride (40 mL) was added dropwise at 0° to a solution of (3-cyclopenten-1-yl)amine (9.3 g, 112 mmol) in dry pyridine (30 mL). The mixture was maintained at + 5° for two days and poured into ice and water. After vigourous stirring, the aqueous phase was extracted with CH_2Cl_2 (3 × 200 mL). The combined organic phases were washed with $NaHCO_3$ (3 × 150 mL), water (3 × 100 mL), and dried ($MgSO_4$). The resulting organic phase was concentrated until disappearance of the odor of pyridine to give an oil that crystallized. The crystals were filtered, washed with cyclohexane, and recrystallized from cyclohexane (16.6 g, 51%), m.p. 91°; ^{1}H-n.m.r. ($CDCl_3$); δ 7.50–7.09 (m, 10 H, 2 Ph), 5.80 (s, 2 H, ethylenic), 5.58–5.22 (m, 1 H, H-1), and 3.13–2.58 (m, 4 H, 2 CH_2).

Anal. Calc. for $C_{19}H_{17}NO_2$: C, 78.33; H, 5.88; N, 4.81. Found: C, 78.24; H, 5.83; N, 4.81.

trans-*3-Dibenzamido-6-oxabicyclo[3.1.0]hexane* (**9**). — To a stirred solution of **6** (10 g, 34.36 mmol) in dry CH_2Cl_2 (150 mL) at 0° was added dropwise a solution of 3-chloroperoxybenzoic acid (51.5 mmol) in CH_2Cl_2 (250 mL). Then the mixture was stirred overnight at room temperature. Solid $Ca(OH)_2$ in excess was added, and the resulting suspension was stirred for 30 min before it was diluted with CH_2Cl_2 (400 mL) and washed with water several times. The organic phase was dried ($MgSO_4$) and evaporated to dryness under reduced pressure to give a colorless oil which crystallized. Recrystallization from abs. EtOH provided pure **9** (8.65 g, 82%), m.p. 133°; ^{1}H-n.m.r. ($CDCl_3$): δ 7.48–7.06 (m, 10 H, 2 Ph), 4.85 (qt, 1H, *J* 8.4 Hz, H-3), 3.64 (degenerated AB system, 2 H, H-1,5), and 2.68–2.26 (m, 4 H, 2 CH_2).

Anal. Calc. for $C_{19}H_{17}NO_3$: C, 74.25; H, 5.58; N, 4.56. Found: C, 74.56; H, 5.47; N, 4.79.

(+/−)-trans-*4-Benzamido-3-cyano-3-phenyl-7-trimethylsilyloxy-2-oxa-4-azabicyclo[3.2.1]octane* (**11**). — A solution of epoxide **9** (5 g, 16.28 mmol) in CH_2Cl_2 (20 mL) was added dropwise to a mixture of trimethylsilyl cyanide (2.4 mL, 17.9 mmol) and diethylaluminum chloride (1 mL of M solution in hexanes) under anhydrous conditions (Ar). The mixture was heated under reflux for 30 min and stirring was continued at room temperature for 24 h. A solution of 2M NaOH (4 mL) was added and stirring continued

* Lists of atomic coordinates, bond lengths and angles, anisotropic thermal parameters, and observed and calculated structure factors have been deposited with, and can be obtained from, Elsevier Science Publishers B.V., BBA Data Deposition, P. O. Box 1527, Amsterdam, The Netherlands. Reference should be made to No. BBA/DD/494/*Carbohydr. Res.*, 228 (1992) 21–27.

