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Organic Synthesis

Synthesis of Bicyclic Proline Derivatives by the Aza-Cope–Mannich Reaction: Formal Synthesis of (±)-Acetylaranotin

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Dedicated to Maria Andreeva on the occasion of her 13th birthday

Abstract: Herein we suggest an approach to oxygenated bicyclic amino acids based on an aza-Cope–Mannich rearrangement. Seven distinct amino acid scaffolds analogous to the natural products were prepared on a gram scale with precise control of stereochemistry. Successful implementation of our strategy resulted in the formal synthesis of acetylaranotin.

Introduction

Oxygenated bicyclic amino acids constitute an important class of secondary metabolites. Many of these nonproteinogenic amino acids[1] are subunits of structurally diverse natural products (Figures 1 and 2).[2,3] Epidithiodiketopiperazines (ETPs) and

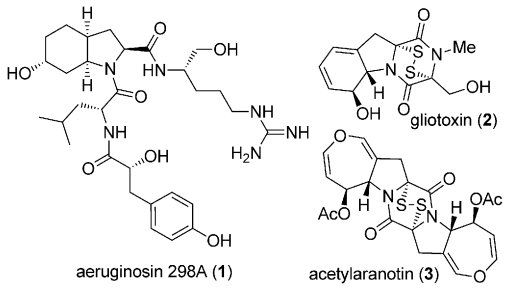

Figure 1. Natural products derived from oxygenated bicyclic amino acids.

bis(methylthio)diketopiperazines with oxygenation at the C5 and C5′-positions and the *cis*-fused ring junction, which are represented by four groups of natural products (epicoccins, epicorazines, rostratins, and brocazines), deserve additional attention (Figure 2).[3] The intriguing structural features of these fungal metabolites together with their antiviral, antibacterial, antiallergic, antimalarial, and cytotoxic properties[3,4] have

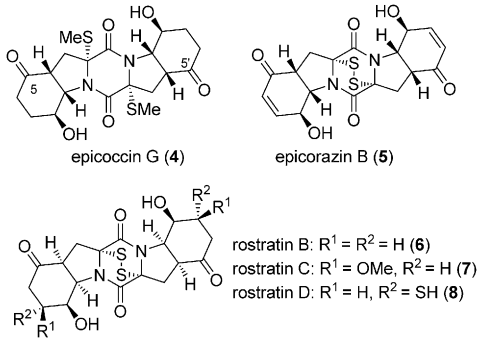

Figure 2. Natural products with oxygenation at 5 and 5′-positions.

stimulated numerous synthetic efforts toward compounds **3**–**8**. Total syntheses of epicoccin G, 8,8′-*epi*-*ent*-rostratin B, and related ETPs were reported by the Nicolaou group.[5] Bräse reported a unified synthetic strategy toward diketopiperazine cores, present in all of these natural products.[6] Recently, the groups of Reisman[7] and Tokuyama[8] completed total syntheses of acetylaranotin. The work in this area stimulated the development of various synthetic methods, such as sulfenylation[9] of 2,5-diketopiperazines, syntheses of bicyclic amino acids,[10] and preparation of diketopiperazines.[11] Moreover, successful efforts were taken to find biologically active analogues of these natural products.[5b,12]

We began planning the synthesis of the above-mentioned scaffolds with the retrosynthetic simplification of compounds **4**–**8** to the less-oxidized[13] C_2-symmetric diketopiperazine intermediate **9** (Scheme 1), which in turn could arise from the dimerization of **10**. It was envisioned that stereoselective formation of *cis*-fused bicyclic amino acid **10** could be achieved by the aza-Cope–Mannich reaction.[14] The requisite building block **11** could in turn be obtained by diastereoselective Grignard addition to a suitably protected α-amino ketone **12**.

