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Asymmetric Synthesis of 1-Aryl-1,2,3,4-tetrahydroisoquinolines Part 1: Addition of Chiral Phenylacetaldehyde Acetals to Acylimines

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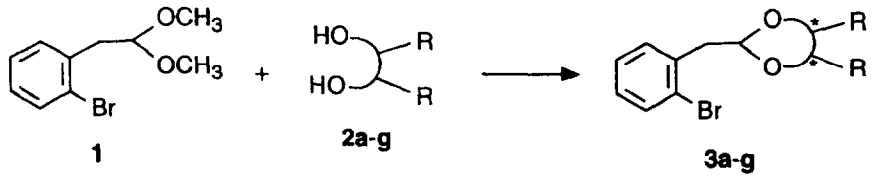
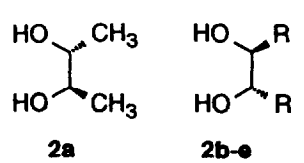
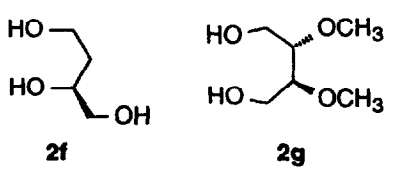
Abstract: The stereoselectivity in the addition of the enantiomerically pure (2-bromophenyl)acetaldehyde acetals **3a-g** to the acylimines **4a,b** is investigated. Based on this reaction a novel asymmetric synthesis for the 1-phenyl-tetrahydroisoquinoline **8** is elaborated.

The great number of alkaloids based on the 1-substituted tetrahydroisoquinoline skeleton has stimulated the development of asymmetric syntheses to obtain enantiomerically pure tetrahydroisoquinolines.[1] Among these syntheses only few methods are suitable for the preparation of homochiral *1-aryl*-tetrahydroisoquinolines.[2-5] The considerable pharmacological properties of 1-aryltetrahydroisoquinolines, which can display antagonistic activity at D_1 receptors[6] and NMDA receptors,[7] prompted us to develop a novel asymmetric synthesis for this heterocyclic ring system. In contrast to the reported procedures, in which the stereogenic centre in position 1 is established after the isoquinoline ring system has been built up,[2-5] we planned to create the stereogenic centre first and then cyclize the chiral intermediate to obtain the isoquinoline ring system. In our strategy the chiral acetal moiety[8] of **3** should control the stereoselectivity during the addition of the aryllithium intermediates generated by halogen-metal exchange at the aryl bromides **3** to the acylimines **4**.





2	R
b	CH_2OCH_3
c	$C(CH_3)_2OCH_3$
d	CO_2CH_3
e	$CON(CH_3)_2$



With exception of the acetal **3e** the acetals **3a-g** were prepared by transacetalization of the dimethyl acetal **1**[9] with the homochiral diols **2a-g**, which are commercially available (**2a**, **2d**, **2f**) or accessible by known procedures (**2b**[10], **2c**[11], **2g**[12]). Aminolysis of the diester **3d** with an excess of dimethylamine furnished the tartaramide derived acetal **3e**. In analogy to the acetal formation of

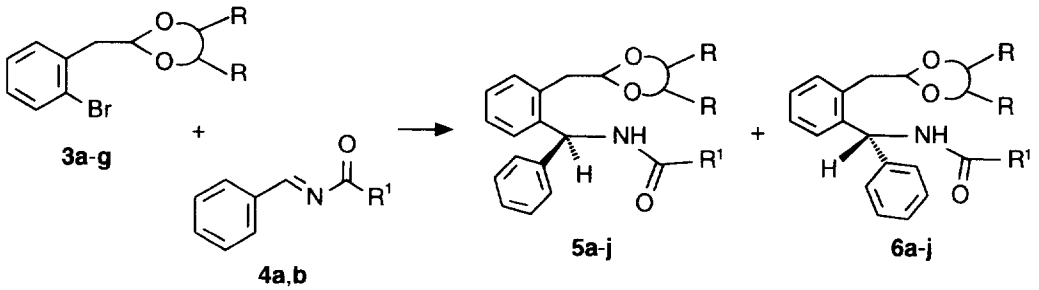
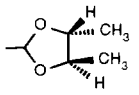
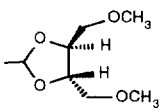
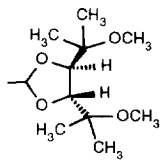
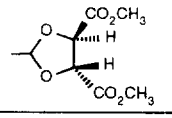
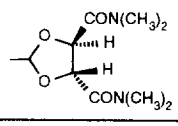
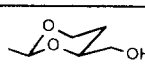
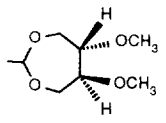


