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188. Total Synthesis of Neplanocin A

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Summary

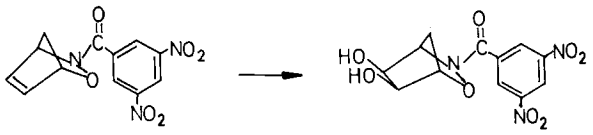
The first total synthesis of racemic neplanocin A (**1**)[1]) from cyclopentadiene and acylnitroso-3,5-dinitrobenzoic acid is described. The synthesis is suitable for specific isotopic labelling of the hydroxymethyl group of neplanocin A.

Neplanocin A (**1**), a carbocyclic analogue of adenosine with antitumor activity was recently isolated [1] [2] from the culture filtrate of *Ampullariella regularis*. Its structure was determined by spectroscopic measurements (IR, NMR, UV, MS), X-ray analysis and correlation with aristeromycin [3]. We report here the first total synthesis of racemic neplanocin A[1]).

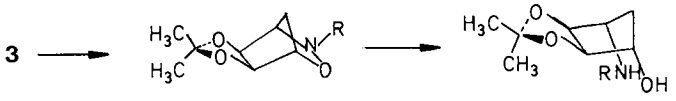
The starting material was (±)-3-(3,5-dinitrobenzoyl)-2-oxa-3-azabicyclo[2.2.1]-hept-5-ene (**2**) which is easily available by *Diels-Alder* condensation of cyclopentadiene with the acyl nitroso derivative of 3,5-dinitrobenzoic acid [4]. Stereospecific *exo-cis* dihydroxylation of **2** with a catalytic amount of OsO_4 in the presence of *N*-methylmorpholine oxide yielded the crystalline diol **3** (92%). The isopropylidene derivative **4** thereof (94%) was submitted to alkaline hydrolysis to furnish compound **5** (86%). Reductive cleavage of the N-O-bond of **5** by Zn/acetic acid [5] afforded triol **6** (88%) the NH_2-group of which was subsequently blocked as benzyloxycarbonyl derivative **7** (92%). Compound **7** was then oxidized with pyridinium chlorochromate [6] to yield ketone **8** (81%) which is a suitable intermediate to introduce the sixth C-atom (isotopically enriched if required) corresponding to C(5′) of D-ribose. In the present synthesis this was achieved by treatment of **8** with dimethylsulfoxomethylene ylide [7]. As inferred from the ^{1}H-NMR spectrum of the oily product **9** (see *Exper. Part*) the carbene addition had taken place stereospecifically and probably from the side not hindered by the bulky isopropylidene protecting group.

The epoxide ring of **9** was easily opened on boiling in glacial acetic acid containing potassium acetate [8]. The crystalline ester **10** was obtained almost quantitatively (97%). The free NH_2-group was regenerated by hydrogenolytic removal of the benzyloxycarbonyl group to yield **11** (95%). The construction of the

[1]) *Note added in proof:* After submitting our paper we learned that *Arita et al.* [J. Am. Chem. Soc. *105*, 4049 (1983)] synthesized the natural enantiomer of neplanocin A.



2 **3**

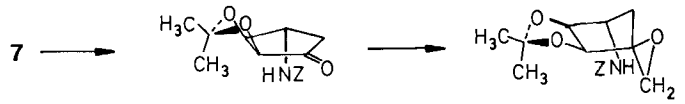


4 R: CO-(2,4-dinitrophenyl)

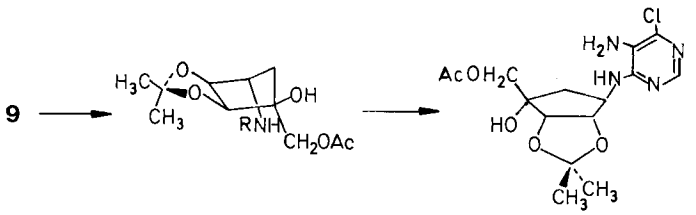
5 R: H

6 R: H

7 R=Z: CO-OCH_2Ph



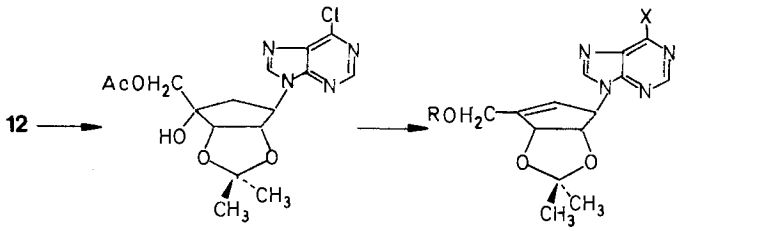
8 **9**



10 R: CO-OCH_2Ph

11 R: H

12



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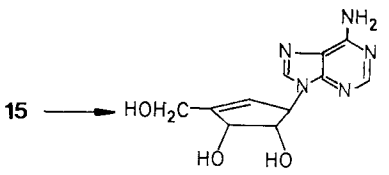
14 R: Ac, X: Cl

