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Synthesis of the alkaloid tyroscherin by an aldol/Curtius strategy

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ABSTRACT

The alkaloid tyroscherin (**2**), which contains a vicinal *anti*-amino alcohol subunit was prepared from 4-hydroxyphenylpropionic acid (**5**) and *meso*-diol **9**. After desymmetrization of diol **9** and suitable protecting group manipulations, one terminus was extended via a Claisen rearrangement giving rise to enoate *ent*-**15**. The missing carbon on the other end could be incorporated using MeMgCl/CuBr·SMe_2 leading eventually to aldehyde *ent*-**22**. The acylated oxazolidinone **32** derived from acid **5** and aldehyde *ent*-**22** were combined in an aldol reaction. A subsequent Curtius rearrangement on the carboxylic group furnished the amino function of tyroscherin (**2**). In a proof of concept study the same strategy was used to prepare tyroscherin analog **28**.

1. Introduction

The β-phenylethylamine substructure is present in a range of natural and man-made molecules.[1] An unique representative of this class of compounds is tyroscherin,[2] which is a hybrid between tyrosine and a polyketide fragment. A possible biosynthetic precursor **3** is shown in Figure 1. In 2008, total synthesis studies led to the conclusion that the original published stereostructure needed revision.[3,4,5] Thus, the *syn*-amino alcohol stereochemistry actually has *anti*-configuration and the C8,C10-stereochemistry is opposite to the originally proposed configurations. The molecule was reported to inhibit the growth of cancer cells that depend on the insulin-like growth factor (IGF). The IC_{50} value for MCF-7 human breast cells containing IGF-1 (30 ng mL^{-1}) was 9.7 ng mL^{-1}. If the growth-stimulating IGF-1 is replaced by fetal bovine serum, tyroscherin had essentially no activity on these cells. Thus, a concise route to tyroscherin and possibly its stereoisomers seemed of interest. In particular derivatives thereof might allow for identification of the cellular target. The approach followed by Watanabe et al.[3,4] uses the Weinreb amide of *N*-Boc-*N*-methyl tyrosine for chain extension. The section containing the two methyl groups was later attached via a Julia olefination. We thought about forming the C2–C3 bond via an asymmetric aldol reaction followed by Curtius degradation of the carboxylic group.[6] In the following we describe the realization of this strategy.

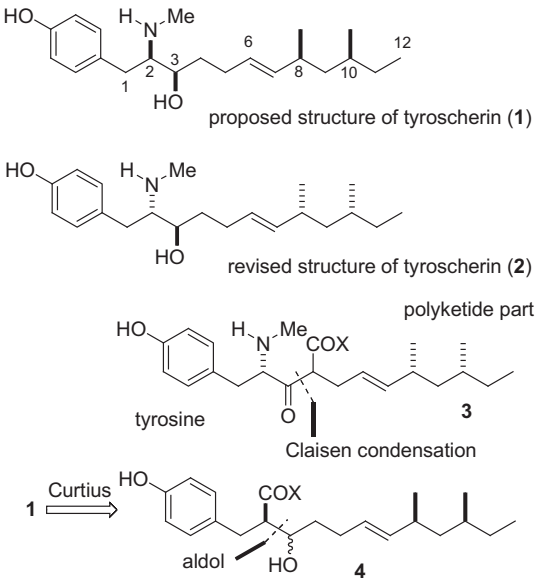

Figure 1. Structures of the proposed (**1**) and revised (**2**) tyroscherin together with the biosynthesis precursor **3** and the retrosynthetic analysis.

2. Results and discussion

The synthesis of the carboxylic acid part for the aldol reaction started with 4-hydroxyphenylpropionic acid (**5**) (Scheme 1). While the corresponding 4-triisopropylsilyl and MOM ether and could

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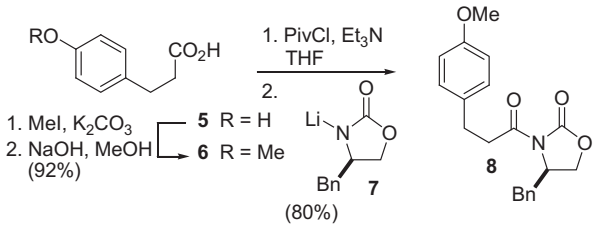
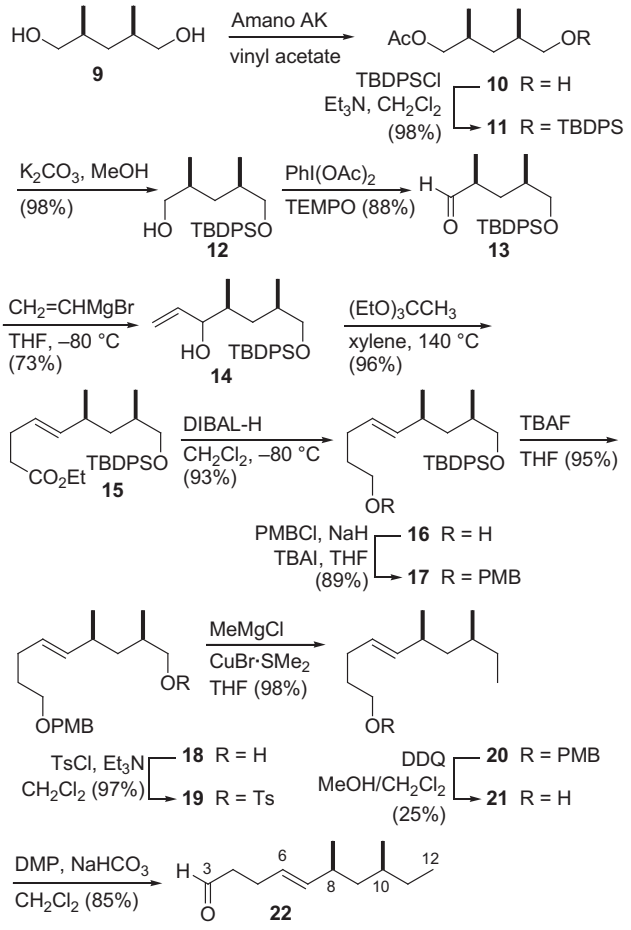
also be prepared, we faced severe problems in acylating the lithiated Evans oxazolidinone **7** via the mixed anhydride.[7] For some reason the acylation with the acid[8] **6** containing a 4-methoxyphenyl group worked nicely. The absolute configuration of the chiral auxiliary was chosen in such a way that the 3-OH group would have to be inverted at a later stage of the synthesis but the carboxyl, respectively, amino group would be correct. Thus, in one step a crucial carbon–carbon bond as well as two stereogenic centers would be formed that would open the way to tyroscherin and analogs. In addition, this strategy would allow for the preparation of oxazolidinone derivatives.[9]



