An Alternative Synthesis of Both Enantiomers of *trans*-3,4-Bis(benzyloxy)cyclopentanone

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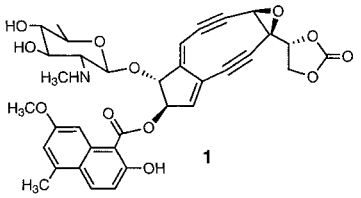
Abstract : An efficient synthesis of both enantiomers of *trans*-3,4-bis(benzyloxy)cyclopentanone **4**, potential precursors to the five-membered (A)-ring of the neocarzinostatin chromophore, was accomplished from diethyl tartrate in 7 steps.

Trans-(3*R*,4*R*)-bis(benzyloxy)cyclopentanone **4a** is an important intermediate in the synthesis of prostaglandin derivatives.[1] This optically active building block appears also in several natural products possessing biological activities. Neocarzinostatin[2] **1** and kedarcidin[3] **2** are representative compounds which are bearing this diol on the five-membered ring.



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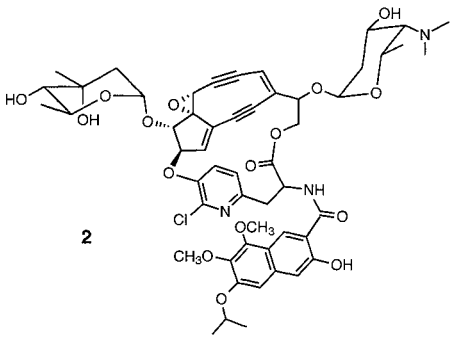

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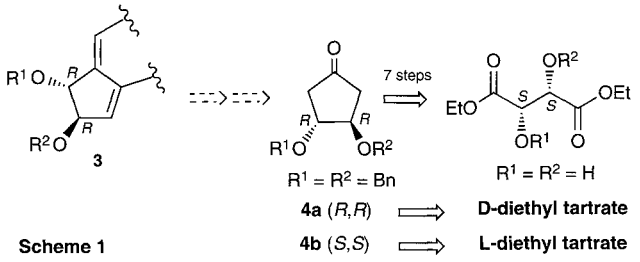
The neocarzinostatin and kedarcidin chromophores **1** and **2** are highly potent antitumor agents. Neocarzinostatin **1** carries an amino sugar[5] which is used as an activating group[6] and a naphthoate moiety[7] which plays an important intercalating role[8] between the DNA pairs bases. It will be interesting to functionalize the A-ring[9] of the already synthesized related analogues[4] of neocarzinostatin in order to introduce groups which can interact with DNA.



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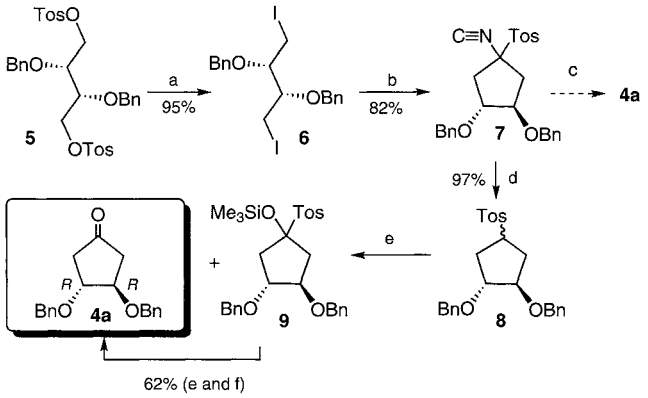
Scheme 1

The presence of these functionalities should increase the efficiency of recognition and intercalation of the analogues before cleavage of the DNA double strand.

In the course of the synthesis of neocarzinostatin analogues[4] we were interested in the search for a more efficient synthesis of *trans*-(3*R*,4*R*)-bis(benzyloxy)cyclopentanone **4a** which could be an interesting precursor to access highly functionalized derivatives of type **3** possessing the absolute 3*R*,4*R* stereochemistry of the natural product (Scheme 1). There is only one reported synthesis[10] of *trans* -(3*S*,4*S*)-bis(benzyloxy)cyclopentanone in the literature starting from tartaric acid. The authors proposed three different routes to this compound in 9 to 12 steps (no overall yield reported). Two other groups[11] have published other approaches to (3*R*,4*R*)-3-(benzyloxy)-4-hydroxy cyclopentanone (9 steps, no overall yield reported) and (3*S*,4*S*)-3,4-dihydroxycyclopentanone (7 steps, 32 % overall yield), respectively.

