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Concise total synthesis of (+)-carpamic acid

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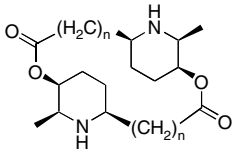
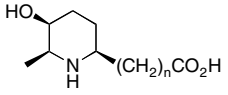
Abstract—We report herein an efficient enantioselective synthesis of (+)-carpamic acid, with nine steps as the longest linear sequence, the key strategy being based on a novel sequence of a cross-metathesis (CM) reaction and a subsequent cyclizing reductive amination to form the piperidine ring.

Piperidine alkaloids are widespread in nature and many compounds of this family exhibit important biological activities.[1] 2,6-Disubstituted 3-piperidinols represent a small subgroup and as a common structure these alkaloids possess a β-hydroxypiperidine ring with a methyl or hydroxymethylene group in position 2 and an alkyl side chain in position 6 of the heterocycle.[2] Due to their interesting structures and their pharmacological properties much effort has been directed towards the stereoselective synthesis of this class of compounds.[3] Carpaine and azimine are two of the macrocyclic dilactones consisiting of two molecules of the characteristic 3-piperidinol structure designated as azimic acid **1** and carpamic acid **2** with a carboxy group in the C-6 alkyl chain and an all-*cis*-configuration of the substituents. We herein describe an enantioselective total synthesis of (+)-carpamic acid **2**.[4] With the conversion of **2** into carpaine being described in the literature, our synthesis represents a formal total synthesis of carpaine.[5]



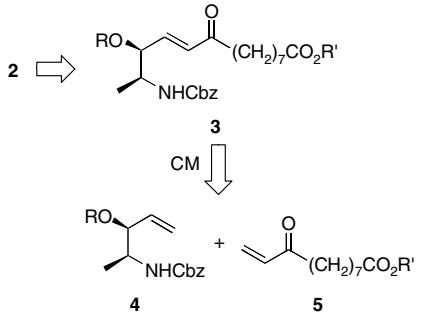
Azimine (n = 5)
Carpaine (n = 7)



1 (+)-Azimic acid (n = 5)
2 (+)-Carpamic acid (n = 7)

We envisaged an aminoketone of type **3** as the retrosynthetic precursor (Scheme 1). Upon treatment with hydrogen and a Pd-catalyst, δ-aminoketones of type **3** bearing an N-protecting group labile to hydrogenation are converted into piperidines with the desired 2,6-*cis*-stereochemistry in a sequence of hydrogenation of the double bond, N-deprotection and cyclizing reductive amination.[6] Compound **3** was envisaged to be synthesized via cross-metathesis (CM) between olefins **4** and **5**. We considered the Cbz group as an appropriate N-protecting group due to both its compatibility with the metathesis step and its lability to hydrogenolysis. Aminoalcohol **4** was envisaged to be synthesized from (L)-alanine.

The addition of vinyl anions to variously N-protected α-alaninals to afford α-vinyl-β-aminoalcohols has been intensively investigated in the literature, but diastereoselectivities obtained were low.[7] Good diastereoselectivities in favour of the desired *syn*-isomer[8] (*syn*/*anti* 15:1) were reported by Yamamoto[9] starting from *N*-Boc-alanine methyl ester **6** by DIBAL-H reduction of the ester moiety and in situ conversion of the reaction intermediate—presumably the aluminoxy acetal—by



Scheme 1. Retrosynthetic analysis of **2**.