Although the preparation of proline derivatives by the aza-Cope–Mannich reaction is known in the literature,[15] no such chemical transformation has ever been applied to derivatives

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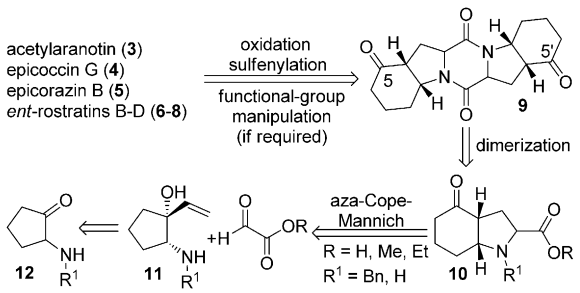


Scheme 1. Retrosynthetic analysis.

of octahydroindol-2-carboxylic acid or other bicyclic amino acids. In addition, recent studies from our group showed that the aza-Cope–Mannich reaction can be easily scaled up to decagram quantities and even more, therefore providing an adequate supply of material for both biological and synthetic studies.[16,17] Moreover, even substrates with α-stereocenters that are prone to epimerization can be used in the rearrangement.[18]

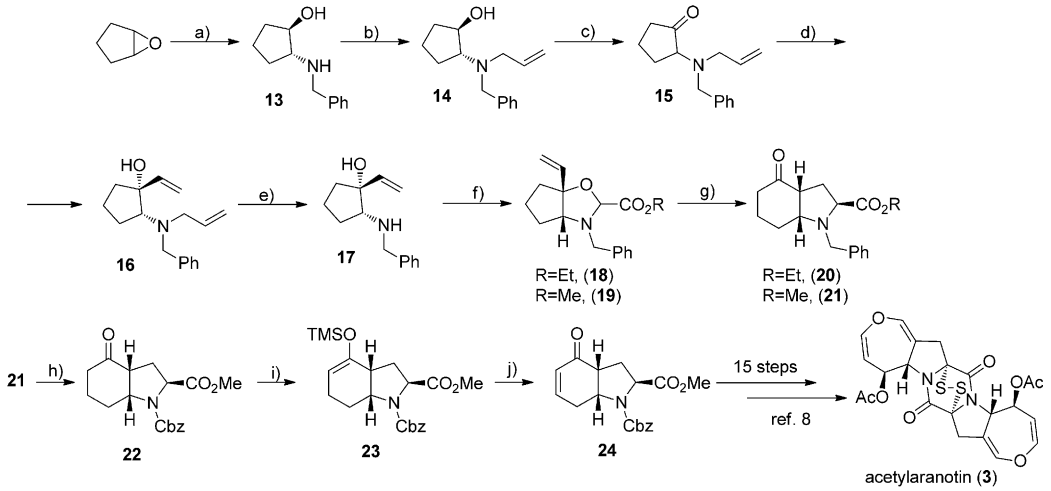
In principle, thiodiketopiperazines (acetylaranotin, gliotoxin) without C5 oxygenation can be prepared from diketopiperazine **9** or amino acid **10** by appropriate keto-group manipulations, oxidation[8] of the carbon framework and sulfenylation[19] (Scheme 1). Herein, we disclose the preparation of amino acid **10** and structural analogues thereof as well as the implementation of our strategy for the formal synthesis of acetylaranotin.

Results and Discussion

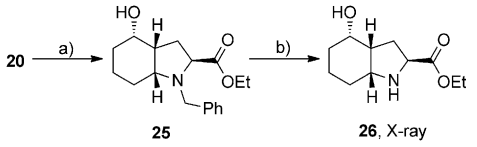
Synthesis of octahydroindol-2-carboxylic esters

