Butorphanol metabolites: Synthesis of cis- and trans-3,14-dihydroxy-N-(3'-hydroxycyclobutylmethyl) morphinan.

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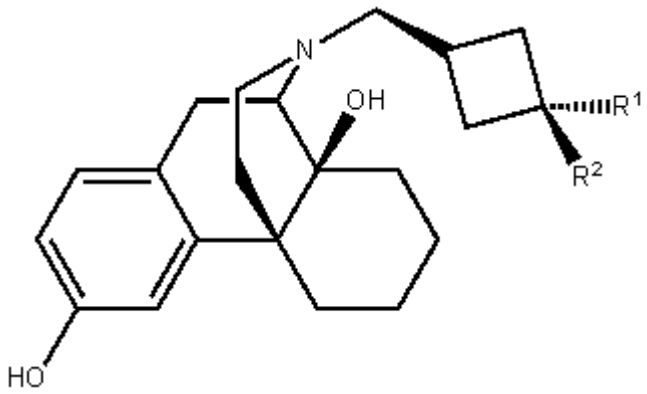
Abstract

The synthesis of hydroxylated butorphanol metabolytes is described.

Keywords

protected hydroxycyclobutane carboxylic acid, morphine derivatives,



butorphanol	R1, R2 = H	1
trans-hydroxybutorphanol (click for 3D structure)	R1 = OH, R2 = H	2

cis-hydroxybutorphanol (click for 3D structure)	R1 = H, R2 = OH	**3**

Introduction:

Butorphanol (**1**), a synthetic opioid analgesic with affinity for μ and κ-opioid receptor sites[1,2] , is used, among others, in treatment of post-surgical and dental pain as well as migraine but also for veterinary applications, e.g. sedation and anaesthesia in captive rhinoceros species[3a,b]. Known metabolites include trans-hydroxybutorphanol 2, norbutorphanol, and its glucuronide conjugates [4].

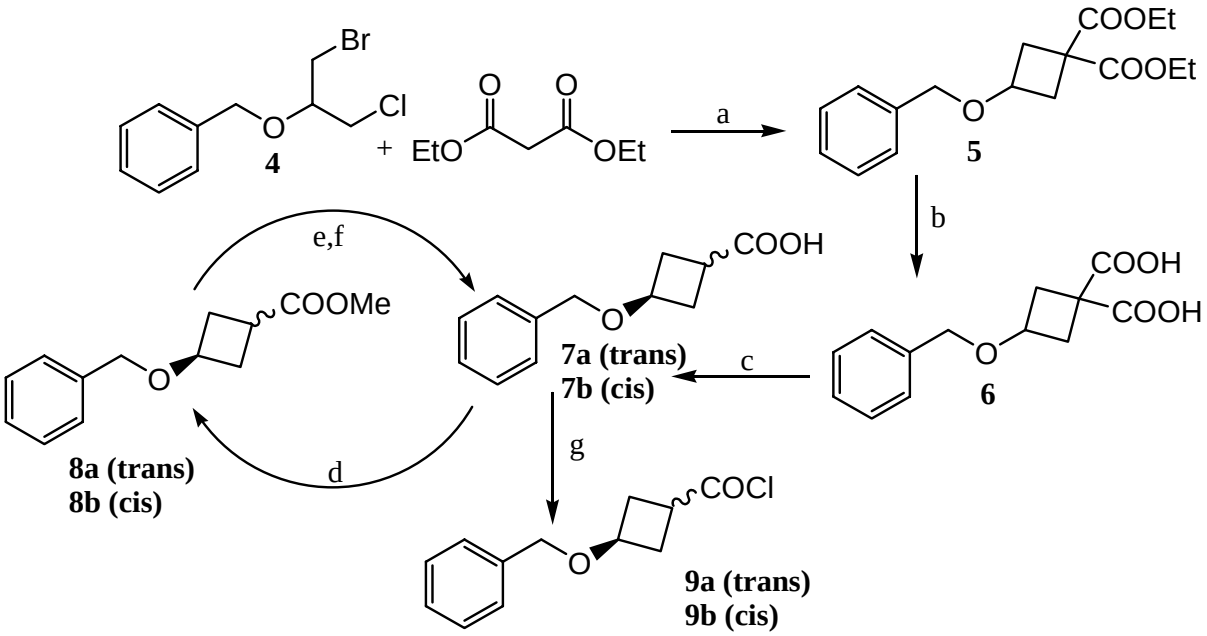
Although several analytical and pharmacological studies are known and trans-hydroxybutorphanol (2) was isolated as the major urinary metabolite of 1, the chemical synthesis has not been described [5] except a short note without any experimental details in a paper describing the metabolism of tritiated 1 [6].

