Approach to Carbocyclic 4-Deoxypyrazofurin through Asymmetrisation of a *meso*-Norbornene Derivative

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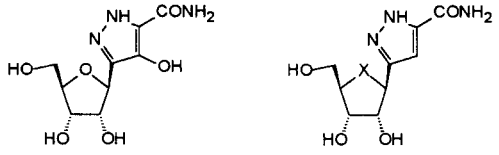
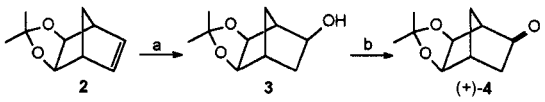
Abstract: The first enantioselective synthesis of carbocyclic 4-deoxypyrazofurin **1a** has been accomplished *via* ketone (+)-**4** which was prepared by asymmetric hydroboration or hydrosilylation reactions.

Carbocyclic nucleosides, particularly in their optically active form have attracted considerable synthetic interest as potential therapeutic agents.[1] Within this context, we report here a synthesis of (-)-3-[(1*S*,2*S*,3*R*,4*R*)-2,3-(dihydroxy)-4-(hydroxymethyl)cyclopentyl]1H-pyrazole-5-carboxamide (**1a**), a carbocyclic congener of 4-deoxypyrazofurin **1b**.[2]



In continuation of our efforts[3] to develop an efficient methodology for the construction of enantiomerically pure compounds with several contiguous stereogenic centres from *meso*-substrates, we wanted to further explore the utility of easily available *meso*-norbornene derivative **2**.[4] We envisaged that its asymmetric transformation to the ketone **4** would represent a shorter access to the lactone **5**, a common precursor of carba*ribo N*- and *C*-nucleosides previously reported.[5] Thus, we examined different means of asymmetric hydroboration[6-8] and hydrosilylation[9] reactions of the olefin **2** (Table 1). The best results regarding chemical and optical yields were achieved by hydrosilylation with trichlorosilane in the presence of a palladium catalyst coordinated with (*R*)-MOP ligand at 0°C (entry 11).[10] Hydroboration with (-)-Ipc_2BH at temperatures below -10°C (entries 1-3)[11] also gave good results. The ee value of ≥ 76% of the ketone **4** could be enriched up to 98% by fractional crystallization from pentane. Hydroborations with Lgf_2BH (entry 5)[12] as well as catecholborane (entries 6-10)[13] in the presence of rhodium (I) catalyst coordinated with different chiral phosphines (+)-DIOP, (-)-BINAP, (-)-CHIRAPHOS resulted, on the other hand, in moderate ee values.



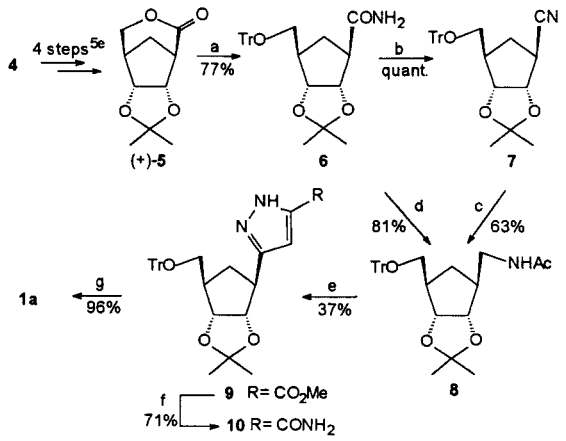
Scheme 1. *Reagents:* (a) i, (-)-Ipc_2BH/THF or Lgf_2BH/THF or catecholborane/homochiral Rh-cat./THF; ii, 30% H_2O_2/*aq.* NaOH; or i, $HSiCl_4$/(*R*)-MOP/$[PdCl(\pi\text{-}C_3H_5)]_2$; ii, KF/$KHCO_3$/30% H_2O_2; (b) PDC/ Py·CF_3CO_2H/CH_2Cl_2

Transformation of the enantiomerically enriched ketone (+)-**4** ($[\alpha]_D^{21}$ = +104.0 (*c* 1.6, $CHCl_3$)) to the lactone (+)-**5** was carried out in four steps.[5e] Having the optically pure (+)-**5** in hand, the synthesis of the "natural" enantiomer of the target compound **1a** was realised in a straightforward manner (Scheme 2). Opening of the lactone **5** with ammonia followed by tritylation gave the protected crystalline amide **6**. This was transformed to the acetamido derivative **8**[14] using two approaches of which the reduction of the amide functionality with BH_3[15] followed by acetylation was more efficient. Treatment of **8** with N_2O_4/AcOH at 0°C easily provided the targeted *N*-nitrosoamide