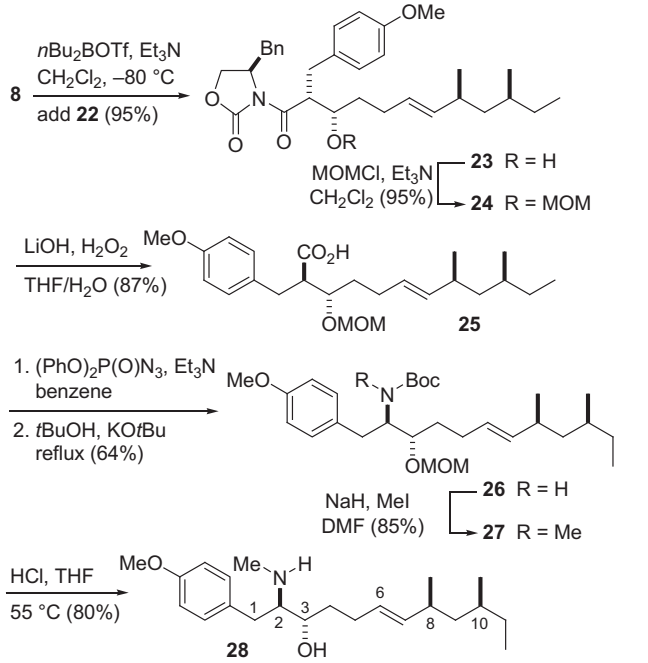
Scheme 1. Synthesis of propionyl oxazolidinone **8**.

For the synthesis of the polyketide segment we started with the known *meso*-diol **9** and relied on a desymmetrization via selective enzyme-catalyzed monoacylation (Scheme 2).[10,11] Simple protecting group manipulations led via the *tert*-butyldiphenylsilylether[12] **11** and **12** to aldehyde **13**. Reaction of aldehyde **13** with vinylmagnesium bromide furnished the vinylic alcohol **14** as a diastereomeric mixture (2:1). This was subjected to a Johnson–Claisen rearrangement[13,14] leading in almost quantitative yield to unsaturated ester **15**. Reduction of the ester **15** to alcohol **16**, protection as PMB ether **17**, cleavage of the silyl ether of compound **17** and tosylation of primary alcohol **18** provided tosylate **19**. Substitution of the tosylate with MeMgCl in presence of $CuBr \cdot SMe_2$ gave an excellent yield of the C3–C12 fragment **20**.[11,15] All these steps went with high chemical yields. In contrast, cleavage of the PMB ether in alkene **20** turned out to be problematic and only proceeded with moderate efficiency. Finally, oxidation of alcohol **21** furnished aldehyde **22**, required for the subsequent aldol reaction. An earlier introduction of the C12 methyl group was possible, but this aldehyde corresponding to **13** turned out to be rather volatile making its isolation and purification difficult.



Scheme 2. Synthesis of alkenal **22**, corresponding to the C3–C12 fragment of tyroscherin.

The propionic acid derivative **8** and aldehyde **22** were combined via an Evans aldol reaction using Bu_2BOTf and Et_3N in CH_2Cl_2 at low temperature (Scheme 3).[16] The fact that we could only observe one set of signals in the ^{13}C NMR indicated the high diastereoselectivity in the aldol reaction. MOM protection of the alcohol **23** followed by saponification of the amide derivative led to acid **25**. The Curtius rearrangement was induced with diphenylphosphoryl azide[17] in presence of *tert*-butanol to provide BOC protected amine **26**. This was followed by *N*-methylation[18] and cleavage of the MOM and BOC protecting group under acidic conditions. The final cleavage of the arylmethyl ether under various conditions (BBr_3,[19] 9-I-BBN) did give the desired product according to LC–MS. However, the product was always contaminated with products resulting from addition of HX (X=Br, I) to the double bond. Therefore, another protecting group was needed. Since at this time the correct structure also became known,[3,4] the synthesis was aimed at this diastereomer. In fact, due to the C2–C3 *anti*-stereochemistry, the aldol/Curtius approach seemed even more suitable.



Scheme 3. Aldol reaction followed by Curtius-rearrangement leading to amino alcohol **26** and tyroscherin analog **28**.

For the phenol protecting group we settled on an allyl ether. This required a small detour since the acylation of the Evans oxazolidinone only worked nicely with the methyl- or benzyl ether (Scheme 4). Thus, after acylation of lithiated oxazolidinone **7** with the mixed anhydride derived from propionic acid[20] **29**, the benzyl group was replaced with the allyl ether via hydrogenation and Williamson etherification to yield amide derivative **32**.