Here we report the synthesis of 3,14-dihydroxy-N-(trans-3'-hydroxycyclobutylmethyl) morphinan (**2**) and the cis-isomer **3**.

Results:

The synthesis starts from the reaction of **4** with diethyl malonate to give **5** which is hydrolyzed to **6** and decarboxylated to a mixture of cis and trans carboxylic acids **7**. Attempts to separate this mixture failed in our hands, however, separation of the methyl esters (**8a** and **8b**) by column chromatography was successful. The pure isomers **7a** and **7b** were than converted to the corresponding acid chlorides (**9a** and **9b**) (Scheme 1).

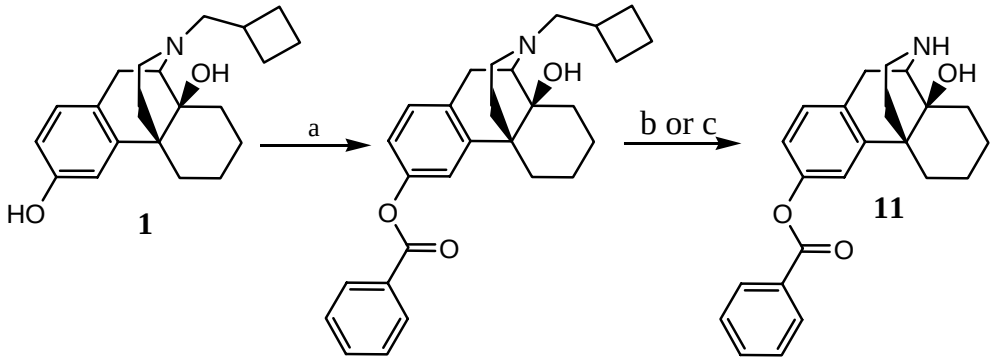
Scheme 1: trans (cis)-3-benzyloxy-cyclobutanecarbonyl chloride



a)NaH, dioxan b) KOH, ethanol/water c) 175°C, 11 mbar, 1 h and 150-165 °C, 0.5 mbar d) MeOH, $SOCl_2$ e) Chromatography (pentan/EtOAc 99:1) f) NaOH, ethanol/water g) $SOCl_2$, $DMF_{kat.}$

Next we tried to prepare **2** from norbutorphanol (**10**) by reaction with **7a**. This synthesis afforded the desired product, but the yield in the last step of the reaction was not satisfactory. Improved yields were obtained by protecting of the aromatic hydroxyl group with a benzoyl group. Dealkylation of the cyclobutylmethyl-residue was accomplished first according Ref.[2] but the yield was not satisfactory (9-30 %). Using methanol as a solvent we were able to improve the yield substantially for the intermediate **11** to 60 % yield (Scheme 2).