Table 1. Asymmetrisation of *meso*-norbornene derivative **2**

entry	source of chirality[a]	conditions	yield (%)[b]	$[\alpha]_D^{21}$[c]	% ee[d]
1	(-)-Ipc_2BH	-30°C, 9d	42	+85.0	80
2	(-)-Ipc_2BH	-20°C, 7d	48	+81.7	77
3	(-)-Ipc_2BH	-10°C, 5d	72	+80.7	76
4	(-)-Ipc_2BH	0°C, 3d	81	+69.0	65
5	Lgf_2BH	0°C, 3d	52	+24.4	23
6	(-)-CHIRAPHOS	0°C, 2d	49	+ 3.2	3
7	(+)-DIOP	0°C, 2d	53	+20.2	19
8	(-)-BINAP	0°C, 2d	48	+24.4	23
9	(-)-BINAP	-15°C, 6d	55	+43.5	41
10	(+)-BINAP	-15°C, 6d	51	-43.0	40
11	(*R*)-MOP	0°C, 2d	67	+97.7	92

[a](-)-Ipc_2BH, (-)-diisopinocampheylborane; Lgf_2BH, dilongifolylborane; (+)-DIOP, (2*S*,3*S*)-2,3-*O*-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane; (-)/(+)-BINAP, (*S*)/(R)-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl; (-)-CHIRAPHOS, (2*S*,3*S*)-bis(diphenylphosphino)butane; (*R*)-MOP, (*R*)-2-(diphenylphosphino)-2'-methoxy-1,1'-binaphthyl. [b]Isolated yield of ketone **4**. [c]*c* 1.6 in $CHCl_3$. [d]The percent enantiomeric excess is based on maximum reported rotation: $[\alpha]_D^{21}$ = +106.2 (*c* 1.6, $CHCl_3$) [5e]



Scheme 2. *Reagents:* (a) i, NH_3/MeOH; ii, TrCl/Et_3N/DMAP/MeCN; (b) $(CF_3CO)_2O$/Py/THF; (c) i, $NaBH_3(OCOCF_3)$/THF; ii, Ac_2O/Et_3N/DMAP/THF; (d) i, BH_3·THF; ii, Ac_2O/Et_3N/DMAP/MeCN; (e) i, N_2O_4/ NaOAc/AcOH/CCl_4; ii, *aq.* KOH/Et_2O; iii, HC≡CCO_2Me; (f) NH_3/MeOH; (g) 60% AcOH

derivative which was treated with a mixture of *aq.* KOH/Et_2O to generate the diazo functionality. 1,3-Dipolar cycloaddition of the diazo dipole to methyl propiolate furnished the carbocyclic pyrazole nucleoside analogue **9**. The pyrazole **9** was the only detectable regioisomer. Its structure was confirmed by detailed ^1H- and ^{13}C-NMR analysis in comparison with **1b**.[2] Ammonolysis of **9** at 60°C in a sealed tube gave the amide **10** that was smoothly deprotected with 60% *aq.* AcOH to afford the target compound **1a**.[16]

To the best of our knowledge, this is the first synthesis of carbocyclic 4-deoxypyrazofurin. The methodology through asymmetric hydrosilylation described in this study is certainly very efficient for preparing both enantiomers of other carbocyclic nucleosides. Work towards extending the scope of this approach to carbocyclic *C*-nucleosides is currently underway in our laboratory.