15 R: H, X: NH_2

16 R: H, X: OCH_3



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purine nucleus was achieved by a procedure used previously in the synthesis of aristeromycin [9]. Reaction of **11** with 5-amino-4,6-dichloropyrimidine gave the oily pyrimidine derivative **12** (59%). The purine nucleus was then completed by treating the purified **12** with triethyl orthoformate in the presence of *p*-toluenesulfonic acid as catalyst. The resulting tetrol **13** (59%) seemed to be the appropriate intermediate for elimination of the tertiary OH-group. Its treatment with phosphorus oxychloride and 4-dimethylaminopyridine led to **14** (82%). The isopropylidene-protected racemic neplanocin A **15** was obtained by heating **14** with liquid ammonia in a sealed tube (autoclave). The substitution of the Cl-atom by ammonia occurred concomitantly with aminolysis of the acetate side chain in 74% yield. The ^{1}H-NMR, UV, and mass spectra of **15** were identical with those of the corresponding derivative of natural neplanocin A. Acid hydrolysis of **15** gave finally racemic neplanocin A which exhibited identical UV, ^{1}H-NMR, and mass spectra as published for the natural compound. The overall yield was 6.4% based on **2**.

In an attempt to substitute the Cl-atom in **14** by treatment with a methanolic ammonia solution instead of the neplanocin A derivative triol **16** was also obtained (29%) and spectroscopically characterized.

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Experimental Part

General. Melting point (m.p.) (not corrected): *Tottoli* apparatus. Prep. TLC plates from *Macherey-Nagel*, Kieselgel *G-100 UV$_{254}$*, 1 mm, column chromatography (CC), *Merck* Kieselgel *60*, 0.040–0.063 mm. UV spectra (λ_{max} [nm] (ε)). *Varian Cary 14* spectrometer. IR spectra (ν [cm^{-1}]), *Beckman IR-8* and *Perkin Elmer 221* spectrometers. ^{1}H-NMR spectra, *Bruker WH-90* or *Bruker WM-250* spectrometers (δ ppm, apparent coupling constant J Hz, number of protons, tentative attribution); *s* = singulet, *d* = doublet, *t* = triplet, *q* = quadruplet, *quint.* = quintet, *m* = multiplet, $\delta_{TMS} = 0.0$ ppm. MS (*m/e* [amu] (% base peak)); *Varian MAT CH-5* spectrometer, T_d temperature at direct probe introduction; Elemental analyses were performed by Mrs. *I. Süß* in our laboratory. Abbreviations: *i.v.* = in vacuo, r.t. = room temperature.

(±)-exo-cis-3-(3,5-Dinitrobenzoyl)-2-oxa-3-azabicyclo[2.2.1]heptane-5,6-diol (**3**). (±)-3-(3,5-Dinitrobenzoyl)-2-oxa-3-azabicyclo[2.2.1]hept-5-ene (**2**) [4] (6 g, 20.6 mmol) and *N*-methylmorpholine *N*-oxide monohydrate (3.34 g, 24.7 mmol) were dissolved in a mixture of acetone (412 ml) H_2O (103 ml) and *t*-BuOH (41 ml). After addition of OsO_4 (47 mg, 0.185 mmol) the mixture was stirred at r.t. for 2 days, then a solution of $NaHSO_3$ (7.08, 68 mmol) in H_2O (412 ml) was added and the solution stirred at r.t. for further 2 h. Neutralisation with 0.5M H_2SO_4 and removal of the acetone *i.v.* was followed by acidification to pH 2 (0.5M H_2SO_4), saturation with NaCl and extraction with EtOAc (5 × 100 ml). The combined org. extracts were dried (Na_2SO_4). Evaporation of the solvent *i.v.* yielded 6.15 g (18.91 mmol, 92%) semi-crystalline crude product, m.p. 128–129° (from $CHCl_3$). IR (KBr): 3400, 3080, 1610, 1540, 1340, 1080, 730, 705. ^{1}H-NMR ($CDCl_3$): 2.03 (*d* of *quint.*, J = 11 and 1.8, 1 H); 2.38 (*d*, J = 11, 1 H); 3.11 (*d*, J = 5.6, 1 H, disappears on exchange with D_2O); 3.40 (*d*, J = 5, 1 H, disappears on exchange with D_2O); 4.23 (*m*, 2 H); 4.64 (*s*, 1 H); 4.96 (*s*, 1 H); 9.00 (*d*, J = 2, 2 H); 9.16 (*t*, J = 2, 1 H). MS (70 eV, T_d = 115°): 325 (3, M^+), 267 (6), 266 (8), 225 (12, ON–CO–$C_6H_3(NO_2)_2^+$), 195 (100, CO–$C_6H_3(NO_2^+)_2$), 130 (5), 103 (17).