Our studies commenced with the preparation of *cis*-amino alcohol **17** in accordance with the previously developed synthetic strategy (Scheme 2).[16] The ring-opening of cyclopentene oxide with benzylamine produced **13**, and N-allylation, followed by the Swern oxidation,[20] afforded ketone **15** in 75% yield over three steps. Ketone **15** was found to be unstable even upon storage at reduced temperature and was immediately consumed in the next stage. After the formation of a nonbasic[21] vinylcerium species, **15** was added at −78 °C to give the tertiary allylic alcohol **16** in 93% yield as a single isomer (*cis*-amino alcohol). It is noteworthy that ketone **15** is added to the preformed vinylmagnesium bromide–cerium(III) chloride reagent, otherwise the yield and the diastereoselectivity of the reaction would be greatly diminished.[22] The careful control of the reaction temperature is also important, because alkenylcerium reagents are unstable above −20 °C.[23] The removal of the allyl group under the action of 1,3-dimethylbarbituric acid (NDMBA) in the presence of catalytic amounts of $[PdCl_2(Ph_3P)_2]$ gave the required *cis*-amino alcohol **17**.[24] The successive treatment of **17** with a freshly distilled ethyl glyoxylate in the presence of camphorsulfonic acid (CSA, 0.1 equiv) furnished the oxazolidine **18** in an excellent yield. The configuration of the C2 stereocenter was not determined in **18** and related oxazolidines (vide infra), because this center was destroyed in the following reaction. Finally, the aza-Cope–Mannich reaction proceeded smoothly at −78 °C upon treatment of **18** with $BF_3{\cdot}Et_2O$ to provide a bicyclic amino ester **20** as a single diastereomer in 83% yield (8.3 g scale). After the Luche reduction and debenzylation, the relative stereochemistry of **20** was unambiguously confirmed by X-ray crystallographic analysis (Scheme 3).[25]

The use of methyl glyoxylate[26] instead of ethyl ester and following with BF_3-catalyzed rearrangement effectively provided amino ester **21** (34% from **17**), the *N*-benzyl group of which was exchanged for an *N*-Cbz group by hydrogenation and sequential treatment with benzyloxycarbonyl chloride in the presence of base (DIPEA). The two-step procedure,



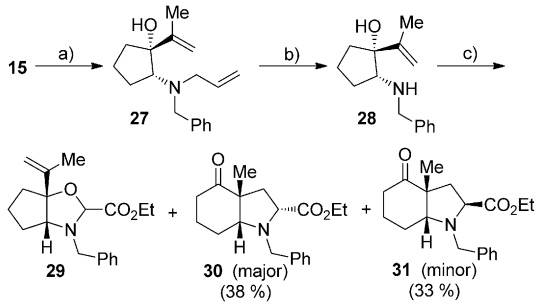
Scheme 2. Synthesis of *cis*-fused amino esters: a) $BnNH_2$ (3 equiv), 150 °C, 81%; b) AllylBr (1.5 equiv), K_2CO_3 (2 equiv), MeCN, Δ, 100%; c) DMSO, $(COCl)_2$, Et_3N, dichloromethane, −78 °C, 92%; d) vinylmagnesium bromide, 1 M in THF (1.5 equiv), $CeCl_3$ (1 equiv), THF, −78 °C, 93%; e) *N*,*N*′-dimethylbarbituric acid (3 equiv), $[PdCl_2(PPh_3)_2]$ 1 mol%, dichloromethane, Δ, 88%; f) ethyl glyoxylate (2 equiv), dichloromethane, CSA 10 mol%, (R = Et, 90%, R = Me, 93%); g) $BF_3{\cdot}Et_2O$ (2 equiv), dichloromethane, −78 °C to RT, (R = Et, 83%, R = Me, 37%); h) 1) 10% Pd/C, H_2, EtOAc; 2) CbzCl, DIPEA, EtOAc, 62%; i) TMSOTf (3 equiv), DIPEA (4 equiv), dichloromethane; j) $Pd(OAc)_2$ (2 equiv), MeCN, 43% over two steps. Cbz = carbobenzyloxy; DIPEA = *N*,*N*-diisopropylethylamine.



Scheme 3. Synthesis of **26**: a) $NaBH_4$ (1 equiv), $CeCl_3 \cdot 7H_2O$ (1 equiv), −78 °C, 66%; b) 10% Pd/C, H_2, EtOH, 94%.

featuring silyl enol formation and Saegusa–Ito[27] oxidation, intercepted an intermediate in Tokuyama's[8] acetylaranotin synthesis, successfully completing our formal synthesis studies.

