A ring-closing metathesis-mediated route to novel enantiopure conformationally restricted cyclic amino acids†

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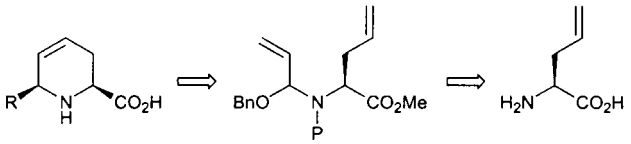
A combination of palladium-catalysed *N,O*-acetal formation, ruthenium-catalysed ring-closing metathesis and *N*-sulfonyliminium ion-mediated C–C bond formation constitutes an efficient and versatile route to a set of enantiomerically pure 2,6-disubstituted unsaturated pipecolic acid derivatives.

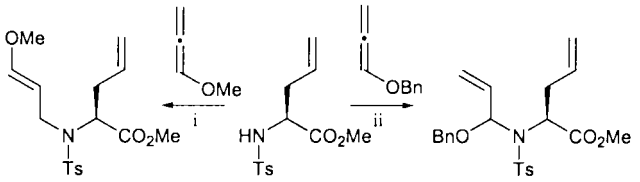
The pipecolic acid derivatives **1**, heterocycles containing a variety of functional groups, constitute an interesting compound class. They are rigid amino acids and may therefore be used to introduce conformational restriction in peptides.[1] Furthermore, this class of cyclic amino acid derivatives is a versatile starting point for the construction of (libraries of) biologically active compounds and for the synthesis of naturally occurring alkaloids.[2] Although a few approaches towards the synthesis of such systems are known,[3] general access to a wide range of these types of amino acids is still rather limited. Here we present an efficient and flexible route to the unsaturated 2,6-disubstituted pipecolic acid derivatives **1** consisting of (i) a novel amidopalladation reaction of an alkoxy-substituted allene to form the allylic *N,O*-acetals **2a** and **2b**, (ii) Ru-mediated ring-closing metathesis of these intermediates and (iii) selective functionalisation at the 6-position *via* allylic *N*-sulfonyliminium ion chemistry (Scheme 1).[4] The starting material is enantiomerically pure allylglycine (**3**), which is commercially available but alternatively can be efficiently prepared in both enantiomeric forms.[5]



1 **2a**: P = Ts; **2b**: P = Ns **3**

Scheme 1 Retrosynthesis.

This route was inspired by previous work in our group on the synthesis of oxygen heterocycles, where one of the key steps consisted of a highly efficient acetal formation *via* oxypalladation of methyl propadienyl ether.[6] We envisioned that formation of the corresponding *N,O*-acetals should be possible in a similar fashion.[7] However, treatment of Ts-protected allylglycine methyl ester (**4**) with methyl propadienyl ether in the presence of $Pd(OAc)_2$ at 80 °C surprisingly led to the undesired enol ether **5**, formed by reaction of the tosylamide at the least hindered γ-position of the allene (Scheme 2). Interestingly, a similar reaction with benzyl propadienyl ether[8] did not require these refluxing conditions to proceed, but instead



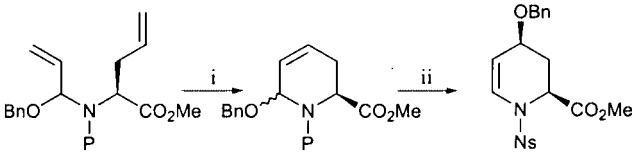
5 **4** **2a**

Scheme 2 *Reagents and conditions*: i, methyl propadienyl ether, $Pd(OAc)_2$, dppp, Et_3N, MeCN, sealed tube, reflux, 50%; ii, benzyl propadienyl ether, $Pd(OAc)_2$, dppp, Et_3N, MeCN, room temperature, 85%.

went to completion in one hour at room temperature to selectively give the desired *N,O*-acetal **2a** in 85% yield.[9] Most probably, at higher temperatures the thermodynamic product is formed, whereas at room temperature the kinetic product is produced.

The *N,O*-acetal formation proceeded well for both the Ts- and Ns (4-nitrobenzenesulfonyl)-protected allylglycine derivatives (yield of **2b**: 84%; both **2a** and **2b** were obtained as *ca.* 1:1 mixtures of diastereomers), but did not work satisfactorily for the corresponding carbamates. It should be stressed that this amidopalladation of benzyl propadienyl ether represents a novel method of generating *N,O*-acetals. More general application of this smooth reaction to convert sulfonylamides into the corresponding *N,O*-acetals[10] in principle paves the way to a large variety of *N*-sulfonyliminium ion precursors.[4]

Having these stable diolefins in hand, the compounds were subjected to standard ring-closing metathesis conditions using the well-established Grubbs Ru–benzylidene catalyst[11] to give the desired cyclic *N,O*-acetals **6a** and **6b** in excellent yields as *ca.* 1:1 mixtures of *cis/trans*-isomers (Scheme 3)



2a: P = Ts; **2b**: P = Ns **6a**: 95%; **6b**: 90% **7**

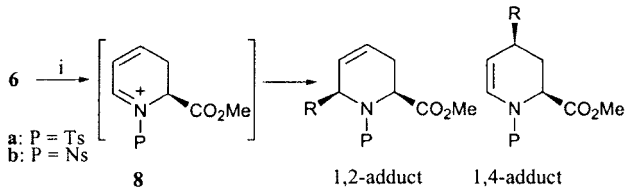
Scheme 3 *Reagents and conditions*: i, $Cl_2(Cy_3P)_2Ru{=}CHPh$, CH_2Cl_2, room temperature; ii, $BF_3{\cdot}OEt_2$, CH_2Cl_2, −78 °C, 90%.