$C_{12}H_{11}N_3O_8$ (325.233) Calc. C 44.32 H 3.41 N 12.92% Found C 44.03 H 3.35 N 12.43%

(±)-exo-cis-3-(3,5-Dinitrobenzoyl)-5,6-O-isopropylidene-2-oxa-3-azabicyclo[2.2.1]heptane-5,6-diol (**4**). A solution of **3** (6.4 g, 19.68 mmol) and *p*-TsOH monohydrate (800 mg, 4.2 mmol) in a mixture of dry acetone (400 ml) and CH_2Cl_2 (400 ml) was heated under reflux for 2 days. The condensate was reintroduced in the mixture through *Sikkon* (Fluka) to remove H_2O. After evaporation of the solvent

i.v. the brownish crystalline residue was chromatographed on silica gel (600 g) with EtOAc. Recrystallization from EtOH yielded 6.75 g (18.48 mmol, 94%) colourless needles of **4** (m.p. 155°). IR (KBr): 3095, 2990, 2940, 1630, 1545, 1345, 1210, 1070, 730, 720, 705. ^{1}H-NMR ($CDCl_3$): 1.33 (*s*, 3 H); 1.47 (*s*, 3 H); 1.92 (*d* of *quint.*, J = 11 and 1.8, 1 H); 2.37 (*d*, J = 11, 1 H); 4.41 (*dt*, J = 5.4 and 1, 1 H); 4.56 (*dt*, J = 5 and 1, 1 H); 4.78 (*s*, 1 H); 5.09 (*s*, 1 H); 9.01 (*d*, J = 2, 2 H); 9.16 (*t*, J = 2, 1 H). MS (70 eV, T_d = 110°): 365 (9, M^+), 350 (24), 308 (5), 195 (88, $CO{-}C_6H_3(NO_2)_2^+$), 179 (5), 149 (40), 103 (15), 43 (100, $H_3C{-}CO^+$).

$C_{15}H_{15}N_3O_8$ (365.298) Calc. C 49.32 H 4.14 N 11.50% Found C 49.31 H 3.97 N 11.39%

*(±)-*exo-cis-*5,6-O-Isopropylidene-2-oxa-3-azabicyclo[2.2.1]heptane-5,6-diol* (**5**). A solution of **4** (1.2 g, 3.28 mmol) was prepared in warm (*ca.* 50°) EtOH (700 ml), was then cooled to r.t. and treated dropwise with 0.1 M ethanolic KOH (41 ml within 0.5 h). The deep red-violet mixture was stirred at r.t. for 40 h. After removal of the solvent at 30° in a rotatory evaporator the brown residue was sublimed at 65°/15 Torr, giving **5** as colourless plates, yield: 0.483 g (2.82 mmol, 86%), m.p. 93°. IR (KBr): 3240, 2980, 2950, 2940, 1380, 1370, 1270, 1200, 1155, 1060, 925, 890, 855, 755, 745. ^{1}H-NMR ($CDCl_3$): 1.24 (*s*, 3 H); 1.40 (*s*, 3 H); 1.58 (*d* of *quint.*, J = 11 and 1.8, 1 H); 2.22 (*d*, J = 11, 1 H); 3.71 (*dd*, J = 1.4 and 1, 1 H); 4.13 (*dt*, J = 5.4 and 1.6, 1 H); 4.24 (*dt*, J = 5 and 1.6, 1 H); 4.37 (*m*, 1 H); 5.4 (br. *s*, 1 H, disappears on exchange with D_2O). MS (70 eV, T_d = 120°): 171 (2, M^+), 156 (9), 138 (5), 95 (6), 54 (10), 43 (100).

