First Examples of a Highly Stereoselective Passerini Reaction: A New Access to Enantiopure Mandelamides

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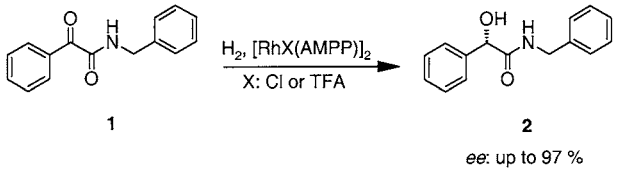
Abstract: Achiral benzaldehydes and isocyanides could be transformed enantioselectively in a Passerini three-component reaction to chiral mandelamides by using a galacturonic acid derivative as chiral inducer.

Key words: α-hydroxy acid derivative, mandelamide, Passerini reaction, multi-component reaction

α-Hydroxy acids and their derivatives play an indisputably important role in chemistry and biology.[2] Among this class of chemical compounds, particularly amides of mandelic acid are gaining in interest because of new opportunities in medicine[3] and agriculture.[4] The fact that such molecules contain a chiral centre clearly underlines the need for an efficient enantioselective synthesis. So far, the preparation of enantiopure mandelamides from achiral precursors has been mainly achieved by catalytic asymmetric hydrogenation of phenylglyoxylamides (Scheme 1). Hereby, the stereoselective reduction of the keto function is accomplished using rhodium(I) complexes with chiral diphosphine ligands, especially of the AMPP-[5] or BICHEP-type.[6]



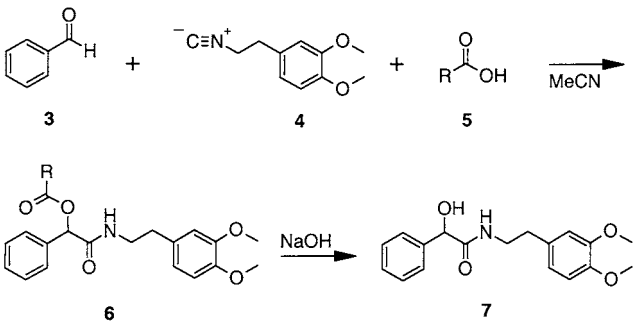
Scheme 1

In this paper we present a new two-step approach to enantiopure mandelamides from achiral building blocks by application of a highly stereoselective multi-component reaction.

Recently, multi-component reactions received much attention as powerful tool for the generation of molecular diversity in combinatorial libraries and for the easy assembly of complex chemical structures.[7] In both classical multi-component reactions operating with isocyanides, the Passerini reaction of a carbonyl compound, an isocyanide and a carboxylic acid to give an α-acyloxycarboxamide, and the Ugi reaction of a carbonyl compound, an isocyanide, an amine and a carboxylic acid to obtain an α-acylaminocarboxamide, the prochiral aldehyde produces the new chiral centre. There are several examples in the literature for stereoselective multi-component reactions. Using glycosylamines[8] or α-ferrocenylalkylamines,[9] high degrees of diastereoselectivity could be achieved in Ugi reactions. Also cases have been described, in which the Passerini reaction was carried out with a chiral aldehyde[10] or isocyanide.[11] Unfortunately, the stereoselectivity here is in most of the cases relatively low. During a research program we required a reliable approach to enantiopure mandelamides. We decided to perform a Passerini reaction with a chiral acid, which would hopefully transfer chiral information during the multi-component condensation, and would be cleaved off afterwards to yield the desired α-hydroxyphenylacetamide. For this purpose, we investigated several different phenylalanine, proline and galacturonic acid derivatives as asymmetric inducing agents from the chiral pool.

It turned out, that 1,2,3,4-tetra-*O*-acetyl-α-D-galacturonic acid[13] (**5d**) gave a Passerini product **6d** with high diastereoselectivity, which after cleavage of the ester linkage led to the mandelamide **7** with impressive enantiomeric excess (Scheme 2, Table 1).[14,15] The analysis of the stereochemical outcome of the reaction was performed by HPLC on a chiralpak AD column (20% isopropanol in hexane as solvent). The correct assignment of the enantiomers was obtained by comparison with the coupling products of commercially available D-(–) and L-(+) mandelic acids with homoveratrylamine.

This stereoselectivity is not surprising, because the initial step of the postulated mechanism of the Passerini reaction



Scheme 2

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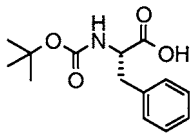
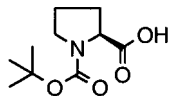
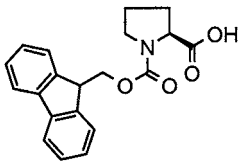
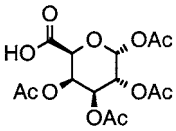
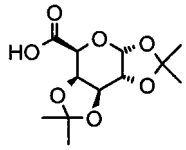
Table 1 Passerini Reactions of Benzaldehyde (**3**) and 2-(3,4-Dimethoxyphenyl)ethyl Isocyanide[12] (**4**) with Different Chiral Acids