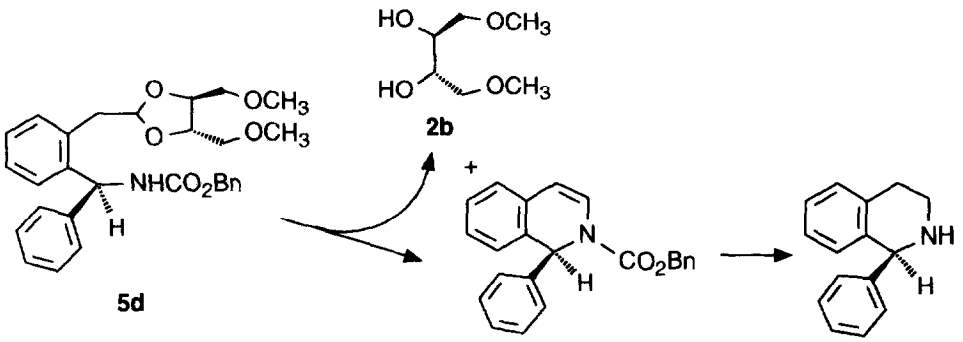
Table 1

Entry	Acetal **3**		Acylimine **4**	R^1	Products	Ratio **5** : **6**	Yield
1	**3a**		**4a**	$C(CH_3)_3$	**5a** : **6a**	36 : 64	76 %
2	**3a**		**4b**	$OCH_2C_6H_5$	**5b** : **6b**	38 : 62	71 %
3	**3b**		**4a**	$C(CH_3)_3$	**5c** : **6c**	68 : 32	78 %
4	**3b**		**4b**	$OCH_2C_6H_5$	**5d** : **6d**	72 : 28	72 %
5	**3c**		**4a**	$C(CH_3)_3$	**5e** : **6e**	55 : 45	66 %
6	**3c**		**4b**	$OCH_2C_6H_5$	**5f** : **6f**	51 : 49	63 %
7	**3d**		**4b**	$OCH_2C_6H_5$	no transformation		0 %
8	**3e**		**4b**	$OCH_2C_6H_5$	no transformation		0 %
9	**3f**		**4b**	$OCH_2C_6H_5$	no transformation		0 %
10	**3g**		**4b**	$OCH_2C_6H_5$	no transformation		0 %

benzaldehyde, benzaldehyde dimethyl acetal, or 2-bromobenzaldehyde dimethyl acetal with the butanetriol **2f**[13] the transacetalization of **1** with **2f** occurred with high regio- and diastereoselectivity affording the (S,S)-configurated 1,3-dioxane **3f** in 79 % yield.[14]

The bromine-lithium exchange at the bromo acetals **3a-g** was performed with n-butyllithium at -105 °C. For trapping of the thus generated aryllithium intermediates the acylimines **4a** with the large pivaloyl group and **4b** with the facile cleavable benzyloxycarbonyl group were selected.[15] Table 1 reveals, that the addition of the dioxolane derivatives **3a-c** to the acylimines **4a,b** resulted in good chemical yields of the amides **5/6** (entries 1 - 6). Introduction of ester (**3d**) or amide groups (**3e**) into the dioxolane moiety or enlargement of the 1,3-dioxolane ring to a 1,3-dioxane ring (**3f**, 2.1 equivalents of n-butyllithium) or a 1,3-dioxepane ring (**3g**) reduced the reactivity of the corresponding aryllithium intermediates so much that addition to the acylimine **4b** could not be observed (entries 7 - 10). Even warming up the reaction mixture to -20 °C or +25 °C did not lead to the addition products **5g-j/6g-j**. The only isolated or detected products were the debrominated phenylacetaldehyde acetals.

The diastereomeric ratios **5** : **6** were determined by integration of separated signals in the 400 MHz ^{1}H-NMR spectra. The best ratio, **5d** : **6d** = 72 : 28 (entry 4), which was confirmed by HPLC analysis, was observed for the addition of the bis(methoxymethyl) substituted acetal **3b** to the benzyloxycarbonyl imine **4b**.



After chromatographic separation of the diastereomers **5d** and **6d** the configuration of the new stereogenic centre of the main diastereomer **5d** was deduced by transformation of **5d** into the known 1-phenyltetrahydroisoquinoline **8**. Thus, heating of a methanolic solution of **5d** with an excess of *p*-toluenesulfonic acid led to acetal cleavage and cyclization affording the dihydroisoquinoline **7** and liberating the chiral auxiliary, the diol **2b**, which could be regained in 89 % yield. Catalytic hydrogenation of **7** (H_2, Pd/C) provided the laevorotatory isoquinoline **8** ($[\alpha]_D^{20}$ = -10.1, c = 0.60 in $CHCl_3$). The laevorotatory 1-phenyl-1,2,3,4-tetrahydroisoquinoine **8** is reported to be (S)-configurated.[16] Therefore, (S)-configuration has to be assigned to the new stereogenic centre of **5d** as well as to the asymmetric centres of **7** and **8**. Since in all addition products **5/6** the ^{1}H-NMR signal of the methin proton between the two aryl substituents of the main diastereomer is downfield shifted in relation to the corresponding signal of the minor diastereomer, we assign the (S)-configuration to the

main diastereomer in the reactions of **3b** and **3c** (entries 3 - 6) and the (R)-configuration to the main diastereomer in the reactions of **3a** (entries 1 and 2).

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16) (S)-**8** is reported to have a specific optical rotation of $[\alpha]_D^{24}$ = -10.2 (c = 0.17 in $CHCl_3$)[4a].

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