$C_8H_{13}NO_3$ (171.196) Calc. C 56.13 H 7.65 N 8.18% Found C 55.98 H 7.40 N 8.01%

*(±)-1β-Amino-2a,3a-*O*-isopropylidene-2a,3a,4β-cyclopentanetriol* (**6**). To a solution of **5** (2.8 g, 16.35 mmol) in Et_2O (125 ml) kept in an ice bath, were added glacial HOAc (29.7 ml) and activated [10] Zn-dust (10.8 g, 165.2 mmol). The vigorously stirred suspension was allowed to warm to r.t. during 24 h, before it was cooled again in an ice bath and treated dropwise with 2 M NaOH (297 ml within 45 min). The precipitate was filtered with suction and washed with CH_2Cl_2 (100 ml). Filtrate and washing phase were combined and evaporated *i.v.* at 70° to dryness. The residue was repeatedly extracted with CH_2Cl_2 (7 × 100 ml). After drying (Na_2SO_4) the combined extracts evaporation of the solvent furnished colourless crystalline **6** (2.5 g, 14.43 mmol, 88%), m.p. 128° (from Et_2O). IR (KBr): 3440, 3340, 3280, 3130, 2980, 2930, 2900, 1590, 1380, 1260, 1205, 1160, 1070, 1040, 985, 905, 860. ^{1}H-NMR ($CDCl_3$): 1.28 (*s*, 3 H); 1.38 (*s*, 3 H); 1.62 (*d*, J = 14, 1 H); 2.09 (*dt*, J = 14 and 4, 1 H); 2.60 (br. *s*, 3 H, disappears on exchange with D_2O); 3.58 (*d*, J = 4, 1 H); 4.08 (*d*, J = 4.2, 1 H); 4.38 (*dd*, J = 5 and 1.6, 1 H); 4.67 (*dd*, J = 5 and 1.6, 1 H). MS (70 eV, T_d = 30°): 174 (0.5, $M^+ + 1$), 173 (1.5, M^+), 158 (5), 115 (9), 43 (100).

$C_8H_{15}NO_3$ (173.212) Calc. C 55.47 H 8.73 N 8.09% Found C 55.44 H 9.03 N 8.07%

*(±)-1β-(Benzyloxycarbonylamino)-2a,3a-*O*-isopropylidene-2a,3a,4β-cyclopentanetriol* (**7**). A cooled (0°) solution of **6** (2.4 g, 13.86 mmol) in toluene (390 ml) was first treated with anh. Na_2CO_3 (14.69 g, 138.6 mmol) then dropwise with a 50% (w/w) mixture (4.87 ml within 5 min) of benzyl chloroformate (14.55 mmol) and toluene. After stirring at r.t. for 1 day the undissolved solid was removed by filtration and washed with CH_2Cl_2 (30 ml). The combined org. phases were washed successively with 1 M HCl saturated with NaCl, sat. $NaHCO_3$ and sat. NaCl solutions. After drying (Na_2SO_4) removal of the solvent *i.v.* at 40° yielded an oily product. Chromatography on 500 g silica gel with EtOAc/hexane 2:1 afforded colourless crystalline 7 (3.9 g, 12.69 mmol, 92%), m.p. 101–102° (from EtOAc/hexane). IR ($CHCl_3$): 3430, 3000, 2945, 1715, 1515, 1390, 1380, 1075, 1050, 870, 695. ^{1}H-NMR ($CDCl_3$): 1.25 (*s*, 3 H); 1.39 (*s*, 3 H); 1.68 (*d*, J = 14, 1 H); 2.28 (*m*, 2 H, half of it disappears on exchange with D_2O); 4.19 (*m*, 2 H); 4.46 (*dd*, J = 5 and 1.6, 1 H); 4.58 (*dd*, J = 5 and 1.4, 1 H); 5.11 (*s*, 2 H); 5.68 (*d*, J = 8, 1 H, disappears on exchange with D_2O); 7.31 (br. *s*, 5 H). MS (70 eV, T_d = 75°): 307 (2, M^+), 292 (6), 249 (13), 108 (23), 107 (14), 92 (27), 91 (100, $C_6H_5CH_2^+$), 77 (14), 43 (34).