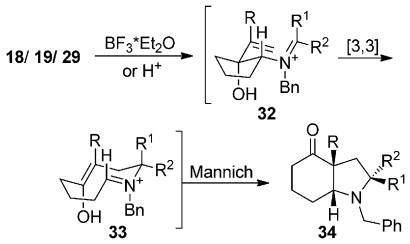
It is a well-known fact that methylated compounds, especially amino acids, are of considerable interest to medicinal chemists due to the "magic methyl effect".[28] Thus, the scope of the reaction was further extended to structures containing methyl substituents (as well as a quaternary stereocenter) at the ring junction. To this end, aminoethanol **28** was prepared (Scheme 4) from ketone **15** by employing the same two-step



Scheme 4. Synthesis of *cis*-fused amino esters: a) 2-propenylmagnesium bromide, 0.5 M in THF (1.5 equiv), $CeCl_3$ (1 equiv), THF, −78 °C, 73%; b) *N*,*N*′-dimethylbarbituric acid (3 equiv), $[PdCl_2(PPh_3)_2]$ 1 mol%, dichloromethane, Δ, 94%; c) ethyl glyoxylate 50% in toluene (2 equiv), CSA 10 mol%, dichloromethane.

procedure as for **17**. In this way, the treatment of **28** with ethyl glyoxylate in the presence of camphorsulfonic acid (CSA, 0.1 equiv) furnished not only the oxazolidine **29** but also two rearranged products, **30** and **31**, in 19, 26, and 41% yield, respectively. The rearrangement of **29** under the action of $BF_3 \cdot Et_2O$ at −78 °C gave a 1:1 mixture of **30** and **31**. To overcome the formation of a complex mixture, we have applied more forcing conditions to **28** (i.e., refluxing in 1,2-DCE), thus achieving the complete consumption of **28** and **29**; however, the yields of **30** and **31** were slightly lower (35 and 24%, respectively). Further extension of the reaction time up to 3 days at an ambient temperature in dichloromethane resulted in a full conversion with improved yields (**30**: 38%, **31**: 33%). The relative configuration of **30** and **31** was assigned on the basis of NMR spectroscopic studies (NOESY). It should be emphasized that **30** and **31** are readily separable by column chromatography (>1 g scale). Compound **30** can, in principle, be transformed to simplified lycoposerramine-S analogues.[29,30]

It is well-known that the stereochemical outcome of an aza-Cope–Mannich reaction is controlled by steric effects in the



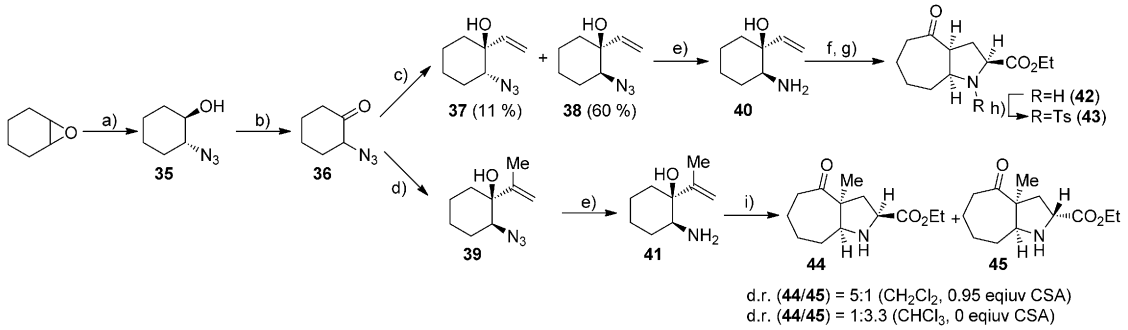
Scheme 5. Transition-state geometry of [3,3]-sigmatropic rearrangements of iminium ions; R = H, Me; R^1, R^2 = H, CO_2Et.

intermediate iminium ion (Scheme 5).[14] When the substituent at the nitrogen atom is large (CH_2Ph) and R = H, the configuration-determining [3,3]-sigmatropic rearrangement (**32**→**33**) occurs preferentially via the (*Z*)-iminium ion to furnish amino esters **20** and **21** (Scheme 2).[31,32] The replacement of vinyl by an isopropenyl group leads to an almost equal stability of (*E*)- and (*Z*)-iminium ions (**30**/**31** 1.1:1, Scheme 4), due to the steric interactions between Me (R) and the ester groups (R^1). However, when an aldehyde substituent decreases in size ($CHOCO_2H$ vs. $CHOCO_2Et$, Scheme 12), the (*Z*)-iminium ion again becomes more favorable (**68**/**67** 9.6:1 vs. 1.1:1, Scheme 12).