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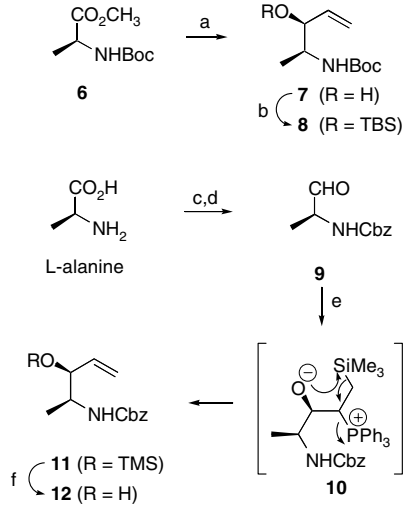
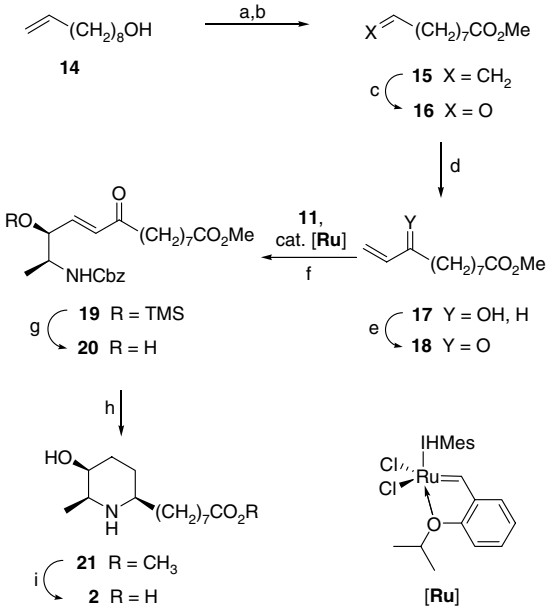
subsequent addition of vinylmagnesium chloride. According to this protocol, **7** was synthesized in 52% yield with a diastereoselectivity of 8:1 (Scheme 3).[10] In order to separate the isomers, they were converted into their corresponding TBS-ethers **8**, which were separable by column chromatography.[9] The difference in R_f values was very small, and the separation turned out to be troublesome. Furthermore, the use of the Boc protecting group would require additional deprotection/protection steps due to the necessary change of the protecting group for the reductive amination. Instead, it would be conceiveable to start directly from Cbz-protected α-alanine methyl ester, but problems might arise due to the limited stability of the Cbz group towards Grignard reagents.

Therefore, we focused our attention on an alternative preparation by Taddei and co-workers[11] who described the syntheses of various α-vinyl-β-aminoalcohols in good *syn*-diastereoselectivities of generally higher than 20:1 by reaction of various *N*-Boc-protected α-amino-aldehydes with the Seyferth–Fleming ylide[12] $Ph_3P{=}CHCH_2TMS$ **13** and subsequent desilylation of the initially formed TMS-ether. The formation of the products was rationalized by a 1,4-shift of the TMS-group and concomitant extrusion of PPh_3 (see intermediate **10**, Scheme 2).[13] Applying the literature protocol to *N*-Cbz protected alaninal **9**, which was synthesized from L-alanine using standard procedures, **11** was obtained in yields of less than 15%, presumably due to the enhanced lability of the Cbz group compared to the Boc-group under the basic reaction conditions. Taking this lability into account, the literature protocol was slightly modified. Instead of allowing the reaction mixture to warm to room temperature after addition of the aldehyde **9** to the ylide **13** at −78 °C, the reaction mixture was only allowed to warm to 0 °C and stirred at



Scheme 2. (a) (i) DIBAL-H, CH_2Cl_2, −78 °C, (ii) C_2H_3MgCl, THF, −78 °C → rt (52%, *syn*/*anti* 8:1); (b) TBS-Cl, imidazole, DMF; (c) (i) MeOH, $SOCl_2$; (ii) CbzCl, $NaHCO_3$ (71%, two steps); (d) DIBAL-H, toluene, −78 °C (68%); (e) **13** (2.5 equiv), THF, −78 °C → 0 °C, then NH_4Cl (aq) (64%, *syn*/*anti* 12:1); (f) TBAF, THF (90%, *syn*/*anti* > 20:1).



