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Tricyclic Benzomorphan Analogues by Intramolecular Oxa-Pictet-Spengler Reaction

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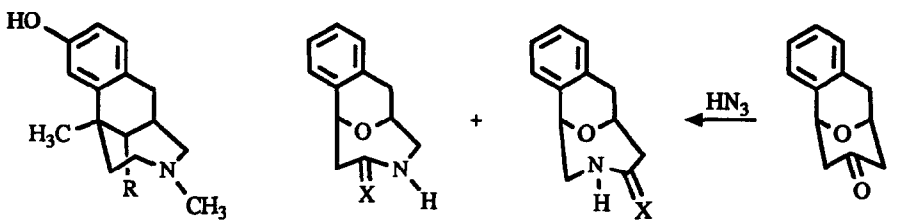
Abstract: The key step in the regio- and stereoselective preparation of the benzomorphan analogues **9**, **10a**, **10b**, **14** and **15** is an intramolecular Oxa-Pictet-Spengler reaction. Masked as an acetal the carbonyl component is connected via an amide to the 2-phenylethanol component (**7**, **12**).

Tricycles with the 1,2,3,4,5,6-hexahydro-2,6-methano-3-benzazocine structure (benzomorphans) are well known as strong analgesics[1]. Ring C homologisation of the benzomorphan ring system leads to the 1,6-methano-4-benzazonines **1** which exhibit strong analgesic activity as well. Thus, in the Haffner test (mouse) and in the hot plate test (mouse) eptazocine (**1a**, racemate) shows half the analgesic potency of morphine and the methanobenzazonine **1b** (racemate) bearing an additional methyl group in β-position is equipotent to morphine[2].

Scheme 1



1a,b **2a,b** **3a,b** **4**

1	R
a	H
b	CH_3

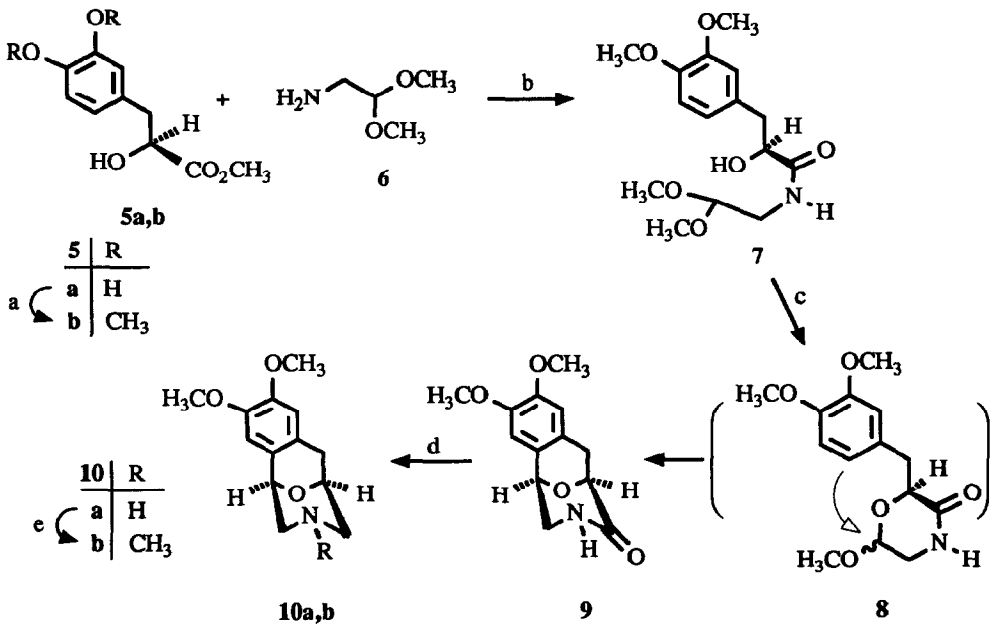
2,3	X
a	O
b	H_2

Recently, we described the preparation and psychopharmacological profile of the regioisomeric *epoxy*benzazonines **2b** and **3b**. In addition to the strong sedative effects caused by both regioisomers in mice (Irwin screen[3]) we found that the regioisomer **2b** has an analgesic activity which is

comparable with the analgesic activity of pethidine and tramadol[4]. However, the introduced synthesis is not very efficient for the preparation of the regioisomer **2b** in a large scale because of the bad regioselectivity in the Schmidt rearrangement of the ketone **4** (**2a** : **3a** = 35 : 65). Additionally, the synthesis of **2b** and **3b** via Schmidt rearrangement of **4** allows only the preparation of racemic test compounds[4].

