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Synthesis of a Head to Head Cholaphane

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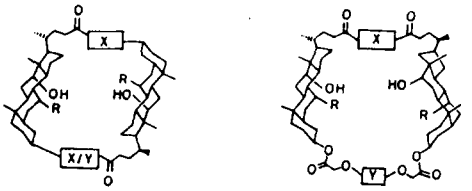
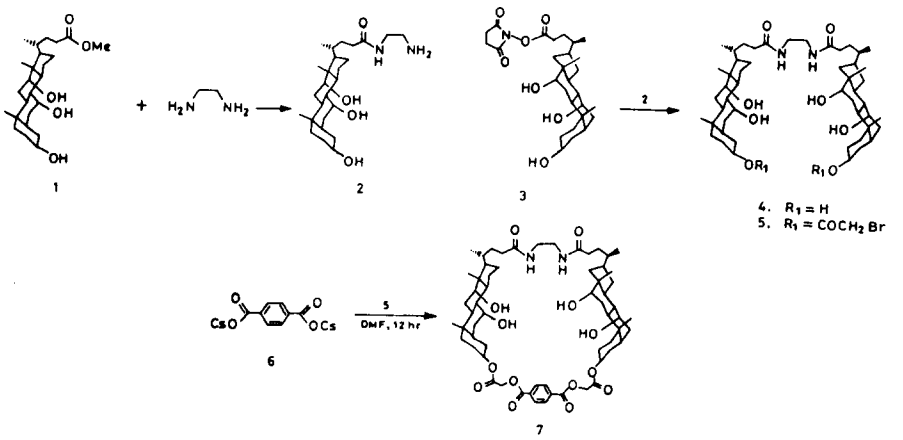
***Abstract*: A general synthetic route for the construction of head to head cholaphanes, a new type of steroidal macrocycles, has been described.** © 1997 Published by Elsevier Science Ltd.

The unique features of the bile acids in terms of their chiral, rigid framework and chemically different hydroxyl groups have made them attractive building blocks for the design of synthetic receptors[1]. As a result, considerable efforts have been made in recent years towards the synthesis of cyclic systems consisting of two,three and four steroidal units[2]. Most of these efforts, however, involve head to tail combination of cholic acids (Type I). As the highly asymmetric and polar nature of the interior of these receptors has been found to be well-suited for diastereo- and enantio-selective binding of polar molecules like carbohydrates[3], the head to head combination of cholic acids (Type II) would be of particular significance for creating a different asymmetric environment in the cavity. Recently, a bicyclic and trimeric head to head system has been reported[4]. However, to our knowledge, such monocyclic and dimeric system has not yet been synthesized. We report here a novel synthesis of a cholaphane involving head to head combination of cholic acids.



The treatment of methyl cholate **1** with a large excess of ethylenediamine in methanol (48h) resulted in the complete conversion of methyl cholate into steroidal amine **2**. The amine **2** on condensation with the activated ester of cholic acid **3** [5] (1:1 eqiv.) in DMF (12 h) gave bis-cholamide **4** in almost quantitative yield. The selective bromoacetylation of both the equitorial 3-OH groups was achieved in 40 % yield by stirring a mixture of bis-cholamide **4** (1 eqiv.), bromo-acetic acid (2.25 eqiv.), DCC (2.25 eqiv.) and a few drops of pyridine in anhydrous CH_2Cl_2 for 48 h. The CH_2Cl_2- insoluble starting material could be easily separated from the product **5** and recycled to improve the yield. The crucial cyclisation step was accomplished remarkably well by using the cesium salt method developed by Kellogg et al[6]. Thus, the treatment of the steroidal bis-bromoacetate **5** (0.1 mM) with bis-cesium terephthalate **6** (0.1 mM) in DMF (5 mL) led to the formation of the cholaphane **7** in 95% yield. The highly non-polar cyclic product was easily purified by column chromatography. All the reactions were performed at room temperature and



the products were characterized by IR and ^{1}H-NMR spectroscopy[7]. No higher oligomer was detected in HPLC.

Our approach has been to develop a general strategy for the synthesis of cholaphanes of type II with a provision of having two different steroidal units. By variation on either side one may control the flexibility and size of the cavity or incorporate catalytic groups to expand their applications to biomimetic chemistry.

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7. Characteristic ^{1}H-NMR (300 MHz, $CDCl_3$-CD_3OD): **2**, δ 3.30 (t, 2H, -CONHC**H**$_2$-), 2.75 (t,2H, -C**H**$_2$-NH$_2$); **4**, 3.40(m, 4H, -CO-NH-C**H**$_2$-); **5**, 4.70(b,2H, 3C**H**-), 3.80(s,4H, -CO-C**H**$_2$-Br), **7**, 8.20 (bs, C_6H_4), 4.80 (bs, 4H, -CO-C**H**$_2$-O-), 4.80 (b, 2H, 3C**H**-).

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