Treatment of this mixture with $BF_3{\cdot}OEt_2$ at −78 °C led to isomerisation of **6b** to the thermodynamically more stable vinylogous *N,O*-acetal **7**,† which consisted of an 8:1 mixture of *cis/trans* isomers. After comparison with literature data[3c] and based on the observed NOE signals in the ^1H NMR spectrum, the major isomer was identified as the *cis*-product. This isomerisation was a useful indication of the feasibility of cationic reactions *via* such types of *N*-sulfonyliminium ions.

To establish CC-bond formation, precursors **6a** and **6b** where treated with a variety of nucleophiles in the presence of different Lewis acids. In Table 1, the results with $BF_3{\cdot}OEt_2$ are shown,

† Electronic supplementary information (ESI) available: characterisation data for compounds **7**, **9** and **16**. See http://www.rsc.org/suppdata/cc/b0/b001253j/

Table 1 *Reagents and conditions*: i, nucleophile, $BF_3{\cdot}OEt_2$, CH_2Cl_2, −78 °C → room temperature; yields were determined after flash column chromatography. The enantiopurity of the products was checked by chiral HPLC (Chiracel OD, heptane–isopropyl alcohol = 80:20)



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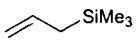
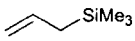
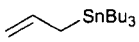
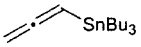
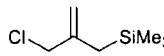
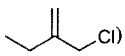
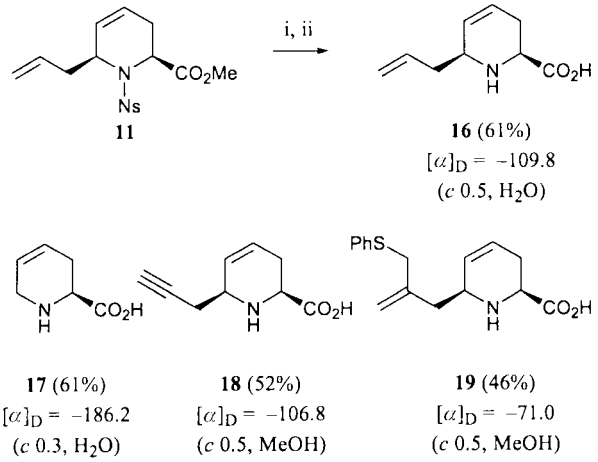
Entry	Substrate	Nucleophile	Product	Ratio (1,2:1,4)	Yield (%)
1	**6b**	Et_3SiH	**9** (R = H)	100:0	88
2	**6a**		**10** (R = Allyl)	90:10	62
3	**6b**		**11** (R = Allyl)	75:25	79
4	**6b**		**11** (R = Allyl)	98:2	94
5	**6a**	$Me_3Si{-}C{\equiv}N$	**12** (R = CN)	100:0	70
6	**6b**	$Me_3Si{-}C{\equiv}N$	**13** (R = CN)	100:0	89
7	**6b**		**14** (R = Propargyl)	100:0	75
8	**6b**		**15** (R = )	80:20	67

since this Lewis acid appeared superior in terms of selectivity and yield. The most simple nucleophile (Et_3SiH, entry 1) provided selectively the unsaturated pipecolic acid **9** in 88% yield. The enantiopurity of the product was checked by analysis of the enantiopure and the racemic product with chiral HPLC (as in all other entries) to confirm that racemisation during the *N*-sulfonyliminium ion reaction does not take place. With allyltrimethylsilane as the nucleophile (entries 2 and 3), mixtures of 1,2- and 1,4-addition products were obtained, both as single diastereoisomers. The stereochemistry of the 1,2-adduct was assigned on the basis of ^1H NMR NOE studies after deprotection to the free amino acid (10% enhancement of H6 upon irradiation of H2 and *vice versa*) and was in accordance with previously published observations.[3a] The *cis*-configuration of the 1,4-adduct was concluded *via* comparison with ^1H NMR data of **7**. The regioselectivity of this reaction could not be influenced by using different Lewis acids, but instead by applying the more reactive nucleophile allyltributyltin a highly selective reaction took place at the six-position. In addition, both trimethylsilylcyanide and 1,2-propadienyltributyltin[12] (entries 5–7) reacted solely and with complete diastereoselectivity at the six-position to give the corresponding cyanide- and propargyl-substituted product, respectively. Inversely, the chloromethyl-substituted allylsilane (entry 8) provided again a mixture of regioisomers.

Eventually, most of the Ns-protected products were converted into the corresponding free pipecolic acid derivatives (Scheme 4). A straightforward sequence involving (i) cleavage of the sulfonamide with K_2CO_3 and PhSH, (ii) LiOH-mediated hydrolysis of the ester and (iii) purification by ion exchange chromatography yielded the cyclic amino acids in good to moderate yields over these two steps without detectable epimerisation of the stereocentres. Thus, a number of differently substituted amino acid building blocks were obtained, including the natural product baikiain (**17**: $[\alpha]_D$ = −182.6 (*c* 0.3, H_2O); lit.,[13] −201.6 (*c* 1, H_2O)) and the allylic sulfide **19**, which arose from nucleophilic substitution of the chloride during the deprotection.

In summary, we developed a practical and concise transition metal-catalyzed route to a variety of substituted pipecolic acid



Scheme 4 *Reagents and conditions*: i, PhSH, K_2CO_3 DMF, room temperature; ii, LiOH, MeOH–H_2O (1:1), room temperature.

derivatives including the natural product baikiain. At present, we are further extending the scope of the cyclic *N,O*-acetals as synthetic intermediates in different (metal-catalysed) types of C–C bond forming reactions and are also exploring the possibilities to apply these building blocks in natural product synthesis.

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Notes and references

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