In this communication we report on the *regioselective* preparation of *homochiral* 1,5-epoxy-3-benzazocines (**9**, **10**) and 1,6-epoxy-4-benzazonines (**14**, **15**) which are related to the analgesic active benzomorphans, methanobenzazonines **1** and the epoxybenzazonine **2b**. An intramolecular Oxa-Pictet-Spengler reaction in the course of which the intramolecularly fixed carbonyl component is masked as an acetal was the key step in the synthesis of **9** and **14**.

Scheme 2



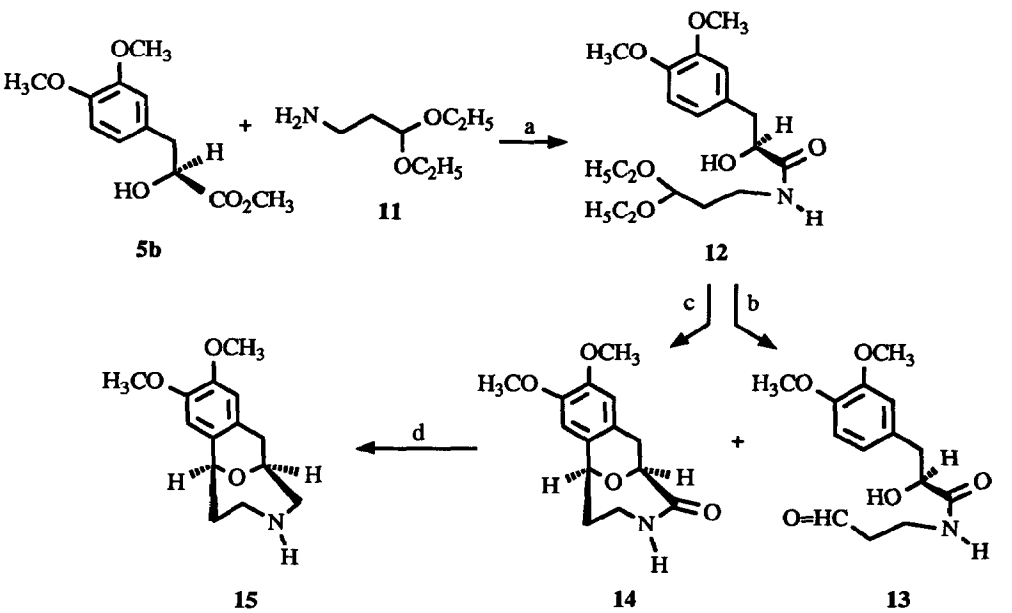
(a) CH_3I, DMF, K_2CO_3, 12 h, 40°C, 67 %.- (b) Neat, p-toluenesulfonic acid, 1.5 h, 140°C, 99 %.- (c) Dioxane saturated with gaseous HCl, 48 h, rt, 60%.- (d) $LiAlH_4$, THF, 19 h, rt, 83 %.- (e) CH_2=O, $NaBH_3CN$, CH_3OH, 4 h, rt, 98 %.

We started the synthesis with the homochiral methyl (S)-3-(3,4-dihydroxyphenyl)lactate **5a** which was derived from the amino acid (S)-tyrosine[5]. In the first step **5a** was methylated with methyl iodide in the presence of potassium carbonate to yield the dimethoxy derivative **5b**[6][7]. A prolonged reaction time (72 h) resulted in an additional methylation of the aliphatic hydroxy group giving a α-methoxy ester derivative (5 % yield). The aminolysis of the ester **5b** with the aminoacetaldehyde dimethyl acetal (**6**)[8] was catalyzed with p-toluenesulfonic acid. Treatment of the "amide-acetal" **7**[9] thus obtained ("amide-acetal" means, that an amide and an acetal functionality are