Synthesis of decahydrocyclohepta[b]pyrrole-2-carboxylic esters

The sequence en route to octahydroindoles was further extended to the synthesis of decahydrocyclohepta[*b*]pyrrole-2-carboxylic acids. These substrates can be viewed as full-carbon analogues of acetylaranotin or conformationally constrained analogues of proline:[33] the related amino acid was found to be a useful intermediate in the total synthesis of didehydrostemofoline.[34] Both *cis*- and *trans*-fused amino acids can be prepared.

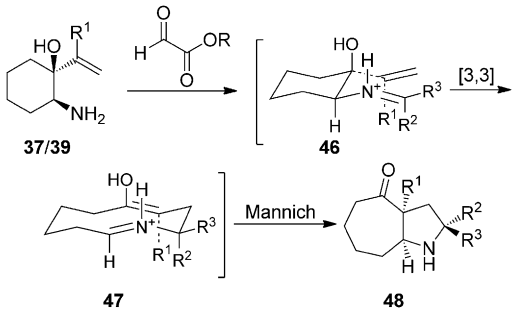
To synthesize *cis*-fused analogues, we have considered an azido group as an ammonia surrogate in place of benzylamine.[35] This tactic was expected to obviate the need for protection–deprotection (e.g. **13**→**14**, **16**→**17**, Scheme 2) and debenzylation steps. The sequence commenced with Swern oxidation[20] of readily available *trans*-2-azido-cyclohexanol **35** (Scheme 6).[36] As the resulting ketone is quite volatile, all manipulation (workup, chromatography) was conducted using low-boiling solvents (dichloromethane, Et_2O, pentane) to ensure high yield (96%). The following Grignard addition proved to be more challenging than anticipated:[37,38] the treatment of **36** with vinylmagnesium bromide in THF at 0 °C provided a 3.5:1 mixture of *trans*- and *cis*-azidoalcohols **37** and **38** in a 52% combined yield. The isomers obtained are readily separable by column chromatography even on a large scale (>10 g).Decreasing the reaction temperature to −78 °C led to an increase of both the combined yield (71%) and the diastereomeric ratio of the products (5.5:1 in favor of **38**). Using a cerium(III)mediated addition[21] further improved the yield to 85% but also dramatically reduced the d.r. to 2:1 in favor of the *trans* isomer. Ketone **36** showed an analogous behavior in the



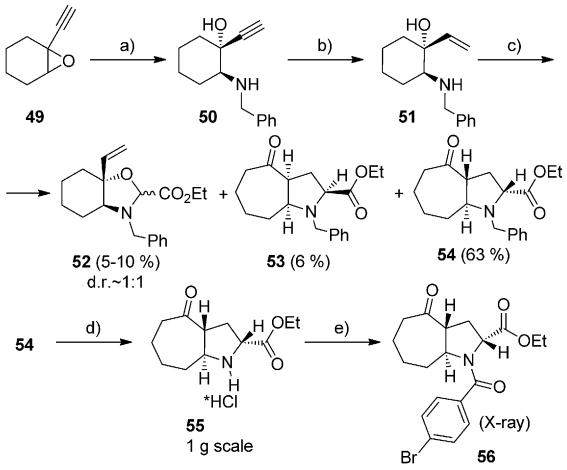
Scheme 6. Synthesis of *cis*-fused amino esters: a) NaN_3 (2.5 equiv), H_2O/acetone, Δ, 99%; b) DMSO (2.5 equiv), $(COCl)_2$ (1.5 equiv), Et_3N (5 equiv), dichloromethane, −78 °C, 96%; c) vinylmagnesium bromide, 1 M in THF (1.5 equiv), THF, −78 °C, 71%; d) 2-propenylmagnesium bromide, 0.5 M in THF (1.5 equiv), $CeCl_3$ (1 equiv), THF, −78 °C, 80%; e) $LiAlH_4$ (2 equiv), Et_2O, 97% for **40**, 93% for **41**; f) ethyl glyoxylate, 50% in toluene (1.1 equiv), CSA 10 mol%, dichloromethane; g) $BF_3{\cdot}Et_2O$ (2 equiv), dichloromethane, −78 °C, 72% over two steps; h) TsCl (1 equiv), Et_3N (1 equiv), DMAP (cat.), dichloromethane, 88%; i) ethyl glyoxylate, 50% in toluene (1.1 equiv), CSA 0–95 mol%, dichloromethane, 95%. DMAP = 4-dimethylaminopyridine.

