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New cycloheptane nucleoside analogues

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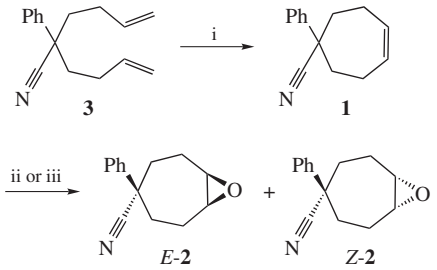
Epoxidation of 1-phenylcyclohept-4-ene-1-carbonitrile gives mostly *E*-isomer of the desired epoxy derivative, whose ring opening with adenine or thymine proceeds stereoselectively providing access to novel cycloheptane nucleoside analogues.

Carbocyclic nucleosides are compounds in which endocyclic oxygen atom of nucleoside sugar is replaced by a methylene group. A large number of five- and six-membered ring nucleoside analogues[1–4] have recently been synthesized as potential chemotherapeutic agents. At the same time, seven-membered analogues possessing promising biological activities,[5,6] are not sufficiently studied.[7]

Ring-closing metathesis is an advanced access to a variety of the substituted cycloheptenes.[8–12] In addition, 1,2-disubstituted cycloheptane nucleoside analogues have been readily obtained through an epoxidation of the cycloheptene double bond followed by epoxide ring opening.[13] However, this approach and other transformations of the double bond have not been applied to the synthesis of highly functionalized cycloheptane nucleoside analogues from substituted cycloheptenes.

Herein, we report a brief study of epoxidation of 1-phenylcyclohept-4-ene-1-carbonitrile **1** leading to diastereomeric 4-phenyl-8-oxabicyclo[5.1.0]octane-4-carbonitriles **2**.



Scheme 1 *Reagents and conditions*: i, DCM, 0.25 mol% 1st generation Grubbs catalyst, reflux, 3 h, 99%; ii, DCM, mCPBA, Na_2HPO_4, 0 °C, 1 h, then 20 °C, 85% overall, *de* 75%; iii, benzene, mCPBA, Na_2HPO_4, 0 °C, 1 h, then 20 °C, 87% overall, *de* 91%.

Cycloheptene **1** was obtained in a quantitative yield by refluxing available[9] diene **3** in dichloromethane in the presence of 1st generation Grubbs catalyst (Scheme 1; for details, see Online Supplementary Materials). Epoxidation of **1** with mCPBA in dichloromethane afforded diastereomeric epoxides **2** as *E* : *Z* = = 7 : 1 mixture in the 85% overall yield.† Similar epoxidation using Oxone[14] or hydrogen peroxide[15] (Table 1) provided lower yields of products **2**.

Table 1 Epoxidation of 1-phenylcyclohept-4-ene-1-carbonitrile **1**.

Epoxidation system	*T*/°C	*t*/h	Overall yield (%)	Ratio *E*-**2** : *Z*-**2**
H_2O_2 (10 equiv.), DMF, 0.2 M $NaHCO_3$ buffer, 1 mol% $MnSO_4$	20	5	25	3:1
H_2O_2 (5 equiv.), DMF, $NaHCO_3$ (0.2 M buffer), 1 mol% $MnSO_4$, 4 mol% salicylic acid	20	5	57	3:1
Oxone (3 equiv.), CH_2Cl_2/H_2O, acetone, 0.2 M Na_2HPO_4 buffer, 18-crown-6 (cat.)	5	5	35	5:2
Oxone (3 equiv.), CH_2Cl_2/H_2O, acetone, 0.2 M Na_2HPO_4 buffer, $[Bu_4N]^+HSO_4^-$ (cat.)	5	5	50	3:1
mCPBA (1.1 equiv.), CH_2Cl_2, 0.2 M Na_2HPO_4	20	5	85	7:1
mCPBA (1.1 equiv.), benzene, 0.2 M Na_2HPO_4	20	5	90	21:1

Diastereomeric ratio *E*-**2** : *Z*-**2** was found to be increased to 21 : 1 by conducting epoxidation with mCPBA in benzene, and the major isomer *E*-**2** was simply isolated by flash chromatography.