in the same molecule) with HCl in dioxane led to the tricyclic amide **9**. This double cyclisation of **7** (intramolecular Oxa-Pictet-Spengler reaction) may be started with an intramolecular transacetalisation of the hydroxy group with the acetal function to give the 6-methoxy-1,4-oxazinan-3-one **8** as intermediate. After protonation and methanol elimination a second ring closure finishs the transformation. Reduction of the amide **9** with $LiAlH_4$ was affected in 19 hours at ambient temperature. The secondary amine **10a** was isolated in a 83 % yield and subsequently methylated with formaldehyde and $NaBH_3CN$[10] to yield the tertiary amine **10b**.

With the experience we had gained with the synthesis of the epoxybenza*zocines* **9** and **10** we projected the preparation of the homologous epoxybenza*zonines* **14** and **15** by a similar pathway. The ester **5b** was converted nearly quantitative into the "amide-acetal" **12** by aminolysis with the 3-aminopropionaldehyde acetal **11**[11]. The reaction conditions we used for the transformation of **7** to **9** only led to the cleavage of the acetal of **12**. Thus, we only isolated the hydroxyaldehyde **13** after work-up. We suppose, that **13** is the reaction product from an intermediate analogous to **8** or the corresponding α-chloro ether with water. But, heating the "amide-acetal" **12** in dioxane saturated with gaseous HCl resulted in the intramolecular Oxa-Pictet-Spengler reaction to afford the tricyclic amide **14**. The reduction of the amide **14** with $LiAlH_4$ in analogy to the reduction of the amide **9** did not proceed to give the secondary amine **15**. Only in the presence of a stoichiometric amount of $AlCl_3$ a clean reduction of the amide **14** was observed.

Scheme 3



(a) Neat, p-toluenesulfonic acid, 2 h, 140°C, 97%.- (b) Dioxane saturated with gaseous HCl, 48 h, rt, 60 % **13**.- (c) Dioxane saturated with gaseous HCl, 12 h, 50°C, then 4 h, 100°C, 20 % **14**.- (d) $LiAlH_4$, THF, Et_2O, $AlCl_3$, 45 min, rt, 74 %.

In contrast to the *inter*molecular Oxa-Pictet-Spengler reaction of chiral 2-phenylethanol derivatives with unsymmetrical carbonyl compounds which in most cases lead to a mixture of diastereomers the formation of only one diastereomer is possible with the presented *intra*molecular version of the Oxa-Pictet-Spengler reaction. Starting with enantiomerically pure educts (**5a**, **5b**) the homochiral tricycles **9** and **14** are obtained in only two steps. Additionally, problems concerning the regioselectivity in the Schmidt rearrangement of the ketone **4** are avoided.

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6) The (R)-configurated enantiomer of **5b** has been isolated after diazomethane methylation of the hydrolysis product of lithospermic acid from the roots of the plant lithospermum ruderale (Lit.[6a]) and after diazomethane methylation of the aqueous extract of Coptidis rhizoma (Lit.[6b]).

6a) C. J. Kelley, J. R. Mahajan, L. C. Brooks, L. A. Neubert, W. R. Breneman and M. Carmack, J. Org. Chem. **1975**, *40*, 1804 - 1815.- 6b) S. Yahara, M. Satoshiro, I. Nishioka, T. Nagasawa and H. Oura, Chem. Pharm. Bull. **1985**, *33*, 527 - 531.

7) **5b**: $[\alpha]_D^{21}$ = +5.7 (c = 0.99, CH_3OH); enantiomer of **5b** (Lit.[6b]): $[\alpha]_D^{32}$ = -4.5 (c = 1.00, CH_3OH).

8) The aminoacetaldehyde dimethyl acetal **6** was purchased from the Fa. Merck.

9) All new compounds gave satisfactory physical and analytical data.

10) R. F. Borch, M. D. Bernstein and H. D. Durst, J. Am. Chem. Soc. **1971**, *93*, 2897 - 2904.

11) The 3-aminopropionaldehyde diethyl acetal **11** was obtained by $LiAlH_4$ reduction of 3,3-diethoxypropionitrile.