reaction with 2-propenylmagnesium bromide (33% at 0 °C, 55% at −78 °C, $CeCl_3$ 80%); however, only minor quantities of *trans*-azidoalcohol were observed (d.r. = 20: 1). The subsequent reduction of azides **38** and **39** with $LiAlH_4$ in Et_2O led smoothly to amino alcohols **40**[39] and **41** in 97 and 93% yields, respectively. Next, the reaction of **40** with ethyl glyoxylate in the presence of 3 Å molecular sieves gave an oxazolidine (not shown on scheme), which was treated in a one-pot fashion with two equivalents of $BF_3{\cdot}Et_2O$. After mild basic workup ($NaHCO_3$), amino ester **42** was obtained in 72% yield as a single isomer (1 g scale). We have noted that **42** forms an inseparable mixture of epimers upon storage (weeks). However, tosylation (TsCl, Et_3N, DMAP cat.) provides a stable crystalline compound **43**, the relative stereochemistry of which was determined by X-ray crystallographic analysis.[25] In contrast, no Lewis or protic acid was needed to initiate the aza-Cope–Mannich rearrangement of **41**: two products were formed, and the diastereoselectivity of the reaction was found to be dependent on the reaction conditions. Thus, **44** was the major product when the reaction was conducted in the presence of 0.95 equivalents of CSA in dichloromethane (**44**/**45** = 5:1). In contrast, **45** was formed predominantly in $CHCl_3$ without any acidic catalysis (**44**/**45** = 1: 3.3). The relative configurations of **44** and **45** were unambiguously confirmed on the basis of COSY and NOESY spectra. Despite significant differences in their chromatographic mobility, compounds **44** and **45** cannot be fully separated by means of column chromatography. Formation of **45** is surprising and cannot be explained fully by steric interactions in the transition iminium ion (Scheme 7).

The synthesis of the *trans*-fused amino acid commenced with a preparation of *trans*-amino alcohol **51** by performing the previously described two-step procedure:[17,40] the nucleophilic ring-opening of the commercially available oxirane **49** followed by the partial reduction of the triple bond in the presence of Lindlar's catalyst furnished the amino alcohol **51** in 80% yield (Scheme 8). The subsequent treatment of **51** with freshly distilled ethyl glyoxylate mediated by CSA (0.3 equiv) furnished a mixture of compounds **52**–**54**.The relative configuration of the main product **54** was determined by X-ray crystal structural analysis based on its derivative **56**. The N-alkylation



Scheme 7. Transition-state geometry of [3,3]-sigmatropic rearrangements of iminium ions; R = H, Et; R^1 = H, Me; R^2, R^3 = H, CO_2Et.

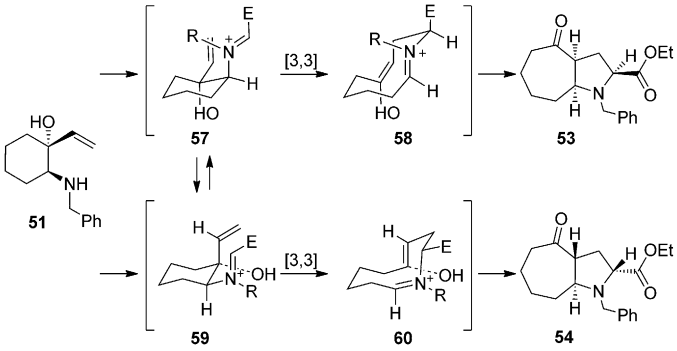


Scheme 8. Synthesis of *trans*-fused amino ester **55**: a) Benzylamine (2 equiv), $LiClO_4$ (1.5 equiv), MeCN, 60 °C, 91%; b) H_2, Pd/$CaCO_3$, EtOH, 96%; c) ethyl glyoxylate (3 equiv), CSA 30 mol%, dichloromethane, 63%; d) 10% Pd/C, H_2, HCl (1 equiv), EtOH, 87%; e) *p*-BrC_6H_4COCl (1 equiv), Et_3N (1 equiv), dichloromethane, 95%.