Apparently, axially oriented nitrile group is close to the double bond in the preferred molecular conformation of compound **1**, thus it considerably inhibits the attack of the epoxidizing species at this molecule surface in epoxidation processes. Structures of epoxides *E*-**2** (Figure 1) and *Z*-**2** (Figure 2) were confirmed by an X-ray crystallographic analysis.‡

† *4-Phenyl-8-oxabicyclo[5.1.0]octane-4-carbonitriles* **2**. Finely pulverized Na_2HPO_4 (35.8 g, 250 mmol) was added to a vigorously stirred solution of compound **1** (9.9 g, 50 mmol) in benzene (400 ml). The suspension was cooled to 0 °C and mCPBA (14.6 g, 85 mmol) was then added portionwise over 0.5 h. The resulting mixture was warmed to room temperature and allowed to stand overnight. Then the saturated aqueous K_2CO_3 solution (300 ml) was added and the mixture was vigorously stirred for 1 h at room temperature. The organic layer was separated and the aqueous layer was extracted with DCM (2×200 ml). The combined organic layers were dried over Na_2SO_4 and the solvent was evaporated under reduced pressure. The crude residue was purified by flash chromatography on silica gel (hexane–EtOAc, 4 : 1) to give 9.0 g (86%) of *E*-**2** and 0.4 g (4%) of *Z*-**2**.

Isomer *E*-**2**: white crystalline solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.63 (m, 2H), 2.25 (m, 2H), 2.50 (m, 4H), 3.25 (m, 2H), 7.25 (t, 1H, *J* 8.5 Hz), 7.35 (t, 2H, *J* 8.5 Hz), 7.5 (d, 2H, *J* 8.5 Hz). MS, *m*/*z*: 214.2 $[M+H]^+$. Found (%): C, 78.88; H, 7.02; N, 6.51. Calc. for $C_{14}H_{15}NO$ (%): C, 78.84; H, 7.09; N, 6.57.

Isomer *Z*-**2**: white crystalline solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.63 (m, 2H), 1.80 (m, 2H), 2.12 (m, 2H), 2.35 (m, 2H), 3.05 (m, 2H), 7.25 (t, 1H, *J* 8.5 Hz), 7.38 (t, 2H, *J* 8.5 Hz), 7.50 (d, 2H, *J* 8.5 Hz). MS, *m*/*z*: 214.2 $[M+H]^+$. Found (%): C, 78.87; H, 7.02; N, 6.51. Calc. for $C_{14}H_{15}NO$ (%): C, 78.84; H, 7.09; N, 6.57.

‡ *Crystal data for* **2**. Single crystals of compounds *E*-**2** and *Z*-**2** ($C_{14}H_{15}NO$, *M* = 213.28) were grown from ethyl acetate. X-ray analysis was performed on a Bruker SMART APEX II diffractometer equipped with a CCD area detector. Using Olex2,[20] the structure was solved with the ShelXS-1997[21] structure solution program using direct methods and refined with the olex2.refine refinement package using Gauss-Newton minimisation. Both structures were refined in anisotropic approximation for non-hydrogen atoms. Hydrogen atoms were refined using 'riding' model.

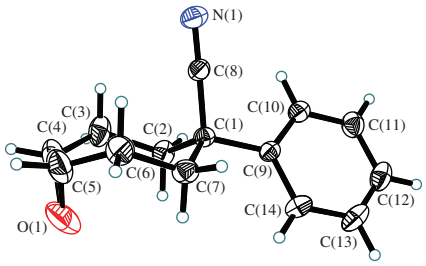


Figure 1 X-ray crystal structure (ORTEP) of *E*-**2**.

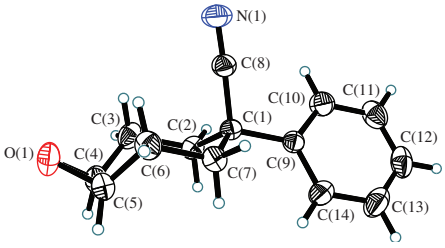


Figure 2 X-ray crystal structure (ORTEP) of *Z*-**2**.

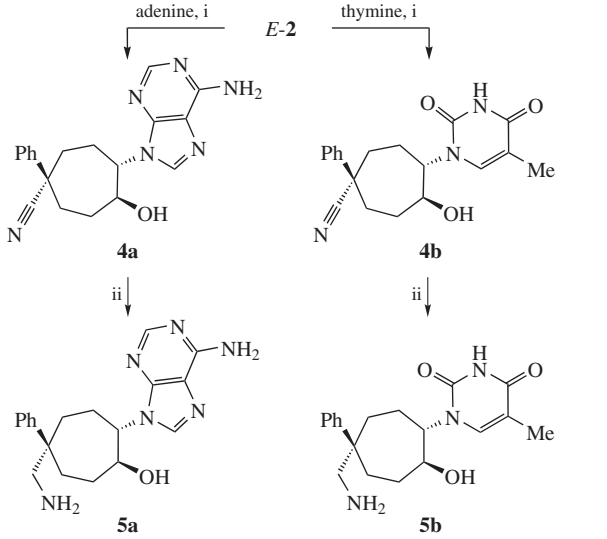
Aiming to obtain new cycloheptane nucleoside analogues, we examined ring opening of epoxide cycle in major diastereomer *E*-**2** with adenine and thymine (Scheme 2).[§]