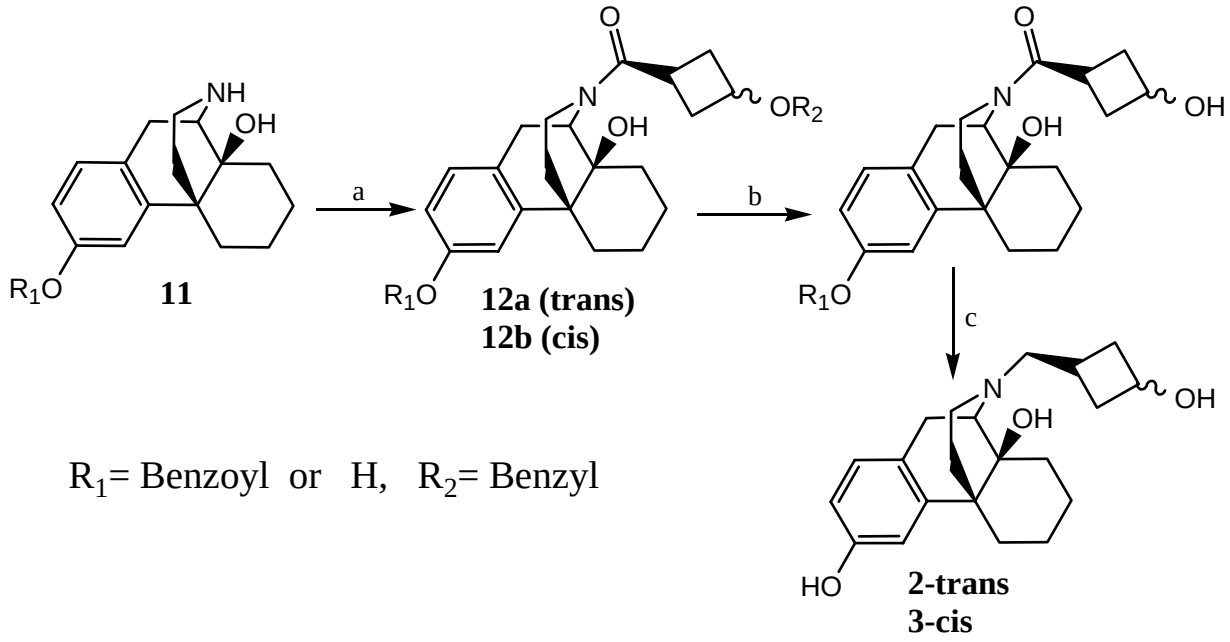
Scheme 2: Dealkylation



a) Benzoyl chloride, triethylamine, dichloromethane; b) 1, MCPBA, Dichlormethane, 2, $FeCl_2.4H_2O$, water, yield 34 % c) 1, MCPBA, methanol, 2, $FeCl_2.4H_2O$, water, yield 60 %

Next **11** was reacted with **9a** or **9b** to afford **12a** or **12b** followed by removal of the benzyl protecting group by catalytic hydrogenation. Diborane reduction afforded both the removal of the benzoyl protecting group and reduction of the amide (Scheme 3).

Scheme 3: 3,14-dihydroxy-N-(trans and cis-3'-hydroxycyclobutylmethyl) morphinan (2, 3)



R_1= Benzoyl or H, R_2= Benzyl

a) trans or (cis)-3-benzyloxy-cyclobutanecarbonyl chloride, Diisoproppylamine, dichlormethane b) Pd/C 10 %, methanol, H_2 40-50 p.s.i. c) B_2H_6.THF, THF

The final products **2** and **3** were purified by chromatography using dichloromethane/methanol/ammonia and the overall yield of the synthesis of **2** and **3** was 48-50% The identity of all products was fully characterized by ^1H and ^{13}C NMR, the purity by HPLC.

Conclusion:

We have successfully prepared 3,14-dihydroxy-N-(trans-3'-hydroxycyclobutylmethyl) morphinan (2) in 48 % yield and the cis-isomer 3 in 50 % yield. Full experimental details will be published in the proceedings of this conference.

References:

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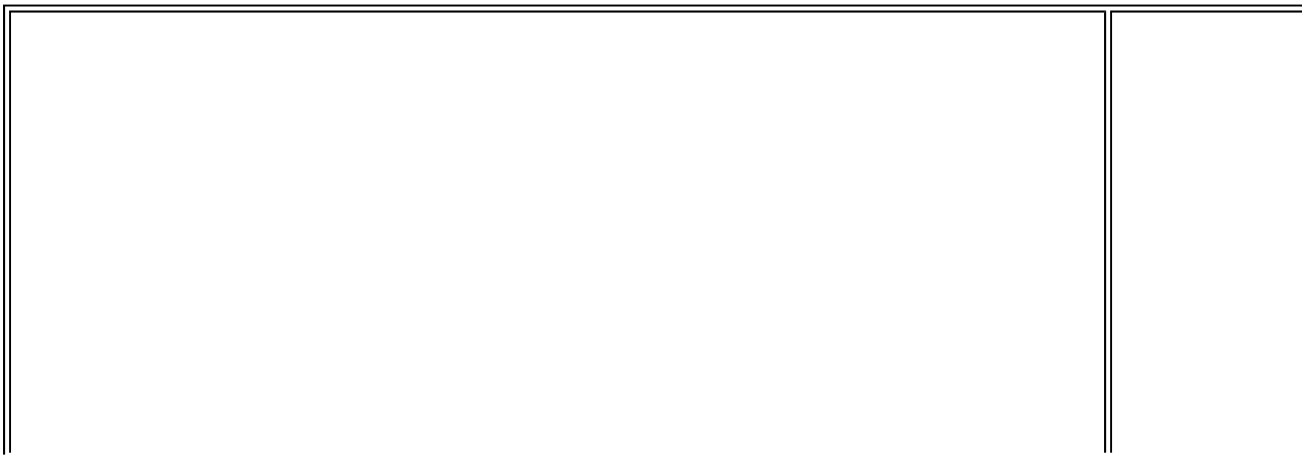
Appendix:

Here are some photographs of our Institute situated in the heart of the City of Vienna



Karlskirche, the main building of our University and the Sezession with the golden roof

The view from the top of the chemistry build