of aminoester **42** with benzyl chloride furnished a product with the same NMR spectra as **53** (Scheme 6). Unfortunately, we failed to increase the yield of **54**. When more forcing conditions were applied to ensure the full consumption of

alkene **51** and oxazolidines **52**, the diastereoselectivity of the reaction decreased.

The rearrangements of iminium ions derived from cyclohexanols with *cis*-oriented amine and vinyl groups are quite complex, because two chair transition states are possible (Scheme 9). In both cases, the carboethoxy group is placed in



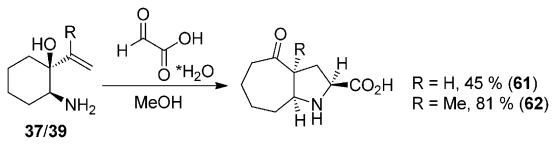
Scheme 9. Transition-state geometry of [3,3]-sigmatropic rearrangements of iminium ions; E = CO2Et, R = Bn.

a pseudoequatorial position (**57**, **59**), but conformation **57** is higher in energy than **59** due to steric interactions between the bulky benzyl group and the cyclohexane ring. As was reported earlier by our group, this steric interaction is one of the major factors contributing to high *trans*-stereoselectivity.[17] It has been previously demonstrated by Overman that alkene substitution is also very important for the stereochemical outcome of the reaction, that is, when an aryl substituent is introduced, the rearrangement gives the *cis*-product analogous to **53** exclusively.[41] It is worth noting that *cis*- and *trans*-substituted amino cyclohexanols can be transformed to the respective *cis*- and *trans*-fused decahydrocyclohepta[b]pyrroles; in contrast, both *cis*- and *trans*-substituted amino cyclopentanols rearrange to *cis*-fused octahydroindoles.[32b]

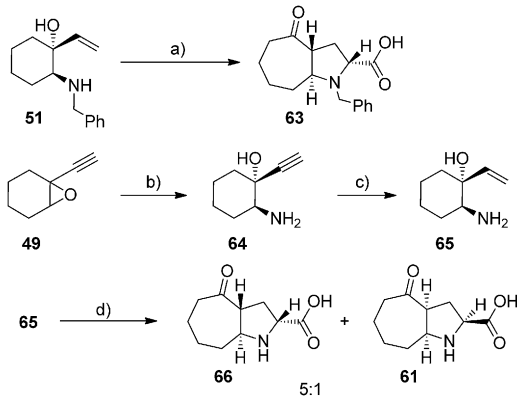
Synthesis of amino acids

For further modification, including diketopiperazine formation, both an N-deprotected aminoester and N-protected amino acid are needed. With these considerations in mind, we attempted to prepare N-protected amino acids by ester hydrolysis. The reaction proved very challenging, and under most conditions, extensive epimerization/decomposition was observed. Preliminary results suggested $Ba(OH)_2 \cdot 8H_2O$ in methanol as a most suitable hydrolyzing reagent.[42] After these unsuccessful experiments, we switched to directly preparing the amino acids by reacting amino ethanols with glyoxylic acid.[15a]

In comparison to the reaction with ethyl glyoxylate (Scheme 6), no diastereomeric mixtures were formed during the reaction of both **37** and **39** with glyoxylic acid in MeOH. Hence, within a few minutes, precipitates of pure amino acids **61** and **62** were formed in 45 and 81% yields, respectively (>1 g scale, Scheme 10).[15] High diastereoselectivity along



Scheme 10. Synthesis of *cis*-fused amino acids.