We present here the synthesis of key intermediates of type **4**. The ketones **4a** (*R*,*R*) and **4b** (*S*,*S*)[10] were synthesized in 7 steps from D and L-diethyl tartrate, respectively. The synthesis of **4a** is shown in Scheme 2. The ditosylate **5** was prepared in 3 steps from D-diethyl tartrate following a known procedure (protection[12], reduction and tosylation[13]) (Scheme 2). Its conversion into diiodo **6** was effected by NaI in acetone[14] under reflux in very high yield (95%).



Scheme 2 : **a)** NaI (5 equiv.), acetone, 60°C, 24 h, **b)** Tosyl methyl isocyanide (TosMIC) (1.0 equiv.), NaH (2.2 equiv.), DMSO/ether, RT, 4 h, **c)** HCl conc, Et_2O/CH_2Cl_2. **d)** *n*-Bu_3SnH (1.5 equiv.), AiBN (0.7 mol-%), PhH, 80°C, 30 min, **e)** *n*-BuLi (1.54 M in hexane, 1.2 equiv.), BTSP (1.4 equiv.), THF, –78°C, 1 h. **f)** **4a** + **9**, NH_4F (55 equiv.), *n*-Bu_4NHSO_4 (0.2 equiv.), CH_2Cl_2/H_2O, RT, 12 h.

Different synthetic equivalents of the formyl group[15] were tested to try to cyclize compound **6** in order to obtain the five-membered ring core. Most of these equivalents gave no or disappointing results. Successfully, the TosMIC[16] dianion reacted well (82%) with compound **6** to give the cyclopentane **7**. Unfortunately, hydrolysis[16] of **7** under strong acidic conditions, simply led to a mixture of decomposed products. To circumvent this foreseeable outcome, an approach to the cyclopentanone **4a** was realized in only 3 steps. At first the sulphone **8** was prepared by radical way[17] (*n*-Bu_3SnH, AiBN, Δ) in excellent yield (97%). The oxidative desulfonylation of **8** was carried out by modifying the Hwu procedure.[18]

Indeed by following this latter procedure, the starting product was decomposed to a complex mixture of side products. Consequently, the anion of sulfone **8** was treated with bis(trimethylsilyl)peroxide (BTSP)[19] at – 78°C to furnish compound **9**[20] and a small amount of **4a** (displayed on TLC). In order to avoid decomposition, the reaction mixture had to be neutralized at the same temperature. A mixture composed of silylated ether **9** and ketone **4a** was isolated from the starting material (30% recovered) and was treated finally with

ammonium fluoride[21]. This last step furnished ketone **4a**[22] in 62% yield for the two steps. The synthesis of ketone **4b** was conducted in the same manner with comparable yields.

In summary, the cyclopentanones **4a** (*R,R*) and **4b** (*S,S*) which possess a C_2 axis have been prepared enantioselectively from D and L diethyl tartrate, a chiral template, in 7 steps. Studies towards the synthesis of functionalized structure of type **3** are in progress in our laboratory and will be reported in due course.

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(20) No separation by flash chromatography on silica gel because **9** partially changes into **4a**.

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(22) All new compounds described in this work have been fully characterized by means of IR-spectra, ^1H and ^{13}C NMR, mass spectra and microanalysis :
4a : **IR** ($CHCl_3$): ν_{max} = 3067 cm^{-1}, 3002, 2920, 2867, 1747, 1601, 1455, 1150, 1089. – **^1H NMR** (200 MHz-$CDCl_3$) : δ = ABX signal (AB part, δ_B = 2.36, δ_A = 2.64, J_{AB} = 17.6 Hz, J_{AX} = 6.4 Hz, J_{BX} = 1.8 Hz, 4H, C$\underline{H}_2$), 4.23-4.28 (X part, m, 2H, C$\underline{H}$, 3-H and 4-H), AB signal (4H, δ = 4.55, δ = 4.61, J = 12.4 Hz, Ph$C\underline{H}_2$), 7.29-7.41 (m, 10H, H aromatic). – **^{13}C NMR** (50 MHz-$CDCl_3$) : δ = 42.48 (C-2, C-5), 71.22 (Ph$\underline{C}H_2$), 79.02 (C-3, C-4), 127.53, 127.81, 128.44, 137.60 (aromatic), 214.56 (C-1). – **MS**, m/z (%) = 296 (0.2) M^+, 219 (0.4), 205 (18.7), 188 (0.7), 108 (16.1), 91 (100.0), 77 (27.3). – **Microanalysis** : $C_{19}H_{20}O_3$ (296.35 g/mol), % C (calcd. = 77.00 - exp. = 76.88), % H (calcd. = 6.80 - exp. = 6.79). – $[\alpha]_D^{23}$ = + 18 (c = 1.50, $CHCl_3$). **4b** : – $[\mathbf{a}]_D^{23}$ = – 19 (c = 1.50, $CHCl_3$).