$C_{16}H_{21}NO_5$ (307.346) Calc. C 62.53 H 6.89 N 4.56% Found C 62.73 H 7.05 N 4.51%

*(±)-1β-(Benzyloxycarbonylamino)-2a,3a-dihydroxy-2a,3a-*O*-isopropylidene 4-cyclopentanone* (**8**). To a solution of pyridinium chlorochromate (7.75 g, 38.07 mmol) in CH_2Cl_2 (80 ml) was added **7** (3.9 g, 12.69 mmol) and the mixture was stirred at r.t. for 3 days. After filtration the tarry residue was washed 3 times with CH_2Cl_2 and the combined org. phases were concentrated *i.v.* Chromatography of the brownish residue on 500 g silica gel with EtOAc/hexane 2:1 furnished colourless crystals of **8** (3.12 g, 10.22 mmol, 81%), m.p. 113–114° (from EtOAc/hexane). IR ($CHCl_3$): 3460, 3035, 3000, 2945, 1765, 1715,

1515, 1390, 1380, 1240, 855, 695. ^{1}H-NMR ($CDCl_3$): 1.31 (*s*, 3 H); 1.40 (*s*, 3 H); 2.30 (*d*, J = 18, 1 H); 2.94 (*dd*, J = 18 and 8, 1 H); 3.92 (*m*, 1 H); 4.49 (*d*, J = 5, 1 H); 4.71 (*d*, J = 5, 1 H); 5.04 (*s*, 2 H); 5.31 (br. *s*, 1 H, disappears on exchange with D_2O); 7.31 (*s*, 5 H). MS (70 eV, T_d = 120°): 305, (2, M^+), 290 (2), 247 (3), 214 (19), 156 (9), 92 (12), 91 (100, $C_6H_5CH_2^+$), 59 (42), 43 (17).

$C_{16}H_{19}NO_5$ (305.330) Calc. C 62.94 H 6.27 N 4.59% Found C 63.04 H 6.60 N 4.59%

*(±)-1β-(Benzyloxycarbonylamino)-2α,3α-dihydroxy-2α,3α-*O*-isopropylidene-4-methylidene-cyclopentane oxide* (**9**). A suspension of NaH (208.5 mg, 60% in oil, 5.21 mmol) in pentane (20 ml) was stirred at r.t. for 15 min in a closed three-necked flask. After stopping the stirrer the liquid was removed by decantation and the residue was resuspended in dry DMSO (17 ml). While a gentle stream of N_2 through the reaction mixture was maintained, two dropping funnels were filled with a solution of **8** (1.56 g, 5.11 mmol) in DMSO (16 ml) and with a solution of trimethylsulfoxonium iodide [11] in DMSO (16 ml), respectively. After stirring the suspension of NaH for 5 min the solution of trimethylsulfoxonium iodide was added within 10 min. The initially vigorous bubbling was gradually terminated while stirring was continued for 20 min. Then the solution of **8** was introduced within 5 min. After a further 30 min a clear yellowish solution resulted which was poured onto ice-chilled water (50 ml). The milky emulsion was extracted with CH_2Cl_2 (5 × 40 ml) and the combined org. phases were dried (Na_2SO_4). After removal of the solvent the residue was chromatographed on 200 g silica gel with EtOAc/hexane 2:1 furnishing a slightly yellowish oil identified as **9** (1.42 g, 4.447 mmol, 87%). IR ($CHCl_3$): 3440, 3000, 2940, 1725, 1510, 1385, 1380, 1260, 1230, 1065, 1045, 865, 695. ^{1}H-NMR ($CDCl_3$): 1.27 (*s*, 3 H); 1.31 (*d*, J = 14, 1 H); 1.44 (*s*, 3 H); 2.69 (*dd*, J = 14 and 6, 1 H); 2.89 (*d*, J = 4, 1 H); 3.00 (*d*, J = 4, 1 H); 4.19 (*m*, 2 H); 4.66 (*d*, J = 6, 1 H); 5.10 (br. *s*, 3 H, one third of which disappears on exchange with D_2O); 7.33 (*s*, 5 H). MS (70 eV, T_d = 55°): 319 (2, M^+), 304 (2), 261 (4), 170 (4), 108 (9), 107 (8), 92 (11), 91 (100, $C_6H_5CH_2^+$), 43 (23).