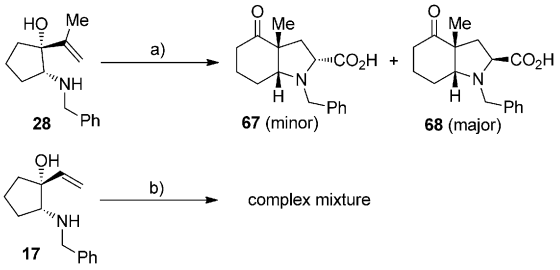


Scheme 11. Synthesis of *trans*-fused amino acids: a) glyoxylic acid monohydrate (1.1 equiv), MeOH, 69%; b) NH_3/MeOH, 60 °C, 61%; c) H_2, $Pd/CaCO_3$, EtOH, 92%; d) glyoxylic acid monohydrate (1.1 equiv), MeOH, 48%.

with a rapid reaction rate might be a result of intramolecular acidic catalysis.[15a]

In analogy with the reactions shown in Scheme 10, the treatment of **51** with glyoxylic acid in MeOH resulted in fast precipitation of a single product—*N*-benzyl amino acid **63** (69%, Scheme 11). N-unsubstituted *trans*-amino acid **66** was prepared from epoxide **49** in three steps (Scheme 11). The aza-Cope–Mannich rearrangement was also fast, but the diastereoselectivity was modest (5:1 in favor to *trans*-fused product, see Scheme 9).

In contrast to the observed behavior of the compounds **37**, **39**, and **51**, the treatment of **28** with glyoxylic acid in MeOH (Scheme 12) provided a 3:1 mixture of diastereomeric amino acids **67** and **68** in 74% combined yield (separable by column chromatography).[15,43] The d.r. was sharply improved to 9.6:1 in favor of **68** by employing trifluoroethanol as a solvent. The reaction of aminoethanol **17** with glyoxylic acid led to a complex mixture under a variety of conditions.



Scheme 12. Synthesis of *cis*-fused amino acids: a) glyoxylic acid monohydrate (1.1 equiv), CF_3CH_2OH, 74%; b) glyoxylic acid monohydrate (1.1 equiv), MeOH, 69%.

Conclusions

We have developed a practical method for the preparation of unnatural bicyclic proline analogues by a tandem cationic aza-Cope rearrangement–Mannich cyclization reaction. Herein, we have prepared seven distinct amino acid scaffolds that could be of interest to medicinal chemists. The experimental simplicity of our procedures allows us to prepare gram quantities of the requisite compounds. Finally, we have demonstrated the applicability of our route to the synthesis of complex natural products by formal synthesis of acetylaranotin. Although our synthesis was less efficient than reported by others[7,8] and intercepted only a racemic intermediate, it demonstrates that diketopiperazine natural products can be accessed by an aza-Cope–Mannich rearrangement. We believe that our route to the diketopiperazine scaffold can be much more efficient when applied to the synthesis of analogues of amino ester **24** for biological examination.

Experimental Section

All the experimental details are gathered in the Supporting Information.

Acknowledgements

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Keywords: amino acids · medicinal chemistry · natural products · rearrangement · total synthesis

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FULL PAPER

Organic Synthesis

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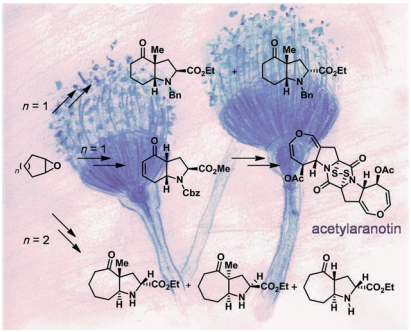
Synthesis of Bicyclic Proline Derivatives by the Aza-Cope–Mannich Reaction: Formal Synthesis of (±)-Acetylaranotin



Rearrangement mimics fungi: An approach to oxygenated bicyclic amino acids based on an aza-Cope–Mannich rearrangement is described. Seven distinct amino acid scaffolds analogous to the natural products were prepared on a gram scale with precise control of stereochemistry. Successful implementation of our strategy resulted in the formal synthesis of acetylaranotin (see scheme).