Treatment of epoxide *E*-**2** with nucleobases in the presence of sodium hydride in DMF[16] yielded complex mixtures of undetectable compounds with the low amounts of desired products **4a**,**b** (Table 2). A brief screening of procedures showed that using DBU as a base[2] in absolute ethanol under microwave irradiation[17] at 140 °C to be the optimal pathway for obtaining compounds **4a**,**b** in good yields and with good stereoselectivity. The configuration of products **4a**,**b** was confirmed by 2D ^{1}H NMR NOESY and ^{1}H-^{13}C HMBC experiments (see Online Supplementary Materials).

The further transformations of nitrile groups in compounds **4a**,**b** are closely connected to the general concept[18] for obtaining versatile building blocks. Unfortunately, attempted basic or acidic

Table 2 Epoxide opening in compound *E*-**2**.

Reactants (1 equiv.)	Conditions	*T*/°C	*t*/h	Product	Yield (%)
Adenine	K_2CO_3 (3.0 equiv.)/DMF	130	4	**4a**	–
Thymine				**4b**	–
Adenine	NaH (1.5 equiv.)/DMF	50–100	4	**4a**	10
Thymine				**4b**	16
Adenine	DBU (1.5 equiv.)/DMF/ microwave irradiation	140	1	**4a**	45
Thymine				**4b**	40
Adenine	DBU (1.5 equiv.)/EtOH/ microwave irradiation	140	1	**4a**	87
Thymine				**4b**	80



Scheme 2 *Reagents and conditions*: i, adenine or thymine (1.0 equiv.), DBU (1.5 equiv.), EtOH, 140 °C, 1 h, microwave irradiation, 80–87%; ii, Raney-Ni, MeOH/NH_3, H_2, 20 °C, 12 h, ~100%.

Crystals of *E*-**2** are monoclinic, space group $P2_1/n$ (no. 14), a = 6.8214(3), b = 8.9966(4) and c = 18.6522(9) Å, β = 89.6379(7)°, V = 1144.65(9) Å^3, Z = 4, T = 296.15 K, μ(MoKα) = 0.078 mm^{-1}, d_{calc} = 1.2375 g cm^{-3}, 13 373 reflections measured (5.02° ⩽ 2θ ⩽ 55.98°), 2745 unique (R_{int} = = 0.0192, R_σ = 0.0156) which were used in all calculations. The final R_1 was 0.0449 [$I \geqslant 2\sigma(I)$] and wR_2 was 0.1307 (all data).

Crystals of *Z*-**2** are monoclinic, space group $P2_1/c$ (no. 14), a = 10.3400(11), b = 9.5196(10) and c = 12.6101(13) Å, β = 111.314(2)°, V = 1156.3(2) Å^3, Z = 4, T = 296.15 K, μ(MoKα) = 0.077 mm^{-1}, d_{calc} = 1.2250 g cm^{-3}, 13 656 reflections measured (5.5° ⩽ 2θ ⩽ 56°), 2789 unique (R_{int} = = 0.0208, R_σ = 0.0180) which were used in all calculations. The final R_1 was 0.0423 [$I \geqslant 2\sigma(I)$] and wR_2 was 0.1296 (all data).

CCDC 978617 and 978618 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* http://www.ccdc.cam.ac.uk.

[§] *Compounds* **4a**,**b**. A solution of epoxide *E*-**2** (3.2 g, 15 mmol), adenine or thymine (15 mmol) and DBU (3.4 g, 22.5 mmol) in anhydrous ethanol (15 ml) was heated under microwave irradiation at 140 °C over 1 h. The mixture was diluted with DCM (250 ml) and washed with brine (150 ml). The organic layer was passed through the pad of celite and dried over Na_2SO_4. The solvents were removed under reduced pressure, the residue was purified by flash chromatography on silica gel (eluent, ethylacetate) to give compounds **4a** or **4b**, respectively.

*(1*RS*,4*SR*,5*SR*)-4-(6-Amino-9*H*-purin-9-yl)-5-hydroxy-1-phenylcycloheptane-1-carbonitrile* **4a**: yield 4.5 g (87%), white crystalline solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.85 (m, 2H), 2.15 (m, 2H), 2.25 (m, 3H), 2.65 (m, 1H), 4.30 (br., 1H), 4.45 (br., 1H), 5.00 (br., 1H), 6.95 (br., 2H), 7.30 (t, 1H, *J* 8.5 Hz), 7.45 (t, 2H, *J* 8.5 Hz), 7.55 (d, 2H, *J* 8.5 Hz), 8.15 (s, 2H). MS, *m*/*z*: 349.2 [M+H]$^+$. Found (%): C, 65.53; H, 5.84; N, 24.32. Calc. for $C_{19}H_{20}N_6O$ (%): C, 65.50; H, 5.79; N, 24.12.