Scheme 3. (a) CrO_3, H_2SO_4, acetone (75%); (b) MeOH, cat. H_2SO_4 (98%); (c) (i) O_3, CH_2Cl_2, −78 °C, (ii) Zn, HOAc (72%); (d) C_2H_3Br, $CrCl_2$, $NiBr_2$ (cat.), DMF (78%); (e) DMP, CH_2Cl_2 (93%); (f) **18**:**11** = 1:1.2, 5 mol % [**Ru**], toluene, 80 °C; (g) TBAF, THF (78%, two steps); (h) H_2, Pd/C, MeOH; (i) KOH, MeOH (quantitative, two steps).

that temperature for 1 h before quenching. This modification involved an increased yield of **11** of 64%. The diastereoselectivity was found to be *syn*/*anti* 12:1. Desilylation using TBAF in THF afforded **12** in 90% yield in diastereomerically pure form.[14]

9-Decen-1-ol **14** served as the starting material for the second CM partner (Scheme 3). Jones oxidation and subsequent esterification furnished ester **15**. We would like to point out that we chose to protect the carboxylic acid functionality as an ester for practical reasons in order to avoid difficulties concerning work-up and solubility problems of the free acid; the following reactions including the metathesis step would not necessarily require this protection. Ozonolysis of **15** followed by reductive work-up afforded aldehyde **16**, which was vinylated using the Nozaki–Hiyama–Kishi reaction[15] to provide the allylic alcohol **17**. Competing vinylation of the ester moiety was not observed. Subsequent Dess–Martin oxidation[16] provided the enone **18**.

Next, the CM step was investigated. Ruthenium complexes bearing N-heterocyclic carbene ligands such as the second generation Grubbs catalyst (IHMes)$(PCy_3)Cl_2Ru(=CHPh)$[17] and its phosphine-free variant [**Ru**][18] have proved to be efficient catalysts for CM reactions between terminal olefins and acceptor-substituted alkenes.[19] Using either catalyst, CM between **18** and **12** afforded the desired product **20** in yields of less than 60% due to competing homodimerization of **12** as the major side reaction. When using the synthetic precursor **11** (*syn*/*anti* 12:1) as the CM partner instead of **12**, gratifyingly, homodimerization could almost completely be suppressed. We assume that the decreased

tendency towards self-metathesis of **11** is based on the high steric demand of the bulky TMS-group. Using 5 mol % of [**Ru**], the mixed CM product **19** could be obtained in good yield. TMS-ether **11** was employed in a slight excess of 1.2 equiv in order to suppress homodimerization of **18**, which occurred to a small extent as the major side reaction in this CM. Subsequent treatment of the crude product with TBAF furnished alcohol **20** in diastereomerically pure form.[20] Treatment of **20** with Pd/C under a hydrogen atmosphere afforded (+)-carpamic acid methyl ester **21** quantitatively and with complete stereoselectivity. Subsequent saponification furnished (+)-carpamic acid **2**. Spectral and analytical data were consistent with those reported in the literature.[4c,f]

In summary, we have described a concise and highly efficient total synthesis of (+)-carpamic acid. The key steps of our convergent synthesis were the highly diastereoselective vinylation of aldehyde **9**, a selective CM reaction and the reductive cyclization of aminoketone **20**. Given the high functional group tolerance of the Ru metathesis catalysts, our concept of CM in combination with a subsequent cyclizing reductive amination in general opens up a facile entry into the class of *cis*-2,6-disubstituted piperidines. Further syntheses based on this strategy are currently underway in our laboratories and will be reported in due course.

Acknowledgements

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14. Desilylation of a mixture of isomers **11** *syn*/*anti* 4:1, which was obtained via column chromatography, afforded **12** as a mixture of *syn*/*anti* 18:1. Since after the reaction, the *anti*-isomer **11** was no longer detected in the reaction mixture, the change in ratio of the diastereomers is not based on kinetic reasons. The product(s) formed from *anti*-**11** could not be determined.
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20. We assume that the change of the ratio of diastereomers is due to the same effect as in the desilylation of **11**, however, the crude metathesis product was not investigated in detail so we cannot be completely sure, which of the two steps is responsible for this finding.