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(10) Hydrosilylation of *meso*-olefin **2**. A mixture of olefin **2** (10.00 g, 60.2 mmol), trichlorosilane (7.3 mL, 72.3 mmol), [PdCl(π-C_3H_5)]$_2$ (22 mg, 0.1 mol%) and (*R*)-MOP[9d] (113 mg, 0.4 mol%) was stirred at 0°C for 2 d (Table 1, entry 11). The excess of trichlorosilane was removed under vacuum and the residue bulb-to-bulb distilled (100°C/0.1 Torr) to obtain 16.8 g of silylated material. This was slowely added to a suspension of $KHCO_3$ (50.18 g) and KF (19.41 g) in THF/MeOH (1:1, 160 mL) at 0°C and treated with 30% H_2O_2 (39 mL). The mixture was stirred at r.t. for 1d, concentrated, and partitioned between CH_2Cl_2 (300 mL) and water (300 mL). The extract was washed with brine (300 mL) and dried ($MgSO_4$). Concentration gave an oil **3** (8.75g, 79%) that was oxidised with PDC as described below to furnish ketone **4**. The ee value of **4** was enriched up to 98% by crystallization from pentane; $[\alpha]_D^{21}$ = +104.0 (*c* 11.6, $CHCl_3$).
Oxidation of alcohol **3** with PDC. To a slurry of pyridinium dichromate (PDC) (35.7 g, 2 eq.) and pyridinium trifluoroacetate (3.7 g, 0.4 eq.) in dry CH_2Cl_2 (10 mL/g PDC) was added a solution of alcohol **3** in the same solvent (2 mL/g of **3**). After stirring at. r.t. for 2 d, the mixture was diluted with Et_2O (40 ml/g of **3**) and filtered. The solid was washed with Et_2O and the combined filtrates concentrated. The residue was boiled with pentane for 20 min, filtered, and concentrated to give ketone **4** (7.34 g, 67%). An analytical sample was purified by flash chromatography using petrolether/EtOAc (5:1) as eluent.

(11) General procedure for hydroboration of *meso*-olefin **2** with (-)-Ipc_2BH. To a stirred suspension of (-)-Ipc_2BH[6b] (7.20 g, 25 mmol) in dry THF (10 mL) was added olefin **2** (4.15 g, 25 mmol) and stirred for the time and at temperature indicated in Table 1 (entries 1-4). The obtained solution was treated with MeOH (2.5 mL), followed by 3M NaOH (10 mL) and careful addition of 30% H_2O_2 (11 mL). The reaction mixture was stirred at 55°C for 2 h, cooled and extracted with Et_2O (4 x 30 mL) to obtain alcohol **3** and 3-pinanol that were oxidised with PDC as described in ref. 10. The resulted mixture was carefully fractionated to remove 3-pinanone (bp 55°C/0.2 Torr) from ketone **4**.

(12) Hydroboration of *meso*-olefin **2** with Lgf_2BH (Table 1, entry 5) was carried out as with Ipc_2BH. Ketone **4** was separated from by-product with column chromatography using petrolether/ EtOAc (8:1) as eluent.

(13) General procedure for rhodium(I)-catalysed hydroboration of *meso*-olefin **2**. Chlorobis(cyclooctene)rhodium(I) dimer (7 mg, 0.01 mmol), chiral ligand (0.02 mmol), and olefin **2** (0.17 g, 1.02 mmol) in dry THF (0.5 mL) were stirred at r.t. for 20 min. The solution was cooled on dry-ice/acetone bath, and a solution of catecholborane (1M in THF, 1.2 mL) was added. After stirring for time and at temperature indicated in Table 1 (entries 6-10), the mixture was warmed up to r.t., diluted with Et_2O (10 mL), and treated with 3M NaOH (0.6 mL) and 30% H_2O_2 (0.15 mL) for 2 h. The organic layer was separated, washed with 1M NaOH (2 x 10 mL), and dried ($MgSO_4$). Concentration gave crude **3** that was oxidised with PDC as described in ref. 10 to furnish ketone **4**.

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(16) Data for **1a** $[\alpha]_D^{21}$ = -63.6 (*c* 0.55, H_2O). IR (KBr) 1657 (CO) cm^{-1}. δ_H (300 MHz, D_2O) 1.40 (ddd, 1H, H-5a'; *J* 12.7. 11.1, 8.2 Hz), 2.21 (m, 1H, H-4'), 2.33 (dt, 1H, H-5b'; *J* 12.7, 8.2 Hz), 3.28 (dt, 1H, H-1'; *J* 11.0, 8.4 Hz), 3.61 (dd, 1H, CH_aH$_b$OH; *J* 11.2, 6.4 Hz), 3.66 (dd, 1H, CH$_a$H$_b$OH; *J* 11.2, 6.4 Hz), 3.86 (dd, 1H, H-3'; *J* 5.5, 3.3 Hz), 4.01 (dd, 1H, H-2'; *J* 8.8, 5.5 Hz), 6.71 (s, 1H, H-4). δ_C (300 MHz, D_2O) 30.13 (C-5'), 40.53 (C-1'), 46.47 (C-4'), 63.80 (CH_2OH), 73.96 (C-3'), 77.85 (C-2'), 103.66 (C-4), 145.06 (C-3), 148.61 (C-5), 166.84 (CO). HRMS: m/z M^+ calcd for $C_{10}H_{16}N_3O_4$ 242.115. Found 242.115.