*(1*RS*,4*SR*,5*SR*)-4-Hydroxy-5-(5-methyl-2,4-dioxo-3,4-dihydro-2*H*-pyrimidin-1-yl)-1-phenylcycloheptane-1-carbonitrile* **4b**: yield 4.1 g (80%), white crystalline solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.70 (m, 1H), 1.78 (s, 3H), 1.85 (m, 1H), 2.05 (m, 2H), 2.15 (m, 1H), 2.25 (m, 2H), 2.38 (m, 2H), 4.00 (br., 1H), 4.25 (br., 1H), 5.00 (br., 1H), 7.25 (t, 1H, *J* 8.5 Hz), 7.50 (t, 2H, *J* 8.5 Hz), 7.53 (d, 2H, *J* 8.5 Hz), 7.60 (s, 1H), 10.70 (br., 1H). MS, *m*/*z*: 340.1 [M+H]$^+$. Found (%): C, 67.27; H, 6.30; N, 12.26. Calc. for $C_{19}H_{21}N_3O_3$ (%): C, 67.24; H, 6.24; N, 12.38.

Compounds **5a**,**b**. The corresponding nitrile (**4a** or **4b**, ~6 mmol) was dissolved in 100 ml of MeOH saturated with NH_3 (15–20 wt%). Raney nickel (0.6 g) was pre-washed twice with methanol and resulting suspension was added to the solution. The formed suspension was flushed with argon and placed into Parr shaker-type apparatus. Hydrogenation was completed in ~18 h at a hydrogen pressure of 2–3 atm and 20 °C. Then the resulting mixture was filtered through the pad of celite. The solvent was evaporated under reduced pressure to give corresponding amine **5a** or **5b** in a quantitative yield.

*(1*S*,2*S*,5*R*)-5-Aminomethyl-2-(6-aminopurin-9-yl)-5-phenylcycloheptanol* **5a**: yield 2.1 g (~100%), reaction time 20 h, white crystalline solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 0.90 (br., 2H), 1.40 (m, 1H), 1.75 (m, 4H), 2.25 (m, 3H), 2.65 (m, 2H), 4.10 (m, 2H), 4.65 (br., 1H), 6.90 (br., 2H), 7.20 (m, 1H), 7.35 (m, 5H), 8.15 (s, 2H). MS, *m*/*z*: 353.3 [M+H]$^+$. Found (%): C, 64.78; H, 6.93; N, 23.62. Calc. for. $C_{19}H_{24}N_6O$ (%): C, 64.74; H, 6.86; N, 23.85.

*1-[(1*S*,2*S*,5*R*)-5-Aminomethyl-2-hydroxy-5-phenylcycloheptyl)-5-methyl-1*H*-pyrimidine-2,4-dione* **5b**: yield 2.0 g (~100%); reaction time 18 h, thick colorless oil. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 0.85 (br., 2H), 1.25 (m, 1H), 1.50 (m, 3H), 1.65 (m, 1H), 1.75 (s, 3H), 2.00 (m, 1H), 2.20 (m, 2H), 2.60 (m, 2H), 3.70 (m, 1H), 3.95 (m, 1H), 4.65 (br., 1H), 7.25 (m, 1H), 7.30 (m, 4H), 7.55 (s, 1H). MS, *m*/*z*: 344.2 [M+H]$^+$. Found (%): C, 66.48; H, 7.27; N, 12.12. Calc. for $C_{19}H_{25}N_3O_3$ (%): C, 66.45; H, 7.34; N, 12.24.

hydrolysis brought about complex mixtures of unidentified compounds. The chemical reduction of nitrile groups in **4a**,**b** occurred simultaneously with the reduction of nucleobase moieties. Luckily, mild catalytic hydrogenation in the presence of Raney nickel and ammonia[19] in methanol cleanly afforded 5-aminomethyl-2-hydroxy-5-phenylcycloheptane nucleoside analogues **5a**,**b** in quantitative yields.[§]

In summary, novel 5-aminomethyl-2-hydroxy-5-phenylcycloheptane nucleoside analogues were synthesized in good yields using simple procedures, the key steps occurring stereoselectively.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.mencom.2015.03.014.

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