*(±)-4β-(Acetoxymethyl)-1β-(benzyloxycarbonylamino)-2α,3α-*O*-isopropylidene-2α,3α,4α-cyclopentanetriol* (**10**). Compound **9** (1.42 g, 4.45 mmol) and KOAc (6.55 g, 66.74 mmol) were heated together with glacial HOAc (28 ml) to 120° for 15 min. The mixture was then cooled to r.t. and treated with solid Na_2CO_3 (26.5 g) and sat. aq. $NaHCO_3$ (60 ml). After extraction with CH_2Cl_2 (6 × 30 ml) the org. phases were combined and dried (Na_2SO_4). Evaporation of the solvent and recrystallization of the residue from EtOAc/hexane yielded colourless needles of **10** (1.64 g, 4.32 mmol, 97%), m.p. 111°. IR ($CHCl_3$): 3590, 3430, 2995, 2940, 1725, 1510, 1385, 1375, 1265, 1230, 1085, 1045, 905, 700. ^{1}H-NMR ($CDCl_3$): 1.24 (*s*, 3 H); 1.40 (*s*, 3 H); 1.61 (br. *d*, J = 14, 1 H); 2.10 (*dd*, J = 14 and 7, 1 H); 2.10 (*s*, 3 H); 2.83 (*m*, 1 H, disappears on exchange with D_2O); 4.0–4.4 (*m*, 4 H); 4.58 (*dd*, J = 5 and 1, 1 H); 5.08 (*s*, 2 H); 5.78 (*d*, J = 9, 1 H, disappears on exchange with D_2O); 7.31 (*s*, 5 H). MS (70 eV, T_d = 115°): 379 (6, M^+), 364 (6), 361 (6), 321 (5), 278 (8), 272 (6), 261 (11), 248 (34), 108 (55), 107 (37), 92 (41), 91 (100, $C_6H_5CH_2^+$), 79 (47), 77 (27), 59 (34), 43 (89).

$C_{19}H_{25}NO_7$ (379.409) Calc. C 60.14 H 6.64 N 3.69% Found C 60.04 H 6.89 N 3.68%

*(±)-4β-(Acetoxymethyl)-1β-amino-2α,3α-*O*-isopropylidene-2α,3α,4α-cyclopentanetriol* (**11**). A solution of **10** (1.59 g, 4.19 mmol) in EtOAc (60 ml) was stirred with *Engelhard*'s catalyst (10% Pd/C, 210 mg) under H_2. After the consumption of H_2 had stopped (6 h) the suspension was filtered through *Celite*. Removal of the solvent *i.v.* yielded colourless crystalline **11** (0.980 g, 3.99 mmol, 95%), m.p. 122° (from EtOAc). IR (KBr): 3375, 3100, 2995, 2920, 1740, 1390, 1380, 1255, 1065, 1045, 960, 880, 610. ^{1}H-NMR ($CDCl_3$): 1.28 (*s*, 3 H); 1.40 (*s*, 3 H); 1.59 (*dt*, J = 13.7 and 1.2, 1 H); 1.98 (*dd*, J = 13.7 and 4.2, 1 H); 2.12 (*s*, 3 H); 2.75 (br., 3 H, disappears on exchange with D_2O); 3.60 (*d*, J = 4.2, 1 H); 4.14 (*d*, J = 11.5, 1 H); 4.32 (*d*, J = 11.5, 1 H); 4.43 (*dd*, J = 5.4 and 1.2, 1 H); 4.57 (*dd*, J = 5.4 and 1.2, 1 H). MS (70 eV, T_d = 55°): 246 (0.8, $M^+ + 1$), 245 (1, M^+), 230 (3), 187 (4), 172 (2), 170 (3), 144 (62), 128 (6), 127 (6), 110 (7), 43 (100, CH_3CO^+).

$C_{11}H_{19}NO_5$ (245.275) Calc. C 53.87 H 7.81 N 5.71% Found C 53.88 H 8.13 N 5.83%

*(±)-4β-(Acetoxymethyl)-1β-(5-amino-6-chloro-4-pyrimidinylamino)-2α,3α-*O*-isopropylidene-2α,3α,4α-cyclopentanetriol* (**12**). A solution of **11** (0.730 g, 2.976 mmol), 5-amino-4,6-dichloropyrimidine (1.464 g, 8.927 mmol) and Et_3N (0.62 ml, 4.464 mmol) in BuOH (35 ml) was heated to 120° for 24 h under exclusion of humidity. After removal of the solvent *i.v.* (45°) chromatography of the oily residue on silica gel with EtOAc/hexane 2:1 yielded colourless oily **12** (0.655 g, 1.757 mmol, 59%). IR ($CHCl_3$): 3585, 3400, 2995, 2940, 1745, 1575, 1385, 1375, 1230, 1050. ^{1}H-NMR ($CDCl_3$): 1.27 (*s*, 3 H); 1.44 (*s*, 3 H);

1.77 (*d*, J = 14, 1 H); 2.13 (*s*, 3 H); 2.24 (*dd*, J = 14 and 6, 1 H); 3.42 (br., 3 H, disappears on exchange with D_2O); 4.29 (*s*, 2 H); 4.39 (*dd*, J = 5 and 1.4, 1 H); 4.58 (*dd*, J = 5 and 1.4, 1 H); 4.69 (*d*, J = 6, 1 H); 6.02 (*d*, J = 9, 1 H, disappears on exchange with D_2O); 8.09 (*s*, 1 H). MS (70 eV, T_d = 120°): 373/375 (11/4, $M^+ + 1$), 372/374 (49/17, M^+), 357/359 (23/8), 297/299 (13/6), 296/298 (40/15), 271/273 (16/6), 241/243 (83/29), 236 (22), 145/147 (50/17), 144/146 (67/26), 43 (100, CH_3CO^+).