Entry	**5**	Yield of **7** (%)	er of **7** (%) (conf.)
a		76	51:49 (*S*:*R*)
b		69	47:53 (*S*:*R*)
c		72	52:48 (*S*:*R*)
d		63	93:7 (*S*:*R*)
e		75	53:47 (*S*:*R*)

is the formation of a hydrogen-bonded adduct from the carbonyl and carboxylic acid components.[7c,17] A non-isolable cyclic intermediate of all three components is then built by α-addition of the electrophilic carbonyl carbon atom and the nucleophilic oxygen atom of the carboxylic acid to the isocyanide carbon atom. This α-adduct rearranges in an intramolecular transacylation to the stable α-acyloxycarboxamide.[7c,17] That means, that the carboxylic acid takes part in the reaction from the beginning on and can therefore influence its stereochemical outcome.

Also, other benzaldehydes and isocyanides[18] could be transformed stereoselectively into the corresponding mandelamides by Passerini reaction with 1,2,3,4-tetra-*O*-acetyl-α-D-galacturonic acid (**5d**) and subsequent ester hydrolysis. Looking at the results in Table 2, it seems that the chiral induction does not work in every case, and that phenethyl isocyanides are preferred as substrates.

In summary, we have developed a new method for the asymmetric synthesis of mandelamides. The enantioselective preparation of other α-hydroxycarboxamides should also be possible using this approach. Maybe the application of other acylated glycuronic acids will result in even higher enantiomeric excesses.

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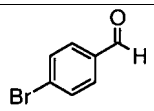
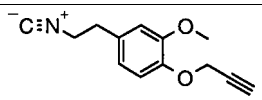
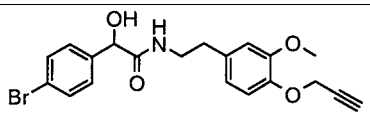
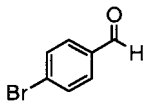
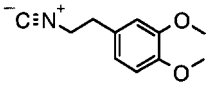
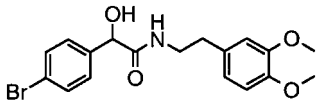
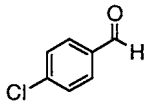
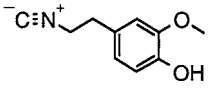
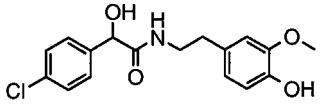
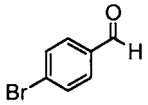
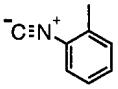
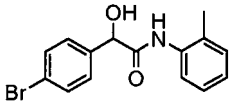
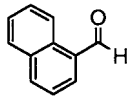
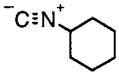
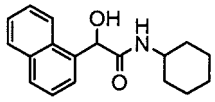
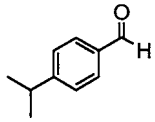
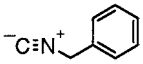
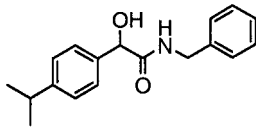
Table 2 Passerini Reactions of 1,2,3,4-tetra-*O*-Acetyl-α-D-galacturonic Acid[13] with Different Aldehydes and Isocyanides[18]

Entry	Aldehyde	Isocyanide	Mandelamide	er (%)
1				98:2
2				94:6
3				71:29
4				56:44
5				91:9
6				90:10

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(15) A typical experimental procedure is as follows: A mixture of benzaldehyde (**3**, 6 mmol), 2-(3,4-dimethoxyphenyl)ethyl isocyanide[12] (**4**, 6 mmol) and 1,2,3,4-tetra-*O*-acetyl-α-D-galacturonic acid[13] (**5d**, 6 mmol) in 15 mL of acetonitrile was stirred for 16 h at r.t. Subsequently, the reaction mixture was diluted with CH_2Cl_2, washed with H_2O, dried over Na_2SO_4 and evaporated. The residue was taken up in a mixture of 1 N NaOH (5 mL) and dioxane (10 mL). This mixture was stirred for 1 h at r.t., acidified to pH 2 with 2 N HCl and extracted with EtOAc. The combined organic layer was dried over Na_2SO_4 and evaporated. The residue was purified by flash chromatography on silica gel (EtOAc/hexane 7:3) to obtain colourless crystals of predominantly (*S*)-*N*-[2-(3,4-dimethoxyphenyl)ethyl]-2-hydroxy-2-phenylacetamide (**7**, 1.2 g, 3.8 mmol, 63%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.74 (q, 2 H, NCH_2), 3.49–3.60 (m, 3 H, $PhCH_2$, OH), 3.83 (s, 3 H, OCH_3), 3.88 (s, 3 H, OCH_3), 5.01 (s, 1 H, CHO), 6.06 (br s, 1 H, NH), 6.57–7.39 (m, 8 H, aromatic H). MS (70 eV): *m/z* = 315 (M^+), 316 ($M^+ + 1$). Mp: 91–92 °C (Lit.[16] 92–93.5 °C).

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