for 30 min. The organic phase was washed with water, dried ($MgSO_4$), and evaporated to give an oil that was purified by chromatography on a silica gel column and elution with 19:1 dichloromethane–ethanol. Crystallization from methanol afforded **11** as colorless needles (4.82 g; 73%), m.p. 132–133°; ν_{max}^{KBr} 846 (s), 887 (m), 912 (m), 939 (w), 1049 (s), 1095 (s), 1135 (s), 1176 (m), 1252 (m), 1331 (s), 1369 (s), 1448 (m), 1664 (s), 1803 (w), 1876 (w), 1948 (w), 2232 (w), and 2490 cm^{-1} (w); ^{1}H-n.m.r. (400 MHz; $CDCl_3$): δ 7.67 (m, 2 H, Ph), 7.39 (m, 3 H, Ph), 7.56 (m, 2 H, Ph), 7.42 (m, 3 H, Ph), 4.62 (br. t, 1 H, $J_{5,6}$ 6.4, $J_{6,8}$ 4.9 Hz, H-5), 4.53 (br. s, 1 H, $J_{1,8}$ 1.56, $J_{1,7}$ 1.22 Hz, H-1), 4.34 (dd, 1 H, $J_{7,1}$ 1.22, $J_{7,6}$ 6.26 Hz, H-7), 3.11 (dd, 1 H, ^2J 14.6, $^4J_{8,6}$ 1.66 Hz, H-8a), 2.8 (m, 1 H, ^2J 14.8, $^3J_{6,7}$ 6.26, $^4J_{8,6}$ 1.66 Hz, H-6a), 2.18 (m, 1 H, ^2J 14.6, $^3J_{8,5}$ 4.90, $^3J_{8,1}$ 1.56 Hz, H-8b), 2.04 (dd, 1 H, ^2J 14.8, $^3J_{6,5}$ 6.4 Hz, H-6b), and 0.12 (s, 9 H, 3 × CH_3); ^{13}C-n.m.r. ($CDCl_3$; 100 MHz): δ 170.6 (s, C = O), 137.8 (s, quatern. C-Ph), 133.95 (s, quatern. C-Ph), 137.74–128 (tertiary C of one Ph), 133.82–125.50 (tertiary C of other Ph), 118.7 (s, quatern. C-N), 81.3 (s, quatern. C-3), 81.10 (d, C-1), 73.72 (d, C-7), 56.05 (d, C-5), 43.76 (t, C-6), 28.77 (t, C-8), and 0 (q, 3 × CH_3).

Anal. Calc. for $C_{23}H_{26}N_2O_3Si$: C, 67.98; H, 6.40; N, 6.89; Si, 6.89. Found: C, 68.07; H, 6.33; N, 7.11; Si, 6.71.

(+/−)-(1α,2β,4α)-4-Benzamidocyclopentane-1,2-diol (**8**). — A solution of **11** (500 mg, 1.23 mmol) in EtOH (30 mL) and concentrated aq. HCl (2 mL) was heated overnight under reflux. The mixture was evaporated to dryness and the residual solvent coevaporated several times with ethanol. On silica gel column chromatography of the residue, elution with 19:1 CH_2Cl_2–EtOH afforded a colorless oil that crystallized on standing (190 mg, 70%), m.p. 136°; ^{1}H-n.m.r. ($CDCl_3$): δ 8.27 (d, 1 H, J 7.6 Hz, NH), 7.87 (m, 2 H, Ph), 7.51 (m, 3 H, Ph), 4.83 (d, 1 H, J 4.1 Hz, OH), 4.68 (d, 1 H, J 3.9 Hz, OH), 4.44 (m, 1 H, J 7.8 Hz, H-4), 3.90 (m, 2 H, H-1,2), 2.33 (m, 1 H, H-5a or 3a), 1.90 (m, 2 H, H-3 or 5), and 1.50 (m, 1 H, H-5b or 3b).

Anal. Calc. for $C_{12}H_{15}NO_3$: C, 65.14; H, 6.83; N, 6.33. Found: C, 64.82; H, 6.74; N, 6.34.

trans-*(+/-)-3-Phenyl-2-oxa-4-azabicyclo[3.2.1]oct-3-en-7-ol* (**12**). — Anhydrous HCl was bubbled for 15 min into a solution of **11** (2g, 4.92 mmol) in dry 1,4-dioxane (60 mL). The solution was kept in the cold (+5°) for 24 h before evaporation to give an oil that was dissolved in CH_2Cl_2, washed with water, and dried ($MgSO_4$). Silica gel column chromatography afforded a colorless oil which solidified on standing. Recrystallization from cyclohexane yielded pure **12** (870 mg, 87%), m.p. 98–100°; ν_{max}^{KBr} 1016 (m), 1115 (s), 1194 (w), 1273 (m), 1350 (m), 1448 (w), 1576 (w), 1634 (s), and 2033 cm^{-1} (w); ^{1}H-n.m.r. ($CDCl_3$): δ 7.78 (m, 2 H, Ph), 7.45 (m, 3 H, Ph), 5.25 (d, 1 H, J 4.4 Hz, OH), 4.57 (m, 1 H, H-5), 4.30 (m, 1 H, H-7), 3.99 (m, 1 H, H-1), 2.40 (m, 1 H, H-6a), 2.14-2.02 (dt, 1 H, H-8a), and 1.27 (m, 2 H, H-8b, H-6b).

Anal. Calc. for $C_{12}H_{13}NO_2$: C, 70.91; H, 6.45; N, 6.89. Found: C, 70.93; H, 6.49; N, 6.95; m.s. (c.i., NH_3): 204 (MH^+ 100%).

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