(±)-4β-(Acetoxymethyl)-1β-(6-chloro-9-purinyl)-2α,3α-O-isopropylidene-2α,3α,4α-cyclopentanetriol (**13**). Compound **12** (102.4 mg, 0.275 mmol) and *p*-TsOH monohydrate (59 mg, 0.310 mmol) were stirred together with triethyl orthoformate (4 ml) at r.t. for 2 days. The resulting suspension was briefly stirred with Et_3N (0.076 ml). The filtered colourless precipitate was recrystallized from EtOAc yielding **13** (62 mg, 0.162 mmol, 59%), m.p. 222–223°. IR (KBr): 3300, 3130, 2985, 2945, 1725, 1595, 1565, 1385, 1375, 1250, 1225, 1210, 1050, 1040, 935, 645, 635. ^{1}H-NMR ($CDCl_3$): 1.33 (*s*, 3 H); 1.56 (*s*, 3 H); 2.13 (*s*, 3 H); 2.20 (*d*, J = 15, 1 H); 2.73 (*dd*, J = 15 and 9, 1 H); 3.99 (*s*, 1 H, disappears on exchange with D_2O); 4.36 (*s*, 2 H); 4.58 (*dd*, J = 4.5 and 1.4, 1 H); 4.97 (*d*, J = 4.5, 1 H); 5.13 (*d*, J = 9, 1 H); 8.53 (*s*, 1 H); 8.77 (*s*, 1 H). MS (70 eV, T_d = 170°): 383/385 (2/1, $M^+ + 1$), 382/384 (2/1, M^+), 367/369 (12/4), 324/326 (18/6), 307/309 (10/4), 282/284 (14/5), 251/253 (100/37, $M^+ - CH_3$, $-CH_3CO$, $-CH_3CO$, $-CH_2O$), 43 (90).

$C_{16}H_{19}ClN_4O_5$ (382.803) Calc. C 50.20 H 5.00 N 14.64% Found C 50.09 H 5.07 N 14.54%

(±)-4-(Acetoxymethyl)-1β-(6-chloro-9-purinyl)-2α,3α-O-isopropylidene-4-cyclopentene-2α,3α-diol (**14**). A solution of **13** (210 mg, 0.548 mmol) and 4-(*N*,*N*-dimethylamino)pyridine (536 mg, 4.383 mmol) in CH_2Cl_2 (4 ml) was cooled to 0° and treated with phosphorus oxychloride (0.1 ml, 1.096 mmol). After stirring at 0° for 1 h the mixture was separated by prep. TLC (R_f = 0.50, solvent EtOAc/toluene 4:1, yielding colourless slowly crystallizing **14** (165 mg, 0.452 mmol, 82%), m.p. 98–100° (from EtOAc/hexane). IR ($CHCl_3$): 3430, 3000, 2935, 1745, 1595, 1565, 1385, 1375, 1225, 1085, 1050, 950, 860, 635. ^{1}H-NMR ($CDCl_3$): 1.38 (*s*, 3 H); 1.49 (*s*, 3 H); 2.13 (*s*, 3 H); 4.73 (*d*, J = 5.4, 1 H); 4.85 (*s*, 2 H); 5.42 (*d*, J = 5.4, 1 H); 5.64 (*m*, 1 H); 5.78 (*m*, 1 H); 8.02 (*s*, 1 H); 8.78 (*s*, 1 H). MS (70 eV, T_d = 140°): 364/366 (0.7/0.3, M^+), 349/351 (4/1.6), 307/309 (8/3), 306/308 (8/3), 277/279 (11/4), 153 (100, M^+ – chloropurine, $-CH_3$, $-CH_3CO$), 110 (7), 43 (62).

(±)-1β-(6-Amino-9-purinyl)-4-(hydroxymethyl)-2α,3α-O-isopropylidene-4-cyclopentene-2α,3α-diol (**15**). Compound **14** (152 mg, 0.147 mmol) and liquid NH_3 was heated to 60° in an autoclave for 4 h. After evaporation of the NH_3 the residual colourless solid was recrystallized from MeOH yielding pure **15** (94 mg, 0.3099 mmol, 74%), m.p. 262–263° (dec.). UV (CH_3OH): 262 (14700), ([3]: 262 (15100). IR (KBr): 3250, 3130, 2990, 1690, 1615, 1575, 1385, 1375, 1340, 1315, 1240, 1205, 1085, 1055, 880, 675. ^{1}H-NMR (CD_3SOCD_3): 1.27 (*s*, 3 H); 1.38 (*s*, 3 H); 4.13 (*m*, 2 H); 4.67 (*d*, J = 5.4, 1 H); 5.07 (*t*, J = 5, 1 H); 5.32 (*d*, J = 5.4, 1 H); 5.44 (*m*, 1 H); 5.72 (*m*, 1 H); 7.27 (br., 2 H, disappears on exchange with D_2O); 7.98 (*s*, 1 H); 8.17 (*s*, 1 H). MS (70 eV, T_d = 180°): 303 (10, M^+), 288 (6.5), 245 (48), 136 (45), 135 (42), 111 (100, M^+ – adenine, $-CH_3$, $-CH_3CO$), 43 (33).

(±)-1β-(6-Amino-9-purinyl)-4-hydroxymethyl-4-cyclopentene-2α,3α-diol (*neplanocin A*, **1**). A suspension of **15** (25 mg, 0.082 mmol) in 1M aq. HCl (20 ml) was stirred at 80° for 8 h. The mixture was then concentrated to 5 ml in a rotatory evaporator. After adjusting the pH to 8 with 15% aq. NH_3 the evaporation was continued to dryness. Recrystallization from H_2O furnished colourless crystals of racemic neplanocin A (**1**) (16.6 mg, 0.063 mmol, 77%), m.p. 221–224° (dec.) ([3]: m.p. 220–222°). UV (H_2O): 262 (14300) ([3]: 262 (15700)). IR (KBr): 3330, 3200, 2850, 1655, 1615, 1585, 1485, 1425, 1335, 1305, 1120. ^{1}H-NMR (CD_3SOCD_3): 4.12 (*m*, 2 H); 4.31 (*q*, J = 5.4, 1 H); 4.44 (*t*, J = 4.2, 1 H); 4.92 (*t*, J = 5.4, 1 H, disappears on exchange with D_2O); 4.97 (*d*, J = 5.4, 1 H, disappears on exchange with D_2O); 5.16 (*d*, J = 6.2, 1 H, disappears on exchange with D_2O); 5.35 (*m*, 1 H); 5.72 (*d*, J = 2, 1 H); 7.24 (br. *s*, 2 H, disappears on exchange with D_2O); 8.09 (*s*, 1 H); 8.16 (*s*, 1 H). MS (70 eV, T_d = 215°): 263 (2.6, M^+), 137 (9) 136 (100, (adenine)$^+$ + 1), 135 (20, (adenine)$^+$).

(±)-4-(Hydroxymethyl)-2α,3α-O-isopropylidene-1β-(6-methoxy-9-purinyl)-4-cyclopentene-2α,3α-diol (**16**). Compound **14** (44 mg, 0.120 mmol) and a sat. methanolic solution of NH_3 (120 ml) were heated to 100° for 15 h in an autoclave. The brown mixture was concentrated *i.v.* and the non-volatile residue purified by TLC with BuOH/AcOH/H_2O 4:1:1. Compound **16** (R_f = 0.61) was obtained as colourless crystals with one mole HOAc as crystal solvent (11 mg, 0.0346 mmol, 29%), m.p. 166–167° (dec.). UV (CH_3OH): 249 (7000). IR (KBr): 3340, 2925, 1600, 1580, 1480, 1225, 1090, 1060, 1040. ^{1}H-NMR (CD_3OD): 1.34 (*s*, 3 H); 1.46 (*s*, 3 H); 1.92 (*s*, 3 H); 4.03 (*s*, 3 H); 4.32 (*m*, 2 H); 4.77 (*d*, J = 6, 1 H); 5.43 (*d*, J = 5.4, 1 H); 5.64 (*m*, 1 H); 5.79 (*m*, 1 H); 8.17 (*s*, 1 H); 8.50 (*s*, 1 H). MS (70 eV, T_d = 120°): 318 (2.7, M^+), 303 (3.1), 261 (9), 260 (15), 231 (15), 151 (21), 111 (100, M^+(O-methylhypoxanthine), $-CH_3$, CH_3CO), 43 (31).

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